The Neuropsychiatry of Epilepsy

Second Edition

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Edited by
Michael R. Trimble

Bettina Schmitz

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Contributors

Albert P. Aldenkamp
Epilepsy Centre Kempenhaeghe, Heeze, The Netherlands; Department of Neurology, Maastricht University Medical Centre, The Netherlands; Head Epilepsy Group in the Division Neurosciences of the Research School MHeNS, Maastrisch, The Netherlands

Fizzah Ali, BMedSc
Honorary Research Fellow, Department of Neuropsychiatry, University of Birmingham and BSMHFT, Birmingham, UK

Frank M.C. Besag, FRCP, FRCPsych, FRCPCH
Bedfordshire and Luton Partnership NHS Trust, Bedford, UK

Penny Blake, MB BCh, MSc
Learning Disability Directorate, Abertawe-Bro Morgannwg University Health Board, Wales, UK

Sarah Broicher, MSc
Swiss Epilepsy Centre, Zurich, Switzerland

Andrea Eugenio Cavanna, MD
Consultant in Behavioral Neurology and Honorary Senior Lecturer, Department of Neuropsychiatry, University of Birmingham and BSMHFT, Birmingham, UK

Thierry Deonna
Unité de Neurologie et de Neuroréhabilitation Pédiatrique, Département Médico-Chirurgical de Pédiatrie, CHUV, Lausanne, Switzerland

Marie-Aline Eden
Research Associate, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Klinikum rechts der Isar der Technischen Universität München, Munich, Germany

Alan B. Ettinger
Neurological Surgery P.C., Lake Success, NY, USA

Christoph Helmstaedter, PhD
Universitatsklinik fur Epileptologie, Bonn, Germany

Dale C. Hesdorffer, MPH, PhD
Associate Professor of Clinical Epidemiology, Columbia University, New York, USA

Hennric Jokeit, PD Dr. rer. Nat.
Head of the Neuropsychology Department, Swiss Epilepsy Centre, Zurich, Switzerland

Kousuke Kanemoto
Aichi Medical University, Neuro-psychiatric Department, Aichi, Nagakute, Japan

Andres M. Kanner, MD
Professor of Neurological Sciences and Psychiatry, Rush Medical College at Rush University; Director, Laboratory of Electroencephalography and Video-EEG-Telemetry; and Associate Director, Section of Epilepsy and Rush Epilepsy Center, Rush University Medical Center, Chicago, USA

Mike Kerr, FRCPsych
Professor of Learning Disability Psychiatry and Honorary Consultant Neuropsychiatrist, School of Medicine, Cardiff University, Cardiff, UK

Steffi Koch-Stoecker
Epilepsy Centre Bethel, Bielefeld, Germany

Ennapadam S. Krishnamoorthy
The Institute of Neurological Sciences, VHS Hospital, Chennai, India

W. Curt LaFrance, Jr., MD, MPH
Director of Neuropsychiatry and Behavioral Neurology, Rhode Island Hospital and Departments of Psychiatry and Neurology, Brown Medical School, Providence, Rhode Island, USA

Marco Mula, MD, PhD
Department of Clinical & Experimental Medicine, Amedeo Avogadro University; Division of Neurology, University Hospital Maggiore della Carità, Novara, Italy

Jane V. Perr, MD
Assistant Attending, Department of Psychiatry, The Zucker Hillside Hospital & North Shore University Hospital, North Shore-Long Island Jewish Health System, Long Island, New York; Staff Psychiatrist, Advantage Care Diagnostic & Treatment Center, Brookville, New York; Psychiatric Consultant, R.E.S. Company, Inc., Medford, New York

Bernd Pohlmann-Eden, MD, PhD
Professor of Neurology and Epilepsy Program Director, Dalhousie University, Halifax, Canada

Eliane Roulet-Perez
Unité de Neurologie et de Neuroréhabilitation Pédiatrique, Département Médico-Chirurgical de Pédiatrie, CHUV, Lausanne, Switzerland

Bettina Schmitz, MD, PhD
Head of the Department of Neurology, the Stroke Unit and Epilepsy Center, Vivantes Humboldt-Klinikum, Berlin, and Professor of Neurology at the Charité University Hospital, Berlin, Germany

Tanvir Syed, MD, MPH
Assistant Professor of Neurology, University Hospitals Case Medical Center, Cleveland, Ohio, USA

Michael R. Trimble, MD, FRCP, FRCPsych
Emeritus Professor of Behavioural Neurology at the Institute of Neurology, Queen Square, London, UK

Juri-Alexander Witt
Columbia University, New York, USA

Chapter 1

Introduction

Michael R. Trimble and Bettina Schmitz

The first edition of this book was published in 2002, at which time there was a growing interest in the psychobiological associations between epilepsy and psychiatry, spurred on by an appreciation of neuroanatomical and neurochemical affinities between them, and the growing recognition of clinical bridges which were relevant to everyday clinical practice. Since then, the neuropsychiatry of epilepsy has become a central focus of epileptology and interest in psychiatric comorbidities has led to much research and publication of peer-reviewed articles. The number of PubMed citations for psychosis and epilepsy doubled between 2002 and 2009, while those for depression and epilepsy quadrupled. Further, epilepsy meetings have given over more time to discussion of these matters, and earlier this year a meeting totally devoted to epilepsy and behavior was held in Prague. Comorbidity, but especially psychiatric comorbidity, is on everyone's lips.

It had been recognized that psychoses in people with epilepsy occurred, but it was not until the links between limbic structures, especially the amygdala and hippocampus, and both medial temporal lobe epilepsy and schizophrenia were clarified that a secure biological foundation for the association became accepted. Yet, even at the time of the first edition, the frequency, presentations and complications of such states as the postictal psychoses were relatively unrealized in clinical practice. The same could be said about the Landolt phenomenon, the alternation between states of psychosis and seizures with a "normalization of the EEG". The former syndrome was one of the many themes which the volume opened out to those interested in managing some of the complications of seizure disorders, while the latter was well discussed in one of our earlier collaborations (Trimble and Schmitz 1998). Such problems are now easy currency in discussion about epilepsy, in contrast to earlier times.

In the intervening years, there has been a clear appreciation in biological psychiatry of the neurobiological bases of such psychopathologies as major depressive disorder, obsessive-compulsive disorder and other anxiety-related conditions, and there has been further development of psychotropic and anticonvulsant drugs (AEDs) (Trimble and George 2010). These advances have brought with them an appreciation of the possible neuroanatomical and neurochemical underpinnings of these comorbid conditions in epilepsy, and a growing number of patients with epilepsy being treated with drugs conventionally more familiar to psychiatrists than neurologists. This has been an important clinical advance, but one which also has some hazards in terms of potential drug interactions and side effects. The potential for AEDs to provoke or exacerbate psychopathology is now well recognized, but in some cases controversial. Such matters, however, emphasize the growing importance of neuropsychiatric debate in epileptology.

This interest in the neuropsychiatry of epilepsy is paralleled by a growth in neuropsychiatry across the neurological spectrum from movement disorders to multiple sclerosis and from head injury to the dementia syndromes. The uncovering of the neurology and genetics of many patients with learning disability, and the CNS abnormalities discovered in disorders such as autism, broadens the spectrum of the interface of neurology and psychiatry even further, especially as many of these problems interface at one or other level with epilepsy.

We have been encouraged by the appreciation and continuing interest in the contents of the first edition of *The Neuropsychiatry of Epilepsy* and have therefore ventured on this second edition. It is composed of two

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main elements. Firstly, some authors from the first edition have been encouraged to update their previous contribution. This is where there have been significant advances in the area to warrant bringing them to attention. Secondly we have asked new authors to write on subjects not addressed in the first edition but which are becoming very important in clinical and research practice.

The new edition starts with epidemiology, which has become a prominent discipline in research attempting to disentangle the extent and variety of psychiatric comorbidities in epilepsy. There are then several chapters that relate to those patients with learning disability, including the links with autism spectrum disorders and, at the other end of life, with dementia. The clinical presentations and the wide spectrum of peri-ictal disorders are then discussed before attending to some of the interictal psychopathologies. Depression in epilepsy may not be quite like depression in the absence of epilepsy, the neuroanatomy giving a special stamp on the phenomenology. In addition, the circuitry involved in seizure spread leads to some distinctive features of the behavioral states that can be seen, which link with newer theories of the "social brain" and how it may be altered in some patients with epilepsy, linking closely with some of the social handicaps that are often problematic in rehabilitation.

Treatments are always clinically relevant, as is the age-old subject of treatment emergent side effects. We have revisited and updated information on the adverse effects of AEDs including the problem of suicidal behaviors, which have important implications for clinical and research practice, updated information on the problems of temporal lobe surgery that can arise in the unwary, and provided an extensive chapter on the use of psychotropic drugs in patients with epilepsy. We conclude with a discussion of the brain mechanisms of consciousness as may be revealed through investigations of patients with seizure disorders.

It was our wish with the first edition of *The Neuropsychiatry of Epilepsy* to enliven the debates surrounding the links between epilepsy and psychiatry, and the intervening years have certainly seen much activity in these areas. We hope that our book played a part in that. With this new edition we hope that those well attuned to the problems discussed will gain even more knowledge, inspiring them to even better clinical practice or more adventurous research. To those less familiar we hope that the contents of this book will enliven their minds to the rich possibilities and important clinical implications of the neuropsychiatry of epilepsy.

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Chapter 2

Neuropsychiatric disorders in epilepsy: epidemiology and classification

Dale C. Hesdorffer and Ennapadam S. Krishnamoorthy

Introduction

The association between epilepsy and psychiatric disorders has a long history. For centuries seizures were considered to be a form of demonic possession. Beginning late in the nineteenth century, considerable attention has been directed towards cataloging, describing and understanding disorders at the interface between epilepsy and psychiatry, particularly by European neurologists and psychiatrists. However, it is only in the past few decades that attention has been paid to the epidemiology of these disorders.

It is increasingly clear that psychiatric comorbidity is common in epilepsy. Additionally, distinct and unique forms of psychopathology occur during the ictal and postictal periods, and a specific dysphoric disorder has been described during the interictal period (Bear and Fedio, 1977; Krishnamoorthy 2000, 2001; Blumer 1995, 2000). The combination of the observed similarities in behavior during and just following seizures and in psychopathological states has strengthened the notion of an affinity between epilepsy and psychiatric disorder.

Most studies examining the comorbidity of epilepsy and psychiatric disorders have been cross-sectional in hospital- and institution-based populations. While these studies early on contributed to the current understanding of psychopathology in epilepsy, the strong selection bias for more severe epilepsies in these studies makes extrapolation of their findings to the majority of patients with epilepsy in the community difficult. More importantly, these studies have led to a potentially incorrect inference that having epilepsy itself leads to the development of psychiatric disorders, which more recent studies that have examined time order of these associations have questioned.

Cross-sectional community-based studies of psychiatric comorbidity in epilepsy

This question of whether psychiatric disorders are more common in epilepsy is important from a public health perspective. Were psychiatric disorders more common in epilepsy, specific mental health resources would need to be created in the community to serve this patient group. On the other hand were there no excess in psychiatric comorbidity, when patients with epilepsy were compared with other illness groups or normal controls, such resources would not be required. In addition to the importance of such information to healthcare planning, because cross-sectional studies concern people with epilepsy, the clinical information they impart is valuable to clinicians. For both of these reasons, community-based studies of psychiatric comorbidity in epilepsy are summarized here (Table 2.1). A subset of these studies has compared cases with controls, some have included standardized instruments to make a diagnosis of different psychiatric disorders, and others have relied upon single questions or ICD codes.

One of the earliest investigations to be carried out was that of Pond and Bidwell (1960), who surveyed patients from 14 doctors' surgeries in the south-east of England. They found that 29% of 245 patients had psychological disorders of sufficient severity to seek treatment, i.e. conspicuous morbidity. While the diagnosis of psychiatric comorbidity was not based upon a standardized questionnaire, the strength of this study lies in recognizing, five decades ago, the importance of an epidemiological approach.

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Table 2.1 Cross-sectional community-based studies and general population surveys of psychiatric comorbidity in epilepsy

Year	Investigators (country)	Results	Methods
1960	Pond and Bidwell (UK)	29% of people with epilepsy had a psychological disorder for which treatment was sought	Study of 245 people with epilepsy ascertained in 14 doctors' surgeries. Interviews conducted by psychiatric social worker. Instruments not standardized
1966	Gudmundsson (Iceland)	55.5% of people with epilepsy had personality changes	Personal survey of 654 people with epilepsy conducted by a single epileptologist. Instruments and diagnosis not standardized
1987	Edeh and Toone (UK)	48% of adults with epilepsy had psychiatric disorders: 22% with depression; 15% with anxiety; 1% with schizophrenia; 3.4% with psychosis; and 2.2% with personality disorder	Primary care-based study of 88 adults with epilepsy. Clinical Interview Schedule used to diagnose psychiatric disorders
1992	Forsgren (Sweden)	Psychiatric disorders were endorsed by 5.9% of adults with epilepsy: 0.8% for schizophrenia; 0.7% for affective psychosis; 0.7% for personality disorders; and 1.7% for alcohol dependence	Multisource registry review of 713 people with active epilepsy in northern Sweden. Each psychiatric disorder was ascertained by a single question on interview
1995	Carlton-Ford et al. & McDermott et al. (US)	Hyperactivity was identified in 28.1% of children with epilepsy and 4.9% of controls ($p<0.05$). Anxiety was identified in 24.0% of cases of epilepsy and 7.5% of controls ($p<0.05$). Antisocial behavior was identified in 18.2% of cases of epilepsy and 8.8% of controls ($p<0.05$). Highly impulsive behavior was identified in 39% of cases of epilepsy and 11% of controls	1988 National Health Interview Survey for children. Behavior problem index used to identify problems in 121 children with epilepsy versus 3950 controls (McDermott). 23 questions about psychological problems in 118 with epilepsy and 11 042 without epilepsy (Carlton-Ford)
1996	Jalava and Sillanpaa (Finland)	Psychiatric disorders present in 24.0% of cases and 0.7% of controls. Psychosis present in 3.1% of cases and 0 controls	Prospective cohort study of 94 people identified at epilepsy onset in childhood with a mean of 35-years follow-up. Compared to 199 population controls. ICD-9 codes used to diagnose prevalent psychiatric disorders
1998	Bredkjaer et al. (Denmark)	16.8% of people with epilepsy had nonorganic nonaffective psychosis	Record linkage study of 67 166 people hospitalized for epilepsy, using the National Patient Register. Prevalent psychiatric disorders are from the Danish Psychiatric Register using ICD-9 codes
1998	Stefansson et al. (Iceland)	Psychiatric diagnosis in 35.3% of 241 epilepsy cases as compared with 29.7% of controls ($p=0.15$). Psychosis in 6.2% of cases and 2.3% of controls ($p=0.01$). Schizophrenia in 1.2% of cases and 0.4% of controls ($p<0.03$). Affective psychosis in 3.3% of cases and 1.7% of controls ($p=0.24$)	Patients with prevalent epilepsy matched to 2 controls with other somatic diseases. Both groups of normal intelligence are drawn from the disability register of the State Social Security Institute. Compared the prevalence of selected psychiatric disorders in cases and controls
2003	Davies et al. (UK)	37% of children with epilepsy had a psychiatric disorder versus 9% of controls. Prevalence comparisons were 19.4% versus	Health survey of British children identified 67 with epilepsy and 10 249 without epilepsy. Development and well-being assessment

Table 2.1 (*cont.*)

Year	Investigators (country)	Results	Methods
		4.7% for conduct disorder and 4.5% versus 2.2% for ADHD	and clinician interview yielded DSM-IV classification
2004	Gaitatzis et al. (UK)	Statistically significant associations for neuroses (OR=1.9; 95% CI=1.8–2.0); obsessive compulsive disorder (OR=2.6; 95% CI=1.6–4.1); anxiety (OR=2.0; 95% CI=1.9–2.1); depression (OR=2.0; 95% CI=1.9–2.1); schizophrenia (OR=4.1; 95% CI=3.1–5.6); organic psychosis (OR=6.1; 95% CI=5.1–7.1); other psychosis (OR=4.0; 95% CI=3.6–4.4); alcohol dependence (OR=5.7; 95% CI=4.8–6.7)	UK General Practice Research Database 1995–1998. 5834 with epilepsy aged 16 and older and 1 035 869 controls. Epilepsy and psychiatric diagnoses based upon codes in the database
2005	Strine et al. (US)	In adjusted analysis, serious mental illness was 2.9-fold more likely in epilepsy than controls (95% CI=2.0–4.2) and being frequently depressed or anxious in the past 12 months was 2.4-fold more likely in epilepsy than controls (95% CI=1.9–3.1)	Adults from the 2002 National Health Interview study; 426 with epilepsy and 30 019 without epilepsy. Epilepsy ascertained by a single question. Psychological distress ascertained by Kessler 6 scale. Single questions used for depression and anxiety in past 12 months
2006	Kobau et al. (US)	Among people with active epilepsy, self-reported depression in the past year was 2.9-fold more common than in controls (95% CI=1.4–6.5) and self-reported anxiety in the past year was 1.9-fold more common than in controls (95% CI=0.9–4.3)	Adults from the 2004 HealthStyles Survey of representative US adults; 131 with epilepsy and 4214 without epilepsy. Epilepsy, anxiety and depression ascertained by single questions
2007	Tellez-Zenteno et al. (Canada)	People with epilepsy were more likely to be classified as having a lifetime history of anxiety disorders (OR=2.4; 95% CI=1.5–3.8) and suicidal thoughts (OR=2.2; 95% CI=1.4–2.3). Lifetime major depression and lifetime panic attack were not significantly associated with epilepsy	Canadian Community Health Survey of 36 984 individuals. World Mental Health Composite International Diagnostic Interview (CIDI) used to assess psychiatric diagnoses. Presence of epilepsy by one question
2009	Lacey et al. (Australia)	High levels of psychological distress in 24% with epilepsy versus 13% of the general population (OR=2.1; 95% CI=1.8–2.6)	Australian national prescription database used to ascertain epilepsy in Tasmania (N=839 adults of whom 652 completed the questionnaire). Comparison was the National Health Interview Survey in Tasmania 2004–2005 (N=2573). Psychological distress according to the K10 for anxiety and depression

OR – odds ratio; 95% CI – 95% confidence interval.

Across community-based studies of prevalent epilepsy that focused upon the wide rubic of psychiatric disorders or personality disorders, the prevalence of psychiatric disorders has ranged from 5.9% to 55.5% in adults (Pond and Bidwell 1960; Gudmundsson 1966; Edeh and Toone 1987; Forsgren 1992; Stefansson et al. 1998) and from 24% to 37% in children (Jalava and Sillanpaa 1996; Davies et al. 2003). This underscores the significant disease burden experienced by people with epilepsy.

Psychiatric disorders are more prevalent in children with epilepsy than in controls without epilepsy (Table 2.1). Hyperactivity is 5.7-fold more common in epilepsy versus controls ($p<0.05$), impulsivity is

3.5-fold more common, and ADHD (attention-deficit hyperactivity disorder) is 2-fold more common (Carlton-Ford et al. 1995; McDermott et al. 1995; Davies et al. 2003). Of these, impulsivity was most prevalent in children with epilepsy. In one study examining conduct disorder and antisocial behavior, conduct disorder was found to be 4.1-fold more common in childhood epilepsy (Davies et al. 2003) and in another study antisocial behavior was found to be 2.1-fold more common (Carlton-Ford et al. 1995; McDermott et al. 1995). Depression has not been studied in community-based studies of children with epilepsy, but anxiety occurs 3.2-fold more often than in controls (Carlton-Ford et al. 1995; McDermott et al. 1995).

The prevalence of anxiety and depression has been addressed in adults with epilepsy compared to controls. Anxiety disorders are 1.9- to 15-fold greater in epilepsy (Edeh and Toone 1987; Gaitatzis et al. 2004; Kobau et al. 2006; Tellez-Zenteno et al. 2007). Anxiety or depression in the past 12 months was 2.4-fold more common in epilepsy (Strine et al. 2005). Interestingly in community-based studies, depression is less often studied. Those studies that have examined depression find either no association for lifetime depression in a study using a standardized interview (Tellez-Zenteno et al. 2007) or a significant 2- to 2.9-fold increased risk in a study using diagnostic codes (Gaitatzis et al. 2004) or a single question (Kobau et al. 2006). Thus, anxiety appears to be more prevalent in adults with epilepsy but data on depression are inconsistent. This inconsistency is intriguing in light of the numerous clinical-based studies that have found a substantially increased prevalence of depression in epilepsy.

Of all the different psychiatric disorders in epilepsy, psychosis is the most studied in cross-sectional studies. In community-based studies of epilepsy, the prevalence of psychosis ranges from 3.1% to 6.2% (Edeh and Toone 1987; Jalava and Sillanpaa 1996; Stefansson et al. 1998; Gaitatzis et al. 2004), the prevalence of affective psychosis ranges from 0.7% to 3.3% (Forsgren 1992; Stefansson et al. 1998), and the prevalence of schizophrenia ranges from 0.7% to 1.2% (Edeh and Toone 1987; Jalava and Sillanpaa 1996; Stefansson et al. 1998; Gaitatzis et al. 2004). In studies with controls (Jalava and Sillanpaa 1996; Stefansson et al. 1998; Gaitatzis et al. 2004), psychotic disorders are at least 2-fold more common in prevalent epilepsy. For a detailed review of studies of psychosis and of the nature and phenomenology of the epileptic psychosis, see Trimble (1991).

Overall community-based studies of epilepsy suggest that psychiatric disorders are more common than in general population controls. Although the first of these studies was conducted five decades ago, and there is increased awareness of this comorbidity in epilepsy, routine screening for psychiatric disorders in epilepsy remains infrequent. Substantially more needs to be done to improve the detection and treatment of these disabling disorders in epilepsy.

Population-based studies examining the time order of associations between psychiatric disorders and epilepsy

While cross-sectional studies of psychiatric disorders and epilepsy provide valuable public health information and inform epileptologists and psychiatrists, they have significant limitations. Most crucial among these limitations is the inability of cross-sectional studies to test hypotheses that might explain the co-occurrence of psychiatric disorders and epilepsy. Psychiatric disorders in epilepsy may reflect the *new onset* of disorders associated with specific neuronal dysfunction that is characteristic of subtypes of epilepsy (e.g. temporal lobe epilepsy), the *new onset* of disorders in response to the stigma and feelings of loss of locus of control in epilepsy, the *recurrence* of disorders such as depression or anxiety present before the onset of epilepsy, or the *persistence* of such disorders after epilepsy onset. Studies of incident cohorts with epilepsy are needed to address these questions, answers to which are crucial to understanding and best treating the underlying reason(s) for the comorbidity observed in cross-sectional studies.

Over the past 20 years, a body of work has emerged examining whether specific psychiatric disorders are associated with an increased risk for developing epilepsy, and assessing the incidence of psychiatric disorders after the onset of epilepsy. These studies are discussed here and can be found in Table 2.2. All follow on from the cross-sectional studies described above that have shown that different psychiatric disorders occur in people with epilepsy more than would be expected by chance. Together

Table 2.2 Studies considering time order of the association between psychiatric comorbidity and epilepsy

Year	Investigators (country)	Results	Methods
Multiple psychiatric disorders and suicidality			
2007	Christiansen et al. (Denmark)	Suicide cases were 1.99-fold more likely to have epilepsy than controls (95% CI=1.71–2.32) in the absence of a history of psychiatric disorders. A history of psychiatric disorders conferred similar risk for suicide in the presence of epilepsy (OR=13.7; 95% CI=11.8–16.0) and in the absence of epilepsy (OR=12.5; 95% CI=12.0–12.9). Among cases with epilepsy, the risk for suicide was highest in the first 182 days after first epilepsy hospitalization	Population-based case–control study conducted from 1981 to 1997 of 21 169 cases of suicide and 423 128 age and gender-matched controls who were alive. Information on past history of epilepsy, psychiatric disorders and socioeconomic status came from different linked Danish registries
Psychosis			
1998	Bredkjaer et al. (Denmark)	After excluding learning disabilities and substance misuse, risk was 2.0-fold increased for incident *nonaffective psychosis* (95% CI=1.7–2.5), 1.5-fold increased for incident *schizophrenia* (95% CI=1.1–1.9) and 2.3-fold increased for incident *schizophrenia spectrum disorder* (95% CI=2.0–2.6). There were no differences by type of epilepsy	Record linkage study of 67 166 people hospitalized for epilepsy, using the National Patient Register. Incident psychiatric disorders after epilepsy onset are from the Danish Psychiatric Register using ICD-9 codes. Epilepsy compared to the Danish general population rates
2005	Qin et al. (Denmark)	Epilepsy increased risk for schizophrenia (RR=2.5 [95% CI=2.2–2.8]); family history of schizophrenia increased risk for schizophrenia (RR=8.4 [95% CI=7.8–9.1]); family history of epilepsy increased risk for schizophrenia (RR=1.3 [95% CI=1.2–1.4])	Population-based study of 2.27 million people followed from their 15th birthday or 1/1/1977 until 31/12/2002: 34 494 with epilepsy and 2.23 million controls. ICD codes were used to identify all diagnoses in medical records
2005	Vestergaard et al. (Denmark)	Risk for developing schizophrenia associated with: febrile seizure (RR=1.4 [95% CI=1.1–1.9]); febrile seizure in the *absence* of epilepsy (RR=1.4 [95% CI=1.0–1.9]); and febrile seizure plus later epilepsy (RR=3.0 [95% CI=1.4–6.8])	Population-based study of 16 429 with febrile seizure and 542 528 controls followed for 2.8 million person-years for development of schizophrenia. Comes from a birth cohort of children born in Denmark between 1/1977 and 12/1986 followed until 12/2001 through nationwide registries. Diagnoses from ICD codes
Depression, bipolar disorder, and suicidality			
1990	Forsgren and Nystrom (Sweden)	Depression 7 times more common among cases than age- and sex-matched controls (p=0.03). Among cases with localized onset seizure, depression was 17 times more common than in controls (p=0.002)	Community-based case-control study of incident epilepsy (N=83) in adults and 166 age- and sex-matched controls. Depression was queried, standardized instruments were not used
2000	Hesdorffer et al. (Rochester, MN, USA)	A history of major depression was associated with a 6-fold increased risk for developing an unprovoked seizure (p=0.03). Adjustment for medical therapies for depression decreased the odds ratio to 3.7	Population-based study of 145 cases with incident idiopathic/cryptogenic seizures, aged 55, and 290 matched controls. Used a modified version of the SCID to abstract data from medical records before the first

Table 2.2 (*cont.*)

Year	Investigators (country)	Results	Methods
			seizure. This was used to make a DSM diagnosis of major depression
2003	Nilsson et al. (Sweden)	Risk of developing epilepsy was increased over a 10-year period in patients with hospitalized *depression* compared with controls (RR=1.3; 95% CI=1.0–1.7). Adjustment for alcohol or drug abuse diminished the increased risk (RR=0.9; 95% CI=0.7–1.2). Similar results were seen for *mania* and for an *affective episode*	A hospital-based retrospective cohort study using record linkage compared the risk of developing epilepsy in 13 748 patients hospitalized for major depression or bipolar disorder to the risk in 81 380 controls hospitalized for osteoarthritis and 69 149 controls hospitalized for diabetes
2006	Hesdorffer et al. (Iceland)	A history of *major depression* was 1.7-fold more common among cases than among controls (95% CI=1.1–2.7). A history of *attempted suicide* was 5.1-fold more common among cases than among controls (95% CI=2.2–11.5) in unadjusted analyses. Attempted suicide increased seizure risk 3-fold even after adjusting for age, sex, cumulative alcohol intake, and major depression or number of symptoms of depression	Population-based study of 324 children and adults, aged 10 years and older, with first unprovoked seizure or newly diagnosed epilepsy and matched 647 controls. History of major depression determined by standardized interviews and diagnosed according to DSM-IV criteria
Attention-deficit hyperactivity disorder (ADHD)			
2001	Austin et al. (US)	Attention problems occurred in: 9.1% of cases versus 7.1% of sibling controls (p=0.0001); 8.1% of children with first unprovoked seizure versus 3.4% of controls; 15.8% with newly diagnosed epilepsy versus 2.2% of controls	Clinic-based study of 224 children (4–14 years) with a first recognized afebrile seizure and 135 healthy sibling controls. The child behavior checklist was used to assess ADHD prior to seizure occurrence
2004	Hesdorffer et al. (Iceland)	History of ADHD was associated with a 2.5-fold increased risk for developing unprovoked seizure (95% CI=1.1–5.5). ADHD-inattentive type (OR=3.7; 95% CI=1.1–12.8); ADHD-hyperactive type (OR=1.8; 95% CI=0.6–5.7); ADHD-combined type (OR=2.5; 95% CI=0.3–13.3). Number of symptoms of ADHD was greater in cases than controls. Age of onset of ADHD was earlier in cases than controls	Population-based study of 109 children aged 3–16 years with unprovoked seizure or epilepsy first diagnosed between 1/12/1995 and 28/2/1999. 218 age and gender-matched controls from the population registry, selected as the next two births. Diagnostic interview schedule for children used to make DSM-IV diagnosis of ADHD
2007	Hermann et al. (US)	ADHD occurred in 31.5% of children with epilepsy versus 6.4% of controls (p<0.001). Among cases with ADHD, ADHD-inattentive type occurred in 52.1% and 82% of ADHD predated epilepsy onset. Frontal lobe volume was increased in ADHD+ cases compared to controls (p=0.0013) and compared to ADHD- cases (p<0.001). This appeared to be due to increased gray matter	Clinic-based study of 75 children aged 8–18 with recent idiopathic epilepsy onset and 62 first degree cousin controls without past neurological disorders, age and gender matched to the cases. Cases and controls all attended regular school. Semistructured Kiddie SADS-PL interview used to make a DSM-IV diagnosis of ADHD

OR – odds ratio; RR – relative risk; 95% CI – 95% confidence interval.
Studies assessing time order.

they suggest that some psychiatric disorders are associated with an increased risk for developing epilepsy, while in others, epilepsy is associated with an increased risk for psychiatric disorder.

Attention-deficit hyperactivity disorder

When time order is examined, ADHD is associated with an increased risk for *developing* epilepsy. This has been shown in case-control studies of children with epilepsy (Austin et al. 2001; Hesdorffer et al. 2004; Hermann et al. 2007) and in cohort studies of select populations of children with ADHD (Hughes et al. 2000; Hemmer et al. 2001; Williams et al. 2001; Holtmann et al. 2003). In one study of 148 children with first unprovoked seizure and 89 seizure-free sibling controls, attention problems as assessed by the Child Behavior Checklist were 2.4-fold more common prior to identification of the first seizure (8.1%) than in controls (3.4%) (Austin et al. 2001). In an analysis of a population-based case-control study conducted among Icelandic children (Hesdorffer et al. 2004), children with incident unprovoked seizure were 2.5-fold more likely than age- and gender-matched controls to have a history of ADHD (95% CI=1.1–5.5), meeting DSM-IV criteria *prior* to seizure onset. The association was restricted to ADHD-predominantly inattentive type (OR=3.7; 95% CI=1.1–13). Most recently, ADHD was found in 31.5% of children with new onset idiopathic epilepsy compared to 6.4% in controls (Hermann et al. 2007). In most cases the ADHD predated epilepsy onset and most were of the inattentive type. Interestingly, frontal lobe volume was increased in children with epilepsy and ADHD compared to controls ($p=0.0013$) and children with epilepsy only ($p<0.001$). When the occurrence of new onset seizures is examined in selected samples with ADHD (Hughes et al. 2000; Hemmer et al. 2001; Williams et al. 2001; Holtmann et al. 2003), 0.2% to 2% of children develop unprovoked seizures. This is 4- to 45-fold greater than the expected rate, because the average annual incidence of seizures is approximately 0.0470% per year in children aged 5–16 years.

Thus, there is an increased risk for *developing* unprovoked seizures in children with ADHD, and the reported increased risk is smaller in case-control studies than in cohort studies, which were limited by the small numbers of ensuing unprovoked seizures during short follow-up periods in selected populations. The development of incident ADHD in a cohort with new onset epilepsy has not been studied yet.

Depression

Depression is associated with an increased risk for developing epilepsy (Table 2.2). Several studies show that a history of major depression is associated with an increased risk for *developing* unprovoked seizures. In the earliest population-based case-control study to examine depression before epilepsy onset, Forsgren and Nystrom (1990) found that a history of "depression" was associated with an increased risk for developing epilepsy, particularly "localized onset" seizures. Additional studies demonstrated that a history of depression, diagnosed according to DSM criteria, increased the risk of developing unprovoked seizures (Hesdorffer et al. 2000; Hesdorffer et al. 2006). In older adults residing in Rochester, Minnesota (Hesdorffer et al. 2000), a history of major depression was significantly associated with a 6-fold increased risk of developing a first idiopathic/cryptogenic unprovoked seizure. In a later Icelandic population-based case-control study (Hesdorffer et al. 2006), a history of major depression diagnosed according to DSM-IV criteria was associated with a 1.7-fold increased risk for developing epilepsy (95% CI=1.1–2.7). Similar results were reported in a hospital-based prospective study (Nilsson et al. 2003), although generalizability was limited, because fewer than half of the people who meet criteria for major depression seek medical care, and even fewer are hospitalized.

Bipolar disorder

Bipolar disorder was associated with a 5-fold increased risk for developing epilepsy in the Icelandic study (Hesdorffer et al. 2006), although this did not reach statistical significance.

Psychosis

Studies examining the time order of the relationship between psychosis or schizophrenia and epilepsy have all been conducted in population-based registries. This is because these studies are examining the first occurrence of a psychiatric disorder that is rare in the general population and a neurological disorder with an overall incidence of about 60 per

100 000 population. Therefore, large numbers of patients with incident epilepsy are needed to observe whether or not there is an association with psychosis. However, there are limitations on relying upon registries, even if they are population-based, because there is a lack of standardized ascertainment for epilepsy and for psychosis. Nonetheless, the accumulated data suggest that epilepsy is associated with an increased risk for psychosis.

Two studies have been conducted in Denmark using record linkage of different national registries to examine the incidence of psychosis following the onset of epilepsy. In the earliest of these (Bredkjaer et al. 1998), the incidence of nonorganic nonaffective psychoses was significantly increased for both men and women with epilepsy, even after excluding all people diagnosed as suffering from a learning disability or substance misuse. The standardized incidence ratio was significantly increased for the entire schizophrenia spectrum ($p<10^{-8}$), nonaffective psychosis ($p<10^{-8}$), and schizophrenia alone ($p<0.0001$). In a second population-based Danish registry study, Qin et al. (2005) found that epilepsy was associated with a 2.5-fold increased risk for schizophrenia in the absence of a family history of psychosis, an important exclusion because family history could explain an increased risk for schizophrenia in epilepsy. In contrast to clinic-based studies of schizophrenia and epilepsy, the risk for developing schizophrenia did not differ by seizure type. However, the risk was dependent upon age at onset of epilepsy with an increasing risk of schizophrenia observed with increasing age at onset ($p<0.001$), suggesting that the median age at onset of schizophrenia after epilepsy is greater than the onset of 22 years reported in the general population (Thorup et al. 2007).

The risk of developing schizophrenia is also increased in the presence of febrile seizures, but only when they are followed by the development of epilepsy (Vestergaard et al. 2005) (RR=1.4 for schizophrenia after febrile seizures only and RR=3.04 for schizophrenia after febrile seizures plus epilepsy). Febrile seizure type was unknown in this study, but it is possible that the association was due to hippocampal damage associated with prolonged febrile seizure.

Suicidality

It is well established that people with epilepsy are at an increased risk for completed suicide. Standardized mortality ratios for suicide in people with epilepsy range from 3.5 (Nilsson et al. 1997) to 5.0 (Rafnsson et al. 2001). In a study examining correlates of the increased risk for completed suicide in Denmark (Christensen et al. 2007), suicide cases were 2-fold more likely than living controls to have epilepsy (95% CI=1.71–2.32) in the absence of a history of psychiatric disorders. Suicide cases were 14-fold more likely to have epilepsy (95% CI=11.8–16.0) than living controls in the presence of psychiatric disorder, but this was no different from the risk of suicide when a history of psychiatric disorder was unaccompanied by epilepsy.

Although the long held explanation for the increased risk for suicide in people with epilepsy was that psychiatric disorders lead to suicide in people with epilepsy, in part because their epilepsy makes them severely depressed or anxious, recent findings make this explanation unlikely. Analysis of the Icelandic case-control study (Hesdorffer et al. 2006) showed that suicide attempt was associated with a 3.5-fold increased risk for *developing* epilepsy (95% CI=1.5–8.6), after adjusting for major depression, bipolar disorder, and cumulative alcohol intake. Parallel to findings on major depression and epilepsy, suicidal behaviors *precede* the occurrence of a first unprovoked seizure. Because others have shown that suicide attempt increases the risk of later completed suicide (Bradvik 2003; Suominen et al. 2004), the increased risk for completed suicide in people with epilepsy may reflect recurrence of premorbid suicidal behavior rather than epilepsy leading to major depression and completed suicide.

The classification of psychiatric disorders in epilepsy

The classification of psychiatric disorders in epilepsy has always been controversial. There are two main schools of thought, which depend upon the perspective taken and questions asked when considering the comorbidity of these conditions.

One perspective takes a clinical point of view and focuses upon psychiatric comorbidity in clinical populations with epilepsy, historically in selected populations drawn from tertiary care centers. This view, most often voiced by neuropsychiatrists with an interest in epilepsy, is that the existing systems of classification are hopelessly inadequate as far as neurological disorders in

general and epilepsy specifically are concerned (Krishnamoorthy et al. 2007). On the basis of this, several investigators have developed their own instruments to permit the identification of epilepsy-specific features of psychiatric disorders (Bear and Fedio 1977; Blumer 1995; Gilliam et al. 2006). The traits that Bear and Fedio (1977) looked for were those identified by Gastaut, and later Geschwind, who described the constellation of personality traits that characterize patients with temporal lobe epilepsy, including hypergraphia, hyposexuality, religiosity, and emotional viscosity. Blumer (1995, 2000) has drawn attention to an interictal dysphoric disorder of refractory epilepsy as being polymorphic, and characterized by a constellation of eight symptoms, typically of short duration and occurring in different permutations and combinations at different times. The depressive traits assessed in the neurological disorders depression inventory (Gilliam et al. 2006) excluded those that could be features of epilepsy in the absence of major depression. These instruments need to be studied in population-based epilepsy cohorts with specific epilepsy characteristics (e.g. refractory epilepsy, temporal lobe epilepsy) to eliminate selection factors that could lead to erroneous conclusions.

In addressing psychopathology in epilepsy, the Neuropsychiatry Commission of the International League Against Epilepsy (Krishnamoorthy et al. 2007) chose to differentiate comorbid psychiatric disorders as classified in DSM-IV (American Psychiatric Association 1994) and ICD-10, all of which could occur in epilepsy, and well-described psychopathology related directly to the ictus, that is, epilepsy-specific psychopathology. Classifying epilepsy-specific psychopathology, the Neuropsychiatry Commission proposal relates it clearly to the ictus (pre-ictal, interictal, and postictal). The report acknowledges the contribution of biological factors like hippocampal sclerosis, psychological factors including memory complaints and cognitive dysfunction, the contribution of antiepileptic drugs both in relieving and in precipitating psychopathology, and EEG changes associated with psychopathology to epilepsy-specific psychopathology. Indeed, this multi-axial nondidactic approach to classification allows a wide conceptualization of epilepsy-specific psychopathology. For example, it allows us to think about nonpsychotic psychopathology (e.g. affective-somatoform) as being associated with forced normalization of the EEG, reflecting an evolving broad understanding of the interface between epilepsy and behavior.

The other perspective on classifying psychiatric disorders in epilepsy arises from a desire to understand more fully the nature of their comorbidity. One line of inquiry has been the time order of the association between epilepsy and various psychiatric disorders. The logic underlying these investigations is if psychiatric disorders are associated with an increased risk for developing epilepsy, then they will be present before epilepsy develops and likely indistinguishable from both the psychiatric disorders of people who will later develop other comorbidities (e.g. migraine, stroke) as well as those of people who will never develop a comorbidity. For such studies, the existing systems of classification in psychiatry, currently the ICD-10 and DSM-IV, are the best choice. They are also the best choice for studies comparing the first occurrence of psychiatric disorders in incident epilepsy and controls and for studies of the familial aggregation of epilepsy and psychiatric disorders.

Conclusions

Our conclusions are as follows:

- Psychiatric disorders are common in epilepsy and encompass the spectrum of conditions.
- There is considerable evidence from epidemiological studies to suggest that ADHD, depression, bipolar disorder, and psychoses are associated with an increased risk for developing epilepsy.
- Suicide attempt is associated with an increased risk for developing epilepsy, even after adjustment for depression, socioeconomic status, age, gender, and cumulative alcohol consumption.
- Continued controversy exists regarding the classification of psychiatric disorders in epilepsy. The use of any classification system must be dependent upon the question being addressed. Whatever classification system is used, studies are needed in unselected cohorts with epilepsy in order for correct inferences to be drawn from the results.
- Routine screening for psychiatric disorders in epilepsy remains infrequent. Much more needs to be done to improve the detection and treatment of these disabling disorders in epilepsy.

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Chapter 3

Genetic disorders associated with intellectual disability

Mike Kerr and Penny Blake

Introduction

The association between intellectual disability and the presence of epilepsy is longstanding. In the main it has been seen as one of an increasing prevalence, worsening severity of the epilepsy, and complexity of clinical management (Kerr and Bowley 2000). This association has in addition much overlap with neuropsychiatric practice especially in terms of assessment of: (1) seizures, (2) the cognitive impact of epilepsy, and (3) behavioral disorders associated with epilepsy and its treatment. Prevalence figures for epilepsy in people with an intellectual disability vary depending on the population source, as hospital or other health service settings frequently have individuals with more severe disability or other comorbidity. More recent community-derived estimates of prevalence are of around 18% (Matthews et al. 2008) as compared with a general population figure of around 0.7% (Linehan 2010). The epilepsy in people with a learning disability frequently commences in childhood and can be refractory to treatment. This combination of early onset and refractory nature means that people with an intellectual disability are represented in a wide range of clinical epilepsy settings across the life span (Mc Grother et al. 2006).

This chapter looks at the management of epilepsy in people with an intellectual disability, which has gained increasing importance over recent years, and the interface between the genotype causing the intellectual disability and potential behavioral and epilepsy phenotypes associated with this genotype. Advances in this area can lead to some important clinical pointers and increasingly etiological considerations should be part of both neuropsychiatric and neurologic formulations for this population.

The phenotypes of individuals with specific causes of intellectual disability, independent of whether there is an association with epilepsy, have also been the subject of increasing academic scrutiny (Butler et al. 2010; Schneider et al. 2009), where the impact of genotype on (1) physical phenotype, (2) epilepsy phenotype and (3) psychological phenotype has been explored. In this chapter how the understanding of a person's epilepsy, its management, and their associated behavioral manifestations may be a product of their genotype will be investigated.

We have taken a broad approach to potential genotypic influence to include issues relating to epilepsy management from diagnosis through to psychological interventions. This reflects the nature of neuropsychiatric input into epilepsy management in which psychiatric assessment and management is interlinked with knowledge of the epilepsy and its treatment. These components are necessary for all neuropsychiatrists though the delivery of seizure management will vary with clinical training.

In order to explore this the genetics of intellectual disability, the genetic association between intellectual disability and epilepsy, behavioral phenotypes, clinical neuropsychiatric issues in intellectual disability, and specific syndromes with clear epilepsy phenotypes are discussed.

Definition

Intellectual disability

Intellectual disability is our preferred term for a population known as those with mental retardation in the USA and with a learning disability in the UK. The American Association for Mental Retardation (American Psychiatric Association 1994) defines "mental retardation" as:

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

> Mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social and practical adaptive skills. . . The disability originates before the age of 18.

It adds five assumptions, which are essential to the application of the definition:

1. Limitations in present functioning must be considered within the context of community environments typical of the individual's age peers and culture.
2. Valid assessment considers cultural and linguistic diversity as well as differences in communication, sensory, motor, and behavioral factors.
3. Within an individual, limitations often coexist with strengths.
4. An important purpose of describing limitations is to develop a profile of needed supports.
5. With appropriate personalized supports over a sustained period, the life functioning of the person with mental retardation generally will improve.

Phenotype

A phenotype is an observable characteristic of an individual as determined by both genetic and environmental factors.

Epilepsy phenotype

Definition of epilepsy phenotype is a complex issue. Winawer (2006) discusses some of the reasons for this, in particular the variety of epilepsy presentations and the various factors that complicate phenotype-genotype correlation (Winawer 2006).

For the purposes of our chapter we will use a working definition of: "The pattern of seizure type, seizure syndrome and treatment response characterized by a specific genotype."

Behavioral phenotype

As described in O'Brien and Yule a behavioral phenotype is "a characteristic pattern of motor, cognitive, linguistic and social abnormalities which is consistently associated with a biological disorder. In some cases the behavioral phenotype may constitute a psychiatric disorder; in others, behaviors which are not usually regarded as symptoms of psychiatric disorders may occur." (O'Brien and Yule 1995).

The genetics of intellectual disability

An evaluation of a population of individuals with an intellectual disability, or global developmental delay, is likely to yield a potential diagnostic category in approximately 40–60% (Curry et al. 1997). This yield is of course dependent on the investigation process. The likely pick up from investigation is reviewed by Moeschler (2008), and summarized in Table 3.1. Genetic investigation as to the cause of intellectual disability may be helpful. Referral to a specialist genetic service may be able to provide a genetic diagnosis for a patient's intellectual disability and epilepsy. However, as previously discussed, not all intellectual disability has an identifiable genetic basis. Moeshler's paper goes on to discuss that chromosome studies or molecular genetic studies are appropriate where a specific diagnosis is suspected. In other individuals where there is no clear suspected diagnosis broader genetic investigation such as fluorescent in situ hybridization (FISH) may be useful. FISH is a cytogenetic method of detecting the presence or absence of specific DNA sequences on chromosomes. Fluorescent probes bind to the parts of the chromosomes which share a similar sequence to itself and then fluorescent microscopy is utilized to determine the exact location of the bound probe.

He also explains that comparative genomic hybridization (CGH) diagnostic studies in individuals with an intellectual disability who have normal karyotype and normal FISH for subtelomere abnormalities may give additional diagnostic results and that this may be an important diagnostic tool of the future. The use of array-CGH is particularly interesting. This process identifies deletions and insertions throughout the genome (Gurnett and Hedera 2007). These so-called copy number changes will be increasingly useful both in identifying potential causes of intellectual disability and in causations of epilepsy. Kim and colleagues (2007) identified copy number alterations throughout the genome in a population of 60 individuals with epilepsy, in which 62 aberrant chromosomal regions were identified.

A full review of the genetics of intellectual disability is beyond the scope of this chapter; for such a review the reader is referred to Ropers (2008). Ropers describes intellectual disability as "one of the largest unsolved problems of healthcare" suggesting that policy issues have hampered scientific investigation. Ropers provides a review of recently identified genes that are associated with intellectual disability. A range of genetic etiologies

Table 3.1 Diagnostic yield in individuals with an intellectual disability

Investigation	Percentage etiologies identified
Dysmorphological investigation	39–81
Cytogenetics	9.5
Fragile X studies	2–5.4
Metabolic studies	<1
Neurological examination	42.9
Neuroimaging	30 (abnormalities)
	1.3 (etiologies)

can contribute to intellectual disability: chromosomal aberrations, X-linked conditions, and autosomal conditions. X-linked genes are particularly important with Fragile X accounting for possibly a quarter of these, and many other new genes are being identified.

Intellectual disability and epilepsy

The prevalence of epilepsy amongst the population of people with an intellectual disability varies between studies from as low as 13% to as high as 40% depending on the inclusion criteria used (see Table 3.2). The majority of studies agree that the prevalence of epilepsy increases with increasing severity of intellectual disability. This is easily recognized in clinical settings but what is also clear is that great variation in severity and type of epilepsy occurs even when level of disability is controlled for. With such diverse etiologies pathogenic mechanisms for the occurrence of epilepsy are not always clear. However, our increasing knowledge of Fragile X syndrome has offered the potential to understand a pathogenic pathway in one defined genetic causation of intellectual disability (please see Figure 3.1). Similar genetic mechanisms may be responsible for epilepsy in other genetic causes of intellectual disability.

Etiological association between intellectual disability and epilepsy

It is in the Fragile X syndrome that a greater understanding of the pathogenetic mechanism of

Table 3.2 Epidemiological surveys of the prevalence of epilepsy in people with intellectual disability (ID)

Prevalence	Sample	Study
20%	Children under 14 years Community SMR	Corbett et al. (1975)
Mild ID 24% Severe ID 44%	Children up to 22 years Community	Richardson et al. (1981)
All 32%	Institution	Mariani et al. (1993)
Mild ID 14% Severe ID 24%	Children 6–13 years Community	Steffenburg et al. (1995)
All ID 22.1%	Adults, community based	Welsh Office (1995)
All ID – 19% by age 10 years and 21% by age 22 years Severe ID – 5-fold risk as compared with mild ID	Community-identified pediatric sample	Airaksinen et al. (2000)
All ID 18.3%	All ages, record-linked health data	Morgan et al. (2003)
Down's syndrome 13.6% Cerebral palsy 40%	Primary care health facilities	
Epilepsy 18%	Primary care	Matthews et al. (2008)

epilepsy in association with an intellectual disability gene can be best seen. This area is expertly reviewed by Hagerman and stafstrom (2009). The scientific pathway to this knowledge may act as a model for further associations between intellectual disability genes and potential epileptogenesis (see Figure 3.1).

A mouse model examined by Huber et al. in 2002 brought about a greater understanding of the molecular basis of Fragile X syndrome (Huber et al. 2002; Hagerman and Strafstrom 2009). It was found that in mice which lacked the Fragile X Mental Retardation protein (FMRP) this led to an accumulation of

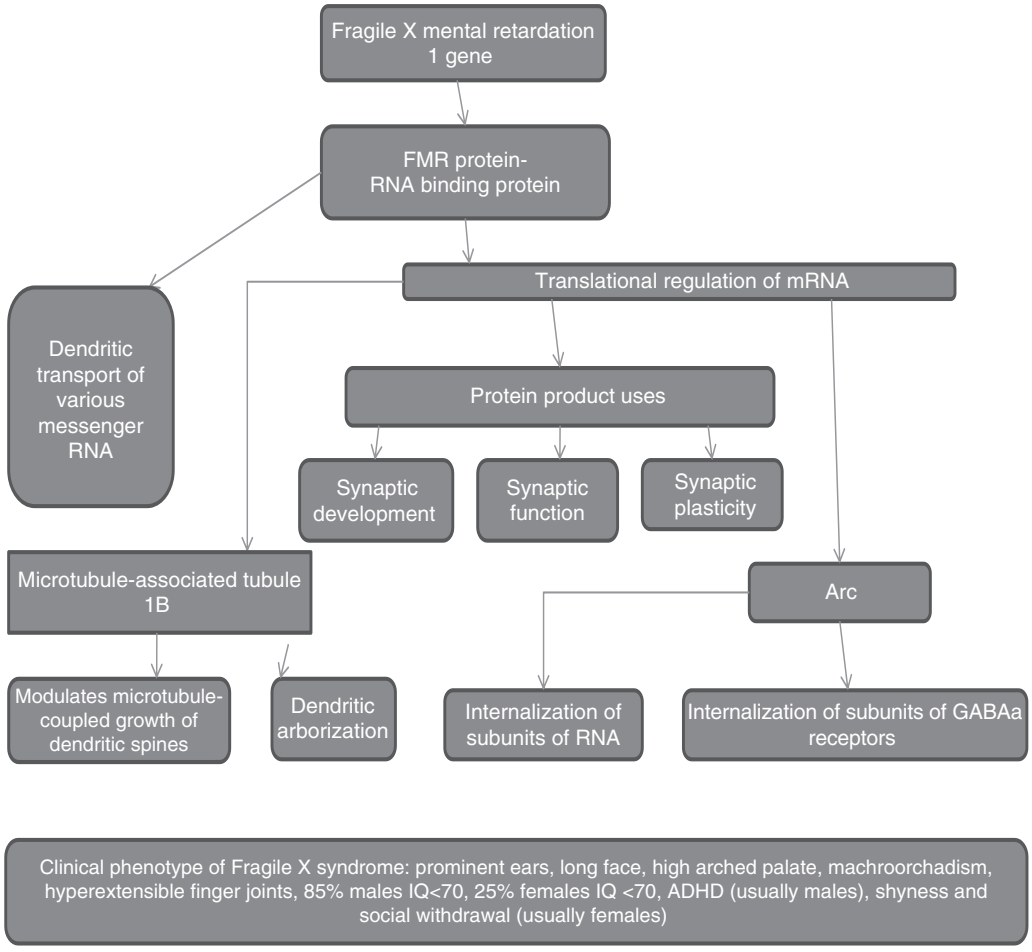

Figure 3.1. Adapted from Hagerman and Strafstrom (2009).

postsynaptic protein translation and eventual weakening of synaptic connections (Huber et al. 2002). This mouse model can be used to give reasons for many of the physical and behavioral phenotypes of Fragile X syndrome. A similar logic may also be applied to the epileptogenic mechanism whereby a voltage-gated inward current on group 1 mGluR is the cause. Activation of mGluR5 in numerous synapses eventually causes neuronal plasticity that has heightened electrical excitability.

