Konstantinos Fountas
Eftychia Z. Kapsalaki *Editors*

Epilepsy Surgery and Intrinsic Brain Tumor Surgery

A Practical Atlas

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Editors
Konstantinos Fountas
Medical School
University Hospital of Larisa Medical School
University of Thessaly
Biopolis
Larisa
Greece

Eftychia Z. Kapsalaki
School of Medicine
University of Thessaly School of Medicine
Biopolis
Larisa
Greece

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To Evie

Foreword

Epilepsy surgery and intrinsic brain tumor surgery share overlapping problems. While neurosurgeons specializing in glioma surgery nowadays know about mapping of brain function, they will not automatically know about the specific problems of epilepsy surgery related to intrinsic brain tumors. Drug-resistant epilepsy is a good indication for a surgical approach, and it is usually performed by specialized members of the neurosurgical team. Whereas the brain tumor surgeon focuses on preservation of function plus complete removal of the tumor, the epilepsy surgeon does the same but also focuses on removal of the epileptogenic area. So the tasks in the two fields are not identical. This book is devoted to the coverage of both, typical brain tumor problems plus the identification and safe removal of the epileptogenic focus related to brain tumors.

Twenty to 30% of all epilepsy surgery cases have involved tumors, mostly those well known to occur in association with drug-resistant epilepsy that in the past were termed long-term epilepsy-associated tumors (LEAT) or more recently low-grade epilepsy-associated tumors. These tumors tend to be more benign; however, a small proportion can turn out to be malignant in the long run. Therefore, complete tumor removal remains an aim also in the field of epilepsy surgery, just like in "normal" intrinsic brain tumor surgery.

Several chapters are devoted to modern diagnostic methods. The two main techniques for functional localization—extraoperative mapping with implanted electrodes and awake craniotomy—are covered, and, in fact, both techniques can also be used for conventional tumor surgery without the presence of drug-resistant epilepsy. For drug-resistant epilepsy, however, they are indispensable.

The book also covers the spectrum of epilepsy surgery including very recently introduced techniques such as responsive stimulation, and it devotes several chapters to specific types of gliomas that may pose specific problems as in insular gliomas.

The covered topics will be of interest for both tumor surgeons and epilepsy surgeons. The book has the potential to increase the interest of brain tumor surgeons in the necessity of including aspects of how to remove the epilepsy focus in low-grade brain gliomas, which are frequently associated with seizures even if these seizures are not drug resistant. The book is thus a contribution to abolish the mental barrier between "pure" glioma surgery and glioma surgery for epilepsy.

Bonn, Germany — Johannes Schramm

Foreword

This book bundles the knowledge and experience of about 40 renowned specialists in the diagnosis, clinical and preoperative setup, and therapy of patients with epilepsy and brain tumors. The editors are Eftychia Kapsalaki (neuroradiologist) and Kostas Fountas (neurosurgeon), both from the University Hospital of Larisa connected to the University of Thessaly in Greece, but both trained in the United States and authorities in their specialty. Not surprisingly, about one third of contributors are Greek, but many authors come from other European countries (Belgium, Croatia, Finland, France, Germany, Italy, Spain, and the United Kingdom), Israel, and the United States. The authors are radiologists, physicists, neurologists, epileptologists, neurosurgeons, and neuro-oncologists (Greece).

The focus of the book is the multidisciplinary diagnostic and therapeutic approach of patients with brain tumors and epilepsy in order to achieve better and safer outcome.

In the preoperative neuroimaging of patients with brain tumors and epilepsy, emphasis is on magnetic resonance imaging (MRI). Both conventional MR imaging as well as advanced imaging techniques such as diffusion-weighted imaging, perfusion imaging, diffusion tensor imaging, and functional MR are discussed in detail. Other novel nonradiological diagnostic preoperative examinations such as magnetoencephalography, surface electroencephalography, cortical stimulation, and others are described.

The therapeutic part of the book discusses all recent techniques such as neuronavigation, intraoperative imaging, stimulation techniques, and all available nonsurgical additional treatment modalities.

The editors should be congratulated not only for their personal input but above all for the excellent choice of authors and the high quality of the contributions.

Emeritus Guido Wilms
Neuroradiologist, University Hospitals Leuven
Leuven, Belgium

Preface

«Περὶ μὲν τῆς ἱερῆς νούσου καλεομένης ὧδ' ἔχει· οὐδέν τί μοι δοκέει τῶν ἄλλων θειοτέρη εἶναι νούσων οὐδὲ ἱερωτέρη, ἀλλὰ φύσιν μὲν ἔχει ἥν καὶ τὰ λοιπὰ νουσήματα, ὅθεν γίνεται.»

Ιπποκράτης (460–370 ΠΧ), Περί ιερῆς νούσου

"In regard to the so-called "sacred disease," the situation is the following: this disease is not more sacred or God-given than any other disease, according to my opinion. Contrariwise, it has exactly the same nature, and the same origin as any other disease."

Hippocrates (460–370 BC), About Sacred Disease

Since the Hippocratic era, the association of epilepsy and brain pathological conditions has been well established. It required, however, several centuries and significant work on animal and human anatomy and physiology before John Hughlings Jackson (1835–1911) postulated that brain tumors might cause focal epilepsy. He observed and described in 1890 olfactory seizures in a patient with a tumor in the right temporo-sphenoidal area and abnormal sensations of smell and taste in a patient with a temporal lobe tumor. His pioneering concept, that epilepsy is a symptom rather than a disease itself, radically changed our approach to the diagnosis and the management of epilepsy.

The recent advances in neuroimaging with the wide clinical application of magnetic resonance (MR) imaging, and all the MR-based imaging modalities provide the opportunity for an early and accurate diagnosis in the majority of epilepsy cases. Furthermore, the emerging hybrid imaging modalities, in which functional parameters are superimposed on highly accurate anatomical imaging studies, allow the identification and the localization of an underlying epileptogenic focus, even in cases in which all structural imaging studies appear normal.

These imaging advances along with the evolution of intraoperative neurophysiological stimulation and mapping techniques, as well as the wide clinical application of neuronavigational devices, allow the safe and aggressive resection of intrinsic brain tumors and the successful management of the associated epilepsy. Moreover, many of these surgical strategies are applicable even in cases of nonlesional epilepsy, when no anatomical abnormalities can be identified despite the exhaustive preoperative imaging workup of these patients. It has become evident in the past years that techniques from the field of epilepsy surgery can be easily transplanted to that of tumor surgery and vice versa.

The purpose of our current atlas is to serve exactly this emerging need for providing a systematic approach for all the available diagnostic and therapeutic modalities for safely managing patients with gliomas and/or epilepsy. The atlas describes in a practical, reader-friendly way all the currently available diagnostic methodologies for establishing an accurate diagnosis in cases of suspected tumor or in cases of epilepsy. In addition, it explores the exact role of all these methodologies in the presurgical planning of these cases. The contemporary intraoperative and extraoperative stimulation and mapping techniques, along with all the available resection surgical techniques, are also presented. The surgical management of gliomas is presented based on their anatomical location, since certain anatomical areas present certain technical difficulties.

We hope that you will find our publishing effort helpful in the management of patients with intracranial gliomas and/or epilepsy. If our current atlas assists you in improving the way you approach these challenging cases, then our goal has been achieved.

Larisa, Greece — Eftychia Z. Kapsalaki
Larisa, Greece — Konstantinos N. Fountas

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The authors wish to gratefully thank all the authors for their valuable contributions. Their time and their will to share their experience are greatly appreciated. Without them, our current publishing effort would have not been possible.

We also want to acknowledge Professors Johannes Schramm and Guido Wilms for their kind Foreword.

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Contributors

Rahul K. Ahluwalia, BS Department of Neurological Surgery, Indiana University, Indianapolis, IN, USA

Ayisha Al-Busaidi Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK

George A. Alexiou, MD, PhD Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece

Garrett P. Banks, MD Department of Neurological Surgery, New York-Presbyterian Hospital, The Neurological Institute, New York, NY, USA

Nicholas M. Barbaro, MD Department of Neurological Surgery, Indiana University Health Neuroscience Center, Indianapolis, IN, USA

Mitchel S. Berger, MD Department of Neurological Surgery, University of California San Francisco Medical Center, San Francisco, CA, USA

Sotirios Bisdas, MD, PhD Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK

John Boockvar, MD Department of Neurosurgery, Hofstra-Northwell School of Medicine, Manhasset, NY, USA

Shamik Chakraborty, MD Department of Neurosurgery, Hofstra-Northwell School of Medicine, Manhasset, NY, USA

Sofia Chatziioannou, MD Department of Nuclear Medicine, University of Athens, Biomedical Research Foundation, Academy of Athens, Athens, Greece

Hans Clusmann Department of Neurosurgery, TWTH Aachen University, Aachen, Germany

Alfredo Conti, MD, PhD Department of Neurosurgery, CyberKnife Center, Messina, Italy

Efthimios Dardiotis, MD, PhD Department of Neurology, University Hospital of Larisa/ Mezourlo Larisa, Larisa, Greece

Riëm El Tahry, MD, PhD Department of Neurology, Cliniques Universitaires St. Luc, Brussels, Belgium

Susana Ferrao Santos, MD Department of Neurology, Cliniques Universitaires St. Luc, Brussels, Belgium

Nicolas Foroglou, MD, PhD Department of Neurosurgery, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece

Konstantinos N. Fountas University Hospital of Larisa Medical School, University of Thessaly, Larisa, Greece

Kyriakos Garganis, MD, PhD Epilepsy Center, St. Luke's Hospital, Panorama-Thessaloniki, Thessaloniki, Greece

Antonio Gonçalves-Ferreira, MD, PhD Department of Neurosurgery, Hospital Santa Maria, Centro Hospitalar Lisboa-Norte, Faculdade Medicina, Universidade Lisboa, Lisbon, Portugal

Jorge Gonzalez-Martinez, MD, PhD, FAANS Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH, USA

Georgios M. Hadjigeorgiou, MD, PhD Department of Neurology, University Hospital of Larisa/Mezourlo Larisa, Larisa, Greece

Shawn L. Hervey-Jumper, MD Department of Neurological Surgery, University of California San Francisco Medical Center, San Francisco, CA, USA

Marcel A. Kamp, MD Department for Neurosurgery, Medical Faculty, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

Eftychia Z. Kapsalaki Department of Diagnostic Radiology, School of Medicine, University of Thessaly, Larisa, Greece

Athanasios P. Kyritsis Department of Neurology and Neurosurgical Institute, University Hospital of Ioannina, Ioannina, Greece

Gregory P. Lee, PhD Department of Neuropsychology, Barrow Neurological Institute, Phoenix, AZ, USA

Pantelis Lioumis, PhD Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Jyrki P. Mäkelä, MD, PhD BioMag Laboratory, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Laura Mancini, PhD Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK

Katerina Markou, MD Department of Neurology, University Hospital of Larisa/Mezourlo Larisa, Larisa, Greece

Robert A. McGovern, MD Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH, USA

Guy M. McKhann II, MD Department of Neurological Surgery, New York-Presbyterian Hospital, The Neurological Institute, New York, NY, USA

Stephen K. Mendenhall, MD Department of Neurological Surgery, Indiana University, Indianapolis, IN, USA

Andrew C. Papanicolaou, PhD Department of Pediatrics, Division of Clinical Neurosciences, University of Tennessee Health Science Center, Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, USA

Thanasis Paschalis Department of Neurosurgery, University Hospital of Larisa, Larisa, Greece

Nikoletta Pianou, MD Nuclear Medicine Division, Clinical Research Center, Biomedical Research Foundation, Academy of Athens, Athens, Greece

Christian Raftopoulos, MD, PhD Departments of Neurosurgery and Neurology, Cliniques Universitaires St. Luc, Brussels, Belgium

Cristina Ramirez-Aubone, PsyD Department of Neurology, Medical College of Georgia, Augusta, GA, USA

Marion Rapp, MD Department of Pediatrics, University of Luebeck, Luebeck, Germany

Roozbeh Rezaie, MD Department of Pediatrics, Division of Clinical Neurosciences, University of Tennessee Health Science Center, Memphis, TN, USA

Pantaleo Romanelli, MD Cyberknife Center, CDI, Milan, Italy

Krešimir Rotim, MD, PhD Department of Neurosurgery, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia

Michael Sabel, MD Department of Neurosurgery, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Tomislav Sajko, MD, PhD Department of Neurosurgery, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia

Johannes Schramm, MD Professor of Neurosurgery, University of Bonn Medical School, Bonn, Germany

Michael Schulder, MD Department of Neurosurgery, Hofstra-Northwell School of Medicine, Manhasset, NY, USA

Demitre Serletis, MD, PhD, FRCSC, FAANS, FACS Section of Neurosurgery, Health Sciences Centre, University of Manitoba, Winnipeg, MB, Canada

Loizos Siakallis, MD, Mres Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK

Panagiotis G. Simos, PhD University of Crete, Voute Campus, School of Medicine, Division of Psychiatry and Behavioral Sciences, Herakleion, Crete, Greece

Joseph R. Smith Department of Neurosurgery, Augusta University, Augusta, GA, USA

Maria Smuga, MD Department of Neurosurgery, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

Maria Sokratous, MSc Department of Neurology, University Hospital of Larisa/Mezourlo Larisa, Larisa, Greece

João Paulo Sant'Ana Santos de Souza, MD Laboratory of Neuroimaging, Teaching Hospital of University of Campinas (UNICAMP), Campinas, São Paulo, Brazil

Patricia Svolos, MSc, PhD Medical Physics Department, Medical School, University of Thessaly, Larisa, Greece

Dorota Tassigny, MD Department of Neurosurgery, Cliniques Universitaires St. Luc, Brussels, Belgium

Abraham Tsitlakidis, MD Department of Neurosurgery, AHEPA University Hospital, Thessaloniki, Greece

Dimitra Tsivaka Medical Physics Department, Medical School, University of Thessaly, Larisa, Greece

Ioannis Tsougos Medical Physics Department, Medical School, University of Thessaly, Larisa, Greece

Kenou van Rijckevorsel, MD, PhD Department of Neurology, Cliniques Universitaires St. Luc, Brussels, Belgium

Dirk Van Roost, MD, PhD Department of Neurosurgery, Ghent University Hospital, Ghent, Belgium

Géraldo Vaz, MD Department of Neurosurgery, Cliniques Universitaires St. Luc, Brussels, Belgium

Katherine Wagner, MD Department of Neurosurgery, Hofstra-Northwell School of Medicine, Manhasset, NY, USA

Guido Wilms, MD, PhD Department of Radiology, University Hospitals Leuven, Campus Gasthuisberg, Leuven, Belgium

Adam Kenji Yamamoto, MBBS, BSc, MRCS, FRCR Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK

Brain-Tumor Related Epilepsy

1

Efthimios Dardiotis, Maria Sokratous, Katerina Markou, and Georgios M. Hadjigeorgiou

Brain tumor related epilepsies (BTREs) account for about 12% of all acquired epilepsies and are a common symptom of brain tumors. The clinical signs and symptoms vary and are mainly focal in onset or secondarily generalized. Their features are indicative of their origin in the region of the brain. BTREs are difficult to manage because they usually are drug-resistant. The patients' characteristics should be carefully evaluated in selecting the appropriate antiepileptic drug (AED) and the therapeutic scheme.

1.1 Epidemiology

Epilepsy represents the most common symptom associated with brain tumors. In 20–40% of patients with brain tumors seizures are the initial symptom that leads to diagnosis, while in another 20–45% seizures appear during the course of the disease. Their incidence varies from 35% to 70% regardless of the type or localization of the tumor. Brain tumor–related epilepsy constitutes 12% of all acquired epilepsies. In patients with brain metastases, the presence of seizures varies from 48% for lung cancer metastases to 67% for metastatic melanoma [1].

Clinical studies have made clear that the presence of epilepsy depends on the histologic type, the site, the grade differentiation, and the growth pattern of the tumor as well as on the patient's special features, such as age and gender. Epilepsy frequency seems to be inversely correlated with tumor malignancy, that is, low-grade tumors such as meningiomas, astrocytomas, and oligodendrogliomas have been associated with a higher incidence of epilepsy (65–95%) in contrast to high-grade gliomas, which are associated with 15–25% of epileptic seizures. A frequency of about 100% has been reported in dysembriobIastic-neuroepithelial tumors. Also, slow-growing tumors seem to be associated with a higher incidence and younger age of onset of epilepsy. The early onset has been linked to better prognosis owing to a better location for surgical intervention or to the slow growth pattern of the tumor [1, 2].

Tumor-induced epileptogenesis has also been correlated with the localization of the tumor within the brain. Tumors situated within or near the cortex, such as meningiomas, are assumed to be more epileptogenic than those infiltrating deeper structures in the brain. Furthermore, higher seizure frequency has been reported in tumors sited in the frontal, parietal, and occipital lobes compared to those in the occipital lobes. Seizure frequency also increases with the proximity to the Rolandic fissure and to the central sulcus. However, tumors in the infratentorial and sellar regions constitute a rare cause of seizures unless they extend to the cerebral hemispheres [2].

1.2 Clinical Features from Neurologic Examination

Seizures appear as a common symptom in patients with brain tumors. Typically, they begin as focal seizures, and their semiology is usually indicative of the tumor localization. Even when a history of generalized seizures is described, the onset is focal, but either the patient cannot remember or these signs are silent. The partial seizure is most commonly motor, and it is usually manifested by limb or face jerking. When it appears in one limb, it may also progress to the ipsilateral limb (Jacksonian march). Focal seizures may secondarily become generalized [3].

Tumors affecting the temporal lobe such as gliomas may manifest partial seizures, including déjà vu sensations, gustatory hallucinations, speech arrest, or depersonalization. Visual hallucinations usually occur in patients with tumors affecting the occipital lobes. A particularly severe consequence of

E. Dardiotis (✉) · M. Sokratous · K. Markou
G. M. Hadjigeorgiou
Department of Neurology, University Hospital of Larisa/Mezourlo Larisa, Larisa, Greece

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partial seizures is the postictal prolonged motor weakness common in Todd paralysis, which may never resolve completely. In brain tumor patients presenting with generalized seizures, irreversible cognitive decline may follow. Also, status epilepticus foreshadows poor diagnosis in these patients and is often difficult to manage [4].

1.3 Classification According to Tumor Localization

1.3.1 Temporal Lobe Epilepsy

Temporal lobe seizures represent the most common form of partial epilepsies. They usually begin with auras, which may include sensory illusions, hallucinations, or visceral sensations such as thoracic, epigastric, or warm ascending sensations. The ictal episode is often manifested by a blank stare, loss of consciousness, vocal or oroalimentary automatisms, upper limb automatisms and tonic or dystonic postures, deviation of the head or eyes, and dysphasia. Oroalimentary automatisms consist of repetitive, stereotypical movements of the lips, mouth, jaw, or tongue, which look like lip-smacking or chewing. These automatisms may also involve swallowing, spitting, or gulping. Upper limb automatisms include repetitive movements, which have the appearance of fumbling, grasping, or searching. Both upper limb and oroalimentary automatisms are indicative of mesial temporal lobe lesions. In determining the lateralization of the lesion, postictal dysphasia and unilateral automatisms are assumed to be the most predictive signs. Unilateral automatisms present a typically ipsilateral allocation to the region of the seizure onset, while postictal dysphasia is characterized by a dominant hemisphere lesion. Seizures resulting from the nondominant hemisphere may preserve speech and responsiveness as well as minimal confusion in the postictal period [5].

The localization of the tumor within the temporal lobe can also be defined from clinical features with a specific semiology. Thus, temporal epilepsy can be divided into the mesial, the mesial-lateral part, and/or the lateral temporal lobe. Seizures deriving from the mesial part often begin with viscerosensory or epigastric sensations, a dreamy state, and fear. They are also characterized by a longer duration as well as by delayed loss of consciousness and automatism (mainly of the oroalimentary areas and upper limb). Seizures from the mesiolateral part of the temporal lobe are similar to those deriving from the mesial part, but the loss of consciousness appears earlier, as do the automatisms, including mainly oroalimentary, vocal, and verbal characteristics. Finally, seizures caused by lesions localized to the lateral temporal lobe usually begin with auditory hallucinations or illusions and loss of consciousness. They are shorter in duration, approximately less than a minute, and they often become secondarily generalized. Mesial (limbic) temporal lobe epilepsy should be distinguished from lateral (neocortical) epilepsy during the differential diagnosis in order to proceed to surgical treatment because each type exhibits differences in seizure relief and complications postsurgically [3, 6].

1.3.2 Frontal Lobe Epilepsy

Seizures caused by lesions in the frontal lobe represent the second most frequent form of partial epilepsies, with a 30% occurrence. They exhibit a peculiar semiology and are often misdiagnosed because they seem to be similar to pseudoseizures. They are usually short, with a duration of less than 30 s and they tend to occur in aggregations and many times in a day. The postictal loss of consciousness is usually minimal or absent. The semiology of frontal lobe epilepsy involves a sudden hypermotoric behavior, usually with vocal, sexual, gestural, and bilateral lower limb automatisms such as pedaling or cycling. Behavior depends on the localization of the lesion into the frontal lobe, which contributes to seizure development. However, clinical semiology cannot always indicate the specific tumor localization owing to extensive intraconnectivity in the frontal lobe, which leads to rapid spread of the seizures [7]. Generally, clinical features can originate from different parts of the frontal lobes, such as from the supplementary motor area (SMA), the mesial frontal lobe, the lateral curvature, the lateral dorsal cortex, the orbitofrontal cortex, and the cingulate gyrus. Seizures caused by lesions in the SMA are mainly characterized by vocal signs and asymmetric tonic extension of the proximal extremities, which may be abrupt and bilateral. The same features are present in seizures originating from the mesial frontal lobe. Seizures coming from the lateral curvature usually involve clonicity, which affects the contralateral limbs. Those originating from the lateral dorsal cortex exhibit speech arrest, strained thinking, and reversive deviation of the eyes and head as well as automatisms, including kicking, laughing, chewing, sniffing, or crying. Seizures from the orbitofrontal cortex are mainly characterized by symptoms from the autonomic nervous system (ANS), such as mydriasis, flushing, and tachycardia. They also manifest loud vocal signs and automatisms. Owing to rapid propagation of the seizures into the frontal lobe, this type of seizure often exhibits similar characteristics to seizures originating from the temporal lobe. Finally, seizures from the cingulate gyrus are quite similar to those coming from the SMA, but they also include behavioral arrest and mood swings as well as automatisms (oroalimentary, gestural, or sexual) and urinary incontinence at times [8].

1.3.3 Parietal Lobe Epilepsy

Seizures caused by lesions in the parietal lobe represent less than 10% of focal epilepsies. They often localize in clinically silent regions within the brain and tend to be symptomatic only when they spread to functional regions in the frontal, temporal, or occipital lobes. The clinical semiology includes somatosensory symptoms such as paresthesia, dysesthesia, and sensations of numbness, pricking, heat, and electricity, usually accompanied by exacerbating pain. Symptoms initially affect the face and the upper limbs on the opposite side of the tumor localization. In seizures resulting from tumors embedded in the parietal lobe of the nondominant hemisphere, patients may manifest hemispatial neglect of the contralesional side of their bodies or their surroundings. In tumor patients with lesions in the parietal lobe of the dominant hemisphere, seizures may include language disorders [3, 8].

1.3.4 Occipital Lobe Epilepsy

Seizures arising from lesions in the occipital lobe also constitute less than 10% of focal epilepsies. Their characteristic symptoms include visual hallucinations of steady or flashing light (white or colored). These delusions begin from the contralesional field of vision. Blackouts or "white-outs" are often referred to in patients' vision. Other symptoms involve eye deviation to the opposite side of the lesion and rapid blinking. The spread of a discharge defines the rest of the clinical semiology. Seizures from the occipital lobe can propagate to the posterior or mesial part of the temporal lobe, the parietal lobe, and the perirolandic regions. Furthermore, this kind of seizure can mimic those originating from the regions they spread to. For example, when a seizure spreads into the posterior part of the temporal lobe where the vision-associated area lies, it may manifest complicated visual hallucinations [9].

1.4 Seizures from Deeper Structures of the Brainstem

The precise effect of deeper structures of the brainstem in seizures is still unclear, although thalamocortical networks have been shown to be involved in some seizures. Up to now, only hypothalamic hamartomas have been proven to cause gelastic seizures. This kind of seizure may also be manifested by lesions in the mesial part of the frontal lobe or from the temporal lobe. They often consist of involuntary laughter, usually accompanied by tonic and bilateral elevation of the upper limb. The laughter is not an expression of joy or happiness. These seizures are also very short. The whole syndrome, which is associated with hypothalamic hamartomas, involves endocrine disorders, premature puberty, and arrested development. Surgical excision of the hamartoma can relieve patients from seizures [10].

1.5 Clinical Features in Children with Brain Tumor–Related Epilepsy

From a medical approach children cannot be considered as little adults; therefore brain tumors and their manifestations differ from those developing in adults. Although high-grade tumors and metastases are more frequent in adults, slow growing, low-grade tumors occur more frequently in children. Seizures appear in about 9–14% of all cases of children with brain tumors. More specifically, in children they occur in 49% of lobar tumors, in 40% of neocortical tumors, and in 22–38% of tumors in the supratentorial region. Also in children, brain tumor–related seizures are mainly focal in 85–100%. Generalized seizures, however, are more common in children than in adults. Seizure semiology has a unique manifestation in children and thus it is often misattributed to imitations or misdiagnosed [11].

Temporal lobe seizures in children present subtle features that may change during the course of the first 10 years of a child's lifetime. Infants usually develop tonic, clonic, motor, or myoclonic signs, whereas in toddlers behavioral arrest is more common. Automatisms, which are common symptoms in seizures from the mesial part of the temporal lobe in adults, such as lip smacking or finger rubbing, are usually absent in under school-age children [10, 11].

Seizures from the frontal lobes in children appear almost exclusively during sleep and are manifested by clonic motions or asymmetric posturing. Hypermotor seizures are less common in children than in adolescents or in adults. In older children, seizures from the frontal lobes may exhibit difficulties in sleeping; such seizures may be new in appearance or worsening and are accompanied by subsidiary nocturnal enuresis as well as personality changes. The latter are characterized by unrestrained and careless behavior. These features are often falsely attributed to sleep disruptions. Brain tumors in children may even be manifested as epileptic spasms consisting of paroxysmal behavior, such as eye deviation upward, upper limb extension, and/or body flexion. Genetic syndromes are often concurrent in such cases [11].

1.6 Features from the Electroencephalogram (EEG)

1.6.1 EEG Characteristics in Partial Seizures

Partial (focal) seizures are initially characterized by focal desynchronization of cerebral rhythms and minor, fast

rhythms of low potential. After that, rhythmic spikes of low potential are focally recorded; their height increases gradually while their frequency decreases. When the primal discharge originates from a special region in the cortex, these spikes may constitute the initial finding seen on the EEG. These features are characteristic of the tonic phase of seizures. They are followed by spike-wave complexes owing to inhibitory mechanisms, which compose the clonic phase of seizures. After the clonic phase, the EEG curves widen owing to depletion of cell bioelectrical activity. In the restoration phase, slow rhythms with increasing frequency appear in order to return to the condition before seizure occurs [12].

The duration of the discharge in partial seizures ranges from milliseconds, when it localizes in the somatomotor cortex, to over 2 min, when it comes from the frontal, temporal, or occipital lobe. Also, the localization of the epileptogenic focus includes cortical or subcortical regions, although the cortex is the most common point of origin for this type of seizure. The specific locus is nearly impossible to define by EEG because of rapid propagation (almost simultaneously) of the discharge into the brain and the lack of the procedure to distinguish between anatomic structures with different cerebral depths [13].

Partial seizures can be subclassified into simple focal, complex focal, and secondarily generalized seizures. Each type exhibits characteristic EEG features.

In simple focal seizures, the EEG diagram is characterized by contralateral discharges in the corresponding region of the cortex. The discharges localize in the primary regions of the cortex, last less than 1 min, and do not affect consciousness.

Complex focal seizures exhibit epileptic discharges that focus or propagate to temporal or frontotemporal regions where the coherence is accomplished. These discharges last longer and affect consciousness. The EEG picture during the seizures is characterized by unilateral or bilateral discharges, which are focal or diffusible in the temporal or frontotemporal regions. In the meantime, between two seizures, there are also focal unilateral or bilateral but they are asynchronous and appear in the frontal or temporal regions [12].

All kinds of partial epileptic seizures may be generalized secondarily and end up in generalized tonic-clonic seizures. The generalization happens so fast (in a few milliseconds) that the focus of the initial discharge is hardly noticeable, giving the impression of primary generalized seizures and thus confusing the differential diagnosis. Studies have shown that in secondarily generalized seizures, the initial discharge most commonly localizes in the frontal lobes and less often in the central structures or the parietal lobes. The rapid propagation mentioned, however, is the reason that these seizures are usually confused with primary generalized seizures [14].

1.6.2 EEG Characteristics in Brain Tumors

In brain tumor patients, the EEG is mainly characterized by slow rhythms and especially by "delta" rhythm. The tumor itself does not produce electric activity, and therefore the EEG disruptions come from functional disorders of neurons from neighboring or more distant regions, which are directly affected by the tumor development into the brain.

These disruptions are related to the localization of the tumor into the cerebral parenchyma and also to the size and the increased rate of growth of the tumor itself; this, in turn, is related to the tumor's histologic form. There are no special findings, however, that help to decipher the nature of the tumor or to discriminate it from other space-conquering lesions.

According to their localization, tumors can be separated into those lying in the posterior cerebral fossa and those localized in the cerebral hemispheres. Tumors of the midline structures are included in the first category because of the corresponding EEG features [15].

1.6.3 EEG Features of Tumors of the Posterior Cerebral Fossa

The value of the EEG in early diagnosis of tumors localized in the posterior cerebral fossa is very restricted, since pathologic features appear almost simultaneously with the main symptoms of the tumors, that is, increased intracranial pressure (ICP) and blurred vision. The increased ICP induces slow waves owing to pressure phenomena caused by the edema in the penetrating vessels of the diencephalon and the brainstem [13, 15].

The EEG at the initial stages of a tumor in the posterior cerebral fossa, when it is pathologic, is characterized by slow rhythm "theta" appearing at the same time at the frontal regions. At later stages, "delta" rhythms appear bilaterally; they are monomorphic, intermittent, and dominate in the side of the lesion, or alternatively when the lesion lies in the midline. These rhythms become more intense with eye-blinking, hyperventilation, and drowsiness. In adults, they plainly dominate in the frontal regions, while in children under 8 years old, they prevail in the occipital regions. "Alpha" rhythm is not affected at the initial developmental stages of the tumor, but it decreases in height and frequency in cases of increased ICP [15].

Similar EEG features appear in tumors localized in the thalamus with lateral slow waves and in the corpus callosum with primary slow rhythm development bilaterally. In distention of the septum pellucidum, however, slow waves, when present, most often prevail in the temporal regions [15].

1.6.4 EEG Features in Tumors of the Cerebral Hemispheres

Pathologic EEG features appear more frequently in tumors of the cerebral hemispheres than in those localized in the posterior cerebral fossa. The site of the tumor in the cerebral hemispheres is typically shown by EEG and reaffirmed with clinical examination of the patient [14, 15].

The typical EEG diagram of tumors localized in the white matter and extending to the surface is characterized by polymorphic "delta" activity, nonrhythmic, with high potential and frequency of about 2–3 waves per second. In tumors lying in the base of the brain or deep into the cerebral parenchyma, the EEG diagram is similar to that from tumors of the posterior cerebral fossa [15].

Apart from slow wave presence in the hemisphere of the lesion, there are also other EEG features contributing indirectly to tumor diagnosis. The most important of them is the disruption of the "alpha" rhythm, which is more profound in occipital tumor regions. "Beta" rhythm also decreases or disappears from the hemisphere of the lesion, especially when the lesion is situated in the fronto-rolandic regions. Sleep increases EEG abnormalities when the tumor extends to the surface of the hemispheres but hides the abnormalities when the tumor is located deeper than 3 cm of the surface [15].

1.7 Medical Treatment of BTRE

The treatment of BTRE is a complex therapeutic procedure and requires a personalized and unique approach because of drug interactions and pharmaco-resistance that patients may develop. Currently, BTREs are mainly treated with antiepileptic drugs (AEDs) [16]. AED treatment is often based on the motto "start low, go slow," starting the patient with a low dose and evaluating him or her with slow titration if possible so as to eliminate side effects. The basic approach is to start with a single AED as monotherapy at the lowest dose of effectiveness in controlling the seizures and continue with one or two AEDs as monotherapy trials, if necessary. Multiple AED treatment is generally avoided and used mainly in refractory epileptic cases [17, 18].

According to the guidelines published in 2000 by the American Academy of Neurolology, AEDs are not recommended as a prophylactic treatment when brain tumor patients have not experienced seizures. They affirm that seizure onset cannot be prevented by AEDs and considering the potential side effects, they suggest that prophylaxis with these drugs should not be routinely followed in such patients. In case the physician decides to use prophylactic treatment in brain tumor patients with no apparent seizures, the proposed practice is to postpone it for a week after surgery and as long as the patient is stable [19].

In patients with BTRE, the new second-generation AEDs seem to have less drug-to-drug interactions and are further subclassified into enzyme inducing (EIAEDs), non-enzyme inducing, and enzyme inhibiting, based on their interaction with cytochrome P450. This is important for BTREs because antineoplastic drugs undergo metabolic modification through the liver and may possibly interact with other drugs metabolized by the same cytochrome. Additionally, second-generation AEDs are far better tolerated by the patients [20].

When choosing AED monotherapy, physicians should consider the special patients' characteristics, such as age, sex, drug intake, and other concurrent diseases. Furthermore, the grade of the tumor is also supposed to affect treatment and AED selection [18]. However, only a few quality studies have been conducted so far involving the effectiveness of AEDs in BTREs, making it difficult to recommend the use of one drug over another. In fact, there has been no real progress in this field for over 20 years despite the high rate of glioma patients with epilepsy. Only a small, randomized pilot study of phase II suggested that it is safe to switch phenytoin to levetiracetam postoperatively in patients with supratentorial gliomas [21].

1.8 Management Focused on Tumor Grade

BTREs should be managed differently according to the grade of the tumor, as patients present differences in demographics, seizure types, clinical semiology, response to treatment, and urgency of the case [22].

1.9 Treatment of Low Grade–Glioma Associated Epilepsy

BTREs in low-grade glioma patients are often managed with a treatment focusing on symptom relief. Surgery may only be recommended in patients with drug-resistant epilepsy with a significant impact on their quality of life. As treatment with chemotherapy or radiotherapy has not proved to expand the lifespan in these patients, neurologists together with oncologists seem to play the critical role in their management [22, 23]. In this direction, the International League Against Epilepsy has recently suggested that levetiracetam and zonisamide have similar effects to carbamazepine and phenytoin, and they can be effectively used as monotherapy in adults with focal seizures [24].

1.10 Treatment of High Grade–Glioma Associated Epilepsy

There is no strong evidence to High Grade–Glioma Associated Epilepsy support using one AED over another in patients with high grade–glioma associated epilepsy. Thus, three main points should be considered in selecting the appropriate prescription: tolerability, drug-to-drug interaction, and potential antitumor effect. Generally, second-generation AEDs are considered to have fewer side effects and pharmacokinetic and pharmacodynamic interactions. Taking into account that glioblastoma patients are mainly elderly and also taking other medications, low doses of new AEDs are presumed to be safer. Furthermore, AEDs such as carbamazepine, phenytoin, and valproate have shown an antitumor effect during laboratory studies. Also, levetiracetam has been shown to improve the response of glioblastoma patients to temozolomide. However, none of these drugs have been tested for glioma [22, 25, 26].

1.11 Drug Resistance in BTREs

BTREs, especially in patients with low-grade gliomas, are often resistant to AEDs. Drug-resistant epilepsy is defined as epilepsy failing to respond to two appropriately selected and tolerated AED schedules, used either in combination or as monotherapies. The drug resistance can be classified as (a) primary, referring to the tumor itself, (b) secondary, dealing with the consequences of BTREs, (c) specific, taking into account the response of the patient to one specific drug, and (d) nonspecific, referring to the response to a variety of drugs [17].

The pathophysiologic mechanisms of drug-resistant BTRE are not yet fully elucidated but two hypotheses seem to be predominant. The first focuses on the receptors targeted by the AEDs, supporting the theory that modifications in their binding sites might be responsible for the lack of sensitivity leading to drug resistance. The second suggests that overexpression of genes, codifying specific transporter proteins, may restrict the access of AEDs into the tumor tissue, resulting in their decreased intraparenchymal levels [17, 19].

Conclusion

BTREs are mainly manifested by partial seizures of focal onset, including a variety of clinical signs and symptoms. Seizures may secondarily be generalized. The specific orientation of the seizure into the brain can be identified by the clinical examination of the patient and the characteristic signs presented. The EEG is considered to be a useful tool, assisting the clinical evaluation in defining the region of epileptogenesis. The management of BTREs requires a personalized approach, showing caution of the interactions and tolerability of AEDs. This is because many patients with BTREs, especially those with low-grade tumors, develop drug resistance. Generally, the new second-generation AEDs are considered to have less side effects and drug-to-drug interactions than the old ones. However, research has yet to reveal which scheme could improve the patients' response and prevent the tumor growth.

References

1. Salmaggi A, Granata T, Rigamonti A. Pathophysiology of brain tumor-related epilepsy. In: Newton HB, Maschio M, editors. Epilepsy and brain tumors. Boston: Academic; 2015. p. 111–8.
2. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. Lancet Neurol. 2007;6:421–30.
3. Rudzinski LA, Shih JJ. The classification of seizures and epilepsy syndromes. Continuum (Minneapolis, MN). 2010;16:15–35.
4. Rogers L. Cancer and the nervous system clinical features and complications. In: Daroff RB, Jankovics J, Mazziotta JC, Pomeroy SL, editors. Bradley's neurology in clinical practice. 7th ed. Philadelphia: Elsevier; 2012. p. 1037–40.
5. French JA, Williamson PD, Thadani VM, Darcey TM, Mattson RH, Spencer SS, et al. Characteristics of medial temporal lobe epilepsy: I. Results of history and physical examination. Ann Neurol. 1993;34:774–80.
6. Berg AT, Scheffer IE. New concepts in classification of the epilepsies: entering the 21st century. Epilepsia. 2011;52:1058–62.
7. Bancaud J, Talairach J. Clinical semiology of frontal lobe seizures. Adv Neurol. 1992;57:3–58.
8. Luders H, Acharya J, Baumgartner C, Benbadis S, Bleasel A, Burgess R, et al. Semiological seizure classification. Epilepsia. 1998;39:1006–13.
9. Giulioni M, Marucci G, Martinoni M, Marliani AF, Toni F, Bartiromo F, et al. Epilepsy associated tumors: review article. World J Clin Cases. 2014;2:623–41.
10. Jobst B, Williamson P. Anatomical-clinical localization of ictal behaviour. In: Kaplan PW, Fisher RS, editors. Imitators of epilepsy. 2nd ed. New York: Springer, Demos Medical Publishing; 2005. p. 47–62.
11. Lopez J. Brain-tumor-related epilepsy in children. In: Newton HB, Maschio M, editors. Epilepsy and brain tumors. Boston: Academic; 2015. p. 65–99.
12. Κάζης Α. Επιληψίες. In: Press US, editor. Κλινική Νευροφυσιολογία. Thessaloniki: University Studio Press; 1984. p. 43–60.
13. Blume TW. Electroencephalography in diagnosis of non-epilectic and epileptic conditions. In: Peter KW, Roberts FF, editors. Imitators of epilepsy. 2nd ed. New York: Springer, Demos Medical Publishing; 2005. p. 33–46.
14. Appleton R, Nicolson A, Smith D, Chadwick D, MacKenzie J. Etiology. Atlas of epilepsy. London: Informa Healthcare; 2007. p. 41–114.
15. Κάζης Α. Όγκοι του εγκεφάλου. In: Press US, editor. Κλινική Νευροφυσιολογία. Θεσσαλονίκη. Thessaloniki: University Studio Press; 1984. p. 61–6.
16. Newton HB, Maschio M. Clinical evaluation of epilepsy in the brain-tumor patient. In: Newton HB, Maschio M, editors. Epilepsy and brain tumors. Boston: Academic; 2015. p. 43.

17. Leslie R, Maschio M, Newton HB. Antiepileptic drugs and brain tumor patients. In: Newton HB, Maschio M, editors. Epilepsy and brain tumors. Boston: Academic; 2015. p. 195–205.
18. Maschio M. Brain tumor-related epilepsy. Curr Neuropharmacol. 2012;10:124–33.
19. de Groot M, Reijneveld JC, Aronica E, Heimans JJ. Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment. Brain. 2012;135:1002–16.
20. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54:551–63.
21. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev. 2008;(2):Cd004424.
22. Grant R. Overview: brain tumour diagnosis and management/royal college of physicians guidelines. J Neurol Neurosurg Psychiatry. 2004;75:ii18–23.
23. Hildebrand J, Lecaille C, Perennes J, Delattre JY. Epileptic seizures during follow-up of patients treated for primary brain tumors. Neurology. 2005;65:212–5.
24. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the quality standards Subcommittee of the American Academy of neurology. Neurology. 2000;54:1886–93.
25. Gallagher P, Leach JP, Grant R. Time to focus on brain tumor-related epilepsy trials. Neuro-Oncol Pract. 2014;1:123–33.
26. Newton HB, Dalton J, Goldlust S, Pearl D. Retrospective analysis of the efficacy and tolerability of levetiracetam in patients with metastatic brain tumors. J Neuro-Oncol. 2007;84:293–6.

The Role of Diffusion Weighted and Diffusion Tensor Imaging in Epilepsy

2

Dimitra Tsivaka, Patricia Svolos, Eftychia Z. Kapsalaki, and Ioannis Tsougos

2.1 Introduction

Epilepsy is a chronic neurologic disorder characterized by unpredictable, recurrent, unprovoked seizures. It is the fourth most common neurologic disorder and affects people of all ages. A substantial number of epilepsies are well controlled with the administration of suitable antiepileptic medication. However, approximately 20–30% of epilepsy cases can be medically intractable, and hence there is an increasing interest in surgical approaches for seizure abolition [1]. It follows that accurate lateralization and localization of the epileptogenic focus are significant prerequisites for determining surgical candidacy once the patient has been deemed medically intractable.

Neuroimaging and especially magnetic resonance imaging (MRI) play a very important role in the identification and localization of the seizure focus. MRI with high-resolution structural imaging has become the modality of choice, and it is essential in detecting hippocampus and temporal pole atrophy as well as structural abnormalities such as cortical dysplasias [2]. Nevertheless, the detection of structural lesions is not always feasible, and the true extent of the abnormality may not be reflected using exclusively conventional MRI [3]. Advanced MR based imaging techniques such as diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), and diffusion MR tractography may also be used as multimodal approaches for the purpose of detection of abnormalities and investigation of the microstructural alterations.

Since these advanced neuroimaging techniques are increasingly established in the clinical routine, the objective of this chapter is to analyze and discuss the meaningful role of diffusion MRI in epilepsy, both in the diagnosis, treatment, and research of the disorder.

D. Tsivaka · P. Svolos · I. Tsougos (✉)
Medical Physics Department, Medical School,
University of Thessaly, Larisa, Greece
e-mail: tsougos@med.uth.gr

E. Z. Kapsalaki
Department of Diagnostic Radiology, School of Medicine,
University of Thessaly, Larisa, Greece

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2.2 Diffusion Imaging

2.2.1 Diffusion Weighted Imaging (DWI): Basic Principles

Water molecules placed inside a medium are in continuous motion because of their thermal energy. Their collisions with other water molecules combined with their motion describe a random walk which is called Brownian motion originating from the Scottish botanist Robert Brown. The phenomenon of diffusion can be observed when a drop of ink is added to a glass of water. Human tissue and especially the human brain has a more complex structure; it contains neuronal axons, macromolecules, and cell membranes, which hinder and restrict water diffusion. As a result the water mobility is anisotropic. When a wealth of neuronal axons are located in a brain area, then the water molecules are forced to move along their axes rather than perpendicular to them.

Additionally, Brownian motion is the natural occurrence on which DWI is based. The insertion of a patient into the MR scanner, namely, into its homogeneous magnetic field, induces alignment of nuclear spins in the same direction of the static magnetic field. The application of a radiofrequency pulse induces protons to spin, while the duration, the strength, and the direction of the pulse define the rate of the spin. If an equal and opposite gradient is applied, protons will be refocused, and thus the signal of the stationary protons will be null in contrast to mobile protons, which will display a signal loss. The factor that reflects the strength and duration of the gradients used to generate diffusion-weighted images is called the b-value [4]. In order to determine the direction of diffusion, the signal from mobile protons should be measured.

Nevertheless, the spin alignment will be ruined because of the different effect the magnetic field will have on every spin. This misalignment of the spins leads to a decline of the total signal, which arises as the sum of signals from every individual spin [5]. The most common pulsed-gradient spin-echo pulse sequence for diffusion imaging is illustrated in Fig. 2.1.

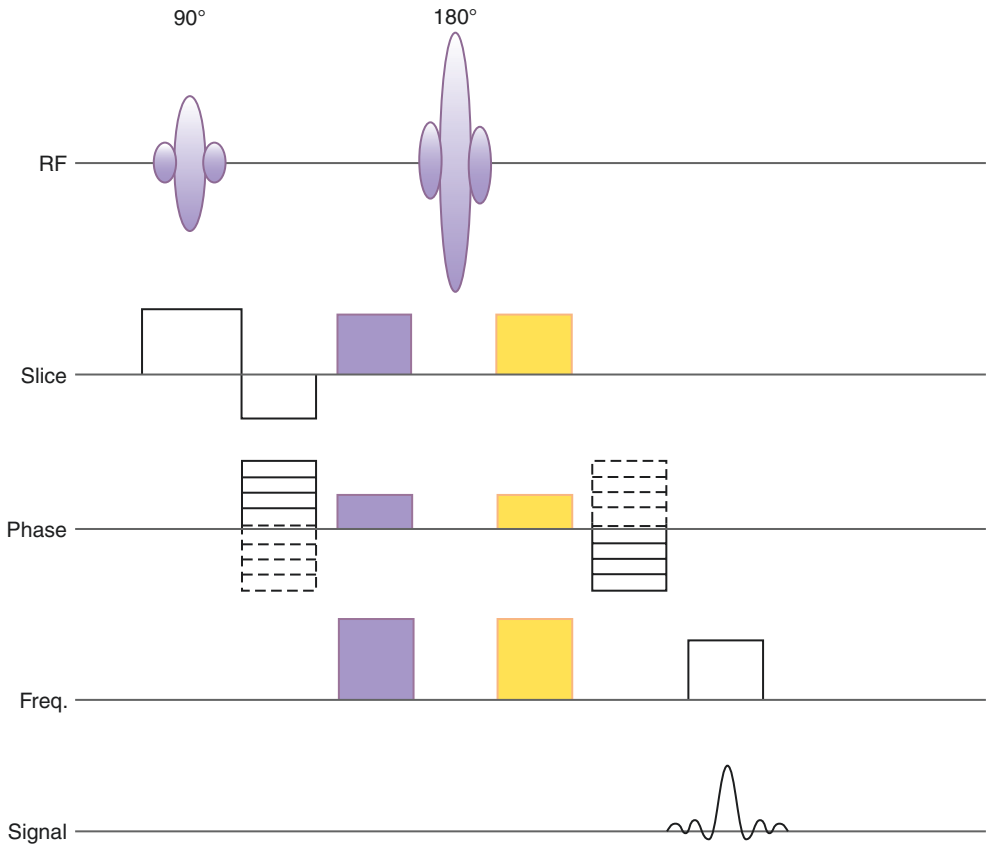

Fig. 2.1 A pulsed-gradient spin-echo pulse sequence for diffusion imaging

The parameter that adequately characterizes DWI is called apparent diffusion coefficient (ADC). The term "apparent" shows that there is often an average measure of a number of complex processes within the tissues and does not always represent the magnitude of the inherent self-diffusivity of water [6, 7].

ADC can measure the magnitude of diffusion within every voxel, and this constitutes the aim of DWI. After processing a number of DWIs with different b-values, a parametric map is created. More specifically, in this parametric map of ADC values the intensity of every pixel represents the strength of the diffusion in it. The interpretation of the ADC values shows that a bright signal corresponds to a high ADC value and reflects free diffusion, while a dark signal corresponds to a low ADC value and denotes restricted water movement [8]. Figure 2.2 depicts a typical ADC parametric color map.

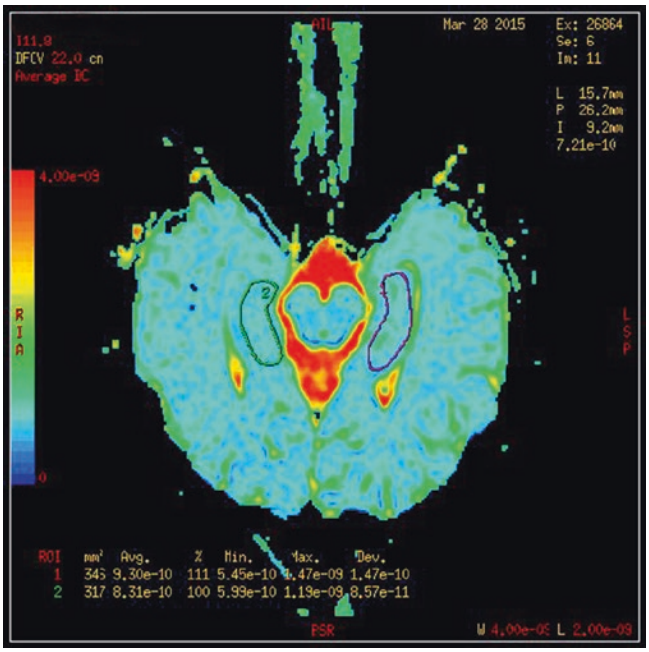

Fig. 2.2 ADC parametric color map

2.2.2 Diffusion Tensor Imaging (DTI): Basic Principles

DWI is undoubtedly a very useful clinical tool, but unfortunately it suffers from a serious limitation. It is only a qualitative type of examination and depends on the direction of the applied diffusion encoding gradient. This means that in certain regions of the brain, ADC will be different, depending on the applied gradient. In other words, ADC is directionally dependent [9, 10], and it follows that an infinite number of ADC measures should be obtained to characterize anisotropic tissue. Inside the brain, the presence of neuronal axons and macromolecules, cell membranes, and several intracellular subunits hinders and limits the diffusion of water. In particular, the preferable direction of water diffusion is along the white matter axons compared to the direction perpendicular to them, and in the first case the diffusion is called anisotropic (Fig. 2.3) [4]. In that sense, different tissue structures affect the diffusion profile of water in different ways.

DTI evolves from DWI and was developed to remedy the aforementioned limitations of DWI, exploiting the preferential water diffusion inside the brain tissue [11, 12]. Diffusion tensor (DT) is a mathematical model that can summarize the measurements of both the magnitude and direction of proton motion, which correspond to individual voxels [8]. Assuming that the probability of molecular displacements follows a multivariate gaussian distribution over the observation diffusion time, DT is defined as a 3 × 3 matrix of numbers corresponding to several diffusion rates for different diffusion directions. The mathematical formulation below represents the DT matrix of an anisotropic and a perfect isotropic diffusion, and it contains nine elements.

$$D = \begin{bmatrix} Dxx\ Dxy\ Dxz \\ Dyx\ Dyy\ Dyx \\ Dzx\ Dzy\ Dzz \end{bmatrix} D_{isotropic} = \begin{bmatrix} D\,0\,0 \\ 0\,D\,0 \\ 0\,0\,D \end{bmatrix}$$

Assuming that the directional motion of water within a voxel can be depicted by an ellipsoid (*see* Fig. 2.3), it can be

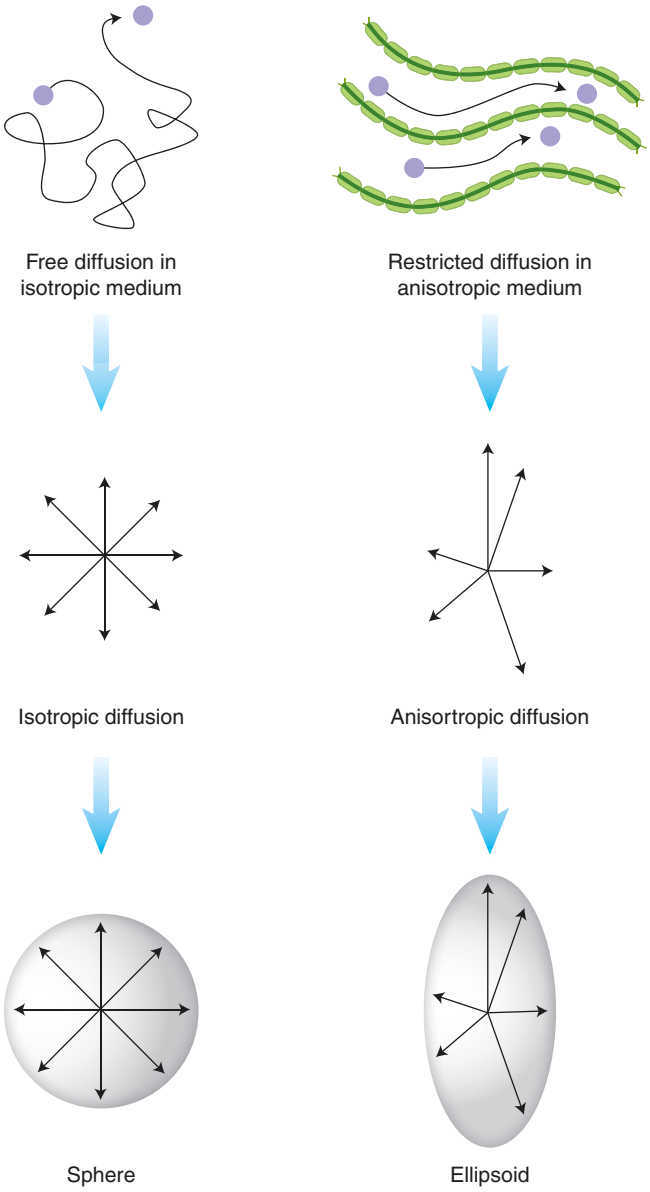

Fig. 2.3 The diffusion of water molecules in an isotropic and in an anisotropic medium

described by the tensor in that particular voxel. This tensor practically is a 3 × 3 matrix derived from measurements of water diffusivity in at least six different directions. The tensor matrix demonstrates diagonal symmetry (Dij = Dji), and that means the complete determination of the matrix by six parameters. If the diffusion tensor is totally aligned with the anisotropic medium, the off-diagonal elements are all zero and the tensor is diagonalized. The outcome of this diagonalization is three eigenvectors—v1, v2, and v3—that describe the orientation of the three axes of the ellipsoid. Additionally, three eigenvalues (λ1, λ2, and λ3) arise and represent the magnitude of the axes (apparent diffusivities) in the corresponding directions (Fig. 2.4). The direction of the major axis is considered to coincide with the direction of maximum diffusivity (λ1) and with the orientation of the tract [4, 13]. Therefore, a conversion occurs from the x, y, z coordinate system defined by the geometric characteristics of the scanner to a new coordinate system where axes are prescribed by the directional diffusivity information.

Local diffusion defines the shape of the ellipsoid, namely, prolate, oblate, or spherical. There are many diffusion parameters offering specific information, but the most common and widely used are the fractional anisotropy (FA) and mean diffusivity (MD). FA is calculated from the standard deviation of the eigenvalues λ1, λ2, and λ3, while MD is the mean of the eigenvalues describing the directionally measured average of diffusivity of water molecules.

The degree of anisotropy, which refers to a particular voxel, is represented by the signal brightness as it is displayed on a FA map. The microarchitecture of the tissue affects the value of FA; it fluctuates between 0 (isotropic diffusion) and 1 (highly anisotropic diffusion). Typical examples of isotropic and anisotropic diffusion are the cerebrospinal fluid (CSF) (value closer to 0) and the corpus callosum (value closer to 1) [4]. In Fig. 2.5, a T2 weighted image, an ADC, an FA map, and a color-coded orientation map are illustrated.

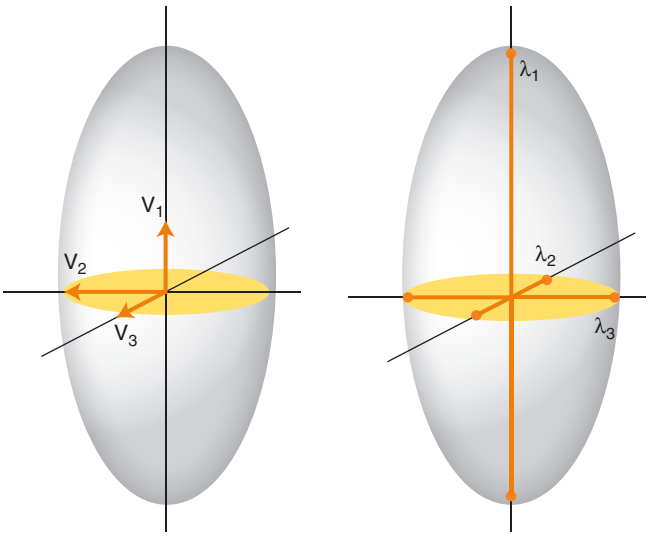

Fig. 2.4 The orientation of the three axes of the ellipsoid is described by three eigenvectors: v1, v2, and v3. The magnitude of the axes of the ellipsoid is represented by three eigenvalues: λ1, λ2, and λ3

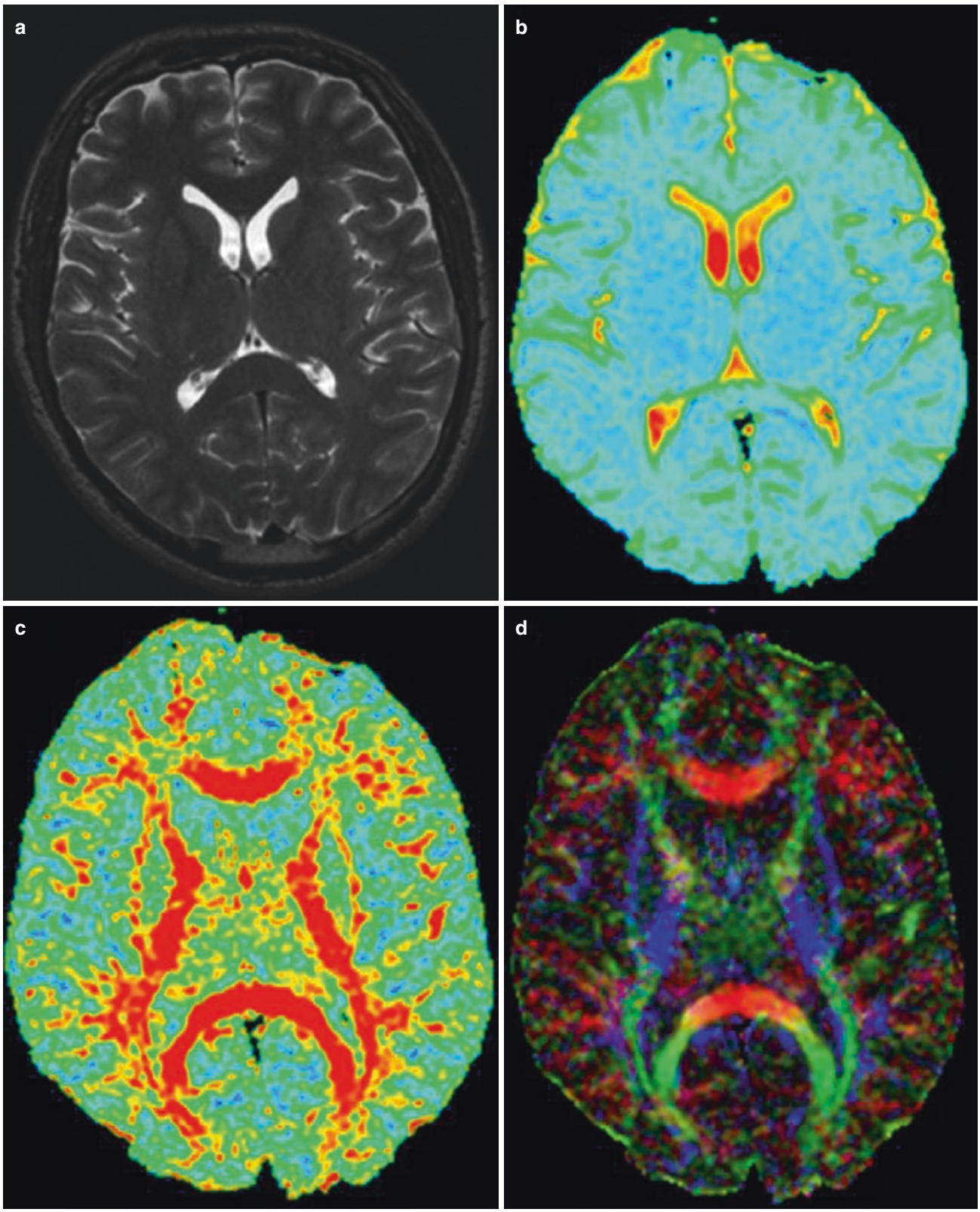

Fig. 2.5 (**a**) T2-weighted image; (**b**) Average DC; (**c**) FA map; (**d**) Color-coded orientation map. Images were acquired using a 3.0 T scanner. The colors (red, green, blue) correspond to different orientations of fibers; red: right–left, green: anterior–posterior, and blue: superior–inferior

2.2.3 Diffusion-Based MRI in Epilepsy

DTI provides information regarding the microstructural arrangement of a tissue and can improve understanding of the structural pathology that induces epilepsy. Epileptic seizures fail to come under control with seizure medication in about one third of cases. A number of terms such as "refractory," "intractable," or "uncontrolled epilepsy" are used to describe this situation. However, the International League Against Epilepsy has proposed the term "drug-resistant epilepsy." According to the League, drug-resistant epilepsy occurs when a person has failed to become seizure free with adequate trials of two seizure medications [14]. This type of epilepsy can be treated with surgical intervention when the seizures are focal and the epileptogenic area can be removed safely. Hence, the detection of a structural brain lesion or/and abnormality is of paramount importance for the presurgical work-up [15]. Advanced MRI techniques offer a noninvasive method for the investigation of underlying neurobiological abnormalities that cause epileptic seizures.

Epileptic seizures are classified into three main types: focal, generalized, and unknown onset. Focal seizures refer to those that affect only one hemisphere of the brain; generalized seizures indicate that both sides of the brain are affected at the start of a seizure; and unknown onset are seizures with no clear seizure focus from the beginning of the event [16].

There is also a list of terms such as epileptogenic zone, status epilepticus (SE), and temporal lobe epilepsy (TLE) that need to be defined because there is a large body of literature on diffusion-based analysis in cases with one of the aforementioned categories of epilepsy. The epileptogenic zone is defined as the area of cortex indispensable for the generation of clinical seizures [17], and SE is defined as a continuous seizure lasting more than 30 min or two or more seizures without full recovery of consciousness between them [18]. TLE is the most common form of partial or localization-related epilepsy, where seizures begin in the temporal lobe.

Especially during SE (prolonged seizures), there is a breakdown of the sodium-calcium pumps on brain cell membranes (cytotoxic edema), which leads to a rapid uptake of water intracellularly and can cause cellular swelling [19]. This cellular swelling in diffusion MRI is reflected as a reduction in the ADC parameter. The vasogenic edema that follows cytotoxic edema allows the penetration of fluid and proteins into the interstitial extracellular space; the extracellular volume increases and the ADC is subsequently increased [20].

There are two different approaches to the evaluation of diffusion MRI in epilepsy. The first category refers to peri-ictal and postictal studies, namely, immediately or shortly after a seizure, while the second category includes interictal studies conducted between seizures.

2.3 Peri-ictal and Postictal Studies

2.3.1 Status Epilepticus (SE)

One of the earliest studies of DWI in SE was that of Wieshmann and colleagues in 1997, which referred to a female patient with focal motor SE (jerking of the right leg). Their diffusion findings denoted a decrease of 27% in ADC in the left motor cortex and a 31% increase of ADC of the subcortical white matter compared to the contralateral hemisphere [21]. Two years later, Diehl and coworkers and Lansberg and associates came to similar results [22, 23]. More specifically, Diehl's group investigated the distribution of ADC in 35 patients with focal motor SE and noticed an ADC decrease of 23% in the frontal region of interest. Additionally, the region of maximal decrease coincided with the area of seizure activity according to the intraoperative EEG [22]. Lansberg and coworkers observed a cortical hyperintensity on T2 images, and their ADC measurements showed a decline of 36% in the affected hemisphere compared to the unaffected one [23]. Other studies associated ADC reduction with diffuse atrophy in both occipital lobes and revealed an osmotic connection between epileptogenic and surrounding areas [24, 25]. In 2004, the findings of Hong and colleagues included an increased signal in T2 images and also increased ADC in the left temporoparietal area, which indicated vasogenic edema. However, in many follow-up scans, "normal" ADC and no atrophy were detected as a result of successful treatment of the seizures [26, 27]. It is important to highlight the fact that the potential etiologic factors of epilepsy can vary widely, since a stroke, encephalitis, or an infection, for example, can provoke epileptic seizures. In that sense, all the aforementioned underlying pathologies can affect the diffusion MRIs, and it is significantly complex to search for diffusion changes that are not caused by epileptic seizures. Every different study implements appropriate protocols and analysis methods that are adjusted to the clinical characteristics of the patient groups.

2.3.2 Temporal Lobe Epilepsy (TLE)/ Drug-Resistant Epilepsy

To measure ADC in patients with TLE, Diehl and coworkers presumed that DWI may detect and delineate the epileptogenic region [28]. Nine patients with intractable epilepsy were scanned after EEG documented seizures (45–150 min). The etiology of TLE was hippocampal sclerosis (HS), left mesial temporal lobe tumor, SE, or unknown. As a consequence, only one of the six TLE patients showed estimable decreases in ADC. Two SE patients exhibited a reduction or no change in ADC, while the patient with an incompletely resected temporal lobe tumor exhibited ADC abnormalities.

Thus, Diehl's group came to the conclusion that only occasionally may postictal DWI help the delineation of epileptic areas in patients with TLE. Similar findings were also derived from the study of Hufnagel and associates, in which after diffusion analysis in a group of nine patients with refractory epilepsy, ADC changes during postictal DWI were complex [29]. DWI scans were acquired 2–210 min after a seizure, and postictal ADC values varied from a 25–31% decrease in the epileptogenic zone (two patients) to widespread bilateral increase after a seizure provoked by flumazenil (one patient). Three of the remaining patients had generalized ADC changes after generalized or prolonged seizures, and the last three revealed no significant changes after short-lived seizures or if the interval between the seizure and the first DWI scan was up to 15 min long. In some cases, estimable differences in ADCs were noticed only in patients with neocortical ictal onset zones or in the neocortical portion of the temporal lobe [30].

Konermann and coworkers [31] implemented a different method in order to cause epileptiform activity. They scanned 12 patients with intractable TLE or/and extratemporal lobe epilepsy interictally and 10 min after seizure after the injection of 1 mg of flumazenil. Their interictal result was a considerable ADC increment in the hippocampus of the epileptogenic area of all TLE patients. Postictal results showed significant ADC reduction in all patients compared to interictal scanning but altered corresponding to the different regions of interest (ROIs). A large decrease of 14.8% was observed in the hippocampus on the seizure-onset side, while this decrease became lower for both the parahippocampal gyrus on both sides and in the cortex on the non-ictogenic side.

More recent studies have investigated DTI measures such as FA and MD in intractable focal epilepsy and inquired into their utility in the preoperative assessment of patients with epilepsy. Diehl and coworkers [32] conducted a representative study and detected a postictal decrease in MD, which is probably associated with cellular swelling in areas of seizure focus and seizure spread; on the other hand, FA appeared less sensitive in changes. Interictal and postictal images were acquired from a group of 18 patients with intractable focal epilepsy. Their results were compared to those of 27 normal controls. Interictal findings revealed an appreciable increase of MD in 72% of patients, whereas 50% of the patients had significant relative decrease in MD (40% of patients had focal changes) postictally. No significant fluctuation in FA was noticed between postictal and interictal data [32]. According to another study performed by Salmenpera and colleagues [33], the evaluation of MD may indicate the networks involved in seizures but it is not an effective method for the accurate delineation of the seizure focus. Interictal scans and a scan after 23 seizures were performed in 21 patients with intractable focal epilepsy. The interval was about 53 min between seizure onset and scanning. The results after comparison with 20 normal controls showed that in 11 patients and in 12 of 23 seizures, increases and decreases of MD were observed. Five patients revealed both increases and decreases postictally, and in four patients the changes co-localized with postulated seizure focus. Taking into account all these postictal studies, it is evident that there are examples of discordance between their results. Different types of seizures, various etiologies, and the small sample size are all factors that complicate the reproducibility and the corroboration of the results.

2.3.3 Interictal Studies

Interictal studies include qualitative and quantitative analysis of diffusion MRIs acquired during the period between seizures. There is a list of interictal studies of DTI in epilepsy that chronologically start in 1999, when Krakow and colleagues [34] analyzed data from one patient with a malformation of cortical development (MCD) in the right hemisphere. They utilized DTI, functional MRI, and CSI to study partial and secondarily generalized seizures of the patient and came to the conclusion that DTI showed the heterogeneous microstructure of the MCD attended by reduced FA and elevated MD. This MR technique provides a wealth of microstructural, biochemical, and functional information regarding the epileptogenic tissue that cannot be obtained with other noninvasive means [34].

Both publications of Eriksson and associates [35] and Rugg-Gunn and coworkers [36] in 2001 investigated the combination of DTI and statistical parametric mapping (SPM) in a group of patients with partial seizures. Eriksson's group [35] compared 22 patients with partial seizures and MCD with 30 normal controls and found areas of reduced FA in 17 out of 22 patients, increased FA in 2 out of 22 patients, and increased MD in 10 out of 22 patients. Rugg-Gunn's group [36] calculated FAs and MDs of 40 patients (10 with partial seizures and acquired lesions and 30 with partial seizures and normal MRIs); they also discovered decreased FAs and elevated MDs in all of the patients. Moreover, there were nine patients in whom the abnormalities identified on conventional MRI concurred with the areas of decreased FA. Both studies indicated changes in tissue beyond the affected area that appeared normal on conventional MRIs.

There is an association between the epileptogenic hippocampal formation and abnormalities in DTI measurements in unilateral TLE [37]. Assaf and colleagues studied 12 patients with unilateral TLE, compared them with a group of 14 healthy controls, and found that FA was lower in contrast to values of the contralateral hippocampus. In addition, the MD of hippocampal formation was significantly greater ipsilateral to the epileptogenic focus. A study of 2005 showed that diffusion abnormalities were localized not only in the areas of the epileptogenic hippocampus but also that a larger network was involved [38]. It was Thivard and coworkers who scanned 35 well-defined medial TLE patients (caused by hippocampal sclerosis) and 36 normal controls in order to examine the impact of mesial TLE on the architecture of a wide cerebral network. Their findings showed decreased FA ipsilaterally in temporal lobe formations and in extratemporal regions and increased MD in the affected epileptic hippocampus. MD of the contralateral normal hippocampus, amygdala, and temporal pole displayed a reduction. Figure 2.6 depicts a T2-weighted image, the ADC and FA maps, and the tractogram of a patient with hippocampal sclerosis.

The expected reduction of FA and increment of MD was corroborated by two more studies: Gross and coworkers [39] and Dumas de la Roque and colleagues [40]. More specifically, Gross' group [40] evaluated five patients with refractory epilepsy and focal cortical dysplasia (FCD) and analyzed their DTI images producing FA maps and calculating MDs. The results revealed decreased FA, increased MD, and white matter hyperintensities on T2-weighted images in three patients and no abnormalities in the other two patients. Dumas de la Roche and coworkers [39], on the other hand, performed a dedicated investigation of FA. They measured FA in the internal capsule, in normal white matter, close to the area affected by the lesion and away from it in 15 patients with a cortical lesion identified on structural MRI. An up to 10% reduction in FA was detected in 12 patients away from the lesion and in 13 patients close to the lesion. Furthermore, FA in the internal capsule was normal, and a lower but significant decrease of FA was observed in the WM adjacent to and away from the lesion. Thus, they came to the same conclusion as did Eriksson and Rugg-Gunn; DTI changes can reveal WM abnormalities that appear normal on conventional MRI [35, 36, 39]. A subsequent study of Salmenpera and associates analyzed high resolution DTI data of 7 patients with unilateral TLE and 13 healthy controls and detected abnormal FA values compared to the control group [41]. High-resolution DTI recognizes lateralizing MD and FA abnormalities in patients with TLE. According to Focke and coworkers (2008), DTI detects extensive alterations in mesial TLE with hippocampal sclerosis [42]. In this study, the affected networks in patients that underwent presurgical evaluation were localized mainly in the limbic system and the ipsilateral temporal lobe.

The utility of ADC interictal measurement as a complementary tool in lateralizing the epileptogenic lesion was investigated in a series of studies [43–47]. Increased ADCs of the affected hippocampi were observed in patients with TLE, mTLE, HS, and in cases of temporal lobe resection. This increase may reflect neuronal loss in the epileptogenic area, gliosis, loss of structural organization, and an expansion of extracellular space (an indicator of HS).

In contrast to postictal studies, the majority of interictal studies corroborate the increase of MD and decrease of FA in the epileptogenic regions. However, the small sample size both of the patients and control group in interictal studies cannot provide experimental results with adequate statistical significance to define their contribution to the presurgical planning.

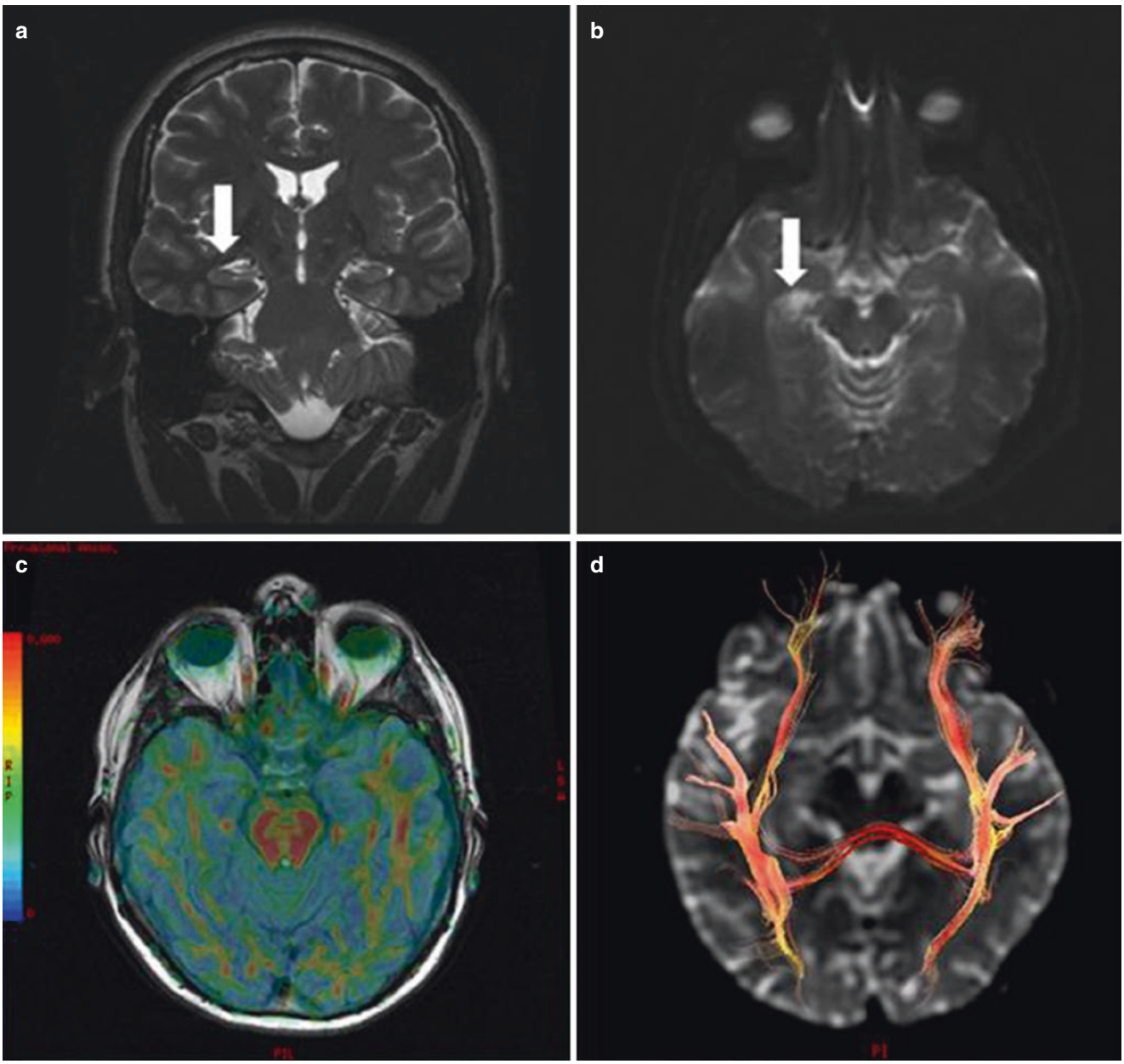

Fig. 2.6 (**a**) High resolution T2-weighted image; (**b**) Apparent diffusion coefficient map; (**c**) FA map; (**d**) Tractography in a patient with hippocampal sclerosis

2.4 Tractography

White matter comprises a highly coherent structure full of neuronal fibers and facilitates the anisotropic diffusion of water. As a result, calculation of fiber orientation can be derived from the combination of FA values with directionality. This concept is the theoretical basis of fiber tractography, which enables a three-dimensional visualization of the white matter networks noninvasively [48].

Fiber tractography algorithms are based on the fact that monitoring the tensor's orientation makes the detection of intravoxel connections more feasible. There are a variety of algorithms; however, all of them concluded on a line propagation approach (Fig. 2.7), which can yield colored maps of fiber tracks. Various tractography techniques have been reported [49–52].

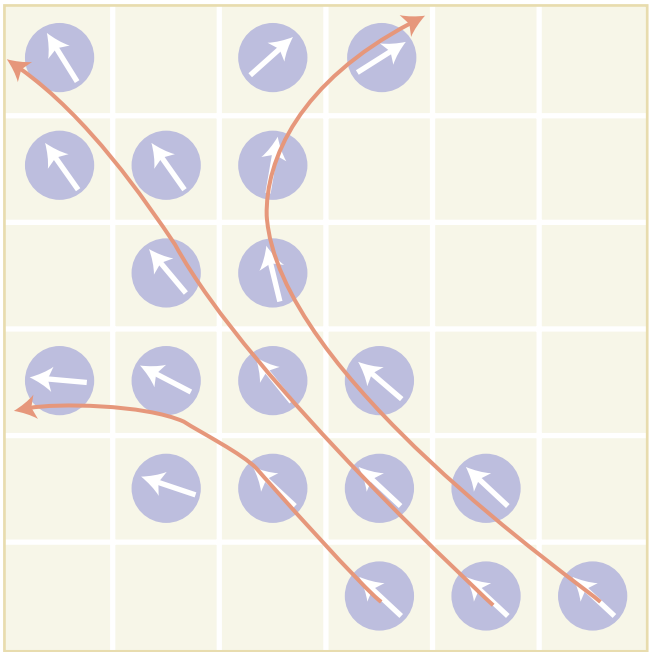

Fig. 2.7 Schematic diagram of the interpolation approach (nonlinear line propagation)

There is also a series of studies that employ DTI and tractography and created atlases of the human brain [53, 54]. Thus, a damage to a given fiber tract (such as disruption or displacement) could be a valuable diagnostic parameter, as it could be evaluated by three-dimensional tractograms [55, 56].

The definition of a "seed" region of interest (ROI) on the color orientation map is required in order to reconstruct and visualize white matter tracts. Most software applications have the option of a "structural view." Placement of a seed ROI leads to a white matter track oriented through the ROI. If the user desires the representation of the fiber pathway that connects one ROI to another one, the placement of a second ROI determined as the "target" ROI on the image should take place. This procedure is pictorially depicted in Fig. 2.8.

Tractography techniques also provide useful information in relation to presurgical planning; nonetheless, they present limitations such as in cases of crossing and kissing fiber tracts, which should be taken into consideration when these methods are used for preoperative guidance.

Diffusion gradients are applied in multiple directions in DTI; therefore the amount of noncollinear gradients applied may range from 6 to 55. Nevertheless, the optimal range is still debatable in the literature, and an optimal number has not yet been defined [57–59]. A principal disadvantage associated with an increase in the number of DTI gradients is scan time. Increasing the number of directions simultaneously increases scan time and may easily exceed the limits of clinical practice [60]. Therefore there is a constant cost-benefit analysis debate between the imaging time and the number of gradients applied in order to acquire adequate diffusion information.

Nevertheless, the wider use of higher field scanners (3T or more) and the further development of acquisition and post-processing techniques should result in the increased role of this promising advanced technique in both research and clinical practice.

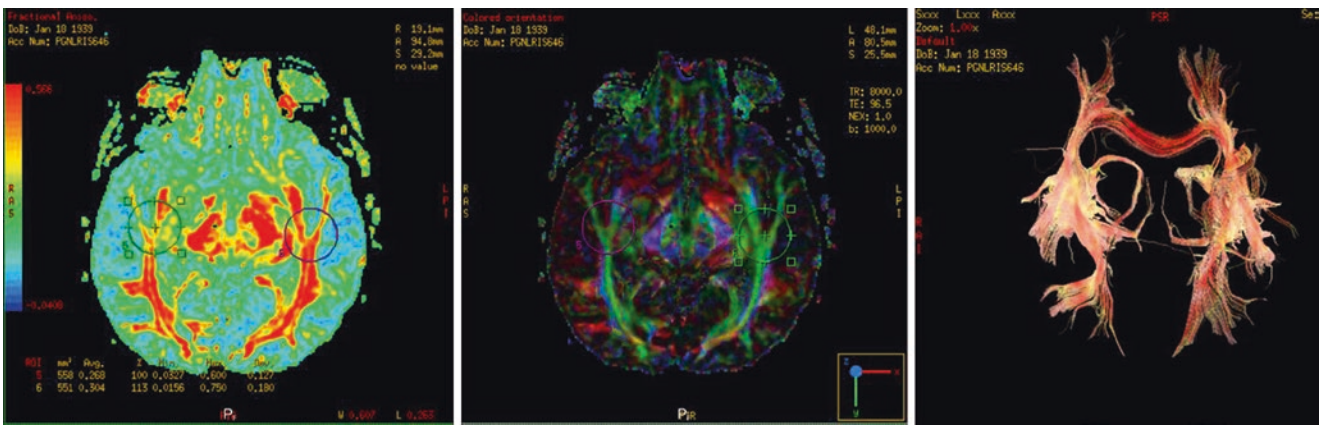

Fig. 2.8 ROI placement on colored orientation map (*left*) fiber tracts (*right*)

2.4.1 Tractography in Epilepsy

The noninvasive technique of fiber tractography deploys data collected by DTI and visualizes a map of white matter tracts after a three-dimensional reconstruction. This neural network determines anatomic connections between different cortical areas, including the epileptogenic zone, and assists the decoding of brain structure and function. Additionally, functional areas of language, memory, and vision, for example, can be delineated and aid the presurgical evaluation of an intracranial mass resection.

The parahippocampal gyrus (PHG) is the link between the hippocampus and neocortical areas; their connections may constitute the plinth of "memory and visual processing" theoretical framework [61]. Powell and associates came to this conclusion after searching the connectivity of the parahippocampal gyrus using DTI and fast marching tractography in a group of ten healthy controls. They found that lingual and fusiform gyri are the link between the parahippocampal gyrus and the orbitofrontal areas, the extra striate occipital lobe and the anterior/posterior temporal lobe. Moreover, their results bore testament of a direct hippocampus and PHG connection for the first time. In 2005 Concha and coworkers [62] studied eight patients with TLE and unilateral mesial temporal sclerosis and related their disorder to the bilateral pathologic limbic system. The results concerning TLE patients demonstrated a bilateral decrease of FA in the fornix, while patients with unilateral mesial temporal sclerosis showed bilateral abnormalities in the fornix and cingulum. In a longitudinal study 2 years later the same authors reported that the eight aforementioned patients underwent an anterior temporal lobe resection [63]. However, their follow-up scan (1 year later) continued to show DTI abnormalities in the genu of the corpus callosum and the contralateral tracts of the fornix, cingulum, and external capsules. The interpretation of this outcome was the presence of an underlying structural impairment in the affected areas.

Despite the fact that tractography appears to have very positive perspectives, it also has limitations. Anatomic structures attended by crossing and kissing fibers can lead to erroneous calculation of fiber orientation. Additionally, the size variation between an actual nerve fiber (μm) and the spatial resolution of DTI (mm) can often be responsible for the wrong estimation of a tract direction [64]. A three-dimensional visualization of a brain network is the outcome of complex data processing; therefore it is difficult to know whether a reconstructed fiber represents an actual one localized in the same place.

2.5 Memory and Language Networks

In 2008 Yoharajah and coworkers [65] evaluated the correlation between FA, volume, and memory performance in 18 patients with TLE before they underwent a surgical intervention. Significantly decreased FA and volume were detected in areas connected ipsilateral to the epileptogenic region in patients with left TLE, while patients with right TLE revealed correlations between verbal and nonverbal memory and left and right FA. In chronic temporal lobe epilepsy, extensive information regarding the integrity of the aforementioned connections may prospectively evaluate lessening of memory [65]. The correlation of memory performance and the uncinate fasciculus can also be evaluated. Memory scores were marked in 28 patients with TLE, and it was established that an increase in radial diffusivity and a reduction in FA were associated with visual delayed memory [66].

Functional lateralization refers to the distinction of a human brain function and can occur both in the right and left hemispheres. Powell and coworkers [67] studied the lateralization of language processes utilizing fMRI and diffusion MR tractography in ten right-handed normal controls. Volume and FA measurements showed that both of them were higher on the left compared to the right brain. This asymmetry is associated with the lateralization of the language function [67]. The same authors published a new study 1 year later in which they observed structural reorganization of WM tracts in patients with left TLE [68]. This was an indicator of change in the lateralization of language, and as a result they concluded that fMRI and tractography are a successful combination for studying the function of language.

A recent study of 2015 investigated the utility of diffusion MR tractography in the detection of fiber tracts linked to language cortices and concerned children with intractable epilepsy [69]. In the presurgical planning they constructed maps of the language network using fMRI and tractography in order to accomplish a more precise resection. In 12 healthy children who were examined, the localization of language activation regions was 77% accurate, and in children with epilepsy the accuracy was up to 82%. This kind of fMRI-tractography analysis could assist the presurgical work-up of pediatric interventions as a useful diagnostic tool [69].

2.6 Visual Networks

A severe lesion of the Meyer loop (disruption) leads to superior vision loss. A superior homonymous quadrantanopia is a complication of anterior temporal lobe resection [70] and is interpreted as the loss of vision in a quarter of the visual field [71]. Diffusion MR tractography was used to evaluate the optic radiation pre- and postsurgically via a three-dimensional reconstruction in one patient with quadrantanopia [70]. It was concluded that imaging of the optic radiation can play a significant role in the prediction of postoperative visual field deficits [70]. Another study investigated the correlation of optic radiation integrity and visual loss in patients with cerebral arteriovenous malformation (AVM) using tractography, and it was demonstrated that this method could constitute a useful tool in the assessment of surgical risk [72].

One in ten patients who undergo an anterior temporal lobe resection (ATLR) suffer a visual fields deficit (VFD) postoperatively. Twenty patients were scanned presurgically 3–12 months after surgery and fiber tractography was used to visualize the optic radiation. The result was that 60% of the patients suffered a VFD. Hence, tractography can provide an accurate delineation of optic radiation in order to potentially reduce the VDF probability [73].

Conclusions

It is evident that the most important aspect of epilepsy surgery is the ability to accurately identify the epileptogenic zone. Structural MRI and clinical, electrophysiologic, and neurophysiologic data have an established role in the localization of the epileptogenic foci. Nevertheless, about 30% of epilepsy patients may have unclear MRI evidence, and the presurgical assessment may remain controversial. It should also be mentioned that even a detailed structural MRI may not reveal the true extent and functional status of the abnormality.

The introduction of DWI, DTI, and diffusion MR tractography has provided an insight into the underlying pathophysiology of epileptogenesis and offers the potential to discover meaningful details of the microarchitecture of the affected tissue. In conclusion, advanced MRI techniques are increasingly becoming an essential part of both the diagnostics and presurgical guidance of epilepsy by accomplishing successful identification of the epileptogenic focus when this area is undetectable on structural MRI or when structural MRI and clinical and electrophysiologic findings are not in agreement.

References

1. Chang SC, Lai PH, Chen WL, Weng HH, Ho JT, Wang JS, et al. Diffusion-weighted MRI features of brain abscess and cystic or necrotic brain tumors: comparison with conventional MRI. Clin Imaging. 2002;26:227–36.
2. De Belder FE, Oot AR, Van Hecke W, Venstermans C, Menovsky T, Van Marck V, et al. Diffusion tensor imaging provides an insight into the microstructure of meningiomas, high-grade gliomas, and peritumoral edema. J Comput Assist Tomogr. 2012;36:577–82.
3. Hakyemez B, Yildirim N, Erdogan C, Kocaeli H, Korfali E, Parlak M, et al. Meningiomas with conventional MRI findings resembling intraaxial tumors: can perfusion-weighted MRI be helpful in differentiation? Neuroradiology. 2006;48:695–702.
4. Price SJ. The role of advanced MR imaging in understanding brain tumour pathology. Br J Neurosurg. 2007;21:562–75.
5. Moritani T, Ekholm S, Westesson PL. Diffusion-weighted MR imaging of the brain. 2nd ed. New York: Springer; 2009.
6. Tanner E. Transient diffusion in a system partitioned by permeable barriers: application to NMR measurements with a pulsed field gradient. J Chem Physiol. 1978;69:1748–54.
7. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology. 1986;161:401–7.
8. Debnam JM, Schellingerhout D. Diffusion MR imaging of the brain in patients with cancer. Int J Mol Imaging. 2011;714021:2011.
9. Doran M, Hajnal J, Van Bruggen N, King MD, Young IR, Bydder GM. Normal and abnormal white matter tracts shown by MR imaging using directional diffusion weighted sequences. J Comput Assist Tomogr. 1990;14:865–73.
10. Chenevert TL, Brunberg JA, Pipe JG. Anisotropic diffusion within human white matter: demonstration with NMR techniques in vivo. Radiology. 1990;177:401–5.
11. Mukherjee P, Berman JI, Chung SW, Hess CP, Henry RG. Diffusion tensor MR imaging and fiber tractography: theoretic underpinnings. Am J Neuroradiol. 2008;29:632–41.
12. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci. 2003;4:469–80.
13. Field AS, Alexander AL. Diffusion tensor imaging in cerebral tumor diagnosis and therapy. Top Magn Reson Imaging. 2004;15:315–24.
14. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy. Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(9):1922.
15. Shah AK, Mittal S. Evaluation of magnetic resonance imaging negative drug-resistant epilepsy. Ann Indian Acad Neurol. 2014;17(Suppl 1):S80–8.
16. Fisher RS. The 2017 ILAE seizure classification. Presented at the American Epilepsy Society Annual Meeting, December 2016, in Houston, TX, USA.
17. Felix R, Hans F. Presurgical evaluation of epilepsy. Brain. 2001;124:1683–700.
18. Cherian A, Thomas SV. Status epilepticus. Ann Indian Acad Neurol. 2009;12:140–53.
19. Rosenberg G. Ischemic brain edema. Prog Cardiovasc Dis. 1999;42:209–16.
20. Vulliémoz S, Meuli R, Maeder P, Seeck M, Delavelle J. Diffusion magnetic imaging applied to epilepsy. Epileptologie. 2007;24:60–5.
21. Wieshmann UC, Symms MR, Shorvon SD. Diffusion changes in status epilepticus. Lancet. 1997;350:493–4.
22. Diehl B, Najm I, Ruggieri P, Foldvary N, Mohamed A, Tkach J, et al. Periictal diffusion weighted imaging in a case of lesional epilepsy. Epilepsia. 1999;40:1667–71.
23. Lansberg MG, O'Brien MW, Norbash AM, Moseley ME, Morrell M, Albers GW. MRI abnormalities associated with partial status epilepticus. Neurology. 1999;52:1021–7.
24. Chu K, Kang DW, Kim JY, Chang KH, Lee SK. Diffusion-weighted magnetic resonance imaging in nonconvulsive status epilepticus. Arch Neurol. 2001;58:993–8.
25. Kim JA, Chung JI, Yoon PH, Kim DI, Chung TS, Kim EJ, Jeong EK. Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: periictal diffusion-weighted imaging. Am J Neuroradiol. 2001;22:1149–60.

26. Hong KS, Cho YJ, Lee SK, Jeong SW, Kim WK, Oh EJ. Diffusion changes suggesting predominant vasogenic oedema during partial status epilepticus. Seizure. 2004;13:317–21.
27. Senn P, Lovblad KO, Zutter D, Bassetti C, Zeller O, Donati F, Schroth G. Changes on diffusion-weighted MRI with focal motor status epilepticus: case report. Neuroradiology. 2003;45:246–9.
28. Diehl B, Najm I, Ruggieri P, Tkach J, Mohamed A, Morris H, et al. Postictal diffusion-weighted imaging for the localization of focal epileptic areas in temporal lobe epilepsy. Epilepsia. 2001;42:21–8.
29. Hufnagel A, Weber J, Marks S, Ludwig T, de Greiff A, Leonhardt G, et al. Brain diffusion after single seizures. Epilepsia. 2003;44:54–63.
30. Oh JB, Lee SK, Kim KK, Song IC, Chang KH. Role of immediate postictal diffusion-weighted MRI in localizing epileptogenic foci of mesial temporal lobe epilepsy and non-lesional neocortical epilepsy. Seizure. 2004;13:509–16.
31. Konermann S, Marks S, Ludwig T, Weber J, de Greiff A, Dorfler A, et al. Presurgical evaluation of epilepsy by brain diffusion: MR-detected effects of flumazenil on the epileptogenic focus. Epilepsia. 2003;44:399–407.
32. Diehl B, Symms MR, Boulby PA, Salmenpera T, Wheeler-Kingshott CA, Barker GJ, Duncan JS. Postictal diffusion tensor imaging. Epilepsy Res. 2005;65:137–46.
33. Salmenpera TM, Symms MR, Boulby PA, Barker GJ, Duncan JS. Postictal diffusion weighted imaging. Epilepsy Res. 2006;70:133–43.
34. Krakow K, Wieshmann UC, Woermann FG, Symms MR, McLean MA, Lemieux L, et al. Multimodal MR imaging: functional, diffusion tensor, and chemical shift imaging in a patient with localization-related epilepsy. Epilepsia. 1999;40:1459–62.
35. Eriksson SH, Rugg-Gunn FJ, Symms MR, Barker GJ, Duncan JS. Diffusion tensor imaging in patients with epilepsy and malformations of cortical development. Brain. 2001;124:617–26.
36. Rugg-Gunn FJ, Eriksson SH, Symms MR, Barker GJ, Duncan JS. Diffusion tensor imaging of cryptogenic and acquired partial epilepsies. Brain. 2001;124:627–36.
37. Assaf BA, Mohamed FB, Abou-Khaled KJ, Williams JM, Yazeji MS, Haselgrove J, Faro SH. Diffusion tensor imaging of the hippocampal formation in temporal lobe epilepsy. Am J Neuroradiol. 2003;24:1857–62.
38. Thivard L, Lehericy S, Krainik A, Adam C, Dormont D, Chiras J. Diffusion tensor imaging in medial temporal lobe epilepsy with hippocampal sclerosis. NeuroImage. 2005;28:682–90.
39. Dumas dR, Oppenheim C, Chassoux F, Rodrigo S, Beuvon F, Daumas-Duport C, et al. Diffusion tensor imaging of partial intractable epilepsy. Eur Radiol. 2005;15:279–85.
40. Gross DW, Bastos A, Beaulieu C. Diffusion tensor imaging abnormalities in focal cortical dysplasia. Can J Neurol Sci. 2005;32:477–82.
41. Salmenpera TM, Simister RJ, Bartlett P, Symms MR, Boulby PA, Free SL, et al. High-resolution diffusion tensor imaging of the hippocampus in temporal lobe epilepsy. Epilepsy Res. 2006;71:102–6.
42. Focke NK, Yogarajah M, Bonelli SB, Bartlett PA, Symms MR, Duncan JS. Voxel-based diffusion tensor imaging in patients with mesial temporal lobe epilepsy and hippocampal sclerosis. NeuroImage. 2008;40:728–37.
43. Hugg JW, Butterworth EJ, Kuzniecky RI. Diffusion mapping applied to mesial temporal lobe epilepsy: preliminary observations. Neurology. 1999;53:173–6.
44. Wieshmann UC, Clark CA, Symms MR, Barker GJ, Birnie KD, Shorvon SD. Water diffusion in the human hippocampus in epilepsy. Magn Reson Imaging. 1999;17:29–36.
45. Kantarci K, Shin C, Britton JW, So EL, Cascino GD, Jack CR Jr. Comparative diagnostic utility of 1H MRS and DWI in evaluation of temporal lobe epilepsy. Neurology. 2002;58:1745–53.
46. Yoo SY, Chang KH, Song IC, Han MH, Kwon BJ, Lee SH, Yu IK, Chun CK. Apparent diffusion coefficient value of the hippocampus in patients with hippocampal sclerosis and in healthy volunteers. Am J Neuroradiol. 2002;23:809–12.
47. Hakyemez B, Erdogan C, Yildiz H, Ercan I, Parlak M. Apparent diffusion coefficient measurements in the hippocampus and amygdala of patients with temporal lobe seizures and in healthy volunteers. Epilepsy Behav. 2005;6:250–6.
48. Westin CF, Maier SE, Mamata H, Nabavi A, Jolesz FA, Kikinis R. Processing and visualization for diffusion tensor MRI. Med Image Anal. 2002;6:93–108.
49. Mori S, Crain BJ, Chacko VP, van Zill PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol. 1999;45:265–9.
50. Jones DK, Simmons A, Williams SC, Horsfield MA. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn Reson Med. 1999;42:37–41.
51. Mori S, van Zijl PMC. Fiber tracking: principles and strategies: a technical review. NMR Biomed. 2002;15:468–80.
52. Parker GJ, Stephan KE, Barker GJ, Rowe JB, MacManus DG, Wheeler-Kingshott CAM, et al. Initial demonstration of in vivo tracing of axonal projections in the macaque brain and comparison with the human brain using diffusion tensor imaging and fast marching tractography. NeuroImage. 2002;15:797–809.
53. Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PCM, Mori S. Fiber tract-based atlas of human white matter anatomy. Radiology. 2004;230:77–87.
54. Jellison BJ, Field AS, Medow J, Lazar M, Salamat MS, Alexander AL, et al. Diffusion tensor imaging of cerebral white matter: a pictorial review of physics, fiber tract anatomy, and tumor imaging patterns. Am J Neuroradiol. 2004;25:356–69.
55. Mori S, Fredericksen K, Van Zijl PC, Stieltjes B, Kraut MA, Solaiyappan M, Pomper MG. Brain white matter anatomy of tumor patients using diffusion tensor imaging. Ann Neurol. 2002;51:377–80.
56. Bello L, Castellano A, Fava E, Casaceli G, Riva M, Scotti G, et al. Intraoperative use of diffusion tensor imaging fiber tractography and subcortical mapping for resection of gliomas: technical considerations. Neurosurg Focus. 2010;28:E6.
57. Hasan KM, Parker DL, Alexander AL. Comparison of gradient encoding schemes for diffusion-tensor MRI. J Magn Reson Imaging. 2001;13:769–80.
58. Jones DK. The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carlo study. Magn Reson Med. 2004;51:807–15.
59. Nucifora PG, Verma R, Lee SK, Melhem ER. Diffusion tensor MR imaging and tractography: exploring brain microstructure and connectivity. Radiology. 2007;245:367–84.
60. Gupta A, Shah A, Young RJ, Holodny A. Imaging of brain tumors: functional magnetic resonance imaging and diffusion tensor imaging. Neuroimaging Clin N Am. 2010;20:379–400.
61. Powell HW, Guye M, Parker GJ, Symms MR, Boulby P, Koepp MJ, et al. Noninvasive in vivo demonstration of the connections of the human parahippocampal gyrus. NeuroImage. 2004;22:740–7.
62. Concha L, Beaulieu C, Gross DW. Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. Ann Neurol. 2005;57:188–96.
63. Concha L, Beaulieu C, Wheatley BM, Gross DW. Bilateral white matter diffusion changes persist after epilepsy surgery. Epilepsia. 2007;48:931–40.
64. Jones DK. Studying connections in the living human brain with diffusion MRI. Cortex. 2008;44:936–52.
65. Yogarajah M, Powell HW, Parker GJ, Alexander DC, Thompson PJ, Symms MR, et al. Tractography of the parahippocampal gyrus and material specific memory impairment in unilateral temporal lobe epilepsy. NeuroImage. 2008;40:1755–64.

66. Diehl B, Busch RM, Duncan JS, Piao Z, Tkach J, Luders HO. Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. Epilepsia. 2008;49:1409–18.
67. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, et al. Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. NeuroImage. 2006;32:388–99.
68. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, et al. Abnormalities of language networks in temporal lobe epilepsy. NeuroImage. 2007;36:209–21.
69. Jeong JW, Asano E, Juhász C, Chugani HT. Localization of specific language pathways using diffusion-weighted imaging tractography for presurgical planning of children with intractable epilepsy. Epilepsia. 2015;56:49–57.
70. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, et al. MR tractography predicts visual field defects following temporal lobe resection. Neurology. 2005;65:596–9.
71. Hanbin WH, Wei Sun W, Zhuang Fu Z, Zhichao Si Z, Yufang Zhu Y, Guode Zhai G, et al. The pattern of visual impairment in patients with pituitary adenoma. J Int Med Res. 2008;36:1064–9.
72. Kikuta K, Takagi Y, Nozaki K, Hanakawa T, Okada T, Miki Y, et al. Early experience with 3-T magnetic resonance tractography in the surgery of cerebral arteriovenous malformations in and around the visual pathway. Neurosurgery. 2006;58:331–7.
73. Winston GP, Daga P, Stretton J, Modat M, Symms MR, McEvoy AW, et al. Optic radiation tractography and vision in anterior temporal lobe resection. Ann Neurol. 2012;71:334–41.

Functional MRI in Epilepsy

3

Sotirios Bisdas, Ayisha Al-Busaidi, Laura Mancini, Loizos Siakallis, and Adam Kenji Yamamoto

3.1 Introduction

In this chapter we attempt to provide a brief but comprehensive overview of functional magnetic resonance imaging (fMRI) as a method for the assessment of brain function and its utilization in the preoperative assessment of patients undergoing brain surgery. The first part of the chapter is devoted to the presentation of the basic principles governing fMRI; this is followed by the presentation of current clinical and research evidence on the implementation of this technique for the preoperative assessment of patients, with emphasis on patients with refractory epilepsy. Finally, a more detailed analysis of the technical aspects of fMRI acquisition with specific recommendations is provided for the interested reader.

3.2 Basic Principles of Functional MRI

Functional neuroimaging methods aim at mapping the living brain activity in space and time. For studies on human subjects, there are two main approaches to noninvasive functional neuroimaging. These are composed of methods based on measuring electrical activity (electrophysiology-based methods) such as electroencephalography (EEG) and magnetoencephalography (MEG) and methods measuring the metabolic/vascular brain status such as positron emission tomography (PET) and fMRI. The electrophysiologic methods have high temporal resolution but poor spatial resolution. The methods measuring the metabolic/vascular properties of the brain tissue are more indirect surrogates of brain activation but provide very good spatial resolution, localization, and delineation of the spatial extent of activated areas; however, they lack temporal resolution.

There are different types of fMRI, among which perfusion-based or arterial spin labelling (ASL) fMRI and susceptibility contrast-based or bold oxygenation level–dependent (BOLD) fMRI are the most widespread. fMRI is often used as a synonym of BOLD fMRI, since this is the most commonly used technique. In the following text, we will use these terms interchangeably while we will explicitly specify if we refer to ASL-based fMRI. Both these methods measure physiologic changes that are correlated with neuronal activity. The main physiologic changes associated with brain cell activity are (i) the association of brain cell activity with local changes in metabolism (i.e., glucose and oxygen consumption), and (ii) the so-called "neurovascular coupling" between cerebral blood flow (CBF) and oxygenation.

3.2.1 Brain Activity and Principles of FMRI

The brain tissue is metabolically "expensive" (it accounts for only 2% of the total body mass but consumes 20% of the body's glucose and oxygen) and has very limited energy deposits; it covers these energy requirements by receiving 20% of the body's blood supply. Although the general principles of brain metabolism and the hemodynamic response to neuronal activity are known, the precise mechanisms linking brain energy metabolism and brain output are not well defined [1].

S. Bisdas (✉) · A. Al-Busaidi · L. Mancini · L. Siakallis
A. K. Yamamoto
Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, University College London NHS Foundation Trust, London, UK
e-mail: s.bisdas@ucl.ac.uk

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Brain activity is associated with increased energy requirements, mostly met by oxidative glucose consumption. The vascular system provides continuous perfusion of blood containing the oxygen and glucose necessary for cellular respiration and metabolism. At rest and over the long term blood flow and cerebral metabolism are well matched. However, after the onset of brain activity, the feeding arterioles dilate, leading to an increase in CBF in downstream capillaries mainly caused by an increase in blood velocity. The increase in blood flow is greater than the increase in oxygen consumption; therefore oxygenation increases, especially at the venular side of the capillary bed and in the venous vessels, resulting in a decrease of deoxy-hemoglobin concentration [2, 3].

The circulating oxygen in the blood is bound to hemoglobin molecules. A hemoglobin molecule has different magnetic properties whether or not oxygen atoms are bound to its heme protein. Oxy-hemoglobin is weakly diamagnetic and has little effect on magnetic fields, while deoxy-hemoglobin is paramagnetic and concentrates magnetic field lines. This paramagnetic property causes a loss of phase coherence in nearby protons and is reflected in a shorter T2* (and therefore lower MR signal) in deoxygenated blood with respect to oxygenated blood. This influences the contrast on T2*-weighted images or susceptibility-weighted images (e.g., gradient-echo images) [4].

3.2.2 Blood Oxygen Level–Dependent (Bold) fMRI

(BOLD) fMRI, first described in the 1990s, maps the changes in blood oxygenation with MRI using T2*-weighted images [5]. The main concept of fMRI is to modulate the oxygenation level at the site of brain activity and detect correlated signal changes; through this process it aims to provide associations between certain tasks and regional brain activity [5].

Rapid scanning of the whole head (repetition time of the order of 2–3 s), usually with echo-planar imaging (EPI), is performed continuously while the subject performs various mental tasks (known as paradigms). In clinical practice, the tasks are usually arranged in a block design with periods of activity alternating with periods of a contrasting activity or rest, for a total acquisition time of 4–5 min. During the course of the experiment, 100 brain volumes or more are typically recorded. The periods of activity might involve motor tasks, stimulus presentation, or cognitive activity (e.g., generating words or doing mental arithmetic). A block length or epoch commonly ranges from 15 to 30 s, and a period of task and baseline blocks would usually be repeated four to eight times depending on the epoch duration. Block design paradigms are robust and simple to arrange. For some mental tasks it may be difficult to generate extended periods of activation. In these cases an alternative paradigm design is the use of event-related fMRI, in which the task is performed for a short period of time (a few milliseconds) and repeated at variable intervals.

One of the complexities of BOLD fMRI is that the detected signal change lags behind the neuronal activation by approximately 6 s and will outlast the neuronal activation by approximately the same amount of time. This is known as the hemodynamic response function. And it limits the fMRI temporal resolution. The exact nature of this process is still subject to debate, but the consensus is that initially the signal drops as oxygen consumption increases, and the subsequent increase in blood delivery causes the detectable BOLD signal [4, 6].

3.2.3 Post-Processing in fMRI

Following data acquisition, some post-processing is required to generate the activation maps that represent the statistical significance of signal changes correlated with the paradigm. The common steps of fMRI post-processing include (i) image realignment, (ii) coregistration to an anatomic image (for the individual patient fMRI in the clinical setting ± or normalization to a template (often the MNI (Montreal Neurological Institute) atlas, similar to the Talairach Brain Atlas), (iii) smoothing of the data, (iv) filtering of the data, and (v) statistical analysis.

Image realignment is performed to correct for head motion during data acquisition. It is needed because even a small shift in voxel position can generate significant signal changes resulting in false-positive or reduced real activations. Co-registration to a structural image allows the anatomic localization of the activation map to a specific region of the brain. Normalization is not usually performed for the clinical use of fMRI but can permit the comparison of a single subject data set to that acquired from other subjects (also known as a second-level analysis). Smoothing (blurring each volume spatially) helps to enhance the signal-to-noise ratio (SNR) and is a step that is required for the statistical analysis but has to be applied carefully to avoid excessive loss of spatial resolution. Filtering of the low and high frequency noise is usually performed to reduce the contribution of physiologic noise.

3.2.4 Statistical Analysis and Models

The statistical analysis is performed to determine which voxels are activated by the stimulation. This can consist of a simple correlation analysis or a more advanced modelling of the expected hemodynamic response to the stimulation. There is a distinction between ‘model-based’ and ‘model-free’ methods. In a model-based method, a model of the expected

response is generated and compared with the data. In a model-free method, effects or components of interest in the data are found on the basis of some specific criteria. Currently, the most popular statistical approach is the general linear model (GLM), which is model-based. An example of a model-free approach is the Bayesian analysis [5].

3.2.5 The General Linear Model (GLM)

In the GLM, the model is derived by the combination of the timing of the stimulation applied to the subject and a function representing the expected signal change following a single neuronal activation (also called the hemodynamic response function). The combination of these two parameters is performed by a mathematical function called convolution. The GLM is usually used in a univariate way, which means that the time series signal from each voxel is considered independently. The predicted model is fitted voxel-by-voxel, and a statistical test is performed to assess the goodness of fit. The obtained statistical map is then thresholded at a given level of significance to show which parts of the brain were activated. In a brain volume there are a large number of voxels, approximately 20,000, and since a statistical test is performed for each voxel, the final results have to be corrected for the multiple comparison problem to reduce the number of false positives. Information on the measured head motion during the acquisition and, if available, the motion due to respiration can be introduced in the GLM to eliminate motion-associated variation in the data.

fMRI brain activation maps are usually presented as colored "blobs" superimposed on a gray-scale anatomic brain image. It is important to remember that the colored blobs do not themselves signify brain activation but represent areas of statistically different MR signals. The intensity of the color represents the degree of statistical confidence that a voxel value or a group of voxels has changed according to the testing paradigm. Actual signal changes are usually small, on the order of 5%.

3.3 Role of Clinical Functional MRI in Epilepsy

Intractable epilepsy is an epileptic disorder in which a patient's seizures cannot be controlled using medical therapy; seizures in this group of patients are also called uncontrolled or refractory. If the seizure origin can be localized in the brain and the region is safe to remove, surgery is a reasonable option for people with refractory epilepsy. The goal is the complete resection or disconnection of the epileptogenic area while preserving the eloquent cortex (language, motor, sensory, memory). The most commonly performed surgical procedure for intractable epilepsy is the partial removal of the anterior temporal lobe (ATL), including removal of the amygdala and hippocampus. Resective epilepsy surgery is highly effective for seizure control and yields favorable psychosocial outcomes. Surgery can improve the quality of life in this group of patients, achieving seizure freedom in around 60–70% of patients [7, 8]. However, up to 4.7% of epilepsy patients develop major postsurgical neurologic complications [7]. Visual field deficits from optical radiation damage and memory deficits caused by involvement of the hippocampus can result from temporal lobe resection [9–12]. Hence, accurate identification of epileptogenic zones along with eloquent brain in presurgical candidates is essential [13].

3.3.1 Methods of Detecting Eloquent Brain Areas

During the past 50 years neurosurgeons have relied upon direct cortical stimulation mapping (CSM), neuropsychologic assessment, and the known Wada test (awake intracarotid catheter injection of sodium amobarbital or propofol selectively into one hemisphere) to address the eloquent brain areas. Today, a variety of functional imaging methods are used for preoperative assessment. Epilepsy patients usually undergo extensive noninvasive assessment including fMRI, seizure semiology analysis, EEG, MEG, structural MRI, and functional/neuropsychiatric assessments [14]. The aims of these assessments are to (i) localize the epileptogenic focus, (ii) map eloquent areas, and (iii) predict postsurgical cognitive functions outcome.

Once the noninvasive studies have been completed, a small percentage of patients proceed to an intracranial recording study with surgically implanted electrodes. Patients who undergo this study are those for whom the various tests may have yielded nonconcordant results or insufficient information to enable focal resection but sufficient information to determine the eloquence of various brain regions [7].

3.3.2 Preoperative fMRI: General Aspects

Preoperative fMRI is routinely used to investigate motor- and sensory-related activity, showing robust activation patterns, which can also be entered into neurosurgical navigation systems. In contrast to research, the objective of presurgical and particularly language fMRI in epilepsy is not to make inferences about the function of specific brain regions but to localize areas of activation in individual patients. It is important to note that the activation elicited by an fMRI task does not indicate that a region is required for the particular

function in a patient; it merely shows that the task resulted in activity in this region [15].

Studies have shown that fMRI has the potential to predict the effects of temporal lobe surgical resection on memory and language, allowing surgeons to better plan their procedures and patients to make informed decisions regarding their care [16, 17]. In well-selected patients, preoperative neuroimaging techniques can lead to seizure-freedom in up to 84% of temporal lobe epilepsy patients and up to 74% of patients with extratemporal lesions [7]. Over 50% of these patients will be seizure-free at long-term follow-up of up to 10 years [7, 8, 18]. Nevertheless, there are imaging challenges that a radiologist may encounter using fMRI, which are discussed in the following sections.

3.3.3 Language

The knowledge of functional anatomy reorganization to the ipsilateral or contralateral hemispheres is essential in surgical resection because it can predict prognosis and postsurgical neurologic deficits. It is well known that in epilepsy patients, atypical language lateralization is more common than in control populations, probably because, depending on the timing when the cause of the epilepsy originated, plasticity may have taken place [19, 20]. Lesions such as cortical malformation, vascular lesions, encephalitis, or neonatal trauma may cause reorganization [21, 22]. The role of fMRI in language hemispheric dominance has been validated; it is a cheaper, noninvasive, and reproducible alternative to the WADA test [5, 23–25] and is an excellent choice in the initial assessment of presurgical candidates [26]. Although localization of language areas with fMRI alone is not routinely clinically practiced and invasive electrocortical stimulation mapping is still required, research studies show promise in identifying the epileptogenic focus in conjunction with other modalities [27]. It has been proven that fMRI also has a prognostic value in the evaluation of verbal and visual memory after ATL resection; as explained in the memory section, posterior medial temporal lobe (MTL) activation on fMRI has been associated with a favorable postsurgical outcome [28, 29].

3.3.3.1 fMRI: WADA Test in Language Lateralization

In addition to its other merits, fMRI potentially provides more information about lateralization than the Wada test as well as being free from the effects of anesthesia [26]. A meta-analysis by Dym et al. looked at 23 studies published between 1996 and 2008. The studies included 422 participants and found more concordance than discordance between the two tests, which varied between 61.5% and 100% [26]. The largest study by Woermann et al. [21] showed around 91% concordance. There was an overall sensitivity of 83.1% and a specificity of 88.1% for atypical language dominance on fMRI compared with the Wada test [26].

The low concordance encountered in some studies can partly be explained by Wada test factors such as inadequate or excessive anesthesia, interhemispheric cross-flow of anesthesia, anomalous vasculature, and short duration of drug effect. Factors that compromise the diagnostic performance of fMRI include motion artefacts, poor task performance, and variability in task design. In addition, some studies were conducted in small samples and with a limited number of patients with atypical language dominance [30].

3.3.3.2 fMRI Paradigms for Language Lateralization

Certain fMRI language paradigms seemed to have improved concordance between fMRI and the WADA test [31–34]. Specificity increased more with word-generating tasks than with semantic decision tasks. A possible explanation was that the latter tasks activated areas in the cortex only indirectly involved in language, such as memory-related areas. Studies that had a global or only frontal assessment were also more specific than those that only assessed the temporal-parietal regions. Assessing a larger area with global evaluation was also found to be more sensitive than temporal evaluation owing to the higher likelihood of identifying atypical language representation. Using word-generating tasks in those studies may have also contributed to their lower sensitivity, which is generally more robust in frontal activation [26].

However, laterality indices (LIs) that can be applied to fMRI activation data have to be interpreted with caution, since lateralization has been shown to be driven by differences in the activation patterns of the right hemisphere rather than the left [35]. For example, three patients may have different LIs but in fact there may be identical activation in the left hemisphere for all patients (Fig. 3.1). An index indicating right lateralization does not mean that the left hemisphere is less important, since patients may depend equally on the left hemisphere for language processing despite the differing LIs. Conversely, two patients with the same LIs may have differing dependency on their left hemisphere activation. Secondly, it has been shown that there may be regional differences in lateralization within each hemisphere of the supratentorial parenchyma, a finding that may be lost when only the global hemispheric LI index is considered [25].

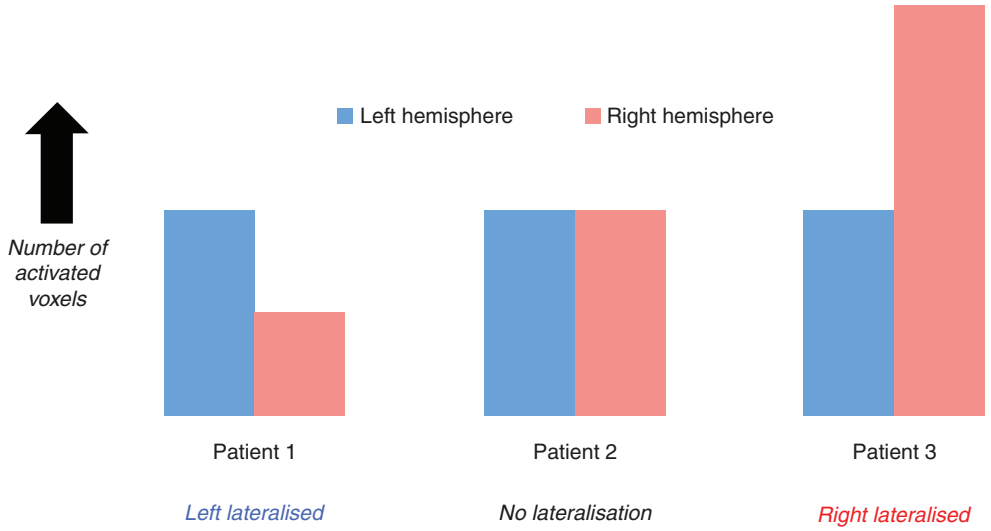

Fig. 3.1 Hemispheric laterality of activation. The figure illustrates an example of why caution is required with the interpretation of an LI calculated from the language fMRI. The relative numbers of activated voxels in the left (*blue*) and right (*red*) hemispheres are shown for a language fMRI task in three different patients. Each patient activates the same number of voxels in the left hemisphere. However, the laterality index is different for all three patients as the number of activated voxels in the right hemisphere varies. Although patient 3 is right lateralized, this result does not imply that the left hemisphere is less critical for language function compared with patient 1 or patient 2; it merely indicates that patient 3 utilized more right hemisphere language centers when performing this particular fMRI task

3.3.3.3 Typical and Atypical Language Representation

Overall fMRI is more specific in right-handed individuals than those who express atypical language representation such as left-handed or ambidextrous individuals [26]. However, there is evidence that fMRI expresses more bilateral language representation compared to the Wada test [30]. A prospective study done in 2013 by Janecek et al. [30] compared the two tests in 229 epilepsy patients and found concordance in 86% of patients, with discordance in bilaterally language represented patients. Discordance between the Wada test and fMRI was higher in cases in which fMRI revealed atypical language dominance. The discordance does not refute the accuracy of fMRI, as there are only a few studies that have looked at the predictive postsurgical language outcome using both methods. Janecek et al. [30] mostly looked at concordant cases and found that the lateralization index of fMRI may be more sensitive than Wada to right hemisphere language processing. Hence, presurgical patients with left language dominance on fMRI do not require a Wada test (Fig. 3.2).

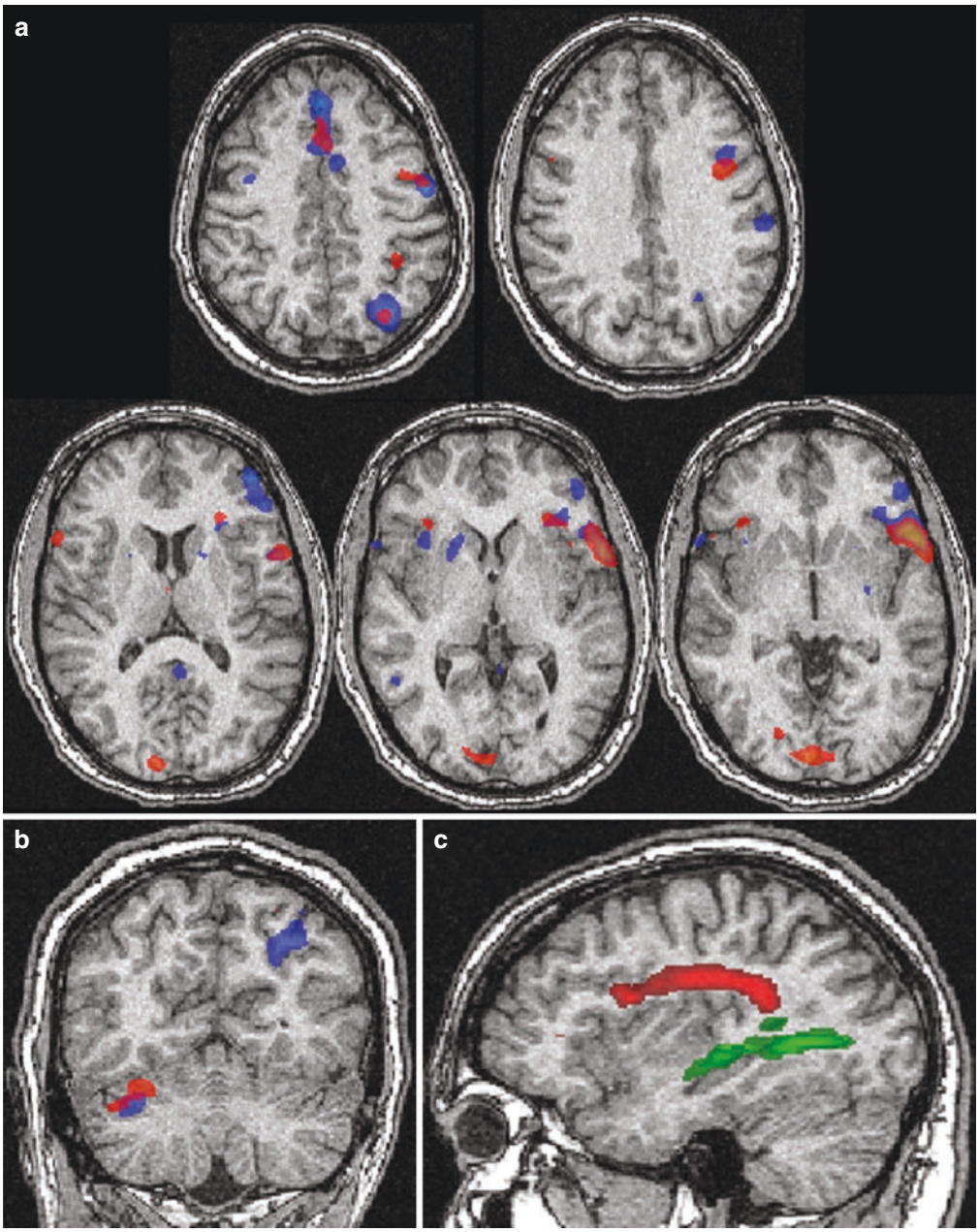

Fig. 3.2 (**a**, **b**) fMRI using language paradigms (verbal fluency (orange) and verb generation (blue)). The data have been analysed with SPM and the maps have been thresholded at $p<0.001$ without correction for multiple comparisons, (**c**), Diffusion tensor imaging (DTI) delineating the arcuate fasciculus (red) and optic radiation (green). The DTI was derived by a probabilistic method. Verbal fluency and verb generation elicited activation in the left inferior frontal gyrus (IFG) and left middle frontal gyrus (MFG) with minimal activation also in the right IFG and right MFG. There was predominant activation in the right cerebellar hemispheres during both tasks. The findings are consistent with left dominance for language. The arcuate fasciculus was derived by drawing regions of interest (ROIs) in the vertical fibers of the arcuate fasciculus and Broca area. The fibers run along their expected trajectories as illustrated on the images provided

3.3.3.4 Cortical Mapping of Language

Test-retest series have shown that localizing language areas activated during a specific language paradigm is less reliable than language lateralization [8]. The sensitivity between language fMRI and cortical stimulation ranged between 59% and 100%, and the specificity between 0% and 97% [15]. In some cases, activated fMRI data did not correlate with language disturbance on electric stimulation [9], whereas language areas were clearly shown in other subjects in fMRI [10, 36]. This may partially be related to the chosen statistical threshold on fMRI. Hence, language area localization by fMRI is not currently ready to be used as a surrogate to cortical mapping for presurgical assessment.

Coregistration with intraoperative or extraoperative electrical stimulation mapping is still required for cortical mapping of language to prevent language deficits in operations proximal to eloquent areas in the clinical setting [7, 37]. Nevertheless, fMRI may have a role in guiding electrical stimulation electrode placement and potentially in prognosis and in developing new rehabilitation strategies when used in conjunction with other modalities [27, 38]. There have been studies on activation patterns in nonsurgical cases during language tasks, such as reading, to identify seizure-generating regions when combined with EEGs [27].

3.3.3.5 Candidates for Language Lateralization with fMRI

A good candidate is a subject with atypical handedness—defined as left-handed individual (especially those with left-sided seizures), patients with left hemispheric lesions, right-handed and left-handed individuals with a left hemispheric lesion or right hippocampal sclerosis, right-handed individuals with aphasia during seizures, and patients with discordance between the anatomic location of the lesion and the clinical semiology [25]. There is a predictive value of fMRI in language lateralization in temporal lobe epilepsy for naming and verbal memory [39, 40]. However, there is currently doubt about the value of using predictive models in routine clinical practice.

3.3.4 Primary Motor and Somatosensory Areas

fMRI is robust and reproducible in identifying motor areas using motor tasks such as finger tapping, tongue wiggling, mouth pouting, or foot movement [41]. Hence, this method has been clinically adopted (Fig. 3.3). In addition to identifying the primary motor cortex area, other areas such as the thalamus, basal ganglia, and ipsilateral cerebellum may be identified on fMRI, as may the supplementary motor cortex [41, 42]. Passive movement may be a viable option in young children and uncooperative or sedated patients. The sensory cortex can also be identified by brushing the face, hand, or foot [43, 44]. Studies have also described paradigms designed for mapping the auditory and visual cortices by introducing tones in the former and flashing a checkerboard pattern in the latter [45]. It is estimated that 9–18% of all epilepsy surgical procedures are performed on extratemporal lesions. A meta-analysis by Téllez-Zenteno et al. [46] found six studies published between 1995 and 2007 on extratemporal epilepsy in which postsurgical seizure freedom was demonstrated in 53% lesional and 26% nonlesional extratemporal epilepsy surgical interventions [18, 46, 47]. Compared with evoked potentials or electrocortical stimulation, Lehericy et al. [32] found agreement with the fMRI activation sites to within 1 cm.

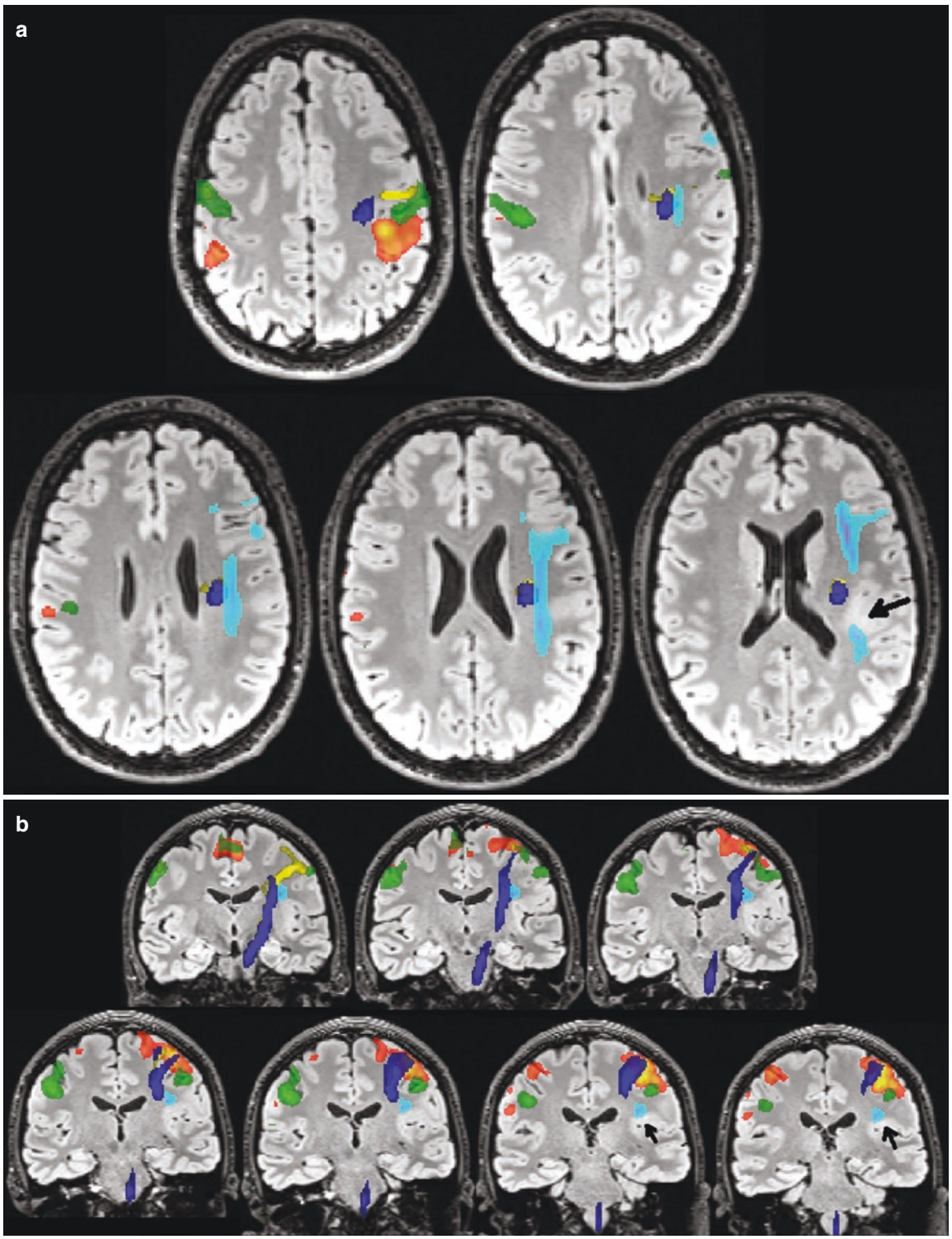

Fig. 3.3 (**a**–**c**) Preoperative fMRI with motor paradigms and DTI study of a patient with left focal cortical dysplasia involving the left parietal operculum and left posterior insula with a deep tail of signal change reaching the lateral ventricular margins and traversing the posterior left insula and left corona radiata (the black arrow point to the lesion). This case illustrates the importance of fMRI, especially in conjunction with DTI in delineating the boundaries of lesions in proximity to eloquent cortical areas or tracts, in this case the CST and arcuate fasciculus. The specific areas activated on fMRI and the white matter tracts (derived by a probabilistic method using the fMRI activation areas as seed points) are color-coded: orange = right hand fMRI, corrected with multiple comparison with family wise error (FWE) and thresholded at p<1e-09; green = lips fMRI, FWE p<0.05, blue = CST right hand, yellow = CST lips, cyan = arcuate fasciculus

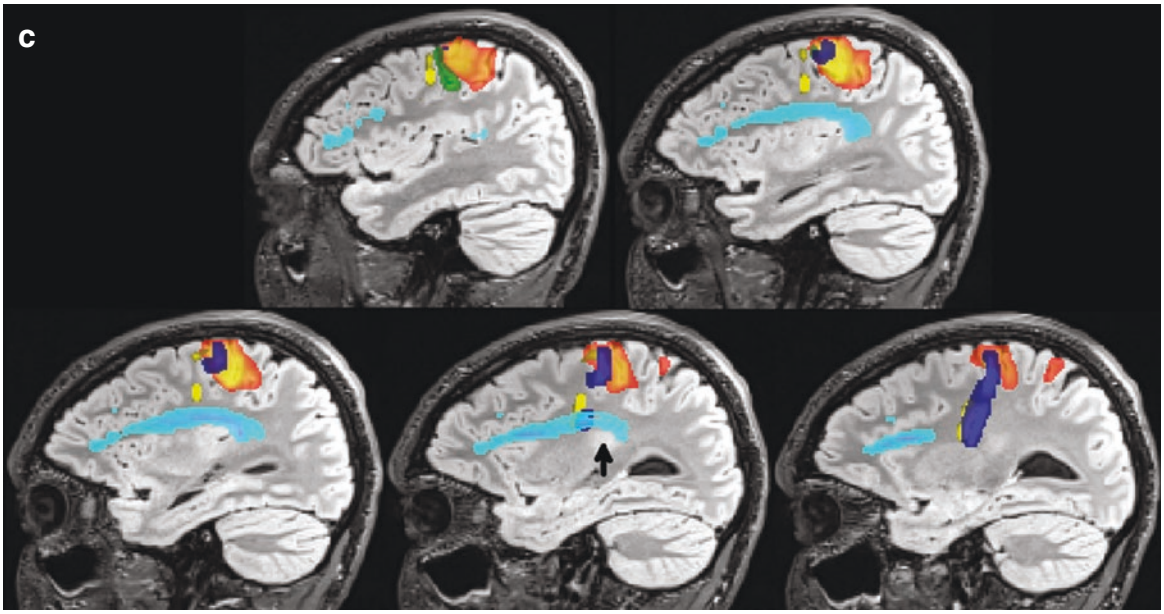

Fig. 3.3 (continued)

3.3.5 Memory

Word finding difficulties were reported in 50% of patients after ATL resection in the dominant hemisphere for language, typically the left [9–12, 48]. Visual memory decline tended to be associated with right ATL resection [29, 49]. As a result of reorganization, patients with unilateral temporal lobe epilepsy may present with material-specific memory impairment, either verbal or visual, and they are expected to show material-specific lateralization of memory on fMRI. Spatial memory, verbal learning, and verbal long-term consolidation and retrieval may be affected by temporal lobe epilepsy surgery as well. Language lateralization on fMRI can predict the risk of postoperative memory decline [34, 50, 51]. Powell et al. studied patients undergoing anterior temporal lobe resection (ATLR) surgery using naming scores pre- and post-treatment. Binder et al. studied 60 patients undergoing left ATLR and showed that lateralization of language on fMRI was better correlated with lateralization of verbal memory than in the Wada test; greater left language dominance on fMRI was associated with a greater verbal decline postoperatively [34]. The patients with greater LIs in the resected hemisphere demonstrated greater decline in naming function [52]. Multiple fMRI paradigms have been used to assess verbal memory, visual memory, or visual complex-scene encoding tasks, and several studies have looked into verbal memory decline compared with a few that studied visual memory impairment [7, 17, 29, 39, 53].

3.3.5.1 Predictors of Postsurgical Verbal and Visual Memory Impairment

Verbal memory decline more likely occurs in surgeries involving language-dominant temporal lobe, and visual-spatial memory decline is more likely in the nondominant hemisphere to language. This was illustrated by Bonelli et al. in their study that included 54 patients with medically refractory temporal lobe epilepsy who underwent temporal lobe resection after preoperative memory fMRI and neuropsychological assessment before and 4 months after surgery [29]. After left ATLR, verbal memory (verbal learning) decline was higher in those patients who showed greater left anterior hippocampal activation compared to right on word encoding. Greater activation of the left posterior hippocampus compared with the right showed better verbal memory outcome postsurgery [29].

Resection of the right anterior temporal lobe was associated with higher visual memory (design learning) decline in patients with right temporal lobe epilepsy in whom preoperative assessment revealed higher anterior right hippocampal activation on face encoding compared to the left [29]. Asymmetry in activation with higher ipsilateral anterior MTL activation was the strongest predictor of verbal and visual memory decline postsurgery. Posterior MTL activation showed favorable verbal and visual memory outcome [29, 40]. Ipsilateral activation in the anterior MTL showed the strongest correlation in terms of predicting verbal and visual memory decline compared to other epilepsy-related variables, including the degree of hippocampal sclerosis, age of onset, and the duration of epilepsy [29, 39, 40]. Other factors that predict low postoperative performance include high preoperative neuropsychological testing scores [9, 12, 28, 54] and less severe hippocampal sclerosis decline [29, 55, 56].

A devised algorithm for memory laterality index was able to predict clinically significant verbal memory decline in all the patients who underwent left ATLR. However, it was not predictive for visual memory [29]. The memory asymmetry index measures may be a robust predictive tool in verbal memory decline, with a significant positive correlation between higher left than right (L > R) posterior MTL activation and a significant negative correlation between a higher left than right (L > R) anterior MTL activation. Hippocampal volume did not show a statistically significant correlation with postoperative memory decline status [29].

3.3.5.2 fMRI Memory Assessment: Challenges

The challenges associated with studying memory fMRI are the low-resolution, geometric distortions, and susceptibility artefacts in the temporal lobe [29]. In early fMRI studies, the anterior hippocampus and parahippocampal regions were not readily shown on fMRI, especially in the inferior frontal and inferior lateral temporal regions, probably because of signal loss from susceptibility artefact and the anterior inferior sloping of the hippocampus. Block experimental designs readily show activation in the posterior regions, with contrast between the two regions. An advantage of event-related designs over block designs is that they capture activation for items that were subsequently remembered as opposed to those forgotten during successful verbal encoding tasks, which may show the activation of the anterior hippocampus and parahippocampal regions [7]. The main limitations of event-related designs include vulnerability to changes in hemodynamic response function and being less able to control for changes in the brain between the events. In addition, they are not entirely practical because they are time-consuming, require cooperation from patients, and are demanding on personnel [29]. A possible alternative is to use memory paradigms assessing both verbal and visual memory in one scanning session [57].

3.3.6 Novel and Adjunct Methods and fMRI in Preoperative Assessment

3.3.6.1 Intracranial EEG and fMRI

Defining the epileptogenic zones anatomically is challenging, even with the use of advanced tests such as MEG, intraoperative electrocorticography, or invasive electrode implantation [47]. fMRI alone is able to identify and locate an epileptic focus during the ictal and the interictal states. However, the technique is improved by EEG-fMRI, which is a noninvasive, highly reproducible research tool that allows simultaneous temporal detection of the epileptic focus, promotes the understanding of epileptic networks, neurovascular coupling, and epileptogenesis and may have a clinical role in identifying the potential surgical target [7]. In around half of patients with epilepsy, EEG-fMRI is found to be superior and more specific than scalp EEG alone in localizing an epileptic focus and can provide complementary information that can affect patient management [7].

Much of the current evidence has been based on individual patients or small case series. In a study by Pittau et al. EEG-fMRI-driven focus localization was higher than with EEG alone in 21 of 33 patients (64%) and concordant in 29 of 33 patients (88%) [58]. Other studies showed that complete surgical removal of the BOLD signal associated with the epileptogenic focus has positive predictive value of seizure freedom of 82–90% during the first year [59, 60] and a negative predictive value of 90.9% if the activation has been outside the resected tissue. Another study in patients with focal cortical dysplasia found that focal BOLD changes (concordant with intracranial EEG findings) predicted good prognosis in four of five patients contrary to diffuse or multifocal BOLD changes [7]. A study comparing interictal fMRI and FDG-PET in 21 patients with interictal epileptiform activity (IEA) found that activations coincided with hypometabolism on fluorodeoxyglucose positron emission tomography (FDG-PET) [7]. Thornton et al. showed that EEG-fMRI is a reliable complementary study to FDG-PET and that it was associated with high long-term seizure freedom [61]. Sierra-Marcos et al. [62] found good concordance between areas of activation during ictal events on EEG-fMRI and the results of structural MRI, PET, Subtraction Ictal SPECT Co-registered to MRI (SISCOM), and invasive EEG.

Interictal fMRI is challenging because it depends on the presence of interictal epileptic discharges during scanning [63]. It is more sensitive in higher field scans [7]. Magnetic-response-encephalography technique provides improved temporal resolution of around 100 ms, which improves the yield of EEG-fMRI and increases the number of patients with BOLD responses correlated with spike topography [7]. Ictal fMRI may be useful in distinguishing the hemodynamics related to the generation and propagation of seizures. It has been suggested that focal epilepsy is caused by abnormal function of a network of cortical and subcortical structures rather than an abnormal epileptogenic focus. EEG-fMRI coupled with other noninvasive techniques is thought to be able to distinguish initiation areas of interictal epileptic discharges from propagated areas [58]. Simultaneous video-EEG recordings during ictal fMRI may help detect BOLD changes in different phases of a seizure in addition to the wealth of data they provide [64]. Combining the analysis of interictal and ictal event data has provided insights into the differences in BOLD signal alterations in different pathologies [64]. The technical challenge in ictal imaging lies in patient movement and the low probability of recording a seizure during an acquisition. Thus, it may only be of value in patients with frequent seizures [58]. In addition, EEG source imaging and EEG-fMRI acquisitions and analysis vary across centers with no guidelines or recommendations [58]. Despite the progress in EEG-fMRI presurgical evaluation, it has not been readily used in clinical practice [23].

3.3.6.2 Functional Neuronavigation and Intraoperative MRI

The gold standard in monitoring eloquent brain areas during surgery has been awake craniotomy and intraoperative cortical brain mapping. However, there is limited information on their safety, efficiency, and pain control due to the lack of randomized controlled trials. In addition, their complications include airway obstruction, neurologic deficits of up to 29%, and surgical complications that reach up to 15% [65–67]. These methods can achieve complete resection in around 71–85% of extratemporal lesions. The addition of functional neuronavigation information and the use intraoperative MRI allows surgical resection within or very close to the eloquent brain and can potentially improve complete resection rates [47]. A retrospective study by Sommer et al., which observed postsurgical morbidly and seizure freedom in patients with drug-resistant extratemporal epileptogenic lesions close to eloquent brain or white matter tracts found that functional neuronavigation and intraoperative MRI achieved complete resection in all 25 cases and seizure freedom in 72% of patients [47]. The most favorable outcome was found after cavernoma surgery (84%), followed by hippocampal sclerosis (79%) and tumors (76%). The group showed improvement in complete resections from 73% to 87% after the introduction of neuronavigation and low field iMRI. The largest group of patients who required second-look surgery were the long-term epilepsy-associated tumors [24]. In addition, there is evidence that the use of these methods is associated with a low rate of complications without additional adverse effects. Roessler et al. reported visual field defects of around 5.2%, dysphasia of around 5.7%, and hemiparesis of 2.7% [24]. Multimodal navigation can provide information helpful to justify surgery, is no worse than using awake craniotomy in terms of neurologic outcome and surgical complication rates, and may be used clinically in epilepsy centers [47].

3.3.6.3 Resting State fMRI

Identifying an epileptogenic focus in nonlesional epilepsy with normal MRI is essential for the best possible postoperative outcome [23]. Resting state fMRI (rsfMRI) is a feasible test for clinical practice [68] and was shown in the literature to be a potential preoperative mapping tool for identifying seizure focus [23, 69, 70]. Intact language networks have been identified by rsfMRI in the absence of verbal testing [23, 71]. An initial disruption of cross-hemispheric networks and an increase in static functional connectivity in the ipsilateral temporal network accompanying the onset of temporal lobe seizures was shown using rsfMRI [35]. This phenomenon is possibly attributable to a compensatory cross-hemisphere mechanism and may allow for identification of the hemisphere of the seizure focus with at least 91% specificity [23, 35]. Weaver et al. suggest that the location of epileptogenic regions in nonlesional focal epilepsy can be accurately estimated from rsfMRI local functional connectivity measurements [23]. Some of the limitations of the studies that looked into rsfMRI are the small sample size of the cohorts and the variable techniques [23].

3.3.7 Considerations and Limitations

Certain inherent limitations of fMRI may weaken its clinical value under certain conditions. In fMRI, spurious activation or false positives cannot easily be distinguished from actual activations, and motion can either introduce artefactual activation and/or reduction in the power and extent of the real activation. There is compromise of the fMRI signal in patients with metal implants, claustrophobia, and morbid obesity, whereas high-flow vascular lesions (e.g., arteriovenous malformations) may cause false activation and thus false focus localization. Moreover, there is a lower signal to noise ratio in areas such as the temporal lobes because of differences in magnetic susceptibility at air-tissue boundaries and signal detection in the proximity to large blood vessels and bones [7, 13]. Furthermore, the presurgical work-up is highly variable across centers and depends on the accessibility to technology and local expertise. When fMRI is incorporated into the presurgical assessment, caution must be taken in the choice of fMRI paradigms and study design. Following covert tasks (as the ones used in fMRI paradigms) is difficult, when the patient's understanding of the tasks and accurate following of instructions and performance affect results [7, 13]. Epilepsy patient safety owing to the limited space and the risk of injury as well as head motion may also be concerns [64]. Patient selection, head restraint, and MRI compatible microphones to monitor speech during the scan can be used. Scanner implemented software for online data analysis can be used to show activation patterns during scanning [64].

During data processing, the sensitivity of activation depends on the statistical thresholding applied to the fMRI data. A high threshold reduces the sensitivity of activation detection, and a low threshold increases the risk of false-positives. Areas of activation may not be essential to perform the fMRI task, and conversely areas involved in language function may not be necessarily activated by the fMRI task being performed. Great caution is required in interpreting the absence of activation in fMRI in presurgical localization of relevant language processing. The extent and magnitude of activation may be affected by the patient's performance, with reduced functional activity often accompanying cognitive impairment [22]. There is also evidence that some rsfMRI techniques may be susceptible to smearing of voxels and underestimation of the epileptogenic zone [23].

The time increase by using fMRI embedded in neuronavigation during intraoperative MRI (iMRI) is minimal. The errors encountered may be related to the spatial resolution, data calculation and thresholds, volumetric brain deformation, navigation target registration, coregistration of the pre- and intraoperative MR images, and intraoperative loss of cerebral spinal fluid resulting in "brain shift" [9, 13]. Notably, techniques to tackle the coregistration inaccuracies have been developed [23, 24, 47].

3.3.8 Clinical Applications of fMRI in Epilepsy: Summary

The use of functional MRI in clinical practice has been validated, especially in identifying sensorimotor or visual areas and in the assessment of language hemispheric dominance (Fig. 3.4). On the other hand, memory paradigms are still making the transition toward their application in the clinical setting, and EEG-fMRI remains a research tool in localizing epileptic zones. Studies have produced data on validating fMRI activation in comparison with direct electrical CSM. The fMRI localization of the sensorimotor cortex is well confined to the peri-Rolandic region and replicates CSM findings. Conversely, fMRI of language identifies regions that are similar yet not identical to those shown by CSM. As a consequence, fMRI for language localization is currently considered complementary to CSM and transcranial magnetic stimulation (TMS), which are considered the ultimate guide for the evaluation of surgical candidates [72, 73]. Further concordance studies between different modalities such as rsfMRI and FDG-PET may increase the diversity of applications of fMRI.

