# Handbook of Medical Neuropsychology

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## Applications of Cognitive Neuroscience

Foreword by Muriel D. Lezak

Springer

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*Carol L. Armstrong*

*This book is dedicated to my mentors, especially Peter Phillips and the Children's Hospital of Philadelphia neuro-oncologists, Muriel Lezak, David Hackney, Robert Lustig, Omar Hijab, and the cognitive neurologists now and once at the University of Pennsylvania, particularly Mark D'Esposito. It is also dedicated to all of the patients who have shown so bravely how injury affects a person's life.*

*Lisa Morrow*

*Having one mentor is a gift, having five is remarkable. Many thanks to my mentors – Francois Boller, Youngjai Kim, Graham Ratcliff, Christopher Ryan, and Steve Slane.*

# Foreword

This handbook celebrates the abundantly productive interaction of neuropsychology and medicine. This interaction can be found in both clinical settings and research laboratories, often between research teams and clinical practitioners. It accounts for the rapidity with which awareness and understanding of the neuropsychological components of many common medical disorders have recently advanced. The introduction of neuropsychology into practice and research involving conditions without obvious neurological components follows older and eminently successful models of integrated care and treatment of the classical brain disorders.

In the last 50 years, with the growing understanding of neurological disorders, neuropsychologists and medical specialists in clinics, at bedside, and in laboratories together have contributed to important clinical and scientific advances in the understanding of the common pathological conditions of the brain: stroke, trauma, epilepsy, certain movement disorders, tumor, toxic conditions (mostly alcohol-related), and degenerative brain diseases. It is not surprising that these seven pathological conditions were the first to receive attention from neuropsychologists as their behavioral symptoms can be both prominent and debilitating, often with serious social and economic consequences.

However, many diseases affect behavior and cognition without directly involving brain substance. Yet only in the last two decades has a scientifically grounded understanding of the neuropsychological implications of such diseases become available as the neuropsychological enterprise broadened its purview from the common brain disorders to clinical care and research with patients whose medical conditions impaired their neuropsychological functioning. Thanks to the relatively recent emphasis on "holistic" medicine, physicians have increasingly become sensitive to the often subtle but functionally important psychological alterations of medical patients without diagnosable brain disease. This has led many to neuropsychology for reliable knowledge about the behavioral ramifications of these patients' disorders. This recent marriage of traditional medicine and neuropsychology has been most fruitful, as attested to in the sections that deal with metabolic and endocrine disorders in particular, but also in chapters concerned with specific vascular and immune-mediated disorders occurring outside the brain.

By including sections on developmental disorders and rehabilitation this handbook effectively covers the full range of conditions with neurocognitive ramifications. It will become apparent to the reader that the interplay of medicine and neuropsychology has made possible the science and skills for today′s best practices in the care of patients with these conditions.

Of the eight sections in this handbook, the first is devoted exclusively to central nervous system disorders: Four of the six diagnostic categories considered in *primary nervous system disease* concern brain conditions in which neuropsychologists have been involved for more than three decades: movement disorders, epilepsy, traumatic brain injury, and neurooncology (e.g., [1–6]). Although these disorders differ greatly in their etiologies, developmental histories, course, and susceptibility to amelioration, what they have in common is the significant role that their neuropsychological symptoms play in determining the conduct and quality of the patient's life. The large body of scientific literature for each of these categories testifies to the value of medical specialists and neuropsychologists working together on patient evaluation and treatment. Much of the research underlying improved care for these conditions comes from this cooperation and cross-fertilization.

A relative newcomer to the categories of neurological disorders with significant behavioral symptom is *autonomic nervous system disorders*. The recency of neuropsychologists' involvement may account for the paucity of neuropsychologically relevant research into this condition. This chapter and others, such as Hydrocephalus, make it evident that understanding subcerebral disorders. Whether psychological interventions may also ease the cognitive and emotional symptoms of these conditions remains to be seen.

The end product of all *cardiovascular diseases* is reduced availability of oxygen. Thus, by their very nature, these diseases breed neuropsychological disorders as a result of insufficient oxygenation of highly oxygen-dependent brain substance. Their neuropsychological symptoms vary, from the sudden, often dramatic, loss of significant abilities due to stroke or the progressive cognitive withering of vascular dementia to the subtle dampening of cognitive acuity that occurs with primary breathing disorders or the intermittent diminution of function accompanying many migraine headaches. The presentation of the broad range of cardiovascular disorders here should give the clinician an increased awareness of the neuropsychological manifestations of vascular disease, especially those all too common respiratory conditions in which subtle but important neuropsychological consequences have been unsuspected or overlooked, such as chronic obstructive pulmonary disease and sleep apnea.

Unlike some of the other conditions discussed in this handbook, neurobehavioral aspects of (the) most *developmental disorders* are too obvious to have been ignored. Thus, for all of these conditions, some references go back 30 or more years; in this handbook one on dyslexia was published in 1891. Decades of study have given these disorders a substantial knowledge base which current studies refine but rarely revise. Treatment options are limited or even nonexistant for many of these lifelong conditions. Still, a full appreciation of their genetic, physiological, and cognitive features should enhance clinicians' abilities to work intelligently and sensitively with the patients and their often overly burdened families.

For example, the review of several well-studied developmental disorders – Down, fragile X, and Williams syndromes – relates specific genetic errors to discrete patterns of cognitive and behavioral dysfunction. Other developmental problems have their origins in a variety of structural anomalies, each impinging on different parts of the developing central nervous system with diverse etiologies and neuropsychological consequences. Like its childhood counterpart, adult-onset hydrocephalus bears many etiologic and structural similarities to the developmental condition but, if untreated,

can evolve into a classical dementia. And then there are the etiologic puzzles presented by the autism – Aspergers range of neurobehavioral disorders which here are considered as neuropathologic phenomena with associated patterns of neurocognitive dysfunction.

The section on *aging* contains, as one might expect, a *Dementia* chapter which reviews not only the most prevalent of dementing diseases but also one of the rarest forms of dementia – the prion diseases. Although the most common prion diseases progress so rapidly as to be of little neuropsychological interest, neurobehavioral symptoms are prominent in a recently identified variant with a longer course.

Since aging and dementia are so often associated in reviews of neurobehavioral disorders, it is a pleasure to find a separate discussion of normal cognitive aging which not only documents the usual deficits that develop in the seventh and eighth decades, but also emphasizes the variability in cognitive functioning within the aging population. The good news is that high-functioning older people contribute to this variability as well as those whose faculties are exceptionally diminished.

The reviews here of multiple sclerosis and the HIV-AIDS complex are expected in a section on *immune-mediated disease*. An appreciation of the impact of multiple sclerosis on patients and families requires an understanding of how the complexity of the most typical symptoms – motor and cognitive deficits, emotional distress and fatigue – can interact to exacerbate the illness experience. Of especial value is a discussion of the importance of family understanding and support for patients' quality of life which, while focussed on the MS patient, speaks for all neuropsychologically impaired patients and their families.