The advances in the understanding of the genetic and molecular basis of epileptogenic activity in Fragile X syndrome enables a targeted treatment to be sought. Hagerman and Strafstrom (2009) suggest that this treatment could be based on blocking the mGluR5 receptor itself, which would then compensate for the absence of FMRP. They also point out that seizures found in Fragile X syndrome are not usually severe and often remit in childhood. The seizures usually respond to conventional anticonvulsants. Hence the type of treatment in Fragile X syndrome must consider these issues against any unfavorable side effects from a new medication.

Behavioral phenotypes

The recognition of an association between behavior and genotype is longstanding, an early recognized example being that of the high rate of self injury in Lesh Nyhan syndrome (O'Brien and Yule 1995), a recessive metabolic disorder. This association between causation of intellectual disability and specific patterns of behavior has been a rich area of scientific enquiry (Dan 2009; Moss et al. 2009). In

Table 3.3 Association between mouse models and behavioral phenotypes

Disorder	Mouse mutation	Behavior seen in mouse
Rett syndrome	MECP2 gene	Repetitive forelimb movements similar to those seen characteristically in girls with Rett syndrome
Prader-Willi syndrome	GABRB3 gene	Increased level of repetitive behavior
Angelman syndrome	GABRB3 gene	Increased level of repetitive behavior

particular the impact of genetic syndromes on a specific pattern of cognitive and behavioral presentation has been explored in a range of conditions, with an aim to establish an etiological pathway for behaviors explained at both a cognitive and neurobiological level (Moss et al. 2009). Mouse models looking at the neurobiological level have revealed potential etiological pathways for repetitive behavior as outlined in Table 3.3. (Moss et al. 2009).

These findings demonstrate the link between genetics and the behavioral phenotype in animals. An increasing number of studies have identified specific behavior characteristics in a range of conditions in humans including: social avoidance in fragile X (Schneider et al. 2009), increased social contact in Williams' syndrome, and psychosis in velocardio facial syndrome (Murphy et al. 1999). In the next section of this chapter we will discuss a range of more specific syndromes where a behavioral or epilepsy phenotype exists that may impact on neuropsychiatric assessment.

Specific genetic causes of intellectual disability and epilepsy

The following gives some examples of common genetic causes of intellectual disability and outlines the physical, behavioral, and epileptic phenotypes associated with them. The list is by no means exhaustive and the field is moving fast.

Angelman syndrome

This is a rare condition. Individuals with Angelman syndrome have severe intellectual disability, ataxia, paroxysmal inappropriate laughter, myoclonic jerks, and seizures (Schachter et al. 2008). In more than 70% of cases it is caused by a deletion of the long arm of chromosome 15 of maternal origin. Seizures present in about 90% of cases and they usually begin in infancy. The seizures tend to be of numerous types including: spasms, myoclonic, myoclonic-atonic, tonic-clonic, simple partial, complex partial, atypical absences, myoclonic absences, and febrile convulsions (Schachter et al. 2008).

Epilepsy often improves over time and can disappear by late childhood. It can however persist or reappear in adulthood and be difficult to control (Dan 2009). Thibert et al. conducted a large-scale study which looked at epilepsy and its treatments in Angelman syndrome (Thibert et al. 2009). Their results supported those of previous studies in that epilepsy was extremely common and more than half of patients had multiple seizure types. Seventy-seven percent of patients had medically refractive epilepsy and response rates to AED therapy were significantly lower than the reported response rate for the general population. The study also found that newer AEDs, levetiracetam and lamotrigine, were perceived to have similar efficacy as older medications in treating epilepsy in Angelman syndrome. It was also found that dietary therapy and vagus nerve stimulation were favorable in efficacy and tolerability but the small sample size for these precludes drawing any conclusions from this.

Genetic testing reveals a molecular mechanism where there is lack of expression of the UBE3A gene on the maternal chromosome 15 in the majority of patients (Dan 2009). The epilepsy phenotype of Angelman's points towards the need for those drugs that are of value in generalized epilepsies. Angelman's has a clear epilepsy phenotype; our understanding of the behavioral phenotype is also increasing. Pelc and colleagues (2008) provide a comprehensive review of the behavioral and neuropsychiatric manifestations of the disorder (Pelc et al. 2008). Many of the features of the condition can be relevant within epilepsy settings. Inappropriate laughter and motor stereotypies may be part of the differential diagnosis of epilepsy. The constellation of inattention, impulsivity, and hyperactivity can be mistaken for treatment side effects and may need behavioral treatment.

Cornelia de Lange syndrome

Cornelia de Lange syndrome (CDLS) is a rare genetic syndrome affecting approximately 1 in 10 000 live births (Dorsett and Krantz 2009). Genetic

abnormalities on chromosomes 5, 10, and X have been identified. The physical phenotype is characterized by short stature, limb abnormalities, distinctive facial features, and chronic respiratory infections. The epilepsy is ill defined though reflex anoxic seizures have been described (Nechay et al. 2006). Oliver and colleagues compared a population of individuals with CDLS with a matched cohort of individuals with intellectual disability; their study showed features of severe autism and those of compulsive behavior to be more common in the CDLS cohort (Oliver et al. 2008). Berney et al surveyed a non-controlled population with CDLS (Berney et al. 1999). They noted the high frequency of daily aggression, sleep disorder, hyperactivity, and self injury.

Down's syndrome

Down's syndrome is the single most common condition causing intellectual disability. The genetic abnormality involves the person having three copies of chromosome 21 and is often referred to as trisomy 21. In Down's syndrome epilepsy has two peaks of onset; the first is the development of epilepsy in infancy and the second is associated with the onset of dementia. Epilepsy semiology is pleomorphic and can include severe infantile encephalopathy such as West syndrome (Kajimoto et al. 2007) and a Lennox-Gastaut-like picture (Ferlazzo et al. 2009). Over 80% of people with Down's syndrome and dementia develop seizures and this may be the presenting symptom of the dementia. There may be a change in seizure frequency, pattern, or severity associated with the dementia compared with their previous epilepsy characteristics (Royal College of Psychiatrists/British Psychological Society 2009). The development of late-onset myoclonic seizures with Down's syndrome (LOMEDS) may be overlooked and take a clinical course not unlike progressive myoclonic dementias (Möller et al. 2001; De Simone et al. 2006). It is felt that seizures in people with Down's syndrome generally respond to a single antiepileptic medication.

The association between late-onset seizures, often myoclonic, and Alzheimer's disease is an important neuropsychiatric marker. Any individual with Down's syndrome and such seizures should have a comprehensive assessment for the presence of loss of skills or other features of cognitive decline.

Fragile X syndrome

Fragile X syndrome is one of the most common causes of inherited intellectual disability although prevalence figures vary among studies. It is caused by a single gene (FXMR 1) with an expanded CGG trinucleotide repeat on the long arm of the X chromosome (Schneider et al. 2009). Seizures are seen in approximately a quarter of children with Fragile X syndrome, but they are relatively benign and usually resolve after childhood (Hagerman and Stafstrom 2009). The phenotypic presentation in this disorder is large ears, narrow face, muscle hypotonia, and macro-orchidism. Lightbody and Reiss (2009) review the Fragile X behavioral phenotype. They define the key features as: gaze aversion, hyperactivity, inattention, anxiety and hyperarousal, and impulsivity. Furthermore individuals can have a range of social difficulties resembling those seen in the autistic spectrum.

Prader-Willi syndrome

Prader-Willi syndrome is caused by a microdeletion leading to the loss of paternally inherited genes on the long arm of chromosome 15. The condition is characterized by eating and satiety abnormalities, including hyperphagia and food seeking (Dykens and Shah 2003). Individuals with Prader-Willi syndrome show increased rates of self injurious behaviors with skin picking and aggression. Where maternal uniparental disomy is the cause of the genetic abnormality psychosis is more prevalent.

Fan and colleagues (2009) explored the characteristics of epilepsy in 56 individuals with Prader-Willi syndrome. Ten of the 56 individuals had seizures, the authors concluding that the seizure disorder was a spectrum of generalized seizure disorder.

Rett syndrome

Rett syndrome is a disorder mostly seen in females caused by a defect at Xq28 in the gene MECP2 (Fraser and Kerr 2003a). There appears to be geographic variation in prevalence with rates of about 0.1/1000 girls seen in some areas (Fraser and Kerr 2003b). The diagnosis is often made by recognizing the classical history of normal early development followed by regression in cognitive ability and a range of classical features. These usually include severe intellectual disability, scoliosis, epilepsy, autonomic dysfunction, abnormal hand function, and stereotypies (Perry 1991).

Seizures are reported in up to 90% of girls with Rett syndrome. However, an important differential diagnosis occurs due to the high level of autonomic dysfunction (Julu et al. 2001). It may sometimes be difficult to differentiate between epilepsy and non-epileptic vacant spells, which include a range of breathing abnormalities. The ideal investigation is telemetry plus autonomic monitoring. It is common for individuals to experience both vacant spells and epilepsy and it is important to ensure patients are not being inappropriately medicated for vacant spells which observers may be assuming are epileptic in origin. A further element of the Rett phenotype that needs recognition is that of motor stereotypy (Temudo et al. 2007). This can lead to self injury and may be misidentified as a seizure disorder.

Tuberous sclerosis

Tuberous sclerosis is usually associated with seizures and intellectual disability and often individuals demonstrate autistic and hyperkinetic activity (Sampson and Harris 1994; Schwarz et al. 2007). The syndrome is a variably expressed, autosomal dominant syndrome with multisystem involvement occurring in about 1 in 6000 live births (Chu-Shore et al. 2010). Two genes have been identified: TSC-1 and TSC-2; two-thirds of patients represent sporadic mutations. Seizures are common and are seen in up to 85% of individuals; they often begin in early childhood and are frequently associated with severe epilepsy syndromes such as infantile spasms and Lennox-Gastaut syndrome. Where infantile spasms occur it is usually indicative of those individuals who will have more severe intellectual disability and the most intractable epilepsy. The site of intracranial tubers is relevant with temporal tubers associated with the presence of autistic spectrum disorder (Raznahan et al. 2007). Muzykewicz et al. (2007) surveyed a large clinic population of individuals with tuberous sclerosis. Psychiatric disorder was common with mood disorder, anxiety, ADHD, and aggressive behavior disorder prevalent. The combination of seizure severity, autistic traits, and behavioral problems can lead to great difficulty in clinical epilepsy settings.

Velocardiofacial syndrome

This disorder is caused by a microdeletion of chromosome 22q11. Clinical features include distinctive dysmorphology, physical abnormalities, intellectual disability, and psychiatric disorders (El Tahir et al. 2004). There are several case reports of people with this disorder presenting with seizures. El Tahir et al. (2004) report on two case studies which both have a diagnosis of velocardiofacial syndrome (VCFS) and generalized epilepsy. They speculate as to whether the underlying genetic abnormality responsible for VCFS may contribute to the pathogenesis of generalized seizures but conclude that this is an area where more research is needed to examine this association. Lemke et al. reported on a case of juvenile myoclonic epilepsy in a girl with a 22q11.2 deletion (Lemke et al. 2009).

The neuropsychiatric profile of VCFS has been widely studied due largely to its strong association with psychosis. However, the breadth of psychiatric impairment is wide with there being high rates in childhood of ADHD, oppositional defiant behavior, and obsessive-compulsive disorder (Gothelf et al. 2008). In later adolescence and adulthood the prevalence of psychotic disorder is as high as 32% compared with 4% in the control population.

Williams syndrome

Also known as the Williams-Beuren syndrome this condition is a microdeletion disorder occurring in approximately 1 in 10 000 births (Pober 2010). Phenotypic presentation is variable but there are major abnormalities of the cardiovascular system (including stenosis of major arteries), the endocrine system (including hypocalcemia), and the nervous system. Intellectual disability is present and there is relatively higher verbal ability present. Anxiety disorders are present in 50–90% of individuals. Data is sparse on the epilepsy phenotype though case studies of infantile spasms exist (Tsao and Westman 1997; Morimoto et al. 2003).

Neuropsychiatric issues in the management of epilepsy in people with intellectual disability

From the chapter so far it is easy to see that for any individual with a genetic etiology their condition may impact on seizure presentation, treatment, and the understanding of any associated psychiatric or behavioral abnormality. However, when speaking more generally about epilepsy management there are two key areas in which neuropsychiatric assessment is

particularly important in assessing epilepsy and intellectual disability. These are (1) the assessment of behavior and (2) the assessment of treatment outcome.

Behavioral assessment in people with an intellectual disability and epilepsy is applied in a range of clinical scenarios (Kerr 2003). Firstly it can be as an aid to diagnosis when observed behavior is mooted to be a seizure. This is particularly important as misdiagnosis is common in this population. The most complex individuals in which to differentiate seizures from behavior disorders are often those with intellectual disability and an associated communication disorder. This difficulty can be seen in several of the specific syndromes we have mentioned to date: vacant episodes in Rett syndrome is one good example. The other important need for behavioral assessment is in the context of treatment outcome assessment. In this case behavioral change is associated with treatment change and the clinician needs to differentiate seizure or antiepileptic drug effects from environmental, physical, and other impacts on an individual's behavior. In both these situations knowledge of the genotypic effects on behavior can add a further useful dimension to the assessment.

Conclusions

There are many genetic disorders that give rise to epilepsy in the affected individuals. The severity and prognosis of the epilepsy varies among disorders and also among individuals. It is useful for both the family and the clinician to have information regarding a genetic cause for the epilepsy as this will give useful predictors of seizure prognosis and likely successful drug treatments, and assist in assessing behavioral and psychological pathology.

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Chapter 4

Epilepsy and autistic spectrum disorders

Thierry Deonna and Eliane Roulet-Perez

Introduction

The fact that this topic is included for the first time in this latest edition of *Neuropsychiatry of Epilepsy* may come as a surprise, because it has been known for some time that epilepsy frequently occurs (with a prevalence up to 30%) in people with autism. It reflects the fact that both epilepsy and autism as clinical concepts are undergoing major changes which modify the way the relationships between both disorders can be thought of. At the same time, the additional burden of epilepsy in an autistic person has become appreciated.

Autism is a disorder of brain development mainly affecting social interaction and verbal and nonverbal communicative functions. Restricted interests and stereotyped behaviors are also key features (Rapin 1991). Cognitive functions in the nonsocial domains may be normal (so-called high-functioning autism) or retarded (i.e. associated with global or specific disabilities of various severity, with notable "islets of ability") (Frith and Happé 2005).

Autism is not a single disease and it can be associated with different brain disorders.

A set of defined clinical diagnostic criteria for autism has been devised (DSM-IV revised or ICD-10 criteria of the WHO) and is considered a *sine qua non* condition to qualify for inclusion in a scientific study. Over the years, however, many children were found to have some but not all of these criteria, or not to be affected severely enough to fit the diagnosis of typical autism. These children were therefore labelled as having an "autistic spectrum disorder (ASD)," an "autistic-like condition," "atypical autism," or a "pervasive developmental disorder." Nowadays these terms are often used interchangeably (Tuchman 2006). The apparent increase in prevalence of autism probably reflects widening diagnostic criteria and increased awareness (Frith and Happé 2005).

One usually distinguishes primary autism (idiopathic autism) from secondary autism (symptomatic autism). This simply acknowledges the fact that in the first situation no specific neurological signs and no specific etiology has been found, be it a brain lesion or malformation, a metabolic disorder, or a genetic syndrome. These children show nothing apart from their abnormal behaviors and their cognitive level is more likely to be preserved (high-functioning autism/Asperger's syndrome). Like with other developmental disorders, some cases initially considered as primary have been found to have a cytogenetic or a metabolic abnormality or a brain malformation using new investigational techniques.

Patients with secondary or symptomatic autism often have associated intellectual disability and abnormal neurological findings. In these cases, the frequency of epilepsy is much higher (Olsson et al. 1988; Volkmar and Nelson 1990; Danielsson et al. 2005).

The basis of autistic spectrum disorders in the brain is still ill-understood and the focus of much research at the anatomical, neuropsychological, and genetic level (Frith and Happé 2005; Abrahams and Geschwind 2010). However, pathological examinations of brains of autistic people, animal experiments on primates, and studies of acquired autistic disorders after focal brain lesions have all contributed to the idea that dysfunction of the limbic system or its connexions do cause symptoms predominantly within the social-communicative and emotional sphere (De Long et al. 1981; Robbins 1999).

Autism and epilepsy: reasons for associations and possible common mechanisms

Observations made in the 1970s that autistic children often developed epilepsy during adolescence were

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

Table 4.1 Epilepsy and autism (classical data)*

Epilepsy is frequent in autism, much more in symptomatic autism and in autism associated with learning disability
Epileptiform EEG abnormalities (mainly in sleep) are very frequent in autistic children with/without seizures
Peak of onset of epilepsy in early childhood and adolescence. Onset past puberty rare (10%)
Complex partial seizures are the most frequent seizure type
Remission can occur at adult age, depending on etiology and epileptic syndrome (like in mental retardation)
Increasing recognition of genetic syndromes combining autistic spectrum disorder and epilepsy (usually with mental retardation)
Epilepsy in people with autism has an additive negative influence on quality of life and behavior (Turk et al. 2009)

**Note: These points do not apply to all persons with autism and deliberately no statistical figures are given since there are large differences between studies (inclusion or exclusion of patients with or without associated mental retardation or other handicaps; varying age at time of study, and severity of autistic symptoms).*

Table 4.2 Association between epilepsy and autism: possible relationships

Both conditions are totally independent (i.e. primary autism and coincidental petit mal epilepsy)
The same brain disorder is at the origin of an autistic phenotype *and* epilepsy (or paroxysmal EEG abnormalities), i.e. Fragile-X, duplication, 15q11–q13
A focal developmental pathology in specific brain networks involved in communication and social behavior ("social brain"; Adolph 2009) is the cause of an autistic phenotype and/or also the site of origin of an epileptic disorder that causes or aggravates the symptoms
The epileptic process causes a specific perceptual (i.e. visual) or cognitive dysfunction (i.e. language: auditory agnosia) contributing to the autistic phenotype in a vulnerable child
Acquired bilateral lesions in the limbic system due to recurrent status epilepticus ("hippocampal sclerosis") in young children may cause severe mental regression with autistic features (DeLong and Heinz 1997)

among the first strong arguments for a biological as opposed to a psychological cause of the disorder (Volkmar and Nelson 1990). Since then, a large number of clinical and EEG studies have been done to define the age of onset, seizure types, EEG findings, and prognosis in children with autism and epilepsy. These are summarized in Table 4.1.

The very different reasons why epilepsy and autism may be associated in a given child are outlined in Table 4.2.

One robust finding is that children with autism who also have a learning disability are more likely to have epilepsy than those at a higher cognitive level. This simply means that they have a more severe or diffuse brain pathology. In a recent study of children with a mean age of 9 years (4–21 years), only 1 in 34 children (3%) with primary autism and with "a higher IQ" had epilepsy, also indicating that epilepsy is not specifically associated with the autism itself but with the associated disorders (Pavone et al. 2004; Danielsson et al. 2005).

All types of seizures are seen in children with an ASD, but "infantile spasms" and temporal lobe seizures are much more frequently reported. The possible reasons for this will be discussed later.

Common genetic and molecular mechanisms that could be responsible for both the epilepsy and the ASD are increasingly looked for (Brooks-Kayal 2010; Tuchman et al. 2010a). While it is true that an increasing number of genetic (such as Fragile X or Rett syndrome) and metabolic conditions are recognized which often have epilepsy and some features of autism in common, they cause learning disability as well (Gurrieri et al. 1999; Scheffer et al. 2008; García-Peñas 2008). It is important to note also that the same conditions most often cause intellectual disability (i.e. most cases of Fragile X syndrome) or severe epilepsy without any autistic symptoms. In tuberous sclerosis, a monogenic disorder causing malformations of cortical development, the pathology may occasionally involve specific structures belonging to the "social brain" (Adolph 2009) and be associated with autism (see below).

To date, there have been no strong data to support the hypothesis that a synaptic dysfunction of genetic origin specifically involving the "social brain" networks and causing autism is closely related to a molecular abnormality responsible for epilepsy. In the future, new genetic disorders in which a close correlation with the clinical phenotype of autism (and not with severe mental retardation as well) and epilepsy may be discovered indicating specific common molecular mechanisms in some families.

Autism spectrum disorder is frequently reported in patients with epilepsy (Matsuo et al. 2010) but at this point it is crucial to note that the majority of children with severe early focal epilepsies who present with developmental delays, and language disturbances, are not autistic (Vasconcellos et al. 2001). This strongly suggests that specific characteristics of the epilepsy, like etiology and time and site of onset, as well as cerebral circuitry involved, must be decisive. Thus, focal cortical dysplasias, which are often highly epileptogenic in young children, not only cause localized or regional disturbances but also functionally and electrophysiologically widespread disturbances (Duchowny 2009; Roulet-Perez et al. 2010). One has to think not only in terms of anatomo-clinical correlations (Jambaqué et al. 1998) but also in terms of functionally and even structurally abnormal networks related to the epilepsy. If these belong to a brain system particularly important for social communicative functions, some or several behavioral anomalies within the autistic spectrum could be observed. Recent (f)MRI (functional magnetic resonance imaging) studies in high-functioning individuals with autism suggest that specialization of many cortical networks has failed to develop fully (Minshew and Keller 2010).

One can thus postulate that a strategically located epilepsy may have such an impact in young children. If seizures start very early in development, the child may present with a developmental disorder with predominantly autistic features. For example, an epileptic focus in cortical areas such as the superior temporal sulcus or the fusiform gyrus involved in the networks relating emotions to higher-level visual representations could interfere with the developing capacity to recognize the emotional signals of faces, which is typically deficient in autism (Leppänen and Nelson 2009). The key components of this network emerge early in life and could be vulnerable, as are for instance some components of the perisylvian language networks in rolandic epilepsy (Halász et al. 2005; Deonna and Roulet-Perez 2010).

The emphasis of this chapter will be to look at epileptic syndromes or types of epilepsies in which autistic symptoms can be a predominant manifestation, and can worsen or improve in direct correlation with the activity of the epilepsy, even though they probably constitute a minority of situations in which both autism and epilepsy co-occur.

It is not intended here to push the point that epilepsy is a frequent causal factor in autism and that treating epilepsy or chasing epileptic EEG abnormalities will improve or cure autism. Excessive hopes and beliefs of this sort have unfortunately led some clinicians to dismiss this issue altogether (Kanner 2000). However, we believe that this link remains theoretically and practically important, and is probably the most interesting way in which autism and epilepsy can be approached. Epilepsy, which is sometimes overlooked, may be the reason for an otherwise unexplainable evolution (positive or negative) in children with an ASD. This is all the more interesting in that recovery from autism is now increasingly recognized and well documented and epilepsy might be involved (Helt Molly et al. 2008).

In addition, recent major changes in the concepts of autism on the one hand and childhood epilepsy on the other have given new foundations for this approach and will be briefly summarized (Table 4.3).

Recent major changes in the concepts of autism and childhood epilepsy (Table 4.3)

Autism

The classical triad of symptoms (impaired social interaction; impaired communication; and restricted–repetitive interests and activities) which was considered a *sine qua non* condition to make the diagnosis of autism is now being challenged, mainly on the basis of clinical-genetic studies (in twins) showing that the different components of the clinical syndrome can be dissociated (Bailey and Parr 2003; Happé et al. 2006). The appearance or disappearance of some symptoms with age and the marked variability in severity (or sometimes the absence) of symptoms in one subset of the triad have become gradually evident, so that one is currently considering autism along a continuum without sharp boundaries, i.e. a move from a quantitative to a more qualitative view.

This change of view came as no surprise to child neurologists who are used to diagnosing rare or complex neurological conditions in which the clinical phenotype is often incomplete.

Although essentially genetic in origin, there is no single gene responsible for autism (Abrahams and Geschwind 2010). Many different genes are likely to be involved in the development of the networks

Table 4.3 Recent changes in the clinical concepts of "autism" and "epilepsy"

Autism
Classical triad (impaired social interaction, impaired communication, restricted–repetitive interests and activities) on which conventional diagnosis is based may be dissociated, challenging the current concept of autism
Dysfunction of different brain networks can lead to behavioral disturbances which have an impact on developing social–emotional competences and give some symptoms seen in autism
No single gene is responsible for autism (Abrahams and Geschwind 2010)
Prenatal or early postnatal lesions (non-genetic causes) may rarely cause an ASD
Impaired competences may improve or even normalize with age; ASD should no longer be considered a life-long disorder
Epilepsy
Epilepsy is not only a paroxysmal disorder, but also can be the cause of persistent, prolonged, or progressive cerebral dysfunction; it may also lead to acquired cognitive-behavioral disturbances in the absence of clinically recognized epilepsy
A prolonged abnormal bioelectrical activity within a developing brain network may lead to a dysfunctional connectivity which may be permanent
Any developing brain function may be selectively affected by epilepsy including social–emotional development and account, partially or fully, for an autistic syndrome

supporting the different functions of the so-called "social brain" (Adolph 2009). This is also true for familial developmental language disorders, where other, but related, brain circuits are affected. Specific language impairments (SLI) and autism are actually highly interconnected (Bishop and Norbury 2002). On the one hand, family studies have shown that SLI *or* autism can occur in the same sibship or twin pair (Bishop and Norbury 2002). On the other hand, some predominantly autistic children have an additional language disorder that affects expression and comprehension much beyond the semantic and pragmatic impairment usually found in this condition. The rare follow-up studies of children with combined SLI and autistic features have shown that either facet of this combination can significantly improve, so that a child initially considered mainly dysphasic or autistic can change diagnostic category with age. This indicates that a developmental pathology of genetic origin can affect different brain systems with a variable potential for improvement and "recovery" for each of these.

Finally, as with other developmental disorders, initially deficient skills may improve markedly with age, so that autism should no longer be considered a life-long disorder in all circumstances. This has been recognized in longitudinal studies in which cases of autism were comprehensively studied early in life (Helt Molly et al. 2008) and it was confirmed that several different biological conditions, in a given life context, can cause an autistic phenotype, with a variable potential for compensation.

Childhood epilepsy

The clinical manifestations defining epilepsy, i.e. recurrent unprovoked seizures, may be due to very different biological abnormalities (neurotransmitters, ion channels, cellular metabolism, etc.) which modify brain excitability at different ages and in different brain locations with different modes of spread according to the affected network. The underlying causes (genetic, acquired brain lesion) are multiple and the potential for recovery or persistence quite variable. This accounts for multiplicity of epilepsy types throughout the life span. Within a developing CNS network, a prolonged abnormal bioelectrical activity may lead to a nonfunctional or aberrant connectivity which may be permanent (Grigonis and Murphy 1994). This has been shown mainly in animal experiments, but there are good reasons to assume that it can also occur in humans (Khan et al. 2010).

Another important change in point of view is that epilepsy is no longer considered only as a paroxysmal disorder but the possible cause of chronic acquired cognitive-behavioral disturbances, sometimes even in the absence of recognized clinical seizures. In the latter case, an epileptiform abnormality on the electroencephalogram (EEG) is the only clue to the diagnosis. A typical example of this situation is the Landau-Kleffner syndrome (LKS) and the related idiopathic partial epilepsies with continuous spike-waves during sleep (CSWS) (Deonna and Roulet-Perez 2005). The term "cognitive epilepsies" is used to refer to those epilepsies in which cognitive or behavioral dysfunction

are the major or main clinical manifestations of epilepsy whatever the underlying causal epileptic disorder (Deonna and Roulet-Perez 2005). Most authors consider the above syndromes as belonging to the "epileptic encephalopathies," a cover term including very different epilepsies which have in common a marked cognitive impact, but usually a permanent one, in addition to severe and frequent seizures (i.e. Dravet syndrome).

This perspective has allowed the observation and reporting of an increasing number of clinical cases showing that epilepsy can actually involve separately, and "dissect", the different cognitive functions supporting a given complex ability and lead to unique clinical pictures. This has been particularly spectacular in the domain of language and memory. When the onset of the process occurs very early in life, it may appear as a developmental disorder with no clue as to etiology (Mayor Dubois et al. 2004). Further it has been difficult to demonstrate that reversible "epileptic" disabilities can also occur predominantly or exclusively in the social-emotional domain (Gillberg and Schaumann 1983; Deonna and Roulet-Perez 2005).

Tuberous sclerosis (TS): an important model

Among the well-defined congenital and highly epileptogenic brain disorders relatively frequently associated with ASD, tuberous sclerosis deserves a special mention, because it highlights several points in the discussion of association versus causality of autism and epilepsy. The fact that some people with TS are also autistic suggests a link between the nature or location of the malformations of brain development and/or the almost constantly associated epilepsy.

Since the advent of brain imaging (MRI), important new data have emerged on that point. Bolton et al. (2002) studied 53 children with TS and tubers in various locations (31 in the temporal areas). Among those with ASD 17 out of 19 had temporal lobe tubers whereas only 14 out of 34 non-ASD subjects had temporal lobe tubers. Of the 17 cases with temporal lobe tubers and ASD, all had a probable or possible temporal EEG focus and several had had a history of infantile spasms. It appeared that it was not only the location of the tubers in the temporal lobes, but also the presence of epilepsy involving these structures that was a determining factor.

In several case reports, the development of an ASD seemed to correlate with the onset and aggravation of the epilepsy, although this was not studied directly (Hunt and Dennis 1987). In a longitudinal study of two children with TS, we demonstrated a direct relationship between the epilepsy and the autistic disorder in one case (Deonna et al. 1993). Recently, Humphrey et al. (2006) were able to document prospectively an autistic regression after normal development between 13 and 24 months in correlation with seizure onset in a child with previously known TS. Although the child did not significantly improve after diagnosis and antiepileptic treatment during the 12 months of follow-up for different possible reasons (Deonna et al. 2007), the coincidence of the onset of epilepsy is very suggestive of a direct cause-effect relationship. This can certainly be further studied, because children with TS are now increasingly diagnosed before or at birth and followed prospectively with EEG recordings before the first occurrence of epilepsy. In these cases, early recognition and treatment of a cognitive-behavioral regression could occur and prevent permanent sequellae due to epilepsy (Bombardieri et al. 2010).

Autistic regression and epilepsy or EEG epileptiform abnormalities

In the last 20 to 30 years, it has been found that epileptiform EEG abnormalities are frequent in children with ASD, even in those who have never had epilepsy (Ballaban-Gil and Tuchman 2000). These occur particularly during sleep and studies continue to be published confirming this fact (Chez et al. 2006). There has been debate and disagreements as to whether epileptiform abnormalities are only markers of the abnormal brain function or whether they could play a more direct causal role. When it was realized that about 25–30% of children diagnosed with an ASD had a history of language and communicative regression during the second year of life, the question arose of a possible role for a "hidden" epilepsy. This was also prompted by the increasing recognition of a very special epileptic syndrome affecting children, namely acquired epileptic aphasia or Landau-Kleffner syndrome (LKS), which could start quite early in life and could be mistaken for a primary ASD (see below). LKS can occur in children who have never had clinical seizures and in whom only epileptiform EEG discharges suggest the diagnosis. Suppression of these abnormal discharges with antiepileptic drugs or

steroids can be followed by a remarkable improvement in some cases. The question of overlap between early Landau-Kleffner syndrome and autistic regression (Stefanatos et al. 2002) has been reviewed by the authors of this chapter in detail (Deonna and Roulet-Perez 2010) and is discussed below.

After more than 25 years of research, the consensus is that in primary autism, even in those patients who have a history of regression, the occurrence of epilepsy or EEG epileptiform abnormalities is not a causal factor (Baird et al. 2006; Tuchman et al. 2010a).

Epilepsies and epileptic syndromes with direct impact on social-communicative development (Figure 4.1 and Table 4.4)

The structures of the limbic system thought to be involved in ASD are highly epileptogenic and are the origin of frequently encountered early childhood epilepsies or epileptic syndromes (Fig. 4.1).

We will now look at these epilepsies and examine if or how frequently an ASD is actually found. Alternatively, in an epileptic child with an associated ASD, especially if symptoms start or worsen when the epilepsy becomes more active, some of its characteristics, i.e. age at onset, site of origin and spread, or change in maximal epileptogenic zone, may suggest that it has a direct role in the ASD.

Infantile spasms (West syndrome)

The association between autism and West syndrome was one of the first findings to support a neurobiological etiology for autism at a time when psychogenic theories were still flourishing. A small but significant number of children diagnosed with autism had a history of infantile spasms in infancy (Taft and Cohen 1971). Autistic children who had infantile spasms also have learning disability (Riikonen 2001). Some autistic children with learning disability who had infantile spasms and were studied by PET (positron emission tomography) at a late stage show bilateral temporal hypometabolism (Chugani et al. 1996), which is of interest considering the brain systems thought to be implicated in autism.

A global lack of interest in surroundings, irritability, sleep disturbances, and poor and fluctuating visual attention sometimes suggesting blindness are commonly noted in the acute phase, which is sometimes not quite accurately described as autistic. The constant epileptic activity (so-called hypsarrhythmia on the EEG) is a sort of "cognitive status epilepticus." The child appears disconnected from all afferant inputs, has no initiative and affect and may thus appear superficially as autistic. However, it may be that a central visual impairment due to a specific dysfunction of posterior cortical areas prevents the recognition of visual clues essential for emotional development.

Table 4.4 Epileptic syndromes, seizure types, or specific pathologies in which autistic features may appear or correlate with the epileptic activity

Infantile spasms and late infantile spasms
Early partial complex seizures, usually symptomatic of frontal or temporal origin
Frontal epilepsy with CSWS ("acquired epileptic frontal syndrome")*
Acquired epileptic aphasia (Landau-Kleffner syndrome) early forms*
Specific pathologies:
Tuberous sclerosis (epileptogenic tubers in temporal lobes)
Hypothalamic hamartoma (early onset, severe seizures; Deonna and Ziegler 2000)

*See text for discussion.

Late epileptic spasms

When epileptic spasms start later (onset 1–3 years of age), the child may have already reached a significant level of cognitive, social, and emotional development and the regression in these children can be much better recognized and studied. This regression may predominantly show autistic features and persist after seizures have subsided. Improvement may however occur in the long term. During the regression phase, the preservation of some cognitive competences (i.e. visuospatial) while social interaction and verbal and nonverbal communication are affected attests to the specificity of the regression (Deonna and Roulet-Perez 2005).

In such cases, focal EEG discharges (after generalized discharges have subsided) are seen predominantly in the frontal or frontotemporal areas.

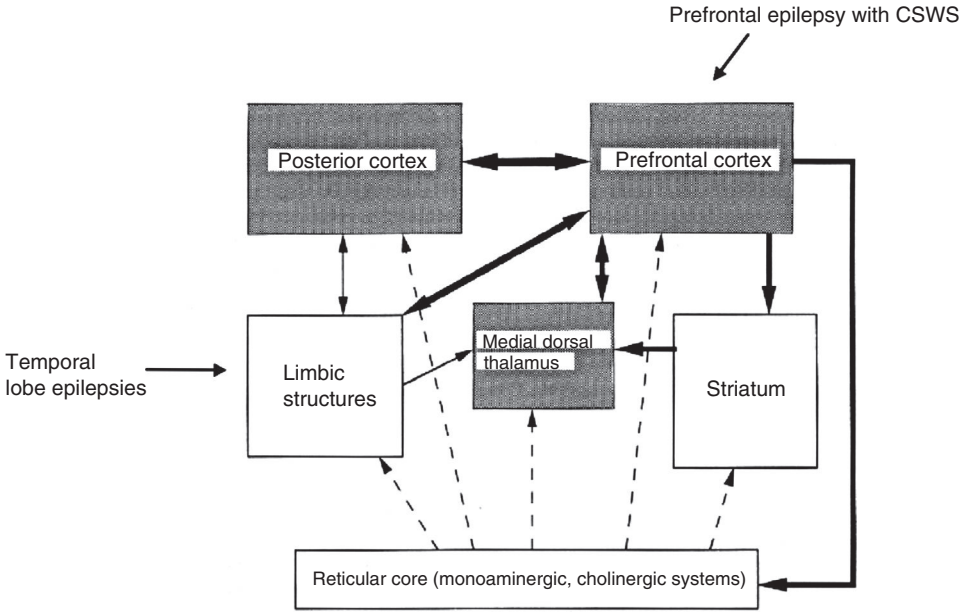

Figure 4.1. Important interconnected brain structures whose dysfunctions (clinical, pathological, and experimental) are associated with an autistic disorder. They are highly epileptogenic and are often at the origin of frequently encountered early childhood epilepsies or epileptic syndromes. CSWS, continuous spike-waves during sleep. Reproduced and modified with permission from Robbins (1999).

Early-onset refractory temporal lobe epilepsies

The high incidence of behavioral disorders in children with temporal lobe epilepsy has been recognized for a long time, much before a clear nosology of the various developmental disorders was accepted and used in clinical research (Lindsay et al. 1979). However, the symptoms are not those of an ASD, apart from some important and interesting exceptions. There have been isolated case reports of children with temporal lobe tumors or cortical dysplasias, in which a behavioral regression of the autistic type could be correlated with onset or aggravation of epileptic seizures, with recovery or at least significant improvement when seizures were controlled (Hoon and Reiss 1992). With the frequent use of surgery for refractory temporal lobe epilepsy in children, which is done at an increasingly younger age, systematic studies of the child's psychopathology before and after successful surgery are beginning to appear (McLellan et al. 2005; Danielsson et al. 2009). Some of these children are clearly in the autistic spectrum; most do improve after surgery and some very rarely worsen. It remains uncertain whether these children were autistic to start with or became so after epilepsy onset and which set of symptoms changed in order to account for the reported improvement. Given the various types of brain pathology, the exact site of maximal epileptogenicity within the limbic system, age at onset of epilepsy and surgery, and short follow-ups (maximum 5 years), it is not surprising that outcomes and severity of autistic profiles are very different. However, these children do represent a unique opportunity to study the possible direct role of epilepsy in causing an ASD. The following case illustrates the complexity of the issue.

E. is a 16-year-old boy with a moderate autistic disorder. He had a right temporal lobectomy at 6 years of age for refractory complex partial seizures which had an onset at the age of 13 months due to hippocampal sclerosis. Full remission was obtained and all medication withdrawn from the age of 9 years. Precise pre- and post-surgical neuropsychological follow-up from 6 to 8 years showed a postoperative significant improvement of autistic symptoms (CARS: Childhood Autism Rating Scale: 36→26 points) mainly due to better "adaptation to change," decreased "level of activity," and "tolerance to frustration" items, rather than to a decrease in more specific autistic traits (Mayor 1999).

His language, which was almost absent at 6 years, improved slowly between 8 and 16 years to become functional. Autistic symptoms also continued to improve markedly, although he is still quite socially impaired. It remains uncertain whether he became autistic as part of his early severe epilepsy (no precise longitudinal follow-up from onset of seizures) and whether there is still a possibility of late improvement of his behavior, by analogy with what happened with his verbal language.

Idiopathic partial epilepsies with cognitive-behavioral symptoms and CSWS

Acquired epileptic aphasia (LKS) of early onset with autistic symptoms

Early-onset LKS, most often an auditory agnosia, may present as a developmental language disturbance and the affected child may sometimes also exhibit autistic features. LKS is now seen as the rare and severe end of a spectrum of cognitive-behavioral symptoms that can be seen in idiopathic (genetic) focal epilepsies of childhood, the benign end being the more frequent rolandic epilepsy. Several recent studies show that some children with rolandic epilepsy have minor developmental cognitive and behavioral problems and that some undergo a temporary deterioration. The severity and type of deterioration correlate with the site and spread of the epileptic spikes recorded on the EEG within the perisylvian region, and continuous focal or diffuse spike-waves during sleep (CSWS) are frequently found (Deonna and Roulet-Perez 2010). Some of these children have pre-existing communication disorders. If early stagnation or regression occurs in these domains, it presumably reflects epileptic activity in networks outside the perisylvian area, i.e. those involved in social cognition and emotions (Nass et al. 1998).

Several clinical, electroencephalographic (including magnetoencephalography), genetic (family studies), and (rare) therapeutic (antiepileptic drugs or steroids) studies suggest that in some children with apparently developmental language delay or very early loss of language, with or without autistic features, the delay may be directly caused by epileptic EEG discharges (Lewine et al. 1999; Rejnö-Habte et al. 2010). How much and which autistic symptoms disappear with antiepileptic therapy has not been well documented. We did not find any report of a child whose clinical picture was incontestably that of a primary autism and who later lost these characteristics when treated within the framework of LKS.

Partial epilepsies with prefrontal foci and dementia and/or psychosis

This clinical symptomatology is probably the most dramatic and severe of all behavioral-psychiatric manifestations of epilepsy in children and some of these children display what has been called an "acquired epileptic frontal syndrome" (Roulet Perez et al. 1993). The regression usually starts around 3–5 years of age and the child's behavior may exhibit some autistic features like inadequate social interaction and use of language, rigidity, and perseverations. However, the children were usually normal prior to onset of the epileptic syndrome, and developed a thought disorder, confabulations, with many preserved emotional capacities, more like psychotic patients (Roulet Perez et al. 1993; Kyllerman et al. 1996). The rare adult follow-ups of these children have shown a marked improvement or disappearance of the behavioral symptoms with variable residual, in particular executive, cognitive deficits but no signs of "sociopathy" or of autism (Seegmuller, unpublished data). These cases are mentioned here because some of the behavioral symptoms in the acute phase can be considered as autistic, if considered in isolation.

Diagnosis and management of epilepsy in autistic children and adults

Diagnosis and differential diagnosis of epilepsy

There are numerous paroxysmal nonepileptic neurological disorders which can be erroneously diagnosed as epilepsy. If an autistic child has already been diagnosed as having epilepsy, it is natural to consider that any new paroxysmal manifestation is epileptic without thinking further. However, the same analysis of paroxysmal symptoms in each new circumstance is necessary as with any child, even more so because of the many possible pitfalls. First, the sensations (fright, vegetative changes, fatigue) that may be experienced during the seizure or more often in the postictal state and their sudden onset can cause an emotional reaction with a marked change in behavior (panic,

regression, aggression, irritability), which can be extreme and more severe than the seizure itself. The autistic child or adolescent is unable to express special sensory, vegetative, or motor symptoms which can be so useful in diagnosis. If the epileptic manifestation has a cognitive component (loss of vigilance, arrest of purposeful activity, loss of language, or a global temporary decrease in cognitive performances), this will be less evident in a child with a basic low level of function or who does not communicate. The work-up may be complicated by the fact that the EEG, which is so important in the diagnosis of specific epileptic syndromes, may be difficult to obtain or gives incomplete information (no sleep record obtained, no photic stimulation done, etc.).

In addition, stereotypies, which are very frequent in autistic people, and their possible relationship to epilepsy must also be discussed. They most often co-occur with seizures but as two different phenomena without any link. Occasionally, complex partial seizures ("epileptic automatisms or epileptic stereotypies"), which are manifestations of epilepsy of frontal or temporal origin, can present with stereotyped movements ("hand clapping", "applause", turning in circle", etc.) and can be mistaken for a nonepileptic autistic stereotypy (Deonna et al. 2002; Fohlen et al. 2004). The problem is likely to arise in young children with developmental delay and autistic behavior in whom the seizures may aggravate the overall functioning or even be a major cause of their deficit (for the details of these manifestations and the difficulty with the diagnosis, see Deonna et al. 2002).

Self-induced syncopes or presyncopes can be seen as the consequence of a respiratory stereotypy with apnea after a forced expiration or a Valsalva maneuver. Abnormal gesturing can follow a brief loss of tone and unconsciousness and convulsive syncope may even ensue. The differential diagnosis with epilepsy may be very difficult because these children may also have an independent epilepsy (Gastaut et al. 1982).

When the symptoms are indisputably epileptic, the question remains to classify the seizure types, to see if they correspond to a known epileptic syndrome and if they can be attributed to the basic brain disorder/pathology which also caused the ASD. Idiopathic-genetic childhood epilepsies are very frequent and may occur by chance in a child with autism (for instance petit mal epilepsy, rolandic epilepsy, juvenile myoclonic epilepsy). This has of course prognostic and therapeutic implications.

Special impact of epilepsy on life and problems of antiepileptic therapy in autistic persons

In autistic children who find it difficult to cope with novelty and adapt to changing circumstances, the experience of seizures themselves, the medical examinations, and special investigations (EEGs, etc.) are difficult to tolerate and can aggravate their behavioral problems. Frequent epileptic seizures in an autistic child can limit the amount of independence that parents and caretakers are willing to give them which is so important to acquire and develop as an adolescent or adult.

Basically, the indication to start or not a continuous antiepileptic therapy in a newly diagnosed epilepsy and which specific drug to use should follow the same principles as in any other epileptic person. However, several considerations are especially important in the context of autism. One might think that, even if the child has had only one or a few seizures, they are likely to recur because of the underlying brain disorder. However, some autistic children have only rare seizures, and not necessarily severe ones, or they may occur only in certain circumstances known to lower the seizure threshold so that chronic therapy may not be mandatory. The worry that neuroleptics (mainly risperidone) increasingly used in autistic persons with severe behavior problems might exacerbate pre-existing epilepsy or favor its development appears rarely justified (Gonzalez-Heydrich et al. 2004; Holzhausen et al. 2007).

The epilepsy itself can aggravate the autistic disorder. An additional decrease of overall functional level may not be immediately noticed if the basic handicap is already severe, but the quality of life and emotional welfare can be much affected.

If therapy is indicated, the potential cognitive and behavioral side effects may occur more often in children with a low functional cerebral "store" and in whom it is difficult to be sure if the observed changes are due to the medication, when many other explanations can be found. Some of these epilepsies may be severe and necessitate more than one drug to achieve control, which is not always possible (refractory seizures). There is a danger of overmedication and therapeutic escalation, without obvious benefit or even aggravation, especially in institutions (Pellock and Hunt 1996).

Occasionally, antiepileptic therapy not only fully controls the seizures, but also some of the autistic symptoms become much less severe. The difficult question that arises here is whether this is a direct effect on the abnormal epileptic networks or an unrelated positive psychotropic effect of the drug (on mood or anxiety) as is well documented with some antiepileptics (Tuchman et al. 2010b).

Epilepsy management is especially difficult when the child or young adult does not live with his or her parents. In this situation, frequent contacts with the same caretakers are necessary to evaluate different therapeutic trials. EEG investigations and blood drug monitoring should be limited but when required, visits to the hospital can be a nightmare. Liaison with institution nurses and direct discussions between neurologists or neuropaediatricians and families or residential staff are a great help in such cases.

Management of acute seizures has been greatly facilitated by the use of buccal or nasal short-acting powerful diazepines, such as midazolam, in the hospital or day-care centers (Jeannet et al. 1999).

High-functioning autism including Asperger's syndrome and epilepsy: how is the impact of epilepsy experienced?

There are almost no data on the long-term prognosis for epilepsy in high-functioning autistic persons and specifically on the effects of epilepsy on the different symptoms of the ASD. One can speculate how such persons might experience and report seizure-related mental phenomena and in what way the transient physiological disturbances before seizures, during seizures, or in the postictal state could influence their perceptions of the outside world or their mood, level of anxiety, and social interactions. In one study, a 23-year-old man with Asperger's syndrome and refractory temporal lobe epilepsy of very early onset (<1 year) showed improvement following vagal nerve stimulation (Warwick et al. 2007). The patient's behavior improved markedly in correlation with a reduction in seizure frequency (from 80 to 30 seizures/month), in the nonverbal social interaction and emotional domains, as documented using ad hoc questionnaires. He was "the best he has ever been" according to his parents. Unfortunately, there were no data on the patient's perception of his new situation and whether he had better insight into his autistic symptoms. One might think that the lack of insight and self-awareness typical of the autistic mind would preclude any sharing of information, but this remains a totally open question. The authors postulated a direct better functioning of the brain systems involved in Asperger's syndrome due to an improvement in his temporal lobe epilepsy. Of course it may have been only a nonspecific improvement of well-being due to seizure reduction. The study of such exceptional cases helps to establish if and how the epileptic activity modifies – either release, exacerbate, or improve – some of the behaviors seen in autistic individuals.

The rarity of such testimonies probably reflects the large gap that still exists between psychiatry and epileptology, which a book such as this tries to address.

Possible "subclinical epilepsy" in young autistic children with or without regression: when is antiepileptic treatment indicated?

When a young child presents with ongoing or recent language and behavioral regression with autistic features and is found to have possible clinical epilepsy or only EEG epileptic discharges, a complete etiological investigation has to be undertaken. Some rare neurometabolic disorders may present with an autistic and cognitive regression without additional neurological or somatic features. Rett syndrome must always be considered because its course may be atypical (for example with a prolonged period of preserved hand use, or late onset of hand stereotypies). An undiagnosed epilepsy with difficult to recognize seizures, or an epileptic disorder without clinical seizures but with sustained epileptic discharges, must always be looked for. This is especially so when regression has occurred after 2 years of age or its pattern or evolution appears unusual (absence of response to sounds that preceded the behavioral changes suggesting auditory agnosia; or severe inattention, abnormal thought, and repetitive behaviors with preserved eye contact and language) or is fluctuating suggesting LKS or a frontal epilepsy with CSWS. In these rare cases, aggressive antiepileptic medication or steroids with the aim of stopping the seizures and/or the epileptic activity on the EEG is mandatory.

In a young child with a developmental disorder and autistic features but no regression and in whom paroxysmal EEG abnormalities are discovered, the probability is very high that the epileptic discharges are only markers of the underlying brain pathology responsible for the developmental disorder or secondary to common genetic factors. When epileptic discharges are very frequent, bilateral, focal, multifocal, or even generalized and there is no detectable underlying brain lesion in an otherwise neurologically normal and nondysmorphic child, they may have interfered with language and social skills so early that they prevented their emergence. This interpretation is only speculative inasmuch as, to the best of our knowledge, no adequate longitudinal study of such cases supports it convincingly and it remains an open question. In this situation, antiepileptic treatment may be attempted, but only with careful neuropsychological and EEG monitoring and regular critical analysis of the results (Roulet-Perez and Deonna 2006).

Prognosis of epilepsy and the issue of drug withdrawal

Full remission or a significant decrease in the frequency and severity of seizures is a general trend of all childhood epilepsies with a few exceptions. However, this is highly variable, depending on many factors, but mainly on the type of epileptic syndrome and specific etiology. The prognosis and the possibility of drug withdrawal after a seizure-free period should be considered individually in any child or adolescent with epilepsy, be it symptomatic or idiopathic. The old idea that epilepsy from focal brain damage or more diffuse brain pathology causing learning disability or autism is life-long and will need continuous antiepileptic therapy has been clearly refuted. Long-term follow-up studies of children with either cerebral palsy or mental retardation have shown that a complete remission can occur after a 5-year seizure-free period in at least 50% of cases.

In a population-based follow-up study of 120 individuals with autism diagnosed in childhood and followed for a period of 13–22 years, a remission of epilepsy was seen in 16%. Of note is that the study excluded individuals with "high-functioning autism or Asperger's syndrome" (Danielsson et al. 2005), so that only the more severe cases were considered.

Late outcome of children with an acquired epileptic autistic regression in early childhood

Rare case reports of children with severe early epilepsy and a developmental regression with predominant autistic symptoms and alleged "recovery" have been published, but with no detailed long-term outcome. We take the opportunity to present here the follow-up of such a child (see details in Deonna and Roulet-Perez 2005).

Case report (Figure 4.2)

This boy was followed prospectively from the age of 13 months when his epilepsy was first diagnosed and treated; he had had seizures for at least 3 months before the diagnosis, mainly sudden fatigue, "eye rubbing," and activity arrest associated with diffuse irregular spike-waves on EEG. After initial therapy with valproate, the diffuse spike-waves disappeared and an intermittent left frontal temporal focus appeared. A brain MRI was normal. The child was followed-up to see if there would be a "catch-up" in his mild developmental delay after control of his epilepsy. Progress was noted for a few months followed by an insidious regression in communication and play reported by the parents and by the early education specialist during home visits: "he is busy with himself without the need of others; his games become too systematic," and "his behavior resembles autism." This regression worsened quite rapidly around the age of 25 months with the occurrence of epileptic stereotypies and late-onset epileptic spasms (for details of this semiology see Deonna et al. 2002) and his behavior became typically autistic. At his worst, he was not lethargic but rather hyperactive and he was able to do embeddings of shapes with ease. This showed a clear dissociation between his much regressed communicative skills and preserved visuospatial capacities. His communication improved rapidly with prednisone. This observation is unusual because the regression happened "under our eyes," was unexpected, and could be documented prospectively.

He has been regularly followed-up since then and has made remarkable cognitive progress (see Fig. 4.2). Social communication status improved with

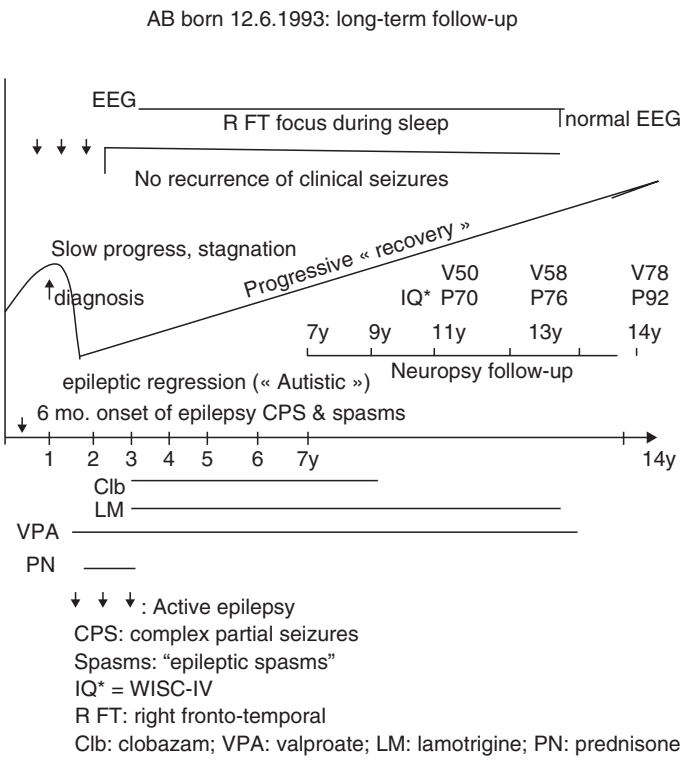

Figure 4.2. Child AB: see case report in text. This graph summarizes the clinical course from 13 months of age (onset of prospective study) until 14 years and shows the evolution of seizures and results of serial IQ tests obtained from 9 to 13 years. Prior to that age, behavior was too disturbed to obtain reliable and complete data.

continuing acquisitions documented between 10 and 14 years, but moderate problems persisted in this domain. At the age of 13 years, a questionnaire on Asperger's syndrome was performed (55 questions). He scored 17 points (just below the cut-off). He had literal comprehension of ambiguous or metaphoric expressions, a tendency to accumulate knowledge without full comprehension, and a particular communication style with relatively monotonous prosody. Cognitive abilities remained dissociated with a better visuospatial than verbal level. He had no ritualistic behavior and his special interests did not have a negative impact on his life.