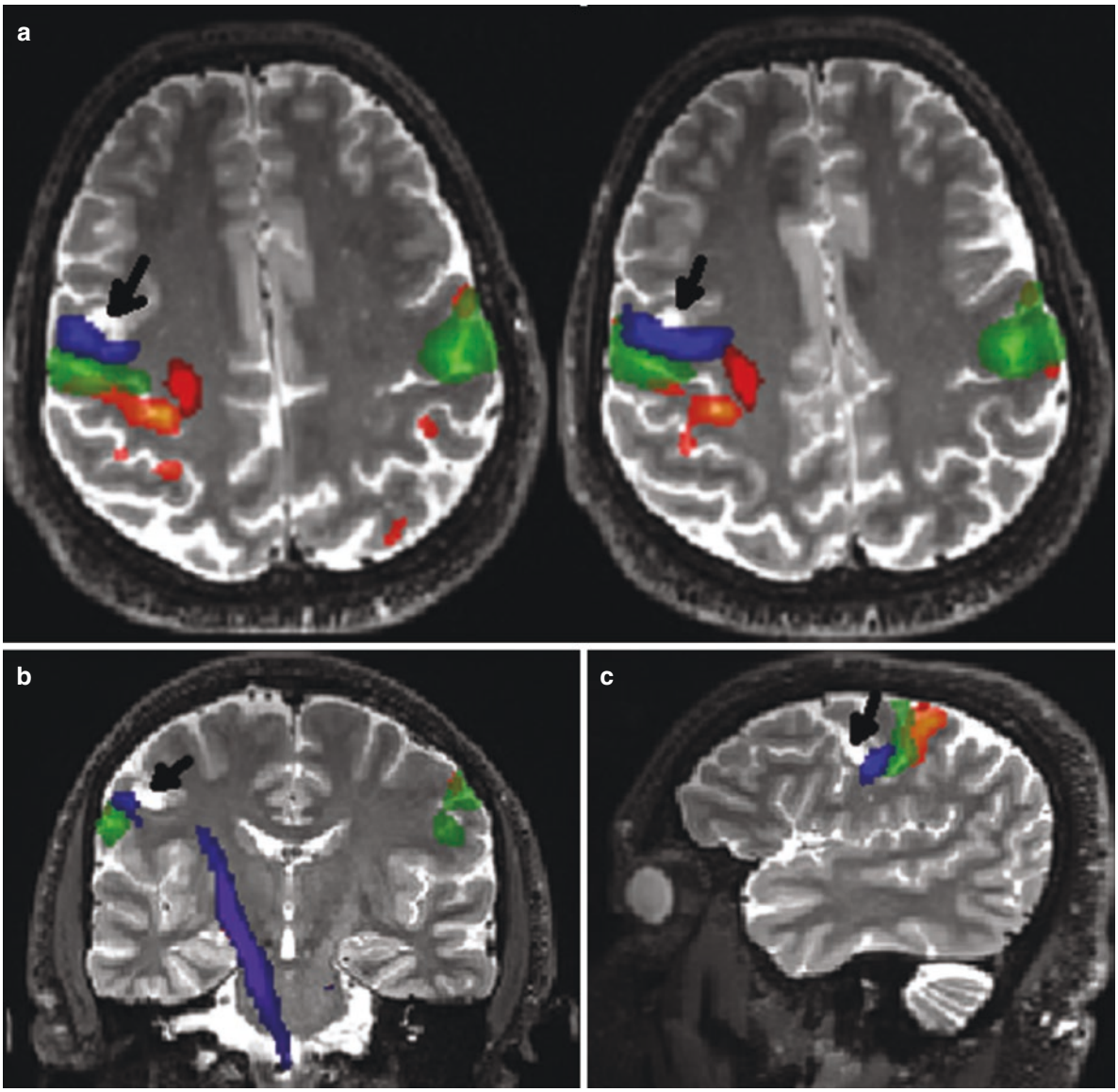

Fig. 3.4 (**a**–**c**) fMRI with motor paradigms and DTI study of a patient with a dysembryoplastic neuroectodermal tumor (DNET) centered onto the lateral genu of the right precentral gyrus (the black arrow point to the lesion). The fMRI data have been analysed with SPM and the maps have been thresholded at $p<0.001$ without correction for multiple comparisons. The specific areas activated on fMRI and the white matter tracts (derived by a probabilistic method using the fMRI activation areas as seed points) are color-coded: orange = left hand fMRI, green = lips fMRI, red = CST left hand, blue = CST lips. The movement of the left hand and the lips elicit activation in the pre- and postcentral gyri. The lips- associated corticospinal tract fascicle runs immediately posterior to the tumor within the precentral gyrus. The hand corticospinal fascicle is at a distance medial to it

3.4 Acquisition and Analysis of Clinical fMRI in Epilepsy

3.4.1 fMRI Acquisition and Patient Performance

In general, fMRI is a demanding study, and care must be taken in the selection of the acquisition parameters and in the detailed explanation of the procedure to the patients since good subject cooperation is required. Any drugs taken by the patients to control their seizures might reduce the BOLD activation, and thus the clinical history should be meticulously investigated. Results may be misinterpreted as a consequence of false-positive and false-negative responses. The clinical interpretation of individual fMRI examinations may be hampered by the fact that the BOLD signal may also decrease. The so-called deactivation may be artefactual or related to pathologic conditions (e.g., small vessel disease), but can be also caused by inhibitory brain processes or the result of the subject's concurrent mental processing on possibly multiple perceptual tasks, mental fatigue, or pathologic conditions [74–76].

3.4.2 fMRI Acquisition: Technical Aspects

From the acquisition point of view, several studies have been performed to optimize the fMRI signal. The MRI SNR increases linearly with field strength, while the BOLD contrast is maximized when using echo time (TE) of similar value to the T2* value of gray matter (TE ~ T2* GM). At 1.5 Tesla, the T2* value of GM is approximately 50–60 ms, while at 3 Tesla, T2* is approximately 30–40 ms [77]. When acquiring susceptibility-based images, issues related to susceptibility such as shimming and distortions (especially at the skull base or in regions near interfaces of susceptibility such as near the sinuses) are more prominent at higher field strengths. The choice of repetition time (TR) is usually dictated by the number of slices and the acquisition speed of the scanner. For lower TR, care must be taken in selecting the appropriate flip angle, which maximizes the signal at a given TR (the Ernst angle). It has been found that functional contrast drops off significantly when a TR of less than 500 ms is used, but the etiology of this phenomenon is yet to be understood. Attempts have also been made to optimize the acquisition voxel volume accounting for the fact that the SNR in MRI is directly proportional to the voxel volume [7, 78, 79]. Functional contrast-to-noise ratio (CNR) is optimized by matching the volume of the active region to the voxel volume. However, since functional region sizes are not well characterized, the optimal voxel size is difficult to predict. Recent studies suggest that the optimal voxel volume dimensions range from 2.8 to 3.5 mm^3, but it is also common practice to match the voxel volume to the cortical thickness (close to 3 mm) [1, 80, 81].

3.4.3 fMRI Post-processing and Interpretation

Physiologic fluctuations are caused by the pulsations following every heartbeat, the respiration-related changes in the magnetic field and in the cardiac frequency, and additional physiologic fluctuations in the 0.1–0.2 Hz range [82, 83]. The impact of the inherent fluctuations should be theoretically eliminated to achieve maximum sensitivity. They are less of an issue at high spatial resolution and in pulse sequences with low contrast sensitivity, where random thermal noise effects are of similar magnitude to the physiologic noise and tend to dominate [1, 84]. An easily implemented post-processing step to eliminate or reduce physiologic noise is to filter out frequencies associated with physiologic processes, which need to be sampled at a rate of at least double that of the highest fluctuation frequency. For the cardiac frequency for instance, this translates into a very short TR. In the most commonly used fMRI designs, TR is of the order of 2 s and therefore the cardiac frequencies cannot be removed by filtering alone. More recent development of multiband or simultaneous multislice acquisitions allow for shorter TR and better removal of cardiac frequencies [45, 85]. On the contrary, the respiration frequency is within the sampling rate of most fMRI acquisitions, thus making it easier to filter out. A more accurate method to remove respiration fluctuation is to obtain direct measurements of the respiration time course and to use them as regressor or reference function in data analysis [82]. From a practical point of view, it is more efficient to rerun a poorly performed fMRI rather than spending time to improve the sampling quality retrospectively. In the meantime, all major MRI scanner vendors include a real-time analysis feature that allows them to monitor the quality of the functional data while they are collected [1].

When reviewing fMRI results there are a number of user options that will dictate the number of voxels displayed as being activated. A voxel is considered activated when the statistical test, which is applied to assess the estimate of the effect of the task, surpasses the statistical threshold. In other words, the user can specify the likelihood that any given voxel identified by the software represents a voxel, which is truly involved with the task rather than representing a false-positive area of activation. The user can also specify the minimum number of voxels that make up any one cluster, a cluster being a group of activated voxels in continuity with one another.

In contrast to neuroimaging research, less stringent statistical thresholds are used for the clinical preoperative application of fMRI because there needs to be a fine balance between maximizing the sensitivity and specificity of the investigation. The disadvantage of using a stringent threshold is that true areas of activation may be missed, resulting in inadvertent damage to functionally important areas as a result of

surgery. Conversely, too low a threshold could result in false-positive areas of activation, leading to overestimation of the extent of the functional area. The benefits of preoperative fMRI have been extensively studied [42, 86]. However, what these studies and others [72, 87] have highlighted is that there are no specific guidelines for the statistical threshold which should be used when interpreting fMRI in clinical practice. Indeed, it has been recommended that thresholding should be individualized on a case-by-case basis [72].

It should be noted, however, that the use of fMRI in the presurgical evaluation of epilepsy patients is slightly different. For neuro-oncologic surgery, fMRI is performed to identify laterality of activation but it can also answer the additional question of whether the tumor margin encroaches into functionally important regions in an attempt to maximize the extent of the resection and avoid postoperative neurologic deficits. For patients with medically refractory temporal lobe epilepsy undergoing ATL resection, the surgical procedure itself is more standardized. Consequently, the main question to be answered relates to lateralization rather than the localization of activation and for this reason, the actual thresholds used may be more flexible but again need to be individualized [15, 35].

3.4.4 fMRI Artefacts Related to Field Heterogeneity

The most prevalent image quality compromise in fMRI data results from image distortion (caused by off-resonance effects induced by the static magnetic field (B_0) inhomogeneities and gradient non-linearities) as well as by signal dropout. Possible solutions to reduce the image distortions are to shorten the readout window, pursue a better shim, and/or map the B0 field in order to subsequently perform a correction for field inhomogeneities. Another potential but less commonly used solution is to use a spiral readout, in which the off-resonance effects appear as image blurring instead of as distortions. Local B0 field inhomogeneities also cause signal dropouts at the interface between tissues with different magnetic susceptibilities (i.e., adjacent to the paranasal sinuses and the auditory canals). To reduce signal dropout, suggested approaches include optimizing the shim, reducing the voxel size, and choosing the slice orientation so that the smallest voxel dimension is oriented perpendicular to the largest B0 gradient [1, 88–91].

3.4.5 Motion-Related fMRI Artefacts

As mentioned previously, good subject cooperation during an fMRI experiment is of paramount importance. The statistical analysis of fMRI data is performed on a voxel by voxel basis whereby the signal intensity in each voxel is compared across consecutive acquisitions. In a typical block design fMRI paradigm this may range from 50 up to 100 volumes, depending on the duration. It is therefore essential that head movement is minimized during the acquisition to ensure that the same voxels are being assessed across the whole acquisition. Imaging analysis software, such as Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Centre for Neuroimaging, London, UK http://www.fil.ion.ucl.ac.uk/spm) allows the realignment of sequential volumes by assuming any motion can be described using a rigid body transformation in the X, Y, or Z axes. For random movement, which would result in false-positive activation up to several millimeters, realignment is an effective method to deal with this. Head motion associated with the task that may occur when the patient tenses or concentrates (also known as stimulus-correlated motion) can be more problematic. This stimulus correlated motion can be more difficult to rectify because the shift of voxels may cause changes in signal intensity similar to those that occur in activation caused by the change in blood flow. Removal of these motion signals may also result in loss of true signal differences (for a comprehensive summary see [92]). During the acquisition we routinely review the whole brain volumes to subjectively assess for any movement. It is recommended that the acquisition be repeated if there is visible gross movement, for example, movement of the cerebellar tonsils in relation to the foramen magnum. One should also consider reacquiring the gradient field map in this situation.

The optimal method for dealing with motion is to limit its occurrence at the time of fMRI acquisition. It is important to ensure that the patient's head is securely but comfortably supported throughout the scan. Even the most compliant patient may move his or her head if it is not adequately supported, and movement should always be considered inevitable when imaging younger patients who may be less compliant with instructions. In our institution this is achieved through the use of at least three supporting sponges placed around the head at the vertex and overlying both pinnas. Multiple sponges shaped to the contour of the head coil, such as those used during structural MRI acquisition, are used and placed in such a manner that the patient's head is limited in its movement. The patient should report that the head feels secure but not uncomfortable. Before the scan we give precise instructions to the patient to keep as still as possible. We advise that if they need to move their trunk or limbs that this should be done during the fMRI task interval. We actively engage the patient before and after the start of each task, giving encouragement, explaining the upcoming task, and reaffirming the importance of keeping as still as possible [1, 83].

3.4.6 Paradigm Design and Related Errors

The design of any fMRI paradigm involves testing to ensure that the task consistently and reproducibly activates the same brain regions across subjects and therefore should not be complex. For subtle cognitive effects, the paradigm has to be psychologically effective, easily transferable to the inside of a scanner, and capable of generating detectable BOLD responses. Occasionally, fMRI paradigm characteristics (e.g., duration) may be tailored to the patient's abilities so that the patient finds the task challenging but is still able to comply with it. It is important to provide clear instructions to the patients, give them adequate time to trial the task, and assess the patient's ability to perform the task before entering the MRI scanner room. While compliance with sensorimotor tasks involving feet and hands can be monitored visually during the acquisition, it might be difficult to monitor the patient's compliance with language or other cognitive tasks. Language tasks involving overt speech can introduce motion artefacts, especially if parallel imaging is used to reduce the repetition time. To enable the patient to listen to the overt speech, special microphones that subtract the scanner noise from the audio tract are needed [93–96].

It is also very important to use accurate timing of the stimulus onset and rest periods and insert these parameters into the SPM in order to produce accurate measurements of the signal changes elicited by each task. Figure 3.5 illustrates a simplified view of a block design fMRI paradigm and how the stimulus onset times are also dependent upon the number of dummy scans, the EPI volumes which are not included in the analysis to allow for T1 equilibration effects [1, 96].

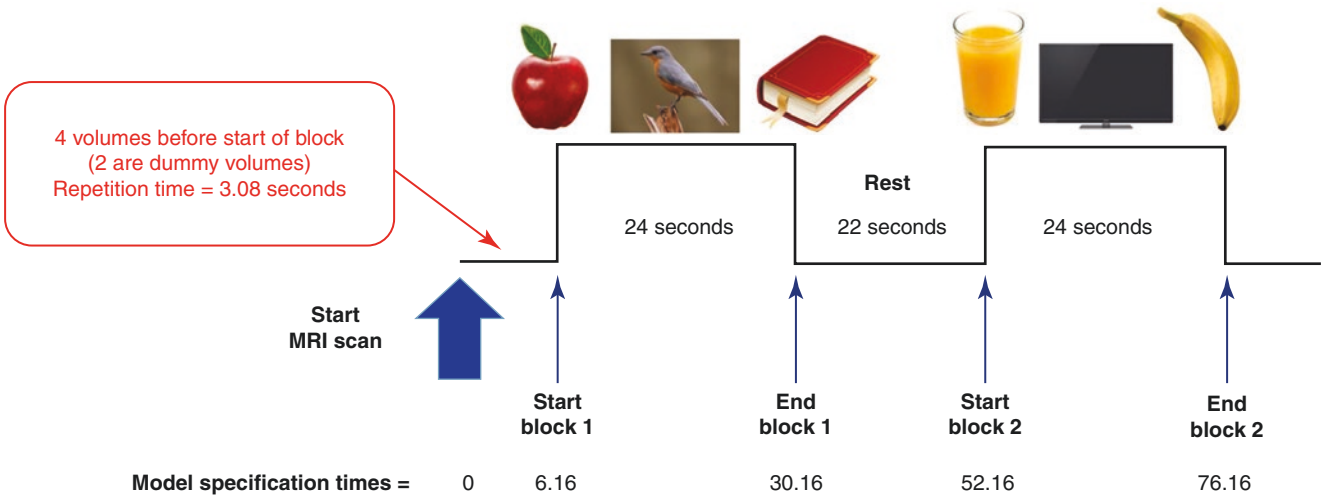

Fig. 3.5 Schematic representation of a block design fMRI paradigm and stimulus onset times. The figure represents a simplified block design fMRI language paradigm involving an object naming task, with the first two blocks of the paradigm shown. The duration of each block is 24 s with an intervening 22 s rest period. The exact stimulus onset time and the duration of the block are required in the fMRI model specification stage of data analysis because the signal change elicited by the task (object naming) is compared to the signal at rest. The main point here is to illustrate the strict attention to the precise time at which the fMRI acquisition and the fMRI paradigm commence. In this example, there are four whole brain acquisitions before the start of the task. As each acquisition has a TR of 3.08 s, this represents a duration of 12.32 s from the time at which the MRI scan is commenced. Two of these volumes are excluded from the analysis to allow for T1 equilibration effects (dummy volumes), and so the paradigm actually starts at 6.16 s. All subsequent model specification times are related to this onset rather than 12.32. Error in timing could lead to the signal elicited by the task being compared to itself rather than the rest period

3.4.6.1 Overt Language Paradigms

The in-scanner task performance is decisive for the success of the MRI experiment and of crucial importance during language fMRI paradigms. Language fMRI paradigms may be performed silently with the patient instructed to think of the response to a task [93–95]. If the fMRI task is performed with overt speech production, there will be bilateral hemispheric activation mainly resulting from motor activation associated with articulation and often superior temporal lobe activation associated with the sound of hearing one's own voice. Although this may be useful for the preoperative evaluation for an epileptogenic focus targeted for resection that may be close to speech centers, subjective assessment of hemispheric laterality of activation may be less obvious than may be achieved during covert tasks [96].

3.4.6.2 Covert Language Paradigms

One major disadvantage of performing the fMRI task covertly is that it may be difficult to subsequently ascertain if absence of the expected activation in a region is pathologic or represents lack of compliance by the patient at the time of fMRI acquisition. This uncertainty may lead to repeat imaging to re-evaluate the pattern of activation. One solution is to engage the patient and to monitor accuracy by including a judgment task embedded within the covert language task; the response may be measured by a button press (Fig. 3.6). For example, an image may be displayed and the patient be required to judge whether the image matches or is different than the image immediately preceding it by pressing a button. These responses can then be assessed after the acquisition to check whether the patient was performing this assessment. Such a method has been described in language fMRI studies, which are specifically designed to be without vocalization [97].

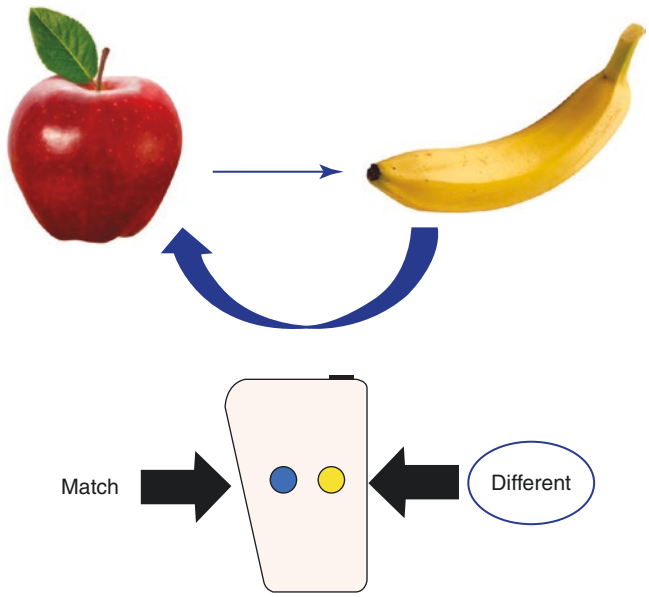

Fig. 3.6 Use of a button press during covert language tasks. The figure illustrates a method of monitoring patient compliance during language fMRI tasks that are performed without speech production or method of monitoring accuracy. In this example, patients are required to silently think of the names of objects presented to them visually, such as an apple. The button press task involves the patient deciding if the next object displayed, the banana, matches or is different from the preceding image by means of a button response. These responses may be checked to monitor the accuracy and is a method of engaging the patient in the task

Conclusion

Imaging cortical function has been continuously pursued, and major breakthroughs have been achieved. Multimodal imaging of brain function is possible and ranges from direct measurements with methods such as EEG and CSM to indirect methods such as FDG-PET and fMRI. Recent advances have allowed for combinations of these techniques in the research and clinical setting and are especially valuable for the preoperative assessment of patients. fMRI has largely improved over the years and has been successfully correlated to the gold standards of brain activation imaging such as CSM. Recent studies provide evidence on the value of this technique as an adjunct and in many cases as a stand-alone technique for the preoperative assessment of patients. Specifically, in patients with epilepsy, the role of fMRI in presurgical assessment is currently undisputable and ranges from investigating language lateralization to predicting the clinical outcome of temporal lobe resection. However, technical and design drawbacks still exist; current and future research is expected to further improve this imaging method and determine its role in the clinical setting.

References

1. Soares JM, Magalhães R, Moreira PS, Sousa A, Ganz E, Sampaio A, et al. A hitchhiker's guide to functional magnetic resonance imaging. Front Neurosci. 2016;10
2. Le Bihan D. Functional MRI of the brain principles, applications and limitations. J Neuroradiol. 1996;23:1–5.
3. Logothetis NK. What we can do and what we cannot do with fMRI. Nature. 2008;453:869–78.
4. Buxton RB, Uludag K, Dubowitz DJ, Liu TT. Modeling the hemodynamic response to brain activation. Neuroimage. 2004;23(Suppl1):S220–33.
5. Moonen CTW, Bandettini PA, Aguirre GK. Functional MRI. Berlin, New York: Springer; 1999. p. xii, 575.
6. Kim SG, Ogawa S. Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. J Cereb Blood Flow Metab. 2012;32:1188–206.
7. Pittau F, Grouiller F, Spinelli L, Seeck M, Michel CM, Vulliemoz S. The role of functional neuroimaging in pre-surgical epilepsy evaluation. Front Neurol. 2014;5:31.
8. Hirsch LJ. Long-term outcome after epilepsy surgery: relapsing, remitting disorder? Epilepsy Curr. 2012;12:140–2.
9. Chelune GJ, Naugle RI, Luders H, Awad IA. Prediction of cognitive change as a function of preoperative ability status among temporal lobectomy patients seen at 6-month follow-up. Neurology. 1991;41:399–404.
10. Hermann BP, Seidenberg M, Haltiner A, Wyler AR. Relationship of age at onset, chronologic age, and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. Epilepsia. 1995;36:137–45.
11. Loring DW, Meador KJ, Lee GP, King DW, Nichols ME, Park YD, et al. Wada memory asymmetries predict verbal memory decline after anterior temporal lobectomy. Neurology. 1995;45:1329–33.
12. Helmstaedter C, Elger CE. Cognitive consequences of two-thirds anterior temporal lobectomy on verbal memory in 144 patients: a three-month follow-up study. Epilepsia. 1996;37:171–80.
13. Woermann FG, Labudda K. Clinical application of functional MRI for chronic epilepsy. Radiologe. 2010;50:123–30.
14. Tracy JI, Tinker JS. Neurocognitive assessment in epilepsy: advanced and challenges. In: Morgan JE, Ricker JH, editors. Textbook of clinical neuropsychology. London: Taylor and Francis Ltd; 2016. p. 449–70.
15. Giussani C, Roux FE, Ojemann J, Sganzerla EP, Pirillo D, Papagno C. Is preoperative functional magnetic resonance imaging reliable for language areas mapping in brain tumor surgery? Review of language functional magnetic resonance imaging and direct cortical stimulation correlation studies. Neurosurgery. 2010;66:113–20.
16. Wasade VS, Elisevich K, Tahir R, Smith B, Schultz L, Schwalb J, et al. Long-term seizure and psychosocial outcomes after resective surgery for intractable epilepsy. Epilepsy Behav. 2015;43:122–7.
17. Janszky J, Jokeit H, Kontopoulou K, Mertens M, Ebner A, Pohlmann-Eden B, et al. Functional MRI predicts memory performance after right mesiotemporal epilepsy surgery. Epilepsia. 2005;46:244–50.
18. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005;128(Pt 5):1188–98.
19. Helmstaedter C, Fritz NE, Gonzalez Perez PA, Elger CE, Weber B. Shift-back of right into left hemisphere language dominance after control of epileptic seizures: evidence for epilepsy driven functional cerebral organization. Epilepsy Res. 2006;70:257–62.
20. Gould L, Mickleborough MJ, Wu A, Tellez J, Ekstrand C, Lorentz E, et al. Presurgical language mapping in epilepsy: using fMRI of reading to identify functional reorganization in a patient with long-standing temporal lobe epilepsy. Epilepsy Behav Case Rep. 2016;5:6–10.
21. Woermann FG, Jokeit H, Luerding R, Freitag H, Schulz R, Guertler S, et al. Language lateralization by Wada test and fMRI in 100 patients with epilepsy. Neurology. 2003;61:699–701.
22. van Houdt PJ, de Munck JC, Leijten FS, Huiskamp GJ, Colon AJ, Boon PA, et al. EEG-fMRI correlation patterns in the presurgical evaluation of focal epilepsy: a comparison with electrocorticographic data and surgical outcome measures. Neuroimage. 2013;75:238–48.
23. Weaver KE, Chaovalitwongse WA, Novotny EJ, Poliakov A, Grabowski TG, Ojemann JG. Local functional connectivity as a pre-surgical tool for seizure focus identification in non-lesion, focal epilepsy. Front Neurol. 2013;4:43.
24. Roessler K, Hofmann A, Sommer B, Grummich P, Coras R, Kasper BS, et al. Resective surgery for medically refractory epilepsy using intraoperative MRI and functional neuronavigation: the Erlangen experience of 415 patients. Neurosurg Focus. 2016;40:E15.
25. Bauer PR, Reitsma JB, Houweling BM, Ferrier CH, Ramsey NF. Can fMRI safely replace the Wada test for preoperative assessment of language lateralisation? A meta-analysis and systematic review. J Neurol Neurosurg Psychiatry. 2014;85:581–8.
26. Dym RJ, Burns J, Freeman K, Lipton ML. Is functional MR imaging assessment of hemispheric language dominance as good as the Wada test? A meta-analysis. Radiology. 2011;261:446–55.
27. Salek-Haddadi A, Mayer T, Hamandi K, Symms M, Josephs O, Fluegel D, et al. Imaging seizure activity: a combined EEG/EMG-fMRI study in reading epilepsy. Epilepsia. 2009;50:256–64.
28. Baxendale S, Thompson P, Harkness W, Duncan J. Predicting memory decline following epilepsy surgery: a multivariate approach. Epilepsia. 2006;47:1887–94.
29. Bonelli SB, Powell RH, Yogarajah M, Samson RS, Symms MR, Thompson PJ, et al. Imaging memory in temporal lobe epilepsy: predicting the effects of temporal lobe resection. Brain. 2010;133(Pt 4):1186–99.

30. Janecek JK, Swanson SJ, Sabsevitz DS, Hammeke TA, Raghavan M, M ER, et al. Language lateralization by fMRI and Wada testing in 229 patients with epilepsy: rates and predictors of discordance. Epilepsia. 2013;54:314–22.
31. Benson RR, FitzGerald DB, LeSueur LL, Kennedy DN, Kwong KK, Buchbinder BR, et al. Language dominance determined by whole brain functional MRI in patients with brain lesions. Neurology. 1999;52:798–809.
32. Lehéricy S, Leclercq D, Duffau H, Van de Moortele P-F, Delmaire C. Presurgical functional localization possibilities, limitations, and validity. In: Stippich C, editor. Clinical functional MRI. 2nd ed. Berlin, New York: Springer; 2015. p. 247–67.
33. Gaillard WD, Balsamo L, Xu B, Grandin CB, Braniecki SH, Papero PH, et al. Language dominance in partial epilepsy patients identified with an fMRI reading task. Neurology. 2002;59:256–65.
34. Binder JR, Sabsevitz DS, Swanson SJ, Hammeke TA, Raghavan M, Mueller WM. Use of preoperative functional MRI to predict verbal memory decline after temporal lobe epilepsy surgery. Epilepsia. 2008;49:1377–94.
35. Morgan VL, Abou-Khalil B, Rogers BP. Evolution of functional connectivity of brain networks and their dynamic interaction in temporal lobe epilepsy. Brain Connectivity. 2015;5(1):35–44. https://doi.org/10.1089/brain.2014.0251.
36. Babajani-Feremi A, Narayana S, Rezaie R, Choudhri AF, Fulton SP, Boop FA, et al. Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation. Clin Neurophysiol. 2016;127:1822–36.
37. Roux F-E, Boulanouar K, Lotterie J-A, Mejdoubi M, LeSage JP, Berry I. Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. Neurosurgery. 2003;52:1335–47.
38. Pal DK. Epilepsy and neurodevelopmental disorders of language. Curr Opin Neurol. 2011;24:126–31.
39. Bonelli SB, Thompson PJ, Yogarajah M, Vollmar C, Powell RH, Symms MR, et al. Imaging language networks before and after anterior temporal lobe resection: results of a longitudinal fMRI study. Epilepsia. 2012;53:639–50.
40. Binder JR, Swanson SJ, Sabsevitz DS, Hammeke TA, Raghavan M, Mueller WM. A comparison of two fMRI methods for predicting verbal memory decline after left temporal lobectomy: language lateralization versus hippocampal activation asymmetry. Epilepsia. 2010;51:618–26.
41. Tyndall AJ, Reinhardt J, Tronnier V, Mariani L, Stippich C. Presurgical motor, somatosensory and language fMRI: technical feasibility and limitations in 491 patients over 13 years. Eur Radiol. 2016:1–12.
42. Bizzi A, Blasi V, Falini A, Ferroli P, Cadioli M, Danesi U, et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology. 2008;248:579–89.
43. Yetkin FZ, Mueller WM, Hammeke TA, Morris GL 3rd, Haughton VM. Functional magnetic resonance imaging mapping of the sensorimotor cortex with tactile stimulation. Neurosurgery. 1995;36:921–5.
44. Rao SM, Bandettini PA, Binder JR, Bobholz JA, Hammeke TA, Stein EA, et al. Relationship between finger movement rate and functional magnetic resonance signal change in human primary motor cortex. J Cereb Blood Flow Metab. 1996;16:1250–4.
45. De Martino F, Moerel M, Ugurbil K, Formisano E, Yacoub E. Less noise, more activation: multiband acquisition schemes for auditory functional MRI. Magn Reson Med. 2015;74:462–7.
46. Tellez-Zenteno JF, Hernandez Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res. 2010;89:310–8.
47. Sommer B, Grummich P, Coras R, Kasper BS, Blumcke I, Hamer HM, et al. Integration of functional neuronavigation and intraoperative MRI in surgery for drug-resistant extratemporal epilepsy close to eloquent brain areas. Neurosurg Focus. 2013;34:E4.
48. Sabsevitz DS, Swanson SJ, Morris GL, Mueller WM, Seidenberg M. Memory outcome after left anterior temporal lobectomy in patients with expected and reversed Wada memory asymmetry scores. Epilepsia. 2001;42:1408–15.
49. Lee GP, Park YD, Hempel A, Westerveld M, Loring DW. Prediction of seizure-onset laterality by using Wada memory asymmetries in pediatric epilepsy surgery candidates. Epilepsia. 2002;43:1049–55.
50. Richardson MP, Strange BA, Duncan JS, Dolan RJ. Memory fMRI in left hippocampal sclerosis: optimizing the approach to predicting postsurgical memory. Neurology. 2006;66:699–705.
51. Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Barker GJ, et al. Imaging language pathways predicts postoperative naming deficits. J Neurol Neurosurg Psychiatry. 2008;79:327–30.
52. Powell HW, Richardson MP, Symms MR, Boulby PA, Thompson PJ, Duncan JS, et al. Preoperative fMRI predicts memory decline following anterior temporal lobe resection. J Neurol Neurosurg Psychiatry. 2008;79:686–93.
53. Rabin ML, Narayan VM, Kimberg DY, Casasanto DJ, Glosser G, Tracy JI, et al. Functional MRI predicts post-surgical memory following temporal lobectomy. Brain. 2004;127(Pt 10):2286–98.
54. Lineweaver TT, Morris HH, Naugle RI, Najm IM, Diehl B, Bingaman W. Evaluating the contributions of state-of-the-art assessment techniques to predicting memory outcome after unilateral anterior temporal lobectomy. Epilepsia. 2006;47:1895–903.
55. Hermann BP, Wyler AR, Somes G, Berry AD 3rd, Dohan FC Jr. Pathological status of the mesial temporal lobe predicts memory outcome from left anterior temporal lobectomy. Neurosurgery. 1992;31:652–6; discussion 6–7.
56. Trenerry MR, Jack CR Jr, Ivnik RJ, Sharbrough FW, Cascino GD, Hirschorn KA, et al. MRI hippocampal volumes and memory function before and after temporal lobectomy. Neurology. 1993;43:1800–5.
57. Powell HW, Koepp MJ, Symms MR, Boulby PA, Salek-Haddadi A, Thompson PJ, et al. Material-specific lateralization of memory encoding in the medial temporal lobe: blocked versus event-related design. Neuroimage. 2005;27:231–9.
58. Pittau F, Dubeau F, Gotman J. Contribution of EEG/fMRI to the definition of the epileptic focus. Neurology. 2012;78:1479–87.
59. Thornton R, Laufs H, Rodionov R, Cannadathu S, Carmichael DW, Vulliemoz S, et al. EEG correlated functional MRI and postoperative outcome in focal epilepsy. J Neurol Neurosurg Psychiatry. 2010;81:922–7.
60. Knowlton RC, Elgavish R, Howell J, Blount J, Burneo JG, Faught E, et al. Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: a prospective study. Ann Neurol. 2006;59:835–42.
61. Thornton RC, Rodionov R, Laufs H, Vulliemoz S, Vaudano A, Carmichael D, et al. Imaging haemodynamic changes related to seizures: comparison of EEG-based general linear model, independent component analysis of fMRI and intracranial EEG. Neuroimage. 2010;53:196–205.
62. Sierra-Marcos A, Maestro I, Falcon C, Donaire A, Setoain J, Aparicio J, et al. Ictal EEG-fMRI in localization of epileptogenic area in patients with refractory neocortical focal epilepsy. Epilepsia. 2013;54:1688–98.
63. Hunyadi B, Tousseyn S, Dupont P, Van Huffel S, De Vos M, Van Paesschen W. A prospective fMRI-based technique for localising the epileptogenic zone in presurgical evaluation of epilepsy. Neuroimage. 2015;113:329–39.
64. De Ciantis A, Lemieux L. Localisation of epileptic foci using novel imaging modalities. Curr Opin Neurol. 2013;26:368–73.

65. Hamer HM, Morris HH, Mascha EJ, Karafa MT, Bingaman WE, Bej MD, et al. Complications of invasive video-EEG monitoring with subdural grid electrodes. Neurology. 2002;58:97–103.
66. Panov F, Levin E, de Hemptinne C, Swann NC, Qasim S, Miocinovic S, et al. Intraoperative electrocorticography for physiological research in movement disorders: principles and experience in 200 cases. J Neurosurg. 2017;126:122–31.
67. Enatsu R, Mikuni N. Invasive evaluations for epilepsy surgery: a review of the literature. Neurol Med Chir. 2016;56:221–7.
68. Fox MD, Greicius M. Clinical applications of resting state functional connectivity. Front Systems Neurosci. 2010;4:19.
69. Jayakar P, Dunoyer C, Dean P, Ragheb J, Resnick T, Morrison G, et al. Epilepsy surgery in patients with normal or nonfocal MRI scans: integrative strategies offer long-term seizure relief. Epilepsia. 2008;49:758–64.
70. Duncan JS. Imaging in the surgical treatment of epilepsy. Nat Rev Neurol. 2010;6:537–50.
71. Shimony JS, Zhang D, Johnston JM, Fox MD, Roy A, Leuthardt EC. Resting-state spontaneous fluctuations in brain activity: a new paradigm for presurgical planning using fMRI. Acad Radiol. 2009;16:578–83.
72. Meier M, Ilmberger J, Fesl G, Ruge M. Validation of functional motor and language MRI with direct cortical stimulation. Acta Neurochir. 2013;155:675–83.
73. Sollmann N, Ille S, Zimmer C, Meyer B, Ringel F, Krieg S. EP 23. Cortical language mapping by rTMS compared to fMRI in healthy volunteers. Clin Neurophysiol. 2016;127:e243.
74. Chiang TC, Liang KC, Chen JH, Hsieh CH, Huang YA. Brain deactivation in the outperformance in bimodal tasks: an FMRI study. PLoS One. 2013;8:e77408.
75. Nakagawa S, Sugiura M, Akitsuki Y, Hosseini SH, Kotozaki Y, Miyauchi CM, et al. Compensatory effort parallels midbrain deactivation during mental fatigue: an fMRI study. PLoS One. 2013;8:e56606.
76. Papma JM, den Heijer T, de Koning I, Mattace-Raso FU, van der Lugt A, van der Lijn F, et al. The influence of cerebral small vessel disease on default mode network deactivation in mild cognitive impairment. NeuroImage Clin. 2013;2:33–42.
77. Peters AM, Brookes MJ, Hoogenraad FG, Gowland PA, Francis ST, Morris PG, et al. T2* measurements in human brain at 1.5, 3 and 7 T. Magn Reson Imaging. 2007;25:748–53.
78. Vitali P, Di Perri C, Vaudano AE, Meletti S, Villani F. Integration of multimodal neuroimaging methods: a rationale for clinical applications of simultaneous EEG-fMRI. Funct Neurol. 2015;30:9–20.
79. Kirilina E, Lutti A, Poser BA, Blankenburg F, Weiskopf N. The quest for the best: the impact of different EPI sequences on the sensitivity of random effect fMRI group analyses. Neuroimage. 2016;126:49–59.
80. Wald LL. The future of acquisition speed, coverage, sensitivity, and resolution. Neuroimage. 2012;62:1221–9.
81. Craddock RC, Jbabdi S, Yan CG, Vogelstein JT, Castellanos FX, Di Martino A, et al. Imaging human connectomes at the macroscale. Nat Methods. 2013;10:524–39.
82. Birn RM. The role of physiological noise in resting-state functional connectivity. Neuroimage. 2012;62:864–70.
83. Murphy K, Birn RM, Bandettini PA. Resting-state fMRI confounds and cleanup. Neuroimage. 2013;80:349–59.
84. Sarkka S, Solin A, Nummenmaa A, Vehtari A, Auranen T, Vanni S, et al. Dynamic retrospective filtering of physiological noise in BOLD fMRI: DRIFTER. Neuroimage. 2012;60:1517–27.
85. McMains S, Hutchison RM, Mair R. Whole-brain, sub-second data collection for task-evoked fMRI studies using simultaneous multi-slice/multiband acquisition. J Vis. 2015;15:233.
86. Wengenroth M, Blatow M, Guenther J, Akbar M, Tronnier VM, Stippich C. Diagnostic benefits of presurgical fMRI in patients with brain tumours in the primary sensorimotor cortex. Eur Radiol. 2011;21:1517–25.
87. Sunaert S. Presurgical planning for tumor resectioning. J Magn Reson Imaging. 2006;23:887–905.
88. Reese TG, Davis TL, Weisskoff RM. Automated shimming at 1.5 T using echo-planar image frequency maps. J Magn Reson Imaging. 1995;5:739–45.
89. Balteau E, Hutton C, Weiskopf N. Improved shimming for fMRI specifically optimizing the local BOLD sensitivity. Neuroimage. 2010;49:327–36.
90. Hutton C, Bork A, Josephs O, Deichmann R, Ashburner J, Turner R. Image distortion correction in fMRI: a quantitative evaluation. Neuroimage. 2002;16:217–40.
91. In MH, Posnansky O, Beall EB, Lowe MJ, Speck O. Distortion correction in EPI using an extended PSF method with a reversed phase gradient approach. PLoS One. 2015;10:e0116320.
92. Poldrack RA, Mumford JA, Nichols TE. Handbook of functional MRI data analysis. Cambridge: Cambridge University Press; 2011.
93. FitzGerald DB, Cosgrove GR, Ronner S, Jiang H, Buchbinder BR, Belliveau JW, et al. Location of language in the cortex: a comparison between functional MR imaging and electrocortical stimulation. Am J Neuroradiol. 1997;18:1529–39.
94. Stippich C, Rapps N, Dreyhaupt J, Durst A, Kress B, Nennig E, et al. Localizing and lateralizing language in patients with brain tumors: feasibility of routine preoperative functional MR imaging in 81 consecutive patients. Radiology. 2007;243:828–36.
95. Kuchcinski G, Mellerio C, Pallud J, Dezamis E, Turc G, Rigaux-Viode O, et al. Three-tesla functional MR language mapping: comparison with direct cortical stimulation in gliomas. Neurology. 2015;84:560–8.
96. Partovi S, Konrad F, Karimi S, Rengier F, Lyo JK, Zipp L, et al. Effects of covert and overt paradigms in clinical language fMRI. Acad Radiol. 2012;19:518–25.
97. Fujimaki N, Hayakawa T, Matani A, Okabe Y. Right-lateralized neural activity during inner speech repeated by cues. Neuroreport 2004;15:2341–5.

Imaging with PET/CT in Patients with Epilepsy

4

Nikoletta Pianou and Sofia Chatziioannou

Functional imaging plays an important role in the management of patients with epilepsy, especially in medically refractory cases. In addition to physical and neurologic examinations, electroencephalograms (EEGs) and blood tests, imaging may be very helpful in surgery candidates in order to accurately localize the epileptic focus.

Magnetic resonance imaging (MRI) and MR spectroscopy are conventional imaging techniques used for that reason, as is single photon emission computerized tomography (SPECT) using brain perfusion imaging. However, SPECT shows a relatively low sensitivity in detecting extratemporal lobe epilepsy (TLE) (66% for the ictal and 40% for the interictal phase) [1, 2]. The sensitivities for TLE SPECT studies are 44%, 75%, and 97% for interictal, postictal, and ictal phases, respectively [3]. The ictal SPECT provides better sensitivity; however, it requires the radiotracer administration within a very short period of time after the onset of seizure, which is clinically difficult to achieve.

Positron emission tomography combined with computerized tomography (PET/CT) is a functional imaging technique widely used in oncology. 18-F Fluorodeoxyglucose (18F-FDG) is the radiotracer mostly used for that purpose. Nevertheless, 18F-FDG PET/CT imaging has been extended in neurologic disorders such as epilepsy. Besides the imaging of glucose metabolism, other PET tracers such as serotonin, oxygen, and receptor binding have been used in imaging of epileptic patients, which will be further analyzed.

N. Pianou
Nuclear Medicine Division, Clinical Research Center, Biomedical Research Foundation, Academy of Athens, Athens, Greece

S. Chatziioannou (✉)
Department of Nuclear Medicine, University of Athens, Biomedical Research Foundation, Academy of Athens, Athens, Greece
e-mail: sofiac@bcm.edu

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4.1 18F-FDG PET/CT Imaging

18F-FDG is a glucose analogue radiotracer which reflects glucose metabolism of the brain. 18F-FDG enters the cells via glucose transporters (GLUT), mainly GLUT1. After entering the cells, 18F-FDG is trapped in the cells because it is being phosphorylated by the hexokinase enzyme, after which it is not further metabolized. Since glucose is the main energy source for brain cells, there is significant physiologic brain 18F-FDG uptake.

The 18F-FDG PET/CT protocol requires patient preparation before injecting the radiotracer. The protocol includes 4–6 h of fasting before the examination and avoiding drugs or substances that might interfere with 18F-FDG brain uptake. Such drugs could be cocaine, narcotics, sedatives, antipsychotic medications, amphetamines, and corticosteroids. Other substances that may affect the brain glucose metabolism such as caffeine and alcohol should also be avoided.

After applying an intravenous channel, the patient remains calm and in a quiet and dimly lit room for about 15 min, avoiding any visual or auditory stimulation. Then the 18F-FDG is injected, and the patient remains at rest for at least another 30 min before the acquisition. The patient should also be hydrated prior to the study, and the blood glucose levels should be at normal limits, at least <150–200 mg/dL. All diabetic patients should have blood glucose values regulated because insulin cannot be used during the uptake phase of the study as it results in low brain and high muscle 18F-FDG uptake [4, 5].

In a normal adult patient 18F-FDG shows high uptake in the cerebral and cerebellar cortices as well as in the subcortical grey matter, while white matter shows lower normal 18F-FDG uptake. The distribution pattern is different in children, depending on the age; in infants the brain exhibits diffusely low metabolic activity [6]. As the children grow older, the 18F-FDG uptake is normally increased, reaching a peak level at the age of 4 years [7, 8].

Static images of the brain are initially visually interpreted, and areas with increased, reduced, or absent metabolic activity are estimated as abnormal areas. However, there is also automated semi-quantitative or quantitative imaging software available in order to reveal regional or global mild abnormalities that are not apparent on visual inspection [9].

Interictal 18F-FDG PET/CT is the most common imaging performed, and the main finding of epileptic focus is a focally hypometabolic area. Ictal 18F-FDG PET/CT is difficult to perform because the majority of the seizures are unpredictable and short lasting. In addition, the long uptake period of 18F-FDG (at least 30 min) may alter the radiotracer distribution, resulting in variant uptake (reduced or even increased), preventing the correct evaluation of the findings. Postictal 18F-FDG PET/CT shows the same complex pattern of 18F-FDG uptake (reduced or increased), depending on the time of the radiotracer injection after the seizure episode.

The value of 18F-FDG PET/CT is in detecting epileptogenic foci in patients with medically refractory partial epilepsy prior to surgery when MRIs and EEGs have failed to identify the epileptogenic focus. The sensitivity of 18F-FDG PET/CT in detecting TLE is reported to be 84%, while the sensitivity for extra-TLE is much lower: 38–55% [10, 11]. Rathore and colleagues investigated the utility of 18F-FDG PET/CT in 194 adult patients with medically refractory focal epilepsy and normal MRI or MRI which was discordant with clinical and EEG data. 18F-FDG PET/CT revealed 64 patients with TLE, 66 with frontal lobe epilepsy (FLE), 26 with temporal-plus epilepsy, and 38 patients with other extratemporal lobe epilepsies (ETE). PET scans were normal in 72 (37%) patients and showed unifocal hypometabolism in 98 (50.5%) and bilateral hypometabolism in 24 (12%) patients. PET data were useful in 103 (53%) patients, more in TLE (63%) than FLE (38%) or ETE (50%). PET scan led directly to surgery in 12 (6%) cases, helped in planning intracranial EEGs in 67 (35%) patients, and excluded 24 (12%) patients from further evaluation. The final conclusion was that 18F-FDG PET/CT helped in decision making in 53% of presurgical patients with normal or discordant MRIs [12]. Another study by da Silva and coworkers showed 18F-FDG PET/CT sensitivity and specificity to be 92% and 62.5%, respectively, in children with FLE [13].

As for predicting surgical outcome, a meta-analysis study by Willmann and coworkers [14] showed that there is a correlation between 18F-FDG PET/CT and surgical outcome in adult patients with TLE. This meta-analysis included 46 studies from the period from 1992 to 2006. Ipsilateral PET hypometabolism showed a predictive value of 86% for good outcome, and the predictive value was 80% in patients with normal MRIs and 72% in patients with nonlocalized ictal scalp EEGs [14] (Figs. 4.1 and 4.2).

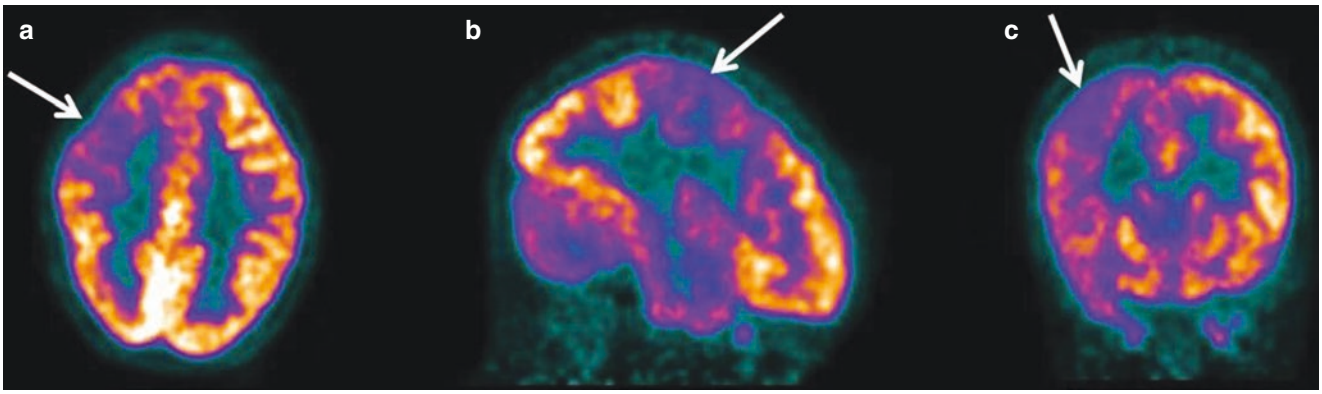

Fig. 4.1 Interictal 18F-FDG PET/CT brain scan of a 7-year-old girl with medically refractory epilepsy. Transverse (**a**), sagittal (**b**), and coronal (**c**) views of the brain showing diffuse hypometabolism at the posterior right frontal lobe extending to the right parietal lobe (*arrow*)

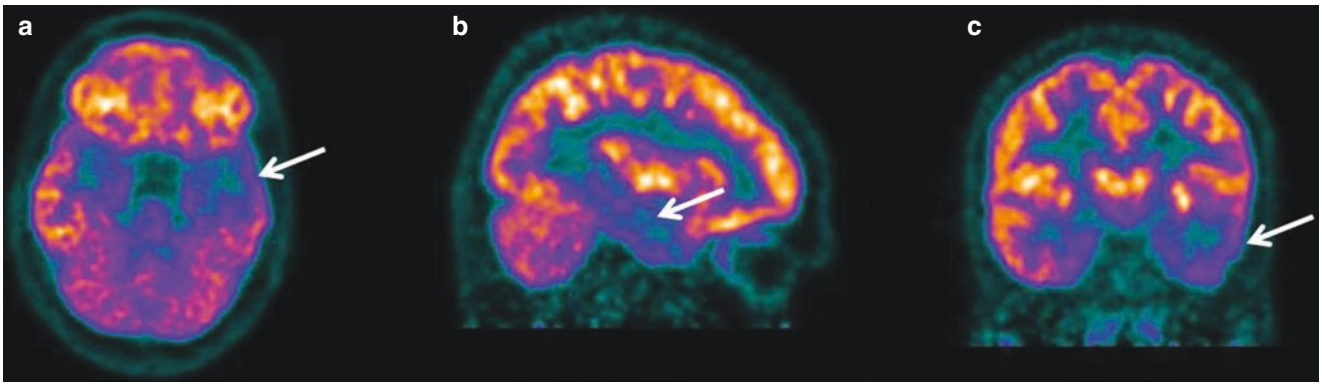

Fig. 4.2 Interictal 18F-FDG PET/CT brain scan of a 22-year-old male patient with medically refractory epilepsy. Transverse (**a**), sagittal (**b**) and coronal (**c**) views of the brain showing diffuse hypometabolism at the left temporal lobe (*arrow*)

4.1.1 Ictal and Postictal 18F-FDG PET/CT

Many technical issues arise in clinical practice when ictal 18F-FDG PET/CT is performed because of the short duration of the seizures. However, ictal 18F-FDG PET/CT is feasible in patients with status epilepticus (SE), in which the duration of the episode may reach 30 min in cases of provoked or induced seizures. Ictal 18F-FDG PET/CT is usually characterized by hypermetabolism of the epileptic foci.

When postictal 18F-FDG PET/CT is performed the findings may vary, showing either hyper- or hypometabolic lesions, depending on the time of injection after seizure. When the 18F-FDG injection was performed within 15 min after the seizure the 18F-FDG PET/CT showed focal hypermetabolism in three pediatric patients in a study by Chugani and associates [15]. Forty-eight hours after the seizure the 18F-FDG PET/CT lesions appeared hypometabolic, while within 24 h after the seizure the findings were intermediate [16].

4.2 18F-FDG PET/CT Versus SPECT

Comparing SPECT to 18F-FDG PET/CT, several studies have reported the superiority of 18F-FDG PET/CT, since the interictal period is characterized by more reduction in regional cerebral glucose metabolic rates than in regional cerebral perfusion [17, 18]. However, 18F-FDG PET/CT cannot define the surgical margin with high precision because the hypometabolic area may be extended further than the epileptogenic foci. Another disadvantage of 18F-FDG PET/CT is the difficulty in differentiating mesial from lateral TLE, since hypometabolism may extend to the lateral aspect of the abnormal temporal lobe [18, 19].

Hwang and colleagues compared interictal 18F-FDG PET/CT with ictal SPECT and MRI in 117 patients with neocortical epilepsy. 18F-FDG PET/CT was most sensitive (71–100%) in detecting all substrates. MR imaging was as sensitive (100%) as PET in detecting tumors but was least sensitive (48.1%) in detecting neuronal migration disorder. Ictal SPECT was more sensitive (75.8%) than MR imaging in detecting neuronal migration disorder [20]. In another study by Won and coworkers, interictal 18F-FDG PET/CT correctly lateralized the lesion in 85%, while SPECT did so in 73% of patients [21].

When the subtraction SPECT technique is applied, better sensitivities are reported for SPECT. In this case the interictal SPECT images are being fused, normalized, and then subtracted from the ictal SPECT images. Fifty-three adult patients were studied, among whom 27 had findings of reduced metabolism on interictal PET scan, whereas all 53 demonstrated a region of relative hyperperfusion on ictal subtraction SPECT suggestive of an epileptogenic zone. The sensitivity of PET was 56%, while the ictal subtraction SPECT appeared to be the more sensitive (87%) [22]. The main disadvantage of ictal subtraction SPECT is that it requires two SPECT studies, one during the ictal and another during the interictal period.

In addition, 18F-FDG PET/CT offers the possibility of semi-quantitative analysis. Drzezga and coworkers evaluated an observer-independent analysis in 27 patients with temporal and 22 patients with extratemporal epilepsy. An automated analysis after anatomic standardization and generation of three-dimensional stereotactic surface projections (SSPs) was used as well as a pixelwise comparison of 18F-FDG uptake with an age-matched reference database, resulting in z score images. The authors concluded that the three-dimensional SSP increased the sensitivity and reduced the observer variability of 18F-FDG PET/CT in patients with extratemporal epilepsy (67% for SSP versus 33–38% for visual analysis). In patients with temporal epilepsy, the sensitivity was comparable for visual and observer-independent analysis (three-dimensional SSP 86%, experienced observers 86–90%, less experienced observers 77–86%) [10].

4.3 Other PET Tracers

Epilepsy is characterized by an abnormally high level of excitatory neurotransmitters and a low level of inhibitory neurotransmitters, resulting in increased and decreased neuronal activity. PET receptor imaging studies are used to investigate the role of neurotransmitters in the epileptogenesis and to identify the epileptogenic regions.

An inhibitory neurotransmitter that plays a role in epilepsy is γ-aminobutyric acid (GABA). A PET/CT study using 11C- flumazenil (FMZ) PET study targets specifically GABAA-central benzodiazepine receptor complex. Patients with partial epilepsy show reduced binding of tracer in epileptic foci, while in patients with TLE and extra-TLE epilepsy FMZ PET is more sensitive and accurate than 18F FDG PET. This is because the abnormal areas are smaller and more circumscribed than the hypometabolic areas in 18F-FDG PET [23]. The same is true for patients with mesial TLE, where FMZ binding was reduced only to the area of hippocampal sclerosis while hypometabolism was more widespread, often involving the lateral temporal complex [24]. Ryvlin and associates evaluated 100 patients before surgery and revealed 73% of patients with FMZ PET abnormalities; these were significantly higher in TLE (94%) than in other types of epilepsy (50%) [25].

Endogenous opioid peptides have anticonvulsant action and limit the spread of electrical activity, playing an important role in epilepsy. 11C- Cerfentanil (CFN) PET and 11C-N1-methylnaltrindole (MeNTI) PET studies target the mu and delta receptor subtypes and are being characterized

by increased uptake in the temporal cortex ipsilateral to the epileptic focus [26]. 11C-Diprenorphine (DPN) PET targets mu, delta, and kappa receptor subtypes showing various results.

Epileptogenic lesions also show increased levels of serotonin, while serotonin exerts antiseizure effects in experimental models mediated by 5-hydroxytryptamine 1A (5-HT1A) receptors. Serotonin 5-HT1A receptor antagonists include 18F-FCWAY, 11C-WAY-100635, and 18F-MPPF PET studies which demonstrate a reduced serotonin 5-HT1A receptor binding in the epileptogenic temporal lobe [27–29].

Alterations of dopamine receptor subtypes, especially D1 and D2, are involved in epilepsy. 18F-Fallypride PET study a is dopamine receptor antagonist, revealing reduced D2 and D3 receptor bindings at the pole and in lateral aspects of the epileptogenic temporal lobe in patients with mesial TLE and hippocampal sclerosis [30].

Other substances believed to be involved in the pathophysiology of epilepsy are adenosine A1 receptor subtype, histamine 3 receptor subtype, and nicotinic and muscarinic acetylcholine receptors (nAChRs and mAChRs). Finally, 15O-H_2O PET has also been used for epileptic focus lateralization with high sensitivity (87%) and specificity (100%). 15O-H_2O PET allows quantitative measurement of regional cerebral blood flow [30].

Conclusion

18F-FDG PET/CT is an imaging method that allows localization of epileptic focus while simultaneously providing additional information on the functional status of the rest of the brain. Hypometabolism is the main finding of the epileptogenic area during the interictal phase, usually exceeding the surgical margins. Other PET radiotracers, beyond FDG, have also been evaluated for the same reason but they are not widely available yet.

References

1. Spencer SS. The relative contributions of MRI SPECT and PET imaging in epilepsy. Epilepsia. 1994;35:S72–89.
2. Weil S, Noachtar S, Arnold S, Yousry TA, Winkler PA, Tatsch K, et al. ECD-SPECT differentiates between temporal and extratemporal epilepsy: confirmation by excellent postoperative seizure control. Nucl Med Commun. 2001;22:233–7.
3. Devous MD Sr, Thisted RA, Morgan GF, Leroy RF. Rowe CC. SPECT brain imaging in epilepsy: a meta-analysis. J Nucl Med. 1998;39:285–93.
4. Varrone A, Asenbaum S, Vander Borght T, Booij J, Nobili F, Någren K, et al. European Association of Nuclear Medicine Neuroimaging Committee. EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. Eur J Nucl Med Mol Imaging. 2009;36:2103–10.
5. Stanescu L, Ishak GE, Khanna PC, Biyyam DR, Shaw DW, Parisi MT. FDG PET of the brain in pediatric patients: imaging spectrum with MR imaging correlation. Radiographics. 2013;33:1279–303.
6. Chugani HT, Phelps ME. Imaging human brain development with positron emission tomography. J Nucl Med. 1991;32:23–6.
7. Kennedy C, Sokoloff L. An adaptation of the nitrous oxide method to the study of the cerebral circulation in children: normal values for cerebral blood flow and cerebral metabolic rate in childhood. J Clin Invest. 1957;36:1130–7.
8. Hikima A, Mochizuki H, Oriuchi N, Endo K, Morikawa A. Semiquantitative analysis of interictal glucose metabolism between generalized epilepsy and localization related epilepsy. Ann Nucl Med. 2004;18:579–84.
9. Drzezga A, Arnold S, Minoshima S, Noachtar S, Szecsi J, Winkler P, et al. 18F-FDG PET studies in patients with extratemporal and temporal epilepsy: evaluation of an observer-independent analysis. J Nucl Med. 1999;40:737–46.
10. Kim YK, Lee DS, Lee SK, Chung CK, Chung JK, Lee MC. (18) F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. J Nucl Med. 2002;43:1167–74.
11. Rathore C, Dickson JC, Teotónio R, Ell P, Duncan JS. The utility of 18F-fluorodeoxyglucose PET (FDG PET) in epilepsy surgery. Epilepsy Res. 2014;108:1306–14.
12. da Silva EA, Chugani DC, Muzik O, Chugani HT. Identification of frontal lobe epileptic foci in children using positron emission tomography. Epilepsia. 1997;38:1198–208.
13. Willmann O, Wennberg R, May T, Woermann FG, Pohlmann-Eden B. The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy. A meta-analysis. Seizure. 2007;16:509–20.
14. Chugani HT, Shewmon DA, Khanna S, Phelps ME. Interictal and postictal focal hypermetabolism on positron emission tomography. Pediatr Neurol. 1993;9:10–5.
15. Leiderman DB, Albert P, Balish M, Bromfield E, Theodore WH. The dynamics of metabolic change following seizures as measured by positron emission tomography with fludeoxyglucose F 18. Arch Neurol. 1994;51:932–6.
16. Zubal IG, Avery RA, Stokking R, Studholme C, Corsi M, Dey H, et al. Ratio-images calculated from interictal positron emission tomography and single-photon emission computed tomography for quantification of the uncoupling of brain metabolism and perfusion in epilepsy. Epilepsia. 2000;41:1560–6.
17. Buch K, Blumenfeld H, Spencer S, Novotny E, Zubal IG. Evaluating the accuracy of perfusion/metabolism (SPET/PET) ratio in seizure localization. Eur J Nucl Med Mol Imaging. 2008;35:579–88.
18. Sarikaya I. PET studies in epilepsy. Am J Nucl Med Mol Imaging. 2015;5:416–30.
19. Hwang SI, Kim JH, Park SW, Han MH, Yu IK, Lee SH, et al. Comparative analysis of MR imaging, positron emission tomography, and ictal single-photon emission CT in patients with neocortical epilepsy. Am J Neuroradiol. 2001;22:937–46.
20. Won HJ, Chang KH, Cheon JE, Kim HD, Lee DS, Han MH, et al. Comparison of MR imaging with PET and ictal SPECT in 118 patients with intractable epilepsy. Am J Neuroradiol. 1999;20:593–9.
21. Desai A, Bekelis K, Thadani VM, Roberts DW, Jobst BC, Duhaime AC, et al. Interictal PET and ictal subtraction SPECT: sensitivity in the detection of seizure foci in patients with medically intractable epilepsy. Epilepsia. 2013;54:341–50.
22. Vivash L, Gregoire MC, Lau EW, Ware RE, Binns D, Roselt P, et al. 18F-flumazenil: a γ-aminobutyric acid A-specific PET radiotracer for the localization of drug-resistant temporal lobe epilepsy. J Nucl Med. 2013;54:1270–7.
23. Szelies B, Weber-Luxenburger G, Pawlik G, Kessler J, Holthoff V, Mielke R, et al. MRI-guided flumazenil- and FDG-PET in temporal lobe epilepsy. NeuroImage. 1996;3:109–18.
24. Ryvlin P, Bouvard S, Le Bars D, De Lamérie G, Grégoire MC, Kahane P, et al. Clinical utility of flumazenil-PET versus [18F] fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. Brain. 1998;121:2067–81.

25. Madar I, Lesser RP, Krauss G, Zubieta JK, Lever JR, Kinter CM, et al. Imaging of delta- and mu-opioid receptors in temporal lobe epilepsy by positron emission tomography. Ann Neurol. 1997;41:358–67.
26. Didelot A, Ryvlin P, Lothe A, Merlet I, Hammers A, Mauguière F. PET imaging of brain 5-HT1A receptors in the preoperative evaluation of temporal lobe epilepsy. Brain. 2008;131: 2751–64.
27. Liew CJ, Lim YM, Bonwetsch R, Shamim S, Sato S, Reeves-Tyer P, et al. 18F-FCWAY and 18F-FDG PET in MRI-negative temporal lobe epilepsy. Epilepsia. 2009;50:234–9.
28. Assem-Hilger E, Lanzenberger R, Savli M, Wadsak W, Mitterhauser M, Mien LK, et al. Central serotonin 1A receptor binding in temporal lobe epilepsy: a [carbonyl-(11)C]WAY-100635 PET study. Epilepsy Behav. 2010;19:467–73.
29. Werhahn KJ, Landvogt C, Klimpe S, Buchholz HG, Yakushev I, Siessmeier T, et al. Decreased dopamine D2/D3-receptor binding in temporal lobe epilepsy: an [18F]fallypride PET study. Epilepsia. 2006;47:1392–6.
30. Tatlidil R, Xiong J, Luther S. Presurgical lateralization of seizure focus and language dom-inant hemisphere with O-15 water PET imaging. Acta Neurol Scand. 2000;102:73–80.

5 Applications of Magnetoencephalography in Epilepsy and Tumor Surgery

Panagiotis G. Simos, Roozbeh Rezaie, and Andrew C. Papanicolaou

Magnetoencephalography (MEG), which represents the most novel example of noninvasive functional mapping techniques, has contributed to the surgical management of epilepsy and brain tumors in two ways. First, in the case of epilepsy, MEG localization of interictal activity has facilitated placement of subdural (grid, strip, and depth) electrodes that are necessary for accurately localizing the ictal onset zone. Second, MEG has emerged as a reliable and accurate tool for localizing motor, somatosensory, and language-specific cortexes as well as determining hemispheric dominance for language in surgical candidates. In this chapter, we first present a general description of MEG, including background on instrumentation, underlying neurophysiology, and its applications in contemporary clinical practice. Subsequently, we review evidence demonstrating the utility of MEG as a noninvasive tool for approximating the ictal onset zone in addition to localizing eloquent cortex and determining the spatial relation of this cortex to epileptogenic tissue and mass lesions. Furthermore, the utility of MEG in presurgical mapping is discussed in light of some methodologic caveats, with recommendations on optimizing its contributions in clinical practice.

P. G. Simos (✉)
University of Crete, Voute Campus, School of Medicine, Division of Psychiatry and Behavioral Sciences, Herakleion, Crete, Greece

R. Rezaie
Department of Pediatrics, Division of Clinical Neurosciences, University of Tennessee Health Science Center, Memphis, TN, USA

A. C. Papanicolaou
Department of Pediatrics, Division of Clinical Neurosciences, University of Tennessee Health Science Center, Neuroscience Institute, Le Bonheur Children's Hospital, Memphis, TN, USA

5.1 Essentials of Magnetoencephalography

MEG is a noninvasive brain imaging method that detects minute variations in the strength and distribution of magnetic flux at the surface of the head. Recordings are performed either at rest (targeting spontaneous abnormal activity associated mainly with epilepsy) or during the performance of specific sensory, motor, or language tasks. In the latter case, recordings and subsequent analyses of the magnetic signals aim to reveal brain regions that significantly contribute to sensation or to the performance of these tasks. Several normative and clinical studies have established the reproducibility and concurrent validity of activation and analysis protocols used for presurgical mapping. The results of these studies support the claim that MEG techniques entail adequate anatomic resolution for the clinical applications discussed in this chapter. Moreover, the temporal resolution of MEG clearly distinguishes it among noninvasive brain imaging methods that rely on hemodynamic measures such as positron emission tomography (PET) and functional MRI (fMRI). While this feature is desirable when the goal is functional brain mapping, it is essential when the objective is to identify the cortical sources of transient abnormal activity. The temporal and spatial resolutions of MEG as well as its demonstrated reliability and external validity have led to its routine use in many neurosurgery centers around the world. Following a brief description of MEG methodology, in this chapter we review the primary clinical applications of MEG, namely, the identification of epileptogenic foci in candidates for epilepsy surgery and the mapping of function-specific cortex prior to resection.

MEG involves the measurement of neuromagnetic signals emanating from the brain (for a detailed discussion, see Papanicolaou [1]). These signals reflect instantaneous changes in intracellular dendritic (primary) electrical currents that take place within populations of pyramidal cells in cortical structures. While the EEG primarily measures the

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secondary currents that spread through the extracellular space and structures, reaching the head surface with significant distortion, the magnetic flux produced mostly by primary currents traverses the brain and other tissues that surround the populations of active neurons that constitute its source with minimal spatial smearing and summation of fields from adjacent sources.

Neuromagnetic signals are measured via an array of superconducting sensors (either magnetometers or gradiometers), each coupled to a special low noise amplifier. State-of-the-art systems are equipped with 150–250 or more sensors that cover the entire head. Recording takes place inside a magnetically shielded room designed to reduce extraneous magnetic fields. Supplementary noise-reduction techniques rely on additional magnetic sensors and special software in order to detect extraneous magnetic fields (mechanical and biological noise) and reduce their contribution to the recorded signal both online and offline. The instantaneous surface distribution of the magnetic flux is registered by the entire array of sensors typically every 1–4 ms during the recording session and is represented as a magnetic isofield map in the sensor-space (i.e., on the surface of the helmet-like sensor array). This distribution is then coregistered on a digital representation of the surface of the patient's head, which is in turn coregistered (with the aid of additional fiducial points) on the patient's high-resolution MRI (typically T1-weighted images).

The final step in the analysis of clinical MEG data entails computing a viable model of the anatomic layout (location and extent) of the intracranial sources producing the observed magnetic flux recordings. A variety of algorithms have been developed in order to obtain an accurate mapping of recorded neuromagnetic activity onto underlying electrical cortical current sources. Most of these algorithms treat intracranial generators of magnetic flux as electrical dipoles representing the coherent activity of tens to hundreds of thousands of neurons. The best solution(s) to this "inverse problem" in source localization is achieved using residual variance minimization algorithms. Key differences among the different approaches concern the number of dipolar sources that can be modeled simultaneously and the geometric characteristics of the model of the brain used. The single-equivalent dipole (ECD) method permits identification of 1–4 relatively independent and spatially distinct point sources at any point in time (i.e., at every 1–4 ms of recorded neuromagnetic activity, depending on the sampling frequency). Typically, single ECD approaches do not take into account the anatomy of the patient's brain in estimating the characteristics of the underlying source (location and strength of the electrical dipole). Once estimates of the coordinates of such sources are made in the MEG coordinate system, they are coregistered with a set of structural images of the patient's brain (MRI) in order to determine the anatomic location of each source. Conversely, multi-source or extended-source modeling algorithms operate on a geometric model of the cortical surface, which is partitioned into several thousand potential sources (cortical patches containing populations of pyramidal neurons that can produce detectable magnetic flux). Minimum-norm estimation algorithms comprise one of two types of extended-source modeling techniques operating on the amplitude distribution of recorded neuromagnetic signals over the entire sensor array. On the other hand, spatial filtering algorithms decompose the recorded signal into frequency bands and project modeled sources of each band onto the patient's cortical surface.

The capacity to identify relatively small cortical patches that show transient increases in neurophysiologic activity renders MEG suitable for a variety of clinical applications. These applications can be classified into two broad categories: those that involve recording and subsequent localization of the intracranial sources of spontaneous, abnormal neurophysiologic activity, and those that target stimulus-evoked activity, either during passive stimulation conditions or while the patient receives auditory, visual, or somatic stimulation or is performing a cognitive or linguistic task.

5.2 Spontaneous Magnetic Activity: Applications in Epilepsy Surgery

Among the clinical applications of MEG that target spontaneous, abnormal brain activity, the localization of the sources of interictal transients (spikes) is the most established one. At different epilepsy centers MEG is part of either the Phase I or Phase II evaluation procedure as an adjunct to noninvasive video- EEG (VEEG) or invasive (intracranial VEEG) techniques. In this context, MEG studies may contribute to the consensus decision of whether a particular patient is a surgical candidate, and they may help guide subdural grid placement. More recent studies have further sought to determine whether resection of the cortical patch that includes the MEG-derived sources of epileptiform activity is sufficient to produce a favorable surgical outcome.

5.2.1 Technical Issues Affecting Clinical Utility

The clinical utility of MEG data is based on a number of factors. It requires, first, that the MEG procedures and algorithms used for the localization of abnormal magnetic activity are sufficiently accurate in identifying the location and extent of the cortical patches that give rise to transient increases in magnetic flux recorded at the surface of the head (magnetic spikes). Second, it requires that a sufficient number of spikes are detected during the MEG recording session (which mostly lasts one-half hour and rarely extends beyond 1 or 2 h). Third is the requirement that the cortical patches, where the generators of magnetic spikes are localized, coincide with the epileptogenic zone(s). It is essential that the MEG study identifies at least a portion of the epileptogenic zone (sensitivity) and that the abnormally active cortical patche(s) identified by MEG cause seizures (selectivity).

With respect to the first requirement, several studies concur that the equivalent current model is sufficient to accurately localize the origin of interictal spikes [2–4]. There have been attempts to use extended-source modeling algorithms to identify the epileptogenic zone utilizing either ictal [5] or interictal spikes [6, 7]. Only the latter studies of 21 and 7 pharmaco-resistant focal epilepsy patients reported correlations with ECoG results. Results were promising, although the samples of patients do not permit conclusions regarding the relative accuracy of the algorithms used (minimum norm estimates and spatial filtering) to identify a clinically useful portion of the epileptogenic zone as compared to the ECD method. Assessment of the reliability of source localization across several spikes and potentially obtaining a second recording session with the same patient may help improve the accuracy of the identification of abnormally active cortical patches.

A second practical problem faced by clinicians using MEG for presurgical epilepsy planning is the rarity of usable, abnormal epileptiform activity during the typically brief recording session. Among the largest scale studies to date, the yield of MEG studies with focal epilepsy patients was 66% (65/98 patients; Pataraia et al. [3]), 78% (103/132 patients; Englot et al. [8]), and 96% (in a sample of 264 patients the majority of whom presented with MRI-positive epilepsy; Rubinger et al. [9]). To optimize the yield of magnetic spikes, some clinicians have sought to evoke epileptiform activity with the use of proconvulsant drugs such as methohexital or clonidine (e.g., Knowlton et al. [2]; Brockhaus et al. [10]). However, the effectiveness of such techniques to increase the diagnostic yield of MEG is still uncertain. Moreover, while the preponderance of MEG applications in epilepsy have relied on spike-like activity, the localization of generators of potentially more abundant focal slow activity in the delta and theta frequency ranges has also been found to be useful for localization of epileptiform activity sources [11–16].

The third prerequisite for the clinical utility of MEG has been addressed in two ways. First, in studies that record and attempt to localize the intracranial origin of ictal magnetic activity [5, 17–22]. These studies can be performed during nonconvulsive seizures because magnetic artifacts associated with electrical muscle activity and movement render abnormal brain activity unusable. Alternatively, brief samples of magnetic activity at the very onset of a convulsive seizure can be fortuitously obtained. The second more common approach to determine the degree of overlap of interictal source localizations obtained by MEG in relation to the epileptogenic zone(s) is to directly compare the results of interictal MEG tests with those of VEEG and electrocorticography (ECoG). An example of this approach is illustrated in Fig. 5.1. Large-scale studies addressing this issue published since 2004 are briefly reviewed in Sect. 5.2.2. The third approach in this line of research is to examine the association between the location of interictal source localizations obtained by MEG and the surgically resected region and with seizure outcome. All studies reviewed in the next two sections used the single ECD method for interictal MEG source localization.

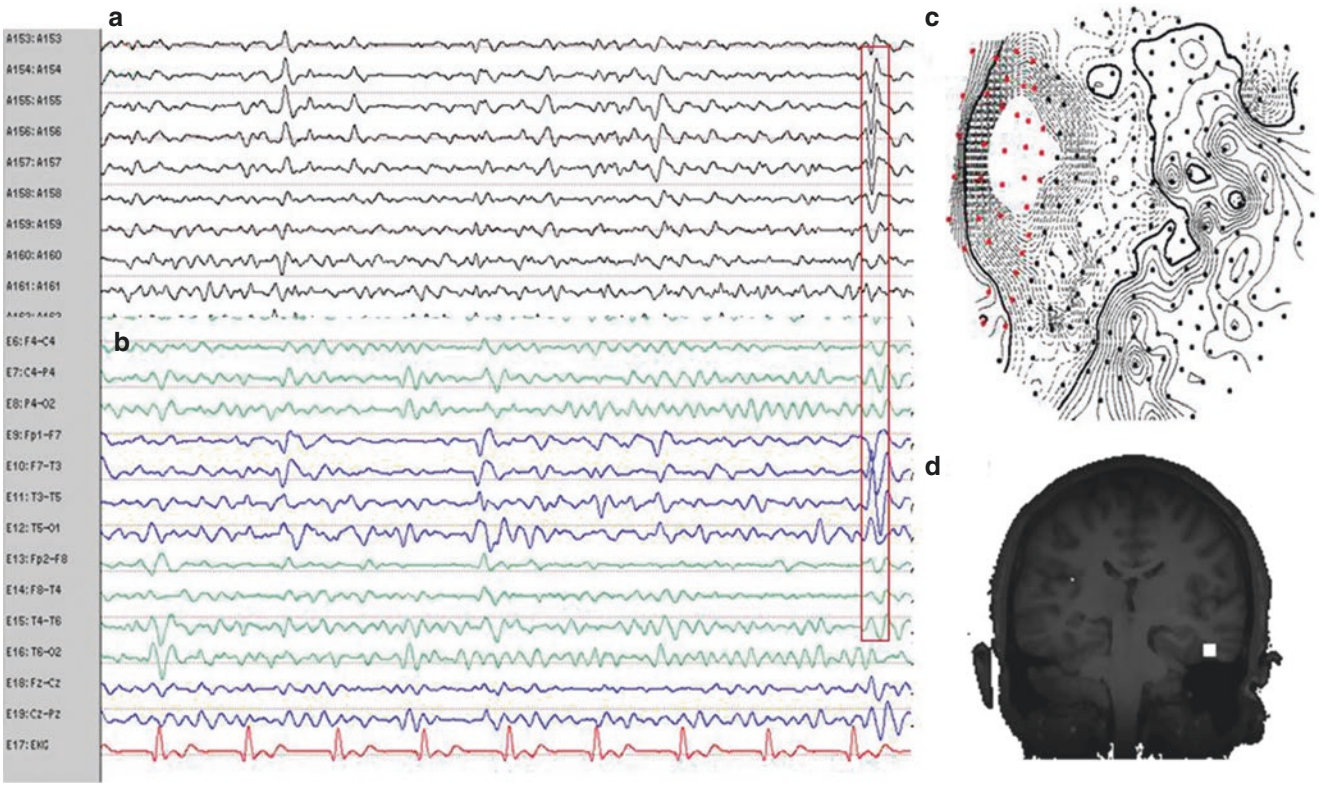

Fig. 5.1 Localization of epileptiform events using MEG. Interictal simultaneous MEG (**a**) and scalp EEG (**b**) tracings recorded during rest in a 16-year-old patient with tuberous sclerosis complex and symptomatic localization-related epilepsy. The topographic distribution of the magnetic fields (**c**) associated with each epileptiform spike over the left hemisphere was used to model underlying activity sources, following coregistration with the patient's MRI (**d**). The MEG-derived source of interictal events (*white square*) was localized to the left inferior temporal lobe

5.2.2 Comparisons of MEG-Versus VEEG/ECoG-Based Localization of Epileptiform Activity

The first large-scale study that directly assessed the utility of MEG in decisions concerning placement of intracranial electrodes and/or surgery compared MEG recordings with both ictal and interictal noninvasive video EEG (VEEG or Phase I EEG) was by Pataraia et al. [3]. The data set included 82 successive patients with medically refractory epilepsy who underwent surgery. The epileptogenic region identified by interictal and ictal VEEG and MEG was defined in relation to the resected area as either (1) perfectly overlapping with the resected area, (2) partially overlapping, or (3) not overlapping. The proportion of extratemporal lobe epilepsy patients for whom interictal events were registered was slightly higher than the proportion of patients with temporal lobe epilepsy (86.7% versus 75%, respectively). On the basis of these MEG data alone, the correct localization of the resected region would have been possible in 72.3% of the patients for whom at least five interictal spikes of similar morphology were registered. This figure was significantly higher than the proportion of correct localizations made on the basis of the surface VEEG results alone (40%). Additionally, as shown in Table 5.1, MEG contributed to the localization of the resected region in 10/17 (58.8%) of the patients in whom VEEG recordings did not provide localization information and in 16/22 (72.8%) of the patients for whom VEEG identified only part of the resected zone. Overall, MEG and VEEG results were equivalent in 32.3% of the cases, and additional localization information was obtained using MEG in 40% of the patients. These results clearly suggest that MEG can be useful for presurgical planning in patients who have either partially localizing or nonlocalizing VEEG results.

The concordance between MEG and ECoG localization results was directly addressed in two recent studies. In the first, Almubarak et al. [23] reported data from a retrospective cohort of 50 patients who underwent ECoG recordings. Among the 36 patients who were subsequently surgically treated, concordance of MEG with the lobe or intralobar region that showed ictal paroxysmal activity in ECoG was found in 14 and 13 cases, respectively. In a more recent study on a larger retrospective cohort of 132 patients, Englot et al. [8] reported a substantially higher lobar concordance between MEG and ECoG (62/92 cases or 67.3%).

Table 5.1 Contribution of MEG data to the identification of the resected region

		MEG[a]			
	N (%)	Improvement	No change	Misidentification	Total
VEEG[b]	Perfect overlap	–	21 (80.8)	5 (19.2)	26 (40)
	Partial overlap	16 (72.8)	3 (13.6)	3 (13.6)	22 (34)
	Nonlocalizable	10 (58.8)	7 (41.2)		17 (26)
	Total	26 (40.0)	31 (47.7)	8 (12.3)	65 (100)

[a]Contribution of MEG to the localization of resected region. (Adapted from Pataraia et al. [3])
[b]Degree of overlap between VEEG-based epileptogenic zone and resected region

5.2.3 Evaluation of MEG Results Against Surgical Outcome

Most studies reviewed in the previous section have more extensively compared the location(s) of interictal source localizations obtained by MEG and ECoG with the surgically resected region in relation to seizure outcome. For instance, Papanicolaou et al. [24] reported data from a subset of 41 patients (29 with temporal and 12 with extratemporal epilepsy) in the Pataraia et al. [3] study for whom it was possible to assess the relative efficacy of MEG and ECoG (both ictal and interictal) in predicting seizure outcome. All patients had positive interictal findings in MEG. The epileptogenic zone was defined separately on the basis of MEG and of ECoG, each in relation to postoperative seizure outcome. The results of each method were separately classified as (1) correct, if the identified epileptogenic area overlapped with the area resected, and the patient was seizure-free postoperatively, (2) incorrect if the identified area was the same as the resected area but the patient was not seizure-free postoperatively or if the localized area identified was different from the resected area but the patient was seizure-free postoperatively, and (3) indeterminate if the identified zone differed from the resected one and the patient was not seizure-free postoperatively. With respect to postoperative outcome, MEG localization was correct in 23 of the 41 patients and ECoG localization was correct in 22 of the 41 patients. The MEG predictions were incorrect for 12 patients and the ECoG predictions for 16 patients. Finally, there were six and three indeterminate cases for ECoG and MEG, respectively. No significant differences between the two methods were found in terms of their ability to predict the localization of the epileptic zone and consequently seizure outcome in individual patients.

The importance of the MEG-defined zone for seizure outcome was highlighted in Almubarak et al. [23]. Whereas favorable seizure outcome was noted in 78.9% of patients who were subjected to complete resection of the zone of MEG interictal sources (15/19 cases), a comparable outcome was observed in only 23.5% patients who received incomplete resection of the MEG source zone (4/17 cases). Using a somewhat different coding of cases, a favorable seizure outcome was found in 85.3% (58/68) of complete or partial resections of the MEG-defined epileptogenic zone and in only 37.1% (13/35) of surgeries that failed to resect a significant portion of this region [8].

A similar conclusion can be drawn from a series of pediatric surgery cases (n = 13) in which the patients were suffering from epilepsy associated with porencephalic encephalomalacia [25] and from a series of patients with insular epileptogenic foci [26].

The efficiency of MEG has been demonstrated for both temporal [3, 13, 27, 28] and nontemporal lobe epilepsy [29–32], although in general, interictal magnetic spikes can be recorded more readily in neocortical epilepsy than in mesial temporal lobe epilepsy [2, 33].

5.2.4 MEG Applications in Lesional Epilepsy

MEG studies have been successfully employed in helping to determine or confirm targets for surgical resection in a variety of epileptic syndromes, such as focal cortical dysplasia [34–42], tuberous sclerosis complex [43–47], pediatric epilepsy [30, 48–55], and conditions that often cause seizures such as cavernomas [56] and mass lesions [50, 57, 58]. Finally, the clinical utility of MEG in guiding surgical resection in pediatric epilepsy patients presenting with a variety of lesions detectable in MRI has been affirmed by Rubinger et al. [9] who reported a positive surgical outcome in 202 of 264 cases (77%) in whom the resected region encompassed the MEG source cluster.

5.3 Evoked Magnetic Activity: Presurgical Mapping of the Eloquent Cortex

MEG recordings performed for the purpose of determining the location and extent of cortex-mediating visual, auditory, somatosensory, motor, and language functions differ from those that aim at the identification of epileptogenic zones in that the phenomenon that exemplifies the function under investigation is repeated several times, while the magnetic flux over the head is sampled at regular intervals. An external stimulus is invariably presented at each instance in order either to induce the phenomenon (in the case of somatosensory and receptive language functions) or to act as a time cue (in the case of expressive language and motor functions). Each segment of recorded activity, beginning a few milliseconds before and extending up to approximately 1000 ms (in the case of language-specific cortex mapping and up to 200 ms in the case of visual, auditory, and somatosensory cortex mapping) after each repetition of the stimulus is stored separately as a MEG epoch. The resulting averaged event-related field (ERF) consists of both early components (50–200 ms poststimulus onset) that correspond to activation of the sensory cortex specific to the stimulus modality and late components (200~800 ms poststimulus onset), which reflect activation of the association cortex or higher functions. The intracranial sources that give rise to the recorded ERFs at each point in time can be estimated and superimposed on an MRI of the patient's brain by applying the same algorithms and procedures used for localizing the sources of abnormal spontaneous activity described previously.

5.3.1 Somatosensory-Evoked Magnetic Fields (SEFs)

The spatial resolution of MEG is adequate to reveal the somatotopic organization of the primary somatosensory cortex with a very high success rate (over 95% for mapping the hand area and between 75% and 80% for the foot area; Schiffbauer et al. [59]; Willemse et al. [60]). Either mechanical stimulation of the fingertips, toes, and lip corner [59, 61–65] or electrical stimulation of the median and tibial nerves is used [60, 66]. The sources of the early and middle-latency components of magnetic responses (occurring <60 ms after stimulus onset) and modeled as successive, single equivalent current dipoles originate in the contralateral primary sensory cortex within the central sulcus.

The efficacy of MEG for somatosensory cortex mapping has been established in large-scale studies with patients sustaining space-occupying lesions [59, 60, 65] and epilepsy patients [67] through direct comparison with the results of intraoperative SEP studies. The average distance between the location of the middle latency mechanically induced SEF peak and the central sulcus (point of intraoperative SEP waveform reversal) is in the millimeter range [66, 67]. Using a different intraoperative method to identify the location of the primary somatosensory or motor cortex, the average (± SD) Euclidean distance between the stimulation site eliciting somatic sensation and the SEF peak source location was estimated at 20.5 ± 1.5 mm [59]. In a similar study, the in-plane distance of the SEF source from the stimulation sites was estimated at 16.3 ± 2.3 mm more lateral, 10.4 ± 2.9 mm more inferior, and 13.3 ± 2.9 mm more anterior [68]. Although SEF recordings and source localization are rather robust in the presence of gross alterations of sulcal geometry owing to large space-occupying lesions [59, 69–74], the aforementioned distance estimates may have been affected in such cases.

Finally, the clinical utility of somatosensory and motor cortex mapping in relation to surgical outcome was directly addressed in a large cohort of 79 consecutively assessed patients suffering from perirolandic glooms [65]. The distance of SEF sources from the tumor border was used to create risk profiles in order to guide the treatment approach. Only four patients (of 42 resected; 9.5%) developed hemiparesis as compared to 21.6% (8/37) of those treated conservatively.

5.3.2 Movement-Related Magnetic Fields (MRFs)

Activation protocols permitting identification of the primary motor cortex contralateral to the moving limb have also been developed [75, 67]. MRF epochs are typically aligned prior to averaging using the onset of clearly defined EMG activity during self-paced movements (i.e., opening and closing of the hand and flexion/extension of the foot: Willemse et al. [60]; finger button-press: Tarapore et al. [76]). These procedures are successful in providing data of adequate quality for clinical use in over 80% of attempted tests (e.g., Willemse et al. [60]). In some studies sources of MRFs preceding EMG onset by approximately 50–100 ms were modeled as single, successive ECDs [66, 77]. In other studies sources were estimated using spatial filtering algorithms focusing on MEG activity in the beta band (13–50 Hz; Willemse et al. [60]; Tarapore et al. [76]). Explicit comparisons between MRF sources in large patient series are scarce, however. Tarapore et al. [76] estimated an average distance of 12.1 ± 8.2 mm between the MEF source and the stimulation site eliciting finger movement in 24 patients, whereas the lateral projections of the MEF source and the central sulcus were found to overlap in 15 patients (Korvenoja et al. [66]; all undergoing resection of perirolandic tumors).

Typically, somatosensory and motor mapping are performed in separate sessions, although a procedure for mapping both somatosensory and motor functions in the same session has been developed [77] (Fig. 5.2). According to this protocol mechanical tactile stimulation is applied to the subject's index finger and serves as a cue for the individual to perform a full wrist extension. Tactile stimulation initially activates the contralateral primary somatosensory cortex followed by activation of the secondary somatosensory cortex, lasting for approximately 150 ms. Activity in the contralateral precentral gyrus is seen next, immediately preceding the onset of electromyographic activity, marking the onset of finger movement. Finally, somatosensory activity is again observed during the movement, presumably the result of proprioceptive input. The location estimates of the motor cortex were subsequently verified in six patients with perirolandic lesions through intraoperative electrocortical stimulation.

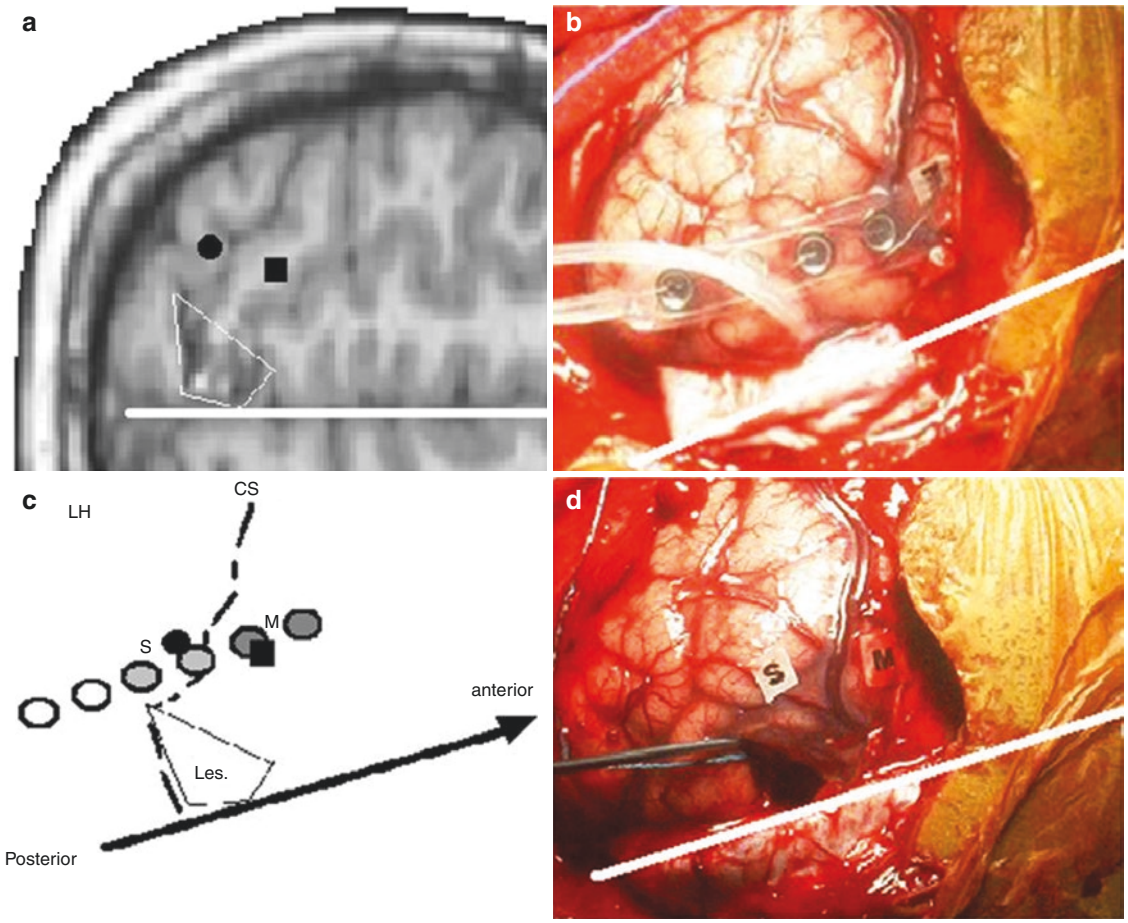

Fig. 5.2 Intraoperative verification of MEG-derived estimates for primary somatosensory (*S*) and motor (*M*) cortex. (**a**): Axial view of patient's MRI. The MEG-derived estimates for sensory (*black circle*) and motor (*black square*) are projected close to the patient's lesion (cavernous angioma). (**b**): Intraoperative photograph showing the placement of a strip of electrodes for sensory and motor mapping. (**c**): Schematic representation of the spatial relation between the lesion (*Les.*), the estimated dipolar sources, and the positive areas for sensory (*S*) and motor (*M*) function as were derived from the invasive recordings. (**d**): Photograph taken after lesion resection showing the identified sensory (*S*) and motor (*M*) areas. (Image reproduced with permission from Castillo et al. [76].)

5.3.3 Visual Evoked Magnetic Fields (VEFs)

Mapping the precise location of the primary visual cortex is often required prior to resecting mass lesions in the vicinity of the calcarine fissure. The intracranial sources that give rise to the early component of the magnetic waveform evoked by rapidly changing patterned stimulation are used as markers of the primary visual area [78–83]. Hemifield or single quadrant stimulation has been successfully used to localize the visual cortex in patients with organic brain diseases before surgical interventions such as craniotomy [65, 84] or stereotactic procedures [85].

5.3.4 Auditory-Evoked Magnetic Fields (AEFs)

Determining the precise location of the primary auditory cortex may be useful for planning resections of mass lesions that encroach on the supratemporal plane [86–88]. In many cases auditory-evoked magnetic fields (AEFs) can be obtained by binaural stimulation with meaningful stimuli in the context of language mapping (see further on).

5.3.5 Language-Related Brain Magnetic Fields (LRFs)

Recording of LRFs has two main clinical indications: (i) to establish the profile of hemispheric involvement in the mechanism that supports basic language functions (hemispheric dominance), and (ii) to identify the location and extent of functionally intact cortex involved in language functions in relation to the area to be resected (epileptogenic zone or mass lesion).

5.3.5.1 Establishing Hemispheric Dominance for Language

With the advent of functional imaging methods, there is great potential for replacing the Wada with a less invasive procedure. Validation studies of the accuracy of fMRI, which is currently the most commonly used hemodynamic imaging technique for mapping eloquent cortex, have shown good concordance with the Wada procedure and with intraoperative electrocortical stimulation mapping (for a recent review and meta-analysis, see Dym et al. [89].

Using MEG as a method of functional imaging, several groups have verified that MEG assessments of hemispheric dominance for language are concordant with those based on the Wada procedure. Using a 148-channel whole-head MEG system, our group established a protocol for eliciting and modeling neuromagnetic activity associated with word-level receptive language functions. Early studies reported excellent concordance with hemispheric dominance estimates provided by the Wada procedures in pediatric and adult patients [90, 91]. The activation protocol consists of an auditory, continuous word recognition task involving 6 blocks of 40 abstract nouns, and the patient is instructed to detect words repeated across blocks (75% of total). The degree of language-specific activity was indexed by the number of consecutive sources (modeled as single, equivalent current dipoles, or ECDs) in perisylvian brain areas. Only late-component activity sources (i.e., between 200 and 600 ms poststimulus onset) that were observed with a high degree of spatial and temporal overlap in two "split-half" data sets were used to compute the MEG laterality index. Pooling data from 85 consecutive surgical candidates with intractable epilepsy aged 8–56 years [92] reported a high degree of concordance (87%) between independent clinical judgments based on MEG and Wada data. MEG laterality judgments had an overall sensitivity of .98 and a selectivity of .83 because of the fact that MEG detected more activity in the nondominant hemisphere than would be predicted on the basis of the results of the Wada procedure. Using identical stimulation and analysis procedures, Doss et al. [93] obtained sensitivity and specificity values of .80 and 1.00, respectively, in determining if the hemisphere to be treated was critical for language functions in a series of 35 consecutive patients with epilepsy or tumors. Excellent concordance between MEG and the Wada results has also been reported by Maestú et al. [94] using a Spanish adaptation of the continuous word recognition task in 8 Spanish-speaking patients. Notably, this activation and analysis protocol may be suitable for uncooperative patients tested under sedation as yielding percentages of left-hemisphere dominant cases similar to those percentages obtained in unsedated patients [95]. Two other groups have used the same analysis method for estimating hemispheric dominance in the context of different activation tasks. Using a silent reading and a naming task agreement with the Wada procedure was noted in 81% of 11 patients with tumors or vascular lesions (and partial agreement in the remaining patients). More recently, Kamada et al. [16, 96] combined laterality estimates obtained with MEG (in the context of an abstract/concrete categorization task with printed stimuli) and fMRI (using a verb generation task) to obtain perfect prediction of hemispheric dominance in a series of 87 surgical candidates suffering from epilepsy or tumors.

Comparable concordance rates regarding hemispheric dominance for speech have been obtained between the results of invasive methods and MEG using a variety of activation tasks and extended-source modeling techniques. In studies relying on spatial filtering algorithms (involving a total of 98 patients with epilepsy, tumors, or AVMs), estimates of complete agreement with the Wada test ranged from 83% (verb generation; Findlay et al. [97]) to 85% (silent word reading task; Hirata et al. [98]), although the likelihood of obtaining usable data was as low as 51%. In smaller samples of patients with epilepsy (total of 43), minimum-norm algorithms have also been applied to model extended patches of cortex that became electrophysiologically active during semantic categorization of printed words [99, 100]. The aggregate concordance rate with Wada results in these studies was 88%. Finally, a concordance rate over 90% (N = 24 patients with epilepsy) has been reported using another extended-source modeling algorithm (MR-FOCUSS) in the context of a verbal generation and a naming task [101].

5.3.5.2 Functional Mapping of the Receptive Language-Related Cortex

Few studies have systematically examined the clinical utility of MEG activation and analysis protocols designed to identify the location and extent of cortical patches critically involved in receptive language functions (i.e., Wernicke area). Early attempts by our group using the protocol described in Sect. 5.3.5.1 defined the language-specific cortex as the region(s) where systematic overlap was found in the activation maps associated with two or more within-session replications of the same continuous auditory word recognition task. As currently utilized, the single ECD approach permits localization of up to three simultaneous activity sources in each hemisphere, provided that they are located at least 3–4 cm apart, and the orientation of each dipolar source results in visually distinguishable surface isofield maps. This method typically reveals one or two sites in the temporal lobe and/or temporoparietal junction of the dominant hemisphere that display consistent activity represented by a series of successive ECDs (source clusters) during the late portion of the LRF. In cases of bilateral language representation, sites demonstrating consistent late activation are typically found in both temporal lobes. The accuracy of these estimates has been verified against the results of invasive intra- or extraoperative electrocortical stimulation mapping (ECS; Simos et al. [102]). Specifically, electrical stimulation of the cortical surface corresponding to these ECD clusters reliably impaired repetition of aurally presented sentences. More recently, spatial filtering has been used to localize receptive language–related brain activity in 47 patients who later underwent ECS [103] (Fig. 5.3). A total of 63 language-specific cortical sites were identified by MEG; 55 of these sites (87%) were verified using ECS (within ~ 1 cm). Verification between MEG and ECS was based most commonly on repetition errors (78%), followed by naming errors (37%).

Other groups have been successful in eliciting reliable activation of temporal lobe sites in the vicinity of Wernicke area using extended-source modeling algorithms: e.g., using silent reading, object naming tasks, spatial filtering [104], and object naming using the MR-FOCUSS source localization technique [101]. The precise location of cortical sites identified using these methods awaits verification by the results of electrocortical stimulation.

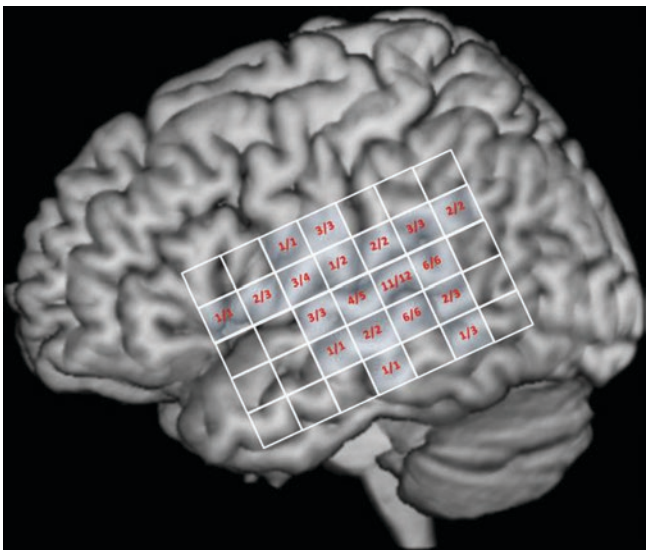

Fig. 5.3 Schematic rendering of 63 cortical sites where language-related activity was detected by MEG and verified by ECS in 47 patients (Castillo et al. [102]). The number of cases displaying activity within a given sector is given in the denominator, and the number of cases confirmed through ECS in the same sector is shown in the numerator

5.3.5.3 Functional Mapping of the Expressive Language-Related Cortex

Although mapping of the receptive language cortex has been found to be sufficient for the purpose of assessing hemispheric dominance for language, it is often necessary to determine the location of the expressive language cortex in relation to a diseased cortex. Several groups have thus far reported success in eliciting frontal magnetic activity in the vicinity of the Broca area associated with the performance of a variety of expressive language tasks.

Castillo et al. [105] employed a picture-naming task and MEG analysis procedures identical to those employed earlier in the context of receptive language mapping to derive maps of activation related to expressive language function. The results for seven normal volunteers and nine patients with epilepsy can be summarized as follows: (1) the task resulted in activation of the expressive language-related cortex (Broca area) in only a fraction of the cases (in three of the nine patients and three of the seven neurologically intact participants). Consequently, the procedure cannot be used alone for routine identification of the Broca area; (2) when frontal activity sources were identified, their location matched very closely with estimates of the location of the Broca area based on electrocortical stimulation mapping [105].

Kober et al. [104] have also reported success in eliciting inferior frontal activity using a picture-naming task and a spatial filtering algorithm to model cortical sources of neuromagnetic activity. Kober et al.'s spatial localization and time course results were consistent with the Wernicke-Geschwind model of language organization [104]. Moreover, they showed a high degree of concordance between results from spatial filtering and single ECD modeling. More recently, promising results were reported by Hirata et al. [96] using spatial filtering to model activity in the beta band recorded during performance of a silent word reading task in 12 patients with epilepsy or tumors. They reported an average distance of 6.0 ± 7.1 mm between the intraoperative stimulation site(s) associated with speech arrest and the cortical patches that displayed significant activation in the inferior or middle frontal gyri.

Clearly, future developments will decide on the most efficient method for assessing laterality as well as the precise location of the cortical circuitry subserving expressive and receptive language. At present the ECD model appears to be the safest to use for all types of presurgical evaluation, from determination of epileptogenic zones to localization of the sensory, motor, and receptive language cortex. There is also accumulating evidence that source modeling algorithms utilizing spatial filtering of task-related middle-to-high frequency neuromagnetic oscillations may provide a viable alternative for both expressive and receptive language mapping.

5.4 Limitations of MEG and Feature Directions

As is common with all functional brain imaging techniques, the utility of MEG as a tool for presurgical mapping is not without some limitations. For example, whereas consistent regional interictal epileptiform discharges may add confirmatory evidence in identifying the area of seizure onset, focal ictal epileptiform discharges preceding the patient's seizures or simultaneous with them are considered the most reliable localizing sign in presurgical evaluation [106]. Thus far there have been only a few reports of ictal MEG recordings [18, 20, 107–109]. MEG localizations of the ictal onset zone showed good agreement with subsequent invasive recordings [20, 108, 109] and seemed to be more accurate than surface EEG localizations [107]. MEG has also helped to resolve some ambiguities concerning the functional organization of the ictal onset zone and to differentiate between distributed and focal seizure onset zones [108]. However, despite the advent of whole-head MEG systems, ictal recordings are difficult to obtain on a routine basis for several reasons. First, the patient must have frequent seizures in order to capture an event during the short time MEG is recorded. Second, if the patients are required to stay in a fixed position in relation to the neuromagnetometer over a prolonged time period, they experience stress and discomfort that few can tolerate. Finally, seizures are usually accompanied by movement and associated artifacts, which can make MEG data difficult to interpret. Moreover, given that MEG recordings are almost exclusively of interictal activity with which one may identify the irritative but not necessarily the ictal onset zone, the practical issue of how well interictal MEG can match inv.VEEG recordings in identifying that zone also requires further study.

With respect to the use of MEG for mapping of the functional cortex, the key limitation concerns specificity of results: Activation profiles feature brain regions that may not be indispensable for a particular target function. This problem is particularly serious in the case of language mapping and to a lesser degree in motor cortex mapping. Replication studies in the same patients may help in this context by reducing (or eliminating) activations attributed to nonsystematic sources of variability in the recorded signals (e.g., certain components of extraneous noise and activity attributable to temporal variations in the realization of language processes involved). Although it is extremely helpful in this respect, within-session replication of the activation task is limited by time constraints and depends heavily upon the patient's level of cooperation, fatigue, and habituation to the task. Employing variations of the activation task (e.g., presenting stimuli in a different modality) may help in this direction.

Sensitivity of results is equally important clinically, although it appears to be less of an issue in MEG applications targeting receptive language functions. Sensitivity of MEG protocols is considerably reduced in motor cortex and expressive language mapping (applications that are also associated with the lowest success rates for obtaining clinically useful MEG test results). In these applications, the nature of the phenomenon being targeted (limb movement or speech) is inherently more difficult to image with MEG than somatic sensation and recognition of an aurally presented word. This difficulty is related to the averaging procedure that MEG entails, whereby several epochs of neuromagnetic activity are recorded, each to one of several repetitions of the same (or a similar) event. In order for the averaged ERF to accurately represent the neurophysiologic activity elicited by each event, the temporal characteristics of this activity have to be identical (or at least very similar) across its successive repetitions. This requirement is met to a large degree in the case of stimulation and processing of somatic and language stimuli and much less in tasks involving planning, programming, and execution of motor acts. Combining results from MEG and fMRI may present a solution to this problem as has been demonstrated in one large-scale study thus far, although activation and analysis protocols ensuring efficient and meaningful integration of data from the two modalities are yet to be established.

References

1. Papanicolaou AC. Fundamentals of functional brain imaging. The Netherlands: Swets & Zeitlinger; 1998.
2. Knowlton RC, Laxer KD, Aminoff MJ, Roberts TP, Wong ST, Rowley HA. Magnetoencephalography in partial epilepsy: clinical yield and localization accuracy. Ann Neurol. 1997;42:622–31. https://doi.org/10.1002/ana.410420413.
3. Pataraia E, Simos PG, Castillo EM, Billingsley RL, Sarkari S, Wheless JW, et al. Does magnetoencephalography add to scalp video-EEG as a diagnostic tool in epilepsy surgery? Neurology. 2004b;62:943–8.
4. Ebersole JS. Classification of MEG spikes in temporal lobe epilepsy. In: Yoshimoto T, Kotani M, Kuriki S, Karibe H, Nakasato N, editors. Recent advances in biomagnetism. Sendai: Tohoku University Press; 1999. p. 758–61.
5. Tenney JR, Fujiwara H, Horn PS, Rose DF. Comparison of magnetic source estimation to intracranial EEG, resection area, and seizure outcome. Epilepsia. 2014;55:1854–63.
6. Jung J, Bouet R, Delpuech C, Ryvlin P, Isnard J, Guenot M, et al. The value of magnetoencephalography for seizure-onset zone localization in magnetic resonance imaging-negative partial epilepsy. Brain. 2013;136:3176–86.
7. Kanamori Y, Shigeto H, Hironaga N, Hagiwara K, Uehara T, Chatani H, et al. Minimum norm estimates in MEG can delineate the onset of interictal epileptic discharges: a comparison with ECoG findings. Neuroimage Clin. 2013;2:663–9.
8. Englot DJ, Nagarajan SS, Imber BS, Raygor KP, Honma SM, Mizuiri D, et al. Epileptogenic zone localization using magnetoencephalography predicts seizure freedom in epilepsy surgery. Epilepsia. 2015;56:949–58. https://doi.org/10.1111/epi.13002.
9. Rubinger L, Chan C, D'Arco F, Moineddin R, Muthaffar O, Rutka JT, et al. Change in presurgical diagnostic imaging evaluation affects subsequent pediatric epilepsy surgery outcome. Epilepsia. 2016;57:32–40.
10. Brockhaus A, Lehnertz K, Wienbruch C, Kowalik A, Burr W, Elbert T, et al. Possibilities and limitations of magnetic source imaging of methohexital-induced epileptiform patterns in temporal lobe epilepsy patients. Electroencephalogr Clin Neurophysiol. 1997;102:423–36.
11. Butz M, Gross J, Timmermann L, Moll M, Freund HJ, Witte OW, Schnitzler A. Perilesional pathological oscillatory activity in the magnetoencephalogram of patients with cortical brain lesions. Neurosci Lett. 2004;355:93–6.
12. Englot DJ, Nagarajan SS, Wang DD, Rolston JD, Mizuiri D, Honma SM, et al. The sensitivity and significance of lateralized interictal slow activity on magnetoencephalography in focal epilepsy. Epilepsy Res. 2016;121:21–8. https://doi.org/10.1016/j.eplepsyres.2016.01.009.
13. Fernandez A, de Sola RG, Amo C, Turrero A, Zuluaga P, Maestu F, et al. Dipole density of low-frequency and spike magnetic activity: a reliable procedure in presurgical evaluation of temporal lobe epilepsy. J Clin Neurophysiol. 2004;21:254–66.
14. Gallen CC, Tecoma E, Iragui V, Sobel DF, Schwartz BJ, Bloom FE. Magnetic source imaging of abnormal low-frequency magnetic activity in presurgical evaluations of epilepsy. Epilepsia. 1997;38:452–60.
15. Ishibashi H, Simos PG, Castillo EM, Maggio WW, Wheless JW, Kim HL, et al. Detection and significance of focal, interictal, slow-wave activity visualized by magnetoencephalography for localization of a primary epileptogenic region. J Neurosurg. 2002a;96:724–30.
16. Kamada K, Saguer M, Moller M, Wicklow K, Katenhauser M, Kober H, Vieth J. Functional and metabolic analysis of cerebral ischemia using magnetoencephalography and proton magnetic resonance spectroscopy. Ann Neurol. 1997;42:554–63.
17. Assaf BA, Karkar KM, Laxer KD, Garcia PA, Austin EJ, Barbaro NM, Aminoff MJ. Ictal magnetoencephalography in temporal and extratemporal lobe epilepsy. Epilepsia. 2003;44:1320–7.
18. Eliashiv DS, Elsas S, Squires M, Fried K, Engel IJ. Ictal magnetic source imaging as a localizing tool in partial epilepsy. Neurology. 2002;59:1600–10.
19. Oishi M, Otsubo H, Kameyama S, Wachi M, Tanaka K, Masuda H, Tanaka R. Ictal magnetoencephalographic discharges from elementary visual hallucinations of status epilepticus. J Neurol Neurosurg Psychiatry. 2003a;74:525–7.
20. Stefan H, Schneider S, Feistel H, Pawlik G, Schuler P, Abraham-Fuchs K, et al. Ictal and interictal activity in partial epilepsy recorded with multichannel magnetoelectroencephalography: correlation of electroencephalography/electrocorticography, magnetic resonance imaging, single photon emission computed tomography, and positron emission tomography findings. Epilepsia. 1992;33:874–87.
21. Tilz C, Hummel C, Kettenmann B, Stefan H. Ictal onset localization of epileptic seizures by magnetoencephalography. Acta Neurol Scand. 2002;106:190–5.
22. Yoshinaga H, Ohtsuka Y, Watanabe Y, Inutsuka M, Kitamura Y, Kinugasa K, Ok E. Ictal MEG in two children with partial seizures. Brain and Development. 2004;26:403–8.
23. Almubarak S, Alexopoulos A, Von-Podewils F, Wang ZI, Kakisaka Y, Mosher JC, et al. The correlation of magnetoencephalography to intracranial EEG in localizing the epileptogenic zone: a study of the surgical resection outcome. Epilepsy Res. 2014;108:1581–90.
24. Papanicolaou AC, Pataraia E, Billingsley-Marshall R, Castillo EM, Wheless JW, Swank P, et al. Toward the substitution of invasive electroencephalography in epilepsy surgery. J Clin Neurophysiol. 2005;22:231–7.

25. Bennett-Back O, Ochi A, Widjaja E, Nambu S, Kamiya A, Go C, et al. Magnetoencephalography helps delineate the extent of the epileptogenic zone for surgical planning in children with intractable epilepsy due to porencephalic cyst/encephalomalacia. J Neurosurg Pediatr. 2014;14:271–8.
26. Mohamed IS, Gibbs SA, Robert M, Bouthillier A, Leroux JM, Khoa Nguyen D. The utility of magnetoencephalography in the presurgical evaluation of refractory insular epilepsy. Epilepsia. 2013;54:1950–9.
27. Iwasaki M, Nakasato N, Shamoto H, Nagamatsu K, Kanno A, Hatanaka K, et al. Surgical implications of neuromagnetic spike localization in temporal lobe epilepsy. Epilepsia. 2002;43:415–24.
28. Stefan H, Schuler P, Abraham-Fuchs K, Schneider S, Gebhardt M, Neubauer U, et al. Magnetic source localization and morphological changes in temporal lobe epilepsy: comparison of MEG/EEG, ECoG and volumetric MRI in presurgical evaluation of operated patients. Acta Neurol Scand Suppl. 1994;152:83–8.
29. Mamelak AN, Lopez N, Akhtari M, Sutherling WW. Magnetoencephalography-directed surgery in patients with neocortical epilepsy. J Neurosurg. 2002;97:865–73. https://doi.org/10.3171/jns.2002.97.4.0865.
30. Otsubo H, Ochi A, Elliott I, Chuang SH, Rutka JT, Jay V, et al. MEG predicts epileptic zone in lesional extrahippocampal epilepsy: 12 pediatric surgery cases. Epilepsia. 2001;42:1523–30.
31. Shiraishi H, Watanabe Y, Watanabe M, Inoue Y, Fujiwara T, Yagi K. Interictal and ictal magnetoencephalographic study in patients with medial frontal lobe epilepsy. Epilepsia. 2001;42:875–82.
32. Stefan H, Hummel C, Hopfengartner R, Pauli E, Tilz C, Ganslandt O, et al. Magnetoencephalography in extratemporal epilepsy. J Clin Neurophysiol. 2000;17:190–200.
33. Baumgartner C, Pataraia E, Lindinger G, Deecke L. Neuromagnetic recordings in temporal lobe epilepsy. J Clin Neurophysiol. 2000;17:177–89.
34. Bast T, Oezkan O, Rona S, Stippich C, Seitz A, Rupp A, et al. EEG and MEG source analysis of single and averaged interictal spikes reveals intrinsic epileptogenicity in focal cortical dysplasia. Epilepsia. 2004;45:621–31.
35. Burneo JG, Bebin M, Kuzniecky RI, Knowlton RC. Electroclinical and magnetoencephalographic studies in epilepsy patients with polymicrogyria. Epilepsy Res. 2004a;62:125–33.
36. Ishibashi H, Simos PG, Wheless JE, Zhang W, Baumgartner JE, Castillo EM, Papanicolaou AC. Somatosensory evoked magnetic fields in hemimegalencephaly. Neurol Res. 2002c;24:459–62.
37. Minami T, Tasaki K, Yamamoto T, Gondo K, Yanai S, Ueda K. Magneto-encephalographical analysis of focal cortical heterotopia. Dev Med Child Neurol. 1996;38:945–9.
38. Morioka T, Nishio S, Ishibashi H, Muraishi M, Hisada K, Shigeto H, et al. Intrinsic epileptogenicity of focal cortical dysplasia as revealed by magnetoencephalography and electrocorticography. Epilepsy Res. 1999;33:177–87.
39. Otsubo H, Iida K, Oishi M, Okuda C, Ochi A, Pang E, et al. Neurophysiologic findings of neuronal migration disorders: intrinsic epileptogenicity of focal cortical dysplasia on electroencephalography, electrocorticography, and magnetoencephalography. J Child Neurol. 2005;20:357–63.
40. Taniguchi M, Yoshimine T, Kato A, Maruno M, Hirabuki N, Nakamura H, et al. Dysembryoplastic neuroepithelial tumor in the insular cortex. Three dimensional magnetoencephalographic localization of epileptic discharges. Neurol Res. 1998;20:433–8.
41. Toulouse P, Agulhon C, Taussig D, Napuri S, Biraben A, Jannin P, et al. Magnetoencephalographic studies of two cases of diffuse subcortical laminar heterotopia or so-called double cortex. NeuroImage. 2003;19:1251–9.
42. Zhang W, Simos PG, Ishibashi H, Wheless JW, Castillo EM, Kim HL, et al. Multimodality neuroimaging evaluation improves the detection of subtle cortical dysplasia in seizure patients. Neurol Res. 2003;25:53–7.
43. Iida K, Otsubo H, Mohamed IS, Okuda C, Ochi A, Weiss SK, et al. Characterizing magnetoencephalographic spike sources in children with tuberous sclerosis complex. Epilepsia. 2005;46:1510–7.
44. Jansen FE, Huiskamp G, van Huffelen AC, Bourez-Swart M, Boere E, Gebbink T, et al. Identification of the epileptogenic tuber in patients with tuberous sclerosis: a comparison of high-resolution EEG and MEG. Epilepsia. 2006;47:108–14.
45. Kamimura T, Tohyama J, Oishi M, Akasaka N, Kanazawa O, Sasagawa M, et al. Magnetoencephalography in patients with tuberous sclerosis and localization-related epilepsy. Epilepsia. 2006;47:991–7.
46. Wu JY, Sutherling WW, Koh S, Salamon N, Jonas R, Yudovin S, et al. Magnetic source imaging localizes epileptogenic zone in children with tuberous sclerosis complex. Neurology. 2006;66:1270–2.
47. Xiao Z, Xiang J, Holowka S, Hunjan A, Sharma R, Otsubo H, Chuang S. Volumetric localization of epileptic activities in tuberous sclerosis using synthetic aperture magnetometry. Pediatr Radiol. 2006;36:16–21.
48. Hattori H, Yamano T, Tsutada T, Tsuyuguchi N, Kawawaki H, Shimogawara M. Magnetoencephalography in the detection of focal lesions in West syndrome. Brain and Development. 2001;23:528–32.
49. Ishibashi H, Simos PG, Wheless JW, Baumgartner JE, Kim HL, Davis RN, et al. Multimodality functional imaging evaluation in a patient with Rasmussen's encephalitis. Brain and Development. 2002b;24:239–44.
50. Morioka T, Nishio S, Hisada K, Shigeto H, Yamamoto T, Fujii K, Fukui M. Neuromagnetic assessment of epileptogenicity in cerebral arteriovenous malformation. Neurosurg Rev. 2000;23:206–12.
51. Otsubo H, Snead OC 3rd. Magnetoencephalography and magnetic source imaging in children. J Child Neurol. 2001;16:227–35.
52. Paetau R, Hamalainen M, Hari R, Kajola M, Karhu J, Larsen TA, et al. Magnetoencephalographic evaluation of children and adolescents with intractable epilepsy. Epilepsia. 1994;35:275–4.
53. Paetau R, Granstrom ML, Blomstedt G, Jousmaki V, Korkman M, Liukkonen E. Magnetoencephalography in presurgical evaluation of children with the Landau-Kleffner syndrome. Epilepsia. 1999;40:326–35.
54. Verrotti A, Pizzella V, Trotta D, Madonna L, Chiarelli F, Romani GL. Magnetoencephalography in pediatric neurology and in epileptic syndromes. Pediatr Neurol. 2003;28:253–61.
55. Yanai S, Minami T, Yamamoto T, Gondo K, Kira R, Tokunaga Y, Ueda K. Magnetoencephalographic analysis of hypsarrhythmia in West syndrome. J Epilepsy. 1997;10:131–8.
56. Stefan H, Scheler G, Hummel C, Walter J, Romstock J, Buchfelder M, Blumcke I. Magnetoencephalography (MEG) predicts focal epileptogenicity in cavernomas. J Neurol Neurosurg Psychiatry. 2004;75:1309–13.
57. Amo C, Saldaña C, Hidalgo MG, Maestú F, Fernández A, Arrazola J, Ortiz T. Magnetoencephalographic localization of peritumoral temporal epileptic focus previous surgical resection. Seizure. 2003;12:19–22.
58. Patt S, Steenbeck J, Hochstetter A, Kraft R, Huonker R, Haueisen J, et al. Source localization and possible causes of interictal epileptic activity in tumor-associated epilepsy. Neurobiol Dis. 2000;7:260–9.
59. Schiffbauer H, Berger MS, Ferrari P, Freudenstein D, Rowley HA, Roberts TP. Preoperative magnetic source imaging for brain tumor surgery: a quantitative comparison with intraoperative sensory and motor mapping. J Neurosurg. 2002;97:1333–42.
60. Willemse RB, Hillebrand A, Ronner HE, Vandertop WP, Stam CJ. Magnetoencephalographic study of hand and foot sensorimotor organization in 325 consecutive patients evaluated for tumor or epilepsy surgery. Neuroimage Clin. 2016;10:46–53.
61. Smith JR, Schwartz BJ, Gallen C, Orrison W, Lewine J, Murro AM, et al. Multichannel magnetoencephalography in ablative

seizure surgery outside the anteromesial temporal lobe. Stereotact Funct Neurosurg. 1995;65:81–5.
62. Ishibashi H, Morioka T, Nishio S, Shigeto H, Yamamoto T, Fukui M. Magnetoencephalographic investigation of somatosensory homunculus in patients with peri-Rolandic tumors. Neurol Res. 2001;23:29–38.
63. Morioka T, Yamamoto T, Katsuta T, Fujii K, Fukui M. Presurgical three-dimensional magnetic source imaging of the somatosensory cortex in a patient with a peri-Rolandic lesion: technical note. Neurosurgery. 1994;34:930–3; discussion, 933–4.
64. Roberts TP, Ferrari P, Perry D, Rowley HA, Berger MS. Presurgical mapping with magnetic source imaging: comparisons with intraoperative findings. Brain Tumor Pathol. 2000;17:57–64.
65. Ganslandt O, Buchfelder M, Hastreiter P, Grummich P, Fahlbusch R, Nimsky C. Magnetic source imaging supports clinical decision making in glioma patients. Clin Neurol Neurosurg. 2004;107:20–6.
66. Korvenoja A, Kirveskari E, Aronen HJ, Avikainen S, Brander A, Huttunen J, et al. Sensorimotor cortex localization: comparison of magnetoencephalography, functional MR imaging, and intraoperative cortical mapping. Radiology. 2006;241:213–22.
67. Ganslandt O, Fahlbusch R, Nimsky C, Kober H, Moller M, Steinmeier R, et al. Functional neuronavigation with magnetoencephalography: outcome in 50 patients with lesions around the motor cortex. J Neurosurg. 1999;91:73–9.
68. Kirsch HE, Zhu Z, Honma S, Findlay A, Berger MS, Nagarajan SS. Predicting the location of mouth motor cortex in patients with brain tumors by using somatosensory evoked field measurements. J Neurosurg. 2007;107:481–7.
69. Breier JI, Simos PG, Wheless JW, Zouridakis G, Willmore LJ, Constantinou JEC, Papanicolaou AC. A magnetoencephalography study of cortical plasticity. Neurocase. 1999a;5:277–84.
70. Burneo JG, Kuzniecky RI, Bebin M, Knowlton RC. Cortical reorganization in malformations of cortical development: a magnetoencephalographic study. Neurology. 2004b;63:1818–24.
71. Oishi M, Fukuda M, Kameyama S, Kawaguchi T, Masuda H, Tanaka R. Magnetoencephalographic representation of the sensorimotor hand area in cases of intracerebral tumour. J Neurol Neurosurg Psychiatry. 2003b;74:1649–54.
72. Papanicolaou AC, Simos PG, Breier JI, Wheless JW, Mancias P, Baumgartner JE. Brain plasticity for sensory and linguistic functions: a functional imaging study using magnetoencephalography with children and young adults. J Child Neurol. 2001;16:241–52.
73. Roberts TP, Zusman E, McDermott M, Barbaro N, Rowley HA. Correlation of functional magnetic source imaging with intraoperative cortical stimulation in neurosurgical patients. J Image Guid Surg. 1995;1:339–47.
74. Vates GE, Lawton MT, Wilson CB, McDermott MW, Halbach VV, Roberts TP, Rowley HA. Magnetic source imaging demonstrates altered cortical distribution of function in patients with arteriovenous malformations. Neurosurgery. 2002;51:614–23; discussion, 623–7.
75. Kassubeck J, Stippich C, Soros P. A motor field localization protocol using magnetoencephalography. Biomed Eng. 1996;41:334–5.
76. Tarapore PE, Tate MC, Findlay AM, Honma SM, Mizuiri D, Berger MS, Nagarajan SS. Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. J Neurosurg. 2012;117:354–62.
77. Castillo EM, Simos PG, Wheless JW, Baumgartner JE, Breier JI, Billingsley RL, et al. Integrating sensory and motor mapping in a comprehensive MEG protocol: clinical validity and replicability. NeuroImage. 2004;21:973–83.
78. Barnikol UB, Amunts K, Dammers J, Mohlberg H, Fieseler T, Malikovic A, et al. Pattern reversal visual evoked responses of V1/V2 and V5/MT as revealed by MEG combined with probabilistic cytoarchitectonic maps. NeuroImage. 2006;31:86–108.
79. Hashimoto T, Kashii S, Kikuchi M, Honda Y, Nagamine T, Shibasaki H. Temporal profile of visual evoked responses to pattern-reversal stimulation analyzed with a whole-head magnetometer. Exp Brain Res. 1999;125:375–82.
80. Hatanaka K, Nakasato N, Seki K, Kanno A, Mizoi K, Yoshimoto T. Striate cortical generators of the N75, P100 and N145 components localized by pattern reversal visual evoked magnetic fields. Tohoku J Exp Med. 1997;182:9–14.
81. Nakamura M, Kakigi R, Okusa T, Hoshiyama M, Watanabe K. Effects of check size on pattern reversal visual evoked magnetic field and potential. Brain Res. 2000;872:77–86.
82. Seki K, Nakasato N, Fujita S, Hatanaka K, Kawamura T, Kanno A, Yoshimoto T. Neuromagnetic evidence that the P100 component of the pattern reversal visual evoked response originates in the bottom of the calcarine fissure. Electroencephalogr Clin Neurophysiol. 1996;100:436–42.
83. Shigeto H, Tobimatsu S, Yamamoto T, Kobayashi T, Kato M. Visual evoked cortical magnetic responses to checkerboard pattern reversal stimulation: a study on the neural generators of N75, P100 and N145. J Neurol Sci. 1998;156:186–94.
84. Alberstone CD, Skirboll SL, Benzel EC, Sanders JA, Hart BL, Baldwin NG, et al. Magnetic source imaging and brain surgery: presurgical and intraoperative planning in 26 patients. J Neurosurg. 2000;92:79–90.
85. Inoue I, Fujimura M, Kumabe T, Nakasato N, Higano S, Tominaga T. Combined three-dimensional anisotropy contrast imaging and magnetoencephalography guidance to preserve visual function in a patient with an occipital lobe tumor. Minim Invasive Neurosurg. 2004;47:249–52.
86. Nakasato N, Kumabe T, Kanno A, Ohtomo S, Mizoi K, Yoshimoto T. Neuromagnetic evaluation of cortical auditory function in patients with temporal lobe tumors. J Neurosurg. 1997;86:610–8.
87. Nakasato N, Fujita S, Seki K, Kawamura T, Matani A, Tamura I, et al. Functional localization of bilateral auditory cortices using an MRI-linked whole head magnetoencephalography (MEG) system. Electroencephalogr Clin Neurophysiol. 1995;94:183–90.
88. Suzuki K, Okuda J, Nakasato N, Kanno A, Hatanaka K, Yamadori A, et al. Auditory evoked magnetic fields in patients with right hemisphere language dominance. Neuroreport. 1997;8:3363–6.
89. Dym RJ, Burns J, Freeman K, Lipton ML. Is functional MR imaging assessment of hemispheric language dominance as good as the Wada test?: a meta-analysis. Radiology. 2011;261:446–55.
90. Breier JI, Simos PG, Zouridakis G, Wheless JW, Willmore LJ, Constantinou JE, et al. Language dominance determined by magnetic source imaging: a comparison with the Wada procedure. Neurology. 1999b;53:938–45.
91. Breier JI, Simos PG, Wheless JW, Constantinou JEC, Papanicolaou AC. Hemispheric language dominance in children determined by magnetic source imaging. J Child Neurol. 2001;16:124–30.
92. Papanicolaou AC, Simos PG, Castillo EM, Breier JI, Sarkari S, Pataraia E, et al. Magnetocephalography: a noninvasive alternative to the Wada procedure. J Neurosurg. 2004;100:867–76.
93. Doss RC, Zhang W, Risse GL, Dickens DL. Lateralizing language with magnetic source imaging: validation based on the Wada test. Epilepsia. 2009;50:2242–8.
94. Maestu F, Ortiz T, Fernandez A, Amo C, Martin P, Fernandez S, Sola RG. Spanish language mapping using MEG: a validation study. NeuroImage. 2002;17:1579–86.
95. Rezaie R, Narayana S, Schiller K, Birg L, Wheless JW, Boop FA, Papanicolaou AC. Assessment of hemispheric dominance for receptive language in pediatric patients under sedation using magnetoencephalography. Front Hum Neurosci. 2014;8(657)
96. Kamada K, Sawamura Y, Takeuchi F, Kuriki A, Kawai K, Morita A, et al. Expressive and receptive language areas determined by a noninvasive reliable method using functional magnetic resonance imaging and magnetoencephalography. Neurosurgery. 2007;60:296–305.

97. Findlay AM, Ambrose JB, Cahn-Weiner DA, Houde JF, Honma S, Hinkley LB, et al. Dynamics of hemispheric dominance for language assessed by magnetoencephalographic imaging. Ann Neurol. 2012;71:668–86.
98. Hirata M, Kato A, Taniguchi M, Saitoh Y, Ninomiya H, Ihara A, et al. Determination of language dominance with synthetic aperture magnetometry: comparison with the Wada test. NeuroImage. 2004;23:46–53.
99. McDonald CR, Thesen T, Hagler DJ Jr, Carlson C, Devinksy O, Kuzniecky R, et al. Distributed source modeling of language with magnetoencephalography: application to patients with intractable epilepsy. Epilepsia. 2009;50:2256–66.
100. Tanaka N, Liu H, Reinsberger C, Madsen JR, Bourgeois BF, Dworetzky BA, et al. Language lateralization represented by spatiotemporal mapping of magnetoencephalography. Am J Neuroradiol. 2013;34:558–63.
101. Bowyer SM, Moran JE, Mason KM, Constantinou JE, Smith BJ, Barkley GL, et al. MEG localization of language-specific cortex utilizing MR-FOCUSS. Neurology. 2004;62:2247–55.
102. Simos PG, Breier JI, Maggio WW, Gormley WB, Zouridakis G, Willmore LJ, et al. Atypical temporal lobe language representation: MEG and intraoperative stimulation mapping correlation. Neuroreport. 1999a;10:139–42.
103. Castillo EM, Breier JI, Wheless JW, Slater JD, Tandon N, Baumgartner JE, et al. Contributions of direct cortical stimulation and MEG recordings to identify “essential” language cortex. Epilepsia. 2005;46:324.
104. Kober H, Moller M, Nimsky C, Vieth J, Fahlbusch R, Ganslandt O. New approach to localize speech relevant brain areas and hemispheric dominance using spatially filtered magnetoencephalography. Hum Brain Mapp. 2001;14:236–50.
105. Castillo EM, Simos PG, Venkataraman V, Breier JI, Wheless JW, Papanicolaou AC. Mapping of expressive language cortex using magnetic source imaging. Neurocase. 2001;7:419–22.
106. Lüders HO. Epilepsy surgery. New York: Raven Press; 1992.
107. Ko DY, Kufta C, Scaffidi D, Sato S. Source localization determined by magnetoencephalography and electroencephalography in temporal lobe epilepsy: comparison with electrocorticography: technical case report. Neurosurgery. 1998;42:414–21; discussion, 421.
108. Sutherling WW, Crandall PH, Engel J Jr, Darcey TM, Cahan LD, Barth DS. The magnetic field of complex partial seizures agrees with intracranial localizations. Ann Neurol. 1987;21:548–58.
109. Ishibashi H, Morioka T, Shigeto H, Nishio S, Yamamoto T, Fukui M. Three-dimensional localization of subclinical ictal activity by magnetoencephalography: correlation with invasive monitoring. Surg Neurol. 1998;50:157–63.

6 Navigated Transcranial Magnetic Stimulation in Planning Epilepsy Surgery

Pantelis Lioumis and Jyrki P. Mäkelä

Navigated transcranial magnetic stimulation (nTMS) is increasingly used for noninvasive functional mapping of eloquent cortical areas in preoperative evaluation for brain surgery. Reliability of nTMS has been studied in healthy populations. Here we describe the methods and protocols for nTMS mapping of motor- and language-related cortical areas and describe results of nTMS in patients going through workups for epilepsy surgery. Clinical evidence indicates that nTMS mapping is a safe and useful tool in planning epilepsy surgery.

Noninvasive transcranial magnetic stimulation (TMS) enables cortical neural excitation by means of brief and strong magnetic field pulses that induce weak intracortical currents in the tissue, resulting in membrane depolarization [1]. The initiation of cortical activation or its modulation depends on the characteristics of the TMS coil, its position and orientation with respect to the head [2], the waveform of the pulse generated by the coil, and the background activation of the neurons of the cortical region to be activated [3]. TMS is an important tool to investigate cortical functions in humans by evoking motor or behavioral responses or by interrupting task-related processing. Cortico-spinal excitability can be evaluated by recording electromyographic (EMG) responses elicited by single TMS pulses over the motor cortex, whereas intracortical excitability can be measured by means of paired pulse TMS. Repetitive TMS can be used as a therapeutic tool and to disturb various ongoing cognitive processes. Furthermore, TMS combined with simultaneous electroencephalography (EEG) enables the study of cortico-cortical excitability and connectivity. When TMS is assisted with neuronavigation (nTMS), precise test-retest paradigms can be executed, and the majority of the cortical mantle can be targeted and stimulated (including areas that do not produce measurable neurophysiologic or behavioral results; "silent" cortical regions). nTMS also enables a precise mapping of cortical functions. This is particularly important in designing epilepsy surgery.

One of the goals in neurosurgery is to preserve the eloquent cortex and to optimize the extent of rejection of pathologic tissue [4]. Estimation of functional eloquence of brain areas based on anatomic landmarks is unpredictable as a result of anatomic, functional, and pathology-related variability [5]. Therefore, neuroimaging and intraoperative/extraoperative brain mapping are needed to limit postoperative functional deficits and to maximize the quality of postoperative life. Resection without intraoperative or extraoperative invasive mapping should not be considered in lesions estimated to be close to eloquent areas [5]. Invasive functional cortical mapping prior to resection is achieved by means of direct electrical cortical stimulation (DCS) utilizing monopolar or bipolar electrode probes to stimulate the exposed cortex of tumor patients [6].

Patients with intractable epilepsy need accurate identification of the epileptogenic area. If the epileptic focus is suspected to be in the eloquent cortex, intracranial recordings and DCS are required. These procedures are done before the actual epilepsy surgery by surgical insertion of subdural grid electrodes (extraoperative direct cortical stimulation [ECS]). Recording and stimulations are then performed on the ward for about 1 week to obtain localization of epileptic foci and functional mapping [7]. This diagnostic surgery is associated with a non-trivial possibility of complications [8, 9], such as ECS-evoked after discharges and induced seizures that put patients at risk and make testing time consuming or even impossible [10]. Moreover, extraoperative procedures require good collaboration by the patient; this is not always easily obtained (e.g., in children or in patients with delayed development caused by the epilepsy). Nevertheless, invasive functional cortical mapping is the gold standard for functional mapping because it is able to localize the primary motor cortex accurately [11]. In addition, it has been well validated for

P. Lioumis (✉)
Temerty Centre for Therapeutic Brain Intervention, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

J. P. Mäkelä
BioMag Laboratory, HUS Medical Imaging Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

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localizing language-related cortical areas during awake craniotomy procedures [12, 13]. It also can be used for mapping of visuospatial and cognitive functions [14].

Lateralization of speech is necessary if the area to be resected is estimated to be near speech-related areas. The standard procedure for the identification of cerebral speech dominance is the WADA test [15], in which sodium amytal is injected into one of the carotid arteries to induce temporary loss of function of one hemisphere. The WADA test, although an efficient way to identify speech lateralization, has a number of constraints and risks [16]. Therefore, noninvasive preoperative neuroimaging methods are of high interest.

Utilization of neuroimaging has increased in work-ups for epilepsy surgery during the last decade. MRI, fMRI, diffusion tensor imaging (DTI), and magnetoencephalography (MEG) are used for preoperative mapping [17–19]. Anatomic MRI is crucial in localizing tumors and other epileptogenic lesions, but it does not necessarily reveal the location of epileptic foci. It can also be used in neuronavigation in the operation theater to guide the neurosurgeon to the cortical site of interest [20]. fMRI is used for localization of motor functions. It has also been widely used to identify speech-dominant hemispheres, although with variable results. Some studies have compared fMRI to DCS results for localization of speech-related areas (for a review, see Rutten and Ramsey [19]). fMRI produces false-positive activations when compared with DCS but may offer valuable information about the sensitivity of different tasks in the demonstration of eloquent cortical speech areas [21]. DTI can image the white-matter fiber tracts that connect different speech-related cortical regions (for review [22, 23]). It can illustrate the different connections in the speech network important for neurosurgical planning [19]. MEG is useful in detecting sources and spread of epileptiform activity [18]. Functional localization of sensorimotor cortex by MEG has been confirmed by DCS and appears to be more accurate than fMRI [24, 25].

Mapping of speech-related cortical areas can be useful for presurgical planning. Recent studies show that fMRI depicts the frontal speech-related activity better than MEG, whereas MEG is more useful in detecting temporoparietal speech-related cortices. MEG combined with fMRI may give valuable and accurate results for localizing speech functions [26].

MEG may turn out to be indispensable in designing surgical resection for epilepsy in accurately locating the epileptogenic zone [27]. MEG localization of epileptiform activity is valuable in predicting the findings of electrocorticography (EcoG), which is also often used in patients with intractable epilepsy. However, availability of MEG is limited, and it requires expertise for the data analysis and interpretation [18].

TMS has been used efficiently for preoperative mapping both in brain tumor [28, 29] and epilepsy patients [30–32]. Although promising results have been obtained in locating the motor cortex by non-navigated TMS [33], the development of nTMS has enabled its extensive use for preoperative mapping. In mapping of motor functions, nTMS is more accurate than fMRI [28, 34], and the results obtained by nTMS agree with DCS findings [29, 34]. Several studies suggest that nTMS mapping improves surgical planning [35] and increases the surgeon's confidence during resection [34]. In speech mapping, early studies [36] inspired several attempts producing variable results [37]. The use of nTMS has, however, opened new possibilities in mapping of speech-related cortex [38]. Comparisons of nTMS results with DCS during awake craniotomy in patients with brain tumors have been promising [39–41]. Mapping of cortical speech-related areas by nTMS is used in more than 40 neurosurgical centers around the world. Its clinical value is being improved by a unified effort from the clinical nTMS community to standardize methodology and compare the nTMS results with those of DCS in a homogeneous manner [42].

6.1 Methods

6.1.1 TMS

TMS induces focal electric fields that generate neuronal activation in the brain. The magnetic field used is approximately 1 tesla; the rise time of the field is usually less than 100 μs.

Conventional non-navigated TMS has a somewhat limited use in clinical applications and in basic research. It can be utilized to stimulate areas that can produce measurable neurophysiologic (e.g., motor-evoked potentials [MEPs]) or behavioral results. In addition, other cortical sites can be identified on the basis of external anatomic landmarks. But even in the motor cortex, where MEP can be easily generated, the precise cortical location of the targeted site is not known. Moreover, the distances of different cortical regions from the scalp may vary. Hence, the induced electric field is not the same in all cortical areas, although the stimulator output remains fixed. The individual variability of brain shape, size, location, and orientation of anatomic structures adds imprecision for the selection of the stimulation site. As a result, cortical functional mapping cannot be implemented reliably with the traditional TMS methodology [43].

6.1.2 Navigated TMS

In the state-of-the-art nTMS equipment, a figure-of-eight-shaped coil is moved manually with the help of optically guided navigation so that cortical sites selected from individual MRIs will be stimulated. In nTMS (Fig. 6.1a, b), individual MRIs are coregistered with the subject's head. For this purpose, an infra-red camera locates the trackers that are attached on the coil and on the subject's head. In aligning the 3-D MRI head model and the head, landmarks that have been set on the MRIs are chosen manually on the head with a digitizing pen. After this procedure, the coil can be visualized over the 3-D MRI head model. In this way, the stimulation site, the

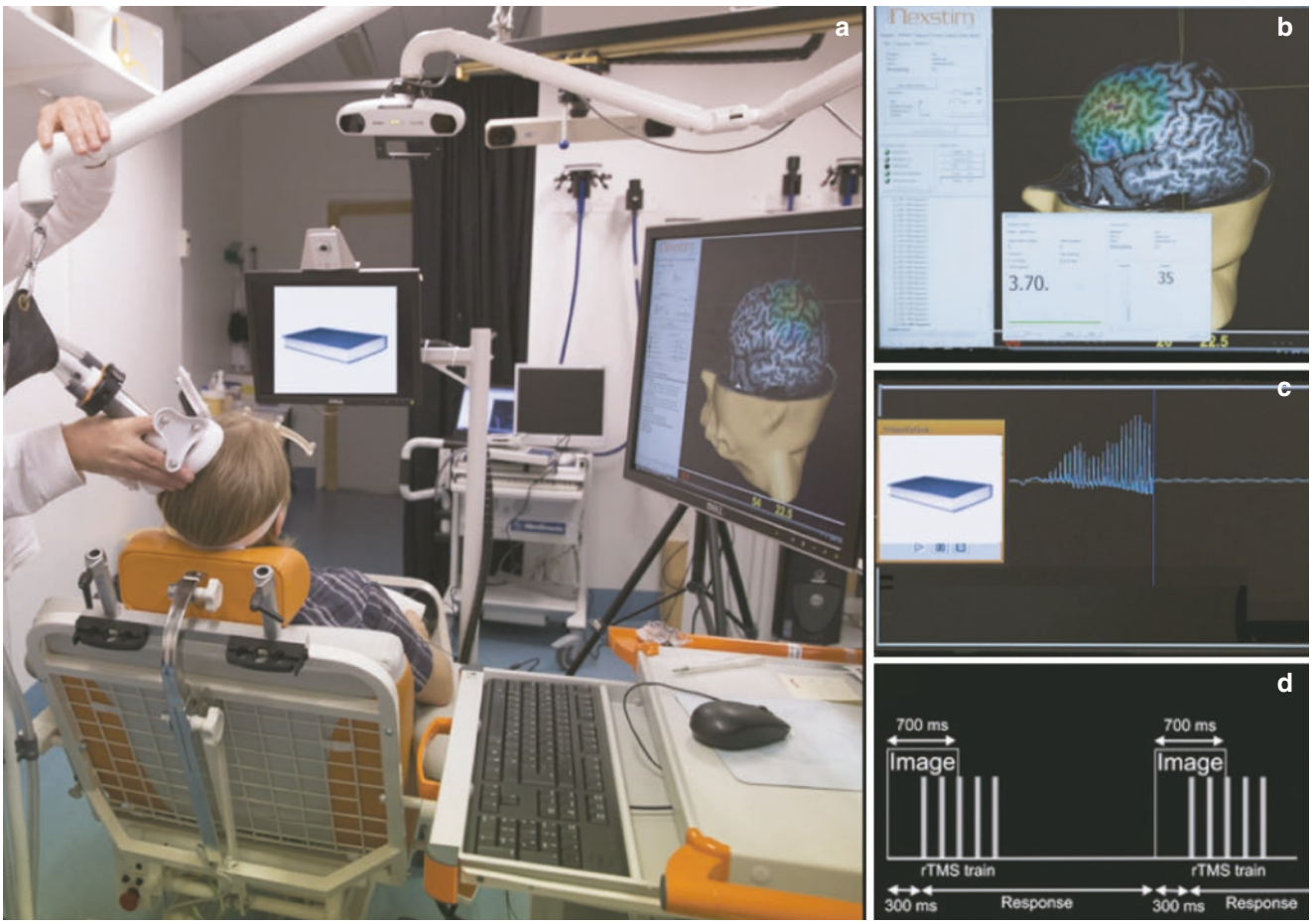

Fig. 6.1 Navigated TMS for cortical motor and speech mapping. (**a**) The subject is seated in a chair wearing a band with head trackers. (**b**) Thereafter, both the coil projection on the individual's cortex and the induced field over the particular cortical site can be visualized in real time [43]. (**c**) For the speech mapping, the visual stimuli as well as the accelerometer signal recorded from the larynx [46] can be visualized simultaneously. (**d**) Schematic presentation of the picture presentation and nTMS trains for the object-naming paradigm. (Courtesy of Dr. Anne-Mari Vitikainen [47])

coil orientation, and the calculated estimate of the induced electric field can be visualized and reproduced in different measurements of the same subject as long as the registration error remains the same [43]. Navigated TMS enables the operator to plan, perform, monitor, and document the experiments in an accurate and reproducible manner [2].

6.1.3 Motor Cortical Mapping with nTMS

Cortical mapping with nTMS is used to determine locations of the eloquent motor and cortical areas. During motor cortical mapping, the TMS coil is moved around motor areas, over the lesion (tumor or suspected epileptogenic area), and in areas in close proximity to the lesion. If a TMS pulse over a cortical site elicits an MEP larger than 50 μV, this site is considered important for motor function. After the motor mapping, all motor-related cortical sites are colored and given to the neurosurgeon (in Helsinki University Hospital [HUH], this is done via radiological picture archiving system (PACS) [44]). This a priori information is used by the neurosurgeon to design the craniotomy and DCS. Motor mapping by nTMS has proved to be very accurate and important; it can potentially replace DCS in several conditions [28–30, 32].

6.1.3.1 Mapping of Speech-Related Cortical Areas with nTMS

In mapping of speech-related cortical areas by nTMS, patients perform cognitive tasks such as object naming [38], and their performance is recorded by video (Fig. 6.1a–d). nTMS cannot elicit speech responses, but when it is used in its repetitive mode (rTMS), it can disturb the task performance if a task-related cortical site is stimulated at the time it participates in the task. The procedure requires a set of pictures that are normalized over linguistic and visual parameters [45]. A baseline naming study without any stimulation is performed first to discard all incorrectly named pictures from subsequent tests. Hence, a subject-validated image stack for the speech mapping is obtained. This aids the off-line analysis of the results, which is preferably done by a neuropsychologist; in HUH, the same person assists the neurosurgeon in speech tests during awake craniotomies. The aim is to identify errors caused by the nTMS and to separate them from those o-wing to a lack of attention or disease-related speech impairment. Lately, an accelerometer attached in the larynx is used to record vibrations associated with vocalization to add information about speech response times in order to get more objective measurements about delays and hesitations during naming (Fig. 6.1c) [46].

After the baseline study, the TMS mapping starts. The investigator has to map large cortical areas, including the contralesional hemisphere, so as to map as many non–speech-related control areas as possible. The times of different protocols and parameters are used by different research groups [38–41]; detailed information about this can be found in Krieg et al. [42].

6.2 Results

6.2.1 Motor Mapping

The applicability of nTMS in mapping cortical motor representations in planning epilepsy surgery was demonstrated in two patients [30]. Localization of the epileptogenic area and somatosensory cortex by MEG was combined with nTMS data to design the insertion of the grid electrodes. For both patients, nTMS results matched with the motorotopy of the precentral gyrus and coincided accurately with the motor responses elicited by the ECS of grid electrodes. The preoperative somatosensory sources by MEG and the subdural cortical stimulation site that produced hand sensation were within 1 cm of distance from each other. The sources of ictal MEG activity for both patients were close or overlapped the cortical stimulation sites by ECS that triggered typical seizures. Histologic examinations of the removed area revealed focal microscopic cortical dysplasia type 2b (FCD; Taylor type) that was not detected preoperatively by 3-T MRI. No postoperative motor impairments occurred, and both patients have been seizure-free for at least 2 years after the surgery.

The feasibility and safety of nTMS as a clinical tool for the noninvasive preoperative localization of M1 in patients with intractable epilepsy have been demonstrated in subsequent studies. For example, 10 patients with different lesion pathologies were evaluated by nTMS before surgery. In 2 young patients nTMS did not elicit motor responses because of the safety limitation of nTMS intensity. In 6 out of 8 adult patients, nTMS localization of M1 was found essential or beneficial for subsequent surgery by changing the resection plan or confirming the safety of the planned resection. In addition, nTMS localized M1 accurately in all adult patients [31].