Rheumatic conditions are widespread with prevalence increasing with age, although many young persons are also affected. The inclusion of chapters on rheumatic diseases may be unexpected but is appropriate and necessary, as cognitive symptoms develop along with the well-known crippling effects of these diseases. Cognitive issues are complicated by pain and compromised mobility making these conditions almost ideal models for neuropsychological and medical cooperation in treatment as well as research. Included in the section on *rheumatologic conditions* are two disorders whose diagnostic validity has been subject to much debate: fibromyalgia and chronic fatigue syndrome. Whether or not these are distinctive diagnostic entities, persons diagnosed with these conditions do suffer cognitive dysfunction which can, in some cases, seriously compromise everyday life. The now documented neuropsychological repercussions of the Guillain–Barré syndrome have also been mostly ignored as it has been essentially considered to be a peripheral neuropathy.

The contributions of stress to neurobehavioral disorders become apparent in the review of *endocrine diseases*. The stress experiences – particularly repeated stress – with its responsive endocrine imbalances and the resulting behavioral and cognitive dysfunction are linked in a causal chain which should be of interest to society's leaders as well as neuropsychologists and endocrinologists. The direct cognitive consequences of medically well-studied endocrine disorders, such as diabetes, tend to be relatively subtle and thus less likely to be identified in these patients. That these cognitive disorders can compromise daily functioning and quality of life makes their recognition important for appropriate patient care.

Some *metabolic disorders* give rise to disease-characteristic behavioral anomalies that, as yet, have not been explained. One interesting example is visuoperceptual disturbances in hepatic disease which, on appropriate examination, show up as gross drawing distortions. On the other hand, some specific patterns of cognitive

dysfunction associated with different toxic sources do have scientifically grounded explanations. Moreover, as in the case of the affinity of organic solvents for fatty tissue or the affinity of carbon monoxide for hemoglobin, these relationships have added to the understanding of brain physiology, tissue vulnerability, and neurobehavioral outcomes. The more or less specific and more or less severe motor abnormalities of mitochondrial disorders have tended to overshadow the associated cognitive disturbances which are – at last – considered here.

Among the latest advances in *rehabilitation* are technological marvels which may substitute for replace, augment, or retrain the impaired functional system. These nontraditional additions or alternatives to more orthodox rehabilitation procedures may open the way for radical rethinking of how to overcome the behavioral impairments due to brain damage.

The inclusion, in many chapters, of assessment recommendations by authors who have had intensive experience in their area of expertise will be appreciated by both newcomers to neuropsychology and older hands confronting patients with unfamiliar conditions. Knowledge of treatment possibilities and procedures – both medical and psychological – is important for neuropsychologists' understanding of and clinical response to these conditions; thus treatment is considered, often extensively, throughout this handbook. Not least of the many values to be found between these covers are the very current reference lists, most containing over 100 references, several more than 200 making this handbook a treasure trove of knowledge for the active seeker.

Despite the rapidity with which new neuropsychological information becomes available, this handbook will remain relevant for some time as its contents are both current and comprehensive. It will serve clinicians and researchers alike as a ready resource for both the facts and the important references for just about all the brain and nonbrain disorders, conditions, and diseases that can affect cognition.

Portland, Oregon Muriel D. Lezak

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# Preface

The burgeoning of molecular and genetic studies of neurological and developmental disorders has contributed to the continuing relevance of neuropsychological studies of medical disorders. Neuropsychologists who follow science have updated and expanded the tools of our field to increase understanding of the functional consequences of disease, disease progression, and treatments. Equally important are the theoretical models of neurocognition that have been developed and refined in conjunction with functional imaging and other tissue or neurotransmitter-specific neuroimaging techniques. Contributing to clinical neuroscience, neuropsychiatry, and developmental neuroscience requires a sophisticated understanding of the medical and biological elements and future directions in which progress is being made in order to remain relevant. The purpose of this book is to provide a current and cutting edge understanding of the various diseases and disorders covered within and their neuropsychological effects. The authors are academic clinicians and researchers who bring insight and carefully constructed explanations about their respective fields of research. The neuropsychological findings of the diseases and disorders that comprise this book are given in the context of the disease mechanisms. Rather than taking the route of quick summarization, the chapters are meant to be intently studied, as they are dense with information. These chapters should remain useful for a long time.

*Handbook of Medical Neuropsychology: Applications of Cognitive Neuroscience* aims to provide understanding of some topics that neuropsychologists confront frequently, such as cerebrovascular disease, dementia, learning disability, normal aging, and traumatic brain injury. These chapters provide incisive reviews of the state of the science, reveal the controversies in diagnosis, and give the current opinions about the most critical factors that characterize these diseases and variations of "normal" brain states (autism, cerebral palsy, and genetic disorders could also be characterized this way). All of the chapters will make the reader who immerses him/herself in the material ready to design a study or understand a clinical evaluation, by helping the reader to be oriented to the key issues, areas that lack clarity, and future directions.

Other diseases covered in this book are confronted less frequently, but are the focus of intense investigation, such as autism, cardiovascular disease, endocrine disease (diabetes), epilepsy, and HIV-AIDS. These chapters are particularly rewarding because of the wealth of information contained in them and the insights that the authors have given us. Those who wish to participate in the cognitive neuroscience of these fields through grant-funded research will find these chapters very valuable. Clinicians will be better able to understand the purposes of treatments and the neuropsychological behaviors of their patients.

Some diseases are included because they are actually relatively common, yet their neuropsychological symptoms and mechanisms are not often examined closely, such as various autoimmune diseases and endocrine disorders, hydrocephalus, migraine, neuro-oncologic disorders, stress disorders, stress/post-traumatic stress disorder, and toxic disorders/encephalopathy. These chapters are reviews that are broadly encompassing yet also focused on the inconsistencies and generalizations that are possible, based on the state of the science.

Today, neuropsychologists must integrate knowledge about neurodevelopmental disorders into their work, whether their focus is adults or children. We are fortunate to have such knowledgeable and elegant chapters about cerebral palsy, pediatric frontal lobe disorders, learning disability, and the language impairments of genetic disorders. These chapters are elucidating and will give the reader new insights.

There are also the chapters on classic, and in some cases not well known, medical diseases that have direct effects on brain functions: autonomic nervous system disorders, hepatic encephalopathy, movement disorders, respiratory disorders, and rheumatologic conditions. Again, these chapters remain true to analyzing their fields through the mechanisms of the disease and how these mechanisms encompass cognitive dysfunction.

There is one other subject of great interest that is still emerging and that is neuropsychologically understudied: mitochondrial disorders. I am grateful to the author, Kevin Antshel, who has taken the proverbial bull by the horns and given us knowledge about the biomedical tools we need to approach the neuropsychological investigation of these diseases.