Comment

His residual symptoms in the communicative-social domains (qualitatively within the autistic spectrum) are most probably a sequel of his epileptic disorder and/or to the underlying brain pathology at its origin. There was no family history of ASD. These symptoms were of a moderate degree considering the initially severe picture. Cases like this are of considerable interest so far as the behavioral phenotype at adolescence resembles high-functioning autism (Asperger's syndrome) of developmental origin.

Conclusions

The growing recognition that epilepsy and/or paroxysmal EEG epileptiform abnormalities are very frequent in children with ASD and the discovery of new genetic disorders in which epilepsy and some features of autism co-occur has given much hope to better understanding the underlying brain dysfunction. At the same time, many changes in the somewhat rigid view of what constitutes autistic symptoms and epileptic manifestations have taken place. These changes have influenced the way in which one looks at some early-onset epilepsies that may affect brain regions or networks supporting emotional and social development and thus occasionally cause or contribute to the ASD.

On the other hand the clinical diagnosis and management of autistic children and adults, while sharing the same principles as those followed with other handicapped persons, have unique features related to the specific symptoms of ASD.

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Chapter 5

Subtle cognitive and behavioral effects of epilepsy

Frank M.C. Besag

Introduction

Both cognitive and behavioral problems are common in people with epilepsy. Epidemiological studies have indicated that around 50% of children with epilepsy have some schooling difficulties and that many have behavioral problems (Pazzaglia and Frank-Pazzaglia 1976; Ross et al. 1980; Sillanpää 1992; Besag et al. 1999). The National Child Development Study in the UK (Ross et al. 1980) revealed that only 67% of children with epilepsy were attending a mainstream school at age 11. Using this broad-brush measure it was evident that a large proportion of the children with epilepsy had significant schooling problems. The work of Pazzaglia and Frank-Pazzaglia in Cesena, Italy (Pazzaglia and Frank-Pazzaglia 1976) also confirmed that a high proportion of children were underachieving at school. The excellent epidemiological studies of Sillanpää (Sillanpää 1992) in Finland showed that 31.4% of this unselected sample of children had mental retardation. Davies et al. (2003), in a British population survey of children with epilepsy, found that 37% had a psychiatric disorder.

In a study carried out in the London Borough of Lambeth, Besag et al. (1999) surveyed 127 children with epilepsy. Sixty-five percent were perceived by their parents to have schooling problems or learning disability and 48% were disturbed according to Rutter Behavioral Scales. Sixty-two percent of the scores indicated a significant impact on quality of life, which was moderate or great in 35%. These studies suggest that schooling and behavioral difficulties constitute a major problem in childhood epilepsy. There is a lack of data, however, to indicate the causes of the problems encountered, both in children and adults.

A systematic framework for assessing behavior

The current author has suggested that when faced with an individual who has epilepsy and behavioral problems, the best approach is to use a systematic framework for assessing the possible cause or causes of the behavioral disturbance (Besag 2002). This framework consists of five main categories: the epilepsy itself, treatment of the epilepsy, reactions to the epilepsy, associated brain damage/dysfunction, and causes equally applicable to people without epilepsy.

The first category, the epilepsy itself, may be broken down into the peri-ictal phenomena of prodrome, aura, automatism and postictal changes, interictal psychoses, focal discharges, and frequent absence seizures. This list is not necessarily comprehensive.

Examples of the way in which the epilepsy itself may affect behavior have been provided elsewhere (Besag 2002). A subtle cognitive or behavioral effect of epilepsy may be defined as an effect that is not immediately obviously attributable to an epileptic seizure. This does not imply that the epileptic activity itself is necessarily "subtle." For example, prodromal mood change preceding a tonic–clonic seizure could be regarded as a subtle effect of the epilepsy, although the seizure itself is not at all subtle. On the other hand, the subtle cognitive and behavioral effects of epilepsy may be the result of subtle seizure activity. In this context, subtle seizure activity is taken to mean a clinical manifestation of epileptiform activity that is not immediately obviously identifiable as a seizure. Absence seizures and many complex partial seizures would fall into this category as would transitory cognitive impairment. There is a growing realization of the fact that epilepsy may affect cognition and behavior in a variety of ways (Stores and Hart 1975;

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

Stores 1978; Trimble 1988; Deonna 1995; Aldenkamp 1997; Besag 1995; 2006; Elliott et al. 2009). There is often an overlap between cognitive and behavioral effects of epileptiform activity.

Frequent frontal discharges may lead to a high degree of social disinhibition and consequent behavioral disturbance.

A teenager had a long history of gross behavioral disturbance. The EEG showed very frequent left frontal discharges, typically occurring every second. He underwent a left frontal lobectomy, following which the epileptiform discharges were abolished, his behavioral disturbance resolved and he returned to his pleasant premorbid personality.

Frequent left temporal discharges may be associated with aggressive behavior. There is evidence from the literature suggesting that young men who have left temporal discharges and subsequently undergo a left temporal lobectomy show improvements both in seizure control and in behavior (Falconer 1973; van Elst et al. 2000).

Further examples of both cognitive and behavioral disturbance that can result from subtle manifestations of epilepsy will be discussed in the next section.

State-dependent cognitive impairment

It is important to distinguish permanent cognitive impairment on the one hand from state-dependent cognitive impairment on the other. The concept of permanent cognitive impairment is readily understood. This may arise from a wide variety of causes of permanent brain damage or dysfunction that may be prenatal, perinatal, or postnatal. The concept of state-dependent cognitive impairment is less widely acknowledged (Besag 1994).

What is state-dependent cognitive impairment? State-dependent cognitive impairment may be defined as cognitive impairment that depends on current factors affecting the individual, for example antiepileptic medication or epileptic activity, that are not necessarily permanent. State-dependent cognitive impairment is potentially reversible and treatable. Failure to treat state-dependent cognitive impairment is failure to provide an adequate service to the patient. Some might put the case even more strongly by suggesting that failure to recognize and treat state-dependent cognitive impairment is a reflection on professional competence.

The first step in managing state-dependent cognitive impairment is to think of the diagnosis. Regrettably, professionals often fail to take this first step. The result is that the condition is neither recognized nor treated. State-dependent cognitive impairment may be divided into two broad categories: drug-induced and epilepsy-induced. As already indicated, the epilepsy itself may cause state-dependent cognitive impairment in a number of different ways.

Frequent absence seizures

Absence seizures were previously thought to have relatively little effect on cognition and behavior. However, Caplan et al. (2008), in a study of 69 children with absence epilepsy, found a high rate of cognitive and behavioral disturbance. Frequent absence seizures, by interrupting awareness, can affect both cognitive performance and behavior. People who are having frequent absence seizures may present as having withdrawn behavior, fragmented thought processes which may be mistaken for a psychosis, attention-deficit disorder with motor overactivity, or, if the frequency of the seizures is variable, attention-seeking behavior. The last of these behaviors tends to be seen when the person emerges from a bout of very frequent absence seizures. It is almost as if the child is "making up for lost time" in being badly behaved when he or she has the opportunity of doing so, having been unable to misbehave when the absence seizures were very frequent.

In some cases the absence seizures may become so frequent as to amount to nonconvulsive status epilepticus. The person is effectively cut off from his or her surroundings because he or she does not have the opportunity to function adequately between the absence seizures. Complex partial seizure status epilepticus may also cause a continuous state of behavioral and cognitive change until the status epilepticus is either treated or resolves spontaneously. Elliott et al. (2009) have recently reviewed the role of mesial temporal complex partial seizure status epilepticus in causing ictal psychosis. The role of epileptiform discharges in autism remains open to debate (Besag 2009).

It is clear that absence seizures can affect both performance and confidence in a major way, particularly if they are occurring frequently. It is not possible to count absence seizures by simple observation alone. To overcome this difficulty, an automatic spike-wave monitor, the "Monolog," was developed (Besag et al. 1989). The Monolog is so-called because it monitors

and logs spike-wave episodes automatically. Using this monitor it has been possible to show that some children have not only hundreds but thousands of spike-wave episodes daily. The device has also confirmed whether treatment was effective or not.

A 13-year-old boy with a history of epilepsy was reported as having reached the stage at which the epilepsy was not a problem for him. He was having relatively infrequent overt seizures. However, he presented as a withdrawn child who would not join group activities. He preferred to sit in the corner of the room sucking his thumb. In the clinic the examiner uttered the child's name on four occasions in succession. On the first three occasions there was no response because he was momentarily unconscious in a subtle absence seizure. On the fourth occasion, when he was not having an absence seizure, he responded promptly and was more than willing to attend to whatever task the examiner asked him to do. Prolonged EEG monitoring revealed that around three thousand spike-wave episodes occurred daily. He responded very well to treatment.

Some individuals have both more obvious seizures, such as tonic-clonic or tonic seizures, and absence seizures. The antiepileptic medication may improve both the obvious and the subtle seizures. However, in other cases the obvious seizures may not be affected by medication while the subtle seizures are greatly reduced. Such individuals may become bright, alert, and in control of their lives as a result of the medication change, even though the obvious seizures have not been reduced in frequency.

When patients are assessed in the outpatient clinic the doctor will typically ask how many seizures have been recorded or will consult the patient's seizure diary. If there has been no reduction in the obvious seizures the doctor may choose to discontinue the medication with which the patient has been treated and try another antiepileptic drug. However, on this basis the doctor might stop a drug that has been highly effective in treating subtle absence seizures, because there has been no major effect on the obvious seizures. Examples are provided in Figures 5.1 and 5.2.

In Figure 5.1 there has been a reduction both in the obvious seizures and in the spike-wave episodes with the addition of lamotrigine. In Figure 5.2, however, the obvious seizures have not decreased. The spike-wave episodes, on the other hand, have been reduced by over 2000 per day. The parents of this teenager were delighted with the transformation. He was able to relate much more readily to the world around him and appeared much more alert. It is important not to discontinue medication on the basis that obvious seizures have not responded if the individual has had a good response in terms of reduction of subtle seizure activity.

Transitory cognitive impairment

A number of papers describing this phenomenon have been published by Binnie and coworkers (Aarts et al. 1984; Marston et al. 1993). The basic concept is that an epileptiform discharge that does not appear, on simple observation, to be manifesting as a seizure, may nevertheless cause a transitory impairment of cognitive function. It has been shown that discharges on the left side may impair language function and those on the right side may impair visuospatial skills. The quality of the impairment is not always straightforward. For example, a child who is having epileptiform discharges during reading may pause or may even read more quickly but make additional mistakes when discharges are occurring.

Binnie and his coworkers have shown that reduction of epileptiform discharges can result in improvement of psychosocial functioning (Marston et al. 1993), although this study was confounded by the fact that obvious seizures had improved as well as the discharges causing the transitory cognitive impairment. Observation of video tapes taken during testing of young people who have transitory cognitive impairment leaves no doubt about the fact that they find their lapses in performance irritating and frustrating. It is highly likely that this phenomenon affects self-esteem and self-confidence. This implies that, although the phenomenon itself is transitory, there may be an ongoing negative effect on the attitude and behavior of the individual.

Not to be confused with the transitory cognitive impairment, is the phenomenon of transient epileptic amnesia (TEA), which has increasingly been recognised as another subtle manifestation of epilepsy. It may present with recurrent transient episodes of memory loss but has also been shown to be associated with accelerated long-term forgetting and remote autobiographical memory loss (Butler et al. 2009).

Frequent localized discharges

Reference has already been made to frequent frontal discharges and frequent left temporal discharges

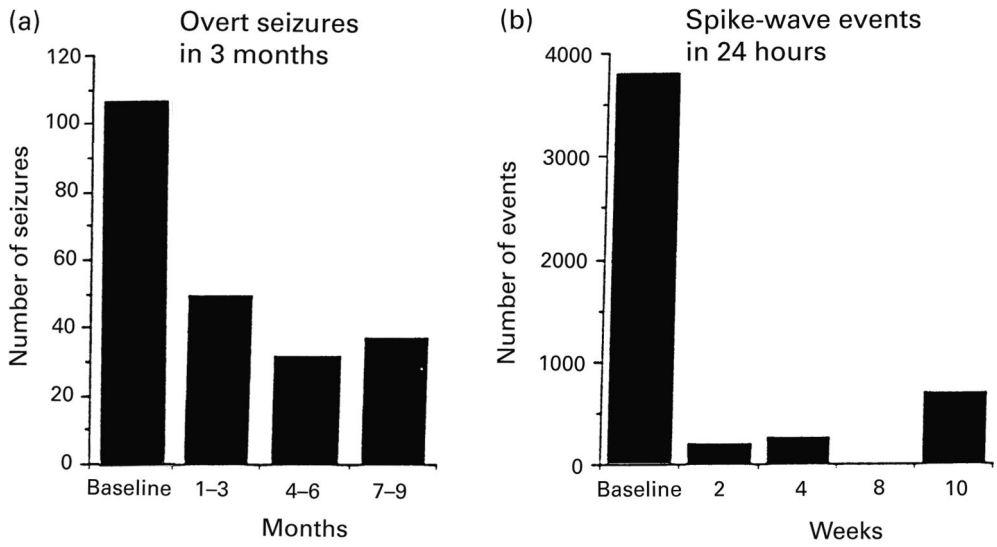

Figure 5.1. The effect of lamotrigine administration on number of overt seizures (a) and spike-wave events (b) experienced by Subject A.

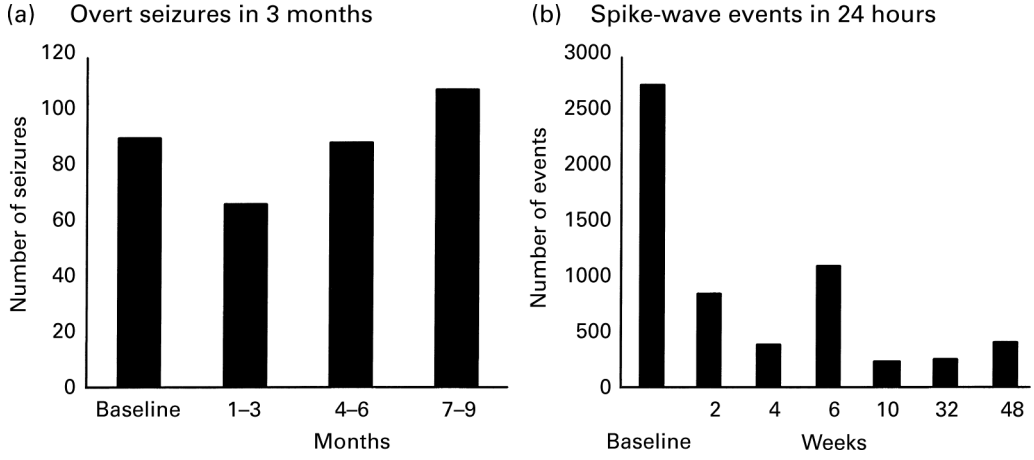

Figure 5.2. The effect of lamotrigine administration on number of overt seizures (a) and spike-wave events (b) experienced by Subject B.

affecting behavior. Localized discharges can also affect ongoing cognitive performance. This effect is more than just transitory if the discharges are frequent.

A girl had a history of a benign left-sided temporal lobe tumor. She had very frequent epileptiform discharges arising from the left temporal lobe. She underwent left temporal lobectomy at 13 years of age. The epileptiform discharges disappeared after the neurosurgery. In a single year her speech development improved from around the 4-year level to the 7-year level. The temporal lobectomy released the remaining brain from the effect of very frequent epileptiform discharges, allowing rapid progress to be made.

Frequent hemispheric discharges

The extreme example of frequent localized discharges is provided by individuals who have an abnormal hemisphere which is the source of such discharges. A number of different pathological conditions can give rise to this phenomenon, including hemimegalencephaly, a porencephalic cyst, and the unilateral cerebral atrophy that accompanies Rasmussen's encephalitis. These individuals often improve markedly after hemispherectomy. Not only are the seizures and epileptiform discharges abolished but the behavior also improves greatly (Goodman 1986). If there is

a gross structural abnormality that is causing very frequent epileptiform discharges then early surgery should be considered. If the lesion responsible has been present from a very early age, for example if it is a congenital porencephalic cyst, then the outcome is likely to be good.

A dilemma arises in the case of the child who develops Rasmussen's encephalitis that is causing progressive hemiatrophy of one hemisphere. The function subserved by the affected hemisphere is likely to worsen and the longer the operation is delayed the less opportunity there will be for the healthy hemisphere to take over function. However, hemispherectomy usually results in loss of finger function on the affected side and there is a tendency to delay the operation until it is clear that the finger function has already been lost, implying that the surgery will not impair function further.

Is it appropriate to wait? Because brain plasticity is greatest when the child is young, there is a better chance that the remaining hemisphere will take over function if the surgery is performed early. There is a strong argument, in such cases, for carrying out the surgery sooner rather than later if the assessment indicates that the disease in the affected hemisphere is progressive.

Postictal state-dependent cognitive impairment

At first sight it might appear trivial to discuss postictal cognitive impairment because this is such an obvious phenomenon. However, it is not always as obvious as one might imagine.

An apparently dementing teenager sat rocking in his chair, not knowing where he was, barely able to carry out a rudimentary conversation and unable to perform his skills of daily living. He had been accepted as a boarding pupil in a special residential center for children with epilepsy and other needs. The staff felt that he had been placed inappropriately. They commented that he could not learn and that he should not have been accepted. At that stage he was having between three and five seizures a day. Following a medication review he became seizure-free. He was then fully orientated and began progressing very well in his educational programs. Both his parents and the staff were delighted with his progress. The staff then commented on how appropriate the placement was. They had previously assumed that his cognitive impairment was permanent whereas, in fact, a large component of the cognitive impairment was state-dependent, treatable, and reversible. When he had been having frequent daytime seizures he had not had the chance to recover from one seizure before he had another. He was in a constant postictal state. When he emerged from this constant postictal state he was able to learn again and progressed rapidly.

It is important to be aware of the possibility of reversible, state-dependent cognitive impairment in an individual who is in a constant postictal state from frequent seizures. Reducing the seizure frequency can improve cognitive function markedly.

Overnight video-telemetry has revealed that some people have very frequent unsuspected and unobserved nocturnal seizures. These seizures may be brief, silent, and easily missed, even by awake night staff. In a series of 15 patients examined by the author and his coworkers, large numbers of nocturnal seizures were recorded by video-telemetry that had been unobserved by awake night staff. In one case over 200 brief nocturnal tonic seizures were recorded. Some individuals are woken by the seizures. Frequent nocturnal seizures may affect daytime performance not only because of the direct after-effects of the seizures themselves but also because they may cause a very broken night's sleep. Since learning appears to depend on good sleep, it would hardly be surprising to find that some individuals with frequent nocturnal seizures have problems with learning.

Electrical status epilepticus of slow wave sleep

The Landau-Kleffner syndrome of acquired epileptic aphasia is classically associated with electrical status epilepticus of slow wave sleep (ESES) (Landau and Kleffner 1957; Beaumanoir 1992). However, a series of six cases of ESES examined by the author and colleagues confirmed that language is not necessarily the function that is impaired. Although some of these children clearly had language impairment in association with the ESES, others did not.

A boy with a right congenital porencephalic cyst and an accompanying left hemiparesis had ESES. He had good language skills but his visuospatial skills became increasingly impaired. He was unable to find his way from his bedroom to the bathroom at home. Following neurosurgery his visuospatial skills improved markedly.

The Landau-Kleffner syndrome provides an important model of state-dependent cognitive impairment. Some of the older textbooks suggested that

antiepileptic treatment was only of value in treating the seizures but would not affect the cognitive impairment. Such statements were probably based on "burnt-out" cases in which the damage had become permanent. It is quite clear that early, energetic treatment may improve the cognitive impairment in some children with Landau-Kleffner syndrome. The implication is that not only may cognition be improved by early treatment but also that permanent impairment may be avoided.

Treatments include antiepileptic medication such as sodium valproate, lamotrigine, high-dose intermittent benzodiazepines, steroid treatment, and neurosurgery. Multiple subpial transection, pioneered by Frank Morrell (Morrell et al. 1989), has been particularly effective in some cases. This can abolish the ESES and allow the language function to return. The results obtained from multiple subpial transection in this condition have made it clear that past statements that antiepileptic treatment could not help cognitive loss were wrong. It is worth repeating that early treatment may not only result in a return of these skills but may also prevent long-term cognitive impairment.

The issues raised by ESES have led to the suggestion that any child who loses skills should be investigated fully and, if another cause is not found, investigations should include overnight EEG monitoring. It should be noted, in this context, that it is said that around 25% of the children with Landau-Kleffner syndrome do not have a previous history of obvious seizures (Beaumanoir 1992).

Preventing cognitive and behavioral problems

In the examples just given, it was emphasized that some children with ESES may present with impaired cognition. They often also present with markedly disturbed behavior. Both the cognitive and behavioral disturbance are reversible with early treatment.

It has become evident that a number of children who present with markedly autistic features have unsuspected epileptiform discharges either during the day or at night (ESES or continuous spike-wave in slow wave sleep – CSWS). Treating these children allows them to emerge from their apparently autistic state.

However, follow-up of teenagers who had very frequent absence seizures in childhood has indicated that some longer-term problems in social interaction or behavior may be evident. Some teenagers who have had very frequent epileptiform EEG discharges earlier in life may subsequently still have autistic features when the epileptiform discharges are no longer present. It would appear that these young people have been unable to interact adequately with the world around them during a critical developmental phase because of the frequent epileptiform discharges at that time. If they have not had the opportunity to develop two-way social interaction during this developmental phase they may present with a very Asperger-like picture during teenage years. This suggests that early treatment of the epileptiform discharges, so as to allow the child to gain fully from the early developmental years, may have avoided these social impairments.

In summary, it appears that there is now an increasing body of evidence to suggest that frequent epileptiform discharges should not be allowed to continue for very long periods because they might cause not only permanent cognitive impairment but also permanent social/behavioral problems.

Conclusions

Systematic assessment of cognitive and behavioral problems often allows the cause to be found and rational management to be provided. It is very important to consider the possibility of state-dependent cognitive impairment, especially in the child who has lost skills. Unless another obvious cause is found, the investigations should include overnight EEG monitoring. If frequent epileptiform discharges are found in association with cognitive or behavioral problems then early, energetic treatment should be initiated. Such treatment may not only improve the impairments at the time but may also prevent permanent cognitive or social impairments.

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Chapter 6

Dementia and epilepsy

Bernd Pohlmann-Eden and Marie-Aline Eden

The study dilemma – an introduction

Dementia and epilepsy are among the most frequent medical conditions in the general population, particularly in the older adult. These conditions deserve special attention because of the demographic shift caused by the rapidly aging population. There is a striking lack of systematic longitudinal studies appropriately addressing the causal relationship between the two disorders. It is obvious that the incidence of seizures and epilepsy will vary among dementia subgroups, based on the underlying illness. To prove that the occurrence of both dementia and epilepsy in one individual is causally related is difficult and complex, as many variables which may accompany reduction of seizure threshold must be considered. These include comorbidities such as cerebrovascular disease, silent post-traumatic scars, depression, anxiety, proconvulsive medication, and metabolic disturbances.

There is very little data on neuropathological findings in patients with dementia-associated seizures. Therefore, it is not surprising that controversies exist with regard to seizure prevalence, type, time course, pathophysiology, and treatment options. This review will focus on the relationship between Alzheimer's disease (AD) and seizure occurrence. There are three reasons for this: (1) AD patients most likely represent the major proportion of patients with dementia and epilepsy; (2) studies of AD patients include a greater number of patients and often include well-documented clinical and neuropathological data; and (3) there is increasing experimental evidence that seizures in AD may be a reflection of pathophysiological processes similar to or overlapping with those responsible for cognitive decline (Larner 2010).

This chapter will not address the inverse relationship which occurs when seizures or the underlying epileptic syndrome and/or their antiepileptic treatment lead to significant cognitive decline and a "dementia-like" clinical picture. These topics are very well covered by other chapters in this book (see Chapters 7 and 17).

Epidemiology of dementia, seizures, and epilepsy

The prevalence of both dementia and epilepsy increases with age. We will first review the epidemiology of dementia and the epidemiology of seizures in the elderly and then will look for the reported coincidence of dementia and seizures.

Dementia

Epidemiological studies of dementia (for review see Mendez and Lim 2003) show that 4–12% of people older than 65 years of age present with some kind of dementing disease (Henderson 1990); if mild forms are included the percentage of dementia found in this population is as high as 15% (Fillenbaum et al. 1998). In European studies, persons over 85 years of age were found to have some form of dementia in 20–30% of cases (Ramaroson et al. 2003, De Ronchi et al. 2005, Helmer et al. 2006). As a general rule, there is a doubling of prevalence rates for dementia every 5 years after age 60 or 65 years (Mendez and Lim 2003). The same authors recently addressed the epidemiology of etiologies: according to their review almost 55–70% of all patients presenting with dementing disease have pure AD or a "mixture" of AD and cerebrovascular disease, about 25% have cerebrovascular changes, and about 15% have dementia with Lewy bodies (Mendez and Lim 2003).

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

Seizures and epilepsy in the elderly

Epileptic seizures are clinical manifestations of sudden abnormal and excessive electrical discharges of neurones. Seizures can present as a variety of clinical phenomena including motor, sensory, or psychiatric symptoms and all degrees of impairment of consciousness (International League Against Epilepsy Commission Report 1997). It is not surprising that seizures occur more frequently in the aging brain. The prevalence and incidence of both single seizures and new-onset epilepsy, which remain constant during adulthood, begin to significantly increase at around the age of 55 years and rise precipitously after the age of 60 years (Pohlmann-Eden 2005).

According to Hauser et al. (1993), the incidence of any type of first seizure is 50 per 100 000 in persons aged 40–59 years and increases to 127 per 100 000 in those older than 60 years (Hauser et al. 1993).

The prevalence of epilepsy shows a similar trend; prevalence increases from approximately 55 years of age and is more than twice that of the general population by >85 years of age (1.2–2.0% *versus* 0.5–1.0%) (Sanders and Murray 1991; Tallis et al. 1991, De la Court et al. 1996). Nursing home studies indicate that up to 8.0% of this population may be suffering from seizures (Chandler and Chandler 1988).

Cerebrovascular disease is the single most common pathological feature underlying epilepsy in elderly people, accounting for 25–30% of all patients with seizures in this age group (Pohlmann-Eden et al. 1997; Pohlmann-Eden 2005). Late-onset seizures frequently signify the presence of otherwise occult cerebrovascular disease, and are associated with a striking increase in the risk of subsequent, often fatal, stroke (Cleary et al. 2004). Other common causes of both single seizures and epilepsy in the elderly include hypoglycemia and other systemic, metabolic, or toxic disorders, head trauma, brain tumors, dementia, and central nervous system infection (Sanders and Murray 1991; Stephen and Brodie 2000). Many widely used drugs are also known to potentially lower seizure threshold and lead to single seizures, including theophylline, tramadol, antihelminthics, some antibiotics, antidepressants, and antipsychotics. Elderly individuals are especially susceptible to seizure activity as a result of age-related impaired drug elimination and reduced seizure threshold (Stephen and Brodie 2000).

Dementia and seizures and epilepsy

Interestingly enough, seizures were not reported among the main clinical features in Alzheimer's first description of AD.

To assess a causal relationship between dementia and seizure threshold and the occurrence of seizures and epilepsy, it is necessary to have congruence in definitions and methodological standards within the published case series. However, most of the available studies (1) are cross-sectional and retrospective, (2) include many different dementing diseases, (3) do not clearly delineate the occurrence of single seizures from the diagnosis of epilepsy, (4) do not have sophisticated neuroimaging studies to allow for differentiation of the most frequent conditions such as cerebrovascular disease (CVD) and AD, (5) do not provide neuropathological data, and (6) use different neuropsychological assessment tools to diagnose dementia.

Etiological assessment in demented individuals by means of imaging data and neuropathological findings is crucial to understand the pathogenetic role of dementia in seizure occurrence. The recognition of vascular lesions in patients with dementia as one possible cause for seizures is particularly important. Subcortical vascular encephalopathy (SVE) occurs frequently in the elderly and is also considered to be the second most frequent etiology of all dementing diseases. This condition can be documented on a computerized tomography (CT) scan of the brain in advanced stages. The imaging method of choice is high resolution MRI (for example Figure 6.1) which is capable of detecting SVE in an early stage. Subcortical vascular encephalopathy and microangiopathic lacunar ischemias are often associated with lowered seizure threshold and seizure occurrence (Schreiner et al. 1995).

The variety of prevalence rates of seizures in AD and dementia, ranging from 5% to 64% (Romanelli et al. 1990; Hauser 1992; Mendez et al. 1994; Volicer et al. 1995; Amatniek et al. 2006), is most likely the result of heterogeneous study populations, including AD patients with vascular changes and severe SVE and patients who have both conditions. The controversy is documented in the following study data.

A case–control study reported that a diagnosis of AD or some other form of dementia was associated with a 6-fold increased risk of unprovoked seizures (Hessdorfer et al. 1996). Ten to twenty-two percent of

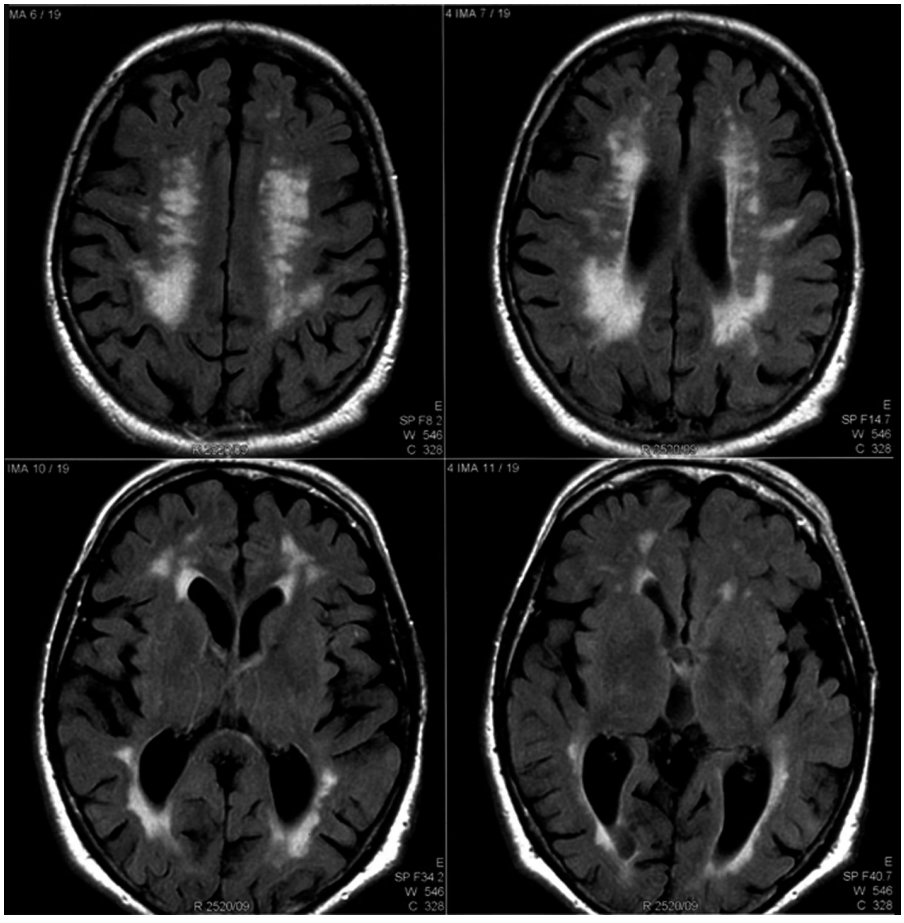

Figure 6.1. Advanced subcortical vascular encephalopathy on a magnetic resonance imaging of the brain in a patient with both dementia and recurrent tonic–clonic seizures.

AD patients have at least one unprovoked seizure (Romanelli et al. 1990; Hauser 1992; Mendez et al. 1994; Volicer et al. 1995; McAreavey et al. 1992). The cumulative incidence of unprovoked seizures in a prospective cohort of mild AD patients followed for 7 years was reported to be nearly 8% (Mendez et al. 1994). In a study with pathological confirmation of the diagnosis, 17% of 446 patients with definite AD developed seizures (Mendez et al. 1994). Thus, in general, patients with definite neuropathologically proven AD (Mendez et al. 1994; Risse et al. 1990) seem to be at higher risk for seizures than cases with probable AD (Larner 2010).

A very recent multicenter study prospectively followed 453 patients with probable AD diagnosed since 1992 (Scarmeas et al. 2009). The study aimed to determine the incidence and predictors of new-onset epilepsy in this population. Among the 52 patients (of the 453) who were considered to possibly have seizures, only 7 were deemed by consensus to have had an epileptic event with certainty (1.5% of the total). This rigorous approach confirmed that AD is a risk factor for late-onset seizures, but emphasized that unprovoked seizures in AD are uncommon. Younger age at diagnosis was the only identified risk-factor for AD-associated seizures. The authors admit that this large study addressing seizure-risk in AD had several inherent methodological limitations, including absence of internal controls, substantial lack of reliable information for diagnostic assignments, and no evaluation of potential subclinical epileptiform activity.

Other dementia disorders

Neuropathological studies have found patients diagnosed with AD only have fewer seizures as compared to those who were found to have dementia with Lewy bodies (Weiner et al. 2003).

Table 6.1 Types of dementia, frequency, and estimated risk for associated seizures

Type of dementia	Estimated relative frequency among all dementias (%)	Associated seizure risk*
Alzheimer's disease (including Lewy body)	50 to 70	xx
Dementia in severe leukoaraisosis ("vascular dementia")	15 to 30	xx
Neurodegenerative movement disorders (MSA, Parkinson's, Huntington's)	5 to 10	x
Frontotemporal dementia and Pick disease	5 to 10	x
Toxic-metabolic diseases (including Hashimoto encephalopathy)	<2	xx
Creutzfeldt-Jakob disease and other prion diseases	<2	xxx
CNS infections (HIV, neurosyphilis, lyme disease, chronic meningitis)	<2	xx
Normal pressure hydrocephalus	<2	xx
Others	<2	x

*Associated risk for seizures (according to published evidence):
x low risk defined as <2%
xx moderate risk defined as 2–15%
xxx high risk defined as <15%
Modified from Mendez and Lim (2003).

Table 6.1 shows various etiologies of dementia, their frequency, and estimated risk for associated seizures. As documented, the spectrum of diseases with dementia and associated seizures ranges from more frequent conditions such as AD and CVD, where seizures occur in a small proportion of patients, to rare conditions such as Creutzfeldt-Jakob disease in which seizures are a common reflection of the underlying epileptogenic neurobiological process. Patients diagnosed with frontotemporal dementia rarely present with seizures (Caramelli and Castro 2005).

Seizure semiology, seizure severity, and time course

Most reported AD studies found a preponderance of generalized seizures (Heyman et al. 1987; Hauser 1992; McAreavey et al. 1992; Mendez et al. 1994; Scarmeas et al. 2009). However, because of the retrospective approach in most of these studies it is not unlikely that a subtle focal onset and mild complex-partial seizures were missed, particularly in mildly impaired dementia patients (Mendez and Lim 2003). It is more likely that focal seizures occur in the setting of demented elderly patients, and acquired "focal" pathology is the most likely cause in these patients. In a recent retrospective analysis of 1738 patients documented in the Mayo Clinic Alzheimer Disease Patient Registry and Alzheimer Research Center, 72% of 63 patients with AD-associated seizures presented with complex-partial seizures. However, 36% of this group were found on MRI to have remote lesions such as stroke or prior hemorrhage (Rao et al. 2009) which may explain the focal nature of their seizures. Nonconvulsive status epilepticus was described as a rare manifestation of AD (Armon et al. 2000).

Seizures can present in an unusual fashion, such as transient epileptic amnesia (Larner 2010). Late-onset epilepsy with myoclonic jerks resembling juvenile myoclonic epilepsy has been described in patients with Down's syndrome (LOMEDS=Late-onset myoclonic epilepsy in Down's syndrome) by several authors (Genton and Paglia 1994; Li et al. 1995).

Most of the studies agree that seizures in AD tend to occur in the advanced stage of the disease, an average 6 years after the onset of the dementia (Hauser et al. 1986; Risse et al. 1990; Romanelli et al. 1990; Mendez et al. 1994). An epidemiological study reported a median elapsed time of 3.3 years after diagnosis of AD at the time of the first seizure occurrence (Hessdorfer et al. 1996).

Rarely, seizures can occur at the time of diagnosis in patients with probable Alzheimer's disease (Lozsadi and Larner 2006). The subgroup of early-onset familial Alzheimer's disease due to autosomal dominant

presenilin I or amyloid precursor protein gene mutation seems to be an exception to the rule with an early manifestation of seizures (Ezquerra et al. 1999; Janssen et al. 2000; Takao et al. 2001; Velez-Pardo et al. 2004).

Unfortunately, the important issue of seizure presentation in AD is not addressed appropriately in the literature. It is suggested from the available studies that chronicity and frequent seizures with decreasing seizure-free intervals over time, as seen in other focal symptomatic epilepsy syndromes, are rarely found in AD patients; most of the available studies emphasize that single seizures or scattered few seizures were the main seizure expressions; seizures usually were easily controlled with antiepileptic drugs. As an example, a recent retrospective study of 453 AD patients documented seven individuals with seizures, four of whom had single seizures only (Scarmeas et al. 2009).

Worsening of clinical status with seizure occurrence was reported; language function declined significantly more rapidly in AD patients with seizures than in controls matched by age and duration of AD (Volicer et al. 1995).

Pathophysiology of seizures in Alzheimer's disease

The mechanisms in AD which induce a lowered seizure threshold and lead to the occurrence of unprovoked seizures in some individuals are still not well understood and remain speculative.

Seizures in AD have been frequently interpreted to have resulted from advanced neurodegeneration in combination with other comorbidities, proconvulsive medication, and aging factors. Data supporting this theory are poor. Neuropathological findings of AD patients with seizures did not differ from those AD patients who had no clinical evidence for seizures; both groups showed the same amount and pattern of neuronal loss, neurofibrillary tangles, beta amyloid plaques (Romanelli et al. 1990; Mendez et al. 1994; Armon et al. 2000), and number of Lewy bodies (Scarmeas et al. 2009).

The role of hippocampal sclerosis which is the most frequent finding in temporal lobe epilepsy is controversial for seizure occurrence in AD. It has been described in a variety of forms of dementia, including frontal temporal dementia and AD, but was not specifically detected in AD seizure patients (Scarmeas et al. 2009; Ala et al. 2000).

One study in 56 histologically proven AD cases reported significantly reduced pyramidal cell counts in the parietal and hippocampal areas in the subgroup of 6 seizure patients (Forstl et al. 1992).

According to a recent comprehensive review by Larner in 2010, obvious candidate mechanisms for the pathophysiology of seizures in AD include: (1) the accumulation of amyloid-related pathology, (2) alterations in neurones, and (3) potential cerebrovascular comorbidity (Larner 2010).

Genetic mechanisms are likely to play a major role for susceptibility to epileptic seizures in some AD patients. Mutations in the presenilin-1 (PSEN1) gene on chromosome 14 predict an early onset of AD and an increased risk of seizures as part of this phenotype (Larner and Doran 2006). Down's syndrome patients (trisomy 21) who overexpress beta-amyloid (Aβ) peptides often develop clinically and neuropathologically proven AD after age 50 years or earlier, with corresponding rapid dementia and new-onset seizures (Puri et al. 2001). Apolipoprotein E4, the most important genetic risk factor for sporadic AD, is associated with subclinical epileptiform activity in carriers without dementia (Puri et al. 2001).

Experimental data support this pathophysiological scenario. Transgenic mouse models demonstrate that those with high levels of beta-amyloid (Aβ) in the brain not only have AD-like pathology and cognitive decline, but also show spontaneous nonconvulsive seizure activity in cortical and hippocampal tissue slices (Palop and Mucke 2009). In another animal model, Aβ peptides induced significant neuronal hyperexcitability and progressive epilepsy (Minkeviciene et al. 2009). The particular relevance of Aβ peptides to seizure pathogenesis is emphasized by Larner 2010; he does not believe in the model of neurodegeneration only as several other neurodegenerative dementing diseases, such as supranuclear palsy, corticobasal degeneration, and Parkinson's disease with dementia, lack Aβ peptides and only seldom present with seizures (Larner 2010).

Forstl et al. (1992) found disproportionate neuronal degeneration in patients with AD-associated seizures, and other experimental results suggest that neuronal abnormalities such as neuronal sprouting and dystrophic neurite growth may play a key role in epileptogenesis of AD-associated seizures (Larner 2010). In particular, aberrant neuritic growth and connections are considered to be candidate mechanisms for lowering seizure threshold in AD; it is

also the typical histopathological correlate in temporal lobe epilepsy (Palop and Mucke 2009; Larner 2010).

Currently, the role of inhibitory molecules for repair and regulation of neuronal sprouting is being examined. It is speculated that collapsin-response mediator protein 2 (CRMP 2) may play a critical role in the acceleration of neuritic regeneration (Larner 2010). This might be of practical relevance as the new antiepileptic drug lacosamide binds to CRMP 2 (Beyreuther et al. 2007).

A recent critical review addressed the pathophysiological role of cerebrovascular lesions (CVL) in both animals and humans for subsequent development of hyperexcitability and seizure occurrence (Pohlmann-Eden et al. 1997). As ischemic events are a frequent comorbidity in elderly patients with dementia, it is surprising that no animal model so far has been established which combines both dementia and CVL to examine the question of lowered seizure threshold. In elderly patients, it is strongly recommended to perform a rigorous standardized protocol of testing in new-onset epilepsy and first seizure presentations, combining high-resolution MRI and early EEG to detect even subtle CVL and assess its role in ictogenesis and epileptogenesis (Pohlmann-Eden and Newton 2008).

Diagnostic strategies

Patients with dementia-associated seizures require a systematic evaluation including history, collateral history, clinical examination, neuropsychological assessment, routine and/or sleep-deprived EEG, and high-resolution MRI of the brain following an epilepsy protocol.

Routine investigations should also include an electrocardiogram, complete routine blood work including electrolytes, liver enzymes, kidney function, and blood cell count.

The key piece for the right diagnosis is the clinical findings. Most of the studies in both the elderly and dementia patient specifically confirm the difficulty of establishing an accurate initial diagnosis (Mendez and Lim 2003). The clinical presentation of epilepsy in the elderly including dementia seems to differ somewhat from that of younger patients (Ramsay et al. 2004). Older individuals frequently present with sudden subtle behavioral changes, confusion, mental slowing, memory disturbance, and syncope-like episodes (Pohlmann-Eden 2005). As Todd's paresis is very common in post-stroke seizures, the postictal state may be misdiagnosed as transient ischemic attack or re-stroke, leading to emergency admission to stroke units. Because of these relatively nonspecific symptoms it is assumed that ictal events are often overlooked or misdiagnosed (Ramsay et al. 2004). This is particularly true for dementia-associated seizures, as the current literature does not yet provide a consistent pattern of seizure semiology.

The role of the electroencephalogram (EEG) has yet to be defined in dementia-associated seizures. The data is poor. A recent review stated that the most frequent finding in AD patients is generalized slowing of the background (Mendez and Lim 2003). The EEG findings in a prospective cohort study of 453 AD patients (Scarmeas et al. 2009) were only available for 21 out of those 52 who were suspected of having a seizure (a definite seizure diagnosis was made in only 7 of the 52!): 38% had normal EEGs, 38% showed diffuse slowing on EEG, focal slowing was documented in 20%, and epileptiform activity (EA) detected in 16% (without any detail or classification of this EA provided). In a retrospective evaluation of 29 patients with dementia-associated seizures, EEGs showed interictal epileptiform activity in 38%, commonly unilateral or with bilateral sharp wave discharges (Rao et al. 2009).

As the EEG is neither sensitive nor specific for AD-associated seizures, its main task is to rule out other causes of dementia with more specific EEG patterns (Creutzfeldt-Jakob disease, herpes simplex encephalitis) or to find regional functional changes prompting sophisticated neuroimaging to look for discrete AD-independent structural changes.

The critical role of MRI for new-onset epilepsy and first seizures (FS) was recently stressed (Pohlmann-Eden and Newton 2008). It is the imaging tool of choice to document focal and diffuse brain pathology in FS of unknown etiology. The additional (or contributing) role of concomitant cerebrovascular disease for ictogenesis and epileptogenesis in AD-associated seizures has to be assessed in the light of EEG findings and interictal epileptiform activity. It would be a serious oversight to miss the most frequent differential diagnosis of AD, vascular dementia; Figure 6.1 shows an MRI of the brain with extensive vascular encephalopathy in a patient both with dementia and seizures.

Treatment strategies

The broad spectrum of psychosocial supports and individually tailored treatment plans in humans who suffer from dementia and seizures is beyond the scope of this chapter. Therefore, the focus will be on medical treatment.

Before antiepileptic drug treatment is considered in the patient with AD-associated seizures, concomitant medication(s) must be evaluated. Many widely used drugs are proconvulsive, potentially lowering seizure threshold and leading to single seizures. These drugs include theophylline, tramadol, antihelminthics, some antibiotics, antidepressants, antipsychotics (Pohlmann-Eden 2005), and also antidementia drugs such as cholinesterase inhibitors (Caramelli and Castro 2005).

Elderly individuals are especially susceptible to proconvulsive effects as a result of age-related impaired drug elimination and reduced seizure threshold (Stephen and Brodie 2000).

When proconvulsive side effects are ruled out, the indication for antiepileptic drug (AED) treatment must be carefully considered.

AED therapy is the mainstay of treatment for epilepsy in the elderly and as a principle should usually be initiated after a proven second unprovoked seizure. In all cases, the potential benefits of AED treatment must always be balanced against the potential disadvantages of long-term side effects.

So far no AED has been identified which specifically targets the reduction of seizure threshold and the mechanisms potentially responsible for producing dementia. The hypothesis that the new antiepileptic drug lacosamide which binds to the inhibitory molecule CRMP 2 may have a positive impact on both seizure control and progression of dementia is entirely speculative (Larner 2010). Given the wide range of AEDs available for treatment, the choice of the correct AED for a particular patient must be individually tailored and based on common practice (Mendez and Lim 2003; Pohlmann-Eden 2005; Hommet et al. 2008).

Initiating AED therapy in elderly individuals with dementia requires careful consideration because of age-specific changes in drug metabolism, the risk of drug interactions, and increased receptor and neuronal sensitivity. Age-related changes in the stomach and bowel, kidneys, and liver can lead to diminished intestinal drug absorption, and a reduction in the renal and/or hepatic clearance of any drugs that are absorbed.

Almost all antiepileptic drugs can lead to cognitive dysfunction, so treatment in demented patients who might be specifically vulnerable to this side effect (Mendez and Lim 2003) has to be very well planned. To our knowledge there has been no controlled comparison trial performed so far with any of the available AEDs, addressing the issue of epilepsy in the demented patient. The extrapolation from studies in the elderly must be done with caution.

The side effects of the older AEDs have been well documented. A large double-blind study evaluated the efficacy and safety of carbamazepine, phenobarbital, phenytoin, and primidone in over 600 adults with partial and secondarily generalized tonic–clonic seizures (Mattson et al. 1992). Intolerable side effects occurred with all four treatments. The high toxicity-related drop-out rates reported in this study (which ranged from 12% with carbamazepine to 33% with primidone) were mainly due to sedation, major cognitive impairment, and depressive symptoms in some patients.

In addition to causing significant treatment-limiting acute side effects, most of the older AEDs are also known to induce hepatic enzymes. This increases the risk of drug interactions, and can adversely affect bone health – both of which are of special concern in the elderly (Stephen and Brodie 2000; Ramsay et al. 2004). Long-term use of enzyme-inducing AEDs which cause hypermetabolism of vitamin D and certain sex hormones can significantly reduce bone mineral density (thus increasing the risk of osteoporosis and bone fractures), and may lead to testosterone deficiency and subsequent erectile dysfunction (Ramsay et al. 2004; Pack et al. 2003).

With the exception of valproate, the older AEDs are not routinely recommended for use in the elderly.

Some of the new AEDs offer significant advantages over the older AEDs, as a result of lack of enzyme induction, fewer drug interactions, and improved tolerability profiles. Several expert groups now recommend the newer AEDs as first-line therapy for elderly patients with epilepsy (Stephen and Brodie 2000; Ramsay et al. 2004; Pohlmann-Eden 2005), although dependence on renal excretion must be taken into account when initiating these treatments. In renal failure or insufficiency, the older AEDs may still have an individual indication.

There have been relatively few controlled clinical trials assessing the comparative efficacy and safety of both older and newer AEDs in the treatment of

Table 6.2 Profiles of AEDs recommended or suitable for use in the elderly with specific focus on demented patients

AED	Advantages	Disadvantages	Doses/ day
Gabapentin	No drug interactions, excellent tolerability, rapid titration	Weak AED, strongly dependent on renal function	2–3
Levetiracetam	Strong AED, no drug interactions, excellent tolerability, rapid titration, effective at low doses	Rarely, insomnia, behavioral disturbances	2
Lamotrigine	Well proven, minimal neuropsychological impairment	Slow titration, allergic reactions, some drug interactions	2
Valproate	"Loadable," parenteral, broad spectrum, no enzyme induction	90% protein binding, enzyme inhibitor, tremor, thrombocytopathy	1

Table 6.3 AED dosing recommendations in the elderly

AED	Initial dose (mg)	Dose increase (mg/day)	Interval (days)	Final dose (mg/day)
Gabapentin	400	400	1	1200–1800
Levetiracetam	500	500	1–3	1000–2000
Lamotrigine	12–25	12–25	14	100–200
Valproate	300	300	2–3	600–1500

epilepsy in the elderly. Of the four published studies, only two have been double blind (Brodie et al. 1999; Rowan et al. 2005). Results suggest that the newer AEDs are at least as effective as the older agents and that their improved tolerability generally translates into higher therapy retention rates in elderly subjects (Brodie et al. 1999; Rowan et al. 2005).

When choosing an AED for use in the elderly, a good safety profile and a low risk of drug interactions are fixed requirements. All of the AEDs selected by the authors for treatment in dementia-associated seizures (three new AEDs and valproate) have advantages and disadvantages in this respect (Table 6.2).

Gabapentin is a very well tolerated AED with no known drug interactions and no risk of allergic reaction but its potency is considered weak as compared to all other AEDs. This limits its use to more benign cases of late-onset epilepsy or special conditions where its lack of idiosyncratic properties may be a crucial advantage (e.g. seizures associated with systemic lupus erythematosus).

Levetiracetam appears to offer a good combination of efficacy, safety, and lack of drug interactions; however, there is only very limited published experience with the use of levetiracetam in the elderly (Ferrendelli et al. 2003).

Lamotrigine is well studied and, because of its positive neuropsychological profile (Chapter 15), may be specifically considered as a useful agent to treat older individuals developing dementia. Lamotrigine does require careful dose titration and is associated with some important drug interactions.

Valproate is the only "old" AED which can still be recommended as a first choice drug in the elderly. It can be rapidly titrated, including parenteral loading, and lacks cardiotoxicity and sedating properties as compared to the enzyme-inducing AEDs carbamazepine, phenytoin, and phenobarbital. The occurrence of tremor, thrombocytopenia, and drug interactions are disadvantages which must be considered.

We do not specifically recommend topiramate in demented individuals with seizures as it can be associated with significant cognitive and language dysfunction, particularly at daily dosages of 200 mg and above (Fritz et al. 2005).

Dosing recommendations for each of these agents are shown in Table 6.3. As a general principle, monotherapy is preferred, titrating slowly and aiming

for a low target dosage (Mendez and Lim 2003; Pohlmann-Eden 2005).

Although there is a significant lack of efficacy data for patients with dementia treated for epilepsy, the authors who have published on the topic are in agreement on the excellent outcome in their patients (class IV evidence, Mendez and Lim 2003; Rao et al. 2009).

Conclusions and future directions

Dementia and seizures occur in a significant proportion of patients with increasing prevalence in the elderly.

There is a striking lack of systematic longitudinal studies appropriately addressing both the epidemiology and the causal relationship between the two disorders. Rigorous etiological assessment by means of clinical assessment, imaging data, and neuropathology is critical.

Conflicting variables which may accompany reduction of seizure threshold must be ruled out on an individual basis. These include frequent comorbidities such as cerebrovascular disease, silent post-traumatic scars, depression, anxiety, proconvulsive medication, and metabolic disturbances.