The nTMS motor cortical representation maps of hand and arm compare well with the results of ECS in patients with epilepsy surgery (Fig. 6.2). In 13 patients with both nTMS and DCS data from the same upper limb muscles, the distance between the average sites of the two maps was 11 ± 4 mm for hand and 16 ± 7 mm (mean ± standard deviation) for arm muscles [32]. These numbers match well with similar comparisons in patients with brain tumors [29, 48]; the reported match between nTMS and DCS (mean distance 7.8 ± 1.2 mm [29] and 3.4 ± 3.0 mm [48] for thenar muscles) corresponds to the match of nTMS and ECS. The slightly higher differences observed in epilepsy patients probably derive from the fact that in ECS the stimulating electrodes have fixed 10-mm distances, whereas in DCS the monophasic or biphasic probe can be moved freely.

nTMS may also reveal epilepsy-induced functional plasticity of cortical motor organization [49]. In one patient nTMS activated the premotor cortex rather than the expected precentral gyrus; the result was in line with the MEG and fMRI localizations of the motor cortex. During the operation, ECS localized finger motor functions into the precentral gyrus. The premotor area containing an FCD was removed,

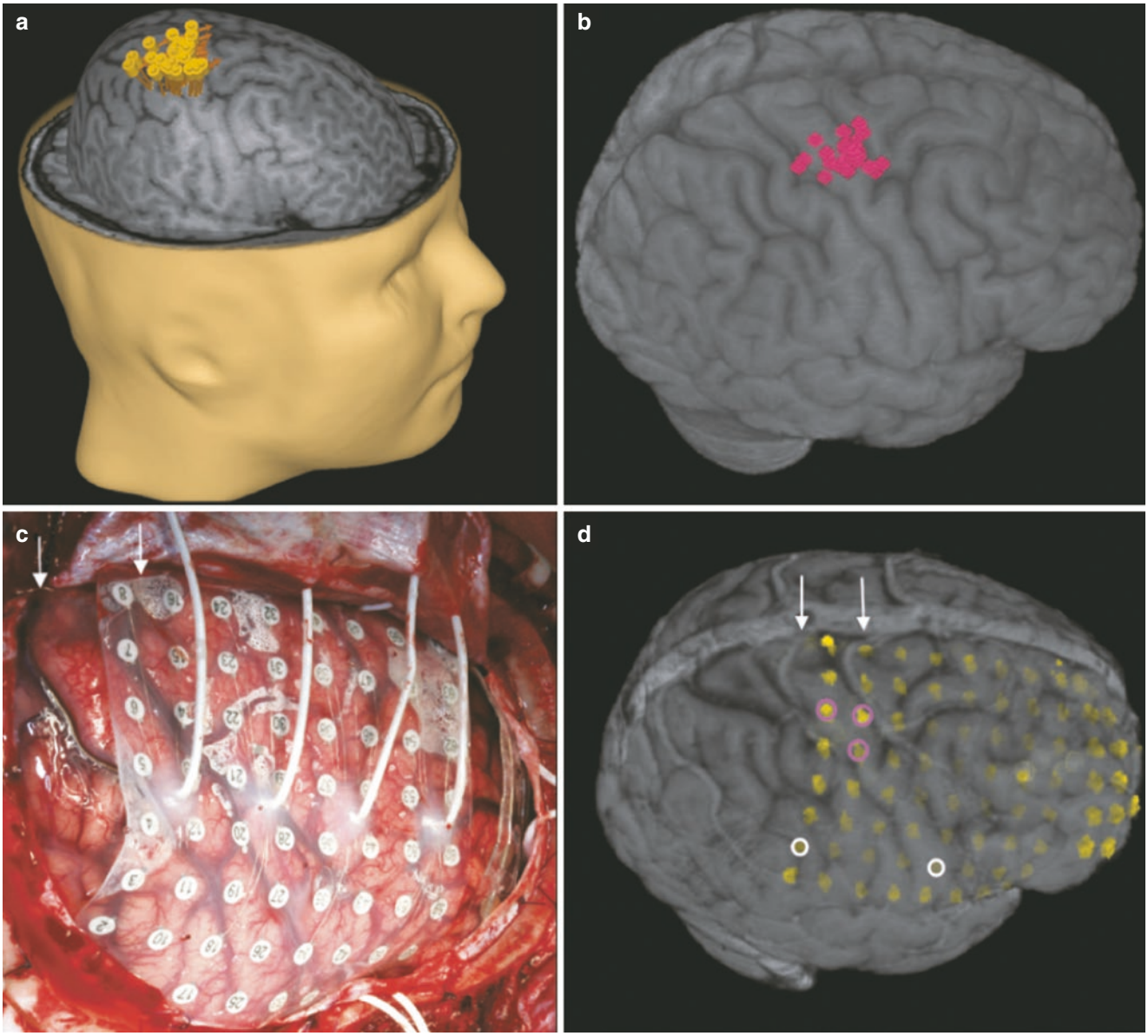

Fig. 6.2 Example from one patient from Vitikainen et al. [32]. (**a**) The nTMS map of the upper arm muscle group from one patient. The estimated TMS-induced electric field maxima at each stimulation point are visualized as small spheres on the brain surface; the orientation and tilt of the stimulation coil are visualized as a stick, and the direction of the induced field is shown as a small arrow on top of each stick (eXimia NBS software, Nexstim Ltd., Helsinki, Finland). (**b**) The same result shown on a 3-D brain volume rendering. The individual response locations are projected to the MR brain surface segmentation. (**c**) A photograph of the intracranial electrode grid before skull closure. Note the cortical veins indicated with arrows. (**d**) The electrode grid (*yellow*) co-registered on the gadolinium-enhanced preoperative MRI brain segmentation; the cortical veins that correspond to those depicted in (**c**) are clearly visualized. The electrodes eliciting motor responses of the stimulations from the upper arm area are marked with *pink circles* and the reference electrodes with *white circles*. The error of a few millimeters in the placement of the electrodes between (**c, d**) can be noticed. (Adapted from Vitikainen et al. [32] with permission of Springer)

and the precentral gyrus was left intact. The patient had no new neurologic or cognitive postoperative impairments. Postoperatively, nTMS mapping was feasible with much lower intensity than preoperatively, and the motor representation was found posterior to the localization seen in the preoperative mapping. A similar change was observed in the postoperative motor mapping by fMRI and MEG. It was proposed that the preoperative absence of nTMS-elicited MEPs from the precentral gyrus resulted from the surrounding inhibition created by the frequently discharging epileptic focus. In another patient in epilepsy surgery work-up, nTMS indicated abnormal ipsilateral hand motor cortex localization and confirmed the functionality of aberrant motor cortical representations of the left foot in the heavily lesioned hemisphere; this was also indicated by fMRI and DTI. Similar findings were also presented in another study, suggesting that pathologic excitability caused by FCD can be located by nTMS with high spatial precision [50].

6.2.2 Speech Cortical Mapping

nTMS enables an extensive mapping of speech areas. Such a large area cannot be studied during awake craniotomy because of time constraints and the limited area of exposed cortex. nTMS speech mapping also helps in designing the craniotomy [51] and may speed up the speech mapping by DCS during surgery.

The methodology for nTMS mapping of speech-related cortical areas was developed in 2012 [38]. This nTMS methodology was validated in brain tumor patients when comparing the results between nTMS and DCS [39, 40] during awake craniotomy. The results have revealed a high sensitivity (90%) [39, 40] but occasionally a low specificity in one study [39]. nTMS may thus depict false-positive cortical sites in comparison to DCS [39, 40]. Nevertheless, nTMS did not produce false-negative activations. This aids in designing the DCS during awake craniotomy and speeds up the intraoperative procedure by limiting the number of sites to be tested by DCS. It is also advantageous that the neurosurgeon and the neuropsychologist have seen the speech performance of the patient before awake craniotomy. Moreover, patients are better prepared for speech tests during the awake craniotomy. Still, the method needs improvement for increasing its specificity.

Babajani-Feremi et al. [52] compared the localization of the language cortex using ECS with subdural grid electrodes, high gamma electrocorticography (hgEcoG), fMRI, and nTMS in patients with epilepsy. All these methods can identify language-related cortical areas. The average sensitivity/specificity of hgEcoG, fMRI, and TMS was 100%/85%, 50%/80%, and 67%/66%, respectively. In comparison to ECS, however, nTMS again indicated a very small amount of false-negative sites; the negative predictive value was 95%. The nTMS results in this study have been somewhat different from the studies performed on brain tumors, mainly because of the differences between ECS and DCS and also the methods used to estimate the sensitivity/specificity [40]. We have studied 20 patients with speech nTMS mapping during epilepsy surgery planning, and our experience suggests similar sensitivity and a small percentage of false-negative sites (Lehtinen et al. submitted). All these studies are in concordance in showing the limitation of nTMS in producing false-positive activations but highlighting its clinical importance for the design of awake craniotomy in producing very few false-negative cortical speech sites.

6.3 Safety

The nTMS mapping protocols for motor and speech functions that have been used in patients with intractable epilepsy did not elicit serious side effects [30–32, 52, 56]. Moreover, EEG recordings during nTMS in 70 patients with Unverricht-Lundborg epilepsy did not reveal nTMS-related epileptiform phenomena [53]. Two recent studies [54, 55] on a large amount of data from brain tumor patients and healthy volunteers are in line with the above-mentioned studies, supporting the notion [42] that as long as the parameters follow the established safety guidelines, nTMS for both motor and language mapping is a safe method without adverse effects. The stimulation parameters need to stay within the established guidelines for safe application of single pulse and repetitive nTMS [54, 55].

Conclusions

The usefulness of nTMS in localizing the cortical motor and language representations in presurgical planning for patients with intractable epilepsy is apparent because of its spatial resolution, accuracy, and reliability. nTMS motor mapping shows excellent accuracy in comparison with ECS, and it could be included in the neurosurgical routine for epilepsy surgery planning. Evidence of nTMS precision in comparison with DCS from tumor patients also supports this notion. However, efficient mapping for epilepsy patients by nTMS may be affected by the plasticity that is produced by the pathophysiology of the epileptogenic area [49, 50]. This plasticity should be taken into consideration in preoperative planning of epilepsy surgeries. Potentially, nTMS can replace ECS under special circumstances as shown by Vitikainen et al. [30], but it should generally be used in combination with ECS or DCS. nTMS language mapping is a new and highly promising clinical tool. It is the only noninvasive method that can simulate the ECS procedure. It can give complementary information, and when combined with other neuroimaging methods it can overcome the limitations of ECS [52]. However, its low specificity should always be taken into consideration. The development of the experimental protocol [42] toward increasing the specificity and maintaining the high negative prediction value of nTMS speech mapping is highly desirable.

References

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1:1106–7.
2. Ilmoniemi RJ, Ruohonen J, Karhu J. Transcranial magnetic stimulation: a new tool for functional imaging of the brain. J Crit Rev Biomed Eng. 1999;27:241–84.
3. Matthews PB. The effect of firing on the excitability of a model motoneurone and its implications for cortical stimulation. J Physiol. 1999;518:867–82.
4. Gil-Robles S, Duffau H. Surgical management of World Health Organization grade II gliomas in eloquent areas: the necessity of preserving a margin around functional structures. Neurosurg Focus. 2010;28:E8.

5. Pouratian N, Bookheimer SY. The reliability of neuroanatomy as a predictor of eloquence: a review. Neurosurg Focus. 2010;28:E3.
6. Kombos T, Süss O. Neurophysiological basis of direct cortical stimulation and applied neuroanatomy of the motor cortex: a review. Neurosurg Focus. 2009;27:E3.
7. Lesser RP, Lüders H, Klem G, Dinner DS, Morris HH, Hahn JF, Wyllie EJ. Extraoperative cortical functional localization in patients with epilepsy. Clin Neurophysiol. 1987;4:27–53.
8. Hamer HM, Morris HH, Mascha EJ, Karafa MT, Bingaman WE, Bej MD, et al. Complications of invasive video-EEG monitoring with subdural grid electrodes. Neurology. 2002;58:97–103.
9. Papanicolaou AC, Rezaie R, Narayana S, Choudhri AF, Wheless JW, Castillo EM, et al. Is it time to replace the Wada test and put awake craniotomy to sleep? Epilepsia. 2014;55:629–32.
10. Blume WT, Jones DC, Pathak P. Properties of after-discharges from cortical electrical stimulation in focal epilepsies. Clin Neurophysiol. 2004;115:982–9.
11. Tharin S, Golby A. Functional brain mapping and its applications to neurosurgery. Neurosurgery. 2007;60:185–201; discussion 201–2
12. Corina DP, Loudermilk BC, Detwiler L, Martin RF, Brinkley JF, Ojemann G. Analysis of naming errors during cortical stimulation mapping: implications for models of language representation. Brain Lang. 2010;115:101–12.
13. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med. 2008;358:18–27.
14. Duffau H. Awake surgery for nonlanguage mapping. Neurosurgery. 2010;66:523–8; discussion 528–9
15. Wada J, Rasmussen TJ. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. 1960. Neurosurg. 2007;106:1117–33.
16. Baxendale S. The Wada test. Curr Opin Neurol. 2009;22:185–9.
17. Majchrzak K, Bobek-Billewicz B, Tymowski M, Adamczyk P, Majchrzak H, Ladziński P. Surgical treatment of insular tumours with tractography, functional magnetic resonance imaging, transcranial electrical stimulation and direct subcortical stimulation support. Neurol Neurochir Pol. 2011;45:351–62.
18. Mäkelä JP, Forss N, Jääskeläinen J, Kirveskari E, Korvenoja A, Paetau R. Magnetoencephalography in neurosurgery. Neurosurgery. 2006;59:493–510; discussion 510–11
19. Rutten GJ, Ramsey NF. The role of functional magnetic resonance imaging in brain surgery. Neurosurg Focus. 2010;28:E4.
20. Willems PW, van der Sprenkel JW, Tulleken CA, Viergever MA, Taphoorn MJ. Neuronavigation and surgery of intracerebral tumours. J Neurol. 2006;253:1123–36.
21. Petrovich Brennan NM, Whalen S, de Morales Branco D, O'Shea JP, Norton IH, Golby AJ. Object naming is a more sensitive measure of speech localization than number counting: converging evidence from direct cortical stimulation and fMRI. NeuroImage. 2007;37:S100–8.
22. Friederici AD. Pathways to language: fiber tracts in the human brain. Trends Cogn Sci. 2009;13:175–81.
23. Weiller C, Bormann T, Saur D, Musso M, Rijntjes M. How the ventral pathway got lost: and what its recovery might mean. Brain Lang. 2011;118:29–39.
24. Inoue T, Shimizu H, Nakasato N, Kumabe T, Yoshimoto T. Accuracy and limitation of functional magnetic resonance imaging for identification of the central sulcus: comparison with magnetoencephalography in patients with brain tumors. NeuroImage. 1999;10:738–48.
25. Korvenoja A, Kirveskari E, Aronen HJ, Avikainen S, Brander A, Huttunen J, et al. Sensorimotor cortex localization: comparison of magnetoencephalography, functional MR imaging, and intraoperative cortical mapping. Radiology. 2006;241:213–22.
26. Kamada K, Takeuchi F, Kuriki S, Todo T, Morita A, Sawamura Y. Dissociated expressive and receptive language functions on magnetoencephalography, functional magnetic resonance imaging, and amobarbital studies. Case report and review of the literature. J Neurosurg. 2006;104:598–607.
27. Shiraishi H. Source localization in magnetoencephalography to identify epileptogenic foci. Brain and Development. 2011;33:276–81.
28. Forster MT, Hattingen E, Senft C, Gasser T, Seifert V, Szelényi A. Navigated transcranial magnetic stimulation and functional magnetic resonance imaging: advanced adjuncts in preoperative planning for central region tumors. Neurosurgery. 2011;68:1317–24; discussion 1324–5
29. Picht T, Schmidt S, Brandt S, Frey D, Hannula H, Neuvonen T, et al. Preoperative functional mapping for rolandic brain tumor surgery: comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. Neurosurgery. 2011;69:581–8; discussion, 588
30. Vitikainen AM, Lioumis P, Paetau R, Salli E, Komssi S, Metsähonkala L, et al. Combined use of non-invasive techniques for improved functional localization for a selected group of epilepsy surgery candidates. NeuroImage. 2009;45:342–8.
31. Säisänen L, Könönen M, Julkunen P, Määttä S, Vanninen R, Immonen A, et al. Non-invasive preoperative localization of primary motor cortex in epilepsy surgery by navigated transcranial magnetic stimulation. Epilepsy Res. 2010;92:134–44.
32. Vitikainen AM, Salli E, Lioumis P, Mäkelä JP, Metsähonkala L. Applicability of nTMS in locating the motor cortical representation areas in patients with epilepsy. Acta Neurochir. 2013;155:507–18.
33. Krings T, Buchbinder BR, Butler WE, Chiappa KH, Jiang HJ, Rosen BR, Cosgrove GR. Stereotactic transcranial magnetic stimulation: correlation with direct electrical cortical stimulation. Neurosurgery. 1997;41:1319–25; discussion, 1325–6
34. Krieg SM, Shiban E, Buchmann N, Gempt J, Foerschler A, Meyer B, et al. Utility of presurgical navigated transcranial magnetic brain stimulation for the resection of tumors in eloquent motor areas. Neurosurg. 2012;116:994–1001.
35. Picht T, Schulz J, Hanna M, Schmidt S, Suess O, Vajkoczy P. Assessment of the influence of navigated transcranial magnetic stimulation on surgical planning for tumors in or near the motor cortex. Neurosurgery. 2012;70:1248–56; discussion, 1256–7
36. Pascual-Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid-rate transcranial magnetic stimulation. Neurology. 1991;41:697–702.
37. Devlin JT, Watkins KE. Stimulating language: insights from TMS. Brain. 2007;130:610–22.
38. Lioumis P, Zhdanov A, Mäkelä N, Lehtinen H, Wilenius J, Neuvonen T, et al. A novel approach for documenting naming errors induced by navigated transcranial magnetic stimulation. J Neurosci Methods. 2012;204:349–54.
39. Picht T, Krieg SM, Sollmann N, Rösler J, Niraula B, Neuvonen T, et al. A comparison of language mapping by preoperative navigated transcranial magnetic stimulation and direct cortical stimulation during awake surgery. Neurosurgery. 2013;72:808–19.
40. Tarapore PE, Findlay AM, Honma SM, Mizuiri D, Houde JF, Berger MS, et al. Language mapping with navigated repetitive TMS: proof of technique and validation. NeuroImage. 2013;82:260–72.
41. Ille S, Sollmann N, Hauck T, Maurer S, Tanigawa N, Obermueller T, et al. Combined noninvasive language mapping by navigated transcranial magnetic stimulation and functional MRI and its comparison with direct cortical stimulation. J Neurosurg. 2015;123:212–25.
42. Krieg S, Lioumis P, Makelä JP, Wilenius J, Karhu J, Hannula H, et al. Current protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. Clin Neurophysiol. 2017;159:1187–95.
43. Ruohonen J, Karhu J. Navigated transcranial magnetic stimulation. Neurophysiol Clin. 2010;40:7–17.
44. Mäkelä T, Vitikainen AM, Laakso A, Mäkelä JP. Integrating nTMS data into a radiology picture archiving system. J Digit Imaging. 2015;28:428–32.

45. Brodeur MB, Dionne-Dostie E, Montreuil T, Lepage M. The Bank of Standardized Stimuli (BOSS), a new set of 480 normative photos of objects to be used as visual stimuli in cognitive research. PLoS One. 2010;5:e10773.
46. Vitikainen AM, Mäkelä E, Lioumis P, Jousmäki V, Mäkelä JP. Accelerometer-based automatic voice onset detection in speech mapping with navigated repetitive transcranial magnetic stimulation. J Neurosci Methods. 2015;253:70–7.
47. Vitikainen AM. Navigated transcranial magnetic stimulation in preoperative functional mapping in patients with epilepsy, University of Helsinki. University of Helsinki, report series in physics, HU-P-D235 (doctoral dissertation). In: Available from; 2016. https://helda.helsinki.fi/handle/10138/160259.
48. Picht T, Mularski S, Kuehn B, Vajkoczy P, Kombos T, Suess O. Navigated transcranial magnetic stimulation for preoperative functional diagnostics in brain tumor surgery. Neurosurgery. 2009;65:93–8; discussion 98–9
49. Mäkelä JP, Vitikainen AM, Lioumis P, Paetau R, Ahtola E, Kuusela L, et al. Functional plasticity of the motor cortical structures demonstrated by navigated TMS in two patients with epilepsy. Brain Stimul. 2013;6:286–91.
50. Schmidt S, Holst E, Irlbacher K, Oltmanns F, Merschhemke M, Brandt SA. A case of pathological excitability located with navigated-TMS: presurgical evaluation of focal neocortical epilepsy. Restor Neurol Neurosci. 2010;28:379–85.
51. Picht T. Current and potential utility of transcranial magnetic stimulation in the diagnostics before brain tumor surgery. CNS Oncol. 2014;3:299–310.
52. Babajani-Feremi A, Narayana S, Rezaie R, Choudhri AF, Fulton SP, Boop FA, et al. Language mapping using high gamma electrocorticography, fMRI, and TMS versus electrocortical stimulation. Clin Neurophysiol. 2016;127:1822–36.
53. Danner N, Julkunen P, Hypponen J, Niskanen E, Saisanen L, Kononen M, et al. Alterations of motor cortical excitability and anatomy in Unverricht-Lundborg disease. Mov Disord. 2013;28:1860–7.
54. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120:2008–39.
55. Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 2015;8:76–87.
56. Henri Lehtinen, Jyrki P. Mäkelä, Teemu Mäkelä, Pantelis Lioumis, Liisa Metsähonkala, Laura Hokkanen, Juha Wilenius, Eija Gaily, (2018) Language mapping with navigated transcranial magnetic stimulation in pediatric and adult patients undergoing epilepsy surgery: Comparison with extraoperative direct cortical stimulation. Epilepsia Open 3(2):224–35.

Neuropsychological Evaluation of Patients with Intrinsic Brain Tumors

7

Cristina Ramirez-Aubone and Gregory P. Lee

This chapter begins with a discussion of the primary purposes of neuropsychological assessment in patients with intrinsic brain tumors and is followed by an overview of the most important tumor characteristics as well as patient status factors that need to be considered when using neuropsychological tests to assess these patients. The cognitive domains that comprise a comprehensive battery of neuropsychological tests are reviewed, along with some representative tests from each domain. In addition, personality testing, assessment of mood, and measures of health-related quality of life designed specifically for patients with brain cancer are briefly covered. Next, a short, standardized battery of neuropsychological tests that have been used internationally in multisite brain cancer clinical trials is described. The chapter concludes with a summary of the salient results of neuropsychological assessments before and after treatment with resective surgery, cranial irradiation, and chemotherapy and the primary cognitive deficits associated with each of these treatment modalities. Finally, there is a brief discussion weighing the clinical decision making trade-offs using health utility measures when there are conflicts between the quantity (survival) and quality (cognition and quality of life).

7.1 Introduction

The neuropsychological assessment of patients with brain tumors has become more common in recent years because it has been more widely appreciated that cognitive impairments can have significant impacts on medical treatment compliance, self-care, and vocational, educational, and social functioning. Consequently, cognition can directly affect the overall quality of life of patients living with brain cancer [1]. Since many intrinsic brain tumors cannot be cured, palliation of symptoms and maintenance or improvement in quality of life are important goals of treatment. Because improvements in treatment in recent years have extended life expectancy considerably, evaluation of treatment outcome needs to be expanded beyond the traditional measures of time to progression of disease and survival. Neuropsychological evaluation is a useful method to measure the direct effects of tumor progression and treatment and is an important estimate of outcome, since even mild cognitive deficits can negatively impact the quality of life [2]. Up to 75% of cancer patients will experience cognitive impairment during or after treatment of their cancer, and in many cases this will persist for years [3, 4].

Many different factors may contribute to the cognitive dysfunction seen in patients with brain tumors, including the direct effects of the tumor on the brain, effects of treatment (i.e., radiotherapy or chemotherapy), adjunctive medical treatment (e.g., steroids, antiepileptic drugs), and patient status factors (e.g., premorbid cognitive capacity, psychological distress, symptomatic epilepsy, tumor grade, size and rate of growth, and tumor lateralization and localization). Most if not all of these factors need to be considered in the individual case when attempting to interpret cognitive test results in patients with brain cancer. When interpreted correctly, neuropsychological testing can identify and diagnose specific neurobehavioral disorders and provide guidance for rehabilitative or psychological intervention. Testing can also serve as an early indicator of disease recurrence and progression, even before signs of disease are apparent on CT or MRI, and this information may be used to help guide clinical decision-making [5–8].

C. Ramirez-Aubone
Department of Neurology, Medical College of Georgia, Augusta, GA, USA

G. P. Lee (✉)
Department of Neuropsychology, Barrow Neurological Institute, Phoenix, AZ, USA
e-mail: GLEE@augusta.edu

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7.2 Purposes of Neuropsychological Assessment in Patients with Brain Tumors

Neuropsychology combines the knowledge base of established brain-behavior relationships with standardized psychometric measures (tests) to assess and diagnose disturbances of mentation and behavior and relates these findings to their neurologic implications and to issues of clinical treatment and prognosis. Standardized measures that assess a broad range of established cognitive domains (such as attention or memory) are compared with normative performance levels of healthy individuals, and negative deviation from these normal population levels may suggest impairment in a given cognitive domain. Focal or multifocal disease in various regions of the brain may result in characteristic patterns of deficit. These patterns are used to generate descriptions of cognitive, psychological-emotional, and functional competence.

7.2.1 Clinical Characterization of Deficits

In patients with brain tumors, one of the primary uses of neuropsychological assessment is to provide a quantitative characterization of the patient's cognitive and behavioral impairments to assist in treatment planning and provide guidance for rehabilitation efforts [9]. The cognitive impairments caused by the direct effects of tumors or to circumscribed resective surgery may be restricted to a single cognitive domain (such as new verbal learning), where the most important determinant of such deficit patterns is the location of the tumor (e.g., in the language dominant [usually left] temporal lobe in the case of new verbal learning). For example, orbitofrontal lobe tumors may result in alterations of emotional control and changes in personality, while dorsolateral prefrontal locations will often cause executive cognitive dysfunction (e.g., poor organization and planning, difficulty switching mental sets). Formal testing can provide clinical characterization and monitoring of cognitive and behavioral disorders that may affect patients' abilities to maintain their occupational, academic, family, or social roles.

7.2.2 Identification of Tumor Recurrence or Disease Progression

Neuropsychological assessment can detect signs of tumor recurrence and disease progression even before signs of disease are present on neuroimaging. Detailed testing of cognitive functioning of patients with high-grade gliomas is more sensitive in gauging the extent of damage to the brain resulting from tumor infiltration than is the structural information provided by CT or MRI [10]. Tests of memory and attentional set-shifting have been shown to predict tumor recurrence in patients with glioblastoma multiforme [8]. Hence, a second purpose of testing is to measure change. Repeat assessments can be valuable in charting progress (e.g., recovery after surgery or radiotherapy) as well as for detecting any decline in cognitive capacity (e.g., from tumor regrowth). Thus, in addition to the clinical value provided by cognitive testing from delineation of the pattern of cognitive and behavioral deficits, neuropsychological assessment also has prognostic value and may serve as an early indicator of disease progression.

7.2.3 Diagnosis of Psychological-Emotional Disorders

In confusing or complex cases, neuropsychological assessment can be useful for teasing out the relative contributions of neurologic conditions (e.g., cellular degeneration, neurochemical disruption), emotional states (e.g., anxiety, depression), and psychiatric illnesses (e.g., personality disorder, psychoses). Abnormal psychological states may be caused by the direct effects of the tumor, secondary effects of treatment (including medications), adjustment reactions to the illness and subsequent alterations in life circumstances, or by some combination of these factors. For example, frontal lobe tumors often cause alterations in personality, emotional control, and comportment. A comprehensive neuropsychological examination will include assessment of mood and personality as well as other aspects of emotional functioning when indicated. This is to ensure that patients' psychological problems are properly identified and addressed through appropriate targeted treatments. Furthermore, the potential contributions of emotional factors in producing spurious abnormal cognitive test results must be considered in test interpretation.

7.2.4 Determining Competency Issues

Cognitive and emotional status both play a role in determining a patient's overall competency. Questions typically involve a patient's ability to exercise rational judgment, make competent decisions, and live in an independent fashion. In addition to cognitive status, assessment of the patients' awareness of their limitations is also important in establishing their ability for independent functioning. Although there is some overlap between neuropsychological test results and inferences about decision-making capacity in cancer patients, additional information must be obtained to make informed

clinical judgments about mental competence. Specific assessment methods that help determine decision-making capacity include formal tests (e.g., MacArthur Competence Assessment Tool for Clinical Research [MCAT-CR]) [11], structured interviews (e.g., Independent Living Scales) [12], or a simple standard clinical interview covering the necessary areas. Complicating this issue is the fact that decision-making capacity is not an all or none phenomenon. As noted by Rodin and Mohile [13], there are gradations of capacity that may not remain stable over time. In many countries, determination of degree of competency has legal consequences, and valid, reliable measures should be used to make such judgments. Most cancer patients will be asked to make crucial life-altering decisions at some point during the course of treatment, and neuropsychology can assist in determining their capacity to make such decisions.

7.2.5 Assist in Formulation of Rehabilitation Strategies and Research

Most patients treated for primary brain tumors will experience some form of cognitive impairment or emotional disturbance, and many of these problems will be present for years to come. Rehabilitation therapies are typically tailored to the specific pattern of deficits for each individual, and a comprehensive neuropsychological assessment may be used to assist with planning targeted rehabilitation interventions.

7.3 Factors Complicating Interpretation of Neuropsychological Results

Cognitive dysfunction is a common complaint among cancer survivors. This is most often caused by the tumor itself or by the effect of cancer-related treatments such as chemotherapy, endocrine treatment, or radiation. Cognitive difficulties seem to be heightened in survivors with primary central nervous system cancers or in those with brain metastases. It has been reported that even survivors who never had primary brain involvement may display cognitive changes [14]. Although there is limited evidence about the mechanisms involved in increasing the risk for chemotherapy-induced cognitive complaints, studies have reported elevated levels of cytokines or DNA damage as possible causes [15]. Additional studies have suggested that neurocognitive impairments from chemotherapy agents are associated with neurotoxicity [16]. Furthermore, emotional distress, fatigue, and psychosomatic effects can influence cognition as well, and patient expectations may also affect test results. For instance, it has been shown that those treated with chemotherapy who were informed in advance of possible cognitive changes were more likely to complain of cognitive difficulties and to produce lower scores on neuropsychological testing than those who were uninformed [17].

7.3.1 Timing of Testing and Location of Tumor

In some cases cognitive impairment is not evident immediately after therapeutic intervention, and as a result assessments in the acute stages are not always informative. However, it has been suggested that children diagnosed with brain tumors may exhibit cognitive changes prior to tumor resection or chemotherapy. Children with cerebellar tumors who underwent neuropsychological testing 3–4 days prior to surgery performed worse on verbal memory testing than healthy controls [18]. When comparing children with brain tumors to those with non–central nervous system cancer before therapeutic intervention, performances in the areas of verbal learning, attention, and working memory were commonly impaired in children with brain tumors. In addition, such children have demonstrated impaired performances (<1 SD) on at least four different cognitive tests compared to those without central nervous system involvement [19]. It appears that performances of those with primary tumors may be affected by compromised brain connectivity, whereas in children without central nervous system involvement cancer-induced mechanisms, such as aberrant immunologic processes, are more likely responsible for reduced cognitive performance [20].

Another concern involved in the neuropsychological assessment of patients with brain tumors is whether damage to brain regions is focal or multifocal. The location of the tumor(s) is the most important factor determining the type of cognitive deficit obtained, while tumor dimension seems to exert a smaller effect [21]. When assessing long-term brain structure and cognitive outcome following cerebellar tumor resections in children, reduced cognitive function, increased gray matter density, and white matter microstructural abnormalities were observed and thought to be related to hydrocephalus [22]. In addition, cerebellar tumors may particularly affect the patient's attention capacity because of their proximity to the ascending reticular activating system, which regulates attention and arousal.

Supratentorial hemispheric tumors appear to be related to lower intelligence quotients (IQs) in children tested before surgery. In addition, factors such as epilepsy and symptom duration are the main issues affecting cognition at the time of diagnosis, whereas age, gender, and neurologic findings seem to be less prominent. Children with supratentorial midline neoplasms have demonstrated deficient memory abilities probably caused by disruption of diencephalic structures

and connections. Linguistic abilities and cortical left-sided tumors have been correlated. Visual-motor integration and planning capabilities have been associated with cortical right-sided tumors [23].

7.3.2 Effects of Treatment Interventions, Comorbidities, and Medications

Neuropsychological deficits may be secondary to a variety of factors, including the focal destructive effects of the tumor, secondary mass effects, acute or late neurotoxic effects of chemotherapy or radiation treatment (type and dosage), or the effects of resective neurosurgery. In addition, some of the medications typically prescribed for patients with primary brain tumors, such as glucocorticosteroids, anticonvulsants, and psychoactive medications, can negatively affect cognition [24]. High-grade glioma patients prescribed corticosteroids have been found to have worse baseline cognition [25]. Radiation-induced cognitive deficits have been found in up to 50% of long-term brain tumor survivors [26]. In addition, those treated with stereotactic radiosurgery and whole-brain radiation therapy experience more severe learning and memory impairments compared to patients with stereotaxic radiosurgery alone [27].

Neuropsychological tests are sensitive to the neurotoxic effects of treatment as well as to the resection of eloquent brain regions. It is estimated that up to half of those who receive cranial irradiation with a longer than 6-month survival rate will experience some type of cognitive impairment [28]. In brain metastases trials, a 4-month post-irradiation neuropsychological assessment was found to assist in establishing the early effects of radiation therapy because the deterioration at this point was reproducible [29]. Some of the cognitive deficits seen in children with acute lymphoblastic leukemia (ALL) treated with cranial irradiation and chemotherapy may only be detected by using specific sensitive neuropsychological tests. For example, in one recent childhood ALL study, 50% of children with white matter abnormalities showed deficits on a test of visual-motor integration [30, 31]. Furthermore, intracerebral calcifications were correlated with the number of intrathecal methotrexate doses and with low performance IQ and significant impairment in attention and visual-spatial-construction. Girls were more vulnerable to the effects of CNS prophylaxis than boys [31]. Thus, neuropsychological assessment can identify specific areas of cognitive dysfunction in brain tumor patients treated with radiation, chemotherapy, or neurosurgical resective treatment.

7.4 Demographic Background and Normative Considerations

Neuropsychological assessment consists of a variety of behavioral measures and tests that are administered in a standardized, controlled fashion, and the results are used to infer a patient's underlying ability and current functioning across a number of broad cognitive domains. The major cognitive domains typically assessed include attention, memory, intelligence, language, visual-perceptual and visual-spatial thinking, psychosensory and motor abilities, personality-emotional functions, and, when indicated, health-related quality of life.

Patient performance on cognitive and psychological-emotional tests are compared with normative performance levels of the general population. Significant negative deviation from these normal population levels may suggest impairment in a given cognitive domain. Major tests have norms that are usually stratified by important moderating demographic variables such as age, gender, education, ethnicity/race, and socioeconomic status. In general, normative comparisons should be made with subgroups that most closely approximate a patient's particular demographic group. Almost all tests provide age-based normative scores, but the availability of norms based on education, ethnicity, race, and culture are less common. Nevertheless, normative comparisons should take these important demographic variables into account whenever possible.

7.4.1 Medical History Considerations

Primary tumors affecting various regions of the brain may result in characteristic patterns of deficit. The pattern of neuropsychological impairment depends upon a number of factors, including the tumor type, size, rate of growth, degree of infiltration, and the specific brain region affected. There are four primary biological mechanisms through which brain tumors can affect brain functions. Brain tumors may cause: (1) increased intracranial pressure that results in generalized symptoms such as headache, nausea and vomiting, and reduced attention capacity; (2) invasion or displacement of brain tissue focally, which in turn may cause isolated sensorimotor or focal cognitive deficits; (3) induction of seizures, usually localization-related complex partial epilepsy; or (4) secretion of hormones or alteration of endocrine patterns, which in turn may affect many different bodily, including brain, functions [32].

After headaches, neurobehavioral changes are the most common presenting symptoms of primary brain tumors [33]. Rapidly growing tumors such as glioblastoma multiforme often cause acute increased intracranial pressure, which will result in widespread neurobehavioral and neurologic effects. In contrast, slow growing, lower grade tumors may produce few or no obvious neurobehavioral or neurologic effects by enabling brain structures to accommodate to surrounding shifting tissue or even reorganize their behavioral functions [34].

From a neurobehavioral perspective, tumors may present in a way similar to other localized lesions and result in behavioral changes in the same way that other discrete brain lesions do. Thus, temporal lobe lesions often result in mem-

ory impairments or psychiatric symptoms. If the tumor invades the temporal lobe language zones, patients typically show deficits in understanding spoken or written language or in their ability to name objects. Frontal lobe tumors affecting the dorsolateral prefrontal regions may cause executive dysfunction with impairments in cognitive flexibility, planning, organization, and generativity as examples. Dominant frontal lobe lesions affecting Broca's area may present conspicuous problems with speech output and fluency. Orbitofrontal tumors, often meningiomas or craniopharyngiomas, can cause disorders of restraint, such as disinhibition of emotional expressiveness or difficulties in the inhibition of socially inappropriate behaviors. Lesions affecting the mesial frontal areas result in apathy, lack of drive, initiative, and motivation and an absence of spontaneity. Brain tumors often disrupt the dopaminergic pathways from the brainstem to the frontal lobe (mesocortical system) or from the brainstem to the limbic regions (mesolimbic pathways) and result in deficits in mental processing speed and attention/concentration and working memory.

Localized tumors in the diencephalon have characteristic neurobehavioral consequences. Tumors that affect the midline limbic structures, such as the dorsomedial nucleus of the thalamus, fornix, and mammillary bodies can result in an anterograde amnesia that may be differentiated from hippocampal memory disorders by neuropsychological testing. Tumors originating in the hypothalamus typically result in disruption of some hypothalamic functions, such as temperature dysregulation, hyperphagia or anorexia, endocrine abnormalities, or hypersomnolence. Thalamic tumors can produce attentional deficits, mental dullness, and memory loss [35].

In addition to the possibility of producing cognitive deficits, brain tumors may also cause behavioral changes, mood disorders, or problems in adaptive behavior. It can be difficult to determine if these psychiatric issues are related to the primary organic effects of the tumor itself (presumably from disruption of corticolimbic interconnections) or to secondary reactive adjustments to the cancer diagnosis and its life-altering consequences. Depression and anxiety reactions are particularly common in tumor patients after diagnosis and treatment. Regardless of the etiology of psychological problems, neuropsychological assessment can identify patients who need psychiatric pharmacotherapy, psychotherapy, or counseling.

7.5 Neuropsychological Assessment

When assessing brain tumor patients, the administration of a comprehensive battery of tests remains standard practice for neuropsychologists. Because the neurocognitive dysfunction caused by tumors and treatments is unpredictable, it is reasonable to establish a testing battery that samples an extensive range of cognitive abilities. Moreover, the severity of cognitive impairments found may be influenced by the rate of tumor growth. Slow tumor growth allows for compensatory plasticity of cognitive functions, which may be associated with only mild or even no deficits. A neuropsychological evaluation should (1) assess several domains found to be most sensitive to tumor and treatment effects, (2) use standardized materials and administration procedures, (3) have published normative data, (4) have moderate to high test-retest reliability, and (5) have alternate forms or be relatively insensitive to practice effects and therefore suitable to monitor changes in neurocognitive function over time. Tests that have been translated into several languages or only primarily require translation of test directions are also useful [5].

The cognitive domains that should be included are general verbal and nonverbal intellectual functions, language, attention, orientation, verbal and nonverbal learning and memory, visual-spatial skills, frontal-executive functions, psychosensory and motor abilities, mood, and health-related quality of life.

7.5.1 General Intellectual Functions

A valuable testing battery will assist in determining an individual's verbal and nonverbal general cognitive abilities through the use of intellectual functioning tests (e.g.,, Wechsler Adult Intelligence Scale, 4th edition [WAIS-IV], Wechsler Intelligence Scale for Children, 5th edition [WISC-V]). Through the use of these composite tests, verbal abilities including verbal concept formation, verbal reasoning skills, and fund of general information can be assessed. Perceptual organization skills include nonverbal reasoning, visuospatial information processing, and visual-motor coordination. The Wechsler scales also include subtests designed to measure attention, concentration, and working memory (digit span and mental arithmetic) and mental processing speed (coding/digit symbol and symbol search).

7.5.2 Language

Language may be affected in cases where the tumor invades eloquent cortical regions that mediate various language functions. The most prominent disorders of verbal functions are the aphasias with associated difficulties in expressive or receptive verbal abilities [36]. Tests that assess language should provide a comprehensive assessment of oral and written language and aural comprehension and reading and may include formal evaluation of spontaneous speech (fluency), naming of objects, auditory comprehension, speech repetition, phonemic associative (letter) fluency, paraphasic errors in speech, and the ability to produce over-learned phrases. A thorough language evaluation often includes testing-associated functions such as oral reading, reading comprehension, written and oral spelling, and speech articulation.

When testing for anomia, the Boston Naming Test requires patients to provide the names of object line drawings. Phonemic (letter) fluency can be measured by asking the examinee to generate words beginning with a specific letter, such as F, A, or S, allowing 1 min for each letter. Semantic fluency assesses the ability to produce words belonging to a specified category (e.g., animals, fruits, or vegetables) in 1 min.

7.5.3 Attention

Neuropsychologists may assess verbal or visual attention. A common measure of auditory attention is the Digit Span subtest from the WAIS-IV and WISC-V. There are many different types of attention, such as sustained attention, selective attention, alternating attention, divided attention, and vigilance, and there are a variety of neuropsychological tasks that may be used to measure these different aspects of attention. Tests of repetition of digits forwards or backwards, sentence repetition, block tapping sequence span, complex mental tracking, mental arithmetic, visual search, cancellation tasks, and continuous performance tasks can all measure different features of attentional capacity.

7.5.4 Orientation

Some commonly used bedside mental status examinations such as the Mini-Mental Status Exam (MMSE) [37] or the Montreal Cognitive Assessment (MoCA) [38] include assessment of orientation to time and place. Orientation requires consistent and reliable integration of attention, perception, and memory and is evaluated by inquiring about the person's knowledge of time, place, and personal information, such as their name, age, and date of birth. Orientation questions are typically part of all mental status examinations and are included in most memory test batteries. It should be noted that mild orientation difficulties may be experienced in individuals with no cognitive impairment, especially in situations such as unemployment, retirement, or when they are hospitalized [39].

7.5.5 Learning and Memory

When examining verbal and nonverbal (visual-spatial) memory, a comprehensive evaluation should include: (1) recall to assess learning and retention of meaningful information (such as stories), which resembles what the examinee has heard in a conversation; (2) rote learning ability across three or more trials, which yields a learning curve and is subsequently tested for both free recall and recognition; (3) visual-spatial memory, which could include copying a complex figure followed by a recognition trial; (4) remote memory, such as fund of information; and (5) personal autobiographical memory [39]. One commonly used memory test battery that contains these necessary memory testing procedures is the Wechsler Memory Scale, 4th edition (WMS-IV), which includes story memory, paired-associates learning, and visual-spatial recall of geometric figures. Some stand-alone measures of visual memory that are not part of a memory test battery include the Rey-Osterrieth Complex Figure Test (ROCFT), and the Brief Visual Memory Test, revised (BVMT-R).

7.5.6 Visual-Spatial-Perceptual Skills

Visual-spatial skills refer to the ability to analyze, discriminate, and synthesize visual stimuli, including visual perception, spatial judgment, and organization of visual materials. Impairments of analysis of visual information can be measured by tests requiring the assembling of objects, drawing, judging the directional orientation of lines, position discrimination, and stimulus orientation [39]. One disorder of visual-spatial processing is hemispatial neglect, which is a deficit in awareness of stimuli contralateral to a lesion [40]. Tests involving line bisection, Judgment of Line Orientation, cancellation, double simultaneous stimulation, and drawing tasks assist in identifying contralateral multimodal neglect in an affected individual. In addition, the Clock Drawing test, Rey-Osterrieth Complex Figure Test, and the RBANS-Figure Copy or the WAIS-IV Block Design subtest may also be useful to assess visual spatial competence.

7.5.7 Executive Functions

Executive cognitive functions are involved in the control and direction of thought and behavior and include such abilities as planning, monitoring, initiating, switching sets, and inhibiting extraneous responses. These cognitive functions are mediated by the prefrontal cortical regions and allow an individual to engage successfully in independent, purposive, self-directed, and self-serving behavior. A standard battery of tests that evaluate these verbal and nonverbal higher cognitive abilities is the Delis-Kaplan Executive Function Scale (D-KEFS). When frontal-executive functions are impaired, both cognition (e.g., planning) and behavior (e.g., impulsivity) may be affected, and completion of activities of self-care, employment, and socialization may not be possible [36]. As a result, a caregiver-rated questionnaire, such as the Frontal Systems Behavioral Scale (FrSBe), may be helpful in capturing both the executive cognitive deficits and personality changes seen with frontal lobe damage and determining

the severity of impairment. The most commonly used executive function test, the Wisconsin Card Sorting Test, assesses higher reasoning skills and requires the patient to form abstract concepts, switch mental sets, and inhibit responses with the use of feedback. Other examples of executive function measures include the Stroop Color Word Test, Trailmaking Test Part B, phonemic fluency, alternating fluency, and the Frontal Assessment Battery [36, 39].

7.5.8 Psychosensory and Motor

Sensorimotor abilities involve receiving and transmitting information to and from the central nervous system. These abilities are usually involved in visually guided behaviors such as hand-eye coordination. Psychosensory disorders include agraphesthesia (inability to recognize symbols drawn on the surface of the skin), astereognosis (inability to recognize an object by touch alone), finger agnosia (inability to identify by touch alone which finger is being stimulated), and right-left disorientation. Disorders of motor functions include apraxia (inability to follow a motor command when this inability is not caused by a primary motor deficit or a language impairment). Ideomotor apraxia can be tested by asking the individual to perform complex pantomimed commands, such as "pretend to comb your hair" [41]. Manual dexterity, fine motor skills, and strength can be assessed by speeded tests of manipulative agility using finger-tapping devices, pegboards, or hand dynamometers [36].

7.5.9 Mood and Personality

Cognitive dysfunction affects physical, psychological, social, and vocational functioning. Many patients with primary brain tumors encounter behavioral, emotional, and intellectual challenges that affect their ability to perform activities of daily living [42]. Personality changes may be attributed to orbital and medial frontal disease or limbic involvement. In addition, mood and anxiety disorders may be primary organic or secondarily reactive. As a result, tests measuring personal adjustment and emotional functioning through the use of questionnaires, such as the Beck series (Beck Depression Inventory, Beck Anxiety Inventory) and objective personality inventories (e.g., Minnesota Multiphasic Personality Inventory) can contribute valuable information to a neuropsychological battery. Objective tests are self-report instruments (such as inventories or scales) in which patients or their informants describe symptoms and emotions by selecting items they claim to be true. Commonly used objective personality tests include the Minnesota Multiphasic Personality Inventory (MMPI-2, MMPI-RF) and the Personality Assessment Inventory (PAI) [36].

7.5.10 A Brief Neuropsychological Battery for Use in Cancer Research

A test battery that meets many of the criteria discussed earlier that has been used in a number of clinical trials, such as the ones conducted by the European Organization for Research and Treatment of Cancer (EORTC), North Central Cancer Treatment Group (NCCTG), National Cancer Institute (NCI-C), Radiation Therapy Oncology Group (RTOG), and the Medical Research Council (MRC), has been described by Klein and colleagues [5]. This brief universal research battery assesses: (1) *memory* using the Hopkins Verbal Learning Test [43], which is a verbal learning and memory test consisting of a list of 12 words in three semantic categories that assesses immediate recall across three trials, recognition of the words from distractors, and delayed free recall; (2) *verbal (phonemic) fluency* using the Controlled Oral Word Association test from the Multilingual Aphasia Examination [44], which requires the production of words beginning with a specific letter for three 1-minute trials; (3) *visual-motor scanning speed* using the Trailmaking Test, Part A [45], which entails connecting dots in numerical order in a timely manner; and (4) *executive function*, using the Trailmaking Test, Part B [45], in which the subject connects dots with alternating numbers and letters as rapidly as possible.

7.5.11 Health-Related Quality of Life

Owing to the effects that a brain tumor and its treatment may have on individuals, Health-Related Quality of Life (HRQoL) or simply Quality of Life (QOL) measures are frequently administered to assist with management of disease. QOL has become an important factor to track when treating brain tumor patients because treatment is not only aimed at maximizing survival but also at improving quality of life throughout the entire course of the disease. There is no universally agreed-upon QOL instrument for use with brain tumor patients, but there are several instruments that have been designed specifically for use with brain cancer patients.

7.5.12 European Organization for Research and Treatment of Cancer (EORTC) Questionnaire

One commonly used instrument, the EORTC QLQ-C30 questionnaire [46], was developed by the European Organization for Research and Treatment of Cancer (EORTC). This measure takes into account five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, nausea and vomiting), "global

health status" and overall "quality of life" items, and six single items for remaining symptoms and problem areas (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). This questionnaire yields a total of 30 QOL items [2]. For a more relevant questionnaire designed specifically for patients with brain cancer (as opposed to tumors elsewhere in the body), the EORTC QLQ-BN20 questionnaire was developed [47]. The brain tumor-specific EORTC QLQ-BN20 questionnaire consists of 20 questions covering four scales (future uncertainty, visual disorders, motor dysfunction, and communication deficit) and seven single items (headache, seizures, drowsiness, hair loss, itchy skin, weakness of legs, and bladder control). Both EORTC inventories require patients to rate their symptoms and problems over a seven-day recall period. With the exception of the "global health" and "overall quality of life" items of the QLQ-C30, all items of both the EORTC QLQ-C30 and the EORTC QLQ-BN20 are rated on a four-point Likert scale ranging from "not at all" to "very much." Answers to the items "global health" and "overall quality of life" are provided on a seven-point Likert scale, ranging from "very poor" to "excellent." Scores of all single item and multi-item scales of the EORTC questionnaires are linearly transformed to a 0–100 scale [48].

7.5.13 Functional Assessment of Cancer Therapy: General (FACT-G) Questionnaire

Another widely used measure to evaluate HRQoL based on a 7 day recall period is the Functional Assessment of Cancer Therapy, General (FACT-G) questionnaire. The FACT-G (version four) includes four domains (physical, social/family, emotional, and functional well-being) and covers a total of 27 items [49]. Additionally, this questionnaire can be used alongside a brain-specific module such as the FACT-Br, which measures specific concerns commonly seen in brain tumor patients [50]. The main difference between the EORTC and the FACT questionnaires is that the latter emphasizes the psychosocial aspects of the disease and its treatment, while the EORTC focuses more on physical functioning and current symptoms [2].

7.5.14 MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)

For those patients requiring a shorter questionnaire, the HRQoL 24-hour recall, the MD Anderson Symptom Inventory (MDASI) was developed [51]. This inventory measures severity of 13 symptoms as well as the interrelation of these activities with daily living (6 items). A specific brain tumor module, MDASI-Brain Tumor, is available as well [52]. This module focuses primarily on symptoms and includes nine items (weakness, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern, and irritability). Items on the MDASI and the MDASI-BT are scored on a numeric rating scale ranging from 1 to 10, where 0 indicates "not present" and 10 is "as bad as you can imagine." Scores are then calculated by averaging the sum of the items in the subscale and for the total questionnaire [53].

Because of the neurologic impairments, cognitive changes, and mood disorders experienced by patients with brain tumors, the validity of the scores on self-rated questionnaires may be questionable at times. Severity of depression has commonly been associated with poorer QOL ratings by patients. In these situations, the inventories should be completed with the assistance of a proxy, family member, or another reliable source. However, the clinician must take into account that the level of agreement between the patient and the proxy may vary. Despite these confounding influences on self-rating inventories, HRQoL questionnaires may nevertheless be valuable in determining the effects of the disease and its treatment on patients' quality of life [2]. Common neuropsychogical, mood, and quality of life tests are listed by cognitive domain in Table 7.1.

Table 7.1 Commonly used neuropsychological tests by cognitive domain

Cognitive domain	Test
Intellectual Functioning	Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV), Wechsler Intelligence Scale for Children, 5th ed. (WISC-V)
Orientation	Montreal Cognitive Assessment (MoCA), Mini Mental Status Exam (MMSE)
Attention	Digit Span; WAIS-IV
Verbal Memory	Rey Auditory Verbal Learning Test, California Verbal Learning Test, Logical Memory & Paired Associates Learning - Wechsler Memory Scale, 4th ed. (WMS-IV)
Visual Memory	Rey-Osterrieth Complex Figure, Brief Visual Memory Test-Revised, WMS-IV Visual Reproduction
Language	Boston Naming Test, Token Test, phonemic (letter) fluency
Executive Functions	Wisconsin Card Sorting Test, Stroop Color-Word Test, Trailmaking Test Part-B, Frontal Assessment Battery, Delis-Kaplan Executive Function System (D-KEFS)
Visuospatial	Clock Drawing, Judgment of Line Orientation, Rey-Osterrieth Complex Figure Test, WAIS-IV Block Design
Sensorimotor	Finger Tapping, Grooved Pegboard, Hand Dynamometer
Mood	Beck Depression Inventory-II, Beck Anxiety Inventory, Beck Scale for Suicide Ideation
Functional Status	European Organization for Research and Treatment of Cancer (EORTC QLQ-C30 or QLQ-BN20), Functional Assessment of Cancer Therapy-General (FACT-G), MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT)

7.6 Neuropsychological Assessment Following Treatment

Patients with primary brain tumors will usually be treated with some combination of neurosurgery, radiation, and chemotherapy. Although neuropsychological assessment is useful for monitoring the effects of these treatments, it is often difficult to identify the separate contribution of each individual treatment because they interact to either produce cognitive deficits or to improve existing deficits. Furthermore, the timing of the neuropsychological testing also matters because the acute effects of surgery and the short-term consequences of irradiation and chemotherapy are often different from their long-term effects.

7.6.1 Neurosurgery

After diagnosis, resective surgery is usually the first treatment undertaken in patients with brain tumors. Resective surgery planning needs to balance the risks of cognitive decline (and medical morbidity) against the benefits of improved survival. The major factors determining cognitive outcome are the location of the brain tumor and the extent of resection. Cognitive deficits may arise from compression of normal brain tissue or through invasion into functional brain tissue, or by disconnecting related functional nodes. Although there is extensive literature about the impact of surgery on neurologic outcome for a variety of brain lesions, there are fewer studies of neuropsychological outcome after neurosurgery for brain tumors [54]. That said, much of the literature on focal neurosurgical resection of noncancerous brain lesions is applicable to neurosurgery for brain tumors.

7.6.2 Cognitive Impairment After Surgery

Much of the literature on focal excisions in epilepsy surgery are generally applicable to brain tumor surgery outcome. Thus, resective surgery in the dominant (left) temporal lobe can result in verbal memory deficits and some language decline, such as anomia, while nondominant (right) temporal lobe resections may be associated with visuospatial memory decline [55, 56]. Orbitofrontal lobe tumors may result in alterations of emotional control and changes in personality. Dorsolateral prefrontal excisions may result in executive cognitive dysfunction. Mesial frontal lobe resections often produce reduced motivation and initiation or apraxia when the supplemental motor area is affected [57]. Parietal and posterior temporal lobe resections may lead to impairments in a variety of higher cognitive functions, including language (e.g., anomia, aphasia, alexia, agraphia), intellectual functions, or visuospatial cognition, as examples [45].

7.6.3 Cognitive Improvement After Surgery

Equally important in this context is the fact that neurosurgical excision of brain tumors may also improve cognitive functioning or leave it unchanged. For example, reduction of compression effects through surgical excision of noninvasive lesions has been shown to improve attentional functioning in patients with frontal meningiomas [58], and long-term improvement in verbal working memory has been reported after removal of low-grade gliomas in frontal premotor and anterior temporal lobe regions (often after transient postoperative worsening) [59]. Patients with high-grade gliomas may also show improvement. Talacchi and coworkers [60] found that approximately one quarter of patients evidenced cognitive decline after surgery, while the majority of patients (~75%) either improved or showed no significant change after surgery. Verbal memory, visuospatial memory, and word (phonemic) fluency were the most frequent negatively affected functions. Moreover, extent of tumor removal did not affect outcome, and postoperative cognitive improvement was correlated with high-grade tumors. Preoperatively, many patients with tumors of the third ventricle have impairments in memory, executive functions, and fine motor speed that are not significantly improved after tumor removal [61]. Similarly, craniopharyngiomas are often successfully treated surgically with limited postoperative cognitive or quality of life consequences as long as nearby hypothalamic structures are not harmed [62].

As may be seen in other chapters in this book, resective surgery for brain tumors generally has a positive impact on future time to tumor progression and survival. Along with these beneficial effects, the long-term postoperative neuropsychological profile tends to be stable when a brain tumor can be removed in its entirety. If the planned surgical resection area is presumed to include eloquent cortex, intraoperative mapping or fMRI evaluation of the at-risk cognitive function(s) may be performed under local anesthesia at the time of surgery. Results of cortical mapping may be used to tailor the extent of resection and preserve as much normal cognitive function as possible.

7.6.4 Radiation Therapy

Radiotherapy attempts to further reduce the size of any residual tumor remaining after surgical excision and to postpone future progression of tumor growth [63]. The immediate effects of radiotherapy on cognition are usually limited, although fatigue, insomnia, general malaise, and symptoms associated with increased intracranial pressure are commonly seen. Significant cognitive deficits have been documented, however, as long-term effects of whole-brain radiotherapy caused by irreversible radiation encephalopathy may occur as late as 20 years after treatment. Long-term radiotherapy cerebral abnormalities have been documented

and include spongiosis of white matter and vascular damage that appear as atrophy and white matter hyperintensities on MRI. These long-term, delayed cerebral abnormalities have been associated with a decline in cognitive functions and health-related quality of life. Although the specific deficits seen vary across patients, impairments in memory and mental processing speed are commonly encountered in patients with low-grade gliomas after radiotherapy [64, 65].

Limited field irradiation appears to cause fewer late-term cognitive impairments than whole brain radiation [66]. More recently, stereotactic radiotherapy has been utilized, and this seems to further limit the amount of radiation delivered to nearby healthy tissue, which, in turn, appears to limit the extent of cognitive impairment. Although radiotherapy-induced cognitive deficits may be expected to have a negative impact on the long-term quality of life in patients with low-grade gliomas, this has not been found in patients with high-grade tumors. Patients with high- grade recurrent tumors reportedly show little deterioration in quality of life over time following treatment with radiation despite their near universal widespread cognitive deficits [67]. This result may be sample-specific or possibly the result of these patients' lowering their expectations of what constitutes positive QOL.

7.6.5 Radiosurgery with or Without Whole-Brain Radiation Therapy

Stereotactic radiosurgery is a common and effective treatment for patients with brain metastases from cancer elsewhere in the body, but when radiosurgery is the sole method of treatment, new metastatic lesions frequently develop [68]. The use of adjuvant whole-brain radiotherapy in conjunction with stereotactic radiosurgery has been shown to improve intracranial tumor control in randomized clinical trials, but unfortunately whole-brain irradiation has also been associated with greater cognitive decline. Unexpectedly none of these clinical trials have shown any significant survival advantage of combining whole-brain radiotherapy with radiosurgery, and one clinical trial reported a survival disadvantage [27, 68, 69]. These data raise the question of whether tumor progression in the brain is more harmful to a patient's well-being than the deterioration of cognition and changes in quality of life that are associated with whole-brain irradiation.

A recent randomized clinical trial [70] examined the effects of adding whole-brain radiotherapy to stereotactic radiosurgery on cognitive functioning, QOL, tumor control, and survival in 213 adults with one to three brain metastases and found that there was significantly less cognitive deterioration (on memory, language, attention, executive function, and motor speed) 3 months after use of stereotactic radiosurgery alone (40 of 63 patients; 63.5%) than after use of radiosurgery plus whole-brain irradiation (44 of 48 patients; 91.7%). In addition, there was better quality of life (QOL) at 3 months with stereotactic radiosurgery alone, including overall QOL and functional well-being.

Although there was less cognitive deterioration and better QOL in patients who only had sterotactic radiosurgery, intracranial tumor control was worse with radiosurgery alone (79 of 105 patients; 75.3%) as compared with radiosurgery plus whole-brain radiotherapy (89 of 95 patients; 93.7%) [70]. Despite the superior intracranial tumor control associated with whole-brain radiotherapy, there was no improvement in survival rates in these doubly treated patients. Median overall survival for surgery plus whole-brain irradiation was 7.4 months, and median survival for surgery alone was 10.4 months. The authors concluded that stereotactic radiosurgery alone may be the preferred treatment strategy for patients with one to three brain metastases.

7.6.6 Chemotherapy

Chemotherapy is part of the standard regimen of treatment among patients with high-grade malignant tumors. As with surgery and radiotherapy, chemotherapy attempts to stabilize the disease and delay tumor progression [4]. It is difficult to quantify the negative cognitive consequences of chemotherapy precisely because it is almost always administered in combination with radiotherapy following surgical resection. This makes it difficult to tease out the relative contribution of chemotherapy to cognitive decline. Similar to radiotherapy, chemotherapy causes neurotoxicity within the brain, which is often reflected in white matter changes and cerebral atrophy seen on neuroimaging. Cancer patients may experience both the direct toxic effects of chemotherapy on the brain as well as indirect CNS disruption from such things as metabolic dysregulation or cerebrovascular changes. Moreover, toxicity from chemotherapy may also differ in its immediate and late-term effects. The cognitive effects of chemotherapy are well known among cancer survivors, as evidenced by their complaints of "brain fog" that causes problems when attempting to perform complex tasks or when multitasking at work or at home. These complaints have anecdotally become known as "chemobrain" by some patients and their caretakers.

Although this area of inquiry is fraught with methodologic problems, the literature in general suggests that long-term survivors of malignant gliomas who have been treated with chemotherapy in conjunction with other treatments typically have significant cognitive deficits that tend to worsen over time [9]. The most frequent cognitive domains reported to show impairment after systemic chemotherapy include memory, executive functions, attention-concentration, and processing speed [71]. After conducting a qualitative review of the literature, Ahles and Saykin [15] concluded that standard dose chemotherapy is associated with subtle decrements in concentration and memory that

can have a significant negative impact on survivors' quality of life. Systemic chemotherapy for tumors originating outside the central nervous system can also affect cognitive function. After conducting a meta-analysis of neuropsychological studies of chemotherapy in patients with non-CNS tumors, Anderson-Hanley, and coworkers [72] reported significant mild to moderate decrements in executive functions, verbal memory, and motor skills.

7.7 Quality Versus Quantity of Life: Health Utility Evaluations

Clinical decisions about treatment options can become difficult when there are conflicts between the quantity (survival) of life versus the quality (cognition and other QOL domains) of life. Health utility measures have been developed in an attempt to quantify this dilemma across populations as well as for the individual patient. Health utility measures are related to health-related quality of life (HRQoL) measurement, and although these measures were originally designed for health economic uses (e.g., cost-effectiveness decisions, resource allocation policies), they may be used by patients and physicians to make difficult treatment decisions in the individual case. Health utility measures differ in one respect from typical QOL measures in that a single value is derived to represent an individual's health status on a scale from 0 (dead) to 1 (perfect health). Health utility measures are designed to be interval measures that reflect an individual's treatment and QOL preferences through calculation of the quality-adjusted life-year (QALY). QALY is a measure of a patient's length of life weighed by an appraisal of their health-related quality of life [73].

There are several approaches to obtain these health utilities. One commonly used direct approach is to ask individual patients to indicate which amount of lifetime they would be willing to sacrifice (number of life-years) in order to live in a better health state (less severe symptoms) across a number of QOL dimensions. Dirven and associates [2] illustrated this with the following example. Treatment A generates one additional year in a health state valued at 1 (best possible health), which results in 1 QALY (1 × 1 = 1). In contrast, Treatment B generates 1.5 additional years of life in a health state valued at 0.5 (mid-level health status), which results in 0.75 QALY (0.5 × 1.5 = 0.75). Thus, in this example, Treatment A would provide 0.25 more QALYs than Treatment B (1–0.75 = 0.25 QALYs) (see Fig. 7.1, which is derived from Dirven et al. [2]).

Several generic measures of health utility have been developed, including some for specific disease states (e.g., childhood cancer, multiple sclerosis, Alzheimer disease). These include the Health Utilities Index (HUI Mark 2 developed specifically for childhood cancer and HUI Mark 3 [samples 8 domains]) [74–78], the EuroQOL (EQ-5D [samples 5 domains]) [76–78], and the SF-6D [samples 6 domains], which was derived from the SF-36 quality of life instrument [76–78]. Although there is no agreed upon best method currently to make health utility treatment determinations in individuals with brain cancer, such approaches hold promise in assisting doctors and patients when weighing difficult treatment decisions.

7.8 Summary

The field of neuropsychology focuses on the information base of recognized brain-behavior associations with standardized psychometric measures (tests). This includes the assessment and diagnosis of impairments in cognition and behavior and relating these findings to their neurologic implications and to issues of clinical treatment and prognosis. Neuropsychological measures are sensitive to the effects of cancer treatment, including the neurotoxic effects of chemotherapy or the consequences of brain tumor resection. When assessing brain tumor patients, a comprehensive battery of tests will aid in providing accurate and precise infor-

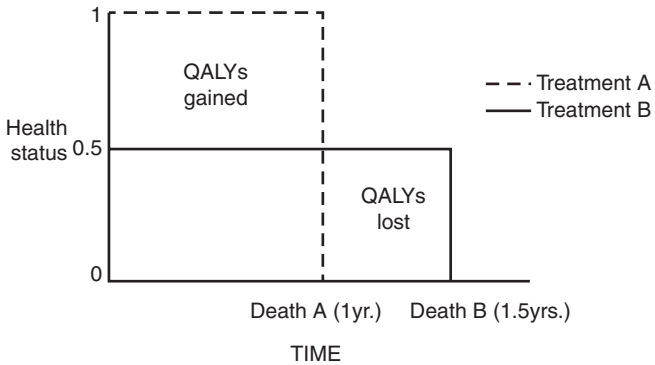

Fig. 7.1 Comparison of two treatments **A** and **B**. Treatment **A** is associated with decreased survival but better health-related QOL than treatment **B**. Quality-adjusted life-years (QALYs) are gained in the short term after treatment A (1 × 1 = 1) but lost in the long term after treatment B (1.5 × 0.5 = 0.75). Thus, treatment **A** would provide 0.25 more QALYs than treatment **B** in this example

mation about the cognitive, behavioral, and quality of life status of patients. Because of the diversity of possible deficits produced by brain cancer and its treatment, a battery capturing a wide range of cognitive abilities should be administered. The most common cognitive domains to be assessed are verbal and nonverbal intellectual functions, language, attention, orientation, verbal and nonverbal learning and memory, visual-spatial skills, executive functions, psychosensory and motor abilities, mood, and health-related quality of life information.

Thought should be given to the timing of neuropsychological testing, since the acute and long-term effects of surgery, radiation, and chemotherapy all vary. With regard to neurosurgery, the main factor determining cognitive outcome is the location of the brain tumor and the extent of resection. It's also important to recall that improvement in cognition also may be seen after surgery when the deleterious effects of the tumor, such as compression mass effects, are removed.

Radiotherapy, especially whole brain irradiation, in patients with brain tumors has been associated with both acute and long-term declines in cognitive function and health-related quality of life. Since chemotherapy is almost always administered in conjunction with radiotherapy and often with surgical resection, it has been difficult to parse out the relative contribution of each of these treatment regimens to patients' cognitive decline.

The neuropsychological assessment is an important component in determining the patient's cognitive and behavioral standing pre- and post-treatment. The patterns of impairment obtained may be used to determine cognitive, psychological-emotional, and functional competence and to assist in treatment planning and rehabilitation recommendations. As a result of the valuable information provided though a neuropsychological evaluation, comprehensive cognitive, behavioral, and quality of life assessment can contribute to the overall wellbeing of cancer patients with brain tumors throughout the course of their disease.

References

1. Mitchell AJ, Kemp S, Benito-Leon J, Reuber M. The influence of cognitive impairment on health-related quality of life in neurological disease. Acta Neuropsychiatrica. 2010;22:2–13.
2. Dirven L, Reijneveld JC, Taphoorn MJB. Health-related quality of life or quantity of life: a difficult trade-off in primary brain tumors? Sem Oncol. 2014;41:541–52.
3. Dwan TM, Ownsworth T, Chambers S, Walker DG, Shum DHK. Neuropsychological assessment of individuals with brain tumor: comparison of approaches used in the classification of impairment. Frontiers Oncol. 2015;5.(Article 56:1–8.
4. Janelsins MC, Kohli S, Mohile SG, Usuki K, Ahles TA, Morrow GR. An update on cancer- and chemotherapy-related cognitive dysfunction: current status. Sem Oncol. 2011;38:431–8.
5. Klein M, Duffau H, De Witt Hammer PC. Cognition and resective surgery for diffuse infiltrative glioma: an overview. J Neuro-Oncol. 2012;108:309–18.
6. Klein M, Postma TJ, Taphoorn MJB, Aaronson NK, Vandertop WP, Muller M, et al. The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. Neurology. 2003;61:1796–9.
7. Meyers CA, Hess KR, Yung WK, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. J Oncol. 2000;18:646–50.
8. Meyers CA, Geara F, Wong PF, Morrison WH. Neurocognitive effects of therapeutic irradiation for base of skull tumors. Int J Radiation Oncol. 2000;46:51–5.
9. Anderson SW, Ryken TC. Intracranial tumors. In: Morgan JE, Ricker JH, editors. Textbook of clinical neuropsychology. New York: Taylor & Francis; 2008. p. 578–87.
10. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. Neurooncology. 2003;5:89–95.
11. Appelbaum PS, Grisso T. MacCAT-CR: MacArthur competence assessment tool for clinical research. Sarasota: Professional Assessment Resources; 2001.
12. Loeb P. Independent living scales manual. San Antonio: The Psychological Corporation; 1996.
13. Rodin MB, Mohile SG. Assessing decisional capacity in the elderly. Semin Oncol. 2008;35:625–32.
14. Denlinger CS, Ligibel JA, Are M, Baker KS, Demark-Wahnefried W, Friedman DL, et al. Survivorship: cognitive function, version 1.2014. National Comprehensive Cancer Network. J Natl Compr Cancer Netw. 2014;12:976–86.
15. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy induced cognitive changes. Natl Rev Cancer. 2007;7:192–201.
16. Salkade PR, Lim TA. Methotrexate-induced acute toxic leukoencephalopathy. J Cancer Res Ther. 2012;8:292–6.
17. Schagen SB, Das E, Vermeulen I. Information about chemotherapy-associated cognitive problems contributes to cognitive problems in cancer patients. Psychooncology. 2012;21:1132–5.
18. Lazareff JA, Castro-Sierra E. Preoperative and postoperative analysis of visual and auditory memory in children with cerebellar tumors. Childs Nerv Syst. 1996;12:81–6.
19. Margelisch K, Studer M, Ritter BC, Steinlin M, Leibundgut K, Heinks T. Cognitive dysfunction in children with brain tumors at diagnosis. Pediatr Blood Cancer. 2015;62:1805–12.
20. Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. J Clin Oncol. 2008;26:971–82.
21. Iuvone L, Mariotti P, Colosimo C, Guzzetta F, Ruggiero A, Riccardi R. Long term cognitive outcome, brain CT scan and MRI abnormalities in children cured for ALL. Cancer. 2002;95:2562–70.
22. Moberget T, Andersson S, Lundar T, Due-Tønnessen BJ, Heldal A, Endestad T, et al. Long-term supratentorial brain structure and cognitive function following cerebellar tumour resections in childhood. Neuropsychologia. 2015;69:218–31.
23. Papazoglou A, King T, Morris R, Krawiecki N. Cognitive predictors of adaptive functioning vary according to pediatric brain tumor location. Dev Neuropsychol. 2008;33:505–20.
24. Klein M, Taphoorn MJ, Heimans JJ, Van der Ploeg HM, Vandertop WP, Smit EF, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. J Clin Oncol. 2001;19:4037–47.
25. Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. Acta Neurochir. 2014;156:1451–9.
26. Crossen JR, Garwood D, Glatstein E, Neuwelt EA. Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. J Clin Oncol. 1994;12:627–42.
27. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole brain irradiation: a randomized controlled trial. Lancet Oncol. 2009;10:1037–44.

28. Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. J Clin Oncol. 2006;24:1305–9.
29. Onodera S, Aoyama H, Tha KK, Hashimoto N, Toyomaki A, Terae S, et al. The value of 4-month neurocognitive function as an endpoint in brain metastases trials. J Neuro-Oncol. 2014;120:311–9.
30. Iuvone L, Peruzzi L, Colosimo C, Tamburrini G, Caldarelli M, Di Rocco C, et al. Pretreatment neuropsychological deficits in children with brain tumors. NeuroOncol. 2011;13:517–24.
31. Iuvone L, Marlotti P, Colosimo C, Guzzetta F, Ruggiero A, Riccardl R. Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cure for acute lymphoblastic leukemia. Cancer. 2002;95(12):2562–70.
32. DeAnglis LM. Brain tumors. N Engl J Med. 2001;344:114–23.
33. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. Am J Phys Med. 2001;80:346–50.
34. Meyers CA. Neurocognitive dysfunction in cancer patients. Oncology. 2000;14:75–8.
35. Mendez MF, Cummings JL. Miscellaneous dementia syndromes-neoplasia-related dementia. In: Mendez M, Cummings J, editors. Dementia: a clinical approach. Philadelphia: Butterworth-Heinemann; 2003. p. 521–6.
36. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment. 5th ed. New York: Oxford University Press; 2012.
37. Folstein MF, Folstein SE, Mchugh PR. "Mini-mental state." a practical method for grading the cognitive state of patients for the clinician. J Psych Res. 1975;12:189–98.
38. Nasreddine ZS, Phillips N, Chertkow H. Normative data for the Montreal cognitive assessment (MoCA) in a population-based sample. Neurology. 2012;78:765–6.; author reply 766. https://doi.org/10.1212/01.wnl.0000413072.54070.a3.
39. Strauss E, Sherman EMS, Spreen O. A compendium of neuropsychological tests: administration, norms, and commentary. 3rd ed. New York: Oxford University; 2006.
40. Heilman KM, Watson RT, Valenstein E. Neglect and related disorders. In: Heilamn KM, Valenstein E, editors. Clinical neuropsychology. 4th ed. New York: Oxford University Press; 2003. p. 296–346.
41. Blumenfeld H. Neuroanatomy through clinical cases. Sunderland: Sinauer Associates; 2010.
42. Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol. 1998;16:2522–7.
43. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test-revised: normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol. 1998;12:43–55.
44. Benton AL, Hamsher K. Multilingual aphasia examination. 2nd ed. Iowa City: AJA Associates; 1989.
45. Lezak MD, Howieson DB, Loring DW. Neuropsychological assessment. 4th ed. New York: Oxford University Press; 2004. p. 68–84.
46. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365–76.
47. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer- specific questionnaires. Qual Life Res. 1996;5:139–50.
48. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 scoring manual. 3rd ed. Brussels: European Organization for Research and Treatment of Cancer; 2001.
49. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The functional assessment of Cancer therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11:570–9.
50. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The functional assessment of Cancer therapy (FACT) scale. Development of a brain sub-scale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer. 1995;75:1151–61.
51. Cleeland CS, Mendoza TR, Wang XS, Chou C, Harle MT, Morrissey M, et al. Assessing symptom distress in cancer patients: the M.D. Anderson symptom inventory. Cancer. 2000;89:1634–46.
52. Armstrong TS, Mendoza T, Gning I, Coco C, Cohen MZ, Eriksen L, et al. Validation of the M.D. Anderson symptom inventory brain tumor module (MDASI- brain tumor). J Neuro-Oncol. 2006;80:27–35.
53. Sloan JA, Dueck A. Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. J Biopharm Stat. 2004;14:73–96.
54. Klein M, Duffau H, De Witt Hamer PC. Cognitive and resective surgery for diffuse infiltrative glioma: an overview. J Neuro-Oncol. 2012;108:309–18.
55. Jones-Gotman M, Zatorre RJ, Olivier A, Andermann F, Cendes F, Staunton H, et al. Learning and retention of words and designs following excision from medial or lateral temporal lobe structures. Neuropsychologia. 1997;35:963–73.
56. Dulay MF, Levin HS, York MK, Mizrahi EM, Verma A, Goldsmith I, et al. Predictors of individual visual memory decline after unilateral anterior temporal lobe resections. Neurology. 2009;72:1837–42.
57. Stuss DT, Benson DF. Neuropsychological studies of the frontal lobes. Psychol Bull. 1984;95:3–28.
58. Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. J Neurosurg. 2003;98:21–31.
59. Teixidor P, Gatignol P, Leroy M, Masuet-Aumatell C, Capelle L, Duffau H. Assessment of verbal working memory before and after surgery for low-grade glioma. J Neuro-Oncol. 2007;81:305–13.
60. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. J Neuro-Oncol. 2011;103:541–9.
61. Friedman MA, Meyers CA, Sawaya R. Neuropsychological effects of third ventricle tumor surgery. Neurosurgery. 2003;52:791–8.
62. Honegger J, Barocka A, Sadri B, Fahlbusch R. Neuropsychological results of craniopharyngioma surgery in adults: a prospective study. Surg Neurol. 1998;50:19–29.
63. Laperrie N, Zuraw L, Cairncross G. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. Radiother Oncol. 2002;64:259–73.
64. Armstrong CL, Corn BW, Ruffer JE, Pruitt AA, Mollman JE, Phillips PC. Radiotherapeutic effects on brain function: double dissociation of memory systems. Neuropsychiatry Neuropsychol Behav Neurol. 2000;13:101–11.
65. Douw L, Klein M, Fagel SS, van den Heuvel J, Taphoorn MJ, Aaronson NK, et al. Cognitive and radiological effects of radiotherapy in patients with low-grade glioma: long-term follow-up. Lancet Neurol. 2009;8:810–8.
66. Torres IJ, Mundt AJ, Sweeney PJ, Llanes-Macy S, Dunaway L, Catillo M, et al. A longitudinal neuropsychological study of partial brain radiation in adults with brain tumors. Neurology. 2003;60:1113–8.
67. Ernst-Stecken A, Ganslandt O, Lambrecht U, Sauer R, Grabenbauer G. Survival and quality of life after hypofractionated stereotactic radiotherapy for recurrent malignant glioma. J Neuro-Oncol. 2007;81:287–94.
68. Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole-brain radiotherapy vs observation after radiosurgery or surgical resection of 1 to 3 cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol. 2011;29:134–41.
69. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy

vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized clinical trial. JAMA. 2006;295:2483–91.
70. Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson K, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases. JAMA. 2016;316:401–9.
71. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA. Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer. 2010;116:3348–56.
72. Anderson-Hanley C, Sherman ML, Riggs R, Agocha VB, Compas BE. Neuropsychological effects of treatment for adults with cancer: a meta-analysis and review of the literature. J Int Neuropsych Soc. 2003;9:967–82.
73. Phillips C, Thompson G. What is a QALY? 2nd ed. London: Hayward Medical Communications; 2009.
74. Duckworth J, Nayiager T, Pullenayegum E, Whitton A, Hollenberg R, Horsman J, et al. Health-related quality of life in long-term survivors of brain tumors in childhood and adolescence: a serial study spanning a decade. J Ped Hematol Oncol. 2015;37:362–7.
75. Torrance GW, Feeny D, Furlong W, Barr RD, Zhang Y, Wang Q. Multi-attribute preference functions for a comprehensive health status classification system: Health Utilities Index Mark 2. Med Care. 1996;34:1–21.
76. Fisk JD, Brown MG, Sketris IS, Metz LM, Murray TJ, Stadnyk KJ. A comparison of health utility measures for the evaluation of multiple sclerosis treatments. J Neurol Neurosurg Psychiatry. 2005;76:58–63.
77. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull. 2010;96:5–21.
78. Lacey L, Bobula J, Rudell K, Alvir J, Leibman C. Quality of life and utility measurement in a large clinical trial sample of patients with mild to moderate Alzheimer's disease: determinants and level of changes observed. Value Health. 2015;18:638–45.

8 Intracranial Electrode Investigations in the Presurgical Evaluation of Drug-Resistant Epilepsy

Kyriakos Garganis

8.1 Intracranial Electrode Studies: An Introduction

In the field of epilepsy surgery, intracranial electrode (ICE) studies can overcome several limitations of surface electroencephalograms (EEGs). To briefly summarize the most important of them:

(a) Conduction of the brain's electrical activity to surface electrodes is significantly hampered by the poor conductivity of the skull [1, 2]. Signals of particular interest (e.g., sharp waves) need to recruit at least a 10–15 square centimeter area of cortical surface in order to be detectable by surface electrodes [3]. Signals recruiting less than that are only recorded by exception. Contamination by muscle and other artifacts is another source of difficulty with signal detection and interpretation.
(b) Initial fast-frequency components of the ictal epileptic discharge (particularly important for ictal-onset region localization) are also attenuated by the intervening layers between the cortex and the skull. An ictal EEG rhythm may be seen only after considerable propagation from the site of origin has taken place following recruitment of extensive cortical surface and evolution to synchronized, lower frequency activity [4, 5].
(c) Signals from "hidden" brain regions at a distance from surface recording electrodes (especially from the interhemispheric fissure and basal and medial frontal regions) are also, barely, recorded [6, 7].

As a result, a significant proportion of epileptic activity passes unnoticed by surface electrodes; in addition, poor or even false localization/lateralization by surface EEGs occurs in a significant proportion of patients (10–30%), especially in those with "hidden" extratemporal epileptogenic zones. Intracranial electrodes record directly from the cortical surface (and in the case of depth electrodes from within the cerebral cortex and subcortical structures if needed). They are thus placed as close to the source of electrical activity as possible, with intervening tissues (cerebrospinal fluid and brain) of high conductivity. They are also free of most artifact types associated with surface EEGs. Thanks to their short distance from the signal generator, they can detect the extremely focal, low-amplitude, and fast frequency discharges often associated with seizure onset. They also provide valuable localizing information before the subsequent spread and transformation of the ictal discharge to neighboring and remote areas that often dominate surface EEG recordings, which may lead to false localization. However, even though the spatial resolution of intracranial electrodes is high, only a small proportion of brain tissue is sampled by each one, corresponding to a sphere of about a 5-mm radius beyond its boundaries. Therefore, localization errors may occur if the electrodes are placed in insufficient numbers or even at a short distance from the epileptogenic zone [1, 8, 9].

There are two main types of intracranial electrodes utilized in epilepsy surgery practice [1, 10]: (a) subdural electrodes, and (b) depth electrodes. They are composed of various materials (platinum, silver, stainless steel, nickel-chromium, and platinum-iridium). Those made of nickel-chromium and platinum-iridium are MRI-compatible and thus favored for chronic implantation.

Subdural electrodes are small, disk electrodes, 4–5 mm in diameter, impeded in flexible material (Silastic) holding them together, at a 5- to 10-mm distance from each one's center, and placed subduraly over the exposed cortical surface to be explored. They are available in arrays of various numbers, configurations (from single row strips of 4–8 electrodes to larger orthogonal grids of 16–128 electrodes), and shapes (e.g., "curvilinear" for interhemispheric fissure placement) tailored to the demands of each investigation. Subdural strips are inserted through burr holes opened above the area of interest and pushed to the target region by the neurosurgeon. Placement of subdural grids requires a larger craniotomy.

K. Garganis
Epilepsy Center, St. Luke's Hospital, Panorama-Thessaloniki, Thessaloniki, Greece

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Depth electrodes are needle electrodes available in different lengths and implanted into the brain parenchyma. They are composed of 5–20 contacts, the superficial ones recording locally from the cortex beneath the entry point and the most distal ones from deeper brain sites (e.g., the amygdala, hippocampus, or medial hemispheric surface). They are placed stereotactically through burr holes with the assistance of a frame or neuronavigation.

Following ICE implantation, appropriate electrode positioning is verified through postoperative MRI or CT scan/MRI fusion. Availability of intraoperative CT is a major advantage because it allows further electrode manipulations and repositioning in case these are not appropriately placed.

8.2 When Are ICE Studies Needed?

ICE investigations are performed either acutely, during the operation (acute intraoperative electrocorticography – acute ECoG), or in a chronic extraoperative setting. Acute ECoG is widely used in most epilepsy centers for purposes of verifying location and extent of the epileptogenic zone and modifying the resection border to include as much epileptogenic tissue as possible [11]. In selected cases, intraoperative electrical cortical stimulation (ECS) may be performed as well to map eloquent cortex borders. The location of the epileptogenic zone is already known from the noninvasive presurgical work-up. The role of acute ECoG is to confirm epileptogenic tissue location through an initial recording (acute preresection ECoG), and in some cases it assists in guiding resection limits. Following resection, ECoG is performed again (acute postresection ECoG) to look for remaining/persistent epileptogenic activity. If such activity is still present, resection borders may be modified until it is abolished or significantly reduced. Acute ECoG is usually performed with subdural electrodes and is practically harmless (it requires only an additional 20–40 min of time in the duration of surgery). As a rule, it detects only interictal epileptiform activity; seizure recording is exceptionally rare. The utility of acute ECoG is well established in cases with focal cortical dysplasia (FCD) [12–14] and perhaps with tumors associated with longstanding epilepsies [15–17], whereas it is less certain with medial temporal sclerosis (MTS) cases [18, 19].

The focus of this chapter is on extraoperative chronic ICE investigations. Understandably, these are performed in more complicated cases, which cannot be brought to surgery based on noninvasive investigations only. If certain prerequisites are fulfilled, these candidates are subjected to a two-stage procedure. They are first implanted with intracranial electrodes according to the noninvasive investigation findings provided that testable localization hypotheses have been formulated from them. The patient is subsequently brought to the Epilepsy Monitoring Unit to undergo a few days of monitoring, which provides the opportunity to record seizures as well as to perform ECS in a relaxed and controlled environment. As soon as the necessary information is obtained, the patient is brought to the operating room again to undergo electrode removal and epilepsy surgery. Obviously, such a process is much more time- and resource-consuming and poses certain risks for the patient.

The majority of suitable surgical patients can be reliably identified through noninvasive evaluation protocols, which include prolonged surface video-EEG monitoring, structural MRIs, neuropsychological testing, and depending on each center's facilities, functional imaging studies (functional magnetic resonance imaging [FMRI], combined electroencephalography with functional MRI [EEG-FMRI]; positron emission tomography [PET]; single photon emission computed tomography [SPECT]; magnetoencephalography [MEG]) as well. Between 60% and 80% of suitable surgical candidates are selected on the basis of converging lines of evidence derived from noninvasive diagnostic studies implicating a particular brain area as the actual source of epileptogenesis [20–23]. This is particularly true for cases with unilateral medial temporal sclerosis and tumors, which currently are only rarely subjected to ICE studies [20, 22, 24]. On the other hand, updates on referral patterns from many established epilepsy programs currently suggest that "easy" cases (such as unilateral temporal sclerosis and tumoral patients) are becoming less [25], and an increasing proportion of "nonlesional" MRI and extratemporal localization patients are brought for investigation; for most of these cases intracranial electrode investigation is imperative, thus compensating for their diminishing use in medial temporal sclerosis and tumoral cases. Considering the whole spectrum of indications for invasive EEG and depending on each center's particular investigative approaches and referred populations, approximately 20–40% of potential surgical candidates require a second, invasive EEG evaluation phase to decide on their surgical suitability.

Before embarking on an ICE investigation, the candidate must have a thorough noninvasive presurgical evaluation, resulting in testable hypotheses regarding localization and resectability of the epileptogenic zone; it is the quality of the noninvasive work-up that largely determines the necessity for and expectations from an ICE study. At times inconclusive or apparently discordant noninvasive data may well be explained considering the limitations of surface EEGs sensitivity and the effects of seizure propagation along an epileptogenic network. ICE investigations are not always required in many of these cases [26]. However, a "core" set of indications is adopted by most centers [27]:

(a) Documenting the presence and localization of an epileptogenic zone when one is suspected but noninvasive localization is poor or not ideally concordant (e.g., when

semiology/surface EEG is localizing but MRI is nonrevealing, or vice versa).

(b) Determining epileptogenic zone localization (or lateralization) when noninvasive findings suggest the existence of more than one zone (for example, with surface EEG evidence of bitemporal epileptogenicity).

(c) Defining the extent of the epileptogenic zone to maximize epileptogenic tissue resection (especially when there are no clear-cut MRI cues) as well as to determine possible overlap with eloquent regions (motor-sensory and language cortices) through ECS and in conjunction with functional imaging studies (e.g., fMRI, DTI) to modify resection borders and avoid damaging functional areas.

8.3 Intracranial Electrode Types: Particular Advantages and Disadvantages

At the very beginning of ICE investigations history, depth electrodes were the most frequently utilized, particularly by the French-Italian school of epileptology, which has generated a strong tradition of stereo-EEG explorations in epilepsy [28]. Depth electrodes are ideally suited to record from deep-seated basal and medial brain areas (particularly useful for sampling the amygdala and hippocampus) as well as from "hidden" structures (such as the insula), which are inaccessible to superficially placed subdural electrodes [29, 30]. They can also record directly from deep parts of the cortex (sulci) and even deeper from subcortical nuclei and subcortical epileptogenic substrates (e.g., heterotopias) if needed, as well as from within a lesion itself when appropriately placed. (This is the case with suspected FCD type IIb lesions, which expose characteristic ECoG patterns in intralesional contacts) (Fig. 8.1) [31]. They can simultaneously record from both lateral and medial parts of the cerebral hemisphere when inserted from the lateral and directed toward the medial hemispheric surface. Given stereotactic methodology, placement is more accurate compared to that of subdurals. They can be placed in different lobes and bilaterally, therefore being particularly suitable for bilateral hemispheric explorations and for depicting seizure propagation pathways and epileptic networks.

Subdural electrodes cover cortical surface like a "blanket" and cannot easily record electrical activity from deeper sulci or closed electrical fields. However, they do record from extensive and contiguous brain areas, and thanks to the orderly and close electrode spacing can provide a more detailed and accurate map of the epileptogenic zone (provided they are correctly placed over it) as well as of eloquent cortex borders through ECS. They are thus perhaps better suited to depths for lateral convexity epileptogenic zones, especially if located close to eloquent cortical regions. Subdural electrodes are also utilized for basal-medial temporal coverage in cases of suspected medial temporal foci; however, underlying bone prominences or adhesions from previous operations may resist ideal placement beneath the temporal lobe and medial temporal structures. Even under optimal conditions, the most distant record is from the parahippocampal gyrus and entorhinal cortex. Although electrical events taking place in hippocampus are often reflected in the parahippocampal gyrus (Figs. 8.2 and 8.3) and thus may be detectable by subdural electrodes, depth electrodes are more sensitive and accurate for hippocampal/amygdala sampling and therefore are preferred over subdurals when it is critical to reliably document ictal onsets from these structures [32–34].

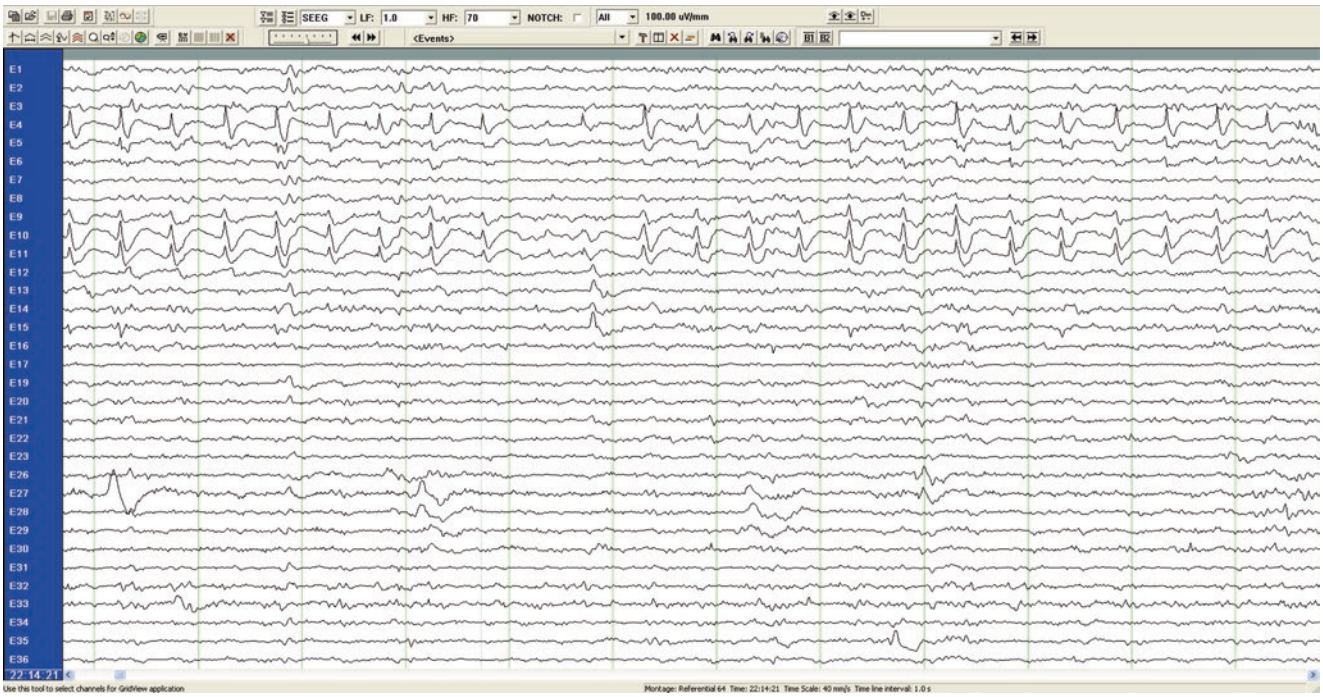

Fig. 8.1 Semicontinuous rhythmic spiking recorded from subdural grid electrodes 4, 5, 9, 10, and 11, located over a type IIb focal cortical dysplasia (FCD), an electrocorticographic pattern frequently encountered with type IIb FCD

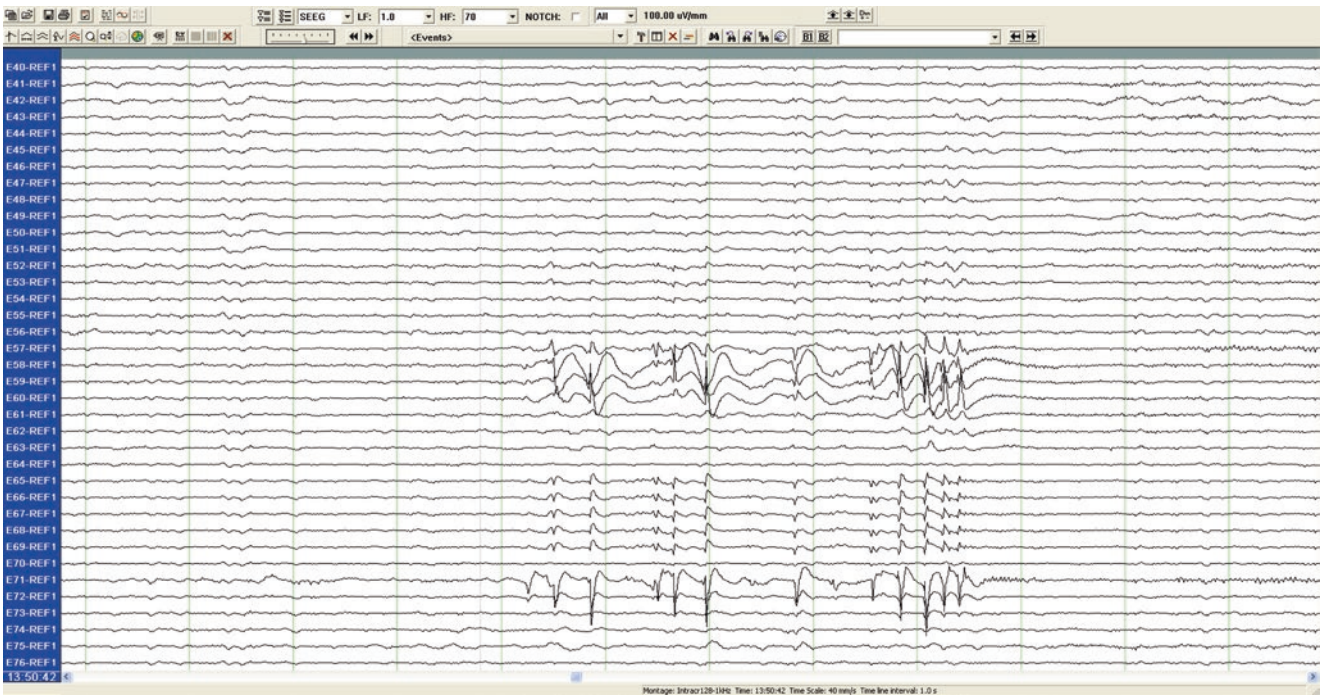

Fig. 8.2 Hippocampal/parahippocampal dyrus onset seizure. Contacts 71–76: depth electrode with contact 71 placed to posterior hippocampus. Contacts 57–64: subdural subtemporal strip with contact 57–58 placed to parahippocampal gyrus. Notice seizure onset with low-frequency repetitive spiking, typically seen with hippocampal onset seizures, in medial temporal sclerosis

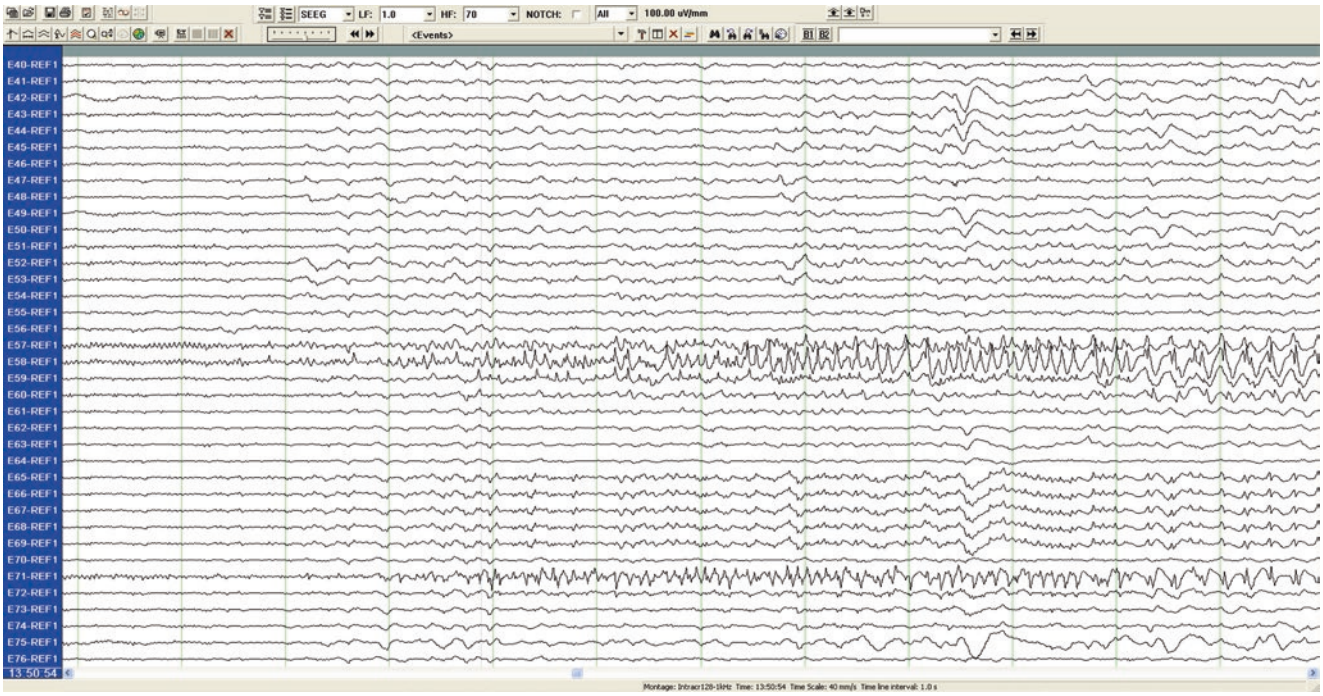

Fig. 8.3 Hippocampal/parahippocampal dyrus onset seizure. Contacts 71–76: depth electrode with contact 71 placed to posterior hippocampus. Contacts 57–64: subdural subtemporal strip with contact 57–58 placed to parahippocampal gyrus. A low-amplitude fast discharge evolves subsequently, suggesting spread and parahippocampal gyrus involvement, latter transforming to lower frequency–higher amplitude rhythmic activity

8.4 Concepts Behind the Use of Depth Versus Subdural Electrodes

It would be an oversimplification to view utilization of depth versus subdural electrodes just as a matter of simple advantage of one type of electrode over the other and/or a team's familiarity and preferences. Under the theoretical framework of stereo-EEG explorations first pioneered by the French and Italian epileptology schools [35, 36] and currently adopted by many centers in Europe and the U.S. as well [37, 38], a quite different concept regarding definition and organization of the ictal onset and epileptogenic zone is proposed as compared to their equivalents adopted by subdural ICE studies. Namely, the ictal onset and epileptogenic zones are not viewed solely as more or less restricted areas where the initial ictal discharge starts from [39] but as a more elaborate neuronal network fostering the "primary organization of the ictal discharge incorporating early spread networks, dependent on connectivity and pathogenic substrate and closely linked to seizure's semiological expressions" [40]. After careful consideration of noninvasive data and formulation of an anatomoelectroclinical hypothesis of seizure organization, depth electrodes are placed at strategic points and nodes of the network [41–43], which may often be at sufficient distances from each other. Given their particular advantage to sample from both lateral and medial hemispheric surfaces, they can provide a three-dimensional approximation of the seizure evolution and trajectory over time. Sophisticated analysis of stereo-EEG studies has substantiated this concept into discrete ictal onset and epileptogenic zone networks along with their semiologic correlates. Among them, the "temporosylvian" [44] one is the most analyzed in this regard, while evidence is also being accumulated supporting the existence of other networks such as the "motor-premotor" [45], the "parietal–rolandic –premotor," [46] and several others within the frontal lobe [47].

On the other hand, subdural electrode investigations, which have been widely utilized (especially in North American centers since middle-late 1980s) [48] proved useful for a wide range of surgical candidates, including nonlesional MRI cases as well. The concept of an ictal-onset zone with subdurals supposes a simpler and more orderly organization, with a primary ictal-onset region spreading, more or less rapidly, to neighboring or remote areas. Although three-dimensional sampling with subdurals placed over both lateral and medial surfaces in experienced hands is feasible, most studies sample from the lateral convexity and/or basal temporal-occipital region. Overall, technical constraints and risk considerations result in fewer explorations of the medial hemispheric and basal frontal regions. In addition, bilateral sampling is a more complex and risk-associated process compared to bilateral stereo-EEG explorations.

For reasons discussed earlier, subdural arrays are preferred by many epileptologists when the issue is about lateral convexity epileptogenic zones and ECS for eloquent cortex mapping. Hybrid techniques combining both types of electrodes are utilized by many centers trying to incorporate their particular advantages [49, 50]. Although they are not equivalent to a stereo-EEG study in the strict sense, they may prove very useful in several circumstances (e.g., with insular-opercular-perisylvian explorations).

It is perhaps premature to evaluate the impact of advances in the field of ICE investigations on management and outcomes of epilepsy surgery candidates. It seems that a greater proportion of cases with nonlesional MRI and extratemporal-neocortical epilepsies are currently brought to investigation and surgery; reported outcomes are satisfactory, very close, or, almost comparable to outcomes of patients brought to surgery following noninvasive assessment only. It is difficult, however, to adjust for confounding factors such as independent information from functional imaging, Electrical Source Imaging (ESI) and MEG, which even in nonlesional MRI cases may provide important clues about epileptogenic zone and eloquent cortex localization and organization, further encouraging and guiding an invasive EEG exploration.

8.5 Indications for Chronic Extraoperative ICE Studies Depending on Specific Epileptogenic Substrates

8.5.1 Nonlesional (or Equivocal) MRI

The presence of an epileptogenic MRI abnormality is a strong localization and prognostic clue; overall, surgical outcomes in normal MRI cases are less successful compared to those with epileptogenic lesions. The reasons may be "hidden" and/or more extensive, atypical, not well-visible substrates, and defying optimal surgical resection. As previously discussed, however, the proportion of nonlesional MRI candidates referred to epilepsy surgery centers seems to rise, and epilepsy teams face the challenge of identifying those suitable for surgery. Most of these cases are therefore subjected to ICE studies to obtain more accurate information regarding localization and extent of the epileptogenic tissue as well as to perform eloquent cortex mapping through ECS in case of close proximity to epileptogenic areas. Exceptions to this rule may be cases with strong semiologic surface EEGs and functional imaging evidence of anteromesial temporal lobe epilepsy provided that acute intraoperative electrocorticography verifies epileptogenicity from the same areas [51]. Although the proportion of operated nonlesional cases has risen and successful surgical outcomes may be quite high in

this group overall, it is still perhaps too early to have a full account of the pathogenetic substrates encountered and of their prognostic significance. New pathologies emerge out of operations in this group that still need to be classified and their cause-versus-effect relationship to the epilepsy itself needs to be further clarified [52, 53]. The fact that such pathologies may also be associated with variable surgical outcomes certainly challenges preoperative counseling.

8.5.2 Medial Temporal Sclerosis (MTS)

There is usually no indication for an ICE study in cases of unilateral MTS on MRI and concordant surface EEG localization. Exceptions to this rule may be cases with "temporal lobe plus" features (according to the French school of epileptology) suggesting involvement of insular and perisylvian structures [54, 55] as well as cases with additional imaging pathology ("dual pathology"). Bitemporal disease, manifesting with various combinations of bilateral MTS on MRI and bitemporal epileptogenicity on surface EEG, is a particularly challenging category, often necessitating ICE investigations [56]. Given that the critical issue is which one of the two mediotemporal regions is primarily responsible for epileptogenesis, it is imperative that these structures are sampled as accurately as possible with the appropriate ICE strategy. Therefore, depth electrodes targeting both hippocampi are more advantageous in this regard compared with subdural strips/grids, which may be pushed up to the parahippocampal gyrus at best [32–34]. Nevertheless, even under optimal ICE investigational conditions of bitemporal epilepsy, surgical results are less satisfactory compared to those of unilateral MTS cases [56]. A particular situation (e.g., a burned-out hippocampus) of deceivingly bitemporal epileptogenicity (or paradoxical lateralization to the presumably healthy side), merits discussion. It is about the paradoxical coexistence of unilateral MTS and surface EEG ictal-onsets from the contralateral (and apparently normal on MRI grounds) temporal lobe. Depth electrode studies in small series of such cases have convincingly shown that seizures, as a rule, start from the sclerotic hippocampus but do not propagate to the ipsilateral temporal neocortex because of the severe sclerotic damage and associated disruption of connections to the ipsilateral temporal neocortex. Instead, they spread to the contralateral normal hippocampus and from there to the temporal neocortex of the same side, thus falsely showing up on surface EEGs as "contralateral" temporal lobe ictal localization [57]. Currently, many centers, when confronted with this scenario, proceed to surgery of the sclerotic side without prior ICE investigations.

8.5.3 Focal Cortical Dysplasia (FCD)

Indications for ICE investigations depend on lesion detectability, type, and location (possible overlap with the eloquent cortex). Between 20% and 50% of FCD (especially the type I and mild malformation of cortical development (mMCD) are not detectable by MRI [58–60]. ICE studies are therefore mandatory in these cases. Even in the presence of focal cortical dysplasia (FCD)-suggesting MRI features, ICE studies are often performed in order to verify lesion epileptogenicity (more so if MRI features are ambiguous), determine epileptogenic tissue extent (which may be more extensive than the imaging abnormality), and perform ECS for mapping nearby eloquent cortices. However, there are situations in which chronic ICE may well be omitted; this is the case with some small, type IIb (bottom of the sulcus) FCDs [61, 62] located at a safe distance from the eloquent cortex. This lesion type is associated with a relatively restricted epileptogenic field within the lesion itself and the proximate area (Fig. 8.4). Resection of the lesion in these cases, with borders possibly being modified by acute intraoperative electrocorticography, may suffice to achieve excellent surgical outcomes in almost 80% of operated patients [63, 64]. Too often, however, type IIb FCD is encountered close to the primary motor-sensory cortex, and ICE studies are felt to be necessary to more accurately define possible overlap between the epileptogenic and eloquent cortices. If such an overlap is present, serious concerns arise as to whether the epileptogenic cortex should be radically resected at the cost of a highly probable postoperative motor-sensory deficit [65] or a partial resection only should be done, saving the eloquent cortex. The latter procedure has fewer chances for excellent seizure control and even a small risk for deterioration [66, 67].

8.5.4 Tumors

As a rule, noninvasive data (semiology and surface EEGs) suffice to provide lesion-concordant localization clues. Accordingly, ICE studies for purposes of documenting epileptogenicity from the lesion area are only needed on rare occasions. However, with anteromesial temporal indolent/low-growth tumors (especially dysembryoblastic neuroepithelial tumor [DNETs] and gangliogliomas) there are often concerns about epileptogenicity of the ipsilateral hippocampus, even if this structure looks normal and not invaded by tumor on MRI [17]. A simple lesionectomy may not suffice for an excellent outcome if an epileptogenic hippocampus is left in place. Many centers proceed to acute intraoperative ECoG investigations (and occasionally to chronic ICE monitoring) of the temporal lobe, and although there is a lack of controlled data, resection of hippocampal/medial temporal structures is favored in addition to tumor surgery if epileptic activity is

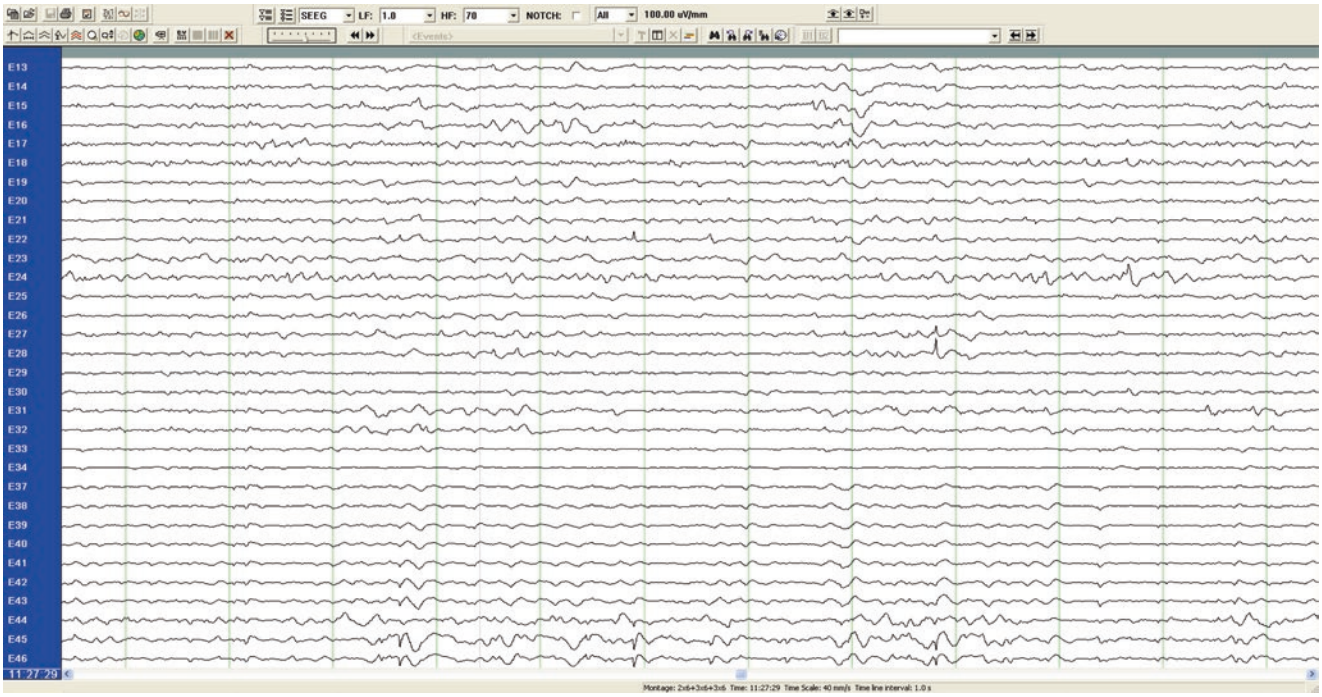

Fig. 8.4 Type IIb FCD recordings from an intralesional depth electrode (contacts 37–46) and a superficial subdural grid (contacts 1–34; non-active contacts 1–12 omitted for higher definition purposes). Depth electrode is placed perpendicularly crossing subdural grid between its contacts 27, 28, 31, and 32. Notice interictal spiking restricted to superficial intralesional depth contacts 46 and 45, without being reflected to nearby subdural contacts

recorded there [68, 69]. Nevertheless, it should be kept in mind that even though ECoG may reveal medial temporal spiking, specific criteria upon which to base a decision for medial temporal resection in the setting of temporal lobe tumor surgery with normal-looking hippocampi/medial temporal structures on MRI are still lacking [70, 71]. Another concern is the presence of additional FCD-like histopathologic features in the tumor vicinity (type IIIb FCD according to the recent International League Against Epilepsy [ILAE] proposal). These are more often encountered with developmental/indolent tumors (long epilepsy associated tumors or LEATs) and are not easily detectable by MRI. Their relevant epileptogenic potential remains unknown; as a result, there is no consensus as to how to approach them from the electrophysiologic point of view. Many centers utilize acute intraoperative ECoG in similar cases, looking for epileptogenic activity from medial temporal structures and perilesional/neighboring cortices in order to modify resection borders [72]. Finally, one more indication for ICE investigations in tumoral patients is lesion proximity to, or, possible overlap with eloquent cortex, necessitating cortical mapping with ECS.

8.5.5 Gross Destructive Gliotic Lesions

Overall, patients with these lesions are not considered ideal surgical candidates given the extensive pathologic substrate and multifocal epileptogenicity often associated with them. The principal lesion may be accompanied by nearby cortical lamination abnormalities (type IIId FCD according to the newly proposed ILAE classification scheme) [73] whose epileptogenic potential is not yet well known. In cases of early-onset catastrophic epilepsies secondary to such lesions, hemispherectomy may be an option in childhood; however, this procedure is rarely performed in adults because of concerns about postoperative neurologic deficits. A yet unknown proportion of such patients may harbor restricted areas of epileptogenicity within that gross pathologic substrate, and noninvasive studies may provide clues in support of this [74–76]. A chronic ICE study (or acute intraoperative electrocorticography) may thus be indicated and suggest successful resective surgery.

8.6 What Do ICE Studies Show?

In principle, the aim of an ICE study is to identify (a) the "gross" area of epileptogenic propensity, defined as the irritative zone, whose electrophysiologic marker is interictal spikes, and (b) the ictal onset zone where the initial ictal discharge starts along with early spread regions and networks. These two zones, along with the lesional zone (which includes the pathologic epileptogenic substrate) largely determine the location and extent of the epileptogenic zone, a theoretical concept meaning the "cortical region needed to be removed to obtain a successful surgical outcome." The accurate prediction of the epileptogenic zone, which is a derivative of the previous three zones), is thus validated a posteriori through the surgical effect [77].

8.6.1 Irritative Zone/Interictal Activity

In the great majority of cases the cortical area of interictal spiking (irritative zone) overlaps, at least partially, with the ictal-onset zone [78–80]. An absolute co-localization of the two zones is exceptional, since interictal spikes are usually recorded not only from the actual ictal-onset zone but also from remote areas and even the contralateral cortex (as is often the case with medial temporal epilepsy) [81–83]. Spiking rate varies, depending on consciousness state, use of anesthetic agents, and underlying epileptogenic substrates [84, 85]. Spike voltage and field are also variable, ranging from low-amplitude spikes restricted to one to two electrodes to high-voltage and wide distribution ones involving many electrodes. Most of the interictal activity recorded by ICE is not reflected on surface EEG recordings. This depends on location and extent of cortex-generating epileptiform activity: for example, spiking from medial temporal structures does not show up on scalp electrodes [86]. Temporal lobe spikes on surface EEG reflect activity originating in the lateral temporal neocortex itself, which is either independent of medial temporal spikes or a result of their propagation to the lateral temporal lobe [4]. It is important to emphasize again that only spikes from the lateral hemispheric surface/convexity can be recorded by scalp electrodes provided they recruit a quite extensive region of neocortical surface (10–15 square cm, as previously discussed).

Although more than one spike population may be recorded, they do not all have the same significance. Several studies across most epileptogenic substrates have shown that regions of frequent spiking with consistent focality and rhythmic features in prolonged trains and associated with local background activity attenuation correlate better with the ictal-onset zone and predict a better surgical outcome if included in the final resection margins [87, 88]. Rare spiking over regions with better organized background activity is less significant in this regard [72].

Spike propagation from one region to another may also be seen when a time lag is consistently shown between spikes seemingly appearing at the "same moment" in different regions. Resecting the areas, including the "leading spike," has been shown in a landmark acute ECoG study to correlate with successful surgical outcome compared with no resection of them or resection of the "propagated" spikes only [89]. Spike propagation may take place along normally existing association pathways (e.g., from medial temporal to basal and lateral temporal neocortex) [4] and/or within the epileptogenic pathology itself [42, 83].

Particular interictal patterns (although somewhat deviant compared to what is typically considered interictal) merit further discussion. In acute ECoG recordings, Palmini et al. [12] described three patterns (repetitive electrographic discharges, bursting pattern, and semicontinuous rhythmic spike-wave), which were found to be strongly associated with focal cortical dysplasia—especially the balloon cell type (IIB). They thought that these patterns might somehow represent the electrographic "signature" of these lesions [12]. Their findings have been variably reproduced by other groups in both acute and chronic ECoG studies, mainly in FCD and in LEATs [16]. In particular, French and Italian groups in their depth electrode studies of patients with FCD have identified semicontinuous spiking and polyspike bursts interrupted by background attenuation as common and specific features for type IIB FCD ECoG pattern. More importantly, they have detected this pattern from depth electrodes placed within the lesion, thus providing direct evidence for its intrinsic epileptogenicity" (Figs. 8.4 and 8.5) [31, 90]. These patterns may be encountered not only from within the lesion, but also from normal-appearing cortex at its vicinity. What is significant from the practical stand-point is that resection of the areas exposing such patterns is associated with a better surgical outcome—thus suggesting an important role for acute and chronic ECoG in detecting such abnormalities and, finally, in guiding resection limits.

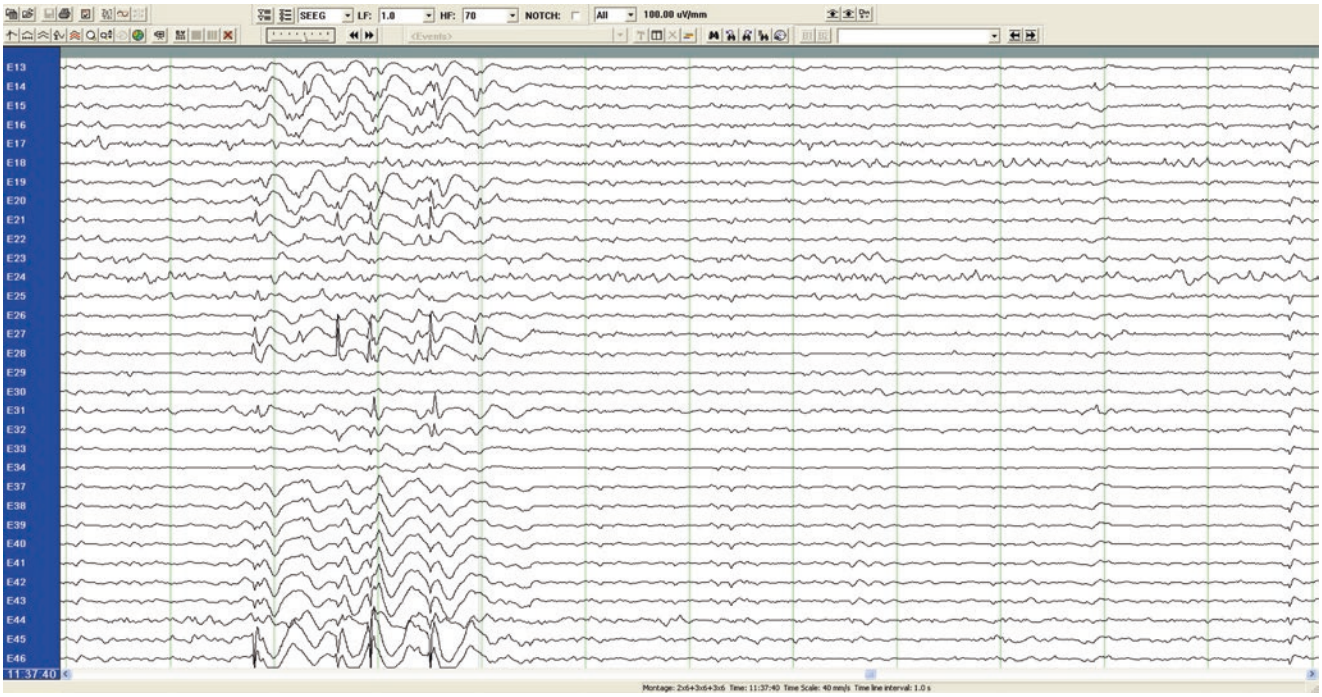

Fig. 8.5 Type IIb FCD recordings from an intralesional depth electrode (contacts 37–46) and a superficial subdural grid (contacts 1–34; non-active contacts 1–12 omitted for higher definition purposes). Depth electrode is placed perpendicularly crossing subdural grid between its contacts 27, 28, 31, and 32. Discharge amplitude and field increase, involving adjacent subdural electrodes

8.6.2 Ictal-Onset Zone

It is important to keep in mind that a given ictal pattern might be considered as indicative of the ictal-onset zone, only if it precedes or at least appears synchronously with the initial clinical manifestations of the seizure. If it appears later than early clinical symptoms and signs, a "propagated" pattern should be suspected rather than one originating from and reflecting the actual ictal onset zone. In such a scenario, it should be questioned whether the intracranial electrodes are appropriately placed over the actual ictal-onset region and not over an ictal-propagation one.

Although ictal electrocorticographic activity is easily recognized in ICE studies, opinions differ as to what components of a given discharge represent true ictal activity. The most common (and simpler) ictal-onset pattern is that of a "low-amplitude fast" discharge (>13–15 Hz). It is encountered especially in neocortical-onset seizures, both temporal and extratemporal, the underlying pathogenic substrate often being focal cortical dysplasia (Fig. 8.6). It is seen, however, across many epileptogenic substrates [91, 92]. Mixed "electrodecrement-low amplitude fast" ictal patterns are also reported. "Low frequency repetitive spiking" (<2 Hz) is typically seen in medial temporal sclerosis [93, 94]. Other ictal-onset patterns include "rhythmic sharp" and "spike-and-wave" activity of unspecified frequency, overall between 2 and 15 Hz. Sinusoidal alpha/theta and delta activities are less frequently encountered and more often represent propagation rather than ictal-onset patterns [94, 95]. Brief epileptiform transients, such as an isolated spike/sharp wave discharge with or without an accompanying electrodecremental response or a brief polyspike discharge may be seen at the very beginning of an ictal pattern. These transients often have a widespread distribution, but this is not necessarily related to a poor surgical prognosis [93]. Among the various ictal-onset patterns, it is the low-amplitude fast one that most reliably predicts accurate localization and successful surgical outcome. (The interested reader is referred to Singh et al. for a comprehensive review of relevant studies) [91].

With medial temporal lobe/hippocampal onset seizures two main ictal patterns are recognized. The first one is the hypersynchronous, with focal hippocampal onset and low frequency periodic spiking less than 2 Hz, transforming subsequently to a low-amplitude fast discharge involving both the amygdalohippocampal complex and the entorhinal cortex (*see* Figs. 8.2 and 8.3) [94, 96, 97]. The second one consists of a low-amplitude fast ictal rhythm from the very beginning, with a wider regionalized onset and early involvement not only of the amygdalohippocampal complex but of the entorhinal/parahippocampal cortices (Figs. 8.7, 8.8, and 8.9). This pattern correlates with entorhinal cortex atrophy in volumetric MRI studies [96]. It is not uncommon for both patterns to coexist in a given patient with medial temporal epilepsy.

Electrodecremental responses (EDs) at ictal onset, either regional or widespread, are also encountered, although there

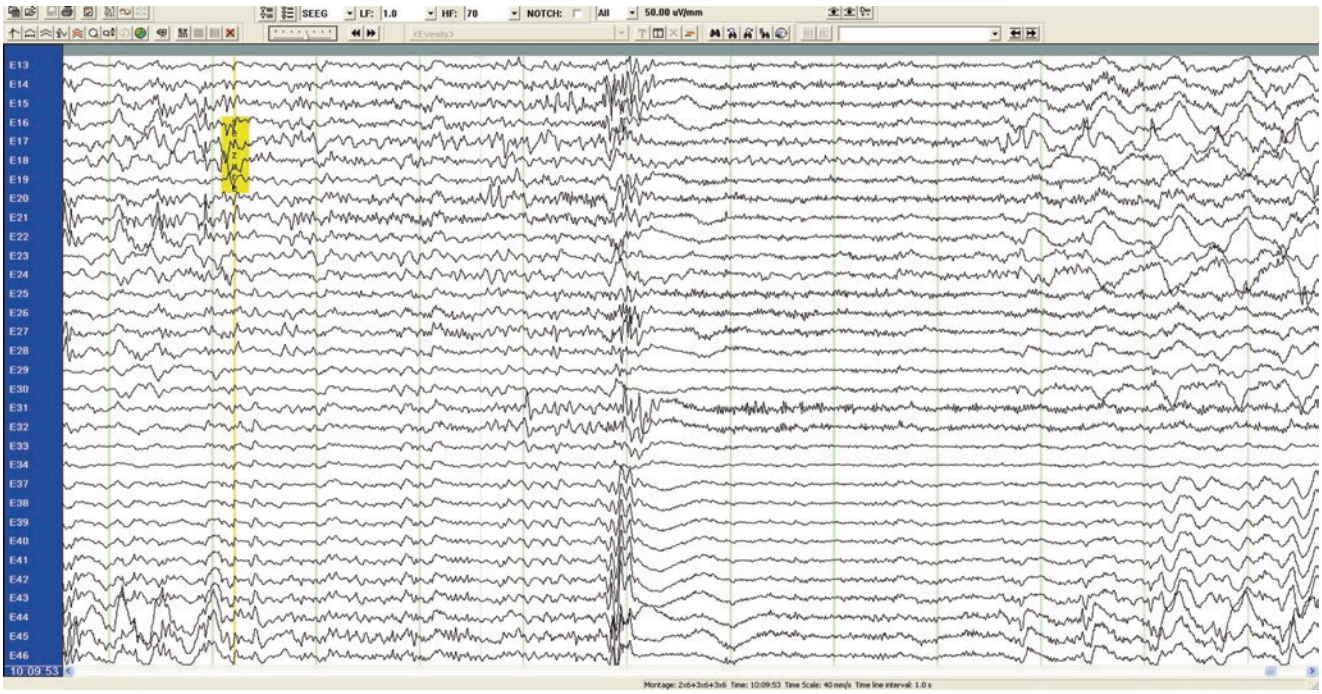

Fig. 8.6 Same patient as in Figs. 8.4 and 8.5. Seizure onset with an initial widespread-polyspike and wave discharge, followed by a low-amplitude fast rhythm; ictal onset pattern typical for FCD

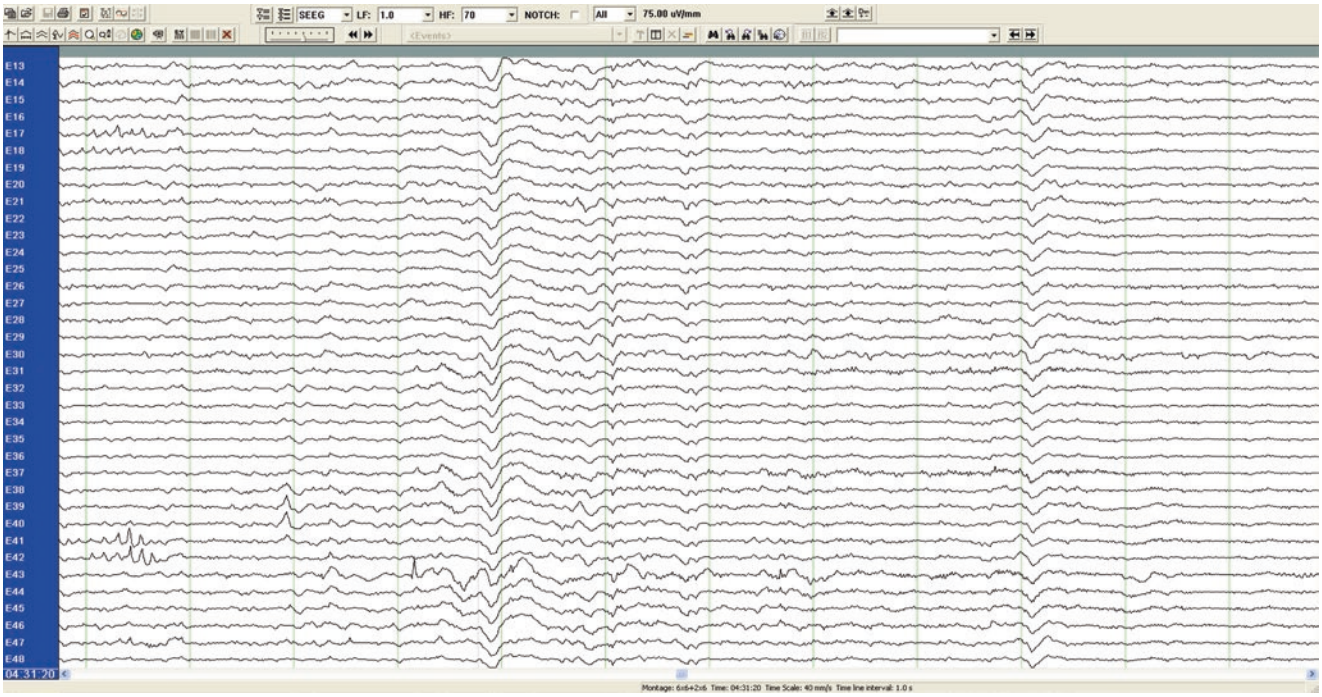

Fig. 8.7 Patient with non-lesional temporal lobe epilepsy. Contacts 31–36: temporopolar subdural strip, with most distal contact 31 located over the mesial temporal cortex. Contacts 37–42: anterior subtemporal subdural strip, with most distal contact 37 located over anterior parahippocampal gyrus. Contacts 43–48: posterior subtemporal subdural strip, with most distal contact 43 located over posterior parahippocampal gyrus

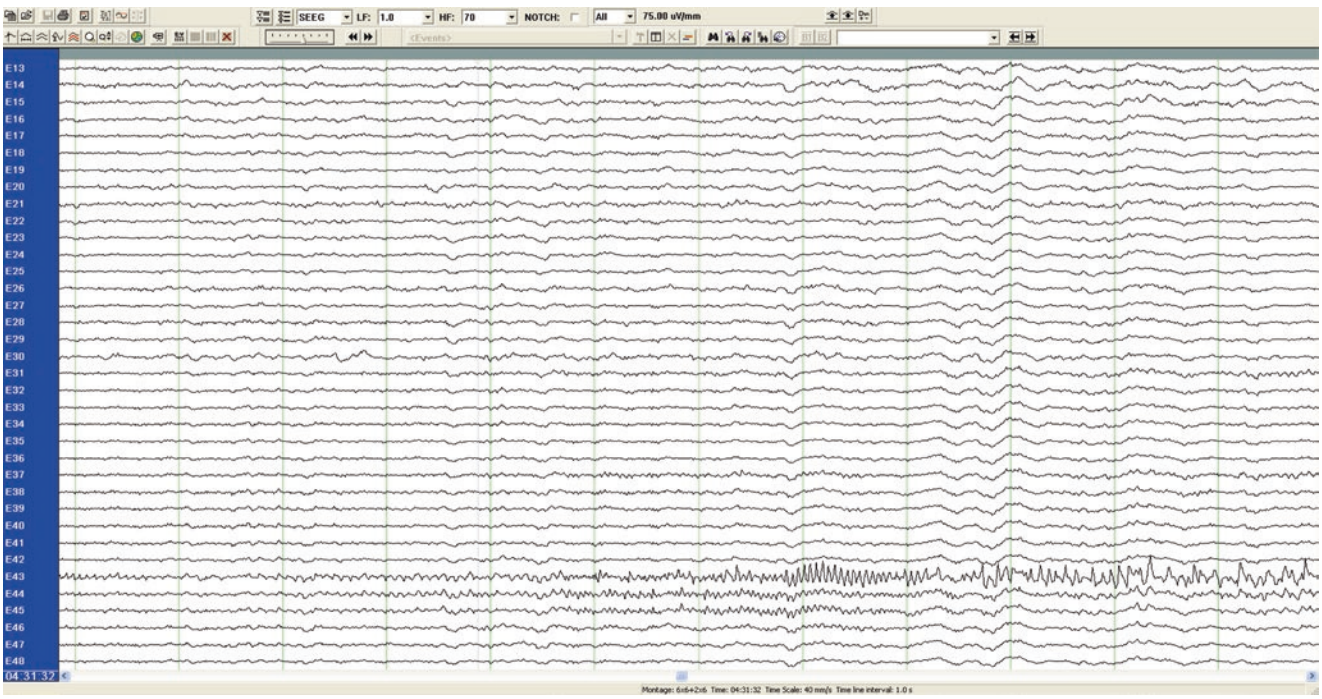

Fig. 8.8 Patient with non-lesional temporal lobe epilepsy. Contacts 31–36: temporopolar subdural strip, with most distal contact 31 located over the mesial temporal cortex. Contacts 37–42: anterior subtemporal subdural strip, with most distal contact 37 located over anterior parahippocampal gyrus. Contacts 43–48: posterior subtemporal subdural strip, with most distal contact 43 located over posterior parahippocampal gyrus. Notice seizure onset with low-amplitude fast rhythm involving distal contacts 31, 37, and 43, sampling from medial temporal/entorhinal and parahippocampal cortices, transforming latter to lower frequency-higher amplitude rhythmic activity (see also Fig. 8.9)

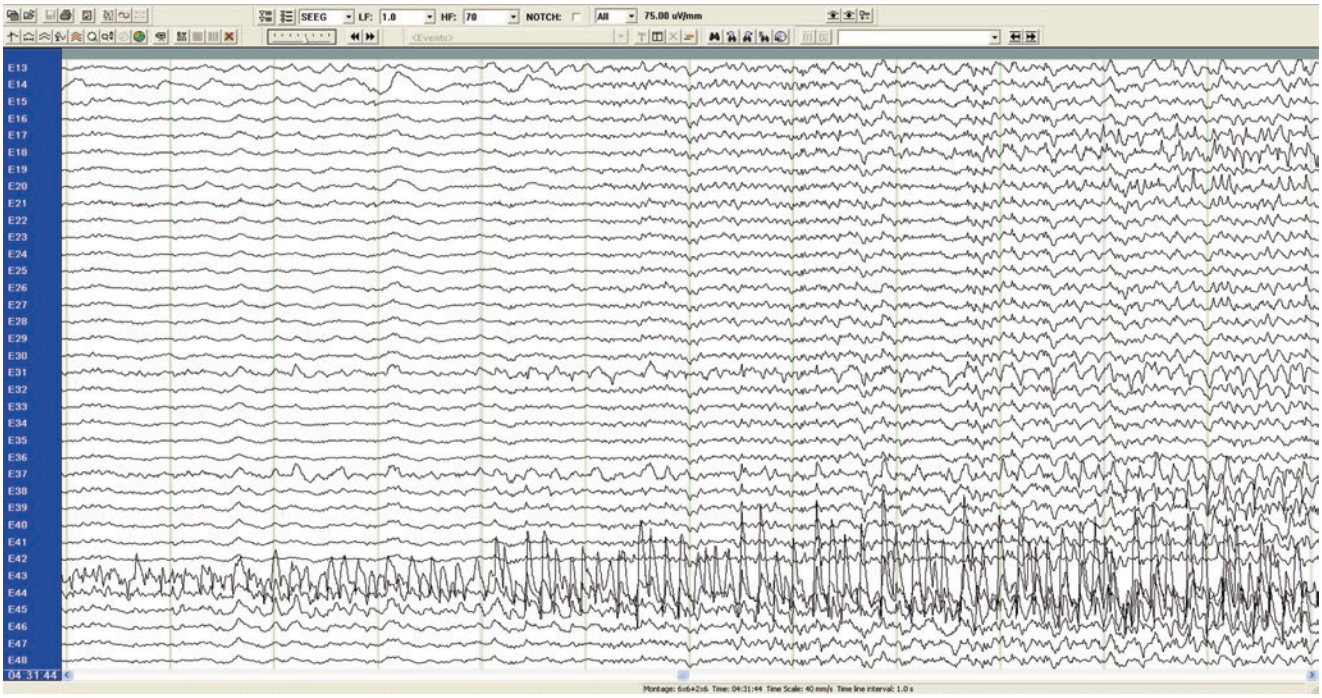

Fig. 8.9 Patient with non-lesional temporal lobe epilepsy. Contacts 31–36: temporopolar subdural strip, with most distal contact 31 located over the mesial temporal cortex. Contacts 37–42: anterior subtemporal subdural strip, with most distal contact 37 located over anterior parahippocampal gyrus. Contacts 43–48: posterior subtemporal subdural strip, with most distal contact 43 located over posterior parahippocampal gyrus

is no consensus about whether they should be considered as belonging to the ictal-onset pattern itself. Some authors suggest that they reflect global cerebral changes that allow particular and susceptible brain areas to be engaged in the epileptic activity rather than bona fide epileptic activity [4]. Although it is not always easily discernible, a concomitant low-amplitude fast rhythm may evolve in parallel with or shortly after EDs [98]. The prognostic significance of the ED pattern still remains controversial. Some studies report poor while others report better surgical outcomes, particularly with mixed EDs—low-amplitude fast patterns [93].

It is still debatable whether there is any relationship between the ictal-onset pattern morphology, the underlying epileptogenic substrate, and the intrinsic organization of the cortical region it arises from. Low-frequency periodic spiking has been specifically assigned to medial temporal sclerosis; it is difficult, however, to disentangle the "pathology" from the "region" effect, as this pattern has occasionally been recorded with ictal onsets from apparently healthy medial temporal structures [94]. Only a few studies have systematically considered electrodecremental patterns [93, 99], perhaps showing a higher predilection for frontal lobe ictal-onset zone localization. Low amplitude fast patterns are related to focal cortical dysplasia and neurodevelopmental tumors, but overall, and with the possible exception of the low frequency periodic spiking, virtually every ictal pattern may be encountered in most pathologic substrates and locations.

Propagation patterns appearing later in the evolution of the seizure may be falsely perceived as the ictal-onset ones, especially if the intracranial electrodes are not appropriately placed over the actual ictal-onset region. Although earlier studies have suggested that propagation patterns most often consist of rhythmic theta and delta activity [95], it is now known that they may be virtually identical to the ictal-onset pattern, including the low-amplitude fast one, typically thought to originate at the ictal-onset region in neocortical epilepsies [94]. The same also holds true for the low-frequency repetitive spiking for the hippocampal onset seizures. Therefore, the morphology of the ictal pattern should not be an absolute criterion for differentiating between ictal-onset and ictal-propagation regions. A particularly challenging situation is when an independent ictal pattern is triggered during the evolution of a seizure at a region of secondary spread/propagation, which may often be at a distance from the actual ictal-onset zone. This phenomenon has been called intra-ictal activation and is related to poorer surgical outcomes if the area of intra-ictal activation is not removed [100].

8.6.3 High-Frequency Oscillations

High-frequency oscillations (HFOs) consist of oscillatory activity above 80 Hz and have attracted much interest in ICE studies because of their significance as an epilepsy biomarker. They are classified as ripples (80–250 Hz) and fast ripples (250–500 Hz) and can be detected only by EEG sampling rates of 2000 Hz and above. Ripples and fast ripples have been related to physiologic memory and somatosensory-evoked potentials. Recent evidence suggests, however, that fast ripples may be a reliable marker of epileptogenic tissue in both medial temporal and neocortical epilepsies [101] and across a variety of pathogenic substrates. Fast ripples are often present in the irritative zone, and although they may be superimposed on interictal spikes, they are also recorded in isolation [102] and seem to correlate better with the ictal-onset zone in comparison to interictal spikes. Including fast ripples in the resection borders has been shown to result in better surgical outcomes [102, 103]; however, it is still uncertain to what extent and which type of ripples should be included in the resection to achieve the best possible outcomes. Perhaps areas with very frequent fast ripples are more important in this regard [103].

8.7 The Prognostic Value of Intracranial Electrode Studies

In lesional epilepsy surgery the principal aim is the radical resection of the structural abnormality causing epileptic seizures. However, the imaging lesion is not always an ideal marker of the underlying epileptogenic zone. This is particularly true with focal cortical dysplasia and sometimes with neurodevelopmental tumor surgery, where a number of studies with acute ECoG and/or chronic ICE recordings have shown that active epileptogenic "spots" may not be present strictly within the lesion itself (intrinsic epileptogenicity) but also be located outside the imaging abnormality borders. In these cases epilepsy surgery aims not only to remove the lesion but also the most active regions of the irritative as well as the ictal-onset zone. This strategy provides better outcomes compared with incomplete lesion resection and/or incomplete epileptogenic zone resection and is associated with excellent postoperative seizure outcomes in 55–70% of operated cases [12, 87, 88, 104]. However, it is not always easy to disentangle an "incomplete epileptogenic zone resection" from an "incomplete lesion resection," so it is difficult to know how much an ICE defined incomplete epileptogenic zone resection may account for a suboptimal outcome independent of lesion resection completeness. In non-lesional surgery, ICE studies results are the most important and perhaps the only available clue for determining localization and extent of tissue to be removed. Regardless of the presence (or absence) of an epileptogenic imaging abnormality, resection of most active and leading interictal spiking spots as well as of the ictal-onset zone (especially if it is manifesting low amplitude fast discharges) predicts a successful outcome. On the other hand, feasibility of resection is largely dependent on the "focality" of the epileptogenic zone; widespread ictal-onset regions and shorter latency to seizure spread and ictal involvement of brain structures beyond the frontal lobe have been shown to be correlated with suboptimal outcomes in a recent series of frontal lobe cases [105]. Inappropriate placement of ICE electrodes, for example of subdural grids placed at the borders of the actual epileptogenic zone (ictal-onsets from the edge of the grid) [9] may identify just part of the epileptogenic zone and lead to incomplete epileptogenic tissue resection. Another critical factor from ICE recordings predicting poor outcome is epileptogenic cortex proximity/overlap with eloquent cortex, rendering complete resections unfeasible.

8.8 Complications of ICE Studies

In a recent meta-analysis of adverse events related to subdural electrode utilization [106], infections emerge as the most common complication with a pooled prevalence estimate of 2.3% for pyogenic neurologic infections, 3% for superficial infections, and 7% for asymptomatic positive cerebrospinal cultures. Intracranial hemorrhage and new-onset transient neurologic deficits occurred with a prevalence of 4% and 4.6%, respectively. Elevated intracranial pressure prevalence was estimated at 2.4%. Permanent neurologic deficits and/or fatalities are exceptional. Electrodes pulled out by the patient represent a much less frequent but unique problem, emphasizing the need for close supervision and monitoring during the recording session. As a result of these adverse events, as many as 3% of patients may require additional unplanned operations. Increasing the number of implanted electrodes and the length of the study correlate positively with the prevalence of adverse events.

Stereo-EEG/depth electrode studies appear to be somewhat less risky compared to subdurals [27, 107], with a pooled prevalence of complications about 1.6% (mostly related to intracranial hemorrhage and infections) and of permanent neurologic deficits about 0.6%. Stereo-EEG studies also appear to be safe in children [36, 108].

8.9 Summary

Invasive EEG studies are an integral part of presurgical investigations in epilepsy and mandatory for a significant proportion of patients for whom standard noninvasive tests are not sufficient to decide on surgery. Invasive EEG studies

should be based upon well-defined and testable localization hypotheses derived from noninvasive work-ups. The aim of an invasive study is not only to document the location of epileptogenic tissue in a certain area but also to define its extent and limits as well as its proximity to eloquent cortical regions by electrocortical stimulation. In most tertiary-level epilepsy centers, subdural electrodes, depth electrodes, and combinations of them are widely utilized, with a trend toward increasing use of stereo-EEG/depth and combined subdural/depth electrode approaches. Identifying and resecting most active interictal spiking areas as well as ictal-onset and early seizure spread zones are important for achieving a successful surgical outcome not only in nonlesional MRI cases but in addition to FCD cases, where epileptogenic tissue may be located beyond the lesion margins which, if not resected, may be responsible for suboptimal outcomes. HFOs, a newly recognized epileptic biomarker, may assist in more accurate mapping and resection of epileptogenic tissue. Invasive EEG procedures in experienced hands appear safe and associated with an acceptable risk of treatable adverse events. An important topic for future research is whether information based on irritative zone mapping, taking into account particular features of recorded spike populations, HFOs, and the whole setting of clinical and imaging features, may be enough to offer surgery without recording seizures in at least a proportion of surgical candidates subjected to invasive EEG explorations, thus bypassing prolonged recording sessions and the associated risks and costs.

References

1. Nair D, Burgess R, McIntyre C, Luders H-O. Chronic subdural electrodes in the management of epilepsy. Clin Neurophysiol. 2008;119:11–28.
2. Pierre G. Neuronal generators and the problem of localization in electroencephalography: application of volume conductor theory to electroencephalography. J Clin Neurophysiol. 1985;2:327–54.
3. Tao J, Ray A, Hawes-Ebersole S, Ebersole J. Intracranial EEG substrates of scalp interictal spikes. Epilepsia. 2005;46:69–676.
4. Alarcon G. Electrophysiological aspects of interictal and ictal activity in human partial epilepsy. Seizure. 1996;5:7–33.
5. Tao J, Baldwin M, Ray A, Hawes-Ebersole S, Ebersole J. The impact of cerebral source area and synchrony on recording scalp electroencephalography ictal patterns. Epilepsia. 2007;48:2167–76.
6. Unnvongse K, Wehner T, Foldvary-Schaeffer N. Mesial frontal lobe epilepsy. J Clin Neurophysiol. 2012;29:371–8.
7. Kriegel M, Roberts M, Jobst B. Orbitofrontal and insular epilepsy. J Clin Neurophysiol. 2012;29:385–91.
8. Lesser R, Krone N, Weber W. Subdural electrodes. Clin Neurophysiol. 2010;121:1376–92.
9. Widdess-Walsh P, Jehi L, Nair D, Kotagal P, Bingaman W, Najm I. Subdural electrode analysis in focal cortical dysplasia: predictors of surgical outcome. Neurology. 2007;69:660–7.
10. Klem G, Nehamkin S. Invasive electrodes in long-term monitoring. In: Luders H-O, editor. Textbook of epilepsy surgery. London: Informa; 2008. p. 623–8.
11. Sanchez-Fernandez I, Loddenkemper T. Electrocorticography for seizure foci mapping in epilepsy surgery. J Clin Neurophysiol. 2013;30:554–70.
12. Palmini A, Gambardella A, Andermann F, Dubeau F, Da Costa J, Olivier A, et al. Intrinsic epileptogenicity of human dyplastic cortex as suggested by corticography and surgical results. Ann Neurol. 1995;37:476–87.
13. Duchowny M. Clinical, functional and neurophysiologic assessment of dysplastic cortical networks: implications for cortical functioning and surgical management. Epilepsia. 2009;50(Suppl 9):19–27.
14. Ferrier C, Alarcon G, Engelsman J, Binnie C, Koutroumanidis M, Polkey C, et al. Relevance of residual histologic and electrocorticographic abnormalities for surgical outcome in frontal lobe epilepsy. Epilepsia. 2001;42:363–71.
15. Tran T, Spencer S, Javidan M, Pacia S, Marks D, Spencer D. Significance of spikes recorded on intraoperative electrocorticography in patients with brain tumors and epilepsy. Epilepsia. 1997;38:1132–9.
16. Ferrier C, Aronika E, Leijten F, Spliet W, Van Huffelen A, Van Rijen P, Binnie C. Electrocorticographic discharge patterns in glioneuronal tumors and focal cortical dysplasia. Epilepsia. 2006;47:1477–86.
17. Zaghloul K, Schramm J. Surgical management of glioneuronal tumors with drug-resistant epilepsy. Acta Neurochir. 2011;153:1551–9.
18. Tran T, Spencer S, Marks D, Javidan M, Pacia S, Spencer D. Significance of spikes recorded on electrocorticography in non-lesional medial temporal lobe epilepsy. Ann Neurol. 1995;38:763–70.
19. Schwartz T, Bazil C, Walczak T, Chan S, Pedley T, Goodman R. The predictive value of intraoperative electrocorticography in resections for limbic epilepsy associated with mesial temporal sclerosis. Neurosurgery. 1997;40:302–11.
20. Gilliam F, Faught E, Martin R, Bowling S, Bilir E, Thomas J, et al. Predictive value of MRI-identified medial temporal sclerosis for surgical outcome in temporal lobe epilepsy: an intent to treat analysis. Epilepsia. 2000;41:963–6.
21. Berg A, Vickrey B, Langfitt J, Sperling M, Walczak T, Shinnar S, et al. The multicenter study of epilepsy surgery: recruitment and selection for surgery. Epilepsia. 2003;44:1425–33.
22. Cendes F, Li M, Watson C, Andermann F, Dubeau F, Arnold D. Is ictal recording mandatory in temporal lobe epilepsy? Arch Neurol. 2000;57:497–500.
23. Jayakar P, Gaillard W, Tripathi M, Liberson M, Mathern G, Cross H. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014;55:507–18.
24. Rosenow F, Menzler K. Invasive studies in tumor-related epilepsy: when are they indicated and with what kind of electrodes? Epilepsia. 2013;54(Suppl 9):61–5.
25. Ryvlin P, Cross H, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol. 2014;13:1114–26.
26. Garganis K, Kokkinos V, Zountsas B. Extratemporal surface EEG features do not preclude successful surgical outcomes in drug-resistant epilepsy patients with unitemporal MRI lesions. Epileptic Disord. 2012;14:275–89.
27. Jayakar P, Gotman J, Harvey S, Palmini A, Tassi L, Schomer D, et al. Diagnostic utility of invasive EEG for epilepsy surgery: indications, modalities and techniques. Epilepsia. 2016;57:1735–47.
28. Chauvel P, Delgado-Esqueta A, Halgren E, Bancaud J. Frontal lobe seizures and epilepsies. New York: Raven Press; 1992.
29. Lhatoo S, Lacuey N, Ryvlin P. Principles of stereotactic electroencephalography in epilepsy surgery. J Clin Neurophysiol. 2016;33:478–582.
30. Afif A, Chabardes S, Minotti L, Kahane P, Hoffman D. Safety and usefulness of insular depth electrodes implanted via an oblique

approach in patients with epilepsy. Neurosurgery. 2008;62(ONS Suppl 2):471–80.
31. Francione S, Nobili L, Cardinale F, Citterio A, Galli C, Tassi L. Intra-lesional stereo-EEG activity in Taylor-type focal cortical dysplasia. Epileptic Disord. 2003;5(Suppl 2):105–14.
32. Alsaadi T, Laxer K, Barbaro N, Marks D, Garcia P. False lateralization by subdural electrodes in two patients with temporal lobe epilepsy. Neurology. 2001;57:532–4.
33. Sperling M, O'Connor M. Comparison of depth and subdural electrodes in recording temporal lobe seizures. Neurology. 1989;39:1497–504.
34. Eisenschenk S, Gilmore R, Cibula J, Roper S. Lateralization of temporal lobe foci: depth versus subdural electrodes. Clin Neurophysiol. 2001;112:836–44.
35. David O, Blauwblomme T, Job A-S, Chabardes S, Hofmann D, Minotti L, Kahane P. Imaging the seizure-onset zone with stereo-electroencephalography. Brain. 2010;134:2898–911.
36. Cossu M, Cardinale F, Castana L, Nobili L, Sartori L, Lo Russo G. Stereo-EEG in children. Childs Nerv Syst. 2006;22:766–78.
37. Nowell M, Rodionov R, Zombori G, Sparks R, Winston G, Kingborn J, et al. Utility of 3D multimodality imaging in the implantation of intracranial electrodes in epilepsy. Epilepsia. 2015;56:403–13.
38. Gonzalez Martinez G, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. Stereoelectroencephalography in the "difficult to localize" refractory focal epilepsy: early experiences from a North American epilepsy center. Epilepsia. 2013;54:323–30.
39. Luders H-O, Najm I, Nair D, Widdess-Walsh P, Bingaman W. The epileptogenic zone: general principles. Epileptic Disord. 2006;8(Suppl 2):1–9.
40. Kahane P, Landre E, Minotti L, Francione S, Ryvlin P. The Bancaud and Talairach view on the epileptogenic zone: a working hypothesis. Epileptic Disord. 2006;8(Suppl 2):16–26.
41. Wendling F, Chauvel P, Biraben A, Bartolomei F. From intracerebral EEG signals to brain connectivity: identification of epileptogenic networks in partial epilepsy. Front Syst Neurosci. 2010;4:154. https://doi.org/10.3389/fnsys.2010.00154.
42. Proix T, Bartolomei F, Guye M, Jirsa V. Individual brain structure and modelling predict seizure propagation. Brain. 2017;140:641–54.
43. Bernhardt B, Hong S, Bernasconi A, Bernasconi N. Imaging structural and functional brain networks in temporal lobe epilepsy. Front Syst Neurosci. 2013;7:624. https://doi.org/10.3389/fnsys.2013.00624.
44. Bartolomei F, Consadier-Rimele D, McGonigal A, Aubert S, Regis J, Gavaret M, et al. From mesial temporal lobe to perisylvian seizures: a quantified study of temporal lobe seizure networks. Epilepsia. 2010;51:2147–58.
45. Bonini F, McGonigal A, Wendling F, Regis J, Scavarda D, Carron R, et al. Epileptogenic networks in seizures arising from the motor cortex. Epilepsy Res. 2013;106:92–102.
46. Bartolomei F, Gavaret M, Hewett R, Valton L, Aubert S, Regis J, et al. Neural networks underlying parietal lobe seizures: a quantified study from intracerebral recordings. Epilepsy Res. 2011;93:164–76.
47. Bonini F, McGonigal A, Trebuchon A, Gavaret M, Bartolomei F, Giusiano B, Chauvel P. Frontal lobe seizures: from clinical semiology to localization. Epilepsia. 2014;55:264–77.
48. Luders H-O, Lesser R, Dinner D, Morris H, Wyllie E, Godoy J. Localization of cortical function: new information from extraoperative monitoring of patients with epilepsy. Epilepsia. 1988;29:556–65.
49. Surbeck W, Bouthillier A, Weil A, Crevier L, Carmant L, Lortie A, et al. The combination of subdural and depth electrodes for intracranial EEG investigation of suspected insular (perisylvian) epilepsy. Epilepsia. 2011;52:458–66.
50. Enatsu R, Bulacio J, Najm I, Wyllie E, So N, Nair D, et al. Combining stereoelectroencephalography and subdural electrodes in the diagnosis and treatment of medically intractable epilepsy. J Clin Neurosci. 2014;21:1441–5.
51. Burkholder V, Sulc V, Hoffman M, Cascino G, Britton J, So E, et al. Interictal scalp electroencephalography and intraoperative electrocorticography in magnetic resonance imaging – negative temporal lobe epilepsy. JAMA Neurol. 2014;71:702–9.
52. Alshafai L, Ochi A, Go C, McCoy B, Hawkins C, Otsubo H, et al. Clinical EEG, MRI, MEG and surgical outcomes of pediatric epilepsy with astrocytic inclusions versus focal cortical dysplasia. Epilepsia. 2014;55:1568–75.
53. Sakuma S, Halliday W, Nomura R, Baba S, Sato Y, Okanari K, et al. Increased subcortical oligodendroglia-like cells in pharmacoresistant focal epilepsy in children correlate with extensive epileptogenic zones. Epilepsia. 2016;57:2031–8.
54. Barba C, Barbati G, Minotti L, Hoffmann D, Kahane P. Ictal clinical and scalp-EEG findings differentiating temporal lobe epilepsies from temporal plus epilepsies. Brain. 2007;130:1957–67.
55. Barba C, Rheims S, Minotti L, Guenot M, Hoffmann D, Chabardes S, et al. Temporal plus epilepsy is a major determinant of temporal lobe surgery failures. Brain. 2016;139:444–51.
56. Thom M, Mathern G, Cross H, Bertram E. Medial temporal lobe epilepsy: how do we improve surgical outcome? Ann Neurol. 2010;68:424–34.
57. Mintzer S, Cendes F, Soss J, Andermann F, Engel J, Dubeau F, et al. Unilateral hippocampal sclerosis with contralateral temporal scalp ictal onset. Epilepsia. 2004;45:792–802.
58. Krsek P, Maton B, Korman B, Pacheco-Jakome E, Jayakar P, Dunoyer C, et al. Different features of histopathological subtypes of pediatric focal cortical dysplasia. Ann Neurol. 2008;63:758–69.
59. Krsek P, Pieper T, Karlmeier A, Hildebrandt M, Kolodziejczyk D, Winkler P, et al. Different presurgical characteristics and seizure outcomes in children with focal cortical dysplasia type I or II. Epilepsia. 2009;50:125–37.
60. Colombo N, Tassi L, Deleo F, Citterio A, Bramerio M, Mai R, et al. Focal cortical dysplasia type IIa and IIb: MRI aspects in 118 cases proven by histopathology. Neuroradiology. 2012;54:1065–77.
61. Hofmann P, Fitt G, Simon Harvey A, Kuzniecky R, Jackson G. Bottom-of-sulcus dysplasia: imaging features. Am J Radiol. 2011;196:881–5.
62. Sisodiya S, Fauser S, Cross H, Thom M. Focal cortical dysplasia type II: biological features and clinical perspectives. Lancet Neurol. 2009;8:830–43.
63. Chassoux F, Landre E, Mellerio C, Turak B, Mann M, Daumas-Duport C, et al. Type II focal cortical dysplasia: electroclinical phenotype and surgical outcome related to imaging. Epilepsia. 2012;53:349–58.
64. Simon Harvey A, Mandelstam S, Maixner W, Leventer R, Semmelroch I, McGregor D, et al. The surgically remediable syndrome of epilepsy associated with bottom-of-sulcus dysplasia. Neurology. 2015;84:2021–8.
65. Van Offen M, Van Rijen P, Leiten F. Central lobe epilepsy surgery – (functional) results and how to evaluate them. Epilepsy Res. 2017;130:37–46.
66. Sarkis R, Jehi L, Bingaman W, Najm I. Surgical outcome following resection of rolandic focal cortical dysplasia. Epilepsy Res. 2010;90:240–7.
67. Garganis K, Kokkinos V, Zountsas B. Limited resection of focal cortical dysplasia and associated epileptogenic cortex may lead to a positive surgical outcome. Epileptic Disord. 2011;13:422–9.
68. Pilcher W, Silbergeld D, Berger M, Ojemann G. Intraoperative electrocorticography during tumor resection: impact on seizure outcome in patients with gangliogliomas. J Neurosurg. 1993;78:891–902.