Last, but most certainly not least, is rehabilitation. This book views this field from two perspectives. One gives the conceptual underpinnings of cognitive rehabilitation as it is carried out in the best brain injury cognitive rehabilitation centers extant. The other approach is the integration of neural brain mechanisms with human perception, to alter the way humans control their movements and balance. The chapter entitled *Sensory Reweighting: A Rehabilitative Mechanism* is included to inspire our present and future generations of neuropsychologists to use neuroscience technologies that integrate sensory information to modify behavior.

Another intent for this book is to provide critiques of the neuropsychological tests that are useful in tracking these diseases. The authors have striven not only to indicate what the tests have shown but also to show that recent research demonstrates that the most informative measures are those with high specificity even in relatively diffuse diseases. The goal was to point to the tests of cognition that are most informative regarding a disease process or disorder.

Finally, we will leave the reader with the insight of a scientist of the past, to remind us that we all can see most clearly if we stand on the shoulders of those who came before us. Neils Bohr, a physicist of the twentieth century whose work was critical for the development of quantum theory, said that the opposite of a truth is a falsity, but the opposite of a deep truth is often another deep truth.

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# Part I
# Primary Nervous System Disease

# Chapter 1

# Epilepsy and Cognitive Plasticity

Joseph I. Tracy, Cynthia Lippincott-Stamos, Karol Osipowicz, and Allison Berman

## Introduction: Why Study Cognition in Epilepsy?

Epilepsy provided neuropsychology with the canonical cases of amnesia and episodic memory disorders. These cases strongly encouraged the development of modular conceptions of memory. As neuropsychology moves to develop non-modular, network approaches to cognition, it is ironic that epilepsy can be seen as providing clear, illustrative examples of a network disturbance in cognition. The key to understanding this shift in thinking is to grasp that the neural mechanism underlying network development (i.e., neuroplasticity) and the neuropathology of seizures are separated by little. Many of the neural mechanisms of learning are key factors in the regulation of seizures, and the highly plastic regions specialized for learning and memory are also prone to seizures. More than characterizing the effects of seizures, and determining the risks and outcomes of brain surgery, there are fundamental cognitive neuroscience reasons for the neuropsychologist to study epilepsy. Neuropsychology traditionally focuses on the clinical symptoms of cognitive disruption caused by epilepsy, but the neuroplastic mechanisms underlying the disorder are important in showing why the cognitive effects of epilepsy are so varied. This chapter will review the biological mechanisms for both epileptogenesis and neural plastic recovery from seizures. It will then review the range of neurocognitive impairments that are associated with epilepsy and associate these with the dynamic changes in neural networks. The epileptogenic factors that affect the development of cognitive impairment are examined because of their importance in understanding how difficult it is to predict cognitive function and dysfunction in epilepsy. The role of neuropsychologists in diagnosis and treatment of epilepsy is explained. An understanding of these new developments in the field of epilepsy will better prepare the neuropsychologist who intends to focus in this area for working with the team of specialists required to diagnose and treat these patients.

Mesial temporal lobe epilepsy (MTLE) is the prototypical epilepsy which has been written about extensively and is well characterized, particularly in terms of episodic memory dysfunction. In this chapter, I will cover some of the lesser known cognitive characteristics of this and other types of epilepsy. The process of developing epileptic foci in the brain (referred to as epileptogenesis), seizure spread, and the development of new epileptogenic foci bring issues of neuroplasticity to forefront for the neuropsychologist. Neuroplasticity and cognitive reorganization complicate neuropsychological assessment as they challenge our normative presumptions about brain/behavior relationships. However, these processes also inform us about the cognitive impact of neural network development and changes that can occur in standard brain/behavior relationships. The responsibilities of a neuropsychologist working in a surgical epilepsy center have evolved with the advent of new imaging technologies. I will discuss this changing role of the neuropsychologist, the new presurgical algorithm

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for epilepsy, and the benefits of combined use of the various imaging techniques.

## Biological Bases for Epilepsy

Epileptogenesis is one model of neural network development. The International League Against Epilepsy (ILAE) defines an epileptic seizure as a "... transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [1]. Epileptogenesis, the process that generates the pathological state, can begin with a single neuron. A seizing neuron recruits adjacent neurons into a hyper-synchronous process, until a critical mass of tissue is acting as a single active unit whose components no longer respond to existing functional network connections. Aberrant though it may be, this process provides some important clues as to how complex brain networks are formed. The development of neural networks, through the classical Hebbian learning mechanisms of long-term potentiation (LTP) and long-term depression (LDP) involving the up- or downregulation, respectively, of communication between two neurons, bears a striking resemblance to the process of epileptogenesis. LTP and LDP are the main plastic processes of learning and remembering, and the temporal lobe contains the most plastic parts of the brain. This plasticity makes the temporal lobe extremely vulnerable to epileptogenesis, which is why pathology of medial temporal lobe (MTL) is so common. The anatomical features of some parts of the MTL also encourage aberrant connectivity; the laminar organization of the hippocampus provides a good architecture for memory but is also conducive to the spread of extracellular currents and hypersynchrony that characterize seizures.

Epilepsy is also connected to cell loss, neurogenesis, and gliosis. Mesial temporal sclerosis (MTS), for example, a common pathology for temporal lobe epilepsy, is characterized by atrophy and possible hardening of the cortex due to reactive gliosis. It also involves aberrant sprouting of glutamatergic axons in the dentate gyrus of the hippocampus and changes in the expression of glutamatergic neurons, the major excitatory neurotransmitter in the brain. Because of these anatomical changes MTLE is often refractory to the chemical alterations offered by medication.

Cellular attributes that promote plasticity, such as neutrophins (cellular growth factors) and factors that affect chemical transmission through the cell membrane, are the focus of intense investigation in epilepsy and the target of drug development. The main neurotransmitters involved in seizures such as GABA and NMDA are crucial to the capacity to learn. NMDA receptor density is high in regions prone to seizures such as the CA 1 and CA 3 regions of the hippocampus. To some degree, NMDA receptor density predicts both the probability of Hebbian learning and epileptogenicity [2]. Thus, the factors that upregulate plasticity also appear to set the stage for seizures.

In summary the process of epileptogenesis and seizure generalization lays down new neural communication networks. These consist of favored pathways that are distinct from developmentally formed neural networks. They can disrupt existing networks by co-opting neurons from them and cutting off connections between distant networks and, in this way, affect the neural communication required for normal cognitive processes and responses. In this manner, the effects of epilepsy are not necessarily limited to the area in and around the seizure focus. These processes help explain the broad and complex scope of the epilepsy–cognition interaction.