Seizures in AD patients were found to be more frequently in the advanced stage (3–6 years after diagnosis) and occur in the range of 3–10% of the total. They most often present as generalized tonic-clonic seizures; focal seizure presentation is suggestive of concomitant vascular disease. Unusual seizure presentations such as amnestic episodes are common.

Current clinical and neuropathological data point to amyloid-related pathology, structural alterations in neurones, and cerebrovascular comorbidity as main pathogenetic factors in Alzheimer-associated seizures. Experimental data suggests that neuronal sprouting and dystrophic neurite growth may play a key role in epileptogenesis of AD-associated seizures. Genetic mechanisms are likely to play a major role in susceptibility to epileptic seizures for those AD patients with mutations in the presenilin-1 (PSEN1) gene on chromosome 14.

The weak clinical data on AD-associated seizures suggest that single seizures or few scattered seizures and a more benign course characterize this syndrome. Seizure outcome seems excellent.

New antiepileptic drugs have major advantages over traditional AEDs, including less sedation and better neuropsychological profile, lack of enzyme induction and minor interactions with both intrinsic (e.g. sex hormones, vitamin D) and extrinsic (e.g. concomitant medication) compounds.

As outlined in detail in this chapter, there is an urgent need for more systematic studies in better defined populations of all clinical, pathophysiological, and experimental dimensions. Future clinically orientated research should focus on a prospective study design of state-of-the art imaging and EEG recordings at an early stage with precisely defined clinical and seizure outcome criteria. Current animal work is encouraging in the further investigation of the overlap between hyperexcitability (and lowered seizure threshold), cognitive decline, and established dementia. It also holds the potential to develop new investigational drugs which impact both dementia and epilepsy.

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Chapter 7

Peri-ictal psychiatric phenomena

Andres M. Kanner

Peri-ictal symptoms as the prototypic psychiatric phenomena of epilepsy

Psychiatric symptoms in epilepsy are classified according to their temporal relation with seizure occurrence. Thus, they are divided into two big classes: interictal and peri-ictal. Interictal symptoms are independent of seizure occurrence. The peri-ictal symptoms are time-locked to the seizure occurrence and hence they are subdivided into symptoms that precede (pre-ictal), follow (postictal), or those that are the expression of the actual seizure (ictal). Peri-ictal psychiatric symptoms have been recognized for a long time; they were described in the writings of Gowers (Gowers 1881) and Hughlings Jackson (1931) in the nineteenth century and by Kraepelin (1923) in the early twentieth century.

Peri-ictal symptoms may occur as isolated symptoms (e.g. only auditory hallucinations or irritability) or as a cluster of symptoms that mimic depressive, anxiety, or psychotic episodes, which may (or may not) be associated with cognitive and neurological signs and symptoms. Despite their relatively high prevalence, they are rarely identified by clinicians and hence systematic investigations of peri-ictal psychiatric phenomena are scarce. Furthermore, failure to recognize the nature of these symptoms leads to frequent misdiagnosis (see below) as interictal psychiatric disorders. The purpose of this chapter is to review the most relevant clinical aspects of peri-ictal symptomatology.

Pre-ictal psychiatric phenomena

It is not unusual for patients to report that they can predict the impending occurrence of their seizure by several hours to up to two days. Parents in particular can become attuned to a change in their child's attitudes or behavior one day before they develop a seizure. Indeed, pre-ictal psychiatric symptoms may precede a seizure by hours to up to 3 days. Despite a relatively frequent awareness by patients and their family members of these symptoms, their actual prevalence has yet to be investigated and established. In one of the few studies available, Mula et al. identified pre-ictal dysphoric-like symptoms in 9 of 143 patients with epilepsy (Mula et al. 2008). One study by Blanchet and Frommer investigated the clinical characteristics of pre-ictal psychiatric symptoms in a systematic manner, in which psychiatric symptoms were monitored daily during 56 days in 27 patients with epilepsy (Blanchet and Frommer 1986). Mood ratings pointed to a dysphoric state three days prior to a seizure in 22 patients. This change in mood was more accentuated during the 24 hours preceding the seizure. A cautionary note is in order: pre-ictal headaches have been identified in 5–11% of patients with epilepsy and it is always possible that the psychiatric symptoms may be worsened by these headaches (Yankovsky et al. 2005; Cai et al. 2008).

Ictal psychiatric phenomena

The classic expression of an ictal psychiatric symptom is an "aura," presenting as feelings of fear, sadness, or euphoria. Investigators have estimated that 25% of auras consist of psychiatric symptoms, 60% of which consist of ictal fear or panic and 15% of mood symptoms (Williams 1956; Weil 1955; Daly 1958).

Ictal panic is one of the most frequently misdiagnosed symptoms in medical practice, as it is often diagnosed as a panic attack (Sazgar et al. 2003). For example, in a series of 112 consecutive patients with epilepsy, Sazgar et al. identified five patients with ictal

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

fear as part of a partial seizure disorder of right mesial temporal origin who had been misdiagnosed with panic disorder (Sazgar et al. 2003). Yet, a detailed history can help distinguish a panic attack from ictal panic. Indeed, ictal panic is typically brief (less than 30 seconds in duration), stereotypical, occurs out of context to concurrent events, and may be followed by other ictal phenomena such as periods of confusion of variable duration, autonomic symptoms such as copious salivations (which has been found to be specific for ictal events), and subtle or overt automatisms when and if the seizure evolves to a complex partial seizure. The intensity of the sensation of fear is mild to moderate and rarely reaches the intensity of a panic attack. On the other hand, panic attacks consist of episodes of 5 to 20 minutes' duration which at times may persist for several hours during which the feeling of fear or panic is very intense, often described as a feeling of impending doom. While panic attacks are associated with a variety of autonomic symptoms also present in ictal fear, including tachycardia, diffuse diaphoresis, and shortness of breath, they are not associated with excessive salivation. During a panic attack, patients may become completely absorbed by the panic experience to the point where they may not be able to report what is going on around them; nonetheless, there is no real confusion or loss of consciousness as in complex partial seizures. Finally, patients with panic attacks are more likely to develop agoraphobia, while this is rare among patients with ictal panic unless they suffer from interictal panic disorder as well (Spitz 1991).

The presence of ictal fear does not exclude the coexistence of an interictal panic disorder. In fact, Mintzer and Lopez reported the case of 12 patients with temporal lobe epilepsy (TLE) with ictal fear, four of whom also suffered from an interictal panic disorder (Mintzer and Lopez 2002). Two other patients had other forms of interictal anxiety disorder and eight patients had depressive disorder.

The misdiagnosis of ictal fear as a panic disorder stems from:

(1) An inaccurate and/or incomplete clinical history.
(2) The absence of epileptiform activity in scalp interictal recordings in patients whose seizures originate from the amygdala, a structure that generates epileptiform discharges with very narrow electric fields. In such patients, the use of video-EEG monitoring studies (VEEG) may be necessary to record the actual seizure. Often, sphenoidal electrodes inserted under fluoroscopic guidance may be necessary to identify the electrographic ictal pattern of the aura (Kanner et al. 1995).
(3) Ictal fear occurs often in the setting of a partial seizure disorder originating in the nondominant hemisphere. In such cases, patients may continue to respond during the ictus (including during a complex partial seizure) and neither witnesses to the seizure nor the patients may be able to identify a period of confusion or loss of awareness of their surroundings, unless a careful testing of the patient is conducted.

Of note, the presence of ictal fear can herald the development of postsurgical mood disorders. For example, Kohler compared the presence of mood and anxiety disorders before and 1 year after temporal lobectomy between a group of 22 patients with ictal fear who underwent an antero-temporal lobectomy for treatment-resistant TLE and a group of matched controls with other types of auras and no auras at all (Kohler et al. 2001). Mood and anxiety disorders declined in the control groups, but not in the ictal fear group after surgery.

Ictal symptoms of depression are the second most frequent ictal psychiatric symptoms; they are of short duration typically, stereotypical, occur out of context, and are associated with other ictal phenomena. The most frequent symptoms include feelings of anhedonia, guilt, and suicidal ideation.

Less frequently, psychiatric symptoms may present as nonconvulsive status epilepticus (SE), either in absence status or in simple partial or complex partial SE (Kaplan 2002). Usually, patients with absence status are alert, attentive, and cooperative. Verbal functioning is relatively well preserved, but may also be slow with stereotypic and usually monosyllabic answers. A variety of behavioral disturbances and psychiatric symptoms can be associated with these cognitive changes, as some patients can become depressed, agitated, and occasionally, hostile. More common are experiential and sensory phenomena such as the following descriptions provided by patients: "sensation of viewing the world through a different medium," "a feeling of not being in the same world as everyone else," "uncontrollable rush of thoughts," "a feeling of fear of losing control of my mind," "a feeling of closeness," "a funny feeling that I can not elaborate," "a strange feeling of not being

myself," "edgy, worried, and uncomfortable," "my character changes completely, I become extremely snappy. . .have a severe headache," or "weird" (Agathonikou et al. 1998).

Nonconvulsive SE of frontal origin occurs frequently with psychiatric symptomatology and without overt confusion. For example, Rohr-Le Floch et al. reported a case series of 60 patients with nonconvulsive SE, 57.5% of whom had SE of frontal origin without confusion (Rohr-Le Floch et al. 1988). Patients were more likely to present behavioral disorders of euphoric type and difficulty in sequential planning as well as confabulation and inappropriate laughter. A similar proportion of patients, however, appeared "indifferent." Furthermore, two different types of nonconvulsive SE of frontal origin were identified by Thomas et al. in 10 patients (Thomas and Mottin 1997; Thomas et al. 1999). Type I included seven patients without clear impairment of consciousness who presented with mood and behavior disturbances as either a mild hypomanic state with affective disinhibition, enhanced word fluency, and familiarity or, on the contrary, a state of affective indifference with blank facial expression, reduced word fluency, and lack of spontaneous activity and emotivity. After the remission of the SE, most patients could recall events that occurred during the episode. Simple gestural automatisms such as picking the clothes, rubbing, or scratching movements were often observed. All patients showed a strictly unilateral spread of ictal activity that involved either the right or the left frontal areas. Three patients presented with a type II, characterized by a confusional state with temporo-spatial disorientation, gross behavioral disturbances, and perseveration. Ictal patterns consisted of recurrent seizures involving frontal and temporal structures bilaterally in two patients and bilateral fronto-central regions in the other patient.

Finally, visual and auditory hallucinations can also be the expression of simple partial SE. In such cases, however, patients are able to realize that the hallucinations are not real.

Finally, Sashi and Wieser described the phenomenon of "aura continua" which represents a prolonged episode of sensory symptoms identical to an aura, but lasting hours to days and considered to be another clinical manifestation of simple partial SE (Wieser et al. 1985; Seshia and McLachlan 2005). For example, cases with prolonged episodes of intense ictal fear and neurovegetative symptoms have been described by various authors (Zappoli et al. 1983; Wieser et al. 1985; Seshia and McLachlan 2005). Most of these cases had an ictal focus in mesial temporal structures. Zappoli et al. reported a clinical case of a woman who had combined simple and complex partial SE of temporal origin (Zappoli et al. 1983). The authors recognized two clinical and electrographic phases. The first phase was characterized by a prolonged feeling of intense fear associated with semirhythmic left temporal epileptiform discharges without apparent impairment of consciousness. In the second phase the left temporal discharges were followed by generalized discharges resulting in a severe impairment of consciousness. Wieser et al. reported four patients with simple partial SE of temporal lobe origin (Wieser et al. 1985). The ictal symptoms associated with neocortical and mesiobasal limbic discharges consisted of various psychosensory and neurovegetative signs. One patient had continuous gustatory aura lasting for several days. The events disappeared after amigdalohippocampectomy. Seshia and McLachlan reported six patients who had prolonged symptoms that were identical, but less intense, than the aura experienced before their typical complex partial seizure (Seshia and McLachlan 2005). Their symptoms lasted between 2 and 8 years. They were not associated with electrographic seizure activity on scalp and subdural recordings. The diagnosis of simple partial SE was established indirectly by the elimination of the "aura continua" after surgery in five patients, and transiently after intravenous lorazepam in the remaining patient.

Postictal psychiatric phenomena

The postictal period can be divided into two phases: an immediate and a delayed phase. The immediate postictal phase refers to the period that follows a seizure and which typically has a duration of a few minutes to 2 hours but may occasionally last for up to 48 and even 72 hours. Cognitive disturbances and headaches are typical of the immediate postictal period. Postictal psychiatric symptoms (PPS) occur characteristically (but not exclusively) during the delayed phase, which occurs after a symptom-free period of 8 hours to 7 days' duration following the seizure. Typically, the postictal delayed period lasts between 12 hours and 7 days but occasionally psychiatric symptoms may persist for up to 3 months.

Postictal psychiatric phenomena may be the expression of: (1) isolated psychiatric symptoms; (2) clusters of PPS mimicking a depressive, anxiety,

or psychotic episode; (3) postictal exacerbation in severity of interictal psychiatric symptoms; and (4) persistence of interictal symptoms into the postictal period.

Postictal psychiatric symptoms

While PPS have been recognized for the last two centuries (Gowers 1881; Hughlings Jackson 1931), there has been only one study in which the prevalence, duration, and clinical characteristics were examined in a systematic manner in 100 consecutive patients with treatment-resistant partial epilepsy. All patients had undergone a VEEG monitoring study, as part of a presurgical evaluation at the Rush Epilepsy Center (Kanner et al. 2004). The PPS were identified with a 42-item questionnaire (The Rush Postictal Psychiatric Questionnaire) designed to identify 30 PPS and five cognitive symptoms. The PPS included symptoms of depression and anxiety disorders (i.e. general anxiety, panic attacks, agoraphobia), obsessions and compulsions, psychotic symptoms, and neurovegetative symptoms. Each question inquired about the frequency of each symptom during the postictal and interictal periods in the course of the last 3 months. The postictal period was defined as the 72 hours that followed a seizure. Only symptoms that were identified after more than 50% of seizures were included in this study, so as to reflect a "habitual" phenomenon. For each symptom, patients were asked to estimate the average duration. For symptoms identified during both interictal and postictal periods, only symptoms reported to be *significantly more severe* during the postictal period were recorded. These were classified as *postictal exacerbation* of interictal psychiatric symptoms.

All patients underwent a psychiatric evaluation to identify previous or concurrent *interictal* psychiatric disorders. Among the 100 patients, 62 were women and 32 were men, with a mean age of 34.1±10 years and a mean duration of the seizure disorder of 21.1±11.5 years. Seventy-nine patients had seizures of temporal lobe origin, and 21 patients had seizures of extratemporal origin. Half of the patients had only complex partial seizures (CPS), and the other half had CPS and secondarily generalized tonic–clonic seizures (GTC). Seventy-eight patients had more than one seizure, and 22 had less than one seizure per month. Fifty-four patients had a past psychiatric history, which consisted of depression, anxiety, and attention-deficit disorders. Eleven patients reported one or more psychiatric hospitalizations.

Among the 100 patients, there were a mean of 8.8±6.5 habitual postictal symptoms (range 0 to 25; median 8.5) corresponding to 2.8±1.8 postictal cognitive symptoms (PCS) (range 0 to 5; median 3) and 5.9±5.3 PPS (range 0 to 22; median 5). Seventy-four patients experienced at least one type of PPS; 68 reported PPS and PCS and 6 only PPS. An additional 14 patients experienced only PCS, whereas 12 did not report any postictal symptom. Sixty (81%) of these 74 patients experienced PPS belonging to more than one symptom category. The most frequent combination of PPS consisted of postictal symptoms of anxiety (PSA), depression (PSD), and neurovegetative symptoms (PNVS).

Postictal symptoms of depression were identified in 43 patients (mean: 4.8±2.4 [range 2 to 9; median = 5]). The type of PSD and median duration are shown in Table 7.1. Thirteen of these patients experienced habitual postictal suicidal ideation; eight experienced passive and active suicidal thoughts, whereas five reported only passive suicidal ideation. No patient ever acted on these symptoms.

With the exception of postictal crying, the median duration of each PSD was 24 hours, while 32 patients experienced PSD of at least 24 hours' duration. In 18 patients a minimum of 6 PSD clustered for a period of at least 24 hours, meeting the definition of a postictal depressive episode.

A prior history of (interictal) mood disorders was identified in 25 patients while 11 experienced a prior anxiety disorder. These patients had a significantly greater number of PSD. Furthermore, postictal suicidal symptoms were significantly associated with a prior history of major depressive episodes and of previous hospitalizations in psychiatric units. Of note, 13 patients who experienced PSD were taking antidepressant medication and had no symptoms interictally (unpublished data).

Postictal symptoms of anxiety were identified in 45 patients (mean: 2±1 PSA [range 1 to 5; median 2]). The type and median duration of anxiety symptoms appear in Table 7.1. Of note, 29 patients experienced postictal agoraphobia; 18 (62%) attributed these symptoms to the fear of seizure recurrence even though the presence of this fear was not related to the actual occurrence of seizures in clusters.

Table 7.1 Prevalence and median duration of PPS

Postictal symptom	Prevalence	Median duration in hours (range)
Symptoms of depression, total	43	
Irritability	30	24 (0.5–108)
Poor frustration tolerance	36	24 (0.1–108)
Anhedonia	32	24 (0.1–148)
Hopelessness	25	24 (1.0–108)
Helplessness	31	24 (1.0–108)
Crying bouts	26	6 (0.1–108)
Suicide ideation	13	24 (1.0–240)
Active suicidal thoughts	8	
Passive suicidal thoughts	13	
Feelings of self deprecation	27	24 (1.0–120)
Feelings of guilt	23	24 (0.1–240)
Neurovegetative symptoms, total	62	
Early night insomnia	11	–
Middle night awakening	13	–
Early morning awakening	11	–
Excessive somnolence	43	24 (2–72)
Loss of appetite	36	24 (2–148)
Excessive appetite	10	15 (0.5–48)
Loss of sexual interest (not related to fatigue)	26	39 (6–148)
Symptoms of anxiety, total	45	
Constant worrying	33	24 (0.5–108)
Panicky feelings	10	6 (0.1–148)
Agoraphobic symptoms	29	24 (0.5–296)
Due to fear of seizure recurrence	20	–
Compulsions	10	15 (0.1–72)
Self consciousness	26	6 (0.05–108)
Psychotic symptoms, total	7	
Referential thinking	5	15 (0.1–108)
Auditory hallucinations	2	6.0 (0.1–108)
Paranoid delusions	4	0.2 (0.1–0.25)
Religious delusions	3	6.0 (0.1–108)
Visual hallucinations	1	36 (6–48)
Hypomanic symptoms, total	22	
Excessive energy	9	2 (0.15–48)
Thought racing	15	2 (0.1–24)

The median duration of PSA ranged from 6 to 24 hours; as is the case with PSD, in the majority of patients (N=30) the duration of at least one PSA was greater than 24 hours, while 15 patients (33%) reported a cluster of four PSA of at least 24 hours. In 15 patients PSA lasted less than 24 hours. As in the case of PSD, there was a significant association between a history of anxiety and depressive disorder and a greater number of PSA.

Postictal hypomanic symptoms (PHMS) included excessive energy and racing thoughts, which were identified in 22 patients: racing thoughts were endorsed by 15 patients and increased energy by nine, while both symptoms were reported only by two. In contrast to PSD and PSA, PHMS had a significantly shorter duration (mean: 2 hours [range: 0.1 to 48 hours]), and only six patients experienced PHMS lasting more than 24 hours. Finally, no psychiatric history was found associated with the occurrence of PHMS.

Postictal psychotic symptoms (PIP) were identified in seven patients (mean 0.6 ± 1.1 [range 1 to 5; median 2]). They included referential thinking (people are staring and talking about me) in five patients, auditory hallucinations in two, paranoid delusions in four, religious delusions in three, and visual hallucinations in one. The median duration of

individual PIP ranged from 0.2 to 36 hours. In four of these patients, at least one PIP lasted a minimum of 24 hours, two patients experienced symptoms lasting between 1 and 23 hours, and one patient reported symptoms of less than 1 hour duration. No patient had experienced a history of interictal psychosis. A psychiatric history was not a risk factor for PIP, but a history of anxiety disorder was associated with a significantly greater number of PIP.

Postictal neurovegetative symptoms (PNVS): Sixty-two patients experienced 2.3 $\pm$ 1.1 PNVS (range 1 to 5; median 2), and in 12, they were the only PPS category reported. Early night insomnia was reported by 11% of patients, middle night awakening by 13%, early morning awakening by 11%, and excessive appetite by 10%. These are four symptoms not typically associated with the postictal state. The median duration of individual PNV ranged from 15 to 39 hours.

There was a high correlation between PSD, PSA, and PNVS. In addition, PSD and PSA were identified in the seven patients who reported PIP. The occurrence of PHMS correlated significantly only with that of PIP. Of note, the presence of PSD was associated with worse postictal cognitive disturbances, as evidenced by a significantly greater number of postictal cognitive symptoms.

Postictal exacerbation in severity of interictal symptoms

In his description of the interictal dysphoric disorder, Kraepelin described the persistence of interictal symptoms during the postictal period (Kraepelin 1923), but did not explicitly describe an exacerbation of interictal symptoms during the postictal period. Mula et al. confirmed these observations in a recent study (Mula et al. 2010). In the study by Kanner et al. (2008), 38 patients experienced interictal symptoms, of whom 24 reported symptoms of depression, 4 symptoms of anxiety, and 6 both types. Interictal symptoms with postictal exacerbation in severity was a common occurrence, being identified in 36 of the 38 (94%) patients; in 19, all recorded symptoms were coded only as such, whereas the other 17 reported symptoms were coded as both interictal symptoms with postictal exacerbation and as interictal symptoms. Furthermore, 30 of these 36 patients (83%) also experienced de novo postictal psychiatric symptoms. In fact, there was a significant association between the occurrence of interictal symptoms of depression and anxiety with postictal exacerbation in severity and the presence of PSD and PSA.

Relation between PSA, PSD, and epilepsy-related variables

As stated above, all patients who were included in this study had undergone a presurgical evaluation, which included a video-EEG monitoring study with recording of interictal epileptiform activity and clinical seizures, high resolution brain MRI study, and neuropsychological testing. There was no relation with the location or lateralization of ictal and interictal epileptiform activity or MRI findings and the occurrence of PSD or PSA.

Impact of PSD and PSA on quality of life

The negative impact of PSD and PSA on the quality of life of patients with epilepsy would not come as a surprise to anyone. Yet, no study has been published to date describing this phenomenon. In an ongoing study of 50 consecutive patients with pharmacoresistant epilepsy, the presence of PSD and PSA were associated with worse scores on the Quality of Life in Epilepsy Inventory-89 (QOLIE-89) (Kanner et al., unpublished data).

Postictal psychiatric episodes

As stated above, postictal psychiatric symptoms can cluster to mimic depressive, anxiety, and psychotic episodes. Postictal depressive and psychotic episodes have been the ones identified.

Postictal depressive episodes (PDE)

The prevalence of PDE has yet to be established. In Kanner's study cited above (Kanner et al. 2004), 18 patients experienced a minimum of six PSD for a period of at least 24 hours; the semiology mimicked a typical major depressive episode, with the exception that the duration of the event was significantly shorter than the required 2 weeks of such episodes. Yet, patients may at times experience PDE of 1–3 weeks' duration.

In a separate study carried out at the Rush Epilepsy Center, 20 patients with PDE lasting more than 24 hours and mimicking major depression were identified. They were compared to 20 age-matched controls also suffering from treatment-resistant partial epilepsy. The 40 patients had undergone a presurgical evaluation. There were no differences in interictal and ictal data, MRI, and neuropsychometric testing between the two groups (unpublished data). However, patients with PID were more likely to have a past psychiatric history than controls.

To date, there are no data on the prevention of PDE or PSD, other than the total prevention of seizures. In fact, in the experience of this author, PDE may occur despite the successful suppression of interictal symptoms of depression with antidepressant medication (unpublished data).

Postictal psychotic episodes

Since the advent of VEEG monitoring studies, postictal psychotic episodes (PIPE) have become the better investigated of the peri-ictal psychiatric episodes. They account for approximately 25% of the cases of psychosis in epilepsy, with prevalence rates estimated to range between 6 and 10% (Dongier 1959). In patients with partial epilepsy who have undergone a VEEG, the yearly incidence of postictal psychosis was reported to be 6.4% (Kanner et al. 1996). In 1988 Logsdail and Toone suggested diagnostic criteria for PIPE which have since become widely accepted. These include:

(1) onset of confusion or psychosis within 1 week of the return of apparently normal mental function
(2) duration of 1 day to 3 months
(3) mental state characterized by:
    (a) clouding of consciousness, disorientation, or delirium
    (b) delusions, hallucinations, in clear consciousness
    (c) a mixture of (a) and (b)
(4) no evidence of factors which may have contributed to the abnormal mental state such as:
    (a) anticonvulsant toxicity
    (b) a previous history of interictal psychosis
    (c) EEG evidence of status epilepticus
    (d) recent history of head injury or alcohol/drug intoxication.

These clinical characteristics of PIPE have been confirmed in several case series (Drake 1987; Savard et al. 1991; Devinsky et al. 1995; Umbricht et al. 1995; Kanner et al. 1996; Kanemoto et al. 1996a; Kanemoto et al. 1996b; Kanemoto et al. 1999; Fukuchi et al. 2002; Kanner and Ostrovskaya 2008a; Alper et al. 2008). Yet, the semiology of PIPE appears to vary widely both within and between series. Logsdail and Toone (1988) found that only one patient had primary delusions and thought disorder, nine had an abnormal mood, and six had paranoid delusions, while hallucinations were mainly visual and auditory. Kanner et al. (1996) reported that most patients exhibited an abnormal affect, depressed in 90% alternating with hypomania in 70%. Seventy percent were irritable and 20% had suicidal ideation. Delusions were experienced by 90% (paranoid, grandiose, somatic, and religious) and hallucinations in 40% (mainly auditory). All patients were orientated in time, place, and person. Kanemoto et al. (1996a) described sexual indiscretions and sudden unprovoked aggressive behavior along with religious and grandiose delusions in patients with PIPE. Fukuchi et al. reported religious delusions in 25% of patients with PIPE, but in only 2% of those with interictal psychoses (Fukuchi et al. 2002). Savard et al (1991) reported that seven of nine patients developed a paranoid delusional syndrome with prominent persecutory delusions. Devinsky et al. (1995) described fluctuating combinations of delirium, persecutory delusions, hallucinations, and affective changes.

Aggressive behavior can occur in PIPE. For example, Kanemoto et al. (1999) described well-directed violent attacks in 13 of the 57 episodes of PIPE (23%) compared with only three of the 62 witnessed episodes of acute interictal psychosis (5%). Violence in PIPE occurs in the setting of a clear or relatively clear consciousness, as opposed to the confusion of the immediate postictal state, characterized by confusion. This clinically is a dangerous situation and suicide in PIPE is one of the reasons why suicide is increased in patients with epilepsy above the population norm.

Other important characteristics worth noticing include: (1) the occurrence of herald symptoms consisting primarily of insomnia and/or agitation which are typically identified 8–24 hours before the appearance of psychotic symptoms; (2) the onset of PIPE follows a 10-year history of a treatment-resistant seizure disorder; (3) a prompt symptom remission follows the administration of a low-dose antipsychotic medication or occasionally benzodiazepines; and (4) secondarily GTC seizures occur, often in clusters (Logsdail and Toone 1988; Savard et al. 1991; Devinsky et al. 1995; Umbricht et al. 1995; Kanner et al. 1996; Kanemoto et al. 1996a; Kanemoto et al. 1996b; Kanemoto et al. 1999).

PIPE can also present with unusual clinical manifestations. Thus, cases of Capgras' syndrome have been described (Drake 1987; Kim 1991) and a case mimicking a Klüver-Bucy syndrome was reported in a patient with persistent seizures following a left temporal lobectomy (Anson and Kuhlman 1993).

In contrast to PDE, PIPE have been associated with various epilepsy-related variables. Several case

series have identified the presence of bilateral independent interictal (Logsdail and Toone 1988; Savard et al. 1991; Devinsky et al. 1995; Umbricht et al. 1995; Kanner et al. 1996; Kanemoto et al. 1996a; Kanemoto et al. 1996b; Kanemoto et al. 1999) and ictal foci (Devinsky et al. 1995, Umbricht et al. 1995, Kanemoto et al. 1996a, Kanner et al. 1996; Kanner and Ostrovskaya 2008a; Alper et al. 2008) with PIPE. In a study of 36 patients with treatment-resistant partial epilepsy, 18 with a history of PIPE, and 36 without, Kanner et al. found that a history of PIPE was predictive of bilateral ictal foci with an 89% accuracy (Kanner and Ostrovskaya 2008a). Alper et al. found that patients with PIPE were significantly more likely than controls to have extratemporal or poorly localized ictal foci, GTC, as well as a history of encephalitis (Alper et al. 2008). Having said this, these data do not imply in any way that patients with a known history of PIPE should not be considered for epilepsy surgery. Firstly, not all patients with PIPE are found to have bilateral ictal foci in their VEEG. Secondly, while the presence of bilateral ictal foci lessens the probability of achieving a seizure-free state after epilepsy surgery, palliative surgery can often be considered, particularly in patients with unilateral mesial temporal sclerosis, provided that a majority of habitual seizures (>80%) originate from the atrophic hippocampus and the neuropsychological data do not predict a high risk of postsurgical memory loss.

Other potential risk factors have been suggested by various investigators: Alper et al. suggested that mood disorders among first- and second-degree relatives could be a predictor of PIPE (Alper et al. 2001). Briellmann et al. found that dysplasias in temporal lobe structures were associated with a higher risk of developing PIPE in a study that compared findings from high-resolution MRI and histopathological studies among six patients who experienced PIPE and 45 controls (Briellmann et al. 2000). Of note, in the patients with PIPE the volume of hippocampal formations was normal. Kanemoto et al., on the other hand, found that hippocampal atrophy was significantly associated with the development of PIPE in a study of 111 patients with TLE (Kanemoto et al. 1996b).

In children, cases of PIPE have been reported *only* following status epilepticus (Nissenkorn 1999; Joshi et al. 2006). One was a case of a 9-year-old boy; the other was a case of a 12-year-old boy. In both children, EEG recordings were obtained during the psychotic episode, documenting that the seizure activity had remitted.

Finally, Kanemoto et al. found a significant risk of experiencing postsurgical mood disorders in patients with a history of presurgical PIPE (Kanemoto et al. 2001), as the preoperative episodes of PIPE were five times more frequent among the patients with postoperative mood disorders (38%) than those who did not experience such complications (7%).

Relation between PIPE and IPE

Various authors have reported on the development of IPE following PIPE (Tarulli et al. 2001; Adachi et al. 2002; Adachi et al. 2003). For example, Tarulli et al. found that 6 of 43 patients with PIPE met all the criteria for both PIPE and IPE (Tarulli et al. 2001). Five of the six patients had multiple documented PIPE before they became chronically psychotic. The range of length of time between PIPE and IPE was 7 to 96 months. Postictal and interictal psychotic symptomatology was similar or identical in five of six cases. Kanner et al. found that 7 of 18 patients with PIPE went on to develop IPE, compared to 1 of 36 controls (Kanner and Ostrovskaya 2008b). Other investigators have reported PIPE preceding and/or following the occurrence of IPE (Adachi et al. 2002; Adachi et al. 2003).

Treatment of PIPE

In contrast to PSD or PDE, PIPE can be readily prevented and treated. Prevention of PIPE is possible in patients who are found to have bilateral ictal foci in the course of a VEEG or who are known to develop PIPE after a cluster of seizures. Indeed, before discharge from the hospital, family members should be warned of the risk of PIPE which can first appear several days after the last seizure and should be instructed to be attentive to the development of insomnia, marked irritability, or agitation as these precede the onset of psychotic symptomatology by up to 24 hours (Dongier 1959). In such cases, a low dose of atypical antipsychotic drugs (i.e. risperidone or quietapine) can be administered for 2–5 days. On the other hand, once psychotic symptoms are identified, a low dose of these antipsychotic drugs can be started, with dose adjustments according to clinical response and tolerability. The duration of treatment will depend on the time it takes to reach full symptom remission, after which the dose can be tapered down over several days.

Conclusions

Postictal psychiatric phenomena are relatively frequent in patients with treatment-resistant epilepsy. PSD and PSA have been associated with a past (or current) history of mood and anxiety disorders, while certain PSD such as postictal suicidal ideation have been found in patients with prior history of severe mood disorders that required inpatient psychiatric hospitalizations. Thus, recognition of PDE, PSD, and/or PSA should serve as red flags for an ongoing or past psychiatric history. While it appears as if PSD may not respond to pharmacotherapy, this question remains unanswered and must be addressed in future prospective studies.

PIPE must not be confused with IPE and must alert clinicians to the presence of bilateral independent ictal foci. They remit readily with low doses of psychotropic drugs which need to be given only for a short period of time. Occasionally, PIPE can evolve into IPE. Finally, it is imperative that the investigation of postictal psychiatric symptoms be included in the evaluation of every patient with epilepsy, just as with postictal cognitive and neurological symptoms.

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Chapter 8

Postictal psychoses: established facts and new clinical questions

Kousuke Kanemoto

Introduction

In the first edition of this book, I reviewed studies on postictal psychosis (PIP) presented up to the turn of the century as comprehensively as possible and also provided renewed data of our own regarding this issue (Kanemoto 2002). At that time, after a century of neglect, this particular state of mental disruption closely related to seizure activity had become rapidly recognized as a distinct clinical entity. This rediscovery has been most often rightly traced back to the paper of Logsdail and Toone (1988). However, without the monograph dedicated to epileptic psychosis written by Michael Trimble in 1991 (Trimble 1991) the significance of that pioneering paper would have remained unnoticed for additional decades. In Table 8.1, multiple case and case–control studies of PIP are listed. Nearly all of the main clinical features of PIP were already reported by the turn of the century (Mendez and Grau 1991; Savard et al. 1991; Devinsky et al. 1995; Umbricht et al. 1995; Kanemoto et al. 1996; Kanner et al. 1996) with most studies thereafter designed to answer specific clinical questions (Lancman et al. 1994; Lui et al. 2001; Adachi et al. 2002; Kanemoto 2002; Oshima et al. 2006; Alper et al. 2008; Falip et al. 2009).

In this revised chapter, after presenting a short history of PIP studies and established clinical pictures of nuclear PIP, clinical questions and answers that have emerged after the turn of the century will be addressed, i.e. the interrelationship between PIP and interictal psychosis (IIP), results of neuro-imaging studies of PIP, premorbid predisposition (including family history) or risk factors, and PIP-related peri-ictal phenomena including discussion of PIP subtypes.

Historical background and definition

Historical background

A short passage on postictal "fury" lasting hours to days that appeared in the textbook of Esquirol in 1839 seems to be the first recognized medical description of PIP (Devinsky 2008). In 1861, the French psychiatrist Farlet attempted to classify epileptic psychosis more systematically and subdivided it into three categories; transient peri-ictal, chronic, and true epileptic psychosis (Farlet 1860). As there was a lack of strict distinction among pre-ictal, intra-ictal, and postictal events at that time, it is not easy to compare Farlet's classification to those of the present. However, while transient peri-ictal psychosis apparently overlaps postictal confusion and chronic psychosis agrees roughly with Slater's psychosis, salient features of Farlet's true epileptic psychosis, such as extreme psychomotor agitation as well as extraordinarily aggressive and self-destructive behavior, have many aspects in common with PIP.

Toward the end of the nineteenth century, Savage and Clouston stressed that such a dramatic outburst of emotional behavior described by Farlet was commonly encountered postictally. This increased attention to postictal behavioral changes culminated in a series of papers written by John Hughlings Jackson (Jackson and Stewart 1899; Hughlings Jackson 1931). At first, he believed that Farlet's true epileptic psychosis directly reflected epileptic discharges per se. However, by 1889 Jackson had gradually shifted his position and considered that this particular variety of psychosis came from some indirect after-effects of seizure discharge. As I will discuss later, these opposing ideas of Jackson still reflect a major question in regard to this topic, that is whether PIP is an "epileptic equivalent" or some

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Table 8.1 Multiple case and case–control studies of postictal psychosis

Authors	N	Style of study	Limited to, in comparison with
Logsdail and Toone (1988)	14	Multiple case study	
Savard et al. (1991)	7	Multiple case study	
Mendez and Grau (1991)	2	Multiple case study	
Lancman et al. (1994)	7	Multiple case study	Recurrent cases
Umbricht et al. (1995)	8	Case–control study	
Devinsky et al. (1995)	20	Case–control study	VEEG
Kanemoto et al. (1996)	30	Case–control study	vs. IIP and CP
Kanner et al. (1996)	10	Case–control study	VEEG
Liu et al. (2001)	12	Multiple case study	
Kanemoto (2002)[a]	51	Case–control study	
Adachi et al. (2002)	36	Case–control study	vs. IIP
Oshima et al. (2006)	8	Case–control study (prospective)	
Alper et al. (2008)	59	Case–control study	VEEG, partial epilepsy
Falip et al. (2009)	5	Case–control study	Temporal lobe epilepsy

[a]Includes patients from 1996 study.
CP – chronic psychosis; IIP – interictal psychosis; VEEG – video-EEG monitoring.

peculiarly modified state of neural network resulting from an after-effect of massive seizure discharges.

However, simultaneously with Jackson's exit, true epileptic psychosis disappeared abruptly from the medical scene, and authors in the early twentieth century began to confuse Farlet's true epileptic psychosis with other types of epileptic psychosis or simple postictal confusion. The true nature of Farlet's psychosis remained misunderstood for more than a century thereafter (Kolb and Brodie 1982; Taylor 1972) and was finally forgotten. For example, multiple case studies with splendid clinical descriptions presented by Levin (1952) vividly introduced readers to PIP. However, he titled the study "Epileptic clouded states," which obscured delineation of the described clinical manifestations from simple postictal confusion and IIP.

Definition

As in cases with other types of epileptic psychosis, PIP is defined in two dimensions: the chronological relationship to seizures and the nature of the psychosis. For the chronological relationship, most authors have adapted the criterion proposed by Logsdail and Toone (1988) i.e. episodes of mental aberration that develop within 1 week after a seizure (or mostly a cluster of seizures) are qualified as PIP. This operational delineation is more rational than it seems and conforms to reality, because, as discussed later in this chapter, PIP occurs mostly within 3 days after the last seizure (Logsdail and Toone 1988; Devinsky et al. 1995; Kanemoto et al. 1996). Indeed, the presence of a lucid interval between the last seizure and the start of mental aberrations guarantees a qualitative difference between PIP and simple postictal confusion, and constitutes an integral part of the clinical picture of nuclear PIP. However, that has not been regarded as essential for diagnosis by most authors. When an aberrant postictal mental state without a lucid interval is also included in PIP, other closely related conditions, such as peri-ictal, ictal (aura continua), and even pre-ictal psychosis (Shukla et al. 2008) can be theoretically considered as a continuum.

The second part of the definition, psychosis, varies among investigators. Mental state characterized by delusion or hallucination in clear consciousness is an original criterion proposed by Logsdail and Toone. However, because severe abnormalities of behavior that result from abrupt mood change are known to constitute one of the basic symptoms of PIP, a definition of psychosis based on ICD-10 criteria is preferred by some. According to those, postictal subacute aggression as well as postictal hypomanic state are included in PIP. Since postictal depression does not accompany bizarre behavior as a rule, it is included in PIP only in the most flexible definitions.

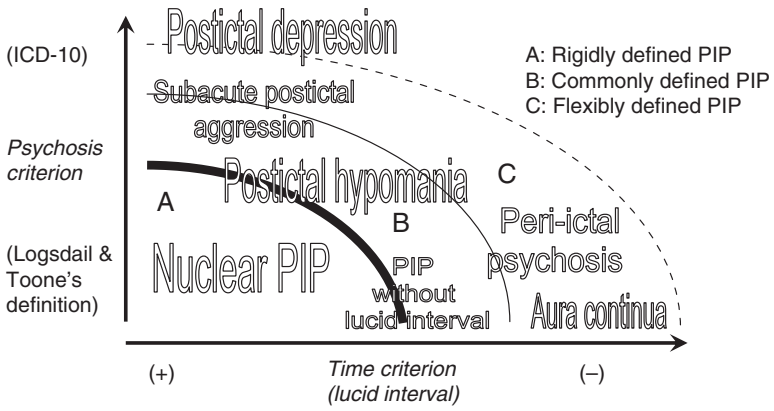


Figure 8.1. Definition of PIP and closely related disorders.

In Figure 8.1, a schema of PIP-related mental disorders using two axes of definition, time (lucid interval) and psychosis criteria, is presented.

Main clinical features

Incidence

Fifty-one (1.7%) of 2905 patients with epilepsy treated at Kansai Regional Epilepsy Center experienced PIP that occurred spontaneously without artificial provocation (Kanemoto 2002). However, this finding cannot be compared simply with those presented in other studies (Table 8.2), because most observations reported as incidents in previous reports were made during seizure monitoring in preparation for epilepsy surgery (Kanner et al. 1996; Alper et al. 2001; Alper et al. 2008; Falip et al. 2009).

Kanner et al. reported that the annual incidence of postictal psychotic events at their monitoring unit was 7.8%. Seven of 13 patients in their series had their first-ever postictal psychiatric event during the monitoring study, leaving 3.6% (6/167) of the cases as spontaneous PIP without artificial provocation (Kanner et al. 1996; Kanner et al. 2004). Considering that their study sample was limited to patients with symptomatic partial epilepsy, this result is nearly the same as ours (3.8%, 49/1279) (Kanemoto 2002).

Data presented in the first edition of this book are reprinted here in Table 8.3. PIP comprises approximately one-fourth of psychoses experienced by patients with epilepsy, which agrees well with data reported by Schmitz and Wolf (1991) while Adachi et al. reported a lower figure (20.2%, 58/282) even after excluding cases with spike-wave-stupor (Adachi et al. 2002). Apparently, and understandably, the relative incidence of PIP to IIP is rated as highest in seizure monitoring units and lowest in tertiary epilepsy centers, which attempt to treat therapy-resistant patients using medication during a relatively long-term follow-up period.

Table 8.2 Incidence of PIP

Author (published year)	Epilepsy in general	Partial epilepsy	Seizure monitoring
Kanner et al. (1996)	–	3.6% (6/167)[a]	7.8% (13/167)
Alper et al. (2001)	–	–	5.9% (29/622)[b]
Kanemoto (2002)	1.7% (51/2905)	3.8% (49/1279)	–
Oshima et al. (2006)	–	7.4% (8/108)[c]	–
Alper et al. (2008)	–	–	4.4% (59/1340)
Falip et al. (2009)	–	5.5% (3/55)[c]	7.3% (4/55)[c]

[a] Only PIP cases prior to artificial seizure provocation were counted.
[b] Patients with complex partial seizures.
[c] Temporal lobe epilepsy alone.

Age at psychosis onset

Since Slater's epoch-making paper, it is well known that there is a long interval (average 15 years) between epilepsy and psychosis onset. Subsequent studies confirmed that the latent period between psychosis and epilepsy onset was more than 10 years in both PIP and IIP, though that in PIP was longer (Kanemoto

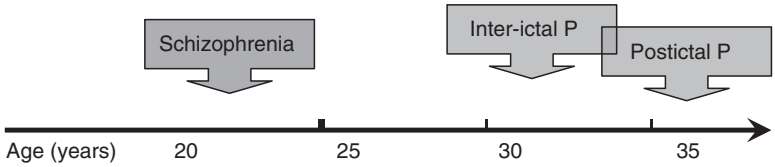


Figure 8.2. Age at psychosis onset. From Kanemoto et al. (1996; 2001), Adachi et al. (2002), Tadokoro et al. (2007).

Table 8.3 Subcategories of epileptic psychoses (N=200)

Postictal psychosis	26.5% (53/200)
AIP as well	2.0% (4/200)
evolving into CP	1.0% (2/200)
Acute interictal psychosis	52.0% (104/200)
evolving into CP	11.5% (23/200)
Chronic psychosis	29.5% (59/200)
Others	5.0% (10/200)

AIP – acute interictal psychosis; CP – chronic psychosis. Reprinted from Kanemoto et al. (2008).

2002; Trimble 1991; Adachi et al. 2002). Independent Japanese studies that directly compared age at psychosis onset between schizophrenia, IIP, and PIP confirmed that the youngest age at onset was in cases of schizophrenia and the oldest in those of PIP (Kanemoto et al. 1996; Adachi et al. 2002; Kanemoto 2002; Tadokoro et al. 2007; Adachi et al. 2008) (Figure 8.2).

Lucid interval, recurrence, and duration

In Table 8.4, lucid intervals presented in previous papers are listed (Levin 1952; Logsdail and Toone 1988; Devinsky et al. 1995; Kanemoto et al. 1996; Lui et al. 2001). In all relevant studies in which the duration of lucid intervals could be traced, the duration was within 72 hours after the last seizure in more than 80% of the cases. In a setting without artificial provocation, lucid interval could not be confirmed in about half of the patients.

In comparison with IIP, the duration of PIP is clearly shorter. In our collaborative study of 48 patients with PIP, approximately 95% of the PIP episodes resolved within 1 month (Adachi et al. 2008). Also in that study, the mean duration of 58 first PIP episodes was 10.5 days. While PIP episodes tend to resolve within 1 week in an overwhelming majority in the setting of seizure monitoring (Devinsky et al. 1995; Kanner et al. 1996), more than one-third of patients exhibit a duration of 1 week or more in retrospective studies (Logsdail and Toone 1988; Kanemoto et al. 1996; Adachi et al. 2007), presented in Table 8.5. Prompt therapeutic intervention in the setting of seizure monitoring may be an explanation for this discrepancy. Repeated recurrence is also a salient feature of PIP in some patients (Lancman et al. 1994) ranging from 49% to 60% of reported cases (Logsdail and Toone 1988; Kanemoto et al. 1996; Kanner et al. 1996; Lui et al. 2001).

Psychopathological features

The affect-laden feature of PIP has been repeatedly demonstrated in the literature. In most previous reports (Logsdail and Toone 1988; Devinsky et al. 1995; Kanner et al. 1996; Lui et al. 2001; Kanemoto 2002) psychiatric manifestations of PIP assumed an affect-laden nature in more than two-thirds of the cases (Table 8.6). In addition, frank manic states were observed in one-fifth to one-fourth of PIP patients, and hypomanic tendency was recognized in half of the PIP patients in our series, as well as in those in the series reported by Kanner.

As Gerard et al. pointed out (Gerard et al. 1998) violent behavior elicited during the course of PIP deserves special comment. Our data as well as those of Kanner revealed that approximately one-third to one-fourth of patients with PIP experienced subacute postictal aggression (Devinsky et al. 1995; Kanemoto et al. 1996; Kanner et al. 1996; Kanemoto 2002), as shown in Table 8.6. It is quite striking that, with only minimal provocation, these patients react extremely aggressively. Just as with a postictal manic or hypomanic state, this abrupt change of mood in a negative direction should be regarded as a phenomenon closely related to PIP. In our previous study (Kanemoto et al. 1999) we compared violent attacks during episodes of PIP, IIP, and postictal confusion immediately following complex partial seizures in patients with TLE, and confirmed that severe violent confrontational behavior toward surrounding people with impending danger occurred only rarely during the postictal confusion, as previous studies have also pointed out. In contrast, patients proved to be quite prone to violent behavior during episodes of PIP.

Table 8.4 Lucid intervals

	<24 hours	<2 days	<3 days	<1 week	LI/total (N)
Levin (1952)	17 (74%)	4 (17%)	2 (9%)		23/52 (44%)
Logsdail and Toone (1988)	8 (67%)		2 (17%)		12/14 (85%)
Devinsky et al. (1995)	11 (58%)	4 (21%)	4 (21%)	0 (0%)	19/20 (95%)
Kanemoto et al. (1996)	4 (27%)	5 (33%)	4 (27%)	2 (13%)	15/30 (50%)
Liu et al. (2001)	(average value [3.5 days])			12/12 (100%)	

LI – lucid interval.

Table 8.5 Duration of PIP

	<24 hours	≤7 days	>7 days	Total (N)
Logsdail and Toone (1988)	7%	50%	43%	14
Devinsky et al. (1995)[b]	16%	74%	11%	20
Kanemoto et al. (1996)	11%	47%	47%	30
Kanner et al. (1996)[b]	10%	90%		10
Liu et al. (2001)	8%	67%	17%	12
Adachi et al. (2007)	37∼66%[a]		34∼63%[a]	(58)[a]

[a]Within 5 days, 37% resolved; within 10 days, 66% resolved.
[b]Recorded in seizure monitoring units for presurgical evaluations.

Table 8.6 Affect-laden psychopathology

	Affect-laden	Manic
Logsdail and Toone (1988)	64%	21%
Kanner et al. (1996)	80%	20% (40%)[a]
Liu et al. (2001)	42%	25%
Kanemoto (2002)	77%	(49%)[a]
	Violence	**Suicide**
Kanner et al. (1996)	30%	20%[b]
Devinsky et al. (1995)		32%[c]
Kanemoto (2002)	28%	8%[d]

[a]Percentages including hypomanic tendency are depicted in parentheses.
[b]Two suicidal ideations.
[c]Three suicide attempts.
[d]Four suicide attempts that led to death.

Suicidal attempts, as an expression of inverted aggression, are also reported to be increased in PIP patients (Devinsky et al. 1995; Kanner et al. 1996; Kanemoto et al. 1999; Fukuchi et al. 2002; Kanemoto 2002).

Hyper-religiosity and mental diplopia (Jackson 1888) also merit special comments. Devinsky and Lai stressed a special role played by PIP in the genesis of epilepsy-related religious conversion (Devinsky and Lai 2008) with ecstatic religious experiences supposed to be related to PIP. In the review of Devinsky and Lau, religious experiences occurred in 2.2% of TLE patients. Also, in an attractive book dedicated to spiritual aspects of the brain, Trimble noted an outstanding proportion of religious experiences reported by patients during PIP episodes (Trimble 2007).

More than a century ago, Jackson and Stewart stressed the triad of illusions of familiarity, mental diplopia, and feelings of impending death as a hallmark of dreamy state (Jackson and Stewart 1899). The first two symptoms of this triad occur almost exclusively in PIP, which seems to be closely related to the marginal type of PIP. In the state of Jacksonian mental diplopia, patients feel as if their stream of consciousness is doubled and even opposed to each other. Kishi et al. (2003) presented a male who felt such a double consciousness preceding a typical hypomanic phase during the course of every episode of PIP. In that case, a strong religious feeling was closely coupled with the mental diplopia.

In Table 8.7, salient psychopathological features of PIP based on our data are presented (Kanemoto 2002). In addition to those, several curious postictal

Table 8.7 Psychopathological salient features (modified SAPS)[a]

	PIP (N=45)	IIP (N=126)
Visual hallucinations	9	2
Grandiose delusions	12	1
Religious delusions	10	3
Pressure of speech	22	1
Illusion of familiarity	13	1
Mental diplopia	8	1

[a]Only features demonstrating a significant difference ($p<0.005$) are listed.
Modified from Kanemoto (2002).

psychiatric symptoms reported recently merit mention, including Capgras syndrome (Drake 1987; Kanemoto 1997), autoscopic phenomenon (Tadokoro et al. 2006), and palinacousis (Di Dio et al. 2007).

Association with TLE

Except for rare exceptions (Chakrabarti et al. 1999; Cutting et al. 2001), previous authors unanimously agree that a seizure (or mostly a cluster of seizures) preceding PIP is either a complex partial or secondarily generalized seizure. As shown in Table 8.8, most previous studies found a close association between TLE and PIP (Logsdail and Toone 1988; Savard et al. 1991; Lancman et al. 1994; Devinsky et al. 1995; Kanemoto et al. 1996; Kanner et al. 1996; Adachi et al. 2002; Kanemoto et al. 2008) except for the most recent report of Alper et al. (2008). While the ratio of TLE among PIP patients in those previous papers amounted to 81.2%, only 25 of 59 patients (42.4%) were diagnosed with TLE in the study of Alper et al. Although differing diagnostic criteria makes it difficult to compare directly between these studies, our comparison between IIP and PIP revealed that patients with PIP exhibited a temporal lobe pathology significantly more often on MR images than those with IIP, while generalized spike-wave complexes were significantly more often recorded in electroencephalograph findings in IIP than in PIP (Kanemoto 2002) as shown in Table 8.9. Two studies, ours and the study of Adachi et al. (2002), demonstrated a higher proportion of TLE in PIP than in IIP (77% [41/53] vs. 53% [74/140], and 75% [27/36] vs. 63% [141/224], respectively).

Table 8.8 Ratios of TLE in patients with PIP

Logsdail and Toone (1988)[a]	79%	11/14
Savard et al. (1991)	100%	9/9
Lancman et al. (1994)[b]	100%	7/7
Umbricht et al. (1995)	–	?/8
Devinsky et al. (1995)[c]	90%	18/20
Kanemoto et al. (1996)[d]	–	[30/30]
Kanner et al. (1996)[c,d]	–	[11/11]
Adachi et al. (2002)[e]	75%	27/36
Kanemoto et al. (2008)	77%	41/53
Total	81.2%	113/139

[a]Partial epilepsy.
[b]Recurrent cases only.
[c]Seizure monitoring unit.
[d]Analysis limited to TLE.
[e]CPS instead of TLE.