69. Looma R, Yeh H, Privitera M, Gartner M. Lesionectomy versus electrophysiologically guided resection for temporal lobe tumors manifesting with complex partial seizures. J Neurosurg. 1995;83:231–6.
70. Mathern G, Babb T, Pretorius J, Melendez M, Levesque M. The pathophysiologic relationships between lesion pathology, intracranial ictal EEG onsets, and hippocampal neuron loss in temporal lobe epilepsy. Epilepsy Res. 1995;21:133–47.
71. Sugano H, Shimizu H, Sunaga S. Efficacy of intraoperative electrocorticography for assessing seizure outcomes in intractable epilepsy patients with temporal lobe mass lesions. Seizure. 2007;16:120–7.
72. Palmini A, Paglioli E, Silva VD. Developmental tumors and adjacent cortical dysplasia: single, or, dual pathology? Epilepsia. 2013;54(Suppl 9):18–24.
73. Bluemcke I, Thom M, Aronica E, Armstrong D, Vinters H, Palmini A, et al. The clincopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. Epilepsia. 2011;52:158–74.
74. Garganis K, Kokkinos V, Zountsas B. Surgical outcome in neocortical type IIId focal cortical dysplasia with accompanying medial temporal pathology. Epilepsy Behav Case Rep. 2013;1:29–31.
75. Iida K, Otsubo H, Arita K, Andermann F, Olivier A. Cortical resection with electrocorticography for porencephaly-related partial epilepsy. Epilepsia. 2005;46:76–83.
76. Burneo J, Faught A, Knowlton R. Temporal lobectomy in congenital porencephaly associated with hippocampal sclerosis. Arch Neurol. 2003;60:830–4.
77. Luders H-O. Textbook of epilepsy surgery. London: Informa; 2008.
78. Asano E, Benedek K, Shah A, Juhasz C, Shah J, Chugani D, et al. Is intraoperative electrocorticography reliable in children with intractable neocortical epilepsy? Epilepsia. 2004;45:1091–9.
79. Asano E, Muzik O, Shah A, Juhasz C, Chugani D, Sood S, et al. Quantitative interictal subdural EEG analyses in children with neocortical epilepsy. Epilepsia. 2003;44:425–34.
80. Greiner H, Horn P, Tenney J, Arya R, Jain S, Holland K, et al. Preresection intraoperative electrocorticography (ECoG) abnormalities predict seizure onset zone and outcome in pediatric epilepsy surgery. Epilepsia. 2016;57:582–9.
81. Marsh E, Peltzer B, Brown M, Wusthoff C, Storm P, Litt B, Porter B. Interictal EEG spikes identify the region of electrographic seizure onsets in some, but not all, pediatric epilepsy patients. Epilepsia. 2010;51:592–601.
82. Bartolomei F, Trebuchon A, Bonini F, Lambert I, Gavaret M, Woodman M, et al. What is the concordance between the seizure onset zone and the irritative zone? A SEEG quantified study. Clin Neurophysiol. 2016;127:1157–62.
83. Mittal S, Barkmeier D, Hua J, Pai D, Fuerst D, Basha M, et al. Intracranial EEG analysis in tumor-related epilepsy: evidence of distant epileptic abnormalities. Clin Neurophysiol. 2016;127:238–44.
84. Spencer S, Goncharova I, Duckrow R, Novotny E, Zaverri H. Interictal spikes on intracranial recordings: behavior, physiology and implications. Epilepsia. 2008;49:881–1992.
85. Goncharova I, Spencer S, Duckrow R, Hirsch L, Spencer D, Zaverri H. Intracranially recorded interictal spikes: relation to seizure onset area and effect of medication and time of day. Clin Neurophysiol. 2013;124:2119–28.
86. Pacia S, Ebersole J. Intracranial EEG substrates of scalp ictal patterns from temporal lobe foci. Epilepsia. 1997;38:642–54.
87. Perry M, Dunoyer C, Dean P, Bhatia S, Bavariya A, Ragheb J, et al. Predictors of seizure freedom after incomplete resection in children. Neurology. 2010;75:1448–53.
88. Kim D, Lee SK, Chu K, Park K, Lee SY, Lee C, et al. Predictors of surgical outcome and pathologic considerations in focal cortical dysplasia. Neurology. 2009;72:211–6.
89. Alarcon G, Garcia Seoane JJ, Binnie C, Martin Mignel M, Juler J, Polkey C, et al. Origin and propagation of interictal discharges in the acute electrocorticogram. Implications for pathophysiology and surgical treatment of temporal lobe epilepsy. Brain. 1997;120:2259–2.
90. Chassoux F, Devaux B, Landre E, Turak B, Nataf F, Varlet P, et al. Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain. 2000;123:1733–51.
91. Singh S, Sandy S, Wiebe S. Ictal onset on intracranial EEG: do we know it when we see it? State of the evidence. Epilepsia. 2015;56:1629–38.
92. Lagarde S, Bonini F, McGonigal A, Chauvel P, Gavaret M, Scavarda D, et al. Seizure onset patterns in focal cortical dysplasia and neurodevelopmental tumors: relationships with surgical prognosis and neuropathologic subtypes. Epilepsia. 2016;77:1426–35.
93. Jimenez-Jimenez D, Nekkare R, Flores L, Chatzidimou C, Bodi I, Honavar M, et al. Prognostic value of intracranial seizure onset patterns for surgical outcome of the treatment of epilepsy. Clin Neurophysiol. 2015;126:257–67.
94. Perucca P, Dubeau F, Gotman J. Intracranial electroencephalographic seizure onset patterns: effects of underlying pathology. Brain. 2014;137:183–96.
95. Schiller Y, Cascino G, Busacker N, Sharbrough F. Characterization and comparison of local onset and remote propagated electrographic seizures recorded with intracranial electrodes. Epilepsia. 1998;39:380–8.
96. Spencer S, Spencer D. Entorhinal-hippocampal interactions in medial temporal lobe epilepsy. Epilepsia. 1994;35:721–7.
97. Bartolomei F, Khalil M, Wendling F, Sontheimer A, Regis J, Ranjeva J-P, et al. Entorhinal cortex involvement in human medial temporal lobe epilepsy: an electrophysiologic and volumetric study. Epilepsia. 2005;46:677–87.
98. Arroyo S, Lesser R, Fisher R, Vining E, Krauss G, Bandeen-Roche K, et al. Clinical and electroencephalographic evidence for sites of origins of seizures with diffuse electrodecremental pattern. Epilepsia. 1994;35:974–87.
99. Dolezalova I, Brazdil M, Hermanova M, Horakova I, Rektor I, Kuba R. Intracranial EEG seizure onset patterns in unilateral temporal lobe epilepsy and their relationship to other variables. Clin Neurophysiol. 2013;124:1079–88.
100. Jayakar P, Duchowny M, Alvarez L, Resnick T. Intraictal activation in the neocortex: a marker of the epileptogenic region. Epilepsia. 1994;35:489–94.
101. Zijlmans M, Jiruska P, Zelmann R, Leijten F, Jefferys J, Gotman J. High-frequency oscillations as a new biomarker in epilepsy. Ann Neurol. 2012;71:169–78.
102. Wu J, Sankar R, Lerner J, Matsumoto J, Vinters H, Mathern G. Removing interictal fast ripples in electrocorticography linked with seizure freedom in children. Neurology. 2010;75:1686–94.
103. Jakobs J, Zijlmans M, Zelmann R, Chatillon C-E, Hall J, Olivier A, et al. High-frequency electroencephalographic oscillations correlate with outcome of epilepsy surgery. Ann Neurol. 2010;67:209–20.
104. Krsek P, Maton B, Jayakar P, Dean P, Korman B, Rey G, et al. Incomplete resection of focal cortical dysplasia is the main predictor of poor surgical outcome. Neurology. 2009;72:217–23.
105. Holtkamp M, Sharan A, Sperling M. Intracranial EEG in predicting surgical outcome in frontal lobe epilepsy. Epilepsia. 2012;53:1739–45.
106. Raviya A, Mangano F, Horn P, Holland K, Rose D, Glauser T. Adverse events related to extraoperative invasive EEG moni-

toring with subdural electrodes: a systematic review and meta-analysis. Epilepsia. 2013;54:828–39.
107. Wellmer J, Von der Groeben F, Klarmann U, Weber C, Elger C, Urbach H, et al. Risks and benefits of invasive surgery work-up with implanted subdural and depth electrodes. Epilepsia. 2012;53:1322–32.
108. Taussig D, Chipaux M, Lebas A, Fohlen M, Bulteau C, Ternier J, et al. Stereo-electroencephalography in 65 children: an effective and safe diagnostic method for presurgical diagnosis independent of age. Epileptic Disord. 2014;26:280–95.

Invasive Electroencephalography in Epilepsy

9

Demitre Serletis

9.1 Introduction and Background

It is estimated that approximately 50 million people worldwide suffer from epilepsy [1]. Recent North American statistics have estimated that at least 1 in 10 adults will experience a seizure event in their lifetime, with at least 1–2% of adults and children developing chronic, persistent, and recurrent seizure activity (i.e., epilepsy) [1, 2]. Medically refractory epilepsy has been recently defined by the International League Against Epilepsy (ILAE) as the "failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug schedules, whether as monotherapies or in combination, to achieve sustained seizure freedom" [3]. In this context, there has been an emphasis on earlier referrals, particularly in childhood and early adulthood, to surgical epilepsy centers to assess potential candidacy for surgical intervention [4].

To date, surgery for epilepsy has been largely underutilized by the medical community despite mounting evidence advocating for earlier surgical intervention [5]. The latter has been bolstered by promising results demonstrating higher incidences for seizure control and/or freedom as compared to continued medical therapy across several well-designed trials in the literature [6–9]. Indeed, the cumulative side effects of chronic epileptic seizures and multiple antiepileptic medications over years lead to substantial medical, cognitive, and behavioral declines in this patient population. Moreover, epilepsy patients face an estimated fourfold higher risk for injury and 12% all-cause mortality within the first 2 years of diagnosis [10]. This is in addition to an ever-present risk for "sudden unexplained death in epilepsy" or SUDEP (estimated at 9% per decade per patient) [11]. Of course, the impact of epilepsy extends beyond the patient, affecting families and society as a whole. Surgical intervention, which often relies on invasive electroencephalography for mapping out the epileptogenic zone prior to resection or ablation, therefore continues to gain interest for its cost-effective approach to delivering an improved quality of life for many patients suffering from intractable epilepsy.

D. Serletis
Section of Neurosurgery, Health Sciences Centre, University of Manitoba, Winnipeg, MB, Canada
e-mail: dserletis@exchange.hsc.mb.ca

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9.2 General Indications for Invasive Electroencephalography

The standard preoperative evaluation for potential epilepsy surgery begins with noninvasive testing. The goal of this comprehensive evaluation is to lateralize and localize the epileptogenic zone, i.e., the regional site of seizure onset and networks implicated in the early spread of seizure activity in the hopes of identifying a suitable target amenable to resection, ablation, or disconnection. This hypothesis-driven approach typically begins with obtaining a detailed clinical history (including review of clinical semiology and assessment of seizure burden and prior treatments), ambulatory and video electro-encephalography (EEG), 3T-magnetic resonance imaging (MRI), and formal neuropsychological testing. Additional tests, as warranted, may include positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetoencephalography (MEG), functional MRI, and Wada testing. For any given patient, his/her clinical profile and collective set of results are then reviewed by a multidisciplinary team encompassing neurologists, neurosurgeons, radiologists, nuclear medicine specialists, neuropsychologists, nurses, EEG technicians, and, on occasion, pathologists. It is here that a hypothesis is made toward localizing the epileptogenic zone, and an all-important decision focuses on the further necessity for invasive implantation of intracranial electrodes, depending on the congruence of the noninvasive results obtained up to that point. In general, of the nearly one third of patients with refractory epilepsy thought to be potential surgical candidates, it is estimated that between 25% and 50% will ultimately undergo invasive EEG monitoring as a means of better characterizing their epileptogenic zone [4, 12].

In essence, general indications for invasive EEG monitoring via implantation of intracranial electrodes include lateralizing/localizing the epileptogenic zone and mapping functional (or eloquent) cortical and/or subcortical regions. More specifically, indications for considering intracranial electrodes include (i) ambiguous or discordant results obtained during the noninvasive work-up (e.g., based on EEG and imaging results); (ii) non-lesional temporal or extratemporal lobe epilepsy; (iii) bilateral temporal lobe epilepsy; and (iv) functional mapping of eloquent cortex and its relation to a potential epileptogenic zone [12–15]. Indeed, intracranial EEG captures refined signals free of external signal artifact and offers higher rates of success for accurately localizing an epileptogenic focus. Two conventional methodologies for performing invasive EEGs include the use of subdural electrodes and/or stereoelectroencephalography electrodes. Here, we present the subdural electrode strategy.

9.3 Subdural Grids

The "North American" approach to invasive EEG monitoring was popularized by Wilder Penfield and Herbert Jasper at the Montreal Neurological Institute (Quebec, Canada) [16], where they expanded intraoperative electrocorticography as a technique for localizing interictal epileptiform activity. Modern-day subdural electrodes evolved during the 1980s from the previous ball-tipped probes used by Penfield and Jasper into thin, flexible, customizable two-dimensional sheets (i.e., grids) or strip arrays of various configurations that could be applied to the surface of the brain [15, 17–19]. The principal indications for grid implantation include lateralizing/localizing the epileptogenic zone and mapping eloquent, functional regions to be spared in the subsequent resection or disconnection. As opposed to intraoperative electrocorticography, grid placement facilitates the collection of long-term, extraoperative EEG recordings of spontaneous seizure events over a period of days to weeks. During this interval, additional testing via safe, extra-operative electrical stimulation may be performed to assess for eloquent cortical tissue (e.g., motor, sensory, speech/language). In this fashion, a tailored cortical resection sparing eloquent cortex may be achieved while minimizing the risk for neurologic morbidity [19, 20]. Subsequently, a therapeutic resective or disconnective procedure is performed at the immediate time of grid removal, all within the same hospital admission.

9.3.1 Strategy and Protocol

9.3.1.1 Preoperative Considerations

Based on the hypothesis conceived for a given patient's epileptogenic zone, appropriately sized and shaped grids (or strips) are selected preoperatively to ensure that the extent of cortical coverage is sufficient for adequate sampling of the region of interest. It is prudent to check with the intraoperative electrophysiologist or technician to ensure sufficient recording channels are available, keeping in mind that an additional number of ground electrode contacts are to be applied at the end of the case as an averaged reference. Conventionally, grids are implanted via a standard neurosurgical craniotomy in the operating room under general anesthesia. Standard intraoperative neuronavigation is also useful for planning purposes, to ensure that the craniotomy is centered on the region of interest. On occasion, our preference is to supplement with frameless stereotaxy for introducing a small number of depth electrodes into a desired target (e.g., hippocampus or amygdala), depending on that

patient's epilepsy hypothesis. Optimal head positioning, hyperventilation, mannitol dosing, and elevating the head of the bed all lead to brain relaxation, which is essential when placing subdural grids with minimal morbidity. The skin incision and underlying craniotomy are planned out beforehand, taking into account the extra room required for tunneling the electrode wires extracranially through the skin. Standard antibiotics and steroids (e.g., dexamethasone) are administered and a safety time-out is performed prior to starting.

9.3.1.2 Intraoperative Procedure

After a standard craniotomy is made, the dura is opened widely in C-shaped fashion to permit access to the cortical surface (Fig. 9.1). In the case of redo procedures the dura may be tightly adherent, in which case microsurgical technique under microscopic or loupe magnification is used to carefully dissect the dura off while sparing the cortical surface and vessels beneath. Following exposure, based on direct visual inspection of anatomic landmarks and concomitant intraoperative neuronavigation, correlation is made between the patient's anatomy, MR imaging, and the anticipated region to be electrographically sampled. In the event that depth electrodes are to be placed, frameless stereotaxy is conventionally used for accurate placement of a limited number of electrodes into specific targets to be sampled (for example into the depth of a sulcus or into the hippocampus or amygdala). It is conventionally easier to perform the depth electrode placement early on, prior to covering the cortical surface with a grid that may interfere with accurate placement in this regard. The pia is gently incised with a 15-blade knife or microscissors instrument, and the depth electrodes are delivered to specific targets using preoperatively defined trajectories under standard neuronavigation.

Measurements are then taken using a soft, flexible ruler, and the chosen grids (or strips) are conformed appropriately such that they lie flat along the cortical surface. Rough grid edges are carefully trimmed to smooth them out, thereby minimizing the chance for cortical laceration. In some cases, large grids must be cut into individual strips while preserving the internal grid circuitry, facilitating placement over a large cortical surface. Ultimately, the grids are gently placed using bayonet forceps under plentiful irrigation, taking care not to damage the grid contacts or wires therein. In many instances, the grid can slide along the cortical surface to be placed beyond the margins of the craniotomy along the convexity or into the basal frontal and/or temporal regions and even into the interhemispheric fissure itself. Great care is taken to protect superficial draining veins, particularly the veins of Labbé or Trolard in addition to the venous sinus system, since venous injury or compression can lead to significant congestion-related morbidity, which often extends beyond the exposed cortical region in view. Regions of adherence may hint at underlying bridging veins, which must be either carefully protected or disconnected. When appropriate individual wires attached to the electrodes are then sutured against the dural margins to reinforce the location of the grid(s) and to prevent against pull-out or shift. Digital photographs are taken to corroborate the relation of the grid(s) to the underlying cortical anatomy. Intra-operative consultation is also sought with the neurology team to confirm proper hardware placement/orientation prior to closure.

The dura is then closed in water-tight fashion. Care is taken to ensure that the wires can easily pass through an open burr hole or exposed bony margin, thereby minimizing the chance for lead kinking and/or fracture prior to securing the bone flap with sutures or plates. Attention is paid to leaving at least one or two borders of the bone flap free to permit outward displacement in the rare event of underlying cerebral edema. The wires are typically externalized through the scalp at a safe distance away from the incision line. These are then secured using purse-string sutures to prevent leakage of CSF fluid. The color coding and numbering of each lead is documented and relayed to the neurology team, again in reference to that grid's position. The scalp flap is approximated in typical fashion and a subgaleal drain is left behind. It is at this time that two to four external ground leads are applied to the scalp prior to careful dressing of the wound and coverage with a formal head wrap. The electrodes are carefully brought out of the wrap and secured within a plastic bag, facilitating access by the EEG technician and neurology teams.

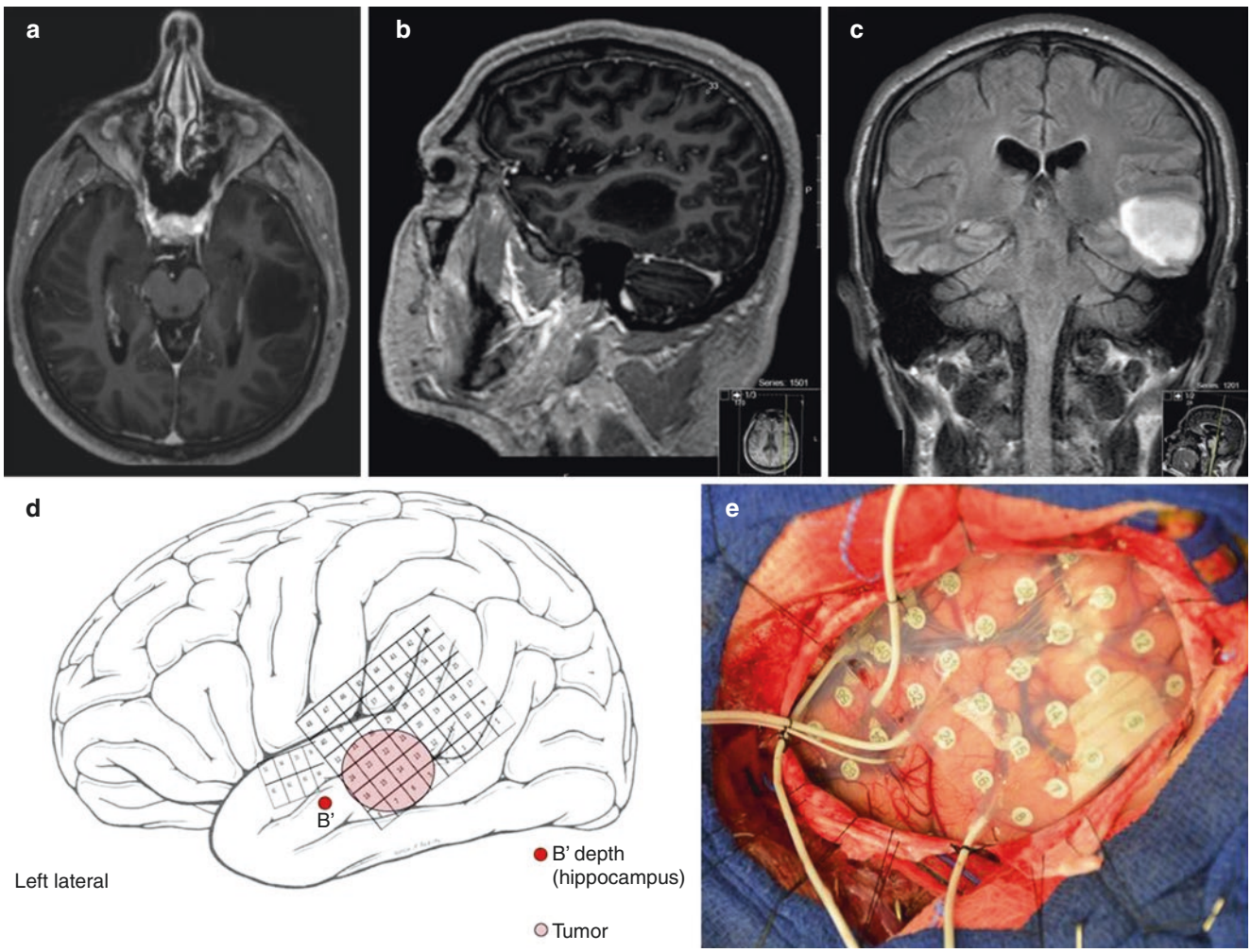

Fig. 9.1 Representative dual-pathology case of medically refractory epilepsy in a 42-year-old male patient with a left temporal low-grade glioma and left-sided hippocampal sclerosis. Axial (**a**) and sagittal (**b**) contrast-enhanced T1-weighted MR images confirmed a nonenhancing, low-grade brain mass situated within the left posterior temporal lobe. (**c**) Coronal T1-FLAIR imaging revealing increased signal within the lesion. (**d**) Implantation map showing the selection of two grids for coverage of the left temporal lobe, with the larger grid strategically positioned over Wernicke's area to assist with language mapping. Note the depth electrode, labelled as *B′*, targeting the head of the hippocampus. (**e**) Open left temporal craniotomy window revealing the implantation of both grid electrodes and a smaller depth electrode. Each electrode has been sutured to the dural edge to minimize displacement prior to externalization through the scalp. Of note, during EEG monitoring the hippocampal depth electrode was not involved in the epileptogenic zone. With this confirmation and subsequent to language mapping, direct lesionectomy (i.e., tumor resection) was therefore performed, resulting in dramatic seizure improvement for the patient

9.3.1.3 Postoperative Considerations

Postoperatively, the patient is taken to recovery and subsequently to the intensive care unit (ICU), where imaging is acquired to confirm the placement of the grid(s). This typically includes skull X-rays, but most importantly CT and MR imaging studies, which are subsequently used for three-dimensional reconstruction purposes. The wires are attached to EEG equipment, permitting real-time EEG analysis and monitoring, and antiepileptic medications are weaned according to the neurology team's protocol. Assuming the first night is uneventful, the patient is then taken to the Epilepsy Monitoring Unit for ongoing monitoring and stimulatory testing purposes, where warranted. Postoperative antibiotics are administered, and in many centers these antibiotics are continued during the monitoring interval [21, 22]. Similarly, postoperative steroids (e.g., dexamethasone) are administered and weaned over several days. The head dressing may be changed sporadically under sterile technique to inspect the lead sites for CSF leakage and/or wound infection, taking care to protect the electrode lead wires during this process.

9.3.1.4 Grid Removal

Once sufficient EEG data are collected and following all stimulatory testing, the patient is returned to the operating room for grid removal. At this time, depending on review again at the Epilepsy Conference, the decision may also be made for concomitant resection. Regardless, the prior surgical incision is opened and great care is taken to avoid shifts in grid placement, as this may serve as the cortical reference or map for resection guided by the seizure data collected for that patient. The grids are delicately removed, again paying close attention to venous preservation, and ample irrigation is applied to aid with this. The wires are disconnected and can be pulled out of the field at this time (provided they have been released at the scalp). The resection may then proceed accordingly, or alternatively in the event of failed localization the craniotomy is simply closed in standard fashion. At the end of the case, care is taken to ensure that all lead exit sites at the scalp have also been closed in order to minimize the chance for CSF leak and infection.

9.3.2 Complications: Avoidance and Management

In general, the overall risk of implanting subdural grids can be as high as 9–22% in some series if not higher, with a separate risk of 5–6% for depth electrode placements [15, 19, 23–25]. Focusing specifically on the craniotomy procedure for grid and/or depth electrode placement, there are a number of inherent risks to be discussed beforehand with the patient and his/her family. A discussion of these risks follows.

9.3.2.1 CSF Leakage and Infections

Leakage of CSF is one established risk factor for infection, namely for meningitis, which must be dealt with promptly at the time of identification. Reported risks for CSF leaks range anywhere from 0.5–2% to as high as 30% in some series [21, 23]. Typically, CSF may be noted to be leaking at electrode exit sites, in which case suture reinforcement and subsequent wrapping of the lead sites with betadine-soaked gauze may help minimize the risk for subsequent infection. In cases of persistent leakage, placement of a temporary lumbar drain for CSF diversion may be beneficial.

In most modern hospitals, the general incidence of infection associated with cranial procedures, as with other types of surgical procedures, is estimated to be approximately 0.5–2%. However, in terms of grid and/or depth electrode implantations (with electrodes externalized through the scalp), the risk of infection rises, given the context of implanted foreign bodies. Thus, the risk for clinically relevant infection is expectedly higher, and based on recent series has been estimated to be approximately 4–5% [19, 21, 23, 25]. These infections may include any of the following: superficial wound infection; meningitis; epi- or subdural abscess; osteomyelitis; and intraparenchymal brain abscess. Other factors identified as contributing to the risk of infection include length of implantation (i.e., days with electrodes in situ) and increased numbers of electrodes owing to increased lead exit sites in the scalp [19, 21].

It should be noted that the degree of subsequent intervention depends on the severity of infection. Superficial wound infections may be addressed by initiating antibiotic therapy for the duration of implantation. Deeper infections, however, must be dealt with by reoperation to remove the grids and/or depth electrodes, culture sampling of the collection, copious irrigation and debridement, and subsequent intravenous antibiotic therapy. In such cases, the treatment decision is delayed and/or modified, often delaying subsequent resection until the infection is resolved.

For chronic infections including those of the bone (e.g., osteomyelitis), these typically appear several weeks to months later with a 2–3% likelihood [15, 25]. In such cases, removal of the bone flap may be indicated followed by aggressive antibiotic therapy. A delayed procedure to replace the open craniotomy site may be pursued using a prosthetic substitute (e.g., titanium mesh or synthetic customized cranial implant).

9.3.2.2 Cerebral Edema

Local irritation and subsequent inflammatory cerebral edema in response to implanted hardware is another common complication associated with grid placement. According to the literature, the risk of clinically significant brain edema may occur in 2–3% of cases [23]. In such instances, the presenting symptoms are usually consistent with headaches and/or progressive neurologic deficits, including contralateral

hemiparesis and/or speech and language disturbances, followed by eventual loss of consciousness and potentially fatal herniation. Pediatric patients, in particular, are generally more susceptible to developing cerebral edema than their adult counterparts. Attempts at minimizing the risk for cerebral edema include opening the dura widely during implantation, closing the bone flap in such a way that it is loosely hinged on one side (through the use of sutures rather than titanium plates), and the perioperative use of steroids. In the most severe cases of refractory brain edema resulting in neurologic compromise, the electrodes should be removed immediately and the patient closely monitored for subsequent resolution of his or her symptoms.

9.3.2.3 Hemorrhage

Intracranial hemorrhage poses another risk for refractory epilepsy patients undergoing grid and/or depth electrode implantation. The rate of radiographic hemorrhage (16%) is known to exceed that of clinically significant hemorrhage (7–8%) [20, 23]. The placement of grids predisposes to risks for cortical injury and venous occlusion/disruption, particularly in close proximity to the sinuses (e.g., in interhemispheric implantations); this can lead to subsequent brain edema and/or subdural hematoma formation [15, 24, 25]. The latter may arise either superficially or deep to the electrodes (directly overlying the cortical surface). In such instances, this may disrupt the acquisition of accurate intracranial EEG signals and could potentially result in mass effect and clinical decline [25].

9.3.2.4 Other Complications

On rare occasion, the implanted grid(s) may fail to capture epileptiform events in their entirety, with part of the seizure activity seen to extend beyond the edge of the hardware. In certain cases, consideration must be given to reoperation to either adjust the current grid(s) in place or perhaps introduce yet another one for more accurate coverage. Theoretically, multiple reopenings may increase the risk for wound infection and other surgical-related problems.

Moreover, as described above, once the grids and/or depth electrodes are placed, the leads are typically sutured at the dural edges before tunneling out through the scalp (where they are again secured at the surface). The intention of these steps is to prevent grid migration or electrode pull-out. Careful attention to electrode care and dressing changes by the nursing and EEG tech team helps to preserve the integrity of the hardware during the implantation phase. Nevertheless, there is a small but very real risk for displacement, removal, or fracture of the implanted electrodes. This is particularly the case for patients who are experiencing violent seizure events with a heavy motor component to their semiology, those in a state of postictal confusion, or at the time of reopening a craniotomy to remove the electrodes. In the latter case, care must be taken by the surgeon to confirm that the grids remain in place while the scalp layers, bone, and dura are reopened so that accurate correlation can be made between the electrode contacts and the electrographically-confirmed epileptogenic zone immediately prior to resection.

Finally, from a medical standpoint, patients implanted in the EMU are conventionally bed- or chair-bound while waiting for sufficient seizure events to be captured. In their state of limited mobility, their risk for deep venous thrombosis, pulmonary embolism, pneumonia, and other medical complications is likely higher than for the typical postoperative population. Careful observation, early diagnosis, and immediate therapeutic intervention help prevent and/or minimize the medical consequences of such events.

9.4 Special Pediatric Considerations

There are several considerations that are uniquely relevant to pediatric patients undergoing work-up and treatment for refractory epilepsy.

From a noninvasive standpoint, despite testing similar to that for adult patients, children require a compassionate and calm approach by trained pediatric-focused hospital staff. Parents, grandparents, and other family members are typically involved, and additional time is often warranted for them to explain each step to the patient in order to ensure more accurate results. In some cases, obtaining a high-resolution 3T-MRI study requires that younger patients be given a general anesthetic to minimize motion artifact-related effects. Interestingly, in certain fMRI studies performed under general anesthesia, it is possible to passively activate eloquent brain regions in the toddler group, thereby mapping the primary motor, sensory, or visual cortices [26]. In contrast, older children may benefit from careful advanced instruction and practicing simple fMRI-related tasks to improve the results obtained with this imaging modality.

With respect to surgical grid implantation for invasive EEG monitoring in pediatric patients, care is taken to use an appropriate head holder specifically designed for children. Examples include the standard use of a donut or horseshoe, or using the Mayfield clamp with age-appropriate pins in cases requiring fixation for image-guidance (such as for placement of depth electrodes). Smaller grids may be required in younger children, and therefore careful consideration for the number of channels and overall grid dimensions should be reviewed prior to each procedure by the neurosurgeon and epileptology team. Upon implantation and tunneling the leads out through the scalp, these must be secured with sutures and dressing material to minimize the chance of the pediatric patient actively reaching up and grasping the electrodes, potentially removing them and/or fracturing them in the process.

Following grid implantation, extraoperative testing for eloquent cortex must utilize age-appropriate language and motor tasks to improve the accuracy of testing results. The subsequent removal of hardware is typically performed in conventional fashion, often in the setting of concomitant surgical resection and/or disconnection of an identified epileptogenic zone.

Conclusions

Invasive EEG monitoring using implanted intracranial grid and/or depth electrode arrays may be safely used in pediatric patients with refractory epilepsy for the purposes of lateralizing and localizing the epileptogenic zone and for functional mapping of eloquent cortical and/or subcortical regions. The concept was expanded by Penfield and Jasper in the 1950s and has evolved into one of two modalities for invasive EEG (the other being stereoelectroencephalography, or SEEG). There are multiple technical considerations to review in planning these procedures, particularly in the pediatric age group, and it is important for the treating physician to gain an appreciation for the utility of the technique and its inherent risks, as described in this chapter. When employed by a trained epilepsy team, grid implantation offers a higher chance for identifying the epileptogenic zone, thereby leading to a more successful postoperative outcome while minimizing the risk for postoperative morbidity.

References

1. Epilepsy: Fact Sheet. World Health Organization, 2016.
2. Annual estimates of the resident population by sex, age, race, and Hispanic origin for the United States, States, and Counties: April 1, 2010, to July 1, 2013. U.S. Census Bureau, Population Division. (Database online.).
3. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the Ad Hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51:1069–77.
4. Albert GW, Serletis D. Surgical management of epilepsy in adolescent patients. J Pediatr Epilepsy. 2015;4:102–8.
5. Engel J Jr. Why is there still doubt to cut it out? Epilepsy Curr. 2013;13:198–204.
6. Jeha LE, Najm IM, Bingaman WE, Khandwala F, Widdess-Walsh P, Morris HH, et al. Predictors of outcome after temporal lobectomy for the treatment of intractable epilepsy. Neurology. 2006;66:1938–40.
7. Engel J Jr, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012;307:922–30.
8. McGovern RA, McKhann GM 2nd. The ERSET trial of early surgery for mesial temporal lobe epilepsy: results and frustrations. Neurosurgery. 2012;70:N23–4.
9. Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness, efficiency of surgery for temporal lobe epilepsy study G. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345:311–8.
10. Jehi L. Neurology's silent killer: drug-resistant epilepsy. Epilepsy Curr. 2016;16:232–3.
11. Jones LA, Thomas RH. Sudden death in epilepsy: insights from the last 25 years. Seizure. 2017;44:232–6.
12. Kuzniecky R, Devinsky O. Surgery insight: surgical management of epilepsy. Nat Clin Pract Neurol. 2007;3:673–81.
13. Serletis D, Bulacio J, Alexopoulos A, Najm I, Bingaman W, Gonzalez-Martinez J. Tailored unilobar and multilobar resections for orbitofrontal-plus epilepsy. Neurosurgery. 2014;75:388–97.
14. Serletis D, Bulacio J, Bingaman W, Najm I, Gonzalez-Martinez J. The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients. J Neurosurg. 2014;121:1239–46.
15. Salazar F, Bingaman WE. Placement of subdural grids. In: Lüders HO, editor. Textbook of epilepsy surgery. London: CRC Press (Taylor & Francis Group); 2008. p. 931–7.
16. Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. London: J. and A. Churchill Ltd.; 1954.
17. Wyllie E, Luders H, Morris HH 3rd, Lesser RP, Dinner DS, Rothner AD, et al. Subdural electrodes in the evaluation for epilepsy surgery in children and adults. Neuropediatrics. 1988;19:80–6.

18. Levy WJ, Hahn JH, Lueders H, Lesser R. Chronic cortical electrode array for seizure investigation. Childs Brain. 1982;9:48–52.
19. Swartz BE, Rich JR, Dwan PS, DeSalles A, Kaufman MH, Walsh GO, et al. The safety and efficacy of chronically implanted subdural electrodes: a prospective study. Surg Neurol. 1996;46:87–93.
20. Behrens E, Zentner J, van Roost D, Hufnagel A, Elger CE, Schramm J. Subdural and depth electrodes in the presurgical evaluation of epilepsy. Acta Neurochir. 1994;128:84–7.
21. Wiggins GC, Elisevich K, Smith BJ. Morbidity and infection in combined subdural grid and strip electrode investigation for intractable epilepsy. Epilepsy Res. 1999;37:73–80.
22. Heuer GG, Bauman J, Storm PB, Baltuch GH. Invasive EEG studies: peg, strip, and grid implantation. In: Baltuch GH, Villemure J-G, editors. Operative techniques in epilepsy surgery. New York: Thieme; 2009. p. 20–4.
23. Schmidt RF, Wu C, Lang MJ, Soni P, Williams KA Jr, Boorman DW, et al. Complications of subdural and depth electrodes in 269 patients undergoing 317 procedures for invasive monitoring in epilepsy. Epilepsia. 2016;57:1697–708.
24. Rahman Z, Bleasel AF, Bartley M, Dexter M, Galea T, Gill D, et al. Reduced complications from intracranial grid insertion by using a small grid size and a precise protocol during monitoring. Acta Neurochir (Wien). 2016;158:395–403.
25. Lee WS, Lee JK, Lee SA, Kang JK, Ko TS. Complications and results of subdural grid electrode implantation in epilepsy surgery. Surg Neurol. 2000;54:346–51.
26. Farmer J-P, Atkinson J. Invasive monitoring in pediatric neurosurgery. In: Cohen AR, editor. Pediatric neurosurgery: tricks of the trade. New York: Thieme; 2016. p. 665–73.

Stereo-Electroencephalography (SEEG) in the Diagnosis and Evaluation of Medically Intractable Epilepsy

10

João Paulo Sant'Ana Santos de Souza
and Jorge Gonzalez-Martinez

10.1 Introduction

Epilepsy surgery aims at the complete resection (or complete disconnection) of the cortical area responsible for generating the epileptic activity and leading to its spread along the brain. This epileptogenic region is classically named the epileptogenic zone (EZ). Since the EZ may eventually overlap with functional cortical areas (the eloquent cortex), preservation of the necessary brain functions is another goal of surgical resection in patients with medically refractory epilepsy [1–7].

Once successful resective epilepsy surgery relies on accurate preoperative localization of the EZ, a presurgical evaluation is necessary to obtain the widest and most accurate spectrum of information from clinical, anatomic, and neurophysiologic aspects, with the ultimate goal of performing an individualized resection for the patient. Briefly, presurgical evaluation tools include the analysis of seizure semiology, video-scalp electroencephalography (video-EEG) recordings, magnetoencephalography (MEG), magnetic resonance imaging (MRI), and other neuroimaging modalities (fMRI, ictal SPECT, PET techniques) [6, 8]. The results of these complementary methods are interpreted in conjunction with each other in an attempt to compose a localization hypothesis of the anatomic limits of the EZ. When the noninvasive data are insufficient to define the EZ, extraoperative invasive monitoring may be indicated.

Stereo-electroencephalography (SEEG) is one of the extraoperative invasive methods that can be applied in patients with medically refractory focal epilepsy in order to anatomically define the EZ and the functional cortical areas that are eventually involved. The clinical aspects of the SEEG method and technique are discussed in this chapter.

João Paulo Sant'Ana Santos de Souza (✉)
Laboratory of Neuroimaging, Teaching Hospital of University of Campinas (UNICAMP) Campinas, Campinas, São Paulo, Brazil

J. Gonzalez-Martinez
Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH, USA

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10.2 Main Concepts and Historical Evolution

Ten years after human cerebral stereotaxis was conceptualized in 1947 by Spiegel and Wycis [9], the SEEG method began to be applied in Paris for the investigation of temporal lobe epilepsy [10, 11]. Both Talairach and Bancaud summed up efforts to create an innovative technique. The debut of SEEG occurred in 1957, when these two physicians first performed the implantation of depth electrodes. The innovation was based on the study of depth brain structures, a procedure very distinct from the superficial cortex analysis applied by Penfield and colleagues.

According to previous European reports, SEEG methodology enabled precise recordings from deep cortical and subcortical structures, multiple noncontiguous lobes, and bilateral explorations while avoiding the need for large craniotomies [5, 10–12]. In 1962 the new technique and method was called "the Stereo-Electro-Encephalography" [13, 14]. Tailarach originally used the stereotactic frame and the double grid system in association with teleangiography [15, 16]. Despite its long-reported successful record, the SEEG technique was still a multiphase and complex method. This may have limited its widespread use outside Europe [17].

The current principles of SEEG methodology remain similar to the principles originally described by Bancaud and Talairach, which are based on anatomo-electro-clinical (AEC) correlations with the main goal of conceptualizing the three-dimensional spatial-temporal organization of the epileptic discharge within the brain [3, 13, 18–31]. The implantation strategy is individualized, taking into consideration patient seizure electroclinical correlations and their relation to a suspected lesion. For these reasons, the formulation of the preimplantation AEC hypotheses is the single most important element in the process of planning the placement of SEEG electrodes. If the preimplantation hypotheses are incorrect, the placement of the depth electrodes will be inadequate, and the interpretation of the SEEG recordings will not give access to the definition of the epileptogenic zone.

10.3 Evaluation Prior to Invasive Monitoring

Medical refractory status for epilepsy has been defined as the failure to achieve seizure control with two or more tolerated drugs, appropriated chosen in terms of posology (maximum recommended dosage) in isolated or in combined regimens [32, 33]. After this condition has been diagnosed, a presurgical evaluation is indicated, directed at

1. Mapping of the AEC network leading to the delineation of the EZ.
2. Functional assessment of the epileptogenic region.

To achieve the above goals, different studies can be used according to their capabilities [6, 8, 34–36]:

- *Scalp-video EEG monitoring*: needed to confirm the diagnosis of focal epilepsy (including interictal and ictal EEG recordings) and to identify the cortical structures of the hypothetical networks that may be involved in seizure organization. The hypothetical networks can be identified through analysis of the recorded clinical and electrical semiology, which leads to the formulation of clear AEC hypotheses.
- *MRI* permits structural identification of the lesion.
- *FDG-PET* identify hypometabolic areas that may point to focal regions of cortical dysfunction.
- *Ictal SPECT* shows hyperperfused regions, which may include the EZ.

Despite being noninvasive tests, these studies are not sufficient to formulate a clear and unique AEC hypothesis in approximately 30% of the cases (unpublished data). In other words, even when combined, such evaluations cannot result in a clear decision among two or three hypotheses in the same hemisphere. In addition, there may also be a sound regional hypothesis but not enough arguments in favor of one hemisphere. Therefore, when the preoperative evaluation does not define the exact location of the EZ, its extent, and/or its overlap with the functional (eloquent) cortex, the patient can be referred for an invasive evaluation with at least one of the following:

- Intraoperative EcoG.
- Extraoperative subdural/grids strips.
- Subdural grids (SBGs) with depth electrodes.
- Stereoelectroencephalography [37].

Therefore the main indications for an invasive evaluation in focal phamaco-resistant epilepsy are to address any of the challenges and limitations listed below:

1. *MRI negative cases:* the MRI does not show a cortical lesion, hampering the confirmation or even questioning

the electroclinical/functional hypothesis generated by the video EEG recordings.

2. *Electroclinical and MRI data discordance:* the anatomic location of the MRI identified lesion (and at times the location of a clearly hypometabolic focal area on PET) is not in agreement with the electroclinical hypothesis. This occurs in cases of **deeply seated brain lesions** such as periventricular nodular heterotopia or deep sulcal lesions. In addition, scalp EEG recordings in 85–100% of patients with focal cortical dysplasia (FCD) show interictal spikes that range in their distribution from lobar to lateralized, from difficult to localize to diffuse (including generalized spike-wave patterns in some cases of subependymal heterotopia) [24, 25, 29, 38–40]. The spatial distribution of interictal spikes is usually more extensive than the structural abnormality, as assessed by intraoperative inspection or preoperative MRI visual analysis [41]. Alternatively, two or more anatomic lesions may be present with the location of at least one being discordant with the electroclinical hypothesis, or both lesions may be located within the same functional network so that it is unclear whether one or more is epileptogenic.
3. *Overlap with the eloquent cortex:* the generated anatomic electroclinical hypothesis (MRI-negative or MRI-identifiable lesion) may involve the highly eloquent cortex. Defining the precise edges of the epileptogenic zone and/or its relationship with the potentially eloquent cortex is not typically resolved in these cases. This situation includes patients with suspected focal cortical dysplasia as the possible pathologic substrate for epilepsy [2, 31, 39, 41–45].

Table 10.1 Selection criteria for SEEG and SBG in refractory epilepsy cases

Clinical scenario	Method of choice	Second option
Lesional MRI: Potential epileptogenic lesion is superficially located, near or in the proximity of eloquent cortex Nonlesional MRI: Hypothetical EZ located in the proximity of eloquent cortex	SBG	SEEG
Lesional MRI: Potential epileptogenic lesion is located in deep cortical and subcortical areas Nonlesional MRI: Hypothetical EZ is deeply located or located in non-eloquent areas	SEEG	SBG with depths
Need for bilateral explorations and or reoperations	SEEG	SBG with depths
After subdural grids failure	SEEG	SBG with depths
When the AEC hypothesis suggests the involvement of a more extensive, multilobar epileptic network	SEEG	SBD with depths
Suspected frontal lobe epilepsy in nonlesional MRI scenario	SEEG	SEEG

10.4 SEEG Versus Subdural Monitoring

In the preceding challenges and limitations, an invasive evaluation is helpful to overcome the remaining doubts regarding the most appropriate resective surgical strategy. The recommendation for invasive monitoring is made during a multidisciplinary patient management meeting that includes neurologists, neurosurgeons, neuroradiologists, and neuropsychologists. Areas and networks of coverage/sampling are determined based on a well-formulated AEC hypothesis, including results of the noninvasive studies.

There is still no clear consensus among "pro-SEEG groups" and "pro-subdural groups." The former group considers that this method can answer any question an invasive method can provide [3, 15, 17–31, 37, 38, 46–76], whereas the latter group, which is unfamiliar with depth electrode explorations, tends to strictly limit its study to the exploration of deep structures such as distinguishing between unilateral or bilateral lobe epilepsy or studying epilepsy related to nodular heterotopia. But differences between SEEG and subdural grids and strips are not restricted to the dichotomy between deep versus superficial mapping. Subdural explorations have been recommended for the invasive study of lesional epilepsy, whereas SEEG initially had little focus on the lesion itself. Therefore SEEG is more suitable for exploration of patients with nonlesional MRIs for whom, in some cases, it is not at all clear that surgery should be performed, although electroclinical evidence is present [17, 37, 69, 70]. In addition, SEEG permits the exploration of remote and multilobar areas without the need for craniotomies and immediate resective surgery. This process allows a prolonged reflection time for the patient and consequently a more complete informed consent process.

The recommendation and resulting analysis of direct electrical stimulation in each method are quite different although potentially complementary [77]. Extraoperative mapping with the subdural method (including grids, strips, and the possible combination with depth electrodes) has the advantage of allowing an optimal anatomic and contiguous coverage and sampling of the adjacent cortex, leading to accurate superficial cortex functional mapping exploration [78, 79]. This is especially the case when there is a need to determine the extension of the EZ associated with a superficial lesion and its anatomic relationship to a close functional area. On the other hand, functional subdural mapping is not applied for the lesion that includes a deep-seated component. Within a surgical perspective, subdural implantations are open procedures with better management of occasional intracranial hemorrhagic complications. The main disadvantages of the subdural method are related to the inability to record and map deep structures such as the insular cortex, orbitofrontal cortex, cingulate gyrus, and depths of sulci and consequently the spatiotemporal

dynamics of the epileptogenic network. In these scenarios, the SEEG methodology may be considered a more adequate and safer option. SEEG has the advantages of allowing extensive and precise deep brain recordings and stimulations (to localize seizure onset) with minimal associated morbidity [17, 31, 64, 69, 70, 76]. It also carries a reduced risk of intracranial infection (compared to open procedures) and a very low risk of bleeding as a result of a pre-implantation imaging-based strategy [80].

Consequently, based on the potential advantages and disadvantages of each method, SEEG appears to be the method of choice. The following reasons contribute to this decision.

1. The possibility of a deep-seated or difficult to cover location of the EZ in areas such as the mesial structures of the temporal lobe, perisylvian areas, cingulate gyrus and mesial interhemispheric regions, ventromedial prefrontal areas, insula, and depths of sulci.
2. Failure of a previous subdural invasive study to clearly outline the exact location of the seizure onset zone**.** This may have been attributable to the lack of adequate sampling from a deep focus or a clinically silent focus upstream from the EZ, among other reasons. Repeated open subdural grid evaluations may also carry risks associated with scar formation and still have limitations related to deep cortical structure recordings. A subsequent evaluation using the SEEG may overcome these limitations, offering an additional opportunity for sustained seizure freedom [76].
3. The need for bihemispheric (normally extensive) explorations as seen in focal epilepsies arising from the interhemispheric or deep insular regions as well as the temporo-parieto-occipital junction.
4. Presurgical evaluation suggestive of an extended network involvement (e.g., temporo-frontal or fronto-parietal) in the setting of a normal MRI (Table 10.1).

The putative disadvantages of the SEEG method are related to a more restricted capability to perform functional mapping. Because of the limited number of contacts located in the superficial cortex, a contiguous mapping of eloquent brain areas cannot be obtained as it can in the subdural method of mapping [30, 64, 76]. It is interesting to note that functional mapping in SEEG cannot be dissociated from the electroclinical localization process and, consequently, a fair comparison between both methods cannot be performed. In addition, the precision of the subdural functional mapping is far from being validated. Last, the functional mapping information extracted from the SEEG method can frequently be complemented with other methods of mapping, such as DTI images or awake craniotomies [31], diminishing the relative disadvantages claimed by the subdural groups.

At the Cleveland Clinic, a final tailored implantation strategy has been generated during a separate presurgical implantation meeting that encompassed a multidisciplinary team (i.e., experienced epileptologists, neurosurgeons, and neuroradiologists) that attempted the formulation of a clear AEC hypothesis. The noninvasive studies performed before the implantation will provide evidence regarding (1) the possible anatomic lesion, (2) more likely structures involved in the epileptic discharge onset, (3) the early and late spread regions, and consequently (4) the interactions with functional networks (e.g., cognitive, sensoriomotor, behavioral). By summing up data collected from noninvasive studies and analyzing the temporal evolution of the ictal clinical manifestations, it is possible to conceptualize a three-dimensional epileptic network to guide depth electrode implantation [81].

Of note is the need to take into account the three-dimensional aspects of depth electrode recordings. Despite a limited coverage (largely compensated for by the interpolation with the electrophysiologic methodology: frequencies, spatial relations, and latencies analyses) of the cortical surface compared with subdural monitoring, these recordings must enable an accurate sampling of the structures along its trajectory, from the entry site to the final impact point. In other words, more important than the entry and target points of the electrodes is their trajectory and their capacity to cover the entire nodes and spreading routes of the epileptic network (multiple lobes/lobules) as much as possible. Consequently, the investigation may include lateral and mesial surfaces of the different lobes and deep-seated cortices such as the depths of sulci, insula, and posterior areas in the inter-hemispheric cortical surface. The implantation should also consider the different cortical cytoarchitectonic areas involved in seizure organization patterns and their connectivity to other cortical and subcortical areas. Furthermore and not less important, exploration strategy should also take into consideration possible alternative hypotheses of localization [17, 66, 82].

Finally, the aim of obtaining all the possible information from the SEEG exploration should not be pursued at the expense of an excessive number of electrodes. In general, implantations that exceed 15 depth electrodes are rare, and the calculated risk of complication per electrode allocated is 0.18% [17]. Additionally, the possible involvement of eloquent regions in the ictal discharge requires their judicious coverage, with the two-fold goal of assessing their role in the seizure organization and defining the boundaries of a safe surgical resection.

10.5 Patterns of Network Explorations

Because SEEG strategy implantation is derived from an individualized AEC hypothesis, standard implantations for specific areas and lobes are difficult to perform. Nevertheless, a number of typical patterns of coverage can be recognized:

Limbic network explorations Cases of temporal lobe epilepsy with consistent anatomo-electro-clinical findings that suggest a limbic network involvement are usually operated on only after noninvasive investigation. In general, the use of invasive monitoring is not necessary when semiologic and electrophysiologic studies demonstrate typical nondominant mesial temporal epilepsy, and imaging studies show clear lesions (e.g., unilateral mesial temporal sclerosis) that fit the initial localization hypothesis. Even tough, invasive exploration with SEEG recordings may be required in patients in whom the supposed EZs (probably involving the temporal lobes) are suspected of involving extratemporal areas as well. In these cases, the implantation pattern points to a preferential spread of the discharge to the temporo-insular-anterior perisylvian areas, the temporo-insular-orbitofrontal areas, or the posterior temporal, posterior insula, temporobasal, and parietal and posterior cingulate areas. Consequently, sampling of extratemporal limbic areas must be wide enough to identify a possible extratemporal origin of the seizures that could not been anticipated with precision by noninvasive methods of investigation.

Frontal-parietal network explorations Because of the large volume of the frontal and parietal lobes, a high number of electrodes is required for adequate coverage of this region. However, specific cases can allow more restricted implantations. The suspicion of orbito-frontal epilepsy, for example, often requires the investigation of the gyrus rectus, the frontal polar areas, the anterior cingulate gyrus, and the temporal pole. Similarly, seizures that are thought to arise from the mesial wall of the premotor cortex are evaluated by targeting at least the rostral and caudal parts of the supplementary motor area (SMA), the pre-SMA area, different portions of the cingulate gyrus and sulcus, the primary motor cortex, and the mesial and dorsolateral parietal cortex. Consequently, the hypothesis-based sampling may localize the EZ in the frontal and/or parietal lobes and also may sometimes allow the identification of relatively small EZs. Eventually, frontal-parietal network explorations may be bilateral and sometimes symmetrical, mainly when a mesial frontal-parietal epilepsy is suspected, and the noninvasive methods of investigation have failed in lateralizing the epileptic activity.

Electrodes in rolandic regions are normally placed when there is a need to define (1) the posterior margin of the resection in frontal network explorations, (2) the anterior margin in parietal-occipital explorations, and (3) when the EZ may be located in or near the rolandic cortex. The main goal here is to evaluate the rolandic participation in the ictal discharge and to obtain a functional mapping by intracerebral electrical stimulation. In this location, depth electrodes are particularly helpful to sample the depth of the central sulcus as well as of the descending and ascending white matter fibers associated with this region.

Posterior quadrant network explorations In the posterior quadrant epilepsies, it is common to find the simultaneous involvement of several occipital, parietal, and posterior temporal structures as well as the multidirectional spread of the discharges to supra and infra sylvian areas or even to the contralateral hemisphere during ictal activity. By this motif, mesial and dorsal lateral surfaces of the occipital lobes are explored, covering both infra-calcarine and supra-calcarine areas in association with posterior temporal, posterior perisylvian, basal temporal-occipital areas, and posterior parietal areas, including the posteroinferior parietal lobule and the posterior precuneus.

10.6 Selecting the Electrodes Trajectory

Volumetric preoperative MRIs are obtained and DICOM (Digital Imaging and Communications in Medicine) format images are digitally transferred to the robot's native planning software. Subsequently, MRI T1-weighted images and contrasted CT images (both ideally acquired no more than 1 day before surgery) are fused in order to achieve better definitions of sulci and gyri as well as less distorted images. Aided by 3-D imaging reconstruction and such fused images, trajectories are selected in accordance with a predefined AEC hypothesis, as already mentioned. The aim is to maximize sampling from superficial and deep cortical and subcortical areas while respecting the vascular idiosyncrasies of the patient. When possible, the electrode trajectories are oriented orthogonally to facilitate the anatomo-electrophysiologic correlation during the extraoperative recording phase and to avoid possible trajectory shifts caused by excessive angled entry points. Notwithstanding, if the orthogonal trajectory passes through or extremely near the vessel trajectory, the entry point must be redefined. In other terms, it is preferable to change the final electrode position as little as possible in favor of avoiding intraoperative vascular ruptures. To reach such a goal, it is fundamental to amplify the coronal, axial, and sagittal views, mainly in the brain surface regions. This precaution is mandatory in order to prevent a vascular lesion, including in small vessels in the surface of the brain. These vessels are more difficult to identify and less mobile than the cisternal vessels and therefore more susceptible to injury during electrode implantation. It is also important to avoid trajectories passing through bone cells in order to prevent further liquor fistulae.

Nevertheless, when multiple targets are potentially accessible via a single nonorthogonal trajectory, these multi-target trajectories are selected in order to minimize the number of implanted electrodes per patient.

A set working distance of 150 mm from the drilling platform to the target is initially utilized for each trajectory; it may be adjusted later on in order to maximally reduce the working distance and consequently to improve the implantation accuracy. The overall implantation schemas are analyzed using the 3-D cranial reconstruction capabilities, and internal trajectories are checked to ensure that no trajectory collisions are present. External trajectory positions are examined for any entry sites that would be prohibitively close (less than 1.5 cm) at the skin level.

10.7 Surgical Technique

10.7.1 Electrode Implantation

After receiving general anesthesia, the patient is placed with the head in a three-point fixation head holder. Ideally, the distance between the base of the robotic arm and the midpoint of the cranium must be 70 cm. Both the robot's and the patient's table are locked into position, and the head holder device is secured to the robot (Fig. 10.1). Then, the robot laser is calibrated using a distance calibration tool, and a semi-automatic laser-based facial recognition is performed to register the preoperative volumetric MRI with the patient. For this recognition, preset anatomic facial landmarks (e.g., inner canthus, outer canthus, midline nasal tip and apex, temples, midline forefront, lateral eyebrow margin) are manually selected with the laser. The facial areas defined by the manually entered anatomic landmarks subsequently undergo automatic registration using laser-based surface scanning. If there is no match between the manually entered landmark and the automatic registered one, the neurosurgeon must reenter this specific landmark until a proper match occurs. Accuracy of the registration process is then confirmed by correlating additional independently chosen surface landmarks with the registered MRI.

The patient is then prepped and draped in a standard sterile fashion. Once the desired trajectory is confirmed using a touch screen, the robotic arm movement is initiated by foot-pedal command. The robotic arm automatically locks the drilling platform (i.e., a 2.5-mm diameter working cannula previously attached) into a stable position when a calculated position for the selected trajectory is reached. A 2-mm diameter handheld drill (Stryker, MFI Medical Equipment, San Diego, CA) is introduced through the platform and used to create a pinhole. After skin perforation, vessels are coagulated using monopolar devices inserted through the platform. The handheld drill is then reutilized to perforate skull bone. Immediately after crossing the inner limit of the bone (when the neurosurgeon feels an abrupt resistance reduction), the length of the drill necessary to reach that point must be measured. The dura is then opened with an insulated dural perforator using a monopolar cautery at low settings. The dural perforator length used is such that it surpasses the drill length measured in one finger tip (i.e., 5–8 mm approximately). Finally, a guiding bolt (Ad-Tech, Racine, WI) is screwed firmly into each pinhole.

The distance from the drilling platform to the retaining bolt is automatically measured, and this value is subtracted from the standardized 150 mm platform to target distance. The resulting difference is recorded for later use as the final

length of the electrode to be implanted. This process is repeated for each trajectory.

The electrode insertion only begins after all the bolts are placed. Changing gloves immediately before electrode insertion is a routine procedure at Cleveland Clinic. A small stylet (2 mm in diameter) is then set to the previously recorded electrode distance. Surgery continues with the stylet being passed gently into the parenchyma in a rotational manner, guided by the implantation bolt. After the stylet has been delicately pulled back, a premeasured electrode is inserted (also guided by an implantation bolt), and further removal of its line guide is manually performed.

In the final phase, the patient must undergo a fluoroscopic examination (anteroposterior incidence; Fig. 10.2) in order to evaluate the trajectory assumed by the electrodes inside the brain. SEEG electrodes must be allocated in a rectilinear trajectory. If curves or tortuosities are noted, the incorrectly positioned electrode is then pulled back and manually reinserted. Ultimately, electrodes are tested to guarantee an adequate recording after the procedure has been completed.

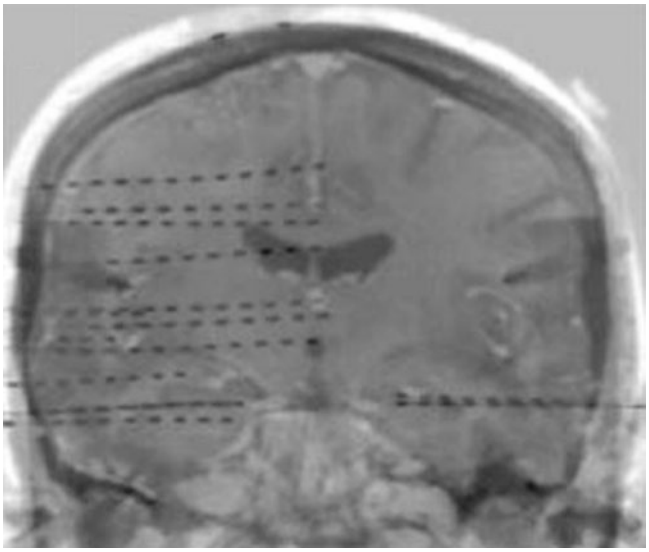

Fig. 10.2 Live fluoroscopic image fused with preoperative MR image during implantation of SEEG electrodes. Note the insertion of hippocampal electrodes bilaterally. The intraoperative images provide the surgeon with an additional degree of certainty and precision regarding the final position of every trajectory. (*From* Alomar et al. [83]; *with permission*)

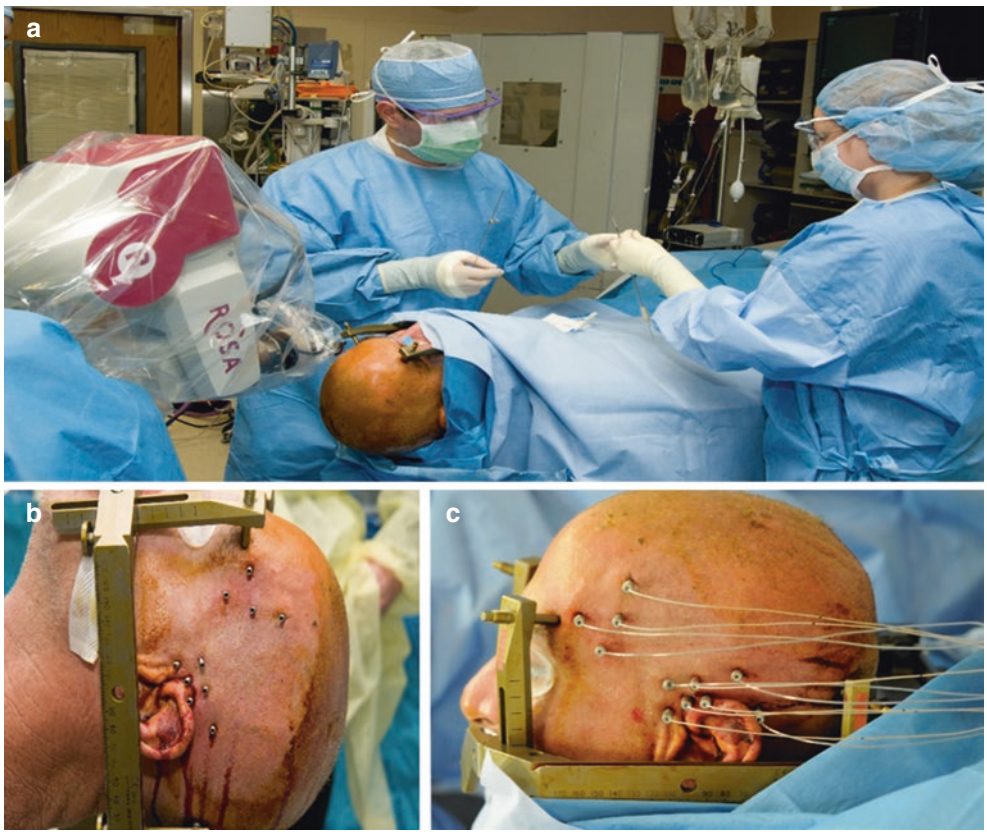

Fig. 10.1 Robotic SEEG technique. (**a**) Operating room "set-up" during left sided SEEG robotic implantation, with surgeon and scrub nurse positioned on each side of the patient and the robot device placed in the middle, at the vertex. (**b**), Intraoperative aspect of left sided frontal-temporal SEEG implantation with the final position of the guiding bolts. (**c**), Left sided frontal-temporal SEEG implantation after the depth electrode implantations. Final aspect. (*From* Alomar et al. [83]; *with permission*)

10.7.2 Electrode Removal

The SEEG electrodes removal corresponds to a very simple procedure normally lasting around 15–20 min. Under general anesthesia, the patient is also prepped and draped in standard sterile fashion. It is recommended that local anesthetic be injected around the bolts before their removal. Electrodes are manually pulled back and guiding bolts are unscrewed using a curved Kelly forceps. In the final phase, each pinhole is closed with a simple suture, and the number of both electrodes and guiding bolts is checked.

10.8 Postoperative Morbidity and Seizure Control

In a recent study, our group reported 200 patients, encompassing a total of 2663 electrode implantations, with the purpose of determining the EZ after defining an AEC hypothesis. In general, the studied individuals posed some challenges for the invasive evaluation because of the paucity of noninvasive data and/or more diffuse pathology suggested by a previous monitoring exploration: around one third of the sample space (58 patients, 29.0%) presented with previous surgery and postoperative repeated seizures. Notwithstanding, the SEEG method confirmed the EZ in 77.0% of the cases (154 patients). Among those who underwent resective surgery based on SEEG findings (137 patients, 87.0%), a considerable sample of 67.8% (61 patients) reached seizure-free outcome (Engel Class I outcome; 90 patients had a minimum of 12 months follow-up).

The most prevalent pathologic diagnosis was focal cortical dysplasia type I (55 patients, 61.1%), and complication rates were minimal, i.e., wound infections (0.08%), hemorrhagic complications (0.08%), and a transient neurologic deficit (0.04%) in a total of 5 patients. The total morbidity rate was 2.5%. Our results are similar to those reported by other independent groups regarding seizure outcome and complications.

Munari et al. [84] reported on their experience with SEEG in 70 patients, summing a total of 712 electrode implantations from which 60 patients (85.7%) were referred to tailored resective surgery as a result of SEEG findings. In the same sample size, these authors identified one permanent complication secondary to the procedure: asymptomatic intracerebral hematoma following the removal of an SEEG electrode (accounting for a morbidity incidence of 1.4%, or 0.1% per electrode).

Guenot [85] presented a series of 100 patients, accounting for total of 1118 SEEG electrode implantations. In this study SEEG was deemed helpful in 84 patients (84%) by either annulling or confirming (and additionally, in the latter case, guiding) surgical resection of the EZ. Moreover, SEEG confirmed the indications for resection in 14 cases (14%) that were previously disputed on the basis of the noninvasive work-up. Again, the rate of complication was quite low (5% of cases): 2 electrode site infections (0.2% incidence per electrode), 2 intracranial electrode fractures (0.2% incidence per electrode), and 1 intracerebral hematoma resulting in death (mortality rate of 1% in the study). In turn, Cossu et al. [86] reported a large series in which morbidity incidence was 5.6%, with severe permanent deficits resulting from intracerebral hemorrhage in 1% of the cases.

Another study conducted by Tanriverdi et al. [87] showed a subgroup of 491 refractory epilepsy patients (total of 2490 intracerebral SEEG electrode implantations and 2943 depth electrode implantations). Derived from this trial, results were obtained as follows: 4 patients (0.8%) with an intracranial hematoma at the electrode site (0.07% per electrode) and 9 patients (1.8%) with an infection arising from electrode placement (0.2% per electrode). There were no deaths secondary to SEEG electrode placement reported in the study.

Additionally, it is possible to quote the data presented by Cardinale et al. in which 482 epilepsy patients (total of 6496 stereotactically electrodes) were studied. Their results identified 2 patients (0.4%, or 0.03% per electrode) with permanent neurologic deficits; 14 patients (2.9%, or 0.2% per electrode) with hemorrhagic complications; 2 patients (0.4%, or 0.03% per electrode) with infections; and one mortality (0.2%) resulting from massive brain edema and concomitant hyponatremia following electrode implantation.

In comparing morbidity, subdural grid electrode implantation has historically been shown to have low permanent morbidity (0–3%) compared with depth electrodes (3–6%), since there is no intraparenchymal passage [7, 34, 88–93]. Although it is difficult to compare morbidity rates between subdural grids and SEEG because of the variability in patient selection, different institutions, and variable numbers of implanted electrodes, the clinical experience among different groups in Europe and North America suggests that the SEEG method provides at least a similar degree of safety when compared with subdural grids or strips [3, 26, 27, 30, 37, 56, 66, 70, 84, 87, 93–96].

Consistent with this idea, a very recent meta-analysis published by our group was responsible for assessing data of 2624 epilepsy patients who underwent SEEG monitoring and, in conjunction, were subjected to 22,085 stereotactic electrode implantations [80]. A total of 121 surgical complications were reported, encompassing in descending order of frequency: 40 patients with hemorrhages (pooled prevalence of 1.0%; most commonly intracerebral hemorrhage), 11 patients with permanent neurologic deficits (pooled prevalence of 0.6%), 28 patients with infections (pooled prevalence of 0.8% —most commonly cerebral abscess), 11 cases of implant malfunction (pooled prevalence of 0.4%), and 5 deaths (pooled prevalence of 0.3%). This study reported a rate of complications substantially lower than the complication rates reported for other extraoperative invasive monitoring. In conclusion, these data alleviate the concerns regarding the safety of the SEEG method, allowing a better decision-making process among different methods of invasive monitoring and ameliorating the fear associated with the insertion of depth electrodes.

Conclusion

The SEEG methodology has been proved to be both efficacious and safe over the last 55 years. The main advantage of the SEEG method is that it presents the possibility of studying the epileptogenic neuronal network in its dynamic and tridimensional aspect, with an optimal time and space correlation with the clinical semiology of the patient's seizures. Such capability leads to a tailored surgical strategy followed by satisfactory seizure control rates.

The main clinical challenge for the near future remains in the further refinement of specific selection criteria for the different methods of invasive monitoring, with the ultimate goal of comparing and validating the results (long-term seizure free outcome) obtained from different methods of invasive monitoring.

References

1. Rosenow F, Lüders H. Presurgical evaluation of epilepsy. Brain. 2001;124:1683–700.
2. Adelson PD, O'Rourke DK, Albright AL. Chronic invasive monitoring for identifying seizure foci in children. Neurosurg Clin N Am. 1995;6:491–504.
3. Cossu M, Chabardès S, Hoffmann D, Lo RG. Presurgical evaluation of intractable epilepsy using stereo-electro-encephalography methodology: principles, technique and morbidity. Neurochirurgie. 2008;54:367–73.
4. Jayakar P. Invasive EEG monitoring in children: when, where, and what? J Clin Neurophysiol. 1999;16:408–18.
5. Jayakar P, Duchowny M, Resnick TJ. Subdural monitoring in the evaluation of children for epilepsy surgery. J Child Neurol. 1994;9:61–6.
6. Winkler PA, Herzog C, Henkel A, Arnold S, Werhahn KJ, Yousry TA, et al. Noninvasive protocol for surgical treatment of focal epilepsies. Nervenarzt. 1999;70:1088–93.
7. Wyllie E, Lüders H, Morris HH, Lesser RP, Dinner DS, Rothner AD, et al. Subdural electrodes in the evaluation for epilepsy surgery in children and adults. Neuropediatrics. 1988;19:80–6.
8. Najm IM, Naugle R, Busch RM, Bingaman W, Lüders H. Definition of the epileptogenic zone in a patient with non-lesional temporal lobe epilepsy arising from the dominant hemisphere. Epileptic Disord. 2006;8(Suppl 2):S27–35.
9. Bancaud J, Dell MB. Technics and method of stereotaxic functional exploration of the brain structures in man (cortex, subcortex, central gray nuclei). Rev Neurol. 1959;101:213–27.
10. Dell MB. Temporal lobe epilepsy. La Press médicale. 1953;61:505–8.
11. Spiegel EA, Wycis HT, Freed H. Stereoencephalotomy in thalamotomy and related procedures. JAMA. 1952;148:446–51.
12. Bancaud J, Bonis A, Talairach J, Tournoux P, Szikla G, Saw V. The value of stereotaxic functional exploration in the localization of expansive lesions. Rev Obstet y Ginecol Venez. 1961;105:219–20.
13. Bancaud J, Angelergues R, Bernouilli C, Bonis A, Bordas-Ferrer M, Bresson M, et al. Functional stereotaxic exploration (SEEG) of epilepsy. Electroencephalogr Clin Neurophysiol. 1970;28:85–6.
14. Talairach J, Bancaud J, Bonis A, Szikla G, Tournoux P. Functional stereotaxic exploration of epilepsy. Confin Neurol. 1962;22:328–31.
15. Talairach J, Bancaud J, Bonis A, Szikla G, Trottier S, Vignal JP, et al. Surgical therapy for frontal epilepsies. Adv Neurol. 1992;57:707–32.

16. Chassoux F, Devaux B, Landré E, Turak B, Nataf F, Varlet P, et al. Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. Brain. 2000;123:1733–51.
17. Gonzalez-Martinez J, Mullin J, Vadera S, Bulacio J, Hughes G, Jones S, et al. Stereotactic placement of depth electrodes in medically intractable epilepsy. J Neurosurg. 2014;120:639–44.
18. Bancaud J, Favel P, Bonis A, Bordas-Ferrer M, Miravet J, Talairach J. Paroxysmal sexual manifestations and temporal lobe epilepsy. Clinical, EEG and SEEG study of a case of epilepsy of tumoral origin. Rev Neurol (Paris). 1970;123:217–30.
19. Bancaud J, Talairach J. Methodology of stereo EEG exploration and surgical intervention in epilepsy. Rev Otoneuroophtalmol. 1973;45:315–28.
20. Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Identification of epileptogenic networks from modeling and nonlinear analysis of SEEG signals. Neurophysiol Clin. 2001;31:139–51.
21. Biraben A, Taussig D, Thomas P, Even C, Vignal JP, Scarabin JM, et al. Fear as the main feature of epileptic seizures. J Neurol Neurosurg Psychiatry. 2001;70:186–91.
22. Bartolomei F, Wendling F, Bellanger JJ, Régis J, Chauvel P. Neural networks involving the medial temporal structures in temporal lobe epilepsy. Clin Neurophysiol. 2001;112:1746–60.
23. Wendling F, Bartolomei F, Bellanger JJ, Chauvel P. Interpretation of interdependencies in epileptic signals using a macroscopic physiological model of the EEG. Clin Neurophysiol. 2001;112:1201–18.
24. Tassi L, Colombo N, Cossu M, Mai R, Francione S, Lo Russo G, et al. Electroclinical, MRI and neuropathological study of 10 patients with nodular heterotopia, with surgical outcomes. Brain. 2005;128:321–37.
25. Battaglia G, Chiapparini L, Franceschetti S, Freri E, Tassi L, Bassanini S, et al. Periventricular nodular heterotopia: classification, epileptic history, and genesis of epileptic discharges. Epilepsia. 2006;47:86–97.
26. Cossu M, Cardinale F, Castana L, Nobili L, Sartori I, Lo RG. Stereo-EEG in children. Childs Nerv Syst. 2006;22:766–78.
27. Sindou M, Guenot M, Isnard J, Ryvlin P, Fischer C, Mauguière F. Temporo-mesial epilepsy surgery: outcome and complications in 100 consecutive adult patients. Acta Neurochir. 2006;148:39–45.
28. Guenot M, Isnard J. Epilepsy and insula. Neurochirurgie. 2008;54:374–81.
29. Guenot M, Isnard J. Multiple SEEG-guided RF-thermolesions of epileptogenic foci. Neurochirurgie. 2008;54:441–7.
30. Devaux B, Chassoux F, Guenot M, Haegelen C, Bartolomei F, Rougier A, et al. Epilepsy surgery in France. Neurochirurgie. 2008;54:453–65.
31. Gonzalez-Martinez J, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. Stereoelectroencephalography in the "difficult to localize" refractory focal epilepsy: early experience from a north American epilepsy center. Epilepsia. 2013;54:323–30.
32. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365:919–26.
33. Cendes F. Mesial temporal lobe epilepsy syndrome: an updated overview. J Epilepsy Clin Neurophysiol. Liga Brasileira de Epilepsia (LBE). 2005;11:141–4.
34. Nair DR, Burgess R, Mcintyre CC, Lüders H. Chronic subdural electrodes in the management of epilepsy. Clin Neurophysiol. 2008;119:11–28.
35. Pataraia E, Baumgartner C, Lindinger G, Deecke L. Magnetoencephalography in presurgical epilepsy evaluation. Neurosurg Rev. 2002;25:141–59. discussion, 160–1.
36. Grouiller F, Jorge J, Pittau F, van der Zwaag W, Iannotti GR, Michel CM, et al. Presurgical brain mapping in epilepsy using simultaneous EEG and functional MRI at ultra-high field: feasibility and first results. MAGMA. 2016;29:605–16.
37. Gonzalez-Martinez J, Najm IM. Indications and selection criteria for invasive monitoring in children with cortical dysplasia. Childs Nerv Syst. 2014;30:1823–9.
38. Marnet D, Devaux B, Chassoux F, Landré E, Mann M, Turak B, et al. Surgical resection of focal cortical dysplasias in the central region. Neurochirurgie. 2008;54:399–408.
39. Lo RG, Tassi L, Cossu M, Cardinale F, Mai R, Castana L, et al. Focal cortical resection in malformations of cortical development. Epileptic Disord. 2003;5(Suppl 2):S115–23.
40. Lüders H, Schuele SU. Epilepsy surgery in patients with malformations of cortical development. Curr Opin Neurol. 2006;19:169–74.
41. Kellinghaus C, Möddel G, Shigeto H, Ying Z, Jacobsson B, Gonzalez-Martinez J, et al. Dissociation between in vitro and in vivo epileptogenicity in a rat model of cortical dysplasia. Epileptic Disord. 2007;9:11–9.
42. González-Martínez JA, Srikijvilaikul T, Nair D, Bingaman WE. Long-term seizure outcome in reoperation after failure of epilepsy surgery. Neurosurgery. 2007;60:873–80. discussion, 873–80.
43. Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, et al. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain. 2002;125:1719–32.
44. Srikijvilaikul T, Najm IM, Hovinga CA, Prayson RA, Gonzalez-Martinez J, Bingaman WE. Seizure outcome after temporal lobectomy in temporal lobe cortical dysplasia. Epilepsia. 2003;44:1420–4.
45. Francione S, Kahane P, Tassi L, Hoffmann D, Durisotti C, Pasquier B, et al. Stereo-EEG of interictal and ictal electrical activity of a histologically proved heterotopic gray matter associated with partial epilepsy. Electroencephalogr Clin Neurophysiol. 1994;90:284–90.
46. Bancaud J, Talairach J, Waltregny P, Bresson M, Morel P. Stimulation of focal cortical epilepsies by megimide in topographic diagnosis. (clinical EEG and SEEG study). Rev Neurol (Paris). 1968;119:320–5.
47. Bancaud J, Talairach J, Waltregny P, Bresson M, Morel P. Activation by megimide in the topographic diagnosis of focal cortical epilepsies (clinical EEG and SEEG study). Electroencephalogr Clin Neurophysiol. 1969;26:640.
48. Talairach J, Bancaud J, Bonis A, Tournoux P, Szikla G, Morel P. Functional stereotaxic investigations in epilepsy. Methodological remarks concerning a case. Rev Neurol (Paris). 1961;105:119–30.
49. Geier S, Bancaud J, Talairach J, Enjelvin M. Radiotelemetry in EEG and SEEG. Technology and material. Rev d'électroencéphalographie Neurophysiol Clin. 1973;3:353–4.
50. Cabrini GP, Ettorre G, Marossero F, Miserocchi G, Ravagnati L. Surgery of epilepsy: some indications for SEEG. J Neurosurg Sci. 1975;19:95–104.
51. Bancaud J, Talairach J, Geier S, Bonis A, Trottier S, Manrique M. Behavioral manifestations induced by electric stimulation of the anterior cingulate gyrus in man. Rev Neurol (Paris). 1976;132:705–24.
52. Musolino A, Tournoux P, Missir O, Talairach J. Methodology of "in vivo" anatomical study and stereo-electroencephalographic exploration in brain surgery for epilepsy. J Neuroradiol. 1990;17:67–102.
53. Engel J, Henry TR, Risinger MW, Mazziotta JC, Sutherling WW, Levesque MF, et al. Presurgical evaluation for partial epilepsy: relative contributions of chronic depth-electrode recordings versus FDG-PET and scalp-sphenoidal ictal EEG. Neurology. 1990;40:1670–7.
54. Baucaud J, Talairach J, Munari C, Giallonardo T, Brunet P. Introduction to the clinical study of postrolandic epileptic seizures. Can J Neurol Sci. 1991;18:566–9.
55. Avanzini G. Discussion of stereoelectroencephalography. Acta Neurol Scand Suppl. 1994;152:70–3.
56. Serletis D, Bulacio J, Bingaman W, Najm I, González-Martínez J. The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients. J Neurosurg. 2014;121:1239–46.
57. Catenoix H, Mauguière F, Guénot M, Ryvlin P, Bissery A, Sindou M, et al. SEEG-guided thermocoagulations: a palliative treatment of nonoperable partial epilepsies. Neurology. 2008;71:1719–26.

58. Abraham G, Zizzadoro C, Kacza J, Ellenberger C, Abs V, Franke J, et al. Growth and differentiation of primary and passaged equine bronchial epithelial cells under conventional and air-liquid-interface culture conditions. BMC Vet Res. 2011;7:26.
59. Kerr MSD, Burns SP, Gale J, Gonzalez-Martinez J, Bulacio J, Sarma SV. Multivariate analysis of SEEG signals during seizure. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2011;2011:8279–82.
60. Centeno RS, Yacubian EMT, Caboclo LOSF, Júnior HC, Cavalheiro S. Intracranial depth electrodes implantation in the era of image-guided surgery. Arq Neuropsiquiatr. 2011;69:693–8.
61. Kakisaka Y, Kubota Y, Wang ZI, Piao Z, Mosher JC, Gonzalez-Martinez J, et al. Use of simultaneous depth and MEG recording may provide complementary information regarding the epileptogenic region. Epileptic Disord. 2012;14:298–303.
62. Yaffe R, Burns S, Gale J, Park H-J, Bulacio J, Gonzalez-Martinez J, et al. Brain state evolution during seizure and under anesthesia: a network-based analysis of stereotaxic EEG activity in drug-resistant epilepsy patients. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2012;2012:5158–61.
63. Antony AR, Alexopoulos AV, González-Martínez JA, Mosher JC, Jehi L, Burgess RC, et al. Functional connectivity estimated from intracranial EEG predicts surgical outcome in intractable temporal lobe epilepsy. PLoS One. 2013;8:e77916.
64. Vadera S, Marathe AR, Gonzalez-Martinez J, Taylor DM. Stereoel ectroencephalography for continuous two-dimensional cursor control in a brain-machine interface. Neurosurg Focus. 2013;34:E3.
65. Wang S, Wang IZ, Bulacio JC, Mosher JC, Gonzalez-Martinez J, Alexopoulos AV, et al. Ripple classification helps to localize the seizure-onset zone in neocortical epilepsy. Epilepsia. 2013;54:370–6.
66. Cardinale F, Cossu M, Castana L, Casaceli G, Schiariti MP, Miserocchi A, et al. Stereoelectroencephalography: surgical methodology, safety, and stereotactic application accuracy in 500 procedures. Neurosurgery. 2013;72:353–66. discussion, 366.
67. Enatsu R, Bulacio J, Nair DR, Bingaman W, Najm I, Gonzalez-Martinez J. Posterior cingulate epilepsy: clinical and neurophysiological analysis. J Neurol Neurosurg Psychiatry. 2014;85:44–50.
68. Enatsu R, Bulacio J, Najm I, Wyllie E, So NK, Nair DR, et al. Combining stereo-electroencephalography and subdural electrodes in the diagnosis and treatment of medically intractable epilepsy. J Clin Neurosci. 2014;21:1441–5.
69. Gonzalez-Martinez J, Lachhwani D. Stereoelectroencephalography in children with cortical dysplasia: technique and results. Childs Nerv Syst. 2014;30:1853–7.
70. Gonzalez-Martinez J, Mullin J, Bulacio J, Gupta A, Enatsu R, Najm I, et al. Stereoelectroencephalography in children and adolescents with difficult-to-localize refractory focal epilepsy. Neurosurgery. 2014;75:258–68. discussion, 267–8.
71. Johnson MA, Thompson S, Gonzalez-Martinez J, Park H-J, Bulacio J, Najm I, et al. Performing behavioral tasks in subjects with intracranial electrodes. J Vis Exp. 2014;92:e51947.
72. Vadera S, Burgess R, Gonzalez-Martinez J. Concomitant use of stereoelectroencephalography (SEEG) and magnetoencephalographic (MEG) in the surgical treatment of refractory focal epilepsy. Clin Neurol Neurosurg. 2014;122:9–11.
73. Cardinale F, Cossu M. SEEG has the lowest rate of complications. J Neurosurg. 2015;122:475–7.
74. Cossu M, Fuschillo D, Cardinale F, Castana L, Francione S, Nobili L, et al. Stereo-EEG-guided radio-frequency thermocoagulations of epileptogenic grey-matter nodular heterotopy. J Neurol Neurosurg Psychiatry. 2014;85:611–7.
75. Enatsu R, Gonzalez-Martinez J, Bulacio J, Kubota Y, Mosher J, Burgess RC, et al. Connections of the limbic network: a corticocortical evoked potentials study. Cortex. 2015;62:20–33.
76. Vadera S, Mullin J, Bulacio J, Najm I, Bingaman W, Gonzalez-Martinez J. Stereoelectroencephalography following subdural grid placement for difficult to localize epilepsy. Neurosurgery. 2013;72:723–9. discussion, 729.
77. Kovac S, Kahane P, Diehl B. Seizures induced by direct electrical cortical stimulation. Mechanisms and clinical considerations. Clin Neurophysiol. 2016;127:31–9.
78. Najm IM, Bingaman WE, Lüders HO. The use of subdural grids in the management of focal malformations due to abnormal cortical development. Neurosurg Clin N Am. 2002;13:87–92. viii–ix
79. Widdess-Walsh P, Jeha L, Nair D, Kotagal P, Bingaman W, Najm I. Subdural electrode analysis in focal cortical dysplasia: predictors of surgical outcome. Neurology. 2007;69:660–7.
80. Mullin JP, Shriver M, Alomar S, Najm I, Bulacio J, Chauvel P, et al. Is SEEG safe? A systematic review and meta-analysis of stereo-electroencephalography-related complications. Epilepsia. 2016;57:386–401.
81. Chauvel P, Mcgonigal A. Emergence of semiology in epileptic seizures. Epilepsy Behav. 2014;38:94–103.
82. Cardinale F, Lo RG. Stereo-electroencephalography safety and effectiveness: some more reasons in favor of epilepsy surgery. Epilepsia. 2013;54:1505–6.
83. Alomar S, Jones J, Maldonado A, Gonzalez-Martinez J. The stereo-electroencephalography methodology. Neurosci Clin North Am. 2016;27(1):83–95.
84. Munari C, Hoffmann D, Francione S, Kahane P, Tassi L, Lo Russo G, et al. Stereo-electroencephalography methodology: advantages and limits. Acta Neurol Scand Suppl. 1994;152:56–67. discussion, 68–9.
85. Guenot M, Isnard J, Ryvlin P, Fischer C, Ostrowsky K, Mauguiere F, et al. Neurophysiological monitoring for epilepsy surgery: the Talairach SEEG method. Stereo electro encephalo graphy. Indications, results, complications and therapeutic applications in a series of 100 consecutive cases. Stereotact Funct Neurosurg. 2001;77:29–32.
86. Cossu M, Cardinale F, Colombo N, Mai R, Nobili L, Sartori I, et al. Stereoelectroencephalography in the presurgical evaluation of children with drug-resistant focal epilepsy. J Neurosurg. 2005;103:333–43.
87. Tanriverdi T, Ajlan A, Poulin N, Olivier A. Morbidity in epilepsy surgery: an experience based on 2449 epilepsy surgery procedures from a single institution. J Neurosurg. 2009;110:1111–23.
88. Lee WS, Lee JK, Lee SA, Kang JK, Ko TS. Complications and results of subdural grid electrode implantation in epilepsy surgery. Surg Neurol. 2000;54:346–51.
89. Rydenhag B, Silander HC. Complications of epilepsy surgery after 654 procedures in Sweden, September 1990–1995: a multicenter study based on the Swedish National Epilepsy Surgery Register. Neurosurgery. 2001;49:51–6. discussion, 56–7.
90. Hamer HM, Morris HH, Mascha EJ, Karafa MT, Bingaman WE, Bej MD, et al. Complications of invasive video-EEG monitoring with subdural grid electrodes. Neurology. 2002;58:97–103.
91. Onal C, Otsubo H, Araki T, Chitoku S, Ochi A, Weiss S, et al. Complications of invasive subdural grid monitoring in children with epilepsy. J Neurosurg. 2003;98:1017–26.
92. González Martínez F, Navarro Gutiérrez S, de León Belmar JJ, Valero SB. Electrocardiographic disorders associated with recent onset epilepsy. Neurol (Barcelona, Spain). 2005;20:698–701.
93. Ozlen F, Asan Z, Tanriverdi T, Kafadar A, Ozkara C, Ozyurt E, et al. Surgical morbidity of invasive monitoring in epilepsy surgery: an experience from a single institution. Turk Neurosurg. 2010;20:364–72.
94. Afif A, Chabardes S, Minotti L, Kahane P, Hoffmann D. Safety and usefulness of insular depth electrodes implanted via an oblique approach in patients with epilepsy. Neurosurgery. 2008;62:ONS471–9. discussion, 479–80.
95. Nobili L, Cardinale F, Magliola U, Cicolin A, Didato G, Bramerio M, et al. Taylor's focal cortical dysplasia increases the risk of sleep-related epilepsy. Epilepsia. 2009;50:2599–604.
96. Serletis D, Bulacio J, Alexopoulos A, Najm I, Bingaman W, González-Martínez J. Tailored unilobar and multilobar resections for orbitofrontal-plus epilepsy. Neurosurgery. 2014;75:388–97. discussion, 397.

Extraoperative Cortical Stimulation and Mapping

11

Konstantinos N. Fountas and Joseph R. Smith

Accurate identification of eloquent cortical areas is of paramount importance for safe surgical resection in cases of medically intractable epilepsy or in glioma cases. Despite all the recent advances in functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) as well as in magnetic source imaging and high-density surface EEGs, direct electrical cortical stimulation remains the gold standard for accurately outlining cortical eloquent areas. Intraoperatively employed cortical stimulation and mapping through an awake craniotomy is not always feasible. Patients with anxiety or fear of undergoing an awake surgical procedure, those with conditions contraindicating an awake procedure, and pediatric patients may not be suitable for mapping through an awake craniotomy. In these cases, and also in cases of medically refractory epilepsy in which invasive EEG monitoring is required for localizing any epileptogenic focus/i, cortical mapping may safely be accomplished through an extraoperative stimulation via implanted subdural and/or depth electrodes. This chapter presents the surgical preparation, the preoperative planning, the surgical procedure, and the extraoperative stimulation and mapping processes and their nuances. The associated complications with the electrode implantation and the invasive EEG monitoring and stimulation are also presented. Moreover, the future perspectives of invasive EEG monitoring and extraoperative cortical stimulation and mapping are briefly presented.

K. N. Fountas (✉)
University Hospital of Larisa, Medical School, University of Thessaly, Larisa, Greece
e-mail: fountas@uth.gr

J. R. Smith
Department of Neurosurgery, Augusta University, Augusta, GA, USA
e-mail: jsmith@mail.mcg.edu

11.1 Introduction

The great positive effect of maximal resection in the overall survival of patients with gliomas has been well documented [1–5]. Gross total resection and even supramarginal resection of low-grade gliomas (LGGs) have been demonstrated to significantly increase the five- and ten-year survival rates and to minimize or significantly decrease the frequency and the severity of any preoperative seizure activity [6–8]. Furthermore, such resection has been demonstrated to decrease the possibility of a tumor recurrence and of its advancement to a higher histologic grade [6–8]. Likewise, it has been shown that maximal tumor resection is associated with prolonged progression-free and overall survival as well as improved functional status in patients with high-grade gliomas (HGGs) [4, 5, 9–11]. However, maximal glioma resection may jeopardize any adjacent cortical areas, particularly in those cases in which gliomas are located in or near eloquent cortical areas.

The definition of eloquent cortical areas has evolved over time, especially during the last two decades with the great advances in the fields of neuroimaging and electrophysiology. Traditionally, the cortical areas associated with motor, sensory, and speech functions are considered eloquent. Anatomic models had outlined the precentral sulcus (Brodmann area 4), and the supplementary motor area (Brodmann area 6) as the main cortical areas associated with motor function, the postcentral sulcus (Brodmann areas 1, 2, and 3) as the main area associated with sensory function, and the Broca (Brodmann areas 44 and 45) and Wernicke areas (Brodmann areas 22, 39, and 40) as the main cortical areas associated with speech functions. However, the landmark study of Ojemann et al. [12] demonstrated that these anatomic models are highly inaccurate, and the functional cortical areas demonstrate significant variation in regard to their exact anatomic location. The wide clinical employment of direct electrical cortical stimulation during neurosurgical procedures practically redefined the boundaries of the

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eloquent cortical areas, especially those associated with speech, and it confirmed that every patient has his or her own unique cortical functional map.

Furthermore, the emergence of functional MRI methodologies (task-generated and resting-state fMRI and diffusion tensor imaging), the evolution of standard electrophysiologic studies (high-density surface EEGs), and the development of hybrid imaging modalities combing neurophysiologic and anatomic data (magnetic source imaging, superimposing magneto-encephalo-graphic data on high-resolution MRIs) significantly enhanced our knowledge regarding the cortical areas involved in the speech process and their complex connectivity. Numerous studies have provided insights into the involvement of several other cortical areas in addition to the Broca and Wernicke areas [13–27]. They have shown that there is involvement in the speech process of cortical areas located in the frontal, temporal, and insular lobes of the dominant hemisphere but also in the temporal lobe of the nondominant hemisphere. It has been proposed that these cortical areas could be the functional components of two interacting loops: a preparatory and an executive one. The key elements of the preparatory loop are the supplementary motor area, the insula, and the superior cerebellum, while the executive loop includes the primary motor cortex, the thalamus, and the inferior cerebellum (Fig. 11.1). It has also been recently demonstrated that these extensive and highly complex cortical networks are interconnected with numerous white matter bundles [13, 23, 28–32]. The arcuate, the uncinate, the inferior fronto-occipital, the superior longitudinal, the middle longitudinal, and the inferior longitudinal fasciculi interconnect these cortical areas and participate in the speech process [13, 23, 28–32]. Interestingly, several investigators have postulated that these complex and interconnecting cortical and subcortical networks may demonstrate plasticity over time and may be variable not only from patient to patient but even in the same patient [33–35].

Intraoperative direct electrical stimulation is considered the gold standard in identifying and outlining cortical and subcortical areas associated with speech [12, 36–39]. However, it requires the patient undergoing surgery to be awake, fully cooperative, and psychologically stable. These conditions may represent limiting factors for employing direct stimulation and cortical/subcortical mapping. In addition, the patient's obesity, pre-existing respiratory difficulties, brain midline structure shift caused by mass effect and edema, stimulation-induced seizures, and occurrence of trigemino-cardiac reflex may be relative contraindications for an awake craniotomy (Table 11.1) [40–43]. It should also be pointed out that during an awake craniotomy only certain language tasks can be assessed, mainly because of time restrictions. The overall failure rate of awake procedures has been reported to range between 0.5% and 6.3% [40, 42, 43].

Extraoperative cortical stimulation and mapping represent a valid alternative option for those patients who cannot undergo an awake procedure. They may be suitable for pediatric patients, for patients who are afraid of undergoing an awake surgical procedure, or for cases in which an extensive stimulation and mapping process is required (multilingual patients, extensive mapping of complex neurocognitive functions). This methodology lends itself to the evaluation and the safe surgical planning of patients with medically refractory epilepsy, gliomas, or metastatic tumors of eloquent areas as well as vascular lesions arterio-venous malformations (AVMs) or cavernous malformations (CMs) of eloquent areas.

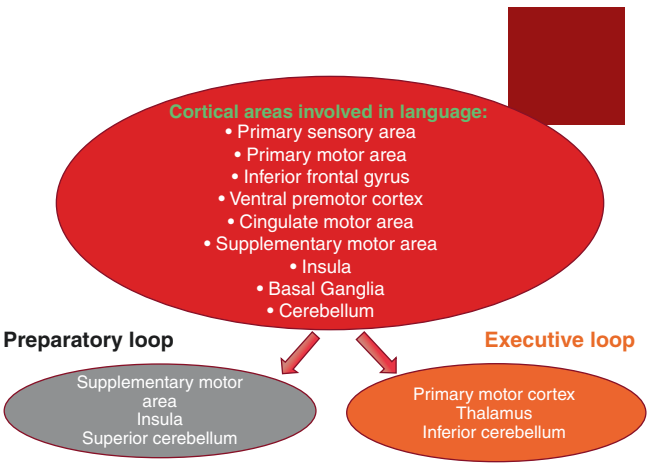

Fig. 11.1 Schematic representation of all cortical areas organized in two loops—a preparatory and an executive one—involved in speech production

Table 11.1 Relative Contraindications for an Awake Craniotomy

Severely obese patient
Pre-existing respiratory difficulty or pathology
Severe brain midline shift caused by mass effect and edema
Pre-existing aphasia
Patient's anxiety, fear, or inability to collaborate/cooperate
Heavy smoking

These conditions constitute relative and not absolute contraindications, depending on the patient and the experience of the involved neurosurgeon with awake procedures

11.2 Preoperative Assessment

The whole process of the two separate surgical procedures and the extraoperative stimulation and mapping session or sessions are adequately explained to the patient and the patient's family. A detailed written consent form is obtained. The patient is carefully evaluated by a neuropsychologist, while all the planned neuropsychological tests and their clinical significance are extensively discussed with the patient. The process of the extraoperative electrical stimulation and mapping is explained to the patient, and special emphasis is given to the fact that seizures may be induced by the electrical stimulation and can be safely managed.

The process of the implantation of the electrodes, the benefits, and the potential complications are also discussed with the patient. The importance of maintaining the implanted electrode tails in a secure position and clean is pointed out to the patient and the caregivers. Also, the fact that there will be a video-EEG recording (in epilepsy cases) is explained.

The patient's conventional MRI, magnetic resonance venography (MRV), or computer tomography venography (CTV), fMRI, and EEG studies are carefully reviewed. In cases in which there are concerns regarding the white matter tracts, a DTI study is obtained. A standard preoperative work-up including a complete blood count, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), bleeding time, and a basic blood biochemical profile are obtained. Especially for epilepsy patients, the chronic use of anticonvulsants may interfere with the patient's clotting profile. The patient is routinely evaluated by a neuroanesthesiologist before surgery.

11.3 Surgical Planning

All the patient's imaging studies (MRI, fMRI, DTI, MRV, or CTV) are uploaded in the navigation computer. In addition, the EEG data are taken into consideration for identifying any areas of epileptogenic activity. The areas of interest are identified, and their proximity to any potential eloquent cortical areas is examined. After confirming the areas that need to be covered by an electrode, the most efficient combination of subdural strip and grid and also depth (if necessary) electrodes is chosen (Fig. 11.2). It must be emphasized that a wide variation in shape and size of subdural electrodes is available for covering practically any cortical area. Furthermore, novel-shaped electrodes especially designed for certain anatomic areas (e.g., the insula) and hybrid electrodes with a combination of standard contacts and microwire arrays embedded in-between the contacts provide additional options for more accurate but also safer monitoring, stimulation, and mapping.

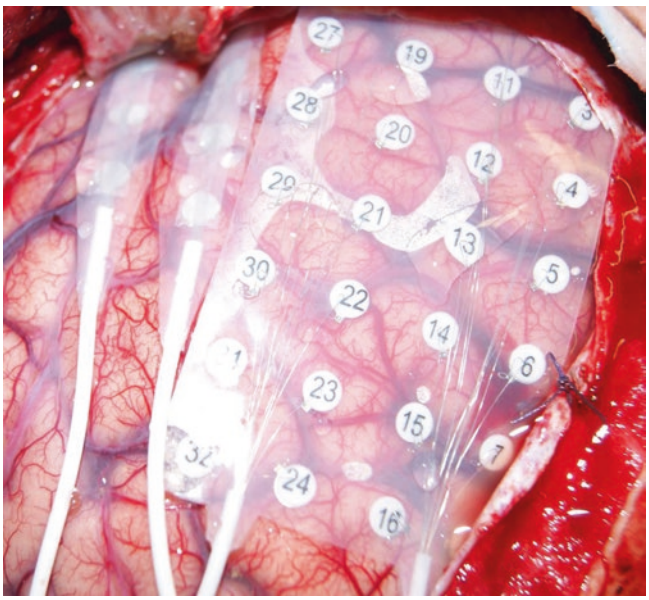

Fig. 11.2 Intraoperative picture demonstrating a combination of implanted subdural grid and strip electrodes for invasive extra-operative EEG recording and cortical electrical stimulation and mapping

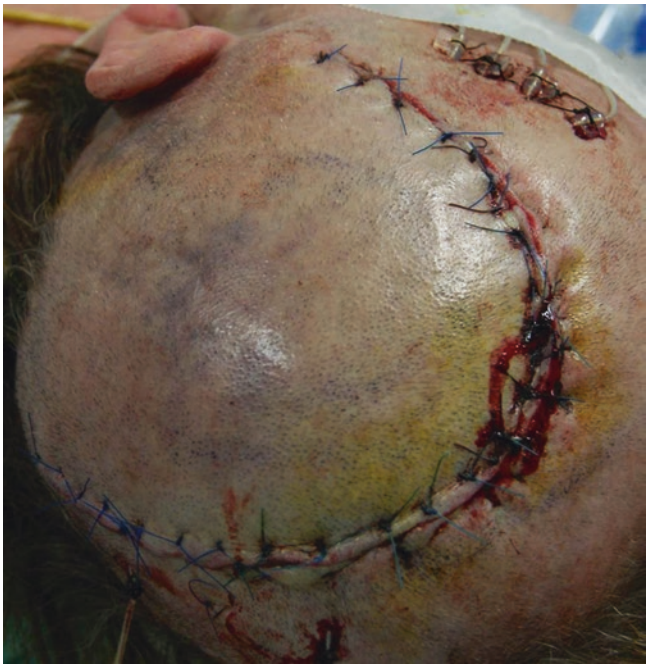

Fig. 11.3 Immediate postimplantation picture in a patient with left-sided temporal subdural electrode implantation for extraoperative EEG monitoring and cortical stimulation and mapping. The exiting electrode tails (*arrow*) are safely secured in the skin, while the exit points are in an adequate distance (at least 2.5 cm away) from the surgical wound skin incision. This will prevent any electrode misplacement and minimizes the risk of any postimplantation infections

The potential entry point for depth electrodes as well as the surface cortical vein anatomy is carefully considered in order to minimize the risk of a venous injury during the insertion of the electrodes. The exit points of the tails of the subdural electrodes are carefully chosen in order to maximize sterility during the procedure and to minimize any mechanical friction, thereby avoiding any electrode migration during the monitoring period (Fig. 11.3). The most optimal surgical plan is finalized and saved for the day of the procedure, thus allowing the selection of the ideal position for the patient's head and the three-point fixation device. Any particular concerns regarding the patient's position during the procedure are discussed with the anesthesiology team.

11.4 Implantation of Electrodes

The day of the first procedure the patient takes all his or her medications early in the morning and is taken into the operating room. After a smooth general endotracheal anesthesia induction, the depth electrodes (if planned) are placed first in order to avoid any cerebrospinal fluid leak and thus minimize any inaccuracies. Subsequently, the planned craniotomy is performed. After the dural opening, the surface venous anatomy is confirmed. The subdural electrodes are carefully implanted, and their exiting tails are tunneled under the skin and exit at a distance of at least 2.5–3.0 cm from the surgical wound incision to minimize the risk of infection (Fig. 11.4). The importance of adequate exposure cannot be overemphasized so as to avoid any venous injuries and postoperative hematomas during the insertion of subdural grids and strips under the dura. The tails of the electrodes are safely anchored and secured at the skin. The bone edges at the exit points are drilled and smoothed in order to avoid any mechanical friction points and potential electrode breakage (Fig. 11.5). The surgical wound is thoroughly irrigated to remove any blood clots, which may interfere with the extraoperative monitoring and stimulation process.

A high-resolution photograph of the implanted electrodes is taken for the extraoperative stimulation process. The watertight closure of the dura is of paramount importance in order to avoid any postoperative cerebrospinal fluid leakages not only to mitigate any postoperative infections but also to avoid any electrode migration and displacement. The local application of collodion at the electrode exiting points serves exactly the same purpose.

A postoperative 1-mm slice thickness CT scan and an MRI are obtained in the immediate postoperative period for verifying the position of the implanted electrodes. The obtained images are fused, reconstructed in three-dimensional models, and used for electrode placement verification (Fig. 11.6).

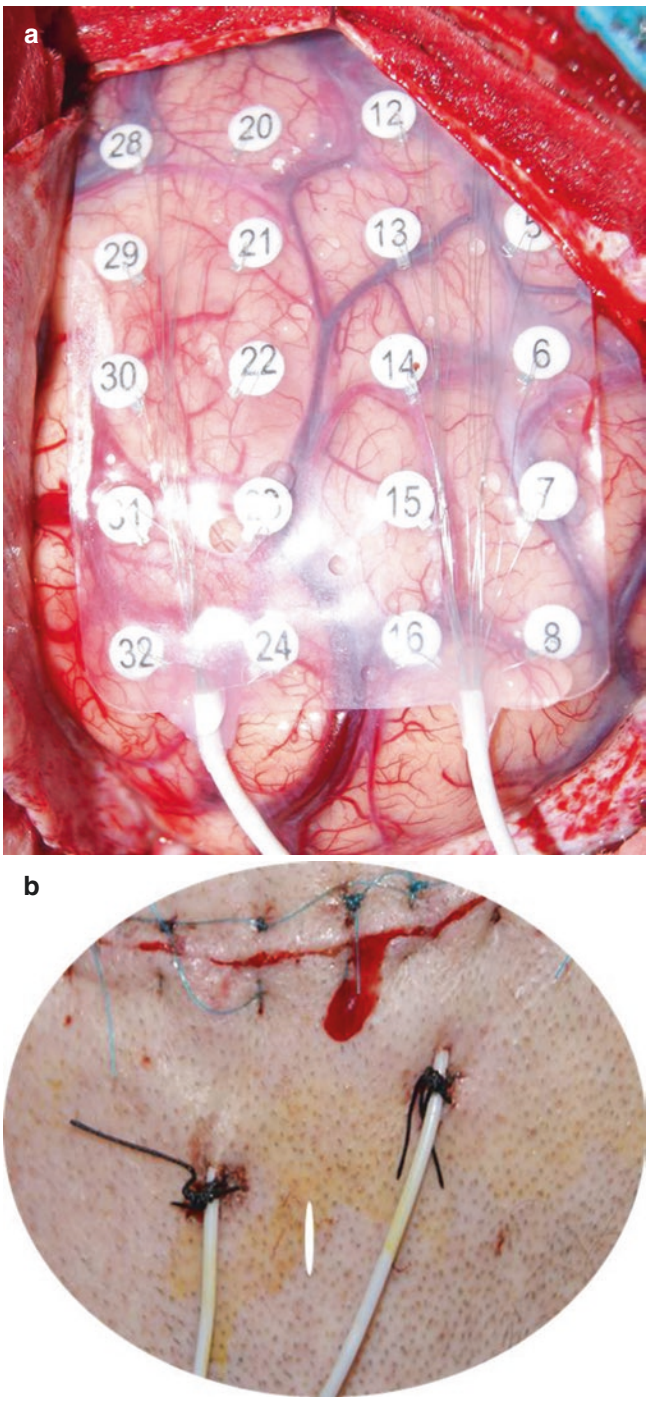

Fig. 11.4 (**a**, **b**) Intraoperative and immediate postoperative pictures demonstrating the implantation of a 32-contact subdural grid electrode and the exiting electrode tails. Collodion is routinely applied around the exiting electrode tail to minimize any cerebrospinal fluid leakage

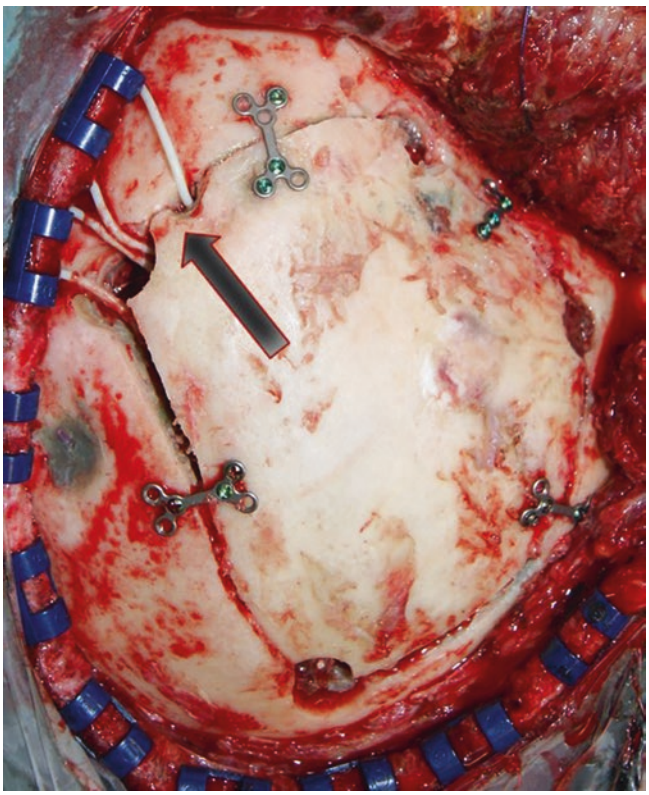

Fig. 11.5 Intraoperative picture taken during closure demonstrating the bone grooving at the electrode tail exiting points (*arrow*). This osseous edge smoothening minimizes any mechanical friction and electrode dysfunction and/or breaking

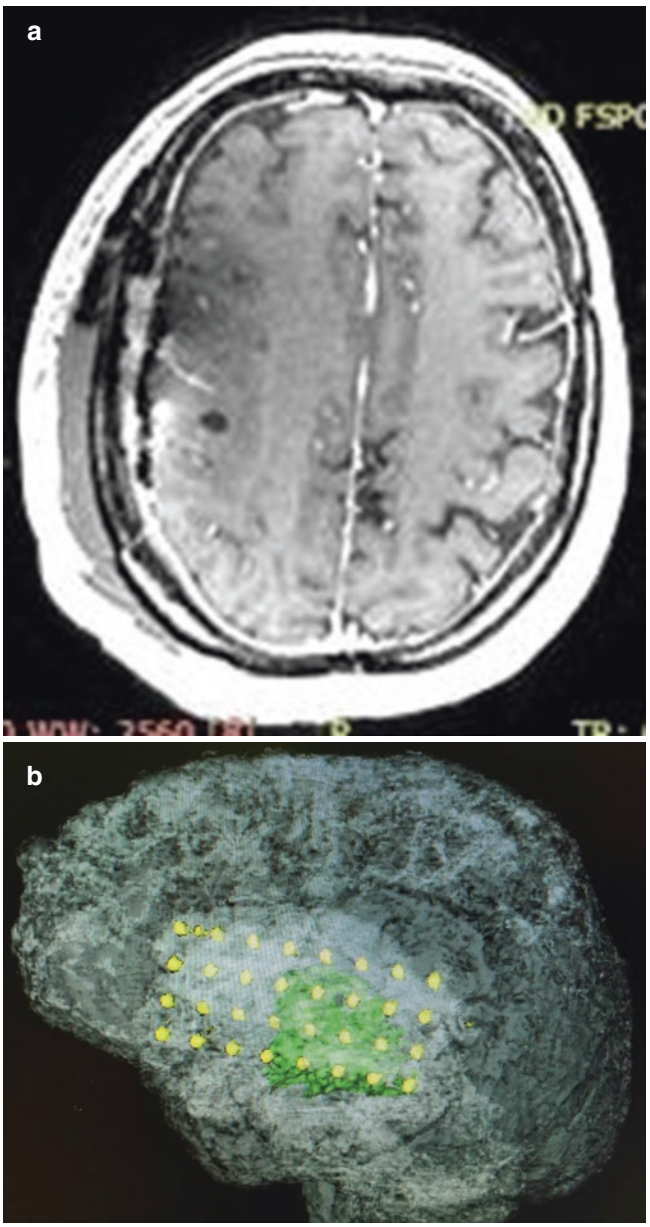

Fig. 11.6 (**a**, **b**) Axial MRI image and three-dimensional reconstruction of postimplantation MRI demonstrating the exact anatomic location of each of the previously implanted subdural grids and the underlying pathology (glioma)

11.5 Extraoperative Stimulation

The extraoperative stimulation in medically intractable epilepsy cases is performed after completing the monitoring period, which usually requires the recording of at least two to three episodes of the patient's habitual seizures. In tumor cases, however, in which EEG monitoring is not necessary, the stimulation and mapping are usually performed 24 to 48 hours after the electrode implantation in order to minimize any implantation-associated artifacts.

The morning of the stimulation, the whole process is explained again to the patient. The patient's comfort and the safe management of any stimulation-induced seizures are very important for the success of the stimulation and the detailed mapping. The whole process is video-recorded for future reference but also for research purposes.

The stimulation parameters may vary among different protocols. We routinely employ electric stimulation of 50 Hz frequency, alternating polarity of 0.2 ms, square-wave pulses, 3 s train, and current intensity of 2–6 mAmp. The initial stimulation may start at 2 mAmp, and then it may be progressively increased by 0.5 or 1 mAmp increments. Whenever there is a speech arrest, a phonemic error, or a paraphasia, a second round of stimulation is performed for confirming these findings after an adequate period of time. It should be pointed out that adequate time needs to be provided between stimuli in order to avoid any after-discharge electrical activity.

Numerous speech or other task tests may be employed during stimulation. We routinely perform at least a minimum menu of the following four speech tests: (i) Boston naming, (ii) listening comprehension of a text, (iii) reading of a text, and (iv) spontaneous speech. This core menu may be expanded to include other more complicated tests such as rehearsing, parroting, opposite/synonym word finding, noun production from a verb and vice versa, counting, and calculating, depending on the patient's background and education level and skills. All these tests may be employed in more than one language for multilingual patients.

Furthermore, memory or other neuropsychological tests may be employed for evaluating certain skills and abilities, thus creating the respective cortical mappings. All other cognitive, psychological, or autonomic responses are recorded and are properly depicted on the generated cortical maps. In those cases in which a task-generated fMRI study has been previously performed, the employed paradigms may be tested for confirming the location of these functions but also for evaluating the accuracy of the fMRI results. The employment of extraoperative stimulation may provide significant clinical information as well as a large amount of electrophysiologic data for research purposes.

The stimulation and mapping can be performed in more than one session if the patient is not comfortable or if stimulation-induced seizures occur and interrupt one of the sessions. In addition, the patient's relatives may be present during the whole process, which may be particularly helpful in cases of pediatric patients. The management of any stimulation-induced seizure activity can be safely done, but both the patient and the involved personnel need to be aware of this possibility. In our experience, including more than 150 tumor and epilepsy cases, the stimulation and mapping process could not be completed in only 3% of our patients. In approximately 15% of our cases this process required more than one session of stimulation and mapping.

11.6 Removal of Electrodes

All the collected data of the stimulation and the generated cortical maps are uploaded on to the navigation workstation and the surgical resection plan is created. The day of the second procedure, before prepping and draping of the surgical field, the electrode's anchoring sutures are removed. After reopening the dural flap, the previously implanted electrodes are carefully removed and are sent for cultures. At the end of the procedure, the electrode exiting points are thoroughly irrigated with antibiotic solution and sutured.

11.7 Complications

The implantation of electrodes has been associated with various complications. In general, depth electrodes are considered safer than subdural electrodes [44–46]. Indeed, the occurrence of any depth electrode–associated complications has been reported to be 2.5% (overall morbidity), while the occurrence of hemorrhagic complications after depth electrode insertion was reported to be 0.2% [47–50].

Various complications have been reported in the pertinent literature in regard to the implantation of subdural strip and/or grid electrodes [44–46, 51–54]. Wellmer et al. [45] reported a cumulative complication rate of 23.1%, while in their recent series Yang et al. found that the subdural electrode–associated cumulative complication rate was 21.7% [54]. The subdural electrode associated mortality rate has been reported to be as high as 2.1% [52]. This is the result of increased intracranial pressure and cerebral edema development in the vast majority of these cases and is more common among children and in cases of interhemispheric, bulky, grid electrode implantation. The development of edema after subdural electrode implantation ranges in the literature between 0.5% and 14% [52]. In pediatric cases, when multiple subdural grid electrodes are planned to be implanted, it may be advantageous to insert an intracranial pressure monitor to properly manage the intracranial pressure.

The occurrence of an infection has been reported to vary from 1.1% to 17% [52]. In the vast majority of cases, the infection can be conservatively managed with systemic antibiotics, with no further consequences. The total number of the implanted electrodes and the duration of monitoring have been strongly associated with the development of postimplantation infection [45]. Likewise, the incidence of postimplantation cerebrospinal fluid leakage has been reported to range between 0% and 20% [52].

The development of postimplantation epidural hematoma has been reported to be 1.8%–2.5%, while that of a subdural hematoma has been 1.1%–14% (Fig. 11.7) [52]. Arya et al. [55], in their meta-analysis study including 21 previously published clinical series, found a 4% incidence of intracranial hemorrhage. They concluded, however, that only a small percentage (3.5%) of the complicated cases required a reoperation for managing their complication [55].

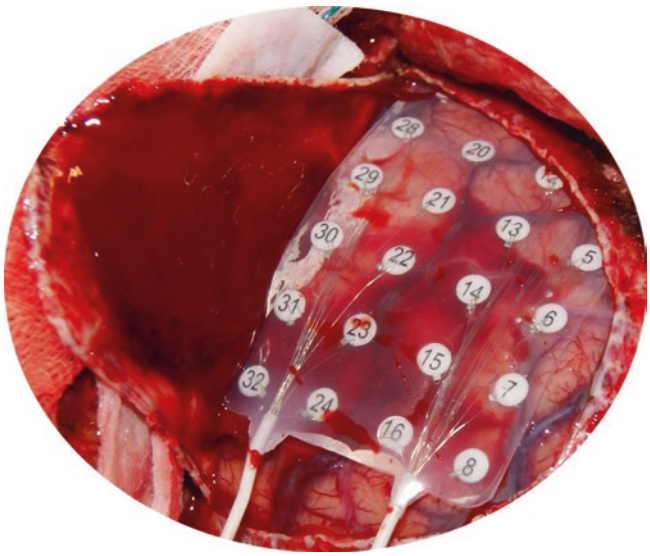

Fig. 11.7 Intraoperative picture taken during reopening of the dural flap for removing the previously implanted subdural grid electrode depicting a small subdural hematoma. In the vast majority of cases these subdural hematomas are of small size and of no clinical significance

We have also previously reported the recording of nonhabitual seizures during the monitoring period in approximately 3% of our implant cases [44]. These findings may be the result of mechanical and/or chemical irritation of the underlying cortex caused by the implanted subdural grid [44]. This may be a confusing and misguiding finding in epilepsy cases, leading to erroneous conclusions regarding the localization of seizure focus/i.

11.8 Future Developments

The designing and the development of novel substrate materials for subdural strip and grid electrodes may further minimize the risk of any complications. Moreover, the wide clinical application of hybrid electrodes may well increase the accuracy of extraoperative stimulation and mapping. The designing and manufacturing of anatomically designated subdural electrodes for certain areas such as the insula and/or the mesial surface of the hemispheres will most probably increase the safety and the overall clinical utility of extraoperative monitoring, stimulation, and mapping strategies. However, thorough knowledge of the implantation surgical technique along with meticulous understanding of the potential complications remains of paramount importance.

References

1. Roelz R, Strohmaier D, Jabbarli R, Kraeutle R, Egger K, Coenen VA, et al. Residual tumor volume as best outcome predictor in low grade glioma - a nine-years near-randomized survey of surgery vs. biopsy. Sci Rep. 2016;6:32286.
2. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the extent of resection with survival in glioblatoma: a systematic review and meta-analysis. JAMA Oncol. 2016;2:1460–9.
3. Suchorska B, Weller M, Tabatabai G, Senft C, Hau P, Sabel MC, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRECTOR trial. Neuro-Oncol. 2016;18:549–56.
4. Hervey-Jumper SL, Berger MS. Role of surgical resection in low- and high-grade gliomas. Curr Treat Options Neurol. 2014;16:284.
5. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery. 2008;62:753–64. discussion, 264–6.
6. Lima GL, Zanello M, Mandonnet E, Taillandier L, Pallud J, Duffau H. Incidental diffuse low-grade gliomas: from early detection to preventive neuro-oncological surgery. Neurosurg Rev. 2016;39:377–84.
7. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: Proposal of a multistage and individualized therapeutic approach. Neuro-Oncol. 2015;17:332–42.
8. Yordanova YN, Duffau H. Supratotal resection of diffuse gliomas: an overview of its multifaceted implications. Neurochirurgie. 2017:pii:S0028–3770(16)30133–3.
9. Lau D, Hervey-Jumper SL, Chang S, Molinaro AM, McDermott MW, Phillips JJ, et al. A prospective phase II clinical trial of 5-aminolevulinic acid to assess the correlation of intraoperative fluorescence intensity and degree of histologic cellularity during resection of high-grade gliomas. J Neurosurg. 2016;124:1300–9.
10. Rasul FT, Watts C. Novel surgical approaches to high-grade gliomas. Curr Treat Options Neurol. 2015;17:369.
11. Almenawer SA, Badhiwala JH, Alhazzani W, Greenspoon J, Farrokhyar F, Yarascavitch B, et al. Biopsy versus partial versus gross total resection in older patients with high-grade glioma: a systematic review and meta-analysis. Neuro-Oncol. 2015;17:868–81.
12. Ojemann G, Ojemann J, Lettich E, Berger M. Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg. 1989;71:316–26.
13. Duffau H. Mapping the connectome in awake surgery for gliomas: an update. J Neurosurg Sci. 2017; https://doi.org/10.23736/S0390-5616.17.04017-6. [Epub ahead of print.].
14. Tussis L, Sollmann N, Boeckh-Behrens T, Meyer B, Krieg SM. Identifying cortical first and second language sites via navigated transcranial magnetic stimulation of the left hemisphere in bilinguals. Brain Lang. 2017;168:106–16.
15. Maurer S, Giglhuber K, Sollmann N, Kelm A, Ille S, Hauck T, et al. Non-invasive mapping of face processing by navigated transcranial magnetic stimulation. Front Hum Neurosci. 2017;11:4.
16. Carota F, Kriegeskorte N, Nili H, Pulvermüller F. Representational similarity mapping of distributional semantics in left inferior frontal, middle temporal, and motor cortex. Cereb Cortex. 2017;1(27):294–309. https://doi.org/10.1093/cercor/bhw379.
17. Middlebrooks EH, Yagmurlu K, Szaflarski JP, Rahman M, Bozkurt B. A contemporary framework of language processing in the human brain in the context of preoperative and intraoperative language mapping. Neuroradiology. 2017;59:69–87.
18. Raffa G, Bährend I, Schneider H, Faust K, Germanò A, Vajkoczy P, Picht T. A novel technique for region and linguistic specific nTMS-based DTI fiber tracking of language pathways in brain tumor patients. Front Neurosci. 2016;10:552.
19. Branco P, Seixas D, Castro SL. Temporal reliability of ultra-high field resting-state MRI for single-subject sensorimotor and language mapping. Neuroimage. 2016: piiS1053–8119(16)30650–4.
20. Lyu B, Ge J, Niu Z, Tan LH, Gao JH. Predictive brain mechanisms in sound-to-meaning mapping during speech processing. J Neurosci. 2016;36:10813–22.
21. Sollmann N, Hauck T, Tussis L, Ille S, Maurer S, Boeckh-Behrens T, et al. Results on the spatial resolution of repetitive transcranial magnetic stimulation for cortical language mapping during object naming in healthy subjects. BMC Neurosci. 2016;17:67.
22. Makris N, Zhu A, Papadimitriou GM, Mouradian P, Ng I, Scaccianoce E, et al. Mapping temporo-parietal and temporo-occipital cortico-cortical connections of the human middle longitudinal fascicle in subject-specific, probabilistic, and stereotaxic Talairach spaces. Brain Imaging Behav. 2017;11(5):1258–77.
23. Negwer C, Ille S, Hauck T, Sollmann N, Maurer S, Kirschke JS, et al. Visualization of subcortical language pathways by diffusion tensor imaging fiber tracking based on rTMS language mapping. Brain Imaging Behav. 2016;20:1–6.
24. Sarubbo S, De Benedictis A, Merler S, Mandonnet E, Barbareschi M, Dallabona M, et al. Structural and functional integration between dorsal and ventral language streams as revealed by blunt dissection and direct electrical stimulation. Hum Brain Mapp. 2016;37:3858–72.
25. Cochereau J, Deverdun J, Herbet G, Charroud C, Boyer A, Moritz-Gasser S, et al. Comparison between resting state fMRI networks and responsive cortical stimulations in glioma patients. Hum Brain Mapp. 2016;37:3721–32.
26. Negwer C, Sollmann N, Ille S, Hauck T, Maurer S, Kirschke JS, et al. Language pathway tracking: comparing nTMS-based DTI fiber tracking with a cubic ROIs-based protocol. J Neurosurg. 2017;126:1006–14.
27. Huang H, Ding Z, Mao D, Yuan J, Zhu F, Chen S, et al. Presurgmapp: a matlab toolbox for presurgical mapping of eloquent functional areas based on task-related and resting-state functional MRI. Neuroinformatics. 2016;14:421–38.
28. D'Andrea G, Trillo' G, Picotti V, Raco A. Functional magnetic resonance imaging (fMRI), pre-intraoperative tractography in neurosurgery: the experience of Sant' Andrea Rome university hospital. Acta Neurochir Suppl. 2017;124:241–50.
29. O'Donnell LJ, Suter Y, Rigolo L, Kahali P, Zhang F, Norton I, et al. Automated white matter fiber tract identification in patients with brain tumors. Neuroimage Clin. 2016;25:138–53.

30. Scaccianoce E, Laganà MM, Baglio F, Preti MG, Bergsland N, Cecconi P, et al. Combined DTI-fMRI analysis for a quantitative assessment of connections between WM bundles and their peripheral cortical fields in verbal fluency. Brain Topogr. 2016;29:814–23.
31. Ivanova MV, Isaev DY, Dragoy OV, Akinina YS, Petrushevskiy AG, Fedina ON, et al. Diffusion-tensor imaging of major white matter tracts and their role in language processing in aphasia. Cortex. 2016;85:165–81.
32. Wassermann D, Makris N, Rathi Y, Shenton M, Kikinis R, Kubicki M, et al. The white matter query language: a novel approach for describing human white matter anatomy. Brain Struct Funct. 2016;221:4705–21.
33. Hartwigsen G. Adaptive plasticity in the healthy language network: implications for language recovery after stroke. Neural Plast. 2016;2016:9674790.
34. Schlaffke L, Rüther NN, Heba S, Haag LM, Schultz T, Rosengarth K, et al. From perceptual to lexico-semantic analysis--cortical plasticity enabling new levels of processing. Hum Brain Mapp. 2015;36:4512–28.
35. Duffau H. The huge plastic potential of adult brain and the role of connectomics: new insights provided by serial mappings in glioma surgery. Cortex. 2014;58:325–37.
36. Austermuehle A, Cocjin J, Richard R, Agrawal S, Sepeta L, Gaillard WD, et al. Language fMRI and direct cortical stimulation in epilepsy preoperative planning. Ann Neurol. 2017;81:526–37.
37. Sollmann N, Ille S, Boeckh-Behrens T, Ringel F, Meyer B, Krieg SM. Mapping of cortical language function by functional magnetic resonance imaging and repetitive navigated transcranial magnetic stimulation in 40 healthy subjects. Acta Neurochir (Wien). 2016;58:1303–16.
38. Sollmann N, Kubitscheck A, Maurer S, Ille S, Hauck T, Kirschke JS, et al. Preoperative language mapping by repetitive navigated transcranial magnetic stimulation and diffusion tensor imaging fiber tracking and their comparison to intraoperative stimulation. Neuroradiology. 2016;58:807–18.
39. Brennan NP, Peck KK, Holodny A. Language mapping using fMRI and direct cortical stimulation for brain tumor surgery: the good, the bad, and the questionable. Top Magn Reson Imaging. 2016;25:1–10.
40. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. J Neurosurg. 2015;123:325–39.
41. Ibrahim GM, Bernstein M. Awake craniotomy for supratentorial gliomas: why, when and how? CNS Oncol. 2012;1:71–83.
42. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, et al. Intraoperative seizures during awake craniotomy: incidence and consequences: analysis of 477 patients. Neurosurgery. 2013;73:135–40. discussion, 140.
43. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, et al. Failed awake craniotomy: a retrospective analysis in 424 patients undergoing craniotomy for brain tumor. J Neurosurg. 2013;118:243–9.
44. Fountas K, Smith J. Subdural electrode-associated complications: a 20-year experience. Stereotact Funct Neurosurg. 2007;85:264–72.
45. Wellmer J, van der Groeben F, Klarmann U, Weber C, Elger C, Urbach H, et al. Risks and benefits of invasive epilepsy surgery workup with implanted subdural and depth electrodes. Epilepsia. 2012;53:1322–32.
46. Hedegard E, Biellvi J, Edelvik A, Rydenhaq B, Flink R, Malmgren K. Complications to invasive epilepsy surgery workup with subdural and depth electrodes: a prospective population-based observational study. J Neurol Neurosurg Psychiatry. 2014;85:716–20.
47. Gonzalez-Martinez J, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. Stereoelectroencephalography in the "difficult to localize" refractory focal epilepsy: early experience from a North American epilepsy center. Epilepsia. 2013;54:323–30.
48. Gonzalez-Martinez J, Mullin J, Vadera S, Bulacio J, Hughes G, Jones S, et al. Stereotactic placement of depth electrodes in medically intractable epilepsy. J Neurosurg. 2014;120:639–44.
49. Bourdillon P, Ryvlin P, Isnard J, Montavont A, Catenoix A, Mauguiere F, et al. Stereotactic electroencephalography is a safe procedure, including for insular implantations. World Neurosurg. 2017;99:353–61.
50. Serletis D, Bulacio J, Bingaman W, Najm I, Gonzalez-Martinez J. The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients. J Neurosurg. 2014;121:1239–46.
51. Hamer H, Morris H, Mascha E, Karafa M, Bingaman W, Bej M, et al. Complications of invasive video-EEG monitoring with subdural grid electrodes. Neurology. 2002;58:97–103.
52. Fountas K. Implanted subdural electrodes: safety issues and complication avoidance. Neurosurg Clin N Am. 2011;22:519–31. vii
53. Vale F, Pollock G, Dionisio J, Benbadis S, Tatum W. Outcome and complications of chronically implanted subdural electrodes for the treatment of medically resistant epilepsy. Clin Neurol Neurosurg. 2013;115:985–90.
54. Yang P, Zhang H, Pei J, Tian J, Lin Q, Mei Z, et al. Intracranial electroencephalography with subdural and/or depth electrodes in children with epilepsy: techniques, complications, and outcomes. Epilepsy Res. 2014;108:1662–70.
55. Arya R, Mangano F, Horn P, Holland K, Rose D, Glauser T. Adverse events related to extraoperative invasive EEG monitoring with subdural grid electrodes: a systematic review and meta-analysis. Epilepsia. 2013;54:828–39.

Awake Craniotomy: Cortical and Subcortical Mapping for Glioma Resection

12

Shawn L. Hervey-Jumper and Mitchel S. Berger

Over 70,000 patients are diagnosed each year with a glioma, and the majority of these tumors are within areas of the brain with presumed functional significance. It has been well established that extent of tumor resection impacts both overall and progression-free survival. Direct stimulation of the cerebral cortex was first employed by Foerster in 1931 and later popularized by Penfield and Ojemann. Intraoperative mapping is the gold standard approach for the identification and preservation of functional areas of the brain. This chapter outlines the evidence supporting the extent of resection for low- and high-grade gliomas, including procedural steps and technical nuances to maximize success and minimize perioperative morbidity.

12.1 Introduction

An estimated 700,000 people in the United States are currently living with a glioma [1]. The role of surgery in the treatment of both low- and high-grade gliomas is to establish the correct histologic and molecular diagnosis, relieve mass effect, and provide maximal safe resection to improve both overall and progression-free survival. More than 50% of gliomas are within areas with presumed functional significance; therefore surgical decisions must balance reduction of tumor volume with preservation of function. Extent of tumor resection impacts outcome. Therefore an awake craniotomy permits maximal extent of resection while minimizing postoperative morbidity [2]. For this reason direct cortical and subcortical stimulation mapping via an awake craniotomy is the gold standard approach for the identification and preservation of functional areas. This chapter will discuss the rationale, indications, and technique for cortical and subcortical mapping during awake craniotomies using the asleep-awake-asleep protocol for patients with low- and high-grade gliomas.

S. L. Hervey-Jumper (✉) · M. S. Berger
Department of Neurological Surgery, University of California San Francisco Medical Center, San Francisco, CA, USA
e-mail: Shawn.Hervey-Jumper@ucsf.edu

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12.2 Cytoreduction Improves Overall and Progression-Free Survival in Low- and High-Grade Glioma Patients

A growing body of literature has established that overall and progression-free survival is strongly influenced by cytoreduction surgery. Additional predictors of longer survival include patient age, oligodendrocyte histopathology, patient performance status, O^6-methylguanine-DNA-methyltransferase promoter methylation status, and the presence of the isocitrate dehydrogenase 1 (IDH1) mutation [1, 3–8]. Intraoperative direct cortical and subcortical stimulation mapping using an awake craniotomy facilitates a greater extent of resection with lower rates of perioperative complications. The goal of intraoperative mapping during awake craniotomy is to balance tumor removal with preservation of function. Intraoperative mapping permits both greater extent of resection and less functional morbidity [2]. A recently published meta-analysis including 8091 glioma patients demonstrated that intraoperative mapping reduced the number of severe neurologic deficits (3.4% late severe neurologic deficits after intraoperative mapping versus 8.2% late severe neurologic deficits without the use of functional mapping) and improved the extent of tumor resection (75% extent of glioma resection with intraoperative mapping versus 58% without intraoperative mapping) [2].

The mean survival for patients with WHO grade II gliomas is 2.2–9.5 years and varies based on isocitrate dehydrogenase, 1p19q codeletion, and ATRX gene mutation status. The median time to malignant progression for WHO grade II gliomas to either WHO III or IV tumors is 5 years [9–12]. The median survival for patients with WHO III gliomas is 3.4 years, again with a strong dependency of extent of resection and molecular markers [9–12]. Many studies have investigated the role of the extent of tumor resection for patients with low- and high-grade gliomas. A survival benefit of 61–90 months with maximal resection can be seen for WHO II and III gliomas [4–7, 11, 13–29]. Similarly, gross total resection of WHO IV gliomas improves overall survival from 11.3 to 18.5 months [1, 3, 10, 30–59]. Perhaps the strongest evidence in support of cytoreduction surgery for gliomas was provided by Jakola et al. [60] in a large population study of Norwegian glioma patients. Neurosurgeons from two adjacent regions offered differing clinical practice patterns. Hospital A favored an initial tumor biopsy followed by watchful waiting, while Hospital B offered early tumor resection at the time of diagnosis. Overall survival was longer for individuals treated at Hospital B. The median survival was 5.9 years for patients receiving tumor biopsy, while the group receiving early resection did not reach median survival by the end of the study period (median follow-up of 7 years) [60]. Five-year survival was 60% for the biopsy group and 74% for those receiving early surgery [60]. This evidence has offered insight about how to manage asymptomatic incidentally found gliomas. These tumors are typically smaller at diagnosis and offer a greater likelihood of achieving a gross total resection, making early resection the favored approach [61, 62].

12.3 Indications and Contraindications to Awake Glioma Surgery

An awake craniotomy is considered for any patient with a supratentorial glioma located within or adjacent to an area presumed to have functional significance. Because safety is of paramount importance during an awake craniotomy, patient selection is critically important. Several factors center on the size and location of the tumor. Amount of mass effect, patient smoking status, patient body-mass index, seizure frequency, and medical comorbidities are associated with increased perioperative risk during awake glioma surgery (Table 12.1) [63, 64]. Absolute contraindications to an awake craniotomy include (1) severe psychiatric illness limiting one's ability to cooperate, (2) severe aphasia with greater than 50% naming errors, (3) large tumors with mass effect resulting in more than 2 cm of midline shift, (4) severe chronic cough, and (5) hemiplegia with less than antigravity motor function resulting in severe limitations in passive or active movement of the extremity to be mapped. As the technique has evolved, a number of strategies have allowed higher risk patients to undergo awake craniotomy despite comorbidities and relative contraindications. Intraoperative nausea can be treated with antiemetic medications (such as ondansetron hydrochloride or scopolamine) prior to induction and throughout the procedure. Severe aphasia may be caused by either tumor infiltration of cortical and subcortical language pathways or pathway irritation from perilglioma edema. Therefore patients with greater than 25% naming errors may be treated with high-dose corticosteroids (dexamethasone, 4–8 mg intravenously every 6 h) and/or osmotic diuretics (mannitol 20%, 30 gm every 6 h for 48–72 h) followed by reassessment prior to surgery. Obesity may be problematic because most sedating and analgesic medications tend to relax the airway, resulting in hypercapnia and cerebral edema. Obese patients (body mass index >35) can be treated with a laryngeal mask airway (LMA) or nasal trumpet to prevent hypercapnia. Patients with generalized anxiety or a severe untreated psychiatric history should be treated with antidepressant and mood-stabilizing medications prior to surgery. Older age is not an absolute contraindication to this procedure. In a study comparing patients over age 65 years to younger individuals, intraoperative mapping proved to be feasible without any increase in perioperative morbidity [65]. Intraoperative seizures are the most common reason for intraoperative failure. Seizures are treated with topical iced Ringer solution applied to the cerebral cortex. Moreover, IV propofol, diazepam, or lorazepam may be used for sustained stimulation-induced intraoperative seizures.

Table 12.1 Contraindications and solutions to awake xraniotomy

Relative contraindications	Solutions
Intraoperative seizures	Iced ringer solution, intravenous lorazepam, or propofol
Mass effect (>2 cm midline shift)	Staged procedure with internal debulking of presumed nonfunctional areas asleep (± functional imaging) followed by reoperation with awake mapping for presumed functional areas
Chronic cough	Light sedation and cough suppressants
Obese patient (BMI >35)	Laryngeal mask airway before and after mapping, intubation after mapping
Severely impaired preoperative function	3–5 days of preoperative high-dose steroids ± mannitol
Emotional instability/ psychiatric history	Presurgical treatment with antidepressants and antipsychotic medications
Chronic or intraoperative nausea	Preoperative medication with antiemetic drugs and dexamethasone

12.4 Imaging and Neuro-Navigation Adjuvants

Initial imaging for a patient with suspected glioma who is being considered for an awake craniotomy begins with a brain magnetic resonance image (MRI) or computed tomography (CT) scan with and without contrast enhancement, including T1, T2, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI (DWI) sequences. MRI spectroscopy or MRI perfusion may offer additional insight into the metabolism and vascularity of the mass to assist in prediction of tumor biology. MRI spectroscopy for gliomas demonstrates raised choline peaks with depressed N-acetyl aspartate peak (increased choline, decreased NAA) [66]. MRI perfusion studies rely on the passage of paramagnetic agents through tumor vasculature to estimate blood volume [67]. A critical aspect of glioma surgery is the identification of functional and nonfunctional areas within and around the tumor. Structural and functional imaging such as functional MRI (fMRI) and diffusion tensor imaging (DTI) MRI tractography illustrates this relationship and is useful for preoperative planning (Fig. 12.1). Changes in regional blood flow and deoxyhemoglobin associated with neuronal activity are known as blood oxygenation level–dependent (BOLD) signal and serve as the hallmark of fMRI. During the MRI, each patient is asked to perform a language or motor task during which a dependent BOLD signal identifies regions of the brain in which there is neuron activation [68, 69]. Another approach involves identifying subcortical tracts of interest using DTI tractography. DTI tractography differentiates the corticospinal tract and dorsal or ventral language in the region of the tumor, which aids preoperative understanding of pathway displacement by the mass [70–72]. Neither fMRI nor DTI tractography are 100% sensitive for the identification of cortical and subcortical functional areas. These studies are challenged by imprecision caused by distortion from mass effect, individual patient anatomic variability, and functional reorganization caused by cortical and subcortical plasticity [73–75]. Furthermore, imaging highly vascular high-grade gliomas can be challenging because of uncoupling of the BOLD signal, making interpretation of fMRI results difficult. Resting state coherence measured with magnetoencephalography (MEG) is a noninvasive measure of functional connectivity of the brain. Malignant brain tumors with decreased resting state connectivity have a lower risk of causing postoperative neurologic deficits, while those with increased resting state connectivity are associated with a higher risk of postoperative neurologic deficits [76].

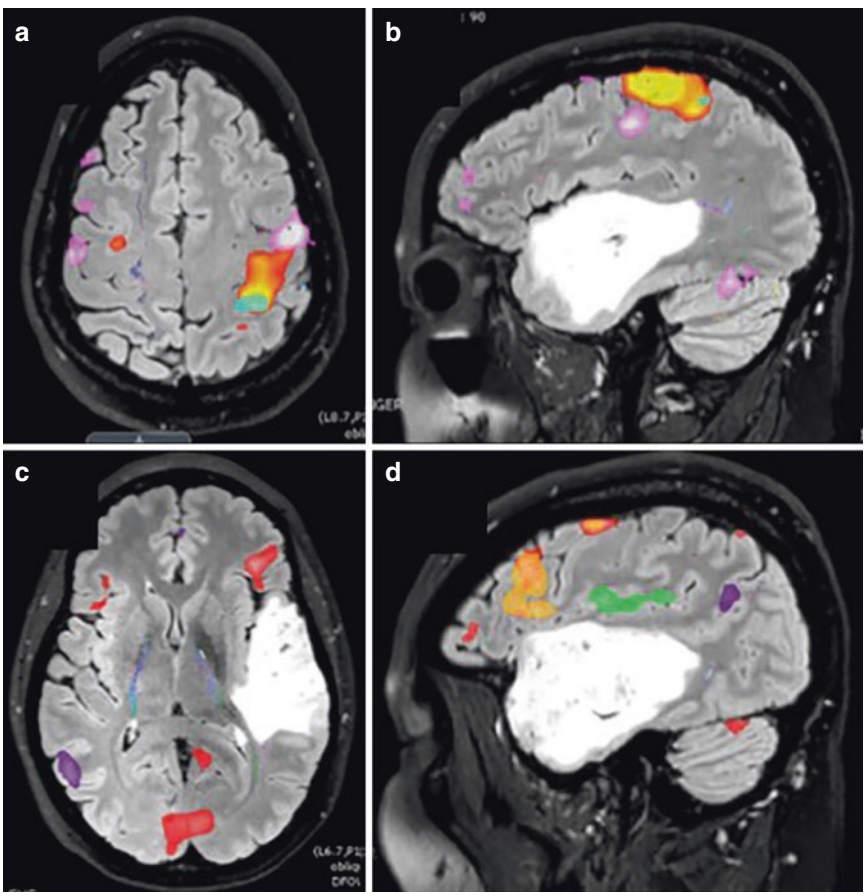

Fig. 12.1 Axial (**a**) and sagittal (**b**) fluid-attenuated inversion recovery (FLAIR) functional magnetic resonance imaging (fMRI) for motor tasks reveals frontal activation above the left temporal nonenhancing glioma (*yellow* and *red*). Axial (**c**) and sagittal (**d**) FLAIR fMRI for language tasks reveals receptive language superior and posterior to the tumor (*green*)

12.5 Planning the Procedure and Preoperative Preparation

Prior to surgery each patient should have a detailed history, physical examination, and review of medications. Preoperatively, each patient should be evaluated by his or her neurosurgeon, anesthesiologist, speech pathologist, neuropsychologist, or intraoperative monitoring specialist. A detailed motor examination, neuropsychological examination, and Boston Naming Test (BNT) are performed at baseline. Patients are counseled about what to expect during the procedure in addition to perioperative risks. Management of seizures is particularly important before intraoperative mapping of craniotomies because stimulation-induced seizures are the most common reason for an aborted mapping procedure. Corticosteroids such as dexamethasone should be administered to control periglioma edema, with doses ranging between 2 and 24 mg daily. Antiepileptic medications such as levetiracetam or Dilantin should be considered preoperatively for patients who will undergo an awake mapping craniotomy [64, 77].