## General Cognitive Characteristics of Epilepsy

The cognitive profiles of various epilepsy syndromes are difficult to define. The impact of epilepsy changes over time due to the accumulative brain effects of recurrent seizure activity. The etiology, number and location of epileptogenic foci, and the spread pattern of seizures will vary across individuals and strongly influence the pattern of cognitive deficits observed in any given patient. Seizures are the final common pathway of a whole host of pathophysiologic processes: viral, fungal, parasitic, metabolic disturbance, ingestion or toxic agent, brain lesion, tumor, congenital defects, cerebral trauma, vascular, alcohol. Each will impose a unique pathophysiology. In addition, pre-existing medical factors and individual differences in skill and intelligence, the amount of cognitive reserve available, all contribute to the diverse neurocognitive

presentation of individuals with epilepsy. Nevertheless, the clinical characteristics of seizures do impart clues about the nature and extent of cognitive deficits. Also, common cognitive patterns emerge from the proclivity of seizures for regions such as the hippocampus and the likely reach of propagation patterns and secondary epileptogenesis.

The location of seizure activity and measurable cognitive deficits will not have a one-to-one correspondence. Often the brain areas recruited by the seizure show worse deficits than the area generating the seizure itself (referred to as the epileptogenic zone). Thus, neuropsychological deficits can greatly mislead about the location of the seizure focus. For instance, outside the epileptogenic zone, areas showing extensive spread with prolonged post-ictal slowing on EEG often display the most pronounced cognitive difficulties [3]. Yet, absence or brief partial onset seizures often show few long-term cognitive effects [4]. With so many regions of the brain connected to the thalamus, it is an ideal structure to generalize and spread a signaling pathology throughout the brain. Yet, standard neuropsychological tests cannot isolate and pinpoint the thalamus as a source of deficit. Generalized seizures tend to produce a wider set of deficits than partial, more focal seizures because of the wider seizure burden, with such individuals often expressing a very low IQ.

The structural lesion and the epileptogenic zone do not refer to the same region, as not all the diseased tissues will likely generate seizures. The symptomatic zone refers to the neurons responsible for clinically observable ictal behaviors and symptoms and comprises a region of gray matter that often extends well beyond the epileptogenic zone. Interestingly, the initial brain insult or pathology that might produce a seizure is often followed by a latency phase of epileptogenesis which can take many years before a threshold is passed and the seizures become observable. Even at that point there may not be demonstrable deficits on neuropsychological testing. This latency phase makes isolation of the cause of the seizures difficult. Once regular seizures begin, the disease can progress even during the subclinical, non-symptomatic interictal state (the period between the acute ictal events). Very little is known about the potentially unique cognitive impact of this interictal period. In animal models, chronic, uncontrolled seizures eventually do produce global deterioration. This is most likely related to excess glutamatergic excitation, a process known as excitotoxicity [5].

The classic cases of amnesia (e.g., HM) were epilepsy patients, helping to establish the hippocampus as a key structure in the consolidation of episodic/declarative memory. While declarative memory deficits in temporal lobe epilepsy are well known and characterized, the preservation of non-declarative memory in these patients has been important in showing that a variety of important memory systems are likely non-hippocampal in their underlying neuroanatomy. For instance, data from my laboratory [6] showed that patients without a hippocampus and surrounding structures (dominant anterior temporal lobectomy patients) produce a clear dissociation between impaired explicit, declarative memory and intact implicit memory. Thus, implicit memory must be reliant on structures outside the hippocampus. Squires and others have shown that these patients also maintain a variety of other non-declarative memory procedures such as procedural or skill-related learning, conditioning, and priming [7, 8].

## Chronicity of Seizures

Still other factors that are important to understanding the neuropsychological status of epilepsy patients include the age at onset of the seizures and the duration of uncontrolled "active epilepsy." Early age seizures put individuals at risk for the effects of chronicity, yet also potentially permit cognitive reorganization, particularly if the seizures start before a critical period (around age 6). The young brain appears more prone to hyperexcitability [9], which is perhaps related to inadequate pruning of neurons. But the immature central nervous system also exhibits greater plasticity potential than the adult, and the best substantiated cases of cognitive reorganization involve individuals with early onset epilepsy [10].

In terms of the effects of chronicity, there is no exact number of seizures required before the cognitive effect of seizures becomes evident, as the impact of frequency and duration can vary widely across individuals. However, long duration events such as status epilepticus (SE) and more frequent seizures are clearly more likely to take a cognitive toll. Interestingly,

animal models have shown that even brief, non-chronic seizures can reduce LTP [11] or cause impairment in spatial and emotional memory in animals [12]. Overall, the duration of active epilepsy is actually a better predictor of the severity of cognitive deficits than type or location of the seizures [13]. Since seizures represent disruption of normal brain activity, chronic seizures will cause more disruptions. Seizure-induced seizure chronicity has been suspected for a long time, but only in recent years have there been any clinical findings in humans to support this. Each seizure seems to increase the likelihood of more seizures [14], leading to a rapid increase in cognitive deficits once a critical threshold of seizure frequency is reached.

## Seizures Initiate Neuroplasticity

The specific ramifications of epileptic activity in the brain include (1) cellular changes (i.e., expression of cellular proteins), (2) injury to cortical pyramidal neurons making membrane ion channels more amenable to excitatory input, (3) axonal sprouting within pyramidal cells that enhance excitatory connections, (4) hyper-innervation, (5) failure to prune immature connections, and (6) changes in glial cells [15] and in the organization of axons and dendrites [16]. All constitute mechanisms of neuroplasticity at different levels of organization. They can cause collateral and terminal axonal bud and dendritic spike sprouting and shifts in sensory receptive fields at the individual neuron level. This may enable unmasking of previously ineffective synapses due to retrieval of vacated synapses by healthy axons after release from inhibition or seizure cessation. These represent alterations in the structure of surviving synapses at the synaptic level and reorganization of surviving neural networks at the network level [17]. For example, Ben-Ari et al. found that newly formed synapses generated by an epileptic seizure had aberrant kainate sensitivity, leaving them more likely to be overstimulated in the future [14]. Both newly formed synapses and the timing of action potentials can disrupt cognition by interrupting normally induced synapse communication. Each level affects the one above it so that changes in individual neurons increase the probability of changes at a cognitive level.

We know neural firing alters the patterning of synaptic connections, but the long-term effects of seizures are not well understood. One means of verifying reorganization is to quantify mossy fiber sprouting within the hippocampus and the new synaptic connections that are formed as a result. Many studies evaluating patients with mesial temporal sclerosis and refractory temporal lobe epilepsy have reported evidence of mossy fiber sprouting in the dentate gyrus. Based on studies with rats, mossy fiber reorganization has been hypothesized to restore inhibition of neural activity after kainate-induced status epilepticus [18].