Treatment

Treatment for PIP consists of two different strategies (Kanemoto 2002; Lancman et al. 1994; Devinsky 2008), acute sedative procedures and preventive measures. Once an episode of PIP breaks out, a direct shortening or alleviation of postictal psychosis should be attempted first. In the nuclear type, PIP begins with an initial hypomanic state. If patients are successfully sedated and made to sleep during this initial stage, the appearance of frank psychosis might be thwarted. Especially in a seizure monitoring unit, where trained psychiatrists can recognize the initial sign without delay, acute sedation is helpful. Second, in contrast to the alternative psychosis of Landolt (1963), control of seizures prevents recurrence of PIP episodes. Thus, successful operative intervention leads to cessation of PIP episodes, except for only rare exceptions (Christodoulou et al. 2002). In exceptional cases, ECT may be helpful in terminating violent PIP attacks (Pascual-Aranda et al. 2001).

New perspectives

Coexisting PIP and IIP

Four different combinations of PIP and IIP have been presented: (1) progression of PIP to chronic psychosis (Kanemoto 2002; Logsdail and Toone 1988; Tarulli et al. 2001; Adachi et al. 2002; Devinsky 2008); (2) PIP changing into IIP without a break during an episode

Table 8.9 Localization in patients with IIP and PIP

	Postictal psychosis (N=45)	Interictal psychosis (N=126)	No pyschotic episodes (N=2728)
EEG findings			
Temporal foci	33	78	
Extratemporal foci	8	15	
Sidedness (L/R)	11/18	43/41	
Diffuse SWC	1	21[b]	
MRI localization			
Temporal[a]	16	25[b]	
Extratemporal[a]	4	14	
Sidedness (L/R)	12/9	34/20	
Epilepsy types			
Idiopathic PE	42		730
Symptomatic PE			
TLE	39	74[b]	422
Extra TLE	10	35	857
Idiopathic GE	–	5	308
Epileptic encephalopathy	–	7	369
Others	2	11	

[a]Patients with both temporal and extratemporal pathology were excluded.
[b]Statistically significant difference ($p<0.05$).
SWC – spike-and-wave complex.
Modified from Kanemoto (2002).

of psychosis (Kwan and Su 2000; Akanuma et al. 2005); (3) PIP and IIP episodes occurring in an alternating manner; and (4) PIP episodes follow after remission of IIP episodes (Adachi et al. 2003).

Most studies that reported mixed cases of IIP and PIP focused on the progression of PIP to IIP, as that mode occurs most frequently. However, in one-third of combined cases, a reversed progression was observed, i.e. after remission of IIP, PIP episodes were reported to follow (Adachi et al. 2003). In rare cases, alternative psychosis was immediately followed by seizure clusters within the same episode. Kwan and Su (2000) reported one such case and Akanuma et al. reported two others (Akanuma et al. 2005).

SPECT studies during PIP episodes

Since the famous and quite polemic paper written by Flor-Henry (1969) attempts to lateralize or localize epileptic psychosis remain controversial. Roughly summarized, Flor-Henry associated transient confusional and chronic schizophreniform psychosis with right and left temporal lobe involvement, respectively, but did not provide sufficient evidence in support of this bold speculation. While the latter corresponds to chronic psychosis as described in the paper of Slater (1963), a substantial proportion of the former seems to overlap with the clinical picture of PIP.

To answer this question, SPECT studies would be of some help (Jibiki and Yamaguchi 1994). In Figure 8.3, four previous SPECT studies of PIP (Nissenkorn et al. 1999; Fong et al. 2000; Leutmezer et al. 2003; Nishida et al. 2006), in addition to five new cases co-presented by our group and Motooka, are summarized. As seen in the figure, independent of whether right- or left-sided pathology was suspected during the non-psychotic states, the relative hyperactivity of the right temporal lobe (or frontotemporal lobe) seems to play a central role in the genesis of PIP. Although this modified version of Flor-Henry's hypothesis still lacks sufficient amplification, just as the original did, it seems to be worth examining in further studies.

Interestingly, the average interval between an end of seizure cluster and SPECT examination is far shorter in cases of increased perfusion limited to the frontal lobe than in those of increased perfusion limited to the temporal lobe. As pointed out by Nishida et al. (2006) the initial hypomanic phase during PIP or isolated postictal manic episodes may be explained by this early frontal hyperactivity.

Bipolar disorder and PIP

Psychopathological features of PIP are highly suggestive of association with bipolar disorder, which is supported by data from different perspectives. According to Alper et al. (2001) while the prevalence of PIP among patients with a positive family history of psychotic illness did not increase, the risk of developing PIP was 3.49 times higher ($p=0.001$) among patients who had a positive family history of mood disorder in their first or second relatives. Our data, derived

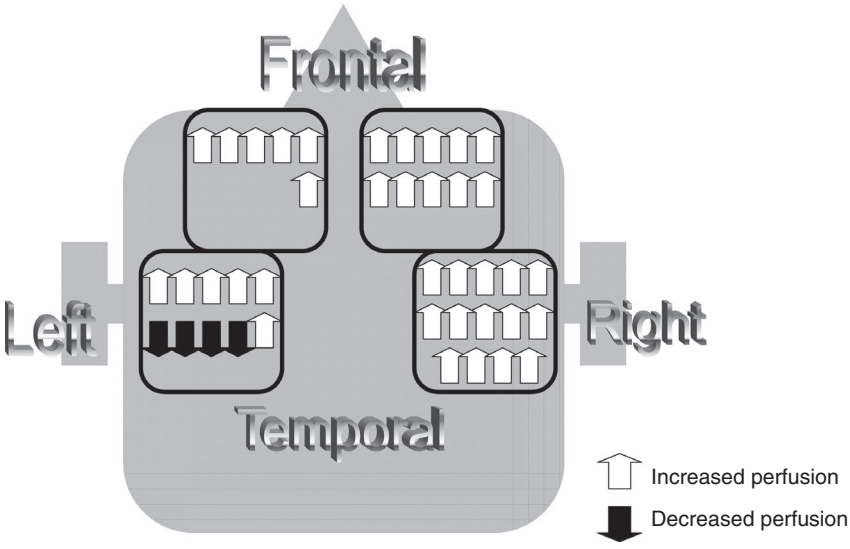


Figure 8.3. SPECT findings during postictal psychosis. From Ohima et al. (in press).

from 52 patients with TLE who underwent a temporal lobectomy and had hippocampal sclerosis, also support a link between mood disorder and PIP (Kanemoto et al. 2001). While a preoperative history of acute IIP is closely associated with schizophreniform disorders after surgery, postoperative mood disorder is significantly more often encountered in patients with a history of PIP or prolonged confusional state prior to surgery. Further, some authors have pointed out close associations between fear aura and PIP (Savard et al. 1991; Kanemoto 2002). In the study of Kohler et al. (2001) the ratios of mood and anxiety disorder tended to increase after a temporal lobectomy in patients with ictal fear; to 55% in the fear aura group, 18% in the non-fear aura group, and 7% in the no aura group.

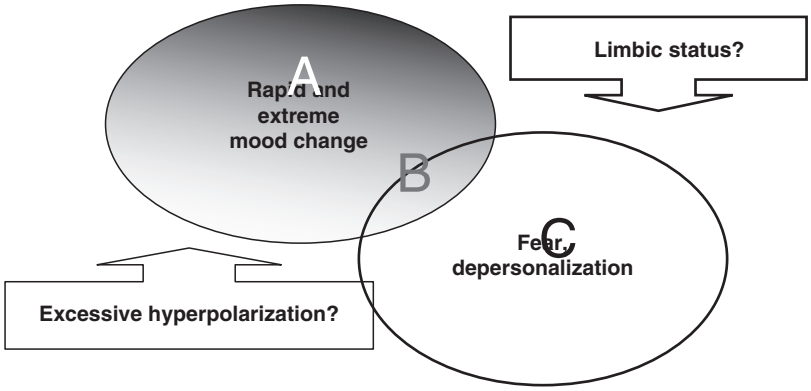
Subtypes of PIP and PIP-related phenomena

As with SPECT studies, only a few depth-EEG studies during active PIP episodes are available, though the results suggest interesting subtypes. So et al. (1990) confirmed the presence of increased spiking activity in the medial temporal region with depth-EEG recording during an episode of PIP. However, they were skeptical about the direct causal relationship between their finding and the occurrence of frank psychosis, since increased spiking is commonly observed as a postictal phenomenon in patients without psychosis (So et al. 1990). In a similar study using depth EEG, Mathern et al. failed to confirm increased postictal spike activity (Mathern et al. 1995). In contrast, psychic symptoms in Wieser's famous case, in which peculiar feelings such as depersonalization, mental diplopia, or déjà vu were prominent, precisely corresponded to subclinical limbic seizure discharge (Wieser et al. 1985). Successful recordings of depth EEG during post- or peri-ictal psychotic episodes are listed in Table 8.10, in which cases shown in boldprint involve direct manifestations of epileptic discharge

Table 8.10 Depth EEG studies during PIP episodes

Authors	Psychiatric symptom	Depth findings
So et al. (1990)	*Psychotic*	*Increased bitemporal spikes (maximally mesial temporal)*
Mathern et al. (1995)	*Psychotic aggressive*	*No change*
Wieser et al. (1985)	Sticky, aggressive	Left unilateral limbic SE
Kanemoto (1997)	*Capgras syndrome, fearful*	*Left unilateral limbic SE*
Takeda et al. (2001)	Psychotic, fearful	Left unilateral amygdala SE

Italics: postictal psychosis; **bold print**: aura continua; *italics* and **bold print**: aura continua and postictal psychosis.



A: Nuclear PIP; B: Subacute postictal aggression
C: Peri-ictal psychosis

Figure 8.4. Subtypes of PIP and related phenomena.

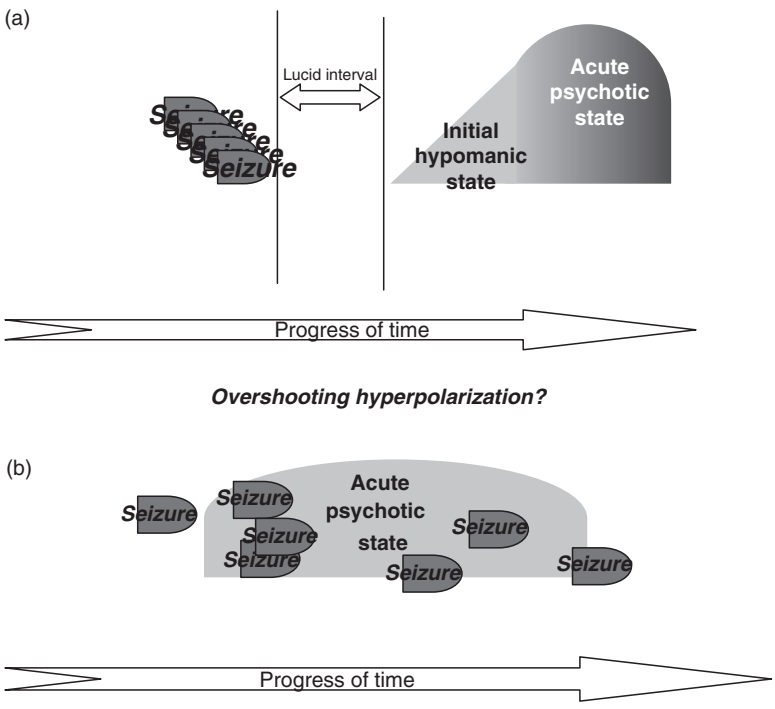


Figure 8.5. (a) Nuclear PIP. (b) Peri-ictal psychosis.

(Wieser et al. 1985; Kanemoto 1997; Takeda et al. 2001) while those noted in italics seemed to appear as an after-effect of epileptic seizures (So et al. 1990; Mathern et al. 1995).

My ideas of nuclear PIP, peri-ictal psychosis, and their mutual relationship are roughly sketched in Figure 8.4. While parts of peri-ictal psychosis are truly "epileptic equivalent," that is to say limbic status epilepticus (Figure 8.5b), nuclear PIP may be explained by overshooting postictal inhibition within a part of the limbic circuits (Figure 8.5a), which is supposed to be a more active process than simple neuronal exhaustion.

Now, we return to the two opposing ideas of PIP suggested by Jackson. Just as PIP itself was revived after a century of oblivion, Jackson's two different images of PIP published more than a century ago may help us go deeper into this peculiar mental state that is indigenous to epilepsy.

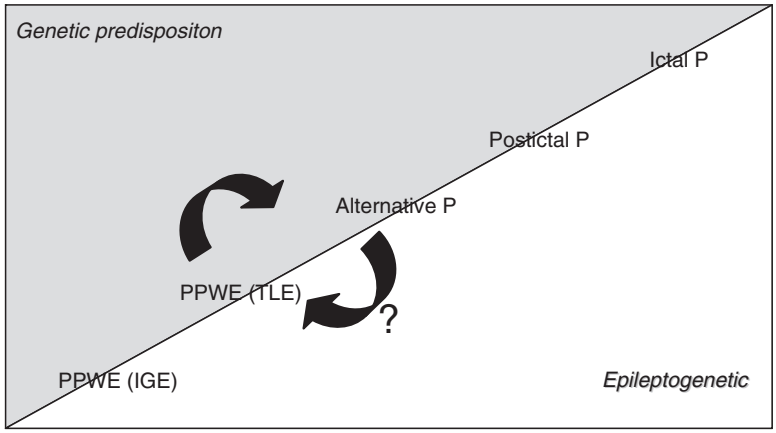


Figure 8.6. Epileptic psychosis or induced schizophrenia? PPWE, psychosis in patients with epilepsy.

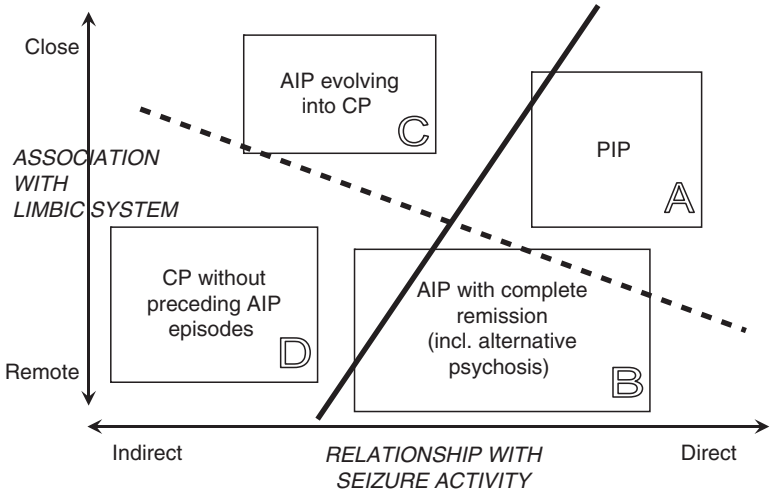


Figure 8.7. Psychosis in patients with epilepsy in association with limbic system and seizure activity.

Pathogenesis of PIP

There are two major streams of explanation for the pathogenesis of epileptic psychosis (Kanemoto et al. 2008). One extreme position is expressed by the opinion that there is no such state as epileptic psychosis and that epilepsy is nothing but a nonspecific precipitating factor leading to psychosis in patients genetically predisposed to psychosis. This explanation can be traced back to the "psychodynamic hypothesis" of Pond (1957) who regarded epilepsy as a risk factor in individuals genetically prone to psychosis. In contrast, the other extreme position is represented by Wieser et al. (1985) who described the first clearly documented case of "limbic status epilepticus" manifesting itself as psychosis. As a matter of course, psychosis observed in this setting may well be directly caused by epileptic activity. In Figure 8.6, the various impacts of genetic predisposition and epileptic activity on different types of psychosis in patients with epilepsy are presented in schematic form.

In a review of epileptic psychosis, Sachdev regarded PIP and alternative psychoses as a large unified group (Sachdev 2007). In his explanation, psychotic episodes are caused by an excessive inhibitory reaction as a sequel to severe ictal activity leading to imbalance within the limbic circuit. This idea develops from a unique theory of excessive inhibitory surround proposed by Stevens (1983) and recent findings of increased hippocampal dynorphin release in PIP and IIP, which serves as a psychotomimetic agent via overstimulation of kappa opioid receptors, providing amplification (Bortolato and Solbrig 2007). This unified group of transient epileptic psychoses can be regarded as true epileptic psychosis, because they are closely associated with epileptic activity, even if the link is inversely related in cases of alternative psychosis. In this perspective, as depicted in Figure 8.7, there is a solid boundary between epileptic

psychosis (A+B) and induced psychosis (C+D) in genetically predisposed patients.

On the other hand, in patients with chronic psychosis, especially when acute psychotic episodes go ahead, a close link with TLE was confirmed in our series. Further, this group of patients and patients with PIP had another important clinical feature in common, a long interval between epilepsy and psychosis onset. In these cases, longstanding seizure activity may modify the nervous system bit by bit and finally prepare settings to make the patient liable to psychotic manifestation. A progressive development of bilateral ictal foci proven to be a potent risk factor for PIP is a known example of such a liability (Kanner and Ostrovskaya 2008) which may also be associated with less favorable surgical outcome in this group of patients (Guarnieri et al. 2009). In this regard, patients with PIP as well as those with a prior history of acute IIP episodes finally changing into CP should be regarded as having epileptic psychosis, which may be partially reversed by removing foci of epileptic activity by surgical intervention. In this case, the dividing line between epileptic psychosis (A+C) and induced psychosis (B+D) should be dotted.

These two perspectives may be supplementary rather than mutually exclusive. On one side, when it comes to individual psychotic episodes, the excessive inhibitory hypothesis by Stevens seems more attractive. On the other, when we focus our attention to how susceptibility to psychosis develops from epilepsy in the long term, the dotted line seems more plausible. Undoubtedly, an attempt to elucidate the pathogenesis of PIP would deepen our understanding of the biological basis of psychosis.

Finally, PIP has become a widely recognized clinical entity in the domain of epileptology (DeToffol 2001; Gélisse et al. 2002; Baum et al. 2007; Elliott et al. 2009; Lambrey et al. 2009), which is expected to help to bridge psychiatry and epilepsy.

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Chapter 9

The interictal dysphoric disorder

Marco Mula

Epilepsy and depression: the nature of the problem

The associations between epilepsy and depression have been well-known and described for a long time. The Greek physician Hippocrates, around 400 BC, observed that *melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy* (Temkin 1971).

The reasons why these two conditions may be closely linked together are both biological and psychosocial. Epilepsy is a chronic disorder and still brings about much social discrimination, thus leading to demoralization and a negative perspective towards life. However, apart from understandable psychosocial explanations, the biological contribution to the association, based on neuroanatomical and neurochemical principles, needs to be taken into account. Limbic system dysfunction is frequently reported in epilepsy and such a neuroanatomical system plays a key role in the processing of emotions. Besides, patients with epilepsy are chronically exposed to antiepileptic drugs that have a high psychotropic potential beyond their anti-seizure effect.

Epidemiological data from community studies confirm that depression is more frequent among patients with epilepsy when compared to the general population. The General Practice UK study reported a 22% prevalence of depression in unselected samples of patients with epilepsy (Edeh and Toone 1987). A Canadian Community Health Survey noted very similar prevalence rates for a lifetime diagnosis of depression (around 22%) that is much higher than those reported in the general population (around 12%) (Tellez-Zenteno et al. 2007). A US survey pointed out that depression is more frequent in patients with epilepsy (36.5%) in comparison to people with other chronic medical conditions such as asthma (27.8%) and healthy controls (Ettinger et al. 2004).

Another relevant issue relates to seizure control suggesting that in a large proportion of subjects, such comorbidity reflects on the intractability of the seizure disorder. Depressive disorders are reported in up to 21% of patients with high seizure frequency, while, in patients with good seizure control (seizure free or less than one seizure per month) prevalence rates are below 10% (Jacoby et al. 1996). Along the same line, other authors pointed out that patients with continuing seizures are significantly more likely to suffer from depression than those in remission (33% vs. 6%) (O'Donoghue et al. 1999).

Although such differences may be easily explained by psychosocial factors resulting from a more disabling seizure disorder, it is plausible to speculate that they may also reflect different biological underpinnings. In this regard, an important finding which has been replicated is that the link between epilepsy and depression is not necessarily unidirectional, in other words that patients with such a comorbidity always present with the seizure disorder before the onset of depression. In fact, it has been noted that the mood disorder can also precede the epilepsy (Forsgren and Nystrom 1990; Hesdorffer et al. 2000). Although it is reasonable to hypothesize that the occurrence of seizures may be related to neurological sequelae due to suicidal attempts, alcohol or drug abuse, and the use of psychoactive drugs, it is tempting to speculate that such a finding may reflect an underlying common pathogenesis, which may relate to some as yet unknown genetic factor, or some link with neurotransmitter function such

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as the serotonin or GABA systems (Kanner and Balabanov 2002; Kanner 2006).

The association of depression with a specific epilepsy syndrome: a still open question

The association between depression and any particular epilepsy syndrome represents a still unsolved issue. It has been suggested that patients with temporal lobe epilepsy are more prone to develop depression than other groups and this association seems to be strictly related to the degree of involvement of the limbic structures (Quiske et al. 2000). However, other authors failed to show any difference between temporal lobe and extratemporal lobe epilepsy in terms of prevalence of depressive disorders (Swinkels et al. 2006). In this regard, it is interesting to note that a number of studies in patients with major depression without epilepsy are pointing out a specific association between hippocampal volume loss and depression (Bremner et al. 2000; Frodl et al. 2002). Thus, although further research in this area is needed, neuroimaging studies are revealing an underlying brain network of mood control, which includes the hippocampus, the amygdala, and the cingulate cortex, nicely in keeping with a number of findings in epilepsy patients.

Another classic topic in neuropsychiatry of epilepsy pertains to the association between depression and the laterality of the EEG epileptiform abnormalities. Flor-Henry hypothesized a relationship between laterality of the seizure focus and psychosis and postulated that depressive disorders were associated with nondominant (right) temporal lobe epilepsy (Flor-Henry 1969). The basis for this still popular hypothesis was, however, relatively weak because it was based on a limited number of patients. In fact, subsequently, many authors have tried to confirm this laterality hypothesis with very mixed and overall equally balanced results favoring neither the right nor the left hemisphere (Lambert and Robertson 1999; Schmitz 2002). Nowadays, it is accepted that depression occurs equally with right- and left-sided temporal lobe epilepsy. Current literature on the neurobiology of depression in epilepsy has focused on frontal lobe dysfunction, the latter being confirmed by brain imaging techniques (PET or SPECT) and neuropsychological testing. In fact, it has been shown that patients with left-sided temporal lobe epilepsy and depression were more likely to perform poorly on frontal lobe tasks (Hermann et al. 1991). Similar results have been reported from neuroimaging studies (Schmitz et al. 1997; Bromfield et al. 1990). Although these findings, of necessity, were on a limited number of patients, the concordance between the conclusions does support an anatomical association between temporal lobe epilepsy, especially left-sided epileptic activity, depression, and frontal lobe dysfunction. These results are of relevance because they further support the view that epileptic foci may have dysfunctional influences on remote areas that may become clinically relevant, for example through the manifestation of psychiatric symptoms.

Atypical phenomenology of depression in epilepsy: the interictal dysphoric disorder

As stated above, interictal depressive disorders have been the most commonly recognized psychiatric comorbidity. There is an ongoing debate as to whether depressive disorders differ between people with and without epilepsy. Modern studies of interictal psychiatric disorders of epilepsy have usually attempted to identify their similarities to the psychiatric disorders that meet current classificatory systems (i.e. DSM-IV and ICD-10). Some authors have emphasized the endogenous features (Betts 1974) while others commented on the reactive nature of depression (Mulder and Daly 1952). In general terms, the spectrum of manifestations is likely to be large and it is reasonable to hypothesize that patients with epilepsy can experience forms of mood disorders identical to those of patients without epilepsy. On the other hand, it is equally reasonable to assume that the underlying brain pathology may influence the final phenomenology of mood disorder symptoms, emphasizing some aspects or attenuating others.

Data favoring the existence of an epilepsy-specific mood disorder come from the clinical observation that the psychopathology of patients with epilepsy often has unique manifestations that are poorly reflected by conventional criteria (Krishnamoorthy et al. 2007). Some authors observed that up to 22% of patients consecutively assessed for the occurrence of depression could be classified as having atypical

features (Mendez et al. 1986) and such percentages can rise up to 71% among subjects with treatment-resistant epilepsy (Kanner et al. 2000; Kanner et al. 2004). At this point it is important to state that a number of potential causes may account for such an atypicality of depressive symptoms in epilepsy such as behavioral peri-ictal symptoms, the psychotropic effects of antiepileptic drugs, the high rates of comorbid anxiety disorders or symptoms, and the spectrum of subclinical and subsyndromic forms of depression which represents, to some degree, an important cause for atypical presentations of primary mood disorders in psychiatric practice. In any case, the possibility that the mood disorders of epilepsy may have unique characteristics has plausibility.

Classic psychiatric authors, such as Kraepelin and Bleuler (Kraepelin 1923; Bleuler 1949), have described a pleomorphic pattern of symptoms, including affective symptoms with prominent irritability intermixed with euphoric moods, fear, and anxiety as well as anergia, pain, and insomnia, typical of patients with epilepsy. Gastaut has confirmed such observations (Gastaut et al. 1955) and, later, Blumer coined the term interictal dysphoric disorder to refer to this type of somatoform-depressive disorder seen in patients with epilepsy (Blumer 2000). Blumer used the term "dysphoria" to emphasize the periodicity of mood changes and the presence of outbursts of irritability and aggressive behavior as key symptoms. Other authors commented on the chronic course of this state of moderate neurotic depression with symptom-free intervals, referring to a dimension close to dysthymia (Himmelhoch 1984; Kanner et al. 2000; Kanner 2003).

It is obvious that the interictal dysphoric disorder may present in our time with features that are different from those described by premodern psychiatry, for example depressed mood and anergia may be much more evident than before because antiepileptic drugs may attenuate mood instability.

In the detailed description of the interictal dysphoric disorder by Blumer, eight key symptoms, grouped in three major categories, are identified: labile depressive symptoms (depressive mood, anergia, pain, and insomnia), labile affective symptoms (fear, anxiety), and supposedly "specific" symptoms (paroxysmal irritability and euphoric moods) (Table 9.1) (Blumer 2000; Blumer et al. 2004). The dysphoric episodes are described as occurring without external triggers and without clouding of consciousness; beginning and ending rapidly and recurring fairly regularly in a uniform manner (every few days to every few months and lasting a few hours up to 2 days). The concept of the interictal dysphoric disorder theorized by Blumer goes beyond the mood disorder per se, to encompass a spectrum of conditions that go from a dysphoric disorder with fleeting symptoms, to a more severe disorder with transient psychotic features, to an even more debilitating disorder with prolonged psychotic states. According to Blumer's view, the schizophrenia-like psychoses of epilepsy can be considered as a severe interictal dysphoric disorder with psychotic features or better a schizoaffective interictal dysphoric disorder (Blumer 2000; Blumer et al. 2004). Such a hypothesis is clearly influenced by a Kraepelinian view of the relationship between manic-depressive illness and schizophrenia (Kraepelin 1923).

Table 9.1 Key symptom categories of the interictal dysphoric disorder of epilepsy according to Blumer's definition

Labile depressive symptoms
Anergia
Depressed mood
Insomnia
Pain
Labile affective symptoms
Anxiety
Fear
Specific symptoms
Euphoric moods
Paroxysmal irritability

During recent years we investigated the clinical and psychopathological features of the interictal dysphoric disorder observing that such a syndrome represents a homogenous construct with specific clinical features (Mula et al. 2008a; 2008b). However, it seems not to be specific of patients with epilepsy, being diagnosed also in subjects with other neurological disorders such as migraine (Mula et al. 2008a). Therefore, it needs to be clarified whether such a condition is an organic affective syndrome that occurs in patients with brain disturbances or whether it can be diagnosed also in subjects with chronic medical conditions not affecting primarily the central nervous system. Theoretically, this issue was partly addressed by Blumer himself who commented on the possibility

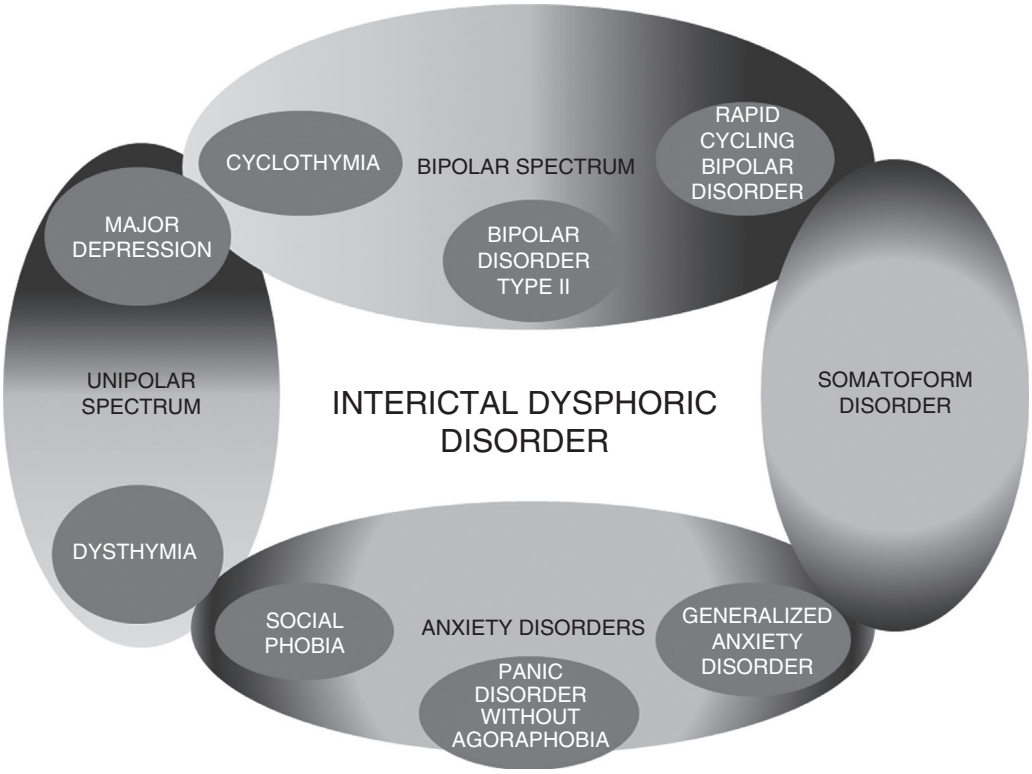

Figure 9.1. Psychiatric diagnoses overlapping with the interictal dysphoric disorder according to current classificatory systems (i.e. DSM-IV-TR).

that this somatoform-depressive disorder could occasionally occur in the absence of clinical seizures, in patients with brain lesions (with or without an abnormal EEG) (Blumer et al. 1988).

Another relevant point relates to the relationship of the interictal dysphoric disorder with current diagnostic categories. It seems evident that its features overlap with a variety of affective disorders seen in clinical psychiatric practice (Figure 9.1). Our data pointed out that the interictal dysphoric disorder is a mood disorder, usually diagnosed during the depressive phase, with comorbid anxiety (social phobia and/or generalized anxiety disorder) and a significant component of mood instability (Mula et al. 2008a). In this regard, it is of relevance to clarify whether such a condition has elements in common with the unipolar or the bipolar mood spectrum because of the implications in terms of prognosis and treatment strategies. In our opinion, the co-occurrence of mood instability and irritability clearly favors closeness with bipolar rather than unipolar depression (Möller and Curtis 2004; Benazzi 2007). This is further supported by the use of standardized clinical instruments for manic and depressive symptoms. In fact, the Mood Disorder Questionnaire, specifically developed to identify manic symptoms (Hirschfeld et al. 2003), has been shown to be more specific for a diagnosis of interictal dysphoric disorder (86.0%) then the Beck Depression Inventory (65.9%) (Mula et al. 2008a). Our clinical impression is that patients with the interictal dysphoric disorder have several features in common with a subset of cyclothymic subjects representing the more unstable form of bipolar disorder type II, where depressive periods and labile-angry-irritable moods dominate the clinical picture (Akiskal and Pinto 1999). Such similarities are further supported by the observation that patients with symptoms of the interictal dysphoric disorder can be misleadingly diagnosed as having a bipolar disorder (Mula et al. 2008b). Notably, Blumer pointed out that a combined therapy with antiepileptic and antidepressant drugs is frequently effective (Blumer et al. 2004), and such association is extensively used in bipolar depression.

The diagnosis of interictal dysphoric disorder in patients with epilepsy

As discussed so far, it seems evident that a diagnosis of depression can be challenging in some patients due to the atypicality and pleomorphic nature of symptoms and the overlap between diagnostic criteria for depression, according to current classifications, and other manifestations related to seizures or side effects of the antiepileptic drug treatment (e.g. loss of energy, insomnia or hypersomnia, increase or decrease in appetite, loss of libido, psychomotor retardation or agitation, diminished ability to think or concentrate). Therefore, clinicians need to explore fully the mental state of the patient in order to identify symptoms that cannot be influenced by epilepsy-related variables.

As for a diagnosis of depression characterized by symptoms identical to those reported by psychiatric populations without epilepsy, a few clinical instruments have been validated in the epilepsy population. Among structured or semi-structured clinical interviews, Mintzer and Lopez (2002) proposed the Epilepsy Addendum for Psychiatric Assessment (EAPA) to be used with the MINI, and a version of the SCID-I adapted for patients with epilepsy, named SCID-E, has been developed (Krishnamoorthy 2005). However, it has to be acknowledged that the relative benefits of these instruments in the assessment of generic psychopathology in community-based studies are still a matter of debate.

Among self-rating screening instruments, the well-known Beck Depression Inventory has been validated in patients with epilepsy showing good sensitivity (0.93), acceptable specificity (0.81), and an excellent negative predictive value (0.98) but a very low positive predictive value (0.47) (Jones et al. 2005). A six-item, self-report, screening instrument, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) (Gilliam et al. 2006), showed an internal consistency of 0.85 and a test-retest reliability of 0.78. A score of 15 or higher has a specificity of 0.90 and a sensitivity of 0.81 for a diagnosis of depression in epilepsy.

However, all these instruments fail to identify atypical manifestations that can be seen in the epilepsy setting and, mostly, cannot identify key symptoms of the interictal dysphoric disorder. The Seizure Questionnaire has been developed by Blumer and collaborators and contains questions for the eight key symptoms (Blumer et al. 2002). Patient and caregiver answer them jointly and the examiner then reviews all answers for completeness and accuracy. A specific instrument, named Interictal Dysphoric Disorder Inventory (IDDI), has been developed in the context of a collaborative German-Italian study (Mula et al. 2008a). It is a 38-item, self-report questionnaire to evaluate all symptoms of the interictal dysphoric disorder in terms of presence, frequency, severity, and global impairment. This questionnaire explores a time-interval of 12 months. The diagnosis of interictal dysphoric disorder is made in accordance with Blumer's criteria (Blumer et al. 2004), namely the presence of at least three symptoms of "moderate" or "severe" severity and causing "moderate" or "severe" distress. It is possible to obtain a total score and three subscale scores that mirror the three major symptom categories described by Blumer: labile depressive symptoms, labile affective symptoms, and specific symptoms. Furthermore, the IDDI allocates also "*severeness*" scores that reflect the degree of interference or distress caused by symptoms. (See Table 9.2.)

The IDDI total and subscale scores showed strong or very strong correlations among themselves (0.68–0.85) and the instrument displayed an acceptable sensitivity and an excellent specificity when compared to a validated questionnaire for the screening of major depression or bipolar disorder (i.e. Beck Depression Inventory and Mood Disorder Questionnaire) (Mula et al. 2008a). Finally, in the Appendix to the questionnaire, six questions investigate the time course of the disorder, the duration of dysphoric symptoms and their associations with seizures or antiepileptic drug therapy. In particular, patients are asked whether dysphoric symptoms are habitually related only to seizures, if yes in what temporal relation they occur, and how long they last. The entire questionnaire has been published and it is fully available (Mula and Trimble 2008).

Recent data from our group pointed out that among patients who satisfy Blumer's criteria for interictal dysphoric disorder, about half of them present with symptoms with a clear-cut relationship with epileptic seizures (Mula et al. 2010). In our opinion, a diagnosis of interictal dysphoric disorder in the strict sense should be limited only to those subjects where psychiatric manifestations are independent from the wide range of behavioral changes

Table 9.2 Interictal Dysphoric Disorder Inventory (IDDI)

Mula and Schmitz 2005 (modified from Krishnamoorthy and Trimble)	
Patient code_____ Date of evaluation:_____	
Some people with epilepsy experience changes in their mood, emotions, and feelings from time to time. We would like to ask you about any such changes you experienced **in the last 12 months**. Please put a cross next to the right answers.	
1. Anergia	
1.1 Do you feel you lack energy from time to time?	No (0) Yes (1)
Further questions about anergia	
1.2 How often does this lack in energy occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
1.3 How severe is this lack in energy usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
1.4 How much do you feel impaired by this lack in energy when it occurs?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
2. Pain	
2.1 Do you suffer from many aches and pains from time to time (e.g. *headaches, stomach-aches, abdominal pain, back pain*)?	No (0) Yes (1)
Further questions about pain	
2.2 How often does pain occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
2.3 How severe is this pain usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
2.4 How much do you feel impaired by this pain, when it occurs?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
3. Insomnia	
3.1 Do you have trouble with your sleep from time to time?	No (0) Yes (1)
Further questions about insomnia	
3.2 How often do these problems occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
3.3 How severe are these problems usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
3.4 How much do you feel impaired by these problems?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
4. Fear/panic	
4.1 Do you experience feelings of fear or feel panicky from time to time?	No (0) Yes (1)
Further questions about fears or panic	
4.2 How often do these feelings of fear or panic occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
4.3 How severe are these feelings of fear or panic usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
4.4 How much do you feel impaired by these feelings of fear or panic, when they occur?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
5. Anxiety	
5.1 Do you have frequent worries, feelings of oppression, agitation, or anxiety from time to time?	No (0) Yes (1)
Further questions about anxiety	
5.2 How often does anxiety occur?	Never (0)
	Rarely (1) Sometimes (2) Often (3)

Table 9.2 (*cont.*)

5.3 How severe is this anxiety usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
5.4 How much do you feel impaired by this anxiety, when it occurs?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
6. Depression	
6.1 Do you feel in low spirits, depressed, or find it difficult to take pleasure in most activities from time to time?	No (0) Yes (1)
Further questions about depressed mood	
6.2 How often does this occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
6.3 How severe is this usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
6.4 How much do you feel impaired by this, when it occurs?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
7. Euphoria	
7.1 Do you feel cheerful, very happy, full of energy without good reasons from time to time?	No (0) Yes (1)
Further questions about euphoric moods	
7.2 How often does this occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
7.3 How severe is this usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
7.4 How much do you feel impaired by this?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
8. Irritability	
8.1 Do you feel irritable, experience bad temper, or fly off the handle easily over little things from time to time?	No (0) Yes (1)
Further questions about irritability moods	
8.2 How often does this irritability occur?	Never (0) Rarely (1) Sometimes (2) Often (3)
8.3 How severe is this irritability usually?	Not present (0) Mild (1) Moderate (2) Severe (3)
8.4 How much do you feel impaired by this irritability?	Not at all (0) Mildly (1) Moderately (2) Severely (3)
Appendix: questions concerning the temporal relations of the above mentioned complaints	
A. Do the above symptoms occur temporally independently from each other?	No ( ) Yes ( )
B. How often do these symptoms occur?	_____times a day _____times a week _____times a month
C. How long do these symptoms last?	A few hours ( ) One day ( ) A few days/less than a week ( ) A week or more ( ) Time periods differ ( ) Chronic ( )
D. Is the occurrence of these symptoms related to seizures in any way?	No ( ) Yes ( )
E. If Yes, in what temporal relation to your seizures do these symptoms occur?	Before seizure ( ) After seizure ( ) During seizure ( ) During periods when you are free of seizures ( )

Table 9.2 (*cont.*)

F. Is the occurrence of these symptoms more noticeable when your therapy is changed?	No ( ) Yes ( )

IDDI scoring

IDD definite diagnosis: at least three symptoms of at least "moderate" or "severe" severity and causing "moderate" to "severe" distress.
Symptoms scoring:
IDDI total score: (Yes answers 1.1+2.1+3.1+4.1+5.1+6.1+7.1+8.1)/8
IDDI labile depressive symptoms score: (Yes answers 1.1+2.1+3.1+6.1)/4
IDDI labile affective symptoms score: (Yes answers 4.1+5.1)/2
IDDI specific symptoms score: (Yes answers 7.1+8.1)/2
Severeness scoring:
Total severeness: total sum of frequency (X.2 for each item), severity (X.3 for each item), and impairment (X.4 for each item) scores
Labile depressive symptoms severeness: sum of frequency, severity, and impairment scores for 1, 2, 3, and 6
Labile affective symptoms severeness: sum of frequency, severity, and impairment scores for 4 and 5
Specific symptoms severeness: sum of frequency, severity, and impairment scores for 7 and 8

that may occur around the epileptic attack and for this reason a distinction between interictal and peri-ictal dysphoric symptoms has been postulated (Mula et al. 2010). Such a distinction was not pointed out or directly addressed in Blumer's papers but has implications in terms of diagnosis, prognosis, and treatment. In fact, although there does not seem to be a difference in the phenomenology of dysphoric symptoms between interictal and peri-ictal manifestations, it is evident that seizure control is determinant for the management of affective manifestations related to seizures while specific psychiatric treatments are needed for interictal symptoms, especially because they are chronic and unremitting in one-third of cases.

One of the most frequent methodological errors in studies of depression in epilepsy is the sole reliance on screening instruments for the diagnosis of depressive disorders. We further support the need for a careful assessment of peri-ictal symptoms because they are frequently reported by patients and may be severe enough to reach clinical attention although they cannot be considered true psychopathology.

Conclusions

Depression in epilepsy represents a frequently encountered psychiatric comorbidity that is likely to be related to a number of variables that are both biological and psychosocial. The arguments for whether or not clinical presentations of depression in epilepsy are similar to those in the general population have been variably prominent across the authors. However, whatever way one views this, the literature suggests that a subgroup of patients may have an affective syndrome with peculiar features which some have referred to as the interictal dysphoric disorder. Such a condition seems to overlap with the bipolar spectrum, with possible consequences in terms of prognosis and therapeutic strategies. However, in a relevant proportion of cases, the number of behavioral manifestations that occur around the seizure play a relevant role in such an atypicality. It is, therefore, essential that clinicians carefully assess the mental state of their patients taking into account a number of variables that are principally related to the underlying neurological disorder.

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Chapter 10

Behavioral and neuropsychological aspects of frontal and temporal lobe epilepsy

Christoph Helmstaedter and Juri-Alexander Witt

Introduction

To date neurobiological interest in the behavioral consequences of epilepsy has been concerned primarily with the neuropsychology of temporal lobe epilepsy (TLE) and of mesial temporal lobe epilepsy (mTLE) in particular. This focus on TLE is mostly due to the fact that this type of epilepsy represents the majority of focal epilepsies. In the Bonn series of surgically evaluated patients, TLE represents about 80% of patients with pharmacoresistant epilepsies and about 60% of these epilepsies originate from temporomesial structures.

MTLE (mesial temporal lobe epilepsy) represents an entity among the temporal lobe epilepsies characterized by a specific pathology (hippocampal sclerosis), a frequent history of febrile convulsions, an early onset of epilepsy, and memory problems as the prominent neuropsychological impairment (Wieser 2004). In TLE, the affected cerebral structures and epileptogenic region are mostly circumscribed, and structural pathology can well be quantified by the analysis of magnetic resonance imaging (MRI) data (T2 relaxometry and volumetry) or by postoperative histopathological examinations of the resected specimen. Frequency, homogeneity, and a circumscribed and quantifiable pathology provide ideal prerequisites for the study of the functional and behavioral correlates of temporal lobe epilepsy. Great progress has been made during recent years at least with respect to the neuropsychological and cognitive aspects of TLE. Recent developments in the field, however, show that it is well recognized that temporal lobe functioning involves more than memory and that its role in emotion and the psychiatric comorbidity of epilepsy is becoming rediscovered.

Despite a long history of research on deviant behaviors in patients with frontal lobe lesions and despite an increasing interest in the cognitive neurosciences in social behavior, the functional correlates of frontal pathology in epilepsy have long been neglected and are yet poorly understood. The major reason for this can be seen in the fact that the frontal lobe, although representing the largest lobe of the human brain, is less frequently affected by focal symptomatic epilepsy than the temporal lobes. In our own series, patients with FLE (frontal lobe epilepsy) represent about 15% of the patients with pharmacoresistant epilepsies. Site and type of the underlying pathology are very heterogeneous. Furthermore, ictal as well as interictal clinical and electrophysiological manifestations of FLE are infrequently localized because multiple connections to most other brain areas enable a fast and widely distributed propagation of epileptic activity.

The behavioral features of the frontotemporal network

To date there is a large body of evidence from studies in animals and man which links social behavior and mood disorders to a functional network which mainly comprises the prefrontal and orbitofrontal cortex, the amygdala, the striatum, the pallidum, the thalamus, the hypothalamus, and parts of the brainstem (Behrens et al. 2009; Price and Drevets 2009).

Correspondent to its cytoarchitectonic structure, the frontal lobe is traditionally divided into two parts, which are important in two major areas. The posterior part controls motor movement and is subdivided into a premotor and a motor area, which control movement preparation and actual execution of movement

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

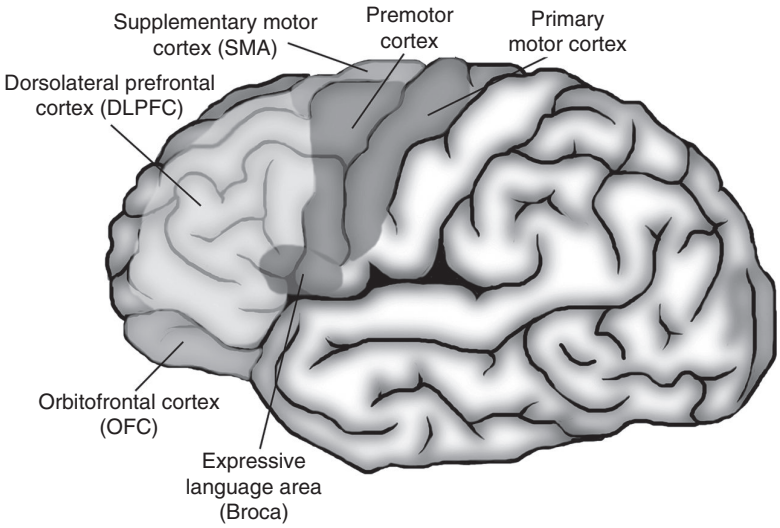

Figure 10.1. Lateral view of the human brain depicting the major divisions of the frontal lobe and the key structures in the mesial temporal lobe. See plate section for color version.

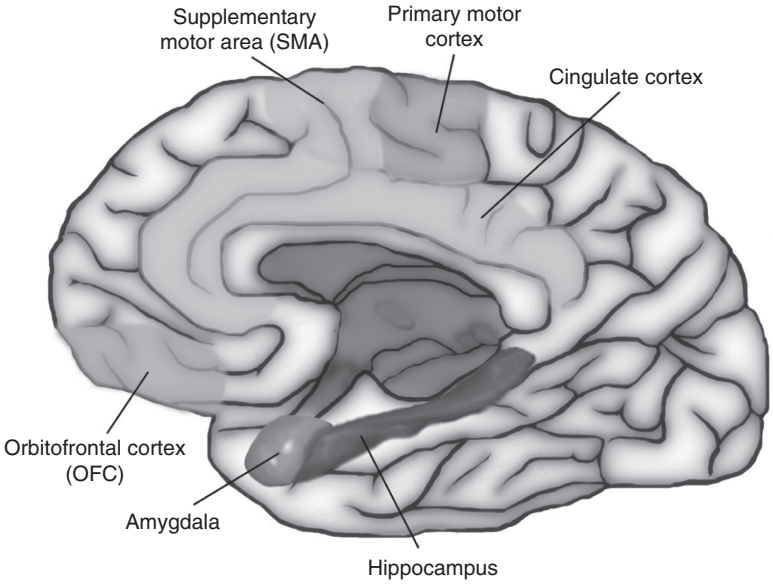

Figure 10.2. Sagittal view of the human brain depicting the major divisions of the frontal lobe and the key structures in the mesial temporal lobe. See plate section for color version.

respectively. The anterior part of the frontal lobe, the prefrontal cortex, is especially important in higher mental functions such as anticipation and planning, initiative, judgment, and in affect control, willpower, and the determination of personality (Bechara et al. 1999; Raine et al. 2000). The prefrontal cortex can be further subdivided into the dorsolateral cortex and the orbitofrontal cortex. This subdivision of the prefrontal cortex is simplified and it should be noted that the orbitofrontal cortex itself is a heterogeneous area connected with a wide range of other prefrontal, limbic, premotor, sensory areas and subcortical nuclei (Cavada et al. 2000). The relevant anatomical areas are shown in Figures 10.1 and 10.2.

For the purpose of this article it is important to know that there is evidence that damage of the dorsolateral part of the prefrontal cortex is more associated with impairment of executive functions like working memory and divergent thinking, whereas damage of the orbitofrontal cortex leads to disinhibition phenomena and impairment of choice behavior, the establishment of emotional valences, and the

evaluation and balancing of the past and future consequences of a given behavior (Bechara et al. 2000; Cummings 1993; Rolls 2000; Rolls and Grabenhorst 2008; Sarazin et al. 1998). In decision-making, the medial prefrontal cortices are rather involved in the process of binary decision-making when choices are requested, whereas the orbitofrontal cortex provides a more continuous representation of reward or affective value (Rolls and Grabenhorst 2008). Areas in which the orbital and medial prefrontal cortex are believed to play a central role are addictive behavior, ADHD, negative emotion, and major depression respectively (Drevets and Price 2005; London et al. 2000; Northoff et al. 2000; Rubia et al. 2000). Davidson and coworkers (2000) propose a key role of the prefrontal cortex in the regulation of emotion in violent subjects and those predisposed to violence.

A third relevant structure for social behavior and behavioral dyscontrol is the cingulum. Dependent on its connections to frontal lobe and mesial structures, the cingulum has been shown to be involved in social interaction, theory of mind, monitoring of action errors and conflict, memory, reward expectation and decision-making, and last but not least in the control of basic aspects of movement (Beckmann et al. 2009; Rushworth et al. 2007). Literature on lesions affecting the cingulum points to apathy as a prominent feature (Cummings 1993) and to deviant social behaviors and affective states (Devinsky et al. 1995).

The cingulum together with the hippocampal formation, the amygdala, and the anterior thalamus belong to the temporo-limbic system, the damage of which traditionally has been associated with impaired emotion processing and behavioral dyscontrol (Papez 1937). Different from frontal lobes and frontal lobe behavior, behavioral abnormalities associated with the temporal lobes and the limbic system are historically connected to epilepsy. Massive medio-temporal lobe damage in monkeys, and damage of the amygdala in particular, has been associated with a loss of fear, a loss of the significance of objects, extreme docility, orality, and hypersexuality (Salloway and Cummings 1994). Klüver found parallels between the oral behaviors he observed and those described by Hughlings Jackson as uncinate fits in temporal lobe epilepsy (Nahm and Pribram 1998). The early formulation of a "temporal lobe syndrome" (Nahm 1997) was also discussed by Henri Gastaut who found that patients with chronic mesial temporal lobe epilepsy – opposite to what is seen with temporal ablation – show intensified emotionality, attention to detail, and hyposexuality (Blumer et al. 2004). This idea is also found in Geschwind's proposition of a "personality change in temporal lobe epilepsy" (Geschwind 1977) which includes increased religious interests, hypergraphia, increased aggression, increased moral and philosophical concerns, viscosity, lack of humor, and hyposexuality. Geschwind's concept was continued by Bear and Fedio (1977) and is still under discussion (Devinsky and Schachter 2009; Devinsky and Najjar 1999).

Within the limbic system the amygdala appears to play a specific role in regard to emotional valence and significance of objects and situations. Furthermore the amygdala is critical for the discrimination of emotions and for fear learning and memory (LeDoux 2003; Nader et al. 2000). Evidence for the involvement of the amygdala in aggressive behavior comes from human and animal stimulation studies, from activating and inhibiting effects of antiepileptic drugs on aggression, and more recently also from direct correlations of amygdala volumes with aggression in patients with mesial epilepsies (Azouvi et al. 1999; Beran and Gibson 1998; Trimble and Van Elst 1999; van Elst et al. 2000). However, aggression associated with the amygdala seems more defensive than offensive in nature (Kalynchuk et al. 1999). Disinhibition phenomena or a loss of impulse control, as is observed with frontal lesions, may be an additional prerequisite for showing impulsive aggressive behavior (Damasio et al. 1994; Dolan 1999; Harlow 1868).

The orbitofrontal cortex as the border zone between the frontal lobes and the limbic system thus appears critical for the linkage of the frontal and limbic aspects of behavioral dyscontrol disorders. The theoretical basis of the role of the prefrontal cortex in the interplay of cognition and emotion has led to the "somatic marker" hypothesis (Damasio 1996) which proposes that responses to external stimuli not only rely on conditioning processes and cognition but also on unconscious autonomic response sets (feelings).

Epilepsy and behavior disorders

Case reports of behavioral and personality disorders in patients with severe frontal or temporal brain lesions often appear dramatic. However, with

respect to focal epilepsies, these reports nevertheless raise the question of whether there might be parallels in the behavior when epilepsy affects the same brain regions. With the exception of rare cases of ictal aggression, postictal confusional states or psychosis (Marsh and Krauss 2000), behavior and personality disorders observed in patients with FLE appear less severe. Furthermore, as with temporal lobe epilepsy, one can hardly expect to find the prototypical "frontal epileptic personality" or "*Wesensänderung*" respectively. Personality is by definition more trait than state dependent and particularly in epilepsy it is quite difficult to determine whether a given behavior really has trait characteristics or not. Conclusion of persistence and continuity requires follow-up observations with longer time intervals. In epilepsy several factors can be discerned, which can lead to dynamic and principally reversible changes in the patient's behaviors and mood states. Thus, for the closer understanding of behavioral abnormalities in epilepsy, differentiation of the more dynamic from the more static factors would be essential (see Table 10.1). The multifactorial etiological model of behavioral dysfunction in epilepsy largely resembles that proposed for cognition (Helmstaedter 2008).