12.6 Awake Craniotomy Procedural Steps and Technical Considerations

12.6.1 Patient Positioning

Clear communication is thought to be the most important aspect of performing a safe awake craniotomy [78]. This early stage requires a great deal of flexibility, as the initial sedation plan can change depending on patient tolerance. In the preoperative area invasive and noninvasive monitors are placed. This includes intravenous and arterial lines, cardiac rhythm monitors, and Foley catheter placement. Many patients benefit from receiving short-acting antianxiolytic medications such as midazolam, or dexmedetomidine [64]. All patients are given supplemental oxygen via nasal cannula or face mask. Positioning the patient must balance patient and surgeon comfort with safety. If possible, even when using an asleep-awake-asleep technique, the patient is briefly awakened to allow active participation in relieving any painful or pressure points. The lateral decubitus or semilateral positions are used with the aid of pillows and a foam mattress placed behind the ipsilateral back and shoulder. Giving the patient a small amount of neck extension ensures easy access to the airway, should placement of an LMA be needed. A nasal trumpet may be placed for the patient who is exhibiting partial airway obstruction.

12.6.2 Initial Sedation

The most common anesthetic technique used during an awake craniotomy for glioma resection is the asleep-awake-asleep approach. Sedation for an awake craniotomy is unique in that it requires the anesthesiologist to alter states of both painlessness and sedation during the procedure. Early in the procedure sedation is often heavier while drilling the calvarium; however, during dural opening sedation can be lighter, although there is a continued need for analgesia. A topical scalp block using a combination of 1% lidocaine with 1:100,000 epinephrine and 0.5% bupivacaine is applied. To avoid burning during delivery, sodium bicarbonate can be added to the local analgesic mixture. When using the asleep-awake-asleep technique, sedation is achieved with intravenous propofol (up to 100 μg/kg/min) or dexmedetomidine (up to 1 μg/kg/min) and remifentanil (0.07–2.0 μg/kg/hr) [79–81]. It is often beneficial to begin sedation prior to placement of the Foley catheter and of the Mayfield headholder pin. Following skin incision and removal of the bone flap, all sedating medications are held or reduced before dural opening. Either 500 mg or 1 gm of intravenous oral acetaminophen is an excellent addition, particularly for patients having continued pain despite intravenous medications.

12.6.3 Craniotomy and Exposure

The goal of exposure is to expose the tumor and surrounding cortical areas with presumed functional significance. This is typically done via a focused exposure encompassing the lesion plus a 2-cm margin. Early intraoperative mapping techniques involved large craniotomies with the goal of finding cortical language and motor sites as positive controls. Over the past decade, however, there has been greater reliance on negative mapping through smaller focused craniotomies, which offer the same degree of perioperative safety. Additionally, a focused craniotomy avoids unneeded exposure of cortical surfaces, thereby preventing injury. Following removal of the bone flap, sedation is held prior to dural opening.

12.6.4 Intraoperative Cortical Mapping

Prior to beginning cortical mapping, it is important to confirm with the neuro-anesthesiologist that a dedicated intravenous line with a 1-mg/kg bolus of propofol is available in the event it is needed for suppression of an intraoperative seizure. However, the first-line agent for treatment of intraoperative stimulation-induced seizures is topical ice-cold Ringer lactate solution. Intraoperative electrocorticography is performed using either a 16-array cortical electrode or a 1 × 6 strip electrode to detect seizure activity and afterdischarge potentials. A bipolar electrode is used for stimulation via 2-mm tips with 5 mm of separation [82]. Typical stimulation parameters include a current of 1.5–2 mA using a constant current generator that delivers 1.25-ms biphasic square waves in 2–4-s trains at 50 or 60 Hz. Cortical stimulation excites local neurons via diffusion of current using both orthodromic and antidromic propagation. Numerical markers are placed 1 cm apart on the surgical field. Intraoperative motor tests may be performed either actively (the patient is asked to tap a finger, wiggle toes, or move the tongue from side to side) or passively (no movement) during stimulation.

12.6.5 Intraoperative Subcortical Mapping

Following mapping to identify cortical language and motor sites, a safe corridor of entry into the tumor is identified, and tumor resection begins. The subpial dissection permits the surgeon to remain within the negatively mapped gyrus and identify the moment a sulcal depth is reached, under which subcortical u-fibers reside. The subcortical map is used to prevent transecting the corticospinal tract or dorsal or ventral language pathways. Intraoperative tasks used for subcortical mapping are similar to cortical tasks. However, stimulation thresholds for subcortical mapping vary but commonly begin with an increase of 1–6 mA above the stimulation threshold used for cortical mapping.

12.6.6 Closure

After the maximal extent of glioma resection has been achieved, sedation is resumed. Sedation for closure may include either resumed monitored anesthesia care (MAC) anesthesia, placement of an LMA, or an endotracheal tube. The patient is then awakened and taken to the postanesthesia care unit for recovery followed by overnight observation in the intensive care unit.

12.7 Complication Avoidance and Perioperative Outcome

The goal of intraoperative mapping for low- and high-grade gliomas is to balance reduction of tumor volume with preservation of language, motor, and neurocognitive functions. Intraoperative mapping offers a greater extent of tumor resection and improved functional outcomes [2]. Postoperative language outcomes following direct cortical and subcortical stimulation mapping of dominant hemisphere low- and high-grade gliomas have been studied in numerous large series [24, 83, 84]. Immediately following surgery (within 2 weeks), language deteriorates in 14–50% of patients [24, 84, 85]. However, after 3 months 78–100% of patients have return of language to baseline preoperative function. Aphasia recovery correlates with structural integrity of the arcuate fasciculus and superior longitudinal fasciculus [24, 84]. After 6 months of aphasia recovery following an awake language mapping craniotomy, only 0–2.4% of patients have worsened language function [24, 84]. Long-term motor outcomes have likewise been examined in a retrospective analysis of 294 patients with peri-rolandic region gliomas following intraoperative motor mapping [86]. Immediately following intraoperative mapping of motor cortex gliomas, 20% of patients experienced a new postoperative motor deficit; however, 58% recovered to their preoperative baseline within 1 month. Three months following motor mapping of rolandic cortex gliomas, contralateral weakness was observed in 4.8% of patients, with the greatest incidence noted in cases in which subcortical motor activity was found during mapping [86].

Conclusion

Both preservation of functional areas and maximal safe resection are critically important in the management of gliomas and impact both overall and progression-free survival. The awake craniotomy is the gold standard procedure for tumors within presumed functional areas. The pursuit of maximal extent of resection must be balanced with careful patient selection to limit perioperative morbidity.

References

1. Hervey-Jumper SL, Berger MS. Role of surgical resection in low- and high-grade gliomas. Curr Treat Options Neurol. 2014;16:284.
2. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 2012;30:2559–65.
3. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, Demonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg. 2001;95:190–8.
4. Lote K, Egeland T, Hager B, Stenwig B, Skullerud K, Berg-Johnsen J, et al. Survival, prognostic factors and therapeutic efficacy in low-grade glioma: a retrospective study in 379 patients. J Clin Oncol. 1997;15:3129–40.
5. Nakamura M, Konishi N, Tsunoda S, Nakase H, Tsuzuki T, Aoki H, et al. Analysis of prognostic and survival factors related to treatment of low-grade astrocytomas in adults. Oncology. 2000;58:108–16.
6. Nicolato A, Gerosa MA, Fina P, Iuzzolino P, Giorgiutti F, Bricolo A. Prognostic factors in low-grade supratentorial astrocytomas: a uni-multivariate statistical analysis in 76 surgically treated adult patients. Surg Neurol. 1995;44:208–21. discussion, 21–23.
7. Scerrati M, Roselli R, Iacoangeli M, Pompucci A, Rossi GF. Prognostic factors in low grade (WHO grade II) gliomas of the cerebral hemispheres: the role of surgery. J Neurol Neurosurg Psychiatry. 1996;61:291–6.
8. Yan H, Parsons DW, Jin G, Mclendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360:765–73.
9. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372:2499–508.
10. Keles GE, Chang EF, Lamborn KR, Tihan T, Chang CJ, Chang SM, et al. Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma. J Neurosurg. 2006;105:34–40.
11. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol. 2008;26:1338–45.
12. Snyder LA, Wolf AB, Oppenlander ME, Bina R, Wilson JR, Ashby L, et al. The impact of extent of resection on malignant transformation of pure oligodendrogliomas. J Neurosurg. 2014;120:309–14.
13. Bauman G, Fisher B, Watling C, Cairncross JG, Macdonald D. Adult supratentorial low-grade glioma: long-term experience at a single institution. Int J Radiat Oncol Biol Phys. 2009;75:1401–7.
14. Claus EB, Horlacher A, Hsu L, Schwartz RB, Dello-Iacono D, Talos F, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer. 2005;103:1227–33.
15. Incekara F, Olubiyi O, Ozdemir A, Lee T, Rigolo L, Golby A. The value of pre- and intraoperative adjuncts on the extent of resection of hemispheric low-grade gliomas: a retrospective analysis. J Neurol Surg A Cent Eur Neurosurg. 2016;77:79–87.
16. Ito S, Chandler KL, Prados MD, Lamborn K, Wynne J, Malec MK, et al. Proliferative potential and prognostic evaluation of low-grade astrocytomas. J Neuro-Oncol. 1994;19:1–9.
17. Johannesen TB, Langmark F, Lote K. Progress in long-term survival in adult patients with supratentorial low-grade gliomas: a population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993. J Neurosurg. 2003;99:854–62.
18. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European organization for research and treatment of cancer (EORTC) study 22844. Int J Radiat Oncol Biol Phys. 1996;36:549–56.
19. Leighton C, Fisher B, Bauman G, Depiero S, Stitt L, Macdonald D, et al. Supratentorial low-grade glioma in adults: an analysis of prognostic factors and timing of radiation. J Clin Oncol. 1997;15:1294–301.
20. North CA, North RB, Epstein JA, Piantadosi S, Wharam MD. Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy. Cancer. 1990;66:6–14.
21. Peraud A, Ansari H, Bise K, Reulen HJ. Clinical outcome of supratentorial astrocytoma WHO grade II. Acta Neurochir. 1998;140:1213–22.
22. Philippon JH, Clemenceau SH, Fauchon FH, Foncin JF. Supratentorial low-grade astrocytomas in adults. Neurosurgery. 1993;32:554–9.

23. Rajan B, Pickuth D, Ashley S, Traish D, Monro P, Elyan S, et al. The management of histologically unverified presumed cerebral gliomas with radiotherapy. Int J Radiat Oncol Biol Phys. 1994;28:405–13.
24. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med. 2008;358:18–27.
25. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a north central cancer treatment group/radiation therapy oncology group/eastern cooperative oncology group study. J Clin Oncol. 2002;20:2267–76.
26. Shibamoto Y, Kitakabu Y, Takahashi M, Yamashita J, Oda Y, Kikuchi H, et al. Supratentorial low-grade astrocytoma. Correlation of computed tomography findings with effect of radiation therapy and prognostic variables. Cancer. 1993;72:190–5.
27. van Veelen ML, Avezaat CJ, Kros JM, van Putten W, Vecht C. Supratentorial low grade astrocytoma: prognostic factors, dedifferentiation, and the issue of early versus late surgery. J Neurol Neurosurg Psychiatry. 1998;64:581–7.
28. Whitton AC, Bloom HJ. Low grade glioma of the cerebral hemispheres in adults: a retrospective analysis of 88 cases. Int J Radiat Oncol Biol Phys. 1990;18:783–6.
29. Yeh SA, Ho JT, Lui CC, Huang YJ, Hsiung CY, Huang EY. Treatment outcomes and prognostic factors in patients with supratentorial low-grade gliomas. Br J Radiol. 2005;78:230–5.
30. Barker FG 2nd, Prados MD, Chang SM, Gutin PH, Lamborn KR, Larson DA, et al. Radiation response and survival time in patients with glioblastoma multiforme. J Neurosurg. 1996;84:442–8.
31. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, Mcdermott MW, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012;117:1032–8.
32. Brown PD, Ballman KV, Rummans TA, Maurer MJ, Sloan JA, Boeve BF, et al. Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. J Neuro-Oncol. 2006;76:283–91.
33. Buckner JC, Schomberg PJ, Mcginnis WL, Cascino TL, Scheithauer BW, O'Fallon JR, et al. A phase III study of radiation therapy plus carmustine with or without recombinant interferon-alpha in the treatment of patients with newly diagnosed high-grade glioma. Cancer. 2001;92:420–33.
34. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Nelson DF, et al. Does extent of surgery influence outcome for astrocytoma with atypical or anaplastic foci (AAF)? A report from three radiation therapy oncology group (RTOG) trials. J Neuro-Oncol. 1992;12:219–27.
35. Dinapoli RP, Brown LD, Arusell RM, Earle JD, O'Fallon JR, Buckner JC, et al. Phase III comparative evaluation of PCNU and carmustine combined with radiation therapy for high-grade glioma. J Clin Oncol. 1993;11:1316–21.
36. Duncan GG, Goodman GB, Ludgate CM, Rheaume DE. The treatment of adult supratentorial high grade astrocytomas. J Neuro-Oncol. 1992;13:63–72.
37. Hollerhage HG, Zumkeller M, Becker M, Dietz H. Influence of type and extent of surgery on early results and survival time in glioblastoma multiforme. Acta Neurochir. 1991;113:31–7.
38. Huber A, Beran H, Becherer A, Prosenc N, Witzmann A. Supratentorial glioma: analysis of clinical and temporal parameters in 163 cases. Neurochirurgia (Stuttg). 1993;36:189–93.
39. Jeremic B, Grujicic D, Antunovic V, Djuric L, Stojanovic M, Shibamoto Y. Influence of extent of surgery and tumor location on treatment outcome of patients with glioblastoma multiforme treated with combined modality approach. J Neuro-Oncol. 1994;21:177–85.
40. Keles GE, Anderson B, Berger MS. The effect of extent of resection on time to tumor progression and survival in patients with glioblastoma multiforme of the cerebral hemisphere. Surg Neurol. 1999;52:371–9.
41. Kowalczuk A, Macdonald RL, Amidei C, Dohrmann G 3rd, Erickson RK, Hekmatpanah J, et al. Quantitative imaging study of extent of surgical resection and prognosis of malignant astrocytomas. Neurosurgery. 1997;41:1028–36. discussion, 36–8.
42. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro-oncol. 2004;6:227–35.
43. Levin VA, Yung WK, Bruner J, Kyritsis A, Leeds N, Gleason MJ, et al. Phase II study of accelerated fractionation radiation therapy with carboplatin followed by PCV chemotherapy for the treatment of anaplastic gliomas. Int J Radiat Oncol Biol Phys. 2002;53:58–66.
44. Mcgirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A, et al. Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg. 2009;110:156–62.
45. Nitta T, Sato K. Prognostic implications of the extent of surgical resection in patients with intracranial malignant gliomas. Cancer. 1995;75:2727–31.
46. Nomiya T, Nemoto K, Kumabe T, Takai Y, Yamada S. Prognostic significance of surgery and radiation therapy in cases of anaplastic astrocytoma: retrospective analysis of 170 cases. J Neurosurg. 2007;106:575–81.
47. Oppenlander ME, Wolf AB, Snyder LA, Bina R, Wilson JR, Coons SW, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg. 2014;120:846–53.
48. Oszvald A, Guresir E, Setzer M, Vatter H, Senft C, Seifert V, et al. Glioblastoma therapy in the elderly and the importance of the extent of resection regardless of age. J Neurosurg. 2012;116:357–64.
49. Phillips TL, Levin VA, Ahn DK, Gutin PH, Davis RL, Wilson CB, et al. Evaluation of bromodeoxyuridine in glioblastoma multiforme: a northern California cancer center phase II study. Int J Radiat Oncol Biol Phys. 1991;21:709–14.
50. Pope WB, Sayre J, Perlina A, Villablanca JP, Mischel PS, Cloughesy TF. MR imaging correlates of survival in patients with high-grade gliomas. Am J Neuroradiol. 2005;26:2466–74.
51. Prados MD, Gutin PH, Phillips TL, Wara WM, Larson DA, Sneed PK, et al. Highly anaplastic astrocytoma: a review of 357 patients treated between 1977 and 1989. Int J Radiat Oncol Biol Phys. 1992;23:3–8.
52. Puduvalli VK, Hashmi M, Mcallister LD, Levin VA, Hess KR, Prados M, et al. Anaplastic oligodendrogliomas: prognostic factors for tumor recurrence and survival. Oncology. 2003;65:259–66.
53. Sanai N, Polley MY, Mcdermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg. 2011;115:3–8.
54. Sandberg-Wollheim M, Malmstrom P, Stromblad LG, Anderson H, Borgstrom S, Brun A, et al. A randomized study of chemotherapy with procarbazine, vincristine, and lomustine with and without radiation therapy for astrocytoma grades 3 and/or 4. Cancer. 1991;68:22–9.
55. Shibamoto Y, Yamashita J, Takahashi M, Yamasaki T, Kikuchi H, Abe M. Supratentorial malignant glioma: an analysis of radiation therapy in 178 cases. Radiother Oncol. 1990;18:9–17.
56. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive radiation therapy oncology group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys. 1993;26:239–44.
57. Stark AM, Nabavi A, Mehdorn HM, Blomer U. Glioblastoma multiforme-report of 267 cases treated at a single institution. Surg Neurol. 2005;63:162–9. discussion, 9.
58. Ushio Y, Kochi M, Hamada J, Kai Y, Nakamura H. Effect of surgical removal on survival and quality of life in patients with supratentorial glioblastoma. Neurol Med Chir (Tokyo). 2005;45:454–60. discussion, 60–1.

59. Vecht CJ, Avezaat CJ, van Putten WL, Eijkenboom WM, Stefanko SZ. The influence of the extent of surgery on the neurological function and survival in malignant glioma. A retrospective analysis in 243 patients. J Neurol Neurosurg Psychiatry. 1990;53:466–71.
60. Jakola AS, Myrmel KS, Kloster R, Torp SH, Lindal S, Unsgard G, et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. JAMA. 2012;308:1881–8.
61. Pallud J, Fontaine D, Duffau H, Mandonnet E, Sanai N, Taillandier L, et al. Natural history of incidental World Health Organization grade II gliomas. Ann Neurol. 2010;68:727–33.
62. Potts MB, Smith JS, Molinaro AM, Berger MS. Natural history and surgical management of incidentally discovered low-grade gliomas. J Neurosurg. 2012;116:365–72.
63. Berger MS. Lesions in functional ("eloquent") cortex and subcortical white matter. Clin Neurosurg. 1994;41:444–63.
64. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. J Neurosurg. 2015;123:325–39.
65. Grossman R, Ram Z. Awake craniotomy in glioma surgery. Eur Assoc Neuro-oncol Mag. 2015;4:1–8.
66. Berger MS, Hervey-Jumper S, Wick W. Astrocytic gliomas WHO grades II and III. Handb Clin Neurol. 2016;134:345–60.
67. Cha S. Perfusion MR imaging: basic principles and clinical applications. Magn Reson Imaging Clin N Am. 2003;11:403–13.
68. Bogomolny DL, Petrovich NM, Hou BL, Peck KK, Kim MJ, Holodny AI. Functional MRI in the brain tumor patient. Top Magn Reson Imaging. 2004;15:325–35.
69. Nimsky C, Ganslandt O, Von Keller B, Romstock J, Fahlbusch R. Intraoperative high-field-strength MR imaging: implementation and experience in 200 patients. Radiology. 2004;233:67–78.
70. Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. Neurotherapeutics. 2007;4:316–29.
71. Bello L, Gambini A, Castellano A, Carrabba G, Acerbi F, Fava E, et al. Motor and language DTI Fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. NeuroImage. 2008;39:369–82.
72. Berman JI, Berger MS, Chung SW, Nagarajan SS, Henry RG. Accuracy of diffusion tensor magnetic resonance imaging tractography assessed using intraoperative subcortical stimulation mapping and magnetic source imaging. J Neurosurg. 2007;107:488–94.
73. Bizzi A, Blasi V, Falini A, Ferroli P, Cadioli M, Danesi U, et al. Presurgical functional MR imaging of language and motor functions: validation with intraoperative electrocortical mapping. Radiology. 2008;248:579–89.
74. Duffau H. New concepts in surgery of WHO grade II gliomas: functional brain mapping, connectionism and plasticity--a review. J Neuro-Oncol. 2006;79:77–115.
75. Thiel A, Herholz K, Koyuncu A, Ghaemi M, Kracht LW, Habedank B, et al. Plasticity of language networks in patients with brain tumors: a positron emission tomography activation study. Ann Neurol. 2001;50:620–9.
76. Guggisberg AG, Honma SM, Findlay AM, Dalal SS, Kirsch HE, Berger MS, et al. Mapping functional connectivity in patients with brain lesions. Ann Neurol. 2008;63:193–203.
77. Trinh VT, Fahim DK, Maldaun MV, Shah K, Mccutcheon IE, Rao G, et al. Impact of preoperative functional magnetic resonance imaging during awake craniotomy procedures for intraoperative guidance and complication avoidance. Stereotact Funct Neurosurg. 2014;92:315–22.
78. Taylor MD, Bernstein M. Awake craniotomy with brain mapping as the routine surgical approach to treating patients with supratentorial intraaxial tumors: a prospective trial of 200 cases. J Neurosurg. 1999;90:35–41.
79. Bekker AY, Kaufman B, Samir H, Doyle W. The use of dexmedetomidine infusion for awake craniotomy. Anesth Analg. 2001;92:1251–3.
80. Herrick IA, Craen RA, Gelb AW, Miller LA, Kubu CS, Girvin JP, et al. Propofol sedation during awake craniotomy for seizures: patient-controlled administration versus neuroleptic analgesia. Anesth Analg. 1997;84:1285–91.
81. Olsen KS. The asleep-awake technique using propofol-remifentanil anaesthesia for awake craniotomy for cerebral tumours. Eur J Anaesthesiol. 2008;25:662–9.
82. Nathan SS, Sinha SR, Gordon B, Lesser RP, Thakor NV. Determination of current density distributions generated by electrical stimulation of the human cerebral cortex. Electroencephalogr Clin Neurophysiol. 1993;86:183–92.
83. Duffau H, Capelle L, Denvil D, Sichez N, Gatignol P, Lopes M, et al. Functional recovery after surgical resection of low grade gliomas in eloquent brain: hypothesis of brain compensation. J Neurol Neurosurg Psychiatry. 2003;74:901–7.
84. Duffau H, Moritz-Gasser S, Gatignol P. Functional outcome after language mapping for insular World Health Organization grade II gliomas in the dominant hemisphere: experience with 24 patients. Neurosurg Focus. 2009;27:E7.
85. Wilson SM, Lam D, Babiak MC, Perry DW, Shih T, Hess CP, et al. Transient aphasias after left hemisphere resective surgery. J Neurosurg. 2015;123:581–93.
86. Keles GE, Lundin DA, Lamborn KR, Chang EF, Ojemann G, Berger MS. Intraoperative subcortical stimulation mapping for hemispherical perirolandic gliomas located within or adjacent to the descending motor pathways: evaluation of morbidity and assessment of functional outcome in 294 patients. J Neurosurg. 2004;100:369–75.

Neocortical Resections

13

Hans Clusmann

Neocortical lesional epilepsy can be caused by a large variety of tumors, ranging from well-circumscribed dysplasia and glioneuronal tumors to infiltrative gliomas. Gross total resection of brain tumors, if possible, is the mainstay of tumor therapy. In particular, glioneuronal tumors can be successfully resected, sometimes with minimal rim, even close to or within the eloquent cortex. The pathology of these focal tumors or also nontumors has a better prognosis than more widespread or diffuse lesions. Differentiation of tumor cases (tumors accompanied by epileptic seizures) and epilepsy cases (refractory epilepsy in the presence of a tumor) is crucial for the definition of the primary treatment goal and thus for the preoperative decision making and the need for further presurgical epilepsy evaluation. Modern diagnostic techniques enable more focused hypotheses of the epileptogenic zone thus making possible more precisely directed resection; however, there is no direct way to determine the epileptogenic zone. Surgical resection has to be adapted to these epilepsy-related findings in order to combine tumor and seizure relief, resulting in lesionectomy, extended lesionectomy, tailored resection, or even lobectomies [1]. The risk-benefit ratio is crucial. Therefore all means to reduce potential morbidity should be regularly applied (e.g., neuronavigation, intraoperative neurophysiologic monitoring, awake craniotomy, and cortical mapping).

H. Clusmann
Department of Neurosurgery, RWTH Aachen University, Aachen, Germany
e-mail: hclusmann@ukaachen.de

13.1 Role of Neocortical Resection to Control Epilepsy

This chapter predominantly deals with approaches and techniques that have been applied to successfully treat various types of neocortical lesional epilepsies. It will not primarily focus on the details of presurgical diagnostics and evaluation. However, success of epilepsy surgery largely depends on thoughtful preoperative evaluation and transfer of relevant data to critical decision making, thus resulting in the chosen surgical strategy. This is not only crucial for seizure control but also for stabilization of health-related quality of life. Tumor patients with gliomas suffer from long-term cognitive effects caused by the tumor itself but also caused by epilepsy and medication. It has been postulated that the effects of epilepsy are worse than the effects of radiation therapy [2].

The cerebral cortex is composed of different layers and cell types, and their respective dendrites and axons constitute a normally balanced network. The neocortex (cerebral cortex) in all mammalian species and humans is a usually a six-layered structure composed of pyramidal (projecting) neurons and local circuit (usually inhibitory GABAergic) interneurons organized in vertical (radial) columns. Whereas the excitatory glutamatergic neurons show a relatively uniform structure and function, the inhibitory GABAergic interneurons differ in their anatomic, molecular, and electrophysiologic function (for review, see DeFelipe et al. [3]). In addition to these neuronal elements, the cortex also consists of different types of glial cells that fulfill a variety of important physiologic functions in the network [4]. Imbalance of these networks by either (1) disturbance of structural or functional maturation of the cortex, or (2) neoplastic lesions may thus contribute to persistent network disturbances underlying hyperexcitability. Pathophysiolologic disturbances such as chloride homeostasis in these networks or induced by perinatal hypoxia and inflammation, traumatic brain injury, or neoplasia may cause long-term alterations in neocortical structure and function, finally leading to single or recurrent focal seizures and the chronic state of a focal epilepsy.

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Although modern imaging techniques may provide an estimate of the structural lesion, the site and extent of the hyperexcitable cortical networks and the epileptogenic zone (EZ) remain elusive [5]. A neocortical lesion may be surrounded by widespread molecular, structural, and functional disturbances that are difficult or not recognized with current imaging technologies. However, modern imaging and electrophysiologic techniques enable focused hypotheses of the neocortical EZ, allowing more specific epilepsy surgery (Fig. 13.1). Focal cortical lesions and tumors can be successfully removed with minimal rim or close to or even within the eloquent cortex with a promising risk-benefit ratio [6]. Molecular, anatomic, and electrophysiologic changes surrounding visible lesions may be rather widespread, and it is currently unclear whether these global modifications are the cause or the consequence of epileptic seizures.

Although modern diagnostic techniques enable more stringent hypotheses of the neocortical EZ thus enabling more precisely directed resection, the exact location and size of the EZ are still difficult to determine [7]. Future methods and studies combining additional parameters such as intraoperative molecular imaging may lead to a further improvement and better identification of the epileptic focus [4, 8].

Epileptogenesis and surgical relief from epilepsy associated with neocortical tumors depend on different factors:

Clinical Factors Absence of generalized seizures has been described as a positive predictor, as are a short history of seizures, early surgery, less severe epileptic fits, and localized EEG abnormalities. However, it should be noted that different studies have identified different predictive factors. The majority of studies have found complete tumor removal to be of benefit for seizure control. In a systematic review of 39 reports and 910 patients with glioneuronal tumors, 79% of patients who underwent gross total resection were described as being seizure-free versus 43% with subtotal resection only [9].

Localization A most prominent group of long-term epilepsy-associated tumors is located in the deeper limbic and paralimbic areas, often associated with refractory epilepsy (e.g., insular gliomas, mesiotemporal tumors) [10]. Mesial temporal lobe epilepsies with or without mesiotemporal lesions are not the topic of this chapter. Superficial cortical location or contact with the cortex is a prerequisite for the development of seizures in smaller tumors. Regarding neocortical tumor-associated epilepsies, the frontal lobe is most often affected, but seizures may also occur with neocortical temporal, perirolandic, and parietal and occipital locations. The frequency of occurrence may correlate with the size of different lobes in the first line [11, 12].

The presence of a focal tumoral lesion in MRI is the most important prognostic factor when treating neocortical epilepsies. Cases with focal frontal lobe epilepsy (FLE) can be treated with good success rates, in some series comparable to results after treatment for temporal lobe epilepsy (TLE) [13]. The necessity of frontal lobectomies implies a more widespread epileptogenic lesion and zone, with the consequence of less promising results [14].

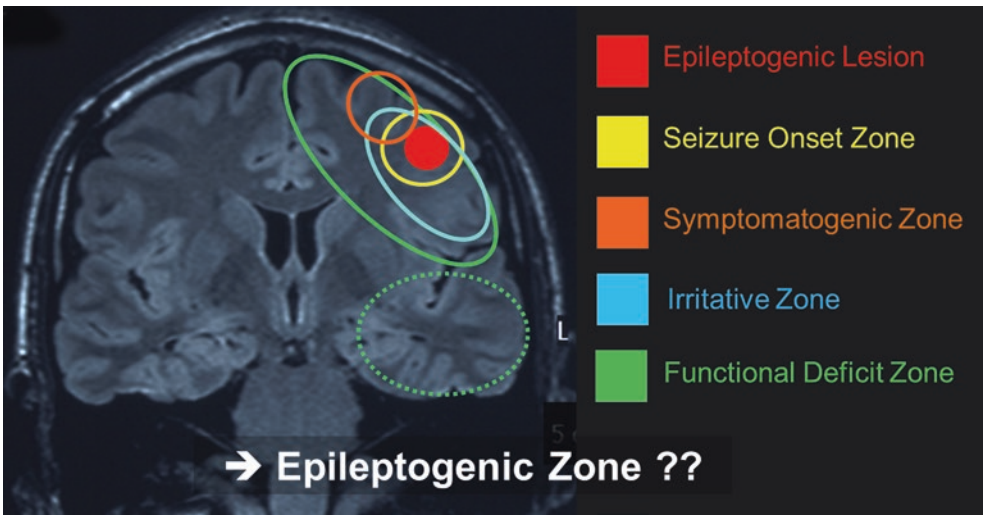

Fig. 13.1 Theoretical concept of different seizure- and epilepsy-related cortical zones, and the hypothesis of the EZ. Schematic illustration superimposed on a coronal MRI: epileptogenic lesion (*red*) surrounded by a potential seizure onset zone (*yellow*). The obvious symptoms may be related to activation of the adjacent cortex, whereas interictal EEG spikes may occur in a noncongruent irritative zone (*blue*). Functional deficits may be caused by impairment in the same lobe (*green solid*), or indirectly in a distant lobe (*green dotted line*). The theoretical construct of the EZ may comprise different aspects including the epileptogenic lesion, seizure-onset zone, and sometimes aspects of the other zones as well. Thus, none of these zones per se defines the necessary area of cortical resection, which is essential for seizure control

Higher cognitive functions and visual fields are the main concerns when operating on patients with parietal lobe epilepsies (PLEs) and occipital lobe epilepsies (OLEs). There are patient series available for parietal, occipital, and multilobar epilepsies with mixed patient cohorts with tumor and nontumor cases [15]. Invasive monitoring is required in a substantial number of cases in order to provide reliable information on the cortical areas that should either be spared or resected to treat epilepsy. However, OLE and PLE patients can be operated on with good success rates [12, 16].

Even rarer forms of epilepsies arise from the cingulate cortex [17]. These areas are considered difficult for evaluation because of their distance from the cortical surface and the variable symptoms that can be associated with cingulate and insular epilepsies.

13.1.1 Tumor Size and Growth

Smaller tumors and those growing less quickly are associated with higher rates of seizures than large, rapidly growing lesions. Moreover, rapidly growing gliomas often occur in the white matter and not primarily in areas prone to cortical epilepsy [18]. One other consideration is that patients with fast growing gliomas often do not survive long enough to develop chronic epilepsy, but first tumor manifestation with an epileptic seizure is frequent. A first seizure in an adult bears an 11% risk for the presence of a tumor [19].

13.1.2 Tumor Histology

Epilepsy is most frequent in low-grade intrinsic lesions. In glioneuronal tumors (often WHO I°: gangliogliomas and dysembryoplastic neuroepithelial tumors [DNT]), the rate is 70–90%. These patients' conditions are often refractory to anticonvulsive medication. Sixty to eighty percent of patients with low-grade gliomas suffer from epilepsy, 25–30% with high-grade gliomas, 20–50% with meningiomas, and 15–35% with metastases. Seizure recurrence can be a first hint at tumor recurrence or progression, even in WHO grade I tumors. Chronic progression of a dysembryoplastic neuroepithelial tumor is shown in Fig. 13.2 [20]. The presence of pathologic neuronal networks ("connectionism") has been described in low-grade gliomas, with plasticity potentially underlying both seizures and cognitive impairment. In addition, postsurgical seizure control is to some degree dependent on histology, and complete tumor removal leads to better seizure control. Especially good seizure control up to 90% can be obtained with glioneuronal tumors [21] and about 60–70% with low-grade gliomas [8, 22]. The main indication for surgery in patients with high-grade gliomas is improving tumor control and survival, but in patients without special consideration of epilepsy about 75% of patients acquire initial seizure control [23].

To uncover the multiple and mostly unclear interactions of tumors and network-driven cortical epileptogenesis, translational research with animals is necessary to further develop and clarify these respective hypotheses [24].

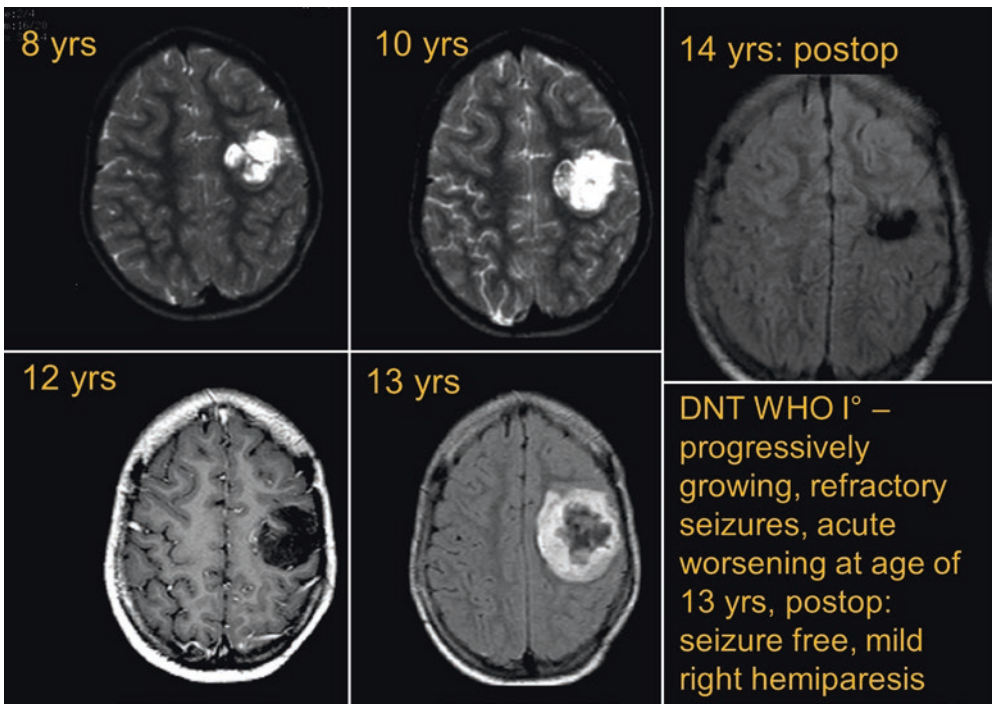

Fig. 13.2 Progressively growing DNT WHO° I. Different axial MRI scans acquired over a period of 6 years in a young patient (8–14 years old) illustrate slow but continuous growth of a dysembryoplastic neuroepithelial tumor (DNT WHO° I). Focal motor seizures became refractory over time. The patient developed a mild but progressive right hemiparesis at the age of 13, and he then underwent surgery with a pure lesionectomy. He became seizure-free after surgery, with a mild but very well-compensated hemiparesis on the right side

13.2 Presurgical Evaluation for Neocortical Resections: Dichotomy of Epilepsy Surgery or Tumor Surgery?

General criteria for successful treatment of cortical tumors associated with epilepsy have been described earlier. Moreover, success largely depends on the type and extent of tumor as seen with MR imaging, on regarding relief from epilepsy on specific preoperative considerations, on the transfer of these factors to decision making, and finally on surgical strategy. Thus surgery in the presence of a tumor seen on MRI is always "lesion-oriented." However, especially for lesional temporal lobe epilepsy, relevant differences have been described with respect to seizure control after tumor and epilepsy surgery. What is the difference? There are two main surgical goals for patients with tumor-related epilepsy: tumor control and seizure control, ideally both achieved with surgery. However, the way to approach such cases varies with respect to criteria and procedures. Most experience has been acquired with temporal lobe epilepsy cases owing to the high epileptogenicity of mesial temporal structures. Thus it is not surprising that strikingly better results were obtained for extended resection, including amygdalohippocampectomies (93% seizure-free) compared to lesionectomies alone (43% seizure-free) [25]. Similar results were obtained in a meta-analysis including 1181 patients from 41 studies [9]. Knowledge about extratemporal tumors and epilepsies is rare. However, recent work has demonstrated the potential to improve results in neocortical lesions [26]. There is also some support from animal series that epileptogenesis can take place predominantly outside the core tumor infiltration area [27]. It is widely accepted that patients with or without lesions on MRI should undergo a formal presurgical evaluation after unsuccessful trials of two anticonvulsants as epilepsy cases [28].

A typical tumor case includes these features:

1. Tumor primarily diagnosed, often WHO° II, III, or IV
2. Oncologic indication for surgery to control tumor: improvement of prognosis
3. Mostly gross total resection desired
4. Additional evaluation applied for analysis of the eloquent cortex if necessary
5. Seizures as one of multiple features in the tumor disease: seizure control a desired side effect of tumor control surgery.

In contrast, a typical epilepsy case has these features:

1. Longstanding epilepsy is often diagnosed first and tumor is then found on MRI
2. Indication for treatment and surgery caused by medically refractory epilepsy
3. Gross total resection potentially not sufficient to control seizures
4. Application of various techniques to analyze seizure generation and eloquent cortex
5. No isolated oncologic indication to remove the tumor (often WHO° I): tumor removal often not necessary per se but surgery to control epilepsy needed

Algorithms have been suggested for tumor cases with chronic and pharmacologically resistant epilepsy. If dedicated epilepsy MRI and video EEG recording reveal congruent results, a lesionectomy should be done. If any incongruences are detected, the indication for invasive EEG recording with individually planned intracranial electrodes should be considered. Moreover, positron emission tomography (PET) and single photon emission computed tomography (SPECT) may aid in decision making, particularly in the decision of which electrodes to implant and where. Results of these extended evaluations may then lead to a recommendation of extended lesionectomy, tailored resection, or even lobectomies. Intraoperative electrocorticography may additionally aid decision making [29].

Many cases are not exactly clear cut and features may be mixed. This supports the notion to consider all aspects when planning diagnostics and treatment in tumor-associated epilepsy. The theoretical basis and the concept of lesion and seizure generation within the EZ will be briefly summarized: Former work resulted in a theory of different zones involved in the epilepsies [7]. In spite of some definition differences, these concepts turned out to be important because they are the fundament of applying multiple diagnostic means to approach the EZ [7]. Six cortical zones that should be defined in the presurgical evaluation of candidates for epilepsy surgery are the symptomatogenic zone (initial ictal clinical symptoms); the irritative zone (interictal EEG spikes); the ictal onset zone (initial EEG ictal seizure activity); the epileptogenic lesion (as seen on MRI, in this context primarily a tumor; the functional deficit zone (persisting neurologic or neuropsychological deficits), and the eloquent cortex (normal adjacent functional cortex) (Fig. 13.1). For epilepsy surgery evaluation, different diagnostic techniques are used in the definition of these cortical zones such as video EEG monitoring and MRI. Presurgical diagnostics should result in an estimate of the EZ, defined as a cortical area, which is inevitably necessary for the generation of clinical epileptic seizures. However, the EZ can only be proved by a circumscribed cortical resection or disconnection leading to seizure freedom [30].

If an epilepsy surgery approach is necessary, the armamentarium comprises multiple features for extra- or intraoperative monitoring. Multiple different electrode types and procedures may be used for chronic invasive monitoring, including depth electrodes either with few electrodes or as stereo EEG recording with multiple depth electrodes (rarely applied for tumor cases) [31], subdural electrodes [32],

epidural electrodes, peg electrodes inserted in the bone, and sphenoidal and foramen ovale electrodes. These electrodes allow interictal and ictal recordings, and if positioned adequately they are able to provide closer hints about the epileptogenic focus.

Intraoperative electrocorticography (ECoG) is often performed in neocortical epilepsy surgery after noninvasive evaluation to determine the border of extended lesionectomy in patients with neocortical lesions. The disadvantages of this method are the poorly defined influence of anaesthetics, the short recording time, and the lack of seizure recording. Basically, intraoperative ECoG is an interictal recording. Therefore, it is restricted to the definition of the irritative zone and thus has limitations for sufficiently delineating the EZ or eloquent cortices [33]. Intraoperative spikes or bursts may indicate the irritative zone. Cessation of these after tumor resection can be taken as an indirect hint that parts of the epileptogenic focus have been resected or disconnected successfully. However, correlation with postoperative seizure control has been weak [34]. High-frequency oscillations (HFOs; ripples, 80–250 Hz; fast ripples, >250 Hz) have been described as a new and potentially even more precise surrogate for the EZ. With the removal of HFO-generating areas, good surgical outcomes were attained in most cases; however, the relevance for tumor cases is still unclear. In the future, HFOs may be used as a promising marker of epileptogenicity, since it is potentially more accurate than spike-generating areas [4].

The MRI documented location of a tumor guides decisions about whether additional measures are necessary. Moreover, this depends on the goal of surgery and the question of whether gross total resection is possible with an acceptable risk of morbidity. These decisions are supported by other tools such as functional MRI [35].

Transfer of presurgical results to surgery follows the above-mentioned concepts. A more precise delineation of the presumed EZ enables smaller additional resections in addition to tumor removal, with the potential for reduced risk for neurologic or neuropsychological deficits. The trend toward smaller resection types should not lead to a decrease in seizure relief rates but will probably improve functional outcomes.

Tools aiding the neurosurgeon to approach his or her target structure precisely are increasingly contributing to epilepsy surgery. Neuronavigation carries the important role of being the direct link between imaging and surgery, which can be characterized as “enhanced reality.” This link can be extraordinarily close if multimodal information is visualized via the surgical microscope. Not only can target structures be visualized but also information derived from electrophysiologic recordings, functional MRI, or diffusion tensor imaging [36, 37].

13.3 Neocortical Resection Techniques

A spectrum of several resective epilepsy surgery types has been used over the last decades and is still being used at the present time such as with corticectomy if no structural lesion is encountered, pure or extended lesionectomy with a variable rim of cortex, tailored resections, and single or multiple lobectomies. Descriptions of disconnective or neuromodulatory procedures are not included in this chapter. Complete removal of an infiltrating brain tumor or resection of the more widespread epileptogenic zone can be compromised by the overlap with the eloquent cortex, for example the primary motor cortex, cortical areas representing speech function, and the visual cortex. Established measures to reliably assess the eloquence of certain cortical areas are cortical mapping via chronically implanted electrodes and intraoperative mapping during awake craniotomy. The aim of these measures is to resect the tumor and as much tissue as thought to be necessary to provide complete seizure relief without causing unacceptable permanent neurologic damage. To achieve this goal, individualized diagnostics and case-based evaluations must be carried out. Severe permanent deficits should be avoided in any case, especially in gliomas WHO °II–°IV, as they generally cannot be cured with surgical methods. Mild or temporary deficits for the sake of improved chances for seizure relief or more substantial tumor resection may be acceptable if they have been discussed with the patient. Frequently there is a close correlation of symptoms (irritative zone and functional deficit zone) and localization in tumor-related epilepsy cases; therefore seizure symptoms may provide a first idea of which function is most at risk.

13.4 Lesionectomy

Pure lesionectomy means the removal of a visible tumoral lesion without any cortical extension of resection. In tumor surgery this means gross total resection, which is always intended if possible to guarantee adequate tumor control rates. Primary resection of tumors has been shown to improve long-term tumor control and survival, including in low grade-gliomas [38]. Pure lesionectomy has proved to be sufficient in selected cases such as glioneuronal tumors and special subtypes of cortical dysplasia [39, 40]. However, as described earlier, overall results in patient series (especially those with temporal lobe epilepsies) show that seizure control rates for lesionectomy are somewhat inferior to rates for more extended resections [9]. Thus, pure lesionectomy with gross total resection of a tumor is mostly promising in cases in which epilepsy constitutes one of the accompanying symptoms but not the major challenge. If there are no hints that epilepsy control can be problematic, such as when it is easy to control seizures with the first anticonvulsant used in a low dose, then pure lesionectomy is a good option. This is especially true if the tumor is located close to or even within the eloquent cortex. An example would be a well-circumscribed lesion in the precentral gyrus or supplemental motor area. If such a lesion is located in a clearly noneloquent area, a more extended lesionectomy may be considered in order to improve chances for long-lasting seizure control. Moreover, more extensive supratotal resections, if possible without permanent sequels, may improve oncologic outcome [41]. The prognosis of pure lesionectomy with respect to seizure control also depends on pathology. Promising results have been obtained for the resection of focal cortical dysplasia type IIb [42].

13.5 Extended Lesionectomy Plus Rim

The above-mentioned criteria for pure lesionectomy are also applied in extended resections. This means that complete lesionectomy and gross total tumor resection are the basis for further epilepsy-driven extension. Corticectomy is thus the technical description for the extension of tumor resection. Corticectomy alone is a possible option in nontumoral and nonlesional epilepsies, but it is not the approach for tumors [9]. The depth of such cortical resection should always include the whole cortical surface and the deep cortical folds. Thus, a resection of 2.5–3 cm in depth is usually sufficient. Deeper resections may be necessary for tumor removal but generally not for improvement of epilepsy control as a cortical phenomenon [30]. Care should be taken not to injure deeper traversing fiber tracts (Fig. 13.3). Vascular compromise in particular may lead to unwarranted complications associated with potential neurologic morbidity. Even more challenging is the difficulty in defining the horizontal extent of resection, and this decision may also depend on the pathology. As already mentioned, extended lesionectomy is very promising in certain developmental tumors such as gangliogliomas and dysembryoplastic neuroepithelial tumors (DNTs), which can be treated with excellent seizure control rates in most patients [9, 43]. Also, certain types of low-grade gliomas (e.g., isomorphic subtype of low-grade astrocytoma, pilocytic astrocytoma) can be operated on with excellent success [44]. In all these lesions it is practically preferred to resect a small rim of adjacent cortex, although there is no significant evidence for such or other strategies. In most cases the extent of resection depends on the epileptologic recommendation as well as on the experience of the surgeon. He or she will be the one to carry the responsibility for the patient's neurologic integrity on one side and for resections considered to be incomplete and thus unsuccessful on the other [30].

What does this mean in practical terms? As a rule of thumb, a rim of about 1 cm neocortex resection to a depth of 2.5–3 cm is probably common practice for "standard" extended lesionectomies. This has not been systematically examined or proved. Extended resections beyond this usually require additional guidance and intra- or perioperative evaluation. Unfortunately, the reliability of for example intraoperative electrocorticography (iECoG) is not high, especially because this is exclusively interictal recording, which may be or may not be congruent with the epileptogenic zone. Other tools such as extraoperative mapping/monitoring with implanted electrodes provide more reliable results but carry other limitations. Taken together, a valid hypothesis supported by clinical or neurophysiologic data should be available for a decision to perform largely extended lesionectomies, since the potential benefit has to be weighed against the additional risk of neurologic or neuropsychological sequels. This is important because these sequels translate into reduced quality of life, even when seizure control is achieved.

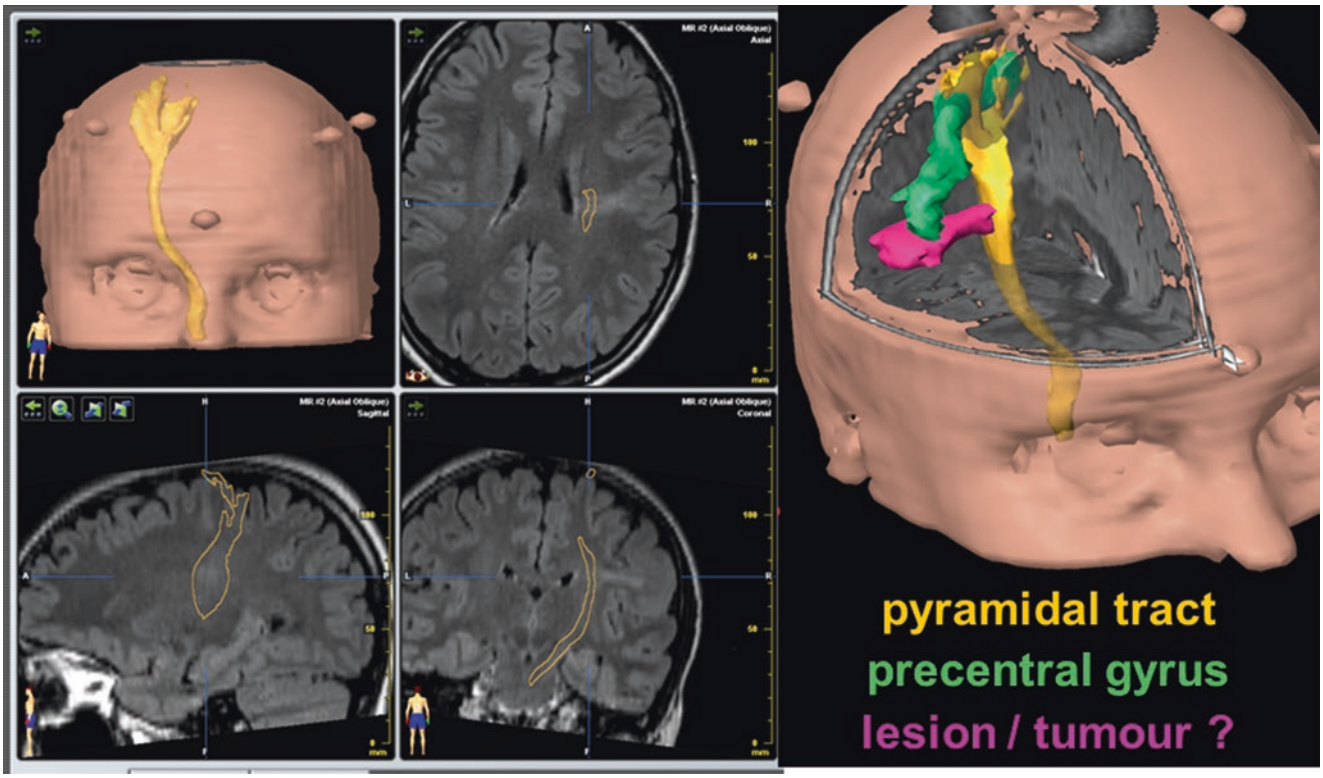

Fig. 13.3 Lesion within the lower right precentral gyrus, intersection with pyramidal tract in depth. Original axial FLAIR MRIs of a young patient with refractory focal epilepsy. Coronal and sagittal images reconstructed by a commercial neuronavigation system (*left*). Object segmentation in these images and in the three-dimensional image (*upper right*) illustrates the right pyramidal tract (*yellow*). The right side shows the head in three dimensions rotated 30 degrees to the left. The virtual cutting planes enable a view into the depth with the pyramidal tract (*yellow*) but also of the segmented objects representing the precentral gyrus (*green*), and the cortical-subcortical lesion (*pink*), representing a tumor or as in this case a developmental lesion. Note the intersection of the lesion and the pyramidal tract in the depth, which is an important aspect for preoperative planning of a resection. Because of the lesion location in the lower 2.5 cm of the precentral gyrus, resection was thought to be sufficiently safe and was well tolerated by the patient. Histology: focal cortical dysplasia with balloon cells, grade IIb Palmini and Lueders

13.6 Tailored Resection

Tailored resections or supratotal resections are even more extensive than simply extended lesionectomies. The idea behind these procedures is different from the question of extension after lesionectomy. The necessity to consider a tailored resection is driven by an extensive and infiltrating glioma. Duffau has suggested supratotal resections of low-grade gliomas where the border of resection is defined by functional limitation, as indicated by intraoperative mapping in awake procedures but not by MRI findings. Thus, this type of resection may exceed a tumoral lesion by several centimeters [41]. On the other hand, tailoring may also stop tumor resection or extension at some point, even when parts of the tumor are still in place in order to avoid deficits. An example is shown in Fig. 13.4 when tumor resection was stopped with some safety "rim" in order to preserve the optic radiation. In this case, the young patient wanted to become seizure-free but was also keen on keeping her driver's license so any larger visual field defect had to be avoided. In a case like this, tailoring of a resection is part of a personalized treatment plan developed during a process of shared decision making in order to follow an individual patient-centered approach.

Epileptologic considerations also may trigger tailored resections. This is the case when extraoperative neurophysiologic monitoring results derived from cortical grid electrodes suggest widespread epileptic signals, and the respective cortex seems to be dispensable. However, this is seen more frequently in non-tumoral epilepsies with widespread cortical malformation or in MRI-negative cases [45].

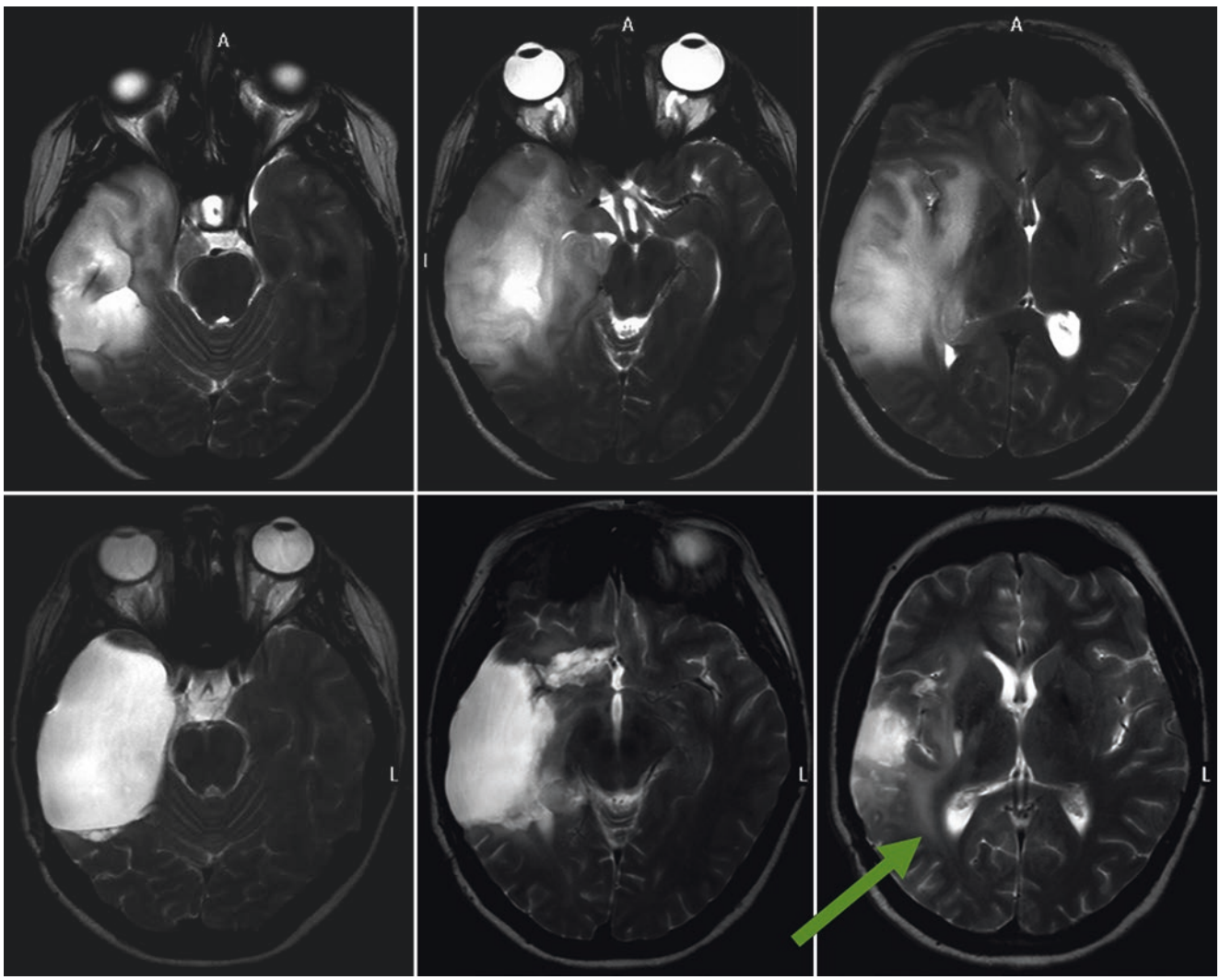

Fig. 13.4 Large right temporal tumor and tailored resection. T2-weighted axial MRIs of a 17-year-old patient. The patient developed epilepsy with simple and complex partial seizures, which were easily controlled with anticonvulsive medication. An infiltrating astrocytoma was suspected, and the patient underwent uneventful subtotal tumor resection. At that time, she had just started to obtain a driving license, and a plan (shared decision making) was made. Her goal was to pursue driving. Thus, a personalized plan was developed to resect as much as possible of the tumor. The goal was to improve the chance for oncologic tumor control and provide a good chance for seizure freedom without sacrificing the optic radiation in order to avoid any relevant visual field defects. The lower images illustrate subtotal tumor resection (astrocytoma WHO°III), with intended preservation of the optic radiation in spite of infiltrative tumor growth (*arrow*)

13.7 Lobectomy and Multilobectomy

Lobectomy or even multilobectomy is rarely performed for tumor-associated epilepsies. These procedures are the domain for widespread brain lesions and associated catastrophic epilepsies. It is rare that a tumor causes such a situation. Gliomatosis cerebri may be such a condition, but this is a domain of radiation and chemotherapy and extensive surgical approaches are mostly neither promising nor indicated [46]. Many large resective procedures have been replaced by disconnective operations such as functional hemispherotomy or hemispherical disconnection, which provide identical epileptologic results but have a better risk profile with much fewer complications [47].

13.8 Intraoperative Adjuncts for Neocortical Resection: Precision, Epilepsy, Safety

As mentioned previously, tumor and neocortical resection may be purely image-guided in simple tumor cases. However, according to extensive presurgical epileptologic evaluation in cases with refractory epilepsies, more intraoperative techniques may have to be brought to the operating room in order to define the extent of resection, to check for sufficient resection, or to control for resection and complications. These adjuncts may be separated into those that provide better orientation or virtual reality (precision), those that guide extension of cortex removal (epilepsy), and safety measures to prevent unintended damage to the eloquent cortex or fibers (safety).

13.8.1 Navigation and Craniotomy Planning: Precision

Frameless navigation has become a standard procedure in neurosurgery. Coregistration and fusion of computed tomography (CT) and MRI provide high accuracy and moreover enable the collection of different MR images, even those acquired at different time points, to be fused with a CT scan acquired before surgery. Moreover, other functional MRI modalities and other information such as SPECT, PET, but also for example amino acid-PET (mostly [18-F]-fluordeoxyglucose (FDG), [11-C]-methionine (MET), or O-(2[18-F]-fluorethyl)-L-tyrosine [FET]) to localize elevated biological tumor activity may be incorporated into the navigation data set. The majority of dedicated imaging data sets are regularly available days before surgery; they are the basis for image-guided planning of surgery. Thus dedicated preplanning is mostly possible in these cases, and the position of the craniotomy, the direction of approach, and object imports with area of resection can be imported into the navigation system to provide the necessary comprehensive information for the surgeon, finally aiming at a resection plan in virtual reality (*see*, for example, Fig. 13.3) [48, 49].

In general, craniotomy needs a sufficient size for any extended lesionectomy. Minimalized keyhole approaches are not suitable to serve the needs of extended cortical resections. Of course, the tumor and the preplanned cortical resection have to be exposed by craniotomy. In cases with intraoperative electrocorticography the area of extension may be larger according to intraoperative recording of interictal spikes. These options have to be kept in mind when planning head positioning, skin incision, and craniotomy. Craniotomies can become extensive in cases of planned supramarginal tumor resection. Pure lesionectomy, i.e., gross total resection, is easily planned, but strategy for patients with a tumor and refractory epilepsy has to be considered in advance according to the tools applied for the case and their potential effects on surgery.

13.8.2 Intraoperative Imaging: Precision

Three-dimensional visualization may further contribute to a valid three-dimensional orientation and resection planning. There are also ideas about an increasing role for intraoperative MRI in immediate resection control of epileptogenic lesions and tumors, as demonstrated in recent patient series resulting in successful treatment with surgery, neuronavigation, and intraoperative high-field MRI. Promising results have been obtained with increasing experience with intraoperative MRI [50]. However, it has to be kept in mind that intraoperative MRI is an expensive and time-consuming tool that at present is only available in a small number of hospitals [51]. The ideas about its more widespread use are still controversial, especially regarding the balance of benefit and expense. Intraoperative imaging can be helpful for precise orientation after the occurrence of brain shift caused by resection and loss of cerebrospinal fluid (CSF). This can affect precision, especially in large and deeper locations. Precise orientation is thus most important at the beginning of cortical resection for reliable initial orientation and transfer of the resection plan to the site. The depth of extended resection in epilepsy surgery is fairly uniform at 2.5–3 cm in depth. This this orientation can be made according to the grey-white matter border or just with a ruler or Cushing cannula. Intraoperative ultrasound is a more widespread tool enabling intraoperative compensation for potential brain shift [52].

Taken together, intraoperative imaging may contribute to preciseness and to completeness of tumor resection, but guidance of additional neocortical resection remains the domain of extra- or intraoperative neurophysiology.

13.8.3 Intraoperative Electrocorticography: Epilepsy

Intraoperative (interictal) electrocorticography (iECoG) can be performed in extratemporal epilepsies after noninvasive evaluation to determine the border of extended lesionectomy in patients with neocortical lesions distant from eloquent areas. The disadvantages of this method are the poorly defined influence of anesthetics, the short recording time, and the lack of seizure recording. Basically, intraoperative ECoG is an interictal recording. Therefore, it is restricted to the definition of the irritative zone and thus has limitations for sufficiently delineating the epileptogenic zone or the eloquent cortices when only looking at interictal spikes [33]. An example of its application is shown in Fig. 13.5. More recent reports have shown that this type of lesion but also patterns of preresection iECoG correlate with postoperative seizure control in lesional epilepsies [53]. Meanwhile, specific fast ripple activity has been shown to be superior to just interictal spikes to forecast seizure control with intraoperative recordings [54]. In practical terms, persisting pathologic activity after lesion or tumor

resection can lead to much more extensive cortical resections than originally planned. This, in turn, constitutes a risk factor allied to the necessity to extend the craniotomy or even to get too close to the eloquent cortex. Thus, other safety measures have to be applied to stop the extension when it is no longer safe for the patient. There are some advantages of extraoperative monitoring with chronically implanted strip, grid, or depth electrodes. These enable recording of interictal and ictal events and thus may provide closer information on the potential epileptogenic zone in addition to exact delineation of the highly eloquent cortex [55]. Respective techniques are described elsewhere. Grid implantation can be especially dangerous in large and space-occupying tumors because of the electrode in place plus swelling, potentially resulting in increased intracranial pressure. Some centers prefer osteoclastic craniectomies for such cases [56].

13.8.4 Intraoperative Neurophysiologic Monitoring (Safety)

Complete yet safe resection close to motor areas in medically intractable epilepsy requires functional information. New deficits may occur despite preservation of the motor cortex, for example through vascular compromise. Continuous motor-evoked potential (MEP) monitoring in focal epilepsy surgery may provide additional safety and should be used in cases close to the motor strip as an alternative or additionally for extraoperative motor cortex mapping via chronically implanted subdural electrodes. Examples of intraoperative continuous monitoring of MEPs are illustrated in Fig. 13.5. It has been shown that MEP changes predict the occurrence and permanence of new paresis. Stable MEP monitoring correlates with unimpaired motor outcome and full seizure control [57]. Alternatively, intraoperative awake mapping can be performed [58].

Somatosensory-evoked potentials can be applied to determine the central sulcus by characteristic phase reversal and may thus serve for the functional verification of the rolandic area and as an adequate stimulation site for MEP monitoring (Fig. 13.5). Modern concepts try to improve integration of intraoperative monitoring into the microscope in order to improve the availability of relevant findings to the surgeon, thereby minimizing potential communication deficits [37]. Warning signs from intraoperative neurophysiologic monitoring should be taken seriously because the time frame to stop resection or to preserve vessels in order to avoid permanent deficits is short, and an immediate reaction is required. The desire to theoretically improve seizure relief cannot accept severe permanent deficits such as hemiparesis. Other important functions, especially language, cannot be sufficiently monitored under anesthesia.

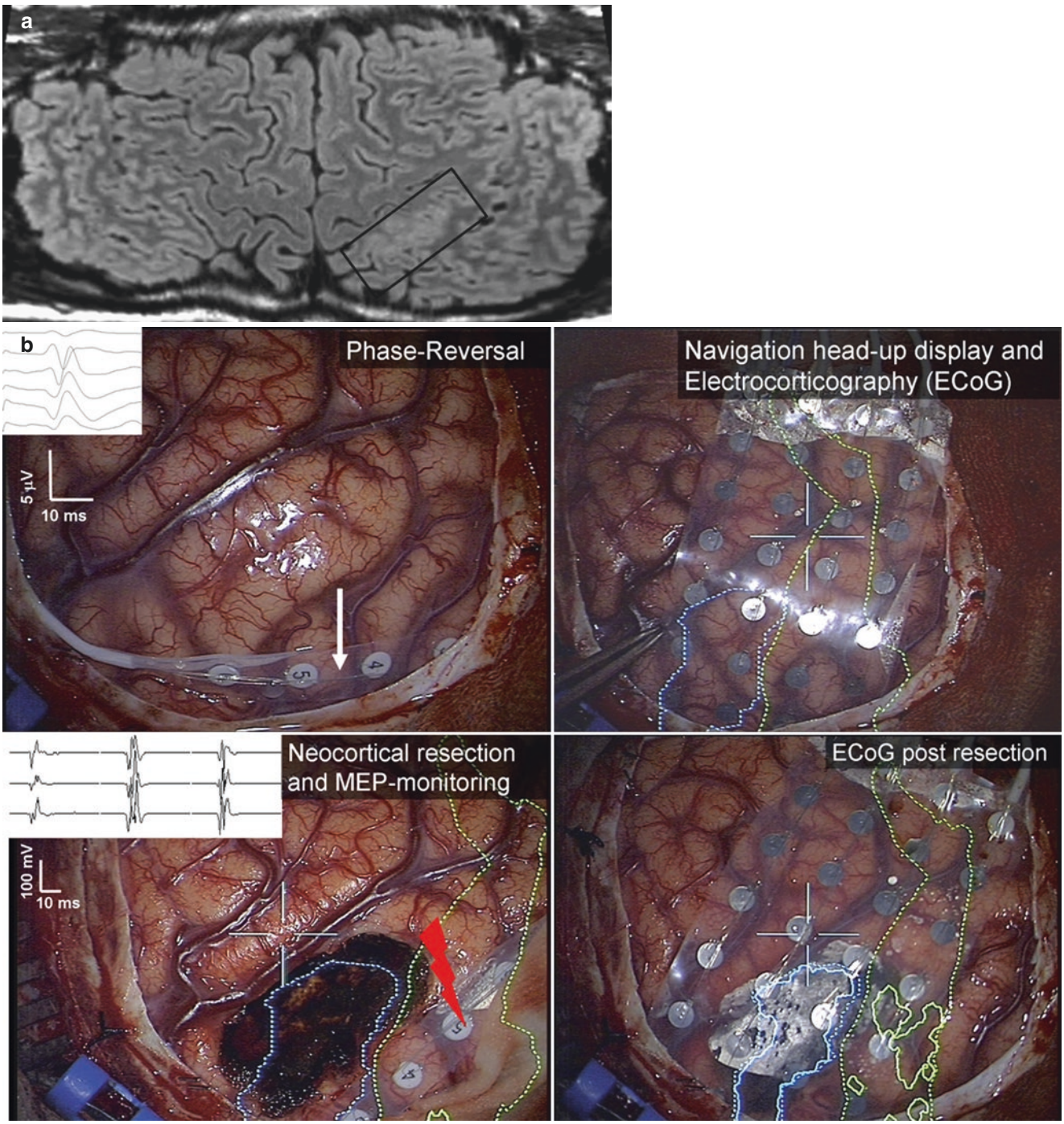

Fig. 13.5 Postcentral lesionectomy. (**a**), An MR FLAIR image of a young adult patient with chronic epilepsy. The planar reformatting (pancake-view) illustrates a structural lesion within the left postcentral gyrus (*box*). (**b**), Four intraoperative photographs acquired by the surgical microscope during resection illustrate the steps of cortical resection and technical adjuncts applied. *Upper left*: View on the intact left central/postcentral cortex. After opening the dura, a six-contact strip electrode is positioned, stimulation of the right median nerve elicits the somatosensory evoked potential (*inset*), and phase reversal indicates the central sulcus (*white arrow*). *Upper right*: Navigation head-up display has been switched on so that preoperatively segmented objects become visible: the lesion (*blue line*) and the precentral gyrus (*yellow line*). In order to record interictal spikes before resection, a 4 × 8 grid electrode is placed over the lesion and adjacent cortex, and the intraoperative electrocorticogram (*not shown*) is recorded for a few minutes. *Lower left*: Cortical resection (lesionectomy) of 2.5 cm in depth is done while motor-evoked potentials are continuously recorded. Stimulation of contact No. 5 (*red lightning*) located on the precentral gyrus has provided reproducible and stable motor-evoked potentials of three forearm muscles (*inset*). Note that for resection the position of the strip electrode has been changed compared to the initial determination of phase reversal. The head-up display confirms the good congruence of the lesion, the precentral gyrus, and their respective objects. *Lower right*: After resection, the ECoG is repeated to check for the absence of interictal spikes

13.8.5 Awake Surgery and Brain Mapping (Safety)

Intraoperative cortical mapping is another important tool that may be used in epilepsy as well as in tumor cases to delineate the eloquent cortex. This is regularly done under awake surgery in patients with lesions in or adjacent to cortical language areas. Details of awake craniotomy and the reliability of language testing with different tasks are described elsewhere; for a review see Szelényi et al. [59]. Resections coming close to classical language areas like Broca and Wernicke require special considerations and intraoperative testing. These regions are highly variable so that neither preoperative functional MRI nor transcranial magnetic stimulation monitoring can provide sufficient safety for the preservation of language function. Furthermore, fibers of the arcuate fascicle can be easily affected by the deeper parts of resection so that cortical and subcortical stimulation are regularly applied in these cases to provide maximal safety [60]. As a rule of thumb, a 1-cm safety margin should be respected for neocortex or fibers with obvious functional impairment with stimulation.

A similar approach can also be taken for the perirolandic cortical areas. Duffau argued for the performance of extraoperative mapping and seizure recording in nontumor epilepsy patients only and extensive intraoperative awake mapping in tumor patients [58]. Intraoperative monitoring or mapping of vision is not yet well established and is in an experimental and developmental state [61, 62].

13.9 Neocortical Resection Complications: Avoidance and Management

Today brain surgery is safe, especially for superficial or neocortical tumors with low complication and mortality rates. But even with increasing use of the developing options, one has to be aware of the limits of brain and epilepsy surgery.

Every tool has its specific limitations and potential to fail. Thus all findings have to be critically reviewed and cross-checked for obvious faults. In neuronavigation systems, left-right orientation is different compared to diagnostic imaging systems. This has to be memorized, particularly when objects from other imaging modalities are imported to and fused within the navigation system. Automated image fusion does not always provide excellent results. Navigation can be imprecise owing to technical failure of the reference clamp, moving of the head during craniotomy, and later during brain surgery by CSF loss and resulting brain shift.

Neurophysiologic recordings may be disturbed by electric or mechanical artefacts. Bipolar forceps, suction device, and ultrasonic aspirator should be set to low energy when approaching critical structures such as arachnoid vessels or cranial nerves. Coagulation should be avoided in the vicinity of perforating white matter vessels and vessels potentially supplying the eloquent cortex, close to cranial nerves, or within the ambient cistern. A large number of uncalculated deficits in tumor and epilepsy surgery seem to correlate with accidental small vessel occlusion; an example is shown in Fig. 13.6 [63].

Generally, with few exceptions (e.g., inferior 3.5 cm of motor strip or extremely well-circumscribed lesions), no resection of diffuse tumors in functional important (eloquent) brain areas is recommended because of potential intolerable neurologic side effects [6]. In general, relevant neurologic impairment should be avoided in every case. Alternative treatment options (e.g., radiation, radiosurgery, physical lesioning) or even observation and medical treatment may be considered in cases where surgery is thought to be too risky [64]. Multiple subpial transections in the eloquent cortex bear the chance of timely recovery of function; however, the chance for permanent seizure control is much less compared with resection [65]. There will always be a low rate of unplanned surgical and neurologic complications, but decision making should aim at minimizing these risks. Temporary and calculated deficits may occur after resection in the supplemental motor cortex (SMA): hemiparesis and also aphasia may occur when operating on the dominant hemisphere, but with the relieving initial sign that the reflexes are not affected. These deficits may resume after few weeks, and other subtle deficits may also persist. The closer the resection comes to the precentral gyrus, the higher the risk of persisting deficits. Permanent deficits have been observed in such cases even if the precentral gyrus was obvi-

ously spared, potentially mediated by a lesion of the mesial interhemispheric parts of the SMA [66]. Effects on subcortical fibers may also explain such findings. Preoperative transcranial magnetic stimulation may uncover areas that require intraoperative mapping in order to avoid permanent deficits [67]. As illustrated in Fig. 13.7, regional developmental abnormalities in gyration may be associated with intraoperative disorientation, especially if safety measures like MEP-monitoring do not provide reliable and stable results.

Intraoperative ECoG may suggest extended resections that come close to or even overlap with the eloquent cortex. If in doubt, a decision should be made by the surgeon that favors safety over ambition. In awake craniotomy and extensive cortical mapping, a safety margin of about 1 cm to the highly eloquent cortex is always aimed at. It has to be kept in mind that cortical language representation cannot be taken from the textbook: it is highly variable in extent, and peritumoral plasticity can shift function to a relevant extent. Furthermore, the underlying networks are not yet well understood. Thus deliberate cortical mapping either extraoperatively or more frequently intraoperatively with awake craniotomy is the mainstay for neocortical resections in the dominant hemisphere close to the eloquent cortex [58].

Resections deeper than 3 cm from the cortical surface may be required for complete tumor removal, but they are not necessary for seizure relief since seizure generation is a cortical and not subcortical (white matter) phenomenon.

When the patient is under anesthesia, use of intraoperative neurophysiologic monitoring (MEP monitoring) is warranted when approaching the perirolandic area or deep white matter pyramidal tract. Warning signs (e.g., increase in latency, reduction in amplitude, demanded increase in stimulation intensity) derived from neurophysiologic safety monitoring should be taken seriously because this is the only chance to avoid permanent deficits in a patient under anesthesia. Sometimes the reason for deterioration of potentials is not initially clear but compromise of fibers by retraction or negative effects on white matter vessels becomes obvious [57].

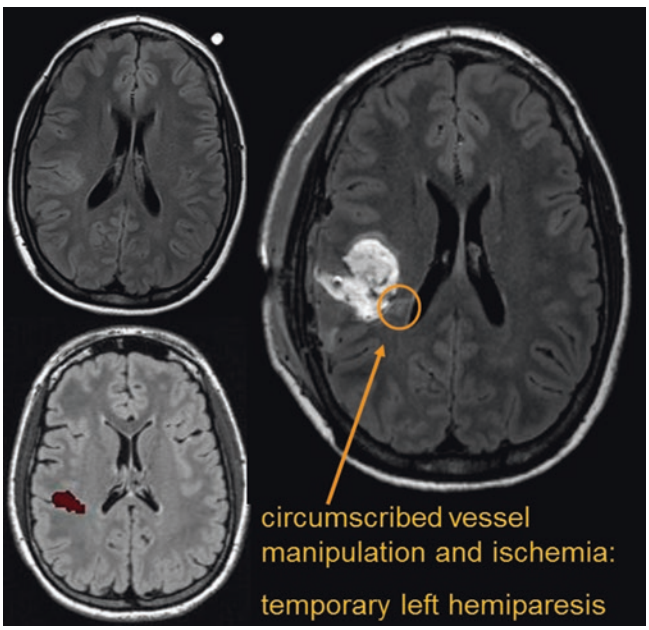

Fig. 13.6 Complication: ischemia after extended lesionectomy. Preoperative axial FLAIR image (*upper left*) and preoperative MRI with segmented object (*dark red area*) indicating an epileptogenic lesion (*lower left*). The postoperative image on the right shows the resection cavity after an extended right lesionectomy as planned but also a circumscribed ischemia (*circle*) medially adjacent to the resection cavity, probably caused by small vessel manipulation or coagulation. The patient suffered a temporary left hemiparesis (leg > arm), but recovered completely after a few weeks

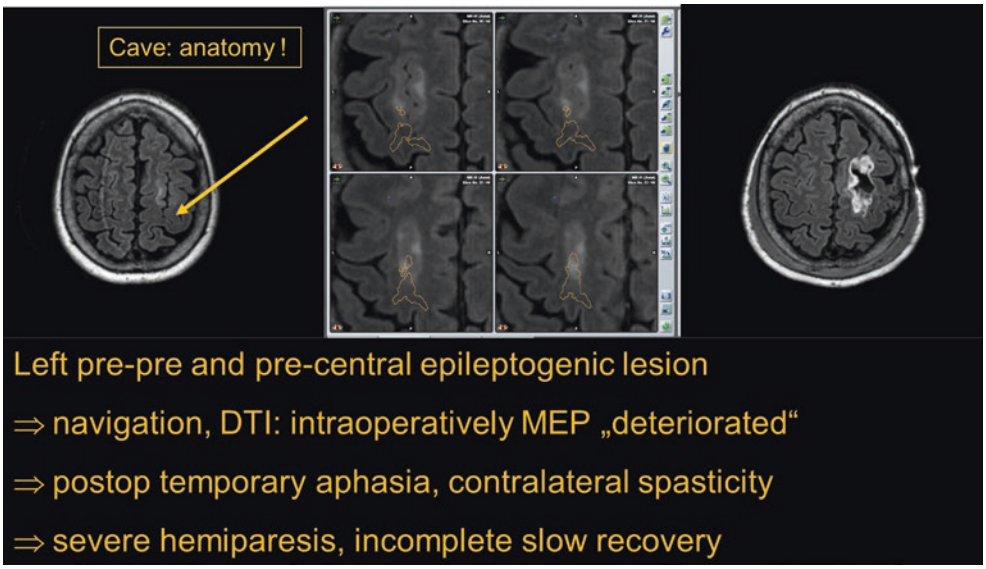

Fig. 13.7 Severe complication: neocortical rolandic resection. Illustration of a severe complication probably owing to anatomic variability: Preoperative MR FLAIR image shows an (epileptogenic) lesion anterior to the precentral gyrus (*upper left*). Note that the cortical and sulcal anatomy of the rolandic area differs when comparing the left and right sides (*arrow*). Images with neuronavigation and integration of the pyramidal tract object indicate some overlap of the lesion and the pyramidal tract starting at a depth of about 2 cm (four images, *upper row middle*). On the right, postoperative MRI for resection control confirms complete lesionectomy and no obvious vascular injury. In the light of intraoperative deterioration of motor-evoked potentials, postoperative aphasia, and severe spastic hemiparesis on the right, structural damage of the pyramidal tract and primary motor cortex, with effects on supplemental motor function, must be assumed as the basis for this unintended severe deficit, which only recovered gradually and slowly

References

1. Clusmann H, Kral T, Schramm J. Present practice and perspective of evaluation and surgery for temporal lobe epilepsy. Zentralbl Neurochir. 2006;67:165–82.
2. Taphoorn MJ. Neurocognitive sequelae in the treatment of low-grade gliomas. Semin Oncol. 2003;30(6 Suppl 19):45–8.
3. DeFelipe J, Lopez-Cruz PL, Benavides-Piccione R, Bielza C, Larranaga P, Anderson S, et al. New insights into the classification and nomenclature of cortical GABAergic interneurons. Nat Rev Neurosci. 2013;14:202–16.
4. Luhmann HJ, Kilb W, Clusmann H. Malformations of cortical development and neocortical focus. Int Rev Neurobiol. 2014;114:35–61.
5. Kral T, Clusmann H, Urbach J, Schramm J, Elger CE, Kurthen M, et al. Preoperative evaluation for epilepsy surgery (Bonn algorithm). Zentralbl Neurochir. 2002;63:106–10.
6. Delev D, Send K, Wagner J, von Lehe M, Ormond DR, Schramm J, et al. Epilepsy surgery of the rolandic and immediate perirolandic cortex: surgical outcome and prognostic factors. Epilepsia. 2014;55:1585–93.
7. Rosenow F, Luders H. Presurgical evaluation of epilepsy. Brain. 2001;124(Pt 9):1683–700.
8. Brogna C, Gil Robles S, Duffau H. Brain tumors and epilepsy. Expert review of neurotherapeutics. Expert Rev Neurother. 2008;8(6):941–55.
9. Englot DJ, Han SJ, Berger MS, Barbaro NM, Chang EF. Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors. Neurosurgery. 2012;70:921–8. discussion 8.
10. Li H, Ren X, Zhang J, Lin S. Mediobasal and lateral temporal gliomas exhibit different growth patterns, surgical outcomes and prognoses. Clin Neurol Neurosurg. 2015;133:90–5.
11. Schramm J, Kral T, Grunwald T, Blumcke I. Surgical treatment for neocortical temporal lobe epilepsy: clinical and surgical aspects and seizure outcome. J Neurosurg. 2001;94:33–42.
12. Binder DK, Von Lehe M, Kral T, Bien CG, Urbach H, Schramm J, et al. Surgical treatment of occipital lobe epilepsy. J Neurosurg. 2008;109:57–69.
13. Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, et al. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. J Neurosurg. 2002;97:1131–41.
14. Kral T, Kuczaty S, Blumcke I, Urbach H, Clusmann H, Wiestler OD, et al. Postsurgical outcome of children and adolescents with medically refractory frontal lobe epilepsies. Childs Nerv Syst. 2001;17:595–601.
15. Urbach H, Binder D, von Lehe M, Podlogar M, Bien CG, Becker A, et al. Correlation of MRI and histopathology in epileptogenic parietal and occipital lobe lesions. Seizure. 2007;16:608–14.
16. Binder DK, Podlogar M, Clusmann H, Bien C, Urbach H, Schramm J, et al. Surgical treatment of parietal lobe epilepsy. J Neurosurg. 2009;110:1170–8.
17. von Lehe M, Wagner J, Wellmer J, Clusmann H, Kral T. Epilepsy surgery of the cingulate gyrus and the frontomesial cortex. Neurosurgery. 2012;70:900–10. discussion 10.
18. Englot DJ, Chang EF, Vecht CJ. Epilepsy and brain tumors. Handb Clin Neurol. 2016;134:267–85.
19. Forsgren L, Bucht G, Eriksson S, Bergmark L. Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study. Epilepsia. 1996;37:224–9.
20. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, et al. Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg. 2008;108:227–35.
21. Englot DJ, Berger MS, Barbaro NM, Chang EF. Factors associated with seizure freedom in the surgical resection of glioneuronal tumors. Epilepsia. 2012;53:51–7.
22. Luyken C, Blumcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J. Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. Cancer. 2004;101:146–55.
23. Chaichana KL, Parker SL, Olivi A, Quinones-Hinojosa A. Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. J Neurosurg. 2009;111:282–92.
24. Kirschstein T, Kohling R. Animal models of tumour-associated epilepsy. J Neurosci Methods. 2016;260:109–17.
25. Giulioni M, Rubboli G, Marucci G, Martinoni M, Volpi L, Michelucci R, et al. Seizure outcome of epilepsy surgery in focal epilepsies associated with temporomesial glioneuronal tumors: lesionectomy compared with tailored resection. J Neurosurg. 2009;111:1275–82.
26. Chandra SP, Bal CS, Jain S, Joshua SP, Gaikwad S, Garg A, et al. Intraoperative coregistration of magnetic resonance imaging, positron emission tomography, and electrocorticographic data for neocortical lesional epilepsies may improve the localization of the epileptogenic focus: a pilot study. World Neurosurg. 2014;82:110–7.
27. Kohling R, Senner V, Paulus W, Speckmann EJ. Epileptiform activity preferentially arises outside tumor invasion zone in glioma xenotransplants. Neurobiol Dis. 2006;22:64–75.
28. Englot DJ, Chang EF. Rates and predictors of seizure freedom in resective epilepsy surgery: an update. Neurosurg Rev. 2014;37:389–404. discussion 405.
29. von Lehe M, Schramm J, Simon M. Chirurgisches Management tumorassoziierter Epilepsie. Z Epileptol. 2012;25:96–103.
30. Schramm J, Clusmann H. The surgery of epilepsy. Neurosurgery. 2008;62(Suppl 2):463–81. discussion 481.
31. Talairach J, Szikla G. Application of stereotactic concepts to the surgery of epilepsy. Acta Neurochir Suppl. 1980;30:35–54.
32. Wyler AR, Ojemann GA, Lettich E, Ward AA Jr. Subdural strip electrodes for localizing epileptogenic foci. J Neurosurg. 1984;60:1195–200.
33. Zentner J, Hufnagel A, Wolf HK, Ostertun B, Behrens E, Campos MG, et al. Surgical treatment of neoplasms associated with medically intractable epilepsy. Neurosurgery. 1997;41:378–86. discussion 86–7.
34. Kuruvilla A, Flink R. Intraoperative electrocorticography in epilepsy surgery: useful or not? Seizure. 2003;12:577–84.
35. Simon M, Schramm J. Surgical management of intracranial gliomas. Recent results in cancer research. Recent Results Cancer Res. 2009;171:105–24.
36. Krakow K, Wieshmann UC, Woermann FG, Symms MR, Mclean MA, Lemieux L, et al. Multimodal MR imaging: functional, diffusion tensor, and chemical shift imaging in a patient with localization-related epilepsy. Epilepsia. 1999;40:1459–62.
37. Stoecklein VM, Faber F, Koch M, Mattmuller R, Schaper A, Rudolph F, et al. Optional real-time display of intraoperative neurophysiological monitoring in the microscopic field of view: avoiding communication failures in the operating room. Acta Neurochir. 2015;157:1843–7.
38. Jakola AS, Skjulsvik AJ, Myrmel KS, Sjavik K, Unsgard G, Torp SH, et al. Surgical resection versus watchful waiting in low-grade gliomas. Ann Oncol. 2017;28:1942–8.
39. Kral T, von Lehe M, Podlogar M, Clusmann H, Sussmann P, Kurthen M, et al. Focal cortical dysplasia: long term seizure outcome after surgical treatment. J Neurol Neurosurg Psychiatry. 2007;78:853–6.
40. Clusmann H, Kral T, Fackeldey E, Blumcke I, Helmstaedter C, von Oertzen J, et al. Lesional mesial temporal lobe epilepsy and limited resections: prognostic factors and outcome. J Neurol Neurosurg Psychiatry. 2004;75:1589–96.
41. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir. 2016;158:51–8.

42. Wagner J, Urbach H, Niehusmann P, von Lehe M, Elger CE, Wellmer J. Focal cortical dysplasia type IIb: completeness of cortical, not subcortical, resection is necessary for seizure freedom. Epilepsia. 2011;52:1418–24.
43. Campos AR, Clusmann H, von Lehe M, Niehusmann P, Becker AJ, Schramm J, et al. Simple and complex dysembryoplastic neuroepithelial tumors (DNT) variants: clinical profile, MRI, and histopathology. Neuroradiology. 2009;51:433–43.
44. Blumcke I, Luyken C, Urbach H, Schramm J, Wiestler OD. An isomorphic subtype of long-term epilepsy-associated astrocytomas associated with benign prognosis. Acta Neuropathol. 2004;107:381–8.
45. Liubinas SV, Cassidy D, Roten A, Kaye AH, O'Brien TJ. Tailored cortical resection following image guided subdural grid implantation for medically refractory epilepsy. J Clin Neurosci. 2009;16:1398–408.
46. Ranjan S, Warren KE. Gliomatosis cerebri: current understanding and controversies. Frontiers Oncol. 2017;7:165.
47. Althausen A, Gleissner U, Hoppe C, Sassen R, Buddewig S, von Lehe M, et al. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. J Neurol Neurosurg Psychiatry. 2013;84:529–36.
48. Mahvash M, Konig R, Urbach H, von Ortzen J, Meyer B, Schramm J, et al. FLAIR−/T1−/T2-co-registration for image-guided diagnostic and resective epilepsy surgery. Neurosurgery. 2006;58(1 Suppl):ONS69–75. discussion ONS69–75.
49. Stadie AT, Kockro RA, Serra L, Fischer G, Schwandt E, Grunert P, et al. Neurosurgical craniotomy localization using a virtual reality planning system versus intraoperative image-guided navigation. Int J Comp Assist Radiol Surgery. 2011;6:565–72.
50. Roessler K, Hofmann A, Sommer B, Grummich P, Coras R, Kasper BS, et al. Resective surgery for medically refractory epilepsy using intraoperative MRI and functional neuronavigation: the Erlangen experience of 415 patients. Neurosurg Focus. 2016;40:E15.
51. Sommer B, Grummich P, Coras R, Kasper BS, Blumcke I, Hamer HM, et al. Integration of functional neuronavigation and intraoperative MRI in surgery for drug-resistant extratemporal epilepsy close to eloquent brain areas. Neurosurg Focus. 2013;34:E4.
52. Prada F, Del Bene M, Mattei L, Lodigiani L, DeBeni S, Kolev V, et al. Preoperative magnetic resonance and intraoperative ultrasound fusion imaging for real-time neuronavigation in brain tumor surgery. Ultraschall Med. 2015;36:174–86.
53. San-Juan D, Alonso-Vanegas MA, Trenado C, Hernandez-Segura N, Espinoza-Lopez DA, Gonzalez-Perez B, et al. Electrocorticographic patterns in epilepsy surgery and long-term outcome. J Clin Neurophysiol. 2017;34:520–6.
54. Hussain SA, Mathern GW, Hung P, Weng J, Sankar R, Wu JY. Intraoperative fast ripples independently predict postsurgical epilepsy outcome: comparison with other electrocorticographic phenomena. Epilepsy Res. 2017;135:79–86.
55. Kral T, Kurthen M, Schramm J, Urbach H, Meyer B. Stimulation mapping via implanted grid electrodes prior to surgery for gliomas in highly eloquent cortex. Neurosurgery. 2007;61(1 Suppl):319–25. discussion 25–6.
56. Arya R, Mangano FT, Horn PS, Holland KD, Rose DF, Glauser TA. Adverse events related to extraoperative invasive EEG monitoring with subdural grid electrodes: a systematic review and meta-analysis. Epilepsia. 2013;54:828–39.
57. Neuloh G, Bien CG, Clusmann H, von Lehe M, Schramm J. Continuous motor monitoring enhances functional preservation and seizure-free outcome in surgery for intractable focal epilepsy. Acta Neurochir. 2010;152:1307–14.
58. Duffau H. Brain mapping in tumors: intraoperative or extraoperative? Epilepsia. 2013;54(Suppl 9):79–83.
59. Szelenyi A, Bello L, Duffau H, Fava E, Feigl GC, Galanda M, et al. Intraoperative electrical stimulation in awake craniotomy: methodological aspects of current practice. Neurosurg Focus. 2010;28:E7.
60. Bello L, Gallucci M, Fava M, Carrabba G, Giussani C, Acerbi F, et al. Intraoperative subcortical language tract mapping guides. Surgical removal of gliomas involving speech areas. Neurosurgery. 2007;60:67–80. discussion 82.
61. Mazerand E, Le Renard M, Hue S, Lemee JM, Klinger E, Menei P. Intraoperative subcortical electrical mapping of the optic tract in awake surgery using a virtual reality headset. World Neurosurg. 2017;97:424–30.
62. Shahar T, Korn A, Barkay G, Biron T, Hadanny A, Gazit T, et al. Elaborate mapping of the posterior visual pathway in awake craniotomy. J Neurosurg. 2018;128:1503–11.
63. Gempt J, Krieg SM, Huttinger S, Buchmann N, Ryang YM, Shiban E, et al. Postoperative ischemic changes after glioma resection identified by diffusion-weighted magnetic resonance imaging and their association with intraoperative motor evoked potentials. J Neurosurg. 2013;119:829–36.
64. Bostrom JP, Delev D, Quesada C, Widman G, Vatter H, Elger CE, et al. Low-dose radiosurgery or hypofractionated stereotactic radiotherapy as treatment option in refractory epilepsy due to epileptogenic lesions in eloquent areas: preliminary report of feasibility and safety. Seizure. 2016;36:57–62.
65. Spencer SS, Schramm J, Wyler A, O'Connor M, Orbach D, Krauss G, et al. Multiple subpial transection for intractable partial epilepsy: an international meta-analysis. Epilepsia. 2002;43:141–5.
66. Ibe Y, Tosaka M, Horiguchi K, Sugawara K, Miyagishima T, Hirato M, et al. Resection extent of the supplementary motor area and postoperative neurological deficits in glioma surgery. Br J Neurosurg. 2016;30:323–9.
67. Moser T, Bulubas L, Sabih J, Conway N, Wildschutz N, Sollmann N, et al. Resection of navigated transcranial magnetic stimulation-positive prerolandic motor areas causes permanent impairment of motor function. Neurosurgery. 2017;81:99–110.

Anterior Temporal Lobectomy and Amygdalo-Hippocampectomy

14

Antonio Gonçalves-Ferreira

The history of surgery for epilepsy is dominated by the treatment of temporal lobe epilepsy (TLE). The studies of Penfield in 1936 [1] on cortical excisions and Penfield and Jaspers in 1954 [2] on the functional anatomy of the temporal lobe are historical landmarks in this field, followed by the development of the temporal lobectomy by Falconer in 1953 [3, 4], the amygdalo-hippocampectomy by Niemeyer in 1958 [5] and, more recently, the microsurgical selective amygdalo-hippocampectomy by Yasargil in 1982 [6–8].

It is widely accepted that 5%–6% of all the pharmacoresistent epilepsies are susceptible to surgical treatment and 70%–75% out of these have limbic mesial or medial TLE frequently with mesial temporal lobe sclerosis; this means that all over the world 20–25 new cases per million habitants per year have TLE with surgical indications [9–11]. That is why the mesial temporal lobe (MTL) is by far the main and most frequent target for the surgical treatment of epilepsy. It is also the best target because its surgical removal or inactivation is the procedure with the highest chance of controlling the refractory mesial TLE. After the MTL resection, epileptogenic conditions like mesial temporal lobe sclerosis (MTLS), hippocampal ganglioglioma, or dysembryoplasic neuroectodermic tumors (DNETs) have long-term epilepsy control rates higher than 80% in most centers (Table 14.1) [12].

To achieve such therapeutic success, the surgical procedure must be safe, complete, and adequate, which means it must be uneventful, comprehend the main MTL structures, and follow the most appropriate approach route. It is worth noting that the hippocampus excision is often restricted to its anterior part on the dominant hemisphere in order to avoid resulting serious verbal memory deficits.

A. Gonçalves-Ferreira
Department of Neurosurgery, Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Faculdade Medicina, Universidade Lisboa, Lisbon, Portugal
e-mail: ajgonfer@medicina.ulisboa.pt

The MTL structures involved in epilepsy [13–17] are the hippocampus proper or *Cornu Ammonis* with the dentate gyrus and fimbria, the parahippocampal gyrus with the entorhinal cortex, and the *amygdala* or amygdaloid nucleus within the uncus (Figs. 14.1 and 14.2). As the amygdala continues medially and upward to the *pallidum* with no clear-cut separation, its removal is usually confined to the ventrolateral part (generally lateral to a straight line drawn between the inferior choroidal point and the M2 segment of the middle cerebral artery). This usually includes the dissection of the uncus, which sometimes falls behind the tentorial notch.

There are several surgical strategies to treat temporal lobe epilepsy. We must distinguish the selective MTL approaches from the enlarged ones; the latter usually involve a temporal lobectomy or at least the removal of the anterior part of the temporal lobe, including the temporal pole or temporal polectomy. In the selective approaches the extent of the hippocampus resection may vary [18, 19], but it usually includes all the MTL structures; the selective cortico-amygdalectomy has been shown to result in less seizure control [20, 21].

The temporal lobectomy is mainly indicated for the neocortical temporal epilepsy and for the mixed origin epilepsy, although in the majority of cases of purely temporal medial epilepsy its practice depends essentially on the operative tradition of each center or even on the preference of the neurosurgeon. For some surgeons it is still regularly performed, whereas for others it is only done when it is suspected that the epileptic zone extends to the temporal neocortex and both the temporal pole and the lateral or the inferior temporal lobe cortex.

Table 14.1 Mesial temporal lobe epilepsy: main pathology and surgical prognosis

	Long-term epilepsy control (%)
Mesial temporal lobe sclerosis	80–95
DNET/ganglioglioma	80–95
Low-grade astrocytoma	70–90
Vascular lesions (cav. angioma)	75–80
Cortical displasia	60–80

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Therefore when an extensive temporal neocortical epileptic focus or lesion is verified, there is a formal indication to perform a temporal lobectomy. We generally use the operative technique of Falconer [3, 4] with good results (Fig. 14.3).

The extension of the temporal lobectomy differs according to the cerebral hemisphere involved: if it is the language-dominant hemisphere, it should be more restricted posteriorly to avoid the Wernicke area that comprehends the posterior part of the superior temporal gyrus (up to 4.5 cm from the temporal pole instead of up to 5.5 cm on the nondominant side). In case of doubt, the functional MRI helps to localize the Wernicke area. In addition, the sodium amytal carotid Wada test may be useful to verify which cortical zone is transitorily inactivated; if necessary, the language may be tested by intraoperative electric stimulation with the patient awake.

The removal or sectioning of the MTL structures is represented in the Fig. 14.4. There are different selective approach routes to the MTL [22–24]. The following should be considered (Fig. 14.5): the superior approach, through the sylvian fissure or along its margins; the anterior one, by the rostral part of the sylvian fissure and the *limen insulae*; the lateral, through the temporal lobe convexity; and the inferior, underneath the temporal lobe. The posterior interhemispheric supratentorial or transtentorial routes provide a more difficult access to the anterior TML structures, which mainly concern the most caudal hippocampal formation [25, 26].

Several anatomic studies made in vitro at the Anatomy Laboratory of the Faculty of Medicine of the University of Lisbon (FMUL) with microdissection of a large number of human brains [22] provided data concerning distances and dimensions of the MTL structures that are useful to consider for the different surgical procedures (Table 14.2). The mean length of the normal human hippocampus is 4 cm, and its maximum width is 1.5 cm at its head and 1 cm in its body; the distance from the temporal horn of the ventricle to the temporal pole is around 3 cm; to the rhinal sulcus, including the entorhinal cortex, the distance is 1.5 cm (*see* Fig. 14.2). The photograph registration of the main operative steps illustrates the most significant features of each approach route, as can be seen in the figures. Furthermore, in vivo observations obtained during surgery of many epileptic patients has led to some relevant conclusions concerning the comparative evaluation of advantages and disadvantages among such approach routes.

The superior approach (access from above) to the MTL includes the subpial anterior trans-T1 (superior temporal gyrus) route of Olivier and the transylvian route of Yasargil [6–8, 21, 27]. Both use a frontotemporal curved (or straight vertical temporal) skin incision and a pterional bone flap (or a well-centered keyhole craniotomy), with the head turned 45 to 60 degrees to the other side. The trans-T1 Olivier route [21, 27] goes through peeling or removing (in variable amounts) the anterior part of T1 along the inferior edge of the sylvian

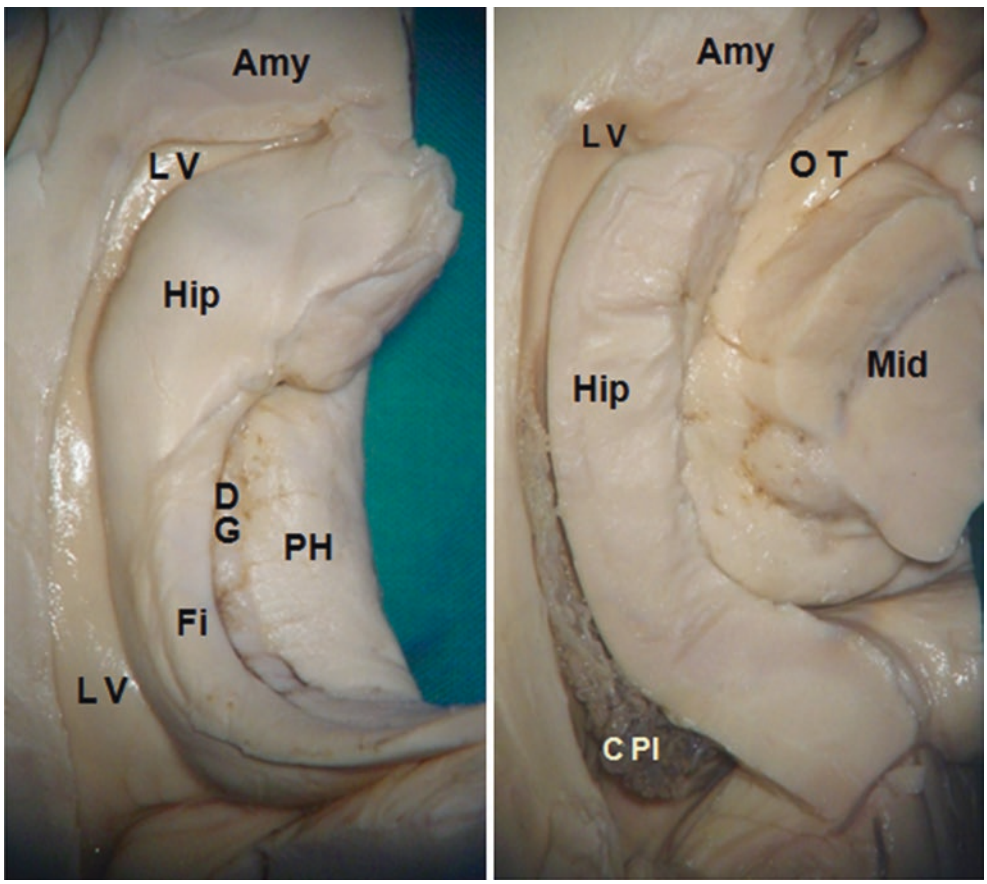


Fig. 14.1 Left hippocampus. Amy – Amygdala; C Pl – Choroidal plexus; DG – Dentate gyrus; Fi – Fimbria; Hip – Hippocampus; LV – Lateral ventricle; Mid – Midbrain; OT – Optic tract; PH – Para-hippocampus

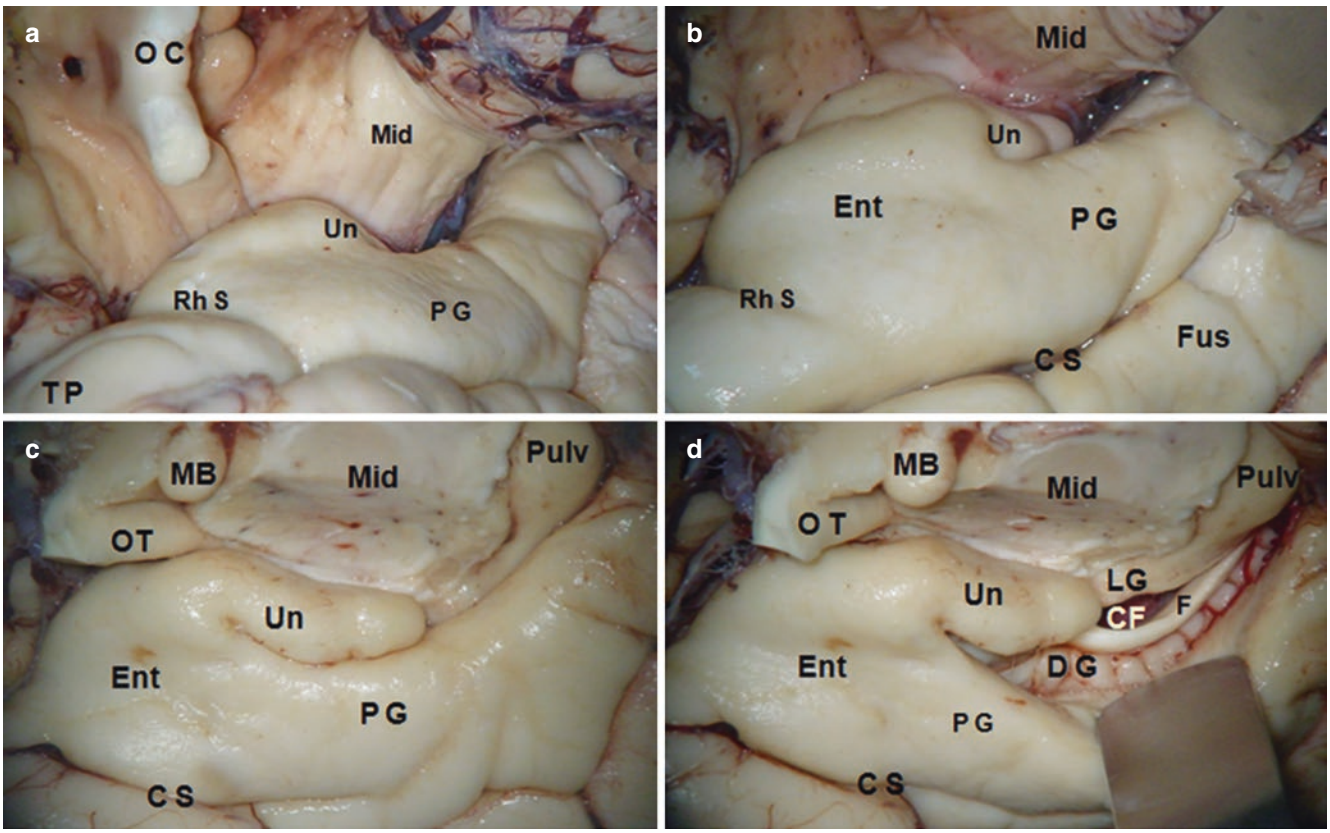


Fig. 14.2 (**a**–**d**), Left medial temporal and neighboring structures: medial view in different angles, from rostral to caudal. CF – Choroidal fissure; CS – Collateral sulcus; DG – Dentate gyrus; Ent – Entorhinal cortex; F – Fimbria; Fus – Fusiform gyrus; LG – Lateral geniculated body; Mid – Midbrain; MD – Mamillary body; OC – Optic chiasm; OT – Optic tract; PG – Para-hippocampal gyrus; Pulv – Pulvinar; Rh S – Rhinal sulcus; TP – Temporal pole; Un – Uncus

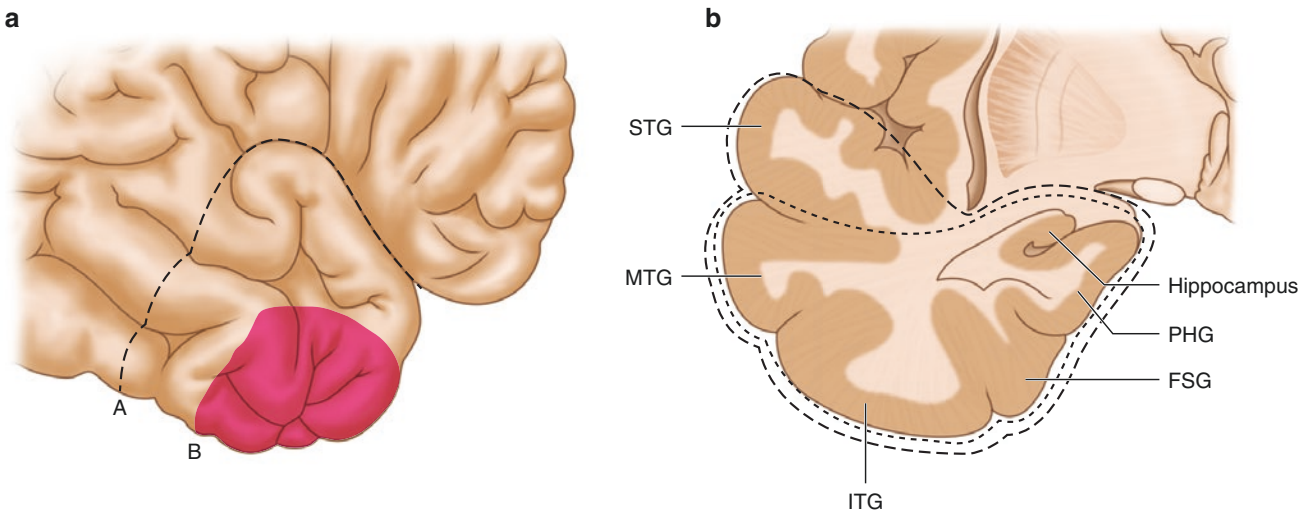


Fig. 14.3 Temporal lobectomy. (**a**), Different extensions (**a**, **b**) delineated on the cerebral convexity. (**b**), Inclusion of MTL structures, with or without the superior temporal gyrus

fissure; it provides an almost direct access to the amygdala and allows a longitudinal exposure of the hippocampus from ahead (it is worth noting that Olivier changed from his initial entry route to a trans-sulcal T1–2 and more recently to a small anterior trans-T2 one [21]). The Yasargil route [6–8] goes through the opening of the middle part of the sylvian fissure and the microdissection between the temporal branches of the middle cerebral artery; it requires the smallest brain tissue (temporal stem) transection to reach the hippocampus (Table 14.2) that is approached more perpendicularly to its main axis. It provides a limited manoeuvering space for the surgical instruments between the sylvian vessels and within the ventricle, which may be difficult for the less experienced neurosurgeon (it may not be easy to move a standard ultrasonic aspirator handpiece through this route). The anterior route used by Schramm [18, 19] is a rostral variant of the previous two, as it goes through the anterior curved part of the sylvian fissure that must be opened and the *limen insulae* that is sectioned laterally. This approach avoids cutting the temporal stem to a large extent but provides a limited angle view to the hippocampal tail.

The lateral approaches comprehend the trans-sulcal T1–2 (or T2–3) routes (probably the most commonly used) and the trans-T2 through the middle temporal gyrus, the widest gyrus of this lobe. This trans-T2 route [5, 21] is the oldest one (Niemeyer) used to reach the hippocampus, still based on an older principle that it was safer to cross the gyrus than to penetrate the "forest" of the sulci vessels; conversely, with the development of microsurgery and other technical refinements, the cerebral sulci became like "highways" that drive the dissection deeper in the attempt to avoid cutting so much brain tissue. These lateral approach routes use a typical curved (or straight vertical) temporal skin incision and a temporal bone flap (or a keyhole flap), with the head in a pure lateral horizontal position, sometimes with a slight posterior tilt. The trans-sulcal approach (Rougier), when performed through the anterior part of the T1–2 sulcus [28] where there is often more space free of important veins, is actually among the shortest and easiest ways to obtain wide access to the lateral ventricle (see distances in Table 14.2).

The inferior, subtemporal approach routes may be performed through the fusiform gyrus [29] or through the collateral sulcus and the parahippocampal gyrus [30]. These subtemporal routes use a temporal curved (or square) skin incision and a low temporal craniotomy, with the head turned laterally and tilted posteriorly toward the surgeon. Even with this head inclination, some degree of temporal lobe retraction from the middle cranial fossa floor is required; this may be hazardous to some major bridging veins draining to the lateral sinus like the Labbé vein.

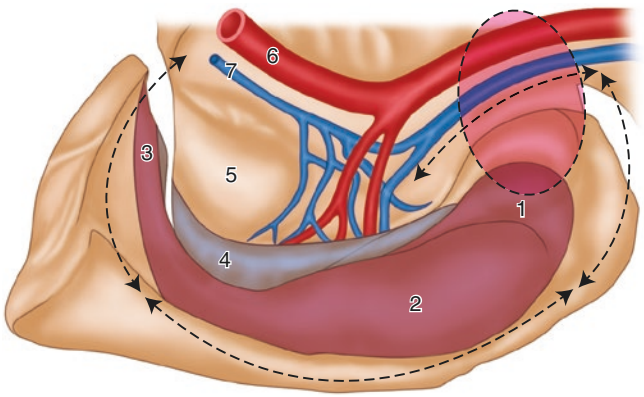


Fig. 14.4 Selective surgery of the hippocampus: in dotted lines with arrows, the peri-hippocampal dissection; in oval, shaded, pink area with dotted limits, the projection of the amygdala. 1 – Head of the hippocampus; 2 – Body of the hippocampus; 3 – Tail of the hippocampus; 4 – Fimbria; 5 – Para-hippocampus; 6 – Posterior cerebral artery; 7 – Basal vein (Rosenthal)

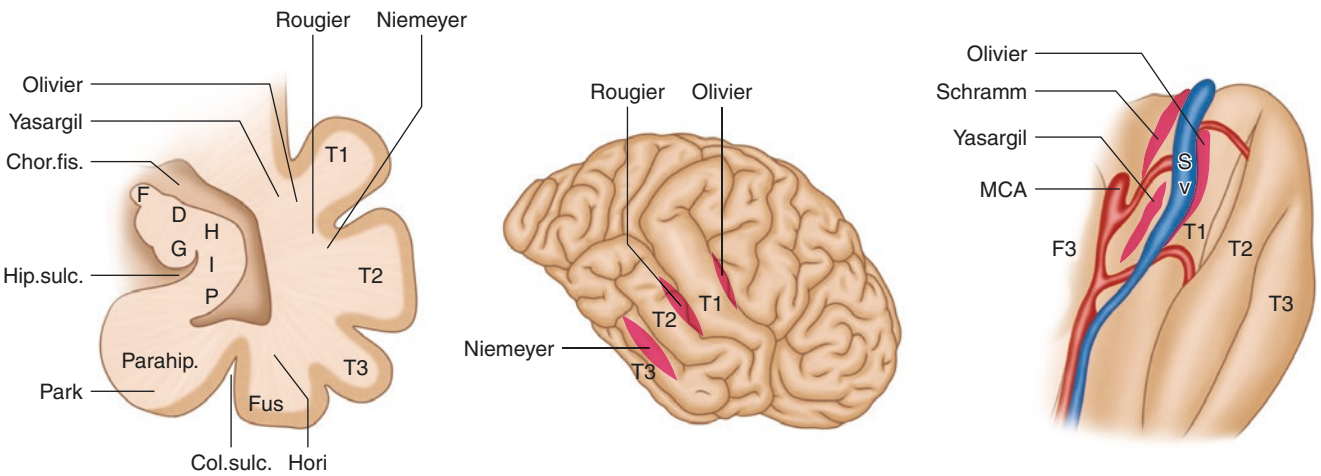
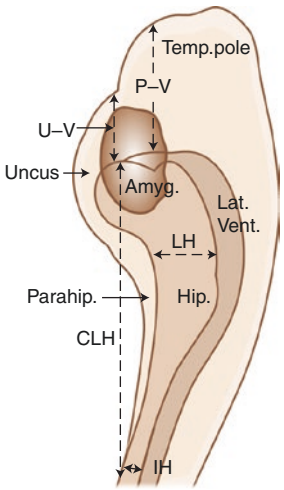


Fig. 14.5 Different approach routes to the medial temporal lobe (for the names of the authors, see text and references). F 3 – Inferior frontal gyrus; T1, 2, 3 – Superior, middle, inferior temporal gyri; Chor Fis – Choroidal fissure; Col Sulc – Collateral sulcus; DG – Dentate gyrus; F – Fimbria; Fus – Fusiform gyrus; HIP – Hippocampus; Hip sulc – Hippocampal sulcus; MCA – Middle cerebral artery; Parahip – Parahippocampal gyrus; SV – Sylvian vein

Table 14.2 Mesial temporal lobe

Measurements (n = 50)	Mean ± SD, mm
Distances	
Sylvian fissure (convexity) to hippocampus	35.3±3.4
Sylvian fissure (depth) to hippocampus	15.5±2.2
1st temporal gyrus to hippocampus	33.1±3.6
Superior temporal sulcus (convexity) to hippocampus	29.5±4.2
2nd temporal gyrus to hippocampus	28.0±4.2
Temporal pole to lateral ventricle	29.0±4.1
Uncus (anterior edge) to lateral ventricle	16.7±4.8
Dimensions of hippocampus	
Length	40.7 ± 4.2
Maximum width (pes hippocampus)	15.4 ± 2.7
Minimum width (tail hippocampus)	10.6±1.7



All these approach routes are much easier to perform with the help of a neuronavigation system (Fig. 14.6). This allows centering of the skin incision and the craniotomy, pointing accurately at the target, and most important a choice of the best route to go through. This can be verified during the operation, provided no excessive brain shift occurs.

The imaging results of the amygdalo-hippocampectomy are well seen on postoperative MRI (Fig. 14.7): in this example, obtained in a left MTL of a right-handed patient, we can see the void resulting from the removal of the anterior half of the hippocampus and the ventral-lateral amygdala.

When evaluating the results and the morbidity of these operations and their mechanisms [12, 31–36], both common and specific features must be looked at. Whichever approach route is used, the MTL resection may result in some common deficits and disorders, which are essentially dependent on the removal of the hippocampus and the amygdala; these mainly concern memory deficits and depression. The memory deficits [21, 34, 35, 37] are dependent on the side of the hippocampus operated on. The verbal memory is mostly affected when the dominant hemisphere for language is involved, usually the left one. That is why by precaution the hippocampal resection on the dominant hemisphere is often restricted to its anterior half to two thirds; this is also why in some cases a selective (cortico)amygdalectomy is performed without a hippocampectomy to avoid additional memory deficits [20, 21]. Indeed, the Wada test for memory with perfusion of the posterior cerebral artery is seldom done to check the effect of the selective inactivation of the hippocampus, and there is not yet an adequate paradigm to selectively label the hippocampus in functional MRI [38]. The depression after the amygdalo-hippocampectomy is a distinct problem because it is mainly a late consequence, and it is not clear whether the left cerebral hemisphere plays a major decisive role in this occurrence [39, 40].

A specific morbidity related to the variable approach routes to the MTL is the optic field defect caused by the sectioning of the temporal stem that includes a segment of the Meyer loop of the optic radiations [41–44]. This is most likely to occur in the superior trans-sylvian and lateral routes because their approach angles are more transverse and require a wider opening of the lateral ventricle; the more anterior the approach to the ventricle, the less the optic radiation is severed. Therefore the rostral and the inferior transparahippocampal routes tend to spare these radiations the most. Nevertheless, the resultant optic field defect is often not clinically significant, even after a wide ventricle opening if it is very anterior.

Whatever approach route is chosen, another most sensible part of these operations is related to the subarachnoidal dissection to complete the MTL removal on the medial side. Such dissection is performed through the choroidal fissure between the plexus and the hippocampus to avoid damaging the brain tissue above. This subarachnoidal space contains many important structures (Fig. 14.8) [16, 21, 45–49]: the basal vein of Rosenthal, the posterior cerebral and the anterior choroidal arteries, more rostrally the third cranial nerve, superiorly the optic tract, and deeper the midbrain. All these structures must be absolutely spared!

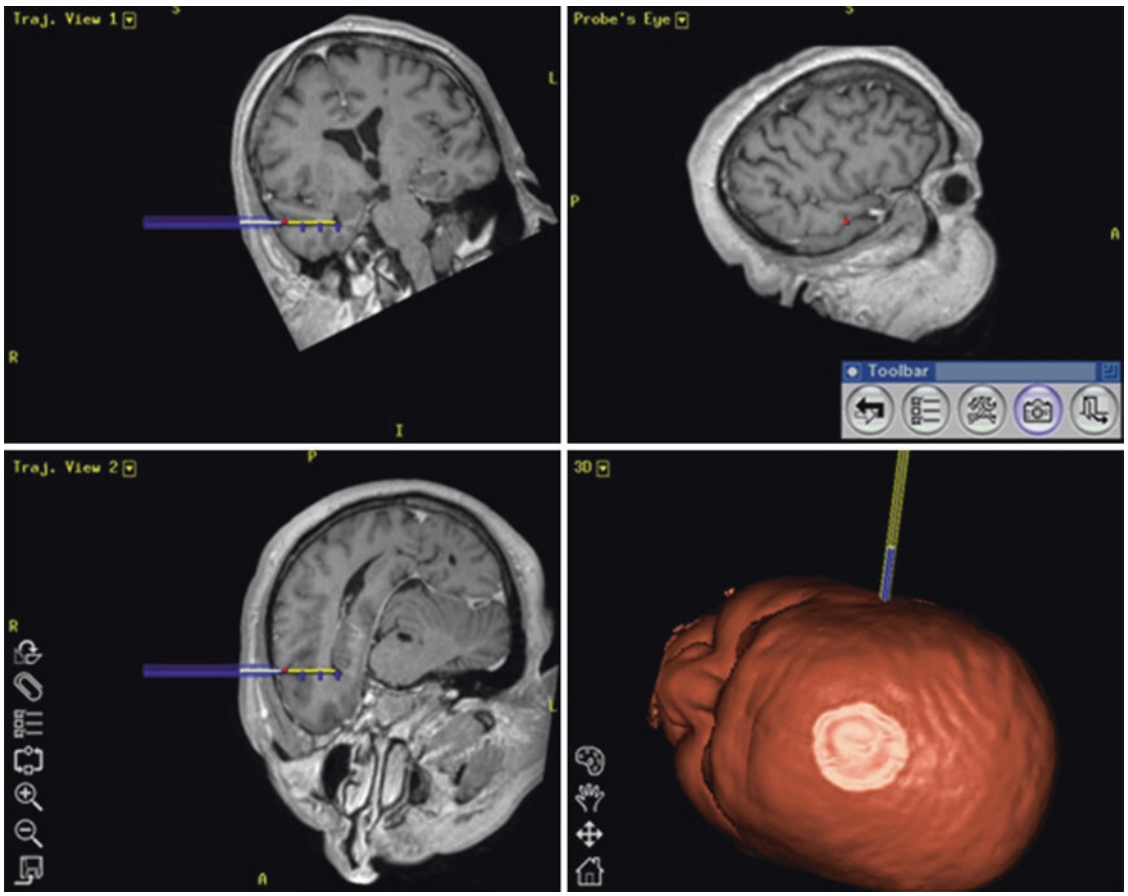


Fig. 14.6 Illustration of neuronavigation guidance through the lateral approach to the MTL (trans-sulcal T1-T2)

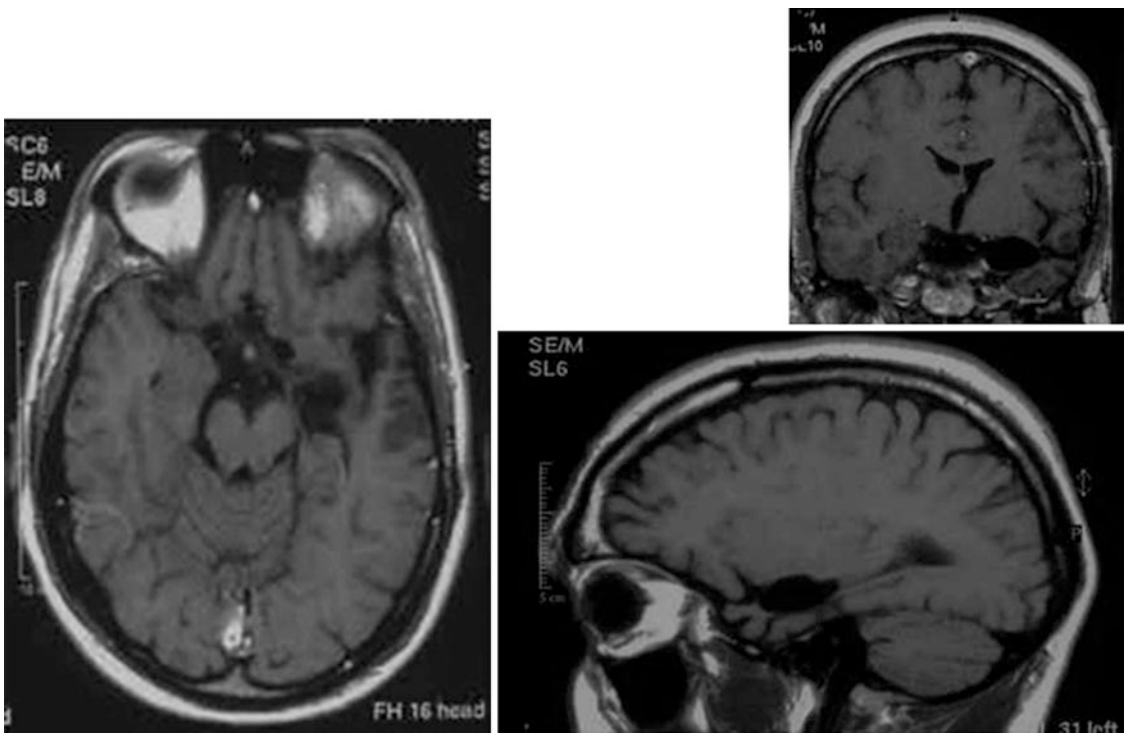


Fig. 14.7 Postoperative MRI after selective amygdalo-hippocampectomy

In an attempt to avoid damaging such intra-arachnoidal structures in those cases where there is no expansive lesion, we have lately developed an alternative technique to the amygdalo-hippocampectomy, the amygdalo-hippocampotomy (Figs. 14.8 and 14.9). With this technique, instead of removing the hippocampus it is disconnected while still removing the lateral amygdala. The principle is the same as that applied to treat other types of epilepsy by disconnecting the epileptogenic brain with the same clinical results as resecting it; well-known examples are the hemispherotomies of Delalande [50], Villemure [51], or Schramm [52], performed instead of the classic hemispherectomy; the temporal lobotomy of Benabid et al. [53] instead of the temporal lobectomy; and the focal disconnections of Ng [54] and Mohamed [55]. The amygdalo-hippocampotomy is a safer operation because the choroidal fissure and the structures inside it are not dissected; the hippocampus is completely separated (from inside the ventricle until the pia mater) around its body and head, and its tail is cut as far as desirable. This way the surgery becomes both easier and somewhat shorter in time. The good results obtained after the first 20 patients operated on with more than 2 years of follow-up are clinically equivalent to the last 100 cases previously operated on with complete MTL removal [56].

A final note to be kept in mind by all neurosurgeons involved in this type of surgery: The key to the success of the surgical treatment of the TLE is to tailor the best operative

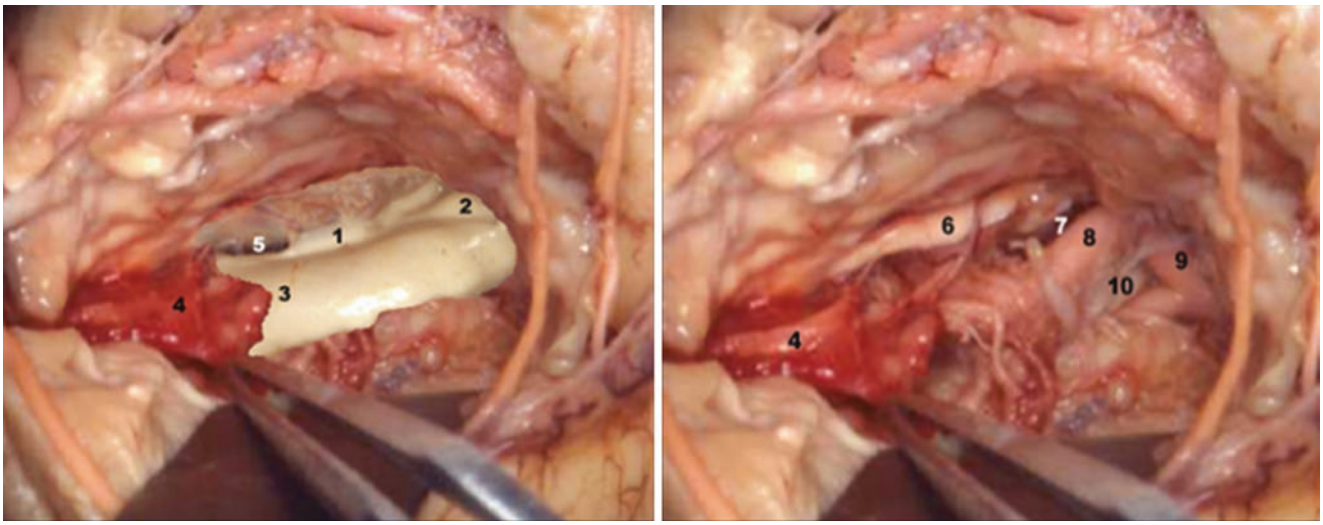


Fig. 14.8 Transventricular features of the mesial temporal region microdissection. *Left*: with the hippocampus in situ; *Right*: after the hippocampus removal. 1 – Fimbria; 2 – Hippocampus head; 3 – Hippocampus body; 4 – Choroidal plexus; 5 – Choroidal fissure; 6 – Optic tract; 7 – Basal vein; 8 – Posterior cerebral artery; 9 – Basilar artery; 10 –Oculomotor nerve

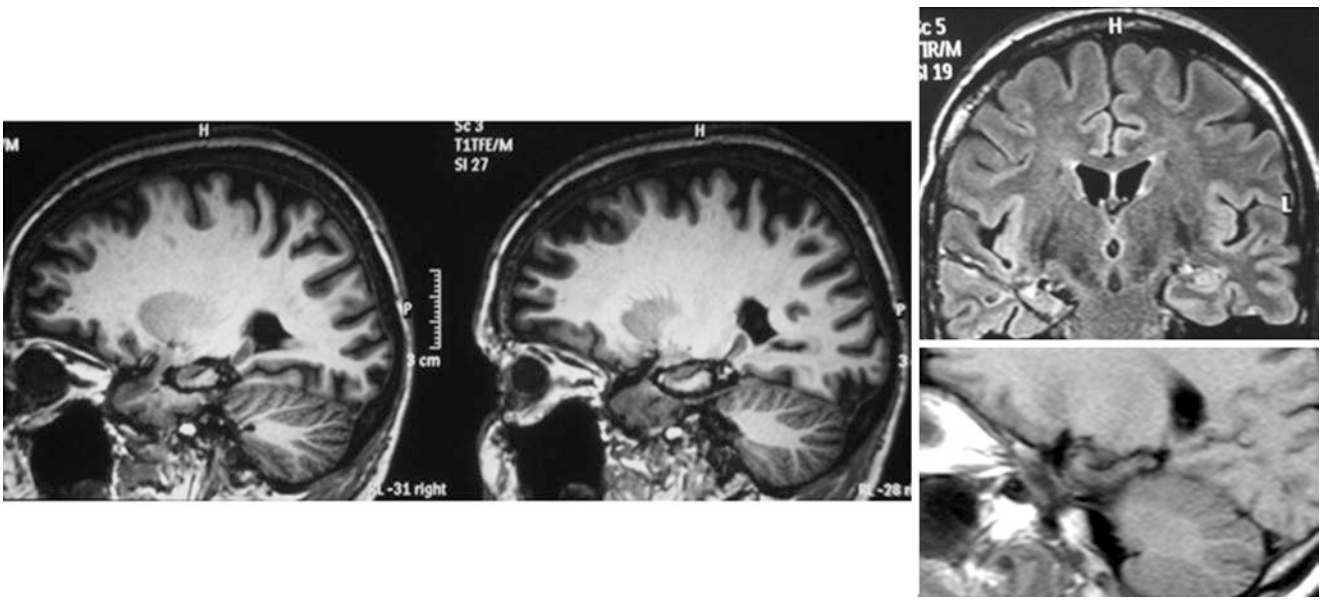


Fig. 14.9 Postoperative MRI after selective amygdalo-hippocampotomy

strategy to each patient; to achieve this, one must be familiar with a variety of surgical approach routes and their relative advantages. It is crucial that every surgeon become acquainted and skilled with one technique that is efficient, secure, and reliable.

References

1. Penfield W. Epilepsy and surgical therapy. Arch Neurol Psychiatr. 1936;36:449–84.
2. Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. London: J & A Churchill Ltd; 1954.
3. Falconer MA, Pond DA, Meyer A, Woolf AL. Temporal lobe epilepsy with personality and behaviour disorders caused by an unusual calcifying lesion. J Neurol Neurosurg Psychiatry. 1953;16:234–44.
4. Falconer MA, Hill D, Meyer A, Mitchell W, Pond DA. Treatment of temporal lobe epilepsy by temporal lobectomy: survey of findings and results. Lancet. 1955;1:827–35.
5. Niemeyer P. The transventricular amygdalohippocampectomy in temporal lobe epilepsy. In: Baldwin M, Bailey P, editors. Temporal lobe epilepsy. Springfield, IL: Charles C Thomas; 1958. p. 461–82.
6. Wieser HG, Yasargil MG. Selective amygdalo-hippocampectomy as a surgical treatment of medio-basal limbic epilepsy. Surg Neurol. 1982;17:445–7.
7. Yasargil MG, Teddy PJ, Roth P. Selective amygdalo-hippocampectomy: operative anatomy and surgical technique. Adv Tech Stand Neurosurg. 1985;12:93–123.
8. Yasargil MG, Wieser HG, Valavanis A, von Amon K, Roth P. Surgery and results of selective amygdalo-hippocampectomy in one hundred patients with nonlesional limbic epilepsy. Neurosurg Clin North Am. 1993;4:243–61.
9. Luders HO. Mesial temporal sclerosis. In: Luders HO, editor. Epilepsy surgery. London: Informa UK Ld; 2008. p. 249–51.
10. Wiebe S, Blume W, Girvin JP, Eliasziw M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345:311–8.
11. Wieser HG. ILAE commission report: mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia. 2004;45:695–714.
12. Jehi L. Mesial temporal lobectomy: post-surgical seizure frequency. In: Luders HO, editor. Epilepsy surgery. London: Informa UK Ld; 2008. p. 1223–35.
13. Duvernoy HM. The human hippocampus. 3rd ed. Berlin: Springer; 2005.
14. Lopes da Silva F, Witter MP, Boeijinga PH, AHM L. Anatomic organization and physiology of the limbic cortex. Physiol Rev. 1990;70:453–511.
15. Sindou M, Guenot M. Surgical anatomy of the temporal lobe for epilepsy surgery. Adv Tech Stand Neurosurg. 2003;28:315–43.
16. Ulm AJ III, Tanriover N, Rothon AL, Roper S. In: Starr PA, Barbaro NM, Larson PS, editors. Surgical anatomy of the temporal lobe. New York: Thieme; 2009. p. 16–28.
17. Bernasconi N, Bernasconi A, Caramanos Z, Antel SB, Andermann F, Arnold DL. Mesial temporal damage in temporal lobe epilepsy: a volumetric study of the hippocampus, amygdala and parahippocampal region. Brain. 2003;126:462–9.
18. Schramm J. Temporal lobe epilepsy surgery and the quest for optimal extent of resection: a review. Epilepsia. 2008;49:1296–307.
19. Schramm J, Behrens E, Entzian W. Hemispherical deafferentation: an alternative to functional hemispherectomy. Neurosurgery. 1995;36:509–16.
20. Kim HI, Olivier A, Jones-Gotman M, Primrose D, Andemann F. Corticoamygdalectomy in memory-impaired patients. Stereotact Funct Neurosurg. 1992;58:162–7.
21. Olivier A. Surgery of temporal lobe epilepsy: cortico-amygdalohippocampectomy, transcortical selective amygdalohippocampectomy. In: Olivier A, Bolling WW, Tanriverdi T, editors. Techniques in epilepsy surgery: the MNI approach. New York: Cambridge University Press; 2012. p. 97–131. (Ch. 9–10).
22. Gonçalves-Ferreira A, Miguéns J, Farias JP, Levy-Melancia J, Andrade M. Selective amygdalo-hippocampectomy: which route is the best? Stereotact Funct Neurosurg. 1994;63:182–91.
23. Campero A, Tróccoli G, Martins C, Fernandez-Miranda JC, Yasuda A, Rhoton AL Jr. Microsurgical approaches to the medial temporal region: an anatomical study. Neurosurgery. 2006;59:279–308.
24. Ojeman JG, Silbergeld DL. Approaches to epilepsy surgery. Neurosurg Clin North Am. 1993;4:183–91.
25. Oliveira JG, Parragua RG, Chaddad-Neto F, Ribas GC, Oliveira GPL. Supracerebellar transtentorial approach: resection of the tentorium instead of an opening – to provide broad exposure of the mediobasal temporal lobe: anatomical aspects and surgical applications. J Neurosurg. 2012;116:764–72.
26. Ture U, Harput MV, Kaya AH, Baimedi P, Firat Z, Ture H, et al. The paramedian supracerebellar-transtentorial approach to the entire length of the mediobasal temporal region: an anatomical and clinical study. J Neurosurg. 2012;20:1–19.
27. Olivier A. Commentary on cortical resections. In: Engel Jr J, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1987. p. 405–16.
28. Rougier A, Saint-Hilaire J, Loiseau P, Bouvier G, Baulac M, Bouthillier A, et al. Evaluation and surgical treatment of the epilepsies. Neurochirurgie. 1992;38(suppl.1):3–112.
29. Hori T, Tabuchi S, Kurisaki M, Kondo S, Takenobu A, Watanabe T. Subtemporal amygdalohippocampectomy for treating medically intractable temporal lobe epilepsy. Neurosurgery. 1993;33:50–6.
30. Park TS, Bourgeois BF, Silbergeld DL, Dodson WE. Subtemporal transparahippocampal amygdalohippocampectomy for surgical treatment of mesial temporal lobe epilepsy. J Neurosurg. 1996;85:1172–6.
31. Behrens E, Schramm J, Zentner J, Konig R. Surgical and neurological complications in a series of 708 epilepsy surgery procedures. Neurosurgery. 1997;41:1–10.
32. Cohen-Gadol AA, Wilhelmi BG, Collignon F, White JB, Britton JW, Cambier DM, et al. Long-term outcome of epilepsy surgery among 399 patients with nonlesional seizure foci including mesial temporal sclerosis. J Neurosurg. 2006;104:513–24.
33. Nayel MH, Awad IA, Luders HL. Extent of mesiobasal resection determines output after temporal lobectomy for intractable partial seizures. Neurosurgery. 1991;29:55–61.
34. Pimentel J, Bentes C, Campos A, Gonçalves-Ferreira A. Long-term and late seizure outcome after surgery for temporal lobe epilepsy. Epileptic Disord. 2010;12:54–8.
35. Rydenhag B, Silander HC. Complications of epileptic surgery after 654 procedures in Sweden, September 1990-1995: a multicentric study based on the Swedish National Epilepsy Surgery Register. Neurosurgery. 2001;49:51–6.
36. Sasaki-Adams D, Hadar EJ. Temporal lobe epilepsy surgery: surgical complications. In: Luders HO, editor. Epilepsy surgery. London: Informa UK Ld; 2008. p. 1288–99.
37. Hermann BP, Seidenberg M, Dohan FC, Wyler AR, Haltiner A, Bobholz J, et al. Reports by patients and their families of memory change after left anterior temporal lobectomy: relationship to degree of hippocampal sclerosis. Neurosurgery. 1995;36:39–45.
38. Ojeman JG. Will fMRI replace the Wada test? In: Miller JW, Silbergeld DL, editors. Epilepsy surgery: principles and controversies. New York: Taylor & Francis; 2006. p. 336–41.
39. Kanner AM, Balabanov AJ. Psychiatric outcome of epilepsy surgery. In: Luders HO, editor. Epilepsy surgery. London: Informa UK Ld; 2008. p. 1254–62.

40. Naylor AS, Rogvi-Hansen B, Kessing L, Krause-Larsen C. Psychiatric morbidity after surgery for epilepsy: short term follow-up of patients undergoing amygdalohippocampectomy. J Neurol Neurosurg Psychiatry. 1994;57:1375–81.
41. Choi C, Rubino PA, Fernandez-Miranda JC, Abe H, Rhoton AL Jr. Meyer's loop and the optic radiations in the transsylvian approach to the mediobasal temporal lobe. Neurosurgery. 2006;59:228–36.
42. Peuskens D, Van Loon J, Van Calenbergh F, Van den Bergh R, Goffin J, Plets C. Anatomy of the anterior temporal lobe and the frontotemporal region demonstrated by fiber dissection. Neurosurgery. 2004;55:1174–84.
43. Rubino PA, Rhoton AL Jr, Tong X, Oliveira E. Three-dimensional relationships of the optic radiations. Neurosurgery. 2005;57(suppl 4):219–27.
44. Sincoff EH, Tan Y, Abdulrauf SI. White matter fiber dissection of the optic radiations of the temporal lobe and implications for surgical approaches of the temporal horn. J Neurosurg. 2004;101:739–46.
45. Bolling WW. Selective amygdalohippocampectomy. In: Baltuch GH, Villemure J-G, editors. Operative techniques in epilepsy surgery. New York: Thieme Medical Publishers Inc.; 2009. p. 41–50.
46. Erdem A, Yasargil MG, Roth P. Microsurgical anatomy of the hippocampal arteries. J Neurosurg. 1993;79:256–65.
47. Renella RR. Microsurgery of the temporo-medial region. Vienna: Springer; 1998.
48. Roper SN, Rhoton AL Jr. Surgical anatomy of the temporal lobe. Neurosurg Clin North Am. 1993;4:223–31.
49. Wen HT, Rhoton AL Jr, Oliveira E, Cardoso AC, Tedeschi H, Baccanelli M, et al. Microsurgical anatomy of the temporal lobe, part I: mesial temporal lobe and its vascular relationships as applied to amygdalohippocampectomy. Neurosurgery. 1999;45:549–92.
50. Delalande O, Pinard JM, Basdevent C, Gauthe M, Plouin P, Dulac O. Hemispherotomy Epilepsy. 1992;33(Suppl 3):99–100.
51. Villemure JG, Mascott CR. Peri-insular hemispherotomy. Neurosurgery. 1995;37:975–81.
52. Schramm J, Lehmann TN, Zentner J, Mueller CA, Scorzin J, Fimmers R, et al. Randomized controlled trial of 2.5 cm versus 3.5 cm mesial temporal resection in temporal lobe epilepsy – part 1: intent-to-treat analysis. Acta Neurochir. 2011;153:209–19.
53. Chabardès S, Minotti L, Hamelin S, Hoffman D, Seigneuret E, Carron R, et al. Temporal disconnection as an alternative treatment for intractable temporal lobe epilepsy. Neurochirurgie. 2008;54:297–302.
54. Ng WH, Valiante T. Lateral temporal lobectomy with hippocampal disconnection as an alternative surgical technique for temporal lobe epilepsy. J Clin Neurosci. 2010;17:634–5.
55. Mohamed AR, Freeman JL, Maixner W, Bailey CA, Wrennal JA, Harvey AS. Temporoparietooccipital disconnection in children with intractable epilepsy. J Neurosurg Pediatr. 2011;7:660–70.
56. Gonçalves-Ferreira A, Rainha Campos A, Herculano-Carvalho M, Pimentel J, Bentes C, Peralta AR, et al. The epilepsy surgery group. Amygdalohippocampotomy, surgical technique and clinical results. J Neurosurg. 2013;118:1107–13.

Selective Amygdalohippocampectomy

15

Dirk Van Roost

Selective amygdalohippocampectomy (sAHE) is an alternative to standard anterior temporal lobectomy as a surgical treatment for medically intractable mesial temporal lobe epilepsy. Variations in the approach have been designed to enhance selectivity, that is, to limit damage to the lateral parts of the temporal lobe. Technically, sAHE is more demanding than anterior temporal lobectomy. The outcome in terms of seizure control is similar for both, but sAHE is claimed to achieve superior cognitive results.

15.1 History

In November 1956 Paulo Niemeyer Soares, a neurosurgeon based in Rio de Janeiro, Brazil, wrote a letter to the eminent epileptologist Henri Gastaut in Marseille, France, and reported that he had successfully operated on seven patients who had been suffering from "psychomotor epilepsy" using a transtemporal -transventricular approach by removing the amygdala, the Ammon horn, and the hippocampal gyrus but no other part of the temporal lobe.

In an enthusiastic reply, Gastaut urged Niemeyer to present his findings at the upcoming meetings in Washington and in Brussels (First International Congress of Neurological Sciences, Brussels, 1957) [1–4]. This was the birth of sAHE. Psychomotor seizures are dyscognitive seizures with automatisms. At present they are classified in a more generic way as "focal seizures with impaired awareness and automatisms" specified by the probable seizure onset zone (i.e. the mesial temporal lobe) [5]. Temporal lobectomy (including sAHE) had been the neurosurgical treatment for the control of psychomotor epilepsy since the 1940s and had arisen from electroencephalographic evidence pointing to the temporal lobe [6, 7]. Already in the late 1920s, Spielmeyer had associated especially vulnerable parts of the hippocampus (the CA1 and CA4 sectors) with psychomotor seizures [8, 9]. Correspondingly, Penfield and Baldwin stressed the removal of the "incisural sclerosis adjacent to the midbrain" as an essential part of temporal lobectomy in an early description of the surgical technique [10]. The interpretation at that time was that the local vascular disposition and the location at the tentorial edge caused hippocampal ischemia. Today the hippocampal alterations are considered to be of excitotoxic origin and to be accompanied by a reorganization of the white matter tracts [11, 12]. The ability of sAHE to control the characteristic temporal lobe seizures suggested that the onset of these seizures is limited to only a small part of the temporal lobe, namely, its mesial or limbic areas.

D. Van Roost
Department of Neurosurgery, Ghent University Hospital,
Ghent, Belgium
e-mail: dirk.vanroost@ugent.be

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15.2 Surgical Techniques

Niemeyer's approach to the hippocampus was a transcortical-transventricular route through the middle temporal gyrus. Subsequent variations were mainly related to the entrance point at the brain surface, while they shared the deeper transventricular part. Yaşargil et al. described an approach through the Sylvian fissure and the limen insulae, Olivier an approach through the anterior tip of the first temporal gyrus, and Rougier et al. one through the first temporal sulcus [13–18]. While the pathway through the brain parenchyma is shortened by a trans-sylvian or trans-sulcal approach, collateral damage can still be produced by the dissection of vessels, a possible release of the pia mater from the cortex, and a variable amount of interruption of white matter tracts within the temporal stem or the temporal lobe, such as Meyer's loop of the optic radiation (*see* Sect. 15.3). Therefore, more selective techniques were conceived, such as the zygomatic, the subtemporal, the trans-sylvian trans-cisternal, and the paramedian supracerebellar transtentorial approaches [19–23]. To avoid excessive retraction of the temporal lobe, Shimizu et al. temporarily took away the zygomatic arch and accessed the mesial temporal lobe through the anterior part of the inferior temporal gyrus [19]. Hori et al. place themselves at the caudal side of the patient's head and direct the microscope upward, parallel to the inclination of the tentorium [20]. At the base of the temporal lobe, they resect or incise the fusiform gyrus in order to gain sight over the hippocampus and amygdala. Park et al. rely on hyperventilation, intravenously administered mannitol, and lumbar cerebrospinal (CSF) drainage to render the brain slack and to reach the hippocampus through the parahippocampal gyrus [21]. CSF bridging veins and especially the Labbé vein remain at risk during a subtemporal approach (Fig. 15.1).

Vajkoczi et al. [22] opened the sphenoidal compartment of the Sylvian fissure, then dissected and exposed the oculomotor nerve to reach the mesial temporal lobe from its cisternal side. This technique may result in a temporary oculomotor nerve palsy, as observed in 9% of their cases [22]. Following earlier suggestions by Yonekawa, Ziyal, de Oliveira, and Yaşargil for the resection of lesions [25–27], Türe et al. described a paramedian supracerebellar transtentorial route to the mesial temporal lobe and used it in 15 patients, six of whom had refractory mesial temporal lobe epilepsy without surgical morbidity or mortality [23]. The same group later specified that the anterior portion of the mesial temporal lobe and the inferior portion of the parahippocampal gyrus may remain hidden in front of the petrous apex in brachycephalic patients, that is, those with high tentorial and occipital angles; the approach is more feasible in dolichocephalic patients [28].