Kindling is known to arise from post-synaptic brain stimulation on the order of tenths of seconds to seconds in length. This makes it likely that even short duration seizure events cause alterations in synaptic networks of the dentate gyrus of the hippocampus for instance [19]. Synapses along the dendritic spines were once thought to be relatively stable, but recent imaging experiments have shown that synapse turnover can actually occur on a timescale of minutes, particularly in response to deprivation or enrichment [20].

Other evidence of epilepsy-driven neural plasticity comes from Koh who showed that environmental enrichment over 7–10 days following induced seizures can improve cognitive activity such as exploratory behavior in rats [21]. Early life neural repair may deplete neural progenitor cells as these have a finite number of divisions in their lifetime. Kolb et al. found that when rats suffered early brain damage, hippocampal neurogenesis at adulthood was far below that of controls [22].

It must also be said that seizures can reduce neuroplasticity by several processes. For instance, seizures can diminish production of neuromodulatory agents that promote neural growth [23]. Anticonvulsant medication may also hinder development of healthy connectivity [24].The forces increasing neuroplasticity seem to exceed those that work to reduce it. Factors such as age, cognitive reserve, and the duration and type of seizures (generalizing versus not) may affect the balance. To transition from the cellular explanation of increased sprouting and loss of inhibition to a cognitive level, we must first see that the end state of this epilepsy-induced neuroplasticity is to alter the established patterns of communication in the brain. This has a direct impact on the construction and deconstruction of cognitive networks.

## Cognitive Deficits Outside the Epileptogenic Zone and the Development of Neural Networks

Declarative memory deficits associated with temporal lobe epilepsy are not the only deficits associated with the syndrome nor even the deficit most commonly reported by patients. Problems with naming and word retrieval are more commonly reported [25]. When localized epileptogenic tissue is malfunctioning it can adversely affect remote cerebral structures, resulting in additional cognitive deficits. There is a growing body of evidence that brain abnormalities in MTLE, even in well-defined cases of unilateral MTLE, are not limited to the epileptogenic region but extend into widespread areas of extrahippocampal and extratemporal regions [26]. Several studies have documented that cognitive dysfunction in MTLE can extend to other cognitive domains, including language and executive functions, that are not ordinarily considered to be affected by strictly mesial temporal lobe pathology [27–32].

There are several mechanisms that offer explanations for the extratemporal deficits, such as undiagnosed seizure activity elsewhere in the brain, or diffuse metabolic pathophysiology set off by seizures such as changes NAA/choline ratios [33]. These processes can potentially result in cognitive deficits in areas outside the known epileptogenic focus. However, several other processes are of particular interest because of their impact on remote neural activity and the cognitive skills they implement. These include diaschisis, seizure propagation, and secondary epileptogenesis.

### *Diaschisis and Inhibition*

The concept of diaschisis, a disorder of connectivity first theorized in the early twentieth century, purports that damage to one part of the nervous system can have distant brain effects due to loss of input from the damaged area [34]. Diaschisis refers to transcallosal suppression and decreased oxygen metabolism between functionally connected sites where loss of input results in suppression of functional activity at the output site. Note, because the disconnection may result in the loss of inhibitory input to a region, diaschisis may actually result in disinhibition and an increase in the functional output of a given region. The effects of diaschisis were thought to occur following acute or sudden onset injury, but it is clear they can emerge from more chronic processes such as the development of seizure networks. For instance, temporal lobe hypometabolism is a common symptom of TLE. Hermann et al. suggested that executive impairment in TLE patients could result from the "spread of temporal lobe hypometabolism to the thalamus secondarily affecting the frontal lobe," or possibly the "direct spread of temporal lobe hypometabolism to the frontal lobe" [35]. This observation suggests that reduction in frontal lobe function is caused by diaschisis and the loss of temporal lobe or thalamic inputs. This is supported by the fact that performance does not decline following resection of epileptogenic lesions, but rather often results in improvement ("normalization") of cognitive functions ipsilateral and contralateral to the damaged area. Frontal lobe function will be restored when surgery allows normal recovery mechanisms to act without interference from the epileptic network, and the disruptive effect of the lesioned tissue is removed. In our own work with the intracarotid amobarbital procedure (IAP) we have observed dysfunction in the unaffected hemisphere, and transient diaschisis from the amytal appears a tenable explanation. There is some evidence of this in studies using single photon emission computed tomography (SPECT) during the Wada exam [36, 37]. Such findings, however, do not fully address the issue of extratemporal deficits in TLE and their potential normalization post surgery.

### *Seizure Propagation*

A simpler and more parsimonious explanation of extratemporal and other remote deficits outside the epileptogenic zone involves seizure propagation or generalization. The direction and extent of propagation can vary not just within individuals but each seizure can be different. In many respects, grasping the cognitive impact of seizure propagation is the Holy Grail of deficit localization in epilepsy. Propagation of ictal discharges to distal brain regions is accomplished through a number of neural pathways that connect one region of the brain to another. Propagation may take advantage of breakdowns in inhibition activity, allowing the seizure to spread. There is an abundance of association fibers within each hemisphere,

as well as commissural fibers between hemispheres that are available as pathways for propagation [38]. Seizure spread is not random, but follows preferred propagation pathways which correspond to the neuroanatomical connections between both gray matter and white matter brain regions [39]. Invasive EEG procedures have demonstrated preferential spread of ictal activity from the mesial temporal lobe to the ipsilateral frontal region, and preferential propagation of interictal spikes from mesial temporal to contralateral mesial and orbitofrontal regions [30].

The mode of transhemispheric propagation is not entirely clear; it might be transcallosal after the ipsilateral frontal lobe is "ictally" activated [39] or after contralateral inhibition breaks down. The hippocampal commissure has also been implicated in interhemispheric propagation [40] and the thalamus seems a crucial structure governing propagation. Mesial structures tend to be propagated earlier than lateral structures [40]. Propagation impairs the functioning of both independent skills (those implemented without communicating with the original epileptogenic region) and dependent functions (cognitive skills that rely on the epileptogenic region for effectively carrying out an activity). In other words, seizure propagation and its enduring, residual effects can stop normal adaptive communication between regions in an otherwise functioning cognitive network.

The electrical burden of seizures is more than just propagation or the spread of excitation. The recruitment of inhibition may be just as important a factor in terms of understanding the cognitive effects of seizures. Non-epileptic brain areas surrounding the epileptic focus are often producing tonically high levels of inhibitory activity [41] in an effort to contain and control the seizure. The unique neural and cognitive burden imposed by this form of "natural" seizure control is quite unknown. Inhibition, because it can be a tonic neural activity as well as a phasic one (responding to individual acute seizures), may contribute significantly to neuronal dysfunction.