Furthermore, although we can now look back at a long history of successful epilepsy surgery, it is still not clear to which degree the fact of having seizures is a prerequisite of behavior and mood disorders in epilepsy.

Table 10.1 Factors affecting behaviors and mood states in epilepsy

States of epilepsy	• Pre-ictal • Ictal • Postictal • Interictal • (seizure free after successful surgery)
Seizures	• Frequency • Generalization • Nonconvulsive status epilepticus
Epileptic dysfunction	• Local versus distant effects
Lesion	• Extent, location, lateralization • Stationary vs. progressive, migration and developmental disorders vs. tumors, encephalitis/autoimmune disease, mitochondrial disease, etc. (confounded with different ages at lesion/epilepsy onset)
AED	• Positive vs. negative psychotropic effects • Individual incompatibility • Drug-induced encephalopathy • Intoxication
Psychiatric comorbidity	• Organic epilepsy related • Organic in addition to epilepsy • Reactive

Seizures

The patient with epilepsy must always be seen in his or her state relative to seizures, e.g. whether he/she is ictal, postictal, or interictal. According to recent findings with regard to seizure prediction by nonlinear measures of complexity loss as recorded by intracranial EEG, significant seizure precipitating drops in complexity, i.e. synchronization, can be recorded long before the seizure starts (Lehnertz et al. 2007). Accordingly, one must assume also pre-ictal states, which would fit well to patients' reports of increased dysphoric mood and cognitive problems before the seizure starts (Figure 10.3). Finally, since a high number of patients can now become permanently seizure free by epilepsy surgery one can suggest an additional state of well-controlled epilepsy after successful epilepsy surgery. This state leaves the patient with his or her past history of epilepsy and a surgical lesion but without the disturbing effects of ictal or interictal epileptic dysfunction.

Lesions

Epileptic activity can affect distant brain areas and cause cognitive and behavioral problems beyond the primary lesion or epileptogenic zone (Shulman 2000). Notwithstanding seizures and epileptic activity one must also differentiate the underlying pathologies, which can be more or less systemic, have different onsets within the life span, and thus have different effects on brain maturation and the development of cognitive functions and personality. Lesions may furthermore be more stationary like post-traumatic lesions, migration disorders, or developmental tumors or they are dynamic and potentially progressive like in limbic encephalitis, mitochondrial encephalopathies, or tumors.

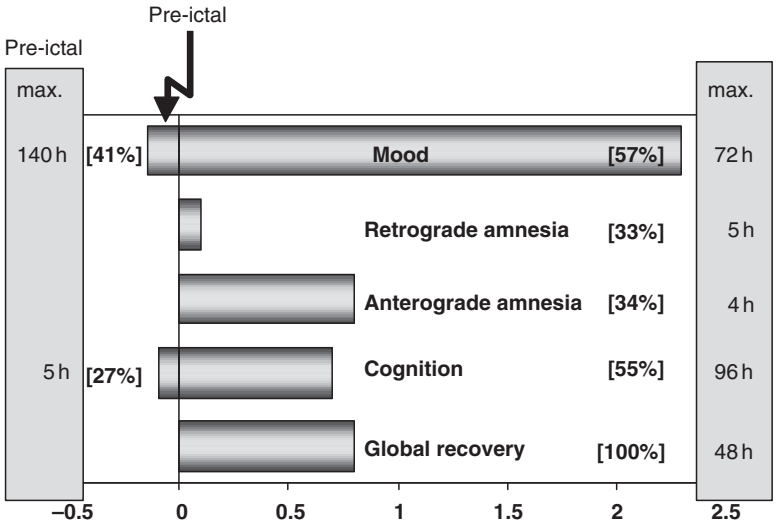

Figure 10.3. Subjectively reported pre- and postictal impairments evaluated in 48 patients with focal symptomatic epilepsies.

Medication

We must finally consider influences of often longstanding antiepileptic medication. Antiepileptic drugs may have positive or negative psychotropic side effects, and can show incompatibilities in the individual patient (Ettinger and Argoff 2007; Ketter et al. 1999). It is understood that interactive effects of pathology, epilepsy, and treatment must be considered. Apart from idiosyncratic actions, drugs can have different effects in lesion and non-lesion patients, and they may act differently dependent on the achieved seizure control.

Psychiatric comorbidity

Finally psychiatric comorbidity must be considered as a factor which directly cuts through our issue here. We may propose psychiatric problems as being part of the epilepsy, as existing in addition and parallel to epilepsy, or as being a reaction to epilepsy and its disabling and stigmatizing consequences.

Taking this into consideration it will be shown in the next sections that there is nevertheless evidence of specific behavioral abnormalities in patients with frontal or temporal lobe epilepsy which can well be interpreted within the above outlined theoretical framework. This will be exemplified by interictal behavior as assessed by neuropsychological examination and self-report measures concerning quality of life (QOL), every day activities, personality, and psychiatric symptoms. In addition seizure semiology and impairment during seizures and nonconvulsive status epilepticus will be considered to convey an idea of what the behavioral consequences of impaired temporal or frontal lobe functions in the respective epilepsies might be.

The neuropsychological features of temporal and frontal lobe epilepsy

While Scoville's and Milner's patient H.M., who after bilateral hippocampectomy suffered from global amnesia, represents a milestone in the development of neuropsychology of temporal lobe epilepsy, Brenda Milner's description of her evaluation of Penfield's patient K.M. may be taken as the frontal counterpart of H.M. This patient had a penetrating head injury in 1928, developed seizures, and underwent surgery of the anterior parts of both frontal lobes. Surgery successfully controlled the seizures and led to improved behavior as well as improved IQ. However, when reevaluated with the newly developed Wisconsin Card Sorting Test in 1962 he showed severe impairment in flexible categorical thinking and concept formation whilst the IQ still was average (Milner 1964). Both cases exemplify how much outcome interpretation depends on the test sensitivity and test selection.

Mainly because of its prevalence, the close relationship between temporal lobe pathology and memory impairment, and because epilepsy surgery often leads to additional memory impairment, the neuropsychology of temporal lobe epilepsy showed

considerable progress over the past decades. Episodic memory impairment is the prominent feature of TLE. Dependent on focus lateralization the impairments tend to be material specific. Dependent on pathology there can be primary or secondary and in part reversible additional dysfunctions in connected, mostly contralateral or frontal brain areas, and there is evidence for developmental hindrance in early onset TLE leading to more generalized intellectual problems (Helmstaedter 2008).

In contrast to TLE there are surprisingly few attempts to apprehend the cognitive characteristics of patients with FLE with group studies. Early data stem from operated patients and often focused on single functions more or less following the rather monistic view of a frontal "central executive" (Baddeley and Hitch 1974). Major impairments indicated by these studies are problems in concept formation, response inhibition (Milner 1964), estimations (Smith and Milner 1984), conditional associative learning (Petrides 1985; Petrides and Milner 1982), and the use of advance information in a choice reaction task (Alivisatos and Milner 1989). Delaney et al. (1980) found no differences in measures of memory when non-operated patients with unilateral frontal lobe foci were compared to healthy controls. In non-resected patients with FLE, we found deficits in attention to be the most significant problem (Kemper et al. 1992).

Later systematic group studies in patients with FLE followed the theoretical suggestion of different frontal subfunctions (Stuss and Benson 1986) and addressed the manifold frontal lobe pathology by the use of a broader range of tests including aspects of attention, motor coordination, psychomotor speed, fluency, response inhibition, conceptual formation and shift, as well as planning, guessing, or estimating. As compared to TLE patients, the 74 non-resected frontal patients in the publications by Upton and colleagues showed poorer motor coordination, guessing, estimation, and response inhibition (Upton and Thompson 1996; Upton and Thompson 1997a; Upton and Thompson 1997b; Upton and Thompson 1999). Our series of 33 patients indicated prominent impairment in motor skills and response inhibition whereas problems in speed/attention and working memory were also observed in TLE (Helmstaedter et al. 1996). Surgery of the frontal lobe did not cause much additional damage as far as eloquent cortex (i.e. language and motor areas) was not concerned. Otherwise, resections may cause aphasia (speech arrest and transcortical aphasia), psychomotor slowing, or a supplementary motor area (SMA) deficiency syndrome (impairment of initiation) (Helmstaedter et al. 1998). When clinical variables which might explain the impairment pattern in non-resected patients are looked at more closely no consistent picture emerges. According to Upton and Thompson (1997b) seizure frequency and the duration of epilepsy have an effect on performance but this appears to be a nonspecific effect rather than a consistent finding over different tests. With the exception of motor skills, which were spared in early right-sided FLE, no systematic effect of the assumed influence of the age at the onset of epilepsy on cognitive development could be concluded from their data (Upton and Thompson 1997a).

The negative impact of epileptic seizures on cognition can well be demonstrated by our postoperative findings indicating that in seizure-free patients adjacent functions recovered after surgery (Helmstaedter et al. 1998). Comparable release effects of frontal lobe functions have also been reported after temporal lobe surgery (Hermann et al. 1988). However, one should not go so far as to conclude that all deficits are due to epileptic dysfunction and thus reversible, as has been suggested by Boone et al. in a single case report in 1988 (Boone et al. 1988).

Summarizing the neuropsychological findings in FLE, impairments in different frontal subfunctions can be differentiated but these appear to converge on the demand of adequate response selection, response initiation, and response inhibition. One may thus hypothesize that the particular problem in FLE is the impairment of response selection/initiation/inhibition with varying emphasis depending on different functional areas. Which area is affected then depends on the type and the precise localization of the underlying lesion including the possibility that symptoms related to distant sites result from spreading epileptic dysfunction or diaschisis phenomena.

The development of appropriate test instruments for the assessment of frontal lobe dysfunction is not yet complete and still represents a challenge for neuropsychologists. Tasks on decision-making, social perception, and social cognition may help to further specify neurocognitive problems in FLE (Helmstaedter 2001; Shulman 2000).

Figure 10.4a,b demonstrates the neuropsychological profiles of a group of 849 patients with frontal or temporal lobe epilepsies: (a) as a function

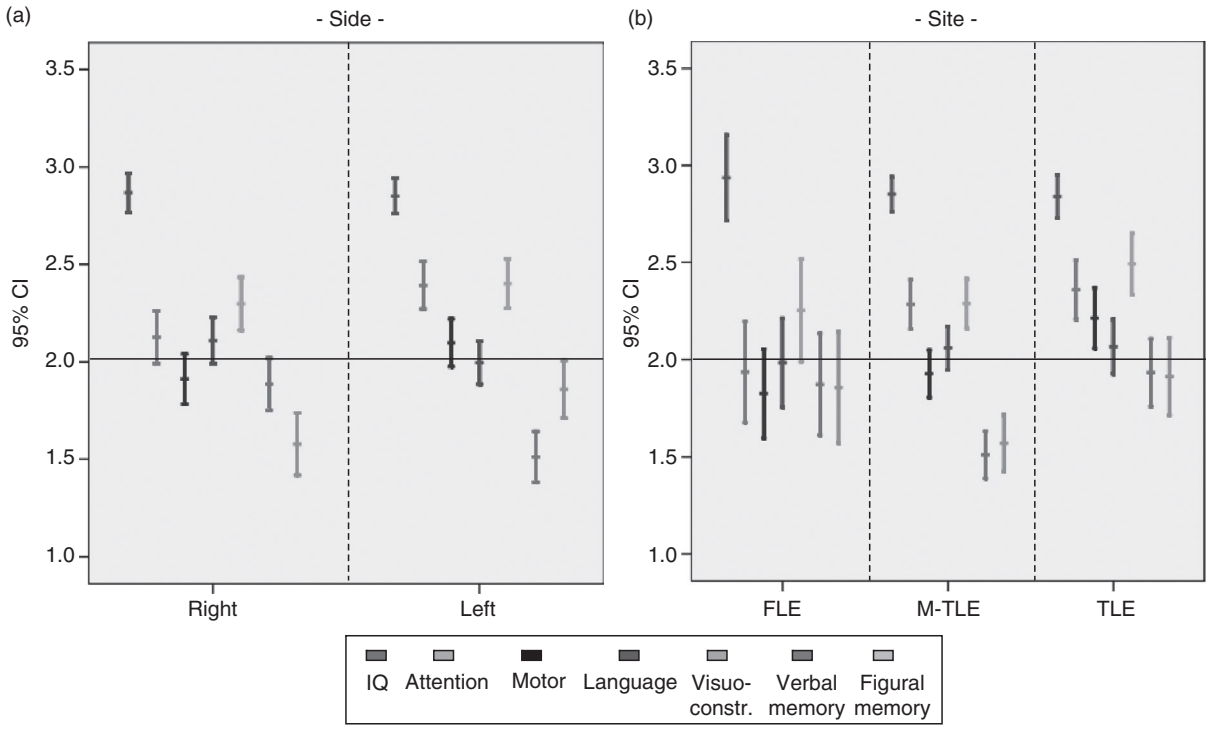

Figure 10.4. (a) Neuropsychological profiles of left versus right hemispheric frontal and temporal lobe epilepsies. (b) Cognitive profiles of patients with frontal lobe epilepsy (FLE) versus temporal lobe epilepsy (TLE) versus mesial temporal lobe epilepsy (mTLE). Values below the line at 2 points fall into the impairment range (mean minus one standard deviation). See plate section for color version.

of the lateralization of the epilepsy (420 left; 429 right), and (b) as a function of the type of epilepsy (117 with FLE, 334 with temporal lobe epilepsy [TLE], 398 with mesial temporal lobe epilepsy [mTLE]). The data stem from a review covering 15 years of epilepsy surgery at the epilepsy center in Bonn (Helmstaedter et al. 2007). All measures are standardized on a scale ranging from 0 to 4. A score of 3 indicates average performance; one point represents about one standard deviation each. Consistent with the literature and our own previous writings the findings demonstrate significantly greater problems in verbal memory and language functions in left hemispheric epilepsies, whereas right-sided epilepsies are accompanied by deficits in attention, motor coordination, and visual memory. Furthermore it becomes evident that FLE in contrast to TLE/mTLE is characterized by impairment in attention, motor-coordination, and visuoconstruction, and that memory problems represent the major impairment of mTLE. FLE and TLE without mesial pathology do not show different memory impairments.

Ictal behavior in temporal and frontal lobe seizures: "positive" and "negative" phenomena

An important source for the behavioral features of temporal and frontal lobe epilepsy is the examination of behaviors related to seizures. In the context of seizures we first of all can differentiate "positive symptoms" like the aura which is a sensation directly experienced by the patient or the observable seizure semiology. In addition we can differentiate "negative symptoms" in terms of impaired functions which cannot be observed without ictal or postictal testing. Seizure semiology and the pattern of impaired and preserved functions during seizures can help to localize the seizure origin and they can tell us something about the functional cerebral organization of cognition and consciousness (Helmstaedter 2007; Lux et al. 2002; Scherrmann and Elger 1999).

Positive ictal phenomena in temporal lobe seizures are oro-alimentary automatisms, gestural automatisms, motor arrest, staring, and dystonic

posturing. Other positive symptoms like internal sensations such as epigastric aura, fear, or more complex emotional, sensory, or cognitive sensations cannot be observed and must be requested from the patient. Negative symptoms like impaired consciousness, speech, mnestic functions, or motor control can only be tested. Seizure semiology differs dependent on whether more mesial or neocortical structures are primarily affected or secondarily involved due to seizure spread into the amygdala or frontal lobes.

Ictal phenomena in frontal seizures are mostly positive phenomena (Table 10.2). On the one hand this means a nearly 1:1 relationship between discharges and motor excitation when direct access to motor neurones is possible, like in primary motor area seizures for example. On the other hand this means release and disinhibition of complex behaviors and behavior chains when premotor and supplementary motor (SMA) areas are involved. Examples are posturing and contraversive movements in SMA and premotor seizures, and explosive, bizarre, and emotional instable behaviors in prefrontal seizures including its mesial parts. Negative phenomena like loss of consciousness are commonly observed in seizures with mesial propagation and secondarily generalization. For frontal seizures one can thus conclude that the prominent feature is impairment of executive control in terms of a pathological "hyperexcitation" or "disinhibition."

Table 10.2 Ictal frontal seizure semiology (N=15)

Localization	Positive symptoms
Primary motor area	Nearly 1:1 manifestation of seizure activity in myoclonic and tonic or clonic motor activity
Supplementary motor area (SMA)	Tonic posturing
Premotor area	Contraversive head and eye movements
Prefrontal (incl. gyrus cinguli)	Explosive and complex motor automatisms (including vocalizations), bizarre & hysterical behavior, mood change
Mesial propagation & sec. generalization	Loss of consciousness
Main feature: impaired executive control: "pathological excitation and disinhibition."	

While classifications of seizures on the basis of seizure semiology are very common, the examination of impairments during seizures has rarely been systematically done. We performed ictal testing in 116 patients, most of them being candidates for epilepsy surgery. These patients underwent ictal examinations which included examination of orientation reflexes (verbal, nonverbal, tactile), expressive and receptive language (commands, naming repetition), nonverbal reception and expression (commands and imitation), and finally awareness and memory (interrogation after the seizure). Testing was comparable to that performed during intracarotid amobarbital tests (WADA test) and it was performed by the video-EEG monitoring staff and started as soon as possible after seizure onset. Functions were tested hierarchically according to their complexity and testing was continued until the seizure ended. About half of the patients had implanted subdural strip and/or hippocampal depth electrodes for invasive EEG recordings.

Table 10.3 shows the resulting impairment pattern when distribution of ictal EEG activity at the time of testing is considered. In comparison to lateralized and bilateral temporal lobe seizures, frontal

Table 10.3 Negative ictal symptoms in focal epilepsy (N=116)

	Location of seizure activity			
% impaired when tested ictally	Frontal N=29	Right temporal N=21	Left temporal N=38	Bitemporal N=28
Orientation reflex	62	10	18	57
Receptive speech (commands)	48	15	59	93
Expressive speech	77	11	47	76
Memory	31	0	46	100
Consciousness	33	12	39	100

lobe seizures are characterized by prominent impairment of orientation reflexes and expressive speech, which are typical frontal functions. Receptive speech is often preserved. Patients can try, for example, to follow body commands even when they appear involved in excessive motor activity. In contrast to left temporal and bitemporal seizures, consciousness (awareness of any kind) and memory for the test situation during the seizures is mostly preserved.

Very special behavioral and neuropsychological conditions are met during nonconvulsive status epilepticus (NCSE), which is defined as an ongoing, electophysiologically assessed, seizure-like epileptic activity without loss of consciousness and without the overt motor signs of a simple partial or complex partial seizure. NCSE may overtly manifest as a psychiatric condition and/or as a condition with predominantly cognitive dysfunctions. However, with invasive depth electrode recordings quite asymptomatic states can also be observed. Systematic observations are rare (Walker et al. 2005). The most prominent feature of frontal NCSE is severe impairment of self-initiated planned behavior (Table 10.4). Bedside testing furthermore reveals that patients in such states show largely preserved, low-level reactive and reflexive behavior, strongly varying attention levels, behavioral loops with stereotyped and perseverative responses, ideomotor apraxia, and generally impaired higher cognitive functions (reasoning, calculating) (Helmstaedter 2007; Profitlich et al. 2008). Testing during NCSE indicates an inhibition of the affected hemisphere but also disinhibition or release of the nonaffected hemisphere has been described (Regard et al. 1985).

Behaviorally, the patients appear irritated and dysphoric. They may react in a defensive manner, but not with directed aggression. Impressive recovery to normal behavior can be observed in these patients when the status is successfully interrupted by injection of diazepam.

Conditions observed in temporal lobe epilepsy and circumscribed bilateral temporo-mesial dysfunction are transient amnestic attacks, which may be recurrent, and which may last from minutes up to an hour. Consciousness and purposeful behavior are preserved but the patients may be irritated about the experienced cognitive disturbance (Butler et al. 2007; Gallassi et al. 1986).

Table 10.4 Ictal symptoms in frontal nonconvulsive status epilepticus (N=6)

Performance	Impairment
Consciousness (impaired in 4 of 6)	• Partly reduced, great fluctuations • Never completely lost
Executive functions (impaired in 6 of 6)	• No self-initiated directed behaviors • Preserved responsiveness, but slowed, reflexive, and restricted to single modalities • Perseverative behaviors • Inadequate intrusive behaviors • Problems with concept formation & response inhibition • Very limited working memory
Higher order functions (impaired in 6 of 6)	• Apraxic signs in object use and imitation • Receptive/expressive dysphasia • Transcortical aphasia • Dyscalculia • Dyslexia • Agnosia • No global amnesia!
Emotion (changed in 4 of 6)	• Emotional instability (dysphoric, irritated, angry)

Main feature: "pathological inhibition" and "negative symptoms" rather than "excitatory" and "positive" symptomatology (frontal dysexecutive?).

Postictal behavior: temporal and frontal lobe epilepsy

After seizures, patients with FLE are usually quickly reoriented, because there often is no ictal loss of consciousness. In this regard they significantly differ from patients with TLE who need much longer time to become accessible.

Figure 10.5 shows the course of verbal memory and decision times in pre- and postictal memory testing after frontal lobe seizures as compared to left versus right temporal seizures and repeated testing in healthy controls. After lateralized temporal lobe seizures material-specific memory impairment can

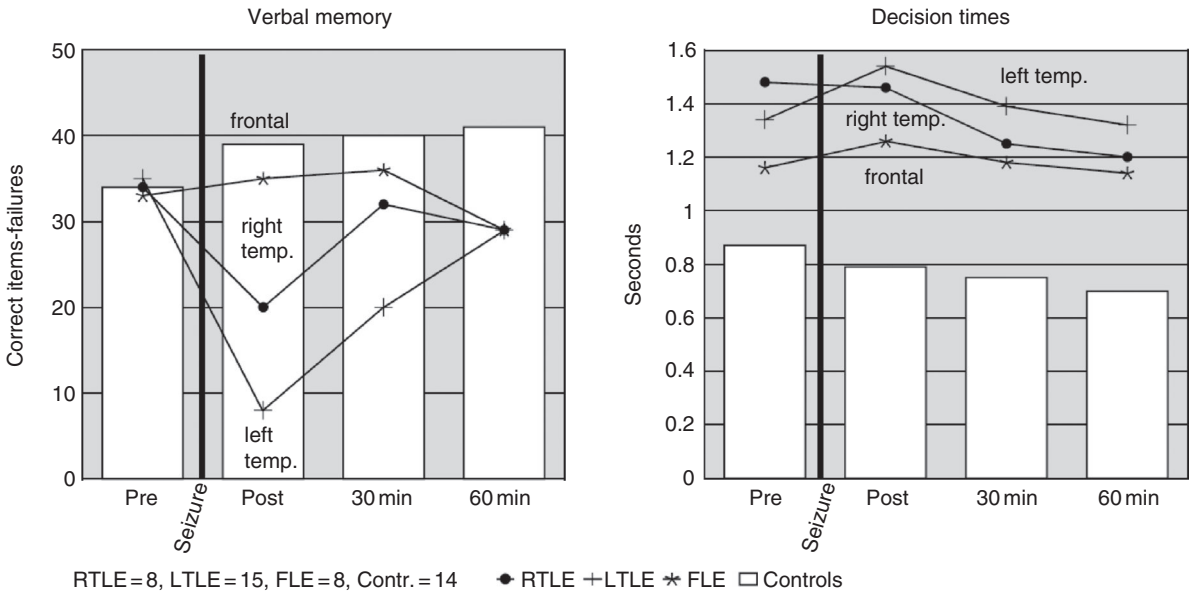

Figure 10.5. Verbal memory and decision times in pre- and postictal testing. The first postictal testing (post) was performed after complete reorientation.

be observed for at least 1 hour after complete reorientation. What is shown for left temporal patients concerning verbal memory in Figure 10.5 has its counterpart for right temporal patients with regard to figural memory. As for frontal lobe seizures it is remarkable that there is no postictal deterioration in memory nor a significant slowing down of the reaction times. However, when seizures originating from the frontal or temporal lobe secondarily generalize, the time needed for reorientation is comparably long. In case of frontal lobe seizures which generalize there is also evidence for lasting postictal memory impairment (Helmstaedter et al. 1994).

It can be concluded that frontal lobe seizures lead to a dysexecutive syndrome with mostly preserved awareness and consciousness, with only reflexive but no self-initiated behavior, and a seizure semiology, which is dominated by a state of hyperexcitation and disinhibition or hyperinhibition. This would confirm the impression from neuropsychological findings that the major problem in FLE is appropriate response selection/initiation and inhibition of behavior respectively. A further differentiation according to lesions or foci within particular sites of the frontal lobes can be suggested but has not yet been proven. For temporal lobe seizures it can be concluded that the major cognitive characteristics are amnesia, disorientation, and unconsciousness.

Interictal behavioral correlates of temporal and frontal lobe epilepsy

If we propose problems with behavior selection/initiation and inhibition as a functional complex which is mainly affected in FLE, the obvious question is whether or not this dysfunction has a correlate in interictal personality and behavior?

As indicated in the introduction section, the question of a personality change ("*Wesensänderung*") due to epilepsy affecting the temporal lobes is still under discussion. It can be very difficult to differentiate this from anxiety and depression, which are the most frequent psychiatric comorbidities in epilepsy, or from the so-called interictal dysphoric mood disorder, which in the tradition of Kraepelin has a characteristic intermittent and pleomorphic symptomatology (e.g. irritability, depressive moods and anxiety, headaches, insomnia, euphoric states) and which together with more positive behavioral features (quiet, modest, devoted, amicable, helpful, industrious, thrifty, honest, and deeply religious) ranges somewhere between clinically manifest depression and personality change (Blumer et al. 2004).

Using a variety of inventories (QOLIE-10, Daily Activity Scale BPSE, the Beck Depression Inventory [BDI], SAS anxiety scale, the NEO-FFI personality inventory) in 77 patients with TLE and 18 patients with FLE we were able to demonstrate poorer quality of life and mood, increased anxiety, less activities, and increased neuroticism (NEO-FFI) in TLE and increased activities and conscientiousness (NEO-FFI) in FLE. Within the QOL domains, more frequently reported impairment of mood, memory problems, and social limitations corresponded well to the features of TLE found with the other instruments in that study. The data thus mainly reflected what has been reported in the literature but at the same time we were disappointed with the results of personality assessment in epilepsy patients. The results demonstrated that psychiatric scales often show a "bottom" effect only detecting extreme patients, and that standard personality inventories developed from healthy subjects appear to miss the specific behavioral features which one experiences in the clinic with the epileptic (Krishnamoorthy 2006). In a subsequent analysis we used a structure equation analysis, but were not able to replicate the factor structure of the widely known NEO-FFI (Costa and McCrae 2000) in our patients. Whilst the German normalization study (N=2112) of the NEO-FFI confirmed the personality structure with five global dimensions (Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism) the Big Five model could not be replicated in 173 epilepsy patients. Only two factors, "Extraversion" and "Openness", out of five could be verified. Hence, our current position is that personality dimensions solely derived from behavioral variations in healthy subjects are not valid for patients with epilepsy. That the NEO-FFI misses specific behavioral features in epilepsy is also indicated by a recent study which demonstrated mildly elevated scores and no differences between patients with lateralized temporal or extratemporal lobe epilepsy (Locke et al. 2010). In the past there had been a tradition of using the Minnesota Multiphasic Personality Inventory (MMPI) in epilepsy patients (Rose et al. 1996), but during recent years this test mostly disappeared in epilepsy research or did at least not provide new insights into the behavioral features of localized epilepsies (Hessen et al. 2007; Locke et al. 2010). The same appears to be true for more specific measures in epilepsy like the Bear-Fedio Inventory (Bear and Fedio 1977; Devinsky and Najjar 1999) or Blumer's questionnaire on dysphoric mood (Blumer et al. 2004).

Presumably because no consistent picture regarding the epileptic personality emerges from the literature and also because of more practical considerations, research in recent years drew back to questions concerned with comorbid depression, anxiety, or nonspecific subjective quality of life issues (Cramer 2002; Kanner 2003).

Depression represents the most common psychiatric comorbidity in epilepsy. Its lifetime prevalence ranges between 40% and 63% which is apparently higher than in other chronic diseases like diabetes or asthma. Sex differences appear less pronounced than usual, and the suicide rate is significantly increased as compared to the general population. Depression and epilepsy appear closely linked to each other and they appear to share a common basis. This is indicated by an overlap of involved morphological structures, by the efficacy of the same pharmacological treatments, and by a close association in the genetically epilepsy-prone rat, which shows epilepsy and depression related behavior and which indicates innate serotonergic and noradrenergic deficiencies as common pathophysiological abnormalities (Jobe 2003). Epidemiological research recently proposed a bidirectional relationship between both diseases (Chapter 2: Hesdorffer et al. 2000; Hesdorffer et al. 2006).

In order to bridge the gap between clinical scales and personality inventories we constructed a new questionnaire in 1999. The "Fragebogen zur Persönlichkeit bei zerebralen Erkrankungen" (FPZ; English: Clinical Personality Scales, CPS (Helmstaedter et al. 2000)) is a self-rating questionnaire with 98 confrontative questions regarding frequencies of behavior occurrence in 14 clinically relevant domains. The inventory aims at identifying behavioral and personality disorders in nonpsychiatric patients with central nervous system (CNS) diseases and epilepsy in particular. Its construction followed four principles (Helmstaedter et al. 2000): (1) items were not taken from existing inventories but empirically collected on the basis of clinical experience with epilepsy patients and secondarily allocated to diagnostic categories; (2) frequencies of actual behaviors instead of feelings, opinions, or positions were requested; (3) questions were kept simple and paragraph headings explicitly name the topic of interest (i.e. anxiety, depression, obsession, addiction); and (4) in order to pick up behavioral features beyond normal personality structures, the factor structure of this test was derived from

a sample pooling epilepsy patients and healthy subjects. Accordingly the inventory assesses 14 first-order areas/factors: Mood, Emotional Lability, Aggression, Addiction, Anxiety, Obsession, Drive, Reward Learning, Self-Determination, Impulse Control, Novelty/Sensation Seeking, Vegetative Symptoms/Somatization, Interpersonal Communication, Perception/Reality Control; and four superordinate second-level areas/factors resembling the "Introversion-Extraversion" dimension and "Neuroticism" as they are found in almost all personality inventories plus "Organic Psycho-Syndrome" and "Addiction." The scales were normalized with the data from healthy subjects and reliable change indices (RCI) based on retest-reliabilities are available for repeated assessment.

The factor structure was confirmed by a validation study in 2006 (Glogau 2006) and again in a more recent validation study in 428 epilepsy patients (Hoppe et al. 2010). The latter sample serves as basis for this section. It consisted of 409 pharmacoresistant inpatients (52% male, age: 39 years $\pm$ 12, onset: 20 years $\pm$ 15, 11 $\pm$ 18 seizures/month) with lateralized TLE (N=151), mTLE (N=191), or FLE (N=67) (left: 57%, right: 43%). About one-quarter of the patients reported a psychiatric history, and 45% had $\leq$10 years of education. Most of the patients (93%) received the BDI in addition to the FPZ. Counting only scales with more than 20% impaired patients as compared to healthy controls, a broad range of impairment in the epileptic patients was indicated (Table 10.5). The BDI indicated depressed mood in 38% of the patients, and elevated scores (>11) were not more frequent in TLE as compared to FLE.

According to data from the FPZ, TLE patients display greater neuroticism and introversion, whereas FLE patients more frequently report problems in interpersonal communication, greater impulsivity, and novelty seeking, and they more often fulfill the criteria of an organic psycho-syndrome. Searching for clinical predictor variables via multiple backward regression (p to remove 0.1) a multi-facetted picture emerges (Table 10.6), indicating a psychiatric history (self/and relatives), low education, female sex, a left-sided epilepsy, mesial pathology, and a higher seizure frequency and antiepileptic drugs as predictor variables. It is important to note that despite high statistical significances the explanatory power in terms of explained variance was low, leaving between 70% and 90% of the variance to sources not covered by the independent variables.

Going into detail: "introversion" was associated with a mesial pathology, a greater number of drugs, and poorer cognition; "neuroticism" appeared connected to a psychiatric history, left lateralization of the epilepsy, and female gender; "organic psycho-syndrome" was associated with a psychiatric history, the number of AEDs, and seizure frequency. Within the subscales of "organic psycho-syndrome," seizure frequency exerted a strong influence on feedback dependent reward learning (learning from past positive or negative experiences). Apart from this, an effect of seizure frequency was observed only on anxiety.

Higher BDI depression scores were related to left lateralized epilepsy, to female sex, poorer education, and cognition (attention and verbal memory). Mesial pathology was not predictive in the regression model, but when analyzed separately from the other predictor variables patients with mesial pathology (BDI: 12 $\pm$ 9) showed higher depression scores than those without (BDI: 10 $\pm$ 8) (F=4.8, p=0.028).

When correlated to the FPZ scales, the BDI shows high correlations to the neuroticism (r=0.58) and organic psycho-syndrome scales (r=0.54), and minor correlations to introversion (r=0.27) or addiction (r=0.17) scales. Thus from a clinical point of view the BDI may be a good indicator for clinically relevant depression, but from a more behavioral point of view the BDI appears to pick up behaviors from different domains.

Since drug load, i.e. the number of AEDs, showed an influence on behavioral data, additionally the impact of the presence or absence of a certain drug alone or in polytherapy was evaluated in regard to the FPZ subscales and the BDI. The drug load showed a significant relation to the BDI, to the global scale "organic psycho-syndrome" of the FPZ, and to the FPZ subscales mood, communication problems, addiction, and eating problems. Further relations of interest were greater aggression, obsession, and drive in the presence of levetiracetam (LEV), and greater neuroticism, less self determination, novelty seeking, and sociability, and greater somatization in the presence of carbamazepine (CBZ), valproic acid (VPA), and clobazam (CLB). With lamotrigine (LTG) greater impulsivity and sensation seeking were reported, the presence of topiramate (TPM) was associated with less addiction, and pregabalin (PGB) with greater anxiety (F between 4.4 and 10.5 with p between 0.048 and 0.000).

Table 10.5 Scales with more than 20% impaired patients as compared to healthy controls

BDI	All patients (N=399)		TLE (N=335)	FLE (N=64)	Chi^2
	N (impaired)	% impaired (BDI >11)			
	150	38%	37%	39%	n.s.
FPZ	All patients (N=428)		TLE (N=361)	FLE (N=67)	
	N (impaired)	% impaired (>84% percentile)			
Neuroticism	73	20%	22%	12%	*
Obsession	110	26%			
Lack of reality control	97	24%			
Lack of drive	97	23%			
Emotional lability	96	23%			
Other determined	90	21%			
Introversion	158	40%	43%	32%	*
Self-determination	206	49%			
Sociability	151	35%			
Mood	133	31%			
Novelty seeking	74	19%	16%	31%	**
OPS	85	22%	21%	31%	*
Communication disorder	130	32%	29%	42%	**
Learning problems	109	26%			
Aggression	97	23%			
Impulsivity	92	22%	21%	31%	*
Insensitivity	84	20%			
Addiction	29	7%			
Pathological	106	24%			

BDI, Beck Depression Inventory; FPZ, Fragebogen zur Persönlichkeit bei zerebralen Erkrankungen; OPS, organic psycho-syndrome.
*$p<0.05$; **$p<0.01$.

Although this analysis was exploratory, the results nicely reflect the negatively stimulating effect of LEV, the positive stimulating effect of LTG, the anti-craving effect of TPM, and the use of PGB to treat anxiety. Furthermore they indicate that CBZ, VPA, and CLB are either preferred in emotionally unstable patients or that inversely such problems arise from these drugs. A causal relationship cannot be determined cross-sectionally, but the results suggest that monitoring drug treatment is important, not only in respect of counting seizures and controlling cognition but also by assessing behavioral changes in domains beyond anxiety and depression.

Summarizing, the major conclusion is that the findings confirm the impact of more static together with more dynamic disease related factors on behavior in epilepsy patients as could be proposed on the basis of the theoretical etiological model (see Table 10.1), and the ongoing controversy about an "epileptic personality" or paroxysmal mood disorder. The behavioral abnormalities are mild to moderate and, mainly because of the multifactorial etiology, prototypic localization related dysfunctional behaviors become evident only as a trend. The impact of AEDs on behavior apart from cognition deserves more consideration in the future.

Table 10.6

Impaired domain	Age	Sex F/M	Psych. history S/F	L-hand	Onset	Seiz. frequ.	Side R/L	Site	N.o. AED	Edu	Language attention memory	F
BDI		F	+/+				L			↓	↓	7.2***
FPZ												
Introversion			/+					AHS	↑	↓	↓	10.9***
Mood			+/					AHS	↑		↓	8.7***
Sociability										↓	↓	11.7**
Novelty	↓	F	+/+					FLE	↓	↑	↑	10.6***
Self-determined		F			↓			AHS	↑	↓	↓	11.8***
Neuroticism		F	+/+				L					11.7***
Lability		F	+/				L					10.2***
Anxiety		F	+/+			↑		AHS				9.6***
Somatization		F	+/				L		↑			9.0***
Vegetative	↑	F	+/	+	↑		L					4.0***
Obsession			+/+						↑			4.1**
Drive			+/+				L					7.2***
Determined									↑		↓	4.1**
OPS	↓		+/+			↑	L		↑	↓		9.4***
Insensitivity		M	+/+				L			↓	↓	11.3***
Aggression	↓		+/+				L					10.7***
Hypoactive	↑		+/				R				↓	5.5***
Impulsivity	↓	F	+/+						↑			6.4***
Learning		F	+/+			↑						44.0***
Communi-cation			+/	+			L		↑	↓		8.0***
Reality control			+/						↑			9.3***
Addiction			+/+				L		↑			5.6***
legal	↓	M	+/		↑		L		↑	↓	↓	3.9**
pathological			+/			↑			↑	↓		7.2***
cultural			+/		↓							6.9**
eating	↓		+/+						↑			6.1***

BDI – Beck Depression Inventory; FPZ – Fragebogen zur Persönlichkeit bei zerebralen Erkrankungen; OPS – organic psycho-syndrome; N. – number; Edu – education; AHS – Ammons horn-sclerosis; FLE – frontal lobe epilepsy.
Backward multiple regression analysis [p to enter = 0.1].
Independent variables: sex, age, handedness, psychiatric history (self/family), age at epilepsy onset, FLE, MTLE with AHS, MTLE with amygdala pathology, side, seizure frequency (CPS + GTCS (Generalized tonic-clonic seizures)), number of AED, education, IQ, verbal/figural memory, language, attention.
**p<0.01; ***p<0.001.

Academic achievement and employment in frontal lobe epilepsy

Patients with frontal lesions may show unimpaired cognitive functions in a very structured test setting, but nevertheless fail on every day demands in their school life and career because of behavioral problems, unsteadiness, difficulties in concentration, increased susceptibility to interference, and problems with timing and planning. Subjective data may not detect such behavioral problems because patients with frontal lobe lesions have been reported to underestimate their impairments. With school achievement and employment, however, we have indirect markers, which may allow us to infer how far patients are adapted to every day life. Different from our findings in previous studies with a smaller number of patients, larger groups of patients with TLE and FLE do not show different levels of education (in both groups 46% vs. 45% with less than 10 years of education). The job situation is also comparable in both groups (rate of employment: 76% TLE vs. 79% FLE).

Trait or state

The previous paragraphs have shown that patients with frontal and temporal lobe epilepsy have behavioral disorders, which in part appear specific for the affected brain regions and which appear mild in expression as compared to those reported in the lesional literature. In addition an influence of subject variables plus static and dynamic disease-related factors on behavior is indicated, which leaves us with the question of how consistent the behaviors in focal epilepsies are over time?

In epilepsy patients the impact of epilepsy and seizures on behavior can be well estimated when comparing patients who, after surgery, still have seizures or became completely seizure free. In 2002 we presented behavioral data from operated and non-operated patients with temporomesial (N=57) or frontal lobe epilepsy (N=30), who participated in a long-term follow-up study (mean follow-up interval: 56 months; range 2–10 years) (Helmstaedter et al., 2002). Seizure outcome was the only predictor variable for BDI scores and quality of life (German modified QOLIE-10) at the time of the long-term follow-up. Only 14% of the seizure-free patients in contrast to 51% of those who still had seizures showed evidence for depressed mood (cut-off score of 11 points), and 45% of the seizure-free patients reported good quality of life as compared to only 11% of those with continuing seizures. It should be noted that 14% is much less than the normally reported ~40–60% depressed patients with focal epilepsy, whereas the 51% is absolutely within this range. These data show quite impressively what a difference the presence or absence of seizures can make. The finding parallels recent findings in children who after successful epilepsy surgery show marked improvement in behavior disorders (Lendt et al. 2000).

Evaluating preoperative to 1-year postoperative data on personality (FPZ) in patients with temporal (N=125) or extratemporal (N=26) lobe epilepsy, the pre- to postoperative changes indicated both dynamic and static aspects of personality and mood (Witt et al. 2008): *Introversion*, which was the only deviant domain before surgery, did not show a postoperative change supporting trait dependency rather than state dependency of this behavioral feature of TLE. Retrospectively this fits to the above reported finding from regression analysis, that *introversion* in particular was related to mesial pathology and less to the more dynamic factors. Although the mean group data did not indicate increased neuroticism or features of an organic psycho-syndrome, significant seizure outcome-related improvements in these domains indicated dynamic state dependency of these features. Differential improvements in seizure-free left temporal resetted patients (enhanced emotional stabilization) versus right temporal resected patients (decreased anxiety and impulsivity, less vegetative symptoms) indicated lateralization-related behaviors in TLE. Since the extratemporal group in this study was very inhomogeneous in respect to the site of the epileptogenic lesion, we examined an additional 33 FLE patients for the purpose of this chapter. These patients underwent epilepsy surgery, and as seen in TLE patients, postoperative seizure freedom was accompanied by improvements in regard to behavior concerned with an organic psycho-syndrome. Improvements were particularly seen after successful right frontal lobe surgery. Different from TLE patients, there was no postoperative change in neuroticism. Again the postoperative changes in TLE and FLE fit to the results obtained by regression analysis which indicated an influence of the more dynamic factors on neuroticism and organic psycho-syndrome.

Conclusion

We can conclude that in temporal and frontal lobe epilepsy dysfunctional behaviors can be discerned which characteristically correspond to the affected brain regions (side and site). Behaviors in the context of seizures (pre-, peri-, postictal) and neuropsychological performance patterns more distinctively reflect the affected functional networks than those behavioral features which one would attribute to personality. "Personality" normally refers to situation independent traits, but the data make clear that in epilepsy morphological and more static as well as dynamic disease and treatment-related factors determine the patients' behavior. Accordingly specificity of behavioral dysfunctions in FLE and TLE is lost on a superordinate level where all these factors converge. There is evidence that active epilepsy (seizures) and antiepileptic treatment (drug load as well as individual agents) not only affect cognition but also the patients' behavior. This calls for an increased attention to these matters in the future.

Independent of the type of epilepsy, the multivariate regression models indicate an increased vulnerability in regard to behavioral problems in patients with left lateralized epilepsies. Additionally a history of psychiatric problems in patients and also in relatives appears to be an excellent predictor for actual behavioral problems. Hyperactivity, impulsivity, conscientiousness, obsession, and behaviors which one could traditionally term as organic psycho-syndrome can be seen as reflecting frontal lobe dysfunction in FLE and taken together with neuropsychological impairments in FLE (attention; motor, executive functions), these behaviors indicate dysfunctional response-selection, -monitoring, and -inhibition as well as impaired learning from feedback (reward) across various behavioral domains.

Introversion, neuroticism, cognitive (memory) impairment and social limitations in contrast seem more a feature of temporal lobe epilepsy. Depression is frequent in TLE but also in FLE. From the presented data it appears that "depression" at least as assessed by the BDI may be adequate to indicate clinically relevant depression but is obviously not suited to pick up the specific behavioral problems in TLE and FLE. However, with TLE it is important to note that the behavioral features in this group become specific mainly because of the patients with mesial pathology. The differentiation between TLE with and without mesial involvement is often neglected but appears very important since TLE patients with neocortical temporal lobe lesions take a position somewhere between mTLE and FLE.

This chapter also reveals the methodological difficulties regarding the adequacy of common clinical measures and the difficulties in disentangling the disease-immanent confounding effects of lesions, epileptic dysfunction, AED, and psychosocial status, which often do not yet allow further distinctions as they are made for example in neurobiological models about the frontal lobes and behavior. Full-blown personality disorders are rare in TLE and FLE and symptoms generally appear rather mild as compared to patients with mass lesions. As regards the state/trait discussion in epilepsy, the consistent seizure control and careful selection of antiepileptic treatment may have beneficial effects for the patients coping with everyday life.

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Chapter 11

Emotional agnosis and theory of mind

Sarah Broicher and Hennric Jokeit

Introduction

Social neuroscience is an emerging interdisciplinary field aimed at investigating the fundamentals of human social and emotional behavior, the quintessence of which is the relationship between the brain and social interaction. Studies on the impact of neurological, psychiatric, and psychological conditions on human social behavior contribute to our understanding of the complexity of social interactions and highlight important social and affective symptoms in brain disorders such as epilepsies which continue to be overlooked in clinical practice.

In patients with epilepsy non-social cognitive functions including memory, language, and executive functions have been studied for many years, whereas social cognitive abilities have received little attention (Kirsch 2006). This is quite astonishing in light of what we know about the remarkable overlap between structures associated with social cognition and anterior brain structures which are frequently affected in patients with epilepsy. The paucity of research becomes more understandable when one considers the lack of readily apparent social deficits in the majority of patients with epilepsies (Phelps and LeDoux 2005).

Nevertheless, comprehensive clinical studies have revealed that psychosocial maladjustment is a serious problem in many patients with chronic epilepsies (Hermann et al. 2000). To what extent these maladjustments are caused by social burdens, stigma, and risk factors of active epilepsy, and to what extent they are due to dysfunctional social cognition, remains an open question (Devinsky and Najjar 1999; Shackleton et al. 2003). However, the fact that psychosocial maladjustment and psychiatric comorbidity are more frequent in certain focal epilepsies compared with other epilepsy syndromes may reflect a specific pathological association (Perini et al. 1996).

In the past, psychiatry and neurology have used different terms and concepts and differed in their diagnostic approaches, research, and treatment methods. Their focus converges to some degree within the framework of the modern neurosciences. As such, social and affective neuroscience provides insight into behavioral disorders in patients with epilepsy via new unifying concepts that can be investigated by means of behavioral tests and structural and functional imaging as well as by neuropsychopharmacological interventions. These opportunities allow us to advance our understanding of brain diseases and how they affect behavior, and raise the hope of new and more efficient therapeutic interventions.

Social cognition

Many patients with epilepsy suffer from communication problems and interpersonal difficulties that have a significant bearing on their quality of life. Imaging and lesion studies have identified cerebral networks associated with social cognitive functions which are frequently affected in patients with temporal or frontal lobe epilepsies. Accordingly, recent studies have demonstrated impairments in social cognition in these patient groups using specific tasks involving emotional recognition and theory of mind (Benuzzi et al. 2004; Fowler et al. 2006; Meletti et al. 2003; Schacher et al. 2006b; Walpole et al. 2008).

Social cognition is a complex and extensive concept that comprises a wide spectrum of sub-processes at different levels of brain functioning (Adolphs 2006). It includes the perception, encoding, organizing, and accessing of a variety of relevant social information.

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

Social cognition is based upon the exchange of signals, whereby the processing of these signals can take place at the automatic and controlled level and is influenced by motivational aspects (Beer and Ochsner 2006). It is noteworthy that these processes rapidly act in different modalities in parallel and draw on implicit as well as explicit memories. Therefore, it is reasonable to assume that lesions in one or more widely distributed independent components may lead to greater or less severe impairments in social cognition.

Adequate social interactions are a prerequisite for normal human development from an anthropogenetical as well as ontogenetical point of view. Social cognition encompasses any cognitive process that involves conspecifics, either as a group or an individual. It encompasses the ability to build representations about others, oneself, and the relationships between oneself and others, and to apply them flexibly to execute social behavior (Beer and Ochsner 2006). Therefore, the success of social interactions depends upon the ability to understand the cognitive and emotional processes of others (Völlm et al. 2006).

Basal social cognitive processes

Within social cognition one can differentiate between more advanced social cognitive abilities, which require the understanding of complex mental conditions, and more basal processes such as the perception and expression of emotional information.

Processing of emotional information plays an important role in many aspects of cognition (Cacioppo and Gardner 1999), including decision-making (Damasio et al. 1994), memory, and attention (Christianson 1992). Furthermore, understanding other people requires relevant information from different modalities which may provide social information about others including speech, facial expression, prosody, lexical information, gaze direction, gestures, and posture. Besides the predominant meaning gleaned from visual information, olfactory, auditory, and tactile sensations can also influence processing of social signals (Adolphs 2006). However, the majority of studies have explored the processing of facial expressions because of longstanding research traditions and well established test materials (Ekman and Friesen 1976).

Brain-damaged patients who exhibit impaired emotional processing, but who are otherwise neuropsychologically intact, show marked deficits in social behavior and in their interpersonal relationships (Damasio et al. 1994). Emotional agnosia, also called expressive or social emotional agnosia, can be seen as an emotion perception deficit and refers to a form of agnosia in which individuals are unable to perceive facial expressions, body language, and intonation, thus making it impossible for them nonverbally to recognize people's emotions and limiting their social interactions. Social emotional agnosias are commonly observed following amygdala and right cerebral lesions, particularly those involving the temporal lobe (Joseph 1988).

Although not a form of agnosia in the narrow sense of the word, alexithymia may be difficult to distinguish from, or even co-occur with, emotional agnosia. Whereas emotional agnosia refers to the inability to recognize affect in others (oriented towards others), alexithymia refers to the inability to recognize affect in oneself (oriented towards oneself). Peter Sifneos introduced the term to describe people who appeared to have impairments in understanding, processing, or describing their own emotions (Taylor 2000).

Despite the importance of emotional expression and processing of emotional information, there are only a few measures available to assess these functions, most of which are not standardized (Borod 2000) or cross-culturally validated.

More detailed information about measures of basal social cognitive functions is provided in the following sections covering methodological issues and imaging.

Theory of mind (ToM)

Humans are by far the most talented species in reading the minds of others. This implies that we constantly make assumptions about the intentions and beliefs of others which form the framework of our complex interpretations of human behavior in daily life. These mentalistic interpretations often seem trivial to us to the point that we fail to perceive them as meaningful, not to mention consider them part of an intuitive psychological theory. Nevertheless they represent a fundamental aspect of social cognition which has been coined theory of mind (ToM) (Premack and Woodruff 1978). ToM is thought to be the proximate mechanism enabling humans to find their way in complex, collaborative social networks.

The terms empathy, social intelligence, and perspective taking are, along with ToM, related abilities and concepts and were often used as equivalents in

the literature as well as in everyday speech. Therefore, social cognition is not equivalent to ToM since there are a number of cognitive abilities which fall within the realm of social cognition which do not involve ToM operations in the narrow sense of the word, e.g. social reasoning and decision-making, the recall of knowledge regarding social schemata, and moral judgment (Greene and Haidt 2002).

According to numerous findings, ToM is considered a specific cognitive domain that needs to be delineated from general intelligence and from executive functions. There are many studies in which social cognition has been shown to be dissociable from general intelligence. For example, Baron-Cohen et al. (1997) showed that very high-functioning adults (HFA) with autism or Asperger's syndrome (AS), despite being of normal or above average IQ, were nevertheless impaired on a subtle theory of mind test. A further example of this dissociation is seen in Down's syndrome where intellectual function is impaired, but individuals perform well on theory of mind tasks (Karmiloff-Smith et al. 1995).

In another study, Baron-Cohen et al. (2001) used a revised version of the "Reading the Mind in the Eyes Test" (Eyes Test) and administered this test to a group of adults with AS or HFA. Again, there was no significant correlation between IQ and the performance in the Eyes Test, confirming that this is independent of general (non-social) intelligence. Using the "Mind in the Voice" Task, which extends the aforementioned test into the auditory domain, Rutherford et al. (2002) found that individuals with AS/HFA have difficulty extracting mental state information from vocalizations. Here, too, no significant correlation was found between verbal IQ and performance on the voice task for either the AS/HFA group or the noncollege control group.

Apart from theory of mind, memory, attention, executive functions (including planning of action), motivation, and decision-making equally contribute to the cognitive and behavioral outputs in social interactions. ToM should be considered a complex neuropsychological function that can be selectively disturbed, but which is correlated with distinct cognitive abilities, in particular executive functions (Rowe et al. 2001).

The first precursors of ToM, including the imitation of intended actions (Meltzoff and Decety 2003) and the distinction between one's own and others' desires and their relation to emotions (Repacholi and Gopnik 1997), can be observed already at the age of 18 months. Also, the beginning of pretend play (Leslie 1987), joint attention skills, and the development of the ability to attribute wishes and emotions to others (Flavell et al. 1999) can be considered as an important milestone in the development of a ToM.

By the age of about 3–4 years children gain the cognitive prerequisite for the comprehension of another person's belief (e.g. that he or she has a false assumption about a certain fact) and thereby the ability to represent mental conditions independent of reality and to derive action predictions from attributions of mental states. This ability requires a conceptual understanding of the mental conditions of another human being (Schult and Wellman 1997).