Minimal invasive stereotactic methods with the intention of even more selective treatment of the mesial temporal lobe structures have a long-standing history and include radiofrequency lesioning as well as gamma knife surgery and MRI-

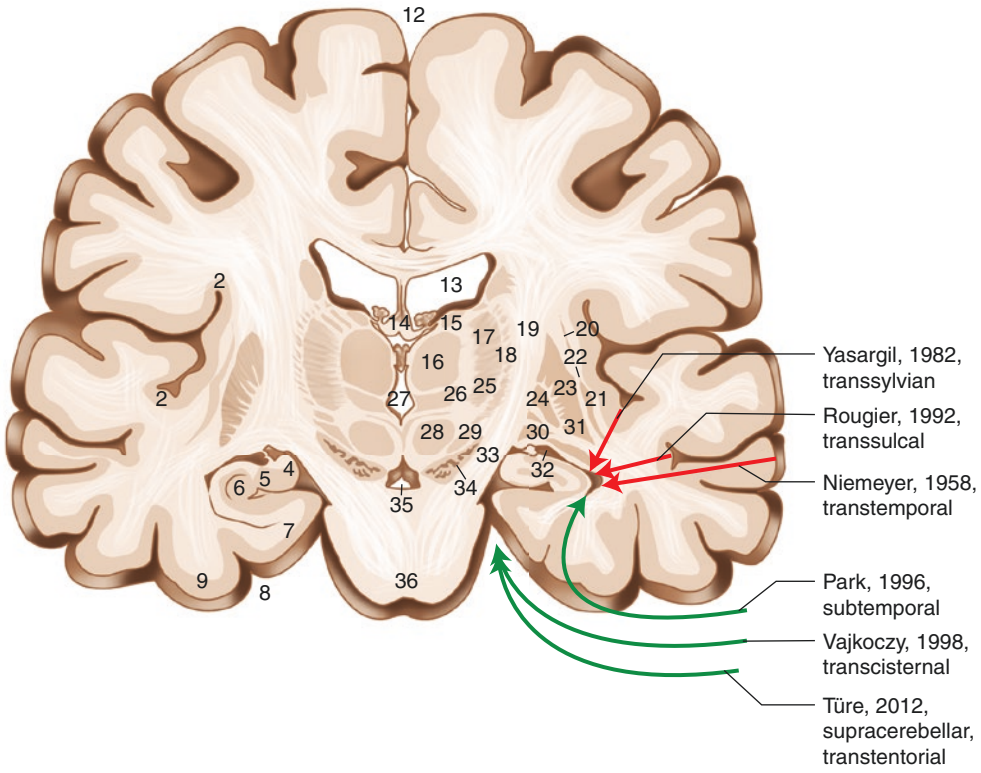

Fig. 15.1 Various approaches for selective amygdalohippocampectomy on coronal cross-section of the brain. (*Modified from* Nieuwenhuys et al. [24])

guided laser ablation [29–34]. Régis et al. claim that gamma knife treatment is dose-optimizable in a way that it modulates rather than destroys the hippocampus and thus avoids memory decline [35]. The drawback of gamma knife treatment is a delay of the seizure-reducing effect of 1 year or up to 1.5 years.

In order to overcome memory decline after resection of an epileptic hippocampus with remaining function, Shimizu et al. applied the principle of multiple subpial transection (MST) to the hippocampus [36]. They accessed the hippocampus via a 2-cm corticotomy on the anterior part of the superotemporal gyrus and aspirated gray matter along the Sylvian fissure to reach the temporal stem. They then traversed the temporal stem to the temporal ventricle horn. Electrocorticography was recorded over the hippocampus and amygdala. Depending on whether the latter showed epileptic discharges or not, it was either resected or only thinned to gain a sufficient view over the hippocampal head. The hippocampus was transected multiple times transversely to its longitudinal axis and with 5-mm intervals using microscissors, a flat ring knife (2 mm), a blunt ring dissector (4-mm in diameter), and an oval transector (4 × 2 mm). The extent of transections was determined and verified by the results of electrocorticography. Twenty-one patients underwent this procedure, 12 left-sided and nine right-sided. Seizure freedom at 1 year follow-up was obtained in 82% of 17 patients. Of the eight patients who were subjected to a neuropsychological assessment before and after surgery, verbal memory was completely preserved in seven cases and transiently worsened but recovered in one. Uda et al. [37] adopted the technique of hippocampal transection using a trans-sylvian approach. They also transected the parahippocampal gyrus and emphasized the need to preserve the fimbria, which is the efferent pathway of the hippocampus. They retrospectively analyzed 37 patients who underwent this procedure. Seizure freedom was achieved in 68%. Patients whose left hippocampus was treated showed no significant change of verbal memory, nonverbal memory, and delayed recall, whereas patients after right hippocampal transection showed a significantly increased verbal memory.

The transgyral, trans-sulcal, and trans-sylvian approaches for sAHE remain, however, popular [15, 38, 39]. The former two can definitely benefit from neuronavigation guidance to reduce their impact on the lateral parts of the temporal lobe and craniotomy size [17]. The target of the transparenchymal dissection is the uncal recess of the temporal horn of the lateral ventricle (Fig. 15.2).

Here the bright alveus of the hippocampus and the anterior choroidal point and bulging of the amygdala are identified. At the level of the anterior choroidal point (and the incisura hippocampi), I transversally divide the head from the body of the hippocampus. At the lateral edge of the alveus hippocampi and using ultrasonic aspiration, the white matter is split from the collateral eminence toward the collateral sulcus, thus comprising the parahippocampal gyrus (T5) within the resection. Splitting is continued along the collateral sulcus in a rostral direction up to the point where the collateral sulcus meets the rhinal sulcus. Both the collateral and the rhinal sulci are part of the limbic fissure, which limits the limbic lobe. The rhinal sulcus is then followed in a medial direction until the internal carotid artery or its bifurcation, covered by the leptomeninges, is identified. The thus rostrally circumscribed uncus is separated from the pia. In the same fashion, the anterior portion of the amygdala is peeled off the leptomeninges that line the Sylvian fissure. The posteroapical portion of the amygdala, however, has to be dissected—by gentle ultrasonic aspiration—from its transition to the lentiform nucleus, in a straight line that connects the carotid artery and the anterior choroidal point. Tiny vessels that cross this cut through gray matter are carefully coagulated and divided. A tissue block that comprises the hippocampal head, the corresponding segment of the parahippocampal gyrus including its uncus, and the amygdala can now be freed subpially. Finally, the vascular pedicle of the hippocampal head is gently pulled out of the hippocampal sulcus, or it is coagulated as close as possible to the hippocampus and divided. The predominantly subpial dissection leaves intact the leptomeninges that separate the medial parts of temporal lobe from the oculomotor nerve, the brainstem, and the surrounding vessels. Therefore for the protection of these, the subpial dissection is an important safety measure. The hippocampal body is also subpially dissected medially along the junction of the fimbria and the choroidal fissure and laterally along the collateral sulcus. The resection is continued up to the hippocampal tail at the level of the quadrigeminal plate. All resected tissue is sent for histologic assessment (Fig. 15.3).

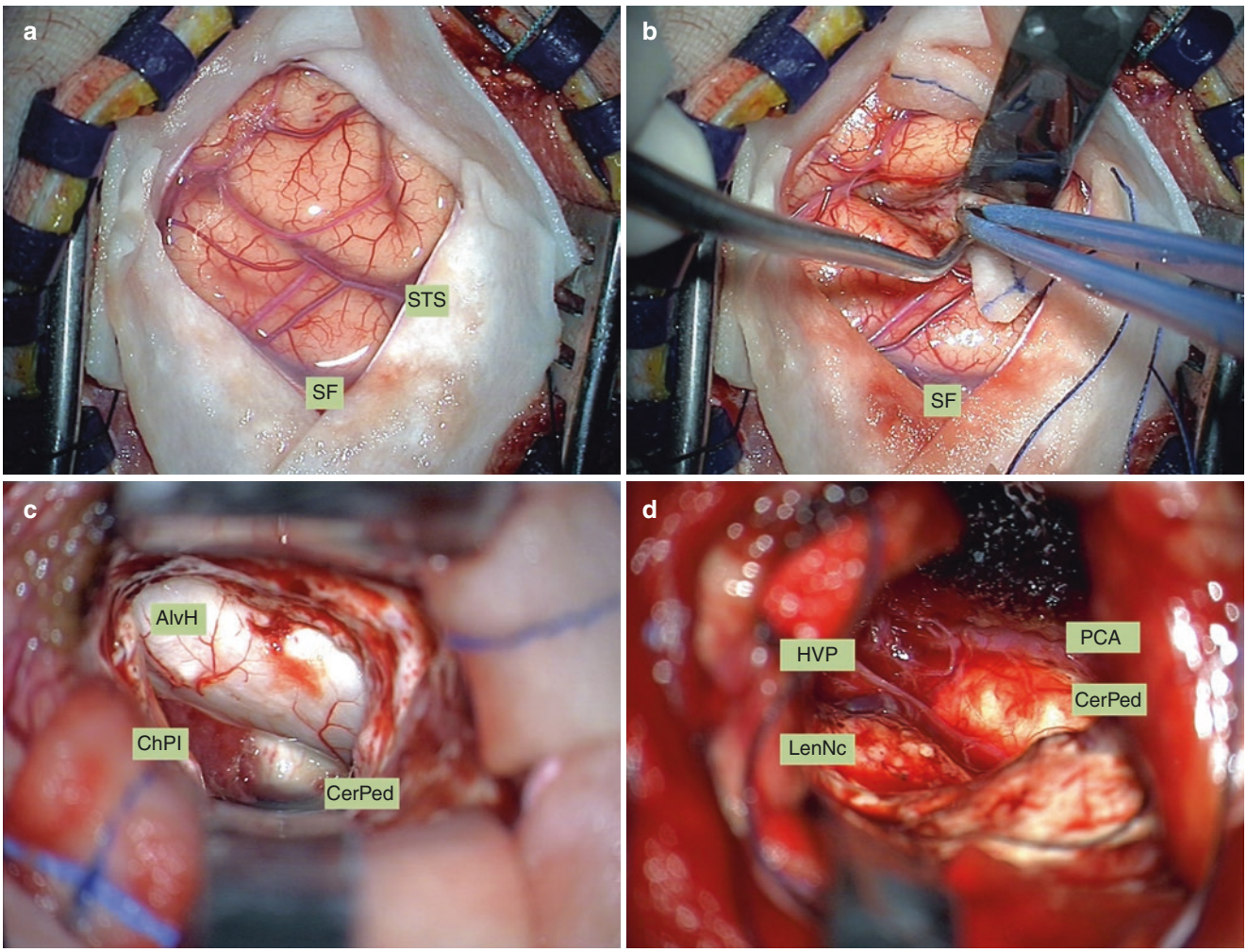

Fig. 15.2 (**a**), Exposure of the right-sided temporal convexity cortex through a 3-cm craniotomy prior to a trans-sulcal selective amygdalohippocampectomy. SF, Sylvian fissure. STS, Superior temporal sulcus. (**b**), Microsurgical dissection of the superior temporal sulcus reaching the sulcal valley. SF, Sylvian fissure. (**c**), Exposure of the uncal recess of the right temporal ventricle horn and within the alveus of the hippocampal head. AlvH, Alveus of hippocampal head. CerPed, Cerebral peduncle. ChPl, Choroid plexus. (**d**), View after en-bloc resection of the hippocampal head, parahippocampal gyrus, uncus, and amygdala, exposing the cerebral peduncle, the posterior cerebral artery, and the vascular pedicle of the hippocampus. CerPed, Cerebral peduncle. LenNc, Lentiform nucleus. HVP, Hippocampal vascular pedicle. PCA, Posterior cerebral artery

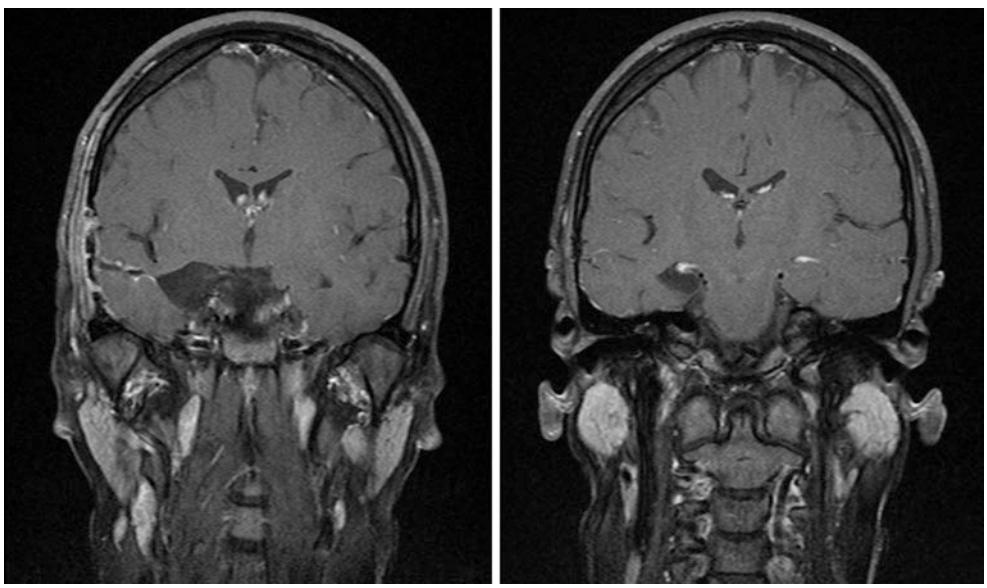

Fig. 15.3 Coronal MRI after right-sided trans-sulcal selective amygdalohippocampectomy

15.3 Anatomic and Functional Considerations

The limbic parts of the temporal lobe serve the processing of emotions and episodic memory. Candidates for sAHE generally suffer from a unilateral (or highly predominant unilateral) mesiotemporal epilepsy. The underlying lesion and/or the epileptic disorder itself often lead to a functional restriction of the hippocampus and amygdala. Prior to an amygdalohippocampectomy, it is an essential part of the presurgical evaluation to determine the residual performance of the diseased hippocampus and, even more important, the performance of the contralateral hippocampus for memory. This evaluation is done by means of neuropsychological assessment, by the intracarotid amobarbital test [40, 41] and increasingly – or even exclusively – by functional magnetic resonance imaging (fMRI). Residual performance of the diseased hippocampus is at risk and will generally be lost after amygdalohippocampectomy. Hence, insufficient memory performance of the contralateral hippocampus constitutes a contraindication for surgery because of the risk of severe or total postoperative amnesia. Multiple hippocampal transection and gamma knife treatment may overcome this contraindication (*see* Sect. 15.2, Surgical Techniques).

The temporal lobe contains important white matter tracts that can be damaged on the surgical pathway to the mesial structures.

The anterior part of the optic radiation (the Meyer loop) covers the anterior tip of the roof of the temporal horn and runs lateral to the inferior one third of the temporal horn and the inferolateral edge of the atrium. Its course is, however, variable. Damage to the Meyer loop causes a contralateral upper quadrantanopia. The central part of the optic radiation runs lateral to the middle one third of the temporal horn and the inferior one third of the atrium and occipital horn [42].

The insular segments of the uncinate fasciculus (UF) and the inferior fronto-occipital fasciculus (IFOF) are part of the temporal stem deep within the limen insulae [43].

The UF connects the frontal lobe (ventrolateral orbitofrontal cortex and prefrontal cortex) to the temporal lobe (temporal pole and uncus). Its anterosuperior part runs inferior and inferolateral to the frontal horn, and its posteroinferior part courses anterior to the temporal horn. The UF plays a role in reward- and punishment-based decisions. It mediates rapid learning of conditional visual associations. Its interruption causes problems of semantic retrieval, a deficit in naming famous individuals, social and/or emotional problems, and difficulties in learning from punishment [42].

The IFOF runs lateral to the temporal horn and the inferior two thirds of the atrium. It connects the frontal lobe (dorsolateral prefrontal cortex and pars orbitalis of the inferior frontal gyrus) to the occipital lobe (superior and middle occipital gyri) [43]. The IFOF serves lexical-semantic processing and visual spatial processing in the nondominant hemisphere. Its disconnection in the dominant and nondominant hemispheres produces semantic paraphasia and a deficit in nonverbal semantic cognition [42, 44].

The middle longitudinal fasciculus (MdLF) courses superior to the temporal horn and lateral to the middle one third of the atrium. It connects the temporal pole with the angular gyrus and the superior occipital lobe. The MdLF mediates the processing of spatial features of sounds [42]. The inferior longitudinal fasciculus (ILF) courses inferolateral to the temporal horn, atrium, and occipital horn. It connects the temporal and the occipital poles [43]. The ILF has a functional role in the recognition and identification of visually perceived objects. Its interruption in the temporal lobe may lead to visual agnosia and alexia [42].

15.4 Therapeutic Outcome

In a randomized controlled trial Wiebe et al. demonstrated that anterior temporal lobe resection is more effective than medical management in the treatment of drug-resistant temporal lobe epilepsy [45]. Anterior temporal lobectomy and sAHE, however, did not significantly differ in terms of seizure control in single-center studies [46]. A meta-analysis that covered 11 prospective and retrospective studies and included 1203 patients found a slight advantage for anterotemporal lobectomy: it appeared 1.32 times more likely to achieve an Engel class I outcome after anterotemporal lobectomy than after sAHE [47]. Another meta-analysis and systematic review of 13 prospective and retrospective studies that included 1511 patients came to similar findings, slightly favoring anterotemporal lobectomy [48]. However, a meta-analysis by Kuang et al. that covered six randomized controlled trials and included 289 and 337 patients who underwent anterotemporal lobectomy and sAHE, respectively, showed a pooled estimate of combined "risk ratio" (of the divergence between the two techniques) of only 1.01 [49]. These results are not surprising, as the resection of the limbic portion of the temporal lobe, being the presumably essential part with respect to seizure generation, is equally well achieved in sAHE and in anterotemporal lobectomy. The question can then be redirected to what exactly this essential part consists of. In a comprehensive review of 53 studies, out of which seven were prospective and four randomized, Schramm concluded that class I evidence is rare concerning seizure outcome related to type and extent of resection of mesial lobe structures [50]. Schramm et al. later specified that possibly not maximum but "adequate" volume resection leads to good seizure freedom. This was concluded from a prospective randomized trial in which 207 patients were allocated to either an intended 2.5-cm or 3.5-cm length of hippocampal resection. The median resection volumes were 72.86% and 83.44% of the initial hippocampus volume, respectively. Seizure outcome Engel class I 1 year after surgery was 74% in the 2.5-cm group and 72.8% in the 3.5-cm group [51].

Clusmann et al. [52] subjected a series of 321 patients who underwent surgery for temporal lobe epilepsy to a uni- and multifactorial analysis to determine the nonsurgical predictors of outcome. Good seizure control correlated with (1) a clear abnormality on MR images, (2) the absence of status epilepticus, (3) MR imaging revealing a ganglioglioma or a dysembryoplastic neuroepithelial tumor, (4) a concordant lateralizing memory deficit, and (5) the absence of dysplasia on MR images. Neuropsychological testing revealed better results after limited resections compared with standard anterotemporal lobectomy, especially with regard to attention level, verbal memory, and calculated total neuropsychological performance [52].

Wieser et al. [53] reported on a single-center series of 369 patients who underwent trans-sylvian sAHE. Seizure outcomes were documented up to 24 years following surgery, with a minimum of 1 year and a median of 7.2 years. In 125 patients, the follow-up period was 10 years or longer. During follow-up, at each point in time more than 49% of patients were free from both seizures and auras (Engel class IA), more than 59% were either free from seizures or experienced only nondisabling seizures (Engel class I), and more than 87% displayed a worthwhile improvement (Engel classes I-III). A state of complete cure was achieved in one third of patients for a period of more than 10 years after sAHE.

Four years after sAHE, seizure outcomes were International League Against Epilepsy (ILAE) class 1 in 79%, class 2 in 13%, class 3 in 0%, class 4 in 4%, class 5 in 4%, and class 6 in 0% of patients with classic hippocampal sclerosis. Outcomes were ILAE class 1 in 59%, class 2 in 9%, class 3 in 0%, class 4 in 9%, class 5 in 23%, and class 6 in 0% of patients with nonclassic hippocampal sclerosis. Four years after sAHE, 33% of patients with classic hippocampal sclerosis and 27% with nonclassic hippocampal sclerosis had attained ILAE class 1a outcomes (no seizures, no auras) [53].

Moreover, this study showed that the outcomes during the first year(s) after surgery statistically predict the outcome distribution after a much longer time. At the individual level, however, seizure recurrences after sAHE with initial seizure freedom did occur and were described as a "running-down" phenomenon. Out of 90 patients with lesional mesiotemporal lobe epilepsy and 77 patients with nonlesional mesiotemporal lobe epilepsy who were free of disabling seizures (Engel class I), during the first year after sAHE, 83.3% and 85.7% remained in the same outcome class for five postoperative years [53]. This decrement compared well with and was certainly not worse than similar observations after temporal lobe resections. The time course of the running-down phenomenon is being discussed as an argument to continue the preoperative regimen of anti-epileptic drugs for two to three years after sAHE [53].

Different approaches were compared by Schmeiser et al. [54] in another single-center retrospective study of 458 consecutive patients. One year after surgery, 72.9% were classified Engel I and in particular 72.8% after anterotemporal lobectomy, 76.9% after keyhole resection, 84.4% after extended lesionectomy, 70.3% after trans-sylvian sAHE, and 59.1% after subtemporal sAHE [54]. These differences were not found to be significant. Rather, the experience of the surgeon was emphasized.

In a series of 389 surgeries Mathon et al. [55] found two factors significantly associated with seizure recurrence: past history of status epilepticus and preoperative intracranial electroencephalographic recording. Surgical approach was not associated with seizure outcome. Risk of cognitive impairment was 3.12 and greater in patients after anterotemporal lobectomy than after transcortical sAHE [55].

15.5 Adverse Effects

In their single-center (Zürich) series of 453 patients who underwent trans-sylvian sAHE, Wieser et al. [53] observed 26 complications (5.74%) in 21 patients (4.63%). Complications were major, that is, affecting activities of daily living for more than 3 months in four patients (0.88%). The authors encountered acute and delayed epidural and subdural hematomas (N = 5), transient oculomotor or trochlear nerve palsies (N = 5), homonymous hemianopia (N = 2), transient (N = 4) and persistent (N = 3) hemiparesis, transient dysphasia (N = 1), persistent disabling memory deficit (N = 1), wound infection (N = 2), meningitis (N = 1), and deep leg venous thrombosis (N = 2) [53].

Seizure outcome and the patient's mental reserve capacity prior to surgery are important determinants of the cognitive outcome after sAHE [56]. With good seizure control attention may improve, which is a major cognitive parameter. Even if there is theoretical reason to assume that selective approaches and resections produce superior functional outcomes compared to standard anterotemporal lobectomy, sAHE is not devoid of the occurrence of collateral gray and white matter damage. Probably because of that, clinical evidence of sAHE's superiority in terms of cognitive performance remains rather weak. Anyhow, if the diseased hippocampus still harbors noticeable function prior to its resection, sAHE will logically have negative consequences for memory, as much as anterotemporal lobectomy. This was observed by Gleissner et al., who subjected 115 patients to neuropsychological assessment before and 3 and 12 months after sAHE. After left-sided sAHE, clinically meaningful losses became evident in 33%–50% of patients without recovery after 1 year. Declines in verbal memory that were observed shortly after right-sided sAHE, on the other hand, seemed to be only temporary [57]. As to the role of the approach, the subtemporal route was not found to be without cognitive side effects in spite of being anatomically very selective. Indeed, von Rhein et al. found a verbal memory decline to a similar degree for both the subtemporal and the transsylvian approaches [58]. Differential effects were seen in verbal recognition memory (more affected by left transsylvian sAHE) as well as in figural memory and verbal fluency (more affected by subtemporal sAHE) [58].

Conclusion

Selective amygdalohippocampectomy has existed for 60 years and has proved to be a valuable therapeutic measure against medically intractable mesial temporal lobe epilepsy. Variations in surgical approach have been suggested to improve the anatomic selectivity and to avoid damage to unrelated white matter tracts in the temporal lobe. However, these technically more demanding techniques have not necessarily resulted in superior outcomes. Multiple hippocampal transection and gamma knife surgery offer the perspective of avoiding postoperative memory decline.

References

1. Niemeyer P. The transventricular amygdala-hippocampectomy in the temporal lobe epilepsy. In: Baldwin M, Bailey P, editors. The temporal lobe epilepsy. Springfield, IL: Charles C Thomas; 1958. p. 461–82.
2. Yacubian EM, Cavalheiro EA. In memoriam Paulo Niemeyer Soares, 1914-2004. Epilepsia. 2004;45:1166–8.
3. Cavalcanti DD, Guasti JAD, Preul MC. Neurological and architectural sinuosities: the Niemeyer brothers. Neurosurgery. 2010;67:1167–79.
4. Gastaut H. Etude électro-encéphalographique du lobe temporal. Rev Otoneuroophtalmol. 1950;22:301–8.
5. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30. https://doi.org/10.1111/epi.13670.
6. Penfield W, Flanigan H. Surgical therapy of temporal lobe seizures. Arch Neurol Psychiatr. 1950;64:491–500.
7. Jasper HH, Kershman J. Electroencephalographic classification of the epilepsies. Arch Neurol Psychiatr. 1941;45:903–43.
8. Sommer W. Erkrankung des Ammon's Hornes als ätiologisches Moment der Epilepsien. Arch Psychiatr Nurs. 1880;10:631–75.
9. Spielmeyer W. Die Pathogenese des epileptischen Krampfes. Z Gesamte Neurol Psychiat. 1927;109:501–20.
10. Penfield W, Baldwin M. Temporal lobe seizures and the technic of subtotal temporal lobectomy. Ann Surg. 1952;136:625–34.
11. Sano K, Kirino T. Ammon's horn sclerosis: its pathogenesis and clinical significance. Tohoku J Exp Med. 1990;161(Suppl):273–95.
12. Pujar SS, Seunarine KK, Martinos MM, Neville BGR, Scott RC, Chin RFM, et al. Long-term white matter tract reorganization following prolonged febrile seizures. Epilepsia. 2017;58:772–80.
13. Yaşargil MG. Operative anatomy. In: Yaşargil MG, editor. Microneurosurgery, vol. 36. Stuttgart: Thieme Publishers; 1984. p. 252–90.
14. Yaşargil MG, Teddy PJ, Roth P. Selective amygdalohippocampectomy. Operative anatomy and surgical technique. In: Symon L, editor. Advances and technical standards in neurosurgery, vol. 12. Vienna: Springer; 1985. p. 553–72.
15. Yaşargil MG, Krayenbuhl N, Roth P, Hsu SP, Yaşargil DC, et al. The selective amygdalohippocampectomy for intractable temporal limbic seizures. J Neurosurg. 2010;112:168–85.
16. Olivier A. Commentary: cortical resections. In: Engel Jr J, editor. Surgical treatments of the epilepsies. New York: Raven Press; 1986. p. 405–15.
17. Olivier A. Transcortical selective amygdalohippocampectomy in temporal lobe epilepsy. Can J Neurol Sci. 2000;27(Suppl 1): S68–S76.
18. Rougier A, Saint-Hilaire JM, Bouvier G, Loiseau P, Baulac M, Bouthillier A, et al. Evaluation and surgical treatment of the epilepsies. Neurochirurgie. 1992;38(Suppl I):3–112.
19. Shimizu H, Suzuki I, Lshijima B. Zygomatic approach for resection of mesial temporal epileptic focus. Neurosurgery. 1989;25:798–801.
20. Hori T, Tabuchi S, Kurosaki M, Kondo S, Takenibu A, Watanabe T. Subtemporal amygdalohippocampectomy for treating medically intractable temporal lobe epilepsy. Neurosurgery. 1993;33:50–7.
21. Park TS, Bourgeois BFD, Silbergeld DL, W. Edwin Dodson. Subtemporal transparahippocampal amygdalohippocampectomy for surgical treatment of mesial temporal lobe epilepsy. J Neurosurg. 1996;85:1172–6.

22. Vajkoczy P, Krakow K, Stodieck S, Pohlmann-Eden B, Schmiedek P. Modified approach for the selective treatment of temporal lobe epilepsy: transsylvian-transcisternal mesial en bloc resection. J Neurosurg. 1998;88:855–62.
23. Türe U, Harput MV, Kaya AH, Baimedi P, Firat Z, Türe H, et al. The paramedian supracerebellar transtentorial approach to the entire length of the mediobasal temporal region: an anatomical and clinical study. J Neurosurg. 2012;116:773–91.
24. Nieuwenhuys R, Voogd J, van Huijzen C. The human central nervous system. Berlin-Heidelberg: Springer Verlag; 1988.
25. Yonekawa Y, Imhof HG, Taub E, Curcic M, Kaku Y, Roth P, et al. Supracerebellar transtentorial approach to posterior temporomedial structures. J Neurosurg. 2001;94:339–45.
26. Ziyal IM, Ozgen T. Transtentorial approach to the posterior temporomedial structures. J Neurosurg. 2001;95:541.
27. Yaşargil MG, Türe U, Yaşargil DC. Impact of temporal lobe surgery. J Neurosurg. 2004;101:725–38.
28. Lafazanos S, Türe U, Harput MV, Gonzalez Lopez P, Fırat Z, Türe H, et al. Evaluating the importance of the tentorial angle in the paramedian supracerebellar transtentorial approach for selective amygdalo-hippocampectomy. World Neurosurg. 2015;83:836–41.
29. Talairach J, Bancaud J, Szikla G, Bonis A, Geier S, Vedrenne C. New approach to the neurosurgery of epilepsy. Stereotaxic methodology and therapeutic results. 1. Introduction and history (in French). Neurochirurgie. 1974;20(Suppl 1):1–240.
30. Nádvornik P, Šramka M, Gajdošová D, Kokavec M. Longitudinal hippocampectomy. Appl Neurophysiol. 1975;37:244–8.
31. Blume WT, Parrent AG, Kaibara M. Stereotactic amygdalohippocampectomy and mesial temporal spikes. Epilepsia. 1997;38:930–6.
32. Régis J, Peragui JC, Rey M, Samson Y. First selective amygdalohippocampal radiosurgery for “mesial temporal lobe epilepsy”. Stereotact Funct Neurosurg. 1995;64(Suppl 1):193–201.
33. Liscak R, Malikova H, Kalina M, Vojtech Z, Prochazkaet T. Stereotactic radiofrequency amygdalohippocampectomy in the treatment of mesial temporal lobe epilepsy. Acta Neurochir. 2010;152:1291–8.
34. Drane DL, Loring DW, Voets NL, Price M, Ojemann JG, Willie JT. Better object recognition and naming outcome with MRI-guided stereotactic laser amygdalohippocampectomy for temporal lobe epilepsy. Epilepsia. 2015;56:101–13. https://doi.org/10.1111/epi.12860.
35. Régis J, Carron R, Park M. Is radiosurgery a neuromodulation therapy? J Neuro-Oncol. 2010;98:155–62.
36. Shimizu H, Kawai K, Sunaga S, Sugano H, Yamada T. Hippocampal transection for treatment of left temporal lobe epilepsy with preservation of verbal memory. J Clin Neurosci. 2006;13:322–8.
37. Uda T, Morino M, Ito H, Minami N, Hosono A. Transsylvian hippocampal transection for mesial temporal lobe epilepsy: surgical indications, procedure, and postoperative seizure and memory outcomes. J Neurosurg. 2013;119:1098–104.
38. Wheatley BM. Selective amygdalohippocampectomy: the transmiddle temporal gyrus approach. Neurosurg Focus. 2008;25:E4.
39. Kovanda TJ, Tubbs RS, Cohen-Gadol AA. Transsylvian selective amygdalohippocampectomy for treatment of medial temporal lobe epilepsy: surgical technique and operative nuances to avoid complications. Surg Neurol Int. 2014;5:133.
40. Wada J. A new method for the determination of the side of cerebral speech dominance. A preliminary report of the intra-carotid injection of sodium amytal in man (Japanese). Igaku to Seibutsugaki (Tokyo). 1949;14:221–2.
41. Wada JA. A fateful encounter: sixty years later – reflections on the Wada test. Epilepsia. 2008;49:715–27.
42. Güngör A, Baydin S, Middlebrooks EH, Tanriover N, Isler C, Rhoton AL. The white matter tracts of the cerebrum in ventricular surgery and hydrocephalus. J Neurosurg. 2017;126:945–71.
43. Zemmoura I, Serres B, Andersson F, Barabtin L, Tauber C, Filipiak I, et al. FIBRASCAN: a novel method for 3D white matter tract reconstruction in MR space from cadaveric dissection. NeuroImage. 2014;103:106–18.
44. Herbet G, Moritz-Gasser S, Duffau H. Direct evidence for the contributive role of the right inferior fronto-occipital fasciculus in nonverbal semantic cognition. Brain Struct Funct. 2017;222:1597–610.
45. Wiebe S, Blume WT, Girvin JP, Eliasziw M. A randomized controlled trial of surgery for temporal lobe surgery. N Engl J Med. 2001;345:311–8.
46. Hemb M, Palmini A, Paglioli E, Paglioli EB, Costa da Costa J, Azambuja N, et al. An 18-year follow-up of seizure outcome after surgery for temporal lobe epilepsy and hippocampal sclerosis. J Neurol Neurosurg Psychiatry. 2013;84:800–5.
47. Josephson CB, Dyckeman J, Fiest KM, Liu X, Sadler RM, Jette N, et al. Systematic review and meta-analysis of standard vs selective temporal lobe surgery. Neurology. 2013;80:1669–76.
48. Hu WH, Zhang C, Zhang K, Meng FG, Chen N, Zhang JG. Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. J Neurosurg. 2013;119:1089–98.
49. Kuang Y, Yang T, Gu J, Kong B, Cheng L. Comparison of therapeutic effects between selective amygdalohippocampectomy and anterior temporal lobectomy for the treatment of temporal lobe epilepsy: a meta-analysis. Br J Neurosurg. 2014;28:374–7.
50. Schramm J. Temporal lobe epilepsy surgery and the quest for optimal extent of resection: a review. Epilepsia. 2008;49:1296–307.
51. Schramm J, Lehmann TN, Zentner J, Mueller CA, Scorzin J, Fimmers R, et al. Randomized controlled trial of 2.5-cm versus 3.5-cm mesial temporal resection in temporal lobe epilepsy – part 1: intent-to-treat analysis. Acta Neurochir. 2011;153:209–19.
52. Clusmann H, Schramm J, Kral T, Helmstaedter C, Ostertun B, Fimmers R, et al. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. J Neurosurg. 2002;97:1131–41.
53. Wieser HG, Ortega M, Friedman A, Yonekawa Y. Long-term seizure outcomes following amygdalohippocampectomy. J Neurosurg. 2003;98:751–63.
54. Schmeiser B, Wagner K, Schulze-Bonhage A, Mader I, Wendling A-S, Steinhoff BJ, et al. Surgical treatment of mesiotemporal lobe epilepsy: which approach is favorable? Neurosurgery. 2017;81:992–1004. https://doi.org/10.1093/neuros/nyx138
55. Mathon B, Bielle F, Samson S, Plaisant O, Dupont S, Bertrand A, et al. Predictive factors of long-term outcomes of surgery for mesial temporal lobe epilepsy associated with hippocampal sclerosis. Epilepsia. 2017;58:1473–85.
56. Helmstaedter C. Cognitive outcomes of different surgical approaches in temporal lobe epilepsy. Epileptic Disord. 2013;15:221–39.
57. Gleissner U, Helmstaedter C, Schramm J, Elger CE. Memory outcome after selective amygdalohippocampectomy in patients with temporal lobe epilepsy: one-year follow-up. Epilepsia. 2004;45:960–2.
58. von Rhein B, Nelles M, Urbach H, von Lehe M, Schramm J, Helmstaedter C. Neuropsychological outcome after selective amygdalohippocampectomy: subtemporal versus transsylvian approach. J Neurol Neurosurg Psychiatry. 2012;83:887–93.

Radiating Multiple Subpial Transection: Operative Techniques, Complications and Outcomes

16

Dorota Tassigny, Riëm El Tahry, Géraldo Vaz, Susana Ferrao Santos, Kenou van Rijckevorsel, and Christian Raftopoulos

Epilepsy is a neurologic disorder affecting nearly fifty million people worldwide [1]. In two thirds of the patients, seizures can be controlled with the right medication. Unfortunately, one third of the patients have drug-resistant epilepsy; for those patients, epilepsy surgery remains a possible life-transforming treatment option.

Nevertheless, epilepsy surgery is limited by the fact that a resective procedure cannot be performed within primary areas without potentially causing severe neurologic deficits. The multiple subpial transection (MST) technique was proposed by Morrell et al. [2] as an alternative method to treat drug-resistant epilepsies whenever the epileptic focus includes the eloquent cortex. This surgical technique interrupts transversal cortical connections to prevent neuronal synchronization and the spread of epileptic discharges while preserving the vertical fibers and vascular supply.

However, MST involves multiple entry points. Each entry point is potentially associated with a risk of bleeding and/or cortical ischemia. To reduce the risk of complications, we use a modified Morrell technique [2] in our Center for Refractory Epilepsy (CRE), performing radiating transections (three to five) from a single cortical entry point. This procedure can be performed alone or in conjunction with other procedures such as lesionectomy or disconnection.

The aim of this chapter is (1) to describe the technique and its evolution over time and detail the operative indications and the different steps of the procedure, (2) to report the complications, and (3) to present functional outcomes in terms of seizure control.

D. Tassigny · G. Vaz · C. Raftopoulos (✉)
Department of Neurosurgery, Cliniques Universitaires St. Luc, Brussels, Belgium
e-mail: christian.raftopoulos@uclouvain.be

R. El Tahry · S. Ferrao Santos · K. van Rijckevorsel
Department of Neurology, Cliniques Universitaires St. Luc, Brussels, Belgium

16.1 Operative Technique

16.1.1 Background

Surgery is considered the treatment of choice in patients with drug-resistant epilepsy. However, whenever the epileptogenic zone includes brain areas with higher functions, resective surgery is limited.

First described in 1989 by Morrell et al., MST is a possible alternative to resection, especially in primary areas [2]. Their aim is to prevent epileptic activity while preserving normal cortical function. This procedure interrupts transversal cortical connections to prevent neuronal synchronization and thereby to prevent the spread of epileptic discharges while preserving the vertical fibers and vascular supply.

In the original Morrell technique, once the suspected epileptogenic area has been electrocorticographically mapped, a small pinhole-sized nick is made in the arachnoid and pia with the point of a small blade in an area of the cortex that is relatively avascular. An attempt is made to reach as deep into the sulcus as possible, but access is often limited by the presence of large vessels. The instrument, a small blunt right-angled hook, is introduced through the pial opening and then swept forward, dipping in an arc-like fashion underneath the gyrus. The blade of the blunt hook is kept in a strictly vertical orientation to avoid cutting the vertical cortical connections. The next transection is made parallel to the first at a distance of 5 mm. Transections are repeated as often as necessary to include the entire area of electrical abnormality and may encompass several gyri. The capillary bleeding associated with each passage of the instrument results in a fine red line useful to gauge the location of the next transection.

However, MST using the Morrell technique involves multiple entry points. Each entry point is potentially associated with a risk of bleeding and/or cortical ischemia. To reduce the risk of complications, we use a modified Morell technique in our CRE. Radiating transections (rMSTs) (three to five) are performed from a single cortical entry point [3, 4].

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16.1.2 Indications for Surgery

The rMST technique is a potential surgical treatment for epilepsy in patients in whom the epileptogenic focus is located in or overlapping with cortical areas with higher functions. The following eloquent cortical areas are possible targets: the motor areas (Brodmann area [BA] 4, 6, 8); the sensory areas (BA 1, 2, 3); the Broca area (BA 44, 45); the Wernicke area (BA 22, 39, 40), and the primary visual area (BA 17). rMSTs is also the treatment of choice for Landau-Kleffner syndrome (acquired epileptiform aphasia) [5].

The surgical strategy is discussed for each patient at a multidisciplinary meeting in our Center, which includes neurosurgeons, neurologists, neuropediatricians, neuroradiologists, psychiatrists, and a nuclear medicine specialist. The surgery is performed whenever the multidisciplinary group decides that the procedure is safe and potentially effective and after informed consent from the patient has been obtained.

In non-lesional epilepsy, rMST alone is performed in or near the eloquent cortical area. In lesional epilepsy, transections are conducted in addition to the resective procedure if epileptiform discharges are still observed after resection, as confirmed by serial intraoperative electrocorticography (ioECoG).

16.1.3 Surgical Procedure

One day before surgery, the patient undergoes a thin-slice magnetic resonance image test for neuronavigation. This imaging enables preparation of the surgical procedure in our surgical planning laboratory by contouring anatomic landmarks, planning the surgical approach, and defining the target. In order for the surgeon to perform the MST correctly, he or she is helped by anatomic and MRI landmarks through the microscope of the computer-assisted navigation system (BrainLAB, Feldkirchen, Germany) and by ioECoG.

To minimize any interference of the anesthesia with the recording of interictal epileptiform discharges during ioECoG, our anesthesiology team has developed an adapted protocol. For this purpose, we avoid using drugs with prolonged effects, such as benzodiazepines. In addition, the anesthesiologists are guided by a contralateral scalp EEGs to monitor the depth of anesthesia. During ioECoG, the scalp EEG shows continuous theta and beta activity.

After endotracheal anesthesia, the patient is usually placed in a supine position, sometimes with one shoulder elevated. The position of the head is fixed using a Mayfield clamp. The degree of head rotation depends on the location of the epileptic focus. The skin incision and the extent of the bone flap are adjusted according to the involved cortex and guided by the landmarks projected through the microscope (neuronavigation using the BrainLAB Curve). After opening the dura mater, the rMST is performed on the top of the gyri. Three to five transections from 10 to 15 mm long are performed radiating from one cortical entry point, either perpendicular to the gyrus axis, parallel to the sulcus at 3–4 mm from it (to avoid the vertical cortical projections), or diagonally. The transector consists of a hook directed caudally at 4 mm depth. Transection is followed visually through the arachnoidopial layers. Each entry point is electrocoagulated to reduce intra- and extra-arachnoid hemorrhage at this level.

The main risk of this procedure is related to the proximity of the transected area to the cortical sulci. Indeed, at this level, the orientation of axonal fibers changes and becomes more perpendicular to the rMSTs. Consequently, when transections are not sufficiently remote from the sulci (minimum 3–4 mm), they may produce axonal sections of the eloquent cortex.

The key to success is based on the resection of the lesion and/or transection of the whole epileptogenic area. For this reason, we recommend use of the ioECoG to map the interictal epileptiform discharges (IEDs) in an eloquent zone. At the end of the procedure, the IEDs are recorded by ioECoG through an electrode placed over and beyond the resected and/or transected areas to check the disappearance or regression of the IEDs. However, there are several limitations: 1. placement of the recording electrode for ioECoG is determined by the size of the craniotomy; 2. the recording time is short; 3. difficulty may be encountered differentiating primary and secondarily propagated epileptic discharge activity. In summary, ioECoG is an important intraoperative tool to help to map IEDs and perform rMSTs but does not predict postoperative evolution (Figs. 16.1 and 16.2) [6].

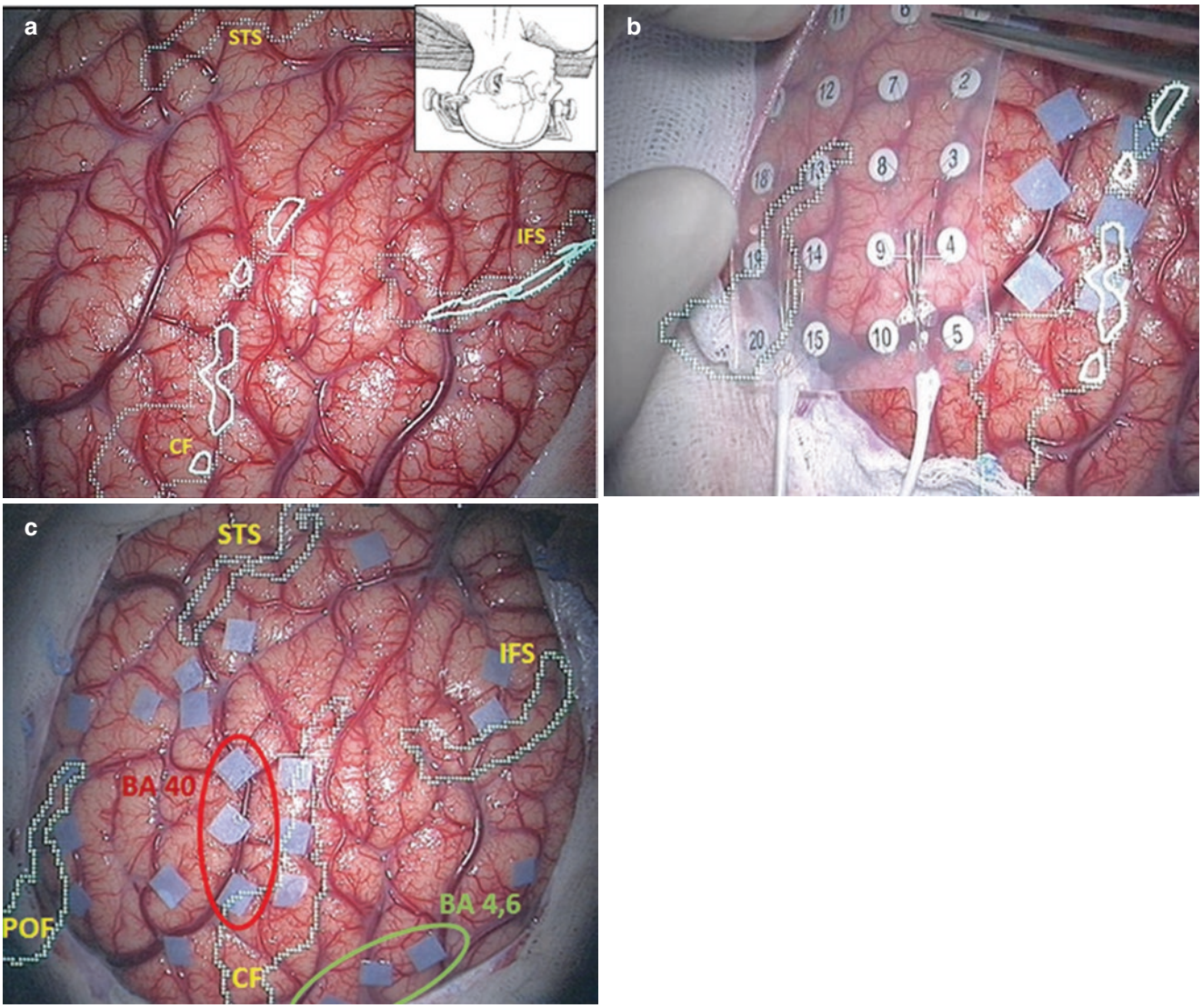

Fig. 16.1 Identification of epileptogenic foci using intraoperative electrocorticography (ioECoG). (**a**), The patient's head was turned to the right side. The anatomic landmarks (STS, superior temporal sulcus; CF, central fissure; IFS, inferior frontal sulcus) were displayed through the microscope by the computer-assisted navigation system. (**b**), ioECoG was used to map the interictal epileptiform discharges in the eloquent zones. Each discharging contact was indicated by a "*blue square*." (**c**), The mapping included motor areas (Brodmann area [BA] 4, 6) and functional language area (BA 40); POF: parieto-occipital fissure

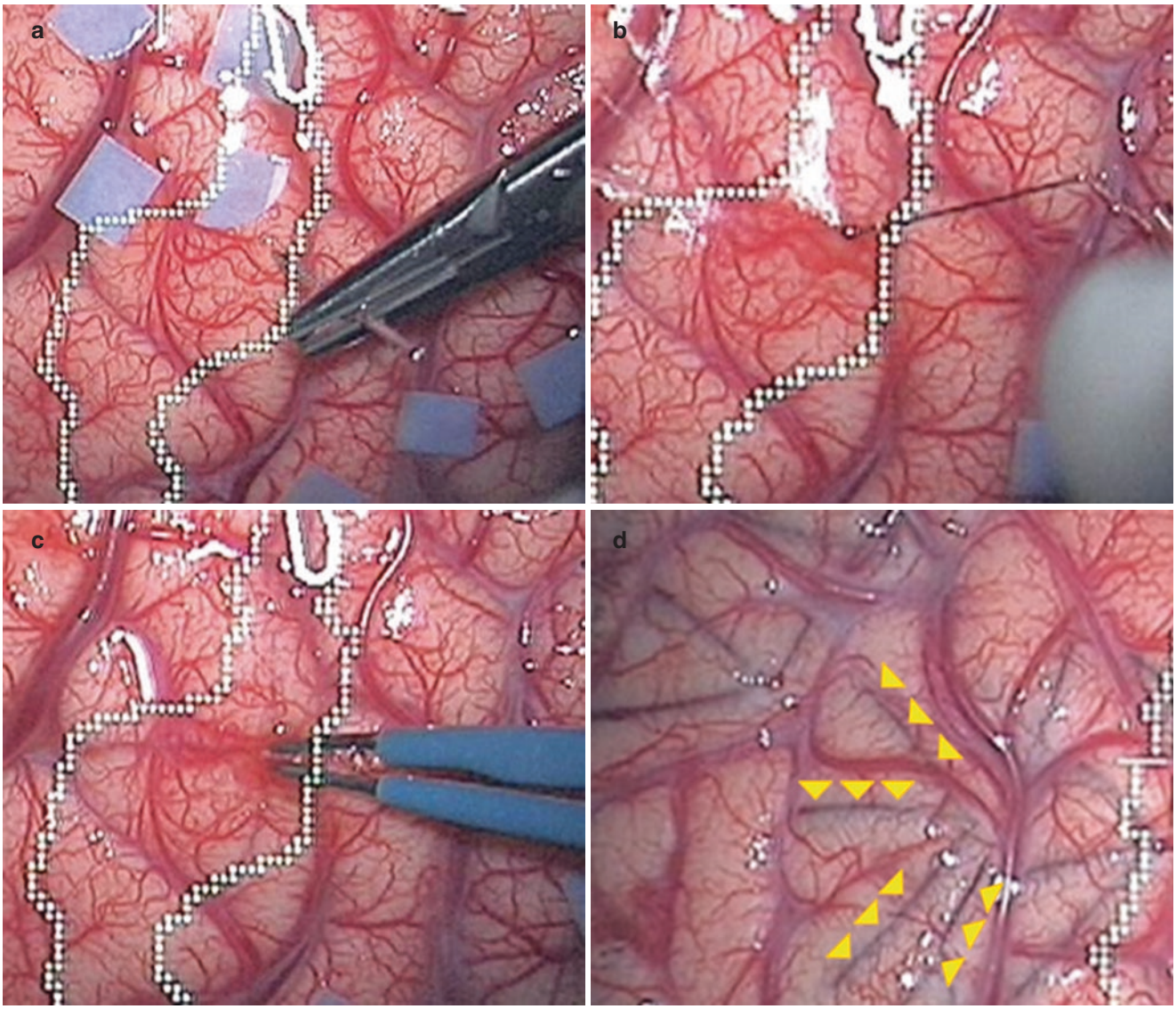

Fig. 16.2 Operative procedure. This figure shows the different steps of the radiating subpial transection technique. (**a**), A small notch was made in the pia mater in a relatively avascular cortex using a needle (27 gauge = 0.40-mm diameter). (**b**), The first transection was performed and followed visually through the arachnoidopial layers (transector is still in place). (**c**), Each entry point was electrocoagulated to reduce intra- and extra-arachnoid hemorrhage at this level. (**d**), Several groups of 3–4 radiating subpial transections (*arrows*) are seen, each group radiating from a single arachnoidopial penetration point; no subarachnoid hemorrhages can be seen

16.2 Complications

In the literature, complications are observed in 19%–42% of cases [7, 8]. The most frequently reported complications are hemorrhage and/or ischemia of the transected cortex. For this reason, we have developed a radiating MST procedure. This modification seems to be the primary factor explaining the lack of subdural or intraparenchymal hematomas and/or cortical infarcts in our patients.

In our last series of 62 consecutive patients, we noted only minor persistent neurologic deficits in four patients (6.4%). Two minor neurologic deficits (3.2%) were related to the radiating MSTs: a slight facial paresis (House-Brackmann grade II) in a patient with a frontal lobe disconnection completed by rMST on residual BA 4 and 6, and a slight (4/5) hemiparesis in a patient with a rolandic unresectable dysembryoplastic neuroepithelial tumor [4]. Visual field deficits were noted in a patient with temporal disconnection (quadranopsia) and one with occipital disconnection (hemianopsia), but these were not related to the rMST. Finally, among 14 patients who underwent rMST in functional language areas (BA 44, 22, 39, and 40), no significant permanent dysphasia was reported.

When studying the consequences of rolandic epilepsy surgery, Behdad et al. [7] observed a 42.9% rate of minor persistent deficits. However, these deficits were mainly related to the cortectomies and lesionectomies and less to the MST. In a meta-analysis by Spencer et al. [8], a 19% rate of permanent deficit related to the MST was reported. In our study, as in others with the same targets, no major permanent neurologic deficits related to the radiating MST were noted [9, 10].

16.3 Outcomes

In our population of 62 patients, 12 patients underwent rMST alone (rMSTa group) and 50 had rMST with another procedure (rMSTs+ group) [4]. The duration of postoperative follow-up ranged from 2 to 9 years. The mean number of transections was 42.2 in the rMSTa group (range, 5–89) and 31.1 in the rMST+ group (range 4–93). The main areas of transection were the frontal ascending gyrus (BA 4 and partially 6; 61%) and parietal ascending gyrus (BA 3, 1, 2; 58%). BA 44 was involved in 11% of cases, and BAs 22, 39, and 40 together accounted for another 11%. Patients were divided into four classes of seizure control: class I (total seizure suppression), class II (99% to 75% fewer seizures), class III (74% to 50% fewer seizures), and class IV (less than 50% fewer seizures) according to the Engel modified classification. A patient was considered a responder when there was a reduction in seizure frequency of at least 50%. After follow-up of at least 2 years, evolution was considered favorable in 49 patients (79.1%), with a reduction in seizures of at least 50% (classes I, II, III). Twenty-six patients (42%) were seizure-free (class I). The success rate of the procedure was slightly higher in the rMST+ group than in the rMSTa group. However, this difference was not statistically significant ($p = 0.8$). The only parameter that was statistically significantly associated with an unfavorable outcome (class IV) was a younger mean age onset of epilepsy ($p = 0.03$).

Our results are comparable to those reported in other published studies [2, 8, 11, 12]. Nevertheless, it is important to note the considerable disparity of results in the various cohorts, a factor that has already been emphasized by Orbach et al. [13], Polkey [11], and Schramm et al. [10]. Different numbers of reported patients, various etiologies, MST of different areas, and different evaluation criteria are the main factors explaining this heterogeneity. The meta-analysis by Spencer et al. [8] reported high rates of seizure suppression (defined by a 95% reduction in seizure frequency, 62% to 87%) but with high rates of neurologic deficit (19% for MSTa; 23% for MST+). Zhao and colleagues [12] reported on the largest group of patients from a single center ($n = 200$) and noted a favorable evolution in 95% with a 63% rate of seizure suppression.

Factors reported in the literature that predict patient outcome vary [10, 14]. In the meta-analysis by Spencer et al. [8], three factors were associated with a good evolution: onset of epilepsy at a younger age, duration of the disease less than 10 years, and specific etiologies such as tumors and congenital and perinatal pathologies. Orbach et al. [13] observed that the absence of MRI or histopathologic lesions was associated with less favorable results. In our series, a less favorable outcome appeared to be associated with an

earlier age of onset of the epilepsy, more frequent generalized seizures, longer mean duration of epilepsy, and a younger mean age; however, only the association with early age of onset was statistically significant. The rate of seizure suppression associated with MSTa was poor compared to patients who received resective surgery, as reported in many studies. Indeed, after performing MSTa, Schramm et al. [10] and Polkey [11] reported that only a small proportion of patients were in class I — 5% and 15% — respectively. Our results with MSTa, that is, 33% of patients with seizure suppression and 75% with significant improvement (class I, II, or III), remain encouraging, even though our percentages are inferior to the results reported by Zhao and Spencer [8, 12]. rMSTa can thus lead to seizure suppression in at least one third of patients.

In conclusion, rMST performed under neuronavigation and guided by ioECoG are a safe and efficient procedure and are associated with rare (3.2%) and minor permanent postoperative neurologic complications. In our series, we report a reduction in the seizure rate of at least 50% in 79% of patients, with 42% becoming seizure-free. For patients who underwent rMSTa, a reduction in the seizure rate of at least 50% was reported in 75% of subjects and one third became seizure-free.

References

1. Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy - a review. Epilepsy Res. 2009;85:31–45.
2. Morrell F, Whisler WW, Bleck T. Multiple subpial transection: a new approach to the surgical treatment of local epilepsy. J Neurosurg. 1989;70:231–9.
3. Vaz G, van Raay Y, van Rijckevorsel K, de Tourtchaninoff M, Grandin C, Raftopoulos C. Safety and efficacy of multiple subpial transections: report of a consecutive series of 30 cases. Neurochirurgie. 2008;54:311–4.
4. Ntsambi-Eba G, Vaz G, Docquier MA, van Rijckevorsel K, Raftopoulos C. Patients with refractory epilepsy treated using a modified multiple subpial transection technique. Neurosurgery. 2013;72:890–8.
5. Buelow JM, Aydelott P, Pierz DM, Heck B. Multiple subpial transection for Landau-Kleffner syndrome. AORN J. 1996;63:727–9. 732–5, 737–9.
6. El Tahry R, Ferrao Santos S, de Tourtchaninoff M, Géraldo Ribeiro Vaz J, Finet P, Raftopoulos C, et al. Post-resection electrocorticography has no added value in epilepsy surgery. Acta Neurol Belg. 2016;116:279–85.
7. Behdad A, Limbrick DD Jr, Bertrand ME, Smyth MD. Epilepsy surgery in children with seizures arising from the rolandic cortex. Epilepsia. 2009;50:1450–61.
8. Spencer SS, Schramm J, Wyler A, O'Connor M, Orbach D, Krauss G, et al. Multiple subpial transection for intractable partial epilepsy: an international meta-analysis. Epilepsia. 2002;43:141–5.
9. Sawhney IM, Robertson IJ, Polkey CE, Binnie CD, Elwes RD. Multiple subpial transection: a review of 21 cases. J Neurol Neurosurg Psychiatry. 1995;58:344–9.
10. Schramm J, Aliashkevich AF, Grunwald T. Multiple subpial transections: outcome and complications in 20 patients who did not undergo resection. J Neurosurg. 2002;97:39–47.
11. Polkey CE. Multiple subpial transection: a clinical assessment. Int Rev Neurobiol. 2001;45:547–69.
12. Zhao Q, Tian Z, Liu Z, Li S, Cui Y, Lin H. Evaluation of the combination of multiple subpial transection and other techniques for treatment of intractable epilepsy. Chin Med J (Engl). 2003;116:1004–7.
13. Orbach D, Romanelli P, Devinsky O, Doyle W. Late seizure recurrence after multiple subpial transections. Epilepsia. 2001;42:1316–9.
14. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol. 2008;7:525–37.

Corpus Callosotomy

17

Stephen K. Mendenhall, Rahul K. Ahluwalia, and Nicholas M. Barbaro

Corpus callostomy is a palliative procedure performed in patients with generalized epilepsy who have failed anticonvulsant therapy and are not candidates for lesionectomy. The corpus callosum is the major pathway for interhemispheric spread of epileptic activity; sectioning it disrupts the spread of epileptic discharges, resulting in decreased clinical seizure activity. The procedure is proven to be safe and efficacious with over seven decades of experience since its creation. Callosotomy is most frequently used for patients suffering drop attacks, but it is effective for all types of generalized tonic-clonic seizures. Future research utilizing newer imaging techniques such as functional MRI may lead to a better understanding of the callosal connections generating and propagating seizures. Deeper understanding of the topographic anatomy of the corpus callosum might allow for more refined callosal sectioning, eliminating many of the side effects of current therapy.

17.1 History

In 1940, Van Wagenen and Herren published a landmark paper evaluating the potential of surgical resection of the corpus callosum as a treatment for generalized seizures [1]. They noted in patients with gliomas of the corpus callosum that generalized tonic-clonic seizures were replaced with partial seizures in the later stages of disease. They hypothesized that destruction of the corpus callosum resulted in decreased generalized convulsive seizures. Their observations led to the theory that surgical division of the corpus callosum could limit seizure propagation between hemispheres in individuals with epilepsy, thereby abolishing secondary seizure generalization. Their observations would markedly influence the development of modern epilepsy surgery.

Even though the practice of corpus callosotomy for treatment of seizures was rarely used until over 20 years later, the procedure gained acceptance in the neurosurgical community following the first case reports of callosal sectioning for seizure control [2–4]. Over the years, surgical modifications of the procedure have been explored. These techniques include the use of an anterior frontal interhemispheric approach for staged callostomy, complete versus partial callosotomy, anterior versus posterior callosotomy, and most recently radiosurgical callostomy [5–8]. The advent of less invasive neurosurgical procedures for epilepsy, the creation of newer, more effective antiepileptic medications and better localization of seizure semiology with electroencephalography (EEG) and magnetic resonance imaging (MRI) have resulted in corpus callostomy's falling out of favor as a primary surgical treatment for epilepsy. Regardless, Van Wagenen and Herren's innovative work [1] has permanently shaped our modern understanding of the functional connections between the cerebral hemispheres.

17.2 Indications

Corpus callosotomy was originally developed for the treatment of generalized seizures. In the modern surgical treatment of epilepsy, it is considered a palliative procedure for

S. K. Mendenhall (✉) · R. K. Ahluwalia
Department of Neurological Surgery, Indiana University, Indianapolis, IN, USA
e-mail: skmenden@iupui.edu

N. M. Barbaro
Department of Neurological Surgery, Indiana University Health Neuroscience Center, Indianapolis, IN, USA

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patients with intractable generalized seizures who are not candidates for focal resection and have failed medical management. Of the different seizure subtypes, drop attacks (both tonic and atonic) remain the primary indication for this procedure. Numerous studies have shown superior outcomes for this seizure subtype [9–13]. Efficacy has also been shown for patients suffering generalized tonic-clonic seizures [14], complex partial seizures [9, 11, 15], absence seizures [14], recurrent episodes of status epilepticus [9, 12], West/Lennox-Gastaut syndrome [16–18], and Rasmussens encephalitis [19–21].

In our experience, selection criteria for callosal section are (1) medically intractable epilepsy of prolonged duration; (2) failure of multiple anticonvulsant regimens with appropriate serum anticonvulsant levels; (3) generalized seizures of the subtypes mentioned above; (4) radiographic and electroencephalographic exclusion of a resectable seizure focus; and (5) potential clinical improvement for the patient if seizure reduction is achieved.

17.3 Preoperative Evaluation

Potential candidates for callostomy require a thorough and comprehensive medical and neurosurgical evaluation in order to accurately select patients with the highest chance of seizure reduction while minimizing potential complications. Patients generally undergo the following assessment:

1. Complete medical history, including seizure history and frequency, antiepileptic drug history, daily functional assessment, and quality of life assessment.
2. Complete and detailed physical examination.
3. Brain MRI.
4. EEG monitoring to confirm seizure type and assess for laterality.
5. Neuropsychological testing.

Many studies have investigated the prognostic factors that are associated with favorable outcome after corpus callosotomy. We will highlight the factors taken into consideration while evaluating patient candidacy for callosal sectioning.

17.3.1 Age

Younger age at the time of surgery (<18 years) has been shown to be an independent predictor for improvement in daily function, psychosocial adjustment, and quality of life [9, 22]. Additionally, the potential adverse effects of callosotomy are less severe in children than adults, although the reduction in seizure frequency is similar [12, 23–25].

17.3.2 Seizure Type

Drop attacks are the most responsive seizure subtype to callosal resection [25]. Numerous studies have shown superior outcomes for this seizure subtype [9–13]. Efficacy has also been shown for patients suffering generalized tonic-clonic seizures [14], complex partial seizures [9, 11, 15], absence seizures [14], recurrent episodes of status epilepticus [9, 12], West/Lennox-Gastaut syndrome [16–18], and Rasmussen encephalitis [19–21].

17.3.3 Magnetic Resonance Imaging

The outcome after callostomy in relation to preoperative MRI is somewhat debated in the literature. Sorenson and colleagues [26] retrospectively reviewed 23 patients who underwent callosotomy and found that the best predictor of good outcome was a normal preoperative MRI. This is in contrast to other studies that observed better outcomes in patients with lateralizing findings on neurologic examination or neuroimaging studies [22, 27]. In addition, other studies show that MRI findings have no influence on surgical outcome [11, 28]. In our patient selection process, those that have a surgically resectable lesion based on MRIs and EEGs are excluded from corpus callostomy surgery because outcomes for lesionectomy are more favorable and have fewer side effects than callosotomy.

17.3.4 Electroencephalography

Ictal EEG is important for identifying patients with drop attacks. Type I ictal EEG, defined as generalized slow spike-wave, electrodecrement, or nonevolving low amplitude fast activity is associated with absence, tonic, and atonic seizures, all of which can cause drop attacks. Hanson and coworkers [29] studied ictal EEG patterns in 41 adult patients undergoing corpus callostomy and found that patients with type I ictal EEGs had better than a 90% chance for total or near total resolution of seizures causing drop attacks. Additionally, patients with interictal EEGs revealing bilateral independent spikes have been associated with poor outcome after callosotomy [24].

17.3.5 Neuropsychological Testing

Epilepsy patients undergo extensive neuropsychological testing prior to operation to identify preoperative deficits. Regarding callosotomy, the presence of significant cognitive

impairment, defined as IQ less than 50, has been associated with poor outcome [24, 25, 30]. Other studies demonstrate that mental retardation is not a contraindication to callosal sectioning [11, 31]. This is especially true in the pediatric population. In their series, Rathore and associates [32] reported that children with severe mental retardation and injurious drop attacks were able to undergo callosotomy with little morbidity and highly favorable outcomes in terms of seizure frequency reduction.

17.4 Corpus Callosum Anatomy

17.4.1 Gross Anatomy

The human brain is divided into two cerebral hemispheres, which are interconnected to control and coordinate activity between contralateral regions. Seven midline structures connect the two hemispheres and include the corpus callosum, anterior commissure, posterior commissure, dorsal and ventral hippocampal commissures, the massa intermedia, and the interforniceal commissure. Human topographic studies show that the corpus callosum is the principal white matter tract interconnecting neocortical areas of the two hemispheres [33]. It is divided into four anatomic parts: rostrum, genu, body, and splenium. Each anatomic region contributes to the walls of the lateral ventricle. The rostrum is found in the floor of the frontal horn. The genu forms the anterior wall of the frontal horn and connects the frontal lobes via the forceps minor tract. The splenium is found in the atrium and occipital horns and connects the occipital lobes via the forceps major tract. The posterior part of the body and splenium give rise to the tapetum fiber tract, which forms the roof and lateral wall of the atrium and temporal/occipital horns [34]. On average, the length of the corpus callosum measures 6.5 cm (from genu to splenium) and is approximately 0.5–1.0 cm in thickness [35].

17.4.2 Topographic Anatomy

Currently, there is debate in the scientific literature about the topographic anatomy of the corpus callosum. New studies utilizing functional magnetic resonance and diffusion tensor imaging are changing the way we view callosal functionality and hemispheric connectivity [33, 36, 37]. In this section we will consider the classic anatomic studies and topographic anatomy that has been used as the framework in which current strategies for corpus callosotomy are based.

The corpus callosum connects approximately 70%–80% of cerebral cortex bihemispherically [38]. Most areas of the cerebral cortex are connected to homologous areas in the opposite hemisphere by axons that bridge the corpus callosum [39]. The callosal axons are organized in an anteroposterior manner, resulting in modality specific regions. The rostrum transfers higher cognitive information [40]. The anterior midbody transfers motor information by connecting the premotor, motor, anterior insular, and anterior cingulate cortices [41, 42]. The posterior midbody connects the somatosensory cortex [40]. The isthmus connects the auditory cortex [40]. The splenium connects the visual cortex [8]. Therefore the anterior regions, specifically the anterior midbody of the corpus callosum, are essential for generalization in atonic, tonic, and tonic-clonic seizures. In fact, the corpus callosum has been demonstrated to be the major anatomic pathway for seizure bilateralization and bisynchronization [43, 44]. The reason most generalized seizures persist but to a lesser degree following callosal resection is explained by other interhemispheric cortical connections. As mentioned earlier, there are seven different commissural pathways that connect the two cerebral hemispheres. Gloor and coworkers [45] provided an excellent illustration of this concept. Using depth electrode EEG recordings, they demonstrated that in some instances of temporal lobe epilepsy, seizure generalization to the contralateral hemisphere occurred via the hippocampal commissure, not the corpus callosum. Several patients with mesial temporal lobe epilepsy were found to have a seizure spread to the contralateral hippocampus before involvement of any other cortical structures. The only such pathway that would allow this type of propagation is the dorsal hippocampal commissure. Thus it is not unreasonable to expect some generalized seizures to occur even following complete sectioning of the corpus callosum.

17.5 Surgical Approach

17.5.1 Rationale

The corpus callosum is considered the most important pathway for interhemispheric spread of seizure activity. Severing the connections between the two hemispheres decreases the likelihood of seizure generalization. In modern epilepsy centers, anterior callosotomy is the most commonly performed initial procedure. The rationale for an anterior callosotomy with splenium sparing is to functionally disconnect the motor cortices while maintaining interhemispheric transfer of sensory information. Performing corpus callostomy in this manner helps reduce the risk of disconnection syndrome and other neuropsychological adverse events, which are discussed later in this chapter [9, 11, 46, 47].

17.5.2 Technique

Patients are maintained on antiepileptic therapy at preoperative doses. Prior to incision, patients are administered prophylactic antibiotics and corticosteroids. The head is placed in three-point cranial fixation, and the patient is positioned in the supine position in a manner that allows adequate exposure and visualization of the genu and splenium without significant brain retraction. This can be accomplished both in the supine lounge-chair and the lateral decubitus positions. Some surgeons prefer the lateral decubitus position because it utilizes gravity to retract the dominant hemisphere [8, 48]. Others feel that it allows additional brain shift that reduces the accuracy of frameless stereotactic navigation. Frameless stereotactic navigation is used for incision planning and to help determine the extent of callosal sectioning. A C-shaped scalp incision is made for interhemispheric exposure, allowing for craniotomy adjacent to the superior sagittal sinus (Fig. 17.1). Burr holes are created in the parasagittal plane spanning the coronal suture to allow the dura over the superior sagittal sinus to be exposed. This creates a bone flap that gives a direct approach to the interhemispheric fissure while reducing the risk of injury to the superior sagittal sinus.

The dura is opened with a C-shaped incision and reflected over the superior sagittal sinus (Fig. 17.2). Dural reflection should take into consideration any dural bridging veins, which are preserved to minimize risk of venous infarction. Dissection of the interhemispheric fissure is done using magnification and microdissection. Self-retaining retractors are used to gently retract the ipsilateral hemisphere. Typically, retraction is attained using a single self-retaining retractor. An additional retractor can be placed on the inferior aspect of the falx in order to widen the surgical corridor. The falx will protect the contralateral medial hemisphere from damage. Care must be taken to avoid bilateral damage when separating the two cingulate gyri.

The pericallosal arteries rest directly on the corpus callosum, which is easily distinguished from the medial hemispheric cortex by its glistening white and relatively avascular appearance (Fig. 17.3). One must be aware of anatomic variations such as fused or adherent arteries. In such cases, sometimes the best route of dissection is lateral to both arteries. If this route is taken, special care should be taken to preserve the delicate perforators originating from the cingulate gyrus. The callosal transection is carried out utilizing microaspiration and bipolar cautery. The most anterior portion of the splenium defines the posterior extent of callostomy. The anterior extent of resection is defined by the dorsal surface of the anterior cerebral arteries and the anterior commissure. The dissection begins posteriorly, working anteriorly with the aid of stereotactic image guidance.

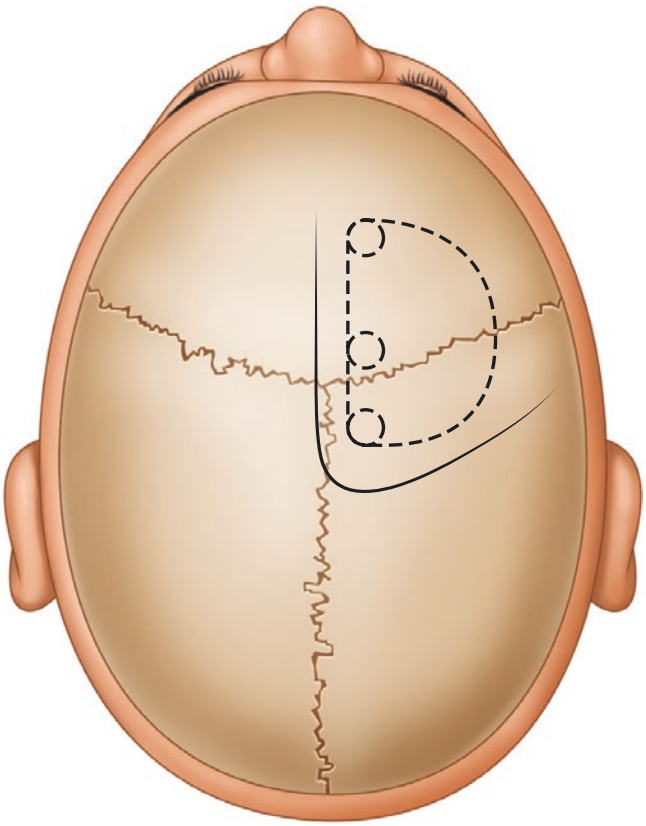

Fig. 17.1 Positioning, incision, and bone flap. The patient can be positioned in the supine or lateral decubitus position depending on surgeon preference. For simplicity, the patient is depicted in the supine position. A C-shaped scalp incision is made for interhemispheric exposure. Preoperative frameless stereotactic guidance is used for surgical planning to ensure adequate exposure and visualization of the genu and splenium. Craniotomy is carried out as close as possible to the superior sagittal sinus to help minimize brain retraction during exposure

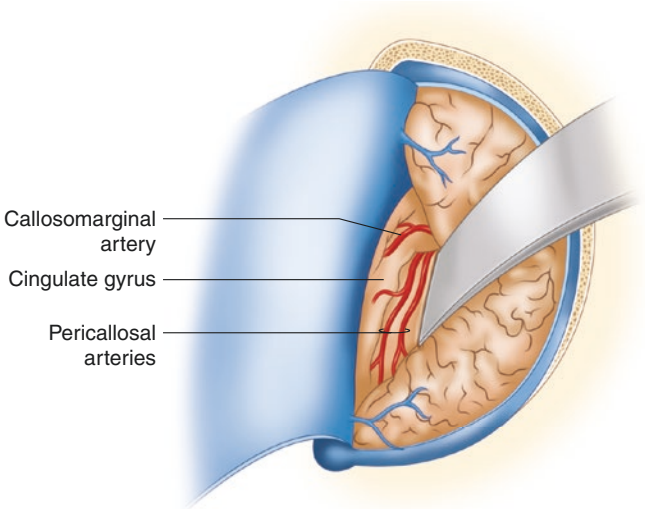

Fig. 17.2 Exposure. The dura is flapped over the superior sagittal sinus after bone flap removal. A retractor is placed on the ipsilateral medial cortex. Interhemispheric dissection proceeds in the pia-arachnoid plane, which if preserved allows visualization of the callosal marginal and pericallosal arteries

Although preservation of the ependyma of the lateral ventricles is ideal in order to prevent entry into the ventricular system, this is rarely possible because complete transection of all commissural fibers takes precedence. Irrigation, meticulous hemostasis, and standard closure are accomplished. The patient is observed in the neurologic intensive care unit overnight and transferred to the ward when stable. The patient is mobilized as soon as possible after surgery. Anticonvulsant medications are left unaltered and the decision regarding completion of callosotomy is revisited approximately 6 months after the initial procedure. Corticosteroids can be tapered based on clinical progress.

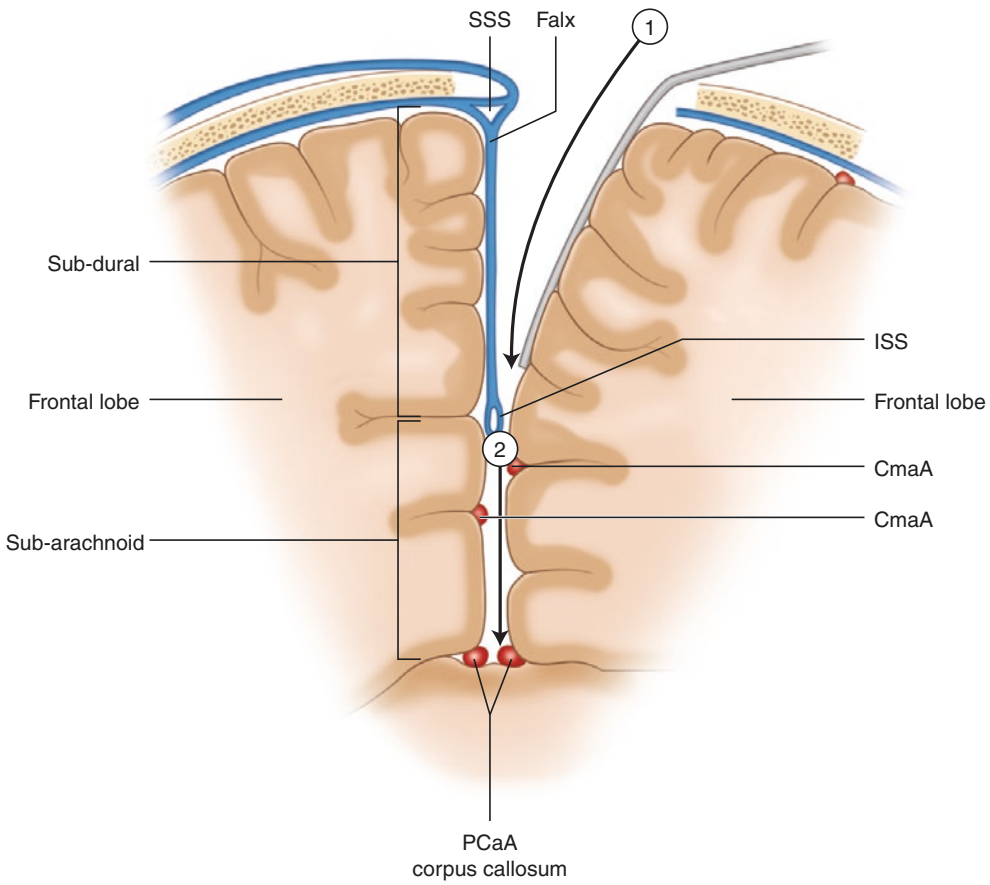

Fig. 17.3 Coronal view of interhemispheric approach. Dissection is first carried out in the subdural plane along the falx. Beyond the falx, dissection proceeds in the subarachnoid plane

17.6 Corpus Callosotomy Complications: Avoidance and Management

Postoperative surgical complications include infection, hydrocephalus, deep vein thrombosis, and epidural hematoma formation. The rates of these complications are as high as 25% in some series, but they rarely cause long-term or permanent effects [9, 12, 49]. The rate of infection is reduced by providing perioperative antibiotics. The incidence of hydrocephalus may be increased if the ventricle is entered and blood products are allowed to accumulate. The risk of deep venous thrombosis is reduced by using mechanical prophylaxis during and chemical prophylaxis after surgery. Dexamethasone may help prevent brain edema caused by retraction and reduce chemical meningitis [8].

Disconnection syndrome occurs as observed episodes in which movement and/or perception of stimuli appear to be under control of one hemisphere without apparent awareness in the other hemisphere. This syndrome is much more common with total resection of the corpus callosum than with anterior sectioning alone [9, 11, 46]. A classic is the alien hand syndrome (AHS), a condition in which a patient's nondominant hand acts without apparent guidance by the patient's own will [50]. The hallmark of AHS is the patient's perception of alienation from and loss of control over the nondominant hand [30]. Several other syndromes of disconnection have been identified after callosal sectioning but are beyond the scope of this chapter [11, 14, 51]. Disconnection syndrome can be minimized by maintaining a more anterior resection of the corpus callosum [30, 46]. Additionally, if a complete callosotomy must be performed, staging the procedure into multiple operations reduces long-lasting disconnection responses [11].

It is not known whether some cases of postoperative language disturbance (in particular extended periods of mutism) are caused by section of the corpus callosum or by retraction on what may be the dominant hemisphere for language. The patients selected for this operation are often those with complex brain dysfunction and organization. Language lateralization may not be easily determined in such patients, and some institutions do not assess language dominance in their preoperative evaluation. Most surgeons prefer to approach the corpus callosum from the right side, which may or may not be the nondominant one. Sass and colleagues [52] retrospectively reviewed all patients in their institution who underwent partial or total corpus callosotomy. Of the 32 patients reviewed, four were found to have clinically significant worsening of language function. Written language skills, verbal memory, and verbal reasoning abilities were impaired to varying degrees. All impairments were associated with crossed cerebral dominance. Three of the patients had severe difficulties and were right hemisphere-dominant for speech and were right-handed. One patient was agraphic after surgery but could speak normally and was left-hemisphere speech-dominant and left-handed. From their study and literature review they concluded that there are three different syndromes of language disturbance that can follow corpus callosotomy: (1) speech difficulty but spared writing, attributable to buccofacial apraxia; (2) speech and writing difficulties involving right hemisphere-dominant right-handed patients; and (3) dysgraphia with intact speech that occurs in left hemisphere-dominant left-handed patients. Thus, it is hard to establish the exact cause of difficulty in speech initiation, language impairment, and mutism [23]. Cases of language dysfunction typically last for only a few weeks [9, 11, 13], but long-term cases have rarely been reported [14]. These facts highlight the importance of preoperative language lateralization to prevent postoperative language deficits.

Transient neurologic deficits including motor dysfunction, nondominant leg and arm paresis or apraxia of varying degrees, decreased grasp in the nondominant hand, gait difficulty, and urinary incontinence have been described. It is postulated that these deficits occur as a result of disconnection or traction of the parasagittal cortex. These deficits are almost always transient and resolve within a few weeks to months [12, 17, 23, 28]. Permanent neurologic deficit following callosal sectioning is rare (<4%), especially since the introduction of microsurgical techniques [12, 28]. Death is an extremely rare occurrence and is typically remote from the operation [49, 53, 54].

17.7 Outcomes

Retrospective analysis has consistently shown that callosotomy is effective at reducing generalized seizures, especially drop attacks. Maehara and coworkers [9] retrospectively reviewed 52 patients at least 2 years following callosotomy. Seizure cessation or greater than 90% seizure reduction was achieved in 85% of patients with drop attacks, 32% of those with generalized tonic seizures, and 31% of those with generalized tonic-clonic seizures. Oguni and coworkers [31] reported similar results. In their study of 43 patients who underwent anterior callosotomy, drop attacks were the most frequent indication for surgery. Of those with drop attacks, 70% had significant benefit from anterior callosotomy. In Rossi's series [46], they found that 9 out of 19 patients with drop attacks were completely cured. In addition to these studies, other series confirm the significant beneficial decrease in seizure activity for patients with drop attacks, generalized tonic-clonic seizures, absence seizures, and myoclonic seizures [11, 17, 22, 54]. It should be noted that most of the studies showing beneficial seizure reduction are short-term studies without long-term follow-up. A meta-analysis studying long-term (greater than 5 years) outcome demonstrated

that only 35% of patients were free from drop attacks [55]. Further studies are needed to reconcile the differences between the short-term and long-term outcomes following callosotomy.

The overall daily function and behavioral consequences following corpus callosotomy have been well studied. Maehara and colleagues [9] showed that overall daily function, as assessed by families, improved in 62%, remained unchanged in 23%, and was impaired in 15% of patients. The changes included improvement in hyperactivity, emotional well-being, social contacts, speech function, and memory function. Turanli and coworkers [22] were able to show that some patients may improve significantly in activities of daily living. IQ scores typically do not change after corpus callosotomy. However, some patients with marked improvement of cognitive and language skills in whom seizure frequency was dramatically reduced had an overall intelligence and language improvement [9, 13, 22, 32]. This is likely attributable to a decrease in seizure frequency and/or a decrease in antiepileptic drug load. This is confirmed by Rougier and associates [25], who demonstrated a close inverse relationship between seizure frequency and improvement in quality of life. Maehara and coworkers [9] also demonstrated that improvement in quality of life occurs more often in children than in adults: greater than 70% versus 45%, respectively. They hypothesize that children have better functional outcomes because younger brains have more "plasticity" and are therefore better able to compensate for the disconnected corpus callosum.

17.8 Role of Corpus Callosotomy in Epilepsy Surgery

Corpus callostomy has demonstrated efficacy in reducing generalized seizures of all types, especially drop attacks, which are the main indication for the procedure today. It is a palliative procedure performed in patients with generalized seizures who have failed anticonvulsant therapy and are without a resectable lesion.

Conclusions

Corpus callosotomy is a safe and effective palliative surgical procedure. Currently, partial anterior resection is favored over total callosotomy because of the risk of developing long-term disconnection syndromes. Future research utilizing newer imaging techniques, such as functional MRI, may lead to a better understanding of the callosal connections generating and propagating seizures. Deeper understanding of the topographic anatomy of the corpus callosum might allow for more refined callosal sectioning, eliminating many of the side effects of current therapy.

References

1. Mathews MS, Linskey ME, Binder DK. William P. van Wagenen and the first corpus callosotomies for epilepsy. J Neurosurg. 2008;108:608–13.
2. Bogen JE, Fisher ED, Vogel PJ. Cerebral commissurotomy. A second case report. JAMA. 1965;194:1328–9.
3. Luessenhop AJ. Interhemispheric commissurotomy: (the split brain operation) as an alternate to hemispherectomy for control of intractable seizures. Am Surg. 1970;36:265–8.
4. Luessenhop AJ, Dela Cruz TC, Fenichel GM. Surgical disconnection of the cerebral hemispheres for intractable seizures. Results in infancy and childhood. JAMA. 1970;213:1630–6.
5. Eder HG, Feichtinger M, Pieper T, Kurschel S, Schroettner O. Gamma knife radiosurgery for callosotomy in children with drug-resistant epilepsy. Childs Nerv Syst. 2006;22:1012–7.
6. Marino JR. Surgery for epilepsy. Selective partial microsurgical callosotomy for intractable multiform seizures: criteria for clinical selection and results. Appl Neurophysiol. 1985;48:404–7.
7. Feichtinger M, Schrottner O, Eder H, Holthausen H, Pieper T, Unger F, et al. Efficacy and safety of radiosurgical callosotomy: a retrospective analysis. Epilepsia. 2006;47:1184–91.
8. Asadi-Pooya AA, Sharan A, Nei M, Sperling MR. Corpus callosotomy. Epilepsy Behav. 2008;13:271–8.
9. Maehara T, Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia. 2001;42:67–71.
10. Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE. Response of multiple seizure types to corpus callosum section. Epilepsia. 1987;28:28–34.
11. Kim DS, Yang KH, Kim TG, Chang JH, Chang JW, Choi JU, et al. The surgical effect of callosotomy in the treatment of intractable seizure. Yonsei Med J. 2004;45:233–40.
12. Maehara T, Shimizu H, Oda M, Arai N. Surgical treatment of children with medically intractable epilepsy--outcome of various surgical procedures. Neurol Med Chir (Tokyo). 1996;36:305–9.
13. Mamelak AN, Barbaro NM, Walker JA, Laxer KD. Corpus callosotomy: a quantitative study of the extent of resection, seizure control, and neuropsychological outcome. J Neurosurg. 1993;79:688–95.
14. Jenssen S, Sperling MR, Tracy JI, Nei M, Joyce L, David G, et al. Corpus callosotomy in refractory idiopathic generalized epilepsy. Seizure. 2006;15:621–9.
15. Purves SJ, Wada JA, Woodhurst WB, Moyes PD, Strauss E, Kosaka B, et al. Results of anterior corpus callosum section in 24 patients with medically intractable seizures. Neurology. 1988;38:1194–201.
16. Pinard JM, Delalande O, Chiron C, Soufflet C, Plouin P, Kim Y, et al. Callosotomy for epilepsy after West syndrome. Epilepsia. 1999;40:1727–34.
17. Cukiert A, Burattini JA, Mariani PP, Camara RB, Seda L, Baldauf CM, et al. Extended, one-stage callosal section for treatment of refractory secondarily generalized epilepsy in patients with Lennox-Gastaut and Lennox-like syndromes. Epilepsia. 2006;47:371–4.
18. Kwan SY, Lin JH, Wong TT, Chang KP, Yiu CH. A comparison of seizure outcome after callosotomy in patients with Lennox-Gastaut syndrome and a positive or negative history for West syndrome. Seizure. 2006;15:552–7.
19. Rasmussen T, Olszewski J, Lloydsmith D. Focal seizures due to chronic localized encephalitis. Neurology. 1958;8:435–45.
20. Rasmussen T. Further observations on the syndrome of chronic encephalitis and epilepsy. Appl Neurophysiol. 1978;41:1–12.
21. Tinuper P, Andermann F, Villemure JG, Rasmussen TB, Quesney LF. Functional hemispherectomy for treatment of epilepsy associated with hemiplegia: rationale, indications, results, and comparison with callosotomy. Ann Neurol. 1988;24:27–34.
22. Turanli G, Yalnizoglu D, Genc-Acikgoz D, Akalan N, Topcu M. Outcome and long term follow-up after corpus callosotomy in childhood onset intractable epilepsy. Childs Nerv Syst. 2006;22:1322–7.

23. Wong TT, Kwan SY, Chang KP, Hsiu-Mei W, Yang TF, Chen YS, et al. Corpus callosotomy in children. Childs Nerv Syst. 2006;22:999–1011.
24. Reutens DC, Bye AM, Hopkins IJ, Danks A, Somerville E, Walsh J, et al. Corpus callosotomy for intractable epilepsy: seizure outcome and prognostic factors. Epilepsia. 1993;34:904–9.
25. Rougier A, Claverie B, Pedespan JM, Marchal C, Loiseau P. Callosotomy for intractable epilepsy: overall outcome. J Neurosurg Sci. 1997;41:51–7.
26. Sorenson JM, Wheless JW, Baumgartner JE, Thomas AB, Brookshire BL, Clifton GL, et al. Corpus callosotomy for medically intractable seizures. Pediatr Neurosurg. 1997;27:260–7.
27. Papo I, Quattrini A, Ortenzi A, Paggi A, Rychlicki F, Provinciali L, et al. Predictive factors of callosotomy in drug-resistant epileptic patients with a long follow-up. J Neurosurg Sci. 1997;41:31–6.
28. Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. Epilepsia. 2006;47:115–22.
29. Hanson RR, Risinger M, Maxwell R. The ictal EEG as a predictive factor for outcome following corpus callosum section in adults. Epilepsy Res. 2002;49:89–97.
30. Geschwind DH, Iacoboni M, Mega MS, Zaidel DW, Cloughesy T, Zaidel E. Alien hand syndrome: interhemispheric motor disconnection due to a lesion in the midbody of the corpus callosum. Neurology. 1995;45:802–8.
31. Oguni H, Olivier A, Andermann F, Comair J. Anterior callosotomy in the treatment of medically intractable epilepsies: a study of 43 patients with a mean follow-up of 39 months. Ann Neurol. 1991;30:357–64.
32. Rathore C, Abraham M, Rao RM, George A, Sankara Sarma P, Radhakrishnan K. Outcome after corpus callosotomy in children with injurious drop attacks and severe mental retardation. Brain and Development. 2007;29:577–85.
33. Zarei M, Johansen-Berg H, Smith S, Ciccarelli O, Thompson AJ, Matthews PM. Functional anatomy of interhemispheric cortical connections in the human brain. J Anat. 2006;209:311–20.
34. Winn R. Youmans neurological surgery. Philadelphia, PA: Elsevier; 2011.
35. Musiek FE. Neuroanatomy, neurophysiology, and central auditory assessment. Part III: Corpus callosum and efferent pathways. Ear Hear. 1986;7:349–58.
36. Hofer S, Frahm J. Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. NeuroImage. 2006;32:989–94.
37. Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, et al. Human motor corpus callosum: topography, somatotopy, and link between microstructure and function. J Neurosci. 2007;27:12132–8.
38. Kaas JH. In: RD RAG, editor. The organization of the callosal connections in primates. New York: Plenum Press; 1995.
39. Waxman SG. Lange clinical neuroanatomy. 25th ed. New York: McGraw-Hill; 2003.
40. Funnell MG, Corballis PM, Gazzaniga MS. Cortical and subcortical interhemispheric interactions following partial and complete callosotomy. Arch Neurol. 2000;57:185–9.
41. Pandya DN, Karol EA, Heilbronn D. The topographical distribution of interhemispheric projections in the corpus callosum of the rhesus monkey. Brain Res. 1971;32:31–43.
42. de Lacoste MC, Kirkpatrick JB, Ross ED. Topography of the human corpus callosum. J Neuropathol Exp Neurol. 1985;44:578–91.
43. Theodore WH, Porter RJ, Albert P, Kelley K, Bromfield E, Devinsky O, et al. The secondarily generalized tonic-clonic seizure: a videotape analysis. Neurology. 1994;44:1403–7.
44. Matsuo A, Ono T, Baba H, Ono K. Callosal role in generation of epileptiform discharges: quantitative analysis of EEGs recorded in patients undergoing corpus callosotomy. Clin Neurophysiol. 2003;114:2165–71.
45. Gloor P, Salanova V, Olivier A, Quesney LF. The human dorsal hippocampal commissure. An anatomically identifiable and functional pathway. Brain. 1993;116:1249–73.
46. Rossi GF, Colicchio G, Marchese E, Pompucci A. Callosotomy for severe epilepsies with generalized seizures: outcome and prognostic factors. Acta Neurochir (Wien). 1996;138:221–7.
47. Volpe BT, Sidtis JJ, Holtzman JD, Wilson DH, Gazzaniga MS. Cortical mechanisms involved in praxis: observations following partial and complete section of the corpus callosum in man. Neurology. 1982;32:645–50.
48. Fuiks KS, Wyler AR, Hermann BP, Somes G. Seizure outcome from anterior and complete corpus callosotomy. J Neurosurg. 1991;74:573–8.
49. Shimizu H. Our experience with pediatric epilepsy surgery focusing on corpus callosotomy and hemispherotomy. Epilepsia. 2005;46(Suppl 1):30–1.
50. Assal F, Schwartz S, Vuilleumier P. Moving with or without will: functional neural correlates of alien hand syndrome. Ann Neurol. 2007;62:301–6.
51. Andersen B, Rogvi-Hansen B, Kruse-Larsen C, Dam M. Corpus callosotomy: seizure and psychosocial outcome. A 39-month follow-up of 20 patients. Epilepsy Res. 1996;23:77–85.
52. Sass KJ, Novelly RA, Spencer DD, Spencer SS. Postcallosotomy language impairments in patients with crossed cerebral dominance. J Neurosurg. 1990;72:85–90.
53. Clarke DF, Wheless JW, Chacon MM, Breier J, Koenig MK, McManis M, et al. Corpus callosotomy: a palliative therapeutic technique may help identify resectable epileptogenic foci. Seizure. 2007;16:545–53.
54. Wilson DH, Reeves A, Gazzaniga M, Culver C. Cerebral commissurotomy for control of intractable seizures. Neurology. 1977;27:708–15.
55. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. Brain. 2005;128:1188–98.

Vagus Nerve Stimulation for Refractory Epilepsy

18

Tomislav Sajko and Krešimir Rotim

18.1 Introduction

Vagus nerve stimulation (VNS) has confirmed its seizure suppression effect by randomized control trials [1]. More than 50% of seizure reductions have been reported in approximately 50% of patients after 2 years of treatment [2]. Independently of the reduction in seizure frequency, it has been reported that VNS improves attention, cognition, behavior, mood, and quality of life [3]. The hypothesis that afferent vagal signals modulate abnormal cortical excitability via various pathways has not been fully clarified. The relevant anatomy and physiology of the vagal nerve as well as indications for its clinical use and the implant operative technique are described.

T. Sajko (✉) · K. Rotim
Department of Neurosurgery, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia

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18.2 Anatomy and Physiology Relevant to the Vagus Nerve

Nervus vagus (N.X) is a mixed parasympathetic efferent nerve consisting of ~80% sensory fibers that provide the brain with visceral sensation from the head, neck, thorax, and abdomen [4, 5]. The right and left vagus nerves, which develop symmetrically, carry different kinds of information as the abdominal and thoracic organs rotate into their adult position. The right vagus nerve becomes more closely associated with the cardiac atria, and the left vagus nerve becomes associated with the cardiac ventricles [6]. Because vagal innervation of the cardiac ventricles is less dense than that of the atria, stimulation of the left vagal nerve is associated with fewer cardiac effects. The right vagus nerve rotates posteriorly in the abdomen and transports information from the hepatic and duodenal branches of the nerve. The left vagus nerve rotates anteriorly to innervate the fundus of the stomach [7].

The *ganglion nodosum* (ganglion inferior n. vagi) contains somatic and visceral sensory neurons. It is located along the course of the nerve just below the jugular foramen. Visceral neurons of the ganglion nodosum relay information to the *nucleus tractus solitarius* (NTS) about internal organ systems. The NTS relays the sensory information through three main pathways [8]. In the first pathway it feeds information back to autonomic preganglionic and related somatic motor neurons located in the medulla and spinal cord [9, 10]. This feedback causes the heart rate to slow when blood pressure increases (the baroreceptor reflex) and respiration to cease as a result of pulmonary stretch (Herring-Breuer reflex, triggered by vagal afferents). The second main NTS output pathway is to the reticular formation of the medulla. The medulla coordinates various autonomic and respiratory reflexes [11]. Activation of these pathways probably causes the respiratory side effects of VNS.

The third main NTS pathway is the ascending projection to the forebrain. Most of the output of the NTS is relayed by the *nucleus parabrachialis*, which is in the dorsal pons lateral to the locus ceruleus [11]. The nucleus parabrachialis gives visceral sensory input to every level of the forebrain [12], particularly the regions of the hypothalamus that control endocrine and visceral functions.

Several major pathways may affect the thalamocortical system and may modulate seizure activity. The nucleus parabrachialis provides direct input to several components of the thalamus. One part of this pathway innervates the *nucleus parvocellularis ventroposterior*, which acts as a relay for visceral sensation to the insular cortex [13]. The insular cortex is a visceral sensory cortex and contains a topographic map of the internal organ systems.

A region of the visceral motor cortex occupies the anterior tip of the cingulate gyrus, termed the infralimbic cortex [14]. The infralimbic cortex receives input from the visceral sensory cortex. Both these cortical areas also receive direct input from the nucleus parabrachialis [15, 16]. Therefore, abnormal visceral sensations from the VNS and reflex responses may be relayed by this pathway.

The nucleus parabrachialis also projects to the thalamic *nucleus intralaminaris* [12]. This pathway has more widespread effects on cortical activity because the nucleus intralaminaris projects widely into the cerebral cortex. Other projections from the nucleus parabrachialis and the NTS provide visceral sensation to the hypothalamus, amygdala, and basal forebrain. Both the lateral hypothalamus and basal forebrain contain neurons that project diffusely to the cerebral cortex, and these pathways also have the potential to influence overall cortical activity [17].

The above-mentioned nuclei have been shown to influence cerebral seizure susceptibility. Vagal modulation of one or more of these nuclei could represent the mechanism for seizure suppression [18].

The immunomodulatory function of the vagus nerve is of particular interest. Afferent signals can activate the so-called cholinergic anti-inflammatory pathway when inflammation occurs. Through this pathway, efferent vagus nerve fibers inhibit the release of pro-inflammatory cytokines and in this way reduce inflammation. In recent years, inflammation has been strongly implicated in the development of seizures and epilepsy; therefore the activation of the anti-inflammatory pathway by VNS could decrease the inflammatory response and thereby explain its clinical effects. In addition to anticonvulsive effects, VNS might have positive effects on behavior, mood, and cognition [19].

It is well known that stimulation of the vagal nerve causes EEG changes [20]. Mechanical vagal or glossopharyngeal stimuli induce EEG slowing [21]. Experiments in animals have demonstrated that repetitive vagal stimulation can cause synchronization or desynchronization of the EEG, depending on stimulus frequency and current strength [22]. High-intensity, high-frequency (>70 Hz) vagal stimulation produces desynchronization of the cortical EEG, but lower intensity stimulation at the same rate causes synchronization.

These findings suggest that each class of vagal afferent feeds in its own way into the pathways that lead to forebrain thalamocortical regulation and that adjustment of the intensity and frequency of vagal stimulation would be necessary to disrupt seizures. The effects of VNS on activation of human central nervous system structures have been studied with positron emission tomography (PET), reporting changes in regional blood flow during VNS in the ipsilateral anterior thalamus and cingulate cortex and the contralateral thalamus and temporal cortex and ipsilateral putamen and cerebellum [23, 24].

VNS may alter cerebral blood flow in ways that are different from changes in local neuronal activation [25]. VNS was tested in several animal models of epilepsy, usually just before or after seizures occurred, because its presumed mechanism of action was transient desynchronization of cortical rhythms [26, 27].

Most vagus nerve fibers are small-diameter unmyelinated *C* fibers; the rest are intermediate-diameter myelinated *B* fibers and large-diameter myelinated *A* fibers. There are direct relationships between vagal fiber diameter and conduction velocity and between fiber diameter and stimulation threshold. The anticonvulsant effect of VNS in experimental animals requires *C* fiber stimulation. There is a direct relationship between effectiveness and the fraction of *C* fibers stimulated as well as between delay of stimulus and duration of seizure.

After seizure onset, the greater the delay before vagal stimulation, the longer the seizure duration. Stimulation is best applied as soon as possible after seizure onset, suggesting that VNS is raising the seizure threshold by releasing y-aminobutyric acid (GABA) and glycine in widespread brain structures [28]. Persisting anticonvulsant action of VNS beyond the stimulation period was demonstrated [29]. Although safety considerations and battery life make it impractical to apply continuous VNS, the results of Takaya et al. [29] suggest that 30-sec on/5-min off intermittent stimulation is reasonable with regard to efficacy and safety.

18.3 Clinical Use and Patient Selection

In 1988, the first human implant of the neurocybernetic prosthesis (NCP) was performed. After the successful implantation of the device, clinical studies were performed and confirmed the long-term safety, efficacy, feasibility, and tolerability of the VNS and durability of the NCP. In 1994, the European Community approved the use of the NCP for VNS in the treatment of refractory epilepsy, and in 1997 the U.S. Food and Drug Administration gave its approval. Other controlled studies followed, including the E05 trial [30]. In this study, 198 patients were assigned blindly to either a high-stimulation group (95 patients) or a low-stimulation group (103 patients). The mean decrease in seizure frequency at 3 months was 28% in the high-stimulation group compared with 15% in the low-stimulation group ($p = 0.039$). A reduction in seizure frequency greater than 75% was noted in 11% of the patients in the high-stimulation group. After the initial phase, 195 of patients were maintained in the research group. All those patients initially assigned to the low-stimulation group were crossed over to receive the high stimulation therapeutic dose. Patients were followed up for at least 12 months. The median reduction of seizure frequency after the completion of the study was 45%. Of the entire group, 35% had a reduction of at least 50%, and 20% had a reduction in seizures of at least 75%. In a retrospective 12-year follow-up study, Uthman et al. found a mean seizure reduction of 26% after 1 year, 30% after 5 years, and 52% after 12 years with VNS treatment. Forty-eight patients were followed up in this study group. The added benefit of prolonged stimulation included drug reduction in this patient population [31].

In terms of efficacy VNS offers a decrease in seizure frequency close to 50% in a third of the patients [32]. All these studies proved the safety, efficacy, and tolerability of VNS in the management of refractory epilepsy.

Epilepsy affects up to 1% of the general population. Despite recent advances in the understanding of the molecular and cellular basis of epilepsy, satisfactory seizure control is not achieved in approximately 30% of patients. Those patients are considered medically intractable and regarding the seizure frequency, seizure type, and overall data potential candidates for NCP implantation. The selection criteria for VNS are still evolving and are influenced by states' health systems, institutional standards, and general guidelines [33].

Good results have been achieved in children with Lennox-Gastaut or other primary generalized seizure syndromes [34, 35]. Patients with idiopathic epilepsy and patients in whom previous surgical procedures failed are considered appropriate candidates [36].

VNS cannot be inserted in patients who have had prior left cervical vagotomy. It is relatively contraindicated in patients with progressive neurologic disease, cardiac arrhythmias, asthma, chronic obstructive pulmonary disease, and insulin-dependent diabetes mellitus.

18.4 Vagus Nerve Stimulation Therapy System

18.4.1 Left Cervical Vagus Nerve Stimulation

The device is composed of a generator attached to a bipolar VNS lead. The generator is powered by a single lithium battery encased in a hermetically sealed titanium module. A handheld computer programs the pulse generator stimulation parameters via a programming wand placed on the skin over the device. The programmable parameters are the current charge (electrical stimulus intensity, measured in milliamperes [mA]), the pulse width (electrical pulse duration, measured in microseconds), the pulse frequency (measured in Herz [Hz]), and the on/off duty cycle (the stimulus on-time and off-time, measured in seconds or minutes). Initial settings for the four parameters can be adjusted to optimize efficacy (for seizure control or for other symptom control, depending on the indication) and tolerability. The generator runs continuously, but patients can turn off VNS temporarily by holding a magnet over the device, and VNS can be turned on and off by the programmer. The pulse generator battery life depends on the stimulus parameters, and it can be replaced or permanently removed in a simple surgical procedure.

The bipolar lead is isolated by a silicone elastomer and can be safely implanted in patients with latex allergies. One end of the lead contains a pair of connector pins that inserts directly into the generator, whereas the opposite end contains an electrode array consisting of three discrete helical coils that wrap around the vagus nerve.

The hand-held magnet performs several functions. When briefly passed across the chest pocket it triggers a train of stimulation superimposed on the baseline output. Such on-demand stimulation can be initiated by the patient or a companion at the onset of an aura in an effort to diminish or even abort an impending seizure.

Patients are instructed to test the function of their device periodically by performing magnet-induced activation and verifying that stimulation occurs.

18.5 Transcutaneous Vagus Nerve Stimulation

The use of transcutaneous vagus nerve stimulation (t-VNS) for treating epilepsy was first proposed in 2000 [37]. The outer ear is supplied by three sensory nerves: the auriculotemporal nerve, the great auricular nerve, and the auricular branch of the vagus nerve [38]. The external auditory meatus and concha of the ear are supplied mainly by the vagus nerve auricular branch, and the cymba conchae is supplied exclusively by the auricular branch. A transcutaneous method of VNS (t-VNS) targets the cutaneous receptive field of the vagus nerve auricular branch. Applying an electrical stimulus to the left cymba conchae (using a stimulus intensity above the sensory detection threshold but below the pain threshold) results in a brain activation pattern similar to that of left cervical VNS [39, 40].

18.6 Operative Procedure for Implanting the Neurocybernetic Prosthesis (NCP)

18.6.1 Anatomy of the Carotid Sheath

The carotid sheath is a tube-shaped fascia wrapping the common carotid artery, internal carotid artery, internal jugular vein, and nervus vagus. It lies anterolateral to the cervical sympathetic trunk behind the sternocleidomastoid muscle (SCM). The sheath blends with the thyroid fascia anteromedially and with the deep surface of sternocleidomastoid muscle anterolaterally. Posteriorly it is attached to prevertebral fascia along the tips of the transverse processes of vertebrae. It ends at the base of the skull, where it attaches around the jugular foramen and carotid canal. Inferiorly, the carotid sheath fuses with scalene fascia, adventitia of great vessels, and the fibrous pericardium. Within the sheath, the common carotid artery is medial, the internal jugular vein lateral, and the nerve posterior and between the vessels.

18.6.2 Operative Procedure

Insertion of the NCP device is performed under general anesthesia. Prophylactic antibiotics are administered preoperatively and maintained for 24 h postoperatively. The patient is in a supine position with a shoulder roll beneath the scapulae to provide mild neck extension. This facilitates connecting separate incisions in the neck and chest using a tunneling tool. The head is rotated 30 ° toward the right, making the left sternocleidomastoid muscle prominent.

A transverse chest incision is made approximately four finger widths below the clavicle. The underlying fat is dissected to the level of the pectoralis fascia, and a subcutaneous pocket is fashioned superiorly. A cervical skin incision is performed in a natural crease for cosmetic purposes. The platysma and subplatysmal fasciae are dissected until the carotid sheath is exposed. After palpation of the carotid pulse, the neurovascular bundle is identified and sharply incised to reveal its contents. Within the carotid sheath the vagus nerve is generally found deep and medial to the internal jugular vein, encased in firm tissue lateral to the common carotid artery.

The nerve trunk is identified and dissected with the aid of the operating microscope. At least 3–4 cm of the nerve must be completely freed from the surrounding tissues. The insertion of a background plastic sheet between the nerve and the underlying vessels greatly facilitates the subsequent steps of the procedure (Fig. 18.1).

A tunneling tool is then used to create a subcutaneous tract between the two incisions. The tool is directed from the cervical to the pectoral site in order to minimize potential injury to the vascular structures of the neck.

A small or large helical electrode is selected, depending on the size of the exposed nerve. The lead connector pins are passed through the tunnel and emerge from the chest incision, whereas the helical electrodes remain exposed in the cervical region. Before applying the electrodes, the lead wire should be directed parallel and lateral to the nerve, with the coils occupying the gap between them. Each coil is applied by grasping the suture tail at either end and stretching the coil until its convolutions are eliminated. The central turn of coil is applied perpendicularly across or beneath the vagus trunk and wrapped around the surface of the nerve. The coil is then redirected parallel to the nerve as the remainder of its loops are applied proximal and distal to this midpoint (Fig. 18.2).

After the preimplant, the testing generator is retracted into the subcutaneous pocket and secured to the pectoralis fascia. To prevent abrasion of the lead it should not be placed behind the pulse generator. Wound closure then proceeds in standard multilayer fashion, using a subcuticular stitch for the skin.

The generator is turned on 10–14 days postoperatively. The current output is adjusted to tolerance, using a 30-Hz signal frequency with a 500-msec pulse width for 30 s of "on" and 5 min of "off" time. A handheld magnet is given to the patient or his/her companion. Stimulation can be modulated or terminated via this magnet. Several generator models have been developed, with each successive model having smaller dimensions to improve cosmetic outcome.

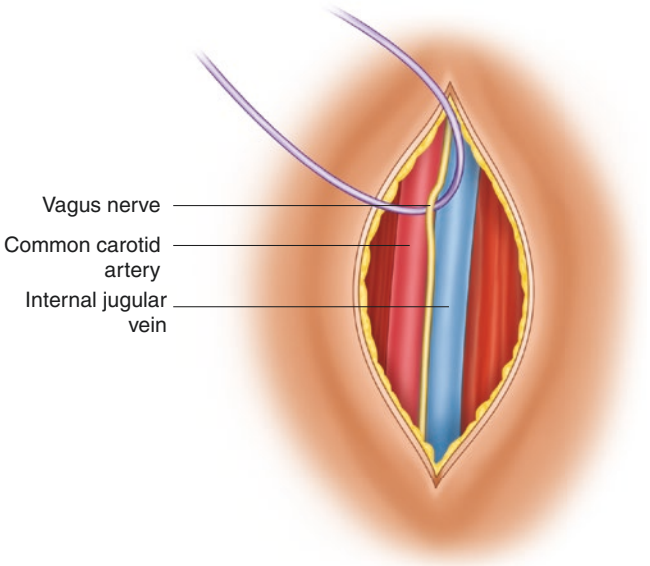

Fig. 18.1 Surgical anatomy of the vagus nerve in the carotid sheath. Nervus vagus, lifted with a elastic band, located between the common carotid artery and the internal jugular vein

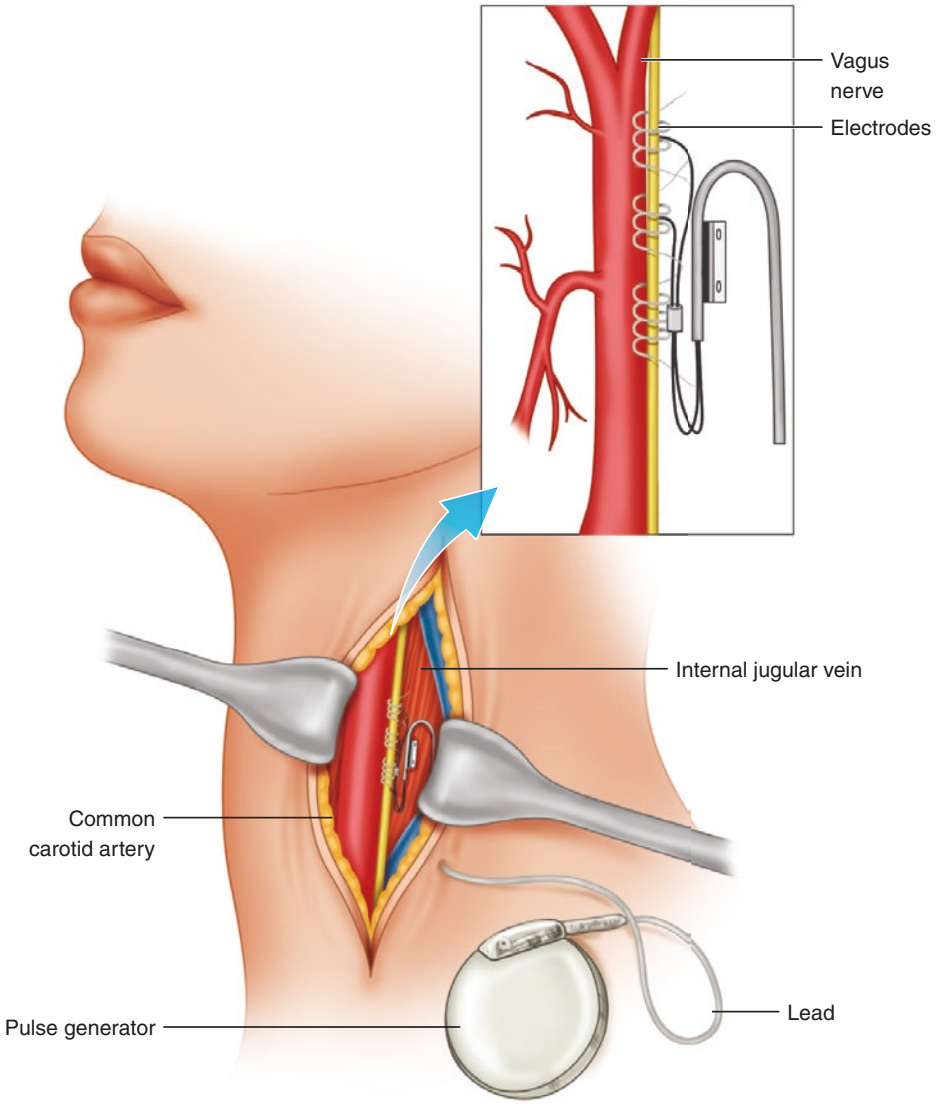

Fig. 18.2 Neck dissection illustrating a vagus nerve system. An infraclavicular seated generator is connected via three leads wrapped around the left vagus nerve. The electrical activity produced by the generator affects the nervus vagus afferent fibers influencing the seizure suppression [41]

18.7 Overall VNS Consideration

In 2015 Panebianco et al. reported a review of five randomized controlled trials that recruited 439 participants [42–48]. Results of the overall efficacy analysis showed that people receiving high VNS stimulation were 1.73 (95% CI, 1.13–2.64) times more likely to have reduced seizures compared to those receiving low stimulation. This effect did not vary substantially and remained statistically significant for both the best and worst cases, accounting for missing outcome data in one study. All included studies were of short duration, so no conclusions can be drawn about long-term efficacy of VNS. Results for treatment withdrawal rates of high and low stimulation groups were similar. The most common adverse events were voice alteration and hoarseness, cough, dyspnea, pain, paresthesias, nausea, headache, and wound infection.

For these adverse effects, voice alteration/hoarseness and dyspnea were more than twice as likely to occur in people receiving high stimulation. Only three out of sixty-four subjects exited early in the study comparing rapid versus mild versus slow stimulation: one developed a device infection, requiring removal, one could not tolerate stimulation (high stimulation group), and one was lost to follow-up. This total percentage withdrawal rate of 4.7% suggests that the treatment is well tolerated.

Experience in epilepsy populations has shown that VNS is effective, safe, and well tolerated in pediatric patients [49]. There are no identified risks when VNS is used during pregnancy. VNS is safe and compatible to use together with psychotropic drugs and with electroconvulsive therapy (ECT). Whole body MRI scans cannot be done with VNS implants, but MRI scans of the head are possible using a transmit/receive head coil [50].

Diagnostic ultrasound is safe, but shortwave, microwave, or therapeutic ultrasound diathermy should not be used. Metal detectors, microwave ovens, cellular telephones, and other electrical or electronic devices will not affect VNS.

Despite all the positive effects, VNS is not an alternative to conventional epilepsy surgery, and it should be considered in patients in whom surgery is not indicated after an extensive presurgical evaluation.

References

1. Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, et al. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Neurology. 1998;51:48–55.
2. Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav. 2011;20:57–63.
3. Hallböök T, Lundgren J, Stjernqvist K, Blennow G, Strömblad LG, Rosén I. Vagus nerve stimulation in 15 children with therapy resistant epilepsy: its impact on cognition, quality of life, behavior and mood. Seizure. 2005;14:504–13.
4. Foley JO, DuBois F. Quantitative studies of the vagus nerve in the cat. I. The ratio of sensory and motor fibers. J Comp Neurol. 1937;67:49–97.
5. Agostini E, Chinnock JE, Daly MD, Murray JG. Functional and histological studies of the vagus nerve and its branches to the heart, lungs, and abdominal viscera in the cat. J Physiol. 1957;135:182–205.
6. Saper CB, Kibbe MR, Hurley KM, Spencer S, Holmes HR, Leahy KM, et al. Brain natriuretic peptidelike immunoreactive innervation of the cardiovascular and cerebrovascular systems in the rat. Circ Res. 1990;67:1345–54.
7. Prechtl JC, Powley TL. Organization and distribution of the rat subdiaphragmatic vagus and associated paraganglia. J Comp Neurol. 1985;235:82–95.
8. Schahter SC, Saper CB. Vagus nerve stimulation. Epilepsia. 1998;39:677–86.
9. Loewy AD, Burton H. Nuclei of the solitary tract: efferent projections to the lower brain stem and spinal cord. J Comp Neurol. 1978;18:421–50.
10. Ruggiero DA, Cravo SL, Arango V, Reis DJ. Central control of the circulation by the rostral ventrolateral reticular nucleus: anatomical substrates. Prog Brain Res. 1989;81:49–79.
11. Saper CB. The central autonomic system. In: Paxinos G, editor. The rat nervous system. 2nd ed. San Diego: Academic; 1995. p. 107–31.
12. Fulwiler CE, Saper CB. Subnuclear organization of the efferent connections of the parabrachial nucleus in the rat. Brain Res Rev. 1984;7:229–59.
13. Cechetto DF, Saper CB. Evidence for a viscerotopic sensory representation in the cortex and thalamus in the rat. J Comp Neurol. 1987;262:27–45.
14. Hurley KM, Herbert H, Moga MM, Saper CB. Efferent connections of the infralimbic cortex of the rat. J Comp Neurol. 1991;308:249–76.
15. Saper CB. Reciprocal parabrachial-cortical projections in the rat. Brain Res. 1982;242:33–40.
16. Allen GV, Saper CB, Hurley KM, Cechetto DF. Organization of visceral and limbic connections in the insular cortex of the rat. J Comp Neurol. 1991;31:1–16.
17. Saper CB. Diffuse cortical projection systems: anatomical organization and role in cortical function. In: Plum F, editor. Handbook of physiology. The nervous system V. Bethesda: American Physiological Society; 1987. p. 169–210.
18. Krahl SE, Clark KB. Vagus nerve stimulation for epilepsy: a review of central mechanisms. Surg Neurol Int. 2012;3(Suppl 4):S255–9.
19. Vonck K, Raedt R, Naulaerts J, De Vogelaere F, Thiery E, van Roost D, et al. Vagus nerve stimulation 25 years later! What do we know about the effects on cognition? Neurosci Biobehav Rev. 2014;45:63–71.
20. Zanchetti A, Wpg SC, Moruzzi G. The effect of vagal stimulation on the EEG pattern of the cat. Electroencephalogr Clin Neurophysiol. 1952;4:357–461.
21. Gamier L. EEG modifications produced by gastric distention in cats. C R Soc Seances Soc Biol Fil. 1968;162:2164–8.
22. Bridgers SL, Spencer SS, Spencer DD, Sasalu CT. A cerebral effect of carotid sinus stimulation. Observation during intraoperative electroencephalographic monitoring. Arch Neurol. 1985;42:574–7.
23. Garnett ES, Nahmias C, Scheffel A, Firnau G, Upton ARM. Regional cerebral blood flow in man manipulated by direct vagal stimulation. Pacing Clin Electrophysiol. 1992;15:1579–80.
24. Ko D, Heck C, Grafton S, Apuzzo ML, Couldwell WT, Chen T, et al. Vagus nerve stimulation activates central nervous system structures in epileptic patients during PET H2150 blood flow imaging. Neurosurgery. 1996;39:426–31.

25. Reis DJ, Iadecola C, Nakai M. Control of cerebral blood flow and metabolism by intrinsic neural systems in brain. In: Plum F, Pulsinelli W, editors. Cerebrovascular diseases. New York: Raven Press; 1985. p. l–25.
26. McLachlan RS. Suppression of interictal spikes and seizures by stimulation of the vagus nerve. Epilepsia. 1993;34:918–23.
27. Woodbury DM, Woodbury JW. Effects of vagal stimulation on experimentally induced seizures in rats. Epilepsia. 1990;3(Suppl 2):S7–19.
28. Ben-Menachem E, Hamberger A, Hedner T, Hammond EJ, Uthman BM, Slater J, et al. Effects of vagus nerve stimulation on amino acids and other metabolites in the CSF of patients with partial seizures. Epilepsy Res. 1995;20:221–7.
29. Takaya M, Terry WJ, Naritoku DK. Vagus nerve stimulation induces a sustained anticonvulsant effect. Epilepsia. 1996;37:111–4.
30. Morris GL, Mueller WM. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. The Vagus nerve stimulation study group E01-E05. Neurology. 1999;53:1731–5.
31. Uthman BM, Reichl AM, Dean JC, Eisenschenk S, Gilmore R, Reid S, et al. Effectiveness of vagus nerve stimulation in epilepsy patients: a 12-year observation. Neurology. 2004;63:1124–6.
32. Lulic D, Ahmadian A, Baaj AA, Benbadis S, Vale FL. Vagus nerve stimulation. Neurosurg Focus. 2009;27:E5.
33. Amar AP, Heck CN, Levy ML, Smith T, DeGiorgio CM, Oviedo S, et al. An institutinal experience with cervical vagus nerve trunk stimulation for medically refractory epilepsy: rationale, technique and outcome. Neurosurgery. 1998;43:1265–80.
34. Amar AP, Levy ML, McComb JG, Apuzzo MLJ. Vagus nerve stimulation for control of intractable seizures in childhood. Pediatr Neurosurg. 2001;34:218–23.
35. Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. J Child Neurol. 2000;15:509–12.
36. Ng M, Devinsky O. Vagus nerve stimulation for refractory idiopathic generalised epilepsy. Seizure. 2004;13:176–8.
37. Ventureyra EC. Transcutaneous vagus nerve stimulation for partial onset seizure therapy: a new concept. Childs Nerv Syst. 2000;16:101–2.
38. Ellrich J. Transcutaneous vagus nerve stimulation. Eur Neurol Rev. 2011;6:254–6.
39. Dietrich S, Smith J, Scherzinger C, Hofmann-Preiss K, Freitag T, Eisenkolb A, et al. A novel transcutaneous vagus nerve stimulation leads to brainstem and cerebral activations measured by functional MRI. Biomed Tech (Berl). 2008;53:104–11.
40. Kraus T, Kiess O, Hosl K, Terekhin P, Kornhuber J, Forster C, et al. CNS BOLD fMRI effects of sham-controlled transcutaneous electrical nerve stimulation in the left outer auditory canal—a pilot study. Brain Stimul. 2013;6:798–804.
41. Friedley J. Brain stimulation for the treatment of epilepsy. Neurosurg Focus. 2012;32(3):e13.
42. Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev. 2015;494(4):CD002896.
43. DeGiorgio C, Heck C, Bunch S, Britton J, Green P, Lancman M, et al. Vagus nerve stimulation for epilepsy: randomized comparison of three stimulation paradigms. Neurology. 2005;65:317–9.
44. Klinkenberg S, Aalbers MW, Vles JSH, Cornips EMJ, Rijkers K, Leenen L, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. Dev Med Child Neurol. 2012;54:855–61.
45. Michael JE, Wegener K, Barners DW. Vagus nerve stimulation for intractable seizures: one year follow-up. J Neurosci Nurs. 1993;25:362–6.
46. Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Stefan H, Mirza W, et al. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. Epilepsia. 1994;35:616–26.
47. Ramsay RE, Uthman BM, Augustinsson LE, Upton ARM, Naritoku D, Willis J, Treig T, et al. First International Vagus Nerve Stimulation Study Group. Vagus nerve stimulation for treatment of partial seizures: 2. Safety, side effects, and tolerability. Epilepsia. 1994;35:627–36.
48. The Vagus Nerve Stimulation Study Group. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. Neurology. 1995;45:224–30.
49. Howland RH. Vagus nerve stimulation. Curr Behav Neurosci Rep. 2014;1:64–73.
50. Gorny KR, Bernstein MA, Watson RE Jr. 3 tesla MRI of patients with a vagus nerve stimulator: initial experience using a T/R head coil under controlled conditions. J Magn Reson Imaging. 2010;31:475–81.

Responsive Stimulation in the Management of Medically Refractory Epilepsy

19

Robert A. McGovern, Garrett P. Banks, and Guy M. McKhann II

19.1 Introduction

It is estimated that epilepsy affects 0.6% of people living in developed countries [1] and 1.6% of all people in more rural undeveloped countries. As a result, epilepsy poses a substantial economic burden for health systems across the globe [2]. While the primary first line therapy for treating this disorder is antiepileptic medication, 20% to 30% of patients are unable to gain seizure control with medication alone [3]. In these patients, further medication trials are of very limited utility, and current guidelines recommend referral of these patients to an epilepsy surgery team.

Surgical approaches for the treatment of epilepsy currently include a wide range of techniques that either seek to remove offending epileptogenic tissue or to use electrical stimulation to disrupt or inhibit seizure activity. While these surgical techniques have been shown to yield reproducible and excellent results compared to medication alone [4], epilepsy surgery techniques are vastly underutilized [5]. The best practice for any patient being considered for epilepsy surgery is to be extensively evaluated by a multidisciplinary epilepsy surgery group. These groups specialize in selecting the best therapy for reducing seizure burden while avoiding the excessive risk of permenant neurologic disability [6].

When seizures are localized to an area of the brain in which they can be removed or ablated with an acceptable patient risk, resective or ablative surgery is the best patient option. However, in many circumstances this is not the case. A patient may have multifocal epilepsy such as multilobar epilepsy or bitemporal epilepsy. Alternatively, when the a patient is found to have an epileptic focus located in an eloquent area of the brain, surgical techniques that result in removal or damage to the target area of the brain may be too high risk for the patient. In these circumstances, techniques that employ neurologic stimulation to treat refractory epilepsy are utilized in order to reduce seizure burden while minimizing neurologic deficits.

The three most commonly used chronic neurologic stimulation techniques for medically refractory epilepsy are responsive neurostimulation (RNS), vagal nerve stimulation (VNS), and bilateral deep brain stimulation (DBS) of the anterior nucleus of the thalamus [7]. RNS is an adjunctive epilepsy treatment approved for disabling medically intractable partial-onset seizures in adults who have either one or two seizure foci. These patients also must have completed two or more full antiepileptic medication trials without seizure relief [8, 9]. The treatment provides closed loop stimulation to the epileptogenic regions of the brain when abnormal electrographic activity thought to predict a seizure is detected. The concept, practice, utilization, and evidence for RNS are covered in this chapter.

R. A. McGovern (✉)
Epilepsy Center, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: mcgover@ccf.org

G. P. Banks · G. M. McKhann II
Department of Neurological Surgery, New York-Presbyterian Hospital, The Neurological Institute, New York, NY, USA

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19.2 Responsive Neurostimulation: Background

One of the first published studies of RNS in patients covered how stimulation could be used to abort persistent afterdischarges that resulted from cortical stimulation mapping [10]. During cortical stimulation to map function in epilepsy surgery patients, application of another electrical stimulation when an afterdischarge was observed significantly reduced the duration of the afterdischarge. This electrical stimulation was also found to decrease the likelihood of an afterdischarge's evolving into a clinical seizure. In some instances, the afterdischarges halted completely upon application of current (Fig. 19.1). While electrically induced afterdischarges are not physiologically equivalent to preictal spontaneous epileptiform activity, the study's results supported the idea that RNS could be utilized to treat seizures in patients.

This concept was advanced several years later using automated responsive neurostimulation in patients implanted with subdural electrode arrays for seizure localization [11]. An automated algorithm was used to deliver high frequency electrical stimulation to areas of the brain exhibiting seizure-like activity. The outcome of this study was that when patients were receiving local responsive stimulation, their seizure rate dropped by an average of 55%. This work demonstrated that a computer could be programmed to detect ictal precursor activity in the absence of human observation and respond automatically with neurostimulation.

While the previous studies capitalized on patients who already had electrodes implanted during their workup for resective surgery for epilepsy, in 2005 a randomized, double-blind, multicenter, sham-stimulation controlled study was performed to evaluate a device specifically designed to detect and stimulate electrical activity predicted to be an ictal precursor [12]. The RNS device consisted of a combined recording device and neurostimulator implanted into the skull and two leads that served to record for both electrical activity predictive of ictal activity and to stimulate the area in order to abolish the abnormal electrical activity (Fig. 19.2) [9]. These leads have four contacts and can either be cortical strip or depth electrodes. The flexibility of the system is somewhat limited because it only allows recording and stimulating the limited brain areas accessed by the two strip or depth electrodes.

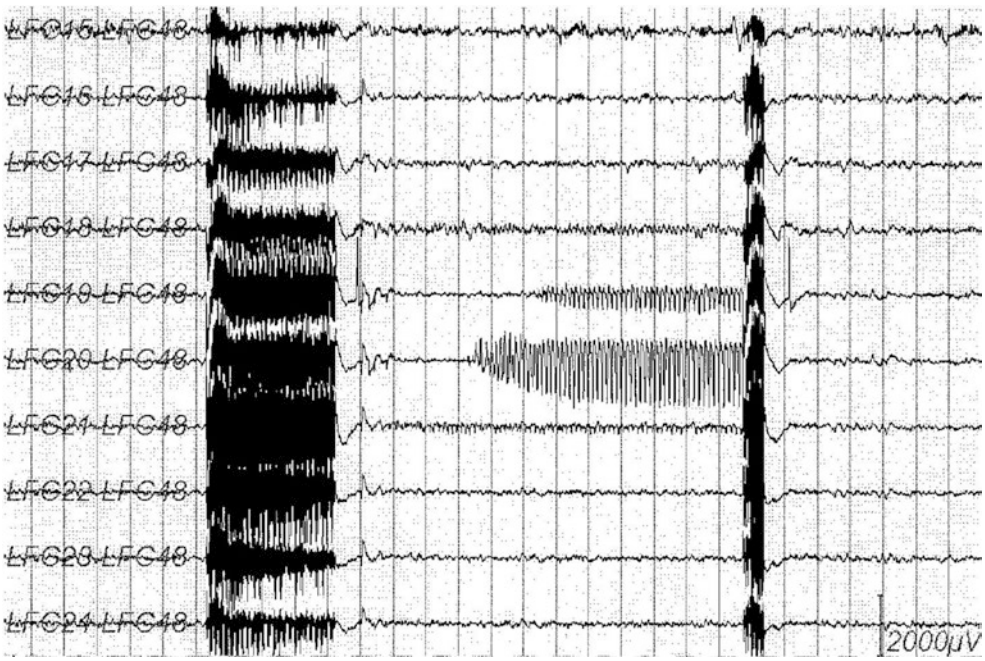

Fig. 19.1 Series of bipolar electrodes showing an afterdischarge (AD) after extraoperative cortical stimulation mapping. In the middle two leads an observable AD is seen. The AD is aborted using an additional short burst of cortical stimulation. (*Adapted from* Lesser et al. [10]; *with permission*.)

In the RNS pivotal trial, 191 adults with medically refractory partial epilepsy and one or two localized seizure foci were implanted with the device. The patients were randomized to receive responsive or sham stimulation. Patients in the treatment group received a 0.5 mA stimulation at 200 Hz for 100 ms when the device detected seizure type activity. The blinded phase continued until 5 months after implant, when all patients entered the open label phase of the experiment and had their devices activated. At the end of the blinded phase, there was a statistically significant reduction in seizure frequency in the stimulation group compared to the sham group. The stimulation group demonstrated a 37.9% reduction in seizure frequency, while the sham group demonstrated a reduction of only 17.3%. During the open label period, once practitioners were able to tailor the parameters used for detection and stimulation, the median reduction in seizure frequency increased to 44% at 1 year, 53% at 2 years, and 66% at 6 years [13, 14]. Notably, these patients achieved a reduction in seizure frequency without any deterioration in neuropsychological function, and most patients had a meaningful increase in quality of life metrics [8, 15].

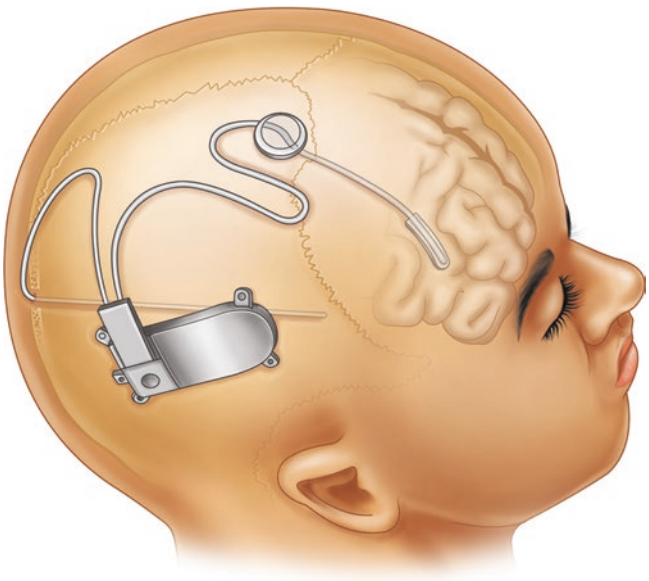

Fig. 19.2 Diagram depicting the neuropace device. The neurostimulator is hooked up to both a depth lead and a strip lead. The depth lead has been inserted through a posterior burr hole deep to the hippocampus, while the strip lead has been placed through a burr hole on a gyrus of the frontal lobe

19.3 Patient Selection

The clinical pathway for selecting a patient to receive RNS for epilepsy is similar to that for any patient undergoing an epilepsy surgery workup. First, patients with medication-resistant epilepsy are referred to a clinical epilepsy neurology group for assessment, characterization of seizure semiology, and assurance that conservative management has been tried and failed. Noninvasive techniques are then used in an attempt to localize the seizure focus. Scalp electroencephalography (EEG) can often provide information about the approximate area and side of the seizure focus. Magnetic resonance imaging (MRI) can demonstrate discrete lesions such as hippocampal sclerosis seen in mesial temporal lobe epilepsy (MTLE), subtle gray and white matter changes in focal cortical dysplasia (FCD), tumors, or vascular malformations. Additional techniques that can be utilized depending on their availability include ictal or interictal single photon emission computed tomography (SPECT), magnetoencephalography (MEG) [16], and computational algorithms for detecting subtle abnormalities on MRI studies initially read as negative [17].

Frequently, the noninvasive workup is insufficient to determine the exact seizure focus. In these cases, invasive surgical monitoring is used to localize the seizure onset zone and guide further treatment. Subdural electrode arrays are implanted via a craniotomy or EEG depth electrodes (Stereo EEG = SEEG) are stereotactically placed in the area(s) of putative seizure onset based on the patient's seizure semiology, imaging results, and scalp EEG findings. Which type of implant is placed depends on the brain area to be evaluated; the possible need for functional mapping; and the epilepsy surgery center's preference and experience. After implantation, the electrodes are monitored extraoperatively for epileptiform interictal spiking and for seizure onset and propagation. These techniques have the advantage of significantly improved spatial and temporal resolution compared to a scalp EEG, given their direct placement on the cortical surface or through the brain parenchyma.

After determining the putative seizure onset zone, selection of the best treatment modality for a patient should be a multidisciplanary discussion that includes the epilepsy neurologist, the neurosurgeon, the neurospsychologist, and most importantly the patient. Removal of the pathologic tissue by means of resection or ablation has been shown to produce

superior seizure freedom rates compared to stimulation-based therapies [17]; however, there are many areas of the brain that will produce either a meaningful or severe neurologic deficit if removed. In those patients in whom the potential for seizure freedom is thought to be outweighed by the potential neurologic deficit, neurostimulation devices can provide the greatest benefit.

Other considerations to be evaluated on a patient-specific basis include the need for future MRIs, the existence of other stimulation devices, the patient's immunologic function, and the patient's social support system [9]. The Neuropace RNS device is currently not MRI compatible, and patients who require frequent MRIs such as those with multiple sclerosis may be poor candidates for RNS. The device also is technically contraindicated for anyone with another device delivering stimulation to the brain, which may make it a poor option for a patient who may also be considering deep brain stimulation for another indication. Also, like all implantable intracranial devices, a serious infection of the device and surrounding tissues including brain, skull, and/or scalp may warrant its removal and treatment of the infection with antibiotics. For patients with immunologic deficiencies, careful consideration should be given to the increased chance for infection. Last, patients are required to frequently upload their seizure information to a central database and must come in for many follow-up visits to fine tune their devices. Unfortunately, patients who are poorly adherent to recommended therapies or do not have a strong social structure to support them may be poor candidates for the device.

19.4 Implantation

Implantation of the device consists of placing strip and/or depth leads and the neurostimulator. The exact surgical procedure varies based on the patient's specific configuration. For patients with depth leads, such as placement into the bilateral hippocampi, the lead placement trajectory is planned on stereotactic software prior to surgery. On the day of surgery, the patient is placed into a stereotactic headframe after being given general anesthesia. A volumetric CT is then acquired and fused to an MRI performed prior to the day of surgery. After image fusion, the patient is placed on the operating room table, with the stereotactic frame base ring fixed to a Mayfield holder. The head is prepped and draped in the usual fashion, bilateral burr holes are made down to the dura, and hemostasis is obtained. After drilling the burr hole, a small trough the width of the lead is made through the side of the burr hole, and a single small "dog bone" titanium plate is affixed with one screw adjacent to the trough for subsequent electrode anchoring. The dura is then incised, hemostasis is achieved, and the depth leads are bilaterally implanted based on the stereotactic coordinates of the trajectories planned on the navigation software. Cannulas that can accommodate a standard 3387 Medtronic lead of 1.27 mm in width can also be used to place the Neuropace lead owing to its similar width of 1.29 mm. After withdrawing the cannula, the depth lead is secured through the trough under the dog bone in order to hold the lead in place and reduce the stress on the lead wire. After securing the electrode, the lead is passed under the skin to the area where the neurostimulator will be implanted. Of note, depending on surgeon preference, frameless stereotaxis or robotic guidance can be used to place the depth electrodes. However, we prefer using a frame-based stereotactic system because of the ease of stereotactic planning and the accuracy of electrode placement.

For strip placement, in almost all instances a previous surgery has been performed for surgical epilepsy localization. In this instance, the patient is placed in a Mayfield clamp, and an incision is made to access the previous craniotomy site. The craniotomy, or a portion of it, is removed, the dura is carefully reopened taking care to carefully dissect the dura from the pia (which may be scarred from the prior surgery), and the strip(s) are slid into position. The dura is then closed, and the craniotomy is replaced. If the strip is not adjacent to the area where the neurostimulator will be placed, the lead is once again passed under the skin to the planned area, and the incision is closed.

For placement of the neurostimulator, the area where the device will be implanted should be toward the back of the head so that the incision and device will be completely obscured by the patient's hair; however, it should not be at a weight-bearing pressure point on the back of the head. The most common location for the implant is the parietal convexity of the skull. A horseshoe incision is made in the scalp large enough to provide

at least 1 cm in all directions around the implant. It is oriented so that the leads do not traverse the incision. Fashioning an incision such that the implant and leads do not lay directly under the incision decreases the chance of infection, wound breakdown, and lead disruption during future device replacements. Following incision and hemostasis, the leads are pulled under the scalp into the area of the incision and wrapped in a moist sponge away from the area to be drilled. Next, the Neuropace ferrule is placed on the surface of the skull, and a marker is used to outline the exact area to be drill. A craniectomy is then drilled and removed in the shape of the ferrule, taking care not to traumatize the underlying dura. Bone wax is used to smooth the edges, and meticulous hemostatsis is performed along with copious irrigation to remove all bone dust from the field. Epidural tenting sutures are placed to minimize the risk of a postoperative epidural hematoma. A partial-thickness craniectomy may be used if the skull is thick enough, minimizing the risk of dural injury or irritation or epidural bleeding. The ferrule is affixed to the skull with four screws provided in the Neuropace kit (Fig. 19.3a). The leads are then passed into the Neuropace stimulator, and the stimulator is affixed to the ferrule (Fig. 19.3b). At this point, we apply a vancomycin powder slurry to decrease the risk of infection, and the incision is closed over the stimulator. The programmer is then draped in a sterile camera sleeve to interrogate the device. Interrogation at this point ensures that the device can be properly accessed through the skin and allows measurement of the impedences of each electrode. Abnormal impedences are greater than 3500 ohms and less than 250 ohms. A CT scan and anteroposterior/lateral x-ray should be obtained postoperatively to document placement (Fig. 19.4).

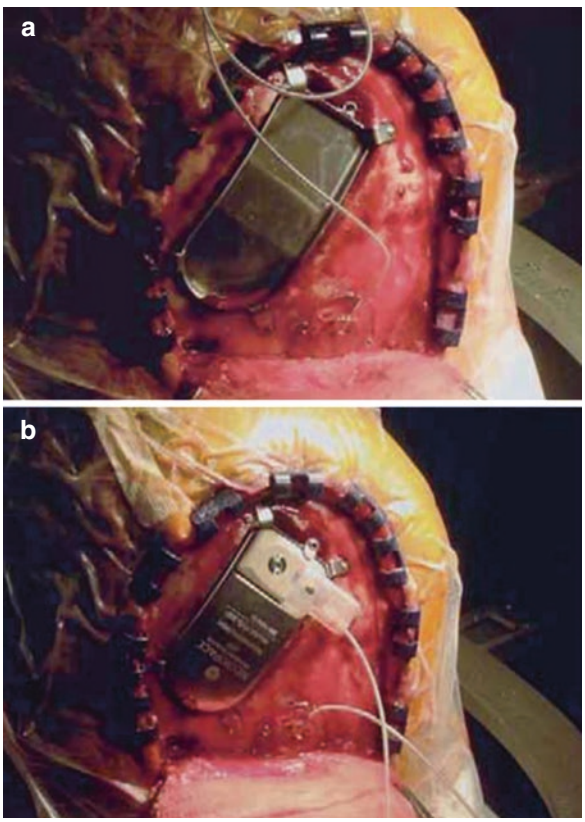

Fig. 19.3 Figure showing the ferrule and the neurostimulator. In part (**a**) the empty ferrule has been placed into the craniectomy site. The craniectomy was made in the same shape as the ferrule to ensure snug placement of the device. In (**b**) the neurostimulator has been placed into the ferrule, and a lead has been inserted into the device. (*Adapted from* Fountas et al. [18]; *with permission*.)

As mentioned previously, the careful planning of each surgical step is imperative and may vary from case to case. In the instance of two depth electrodes, the leads may first be placed with a stereotactic frame and then the frame can be removed. The craniectomy can be performed with the head ring on provided that the ring was placed low enough. If the patient will have two strips implanted, a Mayfield head clamp may be utilized instead without the need for precise stereotactic coordinates. Additionally, if the burr hole or craniotomy incision can be incorporated into the neurostimulator incision area, the incision can be tailored to accommodate both so that fewer incisions are required.

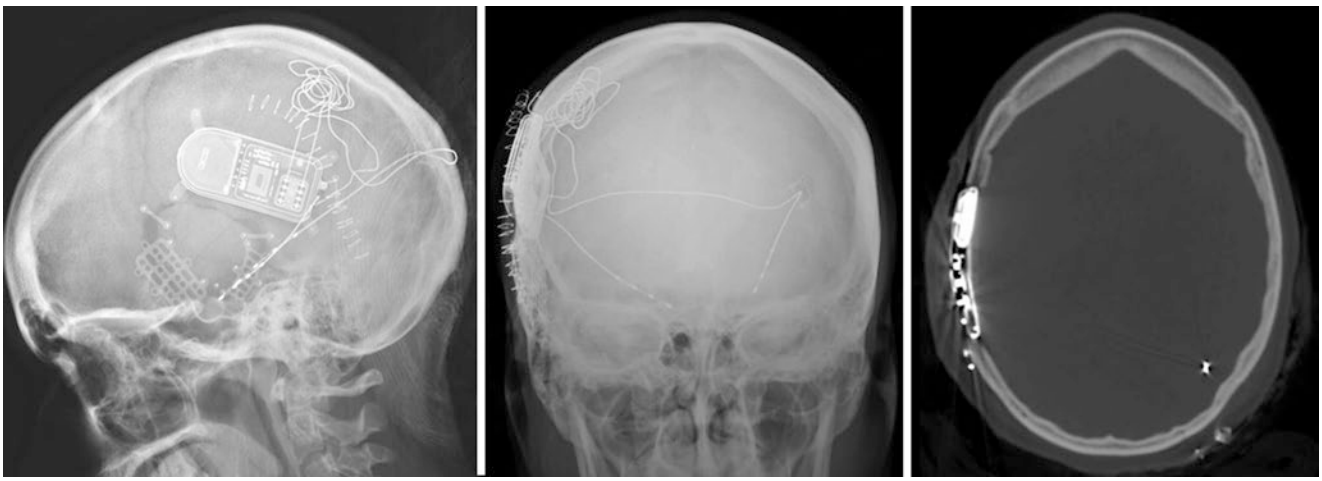

Fig. 19.4 Figure showing plain films and CT scans of an implanted responsive neurostimulator. This patient has bilateral onset mesial temporal lobe seizures and was implanted with bilateral depth electrodes in the parahippocampal region. CT shows the craniectomy and how the ferrule sits within the skull

19.5 Programming of the Device

After implantation in the operating room, the device is usually set to record only. When the device detects specific electrocorticographic patterns, it stores the recording for a set amount of time. There are three ways the device can detect patterns of interest: line length, area, and band pass. Line length is a measure of point-to-point change that is sensitive to both signal amplitude and frequency. As the most globally sensitive of the three methods, it is the recommended initial setting. Area detection is most sensitive to power changes, while bandpass detection is most sensitive to rhythmic and spiking activity. If the patient's seizures were well characterized during the intracranial monitoring evaluation, more specific parameters can be chosen during the placement of the device. Most importantly though, the patient should be counseled on how to store and upload Neuropace information on a daily basis, so that during their first postoperative appointment the information can be used to initiate responsive therapy.

At each follow-up appointment the clinician should first evaluate if ictal events are being captured properly. This can be assessed by comparing the recorded data to patient seizure journals. Of note, continuous ambulatory recording can often reveal that the patient suffers from more frequent electrographic events than are reported in the seizure journals. The detection settings should be changed so that no preictal candidate events are missed. Once the device has been programmed to be sufficiently sensitive to these events, further sessions can be used to carefully tailor the settings to be more specific.

The initial settings for responsive therapy should be left at their default values during the first programming session, and the stimulation should be delivered to the area from which the activity of interest is observed. The default settings are recommended for the initial stimulation phase to allow for a baseline assessment of their effectiveness. After the initial programming phase, 3-month interval visits should be scheduled to better tailor the stimulation to the patient. If the stimulation is not sufficient to abort preictal activity, the initial recommended change is to increase the amplitude of the stimulation by 0.5-mA increments. After changing the current, the stimulation should be trialed in the office to ensure that the stimulation is tolerated by the patient and that it does not induce afterdischarges. If the new stimulation produces a noticeable irritation in the patient, the burst duration can be increased instead of the amplitude.

19.6 Complications and Avoidance

While RNS has a better adverse event profile than resective or ablative surgery, the act of surgical implantation itself still carries a risk. Not including pain and seizure-related complications, the most common adverse events in the pivotal trial were device lead damage, infection, and depression [19]. In approximately 2.6% of patients, the device and/or leads were damaged sometime in the first year. Care must be taken to reduce any potential regions of stress on the device or leads during the implantation in order to decrease the risk of damage. For example, when drilling the burr holes, a trough in the side of the burr hole, as described previously, allows for a more gradual exit from the subdural space and puts less stress on the leads. Sufficient slack should also be placed close to the neurostimulator so that after healing and scarring the lead is not held taut in relation to the neurostimulator.

To decrease infection risk, extra care should be utilized to ensure sterile procedure when prepping and draping. Antibiotic irrigation should be copiously used, and all bone dust should be washed from the field before implantation of any permanent device. We also recommend utilization of vancomycin powder during the implant before closure for additional prophylaxis, and at least one perioperative and postoperative dose of intravenous antibiotics. In the postoperative period, superficial site infections can be treated with antibiotics, but any persistent infection involving the device itself warrants explantation and extended antibacterial therapy. Also, since patients suffering from epilepsy frequently experience comorbid depression, we recommend screening for depression during all postoperative visits [20].

19.7 Limitations and Future Directions

While the RNS device has shown excellent efficacy for reducing seizure frequency in patients with medically refractory epilepsy, the treatment is only able to provide seizure freedom in a very limited number of patients (~10%). Additionally, the therapy is contingent on the ability to localize the ictal focus to one or two specific locations in the brain, a constraint not shared by VNS or anterior thalamic nucleus stimulation. Therefore, while the therapy definitively has a place in the arsenal of treatments for medically refractory epilepsy, it is neither a replacement for resective surgery nor necessarily superior to other electrical stimulation modalities.