### *Secondary Epileptogenesis*

The natural history of epilepsy is progressive, and repeated seizures may promote creation of additional seizure foci, a process known as secondary epileptogenesis [42]. Secondary epileptogenesis occurs when a region, separated from the primary epileptogenic area by at least one synapse, shows signs of seizure creation [43]. Epileptogenesis evolves following plasticity responses in cortex remote from the primary seizure site. It most likely occurs due to kindling, a phenomenon characterized by repeated, brief low-frequency electrical stimulation of brain structures that produce spontaneous epileptiform activity after weeks to months [44]. Pathways in the limbic system and temporal lobes are particularly susceptible to kindling. The theory of kindling, originally described by Goddard, has been extensively studied for over 30 years in animals but has not been directly demonstrated in humans and therefore remains controversial [42, 44, 45]. Epileptogenesis potentiates remote cells for seizure activity, through initially these cells depend on the origin for their firing. These cells become more and more independent over time (e.g., referred to as a mirror focus when the cells are precisely contralateral). Thus, primary seizure activity in the brain initiates a whole host of neuroplastic responses, and through propagation or secondary epileptogenesis potentially forms new neural circuits.

## Seizures as an Example of Maladaptive Plasticity

The adaptation responses that occur in a normal brain may be different than those that emerge from a pathologic brain. Neural plasticity as it emerges from either propagation or secondary epileptogenesis is not always adaptive nor constrained to make neuropsychological sense. For instance, when the cells of the primary focus fire, activation will be potentiated throughout the connected seizure network. The repetition of this epileptiform activity through processes similar to kindling builds up a set of biased, favored pathways in neural communication. Cells downstream will respond to the excitation of seizures as if learning occurred. In this sense, secondary epileptogenesis can be seen to involve processes very similar to LTP [46, 47]. It is possible that these pathologic connections are at work not just during clinically observable seizure activity but also during cognitive stimulation of the brain region that includes the primary epileptogenic site. Thus, plasticity responses in the epileptic brain serve as the

substrate for cognitive activity. In this way, seizures produce a dysfunctional, maladaptive cognitive network by linking brain areas randomly through propagation and secondary epileptogenesis, rather through normal adaptive learning and experience-driven plasticity and connectivity.

## Cognitive Reorganization from Epilepsy

The adult human brain is an adaptive structure and is not fixed in its representation or organization of functional skills. Predicting patterns of neuroplasticity in response to injury is difficult because the principles that govern cortical reorganization of function are unclear. For instance, we do not know the contextual characteristics of the brain that determine which regions might take up full implementation of a skill that is diminished by injury. Nor do we know if the loss of integrity in one region can compel reorganization of a skill whose primary network does not normally include the lost region.

Epilepsy has provided not just the canonical cases of anterograde amnesia and memory disorders but also some of the clearest cases of hemispheric reorganization. Epilepsy patients have much high rates of altered language lateralization (24% versus 6% for normals [10]), with much of the evidence emerging from studies using the intracarotid amobarbital procedure (IAP). Hemispheric dominance for language is thought to be established by age 6, and the onset of dominant temporal lobe seizures prior to that age leads to a more widespread or atypical distribution of language skills, particularly for naming and reading [8, 10, 48, 49]. Factors such as the temporal pattern of the brain insult (slow versus rapid) change the likelihood of both reorganization and the restoration of function, with "slow growing" pathologies increasing the probability and efficiency of reorganization processes [50] particularly in regions more remote from the "at-risk" skill or function.

Language is not a monolithic function and it is not likely all language skills reorganize together. Most IAP-based research studies on language dominance have used a global index of language to determine laterality and have not provided detailed information on the integrity and lateralization of specific language skills such as reading, naming, speech, comprehension, and repetition. In the imaging and neuropsychology literature it is common to presume that language is represented in a monolithic fashion in the brain, with all skills bearing the same degree and pattern of laterality across the hemispheres. We tested this assumption during IAP utilizing five separate language skills: naming, comprehension, repetition, reading, and speech. The rates of atypical representation ranged from 25.8% for reading to 14.5% of the sample for speech [51]. A majority of patients (60%) showing atypical language representation did so on more than one skill. While multiple atypicalities were common, the proportion of patients showing atypical representation on all five skills was strikingly low (5.6% of the total sample). The data suggested that language systems are not independent and do not shift and reorganize in isolation, though no two language skills were coupled and more likely to reorganize than others. The data further suggest that the pressures compelling atypical representation do not affect all language skills equally. We are currently in the process of determining the lateralization patterns and concordance among three types of material-specific memory in order to gain a finer-grained knowledge of which skills are more likely to reorganize in response to intractable seizures.

There are many examples in the literature of cognitive reorganization compelled by epilepsy. Shimizu and colleagues studied hemispherectomized epilepsy patients using transcranial magnetic stimulation and demonstrated that motor cortical excitability of the unaffected hemisphere evoked motor responses not just in the contralateral but also in the ipsilateral muscles [52]. Bittar and colleagues studied hemispherectomized epilepsy patients and found that residual somatosensory function in the hand opposite the lesioned hemisphere was associated with FMRI activity in the secondary somatosensory area of the intact hemisphere [53]. Jokeit and colleagues used the intracarotid amobarbital procedure to show that the right hemisphere mediated memory in adults with left temporal lobe epilepsy in the setting of childhood seizure onset, however, this was not the case in those with adult onset seizures [54]. Thivard and colleagues conducted an FMRI study of left and right temporal lobectomy patients and found that right-sided patients showed responses to language tasks similar to normals but that the left temporal lobectomy patients had a different pattern implicating right hemisphere involvement, i.e., reorganization, of language skills [55].

The ability to predict which patients and what cognitive skills might reorganize following surgery would be a great asset in determining the neurocognitive risk of surgery. We have observed that the integrity of the dominant hippocampus plays a role in determining if language skills will reorganize to the contralateral hemisphere. Using FMRI to examine verbal fluency (verb generation) prior to and after dominant temporal lobectomy, regions in the contralateral, non-dominant hemisphere were recruited. These were standard "en bloc" temporal lobe resections. Results suggested that a reorganization of the cognitive network had occurred, potentially reflecting incorporation of contralateral processing regions into the network providing executive control functions or supplying cognitive reserve [56].

One intriguing possibility is that the hippocampus determines whether reorganization of language is intrahemispheric or interhemispheric. Dominant hippocampal resection necessitates interhemispheric reorganization as the original functional network connecting through the hippocampus is destroyed when the neurons are removed. The remaining hemisphere still has hippocampal neurons which can be reorganized. Along those lines, mesial temporal sclerosis, a common cause of early onset epilepsy, is correlated with a higher incidence of interhemispheric reorganization for receptive language than are focal lesions in the primary language areas alone. In contrast, patients with lesions in language areas alone generally had an intrahemispheric shift, where the processing for those critical language skills was maintained in the same hemisphere in regions adjacent to the lesion [57]. It may be that individuals with a more damaged dominant hemisphere hippocampus are more prone to language reorganization and, if so, it may be more likely that these patients will evolve right hemisphere representation of language.