The comprehension of false beliefs in children can be investigated with the help of so-called "first-order false belief tests," the most prominent of which include the "Sally-Anne-Task" (Baron-Cohen et al. 1985), the "Maxi-Task" (Wimmer and Perner 1983), and the "Smarties-Task" (Gopnik and Astington 1988). The development of an understanding that someone can have a false belief about a false belief begins a bit later towards the age of 6 years (Wimmer and Perner 1985), while the understanding of different perspectives appears between the ages of 12 and 17 (Sodian et al. 1999).

The ability to attribute second-order or embedded mental states (e.g. he thinks that she thinks) is a very socially relevant achievement in the development of a theory of mind. Being able to represent what one person thinks about what a second person thinks allows us to understand not only another's belief about the world (a first-order belief) but also to understand that person's concern about yet another person's belief about the world (a second-order belief). This sort of reasoning is necessary for any sophisticated understanding of the subtleties inherent in social interactions. Perner (Perner and Wimmer 1988) argued that it is at the level of second-order reasoning that social interaction can be understood as an interaction of minds where people are concerned about each other's mental states. Typical second-order false belief tasks are the Ice-Cream Van Task (Wimmer and Perner 1985) or the second-order Sally-Anne-Task (Baron-Cohen et al. 1985).

Tests which go above and beyond simple attribution performances are also called "higher-order" or "advanced" ToM tests and require the understanding of complex mental states (what does x think or

feel?) or also the comprehension of mental states in role-taking activities (e.g. does X also really mean what X says? Why does X behave thus?). The inferences one makes regarding others' mental states include knowledge regarding their thoughts and beliefs ("cognitive ToM component") as well as knowledge and empathic understanding of their emotional states and feelings ("affective ToM component").

Methodological issues

Testing social cognition

The perception and expression of emotional information and ToM abilities have been investigated in numerous studies in a variety of patient groups and healthy persons using a number of experimental paradigms and tests. The following list of selected tests is not intended to be exhaustive, but broadly to cover the most commonly used or representative tests. Short descriptions and behavioral data from a variety of tests are presented below in order to reveal their differences and to highlight recent developments and research perspectives.

Selected tests of basal processes of social cognition

Ekman faces

Test description. Influenced by the work of the psychologist Sullivan Tompkins, Ekman was the first to apply quantitative methods in an effort to clarify the question of the biological basis of emotional facial expression. He showed that facial expressions of emotions are not culturally determined, but universal across human cultures and, thus, biological in origin. Expressions he found to be universal included anger, disgust, fear, joy, sadness, and surprise. Ekman and Friesen (1976) developed the Facial Action Coding System (FACS) to taxonomize every conceivable human facial expression. The FACS has since become the most widely used and validated series of photographs in facial expression research. These photographic representations have been applied in a variety of tests requiring identification, matching, sorting, or rating of facial expression of emotions.

Behavioral data. While initially the question of lateralization of emotional facial expression perception was pursued (Etcoff 1984), the amygdala has increasingly attracted attention with advances in imaging technology. Primarily it was assumed that the perception of fearful expressions depended on the structural and functional integrity of both amygdala (Adolphs et al. 1994). However, subsequent studies have shown that not only facial expressions of fear, but also the perception of other emotions, are affected after bilateral amygdalar lesions (Young et al. 1996; Siebert et al. 2003) and that unilateral lesions can also result in deficits (Adolphs et al. 2002a; McClelland et al. 2006). Disturbances in the perception of emotions from facial expressions have also been reported in patients with traumatic brain injury (TBI) (Milders et al. 2008), in frontotemporal dementia (Diehl-Schmid et al. 2007) as well as in patients with frontal and temporal lobe epilepsy (Meletti et al. 2003; Benuzzi et al. 2004; Farrant et al. 2005; Shaw et al. 2007).

Comprehensive Affect Testing System (CATS)

Test description. Most studies on social cognition have used visual stimuli, but it is clear that real-life social interactions necessarily draw on additional modalities. Audition provides important social signals in addition to language. Accordingly, the intonation of speech – prosody – can signal various emotions, and is recognized using some of the same structures that we use for recognizing facial expressions (Adolphs et al. 2002b). Froming et al. (Froming et al. 2000–2006) took this issue into account and developed a computerized measurement of visual and auditory emotional processing of the six basic emotions – the Comprehensive Affect Testing System (CATS). The CATS consists of thirteen subtests assessing facial identification, emotion matching with and without verbal denotation, emotional tone or prosodic processing with and without verbal denotation, and with conflicting or congruent semantic content.

Behavioral data. The CATS has been administered to patients with AS and comparisons between these patients and healthy controls on CATS subtest results revealed general impairments in the comprehension of facial and prosodic information in the AS group (Froming et al. 2000–2006). Recently, Rocca et al. (2009) applied the CATS to a group of patients with schizophrenia and healthy controls and found that controls performed better on all subtests, the only exception being an affect discrimination task. Data collection is in progress with different groups of patients with brain damage.

Selected tests of theory of mind

Various experimental paradigms exist for evaluating ToM skills. However, a truly theoretically based differentiation of relevant aspects and dimensions of the ToM construct and its test psychological considerations remain absent.

According to the conceptual classification of a "cognitive" and an "affective" ToM component (with overlaps with empathy), some tests require the attribution of epistemic mental conditions such as knowledge, attention or beliefs while other tests investigate the attribution of affective mental conditions, e.g. "feel happy" or "want something" (Stone et al. 2003). According to Shamhay-Tsoory and Aharon-Peretz (2007), performance on second-order false belief tasks requires cognitive components of ToM while "higher-order" or "advanced ToM tests" such as the faux pas test (Stone et al. 1998) require both components. The attribution of intention assumes the recognition of whether an action was executed intentionally or accidentally and can be considered as a further type of attribution, although its inclusion under the attribution of epistemic mental conditions seems to be reasonable as well.

Apart from the classification of ToM tests according to their type of attribution, they also differ with regard to the stimulus modality they employ. While some contain verbal material such as stories and subsequently demand adequate language comprehension, complex visual stimuli are applied in other tests (dynamic and nondynamic); rarely have verbal and visual material been combined.

Moving triangles

Test description. Heider and Simmel (1944) conducted an experimental study over 65 years ago that can be seen as the starting point of attribution theory research. In their experiment healthy subjects were asked to interpret a short film sequence (2.5 min) in which three geometric shapes (a big and a small triangle and a circle) move around at different speeds. Another shape in the field is a rectangle which also acts as a door that can be opened and closed. All in all, Heider and Simmel's (1944) study contained three experiments. In the first experiment subjects freely described what they saw after watching film sequences twice. In a second experiment, subjects were asked to interpret the movements of the figures as human actions and to answer structured interview questions after presentation of the film. In the third experiment the video was shown in reverse and subjects took part in a short, structured interview. The authors observed that people attributed intentions and desires to moving geometric shapes if these actions are of adequate complexity.

Behavioral data. Klin (2000) developed the Social Attribution Task (SAT), a new cognitive procedure based on Heider and Simmel's cartoon animation, and applied it to a group of individuals with autism, a group with AS, and normally developing adolescents and adults. The SAT is adapted for presentation to developmentally disabled individuals by minimizing factors thought to promote ToM task performance but that are absent in real-life social situations. Furthermore, it includes a coding system to examine and quantify different aspects of the subject's social cognitive responses. Both clinical groups showed significant deficits in making social attributions.

Based on the classic Heider and Simmel (1944) paradigm, Abell et al. (2000) aimed to design novel stimuli whose properties of motion would evoke mental state attributions. Protagonists of the new test were two shapes (a big red and a small blue triangle) moving around the screen, which on most trials contained an enclosure. Mental state attributions were restricted to pure movement and interaction in the absence of vocal or facial expression. In their study they presented three different types of animation sequences: random movement in which no interaction occurs (e.g. bouncing), goal-directed (G-D) interactions that elicit attributions of simple actions (e.g. fighting), and ToM interactions that elicit attributions of mental states to the agents (e.g. tricking). The G-D and ToM condition consisted of four animations each, while the random condition had two animations. The computerized animations were presented to high-functioning children with autism, children with general intellectual impairment, normally developing 8-year-olds, and adults. The authors found that high-functioning children with autism frequently used inappropriate descriptions when characterizing the ToM animations. Castelli et al. (2002) used 12 silent animations, four of each of the three types of animations, and here as well the autism group gave fewer and less accurate descriptions of the ToM animations.

Finally, Heberlein and Adolphs (2004) used a video of the original Heider and Simmel (1944) film

in a single case study and found that a patient who acquired bilateral focal amygdala damage during childhood failed to attribute social intent to the moving geometrical objects in the normative manner.

Cartoon task

Test description. Recent research in social cognitive neuroscience has begun to define subcomponents of ToM. One important differentiation is that of "affective" versus "cognitive" ToM, although different terms have been used to describe these and related concepts (Kalbe et al. 2007). This differentiation was taken into account in the "Yoni" paradigm, which was introduced by Shamay-Tsoory et al. (2007a) and is based on a task previously described by Baron-Cohen and Goodhart (1994). It is a computer-controlled test for the assessment of cognitive and affective ToM-performances. In this test the mental state of the main character has to be inferred from the situational context on the basis of verbal cues, eye gaze, and facial expression. There are three main conditions: cognitive, affective, and physical, each requiring either a 1st or 2nd order inference. The cognitive and affective conditions require mental inferences, while the physical condition serves as a control condition and requires a choice based on the physical attributes of the character. In each of the 64 trials a face named Yoni is shown in the middle of a computer screen with four coloured pictures in each corner that either belong to a semantic category (e.g. animals, fruits) or show faces. In the upper range of the screen an incomplete sentence about what Yoni is referring to is presented and subjects are required to decide as quickly as possible which of the four stimuli in the corners best completes the sentence.

Behavioral data. Using the Yoni-paradigm Shamay-Tsoory and colleagues (2007a) were recently able to demonstrate selective deficits in affective as opposed to cognitive ToM in various patient groups. In Shamay-Tsoory et al.'s (2007b) study the performance of patients with schizophrenia was compared to that of patients with localized lesions in the ventromedial (VM) or dorsolateral prefrontal cortex (PFC), patients with non-frontal lesions, and healthy controls. The authors found that patients with schizophrenia and those with VM lesions were impaired on affective ToM tasks, but showed no difficulties in the cognitive ToM conditions. Support for a selective impairment in schizophrenia for the ability to attribute affective mental states comes from another study in which patients with schizophrenia made significantly more errors in the affective conditions as compared to healthy controls (Shamay-Tsoory et al. 2007a). A modified version of the Yoni-paradigm which included additions to the ToM task of gloating, envy, and identification trials ("fortune of others" emotion task) was used with patients with AS and HFA (Shamay-Tsoory 2008) as well as in patients with localized, well-defined brain lesions of various etiologies (Shamay-Tsoory et al. 2007c). The authors showed that, whereas individuals with AS and HFA had no difficulties with first- and second-order ToM tasks, they were impaired in their ability to identify envy and gloating.

In a study with patients with different localized lesions, Shamay-Tsoory and Aharon-Peretz (2007) were able to demonstrate that affective and cognitive ToM processing depends in part on distinct anatomical substrates. While the ventromedial prefrontal cortex (VMPFC) seems to have a special role in processing affective ToM, cognitive ToM may involve both the VMPFC and dorsal parts of the prefrontal cortex. Furthermore, recognition of envy and gloating is impaired in patients with ventromedial prefrontal damage (Shamay-Tsoory et al. 2007c).

Reading the Mind in the Eyes Test

Test description. There are only a few tests which examine ToM skills in adults. So-called "higher-order" or "advanced ToM tests" go far beyond simple attributions and can only be used to study adolescents and adults of normal intelligence, e.g. "Reading the Mind in the Eyes Test" ("Eyes Test") (Baron-Cohen et al. 1997; 2001). The subject's task is to choose which of four words best describes what the person in the picture, that shows only a pair of eyes, is thinking or feeling (e.g. terrified, upset, arrogant, annoyed) (Baron-Cohen et al. 2001).

Behavioral data. The Eyes Test has enjoyed wide use and has demonstrated reduced test performance in patients with psychiatric diagnoses including autism and AS and in patients with schizophrenia.

Further, patients with unilateral or bilateral amygdala lesions (Adolphs et al. 2002a; Stone et al. 2003), with frontotemporal dementia (Gregory et al. 2002) as well as with frontal lobe epilepsy (Farrant et al. 2005) have been found to have impaired performance in the Eyes Test. Farrant et al. (2005), however, presumed that the discovered deficits in the frontotemporal dementia and frontal lobe

epilepsy group are in fact caused by the emotional component rather than ToM itself.

All in all, findings from this widely used test show it to be sensitive for detecting specific ToM impairments in populations that have been found to have deficits in other ToM tests.

Faux Pas Test

Test description. The Recognition of Faux Pas Test (Stone et al. 1998; Baron-Cohen et al. 1999) is another ToM test for adults and estimates the ability to recognize and understand a social faux pas. It was designed to evaluate mentalizing abilities in individuals with high-functioning autism who are able to pass second-order false belief tests. A faux pas is understood as a statement in which the speaker accidentally offends or insults another person. For example, person "A" complains to person "B" about a wedding present without realizing that he is talking to the person from whom he received it. The faux pas test measures several ToM components by including deductions concerning epistemic mental conditions as well as affective mental conditions (Stone et al. 2003; Stone et al. 1998). As verbal materials, in the form of rather complex stories, are used in this task, it makes fairly high verbal demands of the individual.

Behavioral data. Baron-Cohen et al. (1999) administered an age-adapted version of the faux pas test to a group of younger subjects (mean age = 12 years old) with HFA/AS and found that they had difficulties using mental state knowledge and had difficulties in detecting the faux pas. Unlike the children with HFA/AS in the Baron-Cohen et al. study (Baron-Cohen et al. 1999), adults with AS in Zalla et al.'s study (Zalla et al. 2009) and the two adolescents with AS in Shamay-Tsoory et al.'s case-study (2002) reported that something awkward or wrong was perpetrated in the faux pas stories; they were generally unable to provide correct justifications in terms of reasons and intentions and failed to attribute emotions to others.

The adult version of this test has also been applied to patients with orbitofrontal and amygdalar lesions (Stone et al. 1998; 2003), patients with TBI (Milders et al. 2003), patients with mesial temporal lobe epilepsy (Schacher et al. 2006b), patients with Parkinson's disease (Peron et al. 2009), patients with frontotemporal dementia, and patients with Alzheimer's disease (Gregory et al. 2002), all of whom had difficulties recognizing that a faux pas had been committed.

Strange Stories Test

Test description. The Strange Stories Test is concerned with the comprehension of nonliteral statements in hedged expressions, metaphors, irony, sarcasm, and bluff (Happé 1994). In this test subjects are confronted with a set of stories requiring the attribution of complex mental states. There are two conditions in this test consisting of two sorts of materials: social stories, which have to do with mental states, and physical stories, which have to do with physical behavior. There are eight examples of each of these two sorts. Subjects were asked to read these stories and answer a question after each passage.

Behavioral data. Happé (1994) used such a set of stories to test able autistic, mentally handicapped, and normal children and adults in their understanding of story characters' thoughts and feelings. Subjects with autism had difficulties understanding the protagonists' intentions and made context-inappropriate mental state attributions. By contrast, they had no difficulty understanding the physical events in the stories or understanding stories not involving mental states. These results were replicated in other studies of patients with HFA and AS (Baron-Cohen et al. 1997; Jolliffe and Baron-Cohen 1999; Kaland et al. 2005).

Shaw et al. (2004) reported deficits in a number of advanced ToM tests, including Happé's strange stories, in a group of subjects with early damage to the amygdala. These patients made significantly fewer fully accurate mental state attributions compared to a group of patients with late damage to the amygdala and healthy comparison groups.

Imaging of social cognition

Tasks which demand social cognitive abilities appear to activate a consistent set of brain regions. Experiments using imaging techniques have found underlying neural processes in different frontal and temporal localized brain regions (Stone et al. 1998; Amodio and Frith 2006) including particularly the medial frontal cortex (MFC), the anterior cingulate cortex (ACC), the superior temporal sulcus (STS) at the temporal parietal junction (TPJ), the temporal poles (TP), and the amygdala.

Medial frontal cortex and anterior cingulate cortex. For a better understanding of its role in social cognition, one can functionally divide the MFC into a posterior rostral region (prMFC, associated with cognitive processes) and an anterior rostral region (arMFC,

associated with emotional processes), as well as into an orbital region (oMFC, associated with the monitoring of task outcomes). While the prMFC is thought to be engaged in monitoring the value of possible future actions, the oMFC guides behavior regarding the evaluation of possible consequences. The arMFC appears to be activated by a wide range of social cognition tasks that involve thinking about the psychological attributes of people regardless of whether the person was the self, another person, or whether judgments pertained to dispositions or mental states (Amodio and Frith 2006). Thus, activations of the arMFC and ACC were found for the perception of oneself as well as one's own mental conditions (Lane et al. 1997; Vogeley et al. 2001) and for thinking about the mental states of others (Rilling et al. 2004). Based on this knowledge and results which have revealed involvement of the ACC in the control of the attention (Bush et al. 2000), Gallagher and Frith (2003) proposed that the activated parts of the ACC could govern the attention allocated to mental conditions. Thus, the ACC could correspond to the "decoupling" mechanism which was suggested by Leslie (1994) and which differentiates hypothetical conditions from reality (Frith and Frith 2003).

Superior temporal sulcus (STS). Activation in the area of the STS has consistently and robustly been reported in many studies. It is assumed that the STS represents rather elementary processes involved in a variety of ToM tasks and that the posterior STS is particularly sensitive to biological motion (Allison et al. 2000). Overall, the results point to the participation of the STS in the perception of purposeful actions and their attribution as self-caused or other-caused (Brunet et al. 2000; Castelli et al. 2000).

Temporal parietal junction (TPJ). The TPJ appears to be involved in reasoning about the contents of another person's mind (Saxe and Kanwisher 2003). In particular, it has been proposed that the right TPJ is selectively involved in representing the beliefs of others (Saxe et al. 2006). However, this remains a controversial issue as this region has also consistently been activated during spatial reorienting of visual attention (Mitchell 2008).

Temporal pole (TP). The TP may be involved with the retrieval of memory contents, especially autobiographical memories and memories for faces (Gallagher and Frith 2003). Accordingly, the studies which presumably made only negligible demands on the memory or imagination of the test participant were unable to find any activation in the temporal pole (Rilling et al. 2004; Gallagher et al. 2002). Olson et al. (2007) reviewed the literature in both nonhuman primates and humans and their findings indicated that the TP has some role in both social and emotional processes including face recognition and ToM.

Amygdala. The amygdala complex is considered to have a central role in the perception and processing of socially relevant information (Adolphs 2003; Spezio et al. 2007), emotional learning (Phelps et al. 2001), and memory (McGaugh 2004). The amygdala was shown to react to angry and fearful faces (Adams et al. 2003), be involved in gaze monitoring (Kawashima et al. 1999), and is crucial for the recognition of social emotions. Furthermore, there is converging evidence that amygdala structures and their connecting complex of neural systems are at the core of the ability to interpret the mental states of others (Stone et al. 2003, Baron-Cohen et al. 2000). In their current overview of results from different functional imaging studies of the brain basis of ToM skills, Carrington and Bailey (2009) found the amygdala to be less consistently activated. However, its influence on social and emotional reactions (Adolphs et al. 1998) clearly indicates involvement of the amygdala in certain ToM functions.

Task-related imaging. Functional imaging studies on social cognition have used classical ToM tasks (introduced in the preceding section) as well as tasks involving the processing of faces.

Using PET, Morris and his colleagues (1996) were the first to document a specific activation of the amygdala during the presentation of faces with systematically varied expressions (Ekman faces). Thus, a modulation of the neural activation took place depending on the valence and intensity of the emotion. The left amygdala registered significantly more neuronal activity looking at fearful faces than looking at happy faces. Whalen and his colleagues (2001) were able to confirm this finding. They also noticed a significantly stronger activation looking at fearful faces in comparison to neutral or angry ones. Baron-Cohen et al. (1999) were even able to show, using fMRI, that patients with autism and AS did not show amygdala activation in comparison to healthy controls while making mentalistic inferences from the eyes (Eyes Test). These results are in accordance with histopathological studies demonstrating gray matter abnormalities in the amygdala and surrounding temporal areas (Courchesne 1997).

Functional imaging has also been used to study the detection of mental state information in Heider and Simmel's (Heider and Simmel 1944) animations of moving geometric shapes. Castelli et al. (2000), using positron emission tomography, presented an animated sequence in which two triangles interacted with each other. The more strongly the observers attributed mental conditions to the triangles, the stronger the activity in the MPFC, temporal pole, and STS. Schultz et al. (2003) utilized an analogous task and noticed activations in the same areas when using fMRI. In both of these studies where mentalizing was determined by the movements of abstract shapes, the activity in the temporal pole extended into the amygdala and some activity could also be seen in the fusiform gyrus. Each study required explicit mentalizing whenever the test persons were asked to characterize the mental states of another person or to make decisions according to the mental states of others. The only exceptions were studies using passive viewing of animations.

To our knowledge there is only one study to date which has linked structural abnormalities to impaired social cognitive abilities using faux pas tasks. Herold et al. (2009) used voxel-based morphometry (VBM) to compare data of patients with schizophrenia to healthy individuals and found that the poor faux pas performance of patients with schizophrenia correlated with gray matter reduction in the left OFC and right TP. These results correspond to those recently found in a study by Shamay-Tsoory et al. (2005) who revealed that the pattern of ToM deficits in patients with schizophrenia resembled those seen in patients with ventromedial PFC lesions.

A PET study of ToM in autism (Happé and Frith 1996) employed a story comprehension task (Strange Stories Test), replicating a prior study in normal individuals (Fletcher et al. 1995). The authors found displaced and diminished mPFC activation in subjects with autism. However, due to small sample size (six subjects with autism) and relatively poor spatial resolution of PET imaging, these results should be considered preliminary.

Social cognition in temporal lobe epilepsy

Mesial temporal lobe epilepsy (MTLE) is the most prevalent focal epilepsy. It is characterized by recurrent seizures which originate from mesial temporal structures, most frequently within the hippocampus. Therefore, hippocampal sclerosis represents the most common pathological substrate in MTLE (Elger et al. 2004). Neuropsychological examinations often uncover memory impairments which are usually material-specific to the side of ictal onset (Rausch 1987). Resective surgery can be highly effective in obtaining seizure freedom in medically intractable patients with MTLE, but bears a significant risk of memory and language impairments. Accordingly, performances on measures of memory, language, and executive functions have been studied extensively pre- and postoperatively in this patient group. But despite knowledge that cerebral networks associated with social cognitive functions are frequently affected in patients suffering from temporal lobe epilepsies, investigations into social cognitive abilities have been scarce (Kirsch 2006). This paucity of research could be due to the lack of readily apparent social deficits in temporal lobe epilepsy patients (Phelps and LeDoux 2005).

At the same time, TLE is often associated with behavioral disturbances such as psychosocial maladjustments and psychiatric comorbidities including depression and social anxiety (Hermann et al. 2000). However, since anxiety and distress related to epileptic seizures and their consequences, stigmatization, and discrimination as well as a lack of social support can be seen as causative variables in the development of psychiatric afflictions (Devinsky and Najjar 1999; Shackleton et al. 2003), it remains unclear to what extent psychosocial difficulties are caused by these factors and to what extent they are related to deficits in social cognitive functions and, accordingly, to lesions in structures associated with social cognition. The fact that psychosocial difficulties and psychiatric symptoms appear more often in MTLE compared to other chronic epilepsy syndromes (Perini et al. 1996) supports the assumption of an association between MTLE and impairments in social cognition and offers an indication of a possible specific pathology associated with this epilepsy syndrome. Of course, there are other epilepsy syndromes, such as frontal lobe (Farrant et al. 2005) or juvenile myoclonic epilepsy (Piazzini et al. 2008), which may also be at risk of social cognitive impairments, but these have only rarely been investigated and we therefore focus below on TLE.

Several studies of basal aspects of social cognition suggest that the recognition of basic emotions in

facial expressions is frequently impaired in TLE patients (Meletti et al. 2003; Benuzzi et al. 2004; Fowler et al. 2006; Shaw et al. 2007; Walpole et al. 2008). In particular, patients with early seizure onset within the right, non-speech dominant hemisphere showed pronounced difficulties in the recognition of fearful faces (Benuzzi et al. 2004; Meletti et al. 2003). Also, the early-onset right MTLE-HS patients in Hlobil et al.'s (Hlobil et al. 2008) study were impaired in their ability to recognize fear when compared to other MTLE patients and control subjects, indicating that age of damage is an important factor determining this ability.

Moreover, impairments in the recognition of basic emotions with negative valence have also been reported in temporal lobectomy patients with amygdala damage on the basis of facial and vocal expressions (Brierley et al. 2004). The patients in Shaw et al.'s (2007) study who underwent a left anterior temporal lobectomy for medically intractable epilepsy which incorporated the entire amygdala evaluated fearful facial expressions in a more normative manner. By contrast, in right-sided MTLE patients the operation did not have any effect on the level of impairment.

Apart from impairments in the recognition of basic emotions (considered to be a prerequisite for a ToM), deficits in emotional memory (Boucsein et al. 2001) and in ToM abilities (Schacher et al. 2006b) have been associated with MTLE.

Abnormalities in higher-order social cognition were directly attributed to MTLE in a study by Schacher et al. (2006b). The authors compared patients with MTLE to patients with epilepsy not originating within the MTL and healthy controls in their ability to detect a social faux pas. They used a shortened version of the faux pas test (Stone et al. 2003), consisting of three short prose passages, and found that MTLE patients performed significantly worse in this test than patients with epilepsy other than MTLE (extra MTLE) and healthy controls. This finding was not accounted for by variables such as age, age at seizure onset, duration of epilepsy, text comprehension, or IQ and, thus, corroborate earlier findings that ToM abilities are mainly independent of other cognitive functions (Frith and Frith 2003). Considering that the epilepsy control group exhibited no impairments in the ToM task, the authors concluded that the observed deficit comprised a specific impairment in focal epilepsies with lesions in the ToM network.

The question of the role of the amygdala and the affective functions which it mediates is still under debate (Shaw et al. 2004). The amygdala has been associated with ToM processes in numerous studies (Adolphs 2003), whereby it appears to be of particular importance in the attribution of affective mental states (Vollm et al. 2006). To detect a social faux pas, as required in Schacher et al.'s (2006b) study, one has to be able to understand the emotional condition of another person. In patients with MTLE, the amygdala are often part of the epileptogenic zone and in about a quarter of patients with hippocampal sclerosis (HS), the ipsilateral amygdala shows volume reduction or even atrophy (Goncalves Pereira et al. 2005; Salmenpera et al. 2001). Furthermore, neuropathological findings in temporal lobe epilepsy patients point to variable degrees of neuronal cell loss and astrogliosis in the amygdala (Yilmazer-Hanke et al. 2000; Aliashkevich et al. 2003).

Disagreement remains as to what degree the amygdala merely supports the development of ToM abilities (Tager-Flusberg and Sullivan 2000; Frith and Frith 2003; Shaw et al. 2004) or whether it additionally represents an important part of the neural network which underlies ToM processing abilities (Happé et al. 1999; Channon and Crawford 2000; Stone et al. 2003; Sommer et al. 2008). The majority of authors agree with the latter supposition, which receives support in particular from lesion studies that indicate a clear connection between uni- and bilateral lesions of the amygdala and deficits in ToM (Stone et al. 2003; Heberlein and Adolphs 2004).

Apart from these behavioral studies, imaging studies have also been conducted that have detected amygdala dysfunctions. Using an animated fearful face-paradigm in their fMRI study, Schacher et al. (Schacher et al. 2006a) showed that ipsilateral amygdala functioning is impaired in the majority of patients with mTLE. In contrast, the paradigm resulted in symmetrical bilateral amygdala activation in healthy volunteers.

Bonelli et al. (2009) used a fearful face paradigm to study the role of the amygdala in the processing of emotions in patients with mTLE and to examine whether this may be a potential preoperative predictive marker for emotional disturbances following surgery. Healthy control subjects looking at photographs of fearful faces demonstrated left lateralized amgydala activation, while right-sided TLE patients showed bilateral amygdala activations.

Left-sided TLE-patients, however, had significantly reduced activations of either the left or right amygdala in comparison to the control group and the right-sided TLE-patients. During scanning, subjects in Bonelli et al.'s (2009) study were instructed to make judgments of whether photographs of faces were pleasant or unpleasant, a task in which patients with right-sided MTLE were previously shown to have impairments as compared to left-sided MTLE patients and healthy controls (Benuzzi et al. 2004; Meletti et al. 2003). In Bonelli et al.'s (2009) study, the left-sided MTLE patients displayed on average bilaterally reduced fMRI amygdala reactivity. Inspections of scatter plots revealed, however, considerable interindividual variability in the asymmetry of amygdalar responses, even in patients with left-sided MTLE.

Structure–function analyses have also shown an association between impairments in the recognition of facial expressions, especially of fear (Meletti et al. 2003), and reduced fMRI activity in patients with early onset right-sided TLE (Benuzzi et al. 2004). In addition, an association has been observed between fear recognition deficits and the duration of epilepsy as well as the amount of decrease in amygdala volume (Houghton et al. 2000; Reynders et al. 2005).

In sum, the majority of studies suggest that the degree of impairment and which aspects of social cognition are impaired is influenced by amygdala pathology in addition to mediating factors such as the age at which and side of which a lesion was acquired, age at seizure onset, and the expansion of the symptomatogenic zone as well as the functional deficit zone.

Conclusions

Today, we remain unsure as to whether we should consider deficits in social cognition as defining symptoms of the MTLE syndrome. However, the current state of research convincingly demonstrates that a considerable number of patients with MTLE demonstrate impairments in social cognition. These impairments may have a devastating impact on interpersonal relationships, social functioning, and quality of life and may promote the occurrence of the frequently reported comorbid symptoms of depression and anxiety. Yet, aspects of social cognition are not often part of the psychiatric or neuropsychological assessment of patients with epilepsies. We strongly recommend the expansion of cognitive assessment batteries to include tests of social cognition. As acute difficulties in social cognition are not necessarily evident in brief interactions between physician and patient, and these symptoms are often subclinical in nature and, therefore, psychometrically difficult to ascertain, it is important to develop sensitive and standardized instruments to analyse social cognition in different modalities. Identifying deficits in social cognition would allow for the development of more specific treatment strategies aimed at improving social-cognitive abilities in terms of training or within the scope of postoperative rehabilitation. As intact social-cognitive skills are of everyday relevance in that they allow for adequate social functioning in interpersonal relationships as well as in wider society, further insights into social cognition in epilepsy patients are required.

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Chapter 12

Nonepileptic seizures

Tanvir Syed and W. Curt LaFrance, Jr.

Introduction

Psychogenic nonepileptic seizures (PNES) are paroxysms of altered bodily/mental function, such as movement, behavior, or sensations, that are of psychological etiology. PNES can resemble epileptic seizures, although the latter, by definition, are a manifestation of abnormal synchronized cortical neuronal activity (epileptiform discharges) usually visualized on electroencephalography. The descriptor *psychogenic* distinguishes PNES from *physiological* nonepileptic events, which are seizures associated with medical or environmental disturbances (e.g. convulsive syncope, electrolyte disturbances, or substance intoxication/withdrawal seizure) (Gates and Mercer 1995; Vossler 1995; Rothner 1989). The adjective *nonepileptic* distinguishes PNES from psychologically triggered *epileptic* seizures (e.g. mental activity, emotion- or stress-triggered) (Fenwick 1981; Ritaccio et al. 2002; Woods and Gruenthal 2006; Sperling et al. 2008; Nakken et al. 2005; Mattson et al. 1970). Recent literature has abandoned the use of older PNES synonyms such as pseudoseizures, hystero-epilepsy, and psychological seizures, possibly because of definition ambiguity or derogation (i.e. accusations of feigning illness) (Scull 1997). PNES have been conceptualized as "panic attacks without panic" by some; however, the two disorders are clearly distinct, sometimes even co-occurring in individuals. Panic attacks are distinguished from PNES in their characteristic discrete periods of fear of dying or anxiety (Vein et al. 1994) and accompanied by "sympathetic nervous system" symptoms such as heart palpitations, diaphoresis, dizziness, tachypnea, choking feeling, and/or numbness/tingling. WHO International Classification of Diseases classifies PNES as a "Dissociative [conversion] disorder" (ICD-10 code F44.5), whereas DSM-IV-TR (Task Force on DSM-IV TR 2000) describes PNES under conversion disorders "with seizures," in the somatoform disorders category (DSM-IV code 300.11). Malingering, or feigning seizures for tangible gain (e.g. monetary, release from prison), is not a psychiatric diagnosis or under the rubric of PNES.

Potential etiologies of PNES have been reviewed extensively (LaFrance and Bjørnæs 2010), and the most elemental conceptualizations include post-traumatic PNES and developmental PNES (Kalogjera-Sackellares 1996). Reported in up to 80% of patients with PNES (Bowman and Markand 1996), trauma, including physical abuse, sexual assault, or observing of violence, is a recurring premise in the discussion of PNES etiology. The most commonly postulated mechanisms of PNES include dissociation, somatization, and symptom modeling. The dissociation hypothesis explains PNES as a manifestation of an intense dissociated state that functions as a coping mechanism for individuals who are not able to contend with memories of traumatic incidents (Bowman 1993). Under the somatization paradigm, PNES are an outward expression of unresolved internal conflicts typically related to isolated or accumulated stressors (Kapfhammer et al. 1998). Symptom modeling was proposed when the presence of a family history of epilepsy was noted in patients with PNES (Lancman et al. 1993; Lancman et al. 2001). Symptom modeling is a conceptually straightforward, thus attractive, hypothesis that elucidates PNES as a patient's conscious or unconscious attempt to mimic observations of others having epileptic seizures. In support of this hypothesis, a recent study demonstrated that patients with PNES were significantly more likely than patients with epilepsy to have witnessed a seizure prior to onset of their own seizures (Bautista et al. 2008). Based on case studies and review of the literature, Rosenbaum (2000) proposed a hypothesis that

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PNES in women are an expression of rage, fear, and helplessness against the dominant and abusive male. While acknowledging that PNES occur significantly more often in women, the prevalence in men occurring in 20% of the PNES population challenges this feminist theory-influence framework.

Epidemiology

PNES incidence and prevalence in the general population are difficult to accurately estimate. Published studies extrapolate estimates based on referrals to neurological centers and VEEG confirmed diagnosis, indicating that actual incidence and prevalence of PNES in the general population is likely higher than reported. Population-based studies have reported comparable incidences ranging from 1.5 to 3 per 100 000 per year (Sigurdardottir and Olafsson 1998; Szaflarski et al. 2000). Prevalence of PNES in outpatient epilepsy populations is 5–20% (Ramani 1986), whereas PNES may constitute 20–40% of inpatient epilepsy monitoring units (Wada 1985; Benbadis et al. 2004). A prospective study at two comprehensive epilepsy centers in Cleveland identified VEEG-confirmed PNES in 36–43% of 227 consecutively monitored inpatients, although cognitively impaired and encephalopathic patients were excluded (Syed et al. 2009). Benbadis and Hauser (2000) extrapolated a range of PNES prevalence to be 2–33 per 100 000 by combining lower and upper reported estimates of four fractions: epilepsy prevalence in the general population, proportion of intractable epilepsy, percentage referred to epilepsy centers, and PNES prevalence in epilepsy centers.

The female predominance is repeatedly observed in PNES, as women comprise 70–90% of most studies (van Merode et al. 1997). However, practitioners should exercise caution when using gender to distinguish PNES from epilepsy patients because the degree of female predominance in PNES may not be much higher than in concurrent epilepsy populations (Cragar et al. 2002). PNES manifests in all age groups, including children and the elderly (Lempert and Schmidt 1990), although existing literature suggests highest incidence between age 18 and 40 years, followed by children, and adults over 40 years old. Compared to their younger counterparts, patients with PNES with onset after 55 years of age are more likely to be men with severe physical health problems and health-related trauma (Duncan et al. 2006). Data pertaining to racial/ethnic composition of PNES populations is scarce, although existing literature reveals that PNES occur across races and ethnicities and indicates no significant difference from concurrently studied epilepsy populations. Excluding intellectual disability populations, most PNES patients have completed high school, and are educated equivalent to their epilepsy counterparts (Syed et al. 2009). A recent study reported that 56% of patients with PNES were married, compared to 40% of unmatched epilepsy patients, while divorce/separation rates were similar between the two groups (Syed et al. 2009). Other studies report comparable marital rates between PNES and epilepsy populations (Alper et al. 1993). US-based studies report unemployment rates in the PNES population ranging from 57% (Syed et al. 2009) to 67%, with 37% receiving disability (LaFrance and Syc 2009), whereas a UK-based study reports a strikingly similar rate of 58% when combining "unemployed," "receiving disability benefits," and "retired on health grounds" subgroups (Lawton et al. 2009).

Careful history-taking can elicit most risk factors for PNES. A history of traumatic life events, as noted above, is probably the most notorious risk factor for PNES. Comorbid psychiatric diagnoses including depression, anxiety, and personality disorder, and family history of psychiatric disorders are also PNES risk factors (Kanner et al. 1999). Chronic pain and fibromyalgia appear to be risk factors for PNES (Benbadis 2005), although their precise psychopathophysiological role in the development of PNES is uncertain. Family dysfunction (Wood et al. 1998; Griffith et al. 1998) and prior neurological insult (Conder and Zasler 1990) may also contribute to the biopsychosocial makeup of the PNES population (Moore and Baker 1997; LaFrance and Barry 2005).

Diagnosis

Seizure semiology is crucial for raising the clinician's suspicion of PNES, and is often the first step towards making the correct diagnosis (Benbadis and LaFrance 2010). Some PNES-suggestive features include emotional or situational triggers, gradual onset and offset, forward pelvic thrusting, ictal weeping, waxing and waning motor activity, side-to-side head movements, and ability of observer to modify patient's motor activity (Bodde et al. 2009). Recent studies examined postictal breathing patterns in convulsive PNES.

Compared to convulsive epileptic seizures, postictal breathing pattern in convulsive PNES is characterized by increased respiratory rate, short inspiratory and expiratory phases, quiet/shallow breathing sounds, and overall shorter period of altered breathing. Postictal breathing patterns in convulsive epileptic seizures are loud and stertorous (Azar et al. 2008).

Although clinicians refer to a plethora of suggestive clinical features, only a limited number of these features have been systematically and prospectively assessed for diagnostic accuracy and clinical utility (Hoerth et al. 2008). Most studies that assess seizure semiology are structured as retrospective analyses of long-term VEEG. In these studies, video-recordings are reviewed to assess the presence or absence of particular clinical features, and EEG tracings are used to ascertain PNES, or epilepsy, diagnosis. Patients with PNES and epilepsy are statistically compared for the prevalence of the particular clinical feature being studied, and results are typically reported in the form of *p*-values or epidemiological parameters (sensitivity, specificity) (Hoerth et al. 2008). Table 12.1 gives an overview of ictal semiology that may help differentiate psychogenic nonepileptic seizures from epileptic seizures.

Video EEG studies

Despite seemingly accurate methods of semiology and diagnosis assessment, there are theoretical and practical limitations that obscure the clinical utility of findings from these studies. As an example, one prototypical VEEG study concluded a very high sensitivity and specificity of ictal eye closure as a diagnostic feature of PNES (Chung et al. 2006). Clinically, however, if a VEEG-recorded event exhibits ictal eye closure in the context of an epileptiform EEG pattern, the event will be characterized as epileptic, based on the epileptiform EEG rather than the presence of ictal eye closure. On the contrary, if a recorded event exhibits ictal eye opening in the context of a normal EEG pattern, the event will likely be characterized as nonepileptic, based on the normal EEG rather than the absence of ictal eye closure. Thus, during VEEG studies, seizure phenotype plays a secondary role in diagnosis (secondary to EEG), with relatively limited clinical utility. In order for a semiological feature to be clinically useful, it must be accurately obtained during history-taking, prior to VEEG. Its utility, therefore, critically depends upon the accuracy of report from a witness or observer of a patient's seizure. That is, regardless of how specifically or sensitively a feature identifies PNES during VEEG, failure to witness accurately that feature prior to VEEG (e.g. outpatient setting) significantly lowers its clinical usefulness.

Continuing on the example of ictal eye closure, one study (Syed et al. 2008) prospectively assessed observer reports of ictal eye closure as a screening tool for PNES, and concluded that reports were inaccurate, and actually predicted PNES diagnosis worse than chance. With respect to ictal semiology, the diagnostic significance of a sign or symptom is one side of the coin, and equally important, the accuracy of a historically reported description is another, which future studies assessing clinical features should include. One study evaluating interrater reliability (IRR) of VEEG revealed substantial agreement for the diagnosis of epilepsy and moderate IRR for PNES, but low IRR for physiological nonepileptic events (Benbadis et al. 2009). The less than perfect IRR among epileptologists was attributed to the study design, where diagnostic choices were made intentionally but artificially, based solely on viewing VEEG recordings. Clinically, the actual diagnosis of epilepsy or PNES is made by a combination of patient history (neurological and psychiatric), examination, and VEEG monitoring. This process amounts to the mixture of "the science and art of medicine" and ultimately informs the accurate diagnosis. The discussion on monitoring and semiology underscores the importance of putting the history and physical examination in context as summarized in the truism that "one sign or symptom does not a diagnosis make."

Capturing a patient's habitual event during VEEG monitoring remains the gold-standard for PNES diagnosis (Smolowitz et al. 2007, Ghougassian et al. 2004). However, it is important to consider some basic principles of VEEG interpretation to prevent an "expensive" misdiagnosis (LaFrance and Benbadis 2006). First, scalp EEG may not detect epileptic seizure activity if the ictal cortical region is less than 10 cm^2 (Toe et al. 2007). Such may be the case with epileptic auras, focal motor epileptic seizures, or aphasic epileptic seizures, where ictal discharges may recruit a relatively small region of cortex, yet produce dramatic clinical manifestations. Second, ictal cortical activity situated in areas nonadjacent to electrode positions, such as mesial or basal cortex, may evade scalp EEG.

Table 12.1 Ictal semiology that may help differentiate psychogenic nonepileptic seizures from epileptic seizures

	Psychogenic nonepileptic seizures	Epileptic seizures
Observation		
Situational onset	Occasional	Rare
Gradual onset	Common	Rare
Precipitated by stimuli (noise, light)	Occasional	Rare
Purposeful movements	Occasional	Very rare
Opisthotonus "*arc de cercle*"	Occasional	Very rare
Tongue biting (tip)	Occasional	Rare
Tongue biting (side)	Rare	Common
Prolonged ictal atonia	Occasional	Very rare
Vocalization during "tonic-clonic" phase	Occasional	Very rare
Reactivity during "unconsciousness"	Occasional	Very rare
Rapid postictal reorientation	Common	Unusual
Undulating motor activity	Common	Very rare
Asynchronous limb movements	Common	Rare
Rhythmic pelvic movements	Occasional	Rare
Side-to-side head shaking	Common	Rare
Ictal crying	Occasional	Very rare
Ictal stuttering	Occasional	Rare
Postictal whispering	Occasional	Not present
Closed mouth in "tonic phase"	Occasional	Very rare
Closed eyelids during seizure onset	Very common	Rare
Convulsion >2 minutes	Common	Very rare
Resisted lid opening	Common	Very rare
Pupillary light reflex	Usually retained	Commonly absent
Lack of cyanosis	Common	Rare
Ictal grasping	Rare	Occurs in FLE and TLE
Postictal nose rubbing	Not present	Occurs in TLE
Stertorous breathing postictally	Not present	Common
Self-injury	May be present	May be present
Incontinence	May be present	May be present

FLE – frontal lobe epilepsy; TLE – temporal lobe epilepsy; Reproduced with permission from p. 41, Benbadis SR, LaFrance Jr WC. Chapter 4. Clinical Features and the Role of Video-EEG Monitoring. In: Schachter SC, LaFrance Jr WC, editors. *Gates and Rowan's Nonepileptic Seizures*. 3rd ed. Cambridge: Cambridge University Press; 2010.

For example, seizures arising from mesial frontal cortex may give rise to flailing, chaotic movements of extremities, without accompanying epileptiform discharges on scalp EEG. Third, even though PNES may be correctly identified during VEEG, the practitioner should keep in mind that concomitant epilepsy is reported as occurring in from 5% to 40% of patients with PNES, although more stringent studies reveal that epilepsy occurs in only 10% of patients with PNES (Lesser et al. 1983; Benbadis et al. 2001). In our experience, medical history usually suggests that epilepsy onset precedes PNES onset, although no prospective studies have systematically examined this phenomenon.

Certain measures can be taken to overcome these issues and potential pitfalls of VEEG use for PNES diagnosis. Capturing several events over 3–7 days of VEEG LTM with AED tapering or on ambulatory EEG with video has advantages over short-term (<24 hour) recordings. One may uncover that a seizure, which at first appeared nonepileptic, is actually epileptic, by way of secondary generalization or more recognizable seizure patterns (i.e. on viewing the same EEG pattern several times). Conversely, a nonepileptic seizure initially thought to be epileptic may semiologically evolve

over a few days, revealing non-epileptogenicity. For example, focal clonic hand movements on day 1 of VEEG monitoring may last 30–60 seconds, suggesting epileptogenicity in the contralateral primary motor cortex; whereas over 2–3 days the events might evolve in duration (10–20 minutes without secondary generalization), exhibit stop-and-go pattern, and recruit other limbs asynchronously, all suggesting psychogenicity. Furthermore, long-term monitoring improves the likelihood of detecting concomitant interictal epileptiform activity or frank epileptic seizures, especially when AEDs are withdrawn. When seizures occur infrequently, inpatient LTM may not be an option, and ambulatory monitoring with video can be used. In areas where video monitoring is not available, capturing the patient's typical event on home video can aid in diagnosis. Caution must be exercised, however, with the coexistence of PNES and epilepsy and this can be a major pitfall when relying on history alone, or eyewitness/home-video of events.

Other tests

A comprehensive review of adjunctive laboratory, imaging, and neuropsychological testing concluded that these tests were helpful as adjuncts to diagnosis, but did not replace VEEG as the gold standard for PNES diagnosis (Cragar et al. 2002). More recent studies are examining neuropsychological and psychological testing in attempts to distinguish PNES from epilepsy. While these adjunctive tests potentially lead to conceptual frameworks for patients with seizures, the consistent finding among studies on neuropsychological batteries overall is that PNES and epilepsy differ from healthy controls on tests, but not from each other (Cragar et al. 2006; Dodrill 2008). Although depression is prevalent among both patients with PNES and epilepsy (Szaflarski and Szaflarski 2004), patients with PNES may report a higher level of physiological symptoms of depression (Asmussen et al. 2009). PNES patients were found to overestimate their degree of cognitive functioning, despite outperforming epilepsy patients on the Boston Naming Test (Prigatano and Kirlin 2009). Personality measures also have been used to attempt to differentiate patients with PNES from epilepsy; however, a large number of false positive diagnoses of PNES may result depending on the decision rules used in the MMPI/MMPI-2 interpretation (Cragar et al. 2003).

Treatment and prognosis

While much is known about the semiology and comorbidities in PNES, treatment for PNES remains the greatest hurdle for clinicians and patients. A variety of reviews consistently reveal the absence of class I data for PNES treatments (LaFrance and Barry 2005; LaFrance and Devinsky 2004; Baker et al. 2007). Preliminary evidence exists, however, for psychotherapeutic and pharmacological interventions. The strongest evidence, thus far, exists for cognitive behavioral therapy (CBT). Goldstein et al. published an open label trial of CBT for "dissociative seizures" revealing improvements in seizure frequency and in psychosocial outcomes (Goldstein et al. 2004). LaFrance et al. (2009) conducted an open label trial of CBT for PNES based on a psychotherapy for epilepsy (Reiter et al. 1987; Reiter and Andrews 2000). The CBT for the PNES trial revealed 11 of 17 completers were seizure free by the end of the treatment, and comorbid symptoms including depression and anxiety were also significantly improved. Other open label trials of group therapy (Barry et al. 2008) and psychoeducation (Zaroff et al. 2004) show potential. Finally, hypnosis is used in diagnosis of PNES and may be useful in its treatment (Moene et al. 2002).

Pharmacological interventions for PNES have been reviewed (LaFrance and Blumer 2010), and a number of medications show potential for symptomatic treatment but will likely need to be combined with psychotherapy to address underlying issues in patients with PNES. Oral benzodiazepines have been shown to reduce seizure counts and anxiety, but not as much as paradoxical intention therapy when compared in an open label trial (Ataoglu et al. 1998). Analgesics in combination with antidepressants and beta-blockers are described in anecdotal reports with benefit (Blumer 2000). An open label and pilot blinded RCT using SSRIs (selective serotonin reuptake inhibitors) have yielded preliminary data showing potential as adjunctive treatment (LaFrance et al. 2007, LaFrance et al. 2010). AEDs do not treat PNES and they may exacerbate the condition (Niedermeyer et al. 1970; Oto et al. 2005). Many epilepsy monitoring units taper AEDs for diagnosis and hope for seizure freedom based on the notion that sharing the diagnosis "treats" PNES. One study found that telling the patient that he/she had PNES in the epilepsy monitoring units resulted in a drop in seizures among 22 patients with PNES in

the 24 hours after the diagnosis was given (Farias et al. 2003). A follow-up of patients with PNES, however, revealed that 80% of the patients continued to have seizures or other symptoms up to 1 year after the diagnosis (Wilder et al. 2004). Thus, merely communicating the diagnosis is a starting point, but is not a sufficient treatment in the complexity of patients with PNES.

Various prognostic indicators have been reported including clinical and psychological factors (Reuber et al. 2003). Poorer prognosis is associated with the presence of chronic depression, an Axis II personality disorder, and a history of abuse or trauma (Kanner et al. 1999). The prognostic relevance of the significant diagnostic delay from the onset of seizures to the accurate diagnosis of PNES (Reuber et al. 2002) manifests in the finding that the shorter time to diagnosis was associated with requiring fewer therapy sessions (Rusch et al. 2001).

Conclusion

PNES are likely the result of a complex interaction between psychiatric disorders, psychosocial stressors, dysfunctional coping styles, and CNS vulnerability (Mokleby et al. 2002). The main comorbid diagnoses found in patients with PNES include major depressive disorder, post-traumatic stress disorder, and cluster B personality traits characterized by impulsivity/hostility (Bowman and Markand 1996; Rechlin et al. 1997). Three additional critical areas of dysfunction in the PNES population are: emotional regulation, family dynamics, and unemployment/disability (Walczak et al. 1995; Griffith et al. 1998; Holmes et al. 2001). Poorer outcomes to treatment may be associated with the high number of comorbid psychiatric disorders and psychosocial stressors (McKenzie et al. 2010). Therefore, therapy for patients with PNES may require combined psychological education, psychotherapy, and pharmacotherapy, while simultaneously eliminating ineffective AEDs in lone PNES (LaFrance and Devinsky 2002). To determine treatment efficacy, these interventions need to be studied in a randomized, controlled trial (LaFrance et al. 2006). Clinical experience and prior-published treatment reports reveal that coordination between neurologists and psychiatrists/psychologists, with accurate diagnosis and prompt initiation of psychotherapy and communication between care providers, patient and family, yields higher treatment success.

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Chapter 13

The effects of antiepileptic drugs on behavior

Bettina Schmitz

Introduction

Central effects of antiepileptic drugs (AEDs) are not restricted to the modulation of cortical excitability. AEDs may also modify systems which regulate mood and behavior. Anticonvulsant and psychotropic effects are however not independent. Effects on seizure control have indirect effects on the mental state. Patients who are seizure free have no risk of developing seizure-related psychiatric complications. On the other hand sudden cessation of seizures may lead to an imbalance in the mental state as in "forced normalization" (FN). Some AEDs have dose related paradoxical proconvulsive properties which may cause behavioral disturbances with underlying non-convulsive status epilepticus.

Psychotropic effects may be negative or beneficial in individual patients. These effects depend on the antiepileptic effect and the mode of action of the AED and the patient's biological and psychological predisposition. With the growing number of new AEDs, behavioral drug profiles have become increasingly important for optimal treatment choices in epilepsy. Quality of life studies have shown that measurements of depression and tolerability of AEDs may be more important to patients than seizure reduction (Gilliam 2002). Furthermore, the high psychiatric comorbidity in epilepsy often requires psychopharmacological interventions, which may be avoided when anticonvulsants are used which have positive psychotropic properties.

In clinical practice adverse psychiatric effects of AEDs are often not recognized. Many patients do not complain about behavior or mood changes unless they are specifically interviewed or unless these problems become clinically dramatic as in productive psychosis. Many neurologists are not competent in the exploration of a mental state, or they do not have the additional time needed. Many depressed patients are not primarily troubled by obvious depressive symptoms such as sadness or feelings of guilt. Depression in epilepsy often presents with sleep disorders or somatoform complaints and memory problems, which make the diagnosis difficult unless the full psychopathological status is explored. If delayed psychiatric adverse effects occur after months or years of exposure, the causal relationship with drug treatment is often not considered and is in fact difficult to prove, unless drug withdrawal is followed by remission of psychiatric symptoms.

The exact prevalence of psychiatric AED events is difficult to estimate. In a consecutive series of patients with epilepsy and significant depression about 30% were considered AED-related (Schmitz et al. 1999; Kanner et al. 2000). With respect to psychoses the percentage of episodes triggered by AEDs has been calculated to be 40% in a Japanese study (Matsuura 1999).