Future research will seek to improve the efficacy of the device by utilizing the vast amount of outpatient intracranial recording collected by the RNS device. Research aimed at identifying ideal candidates for responsive neurostimulation and improving seizure detection algorithms will likely improve the efficacy and utility of the RNS device. Additionally, research into preoperative predictors of which candidates will respond best to neurostimulation will naturally improve the device's efficacy. Interestingly, now that hundreds of devices are implanted, we are starting to see that far more epileptic events occur in the human brain than are normally reported. This new vast collection of data can potentially be used to further our understanding of the pathophysiology of epilepsy and allow us to better implement appropriate epilepsy therapies.

References

1. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia. 2010;51:883–90.
2. Allers K, Essue BM, Hackett ML, Muhunthan J, Anderson CS, Pickles K, et al. The economic impact of epilepsy: a systematic review. BMC Neurol. 2015;15:245.
3. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365:919–26.
4. Wiebe S, Blume WT, Girvin JP, Eliasziw M. Effectiveness, efficiency of surgery for temporal lobe epilepsy study G. A randomized, controlled trial of surgery for temporal-lobe epilepsy. N Engl J Med. 2001;345:311–8.
5. Jette N, Wiebe S. Update on the surgical treatment of epilepsy. Curr Opin Neurol. 2013;26:201–7.
6. Sauro KM, Wiebe S, Dunkley C, Janszky J, Kumlien E, Moshe S, et al. The current state of epilepsy guidelines: a systematic review. Epilepsia. 2016;57:13–23.
7. Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;51:899–908.
8. Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. Epilepsia. 2015;56:1836–44.
9. RNS® system user manual 2013 [Internet]. Available from: https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/medicaldevices/medicaldevicesadvisorycommittee/neurologicaldevicespanel/ucm340260.pdf.
10. Lesser RP, Kim SH, Beyderman L, Miglioretti DL, Webber WR, Bare M, et al. Brief bursts of pulse stimulation terminate after discharges caused by cortical stimulation. Neurology. 1999;53:2073–81.
11. Osorio I, Frei MG, Sunderam S, Giftakis J, Bhavaraju NC, Schaffner SF, et al. Automated seizure abatement in humans using electrical stimulation. Ann Neurol. 2005;57:258–68.
12. Morrell MJ, Group RNSSiES. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. Neurology. 2011;77:1295–304.
13. Heck CN, King-Stephens D, Massey AD, Nair DR, Jobst BC, Barkley GL, et al. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS system pivotal trial. Epilepsia. 2014;55:432–41.
14. Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015;84:810–7.
15. Meador KJ, Kapur R, Loring DW, Kanner AM, Morrell MJ, Investigators RNSSPT. Quality of life and mood in patients with medically intractable epilepsy treated with targeted responsive neurostimulation. Epilepsy Behav. 2015;45:242–7.
16. Pellegrino G, Hedrich T, Chowdhury R, Hall JA, Lina JM, Dubeau F, et al. Source localization of the seizure onset zone from ictal EEG/MEG data. Hum Brain Mapp. 2016;37:2528–46.
17. Wang ZI, Jones SE, Jaisani Z, Najm IM, Prayson RA, Burgess RC, et al. Voxel-based morphometric magnetic resonance imaging (MRI) postprocessing in MRI-negative epilepsies. Ann Neurol. 2015;77:1060–75.
18. Fountas KN, Smith JR, Murro AM, Politsky J, Park YD, Jenkins PD. Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note. Stereotact Funct Neurosurg. 2005;83:153–8.
19. Morrell MJ. In response: the RNS system multicenter randomized double-blinded controlled trial of responsive cortical stimulation for adjunctive treatment of intractable partial epilepsy: knowledge and insights gained. Epilepsia. 2014;55:1470–1.
20. Kanner AM. Depression in epilepsy: a neurobiologic perspective. Epilepsy Curr. 2005;5:21–7.

Image-Guided Robotic Radiosurgery for the Treatment of Drug-Refractory Epilepsy

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Pantaleo Romanelli and Alfredo Conti

Stereotactic radiosurgery provides a safe nonresective option to treat medically refractory epilepsy. The radiosurgical ablation of an epileptic focus, especially when performed through frameless image-guided radiosurgery, is a thoroughly noninvasive treatment devoid of the risks of open surgical procedures. Radiosurgery can be offered to patients harboring neocortical, hippocampal, or diencephalic seizure foci not requiring invasive mapping. Disconnective procedures such as radiosurgical callosotomy can be performed as well. This chapter will review the state of the art of radiosurgery for epilepsy, with special emphasis placed on robotic image-guided frameless delivery.

20.1 Introduction

Epilepsy is the most common neurologic disorder, with an incidence reaching 0.5% of the population. Approximately one third of patients with epilepsy are affected by medically refractory seizures: seizures are unaffected or only partially improved by prolonged treatment with multiple drugs at therapeutic or even toxic doses. Patients with medically refractory seizures are exposed to the risk of dying as a consequence of uncontrolled seizures. They can develop severe traumatic, metabolic, and neuropsychological sequelae and often bear a serious social stigma. Epilepsy surgery aiming to resect the epileptic focus is offered by qualified medical centers to medically refractory patients. However, the surgical risk to induce severe neurologic and neuropsychological deficits becomes remarkable when the epileptic focus is near or interspersed with eloquent cortex, such as speech or primary motor areas, or if the dominant hippocampus is involved.

Stereotactic radiosurgery (SRS) is an emerging treatment for highly selected cases of medically refractory epilepsy [1, 2]. A noninvasive treatment such as SRS is an attractive option for those cases in which invasive monitoring to localize the epileptogenic focus is not required. Deep-seated epileptogenic foci requiring complex and extensive neurosurgical procedures can also benefit from SRS. Seizure control is obtained through the delivery of high doses of radiation to the seizure focus, with longstanding edema being the most common complication after treatment. The main limit of the radiosurgical treatment of epilepsy, as compared to surgical resection, is the delay (sometimes up to 2 years) between treatment and seizure control. During this time the patient remains exposed to the seizures and to the effects of antiepileptic drugs.

The exact mechanism of seizure abolition after radiosurgery is unknown. Depending on the target volume, radiosurgery can induce necrosis and consequent destruction of the epileptic focus and its pathways of spread. Suppression of epileptic activity by a neuromodulatory effect at nonnecrotizing doses has been proposed as a possible mechanism of action [3–5]. Parcellation and disconnection of the epileptic focus have also recently been described as a novel experimental approach to achieve seizure control [2, 6, 7]. Doses of 20 Gy or less delivered to volumes less than 7 mL do not seem to produce necrosis, but reduced neuronal density and perivascular sclerosis have been noted on hippocampal specimens resected because of poor clinical efficacy [8].

Favorable seizure outcomes have been reported following SRS to treat seizures induced by hippocampal sclerosis, brain tumors, arteriovenous malformations, cavernomas, and deep-seated epileptogenic lesions such as hypothalamic

P. Romanelli (✉)
Cyberknife Center, CDI, Milan, Italy

A. Conti
Department of Neurosurgery, CyberKnife Center, Messina, Italy

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hamartomas (for a review see [1, 2]). Most of these reports illustrate Gamma-Knife cases requiring the placement of a stereotactic frame.

Frameless radiosurgery using the Cyber Knife is a novel treatment modality providing increased patient comfort and safety but also an unrestricted range of beam trajectories along the skull base and splancnocranium [9]. This chapter describes current applications of SRS in the treatment of selected cases of medically refractory epilepsy and highlights the use of frameless image-guided radiosurgery. A brief description of evolving research on the treatment of epileptogenic foci located over eloquent cortex using microradiosurgical transections will be provided as well.

20.2 Stereotactic Radiosurgery for Mesial Temporal Lobe Epilepsy

Jean Régis and coworkers began to perform selective amygdalohippocampal radiosurgery for mesial temporal lobe epilepsy in 1993 [4, 10–14]. Patients were selected for Gamma Knife radiosurgery following the same criteria used for microsurgical amygdalohippocampectomy, including the presence of hippocampal sclerosis and the absence of space-occupying lesions. An approximate volume of 7 mL, including the head and body of the hippocampus, the anterior part of the parahippocampal gyrus, and the basolateral region of the amygdaloidal complex (sparing the upper and mesial part) received 25 Gy to the 50% isodose line. Common post-treatment MR findings included transitory hippocampal swelling, with an increased T2 signal followed by the development of a contrast-enhancing ring demarcating the 50% isodose line and a diffusely increased T2 signal spreading from the hippocampus to the temporal lobe and adjacent white matter. Image changes appeared on MRI scans at approximately 12 months (range, 8–15 months) and were occasionally associated with headaches, nausea, and vomiting, which resolved with corticosteroid treatment. All abnormal MRI findings resolved within 24 months post-treatment [4, 10–14]. Analysis of seizure control after 2 years follow-up showed that 65% (13 of 20 patients) of this cohort of patients treated in three different centers were seizure free, with a reduction of the median number of seizures per month from 6.2 to 0.3 [13]. Ten patients out of 20 (50%) developed visual field deficits consisting of a quadrantanopia (8 cases), hemianopia (1 case), or a mixed deficit (1 case) [13]. These results have been confirmed by a recent prospective multicenter pilot trial delivering radiosurgery to epileptic patients with mesial temporal sclerosis. The overall seizure remission rate was 69% during the third follow-up year after treatment, which is comparable to that reported for resective temporal lobectomy [15].

The efficacy of radiosurgery in cases of mesial temporal tumors associated with longstanding epilepsy has been specifically analyzed in a retrospective study of 19 cases treated by Gamma Knife radiosurgery (GKRS) [16]. All tumors were within the mesial temporal structures and the histology (proven by biopsy or by a resective procedure) included 15 (79%) low-grade astrocytomas, 3 (16%) gangliogliomas, and 1 (5%) cavernoma. GKRS was performed in order to obtain local growth control and alleviation of epilepsy. The latter aim was achieved by irradiating the epileptic foci placed over the gray matter located immediately outside the tumor volume. The mean 50% isodose volume surrounding the tumor was 6.2 mL (range, 1.1–18 mL). The mean marginal dose was 17.3 Gy (range, 12–30 Gy). After a follow-up of 1.7–9.7 years (mean, 6.5 years), 11 patients (57.9%) were significantly improved (Engel I and Engel II), 7 patients (36.8%) had worthwhile improvement (Engel III), and 1 patient (5.3%) was unchanged.

Barbaro et al. [17] reported results of a pilot multicenter trial describing seizure freedom in 77% of 13 patients who received high-dose (24 Gy) treatment and in 59% of 17 individuals who received low-dose (20 Gy) therapy at 1 year. Verbal memory impairment was described in 15% of patients, although none declined on more than one measure, while verbal memory improvement was seen in 12% of individuals [17, 18]. Side effects were reasonable in most cases, including headache and visual field deficits requiring a brief period of steroid administration. Only one patient suffered from malignant edema after treatment, including severe headaches, visual field deficit, and papilledema not responsive to steroids, and this patient eventually underwent temporal lobectomy [17]. The final results are awaited from a prospective randomized trial of SRS versus open temporal lobectomy (Radiosurgery or Open Surgery for Epilepsy [ROSE] trial) [18, 19].

Unlike resection, the beneficial effects of SRS on seizures are typically delayed up to 12 months or more after treatment. Chang and colleagues found that MRI characteristics during the first year following SRS might serve as a predictor of seizure outcome at 3 years after therapy [18]. Specifically, T2 hyperintensity volumes 9 months after the procedure were found to be highly related to seizure remission and were more pronounced in patients who received 24 Gy SRS compared to lower dose 20 Gy treatment [15, 17].

There are currently no published reports dedicated to the use of Cyber Knife radiosurgery for the treatment of epilepsy caused by mesial temporal sclerosis. Figure 20.1 illustrates the case of a 12-year-old boy with right mesial temporal sclerosis who was treated with Cyber Knife radiosurgery. This child was affected by multiple daily complex partial seizures that were refractory to medical therapy. The MRI was remarkable for atrophy of the right anterior temporal lobe and mesial temporal sclerosis. A frameless image-guided Cyber Knife treatment prescribing 23 Gy to the 81% isodose was delivered using 181 nonisocentric beams. The maximum dose was 28.4 Gy. Treatment volume was 6.49 cc and included the head and body of the hippocampus, the anterior part of the parahypocampal gyrus, and the amygdala. Treatment delivery required 56 min and was uneventful. The patient received an intramuscular injection of dexamethasone (8 mg) immediately after the treatment and was discharged. A temporary increase of the seizures was observed 6 weeks after the treatment. Oral dexamethasone was given, with immediate seizure resolution. Since then and for the last 9 months the patient has been seizure free. Follow-up MRI 6 months after the treatment was unremarkable.

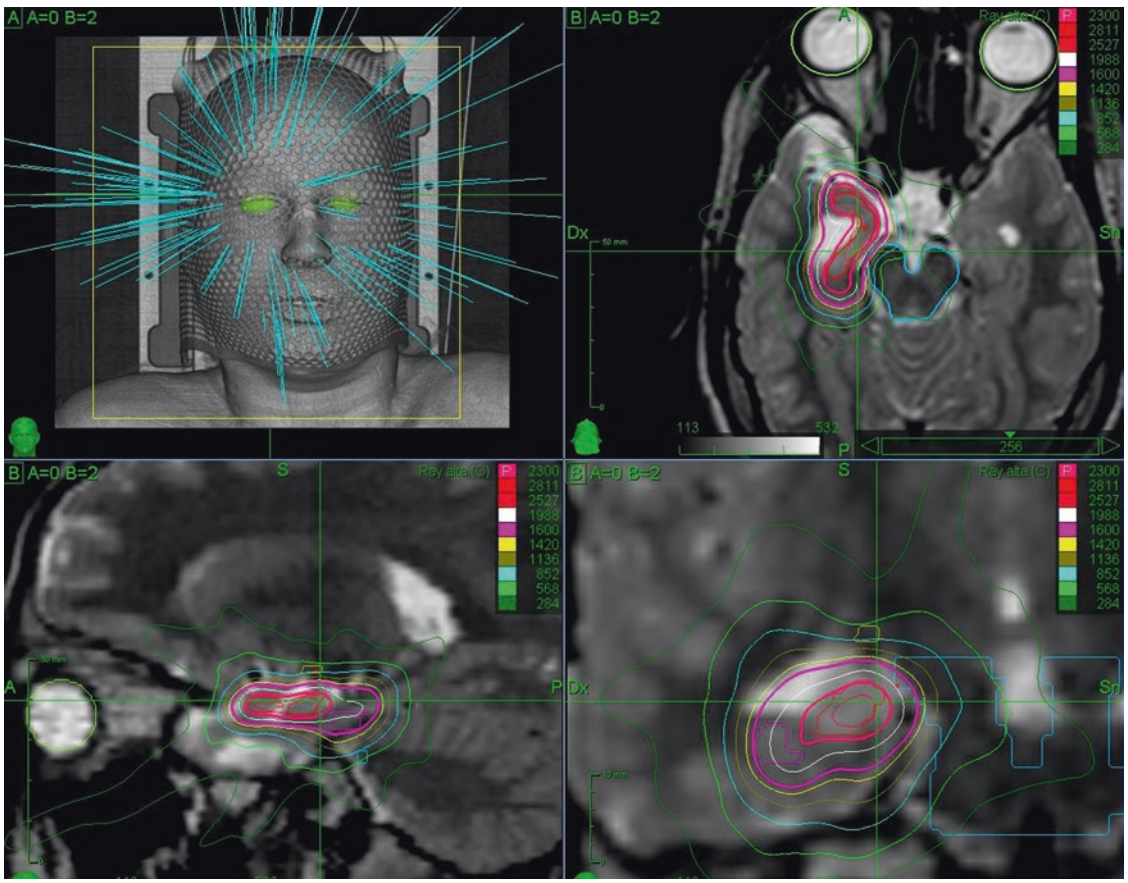

Fig. 20.1 Cyber Knife radiosurgery for mesial temporal sclerosis. The maximum dose was 28.4 Gy. Treatment volume was 6.49 cc and included the head and body of the hippocampus, the anterior part of the parahypocampal gyrus, and the amygdala

20.3 Stereotactic Radiosurgery for Neocortical Epilepsy

Radiosurgery has been widely used to treat neocortical seizures associated with arteriovenous malformations and cavernous angiomas. It has provided a useful tool for ablation of seizure foci located in eloquent or surgically challenging brain regions, where open surgery is associated with an unacceptably high incidence of complications. The combination of noninvasive seizure focus localization with radiosurgery is an attractive alternative approach to conditions traditionally treated with brain resection when a thoroughly noninvasive approach to map and treat a cortical epileptic focus is provided. Magnetoencephalography (MEG) can be used to guide stereotactic irradiation in refractory seizures arising from eloquent cortical areas [20–22]. Current developments toward MEG ictal [23] and interictal mapping [24] as well as the use of epileptic network analysis [25] are likely to further boost the application of radiosurgery to treat epilepsy. Figure 20.2 illustrates an MEG-driven Cyber Knife procedure performed on a 23-year-old patient with severe medically refractory seizures (secondarily generalized tonic-clonic seizures) originating from the right frontal opercular region.

One of the earliest papers reporting the use of radiosurgery to treat neocortical epileptic foci was published by Barcia and coworkers [26–28]. Eleven patients with epileptic foci localized by neuroimaging and invasive electrode recordings underwent SRS for focus ablation. Nine subjects were treated with a ^{60}Co source receiving doses ranging from 10 to 20 Gy, while the remaining 2 patients received an estimated dose of 10 Gy delivered through a 10–15 MeV single beam betatron. At a mean follow-up of 102.5 months, 4 patients were off medication and seizure free, five had a marked reduction in seizure frequency (75–98%), while 2 had no response (supposedly related to inaccuracy of seizure focus localization). No complications were reported.

A large amount of retrospective data are available regarding seizure outcomes following the treatment of arteriovenous malformations (AMVs) with SRS. Pollock and coworkers [29] retrospectively studied 67 patients with small AVMs, Spetzler-Martin Grade I or II, who refused to undergo an open surgical procedure and elected to receive a radiosurgical treatment. Thirty-one patients had experienced seizures prior to radiosurgery, which was performed with a 201 source Gamma Knife system. Mean AVM volume was 3.1 mL, with a mean marginal dose of 21 Gy (maximum dose: 36 Gy). Sixteen patients (52%) had seizure frequency reduced to less than 1 seizure per year, while 15 had no change in seizure control. No patients developed new seizures following treatment. There was a 7.7% record of hemorrhage and a 3% mortality rate (caused by hemorrhage) within 8 months following radiosurgery; however, there was no risk of bleed if there was total obliteration or subtotal obliteration with patency of early draining veins only.

Thirty-three patients with AVMs of the precentral gyrus were selected for retrospective study from a group of 770 patients who had been treated with Gamma Knife radiosurgery for AVMs [30]. Median AVM volume was 3 cm^3, and the median dose to the margin was 20 Gy. Twenty-seven (87%) of the patients had presented with seizures. After a mean follow-up of 54 months, there was a 63% seizure free rate. The remaining 37% continued to experience seizures at a frequency no greater than before radiosurgery.

A retrospective review of 40 pediatric cases of AVMs treated by a multimodality approach and followed for a mean of 38.7 months has been reported by Hoh et al. [31]. Ten patients with AVM-related seizures were treated with proton beam radiotherapy if lesions were located in eloquent areas or had a particular pattern of venous drainage. Mean dose was 15.9 Gy to a mean volume of 9.9 cm^3. Nine out of ten patients (90%) became seizure free following treatment. It should be noted that AVM embolization was also performed concurrently, and seizure outcome was not analyzed in detail to assess the respective weight of radiosurgery versus embolization in the outcome of seizure freedom. The authors reported no radiosurgery-related complications or morbidity. One patient had a hemorrhage after radiosurgery before the AVM had been obliterated.

A further retrospective study published by the same group in 2002 reported on 141 patients with AVMs and seizures, representing 33% of 424 patients treated for AVM over an eight-year period [32]. Follow-up data have been available for 110 patients out of 141.These patients were treated with a multimodality, multidisciplinary approach, including various combinations of surgery, radiosurgery, and embolization. The mean follow-up period was 34.8 months. Those who received radiosurgery were treated with proton beam therapy with a mean dose of 15.5 Gy to a mean volume of 7.7 cm^3. These investigators identified the following pretreatment risk factors for the development of symptomatic seizures with AVM: male gender, age less than 65 years, AVM size larger than 3 cm, and temporal lobe AVM location. Of the 110 patients treated with the multiple modalities, 73 (66%) were seizure free (Engel Class I), 11 (10%) were Class II, 1 (0.9%) was Class III, and 22 (20%) were Class IV. Treatment-specific analysis revealed that surgery had the highest number of patients with Class I outcome (81%), followed by embolization (50%), and then radiosurgery (43%). However, if the AVM was completely obliterated, then all treatments yielded the same percentage of patients with a Class I outcome. The following factors were associated with a Class I outcome: short seizure history, associated intracranial hemorrhage, generalized tonic-clonic seizure type, deep and posterior fossa AVM location, surgical resection, and complete AVM obliteration. In addition, 5.7% of patients who did not have pretreatment symptomatic seizures developed seizures.

Seizure improvement has also been reported after SRS for cavernous malformations (CMs). Ninety-five patients were treated for CMs by proton-beam therapy at the Massachusetts General Hospital [33]. Eighteen of the subjects had seizures prior to treatment. There was a significant improvement in seizure control after treatment, and no patients developed new-onset seizures or intractable epilepsy after treatment. Regis et al. [34] published a retrospective multicenter report of 49 patients treated for CMs with Gamma Knife radiosurgery. All patients had drug-resistant epilepsy and were followed for longer than 12 months after treatment. Mean marginal dose and volume were 19.17 Gy and 2.4 cm^3, respectively. Seizure outcome was favorable: 53% became seizure-free (Engel Class I), 20% experienced a significant decrease in number of seizures, and 26% had little or no improvement. The average time to seizure remission was 4 months. Five of the patients who failed to improve following radiosurgery were treated with microsurgery: three of these later became seizure free; one has rare seizures. One patient experienced no change in seizure control. Seven patients developed major post-treatment edema but fully recovered. Better outcome was associated with simple partial seizures compared with complex partial ones. Mesiotemporal location was associated with a poor outcome, while laterotemporal and central locations were associated with a good outcome. Based upon their results, Regis et al. recommended that Gamma Knife radiosurgery be considered for CMs associated with seizures arising from eloquent cortex surrounding the lesion.

Seizures associated with tuberous sclerosis can also respond well to radiosurgery, as illustrated by a report on a patient with intractable seizures related to a frontal subependymal nodule who did not improve after subtotal resection but experienced seizure freedom following radiosurgical treatment of the residual lesion [35].

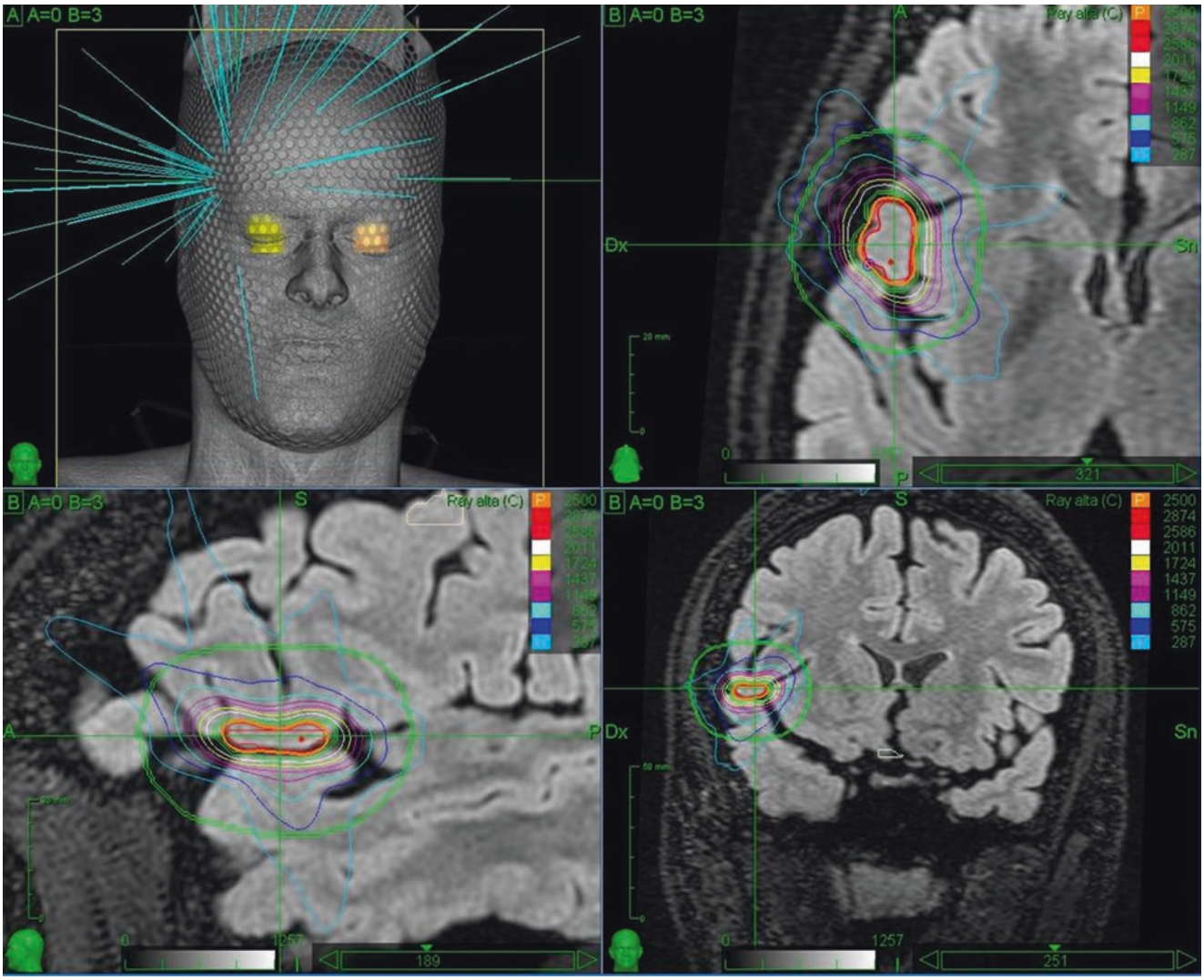

Fig. 20.2 Cyber Knife radiosurgery performed on neocortical seizure focus identified through MEG imaging in a patient with severe medically refractory seizures who refused invasive monitoring

20.4 Stereotactic Radiosurgery for Hypothalamic Hamartomas

Hypothalamic hamartomas (HHs) are deep-seated epileptogenic lesions requiring a complex microsurgical procedure often bound by the limits placed by the hypothalamic gray to lead to incomplete resection and seizure persistence [36]. HHs can be associated with a wide range of neurologic or endocrine manifestations: pedunculated HHs are occasionally associated with endocrine deficits, while intrahypothalamic hamartomas are often associated with gelastic seizures (GSs) and severe medically refractory epilepsy [37]. SRS provides an excellent treatment option for small to medium-sized HHs causing catastrophic epilepsy and is best performed in the early years of childhood before the development of secondarily generalized epilepsy, developmental delay, and behavioral problems. Best results of seizure control are associated with prescribed doses equal or superior to 16 Gy [38, 39]. Temporary worsening of seizures is often observed weeks to months after SRS and is a good predictor of the final success of the procedure [38, 39]. There are no severe neurologic complications following SRS for HHs; a remarkable improvement not only of seizures but also of learning, memory, behavior, and sleep is frequently observed. The main limit of radiosurgery is its delayed effect, since seizures start to decrease 3–6 months after the procedure in most patients and with great variability in the timing of response.

Gamma Knife, Novalis, and Cyber Knife radiosurgery provide safe and effective treatment options for HHs, including for small children [38–41]. Frameless radiosurgery using the Cyber Knife may further facilitate the use of radiosurgery in children, offering a totally noninvasive option devoid of major complications [1, 39]. Surgical and radiosurgical treatments can be optimally integrated in patients with large HHs. In such cases, a surgical debulking procedure can be followed by SRS delivered to the unresectable epileptogenic intrahypothalamic component. Figure 20.3 illustrates a frameless Cyber Knife treatment performed uneventfully and with full seizure resolution in a 9-year-old child with an intrahypothalamic hamartoma associated with catastrophic epilepsy.

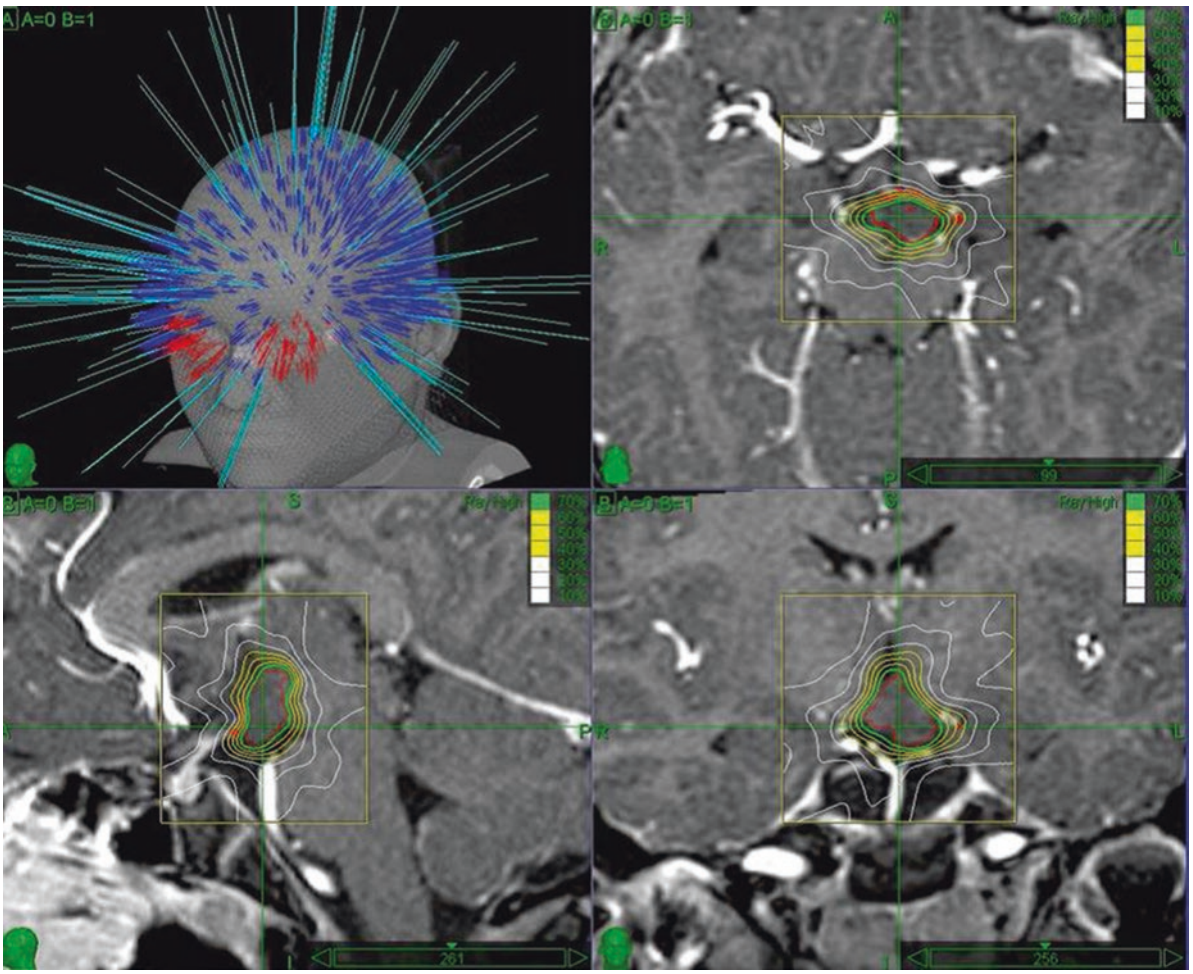

Fig. 20.3 Cyber Knife treatment planning for a medium-sized sessile HH located in the interpeduncular fossa extending into the interpeduncular cistern. The lesion is adjacent to the optic chiasm. The treatment was performed through the delivery of 151 beams. Sixteen Gy prescribed to the 70% isodose were delivered with a maximum dose of 22.85 Gy. Near-seizure freedom (Engel grade Ib) was achieved after 1 year, complete seizure freedom (Engel grade Ia) was achieved after 2 years

20.5 Radiosurgical Callosotomy

The microsurgical section of the corpus callosum prevents the propagation of seizures from one hemisphere to the other, providing an efficacious way to avoid the fast generalization leading to life-threatening drop attacks. Callosotomy is performed as a palliative procedure in patients with severe generalized epilepsy who are not candidates for seizure focus resection. The aim of callosotomy is to control drop attacks caused by generalized tonic or atonic seizures, but a benefit has also been reported for secondarily generalized tonic-clonic seizures, myoclonic seizures, and simple and complex partial seizures. Callosotomy utilization has decreased since the introduction of vagal nerve stimulation, which also helps to prevent tonic and atonic seizures, although there is disagreement regarding which intervention has the best efficacy/risk profile for this purpose [42]. Radiosurgical callosotomy induces a slow and progressive axonal degeneration of white matter fibers as a consequence of neuronal and/or axonal injury. Diffusion tensor imaging (DTI) acquired 3 and 9 months after radiosurgery showed a progressive decrease of the fractional anisotropy in the irradiated region, indicating a progressive disconnection of callosal fibers [43]. Feichtinger and coworkers [44] have described the long-term results of Gamma Knife callosotomy on 8 patients with severe generalized epilepsy and drop attacks. Six patients underwent anterior callosotomy (involving the rostral third of the corpus callosum), while two patients received a posterior callosotomy following hemispherotomy. In one patient a second procedure was performed involving the middle third of the corpus callosum. The treatment was performed using a 4-mm collimator and placing three to five isocenters along the selected region (anterior, middle, or posterior third of the corpus callosum). The maximum dose ranged from 110 to 170 Gy. The prescribed 50% isodose ranged from 55 to 85 Gy. General anesthesia was required in five patients. Target volume ranged from 0.1 to 0.7 mL. Three patients experienced a complete disappearance of drop attacks, while 2 more experienced a 60% reduction. Generalized tonic-clonic seizures disappeared in 2 patients, while 2 others experienced a 50% and 60% decrease. Subacute transient headache and nausea appeared 4–6 months after the treatment in 2 patients. These symptoms were related to mild radio-induced edema in one case and to radionecrosis within the target region associated with bifrontal edema (this case received 55 Gy prescribed in the 50% isodose) in the second. Steroid administration induced symptomatic remission in both cases. Later MRI controls showed edema regression, while the radionecrosis remained limited to the callosal region. On the basis of this experience, the authors recommend prescribing a 50% isodose delivering 45 to 50 Gy to the selected callosal region and then, if needed, adding a further segment to the treatment.

Figure 20.4 shows a Cyber Knife callosotomy administered to a 22-year-old patient with daily drop attacks plus other seizure types (multiple daily complex partial seizures and tonic-clonic generalized seizures twice a week). Presurgical evaluation could not identify a resectable seizure focus: prolonged video EEG monitoring was remarkable for showing a bilateral interictal activity localized over the parietal and occipital lobes; no ictal onset could be identified. A dedicated MRI study failed to show structural lesions. The target region (posterior third of the corpus callosum) received 40 Gy prescribed to the 82% isodose. Target volume was 0.4 mL. Maximum dose was 48.76 Gy. Total number of beams was 193. Beam delivery was nonisocentric, with a large number of beams penetrating around or below the orbito-meatal line. The use of these penetration trajectories would have been banned by the presence of a rigid frame. Treatment duration was 76 min. The patient was discharged home uneventfully immediately after the treatment. A single dose of dexamethasone (8 mg intramuscularly) was administered before discharge. This patient developed mild brain edema associated with worsening of the seizures 3 months after the treatment. Steroid administration was needed to improve seizure control. Six months after the treatment, no further drop attacks and tonic-clonic generalized seizures occurred.

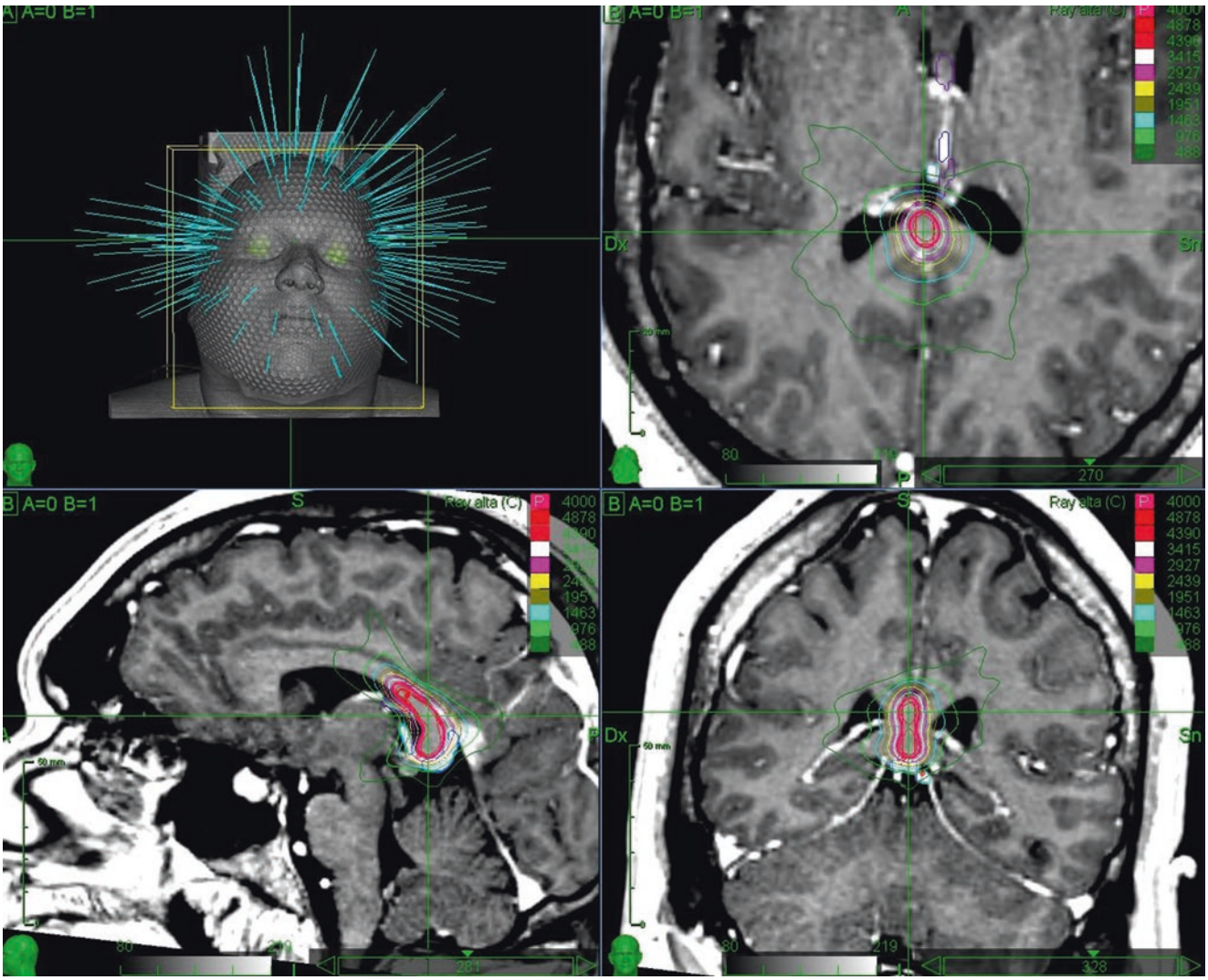

Fig. 20.4 Cyber Knife posterior callosotomy: the absence of a stereotactic frame facilitates a wide array of beam trajectories. Venous structures surrounding the splenium are protected from radiation injury by the tight dosimetry

20.6 Synchrotron-Generated Cortical and Hippocampal Transections

Microscopic arrays of radiograph beams (microbeams) originating from a synchrotron source can induce the equivalent of a microsurgical neocortical or hippocampal incision by delivering very high doses of radiation to tissue slices of microscopic thickness. Neurons, glia, and axons along the penetration path receive peak doses up to 1000 Gy and die immediately, while the immediately adjacent tissue is exposed to much lower valley doses (<6 Gy) that are unable to induce histologically evident tissue damage [6]. In essence, synchrotron-generated cortical transections provide a microradiosurgical equivalent of multiple subpial transections (MSTs), a nonresective surgical technique developed to treat patients with medically refractory epilepsy involving eloquent cortex [45–47]. This technique requires the placement of vertical incisions through the epileptic cortex in order to cut the horizontal axons responsible for the propagation of seizures while preserving the vertical axons subserving neurologic functions. The vertical columns working as the basic unit of cortical function are disconnected but not injured by MSTs, allowing the treatment of epileptic foci located over the sensorimotor or language cortex not amenable to surgical resection. Microbeam transections have been performed over an epileptogenic focus located in sensorimotor cortex, with almost immediate cessation of seizures and excellent preservation of motor function [7, 48–50]. Hippocampal transection has been investigated as well in a rat model (Fig. 20.5), and further studies are ongoing to characterize the ability of hippocampal transections to control seizures originating from this region. These results suggest further investigations directed to assess the potential of microbeam transections to modulate cortical functions and to treat focal epilepsy. Microbeam transection, either placed over neocortical seizure foci or through the hippocampus, could prove to be an excellent tool to add to the current radiosurgical techniques used to control seizures. The development of clinical devices delivering submillimetric beams able to generate cortical transections might add a powerful new tool to the clinical treatment of epilepsy and, more in general, to modulate cortical functions in a wide variety of neuropsychiatric disorders (Fig. 20.5).

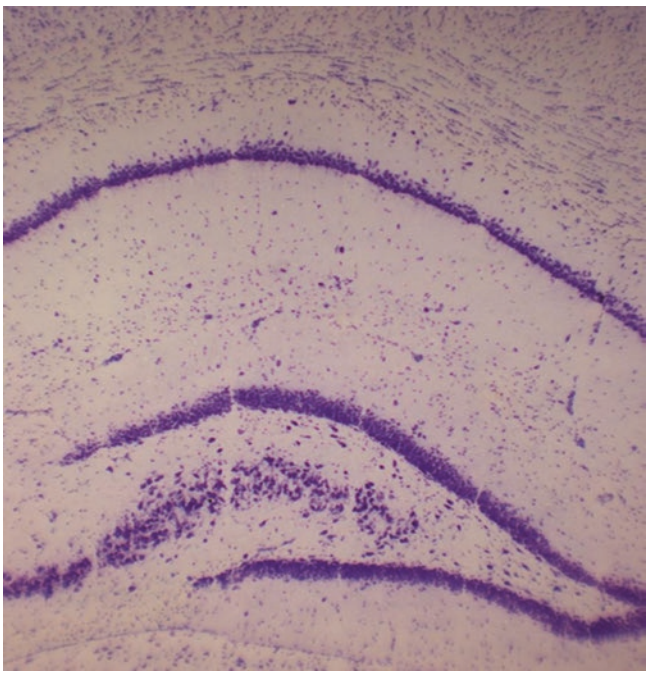

Fig. 20.5 Synchrotron-generated hippocampal transection shown on Nissl staining obtained 3 months after delivery of an array of 9 parallel microbeams to a healthy Wistar rat. Microbeam size was 75 μm, and spacing across the beams was 400 μm. Incident dose was 600 Gy. The treatment was well tolerated, causing no radionecrosis or edema or evident behavioral or cognitive deficits

Conclusions

SRS is an emerging option for selected cases of medically refractory epilepsy. Cyber Knife radiosurgery provides a frameless and thoroughly noninvasive treatment, offering an attractive alternative to a wide variety of patients who refuse or who are not candidates for conventional ablative surgery. Synchrotron-generated microbeams offer a novel research approach to the field of epilepsy surgery, providing the unique ability to generate cortical and hippocampal transections at a microscopic level.

References

1. Romanelli P, Anschel DJ. Radiosurgery for epilepsy. Lancet Neurol. 2006;5:613–20.
2. Romanelli P, Striano P, Barbarisi M, Coppola G, Anschel DJ. Non-resective surgery and radiosurgery for treatment of drug-resistant epilepsy. Epilepsy Res. 2012;99:193–201.
3. Regis J, Bartolomei F, Hayashi M, Chauvel P. Gamma knife surgery, a neuromodulation therapy in epilepsy surgery! Acta Neurochir Suppl. 2002;84:37–47.
4. Regis J, Carron R, Bartolomei F, Chauvel P. Seeking new paradigms in epilepsy: stereotactic radiosurgery. Clin Neurosurg. 2012;59:59–69.
5. Regis J, Carron R, Park M. Is radiosurgery a neuromodulation therapy?: a 2009 Fabrikant award lecture. J Neuro-Oncol. 2010;98:155–62.
6. Romanelli P, Bravin A. Synchrotron-generated microbeam radiosurgery: a novel experimental approach to modulate brain function. Neurol Res. 2011;33:825–31.
7. Romanelli P, Fardone E, Battaglia G, Brauer-Krisch E, Prezado Y, Requardt H, et al. Synchrotron-generated microbeam sensorimotor cortex transections induce seizure control without disruption of neurological functions. PLoS One. 2013;8:e53549.
8. Srikijvilaikul T, Najm I, Foldvary-Schaefer N, Lineweaver T, Suh JH, Bingaman WE. Failure of gamma knife radiosurgery for mesial temporal lobe epilepsy: report of five cases. Neurosurgery. 2004;54:1395–402. discussion, 402–4.
9. Romanelli P, Schweikard A, Schlaefer A, Adler J. Computer aided robotic radiosurgery. Comput Aided Surg. 2006;11:161–74.
10. Regis J, Bartolomei F, Metellus P, Rey M, Genton P, Dravet C, et al. Radiosurgery for trigeminal neuralgia and epilepsy. Neurosurg Clin N Am. 1999;10:359–77.
11. Regis J, Bartolomei F, Rey M, Genton P, Dravet C, Semah F, et al. Gamma knife surgery for mesial temporal lobe epilepsy. Epilepsia. 1999;40:1551–6.
12. Regis J, Bartolomei F, Rey M, Hayashi M, Chauvel P, Peragut JC. Gamma knife surgery for mesial temporal lobe epilepsy. J Neurosurg. 2000;93(Suppl 3):141–6.
13. Regis J, Rey M, Bartolomei F, Vladyka V, Liscak R, Schrottner O, et al. Gamma knife surgery in mesial temporal lobe epilepsy: a prospective multicenter study. Epilepsia. 2004;45:504–15.
14. Regis J, Semah F, Bryan RN, Levrier O, Rey M, Samson Y, et al. Early and delayed MR and PET changes after selective temporomesial radiosurgery in mesial temporal lobe epilepsy. Am J Neuroradiol. 1999;20:213–6.
15. Chang EF, Quigg M, Oh MC, Dillon WP, Ward MM, Laxer KD, et al. Predictors of efficacy after stereotactic radiosurgery for medial temporal lobe epilepsy. Neurology. 2010;74:165–72.
16. Schrottner O, Unger F, Eder HG, Feichtinger M, Pendl G. Gamma-knife radiosurgery of mesiotemporal tumour epilepsy observations and long-term results. Acta Neurochir Suppl. 2002;84:49–55.
17. Barbaro NM, Quigg M, Broshek DK, Ward MM, Lamborn KR, Laxer KD, et al. A multicenter, prospective pilot study of gamma knife radiosurgery for mesial temporal lobe epilepsy: seizure response, adverse events, and verbal memory. Ann Neurol. 2009;65:167–75.
18. Quigg M, Broshek DK, Barbaro NM, Ward MM, Laxer KD, Yan G, et al. Neuropsychological outcomes after Gamma Knife radiosurgery for mesial temporal lobe epilepsy: a prospective multicenter study. Epilepsia. 2011;52:909–16.
19. Rolston JD, Quigg M, Barbaro NM. Gamma knife radiosurgery for mesial temporal lobe epilepsy. Epilepsy Res Treat. 2011;2011:840616.
20. Kurita H, Suzuki I, Shin M, Kawai K, Tago M, Momose T, et al. Successful radiosurgical treatment of lesional epilepsy of mesial temporal origin. Minim Invasive Neurosurg. 2001;44:43–6.
21. Stefan H, Hummel C, Grabenbauer GG, Muller RG, Robeck S, Hofmann W, et al. Successful treatment of focal epilepsy by fractionated stereotactic radiotherapy. Eur Neurol. 1998;39:248–50.
22. Heers M, Rampp S, Stefan H, Urbach H, Elger CE, von Lehe M, et al. MEG-based identification of the epileptogenic zone in occult peri-insular epilepsy. Seizure. 2012;21:128–33.
23. Tovar-Spinoza ZS, Ochi A, Rutka JT, Go C, Otsubo H. The role of magnetoencephalography in epilepsy surgery. Neurosurg Focus. 2008;25:E16.
24. Wu XT, Rampp S, Buchfelder M, Kuwert T, Blumcke I, Dorfler A, et al. Interictal magnetoencephalography used in magnetic resonance imaging-negative patients with epilepsy. Acta Neurol Scand. 2013;127:274–80.
25. Stefan H, Lopes da Silva FH. Epileptic neuronal networks: methods of identification and clinical relevance. Front Neurol. 2013;4:8.
26. Barcia JA, Barcia-Salorio JL, Lopez-Gomez L, Hernandez G. Stereotactic radiosurgery may be effective in the treatment of idiopathic epilepsy: report on the methods and results in a series of eleven cases. Stereotact Funct Neurosurg. 1994;63:271–9.
27. Barcia-Salorio JL, Barcia JA, Hernandez G, Lopez-Gomez L. Radiosurgery of epilepsy. Long-term results. Acta Neurochir Suppl. 1994;62:111–3.
28. Barcia-Salorio JL, Barcia JA, Roldan P, Hernandez G, Lopez-Gomez L. Radiosurgery of epilepsy. Acta Neurochir Suppl (Wien). 1993;58:195–7.
29. Pollock BE, Lunsford LD, Kondziolka D, Maitz A, Flickinger JC. Patient outcomes after stereotactic radiosurgery for "operable" arteriovenous malformations. Neurosurgery. 1994;35:1–7. discussion, 8.
30. Hadjipanayis CG, Levy EI, Niranjan A, Firlik AD, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for motor cortex region arteriovenous malformations. Neurosurgery. 2001;48:70–6. discussion, 6–7.
31. Hoh BL, Ogilvy CS, Butler WE, Loeffler JS, Putman CM, Chapman PH. Multimodality treatment of nongalenic arteriovenous malformations in pediatric patients. Neurosurgery. 2000;47:346–57. discussion, 57–8.
32. Hoh BL, Chapman PH, Loeffler JS, Carter BS, Ogilvy CS. Results of multimodality treatment for 141 patients with brain arteriovenous malformations and seizures: factors associated with seizure incidence and seizure outcomes. Neurosurgery. 2002;51:303–9. discussion, 9–11.
33. Amin-Hanjani S, Ogilvy CS, Candia GJ, Lyons S, Chapman PH. Stereotactic radiosurgery for cavernous malformations: Kjellberg's experience with proton beam therapy in 98 cases at the Harvard Cyclotron. Neurosurgery. 1998;42:1229–36. discussion, 36–8.

34. Regis J, Bartolomei F, Kida Y, Kobayashi T, Vladyka V, Liscak R, et al. Radiosurgery for epilepsy associated with cavernous malformation: retrospective study in 49 patients. Neurosurgery. 2000;47:1091–7.
35. Romanelli P, Verdecchia M, Rodas R, Seri S, Curatolo P. Epilepsy surgery for tuberous sclerosis. Pediatr Neurol. 2004;31:239–47.
36. Calisto A, Dorfmuller G, Fohlen M, Bulteau C, Conti A, Delalande O. Endoscopic disconnection of hypothalamic hamartomas: safety and feasibility of robot-assisted, thulium laser-based procedures. J Neurosurg Pediatr. 2014;14:563–72.
37. Arita K, Kurisu K, Kiura Y, Lida K, Otsubo H. Hypothalamic hamartoma. Neurol Med Chir (Tokyo). 2005;45:221–31.
38. Regis J, Scavarda D, Tamura M, Villeneuve N, Bartolomei F, Brue T, et al. Gamma knife surgery for epilepsy related to hypothalamic hamartomas. Semin Pediatr Neurol. 2007;14:73–9.
39. Romanelli P, Muacevic A, Striano S. Radiosurgery for hypothalamic hamartomas. Neurosurg Focus. 2008;24:E9.
40. Selch MT, Gorgulho A, Mattozo C, Solberg TD, Cabatan-Awang C, Desalles AA. Linear accelerator stereotactic radiosurgery for the treatment of gelastic seizures due to hypothalamic hamartoma. Minim Invasive Neurosurg. 2005;48:310–4.
41. Unger F, Schrottner O, Feichtinger M, Bone G, Haselsberger K, Sutter B. Stereotactic radiosurgery for hypothalamic hamartomas. Acta Neurochir Suppl. 2002;84:57–63.
42. Englot DJ, Birk H, Chang EF. Seizure outcomes in nonresective epilepsy surgery: an update. Neurosurg Rev. 2017;40:181–94.
43. Moreno-Jimenez S, San-Juan D, Larraga-Gutierrez JM, Celis MA, Alonso-Vanegas MA, Anschel DJ. Diffusion tensor imaging in radiosurgical callosotomy. Seizure. 2012;21:473–7.
44. Feichtinger M, Schrottner O, Eder H, Holthausen H, Pieper T, Unger F, et al. Efficacy and safety of radiosurgical callosotomy: a retrospective analysis. Epilepsia. 2006;47:1184–91.
45. Devinsky O, Romanelli P, Orbach D, Pacia S, Doyle W. Surgical treatment of multifocal epilepsy involving eloquent cortex. Epilepsia. 2003;44:718–23.
46. Morrell F, Whisler WW, Bleck TP. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. J Neurosurg. 1989;70:231–9.
47. Morrell F, Whisler WW, Smith MC, Hoeppner TJ, de Toledo-Morrell L, Pierre-Louis SJ, et al. Landau-Kleffner syndrome. Treatment with subpial intracortical transection. Brain. 1995;118:1529–46.
48. Anschel DJ, Bravin A, Romanelli P. Microbeam radiosurgery using synchrotron-generated submillimetric beams: a new tool for the treatment of brain disorders. Neurosurg Rev. 2010;34:1330–42.
49. Romanelli P, Fardone E, Bucci D, Battaglia G, Brauer-Krisch E, Requardt H, et al. Microradiosurgical cortical transections generated by synchrotron radiation. Phys Med. 2015;31:642–6.
50. Fardone E, Bravin A, Conti A, Brauer-Krisch E, Requardt H, Bucci D, et al. Rat sensorimotor cortex tolerance to parallel transections induced by synchrotron-generated X-ray microbeams. Sci Rep. 2017;7(1):14290.

Surgical Resection Techniques of Central Area Gliomas

21

Michael Sabel, Marion Rapp, Maria Smuga, and Marcel A. Kamp

The resection of eloquent located infiltrating brain tumors still presents one of the most formidable challenges in neurosurgery. The need to perform complete (and hence aggressive) resections of high-grade gliomas has been strongly supported by level II evidence of the impact of a complete resection on survival [1–3] and stands in contrast to the need to preserve the patients' integrity and the general principle of medicine to " first do no harm." Fortunately, recent developments in neuro-oncologic neurosurgery provide technologies that can allow for a safe and still aggressive resection even in the central motor area. Among these developments are:

- Improved preoperative imaging (metabolic and functional/anatomic) that allows for improved planning,
- Intraoperative visualization of the tumor (5-aminolevulinic acid [ALA], ultrasound, and intraoperative magnet resonance tomography [iMRI])
- The identification of functional and nonfunctional areas (i.e., resectable areas) by intraoperative monitoring.

Once resectable tissue has been identified, technologies for a safe removal are now available (e.g., ultrasound aspirators). The introduction of subpial resection techniques allows for a more complete resection that preserves the subarachnoid vessels and therefore prevents vascular injuries. Taking advantage of these methods enables the neurosurgeon to limit the resection to functionality and not the tumor margin per se, thereby allowing for a potential supramarginal resection concept. Based on these considerations, this chapter discusses surgical strategy and resection techniques of central area gliomas, the avoidance and management of complications, and the anticipated future development of neuro-oncologic neurosurgery.

21.1 The Need to Perform Complete Resections of Intrinsic Brain Tumors

21.1.1 The Evidence for High-Grade Gliomas

Currently available randomized and controlled studies advocate a surgical resection of malignant gliomas. The prospective randomized 5-ALA study with a total of 270 patients compared the 5-ALA-fluorescence-guided resection of glioblastomas with the conventional white light assisted surgery [1]. The 5-ALA-fluorescence-guided resections resulted in a higher frequency of complete surgical resections of the contrast-enhancing tumor parts on magnetic resonance tomography (MRT). This 29% higher frequency of complete resections after 5-ALA-guided resection resulted in a significantly improved 6-month progression-free survival [1, 2]. Although this study was not directed at an analysis of the overall survival (OAS), a non-significant trend toward a better OAS was observed in the 5-ALA-group [1]. The additional

M. Sabel (✉) · M. Smuga · M. A. Kamp · M. Rapp
Department of Neurosurgery, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany
e-mail: Michael.Sabel@med.uni-duesseldorf.de

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analysis, which included biases and imbalances, suggested a relationship between survival and degree of surgical resection of glioblastoma patients [2]. Next to the 5-ALA study, the prospective randomized and controlled Frankfurt iMRT study demonstrated the benefit of a complete surgical resection of glioblastomas on the patient progression-free survival [4]. Furthermore, it was speculated that the degree of the surgical resection may enhance the efficiency of adjunct and adjuvant therapies [3]. Therefore, this evidence suggests a significant benefit of surgical cytoreduction in malignant gliomas.

21.1.2 The Evidence for Low-Grade Gliomas

Based on the fact that the majority of low-grade glioma (LGG) patients are young adults without major neurologic deficits who enjoy normal life [5], historically these patients have been offered a "wait-and-see" observation of the lesion or just a diagnostic biopsy [6]. But this approach does not take into account the nature of LGGs as a slow-growing process, invariably progressing to high-grade gliomas. LGGs grow continuously about 4–5 mm per year [7], with an inverse correlation between growth rate and overall survival [8]. Recent studies clearly demonstrate a significant increased overall survival following "complete" resection [6, 9–12]. The largest surgical series to date published by the French glioma network identifies the extent of resection as an independent prognostic factor significantly associated with longer survival [13]. At the same time residual tumor volume (of less than 5–10 cm^3) acts as a predictor of malignant transformation [12]. Therefore, according to the current European guidelines, maximal resection represents the first therapeutic option in LGGs [14]. However, a widely accepted definition of maximal resection of LGG has yet been established. Biopsy studies detected tumor cells at a distance of 10–20 mm of the MRI-defined tumor margins [15], suggesting a supramarginal resection with a 2-cm margin around the LGG visible on MRI [16]. In recent studies an increased epilepsy control by supramarginal resection is discussed based on the hypothesis that epileptic seizures arise from the peritumoral tissue and not from the tumor core itself [17].

Therefore, our surgical aim should be to resect the T2/FLAIR-weighted MRT-affected tissue to provide the best chance for stabilizing the disease by controlling epilepsy, delaying malignant tumor transformation, and increasing overall survival.

21.2 The Biological Need for a Supramarginal Approach

Maximum resection of low-grade and high-grade gliomas can obviously prolong the progression-free survival (PFS) and overall survival (OAS). However, as a consequence of the infiltrating growth pattern of gliomas, local tumor recurrence surrounding the resection cavity is almost inevitable (Fig. 21.1). Therefore, modern neurosurgical-neuro-oncology needs to address the issue of resection within the infiltration zone by adopting a supramarginal approach, extending the resection beyond the lesion itself. This approach is highly dependent on the intraoperative evaluation of tissue functionality and has therefore promoted the use of intraoperative monitoring (IOM).

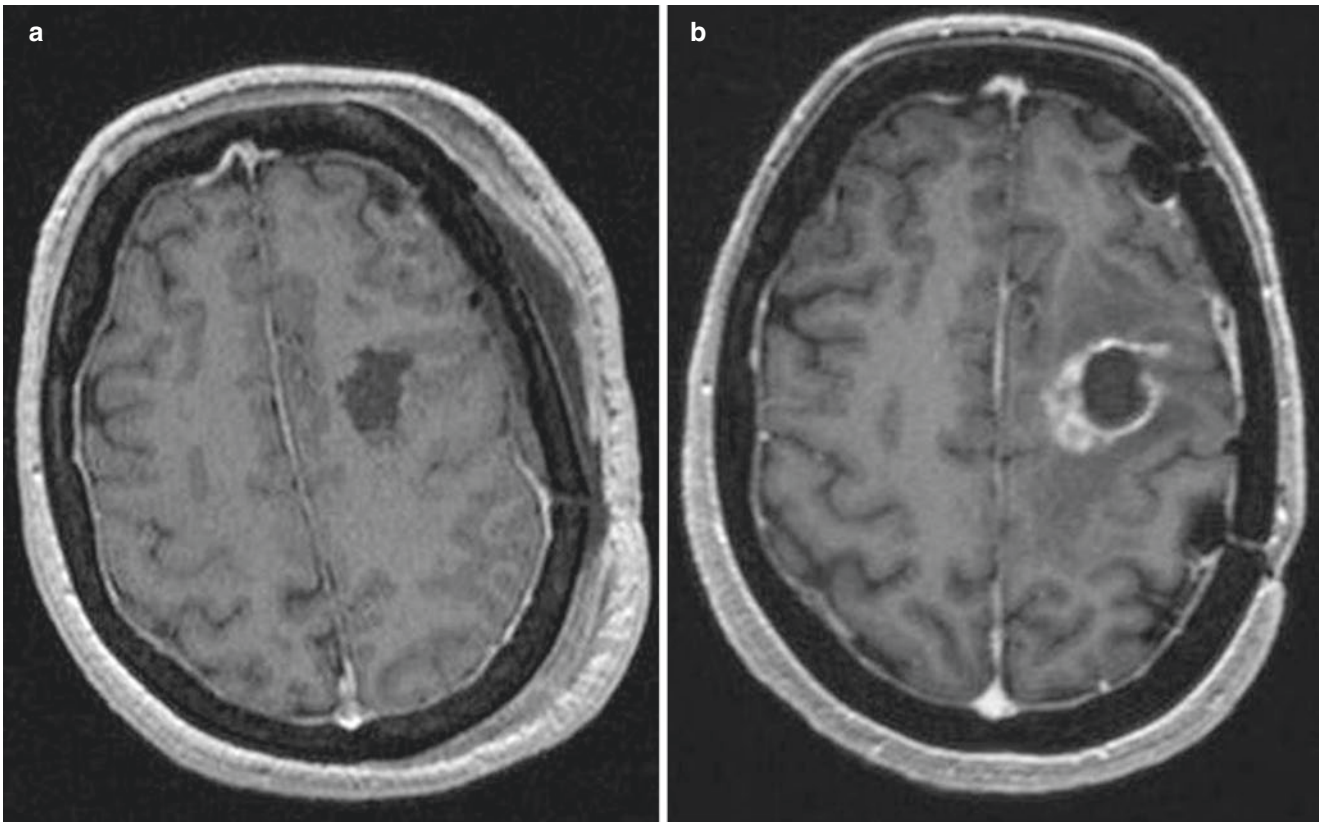

Fig. 21.1 Recurrence of a glioblastoma after complete surgical resection. (**a**), This illustrates the case of a 50-year-old male patient suffering from recurrent glioblastoma (glioblastoma, WHO°IV; IDH wildtype). (**b**), Fourteen months following complete surgical resection

21.3 Surgical Resection Techniques of Central Area Gliomas: Strategy and Technique

We define the central area of the brain as the structure that involves the primary motor cortex, the superior part of the cortical-spinal tract, and the primary sensory cortex, including the thalamo-cortical areas. Surgery in these areas has therefore to take into account the potential damage to motor functions and disturbances of somatosensory functions.

In many centers sophisticated preoperative imaging, including functional MRI, fiber tracking, and metabolic imaging, is available and enables the surgeon to define the anatomic and functional localization of the lesion, thereby providing valuable information that helps to define the risk of causing permanent damage. At this point the detailed goals of surgery must be defined and involve several considerations. First, the individual situation of the patient must be known and considered. Especially in elective (low-grade glioma) surgery, the timing of surgery must be discussed. Is the patient able to accept a temporary deficit in this period of his or her life? Is a minor permanent deficit after a resection of a high-grade glioma compatible with an acceptable quality of life? Is the family ready to provide support if a major deficit occurs? The surgeon needs to define the goals of surgery within this social framework.

21.4 Defining the Surgical Strategy

Under the perspective of maximum prolongation of survival, the primary surgical goal should be the removal of the contrast-enhancing part in the case of a high-grade glioma and the T2 or FLAIR-defined lesion in the case of LGGs. Considering the biological perspective of infiltrating brain tumors, this will not result in a complete resection of the neoplastic tissue. It is therefore necessary to consider a supramarginal approach, thus putting eloquent structures at a high risk for permanent neurologic deficits (Fig. 21.2).

By planning the resection of infiltrating tumors, the surgeon is subject to antithetical endpoints: do no harm versus the removal of deadly neoplastic tissue. Therefore the surgical strategy is aimed at a trade-off between both endpoints.

To resolve this conflict, the surgeon must involve several technical and ethical aspects:

- the indications for surgery and informed consent,
- optimized surgical planning aiming at a supramarginal resection,
- avoidance of permanent neurologic injuries by minimizing the risk of vascular or tissue-related neurologic deficits.

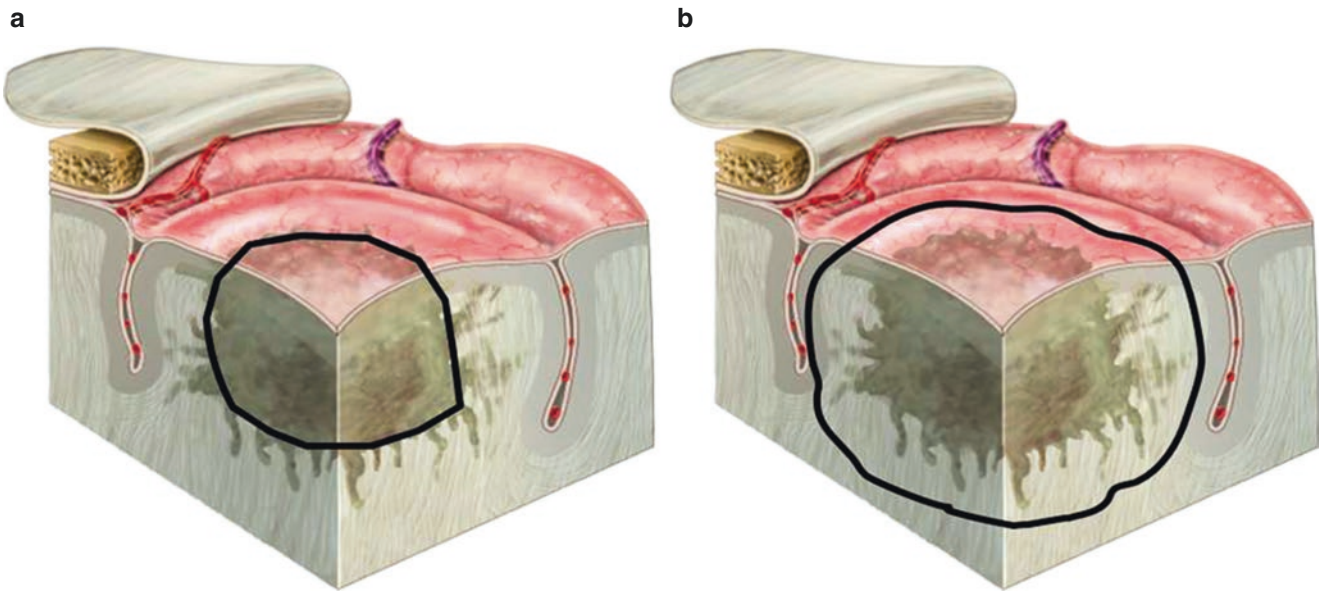

Fig. 21.2 Different surgical approaches to resect an infiltrating intracerebral tumor. (**a**), A common neurosurgical approach to resect infiltrating intracerebral lesions is to remove only the lesion. This approach might result in a complete surgical resection as defined by complete removal of the contrast-enhancing part in the case of a high-grade glioma and the T2 or FLAIR-defined lesion in the case of low-grade gliomas. In the light of the biological perspective of infiltrating brain tumors, this will not result in a complete resection of the neoplastic tissue. (**b**), A supramarginal approach addresses the infiltration zone but has a higher risk for causing permanent neurologic deficits. (Under the perspective of maximum prolongation of survival, the primary surgical goal should be the removal of the contrast-enhancing part in the case of a high-grade glioma and the T2- or FLAIR-defined lesion in the case of low-grade gliomas. In light of the biological perspective of infiltrating brain tumors, this will not result in a complete resection of the neoplastic tissue. It is therefore necessary to consider a supramarginal approach, thus putting eloquent structures at a high risk for permanent neurologic deficits

21.5 The Indications for Surgery and the Informed Consent

It is crucial for the surgical strategy that the risks of causing a permanent deficit must be discussed with the patient and the family and adapted to the patient's individual situation. It is very important to weigh the potential course of the disease without cytoreductive surgery versus the likely outcome of an aggressive surgical approach. Finding the indications for surgery of an infiltrating brain tumor is often more difficult and lengthy than the surgery itself. In this discussion adjuvant treatment options must be considered as well (i.e., glioma with 1p19q co-deletion, isocitrate dehydrogenase-(IDH) mutated and yet no chemotherapeutic treatment). The patient must also be prepared for the possibility of a temporary deficit, which may occur from a high-risk procedure. If the patient agrees in a surgical approach in principle, details of the surgical strategy need to be discussed, such as an awake approach.

21.6 Optimized Surgical Planning Aiming at a Supramarginal Resection

By treating infiltrating brain tumors and thus resecting highly malignant tissue, a pure lesionectomy as defined by the removal of the CE/FLAIR-defined lesion is insufficient. By thoroughly analyzing the preoperative functional and anatomic imaging available, the risks of a pure lesionectomy versus a supramarginal approach versus only a biopsy may be defined.

We recommend a systematic approach:

- cortical or subcortical lesion?
- relationship to the landmarks of the central region: precentral sulcus, M1/S1
- central veins
- relationship to subcortical structures: fiber tracts/vessels.

This analysis should answer the following questions: Which neurologic functions are at risk by

- approach to the lesion,
- resection of the lesion only (lesionectomy),
- supramarginal resection.

If supramarginal resection seems feasible, the extent of additional resection (until functional tissue is involved) must be defined.

We recommend performing this analysis at the latest the day before surgery. This will allow for a final check with the patient and better preparation of the surgical team. In the postoperative phase it is important that the team checks whether the surgical endpoint has been reached (early postoperative MRI) or if a second look operation should be considered.

21.7 Technical Aspects

21.7.1 Presurgical Preparation of the Patient for Awake Craniotomy

The patient must be thoroughly prepared if awake surgery is being considered. This involves training of the tasks he or she will have to perform during surgery. For central area tumors these tasks will mainly involve motor skills and simple motor language tasks (e.g., counting, naming) that will monitor facial, lip, and laryngeal motor involvement. Simple motor tasks for upper and lower extremities must be taught. We suggest training movements that globally screen the relevant motor functions and in addition prepare specific tasks evaluating single muscle functions. The patient should be completely aware of the details of positioning, potential pain management, use of a bladder catheter, and duration of the awake phase. In our experience, a specific neuropsychological preparation of the patient is not necessary [18].

21.7.2 Presurgical Preparation of the Patient for IOM

The neurophysiologist or technician who is responsible for the IOM setup must be briefed about the specific requirements for IOM in the individual case. Depending on the localization of the lesion, it may be necessary to vary the standard setup. For example, planning the resection of a lesion near the midline may require motor-evoked potentials (MEP) monitoring for the lower extremity compared to planning for a more lateral lesion.

21.7.3 Positioning

We recommend the lateral position (Fig. 21.3) for central region tumors with a parallel position of the anteroposterior line to the floor. The advantages of this positioning are:

- simple and fast to perform,
- brain shift in one dimension only,
- good anatomic orientation.

In cases of awake surgery strict axial positioning provides for easy access to laryngeal structures if reinsertion of a laryngeal mask or intubation is required.

Fig. 21.3 Positioning of patients with central region tumors in the operating room. We recommend the lateral position for patients suffering from central region tumors with a parallel position of the anteroposterior line to the floor. (**a**), lateral view. (**b**), coronal view

21.7.4 Skin Incision and Planned Craniotomy

The craniotomy should be sufficient to expose all superficial parts of the tumor. In addition, the craniotomy should also expose the primary motor cortex. This is of utmost importance for the positive control of MEP or bipolar stimulation (see farther on). In most cases linear incisions are sufficient. Since transcranial stimulation is influenced by the position of the electrode placement, a potential shift of electrode position after the skin incision and insertion of the spreader must be anticipated.

21.7.5 Use of Intraoperative Ultrasound

We recommend the use of intraoperative ultrasound as an available and very efficient tool for exact tumor localization. For superficially located lesions the identification of the tumor-bearing gyrus can be performed with high precision, independent of intraoperative brainshift. In more experienced hands the ultrasound might also serve for resection control.

21.7.6 Intraoperative Monitoring: Awake Surgery

Although awake craniotomies are most often indicated for monitoring of higher cortical functions (i.e., language perception, calculation, reading), this method can also be employed for monitoring of pure motor functions. For evaluation of post central lesions, mapping of somatosensory functions is best done in the awake setting. Here we will focus on motor mapping. Awake surgery is most commonly performed in the asleep/awake/asleep or lightly sedated setting. Usually a laryngeal mask under total intravenous anesthesia (TIVA) with propofol and remifentanyl is used for the initial asleep phase. In combination with a field block (0.5% bubivavain plus adrenalin for local vasoconstriction), this provides for sufficient pain control in the initial phase of the operation. As soon as the dura is exposed and palpation of the brain indicates a relaxed brain, the patient can be awakened and the dura opened. The patient will usually require several minutes to awaken after cessation of TIVA. After sufficient compliance is established, testing of the relevant motor functions is started. It is essential that a steady rhythm of movement is established, and quality of performance is communicated with the neurophysiologist and the surgeon.

Stimulation in awake surgery is usually performed with a 60-Hz bipolar stimulator (Fig. 21.4). Stimulation intensity varies between 1 and a maximum of 6 mA. The exposed area should be subdivided into 5-mm^2 areas corresponding to the 5-mm distance between both poles of the stimulator. Systematic mapping of the cortical areas is performed by gradually increasing the stimulation intensity by 0.5 mA, starting with 1 mA. Stimulation should be performed 2 s before a motor task is initiated. Application time of the probe is usually 4 s for testing of motor functions. Since bipolar stimulation blocks motor functions, the observer needs to immediately report changes in motor performance. The initial testing aims at identification of the motor cortex. The minimal intensity that blocks functions is the reference intensity or threshold that is used to evaluate the functionality of the tested tissue. As this reference intensity might change because of increased or decreased awareness of the patient, it is important that repeated stimulation of the motor cortex is performed to identify changes. For subcortical stimulation in the fiber tracts, the surgeon should be able to mentally visualize the assumed course of the tracts. It important to define cut-off values for the stimulation intensity that identify the tissue as resectable. Usually a stimulation intensity of an additional 2 mA of the intensity established on the motor cortex is sufficient for a safe subcortical resection. Because every stimulation can induce a focal or even generalized seizure, the team must be prepared to stop the seizure by irrigation of the exposed brain with ice-cold sodium chloride (NaCl) solution that needs to be available in sufficient quantities (>6 l). Only in very rare cases will irrigation not control the seizure, and treatment with a bolus application of propofol will be needed. Seizure treatment with barbiturates should avoided due to their longer half-life.

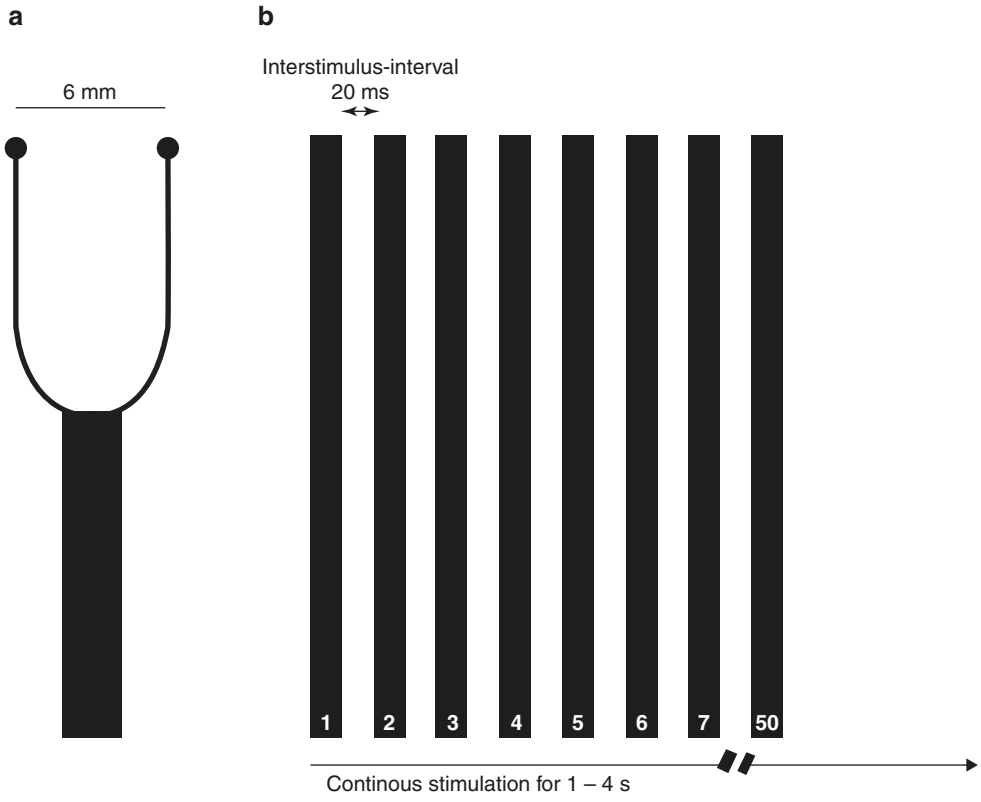

Fig. 21.4 Method of bipolar stimulation. (**a**), Stimulation in awake surgery is usually performed with a 60-Hz bipolar stimulator. (**b**), A cortical area of about 5 mm^2 is stimulated with a stimulation intensity of up to 6 mA over about 4 s

21.7.7 Intraoperative Monitoring: Asleep

The traditional monitoring with transcranial somatosensory-evoked potential (SSEPs) and MEPs is needed and useful but not sufficient for state of the art resection in the central area. This method only offers passive monitoring and identifies problems that are often at an irreversible stage. Monopolar stimulation (Fig. 21.5) should be employed for direct identification of functional cortical or subcortical structures. To this end, in the asleep setting a systematic cortical mapping with a monopolar stimulator should be the first step after dural opening. The technique is in principle similar to the approach described for 60 Hz stimulation. Again, given the considerable risk of stimulation-induced seizures, the surgeon should start with a low current intensity and have an ample quantity of ice-cold irrigation available. As for 60-Hz stimulation, the first step is the reliable identification of the primary motor cortex to determine the minimal current necessary to stimulate the motor system and thus establish the threshold for stimulation. If the motor cortex is identified, a grid can be placed on the exposed cortical area and if necessary subdurally following the respective gyrus. This provides for the options of direct cortical monitoring with MEPs and SSEPs and can compensate for technical problems of transcranial stimulation such as increasing distance between the cortex and skin caused by brain shift. A systematic mapping of the cortical structures identifies the region of safe corticotomy. In due course of the resection subcortical functional areas may be reached and will be identified by subcortical monopolar mapping. Again, a threshold for safe resection needs to be defined. We usually stop if electromyographic (EMG) responses are triggered by stimulation with 2 mA.

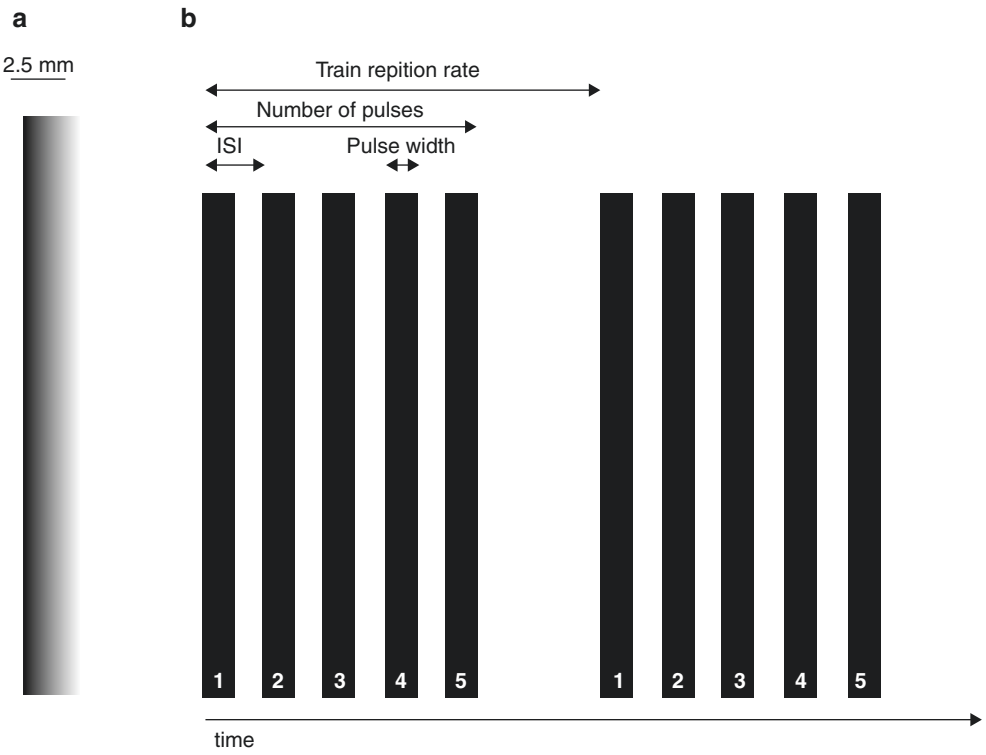

Fig. 21.5 (**a**), Method of monopolar stimulation. Stimulation in awake surgery is usually performed with a 60-Hz bipolar stimulator. (**b**), A cortical area of about 5 mm^2 is stimulated with a stimulation intensity of up to 6 mA over about 4 s

21.7.8 Use of 5-Aminolevulinic Acid

For high-grade gliomas the use of 5-aminolevulinic acid (5-ALA) is correlated with an increased rate of gross total resection and thus with a higher mPFS and mOAS [1–3]. The fluorescence-guided resection of high-grade gliomas with 5-ALA has thus become the standard of care in many centers. An experienced user of 5-ALA can distinguish different qualities of 5-ALA-induced fluorescence (ALIF) [19, 20]: the high intensity "deep red" fluorescence correlating with malignant tumour tissue areas with very high tumor cell content. Here functionality of the tissue can be nearly excluded. At the margin of the lesion the ALIF diminishes to a faint "salmon-like" staining (Fig. 21.6). Here ALIF is helpful to identify the infiltration zone of the tumor as well as functional "danger zones." When approaching these regions the aggressiveness of the resection must be adapted and stimulation should be employed.

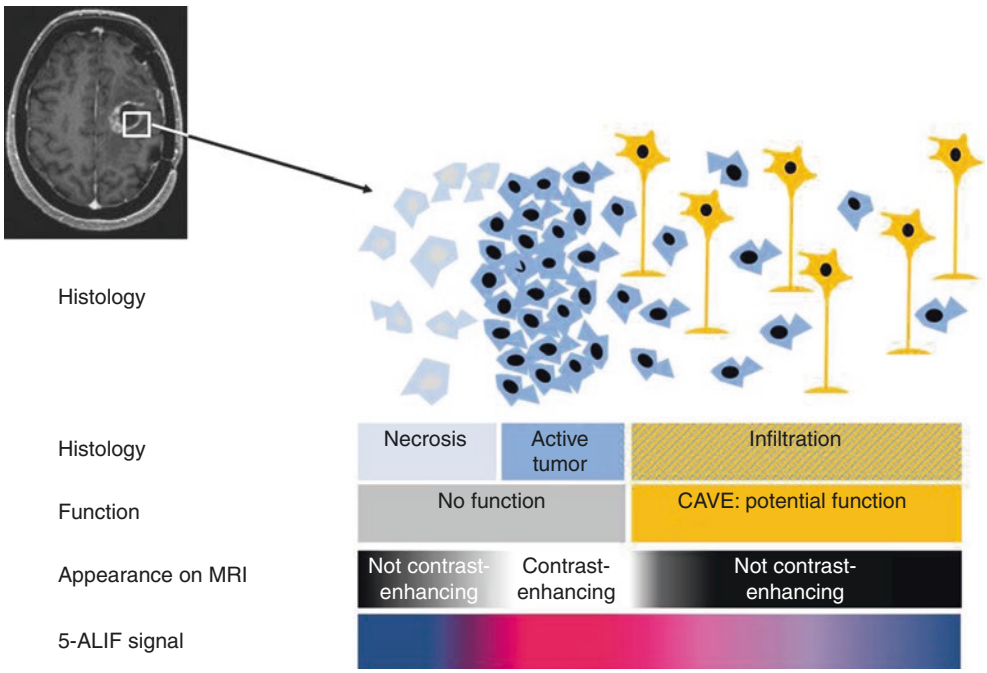

Fig. 21.6 Correlation of the tumor histology, appearance on MRI, neurologic functioning of the particular tissue, and 5-ALA signal in malignant brain tumors

21.7.9 Resection Technique/Tissue Ablation/ Cavitron Ultrasonic Surgical Aspirator

Once resectable tissue has been identified, the removal techniques need to be so precise that only the identified target is removed and vascular injuries are avoided. The traditional resection techniques with bipolar coagulation, suction, and dissector are often too blunt to allow for the necessary precise limitation of tissue ablation. In addition, vascular injuries are often caused by crossing the pial border and thus interfering with the sulcal arteries. We therefore recommend using ultrasound aspiration. This technology allows for the efficient resection of non-eloquent parts of the lesion, and if the right parameters are employed offers a gentle, controlled, and precise ablation of the targeted tissue. In addition, with low-power settings the pia can be preserved and a safe resection can be performed up to the pial border of the adjacent gyrus (Fig. 21.7).

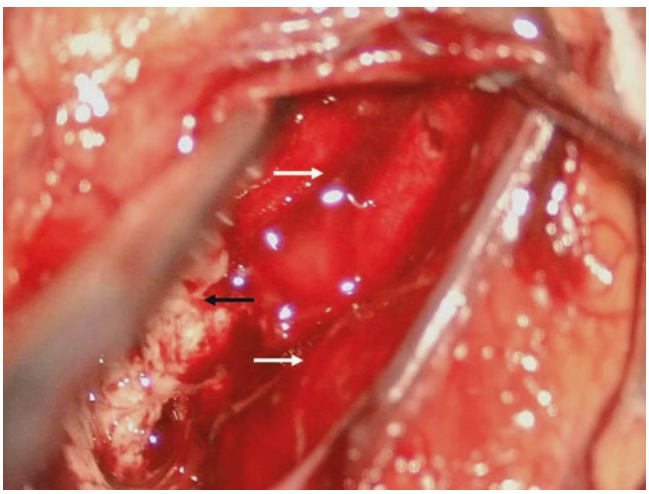

Fig. 21.7 Technique of subpial resection, during which tumor tissue (*black arrow*) is completely removed until the pial boarder appears. Malignant gliomas usually respect the pial boarders without infiltrating them. Vascular injuries of sulcal and pial vessels have to be avoided as they may lead to infarction and subsequent neurologic deficits. Use of the ultrasound aspiration device may help to prevent injury of the pial layer

21.7.10 Hemostasis

In patients with intact coagulation, bleeding usually stops after tumor removal. Since rebleeding in eloquent localizations is almost inevitably associated with severe deficits, a safe hemostasis is compulsory. Because of the destructive tissue effect of and permanent closure of vessels, bipolar coagulation is often not an option. We recommend that for final hemostasis the blood pressure should be raised at least 20 mm Hg above the assumed constitutional blood pressure of the patient. If severe arterial bleeding occurs, bipolar closure of the vessels must be carefully considered. However, in many cases gentle irrigation and covering the area with cottonoids are sufficient. For minor arterial and venous oozing, the application of a hemostat (i.e., oxidized cellulose) is feasible.

21.8 Associated Complications of Surgical Resection Techniques of Central Area Gliomas: Avoidance and Management

Complications associated with the resection of eloquent located lesions often result in severe and disabling neurologic deficits. Measures to prevent this have been described previously. In summary:

- Careful planning with precise definition of danger zones: preoperative identification of eloquent areas (cortical/subcortical) and of potential vascular conflict,
- Intraoperative identification of functional tissue by employing cortical and subcortical stimulation techniques,
- Safe tissue ablation techniques that allow for preservation of pial borders,
- Meticulous hemostasis.

Even with strict adherence to state-of the-art procedures, complications occur at a rate of approximately 6%. Unfortunately, since most of the complications are caused by vascular injury, an effective causal therapy is not available.

21.9 Future Developments of Surgical Resection Techniques of Central Area Gliomas

To improve progression of the tumor and overall survival in patients with central area gliomas, the resection limits should be pushed toward a supramarginal resection. However, this is dependent on the quality and availability of intraoperative monitoring. Neurosurgeons should make every effort to have IOM available. Understanding and being able to practice IOM should be part of basic resident training. Recent advances in the understanding of moleculargentic subtyping of gliomas will lead to a more differential prediction of prognosis. This could influence resection techniques; for example, a tumor with 1p/19q mutation with a likely response to adjuvant treatment might need a less aggressive surgical approach than a non-deleted IDH-1 negative glioma.

In addition, as advances in the understanding of brain connectivity have been identified, the shift from evaluating the functionality of brain areas by topologic considerations to additional hodologic aspects might also influence surgical strategies.

References

1. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006;7:392–401.
2. Stummer W, Reulen HJ, Meinel T, Pichlmeier U, Schumacher W, Tonn JC, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. Neurosurgery. 2008;62:564–76. discussion 76.
3. Stummer W, Kamp MA. The importance of surgical resection in malignant glioma. Curr Opin Neurol. 2009;22:645–9.
4. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V. Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. Lancet Oncol. 2011;12:997–1003.
5. Rueda E, Sierra M, Infante J, Berciano J, Vazquez-Barquero A, Ciordia R, et al. Controversial aspects in WHO grade II gliomas management: review of recent literature. Rev Neurol. 2011;53:747–57.
6. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. Nat Rev Neurol. 2015;11:255–65.
7. Pallud J, Blonski M, Mandonnet E, Audureau E, Fontaine D, Sanai N, et al. Velocity of tumor spontaneous expansion predicts long-term outcomes for diffuse low-grade gliomas. Neuro-Oncol. 2013;15:595–606.
8. Pallud J, Mandonnet E, Duffau H, Kujas M, Guillevin R, Galanaud D, et al. Prognostic value of initial magnetic resonance imaging growth rates for World Health Organization grade II gliomas. Ann Neurol. 2006;60:380–3.
9. Duffau H, Taillandier L. New concepts in the management of diffuse low-grade glioma: proposal of a multistage and individualized therapeutic approach. Neuro-Oncol. 2015;17:332–42.
10. Ius T, Isola M, Budai R, Pauletto G, Tomasino B, Fadiga L, et al. Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients: clinical article. J Neurosurg. 2012;117:1039–52.
11. Jakola AS, Unsgard G, Myrmel KS, Kloster R, Torp SH, Lindal S, et al. Low grade gliomas in eloquent locations: implications for surgical strategy, survival and long term quality of life. PLoS One. 2012;7:e51450.
12. Smith JS, Chang EF, Lamborn KR, Chang SM, Prados MD, Cha S, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol. 2008;26:1338–45.
13. Capelle L, Fontaine D, Mandonnet E, Taillandier L, Golmard JL, Bauchet L, et al. Spontaneous and therapeutic prognostic factors in adult hemispheric World Health Organization Grade II gliomas: a series of 1097 cases: clinical article. J Neurosurg. 2013;118:1157–68.
14. Soffietti R, Baumert BG, Bello L, von Deimling A, Duffau H, Frenay M, et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO Task Force. Eur J Neurol. 2010;17:1124–33.
15. Pallud J, Varlet P, Devaux B, Geha S, Badoual M, Deroulers C, et al. Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. Neurology. 2010;74:1724–31.
16. Duffau H. Long-term outcomes after supratotal resection of diffuse low-grade gliomas: a consecutive series with 11-year follow-up. Acta Neurochir. 2016;158:51–8.
17. de Groot M, Reijneveld JC, Aronica E, Heimans JJ. Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment. Brain. 2012;135(Pt 4):1002–16.
18. Beez T, Boge K, Wager M, Whittle I, Fontaine D, Spena G, et al. Tolerance of awake surgery for glioma: a prospective European Low Grade Glioma Network multicenter study. Acta Neurochir. 2013;155:1301–8.
19. Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ. Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: a prospective study in 52 consecutive patients. J Neurosurg. 2000;93:1003–13.
20. Kamp MA, Krause Molle Z, Munoz-Bendix C, Rapp M, Sabel M, Steiger HJ, et al. Various shades of red—a systematic analysis of qualitative estimation of ALA-derived fluorescence in neurosurgery. Neurosurg Rev. 2016. [Epub ahead of print.].

Surgical Management of Occipital Gliomas

22

Thanasis Paschalis and Konstantinos N. Fountas

Gliomas located in the occipital lobe represent a rare pathologic entity. The importance of their early and accurate diagnosis cannot be overemphasized, since it may affect the overall outcome of these patients. Although extensive resection constitutes the standard management of these tumors, the selection of the best surgical approach remains controversial. Resection through an awake patient craniotomy guarantees maximal resection with great safety. However, it poses significant difficulties associated in large part with the patient's surgical positioning. The employment of visual evoked potential monitoring during general anesthesia craniotomy may provide important information regarding the integrity of the visual pathway and visual cortex; however, its accuracy and reproducibility remain ill defined. The nuances of the employed surgical strategy are presented in this chapter.

22.1 Overview

Gliomas of the occipital region generally constitute a rare clinicopathologic entity representing only 3% of all intracranial gliomas [1]. Their surgical approach remains controversial, as it has been frequently associated with postoperative permanent visual deficits. Often the risk must be thoroughly discussed with the patient and her/his family, regarding the weighing of a permanent visual deficit versus the tumor's gross total or even supramarginal (in cases of a low-grade glioma) resection. There are not that many published series regarding this rare entity. The vast majority of the published ones have suggested an awake surgical resection (whenever the patient meets the requirements for undergoing an awake craniotomy) or resection under general anesthesia, with visual evoked potential monitoring via intraoperative application of specially designed goggles.

22.2 Clinical Presentation

The vast majority of occipital gliomas arise from the parieto-occipital junction. When these tumors affect the nondominant hemisphere, symptoms are usually subtle and can be easily ignored by the patient, until tumor infiltration or tumor-induced edema causes homonymous hemianopia. This delay in the diagnosis may have a negative impact on the prognosis and the overall clinical outcome of these patients [2]. Lesions located on the dominant hemisphere, which usually present with dominant parietal lobe syndromes, are more easily recognized and are diagnosed at an earlier stage [2]. This early diagnosis may have a positive impact on their overall prognosis as well as on the patient's functional outcome. Thus, it is no surprise that the vast majority of the newly diagnosed dominant-hemisphere glial tumors are low-grade gliomas.

T. Paschalis
Department of Neurosurgery, University Hospital of Larisa, Larisa, Greece

K. N. Fountas (✉)
University Hospital of Larisa, Medical School, University of Thessaly, Larisa, Greece
e-mail: fountas@uth.gr

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22.3 Preoperative Evaluation

A blood laboratory work-up should be preoperatively performed, including a complete blood count, a coagulation profile, and baseline biochemical values. Cardiac and pulmonary studies should be done, and the anesthesiologist should take into consideration the complexities of the patient's positioning during surgery (prone, semi-sitting, or modified park-bench position), in order to avoid any adverse perioperative events. A precordial Doppler monitoring as well as a central line insertion need to be considered in cases of patients undergoing surgery in a semi-sitting position.

A recent thorough ophthalmologic examination with emphasis on visual fields must have been performed preoperatively. Imaging evaluation with a gadolinium-enhanced MRI scan (Fig. 22.1), along with a diffusion tensor imaging (DTI) study (Fig. 22.2) should be performed preoperatively, in order to outline the tumor and any adjacent white matter tracts. The exact role of the DTI in identifying and accurately outlining the visual pathway remains highly controversial. Likewise, the role of functional MRI in identifying any visual cortical areas is also highly controversial [3–5]. Data from resting-state functional magnetic resonance imaging (fMRI) studies may provide further information regarding the exact functional topographical anatomy of the occipital cortex.

The majority of the published series advocate the employment of an awake procedure. It allows the surgeon to safely but also aggressively resect the tumor, maximizing thus not only the boundaries of cortical resection but also the boundaries of resection in subcortical areas, while at the same time preserving white matter tracts. Of course patients with occipital gliomas are no different from patients with gliomas in other anatomic areas, and should meet all the requirements and the indications for going through an awake craniotomy. The patient should spend several hours with the neuropsychologist preoperatively in order to familiarize him/herself with the tests employed during the procedure, so that during the procedure collaboration with the neuropsychologist will be as smooth as possible [1].

The whole procedure must be explained in detail to the patient, and all potential risks and complications should be presented to the patient and her/his family before obtaining a written consent.

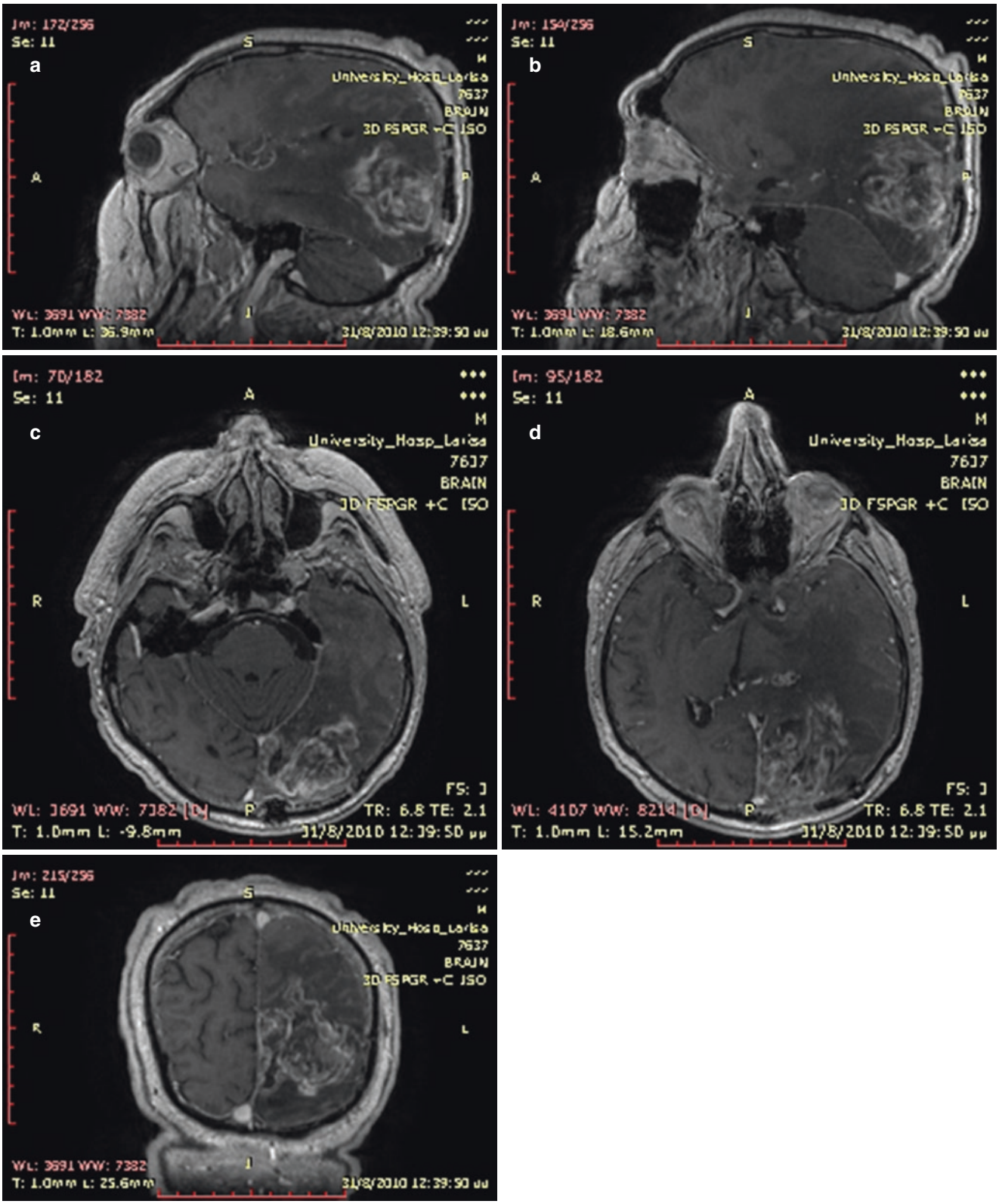

Fig. 22.1 Conventional T1-weighted, sagittal (**a**, **b**), axial (**c**, **d**), and coronal (**e**) images after contrast administration demonstrating a large glioblastoma multiforme (GBM) of the left occipital lobe with surrounding edema and necrotic characteristics

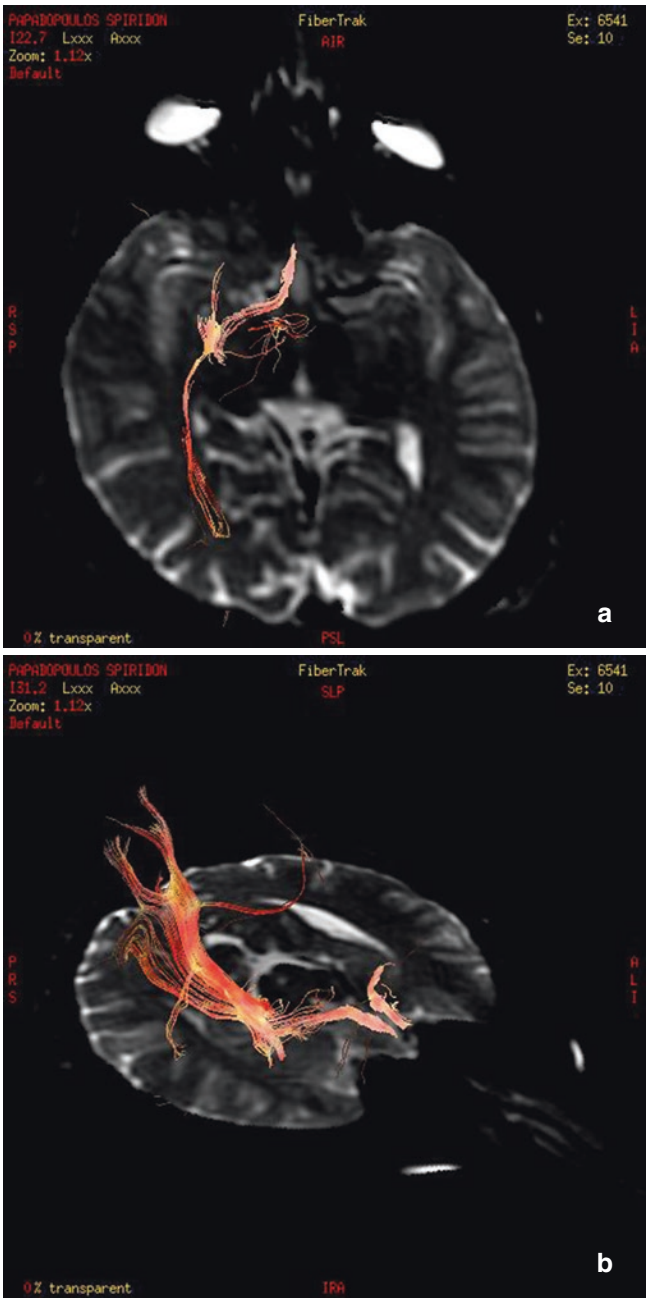

Fig. 22.2 (**a**, **b**) MR-based diffusion tensor imaging depicting the visual pathway

22.4 Surgery Tenets and Considerations

22.4.1 Positioning

As in every other neurosurgical procedure, the optimal positioning of the patient is of paramount importance. There is significant controversy regarding the best surgical position for these patients. There are those surgeons who favor the supine position, with the patient's head in a three-point fixation device rotated up to 70°. The presence of cervical spondylosis, particularly among elderly patients, needs to be taken into consideration.

Many surgeons prefer the prone position when large tumors are present, and of course in asleep procedures. A modified semi-sitting or a modified park-bench position may be used during an awake procedure. During awake procedures special attention needs to be paid to proper nerve block, and every possible effort needs to be made to ensure that the patient has a comfortable position.

22.4.2 Tenets

Gliomas of the occipital lobe or of the parieto-occipital junction are not an exception to the general rules; therefore a maximal initial resection should be the goal in these cases [6, 7]. In order to accomplish this, the visual cortex and all the subcortical visual pathways should be accurately identified. Most experts strongly advocate an awake procedure, which will maximize the tumor resection, while at the same time will mitigate the possibility of a permanent homonymous hemianopia and/or a visual-spatial neglect (which depends on whether the treated glioma is located in the dominant or the nondominant hemisphere). Those patients who are good surgical candidates for an awake craniotomy should undergo surgery in a lateral position under local anesthesia so that functional cortical and subcortical mapping may be carried out using direct brain stimulation. Then the patient is permitted to speak freely with the neuropsychologist, in an attempt to identify and recognize common pictures that have been thoroughly discussed before the procedure.

In awake procedures the cortical mapping is usually followed by subcortical mapping, which is of vital importance because it allows the surgeon to maximize the extent of resection. It has been previously suggested that picture naming to be used in the second stage of the procedure, with pictures situated in the visual quadrant. These are saved and another picture is situated in the opposite quadrant in order to avoid homonymous hemianopia (since quadrantanopia may be well tolerated by the patient) [8]. The role of the neuropsychologist during intraoperative testing is of paramount importance. She/he has to adequately inform and train the patient preoperatively, and smoothly and accurately assess him or her intraoperatively. Special care should be given to provide the patient with information about eye movements, as peripheral vision should be preserved [8].

Various modules have been suggested, such as marking pictures with a red cross in the center [6, 8, 9]. Then the patient is asked to name both items on the picture. This provides the neuropsychologist with the opportunity to test not only language but also the integrity of the overall visual field [8]. Indeed, the patient may frequently experience subjective transient visual disturbances within the contralateral visual hemi-field (blurred vision, phosphenes, or shadow, as previously reported by Duffau et al. [8]), which prevents the naming of the picture situated in the contralateral quadrant but not the picture situated in the ipsilateral quadrant. This indicates a visual field deficit and not a language disorder.

Another important tenet that was widely used before the "awake craniotomy era" is the employment of visual evoked potentials (VEPs). The reliable use of VEPs to diagnose demyelinating and other conditions clinically has suggested, that monitoring visual potentials during neurosurgical procedures involving the visual pathways may serve as a valuable tool, to help guide the surgeon during the procedure and thus preserve visual function. When an awake procedure is not feasible, VEPs remain the last but not the least monitoring modality in a neurosurgeon's armamentarium. Recording evoked potentials relies on the fact that stimulation of sense organs (vision) evokes an electrical response in the corresponding cortical receptive areas and subcortical relay stations. Flash VEPs can be reliably monitored. In these instances, the flash stimulus is transmitted through goggles placed over the patient's closed eyes (Fig. 22.3). Although throughout the years monitoring optic radiation with VEPs has remained a serious controversy, it is still one of the available methodologies for monitoring patients operated on in the occipital region, who cannot be monitored in any other way. While evoked potential recording and anesthesia protocols have remained unchanged, possibly the introduction of high-luminance devices with supramaximal stimulation has contributed to the success of VEP by improving the constant stimulus delivery. New data in the literature support the use of VEPs in association with preoperative DTI imaging for best outcomes and maximal safe resection of gliomas located in the occipital lobe. Although the accuracy of VEP monitoring still remains controversial, there is a recent shift in the literature advocating the use of VEPs, since technical ameliorations have taken place and have minimized the incidence of false-positive and false-negative results.

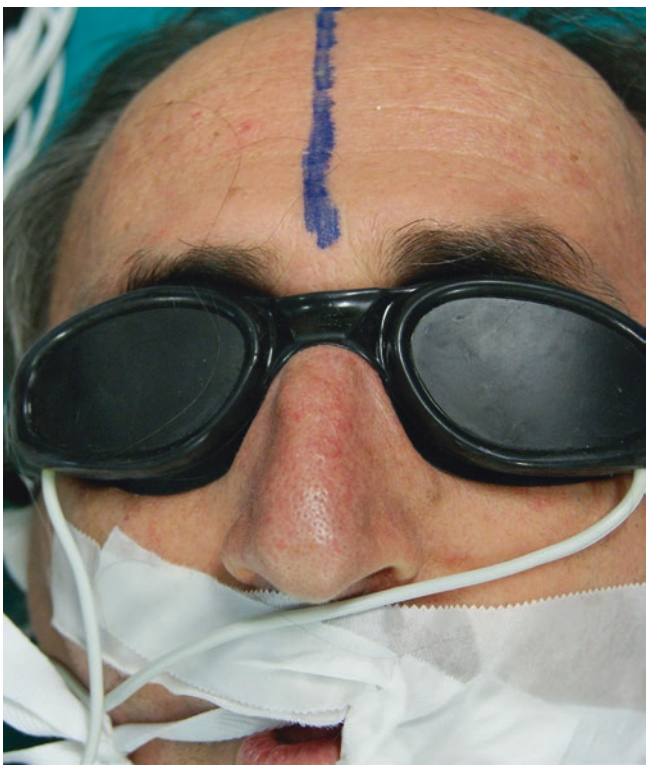

Fig. 22.3 Goggles for intraoperative VEP monitoring on a patient undergoing craniotomy for occipital glioma resection before positioning him in the prone position

22.5 Postoperative Care

Postoperative care does not differ from that of any other neurosurgical patient. However, special attention needs to be given to the psychological support of these patients, as they may be depressed, especially when they face new postoperative visual deficits. The involved neurosurgeons and also the nursing staff need to be aware of any possible behavioral changes, which may also affect the patient's compliance with her/his medications. Early ambulation and avoidance of bed rest becomes extremely important for better surgical wound healing in these patients, since compression of the occiput may affect the healing process. The patient needs to be prepared, and to be properly guided for adjuvant radiation therapy and chemotherapy.

References

1. Viegas C, Moritz-Gasser S, Rigau V, Duffau H. Occipital WHO grade II gliomas: oncological, surgical and functional considerations. Acta Neurochir. 2011;153:1907–17.
2. Edmund J. Visual disturbances associated with gliomas of the temporal and occipital lobe. Acta Psychiatr Scand. 1954;29:291–310.
3. Coenen VA, Huber KK, Krings T, Weidemann J, Gilsbach JM, Rohde V. Diffusion-weighted imaging-guided resection of intracerebral lesions involving the optic radiation. Neurosurg Rev. 2005;28:188–95.
4. Fried I, Nenov VI, Ojemann SG, Woods RP. Functional MR and PET imaging of rolandic and visual cortices for neurosurgical planning. J Neurosurg. 1995;83:854–61.
5. Hirsch J, Ruge MI, Kim KH, Correa DD, Victor JD, Relkin NR, et al. An integrated functional magnetic resonance imaging procedure for preoperative mapping of cortical areas associated with tactile, motor, language, and visual functions. Neurosurgery. 2000;47:711–22.
6. Mandonnet E, Gatignol P, Duffau H. Evidence for an occipitotemporal tract underlying visual recognition in picture naming. Clin Neurol Neurosurg. 2009;111:601–5.
7. Berger MS, Deliganis AV, Dobbins J, Keles GE. The effect of extent of resection on recurrence in patients with low grade cerebral hemisphere gliomas. Cancer. 1994;74:1784–91.
8. Gras-Combe GI, Moritz-Gasser S, Herbet G, Duffau H. Intraoperative subcortical electrical mapping of optic radiations in awake surgery for glioma involving visual pathways. J Neurosurg. 2012;117:466–73.
9. Nguyen HS, Sundaram SV, Mosier KM, Cohen-Gadol AA. A method to map the visual cortex during an awake craniotomy. J Neurosurg. 2011;114:922–6.

Surgical Resection Techniques of Insular Gliomas

23

Abraham Tsitlakidis and Nicolas Foroglou

The insula of Reil, always considered challenging from the neurosurgical perspective, has a predilection for glioma development. Insular gliomas consist of a unique group compared to the rest of brain gliomas because of their peculiarities of the surgical/functional anatomy and clinical presentation. The surgical resection of insular gliomas has been proven to be a safe and effective treatment. Nevertheless, to achieve a favorable outcome, the appropriate surgical planning strategy should take into consideration the individual functional anatomy of the region and the extent of the tumor. Moreover, intraoperative adjuncts such as neurophysiology and image guidance are particularly useful to reveal functionally eloquent areas and tumor residue, thus directing the resection and delineating the surgical cavity.

23.1 General Philosophy and Procedures

23.1.1 Approaches

The insula often develops low-grade and high-grade gliomas, with a unique over-representation of low-grade gliomas in comparison to other regions of the brain [1]. Gliomas may grow slowly, compressing the basal ganglia, because they remain within the limits of the allocortex, which constitutes a major part of the insular cortex. Thus, frequently and especially in the case of a low-grade glioma, the lesion does not invade the deeper basal ganglia [2]. Still, many gliomas infiltrate the underlying white matter tracts, the claustrum, and the putamen, rendering their dissection tiresome [3]. Broadly, they can be restricted to the insula per se or extend toward the frontal or/and temporal lobes (Fig. 23.1).

Historically, according to Yasargil's classification of limbic and paralimbic gliomas [4] as outlined by Zentner et al. [5], insular gliomas are classified in group 3. According to this classification, purely insular lesions (type 3A) represent 16.7% of insular gliomas, and type 3B gliomas (30%) involve the opercula simultaneously. Insular gliomas may also extend into the paralimbic areas such as the fronto-orbital or the temporopolar (type 5A, 30%), or they can infiltrate the limbic system (type 5B 23.3%) (Fig. 23.2).

More recently, Sanai et al. have suggested a topographic classification of insular gliomas into four zones: I (anterior-superior), II (posterior-superior), III (posterior-inferior) and IV (anterior-inferior). This is based on a plane parallel to the sylvian

A. Tsitlakidis
Department of Neurosurgery, AHEPA University Hospital, Thessaloniki, Greece

N. Foroglou (✉)
Department of Neurosurgery, Aristotle University of Thessaloniki, AHEPA University Hospital, Thessaloniki, Greece
e-mail: nforoglou@auth.gr

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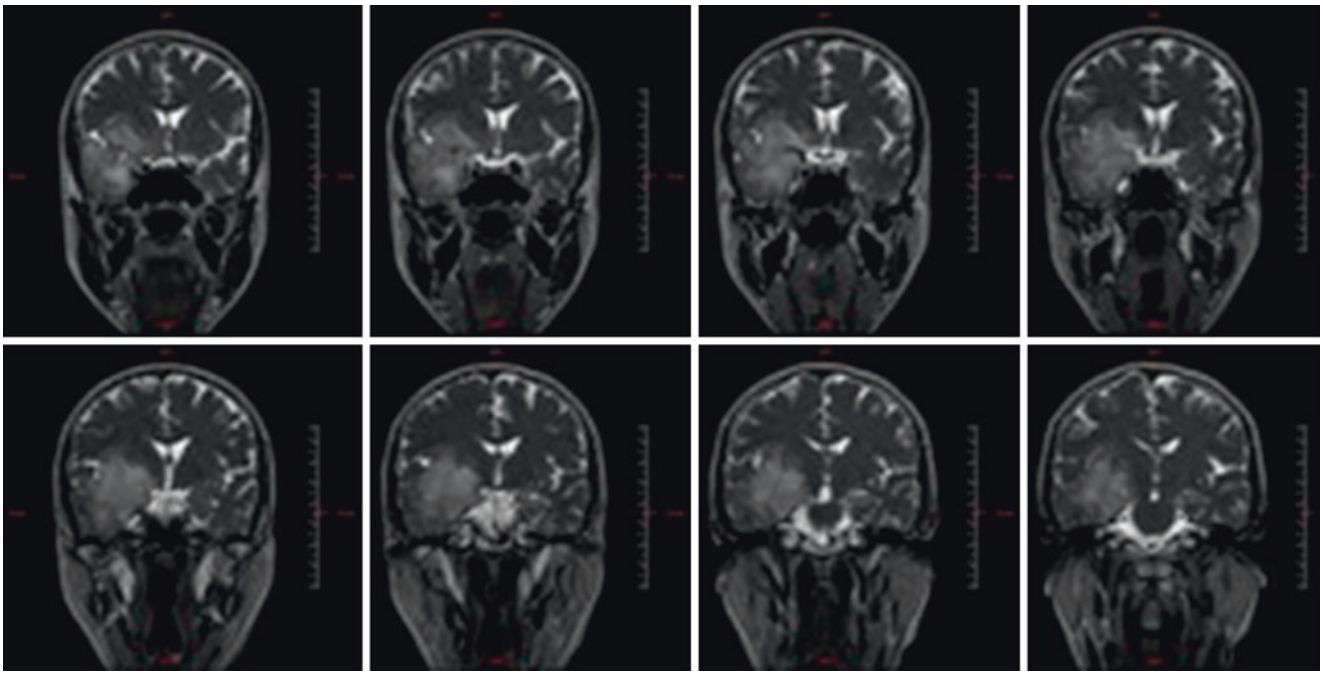

Fig. 23.1 Coronal T2 MRI sections of a right insular glioma extending into both the frontal and the temporal lobes. The hippocampus is infiltrated (Yasargil type 5B)

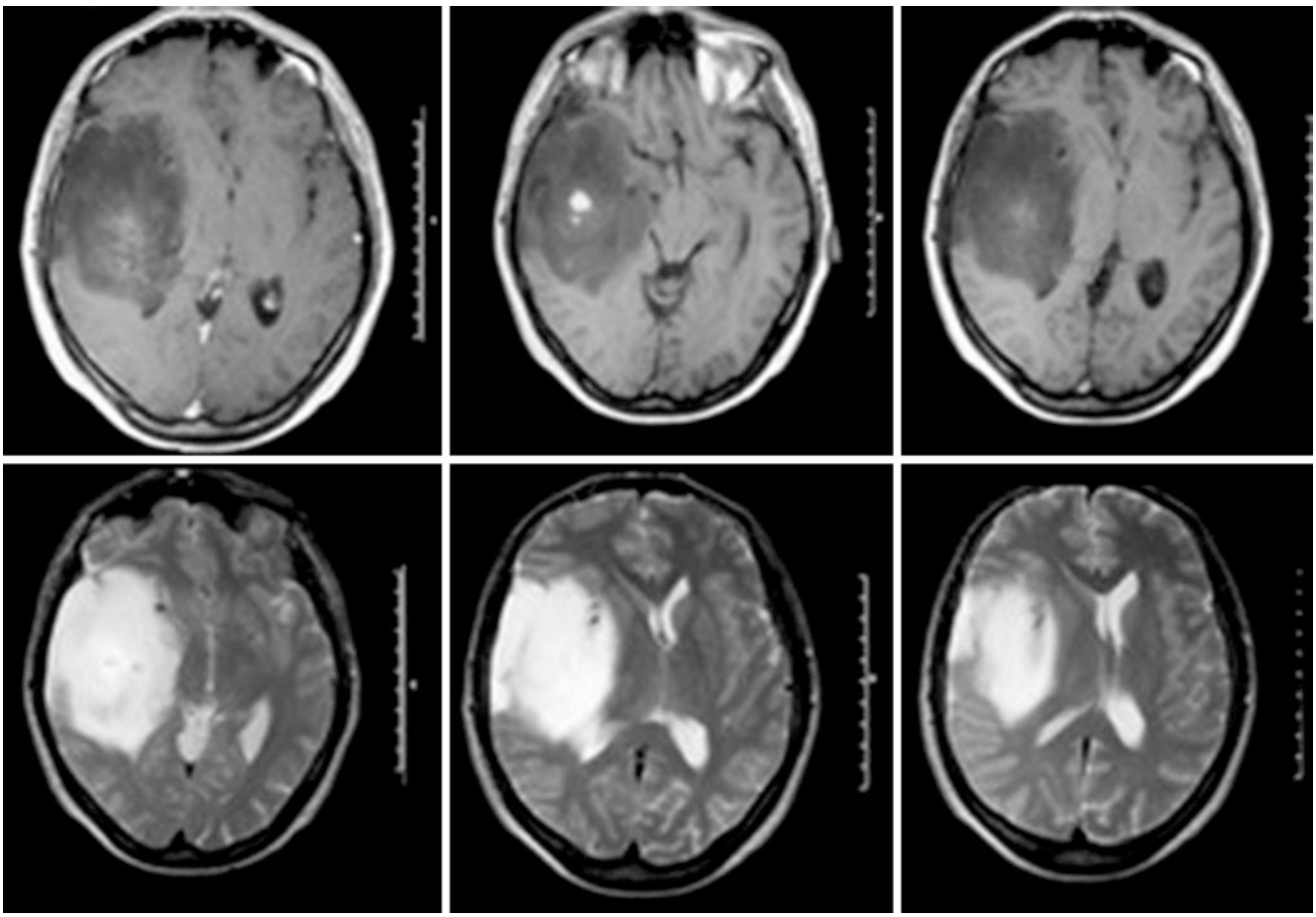

Fig. 23.2 Axial MRI sections of a right insular glioma with temporal expansion and infiltration of the hippocampus (Yasargil type 5B)

fissure and a second plane perpendicular to the first crossing of the foramen of Monro (Fig. 23.3). According to the location, different degrees of resection can be achieved, favoring zone I (93.8%), followed by zones III (90%), IV (88.8%), and II (67.4%) [1]. However, it has been noted that only 31% of gliomas are restricted to zone I, 1.6% to zone II, 13.2% to zone III, and 10.9% to zone IV. In general, in insular gliomas zone I is involved in 59.7%, zone II in 19.4%, zone III in 37.2%, and zone IV in 45.8% [6]. Thus, gliomas of the posterior insula are quite rare in comparison to those of the anterior insula.

The clinical course of insular gliomas usually exhibits a slow progression, with intractable epilepsy as the most common presenting symptom [4]. Other symptoms include headache, sensory or motor dysfunction, aphasia, cognitive dysfunction, memory deficits, attention disorders, or visual dysfunction [7].

Surgery for insular gliomas has two objectives. The first is to achieve the maximal degree of resection in order to maximize survival, as supported from recent accumulating data. The second is to preserve functional integrity. Important structures around the insula are involved, such as white matter tracts, basal ganglia, branches of the middle cerebral artery, and lenticulostriate arteries. It is globally recognized that insular surgery carries a higher surgical morbidity rate than other cerebral areas.

In terms of surgical approach, there are two options when tackling tumors of the insula. The surgeon can either open the sylvian fissure (trans-sylvian approach) [8] or gain access through the opercular cortex (transcortical approach) [2]. Based on a cadaveric study comparing the two approaches, it has been supported that the transcortical approach allows better surgical results [9].

Irrespective of the preferred approach, the surgeon should evaluate several features from the preoperative imaging studies. Preoperative hemispheric dominance is usually explored with functional magnetic resonance imaging (fMRI) and/or neuropsychological examination [10], but there is a recent trend to favor awake patient surgery and map for language and spatial cognition irrespective of side. Appropriate intraoperative mapping and monitoring allow for a safe approach and maximal resection respecting functional integrity. Important factors of surgical outcome are the presence of a sharp border between the tumor and the basal ganglia, the location of the tumor, and the extension of the tumor into the frontal and/or temporal lobes. Frontal extension frequently progresses to the midline structures toward the anterior commissure, and posterior temporal involvement is challenging to the resection [1, 9, 11].

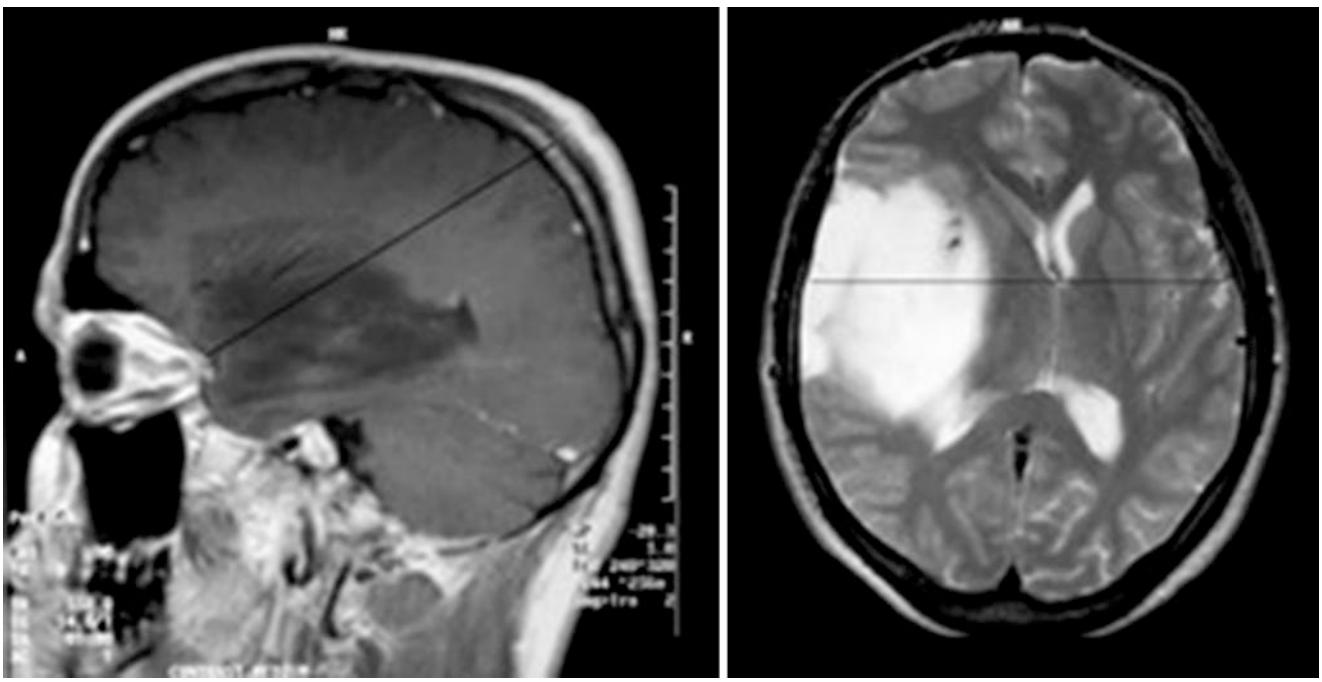

Fig. 23.3 A right insular glioma with a large temporal expansion. On the left, a sagittal T1 MRI section where the plane parallel to the (expected) sylvian fissure is drawn. On the right, an axial T2 MRI section where the plane crossing the Monro foramen is drawn. The tumor invades all four zones of the insula; therefore it is classified as a giant insular glioma according to the Berger-Sanai classification scheme

23.2 Surgical Anatomy

The insula of Reil is the region of cortex underlying the sylvian fossa. The structures beneath it comprise the central core of the cerebrum. A handful of landmarks in the anatomy of the insula are surgically significant. The most prominent are the limen insulae, the apex insulae, which lies directly medially to the anterior sylvian point, and the circular or peri-insular sulcus, which surrounds the insula and constitutes its limits. The circular sulcus is split into the anterior, superior, and inferior peri-insular sulci. The insula, as it lies in the depth of the sylvian fossa, is covered by the fronto-orbital, the frontoparietal, and the temporal operculum [12].

Various functions that have been attributed to the insula include auditory functions, vestibular functions, somatosensory functions, pain and temperature perception, interoception (viscerosensation, bodily awareness, self-recognition), taste, olfaction, several motor functions (visceromotor control, somatomotor control, motor plasticity, speech production), cognitive control, homeostasis, several emotions (individual emotions, social emotions such as empathy), the regulation of attention and alertness, and functions included in the framework of memory and learning. The insula has been associated with disorders such as schizophrenia, conduct disorder, frontotemporal dementia, and drug addiction [13].

The sylvian or lateral fissure is the most prominent landmark on the lateral surface of the cerebrum and is the superficial part of the sylvian cistern. It can be studied preoperatively on sagittal MRI sections based on the morphology of the gyri. The surgeon should be well acquainted with its rami and the gyri that make up the opercula. Based on the anterior sylvian point, which lies directly inferior to the triangular part of the inferior frontal gyrus, the sylvian fissure can be divided into a proximal and a distal part. The sylvian fissure extends medially to the sylvian sulcus, which lies between the frontoparietal and the temporal opercula, while the sylvian fossa lies at the bottom of the sylvian cistern. The sylvian fossa is divided into a proximal, a middle, and a distal part. The proximal part is transversely oriented. The sylvian fossa in this part is called the vallecular, and it corresponds to the anterior perforated substance. The middle or insular part lies directly over the insula and is the widest. The distal or retroinsular part lies posterior to the insula, and it is the deepest part.

The central core is the deep region of the hemisphere. It consists of the thalamus and the caudate nucleus medially (Fig. 23.4). The internal capsule (IC) lies laterally of these. The globus pallidum and the putamen belong to the basal ganglia, along with the caudate nucleus, and they are surrounded by the external capsule. The external capsule consists of the dorsal and the ventral parts. The dorsal part contains fibers that connect the claustrum with the cortex and should be protected in the case of a bilateral lesion. The ventral part contains the uncinate fascicle (UF) and the inferior fronto-occipital fascicle (IFOF). The dorsal part of the claustrum lies lateral to the external capsule, while its ventral part lies within the ventral part of the external capsule. The extreme capsule contains short association fibers that connect the insular gyri to each other and the insula with the rest of the cerebral cortex [14]. The isthmi bridge the central core with the rest of the cerebrum and lie between the peri-insular sulcus and the lateral ventricle. The anterior isthmus lies between the frontal horn and the anterior peri-insular sulcus. The superior isthmus lies between the superior peri-insular sulcus and the body of the lateral ventricle, while the inferior isthmus or temporal stem lies between the inferior peri-insular sulcus and the temporal horn.

The fundamental anatomy of the middle cerebral artery is relatively simple. From its origin to its bifurcation, it is called M1 or the sphenoidal segment. Its bifurcation usually lies directly on the limen insulae. Thereafter and on the insular surface it is called M2 or the insular segment. Around the opercula it is called M3 or the opercular segment, while on the lateral surface of the cerebral hemispheres it is called M4 or the cortical segment. The bifurcation usually results in a superior and an inferior trunk. Several anatomic variations of the M1 have been described [15]. Although the usual cases regarding its direction and morphology involve only one or two variations, the surgeon should also be acquainted with less common variants. Regarding its branching, the usual pattern is the bifurcation, although there are also less common variations. The lenticulostriate arteries arise from the M1, and they enter the parenchyma through the anterior perforated substance to irrigate a major part of the putamen, the caudate nucleus, and the IC as well as a part of the corona radiata. The M2 has its own anatomic variations. In 50% of the cases there are two symmetric branches, but occasionally there might be several asymmetries. The cortical branches of the middle cerebral artery irrigate almost the entire lateral surface of the cerebral hemisphere. A rim on the periphery consists of the exception because it is irrigated by the anterior and posterior cerebral arteries. The perforating branches of M2 arise on the surface of the insula. The vast majority (85%) are short segments and irrigate the insula and extreme capsule, 10% have medium length and irrigate the claustrum and the external capsule, and only 5% are long perforating arteries that usually arise close to the superior peri-insular sulcus, irrigating a major part of the corona radiata. For this reason, the surgeon should be very cautious when the resection approaches the posterior part of the superior peri-insular sulcus. The M1 and the M2 perforators form two distinct systems of arteries that irrigate different areas without anastomoses between them [16].

The deep sylvian vein drains the insular cortex and ends up in the basilar vein of Rosenthal. Also present on the lateral surface of the cerebral hemisphere are the superficial anastomotic vein system with the unique or multiple

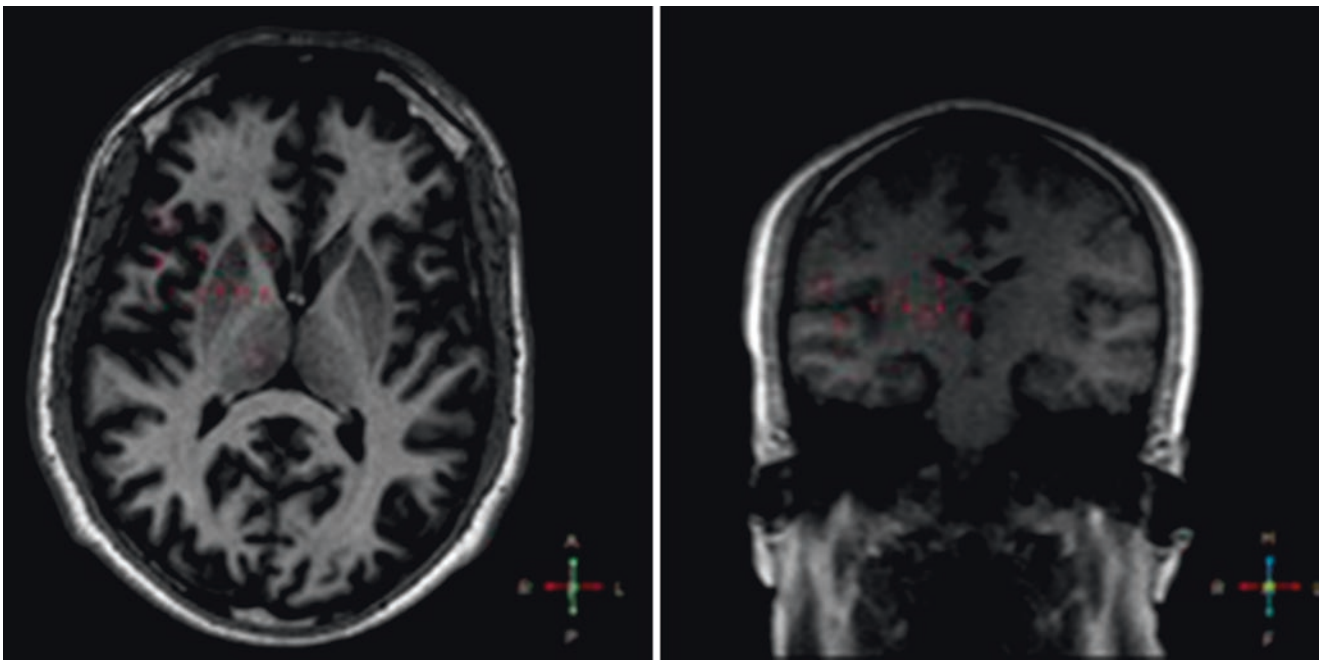

Fig. 23.4 The insula (1) lies beneath the sylvian cistern. The central core consists of the caudate nucleus (2), the thalamus (3), the internal capsule (4), the globus pallidum (5), the putamen (6), the external capsule, the claustrum (7) and the extreme capsule. The frontal (8) and temporal opercula (9) cover the insula

superficial sylvian veins and the veins of Labbe and Trollard, which anastomose in various ways [15]. The two systems are therefore not independent of one another.

The anatomy of the white matter is particularly important for the surgery of insular gliomas. The main association fascicles concerning the surgery of insular gliomas are the UF, the arcuate fascicle (AF), and the IFOF. The UF passes beneath the limen insulae, connects the temporal pole with the basal frontal lobe, and belongs to the limbic system. The IFOF, a major element of the ventral semantic language stream, connects the lateral surface of the temporal and occipital lobes with the frontal lobe. It lies dorsally and posterior to the UF. It passes through the ventral part of the external capsule and deals with the semantic content of language as well as with other functions that may be associated with vision. Both the UF and the IFOF cross the anterior isthmus and the anterior portion of the superior isthmus anteriorly and superiorly and the inferior isthmus inferiorly and posteriorly. It should be noted that the IFOF lies directly lateral to the optic radiation in the temporal lobe. In consequence, if the IFOF is preserved, it may be assumed that the optic tract is preserved as well. The AF, the main contributor of the dorsal language stream, forms a complex with the superior longitudinal fascicle (SLF). It serves some language functions, mainly in the dominant hemisphere, and other functions as well. It begins from the temporal lobe, surrounds the distal rami of the sylvian fissure, passes through the parietal lobe, and ends up in the frontal lobe. Regarding the commissural and the projection fascicles, the surgeon is concerned with the anterior commissure (AC) and the IC. The AC connects the two hemispheres, the frontal and the temporal lobes. It mainly connects the amygdala, while its posterior part reaches the occipital lobe and serves functions associated with vision [14]. The IC is perhaps the most significant fascicle because the pyramidal tract passes through it. All projection fibers from the cortex to the periphery as well as all thalamocortical tracts pass through the IC. The posterior limb of the IC lies a few millimeters from the insular cortex [12].

23.3 Intraoperative Monitoring

Preoperative knowledge of individual surgical anatomy of the region is not enough for safe resection if not combined with appropriate intraoperative neurophysiologic monitoring. The functional sites of the area cannot be localized accurately based on anatomic landmarks only. For example, the language functions are based on various epicenters that communicate with each other, and significant diversity among patients has been observed.

Several functional imaging modalities such as fMRI, magnetoencephalography (MEG), navigated transcranial magnetic stimulation (nTMS), and positron-emission tomography (PET) attempt an estimation of the localization of functional areas around the insula with low sensitivity and specificity when compared with direct brain stimulation. Furthermore, diffusion tensor imaging MRI (DTI MRI), which provides a road map of white matter tracts around the insula, could be suggested as an adjunct to intraoperative neurophysiology. However, the distance between DTI and the findings of the intraoperative neurophysiologic recording may be affected by various factors, such as both DTI and the intraoperative recording [17]. In consequence, it should be underlined that, at one point, intraoperative recording is absolutely necessary.

23.3.1 Brain Mapping with Direct Electrical Stimulation

Intraoperative brain mapping is usually performed with cortical and subcortical electrical stimulation during awake surgery. Cortical stimulation is usually achieved with a bipolar electrode with an interelectrode distance of 5 mm (frequency 60 Hz, 1 ms square wave pulses in 4 s strains, current amplitude 1–6 mA) at 5-mm intervals [18]. It should be noted that during cortical stimulation, epileptic seizures may arise. They should be readily dealt with by irrigating the cortex with cold Ringer solution and, if needed, administering short-acting anticonvulsants intravenously. Cortical mapping is performed after opening the dura with a stimulation current of 1 mA and progressively increased until a motor response is observed. When a response is observed, a tag is placed on the stimulation site. If the patient is awake, a current of 1–6 mA usually suffices to produce a motor response. Electrocorticography is also used to detect direct cortical stimulation induced after-discharge activity. When the mapping motor cortex is under general anesthesia, the current required for a motor response is usually greater. If no motor response is observed with a current of 16 mA, it can safely be deduced that the stimulation site is not part of functional cortex [19].

In the awake patient, it is possible to map the primary somatosensory cortex as well. Usually, the current applied to produce a sensory response is lower than in the case of the motor cortex.

Language mapping in the awake patient starts at 1 mA and the current rises by 1 mA until the after-discharge threshold is reached. It is not unusual that the necessary intensity of the current applied in the vicinity of the tumor is lower [20]. During mapping, continuous electrocorticography is used to alert for potential after-discharge activity indicative of subclinical fits. Naming tasks lasting 4 s each are performed, and the cortex is stimulated. The electrode should remain in contact with the cortex until a correct answer is given by the patient or the next picture appears. Word reading and number counting tasks are also performed with the same process. The stimulated site is tagged and any error is recorded, such as speech arrest, anomia, alexia, and aphasia. Speech arrest is the disruption in number counting without involuntary muscle contraction. Anomia is the inability of the patient to name objects, with speech fluency and sentence repetition untouched. Alexia is the dysfunction of reading capability, without difficulties in spelling and writing. In expressive aphasia, speech and/or writing is impaired, while in receptive aphasia there is inability in written or spoken word comprehension and incoherent speech production with retained fluency. Speech arrest may occur with stimulation of the frontal cortex, while anomia and alexia may occur with stimulation of the frontal, parietal, or temporal cortex. Every site is stimulated at least twice, but not in a row. The site is regarded as positive when a language error is repeated in the same site [18].

Direct subcortical stimulation is performed with the same method repetitively during tumor resection, with which it is regularly alternated. It is a valuable tool that allows maximal tumor resection of insular gliomas with concurrent protection of the pyramidal tract and the subcortical language network, thus minimizing morbidity.

23.3.2 Awake Craniotomy

Under general anesthesia, only motor cortical and subcortical mapping can be performed using cortical or transcranial motor-evoked potentials and subcortical direct stimulation. In awake craniotomy, the spectrum of brain mapping is further enriched at least with language and somatosensory examination. In the awake patient, cortical and subcortical mapping are performed with a specific procedure.

Preoperatively, language function is assessed with naming testing, and all objects not named are eliminated from the intraoperative test. Counting from 1 to 50, single word and short phrase reading are also assigned to the patient. Tasks that will not be assigned intraoperatively, such as complex sentence repetition and word and sentence writing, may also be included in the preoperative language function assessment protocol.

We prefer the asleep-awake-asleep technique. The patient is in the lateral position and intubated with a laryngeal mask under light general anesthesia. Sedation is achieved with propofol and remifentanyl. The skin around the incision, the pin sites, and the occipital and the supraorbital nerves are infiltrated with an anesthetic solution composed of a 1:1 mixture of 0.5% lidocaine with epinephrine and 0.25% bupivacaine with epinephrine This maintains local anesthesia during the awake phase. After the skin incision, further anesthetic is administered into the temporal muscle. The craniotomy is performed in the usual fashion. Lidocaine is injected into the dura [18] along the middle meningeal artery. After the dural opening, the patient is awakened and the laryngeal mask is removed. The area of Broca and the motor area for the face and the upper extremity are mapped with direct cortical stimulation. During further stages of the operation, speech and movement are continuously monitored by talking with the patient, periodically testing movement ability [11], and direct subcortical stimulation. At the end of the resection, the patient is sedated again until the end of wound closure.

Awake craniotomy is the preferred anesthetic technique in the resection of all insular gliomas. However, in patients with severe language deficits, decreased level of consciousness, or emotional instability, severe obstacles are encountered in its application and general anesthesia may be the only available option [18].

23.3.3 Motor-Evoked Potentials

In addition to intermittent direct cortical and subcortical stimulation, motor-evoked potentials should be continuously recorded [21] so as to recognize the presence of the pyramidal tract in time when it is approached, as the resection goes deeper and especially close to the superior peri-insular sulcus (Fig. 23.5). Motor-evoked potentials can also warn about eminent ischemia of the pyramidal system caused by disruption and/or vasospasm of feeding arteries like the lenticulostriates or M2/M3 branches [22].

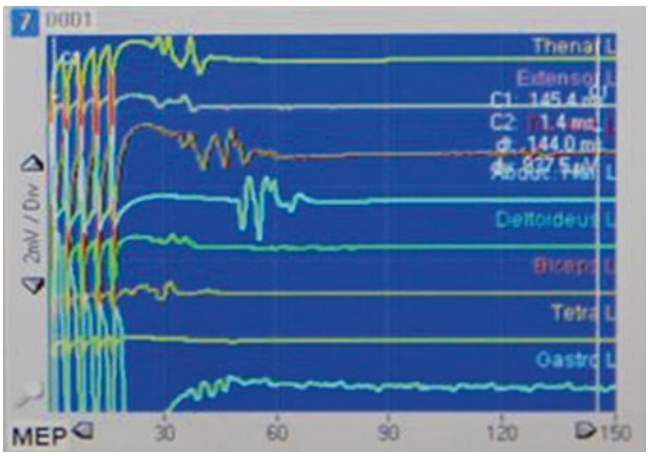

Fig. 23.5 Recordings of motor evoked potentials (MEPs) from the left upper and lower limbs during a right insular glioma resection

23.4 Neuronavigation

Neuronavigation is regarded as a useful tool during planning of the skin incision and the craniotomy. However, brain shift after dural opening and tumor resection renders the preoperative imaging data inaccurate [11]. Future technical developments calculating intraoperative brain shift and modifying preoperative imaging will further boost the use of neuronavigation [23].

23.5 Intraoperative Imaging

Intraoperative imaging tries to compensate for the inaccuracy of neuronavigation during tumor resection. Different modalities have been used such as computed tomography (CT), MRI, and ultrasound with various advantages and disadvantages. In general, intraoperative MRI is accurate; however, it requires special equipment and MR-friendly configuration of the operation theater. Consequently, its cost is regarded as high for many neurosurgical departments around the world. Another disadvantage is the time delay for image acquisition and image quality. Taking these limitations into consideration, when available it may be used to update neuronavigation data and thus optimize the extent of resection and reduce postoperative morbidity [24]. Intraoperative ultrasound, on the other hand, is easily accessible for most neurosurgeons, it can be repeated as many times as required during the operation and it can safely delineate the transition between tumor and brain tissue. However, its accuracy diminishes during tumor resection [11]. Despite this drawback, its availability and feasibility have led to its establishment as an indispensable imaging modality in insular glioma surgery.

23.6 Transcortical Approach

The transcortical approach has been proposed as an alternative to the traditional trans-sylvian one. By mapping the opercular cortex, one can identify safe entry points to the brain and get to the insula subpially through transcortical corridors.

Access to the tumor through nonfunctional areas of the frontal or temporal opercula achieves adequate surgical exposure without any manipulation of M2 branches, with the exception of those that enter the tumor. At the same time, retraction of the eloquent areas of the opercula is also avoided [1]. Practically, the operation is performed under the plane of the sylvian fissure, avoiding manipulation of the vessels.

The operation is performed using the asleep-awake-asleep technique.

23.7 Indications

- Insular glioma in a patient appropriate for awake craniotomy, with or without extension into the opercula.
- Glioma in the posterior insula (zones II and III according to the Berger and Sanai classification).
- Glioma close to the peri-insular sulcus.
- Insular glioma in an adult where sylvian bridging veins cannot be sacrificed.

23.8 Anatomic Landmarks

- Sylvian fissure and its rami
- Foramen of Monro
- Middle cerebral artery and its branches
- Rolandic artery
- Superficial sylvian vein
- Bridging sylvian veins
- Lentiform nucleus
- Internal capsule
- Arcuate fascicle
- Inferior fronto-occipital fascicle
- Uncinate fascicle

23.9 Positioning and Skin Incision

The patient is placed in the lateral position for awake surgery. The head is rotated to the contralateral side so that it is parallel to the floor and rotated 15° to the ipsilateral side if the tumor lies in zone II or III of the Berger-Sanai classification (posterior insula). Furthermore, the head is tilted 15° toward the floor if the tumor lies in zone III or IV (inferior insula), or away from the floor if the tumor lies in zone I or II (superior insula) [1].

The skin is scrubbed with povidone iodine solution, draped in the usual manner, and incised with a scalpel blade with a curved cutting edge. The galea is divided with a pair of scissors, and Raney clips are applied. Care to maintain the superficial temporal artery is taken when the dissection approaches the zygomatic arch (Fig. 23.6).

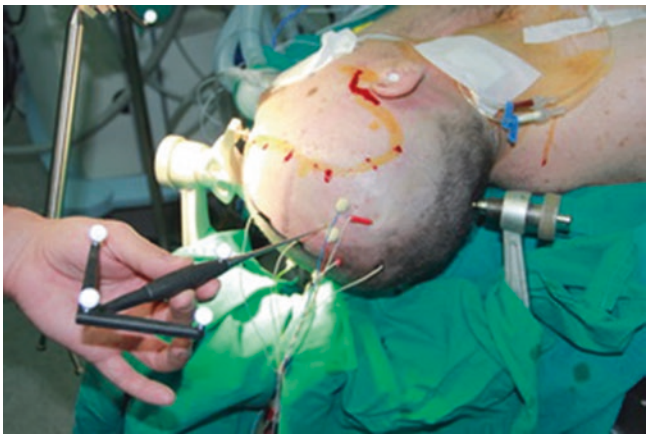

Fig. 23.6 Setup for a right extended pterional craniotomy for transcortical resection of an insular glioma with frontal and temporal extension. General anesthesia has been induced, electrodes for MEP and SSEP have been placed, a large question mark skin incision has been scored, and the neuronavigation system has been registered and is tested

23.10 Soft-Tissue Dissection

The scalp flap is elevated and reflected anteriorly around a piece of gauze. The temporal muscle and its aponeurosis are cut below the temporal line, and the temporal muscle is mobilized from the underlying skull. The pericranium is divided along the borders of the craniotomy.

23.11 Craniotomy

A small craniotomy is not enough to approach insular gliomas if mapping under patient awake conditions is considered. A wide frontotemporoparietal craniotomy should be performed to expose the sylvian fissure from the orbital part of the inferior frontal gyrus to the postcentral sulcus and to provide enough space for cortical mapping. The tumor boundaries are outlined with ultrasound and neuronavigation. In the case of general anesthesia craniotomy a smaller flap can be performed under neuronavigation over the tumor boundaries.

23.12 Dural Opening

The dura is incised in a semicircular fashion and reflected anteriorly. The projection of the tumor boundaries on the cortical surface is outlined with neuronavigation and ultrasonography.

23.13 Opercular Resection

Access to the insula is achieved through the cortical windows, which are corridors to approach the insula by subpial dissection of the opercular cortex [1]. They are defined with cortical mapping.

To outline the limits of the cortical windows, a margin of at least 1 cm around functional areas should be maintained [1]. After outlining a cortical window, multiple openings on the gyral surface are created, demarcated by the superficial arteries and veins. The arachnoid and pia overlying the gyrus are cauterized with the bipolar electrocautery and divided with microscissors. Caution should be taken to protect the surrounding cortex, the bridging veins, and the arterial branches, as they emerge on the cerebral surface. The pia is elevated. Subpial dissection and resection of the opercular cortex are performed with the suction at low setting. Care should be taken not to damage the superficial arteries and veins and the pia of the sylvian cistern. Avulsion of the intrasylvian vessels is avoided by cauterizing small vessels as they enter the cortex. Otherwise, the use of electrocautery should be avoided. The use of cavitron ultrasonic surgical aspirator (CUSA) should also be avoided because it may

interfere with cortical and subcortical mapping. During cortical resection, the pia of the sylvian cistern is treated as a net of protection for the deep sylvian venous tributaries, the M2 and M3 arterial branches, and the cortex of the operculum beyond the cistern. If the pia is damaged by inadvertent manipulations or infiltration by the tumor, healthy pia around the injury should be dissected first in order to reach the damage more efficiently. The opercular resection is accomplished when the base of the peri-insular sulcus is reached [25].