(1) Focal lesions are more constrained in effect than focal epilepsy and (2) ipsilateral regions are generally capable of taking on the function of the damaged region but we are illustrating why the mirror region is also likely to reorganize; the mirror region is more likely to be involved when a central processing area like the hippocampus is affected so that reorganization will occur on the side with the more intact central processing. The nature of this effect is unclear but it may reflect the dependence of language processors in the brain on the parsing, binding, and re-analyzing capabilities of medial temporal structures in order to understand or produce complex speech. The fact that reorganization is fairly common in temporal lobe epilepsy suggests there may be a dynamic force to reorganize. That is, an inherent drive is to seek out the input and computations typically provided by ipsilateral medial temporal structures in order to make sure such skills are available. More studies need to be undertaken to understand the role of medial structures in language processing networks so that care can be taken to spare these structures during temporal lobe resections whenever possible.

## The Role of Neuropsychology in Epilepsy

Neuropsychology plays a limited role in epilepsy diagnosis. The clinical signs of seizures are typically strong, so early detection is common, and no neuropsychological markers of early seizure activity have been found. Neuropsychological deficits tend to come after a period of chronicity, although that period has not been specified. Neuropsychology does play a strong role in characterizing the chronic impact of seizures, determining the cognitive and behavioral effects from treatment (e.g., surgery, medication), and differentially diagnosing true versus psychogenic seizures.

Neuropsychology serves several purposes in the care of epilepsy patients. An important feature of neuropsychological data is that it brings corroborating information regarding the location of dysfunction (i.e., the possible seizure generators), particularly when a lesion is not observable on MRI. Thus, it can often lateralize and make broad neuroanatomical distinctions, but can rarely specifically localize dysfunction. For instance, certain patterns on memory testing can provide clues as to the likely location of the primary epileptogenic pathology. The medial temporal lobe system is preferentially involved in fast and time-limited consolidation processes of memory contents. A medial temporal pattern of dysfunction would show a rapid rate of forgetting. A more dorsolateral frontal–temporal pattern would involve data showing breakdown in the learning and acquisition phase of memory, also working memory. A more lateral neocortical temporal pattern would likely be associated with greater semantic knowledge deficits, and more anterior temporal and inferior frontal dysfunction would more likely

relate to problems in word retrieval and verbal fluency. These distinctions are useful, but are also too simple. For instance, there is increasing evidence that medial temporal structures are involved in retrieval processes, not just the consolidation step in episodic memory [8].

Dichotomies of dysfunction are often present in epilepsy related to the geographical dynamics of neural recruitment into the pattern of hypersynchrony. One should always try to distinguish between anterior/posterior, dominant/non-dominant, left/right, and in the case of temporal lobe epilepsies, between medial versus neocortical deficits. A pathology affecting the left temporal lobe will more likely create a predominantly left hemisphere picture of deficits, but not solely so. Similarly, frontal lobe seizures will most likely disrupt frontal functions (e.g., motor skill) before affecting other functions. These distinctions will also affect understanding of the potential for reorganization and compensation of deficits. Some aspects of language functioning may have less redundancy and be less readily compensated for perhaps because they involve dedicated modules in the left hemisphere (e.g., inflectional morphology, parsing linguistic representations, syntactic comprehension such as odd word order), whereas other language functions (retrieval of whole words) may be more susceptible to reorganization because they invoke a broader network of cognitive components.

Early neuropsychological characterization of deficits can lead to early intervention (e.g., make clear the pressing need for surgery or lead to educational interventions and accommodations). Neuropsychological testing can help determine the risk for debilitating functional impairments post-surgery and identify "at-risk" skills. This supports a more accurate and specific informed consent process prior to surgery. For instance, neuropsychological assessment can gauge the level of memory, language, motor, or executive function skill and provide a rough estimate of the likelihood of lost function should surgery resect the eloquent tissue subserving these functions. Post-surgical neuropsychological assessments can be used to quantify and verify functional outcome both cognitive and emotional/psychiatric. Additional roles for neuropsychology reside in its ability to verify iatrogenic medication side effects. Lastly, neuropsychology is instrumental to setting expectations that guide vocational and life planning.

What are the predictors of a good cognitive outcome post-surgery? Shorter duration of seizures, focality/unilaterality of lesions, non-dominant hemisphere surgery, relatively preserved integrity of the contralateral brain tissue which provides cognitive reserve, earlier age of onset, strength of premorbid general neuropsychological skills, and integrity of specific "at-risk" cognitive functions housed near surgical target (high skill more to lose, less skill less to lose) are some of the factors associated with good outcome [36, 58]. A larger resection is also associated with greater impairment. Patients with bilateral temporal lobe damage are at greater risk than those with unilateral damage for postoperative memory impairment if memory skills are still present. Non-verbal memory measures (and other non-dominant cognitive skills) show less consistent change following non-dominant ATL, suggesting that these skills are less sensitive to non-dominant temporal lobe changes than verbal memory is to dominant temporal lobe changes. Neuropsychology with functional neuroimaging can help identify individuals who have undergone cerebral reorganization of cognitive skills as a result of early brain insult such as malformations, but ultimately the goal is to predict who will cognitively reorganize post-surgery.

## The Changing Surgical Algorithm and Neuroimaging

At most centers the procedure followed for selecting patients for temporal lobe surgery involves an algorithm that includes scalp/sphenoidal ictal EEG (rhythmic 3–8 Hz over the temporal lobe within the first seconds of seizure onset), scalp interictal EEG (state-dependent localized spikes or focal slow wave activity), and MRI with evidence of spell out – MTS or gliosis (hippocampal atrophy and increased T2 signal). Additional criteria include FDG PET interictal hypometabolism in the temporal lobe, asymmetric language and memory findings from both the neuropsychological testing and the IAP implicating deficits on the surgery target side along with integrity in the contralateral side, semiology and EEG findings consistent with temporal lobe seizures, ictal SPECT hypoperfusion in the temporal lobe, and localized

background EEG abnormalities in the temporal lobe. If the localization of seizures is equivocal, then cortical surface and possibly depth electrodes and electrocorticography procedures are used to better localize the epileptogenic zone. With implants in place, often as part of the same surgical procedure, electrocortical stimulation (ECS) is undertaken to map out functions associated with the neural tissue adjacent to the implanted electrode.

FMRI and other functional imaging modalities are becoming part of the surgical algorithm. The most beneficial interaction of these different modalities is still unsettled and emerging. The choice of procedures undertaken emerges from a risk/benefit analysis, with the process halted once an adequate degree of confidence about seizure focus, surgical and neurocognitive risk, and projected outcome is reached. The major difference from the anatomical work-ups is that the future model will likely utilize diffusion tensor imaging (DTI) as part of the visual rendering of the anatomy.