A cortical window has been described for each of the zones of the Berger and Sanai classification system [1]. However, the particular corridor to the tumor and the extent of its resection are determined intraoperatively by direct cortical and subcortical stimulation. Therefore, they cannot be predicted accurately preoperatively but are tailored according to intraoperative functional mapping in each patient [9]. An obvious transcortical route may be indicated by potentially infiltrated opercula after direct cortical mapping [2].

Zone I is approached mainly through the base of the anterior peri-insular sulcus and the anterior part of the superior peri-insular gyrus. The anterior peri-insular sulcus is accessed through the opercular cortex in front of the anterior ascending ramus of the sylvian fissure. In order to completely expose the entire zone I, 60% of the orbital and opercular parts and 20% of the triangular part should be resected [9]. It should be noted that the brain parenchyma can be entered even at the inferior frontal gyrus. Traditionally, the triangular and opercular parts of the inferior frontal gyrus have been regarded as the speech motor area. However, it has been observed that only the posterior portion of the opercular part in the dominant hemisphere is significantly associated with language, and surgery of gliomas of the frontal operculum is characterized by low language morbidity [26], while in 39.1% of patients no language site can be identified on the frontal lobe [27]. In consequence, if mapping of the region is performed, the brain parenchyma can safely be entered through the frontal operculum. If mapping is performed to exclude the presence of any function that could be harmed, lesioning the cortex to approach the insula can be regarded as safe [9].

The superior peri-insular sulcus is accessed through the frontoparietal operculum. Since complete exposure of zone II requires resection of the opercular portion of the precentral gyrus and part of the postcentral gyrus [9], the resection of tumors residing in zone II of the Berger-Sanai classification is quite difficult. On the nondominant side, recovery has been observed after resection of the opercular portion of the precentral gyrus, namely, the primary motor area for the face [28]. However, on the dominant side, the lower motor cortex takes part in speech function. In the aftermath of its resection, only transient central facial paralysis is regarded as an acceptable outcome. Nevertheless, through cortical and subcortical mapping during awake craniotomy, it is usually possible to identify noneloquent areas on the frontoparietal operculum and use them as a corridor to the tumor [29].

The inferior peri-insular sulcus is accessed through subpial dissection and resection of part of the temporal operculum. It should be noted that access to the entire zone III requires resection of 90% of the Heschl gyrus but not the areas posterior to it such as the angular gyrus. Even if unilateral resection of the Heschl gyrus is regarded as safe for hearing, its vicinity containing crucial structures for language render direct cortical and subcortical stimulation indispensable during corticectomy, at least on the dominant side [9].

Zone IV is also approached through the temporal operculum. Specifically, the anterior part of the superior temporal gyrus is used as a cortical corridor to the inferior peri-insular sulcus [9]. It should be noted that purely anatomic landmarks, such as keeping a certain distance from the temporal pole, cannot be used as a reference to avoid language deficits. Indeed, the primary language cortex has been found within a distance of 3 cm from the temporal pole [30]. Therefore, only intraoperative mapping can localize language sites and avoid permanent language deficits.

23.14 Resection at the Isthmus

After opercular resection, the M3 branches of the middle cerebral artery are identified. The subpial resection proceeds in the isthmus. The tumor underneath the peri-insular sulci is resected to provide access to the insula. Tumor resection is regularly alternated with direct subcortical stimulation to avoid disruption of the white matter fiber tracts. It should be noted that usually the presence of tumor expands the isthmi and displaces the fiber tracts medially [3], facilitating the creation of the surgical corridor to the insula.

23.15 Resection at the Insula

Subsequently, subpial dissection and resection proceed with the tumor in the insula, alternated with direct subcortical stimulation of the association and projection fascicles of the area [2].

Beneath the anterior insula, stimulation of the IFOF in the temporal stem results in verbal semantic paraphasia on the dominant side and nonverbal semantic dysfunction on the nondominant side [31]. Gliomas in this area generally emerge between the IFOF/UF complex and the insular cortex. Consequently, at least on the dominant side, the IFOF is the medial border of resection in the inferior and anterior insulae, as indicated by subcortical mapping [3]. Moreover, its preservation ensures the preservation of the underlying optic radiations as well [14]. In general, the tumor is removed

along the course of the UF/IFOF complex. Resection cavities are created above and below the sylvian fissure. As resection proceeds, these cavities are connected to each other. In the end, the skeletonized sylvian vessels remain untouched and wrapped in the sylvian cistern above the unified resection cavity. Particular attention should be given to the identification of the lenticulostriate arteries, as any damage to them could result in hemiplegia [1]. The lenticulostriate arteries are parallel to the medial border of the tumor; however, it may be quite difficult to identify and follow them in the parenchyma [2], while the anterior perforated substance, through which they pass, may also be infiltrated by tumor. In such a case, it has been suggested that it may be wise to leave a tumor residue on the IFOF/UF complex [4].

During resection of tumors in zones II and III, stimulation of the fascicles that compose the AF/SLF complex underneath the cortex of the angular, supramarginal, postcentral, and precentral gyri and close to the peri-insular sulcus [14] results in phonologic paraphasia, repetition disorder, and speech apraxia; these can occur even on the nondominant side [32]. Moreover, stimulation of the posterior insula on the dominant side may result in anomia [33]. To monitor the integrity of the pathways associated with language and discontinue resection before causing inadvertent damage during tumor dissection, the patient performs counting and naming tasks, alternated with subcortical stimulation [2]. Speech dysfunction reveals the vicinity of a language-associated area or tract.

The posterior limb of the IC lies very close to the posterior portion of the superior peri-insular sulcus and descends medially to the tumor and the basal ganglia. Aids that may help to outline the medial limit of resection are the level of the bottom of the peri-insular sulci, the most lateral lenticulostriate artery, the direction of the perforating arteries, and differences in color, consistency, and texture between the tumor, white matter, and basal ganglia. Neuronavigation and especially intraoperative ultrasound may also assist in defining the medial limit of resection, but they significantly decrease in accuracy as tumor resection proceeds. These aids assist the surgeon to rest oriented during tumor resection, it has been stated that preservation of the IC using anatomic criteria alone is not possible [2]. In contrast, subcortical mapping of the IC reliably allows its identification and preservation. Both the motor pathways of the pyramidal tract, both under general anesthesia or during awake craniotomy, [22] and particularly the more laterally localized somatosensory thalamocortical tracts during awake craniotomy, [34] can be mapped. Somatotopy of the fibers in the posterior limb may be modified by the tumor. In posterior insula, resection of the tumor follows a posteroanterior direction. Furthermore, if the lower precentral gyrus was removed during the approach to zone II, dissection would follow the corticobulbar fibers for face movement from the corona radiata down to the IC. Tumor resection is frequently alternated with direct subcortical stimulation of the IC and simple commands to the patient regarding movement of the limbs. In any case, the rolandic artery should be identified and protected [2] from the cerebral surface, around the fronto-parietal operculum, into the sylvian fissure, and down to the artery of the central insular sulcus [9]. The long insular perforators irrigating the corona radiata should also be identified and maintained [16]. It should also be noted that stimulation of the lenticular nucleus results in articulatory disturbances, an observation that may aid in the protection of the medially lying IC [31, 32].

Meticulous hemostasis is achieved, avoiding the use of the electrocautery as much as possible.

After tumor resection has been accomplished, direct cortical stimulation of the inferior motor cortex is performed for one last time in order to verify the integrity of the motor pathways. Alternatively, during awake craniotomy the patient may perform motor and language tasks [34].

23.16 Closure

The dura is sutured in a watertight fashion with nonabsorbable sutures. The bone flap is put back and held in place with titanium plates or cranial fixation clamps. The temporal muscle is sutured to the temporal line with absorbable sutures. A Redon drain is put subcutaneously under a vacuum. The galea is sutured with absorbable sutures. The skin is sutured with a nonabsorbable continuous interlocking suture.

23.17 Pitfalls and Complications

- Injury of the rolandic artery during dissection may lead to permanent hemiparesis, if it is not protected.
- During the medial dissection of the tumor, injury of the lenticulostriate arteries leading to permanent hemiparesis may occur if the most lateral lenticulostriate artery is not identified. If it cannot be identified, it has been suggested that some tumor should be left on the UF. In the same region, damage of the UF may cause behavioral disturbances, while damage to the IFOF is associated with semantic paraphasia. Direct subcortical stimulation of the IFOF during tumor resection can assist in avoiding its disruption as well as damage to the lenticulostriate arteries.
- Direct injury to the pyramidal tract in the corona radiata near the superior peri-insular sulcus during dissection can lead to permanent hemiparesis if continuous subcortical monitoring is not performed. Special attention should be given to dissection at the superior aspect of the posterior insula.
- Disruption of the long M2 perforators can lead to permanent hemiparesis as a result of ischemia of the corona radiata if continuous subcortical monitoring is not performed. Special attention should be given to dissection at

the superior part of the posterior insula, where these vessels usually reside.
- Direct injury of the posterior limb of the IC can lead to permanent hemiparesis, although it is quite rare. It may occur if continuous subcortical monitoring is not performed.
- Transient postoperative paresis may be observed. However, if the direct cortical stimulation of the primary motor areas after tumor resection produce the same motor responses as before the resection, it will fully resolve.
- Injury of M2 or M3 branches or the deep middle cerebral or the basal vein in the sylvian cistern can happen if the pia is transgressed during dissection.
- Permanent aphasia is quite rare. Injury of the AF may result in transcortical motor aphasia, phonologic paraphasia, and repetition disorder. Aphasia may be avoided by means of cortical mapping of speech while performing awake craniotomy.
- Instead, transient dysphasias with speech disturbance may be observed (articulatory disturbance, phonemic paraphasia) but they resolve in weeks to months.
- Transient athymhormic syndrome (inertia and loss of interest and affect with preservation of executive functioning) that resolves in weeks to months.
- Transient Foix-Chavany-Marie syndrome (facio-pharyngo-glosso-masticatory diplegia with bilateral facial weakness and anarthria) that resolves in a short time.

23.18 Trans-Sylvian Approach

The trans-sylvian has been the traditional approach in the surgery of insular gliomas, since it provides direct access to the insula and the neurosurgeons are quite familiar with splitting the sylvian fissure. Nevertheless, the risk of vascular injury and vasospasm is considerable in this procedure. The operation is performed under general anesthesia, and a minimum level of safety for the pyramidal pathway should be ensured with motor mapping. Even though direct electrical stimulation may not be feasible in the pediatric population [20], somatosensory motor potential phase reversal is easily attainable, and continuous recording of motor-evoked potentials should be used to monitor for pending damage to the primary motor cortex or the pyramidal tract during the operation.

23.19 Indications

- Insular glioma in persons who cannot submit to awake craniotomy, with or without extension into the opercula.
- Glioma in the anterior insula (zones I and IV according to the Berger-Sanai classification).

23.20 Anatomic Landmarks

- Sylvian fissure
- Anterior sylvian point
- Middle cerebral artery
- M1 bifurcation
- Limen insulae
- Superficial sylvian vein
- Bridging sylvian veins
- Peri-insular sulcus
- Rolandic artery
- Insular gyri
- Insular sulci

23.21 Positioning and Skin Incision

The patient is placed in the supine position with the ipsilateral shoulder elevated and the head rotated 30–45° to the contralateral side in order to facilitate access to the posterior insula. The head is extended in order to assist the approach to the superior peri-insular sulcus [11]. The neuronavigation system is put into place and registered. A question mark–shaped frontotemporal skin incision behind the hair line and above the ear is marked. The skin is scrubbed with povidone iodine solution, draped, and incised with a scalpel blade with a curved cutting edge. The galea is divided with a pair of scissors, and Raney clips are put on the scalp flap edges. Care to maintain the superficial temporal artery is taken when the dissection approaches the zygomatic arch. Soft-tissue dissection is performed as usual.

23.22 Craniotomy

Pterional (frontotemporal) craniotomy is extended posteriorly over the ear. Drilling of the lesser wing of the sphenoid (sphenoid ridge) is done in order to facilitate access to the proximal sylvian fissure. The extent of the craniotomy can be determined with the help of neuronavigation.

23.23 Dural Opening

Hitch stiches are put on the dura around the rim of the craniotomy. Intraoperative ultrasound can help to validate the borders of the tumor and their projection on the dura. Opening of the dura is done in an arcuate fashion with the concave side toward the pterion.

23.24 Opening of the Sylvian Fissure

Cerebrospinal fluid is released from the basal cisterns. It is accomplished by retraction of the frontal lobe, identification of the olfactory and optic nerves, and division of the arachnoid of the chiasmatic, carotid, and interpeduncular cisterns.

A broad opening of the sylvian fissure from the ICA bifurcation to the supramarginal gyrus should be achieved. The objectives of the dissection of the sylvian fissure are splitting the sylvian fissure, exposing the MCA and all its branches, and splitting the peri-insular sulcus to its base.

Dissection of the proximal part of the sylvian fissure starts at the anterior sylvian point and proceeds proximally. Sharp division of the arachnoid of the proximal part of the sylvian fissure keeping the superficial sylvian vein attached to the temporal lobe is performed. An effort to preserve all the veins of the sylvian fissure should be made at this stage, especially the large veins that lie distally along the length of the fissure. However, sacrifice of some small veins from the frontal lobe to the superficial sylvian vein may be inevitable; however, it should be performed as dissection of the fissure goes further and only when access to the sylvian cistern is hindered. As dissection approaches the pterion, its plane changes from horizontal to vertical toward the bifurcation of the ICA. After the arachnoid of the proximal sylvian fissure has been divided, the dissection can be deepened. M3 branches are identified at their transition to M4 as they emerge to the surface of the cerebrum. They are followed into the sylvian sulcus, and the arachnoid trabeculae between the fronto-orbital and the temporal opercula are divided. The space around each artery is widened like a funnel and joined to the space around neighboring arteries. M3 branches lead to their origin from larger arteries and the sylvian fossa. M2 branches are identified. Once the bottom of the sylvian cistern is reached, the operculae can be further separated from each other from inside out. The M1 bifurcation and the M1 main trunk are identified. Once the fronto-orbital and temporal operculae are separated, the M2 arteries of the sylvian cistern are untangled. As each artery irrigates either the temporal or the frontal lobe but not both, they are mobilized to their respective sides. Untangling the arteries not only makes mobilizing the opercula possible but it also facilitates the identification of the perforators that arise from the deep side of M2. The limen insulae, the origin, and the course of the most lateral lenticulostriate artery are identified. The deep middle cerebral vein and the basal vein are identified.

The arachnoid of the distal part of the sylvian fissure is sharply divided up to the supramarginal gyrus, keeping the superficial sylvian vein attached to the temporal lobe. The M3 branches are followed from their transition to M4 to the depth of the sylvian sulcus to separate the frontoparietal and temporal operculae from each other.

The peri-insular sulci are opened to their base. The M2 branches on the bottom of the opened cistern are followed distally to open the distal part of the sylvian fissure, separating the opercula from the insular cortex. The inferior peri-insular sulcus is dissected quite easily because M2 arteries are parallel to it. The insular vein that lies in the sulcus may usually be sacrificed. The anterior peri-insular sulcus can also be identified easily, following M2 branches that irrigate the frontal lobe. The dissection of the superior peri-insular sulcus is more cumbersome and may require some retraction, as the M2 and M3 branches are perpendicular to it and it is quite deep. It should be noted that the presence of a sizable tumor in the insula usually results in deeper anterior and superior peri-insular sulci, which add some difficulty to their dissection [11, 35].

23.25 Resection at the Insula

In the case of a large tumor, internal decompression of the insular tumor within each gyrus may assist further dissection. Gentle separation of the tumor from the M2 perforators by subpial dissection follows. Care should be taken not to pull the M2 perforators. Devascularization of the tumor by coagulating and dividing each short and medium M2 perforator is performed. The long M2 perforators usually encountered on the posterior insula are wider, do not narrow, and should be protected because they irrigate the corona radiata [16]. Papaverine may be used on the MCA branches to minimize the risk of vasospasm. Resection of the tumor is achieved in a gyrus-by-gyrus fashion subpially between the vessels [4]. Subcortical mapping indicates the presence of important fascicles and enables the surgeon to avoid injuring them [35].

The anterior, superior, and inferior limits of the resection are the respective peri-insular sulci. The medial limit is determined by the level of the bottom of the peri-insular sulci, the most lateral lenticulostriate artery, the direction of the perforating arteries (lenticulostriate arteries are parallel to the medial border of the tumor), as well as differences in color, consistency, and texture between the tumor, white matter, and basal ganglia. Neuronavigation and especially intraoperative ultrasound may assist in defining the medial limit of resection. Resection starts in the anterior part of the tumor, follows in the central part of it, and the posterior part is resected last, to minimize the necessity for retraction. Uneven resection of the tumor with pits and piles should be avoided [11].

23.26 Resection at the Opercula

Removal of the frontal and/or temporal opercular portion follows if there is an extension to these areas, which is the usual case [4]. The opercular resection is performed using the methodology followed by the transcortical approach. Meticulous hemostasis is achieved and closure of the wound is performed in the usual fashion.

23.27 Pitfalls and Complications

- Operating on edematous brain may lead to injury of the superficial sylvian veins, opercula, and MCA branches if early release of cerebrospinal fluid from the basal cisterns is not performed.
- Injury to the superficial sylvian vein at the point it merges with the sphenoparietal sinus will occur if it is mobilized to the frontal side of the sylvian fissure during opening of the fissure.
- Brain edema caused by increased venous pressure will occur if too many tributaries to the superficial sylvian vein are sacrificed during opening of the sylvian fissure and poor outflow occurs through the veins of Labbe and/or Trollard.
- There will be injury of interdigitating opercula during opening of the sylvian fissure if inside-out fashion is not followed.
- Injury of the rolandic artery during splitting of the sylvian fissure may lead to hemiparesis if the M2 branches and their transition to M3 are not identified.
- Injury of the opercula with the edge of the retractor or the sucker may occur if the sylvian fissure is not opened broadly. Excessive retraction may result in ischemia, edema, and/or direct cortical injury.
- Injury of M2 branches on the surface of the insula may take place if the initial internal decompression in each insular gyrus followed by subpial dissection of the tumor is not performed.
- The deep middle cerebral or the basal vein may be injured if they are not identified.
- During the medial dissection of the tumor, injury of the lenticulostriate arteries may lead to hemiparesis if the most lateral lenticulostriate artery is not identified. If it cannot be identified, it has been suggested that some tumor should be left on the UF. In the same region, damage of the UF may cause behavioral disturbances, while damage to the IFOF is associated with semantic paraphasia.
- Direct injury to the pyramidal tract in the corona radiata near the superior peri-insular sulcus during dissection that can lead to hemiparesis may occur if continuous subcortical monitoring is not performed. Special attention should be given to dissection at the superior aspect of the posterior insula.
- Disruption of the long M2 perforators that can lead to hemiparesis owing to ischemia of the corona radiata may take place if continuous subcortical monitoring is not performed. Special attention should be given to dissection at the superior aspect of the posterior insula, where these vessels usually reside.
- Although it is rare, direct injury of the posterior limb of the IC leading to hemiparesis may happen if the borders between the tumor and the basal ganglia are not identified, and continuous subcortical monitoring is not performed.
- Permanent aphasia is quite rare. However, transient dysphasia may occur from use of retraction and vasospasm of MCA branches. Injury of the AF may result in transcortical motor aphasia, phonologic paraphasia, and repetition disorder. Aphasia may be avoided by means of cortical mapping of speech while performing awake craniotomy, meticulous dissection, untangling the MCA branches in the sylvian cistern, and avoiding unnecessary retraction.

References

1. Sanai N, Polley MY, Berger MS. Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. J Neurosurg. 2010;112:1–9.
2. Duffau H, Capelle L, Lopes M, Faillot T, Sichez J-P, Fohanno D. The insular lobe: physiopathological and surgical considerations. Neurosurgery. 2000;47:801–10. discussion, 810–1
3. Martino J, Mato D, Marco de Lucas E, Garcia-Porrero JA, Gabarros A, Fernandez-Coello A, et al. Subcortical anatomy as an anatomical and functional landmark in insulo-opercular gliomas: implications for surgical approach to the insular region. J Neurosurg. 2015;123:1081–92.
4. Yasargil MG, von Ammon K, Cavazos E, Doczi T, Reeves JD, Roth P. Tumours of the limbic and paralimbic systems. Acta Neurochir. 1992;118:40–52.
5. Zentner J, Meyer B, Stangl A, Schramm J. Intrinsic tumors of the insula: a prospective surgical study of 30 patients. J Neurosurg. 1996;85:263–71.
6. Hervey-Jumper SL, Li J, Osorio JA, Lau D, Molinaro AM, Benet A, et al. Surgical assessment of the insula. Part 2: validation of the Berger-Sanai zone classification system for predicting extent of glioma resection. J Neurosurg. 2016;124:482–8.
7. Kim YH, Kim CY. Current surgical management of insular gliomas. Neurosurg Clin N Am. 2012;23:199–206. vii
8. Lang FF, Olansen NE, DeMonte F, Gokaslan ZL, Holland EC, Kalhorn C, et al. Surgical resection of intrinsic insular tumors: complication avoidance. J Neurosurg. 2001;95:638–50.
9. Benet A, Hervey-Jumper SL, Sanchez JJ, Lawton MT, Berger MS. Surgical assessment of the insula. Part 1: surgical anatomy and morphometric analysis of the transsylvian and transcortical approaches to the insula. J Neurosurg. 2016;124:469–81.
10. Desmond JE, Sum JM, Wagner AD, Demb JB, Shear PK, Glover GH, et al. Functional MRI measurement of language lateralization in Wada-tested patients. Brain. 1995;118(Pt 6):1411–9.
11. Hentschel SJ, Lang FF. Surgical resection of intrinsic insular tumors. Neurosurgery. 2005;57(1 Suppl):176–83. discussion, 176–83

12. Ture U, Yasargil DCH, Al-Mefty O, Yasargil MG. Topographic anatomy of the insular region. J Neurosurg. 1999;90:720–33.
13. Nieuwenhuys R. The insular cortex: a review. In: Michel AH, Dean F, editors. Evolution of the primate brain. Progress in brain research. 195. Amsterdam: Elsevier; 2012. p. 123–63.
14. Yagmurlu K, Vlasak AL, Rhoton AL Jr. Three-dimensional topographic fiber tract anatomy of the cerebrum. Neurosurgery. 2015;11(Suppl 2):ONS-274–305.
15. Rhoton AL Jr. Cranial anatomy and surgical approaches. Hagerstown, MD: Lippincott Williams & Wilkins; 2003.
16. Ture U, Yasargil MG, Al-Mefty O, Yasargil DC. Arteries of the insula. J Neurosurg. 2000;92:676–87.
17. Leclercq D, Duffau H, Delmaire C, Capelle L, Gatignol P, Ducros M, et al. Comparison of diffusion tensor imaging tractography of language tracts and intraoperative subcortical stimulations. J Neurosurg. 2010;112:503–11.
18. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. N Engl J Med. 2008;358:18–27.
19. Berger MS. Functional mapping-guided resection of low-grade gliomas. Clin Neurosurg. 1995;42:437–52.
20. Berger MS, Kincaid J, Ojemann GA, Lettich E. Brain mapping techniques to maximize resection, safety, and seizure control in children with brain tumors. Neurosurgery. 1989;25:786–92.
21. Kombos T, Suess O, Ciklatekerlio O, Brock M. Monitoring of intraoperative motor evoked potentials to increase the safety of surgery in and around the motor cortex. J Neurosurg. 2001;95:608–14.
22. Neuloh G, Pechstein U, Schramm J. Motor tract monitoring during insular glioma surgery. J Neurosurg. 2007;106:582–92.
23. Drakopoulos F, Yao C, Liu Y, Chrysochoides N. An evaluation of adaptive biomechanical non-rigid registration for brain glioma resection using image-guided neurosurgery. In: Wittek A, Joldes G, PMF N, Doyle BJ, Miller K, editors. Computational biomechanics for medicine. Cham: Springer International Publishing AG; 2017. p. 111–22.
24. Chen LF, Yang Y, Ma XD, Yu XG, Gui QP, Xu BN, et al. Optimizing the extent of resection and minimizing the morbidity in insular high-grade glioma surgery by high-field intraoperative MRI guidance. Turk Neurosurg. 2017;27:696–706.
25. Duffau H. A new concept of diffuse (low-grade) glioma surgery. Adv Tech Stand Neurosurg. 2012;38:3–27.
26. Rolston JD, Englot DJ, Benet A, Li J, Cha S, Berger MS. Frontal operculum gliomas: language outcome following resection. J Neurosurg. 2015;122:725–34.
27. Sanai N, Berger MS. Glioma extent of resection and its impact on patient outcome. Neurosurgery. 2008;62:753–64. discussion, 264–756
28. LeRoux PD, Berger MS, Haglund MM, Pilcher WH, Ojemann GA. Resection of intrinsic tumors from nondominant face motor cortex using stimulation mapping: report of two cases. Surg Neurol. 1991;36:44–8.
29. Michaud K, Duffau H. Surgery of insular and paralimbic diffuse low-grade gliomas: technical considerations. J Neuro-Oncol. 2016;130:289–98.
30. Heilman KM, Wilder BJ, Malzone WF. Anomic aphasia following anterior temporal lobectomy. Trans Am Neurol Assoc. 1972;97:291–3.
31. Duffau H. Stimulation mapping of white matter tracts to study brain functional connectivity. Nat Rev Neurol. 2015;11:255–65.
32. Duffau H, Moritz-Gasser S, Gatignol P. Functional outcome after language mapping for insular World Health Organization Grade II gliomas in the dominant hemisphere: experience with 24 patients. Neurosurg Focus. 2009;27:E7.
33. Ojemann GA, Whitaker HA. Language localization and variability. Brain Lang. 1978;6:239–60.
34. Duffau H. A personal consecutive series of surgically treated 51 cases of insular WHO Grade II glioma: advances and limitations. J Neurosurg. 2009;110:696–708.
35. Safaee MM, Englot DJ, Han SJ, Lawton MT, Berger MS. The transsylvian approach for resection of insular gliomas: technical nuances of splitting the Sylvian fissure. J Neuro-Oncol. 2016;130:283–7.

Systemic Chemotherapy in Brain Gliomas

24

George A. Alexiou and Athanasios P. Kyritsis

Gliomas constitute the most common and difficult to treat primary brain tumors, accounting for over 50% of all primary central nervous system tumors. The glioblastoma is by far the most frequently occurring and most malignant of the glial tumors, with a median patient survival of 15 months. Current treatment involves maximal surgical resection followed by radiotherapy with concomitant and adjuvant chemotherapy. However, over the last decade much has changed regarding the role of chemotherapy in gliomas. This is the result of several trials that reported survival benefit with a combination of agents and the incorporation of molecular genetic markers as predictors of response to chemotherapy. Herewith we discuss the chemotherapy regimens currently used for glioma treatment as well as the associated toxicities and try to provide an insight into future advancements.

24.1 Introduction

Gliomas constitute the most common primary brain tumors, accounting for over 50% of all primary central nervous system (CNS) tumors and including tumors of astrocytic, oligodendroglial, and ependymal lineage. Among gliomas, astrocytomas occur predominantly in the cerebral hemispheres and less commonly in the cerebellum, brainstem, spinal cord, and optic pathways [1, 2]. Oligodendroglial tumors usually are localized to the cerebral hemispheres. Ependymal tumors are more likely to occur in an infratentorial location such as the floor of the fourth ventricle in children, the spinal cord and cauda equina in adults, and much less commonly in the supratentorial compartment [3].

G. A. Alexiou (✉)
Department of Neurosurgery, University Hospital of Ioannina, Ioannina, Greece
e-mail: galexiou@cc.uoi.gr

A. P. Kyritsis
Department of Neurology and Neurosurgical Institute, University Hospital of Ioannina, Ioannina, Greece

High-grade gliomas (WHO grades III and IV) and especially glioblastomas are among the most difficult cancers to treat, with a dismal prognosis and poor response to chemotherapeutics [4]. This has been attributed to the blood-brain barrier (which forms a pharmacologic sanctuary), the expression of multidrug resistance proteins in malignant cells and associated capillaries [5], the genetic, molecular, and metabolic heterogeneity of glioma cells [1], a resistance mechanism to commonly used alkylating agents, and the ability of tumor cells to evade immune surveillance [6]. Furthermore, tumor stem cells within malignant gliomas have been linked to glioma development, perpetuation, and resistance to both chemotherapy and radiation, accounting for the failure of conventional therapies and tumor recurrence [7]. In addition, chemotherapy and radiation therapy may trigger several signal transduction pathways and toxic events to the tumor cells, such as direct DNA damage which apart from cell death can lead to mutations in the surviving tumor cells that might result in therapy-driven evolution of recurrent gliomas [8]. Herewith we discuss how to treat an individual patient with glioma, the chemotherapeutic drug-related toxicities and their management, and other potential useful approaches for glioma treatment that may emerge in the near future.

24.2 Systemic Chemotherapy for Brain Gliomas: Strategy and Technique

Because glioma cells infiltrate widely in the brain ahead of or independent of new vessel formation (angiogenesis), drug delivery can be highly compromised unless chemotherapeutic agents have a molecular weight of less than 600 Da in order to cross the blood-brain barrier [4]. The blood-brain barrier is formed by brain endothelial cells, which are connected by tight junctions and extremely high electrical resistivity that tend to keep the brain extracellular fluid free of complex organic compounds such as those found in many anticancer drugs.

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In addition to size and charge concerns, another shortcoming of the anticancer agents is the severe side effects on normal tissues and/or because their pharmacokinetics and biotransformation are too fast to permit distribution of chemotherapeutic agents at therapeutic levels within most tumors [9].

24.3 Low-Grade Astrocytoma

Based on the latest WHO 2016 classification, diffuse astrocytomas are now categorized into isocitrate dehydrogenase (IDH) wildtype, IDH-mutant, and not otherwise specific (NOS) in cases in which IDH evaluation cannot be performed [10]. The incidence of these tumors decreases progressively from childhood into late adult life. Although they have a prolonged natural history, indolent behavior, and may not need immediate therapy, these tumors always recur and often dedifferentiate into anaplastic astrocytomas or glioblastomas. Since it is difficult to perform prospective clinical trials with astrocytoma patients because they constitute a small number of glioma patients, gross total excision for both diagnostic and therapeutic purposes is the treatment of choice. Radical excision reduces the risk of malignant transformation. Patients over 40 years of age in need of subtotal excision of a tumor over 6 cm, the presence of neurologic deficits, and diffuse astrocytoma subtype have been associated with unfavorable outcomes, but further treatment had a beneficial effect in these patients [11].

Adjuvant radiotherapy for a total dose of 50.4 Gy is the accepted standard of care, since higher or lower doses were found to have similar effect to the higher dose with less toxicity [12, 13]. Thus, from a survival viewpoint, radiation following surgery is of value, especially for patients with three or more of the above risk factors. What is debatable, however, is whether the impairment in cognitive and emotional function secondary to irradiation for low-grade astrocytoma is worth the increase in lifespan. In this decision-making process, patient age, life-style expectations, and potential effects on cognitive and emotional function need to be considered for each patient.

Mounting evidence from molecular and genetic profiling of low-grade gliomas have resulted in more accurate prognosis assessment. The effectiveness of PCV (procarbazine, lomustine [CCNU] and vincristine) was assessed by RTOG 9802 (a phase III trial that randomized adults with low-grade glioma (LGG) to fractionated radiotherapy with or without six cycles of PC) and showed a substantial improvement in overall survival in the PCV arm (13.3 versus 7.8 years) [14]. Temozolomide (TMZ), owing to its favorable side-effect profile, may be effective in treating progressive WHO grade II astrocytomas. Repeat surgery was suggested for patients with wild-type IDH1 regardless of the histopathologic diagnosis. Although complete tumor resection is generally the goal in the management of these lesions, this can prove difficult to achieve because tumor margins may blend into the surrounding brain tissue. Nonetheless, recent evidence has shown that the median survival of low-grade astrocytomas is 7–10 years [15].

The author's approach has been to treat adults with contrast-enhanced low-grade astrocytomas with radiotherapy and chemotherapy postoperatively. This is based on three clinical observations: (1) in patients over 15 years, survival is inversely correlated to age at diagnosis; (2) noncontrast-enhanced low-grade astrocytomas have a better prognosis than contrast-enhanced low-grade astrocytomas (3.9 versus. 7.8 years' survival); and (3) 70% of patients with contrast-enhanced low-grade astrocytomas who received postoperative chemotherapy and irradiation survived nearly 7 years.

When low-grade astrocytomas first recur, approximately 50% have the original low-grade histology, while the rest recur as more aggressive anaplastic astrocytomas or glioblastomas [11].

24.4 Anaplastic Astrocytomas and Glioblastomas

Based on the latest WHO 2016 classification, anaplastic astrocytomas are now categorized into IDH-mutant, IDH-wildtype, and NOS categories. IDH-mutant cases have a more favorable outcome [10]. In anaplastic astrocytomas, the gains of treatment have been much greater. Standard therapy entails adjuvant radiotherapy up to 60 Gy after surgical excision. However, chemotherapy instead of radiotherapy may be used in some cases, especially when the long-term cognitive effects of radiotherapy are of concern. Upon recurrence, chemotherapy with either TMZ or PCV may be used. Recent evidence showed no difference in time to failure if chemotherapy or radiation was administered first and no significant difference between PCV or TMZ chemotherapy [16].

Based on the latest WHO 2016 classification glioblastomas are now categorized into IDH-wildtype, the most frequent (nearly 90% of cases) of which correspond to primary glioblastoma; IDH-mutant, which corresponds more frequently to secondary glioblastoma; and glioblastoma NOS, in cases in which IDH evaluation cannot be performed [10]. The role of surgery in glioblastoma is mainly cytoreduction, to relieve mass effect, to obtain tissue for establishing diagnosis, and to assess the tumor's molecular profile (LOH 1p/19q, MGMT promoter methylation, IDH mutation). Furthermore, the extent of resection has a prognostic significance [17]. An improvement in progression-free survival (PFS) and increase in the complete resection rate has been

verified when surgery is performed by 5-amino-laevulinic acid (5-ALA), a fluorescence that marks the tumor under blue light [18]. Gliadel wafer-bearing carmustine (BCNU) can be applied in situ only for patients in whom 90% or more of the tumor has been resected. This exposes the remaining tumor cells to a much greater concentration of BCNU compared to systemic administration. In a study, carmustine wafers increased median survival from 11.6 to 13.8 months in patients with newly diagnosed glioblastoma (GBM) [19]. However, in recurrent tumors carmustine wafers had no survival benefit.

The Stupp protocol consisting of external beam radiation and concomitant TMZ has become the gold standard. The use of a radiation dose of 60 Gy in conventional daily fractions of 1.7–2.0 Gy is based on data from clinical studies and on the radiation tolerance of normal brain tissue. Higher total doses by conventional (to 70 Gy) or hyperfractionated (to 80 Gy) regimens did not increase survival. Trials using 1.6–2.0 Gy three times per day have been conducted, but none has shown a survival benefit [20]. Concomitant TMZ consists of 75 mg/m^2/day, 7 days per week until the end of radiation therapy. One month later, six cycles of adjuvant chemotherapy starts. Every cycle consists of 5 days of TMZ repeated every 28 days. The dose is 150 mg/m^2/day for the first cycle and increases up to 200 mg/m^2/day in the following cycles. In a phase III trial of dose-dense TMZ at 100 mg/m^2, days 1 through 21 of a 28-day cycle showed no significant benefit compared to standard dosing in both PFS or overall survival (OS) [21]. With the Stupp protocol the median survival was 14.6 months compared to 12.1 months with radiotherapy alone. The 5-year survival rate was 9.8% compared to 1.9% with radiotherapy alone. The authors extend TMZ chemotherapy after the standard 6-month regimen until tumor recurrence. This has resulted in one study in an increase of the median survival from 16.5 to 24.6 months [22]. In the first phase II glioblastoma study that used this approach, TMZ achieved a 21% PFS at 6 months [2]. The addition of 13-*cis*-retinoic acid to TMZ improved PFS_6 to 32%; the addition of marimastat, a matrix metalloprotease inhibitor, moved PFS_6 to 39%. For BCNU with thalidomide PFS_6 was 27% [2].

Antioangiogenesis agents such as bevacizumab have been administered in addition to standard treatment for newly diagnosed GBM (AVAglio study), but although it showed improved PFS, there was no significant improvement in OS. Furthermore, the rate of adverse events was higher with bevacizumab than with placebos [23]. However, a retrospective analysis of AVAglio data reported that patients with IDH1 wild-type primary glioblastoma had better OS from first-line bevacizumab treatment than from placebo (17.1 versus 12.8 months) [24]. The addition of bevacizumab to standard glioblastoma treatment prolongs PFS and OS for patients with progressive disease who do not receive second-line therapy [25]. Another antioangiogenic agent, cilengitide, in a phase III trial showed no increase in either PFS or OS.

Assessment of MGMT status has a prognostic significance and assists in patient management. Patients with MGMT promoter methylation had 23.4 months median survival compared to 12.6 months in the nonmethylated group. The Stupp protocol in the unmethylated group increased survival from 11.8 to 12.6 months. Thus, alternative treatments for patients with nonmethylated MGMT are proposed as part of ongoing clinical trials. Recently, a phase II study, the GLARIUS trial, explored the efficacy of bevacizumab plus irinotecan as an alternative to TMZ in primary glioblastomas with nonmethylated MGMT. The primary end point was the PFS rate at 6 months. The results showed that PFS was increased from 42.6% with TMZ to 79.3% with bevacizumab plus irinotecan. Thus, PFS was prolonged for 3.7 months. However, no difference in OS was found, and this was attributed to the high crossover rate [26].

Another important issue constitutes the finding from several uncontrolled retrospective case series and a post-hoc analysis of an association between valproic acid (VPA) use and increased survival in patients with newly diagnosed glioblastomas.

A recent combined analysis of the effect of antiepileptic drug use and overall survival was performed in the pooled patient cohort of four randomized clinical trials. The results showed no difference in patients' outcomes between VPA and levetiracetam [27].

Since treatments for glioblastoma add little to survival, especially for the elderly, quality-of-life issues need to be addressed in this group. This is particularly true for patients over 60 years of age in whom median survivals are closer to 35 weeks [2]. This is not to say that surgery should not be carried out aggressively but is rather to express caution about expectations from radiation and chemotherapy. Patients over 70 years of age with reasonable Karnofsky performance status should receive hypofractionated radiotherapy such as 40 Gy in 2.66 Gy fractions over 3 weeks. Preliminary evidence suggests that concurrent and adjuvant TMZ might also be of benefit [28]. As with glioblastoma patients, age is an important variable that negatively influences survival of anaplastic astrocytoma patients. Unlike glioblastoma patients, however, chemotherapy can increase survival substantially.

24.5 Oligodendroglioma and Anaplastic Oligodendroglioma

Based on the WHO 2016 classification, the diagnosis of oligodendroglioma and anaplastic oligodendroglioma mandates the identification of both an IDH gene family mutation and combined whole arm losses of 1p and 19q (1p/19q

codeletion). NOS oligodendrogliomas are histologically typical oligodendrogliomas without the capability of testing IDH and 1p/19q codeletion. The term oligoastrocytomas is now strongly discouraged [10].

Regarding treatment, after surgical resection chemotherapy is the primary treatment modality. Radiotherapy is usually reserved for anaplastic transformation if it occurs. Chemotherapy with PCV given on a 29-day cycle (repeated every 6 weeks) is a standard treatment. Two randomized controlled trials reported that chemoradiotherapy with PCV doubled the median survival of patients with 1p/19q codeleted tumors compared to radiotherapy alone [29, 30]. Cairncross et al. [30] have conducted a series of consecutive phase II studies to examine the rate and duration of response of anaplastic oligodendrogliomas to PCV. Among 24 eligible patients, 38% achieved complete responses (CRs), 38% partial responses (PRs), and 17% stable disease (SD). The median time to progression was less than 25 months for CRs, 14 months for PRs, and 6.8 months for SD patients. Recent analysis showed that patients with 1p/19q noncodeleted IDH-mutated tumors also lived longer after chemoradiotherapy with PCV [31].

TMZ for recurrent anaplastic oligoastrocytoma also showed some efficacy [32–34]. In an EORTC study of 35 oligodendroglioma and oligoastrocytoma patients treated at first recurrence with TMZ, 29% had a CR, 26% a PR, and 31% SD; the 54% of responding patients had a median time to progression of 13.2 months; and the PFS_{12} for all patients was 40% [2]. Van Den Bent and colleagues found that 50% of oligodendroglioma and oligoastrocytoma patients initially responded to PCV chemotherapy, and of 28 patients 25% of oligodendroglioma patients at recurrence responded to TMZ with a median time to progression of 8 months [2].

24.6 Systemic Chemotherapy–Associated Complications: Avoidance and Management

The majority of chemotherapy regimens may produce toxicities that require reduction of dosages or cessation of the responsible chemotherapeutic agent. At times if the toxicity is not recognized early it cannot be reversed, further affecting the quality of life of the patient. Although several compounds have been reported as neuroprotective agents, few have been shown to be active against the chemotherapy-induced toxicity.

24.6.1 Temozolomide

Although TMZ shows many types of toxicities, the majority of them represent either grade 1 or 2 and are tolerable for patients. Fatigue, anemia, leukopenia, thrombocytopenia, and gastrointestinal troubles such as nausea and vomiting are exceedingly common [35, 36]. These may affect the quality of life of patients and thus aggressive monitoring of gastrointestinal toxicities and administration of prophylactic antiemetics may be needed. More toxicities are usually observed in concurrent chemoradiotherapy than in chemotherapy alone.

24.6.2 Vincristine

Vincristine is a neurotoxic agent and can produce dose-dependent and cumulative peripheral neuropathy. Among the most common symptoms and signs are paresthesias, loss of tendon reflexes, and progressive weakness. Less frequently reported are sensory impairment, cranial nerve palsies, gastrointestinal disturbances, and autonomic dysfunctions, including orthostatic hypotension, atonic bladder, and erectile dysfunction. In addition, the efferent olivocochlear system is usually affected by vincristine [37]. Seizures may also occur, and bihemispheric lucencies on brain MRI may be found. However, the latter are reversible after cessation of vincristine [38]. Abducens nerve palsy can be also a presenting sign of a toxic neuropathy associated with vincristine use [39].

24.6.3 Lomustine (CCNU)

Lomustine is an alkylating nitrosourea compound and highly lipid-soluble agent that can cross the blood-brain barrier. Chemotherapy-associated toxicity with this agent is generally mild, is more pronounced in females, and does not increase in older patients. The usual toxicities are gastrointestinal disturbances, hematologic toxicities, and renal impairment that may resolve after discontinuation [40].

24.6.4 Antiangiogenic Therapy

Bevacizumab, a recombinant humanized IgG1 monoclonal antibody, is the first antiangiogenic agent approved for clinical use in brain tumors; however, several treatment-associated toxicities have been reported. Hypertension and proteinuria are frequent toxicities. A three-fold increase of any grade hypertension by low-dose (<10 mg/kg/dose) bevacizumab has been reported, whereas high-dose (≥10 mg/kg/dose) bevacizumab increased such incidence by 7.5-fold [41]. Management of hypertension in these cases should follow the general guidelines for hypertension treatment. Other risk factors associated with hypertension should be assessed, but a single antihypertensive agent is typically sufficient to reduce blood pressure within normal limits [42]. Reversible posterior leukoencephalopathy syndrome has also been associated with antiangiogenic therapy and usually mani-

fests with headaches, confusion, and seizures. Cortical blindness is not a rare sequela. Hyperintensities predominating in the white matter can be seen in brain imaging. Symptoms can be reversible upon cessation of the agent. Another devastating toxicity is the increased risk of both systemic and intracerebral hemorrhage, which are common within the first 5 months of treatment. In a meta-analysis that included 12,617 patients, bevacizumab was associated with an increased risk of hemorrhage (RR 2.48 [95% confidence interval (CI)], 1.93–3.18) compared with the controls [43]. Antiangiogenic therapy also compromises wound healing and has been associated with bowel perforation.

24.7 Future Developments in Systemic Chemotherapy for Brain Gliomas

In human gliomas, expression of hepatocyte growth factor (HGF) receptor (HGFR or MET) was found in up to 29% of cases and is associated with higher grade and more serious clinical outcome. The anaplastic lymphoma kinase (ALK) is a tyrosine kinase that can potentially function as an oncogene. High-grade tumors such as glioblastomas and anaplastic oligodendrogliomas showed an increased expression of ALK relative to normal brain tissues [44]. This is important since crizotinib, an orally available ATP-competitive selective inhibitor of ALK and MET tyrosine kinases, can inhibit tyrosine phosphorylation on these receptors at nanomolar concentrations. Currently a phase Ib study evaluating the safety and activity of crizotinib with TMZ and radiotherapy in newly diagnosed glioblastomas is under way.

The *BRAFV600E* mutation occurs frequently in tumors such as pleomorphic xanthoastrocytomas, gangliogliomas, and pilocytic astrocytomas. It is found less frequently in glioblastoma. Inhibitors of B-Raf protein kinase activity may serve as efficacious drugs for treating patients with *BRAF V600E*-positive GBM. A case of complete response in a *BRAF V600E*-mutated pediatric glioblastoma to vemurafenib (BRAF inhibitor) therapy has been reported [45]. However, more studies are needed to explore the incidence of *BRAFV600E* mutation in this tumor type.

TRAIL is a proapoptotic molecule that induces apoptosis to varying degrees in different tumor cell types and to a lesser degree in normal cells. Furthermore, several agents have been found that sensitize cancer cells to TRAIL-mediated apoptosis [46]. TRAIL requires systemic delivery because of its short half-life. Over the last years recombinant human TRAIL/Apo2L has been tested in phases I, II, and III clinical trials. Regarding toxicity, this agent exhibited minimal adverse effects, and peak serum concentrations were identical to those seen with preclinical antitumor efficacy. Nevertheless, the clinical results were not encouraging. Thus, combination treatments are under way with this agent [47].

p38α Mitogen-activated protein kinase (MAPK) is activated in cancer cells and plays a pivotal role in tumor growth, invasion, metastasis, and resistance to chemotherapy. LY2228820 is a potent and selective inhibitor of the α- and β-isoforms of p38 MAPK and reduces phosphorylation of its cellular target, MAPK-activated protein kinase 2. In several in vivo cancer models, LY2228820 produced significant tumor growth delay in several cancers such as melanoma, non–small cell lung cancer, and glioma [48]. Currently a Phase I/II Study of LY2228820 with radiotherapy plus concomitant TMZ in the treatment of newly diagnosed glioblastoma is recruiting patients [ClinicalTrials NCT02364206].

Epidermal growth factor receptor (EGFR) overexpression and/or amplification can be found in up to 40% of primary GBM cases, the most frequent being the EGFRvIII. Cetuximab, a chimeric monoclonal antibody against EGFRvIII, failed to be more effective than bevacizumab and irinotecan alone in recurrent GBM [49]. ABT-414, an ABT-806 monomethyl auristatin F conjugate, has exhibited in vitro and in xenograph models of selective activity for cancer cells that overexpress wild-type or mutant forms of EGFR [50]. Based on these promising results a randomized phase II study of the EORTC Brain Tumor Group (EORTC Protocol 1410-BTG) study comparing ABT-414 alone or ABT-414 plus TMZ versus lomustine or TMZ for recurrent GBM is currently recruiting patients.

Conclusion

In this chapter we have referenced primarily newer articles and used our own experience to supplement the literature. Certainly, improvements in survival have been made in the treatment of gliomas over the last years. However, radiotherapy and chemotherapy have an impact on surviving patients, causing intellectual and emotional impairment because of toxicity to the CNS. Hopefully, in the near future more specific and selective therapies may emerge that will achieve better tumor control and less toxicities. Until then, we must be thoughtful, creative, and compassionate in our care of brain tumor patients so that we match patients with the most effective treatment that can help them achieve a long life with minimal toxicity.

References

1. Kyritsis AP, Zhang B, Zhang W, Xiao M, Takeshima H, Bondy ML, et al. Mutations of the p16 gene in gliomas. Oncogene. 1996;12:63–7.
2. Levin VA, Giglio P, Kyritsis AP. The management of gliomas, medulloblastomas, CNS germ cell tumors and carcinomas metastatic to the CNS. In: Cavalli F, Hansen H, Kaye S, editors. Textbook of medical oncology. 3rd ed. New York: Taylor & Francis; 2004. p. 313–33.

3. Alexiou GA, Moschovi M, Stefanaki K, Panagopoulos D, Tsotra M, Siozos G, et al. Supratentorial ependymomas in children: analysis of nine cases. J Pediatr Neurosci. 2013;8:15–8.
4. Levin VA. Personalized medicine in neuro-oncology. CNS Oncol. 2016;5:55–8.
5. Alexiou GA, Goussia A, Kyritsis AP, Tsiouris S, Ntoulia A, Malamou-Mitsi V, et al. Influence of glioma's multidrug resistance phenotype on (99m) Tc-tetrofosmin uptake. Mol Imaging Biol. 2011;13:348–51.
6. Alexiou GA, Kyritsis AP. Immunotherapeutic strategies for glioma treatment. Neuroimmunol Neuroinflammation. 2016;3:51–6.
7. Assimakopoulos A, Polyzoidis K, Kyritsis AP. Stem cells in gliomas. J Stem Cells Res Rev Rep. 2014;1:1009.
8. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY, et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science. 2014;343:189–93.
9. Meyers CA, Weitzner MA, Valentine AD, Levin VA. Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. J Clin Oncol. 1998;16:2522–7.
10. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol. 2016;131:803–20.
11. Nitta M, Muragaki Y, Maruyama T, Ikuta S, Komori T, Maebayashi K, et al. Proposed therapeutic strategy for adult low-grade glioma based on aggressive tumor resection. Neurosurg Focus. 2015;38:E7.
12. Karim AB, Maat B, Hatlevoll R, Menten J, Rutten EH, Thomas DG, et al. A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma: European Organization for Research and Treatment of Cancer (EORTC) study 22844. Int J Radiat Oncol Biol Phys. 1996;36:549–56.
13. Shaw E, Arusell R, Scheithauer B, O'Fallon J, O'Neill B, Dinapoli R, et al. Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol. 2002;20:2267–76.
14. Buckner JC, Pugh SL, Shaw EG, Gilbert MR, Barger G, Coons S, et al. Phase III study of radiation therapy (RT) with or without procarbazine, CCNU, and vincristine (PCV) in low-grade glioma: RTOG 9802 with Alliance, ECOG, and SWOG. Paper presented at American Society of Clinical Oncology (ASCO) Annual Meeting; June 2, 2014. Abstract number 2000.
15. Stupp R, Brada M, van den Bent MJ, Tonn JC, Pentheroudakis GESMO. Guidelines Working Group. High-grade glioma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25:93–101.
16. Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol. 2009;27:5874–80.
17. Alexiou GA, Goussia A, Voulgaris S, Fotopoulos AD, Fotakopoulos G, Ntoulia A, et al. Prognostic significance of MRP5 immunohistochemical expression in glioblastoma. Cancer Chemother Pharmacol. 2012;69:1387–91.
18. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol. 2006;7:392–401.
19. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro-Oncology. 2003;5:79–88.
20. Shenouda G, Souhami L, Freeman CR, Hazel J, Lehnert S, Joseph L. Accelerated fractionation for high-grade cerebral astrocytomas. Preliminary treatment results. Cancer. 1991;67:2247–52.
21. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, et al. Dose dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. 2013;31:4085–91.
22. Roldan Urgoiti GB, Singh AD, Easaw JC. Extended adjuvant temozolomide for treatment of newly diagnosed glioblastoma multiforme. J Neuro-Oncol. 2012;108:173–7.
23. Chinot OL, Wick W, Mason W, Stupp R, Hegi ME, Jaeckle KA, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370:709–22.
24. Sandmann T, Bourgon R, Garcia J, Li C, Cloughesy T, Chinot OL, et al. Patients with proneural glioblastoma may derive overall survival benefit from the addition of bevacizumab to first-line radiotherapy and temozolomide: retrospective analysis of the AVAglio trial. J Clin Oncol. 2015;33:2735–44.
25. Chinot OL, Nishikawa R, Mason W, Henriksson R, Saran F, Cloughesy T, et al. Upfront bevacizumab may extend survival for glioblastoma patients who do not receive second-line therapy: an exploratory analysis of AVAglio. Neuro-Oncology. 2016;18(9):1313–8.
26. Herrlinger U, Schäfer N, Steinbach JP, Weyerbrock A, Hau P, Goldbrunner R, et al. Bevacizumab plus irinotecan versus temozolomide in newly diagnosed O6-methylguanine-DNA methyltransferase nonmethylated glioblastoma: the randomized GLARIUS trial. J Clin Oncol. 2016;34:1611–9.
27. Happold C, Gorlia T, Chinot O, Gilbert MR, Nabors LB, Wick W, et al. Does valproic acid or levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials in newly diagnosed glioblastoma. J Clin Oncol. 2016;34:731–9.
28. Cabrera AR, Kirkpatrick JP, Fiveash JB, Shih HA, Koay EJ, Lutz S, et al. Radiation therapy for glioblastoma: executive summary of an American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. Pract Radiat Oncol. 2016;6:217–25.
29. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC Brain Tumor Group study 26951. J Clin Oncol. 2013;31:344–50.
30. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol. 2013;31:337–43.
31. Cairncross JG, Wang M, Jenkins RB, Shaw EG, Giannini C, Brachman DG, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendroglial tumors is associated with mutation of IDH. J Clin Oncol. 2014;32:783–90.
32. Glass J, Hochberg FH, Gruber ML, Louis DN, Smith D, Rattner B. The treatment of oligodendrogliomas and mixed oligodendroglioma-astrocytomas with PCV chemotherapy. J Neurosurg. 1992;76:741–5.
33. Yung WK, Prados MD, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group J Clin Oncol. 1999;17:2762–71.
34. Levin VA, Edwards MS, Wright DC, Seager ML, Schimberg TP, Townsend JJ, Wilson CB. Modified procarbazine, CCNU and vincristine (PCV-3) combination chemotherapy in the treatment of malignant brain tumors. Cancer Treat Rep. 1980;64:237–44.
35. Khasraw M, Bell D, Wheeler H. Long-term use of temozolomide: could you use temozolomide safely for life in gliomas? J Clin Neurosci. 2009;16:854–5.
36. Panet-Raymond V, Souhami L, Roberge D, Kavan P, Shakibnia L, Muanza T, et al. Accelerated hypofractionated intensity-modulated radiotherapy with concurrent and adjuvant temozolomide for patients with glioblastoma multiforme: a safety and efficacy analysis. Int J Radiat Oncol Biol Phys. 2009;73:473–8.

37. Riga M, Psarommatis I, Korres S, Varvutsi M, Giotakis I, Apostolopoulos N, Ferekidis E. Neurotoxicity of vincristine on the medial olivocochlear bundle. Int J Pediatr Otorhinolaryngol. 2007;71:63–9.
38. Hurwitz RL, Mahoney DH Jr, Armstrong DL, Browder TM. Reversible encephalopathy and seizures as a result of conventional vincristine administration. Med Pediatr Oncol. 1988;16:216–9.
39. Toker E, Yenice O, Ogut MS. Isolated abducens nerve palsy induced by vincristine therapy. J AAPOS. 2004;8:69–71.
40. Piribauer M, Fazeny-Dörner B, Rössler K, Ungersböck K, Czech T, Killer M, et al. Feasibility and toxicity of CCNU therapy in elderly patients with glioblastoma multiforme. Anti-Cancer Drugs. 2003;14:137–43.
41. Zhu X, Wu S, Dahut WL, Parikh CR. Risks of proteinuria and hypertension with bevacizumab, an antibody against vascular endothelial growth factor: systematic review and meta-analysis. Am J Kidney Dis. 2007;49:186–93.
42. Armstrong TS, Wen PY, Gilbert MR, Schiff D. Management of treatment-associated toxicites of anti-angiogenic therapy in patients with brain tumors. Neuro-Oncol. 2012;14:1203–14.
43. Hapani S, Sher A, Chu D, Wu S. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology. 2010;79:27–38.
44. Wellstein A. ALK receptor activation, ligands and therapeutic targeting in glioblastoma and in other cancers. Front Oncol. 2012;2:192.
45. Robinson GW, Orr BA, Gajjar A. Complete clinical regression of a BRAF V600E-mutant pediatric glioblastoma multiforme after BRAF inhibitor therapy. BMC Cancer. 2014;14:258.
46. Alexiou GA, Tsamis KI, Vartholomatos E, Peponi E, Tzima E, Tasiou I, et al. Combination treatment of TRAIL, DFMO and radiation for malignant glioma cells. J Neuro-Oncol. 2015;123:217–24.
47. Alexiou GA, Tsamis KI, Kyritsis AP. Targeting tumor necrosis factor-related apoptosis-inducing ligand (TRAIL): a promising therapeutic strategy in gliomas. Semin Pediatr Neurol. 2015;22:35–9.
48. Campbell RM, Anderson BD, Brooks NA, Brooks HB, Chan EM, De Dios A, et al. Characterization of LY2228820 dimesylate, a potent and selective inhibitor of p38 MAPK with antitumor activity. Mol Cancer Ther. 2014;13:364–74.
49. Hasselbalch B, Lassen U, Hansen S, Holmberg M, Sørensen M, Kosteljanetz M, et al. Cetuximab, bevacizumab, and irinotecan for patients with primary glioblastoma and progression after radiation therapy and temozolomide: a phase II trial. Neuro-Oncology. 2010;12:508–16.
50. Phillips AC, Boghaert ER, Vaidya KS, Mitten MJ, Norvell S, Falls HD, et al. ABT-414, an antibody-drug conjugate targeting a tumor-selective EGFR epitope. Mol Cancer Ther. 2016;15:661–9.

Novel Focal Treatment Modalities in Glioma Management

25

Shamik Chakraborty, Katherine Wagner, John Boockvar, and Michael Schulder

Malignant gliomas, including glioblastomas (GBMs) and anaplastic astrocytomas (AAs), remain difficult to treat. Overall prognosis for patients harboring these tumors is poor despite maximal surgical resection with appropriate chemotherapy and radiation. Here we outline several novel treatment modalities for focal control of malignant gliomas. The first set of therapies described rely on bypassing the blood brain barrier (BBB) to better deliver chemotherapeutics directly to the tumor and tumor cells infiltrating into the brain parenchyma. These include convection-enhanced drug delivery, intra-arterial (IA) chemotherapy, focused ultrasound, and laser interstitial thermal therapy. Another modality that has shown promising tumor control is tumor treatment fields therapy, which disrupts tumor mitosis and has increased survival in some studies. We also discuss the challenges associated with these treatments and examine the future of these and other glioma management strategies.

25.1 Introduction

The high-grade malignant brain tumors, which are AAs (WHO grade III) and GBMs (WHO grade IV), affect the majority of adult patients with primary brain tumors. Over 50% of these tumors are GBMs, which have an incidence of approximately three per 100,000 adults per year. The National Cancer Institute estimates that for 2017 there will be nearly 24,000 newly diagnosed patients with GBMs and nearly 17,000 GBM patient deaths in the United States [1]. GBMs and AAs are aggressive tumors, with GBM patients having a median overall survival of 15 months despite maximal surgery, chemotherapy, and radiation. Lower grade gliomas have the potential to become malignant over time, and once transformed, carry a similar dismal prognosis for affected patients. Therefore, efforts to develop safe and effective treatments for glioma have been of paramount concern for neuro-oncologists for some time.

To a limited extent, survival and prognosis for patients with gliomas are dependent on the extent of primary tumor resection. Many new surgical modalities have been developed to increase the extent of safe maximal tumor resection, including navigation systems highlighting important tracts and structures and fluorescent dyes that reveal tumor remnants. However, because of the insidious nature of these tumors, they typically intercalate deep within the brain parenchyma, and complete surgical cure is impossible. Therefore, the efficacy of postoperative treatments becomes as important as surgical resection. The bulk of much of the newest research is in the treatment of malignant gliomas with numerous clinical trials testing new chemotherapeutics, immunotherapies, and other drugs. The efficacy and safety of these treatments may be improved with more focal and guided therapy. Some of these treatment modalities bypass the BBB to improve drug penetration into the tumor and limit exposure of the rest of the brain and body to drug side effects. Other innovations include tumor treatment fields, a novel means to limit

S. Chakraborty · K. Wagner · J. Boockvar · M. Schulder (✉)
Department of Neurosurgery, Hofstra-Northwell School of Medicine, Manhasset, NY, USA
e-mail: mschulder@northwell.edu

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tumor growth that has improved survival by supplementing current treatments. We examine these novel focal treatment modalities below.

25.2 Bypassing the Blood Brain Barrier

Despite significant progress in the molecular mechanisms underlying the pathophysiology of GBMs and related new drug targets, current treatment options remain largely ineffective. Numerous promising new therapeutic agents are under investigation, and in parallel there are many new methods of drug delivery under development to bypass the BBB in order to more effectively target the tumor.

25.2.1 Convection Enhanced Delivery

A direct method of exposing tumors to drugs is via intratumoral drug administration. Convection enhanced delivery (CED) promotes improved diffusion and distribution of a drug by utilizing a pressure gradient during interstitial infusion [2, 3]. Typically, a catheter is stereotactically placed into the tumor cavity and is connected to a pump that creates a constant infusion pressure gradient (Fig. 25.1) [4]. This allows for bypassing the BBB and for administration of large molecular drugs into the tumor up to many kilodaltons as opposed to the normal 200 Da limit of the BBB. Because of the constant pressure gradient, infusates are more homogeneously distributed, and the effective diffusion distance can be up to 3 cm from the catheter [4].

CED has been used to administer not only traditional chemotherapeutics but also toxins, antibodies, and vectors. A large phase III trial was the PRECISE trial, which utilized CED of cintredekin besudotox, a recombinant cytotoxin of interleukin-13 fused to a mutated *Pseudomonas* exotoxin that kills tumor cells expressing IL-13 receptors typically overexpressed on malignant gliomas. This trial was conducted in 296 patients with recurrent GBMs in two centers, with patients randomized to a CED of either cintredekin or Gliadel wafers. The primary endpoint was overall survival, with a median overall survival (OS) for CED of 9.1 mo, and 8.8 mo for Gliadel ($p = 0.476$) [5]. Not only was CED found to be nonsuperior but it was also associated with a nearly eight-fold higher incidence of pulmonary embolism.

Despite the disappointing result, there was some evidence for the efficacy of CED. The progression-free survival (PFS) was 17.7 weeks versus 11.4 weeks for Gliadel. New agents, such as liposomes and nanoparticles, are under preclinical study with CED [4]. A newer IL-13/*Pseudomonas*-toxin drug is under development and study by Targepeutics Inc. (Hershey, PA) in both preclinical and phase-I trials utilizing CED [6]. Innovations in catheter design such as multiport catheters may also improve CED. Numerous phase I and phase II trials are underway and may yield promising results for this focal treatment modality [7]. The biggest downside to CED is its invasive nature, requiring a craniotomy or at least a burr-hole for implantation. This necessitates prolonged hospitalization and meticulous maintenance of the external catheter to prevent potentially serious complications [8]. As a result, it is still a rarely used treatment modality and remains investigational.

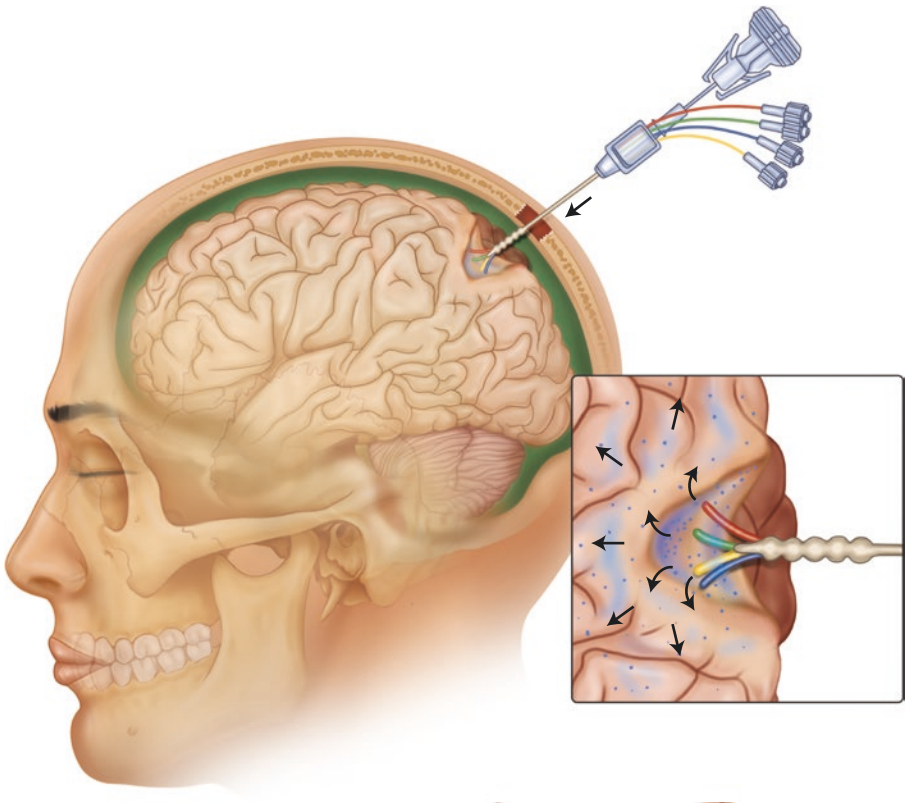

Fig. 25.1 This illustrates a CED catheter implanted into a tumor cavity, with a constant pressure gradient allowing for drug delivery up to 3 cm away from the catheter, thus bypassing the BBB and potentially treating infiltrating tumor cells

25.2.2 BBB Disruption with Osmotic Agents and Intra-arterial Chemotherapy

The BBB limits the passage of molecules above 400–600 Da into the brain tissue [9]. The passage of higher molecular weight agents, such as monoclonal agents and many other chemotherapeutics, is diminished. The BBB around malignant gliomas is heterogeneously disrupted, and many tumor cells may be protected from chemotherapeutics by the BBB [10]. Many preclinical [11–13] and clinical studies [9, 14–16] have shown that the BBB can be transiently disrupted, leading to a significantly higher uptake of IA infused drugs. One of the most studied methods of BBB disruption is the use of hypertonic agents such as mannitol to reversibly increase cerebrovascular permeability [9, 17–21].

Many novel microcatheters and endovascular assistance devices have been developed within the past decade for the treatment of stroke and other vascular disorders. These have also led to more effective focal treatments of cancers throughout the body. Selective IA cerebral infusion (SIACI) techniques allow for focused delivery of chemotherapeutic agents with less brain and systemic toxicity [21, 22]. IA treatment for malignant brain tumors has been administered since the 1960s, and experiments by Neuwelt beginning in the 1980s have demonstrated increased efficacy when combined with BBB disruption [14, 18, 23]. Unlike many IA trials in the past that were typically carotid or vertebral infusions, modern IA infusions are able to accurately target the blood supply of a tumor and catheterize only those affected vessels, sparing the rest of the brain exposure to chemotherapeutic agents [24]. They also potentially permit a lower dose compared to IV or PO medications because they circumvent first-pass metabolism.

The combination of SIACI of chemotherapy in conjunction with osmotic BBB disruption for malignant gliomas has been under study for the past two decades. In 2000, Chow et al. showed a 32% rate of progression-free survival of 3 months using a combination of SIACI of carboplatin following BBB disruption with cereport [25]. Other similar studies by Gobin et al. and Qureshi et al. also using carboplatin helped characterize some of the side effects of this treatment modality, such as seizures, transient neurologic attacks, and stroke [26, 27].

Recent clinical trials by Boockvar have investigated the dosing, safety, and efficacy of SIACI of newer chemotherapeutics in treating malignant gliomas by disrupting the BBB to better target the perivascular glioma stem cell niche (NCT00968240, NCT01238237, NCT01180816). The vascular endothelial growth factor (VEGF) inhibitor bevacizumab can be administered via SIACI and BBB disruption up to a dose of 15 mg/kg safely along with standard therapy for a median progression-free survival of 10 months in patients with recurrent malignant gliomas [28, 29]. Figures 25.2 and 25.3 demonstrate this treatment modality. The durability of a single IA dose is approximately 4 months [30], and this method can potentially have cost savings compared to standard intravenous dosing [31]. Chakraborty et al. showed that SIACI of the epidermal growth factor receptor (EGFR) inhibitor cetuximab can be safely administered up to a dose of 250 mg/m^2 in patients with recurrent GBMs [32]. In a similar phase I SIACI trial of 22 patients with newly diagnosed GBMs who received the alkylating agent temozolomide, Chakraborty et al. found that it can be safely delivered up to a dose of 250 mg/m^2, with a median survival of nearly 24 months; 26% of patients survived for 3 years [33].

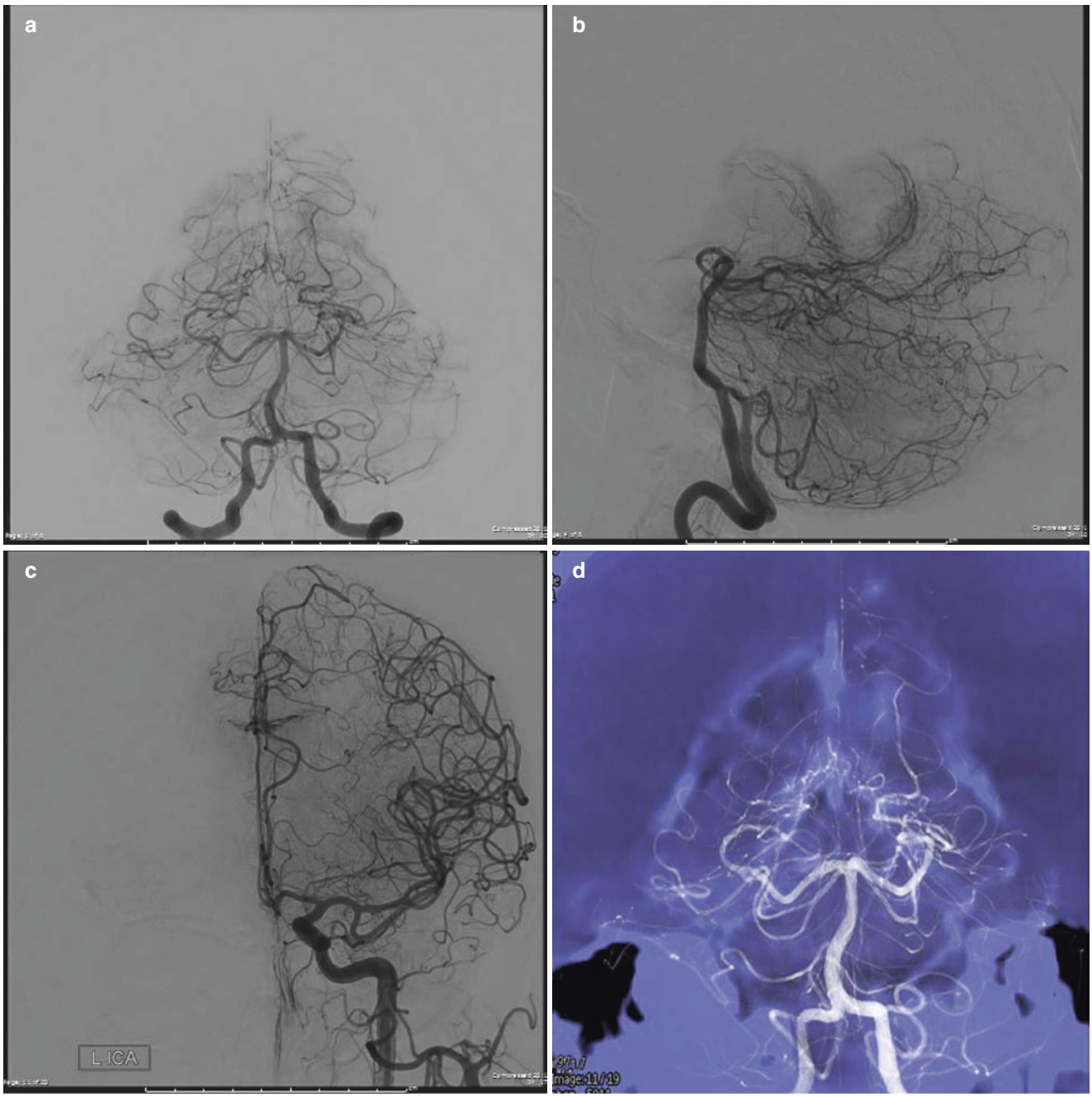

Fig. 25.2 A 60-year-old woman with a GBM of the splenium underwent selective IA cerebral infusion of mannitol for BBB disruption, followed by infusion of bevacizumab. This shows a digital subtraction angiogram with tumor blush and a three-dimensional CT angiogram merged with MRI showing the arterial supply to the tumor

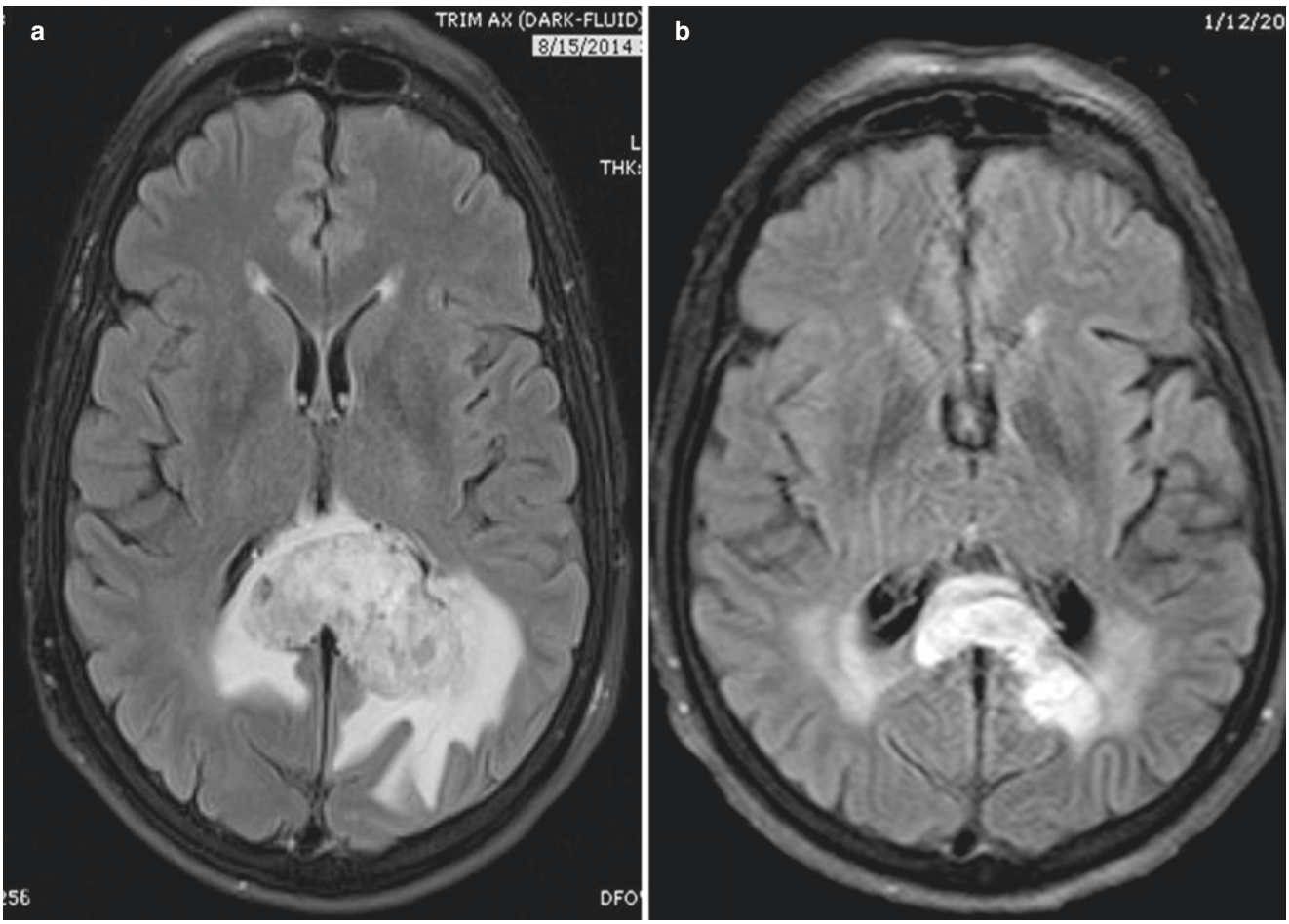

Fig. 25.3 This figure shows the reduction in size of the GBM and tumor control 10 months post-procedure

25.2.3 BBB Disruption with Focused Ultrasound

Focused ultrasound has been recently gaining popularity as a noninvasive way to ablate intracranial lesions. It has been investigated for both functional ablations as well as for the treatment of brain tumors [34]. By combining ultrasound with MRI guidance, these lesions can be quite precise, and it has been shown that MRI-guided focused ultrasound, when used in conjunction with intravenous microbubbles for cavitation, can be used to transiently disrupt the BBB. The BBB disruption can be localized to just the area of the tumor, and the endothelial gap junctions that form the BBB are transiently disrupted for up to 3 days [35, 36]. Numerous preclinical studies have shown some efficacy in improving chemotherapy penetration into the tumor and improved tumor control [35–39]. Currently a clinical trial is under way (NCT02343991) to investigate MRI-guided focused ultrasound to disrupt the BBB and then treat brain tumors with doxorubicin.

25.2.4 BBB Disruption with Laser Interstitial Thermal Therapy

Stereotactic laser interstitial thermal therapy (LITT) is a minimally invasive treatment method for intracranial lesions. It is primary used as an ablative technique using a laser catheter to produce high temperatures that lead to tissue coagulation, necrosis, and cellular apoptosis [8, 40]. This is monitored in an MRI, providing excellent targeting as well as real-time monitoring of the procedure (Fig. 25.4). The LITT temperature within the tumor is over 70 °C but in the peritumoral region it is around 40 °C, which does not induce cell death but is enough to disrupt the BBB. This has been demonstrated by extravasation of dyes, antibodies, and chemotherapy; it can additionally be seen radiographically by new peritumoral contrast enhancement extending several centimeters from the tumor edge compared to pre-procedure tumor enhancement [8, 41–44]. This effect seems to last for several weeks, during which time drug delivery to the tumor could potentially be enhanced. Clinical trials are underway (NCT01851733) to investigate the use of LITT to enhance delivery of chemotherapy for residual disease [43]. This use of hyperthermia shows greater promise than applying it as a purely ablative tool, since reported results have not shown impressive results using LITT as a surrogate for surgical resection [8, 45, 46].

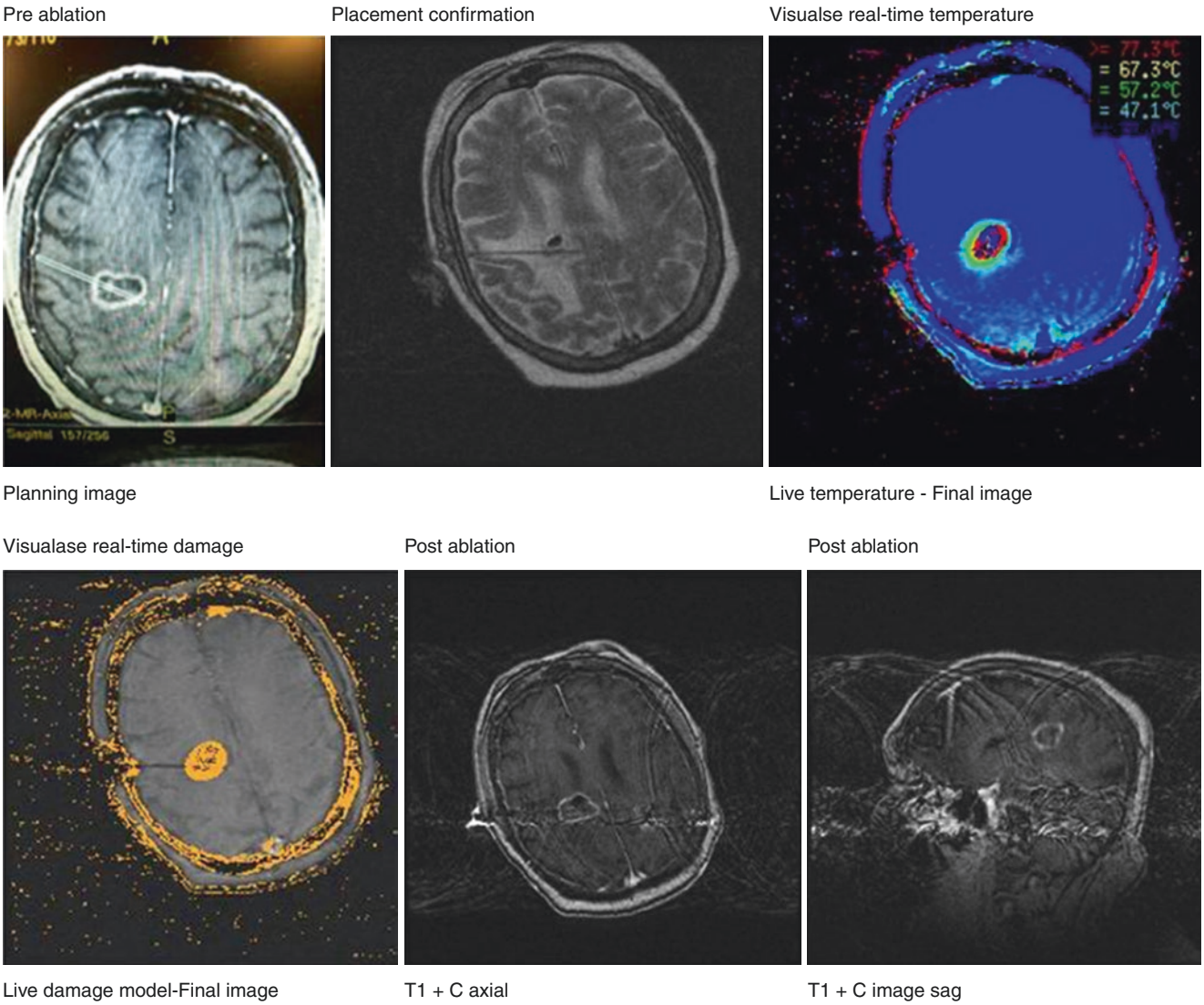

Fig. 25.4 The treatment of a right GBM with the Visualase laser interstitial thermal therapy (LITT) system. MRI was used to confirm catheter placement, followed by real-time monitoring of the temperature and tissue damage zone and final postablative imaging, all done in a single sitting

25.3 Tumor Treatment Fields

In April 2011, the United States Food and Drug Administration approved the use of tumor-treatment fields (TTFs) for use in GBM patients. The potential of this treatment modality was first seen in vitro when studies showed that cells exposed to alternating electromagnetic fields in the kilohertz range underwent membrane blebbing during mitosis [47, 48]. This is thought to be caused by disruption of the alpha and beta tubulin components of mitotic spindles, and it results in a failure to proceed beyond anaphase and subsequent G_0/G_1 arrest and p53-dependent apoptosis [49]. TTFs may also promote an immunogenic response to GBMs, as studies have found that TTF therapy results in high mobility group box 1 (HMGB1) secretion, calreticulin upregulation, and annexin V binding [50, 51]. Patients treated with dexamethasone, an immunosuppressive anti-inflammatory steroid, do not respond as well to TTF therapy, and those with increased levels of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes are more likely to have a better outcome [52].

TTF therapy for GBMs is delivered via two pairs of transducer arrays that are placed on a patient's shaved scalp, which is adhered by a layer of conductive gel [53]. The alternating TTFs are generated with a battery, operating at 200 kHz, with voltages alternating from +50 to −50 V. Gliomas with large necrotic cores are likely to have higher field intensities in the tumor volume as a result of capacitive reactance, while tumors with less necrosis are likely to have lower field intensities [49]. The first TTFs trials for safety were conducted in Europe between 2004 and 2007 in patients with both recurrent and newly diagnosed GBMs [54, 55]. The most common adverse event was contact dermatitis, with no toxicity seen. The median overall survival for patients with recurrences was 14.4 months and for newly diagnosed patients was longer than 39 months. The median progression-free survival (PFS) for newly diagnosed patients was nearly 36 months.

The phase III trial of TTFs for recurrent GBMs was conducted from 2006 to 2009 and showed that the median OS was 6.6 months for TTF patients versus 6 months for chemotherapy [56]. The PFS at 6 months was 21.4% versus 15.1 for chemotherapy. These outcomes indicated that TTFs have an efficacy comparable to that of chemotherapy and bevacizumab. Again, the most common adverse events were scalp irritation, solved mainly by shifting the scalp arrays and applying topical steroids. Importantly, TTFs achieved comparable survival to chemotherapy with far less hematologic toxicity, GI symptoms, fatigue, and pain. The comparable efficacies and the absence of serious toxicities prompted FDA approval for TTF therapy for recurrent GBMs, despite some criticism that all this trial showed was that none of the examined methods had any real effect. Subsequently, the Patient Registry Data Set (PRiDe) was developed to examine the use of TTFs. PRiDe consisted of 457 recurrent GBM patients treated at 91 U.S. centers with TTFs and adjuvant therapy, and patients had a median OS of 9.6 months and a 1-year survival rate of 44%, which compared favorably to the previous trial [57].

A phase III randomized study for TTFs in patients with newly diagnosed GBMs was conducted between 2009 and 2014. After initial radiotherapy and administration of temozolomide, patients were randomized to receive either TTFs and standard therapy or standard therapy alone. An interim analysis approximately halfway through the trial found a PFS of 7.1 months in the TTFs group compared to 4.0 months in the standard therapy alone group. The median OS was 20.1 months versus 15.6 months, and additionally the toxicities seen were similar between the two groups. The trial was subsequently terminated early based on these results [58]. Again, based on these favorable efficacy and toxicity results, the U.S. FDA granted approval in October 2015 for the use of TTFs in conjunction with standard radiation and temozolomide therapy as an adjuvant treatment for patients with newly diagnosed GBMs.

Currently, numerous clinical trials are under way on the use of TTFs in GBMs: (1) TTFs with a combination of temozolomide and bevacizumab with newly diagnosed GBMs (NCT02343549); (2) TTFs in combination with bevacizumab and carmustine in patients with the first recurrence of GBMs (NCT02348255); (3) TTFs with bevacizumab and stereotactic radiotherapy in recurrent GBMs (NCT01925573); and (4) genetic features of GBMs that may prognosticate a response to TTFs (NCT0194576) [49]. These studies and others will help continue to develop this promising mode of focal glioma control.

Conclusions

Although GBMs and malignant AAs remain insidiously difficult tumors to treat, there have been numerous recent breakthroughs that have improved focal tumor control. Despite this, however, the 5-year survival for GBMs still remains only approximately 33% [1]. The new treatment paradigms described here, along with many different chemotherapeutic and immunologic agents under investigation, may be combined to more effectively control malignant gliomas. The results of the clinical trials described above will help guide the future treatment of malignant gliomas and will refine their focal management.

References

1. National Cancer Institute SEER Cancer Statistics Factsheets: Brain and Other Nervous System Cancer. In: Cancer stat facts: brain and other nervous system cancer. https://seer.cancer.gov/statfacts/html/brain.html. Accessed 3 Apr 2017.
2. Bobo RH, Laske DW, Akbasak A, Morrison PF, Dedrick RL, Oldfield EH. Convection-enhanced delivery of macromolecules in the brain. Proc Natl Acad Sci U S A. 1994;91:2076–80.
3. Vogelbaum MA, Aghi MK. Convection-enhanced delivery for the treatment of glioblastoma. Neuro-Oncol. 2015;17(Suppl 2):ii3–8.
4. Abdullah KG, Burdick J. Local and topical treatment of glioblastoma. In: Brem S, Abdullah KG, editors. Glioblastoma. Philadelphia: Elsevier; 2017. p. 207–11.
5. Kunwar S, Chang S, Westphal M, Vogelbaum M, Sampson J, Barnett G, et al. Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma. Neuro Oncol. 2010;12:871–81.
6. Targepeutics Inc. Development of GB-13 as a novel glioblastoma therapy. In: Small business innovation research/small business technology transfer. https://www.sbir.gov/sbirsearch/detail/372598. Accessed 28 Feb 2017.
7. Infuseon Therapeutics Inc. Cleveland Multiport Catheter. In: Cleveland multiport catheter. http://www.infuseontherapeutics.com/Product.aspx. Accessed 28 Feb 2017.
8. Hawasli AH, Kim AH, Dunn GP, Tran DD, Leuthardt EC. Stereotactic laser ablation of high-grade gliomas. Neurosurg Focus. 2014;37:E1.
9. Iwadate Y, Namba H, Saegusa T, Sueyoshi K. Intra-arterial mannitol infusion in the chemotherapy for malignant brain tumors. J Neuro-Oncol. 1993;15:185–93.
10. Oberoi RK, Parrish KE, Sio TT, Mittapalli RK, Elmquist WF, Sarkaria JN. Strategies to improve delivery of anticancer drugs across the blood-brain barrier to treat glioblastoma. Neuro Oncol. 2016;18:27–36.
11. Rapoport SI, Hori M, Klatzo I. Testing of a hypothesis for osmotic opening of the blood-brain barrier. Am J Phys. 1972;223:323–31.
12. Neuwelt EA, Frenkel EP, Rapoport S, Barnett P. Effect of osmotic blood-brain barrier disruption on methotrexate pharmacokinetics in the dog. Neurosurgery. 1980;7:36–43.
13. Neuwelt EA, Barnett PA, Frenkel EP. Chemotherapeutic agent permeability to normal brain and delivery to avian sarcoma virus-induced brain tumors in the rodent: observations on problems of drug delivery. Neurosurgery. 1984;14:154–60.
14. Neuwelt EA, Howieson J, Frenkel EP, Specht HD, Weigel R, Buchan CG, Hill SA. Therapeutic efficacy of multiagent chemotherapy with drug delivery enhancement by blood-brain barrier modification in glioblastoma. Neurosurgery. 1986;19:573–82.
15. Neuwelt EA, Specht HD, Howieson J, Haines JE, Bennett MJ, Hill SA, Frenkel EP. Osmotic blood-brain barrier modification: clinical documentation by enhanced CT scanning and/or radionuclide brain scanning. Am J Roentgenol. 1983;141:829–35.
16. Miyagami M, Tsubokawa T, Tazoe M, Kagawa Y. Intra-arterial ACNU chemotherapy employing 20% mannitol osmotic blood-brain barrier disruption for malignant brain tumors. Neurol Med Chir. 1990;30:582–90.
17. Doolittle ND, Miner ME, Hall WA, Siegal T, Hanson EJ, Osztie E, et al. Safety and efficacy of a multicenter study using intraarterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with malignant brain tumors. Cancer. 2000;88:637–47.
18. Jahnke K, Kraemer DF, Knight KR, Fortin D, Bell S, Doolittle ND, et al. Intraarterial chemotherapy and osmotic blood-brain barrier disruption for patients with embryonal and germ cell tumors of the central nervous system. Cancer. 2008;112:581–8.
19. Guillaume DJ, Doolittle ND, Gahramanov S, Hedrick NA, Delashaw JB, Neuwelt EA. Intra-arterial chemotherapy with osmotic blood-brain barrier disruption for aggressive oligodendroglial tumors: results of a phase I study. Neurosurgery. 2010;66:48–58. discussion 58.
20. Hall WA, Doolittle ND, Daman M, Bruns PK, Muldoon L, Fortin D, Neuwelt EA. Osmotic blood-brain barrier disruption chemotherapy for diffuse pontine gliomas. J Neuro-Oncol. 2006;77:279–84.
21. Riina HA, Fraser JF, Fralin S, Knopman J, Scheff RJ, Boockvar JA. Superselective intraarterial cerebral infusion of bevacizumab: a revival of interventional neuro-oncology for malignant glioma. J Exp Ther Oncol. 2009;8:145–50.
22. Burkhardt J-K, Riina HA, Shin BJ, Moliterno JA, Hofstetter CP, Boockvar JA. Intra-arterial chemotherapy for malignant gliomas: a critical analysis. Interv Neuroradiol. 2011;17:286–95.
23. Kroll RA, Neuwelt EA. Outwitting the blood-brain barrier for therapeutic purposes: osmotic opening and other means. Neurosurgery. 1998;42:1083–99. discussion, 1099–100.
24. Riina HA, Knopman J, Greenfield JP, Fralin S, Gobin YP, Tsiouris AJ, et al. Balloon-assisted superselective intra-arterial cerebral infusion of bevacizumab for malignant brainstem glioma. A technical note. Interv Neuroradiol. 2010;16:71–6.
25. Chow KL, Gobin YP, Cloughesy T, Sayre JW, Villablanca JP, Viñuela F. Prognostic factors in recurrent glioblastoma multiforme and anaplastic astrocytoma treated with selective intra-arterial chemotherapy. Am J Neuroradiol. 2000;21:471–8.
26. Gobin YP, Cloughesy TF, Chow KL, Duckwiler GR, Sayre JW, Milanese K, Viñuela F. Intraarterial chemotherapy for brain tumors by using a spatial dose fractionation algorithm and pulsatile delivery. Radiology. 2001;218:724–32.
27. Qureshi AI, Suri MF, Khan J, Sharma M, Olson K, Guterman LR, Hopkins LN. Superselective intra-arterial carboplatin for treatment of intracranial neoplasms: experience in 100 procedures. J Neuro-Oncol. 2001;51:151–8.
28. Boockvar JA, Tsiouris AJ, Hofstetter CP, Kovanlikaya I, Fralin S, Kesavabhotla K, et al. Safety and maximum tolerated dose of superselective intraarterial cerebral infusion of bevacizumab after osmotic blood-brain barrier disruption for recurrent malignant glioma. Clinical article. J Neurosurg. 2011;114:624–32.
29. Burkhardt J-K, Riina H, Shin BJ, Christos P, Kesavabhotla K, Hofstetter CP, Tsiouris AJ, Boockvar JA. Intra-arterial delivery of bevacizumab after blood-brain barrier disruption for the treatment of recurrent glioblastoma: progression-free survival and overall survival. World Neurosurg. 2012;77:130–4.
30. Chakraborty S, Filippi CG, Burkhardt J-K, Fralin S, Ray A, Wong T, et al. Durability of single dose intra-arterial bevacizumab after

blood/brain barrier disruption for recurrent glioblastoma. J Exp Ther Oncol. 2016;11:261–7.
31. Burkhardt J-K, Shin BJ, Schlaff CD, Riina H, Boockvar JA. Cost analysis of intra-arterial versus intra-venous delivery of bevacizumab for the treatment of recurrent glioblastoma multiforme. J Exp Ther Oncol. 2011;9:183–6.
32. Chakraborty S, Filippi CG, Wong T, Ray A, Fralin S, Tsiouris AJ, et al. Superselective intraarterial cerebral infusion of cetuximab after osmotic blood/brain barrier disruption for recurrent malignant glioma: phase I study. J Neuro-Oncol. 2016;128:405–15.
33. Chakraborty S, Fralin S, Ray A, Wong T, Demopoulos A, Filippi C, et al. Superselective intraarterial cerebral infusion of temozolomide after osmotic blood/brain barrier disruption for newly diagnosed malignant glioma: phase I study. J Neuro-Oncol. 2016;128(3):405–15.
34. Leinenga G, Langton C, Nisbet R, Götz J. Ultrasound treatment of neurological diseases--current and emerging applications. Nat Rev Neurol. 2016;12:161–74.
35. Sheikov N, McDannold N, Vykhodtseva N, Jolesz F, Hynynen K. Cellular mechanisms of the blood-brain barrier opening induced by ultrasound in presence of microbubbles. Ultrasound Med Biol. 2004;30:979–89.
36. Hynynen K, McDannold N, Sheikov NA, Jolesz FA, Vykhodtseva N. Local and reversible blood-brain barrier disruption by noninvasive focused ultrasound at frequencies suitable for trans-skull sonications. NeuroImage. 2005;24:12–20.
37. Chen P-Y, Liu H-L, Hua M-Y, Yang HW, Huang CY, Chu PC, et al. Novel magnetic/ultrasound focusing system enhances nanoparticle drug delivery for glioma treatment. Neuro-Oncology. 2010;12:1050–60.
38. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive opening of BBB by focused ultrasound. Acta Neurochir Suppl. 2003;86:555–8.
39. Mesiwala AH, Farrell L, Wenzel HJ, Silbergeld DL, Crum LA, Winn HR, Mourad PD. High-intensity focused ultrasound selectively disrupts the blood-brain barrier in vivo. Ultrasound Med Biol. 2002;28:389–400.
40. Sakai T, Fujishima I, Sugiyama K, Ryu H, Uemura K. Interstitial laserthermia in neurosurgery. J Clin Laser Med Surg. 1992;10:37–40.
41. Bettag M, Ulrich F, Schober R, Fürst G, Langen KJ, Sabel M, Kiwit JC. Stereotactic laser therapy in cerebral gliomas. Acta Neurochir Suppl. 1991;52:81–3.
42. Nakagawa M, Matsumoto K, Higashi H, Furuta T, Ohmoto T. Acute effects of interstitial hyperthermia on normal monkey brain--magnetic resonance imaging appearance and effects on blood-brain barrier. Neurol Med Chir. 1994;34:668–75.
43. Leuthardt EC, Duan C, Kim MJ, Campian JL, Kim AH, Miller-Thomas MM, et al. Hyperthermic laser ablation of recurrent glioblastoma leads to temporary disruption of the peritumoral blood brain barrier. PLoS One. 2016;11:e0148613.
44. Sabel M, Rommel F, Kondakci M, Gorol M, Willers R, Bilzer T. Locoregional opening of the rodent blood-brain barrier for paclitaxel using Nd:YAG laser-induced thermo therapy: a new concept of adjuvant glioma therapy? Lasers Surg Med. 2003;33:75–80.
45. Thomas JG, Rao G, Kew Y, Prabhu SS. Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma. Neurosurg Focus. 2016;41:E12.
46. Mohammadi AM, Hawasli AH, Rodriguez A, Schroeder JL, Laxton AW, Elson P, et al. The role of laser interstitial thermal therapy in enhancing progression-free survival of difficult-to-access high-grade gliomas: a multicenter study. Cancer Med. 2014;3:971–9.
47. Kirson ED, Gurvich Z, Schneiderman R, Dekel E, Itzhaki A, Wasserman Y, et al. Disruption of cancer cell replication by alternating electric fields. Cancer Res. 2004;64:3288–95.
48. Fonkem E, Wong ET. NovoTTF-100A: a new treatment modality for recurrent glioblastoma. Expert Rev Neurother. 2012;12:895–9.
49. Swanson KD, Lok E, Wong E. Tumor-treating electric fields for glioblastoma. In: Brem S, Abdullah KG, editors. Glioblastoma. Philadelphia: Elsevier; 2016. p. 213–24.
50. Chaput N, De Botton S, Obeid M, Apetoh L, Ghiringhelli F, Panaretakis T, et al. Molecular determinants of immunogenic cell death: surface exposure of calreticulin makes the difference. J Mol Med. 2007;85:1069–76.
51. Gera N, Yang A, Holtzman TS, Lee SX, Wong ET, Swanson KD. Tumor treating fields perturb the localization of septins and cause aberrant mitotic exit. PLoS One. 2015;10:e0125269.
52. Wong ET, Lok E, Gautam S, Swanson KD. Dexamethasone exerts profound immunologic interference on treatment efficacy for recurrent glioblastoma. Br J Cancer. 2015;113:232–41.
53. Lok E, Swanson KD, Wong ET. Tumor treating fields therapy device for glioblastoma: physics and clinical practice considerations. Expert Rev Med Devices. 2015;12:717–26.
54. Kirson ED, Dbalý V, Tovarys F, Vymazal J, Soustiel JF, Itzhaki A, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. Proc Natl Acad Sci U S A. 2007;104:10152–7.
55. Rulseh AM, Keller J, Klener J, Sroubek J, Dbalý V, Syrůček M, et al. Long-term survival of patients suffering from glioblastoma multiforme treated with tumor-treating fields. World J Surg Oncol. 2012;10:220.
56. Stupp R, Wong ET, Kanner AA, Steinberg D, Engelhard H, Heidecke V, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. Eur J Cancer. 2012;48:2192–202.
57. Mrugala MM, Engelhard HH, Dinh Tran D, Steinberg D, Engelhard H, Heidecke V, et al. Clinical practice experience with NovoTTF-100A™ system for glioblastoma: The Patient Registry Dataset (PRiDe). Semin Oncol. 2014;41(Suppl.6):S4–S13.
58. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma: a randomized clinical trial. JAMA. 2015;314:2535–43.

Management of Glial Tumor Recurrence

26

Konstantinos N. Fountas and Eftychia Z. Kapsalaki

This chapter outlines the basic principles of management of patients with recurrent gliomas. These procedures pose certain technical, clinical, and psychological challenges. The diagnosis of glioma recurrence and its differentiation from a radiation and/or chemotherapy effect remain problematic despite the use of all advanced imaging methodologies. The role of conventional magnetic resonance imaging (MRI), MR-advanced techniques, positron emission tomography (PET), single photon emission computed tomography (SPECT), and emerging imaging techniques is evaluated, along with the advantages, disadvantages, and limitations of each imaging method. The surgical resection of a recurrent high-grade but also low-grade glioma as a treatment option is assessed. Special emphasis is given to the recognition of any prognostic factors that may identify good candidates for a reoperation. The potential role of reirradiation, either in the form of conventional or stereotactic radiation, chemotherapy (either systemic or local), immunotherapy, and combined salvage therapies is also examined.

26.1 Introduction

The surgical management of patients with recurrent glial tumors constitutes a real challenge for neurosurgeons. The patient has already undergone a major craniotomy and most probably some form of adjunctive treatment, which may result in enhanced technical surgical difficulties but also severe systemic limitations. Additionally, the possibility of involvement of eloquent cortical areas is significantly higher in recurrent gliomas. Moreover, the patient's psychological state is significantly worse after failing the first-line treatment while facing another round of treatment.

It is well known that gliomas, despite prompt and aggressive treatment, have the tendency to recur in the vast majority of cases. It has been demonstrated that even in cases of complete radiographic resection of a glioma recurrence is very frequent. In more than 90% of these cases the tumor recurrence occurs within 2 cm from the initial tumor resection cavity [1]. The employment of adjunctive radiation therapy and/or chemotherapy and their effects on the resection area frequently make the differentiation of tumor recurrence from post-treatment effects quite problematic and often very difficult.

This chapter presents an outline of our approach to patients with possibly recurrent gliomas and an examination of the treatment options for these patients. We also attempt to give a concise summary of most of the available diagnostic and treatment options as these have been reported in the pertinent literature.

K. N. Fountas (✉)
University Hospital of Larisa, Medical School,
University of Thessaly, Larisa, Greece
e-mail: fountas@uth.gr

E. Z. Kapsalaki
Department of Diagnostic Radiology, School of Medicine,
University of Thessaly, Larisa, Greece

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26.2 Diagnostic Approach

The vast majority of patients with previously resected gliomas are followed up quite regularly, with frequent clinical and imaging evaluations. Any new, even subtle symptoms or neurologic findings should alert the patient and physicians to potential problems and definitely require imaging investigation. Both post-treatment effects and tumor recurrence often present on a conventional post-contrast MRI as enhancing lesions [2]. However, the employment of antiangiogenic chemotherapeutic agents such as bevacizumab may well decrease contrast enhancement owing to its potent vascular normalization effect [3, 4]. Various different MR sequences have been proposed for differentiating tumor recurrence from post-radiation necrosis [5–17]. It has been suggested that T1- and T2-weighted images, FLAIR, apparent diffusion coefficient (ADC), and dynamic-susceptibility contrast-enhanced perfusion along with normalized cerebral blood volume (nCBV) may be sensitive to such differentiation [5–17]. The involvement of the corpus callosum and/or the presence of multiple lesions indicate tumor recurrence rather than post-radiation necrosis [7]. However, the reported accuracy has remained highly variable and problematic [2]. Advanced MR techniques and methodologies have been proposed for increasing the accuracy and the reproducibility of MRI evaluation [5, 6, 8, 11]. The employment of temporal digital subtraction methodology of T1, FLAIR, and ADC images has been suggested to provide accurate differentiation of post-radiation necrosis from tumor recurrence [5]. The employment of radiomics (computer-extracted image texture characteristics) has also been proposed as a promising, differentiating imaging modality [8]. However, in daily clinical practice and when such advanced imaging protocols are not available, the performance of another sequential conventional MRI study in approximately 4 weeks may provide an accurate solution to this diagnostic dilemma.

The role of MRI in the evaluation of treatment response to immunotherapy needs to be taken into consideration, since an exponentially increasing number of clinical experimental protocols examine the role of various targeted immunotherapies in the management of patients with recurrent high-grade gliomas. Qin et al. have outlined the potential role of selected sequences (post-contrast T1-weighted images, T2 WI, FLAIR, and ADC maps) in the treatment evaluation of patients with recurrent glioblastoma multiforme (GBMs) undergoing therapy with anti-PD1 along with or without anti-CTLA4 therapy [18]. They found that MRI demonstrated an initial increase in volumes of abnormal tissue with contrast enhancement, edema, and intermediate ADC changes indicating hypercellularity during the first 6 months of treatment [18]. Subsequent imaging improvement may suggest a response to the administered immunotherapy and possibly stabilization of the underlying disease [18].

We usually employ proton MR spectroscopy (^{1}HMRS) in the evaluation of these patients (Fig. 26.1). Numerous ^{1}HMRS techniques have been proposed with varying accuracy [6, 7, 10, 19]. The most frequently examined metabolites are choline (Cho), creatine (Cr), N-acetyl-aspartate (NAA), lactate (Lac), lipids (Lip), and several metabolic ratios. It seems that there is a consensus regarding the most preferable metabolic ratios (Cho/NAA, Cho/Cr, NAA/Cr). In cases of glioma recurrence Cho concentration is significantly elevated, while the Cho/NAA and Cho/Cr ratios are also elevated (Fig. 26.2). Our clinical data demonstrate that the diagnostic accuracy of MRI and ^{1}HMRS can establish an accurate diagnosis in more than 90% of the cases. Our findings are supported by several reports in the literature which have shown accuracy rates between 90% and 96.2% [7, 10, 19].

Metabolic imaging modalities such as PET, CT/PET, MR/PET, and SPECT have been employed in the evaluation of patients with possible glioma recurrence [2, 20–25]. Various PET techniques and tracers have been used (^{11}C-L-methionine, ^{18}F-fluoroethyl-L-tyrosine, 6-[fluoride-18] fluoro-levodopa, 3′-deoxy-3′-[^{18}F] fluorothymidine) with significantly varying accuracy rates. A recently published study using hybrid MR/PET imaging with a ^{18}F-fluoro-ethyl-tyrosine (^{18}F-FET) tracer reported that their diagnostic accuracy ranged between 81.3% and 96.9% [2]. Likewise, a recent study employing thallium-201 and ^{99m}Tc-hexamethyl-propylene-amine oxime (HPMAO) reported a diagnostic accuracy of 93.3% [20].

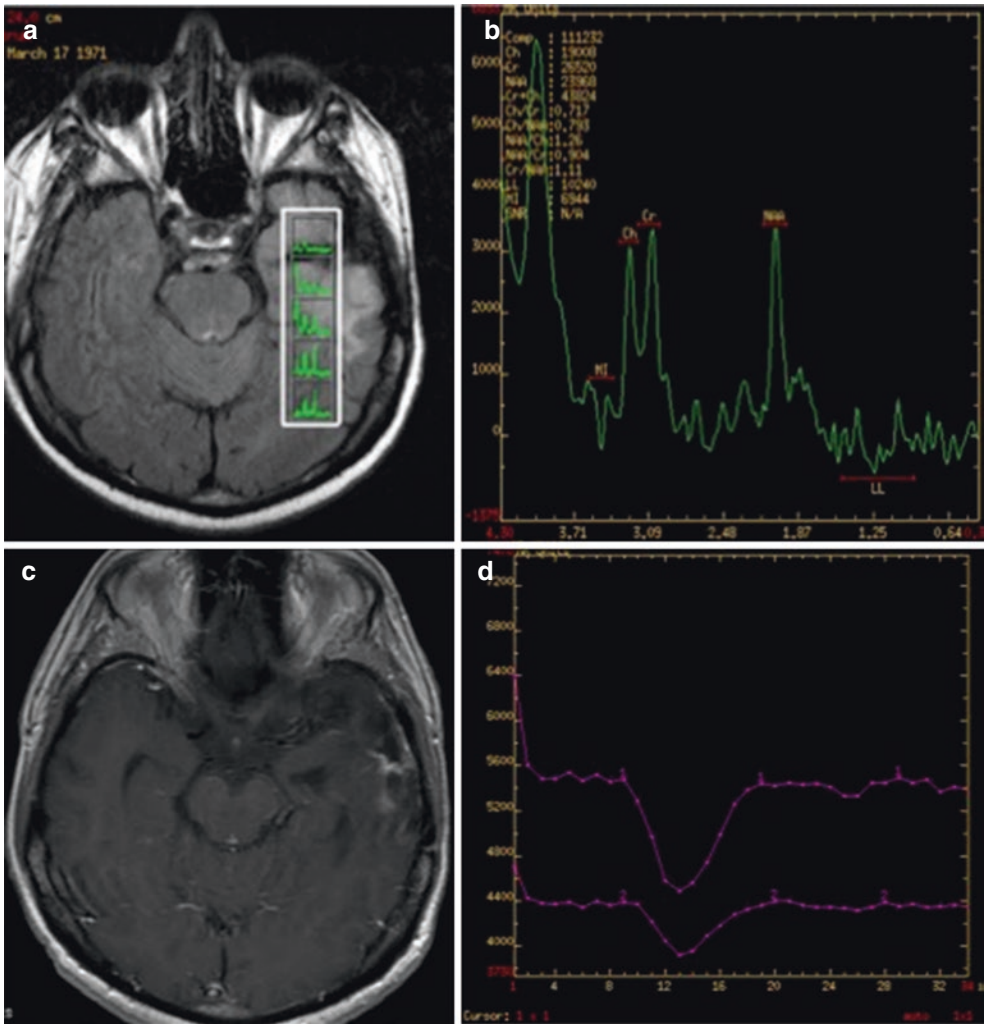

Fig. 26.1 (**a**, **b**) Postoperative MRI study performed at 8 months after surgery showing postoperative changes in the left temporal lobe after surgical excision of a grade III glioma. Proton MR spectroscopy and (**c**, **d**) MR perfusion were performed to differentiate between radiation necrosis and tumor recurrence. The proton MRS shows decreased N-Acetyl-Aspartate (NAA) but no increased Cho/Cr metabolic ratio, and the MR perfusion shows no signal drop. None of the obtained imaging studies show findings suggestive of tumor recurrence. It was decided not to surgically intervene at that point (taking into consideration the patient's excellent neurologic status), and a follow-up imaging study was suggested. No tumor recurrence was identified at 6 and 12 months later

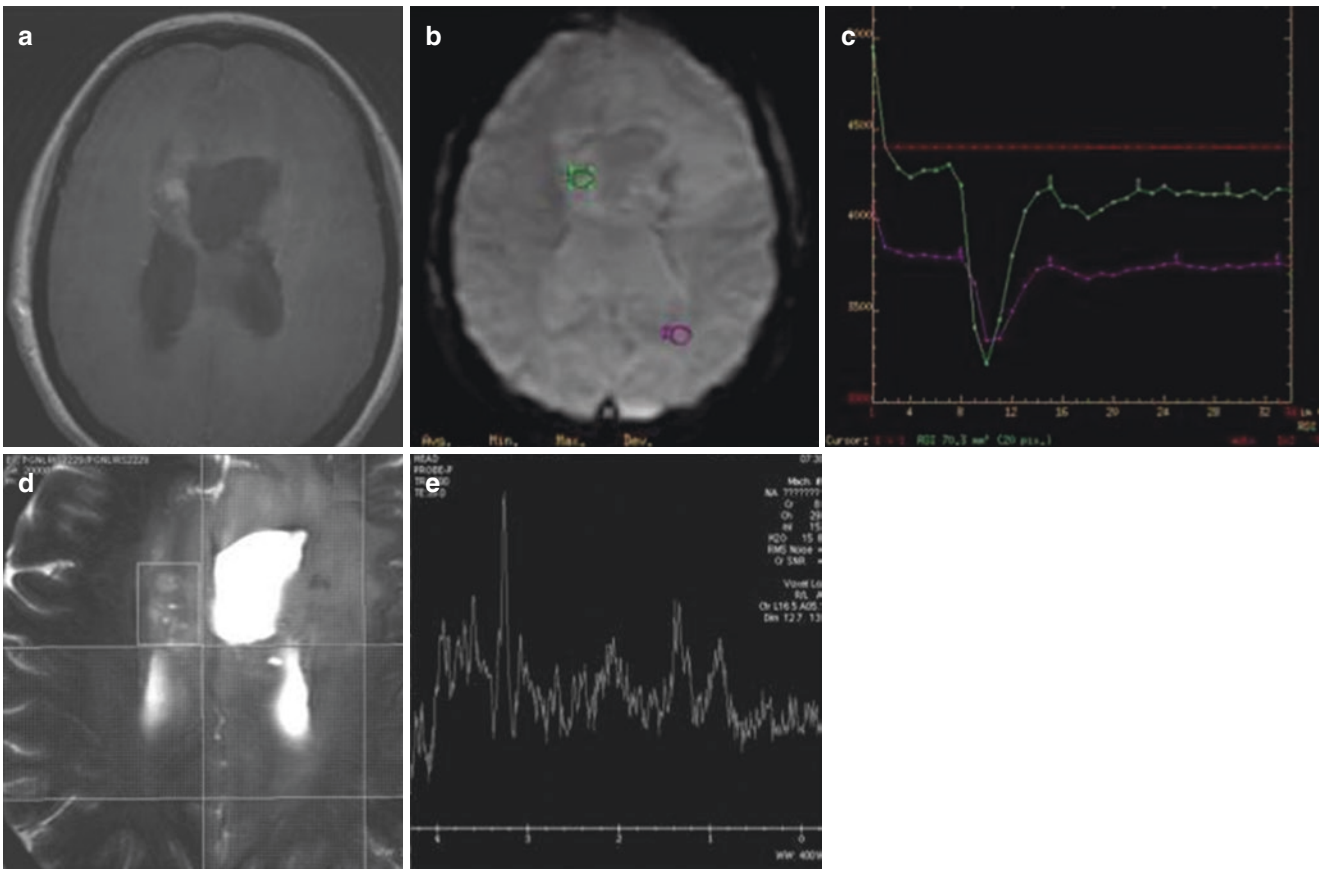

Fig. 26.2 (**a**) An MRI study showing postoperative changes in the left frontal lobe and the corpus callosum. (**b–e**), Axial T1 post-contrast image shows a postoperative porencephalic area surrounded by edema without mass effect. However, an enhancing nodular area is identified at the mesial border of the porencephalic cyst. This finding was not present on the patient's previous MRI, which had been performed 4 months earlier. (**b**, **c**)**,** Advanced MRI techniques were performed to differentiate radiation necrosis from tumor recurrence. (**d**, **e**)**,** T2 MR perfusion (dynamic susceptibility contrast) shows a signal drop at the area of enhancement, while single voxel proton MR spectroscopy shows increased choline concentration and a significantly increased Cho/Cr ratio. These findings were suggestive of tumor recurrence. These imaging findings were histologically confirmed after a surgical re-resection

26.3 Surgical Management of High-Grade Gliomas (HGGs)

The surgical resection of recurrent HGGs (anaplastic astrocytoma or glioblastoma multiforme) has remained highly controversial. Several clinical studies have been published reporting a significant increase in the mean overall survival, the progression-free survival, and improved functional status of patients undergoing reoperation for resection of their recurrent glioma [26]. Harvey-Jumper and Berger, in a systematic review study, summarized all previously published series which, in a vast majority of cases, showed a significant increase in mean overall survival [26]. They identified the patient's age when less than 50 years, Karnofsky performance scale (KPS) score when greater than 70, small tumor volume, tumor histologic grade (anaplastic astrocytoma grade better than glioblastoma grade), longer interval between operations, and greater extent of resection as favorable prognostic factors [26]. Although many studies indicate that patients under 50 years have a better prognosis, it needs to be taken into consideration that the vast majority of patients with HGGs are older than 50. There are series reporting favorable prognosis even in patients under 60 years [26]. It has been demonstrated that the extent of resection during reoperation may play a really important role and even overcome an initial subtotal resection [27]. Park et al. proposed a four-tier prognostic scoring system (0–3) for identifying those patients who can benefit from a reoperation [28].

In cases of reoperation, the use of 5-aminolevulinic acid (5-ALA) has been shown to be advantageous for increasing the extent of resection [29]. Hickmann et al. have reported that the use of 5-ALA in their cohort resulted in a statistically significant increase of the mean overall survival of patients with recurrent GBMs [29]. Previous reports have shown that the perioperative complication rate was higher during the reoperation compared with the initial procedure; however, this difference did not have statistical significance [30]. Likewise, the incidence of a new postoperative neurologic deficit or worsening of the preoperative neurologic status after a reoperation has been reported to be 18% [30]. The increasing use of bevacizumab has shown increased perioperative risk and increased perioperative complication rates [31]. However, its discontinuation at least 4 weeks before any surgical intervention and its restart after the third postoperative week has been reported in order to avoid any hemorrhagic adverse events [31].

It must be emphasized that there are a few studies reporting no benefit in patients undergoing reoperation for resection of an HGG [32–34]. Stromblad et al. [33] found that reoperation was not an independent prognostic factor in their randomized clinical trial, and these patients had no significantly increased mean survival rate. Similarly, Skeie et al. [32] found no advantage of reoperation in their retrospective study. Palmer et al. [34] also found no significant difference in the median overall survival between patients undergoing and those not undergoing reoperation.

Meticulous analysis of the literature leads to the conclusion that a reoperation needs to be reserved for carefully selected younger patients with good KPS scores (>70) and a high probability of accomplishing a gross total resection (Fig. 26.3). The patient needs to undergo a careful preoperative evaluation, particularly in those cases in which bevacizumab has been previously administered.

26.4 Radiation Salvage Therapy

The exact role of the reirradiation of patients with HGGs, the most efficient radiation modality, and its dosage may be defined by the RTOG 1205 ongoing clinical trial [35]. However, numerous clinical series have reported their results from employing different modalities of radiation for recurrent HGGs [Z6].

A reasonable approach to the role of reirradiation of patients with HGGs should take into consideration the tumor volume, the tumor's proximity to vital and radiosensitive structures, the patient's functional status, and previously employed radiation therapy [36]. As a general rule, in cases of large-volume tumors or tumors located close to radiosensitive structures fractionated stereotactic radiosurgery (SRS) may be advantageous [36]. In patients with poor functional status, hypofractionated SRS may provide an alternative salvage therapy with short treatment time, while newer techniques such as pulsed reduced dose rate radiotherapy may be suitable for patients with large-volume tumors [36].

Several clinical investigators have reported their experience and their results from the employment of γ-knife SRS in the management of patients with recurrent HGGs [37–43]. All of them have reported encouraging results, low toxicity, and variably increased progression-free and overall survival. Similarly, there is a significant variation in the employed radiation dosage, with median doses ranging from 10 to 30 Gy at the 50% isodose line in the vast majority of cases [38, 43]. Larson et al., in their review study, found that the previously published γ-knife SRS series reported a median overall survival from diagnoses ranging from 16.7 to 33.2 months, while the median overall survival from the SRS salvage treatment varied from 9 to 17.9 months [39]. The observed complication and adverse event rates were reported from 0% to 46% [39]. A series of factors have been identified for predicting patients' responses to γ-knife SRS [38, 40, 44]. It has been postulated that the patient's age (<50 years), the KPS score (>70), the absence of any neurologic deficits, the tumor volume at recurrence, the histologic grade (grade III versus grade IV), the recursive partitioning analyses classification, and the margin to the planning target volume may influence the patient's response and his or her overall survival time [38, 40, 44].

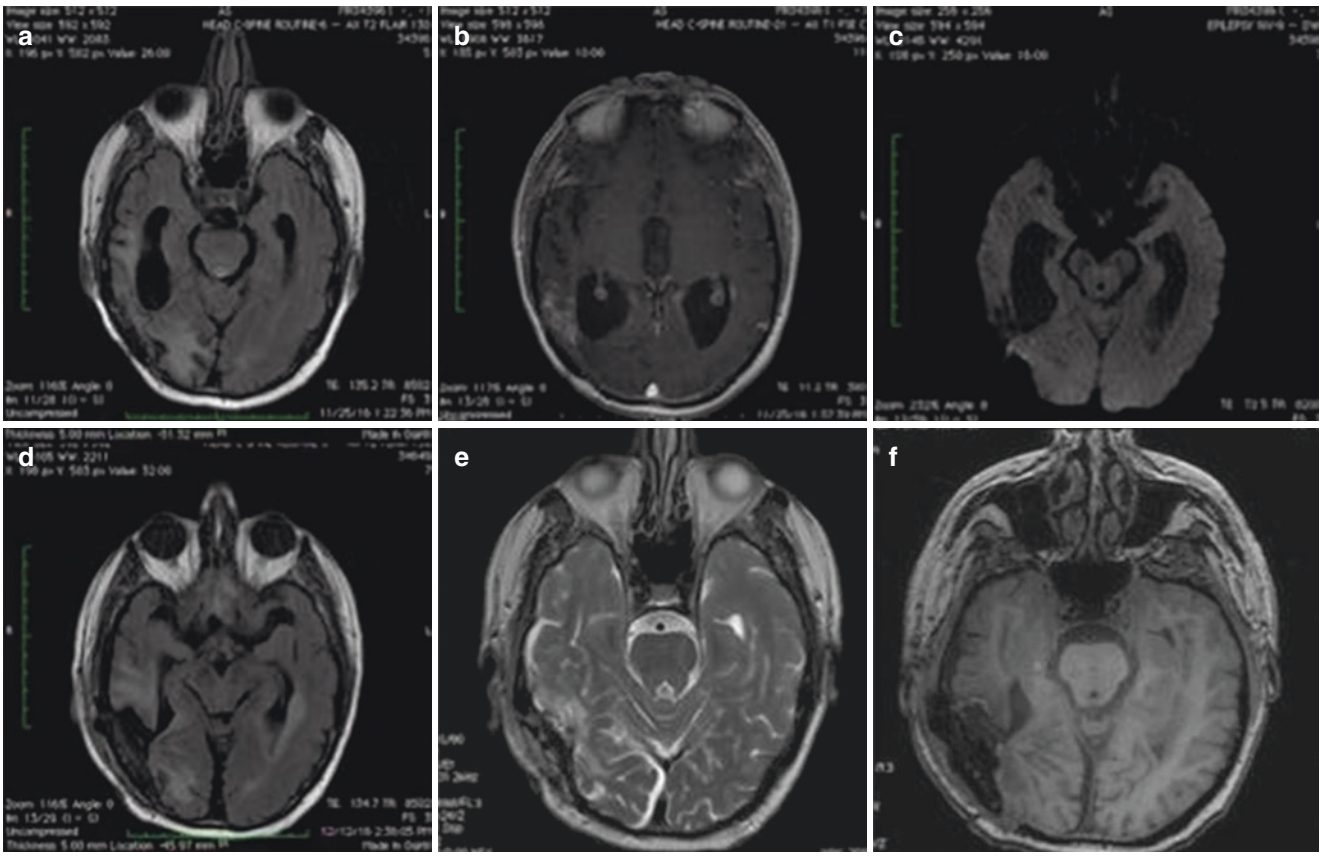

Fig. 26.3 Top row images (**a–c**): Axial FLAIR (**a**), T1 post contrast (**b**), and diffusion-weighted (**c**) images showing postoperative changes at the right temporal lobe. Edema is identified on the FLAIR (**a**) images, along with an enhancing lesion (**b**) located in the right temporal lobe surrounding the trigone of the lateral ventricle. No diffusion restriction is identified (**c**). These findings were suggestive of glioma recurrence. Bottom row (**d–f**): axial FLAIR (**d**), T2 (**e**), and T1 post-contrast (**f**) images obtained immediately after surgical excision of the recurrent lesion show edema and postoperative changes at the posterior part of the right temporal lobe. No residual tumor is identified on the T1 post-contrast images

There is also limited experience with different forms of SRS such as linear accelerator (LINAC) and CyberKnife in the management of patients with recurrent HGGs [44, 45]. Their results and rates are comparable to the γ-knife SRS survival and toxicity rates. Moreover, fractionated and hypofractionated stereotactic radiotherapy (SRT) has been employed as salvage therapies for patients with recurrent HGGs with promising results [46–51]. All these studies have reported improved progression-free and overall survival rates. However, patients undergoing any reirradiation treatment must be very carefully selected.

Furthermore, local interstitial brachytherapy delivered by surgically implanted balloon catheter devices (GliaSite) has been proposed as a salvage treatment for recurrent HGGs. Gobitti et al. [52] reported their institutional experience with GliaSite brachytherapy protocol in a series of patients with recurrent HGGs. They encountered no significant side effects during the treatment period, although 20% of their study participants developed post-treatment radiation necrosis [52]. Further clinical experience is required for exploring the potential role of GliaSite brachytherapy as a stand-alone or adjuvant treatment for recurrent HGGs.

26.5 Local Chemotherapy as Salvage Treatment

It has been well demonstrated that the vast majority of HGGs tend to recur in close proximity to the initial tumor resection site. Therefore the implantation of progressively releasing carmustine wafers (Gliadel) at the resection bed seems to be an appealing treatment option for patients with recurrent HGGs (Fig. 26.4). Indeed, Chowdhary et al. systematically reviewed the pertinent literature for the effectiveness and safety of Gliadel as a salvage therapy for recurrent GBMs [53]. They reported that the one-year overall survival was 37% for the patients treated with Gliadel wafers, while the respective survival for the control group was 34%. The two-year overall survival was reported to be 15% for the Gliadel group, whereas the rate for the control group was 12%. The mean overall survival for the Gliadel group was 9.7 months versus 8.6 months for the control group. The most commonly observed complication associated with the wafer implantation was a postoperative surgical site infection, although hydrocephalus, mass effect, acute or delayed postoperative hematoma, and brain parenchyma necrosis have also been encountered and reported [53]. Special emphasis needs to be given to the potential effect of the implanted Gliadel wafers in the postoperative MRI studies, findings that may be misinterpreted as indicative of brain abscesses.

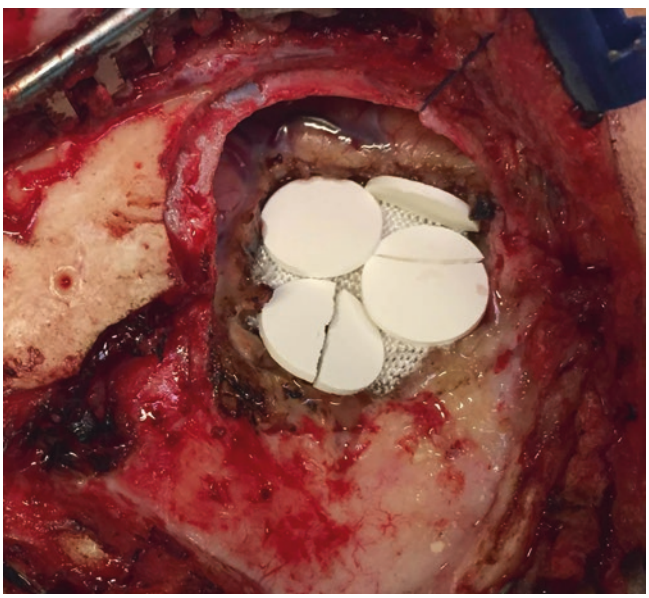

Fig. 26.4 Intraoperative picture taken immediately after the reresection of this GBM depicting the resection cavity and the implanted Gliadel wafers. The number of the implanted wafers each time depends on the volume of the resection cavity. A useful practical tip for securing the implanted wafers in an optimal position is to cover them with a sheet of oxidized cellulose

26.6 Immunotherapy as Salvage Treatment

Several experimental immunotherapy protocols have emerged and been implemented into clinical research as salvage therapy for recurrent HGGs [54–56]. Schijns et al. have reported their early results from the intradermal administration of Gliovac along with human granulocyte–macrophage colony-stimulating factor (GM-CSF) after a previous regimen of regulatory T-cell-depleting and low-dose cyclophosphamide [54]. They found minimal toxicity and increased overall survival in their patients [54]. Pollack et al. reported their initial results from employing a trial of intramuscular vaccinations with peptide epitopes derived from glioma-associated antigens in children with recurrent HGGs [56]. They encountered no toxicity or any other adverse events [56]. The median progression-free survival from the start of vaccination was 4.1 months, and the median overall survival in their series was 12.9 months [56]. It must be emphasized, however, that these promising results need to be validated by large-scale prospective clinical trials and their low-toxicity profile confirmed by long-term follow-up studies.

26.7 Combined Salvage Therapies

Various combinations of treatment modalities have been proposed as salvage therapies for the management of patients with recurrent HGGs [57, 58]. Archavlis et al. reported their experience from employing a combined scheme consisting of reoperation, interstitial brachytherapy, and chemotherapy with temozolomide [57]. They reported that the patients enrolled in this protocol demonstrated a 3-month increase in mean overall survival compared to the group of patients receiving only temozolomide [57]. Muller et al. compared reoperation along with dendritic cell vaccination versus reirradiation and found no difference in the outcome of these two groups [58]. Likewise, Hasan et al. reported on their experience applying fractionated stereotactic radiosurgery along with temozolomide and bevacizumab [59]. They identified that the tumor volume (smaller volume), its anatomic location (frontal lobe), the patient's functional status, and the long interval from initial diagnosis until treatment were positive predictive factors [59].

Similarly, Cuneo et al. reported their experience from employing a combined treatment of SRS and bevacizumab in patients with recurrent HGGs [37]. They found that the use of their salvage therapy resulted in a significant increase of the overall survival of their patients. The one-year survival was 50% among patients receiving both SRS and bevacizumab, whereas it was 22% in the group of patients receiving only SRS as salvage therapy. However, the functional performance of their patients showed no difference between the two groups [37]. Park et al. reported an 18-month median overall survival after the employment of a salvage therapeutic scheme of γ-knife SRS, bevacizumab, and irinotecan [60]. They found that 73% of their study participants with recurrent GBMs had a one-year overall survival rate from the SRS treatment [60].

Likewise, Schuessler et al. [61] reported preliminary results from a series of patients with recurrent GBMs treated with autologous cytomegalovirus (CMV)-specific T cells along with a combination of standard radiation therapy, temozolomide, and various other chemotherapeutic agents. They found that the median overall survival time in their study was 13.6 months, and 40% of their study participants remained progression-free during the immunotherapy treatment period [61].

Novel treatment modalities have been proposed for managing patients with recurrent HGGs. The employment of MR-guided laser interstitial thermal therapy (LITT) has been recently suggested as a one-day salvage treatment for HGG patients [62]. Carpentier et al. reported their early experience from a small series of carefully selected GBM patients treated with LITT. Their patients had a mean survival time of 10.5 months and minor periprocedural complications [62]. The exact role of LITT as a salvage therapeutic option, particularly for deep-seated HGGs, remains to be examined.

26.8 Management of Recurrent Low-Grade Gliomas (LGGs)

The role of surgery in the management of recurrent LGGs remains to be defined. There is a growing body of evidence that supports the role of reoperation in these cases, since many clinical series have reported that maximal resection of a recurrent LGG may improve both the progression-free and the overall survival rates [63, 64]. The vast majority of these studies have concluded that the absence of a residual tumor after the initial resection was a strong prognostic factor for progression-free survival and lack of tumor recurrence [64]. In their retrospective study, Martino et al. found that reoperation is a safe and efficacious method for managing patients with recurrent LGGs, even when they are located in eloquent cortical areas [63]. They reported that they were able to accomplish a total resection of the recurrent tumor in 5.3% and a subtotal resection in 68.4% of their cases. The majority of their patients (68.4%) remained neurologically stable while 15.8% showed improvement in their preoperative neurologic status; however, the remaining 15.8% demonstrated postoperative worsening of their neurologic examination. They also reported that 82.3% of their patients had postoperative improvement of their preoperative seizure symptoms after the second resection. In their series they found that 57.9% of their cases had a higher tumor histologic grade at reoperation [63].

The identification of any prognostic factors becomes of paramount importance in identifying those LGG patients

who are at risk for a recurrence. There are currently several genetic factors that may predispose to a higher possibility of recurrence [65]. There is class III evidence that isocitrate dehydrogenase (IDH) mutation in an LGG patient indicates a shortened time to recurrence and that loss of CDK2NA expression is associated with a higher possibility of histologic progression of an LGG to a higher grade [65]. Moreover, flow cytometry indices such as MIB-1 and/or BUdR may predict the possibility of a recurrence in a LGG case, since their increased values have been associated with higher recurrence rates [65]. Likewise, O^6-methylguanine–DNA methyltransferase (MGMT) status may be used as a predictor, since LGGs with promoter methylation demonstrate shorter progression-free survival but longer post-recurrence survival after temozolomide treatment [65]. It has been shown that there is not enough evidence to support the use of TP_{53} mutation as an outcome-predicting factor in LGGs [65].

The currently available body of evidence supports the employment of systemic chemotherapy (temozolomide and/or temozolomide and/or procarbazine, lomustine, vincristine [PCV]) and of targeted external radiation therapy. However, the role of surgery is not clearly defined in cases of a possible safe total resection of a recurrent LGG, although there is emerging evidence that progression-free and overall survival times may be increased [63, 64]. Additionally, there are several reports in the pertinent literature demonstrating improved functional status of the patients undergoing reoperation for a LGG [63, 64]. It has to be emphasized that the expected benefit of a reoperation needs to outweigh the risks of surgery, especially in cases in which chemotherapy and radiation therapy have been previously employed.

References

1. Santra A, Kumar R, Sharma P, Bal C, Kumar A, Julka PK, et al. F-18 FDG PET-CT in patients with recurrent glioma: comparison with contrast enhanced MRI. Eur J Radiol. 2012;81:508–13.
2. Jena A, Taneja S, Gambhir A, Mishra AK, D'Souza MM, Verma SM, et al. Glioma recurrence versus radiation necrosis: single-session multiparametric approach using simultaneous O-(2-18F-fluoroethyl)-L-tyrosine PET/MRI. Clin Nucl Med. 2016;41:e228–36.
3. Daniels D, Guez D, Last D, Hoffmann C, Nass D, Talianski A, et al. Early biomarkers from conventional and delayed-contrast MRI to predict the response to bevacizumab in recurrent high-grade gliomas. Am J Neuroradiol. 2016;37:2003–9.
4. Zuniga RM, Torcuator R, Jain R, Anderson J, Doyle T, Ellika S, et al. Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. J Neuro-Oncol. 2009;91:329–36.
5. Yanagihara TK, Grinband J, Rowley J, Cauley KA, Lee A, Garrett M, et al. A simple automated method for detecting recurrence in high-grade gliomas. Am J Neuroradiol. 2016;37:2019–25.
6. Fink JR, Carr RB, Matsusue E, Iyer RS, Rockhill JK, Haynor DR, et al. Comparison of 3 Tesla proton MR spectroscopy, MR perfusion and MR diffusion for distinguishing glioma recurrence from posttreatment effects. J Magn Reson Imaging. 2012;35:56–63.
7. Seeger A, Braun C, Skardelly M, Paulsen F, Schittenhelm J, Ernemann U, et al. Comparison of three different MR perfusion techniques and MR spectroscopy for multiparametric assessment in distinguishing recurrent high-grade gliomas from stable disease. Acad Radiol. 2013;20:1557–65.
8. Tiwari P, Prasanna P, Wolansky L, Pinho M, Cohen M, Nayate AP, et al. Computer-extracted texture features to distinguish cerebral radionecrosis from recurrent brain tumors on multiparametric MRI: a feasibility study. Am J Neuroradiol. 2016;37:2231–6.
9. Chang PD, Chow DS, Yang PH, Filippi CG, Lignelli A. Predicting glioblastoma recurrence by early changes in the apparent diffusion coefficient value and signal intensity on FLAIR images. Am J Roentgenol. 2017;208:57–65.
10. Zenq QS, Li CF, Liu H, Zhen JH, Fenq DC. Distinction between recurrent glioma and radiation injury using magnetic resonance spectroscopy in combination with diffusion-weighted imaging. Int J Radiat Oncol Biol Phys. 2007;68:151–8.
11. Kim HS, Kim JH, Kim SH, Cho KG, Kim SY. Posttreatment high-grade glioma: usefulness of peak height position with semiquantitative MR perfusion histogram analysis in an entire contrast-enhanced lesion for predicting volume fraction of recurrence. Radiology. 2010;256:906–15.
12. Hygino da Cruz LC Jr, Rodriquez I, Dominques RC, Gasparetto EL, Sorensen AG. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. Am J Neuroradiol. 2011;32:1978–85.
13. Bobek-Billewicz B, Stasik-Pres G, Majchrzak H, Zarudzki L. Differentiation between brain tumor recurrence and radiation injury using perfusion, diffusion-weighted imaging and MR spectroscopy. Folia Neuropathol. 2010;48:81–92.
14. Lee HY, Na DG, Song IC, Lee DH, Seo HS, Kim JH, et al. Diffusion-tensor imaging for glioma grading at 3-T magnetic resonance imaging: analysis of fractional anisotropy and mean diffusivity. J Comput Assist Tomogr. 2008;32:298–303.
15. Hu LS, Baxter LC, Smith KA, Feuerstein BG, Karis JP, Eschbacher JM, et al. Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements. Am J Neuroradiol. 2009;30:552–8.
16. Voglein J, Tuttenberg J, Weimer M, Gerigk L, Kauczor HU, Essig M, et al. Treatment monitoring in gliomas: comparison of dynamic susceptibility-weighted contrast-enhanced and spectroscopic MRI techniques for identifying treatment failure. Investig Radiol. 2011;46:390–400.
17. Hamstra DA, Galban CJ, Meyer CR, Johnson TD, Sundgren PC, Tsien C, et al. Functional diffusion map as an early imaging biomarker for high-grade glioma: correlation with conventional radiologic response and overall survival. J Clin Oncol. 2008;26:3387–94.
18. Qin L, Li X, Stroiney A, Qu J, Helgager J, Reardon DA, et al. Advanced MRI assessment to predict benefit of anti-programmed cell death 1 protein immunotherapy response in patients with recurrent glioblastoma. Neuroradiology. 2017;59:135–45.
19. Zeng QS, Li CF, Zhang K, Liu H, Kang XS, Zhen JH. Multivoxel 3D proton MR spectroscopy in the distinction of recurrent glioma from radiation injury. J Neuro-Oncol. 2007;84:63–9.
20. Schwartz RB, Carvalho PA, Alexander E 3rd, Loeffler JS, Folkerth R, Holman BL. Radiation necrosis vs high-grade recurrent glioma: differentiation by using dual-isotope SPECT with ^{201}TI and ^{99m}Tc-HMPAO. Am J Neuroradiol. 1991;12:1187–92.
21. Tie J, Gunawardana DH, Rosenthal MA. Differentiation of tumor recurrence from radiation necrosis in high-grade gliomas using ^{201}Tl-SPECT. J Clin Neurosci. 2008;15:1327–34.

22. Xiangsong Z, Weian C, Dianchao Y, Xiaoyan W, Zhifeng C, Xiongchong S. Usefulness of (13)N-NH (3) PET in the evaluation of brain lesions that are hypometabolic on (18)F-FDG PET. J Neuro-Oncol. 2011;105:103–7.
23. Pauleit D, Floeth F, Hamacher K, Riemenschneider MJ, Reifenberger G, Muller HW, et al. O-(2[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. Brain. 2005;128(Pt 3):678–87.
24. Tripathi M, Sharma R, Varshney R, Jaimini A, Jain J, Souza MM, et al. Comparison of F-18 FDG and C-11 methionine PET/CT for the evaluation of recurrent primary brain tumors. Clin Nucl Med. 2012;37:158–63.
25. Piroth MD, Pinkawa M, Holy R, Klotz J, Nussen S, Stoffels G, et al. Prognostic value of early [18F]fluoroethyltyrosine positron emission tomography after radiochemotherapy in glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 2011;80:176–84.
26. Hervey-Jumper SL, Berger MS. Reoperation for recurrent high-grade glioma: a current perspective of the literature. Neurosurgery. 2014;75:491–9. discussion, 498–9
27. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. J Neurosurg. 2012;117:1032–8.
28. Park JK, Hodges T, Arko L, Shen M, Dello Iacono D, McNabb A, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. J Clin Oncol. 2010;28:3838–43.
29. Hickmann AK, Nadj-Ohl M, Hopf NJ. Feasibility of fluorescence-guided resection of recurrent gliomas using five-aminolevulinic acid: retrospective analysis of surgical and neurological outcome in 58 patients. J Neuro-Oncol. 2015;122:151–60.
30. Chang SM, Parney IF, McDermott M, Barker FG 2nd, Schmidt MH, Huang W, et al. Glioma Outcomes Investigators. Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. J Neurosurg. 2003;98:1175–81.
31. Clark AJ, Lamborn KR, Butowski NA, Chang SM, Prados MD, Clarke JL, et al. Neurosurgical management and prognosis of patients with glioblastoma that progresses during bevacizumab treatment. Neurosurgery. 2012;70:361–70.
32. Skeie BS, Enger PO, Brogger J, Ganz JC, Thorsen F, Heggdal JI, et al. γ knife surgery versus reoperation for recurrent glioblastoma multiforme. World Neurosurg. 2012;78:658–69.
33. Stromblad LG, Anderson H, Malmstrom P, Salford LG. Reoperation for malignant astrocytomas: personal experience and a review of the literature. Br J Neurosurg. 1993;7:623–33.
34. Palmer JD, Siglin J, Yamoah K, Dan T, Champ CE, Bar-Ad V, et al. Re-resection for recurrent high-grade glioma in the setting of re-irradiation: more is not always better. J Neuro-Oncol. 2015;124:215–21.
35. RTOG 1205 protocol: randomized phase II trial of concurrent bevacizumab and re-irradiation versus bevacizumab alone as treatment for recurrent glioblastoma. Ann Arbor;1001:48109. https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1205.
36. Dong Y, Fu C, Guan H, Zhang Z, Zhou T, Li B. Re-irradiation alternatives for recurrent high-grade glioma. Oncol Lett. 2016;12:2261–70.
37. Cuneo KC, Vredenburgh JJ, Sampson JH, Reardon DA, Desjardins A, Peters KB, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys. 2012;82:2018–24.
38. Bir SC, Connor DE, Ambekar S, Wilden JA, Nanda A. Factors predictive of improved overall survival following stereotactic radiosurgery for recurrent glioblastoma. Neurosurg Rev. 2015;38:705–13.
39. Larson EW, Peterson HE, Lamoreaux WT, MacKay AR, Fairbanks RK, Call JA, et al. Clinical outcomes following salvage gamma knife radiosurgery for recurrent glioblastoma. World J Clin Oncol. 2014;5:142–8.
40. Martinez-Carrillo M, Tovar-Martin I, Zurita-Herrera M, Del Moral-Avila R, Guerrero-Tejada R, Saura-Rojas E, et al. Salvage radiosurgery for selected patients with recurrent malignant gliomas. Biomed Res Int. 2014;7:1–10.
41. Frischer JM, Marosi C, Woehrer A, Hainfellner JA, Dieckmann KU, Eiter H, et al. Gamma knife radiosurgery in recurrent glioblastoma. Stereotact Funct Neurosurg. 2016;94:265–72.
42. Elaimy AL, Mackay AR, Lamoreaux WT, Demakas JJ, Fairbanks RK, Cooke BS, et al. Clinical outcomes of gamma knife radiosurgery in the salvage treatment of patients with recurrent high-grade glioma. World Neurosurg. 2013;80:872–8.
43. Dodoo E, Huffmann B, Peredo I, Grinaker H, Sinclair G, Machinis T, et al. Increased survival using delayed gamma knife radiosurgery for recurrent high-grade glioma: a feasibility study. World Neurosurg. 2014;82:e623–32.
44. Yazici G, Cengiz M, Ozyigit G, Eren G, Yildiz F, Akyol F, et al. Hypofractionated stereotactic reirradiation for recurrent glioblastoma. J Neuro-Oncol. 2014;120:117–23.
45. Sirin S, Oysul K, Surenkok S, Sager O, Dincoglan F, Dirican B, et al. Linear accelerator-based stereotactic radiosurgery in recurrent glioblastoma: a single center experience. Vojnosanit Pregl. 2011;68:961–6.
46. Combs SE, Gutwein S, Thilmann C, Debus J, Schulz-Ertner D. Reirradiation of recurrent WHO grade III astrocytomas using fractionated stereotactic radiotherapy (FSRT). Strahlenther Onkol. 2005;181:768–73.
47. Ciammella P, Podgornii A, Galeandro M, D'Abbiero N, Pisanello A, Botti A, et al. Hypofractionated stereotactic radiation therapy for recurrent glioblastoma: single institutional experience. Radiat Oncol. 2013;8:222.
48. Patel M, Siddiqui F, Jin JY, Mikkelsen T, Rosenblum M, Movsas B, et al. Salvage reirradiation for recurrent glioblastoma with radiosurgery: radiographic response and improved survival. J Neuro-Oncol. 2009;92:185–91.
49. Maranzano E, Anselmo P, Casale M, Trippa F, Carletti S, Principi M, et al. Treatment of recurrent glioblastoma with stereotactic radiotherapy: long-term results of a mono-institutional trial. Tumori. 2011;97:56–61.
50. Greenspoon JN, Sharieff W, Hirte H, Overholt A, Devillers R, Gunnarsson T, et al. Fractionated stereotactic radiosurgery with concurrent temozolomide chemotherapy for locally recurrent glioblastoma multiforme: a prospective cohort study. Onco Targets Ther. 2014;7:485–90.
51. Fokas E, Wacker U, Gross MW, Henzel M, Encheva E, Engenhart-Cabillic R. Hypofractionated stereotactic reirradiation of recurrent glioblastomas: a beneficial treatment option after high-dose radiotherapy? Strahlenther Onkol. 2009;185:235–40.
52. Gobitti C, Borsatti E, Arcicasa M, Roncadin M, Franchin G, Minatel E, et al. Treatment of recurrent high-grade gliomas with GliaSite brachytherapy: a prospective mono-institutional Italian experience. Tumori. 2011;97:614–9.
53. Chowdhary SA, Ryken T, Newton HB. Survival outcomes and safety of carmustine wafers in the treatment of high-grade gliomas: a meta-analysis. J Neuro-Oncol. 2015;122:367–82.
54. Schijns VE, Pretto C, Devillers L, Pierre D, Hofman FM, Chen TC, et al. First clinical results of a personalized immunotherapeutic vaccine against recurrent, incompletely resected, treatment-resistant glioblastoma multiforme (GBM) tumors, based on combined allo- and auto-immune tumor reactivity. Vaccine. 2015;33:2690–6.
55. Polivka J Jr, Polivka J, Holubec L, Kubikova T, Priban V, Hes O, et al. Advances in experimental targeted therapy and immunotherapy for patients with glioblastoma multiforme. Anticancer Res. 2017;37:21–33.

56. Pollack IF, Jakacki RI, Butterfield LH, Hamilton RL, Panigrahy A, Normolle DP, et al. Antigen-specific immunoreactivity and clinical outcome following vaccination with glioma-associated antigen peptides in children with recurrent high-grade gliomas: results of a pilot study. J Neuro-Oncol. 2016;130:517–27.
57. Archavlis E, Tselis N, Birn G, Ulrich P, Zamboglou N. Combined salvage therapies for recurrent glioblastoma multiforme: evaluation of an interdisciplinary treatment algorithm. J Neuro-Oncol. 2014;119:387–95.
58. Muller K, Henke G, Pietschmann S, van Gool S, De Vleeschouwer S, von Bueren AO, et al. Re-irradiation or re-operation followed by dendritic cell vaccination? Comparison of two different salvage strategies for relapsed high-grade gliomas by means of a new prognostic model. J Neuro-Oncol. 2015;124:325–32.
59. Hasan S, Chen E, Lanciano R, Yang J, Hanlon A, Lamond J, et al. Salvage fractionated stereotactic radiotherapy with or without chemotherapy and immunotherapy for recurrent glioblastoma multiforme: a single institution experience. Front Oncol. 2015;5:106.
60. Park KJ, Kano H, Iyer A, Liu X, Niranjan A, Flickinger JC, et al. Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: a case-control study. J Neuro-Oncol. 2012;107:323–33.
61. Schuessler A, Smith C, Beagley L, Boyle GM, Rehan S, Matthews K, et al. Autologous T-cell therapy for cytomegalovirus as a consolidative treatment for recurrent glioblastoma. Cancer Res. 2014;74:3466–76.
62. Carpentier A, Chauvet D, Reina V, Beccaria K, Leclerq D, Mcnichols RJ, et al. MR-guided laser-induced thermal therapy (LITT) for recurrent glioblastomas. Lasers Surg Med. 2012;44:361–8.
63. Martino J, Taillandier L, Moritz-Gasser S, Gatignol P, Duffau H. Re-operation is a safe and effective therapeutic strategy in recurrent WHO grade II gliomas within eloquent areas. Acta Neurochir. 2009;151:427–36.
64. Uppstrom TJ, Singh R, Hadjigeorgiou GF, Magge R, Ramakrishna R. Repeat surgery for recurrent low-grade gliomas should be standard of care. Clin Neurol Neurosurg. 2016;151:18–23.
65. Nahed BV, Redjal N, Brat DJ, Chi AS, Oh K, Batchelor TT, et al. Management of patients with recurrence of diffuse low grade glioma: a systematic review and evidence-based clinical practice guideline. J Neuro-Oncol. 2015;125:609–30.

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