In terms of functional assessments, FMRI and functional connectivity MRI (fcMRI) as brain mapping techniques may become as common an early step as neuropsychological testing, reducing the need for the IAP, which, because of its inherent risks, would be the last to use of the functional techniques. Also, repetitive transcranial magnetic stimulation (RTMS), or more recent versions involving direct brain stimulation (DBS), may be used as a tool to determine functional necessity and is less risky than the IAP. In terms of ictal source localization, magnetic source imaging (MSI) may be used more regularly as a means of gauging the levels of key neurotransmitter systems such as glutamate or GABA. Magnetic source imaging will be incorporated as MEG and MRI become seamlessly integrated.

Electrocortical stimulation will more systematically rely on neuropsychological testing and FMRI, in particular, as these techniques will generate hypotheses about cognitive functions potentially at risk from the surgery, and thereby guide both choice of the cognitive task and selection of the electrodes to be stimulated. For instance, if there is a right-sided lesion with expressive language deficits on NP testing and signs of right-sided dominance for speech and naming, then FMRI expressive language testing will be undertaken to verify the hypothesis of altered language representation and specify the exact regions involved. The IAP would also likely be undertaken to lateralize language. With all this information in mind, ECS in the right hemisphere would then be done to verify language skill knockout in specific regions. The hope is that techniques such as DTI and fcMRI will yield important information about the connectivity (network of white matter fibers linking gray matter regions from DTI, and resting state maps of communicating gray matter regions from fcMRI) that subserve the investigated cognitive functions and give anatomical grounding to the network of activation implied by FMRI. To the degree that MEG (or MSI) is utilized, the sequencing and timing of regional activations, along with their associated cognitive events, can be identified and depicted.

The added value of techniques such as FMRI depends on the validity of the tasks used and their reliability. It is important to develop a set of norms and expectations regarding the localization/activation properties of the tasks used, as well as their reliability (reproducibility). An important caveat is that the nature of the logical inference permitted by each brain mapping technique is different. For example, ECS and other functional knockout paradigms, such as RTMS, carry the causative power of lesion studies and indicate the necessity of a region. FMRI and other imaging modalities such as PET carry only the power of association (correlation) between the cognitive/behavioral function and the underlying structure. Given these differences, there is no reason to think that the techniques will yield completely overlapping and concordant results.

A goal in most centers conducting presurgical brain mapping is to render the numerous pieces of both structural (MRI, DTI, MRA) and functional (ECS, FMRI, fcMRI, PET, MEG) information in one accurately registered, high-resolution three-dimensional volume. However, as noted, the registration issues in doing so accurately are not minor because each technique is sensitive to different types of distortion (e.g., DTI, white matter around CSF; FMRI, near large arteries and veins) that produce inevitable co-registration errors. When post-surgical imaging studies are conducted, surgical centers are hoping to develop a database that will permit retrospective identification of the presurgical structural and functional neuroimaging markers of positive outcome both in terms of neurocognitive status and seizure control.

## FMRI and Other Neurocognitive Tools in Epilepsy

While FMRI is safer, cheaper, and able to provide a depiction of the full circuit of regions involved in a task, it has disadvantages. FMRI is a noninvasive technique that does not involve the use of contrast injection dye and is therefore the ideal modality to use in both children and for longitudinal studies requiring multiple scans of the same individual. FMRI activation maps are often rich with significant areas of activation even after thresholding. Determining the role of all these structures during a given task is quite difficult. It is not likely that all of the areas of activation represent areas necessary for carrying out the task. Many may involve basic brain responses to the particular conditions of your task presentation (e.g., pictures versus three-dimensional objects for a naming task, mode of input, nature of instructions given – was the subject told to guess if they did not know the answer).

Also, the MRI scanner is a difficult environment. There are emotional responses to this environment, and the level of effort and cooperation are large factors capable of influencing the activation pattern in significant ways. Processing parameters such as the statistical threshold can play a role. The lack of significance does not mean that a region is not involved, and among the regions of activation there is no way to rank their importance to the task. There is also the risk of subtracting out important task components with the control task. There is intra-subject variability in networks, particularly in abnormal, diseased brains. Depiction of the full extent of activity is likely to instill unnecessary caution in the neurosurgeon for fear of taking out areas presumed to be important because they are active in the FMRI map. Primarily, FMRI does not answer questions of necessity: can a task be performed without the affected brain area? FMRI does not test for necessity and may actually point to activation that is not completely necessary. If used with intraoperative cortical and subcortical stimulation to understand underlying anatomical–functional links, FMRI can play a major role in determining surgical options.

Intraoperative electrocortical stimulation (ICS) is the gold standard for localization in eloquent cortex. A craniotomy procedure is used and then in a stepwise fashion, voltage is applied to knockout function while the patient is awake. This shows necessary regions, not full circuits, but it too has problems. Time constraints and the limited spatial coverage of the craniotomy mean that the procedure maps only a limited area of brain (placement of the electrodes is often based on prior knowledge of the FMRI results). The depth of the electrical pulse is not known and the technique is also time consuming. The technique is stressful for the patient and requires their cooperation. ICS can also precipitate seizures which can then make identification of spontaneously generated epileptogenic region difficult. Using ICS as the gold standard, if the FMRI activation is off by more than 1 cm from the ICS mapping of the same skill, one should question the validity of the FMRI.

Brain stimulation techniques may usher in a new wave of cognitive rehabilitation therapies and may be of great help in sorting out the timing of different regions as they contribute to a task. In healthy adult volunteers, RTMS given in time with movement has been found to enhance the encoding of a motor memory in the primary motor cortex (M1) and to increase excitation in both local and remote brain regions. An even newer technique is transcranial direct current stimulation (TDCS), which modulates spontaneous firing rates of neurons, rather than excites neurons to fire directly, has the potential to produce longer effects, and appears to more clearly have the potential to improve behavior and functioning. For instance, TDCS applied to Wernicke's area in healthy adults has produced a transient improvement in a confrontation naming task administered immediately afterward [59].

Depth electrode placements in areas such as the hippocampus are done routinely to locate seizure foci through passive EEG recordings. Depth electrodes are typically used when patients have a suspected focal seizure onset but surface EEG is equivocal. Presurgical mapping of cognitive function of eloquent neural regions near the sites of planned hippocampal surgery, however, is not routinely done. This may result in the assumption that surrounding subregions are not functionally important and, therefore, are potentially respectable. Electrical stimulation of such electrodes (i.e., DBS) provides the means to demonstrate the necessity of a particular pool of neurons for carrying a specific cognitive task. In contrast, FMRI has the ability to provide a complete map of the brain regions implementing a given task. In this sense, techniques such as DBS and FMRI are complementary. DBS can indicate the structures necessary for a task,