Adverse psychiatric effects of specific AEDs

Conventional drugs

Barbiturates

Several studies suggested a link between depression and treatment with barbiturates both in adults and in children (Brent 1986; Robertson et al. 1987). In one study, 40% of school children treated with barbiturates were diagnosed with "major depression", as compared to only 4% of children treated with carbamazepine (Brent et al. 1987). In children, a conduct disorder resembling the attention-deficit hyperactivity disorder may be provoked by many AEDs, the most frequently

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implicated drug being phenobarbitone. Irritability and aggressive behavior are side effects particularly often seen when barbiturates are used in learning disabled patients. Withdrawal problems which present with nervousness, dysphoria, and insomnia may occur even when barbiturates are very slowly tapered down.

Phenytoin

Phenytoin may provoke schizophrenia-like psychoses at high serum levels (McDanal and Bolman 1975). These psychoses are dose related, thus toxic syndromes. Interestingly, they are often not associated with other toxic signs such as cerebellar symptoms which are the most common central nervous system side effects of phenytoin. In a study on 45 patients with drug-related psychoses, 25 [56%] were attributed to treatment with phenytoin (Kanemoto et al. 2001). A chronic encephalopathy has also been described with phenytoin and has been referred to as "dilantin dementia" (Trimble and Reynolds 1976).

Ethosuccimide

Psychoses typically following cessation of seizures and associated with a normalization of the EEG occur in 2% of children treated with ethosuccimide. The risk of "forced normalization" is higher (8%) in adolescents and adults treated with ethosuccimide for persisting absence seizures (Wolf et al. 1984).

Carbamazepine

Affective problems are rare complications of treatment with carbamazepine (Dalby 1975). These are either depressive disorders or mania, the latter being explained as a paradoxical effect due to the antidepressant properties of carbamazepine, which is chemically related to tricyclic antidepressants (Drake and Peruzzi 1986).

Valproate

Rarely, valproate is associated with acute or chronic encephalopathies (Sackellares et al. 1979; Zaret and Cohen 1986; Schöndienst and Wolf 1992). These encephalopathies are related to dose and perhaps polytherapy and are reversible with dose reduction. Otherwise, valproate has rarely been associated with significant psychiatric side effects.

Newer AEDs

Table 13.1 summarizes data from premarketing controlled trials suggesting a relatively high frequency of depressive reactions in vigabatrin, tiagabine, zonisamide, and topiramate, and relatively low rates for lamotrigine, gabapentin, levetiracetam, pregabalin, and lacosamide. Obviously psychiatric risks of the newer AEDs are not the same for all compounds. Some of the drugs seem to have neutral effects, some have a relevant risk for negative effects, and some may have predominantly beneficial psychotropic effects. A general comment is that the overall psychiatric risks of newer AEDs are not lower than those of older AEDs.

Table 13.1 Incidence rates of psychoses and depression in controlled trials

	Psychoses (%)	Depression (%)
Vigabatrin	2.5	12.1
Lamotrigine	0.2	–
Felbamate	0.02	–
Gabapentin	0.5	–
Topiramate	0.8	9–18
Tiagabine	0.8–2	5
Levetiracetam	0.3–0.7	0.5–2
Pregabalin	–	–
Zonisamide	1.9–2.3	7.4
Lacosamide	0–0.6	–

From Besag (2001), Janssen Cilag (1996), Levinson and Devinsky (1999), Matsuura and Trimble (1997), French et al. (2003), Arroyo et al. (2004), Schmidt et al. (1993), Faught et al. (2001), Chung et al. (2010), Halász et al. (2009), Ben-Menachem et al. (2007).

Vigabatrin

The risk of psychiatric complications caused by vigabatrin has been analyzed in two meta-analyses. The overall incidence of psychoses and severe behavioral reactions leading to drug discontinuation in seven placebo-controlled European studies was 3.4% in the vigabatrin group and 0.6% in the placebo group (Ferrie et al. 1996). Another meta-analysis on the psychiatric risks of vigabatrin (Levinson and Devinsky 1999) translated psychopathological symptoms described in the investigator forms into standardized psychiatric terminology, which was then summarized into a syndromatic diagnosis. This analysis of US and non-US double-blind studies demonstrated a significantly increased risk for psychosis and particularly for depression. Psychoses occurred in 2.5% of patients

treated with vigabatrin compared to an incidence of 0.3% in the placebo group ($p<0.05$), and depression occurred in 12.1% of patients treated with vigabatrin in contrast to only 3.5% in the placebo group ($p<0.001$).

Lamotrigine

Severe psychiatric complications are rare with lamotrigine, and psychosis and depression occurred only in very few cases in the trials (Fitton and Goa 1995). Insomnia, which may be associated with irritability, anxiety, or even hypomania, is the only significant psychiatric side effect, occurring in 6% of patients treated in monotherapy, compared to 2% in patients treated with carbamazepine and 3% in patients treated with phenytoin (Brodie et al. 1995).

When there were first reports that carers complained as handicapped patients became more alert and demanding on lamotrigine, this was interpreted to reflect inadequate rehabilitation facilities rather than being a negative side effect (Binnie 1997). Besag refers to this as a "release phenomenon" (Besag 2001). There are however a number of reports that children and adults with learning difficulties have developed behavioral problems such as aggression (Beran and Gibson 1998; Ettinger et al. 1998) and there have been reports on the induction of a reversible Tourette's syndrome which in some cases was accompanied by obsessive-compulsive symptoms (Lombroso 1999).

Felbamate

Felbamate is at present only used in a minority of patients particularly with Lennox-Gastaut syndrome due to its hematological and hepatic toxicity. Felbamate may lead to increased alertness, inducing sleep problems and behavioral problems related to agitation in some patients, again, particularly in children with learning disabilities (McConnell et al. 1996).

Gabapentin

Beyond somnolence, negative psychotropic effects have not been demonstrated in the controlled studies with gabapentin. However, there are a number of studies suggesting that gabapentin may induce behavioral problems such as aggression in children and adults with learning disabilities (Lee et al. 1996; Wolf et al. 1995; Tallian et al. 1996), possibly related to rapid titration. In elderly people with reduced creatinine clearance gabapentin may cause various neurotoxic symptoms due to its renal elimination.

Tiagabine

A specific problem with tiagabine is the paradoxical provocation of de novo nonconvulsive status epilepticus due to a relatively narrow therapeutic window (Schapel and Chadwick 1996). Therefore, EEG examinations are necessary when behavioral problems arise, particularly when clinical signs such as mutism, qualitative change in consciousness, autism, or myoclonia suggest status epilepticus.

In the placebo-controlled add-on studies, nervousness and depressed mood were both increased in the tiagabine group (Leppik 1995) (12% versus 3%, 5% versus 1%). The incidence of serious adverse events presenting as psychosis was 2% versus 1% in the placebo group.

Topiramate

In the premarketing studies and possibly related to aggressive titration schemes, topiramate was associated with a relatively high rate of neurotoxic side effects. Psychotic reactions were however relatively infrequent with a prevalence of 0.8%. In a postmarketing study comparing psychiatric side effects of topiramate, lamotrigine, and gabapentin, psychotic episodes occurred in 12% of patients treated with topiramate compared to 0.7% of patients treated with lamotrigine and 0.5% of patients treated with gabapentin (Crawford 1998). These data suggest an increased vulnerability in selected patient groups. A significant proportion of topiramate-associated psychoses are explained as alternative syndromes in patients who become seizure free (Mula et al. 2003a).

The rate of affective symptoms is clearly dose dependent with an incidence of 9% and 19% with a daily dose of 200 mg and 1000 mg, respectively, in one premarketing study (Janssen-Cilag 1996). In an analysis of topiramate-related psychiatric complications, depression was significantly correlated with rapid titration and high dosages (Mula et al. 2009). Two studies demonstrated a correlation between psychiatric adverse events and cognitive side effects, suggesting that neuropsychological and affective problems are closely interlinked (Mula et al. 2003a; Mula et al. 2009). One study showed that cotherapy with lamotrigine was a significant protective factor (Mula et al. 2009). The neuropsychological disorders caused by topiramate resemble a frontal lobe problem and have been interpreted as regional behavioral toxicity. It would be

interesting to investigate whether patients with epilepsies and frontal lobe dysfunction are more vulnerable to these effects.

Levetiracetam

In the regulatory trials levetiracetam was not associated with high risks for either psychotic or depressive reactions. Significant affective episodes were reported in 2% and psychoses in 0.7% of patients treated in preclinical trials. Some of the levetiracetam-associated psychoses were explained as a manifestation of forced normalization. An observational postmarketing study of 517 patients (Mula et al. 2003b) and a case–control study (White et al. 2003) showed similar incidence rates of depression: 2.5% and 2.8%, respectively. There is no clear relationship to titrations schemes, but previous psychiatric history is associated with higher complication rates suggesting that biological vulnerability may play an important role.

A clinically relevant psychiatric side effect of levetiracetam is the provocation of aggressive behavior and irritability which occurs both in adults and children. In an English series of 517 adult patients treated with levetiracetam 10% developed a psychiatric complication, most frequently presenting with aggressive behavior (Mula et al. 2003b). Aggression occurs particularly often, but not exclusively, in patients with pre-existing irritability and dysphoria. Mesad and Devinsky (2002) analysed cases of severe aggressive behavior, defined by objective verbal or physical aggression leading to withdrawal of levetiracetam. The prevalence was 18 out of 460 consecutive patients (3.9%). Seven patients had previous episodes of aggressive behavior.

Children may be at an even higher risk to develop aggression including suicidal behavior, with prevalence rates up to 68% (Estrada et al. 2002). In children with pre-existing neuropsychiatric symptomatology levetiracetam may provoke an exacerbation of behavioral problems (Gustafson et al. 2002). Kossoff and colleagues (Kossoff et al. 2001) reported on four adolescents who developed a psychosis secondary to treatment with levetiracetam, all of which were reversible following withdrawal. All patients had pre-existing behavioral problems, and two had become seizure free, supporting the role of FN.

Zonisamide

Beyond Japan and USA, there is still limited experience with this broad spectrum AED. There are however indications of significant psychiatric adverse events including affective problems and psychoses. In three placebo-controlled trials, depression was reported in 7.4% of treated patients compared to 3% in the placebo group. The incidence was dose dependent with incidence rates of depression of 0.8% in patients taking less than 200 mg daily, 1.9% with 200–400 mg daily, and 5.8% in patients taking more than 400 mg (Schmidt et al. 1993; Faught et al. 2001; Sackellares et al. 2004).

According to a review by Matsuura and Trimble (1997) the incidence of psychoses ranged from 1.9% to 2.3% across studies. In Japan, where until recently zonisamide has been the only new anticonvulsant for many years, a case series of patients with psychotic episodes showed that half of drug-related episodes were triggered by zonisamide (Matsuura 1999).

In a retrospective analysis of 74 patients with a history of zonisamide treatment, 14 had developed psychotic episodes. The risk of psychotic episodes was higher in younger patients. In children, obsessive-compulsive symptoms appeared to be related to psychotic episodes (Miyamoto et al. 2000).

Whether psychiatric problems of zonisamide are linked to cognitive side effects as with topiramate has not been studied so far. Because of the similarities to topiramate it would be interesting to know whether there are differences with respect to their psychiatric risks.

Pregabalin

Pregabalin has been shown to have several favorable psychotropic effects and there is no evidence for significant psychiatric adverse events from the regulatory studies. In these trials there have been no reports of psychoses. Summarizing the three pivotal trials including more than 1000 patients the overall incidence for depression was lower than 1%. In one study depression was reported in four patients in the placebo group and in two patients in any pregabalin group (Arroyo et al. 2004). In the second study it was noted that there were only isolated reports of anxiety, depression, and other events linked to fluctuation in mood (Beydoun et al. 2005). In the publication from the third placebo controlled study psychiatric side effects are not mentioned (French et al. 2003).

However, clinical experience with this drug is still limited to add-on therapy in patients with epilepsy, since the drug has no monotherapy licence for epilepsy and is predominantly used in patients with neuropathic pains.

Lacosamide

This is a new anticonvulsant which selectively enhances slow inactivation of voltage-gated sodium channels and also modulates collapsing response mediator protein 2 (CRMP-2). The side effect profile resembles other sodium channel blockers such as carbamazepine. In the three published controlled trials psychiatric complications have been rare. In one study comparing 200, 400, and 600 mg daily dosages, the authors commented that there was no clinically important difference in the rate of psychiatric adverse events between patients receiving lacosamide or placebo (Chung et al. 2010). In another study comparing 200 and 400 mg lacosamide with placebo, from 318 patients who received lacosamide two developed a psychosis (with 400 mg/day), compared to none in the placebo group (Ben-Menachem et al. 2007). In a third controlled study the publication does not mention psychiatric side effects (Halász et al. 2009).

The clinical experience with this drug is still limited. In a postmarketing study including 25 patients with difficult to treat focal epilepsies, there were five cases of depression and two with irritability (Wehner et al. 2009).

Oxcarbazepine, eslicarbazepine

Oxcarbazepine is a derivate of carbamazepine which is claimed to be better tolerated than carbamazepine because of a different metabolism. Eslicarbazepine is a recently introduced drug which is activated to the active metabolite of oxcarbazepine. There are no specific data with respect to psychiatric side effects of oxcarbazepine or eslicarbazepine. However, it is likely that their psychiatric profiles are similar to that of carbamazepine. The risk for hyponatremia is higher with oxcarbazepine and this may be associated with psychiatric symptoms.

Positive psychotropic effects of AEDs

Carbamazepine and valproate are established drugs for affective disorders and all novel anticonvulsants have been tested in primary psychiatric disorders with respect to potential mood stabilizing properties. Advantages of anticonvulsants compared to classical mood stabilizers are the lack of proconvulsive risks, the lower potential to induce a switch from depression into mania, and a superior efficacy in atypical syndromes such as rapid cycling bipolar disorder. So far, lamotrigine has been approved for bipolar disorder and pregabalin for general anxiety disorders (Table 13.2) in 2007. Lacosamide had shown anxiolytic effects in animal models; so far these effects have not been confirmed in humans (Higgins et al. 2009).

Table 13.2 Positive psychotropic effects of antiepileptic drugs demonstrated in controlled trials

	Depression	Mania	Bipolar disorder	Anxiety
Carbamazepine	0	+	+	0
Oxcarbazepine	0	+	0	0
Valproate	0	+	+	0
Lamotrigine	0	0	+	0
Gabapentin	0	−	−	+/−
Topiramate	0	−	0	0
Tiagabine	0	−	0	0
Levetiracetam	0	0	0	−
Pregabalin	0	0	0	+
Zonisamide	0	0	0	0

+, positive results; −, negative results; 0, no published data.

The potentially positive psychotropic effects of AEDs have not been systematically studied in patients with epilepsy. This is unsatisfactory because the experience with primary psychiatric patients cannot easily be transferred to epilepsy. Many psychiatric disorders in epilepsy are different in their phenomenology and most likely also in their pathogenesis from "endogenous" disorders.

The evidence for mood stabilizing effects of carbamazepine and valproate when used in patients with epilepsy is based on few observations (Robertson et al. 1987; Trimble and Reynolds 1976; Schmitz et al. 1999). With respect to the newer AEDs the only convincing evidence with respect to positive psychotropic effects relates to lamotrigine (Edwards et al. 2001; Gillham et al. 2000; Kalogjera-Sackellares et al. 2002; Baker et al. 2000).

Risk factors for psychiatric adverse events

Patients with a biographic or genetic predisposition for psychiatric disorders are presumably more at risk to develop AED-related psychiatric complications such as depression and psychosis (Table 13.3). Patients

Table 13.3 Risk factors for depression and psychosis with vigabatrin, topiramate, and levetiracetam

	Vigabatrin[a] Depression/psychoses N=22/28	Topiramate[b] Depression/psychoses N=46/16	Levetiracetam[c] Depression/psychoses N=13/6
Psychiatric history	+/+	+/+	+/+
Febrile seizures	?/?	+/?	+/?
Status epilepticus	?/?	?/?	+/?
Titration/dosage	+/−	+/−	−/−
Seizure freedom	−/+ (13 cases)	−/+ (10 cases)	−/+ (4 cases)
Severity of epilepsy	−/+	+/?	−/?
Cognitive side effects	?/?	+/−	−/−

[a]Thomas et al. (1996);
[b]Mula et al. (2003a);
[c]Mula et al. (2003b).
+, significant relationship; −, no relationship; ?, not studied or too small numbers.

with previous depressive episodes are more likely to develop an affective disorder while patients with previous schizophrenia-like psychoses are more likely to present with a psychotic reaction, suggesting that the clinical presentation of psychiatric adverse reactions depends on the individual psychopathological predisposition. In patients with previous psychiatric problems rapid titration should therefore be avoided, since aggressive titration schemes further increase the risk of behavioral toxicity.

Some studies have shown that patients with severe epilepsies are at a higher risk for psychiatric side effects. Mula et al. (2003a) demonstrated that hippocampal sclerosis is more common in patients who develop depressive episodes secondary to treatment with topiramate as compared to patients without affective side effects, another indication for the close links between limbic dysfunction and affective disorders.

Children and adults with learning disability and multiple handicaps are particularly vulnerable to behavioral adverse effects of AEDs. In these patients, the exact psychiatric diagnosis may be difficult, and both depression and psychosis may manifest with aggressive behavior. Also nonpsychiatric adverse events may lead to disturbed behavior because patients may have difficulties in expressing their discomfort otherwise. In these patients drug changes should be monitored carefully, and it is recommended that the behavioral changes are carefully discussed with the caring team. Sometimes interpretations of behavior changes are different within the team and particularly when patients become more alert and active because of positive psychotropic AED effects these changes may be regarded as negative because they request adaptations in the attitude of carers and make new treatment programs necessary.

Mechanisms

There are four major mechanisms which explain behavior effects of AEDs: (1) dosage-dependent toxicity, (2) dose-independent idiosyncratic drug effects, (3) withdrawal effects, and (4) indirect effects via anticonvulsive actions. Of these, the two most important mechanisms are pharmacodynamic side effects related to the drug's mode of action and effects which arise with seizure control, so-called alternative syndromes associated with the phenomenon of forced normalization.

Trimble's hypothesis of a link between psychiatric complications and GABAergic mechanisms of AEDs was extended by Ketter (Ketter et al. 1999) who distinguished two categories of AED, the first being GABAergic with sedating, anxiolytic, and antimanic properties. This category comprises barbiturates, benzodiazepines, valproate, vigabatrin, tiagabine, and gabapentin. The second category comprises antiglutamatergic drugs which are claimed to have activating, anxiogenic, and antidepressive effects: felbamate and lamotrigine. The

Table 13.4 Potential psychiatric risks of antiepileptic drugs in patients with psychiatric comorbidity

Patient's pre-existing mental state	AEDs which should be used carefully	Possible side effect	AEDs which should be considered
Emotional lability	**PHB, VGB, TPM, TGB, ZNS, LEV**	Major depression	LTG, CBZ, VPA
Anxious	**LTG, LEV**	Anxiety disorder	PGB, GBP, BZD
Paranoid	**DPH, VGB, TPM, LEV**	Schizophrenic psychosis	CBZ, VPA
Agitation	**LTG**	Insomnia, anxiety, hypomania	GBP, PGB, BZD
Hypermotor	**LTG**	Tourette's syndrome	GBP, PGB, BZD, CBZ, VPA
Irritable	**LEV, PRM, PHB**	Aggression	GBP, PGB, BZD, CBZ, VPA
Learning disability	**All AEDs**	Behavior disorders	ALL AEDs: start low, go slow

PHB, phenobarbitone; PRM, primidone; LEV, levetiracetam; LTG, lamotrigine; TGB, tiagabine; TPM, topiramate; VGB, vigabatrin; DPH, phenytoin; ZNS, zonisamide; BZD, benzodiazepines; PGB pregabalin.

authors suggest that anticonvulsant drugs have different psychiatric effects depending on the pre-existing mental status of patients. They predict that patients who are primarily "activated" may benefit from drugs which belong to the "sedating" category and may become worse with "activating" drugs. On the other hand, patients who are primarily sedated would benefit from a drug from the "activating" category, while the same patients would worsen with a "sedating" anticonvulsant. Taking the primary psychopathological status of patients into account explains the sometimes unexpected and seemingly paradoxical effects of some AEDs in individual patients. Based on clinical experiences Table 13.4 suggests some "predictable" psychiatric AED risks depending on baseline psychopathology.

Forced normalization

The concept of forced normalization goes back to the publications of Landolt (Landolt 1958). Cases of FN or alternative psychiatric syndromes have been reported with all conventional and novel anticonvulsants but seem to be particularly common with the more potent drugs such as vigabatrin, topiramate, and levetiracetam. FN has rarely been reported with tiagabine and lamotrigine, and is extremely rare with gabapentin. There are no reports of FN in the context of treatment with zonisamide or pregabalin. The best known manifestation of FN is a psychotic state. However, in a consecutive series by Wolf and colleagues (1984), 50% of 36 patients presented with predominating affective symptomatology. FN is a complication not exclusively of AED treatment but of all successful therapeutic interventions including epilepsy surgery and vagus nerve stimulation. FN is rarely observed in new onset of epilepsy. Patients who develop FN usually suffer from long-lasting treatment-resistant epilepsies and experience a sudden and complete cessation of seizures.

Conclusions

The risk of psychiatric complications of AEDs is likely to be linked to the severity of epilepsy, polytherapy, rapid titration, and high dosages of drugs (Table 13.5). Patients with previous psychiatric problems or a familial predisposition seem to be especially prone to behavioral side effects. Other risk groups are children and adults with learning disabilities, and perhaps elderly patients. It is important to recognize patients at risk in order to inform them and their families about the possibility of psychiatric side effects. In these patients AEDs should be slowly titrated. Patients should be seen frequently and screened for behavioral or mood changes. When recognized at an early stage, psychiatric AED complications are mild and reversible in most cases. Risk factors for psychiatric complications are not a strict contraindication for any particular drug, and it is not always necessary to completely withdraw the responsible drug. Depending on the pathophysiology and the severity of the syndrome, a dose reduction or a comedication with an antipsychotic or antidepressive drug may be

Table 13.5 Recommendations for clinical practice

• Psychiatric adverse events are often overlooked (particularly affective disorders, forced normalization, and delayed effects)
• The two main recognized mechanisms are GABAergic effects in the development of AED-induced depression and seizure free forced normalization in patients (psychosis)
• The direction of psychotropic effects may be positive or negative depending on the patient's pre-existing mental state
• The vulnerability is different in specific patient groups, e.g. patients with learning disability, children, elderly
• Psychiatric adverse effects of AEDs may be related to epileptic syndromes and underlying pathology (e.g. increased depressogenic effects of GABAergic drugs in patients with hippocampal sclerosis)
• Psychiatric adverse events are usually reversible with appropriate management, which includes the adjustment of anticonvulsants and/or psychopharmacological treatment

a good compromise. The use of such medications is discussed in Chapter 16.

Behavioral drug effect profiles, both negative and positive psychotropic effects, ought to be considered in the choice of the optimal drug for an individual patient. There is a need for more studies specifically devoted to the psychiatric effects of AEDs in patients with epilepsy. We need these studies in order to identify patients at risk of severe behavioral reactions with specific drugs and also in order to identify patients who have a good chance of benefiting from potentially positive psychotropic effects of AEDs.

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Chapter 14

Antiepileptic drugs and suicide

Michael R. Trimble

Introduction

On the 23rd May 2008, the American Food and Drug Administration released its analysis on the relationship between anticonvulsant drugs (AEDs) and suicidal behaviors. This was an analysis of data following a request sent to manufacturers of AEDs for data from randomized parallel-arm placebo, low-dose placebo, and active control arm clinical trials. They analyzed data for 11 compounds, the endpoints being a range of behaviors from self-injurious behavior, suicidal ideation, and suicide attempt through to completed suicide. In total 199 placebo-controlled trials consisting of 27 863 patients were collated, and the drugs involved and the key forest plot are shown in Figure 14.1. There were four completed suicides; 0.37% of the drug-treated patients and 0.24% of placebo patients had a suicidal behavior.

As a result of this research, the FDA concluded that AEDs were associated with a risk of suicidality, that this was effectively a class effect, and from that point insisted that manufacturers included a warning in their data and information sheets on the potential for suicidality.

Epilepsy and suicide

There is an association between epilepsy and suicide which had been reviewed in previous communications, including the first edition of this book (Blumer 2004). It is accepted that the risk of suicide is increased in epilepsy, and that in some studies, patients with a temporal lobe focus have the highest risk (Barraclough 1981). These data are accumulated from epidemiological studies, but there are also anecdotal reports of suicidal behaviors noted as a complication of treatments, especially with the sudden cessation of seizures, as with the syndrome of Forced Normalization, and with postictal states of psychosis or depression (Kanemoto et al. 1996).

However, the relationship between epilepsy and suicide is more complicated in that recent epidemiological data has revealed that suicide attempts are themselves a risk factor for the development of epilepsy. Further, the risk of completed suicide in epilepsy is influenced by the comorbid presence or absence of psychiatric disorders (Hesdorffer et al. 2006; Christensen et al. 2007; Chapter 2).

The FDA alert has drawn attention to possible effects of AEDs on suicidal behaviors. This has stimulated several epidemiological investigations, and a search for possible mechanisms. These are reviewed in this chapter.

Antiepileptic drugs and suicide

Collins and McFarland (2008) compared suicidal behaviors in 12 662 bipolar patients treated with either lithium, gabapentin, carbamazepine, or valproate. Compared with lithium, there were higher reports of suicide attempts with valproate and higher rates of suicide completion with gabapentin. Goodwin et al. (2003) compared data on suicide attempts in 20 638 bipolar patients, and noted higher rates with valproate compared with lithium.

Gibbons et al. (2009) examined the data on lithium and the 11 AEDs selected by the FDA in association with suicide attempts in a database of 47 918 patients with bipolar disorder. They found no significant overall difference for the AED group compared with those not receiving one of the drugs or lithium. This held for the individual drugs, with the exception of topiramate and carbamazepine, which showed a greater post-treatment risk compared with no treatment, a finding also noted for lithium. The rate of

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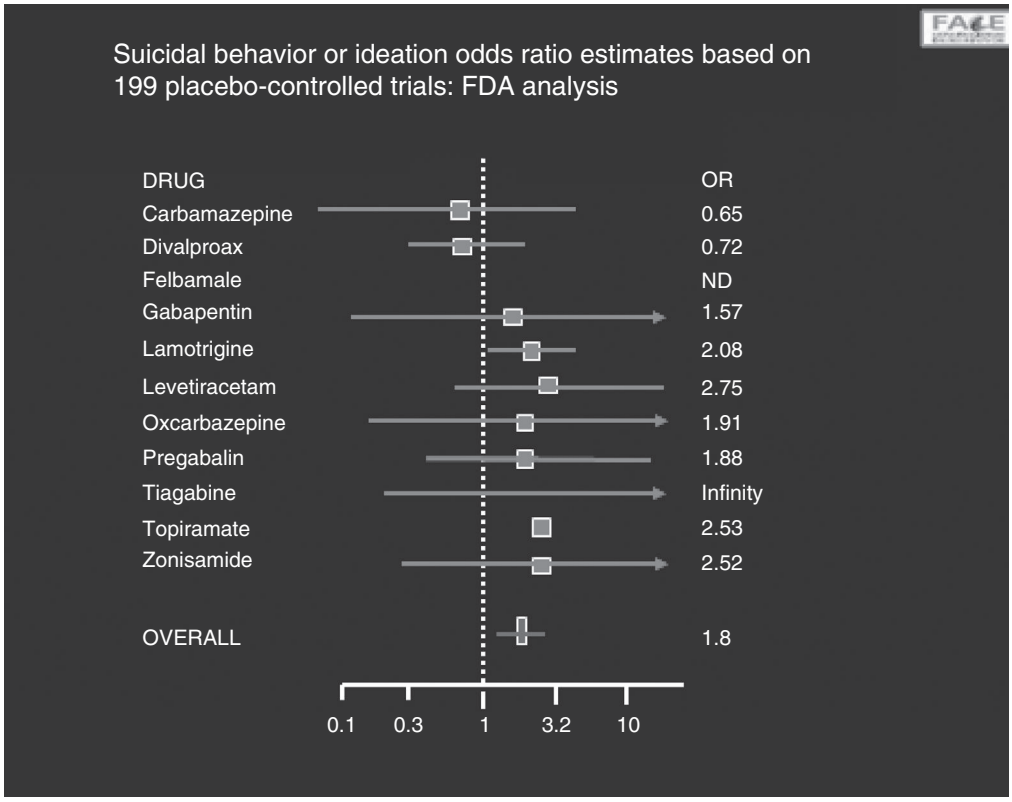

Figure 14.1. Forest plot as published by the FDA (2008) on the relationship between anticonvulsant drugs and suicidal behaviors.

suicide attempts was significantly lower in the time period after treatment compared with before treatment, although the authors failed to adjust for the course of bipolar disorder, a likely indication for the use of AEDs.

Patorno et al. (2010) also used a medical and pharmacy claims registry from the USA, choosing either topiramate or carbamazepine as reference drugs. Follow-up was 180 days after drug prescription, or until drug discontinuation, and suicide attempts, completed suicide, and violent deaths were identified. There were 297 620 new treatment episodes, with a variety of clinical indications for prescription. Compared to topiramate, gabapentin, lamotrigine, oxcarbazepine, tiagabine, and valproate were associated with a non-significant increased risk for attempted or completed suicide. Gabapentin was associated with a significantly higher risk of suicidal events, combined suicidal acts, and violent deaths.

Olesen et al. (2010) used linked patient databases from Denmark to identify 6780 suicides in a 10-year study period, 422 of which were receiving an AED at the time of death; in 86% this was as monotherapy. Comparing the period before suicide to the time of suicide, AEDs were associated with a 1.84 increased suicide risk. Those drugs with an increased odds ratio for suicide were gabapentin, clonazepam, valproate, lamotrigine, phenobarbital, and topiramate, significant for the latter four. Carbamazepine was associated with a lower risk. In a separate analysis, using carbamazepine as a reference drug, and a Cox proportional hazard analysis, they showed the risk to be significantly greater for clonazepam, lamotrigine, levetiracetam, phenobarbitone, and valproate.

All of these studies have been derived from databases (medical claims data or records linkage), which, while quite large in total, have dubious validity in terms of the data collected and were not collected in any systematized way. The Collins et al. and the Gibbons et al. studies were carried out in patients with bipolar disorder. The Danish study was more

inclusive, including patients with epilepsy, and used data more systematically collected and examined completed suicides, but failed to account for confounding by indication for prescription.

Neurochemical associations – depression

That there is a link between GABA and affective disorders has been discussed in biological psychiatry for years (Trimble and George, 2010). Lower CSF GABA levels have been found in patients with depression, and plasma GABA has been reported to be low in euthymic bipolar patients (Berrettini et al. 1983). Petty (1995) has outlined considerable evidence implicating GABA in the biochemical pathophysiology of mood disorders, including the animal models of depression which show regional brain GABA deficits. He opines that low GABA itself is not a marker for any particular mood state, but an inherited biological vulnerability marker for the development of mood disorders. When GABA levels are increased in those with low GABA, owing to interactions between GABA and serotonin, the increased GABA results in lowered release of serotonin from the raphe nuclei. This link between GABA and serotonin is well established in experimental neurobiology (Nishikawa and Scatton 1983; Bowery 1997), and this neurochemical shift in individuals with a prior mood disturbance or current mood disturbance has the potential to make adapting to anxiety or stress more difficult, provoking a further episode of depression (Petty 1995).

There are many studies linking the serotonin system to the regulation of affect, and the serotonin agonists, such as the selective serotonin reuptake inhibitors (SSRIs), are well known antidepressants (Trimble and George 2010). Early observations were that drugs which depleted the brain's reserves of monoamines (serotonin, dopamine, and norepinephrine, in particular) led to depression; that administration of precursor products of serotonin such as L-tryptophan and 5-hydroxytryptophan to patients and volunteers elevated mood; that in patients with Parkinson's disease depression was associated with low levels of CSF 5-HIAA; that drugs which are antidepressant (from the earlier introduced tricyclic drugs to the still widely used SSRIs) enhance serotonin activity; and that measures of serotonin turnover in the brain as measured by cerebrospinal fluid estimations of breakdown products revealed decreased release of serotonin in a subgroup of depressed patients (for further review of this field, see Trimble and George 2010).

The literature on links between serotonin and depression is paralleled by studies linking suicide to low serotonin turnover. This relationship has been observed many times, and is one of the most replicated in the whole of biological psychiatry. Patients with low turnover are more likely to die from suicide at follow-up, and similar biochemical findings are noted in impulsive alcoholic offenders, and people with aggressive personality disorders without depression (Trimble and George 2010). In post mortem samples of brains from those who have committed violent suicide, serotonin levels are interpreted as low (Stanley and Mann 1983; Mann and Malone 1997). Thus, the low serotonin or serotonin turnover relates not only to depressed affect but also to aggression, impulsivity, and suicidal behaviors.

More recent work on this association has confirmed the link between hostility, aggression, and low serotonin, to the extent of noting an inverse relationship between the serotonin levels and the measures taken of aggression (Stanley et al. 2000). These clinical data receive substantial support from investigations of rodents which link low serotonin with enhanced aggression (Miczek et al. 1975), and of non-human primates, in which reduced serotonin turnover is associated with severe forms of aggression and a greater frequency of high-risk behavior (Mehlman et al. 1994.)

These data reveal the importance of altered serotonin function in aggressive, violent behaviors which includes impulsive and suicidal acts. Further, the findings do not apply only to people with personality disorders, but also across a spectrum of psychiatric diagnoses. One hypothesis put forward is that the serotonin link to aggression is mediated via neuronal excitability in the amygdala, a structure known to be associated, along with frontal areas, with the circuitry linked with aggressive displays (Keele, 2005). In this model, serotonin is viewed as an activating system for inhibiting behavior, the former being impaired when serotonin levels are low.

In the biochemical studies of the biology of mood disorders, investigators have moved beyond a simple model of the one neurotransmitter–one disorder kind and now seek for interactions; and balances between monoamines, GABA, and other neurotransmitters such as glutamate are discussed. Glutamate is, in contrast to GABA, the brain's main excitatory transmitter. It is ubiquitous, it interacts with monoaminergic

output and in some brain regions there is a reciprocal interaction with GABA. Sanacora et al. (2004), in an MRI spectroscopy study, reported higher cortical levels of glutamate and lower GABA levels in patients with depression. Although there are a growing number of scientific papers on links between glutamate activity and mood, the results are less clear than the data with GABA and serotonin.

In summary, the neurotransmitters best established as related to suicidal behaviors (linked either through aggression, mood instability, or depression, or all three) are GABA and serotonin. Thus, a relationship especially between suicidal behaviors and drugs which affect the GABA and serotonin systems is predictable.

The neurochemistry of AEDs

The neurochemical systems noted above are influenced by many of the AEDs in clinical use, and may therefore be of relevance in understanding the FDA data. It has been noted from the epilepsy literature how AEDs that seem most likely to provoke affective disorders increase, in one way or another, CNS GABA (Schmitz 2006 and Chapter 13; Trimble and George 2010). Older agents such as the barbiturates and benzodiazepines have GABAergic properties and are associated with negative mood states, especially with prolonged use, in epilepsy and in nonepileptic patients (Schmitz 2006). One of the main neurochemical targets of antiepileptic drug development, especially in the 1980s, was GABA, based on an assumption that in epilepsy increasing CNS levels of the inhibitory neurotransmitter would have an antiseizure effect. Vigabatrin, tiagabine, gabapentin, and topiramate all increase CNS GABA, and some of these have also been shown to alter the turnover of monoamines, including serotonin.

There is much use of AEDs in psychiatric practice to stabilize mood disorders, and it is of interest that none of these GABAergic drugs has found use or been approved by regulatory authorities for the treatment of mood disorders in psychiatry, unlike for example carbamazepine or valproic acid. While the mechanism of action in epilepsy or in mood stabilization of these latter two compounds remains unclear, neither are considered to act via the GABA system, and the tricyclic structure of carbamazepine may confer some properties relevant to the mood stabilization.

There have been a number of studies of patients with epilepsy that link the prescription of AEDs to depression, although the etiology is often not well explored. Polypharmacy and the use of barbiturates were well known problems in the past (Schmitz 2002). Some of the standard AEDs, such as carbamazepine, appear to have been less associated with these problems, but it is with the introduction of a new generation of anticonvulsant drugs in the last 20 years that there has been a resurgence of interest in the association between epilepsy, antiepileptic drugs, and mood disorders.

The first of the new generation of AEDs reliably associated with depression as a treatment emergent effect was *vigabatrin*, a GABA transaminase inhibitor which significantly increased CNS levels of GABA (see below) (Thomas et al. 1996). More recently *tiagabine* and *topiramate* have also been associated with a similar spectrum of behavior changes in epilepsy, these drugs too increasing CNS GABA (Trimble and George 2010; Mula et al. 2003a). In this context it is interesting that drugs not acting on the GABA system, such as levetiracetam, appear to be much less associated with treatment emergent psychiatric problems, particularly depression, although suicide attempts are noted even with this drug (Mula and Sander 2007a,b). Further, when psychiatric problems emerge with these latter drugs, they are often in association with cessation of seizures, the phenomenon of alternative psychosis, linked with Forced Normalization of Landolt (Mula and Sander 2007a).

GABAergic antiepileptic drugs and suicide

Data from the placebo-controlled drug trials may be expected to give some information in this regard. However, the trials are set up to determine seizure-modifying effects, and not psychiatric events. Study subjects will have rating scales for side effects, such as COSTART data. However, in the published papers, it is usual to report only events monitored that occur in over a particular percentage of the population, such as 5% or even 10%. In the limited time of monitoring (usually only a few weeks), while depression is often noted, suicide and suicidal ideation fall below this level of reporting, even if increased above placebo figures. This is likely to lead to an underevaluation of these events in clinical trials.

Associations between antiepileptic drugs and attempted suicide have been noted associated with the ingestion of barbiturates (Hawton et al. 1980). Brent (1986) reported the high frequency with which adolescents with epilepsy presented to the emergency room having taken an overdose of barbiturates. Major depressive disorder was diagnosed in 40% on phenobarbitone, a known GABAergic agent, in contrast to only 4% on carbamazepine. In a study of gender differences of suicidal behavior in epilepsy, Kalinin and Polyanskiy (2005) observed that of 105 epileptic patients, the total daily dose of "classic" AEDs (phenobarbitone, phenytoin, and primidone) was not associated with suicidal behavior, whereas the daily dose of phenobarbitone alone was. This was noted in both males and females. In contrast, the daily dose of carbamazepine and sodium valproate was inversely correlated with such behaviors, in females only. These data tend to support associations between phenobarbitone and suicidal behaviors.

Regarding the new generation of AEDs, the data analyzed by the FDA has drawn attention to the link between suicidal behaviors and AEDs. In their analysis, those agents increasing brain GABA, which as noted may lead to negative effects on mood and behavior, seem prominent, and include gabapentin, tiagabine, topiramate, vigabatrin, and zonisamide.

Vigabatrin is a gabatransaminase inhibitor, associated with the development of depression (Ring et al. 1993). Levinson and Devinsky (1999) reviewed the US and non-US double-blind placebo-controlled studies for evidence of psychiatric side effects with this drug, and examined suicide attempts. Depression was identified as a treatment emergent effect in 12–20% on vigabatrin compared with 2.4–5.7% of placebo-treated patients. However, in that analysis, suicidal attempts were not elevated overall in the drug groups. In a separate analysis of psychiatric adverse events on vigabatrin, 0.4% of 2686 evaluated patients were noted to have attempted suicide. This can be compared with the frequency of such events given as 0.05% in patients not taking the drug, for example in the placebo wing of studies.

Tiagabine increases CNS GABA by acting as an inhibitor of neuronal GABA reuptake, acting at reuptake sites on presynaptic neurones. In clinical trials against placebo this drug was reported to cause increased nervousness and depression (12% v 3%: 5% v 1%), and was also associated with an increased reporting of psychoses (Schmitz 2006). Although cases of overdose are noted in the literature, the relationship of this drug to suicidal behaviors is unclear.

Gabapentin was developed to be a GABAergic compound. There is evidence that gapapentin alters GABA release or metabolism, although exactly how this occurs is unclear. Various investigators have noted effects in animal models, showing agonism at a subtype of GABAb receptor (Bertrand et al. 2001; Parker et al. 2004; Sills 2006). The drug has in addition been shown to increase the activity of GAD (involved in the synthesis of GABA), to decrease activity of GABA transaminase (the enzyme which breaks down GABA in the synaptic cleft), and to increase the release of GABA (Loescher et al. 1991; Gotz et al. 1993; Honmou et al. 1995). Explanations of the GABA effect have included alteration of GABA transporter proteins from the cytosolic pool to cell membranes, and a search for extrasynaptic receptor mechanisms.

Human studies using NMR spectroscopy have shown that gabapentin not only increases brain GABA concentrations in patients but also in volunteers (Petroff et al. 2000a; Kuzniecky et al. 2002).

Gabapentin administration has been shown to alter the turnover of serotonin in humans with CSF analysis of 5-HIAA, the breakdown product of serotonin. This effect was also found to be the case with one of the other GABAergic AEDs that led to a high frequency of depression, namely vigabatrin (Ben-Menachem et al. 1992; 1995).

The association between gabapentin and suicidal activity is suggested from the FDA analysis and backed up by some of the epidemiological data. Depression is a treatment emergent effect in 5% of patients, but aggressive behavior is also consistently reported especially in younger patients (Cugley and Swartz 1995).

Topiramate has several mechanisms of action. More specifically with regards to its effects on mood, it alters glutamate excitatory neurotransmission, but not at the NMDA (*N*-methyl-D-aspartate) receptor, which is the target of some antiepileptic compounds (such as felbamate), acting at kainate receptors (Gryder and Rogawski 2003). Topiramate is also GABAergic, acting at GABAa receptors, which, as already noted, can decrease serotonin activity in the raphe neurones. Thus while topiramate has not been shown in humans to alter serotonin turnover, it has the potential to do so.

Topiramate has a wide spectrum of adverse effects and psychiatric problems are a significant problem. The psychiatric problems relate not only to changes of mood, but also to clear effects on cognition. The latter include targeted side effects such as "thinking abnormal" or "concentration impaired" through to more obvious impairments on structured cognitive tests of particularly verbal memory tasks, and in some patients the onset of an aphasia (an acquired disorder of speech) and a decline in word fluency (Gomer et al. 2010; Mula et al. 2003a,b).

Mula et al. (2003b) analyzed the psychiatric adverse events in 431 patients with epilepsy who were prescribed topiramate. These occurred in 23.9% of the patients: in 10.7% this was an affective disorder, in 5.6% it was aggressive behavior, and 3.9% other behavioral abnormalities were noted, such as agitated behavior, anger, hostility, or anxiety. Demographic variables revealed that the patients who developed psychiatric adverse events were more likely to have a family history of a psychiatric disorder, a personal history of psychiatric disorder, and a higher dose and more rapid titration schedule. Of the patients who developed an affective disorder and aggressive behavior, only a minority became seizure free, and the depression developed with a median of 60 days following the initiation of the prescription. Nearly 50% of these patients required the institution of some psychiatric treatment.

The effect of topiramate on frontal lobe activity has been examined by *f*MRI combined with neuropsychological testing (Jansen et al. 2006). Relative to a control group, the topiramate-treated patients showed significant underactivation of the anterior areas of the left side of the brain, in the context of a significant underactivation of the whole brain. This was thought to be related to the GABA effect of topiramate, an increase shown with the MRI spectroscopy data from Petroff et al. (1999).

Specifically with regards to suicide, the following side effects are cited as "frequent" in patient information sheets provided by the manufacturers: impotence, hallucination, psychosis, and suicide attempt. Individual cases are reported in the literature (Faubion and Christman 2007). In the double-blind trials of topiramate, suicide attempts occurred at a rate of three per thousand patient years on topiramate versus nil on placebo. There was one completed suicide per thousand patient years (Topamax Macneil Neurologics Inc revised July 2005).

The interesting profile of toxicity with topiramate is in keeping with the known biochemical effects, but the clear effects on cognition, linked to alteration of frontal activity, may well relate to the effects on mood and suicidality.

Lamotrigine is generally regarded as a drug with mood stabilizing properties, and to have beneficial effects on behavior in epilepsy. It has wide use in psychiatric practice, especially in patients with bipolar disorder. There are reports of patients with learning disability developing outbursts of aggression (Schmitz, 2002), even with violent and self-injurious behaviors (Cardenas et al. 2010). While not usually discussed as associated with suicidal behaviors, it was included in the FDA analysis, with an odds ratio of 2.08. Even by the time of the FDA analysis, the manufacturers had included a warning regarding suicidality in their package inserts (Hesdorffer and Kanner 2009). In view of these comments on the associations between GABA and adverse effects on mood, it is of interest in this regard that the NMR spectroscopy studies of Petroff and colleagues noted that lamotrigine increased brain GABA, albeit less than gabapentin and topiramate (Petroff et al. 2000b).

Levetiracetam seems less associated with psychiatric adverse events than topiramate, but the psychiatric reactions when they occur can be severe, and include suicidal behaviors and psychoses (Mula et al. 2003c; Mula and Sander 2007b). The drug is not linked to GABA or serotonin effects, and is not used in psychiatric populations, and the data suggest that the more severe behavioral effects may be interlinked with seizure suppression and therefore the phenomenon of Forced Normalization.

One fact which emerged from several studies quoted above is that patients who become depressed with these agents often have in their histories earlier episodes of depressive disorders, and in some studies a family history of such disorders (Mula and Sander 2007a). These data suggest that some patients are more vulnerable than others to the development of these behavioral problems on account of biological predispositions.

Reaction to the FDA alert

Following the FDA alert, an update of 16 December that year required all manufacturers of the class of

drugs (which was quite ill defined) to include a warning about suicidal behaviors to patients and doctors, although the FDA's scientific advisory committee voted against instituting a black box. In view of the analysis undertaken by the FDA, several pharmaceutical companies had already by then altered their data and information sheets to include warnings about suicide-related events.

Hesdorffer and Kanner (2009) commented on three particular problems with the alert. These were that the adverse reaction data were not systematically collected; that the 11 drugs selected had different mechanisms of action and different relative risks, and they challenged the idea that they could represent a class; and that there would be problems of prescribing, such that epilepsy patients may withdraw from their drugs. The risk of death from uncontrolled seizures would probably outweigh the risk of death from suicide.

Bell et al. (2009) reviewed the literature on AEDs and suicidality in some detail. They pointed out the methodological flaws of studies in this area, especially with the confounding factors in epilepsy, such as Forced Normalization and social stigmatization. Noting that the majority of suicidal events are linked with mood disorders, especially depression, and that AEDs fell broadly into two groups, those that are sedating and those that are "activating," they highlighted the AEDs that act at the benzodiazepine-GABA receptor, the more sedating, as associated with depression, and hence associated with suicidal behaviors. In a discussion of the FDA data, they drew attention particularly to the figures for lamotrigine and topiramate, but noted that in both cases the majority of the patients were prescribed the drug for nonepileptic conditions.

What has become clear is that many neurologists treating epilepsy have little knowledge of the frequency of depression in their patients, and often have scant knowledge when it comes to detection, diagnosis, and treatment. It is now recommended that all patients with epilepsy should be routinely evaluated for depression, anxiety, and suicidality, and that, in clinical trials of AEDs, proper psychiatric evaluation is a part of the assessment, and validated behavioral rating scales be used as measurement (Hesdorffer and Kanner 2009). Attempts are being made at the time of writing to develop reliable, valid, user-friendly instruments for outpatient office use.

Summary

The above review leads to the following conclusions. First, AEDs can have negative effects on mood, and the reporting of disturbances of mood with certain drugs of this class is a well accepted scientific observation first made many years ago. These observations have been made mainly on people with epilepsy, but a similar profile of side effects occurs when AEDs are used in nonepilepsy populations. The FDA analysis has specifically drawn attention to suicidal behaviors, including completed suicide, that are associated with the prescription of at least some of these drugs.

Not all AEDs have the same neurochemical profile, and drugs most implicated are those which are GABAergic. This links with the literature in biological psychiatry, which has consistently shown an association between GABA and mood, and one potential intermediate link with suicidal behavior is through alteration of serotonin turnover.

Depression is only one of the psychiatric presentations associated with suicidal behaviors, but links have been shown between depression, attempted suicide, and completed suicide. A second important link of prescription of AEDs is with personality changes, including irritability, aggression, anxiety, dysphoria, hostility, impulsivity, and violent outbursts.

The adverse mood reactions seem more likely to occur in those with a past or a family psychiatric history of depression. They are not in most cases directly related to suppression of seizures (although suicidal behaviors can be seen as part of a psychosis in Forced Normalization).

One consequence of the FDA alert is that neurologists who treat epilepsy need to pay attention to psychiatric comorbidities. A further consequence is that the links between neurology and psychiatry are again emphasized and invigorated.

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Endnote

Since this chapter went to press two other epidemiological studies on the relationship between suicidal behaviors and AEDs have been published. The first by Andersohn et al. (2010) was a nested case–control study drawn from a cohort of patients from the British

General Practice Research Database who had epilepsy and were treated at some time with AEDs. In the study 453 cases with epilepsy and self harm or suicidal behavior were matched to 8962 controls on age, gender, and duration of the database data. Compared to no drug in the 14 days before the index date, AEDs which in the literature had been associated with depression were associated with a 3-fold increased risk for self harm and suicidal behavior; other AEDs not previously identified as linked with depression were protective. When individual drugs were examined only levetiracetam was associated with an increased risk for self harm or suicidal behavior. In the second paper Arana et al. (2010) also using a UK-based database (THIN) did a nested case–control analysis from a cohort of over 5 million patients. The use of AEDs was significantly associated with an increased risk among patients with depression and amongst patients who did not have epilepsy, depression, or bipolar disorder but were receiving the drugs for other conditions.

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Chapter

15 Antiepileptic drugs and cognitive disorders

Albert P. Aldenkamp

Introduction

Cognitive impairment is the most common comorbid disorder in epilepsy (Aldenkamp and Dodson 1990; Dodson and Pellock 1993). Memory impairments, mental slowing, and attentional deficits are the most frequently reported cognitive disorders (Dodson and Trimble 1994; Aldenkamp et al. 1995). Such consequences may be more debilitating for a patient than the seizures; thus, it is worthwhile to explore the factors that lead to cognitive impairment. The exact cause of cognitive impairment in epilepsy has not been explored fully, but three factors clearly are involved: etiology, the seizures, and the "central" side effects of drug treatment (Aldenkamp 2002). Here we concentrate on the unwanted effects of antiepileptic medication on cognitive function. When evaluating this factor separately, it is imperative to realize that in clinical practice most cognitive problems have a multifactorial origin and that, for the most part, the three aforementioned factors, combined, are responsible for the "makeup" of a cognitive problem in an individual patient. Moreover, the factors are related, which causes therapeutic dilemmas in some patients when seizure control can only be achieved with treatments that are associated with cognitive side effects.

The interest in the cognitive side effects of AED treatment is of recent origin. The possibility that cognitive impairment may develop as a consequence or aftermath of epilepsy was raised as early as 1885 when Gowers described "epileptic dementia" as an effect of the pathological sequela of seizures. Nonetheless the topic was not coupled to AED treatment until the 1970s (Ideström et al. 1972; Dodrill and Troupin 1977) probably stimulated by the widening range of possibilities for drug treatment during that period (i.e. the introduction of carbamazepine and valproate). Since then, a plethora of studies have been published, the majority on the commonly used AEDs: valproate (VPA), carbamazepine (CBZ), and phenytoin (PHT).

In the last decade, several new AEDs have been introduced. Although it is claimed that these drugs have different efficacy profiles and that some drugs are particularly efficacious in specific syndromes (e.g. vigabatrin [VGB]), head-to-head comparisons between the new AEDs and between the newer drugs and the commonly used drugs (such as CBZ and VPA) are rare. Nonetheless, meta-analyses such as the influential Cochrane reviews (Marson et al. 1997; Jette et al. 2002) do not show significant differences in efficacy between the newer drugs or between newer and commonly used drugs. Also, studies analyzing long-term retention do not show differences between the drugs (Wong 1997; Stefan et al. 1998).

Several studies have shown retention rate to be the best parameter of the long-term clinical usefulness of a particular drug (Lhatoo et al. 2000). Retention rate is considered to be a composite of drug efficacy and drug safety and expresses the willingness of patients to continue drug treatment. It is therefore the best standard for evaluating the clinical relevance of side effects. The 1-year retention rate is reported to be not higher than 55% for topiramate (TPM) (Kellet et al. 1999), 60% for lamotrigine (LTG), 58% for VGB, and 45% for gabapentin (GBP) (Marson et al. 2000). Long-term (mostly 3-year) retention is about 35% for all newer AEDs (Marson et al. 2001). Side effects appear to be the major factor affecting long-term retention for most drugs (Chadwick et al. 1996; Aldenkamp 2001). In clinical practice, tolerability is therefore a major issue and the choice of a certain AED is at least partially based on comparison of

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tolerability profiles of the drugs. Also, the tolerability profiles of the newer drugs have become a more important issue in drug development, stimulated by the interest of regulatory agencies (Aldenkamp 2001). Cognitive side effects have been demonstrated to be one of the most important tolerability problems in chronic AED treatment.

Method

In evaluating studies of the cognitive effects of AEDs, we will follow an evidence-based approach (Vermeulen and Aldenkamp 1995; Aldenkamp et al. 2003). Randomized clinical trials with monotherapy in patients with newly diagnosed epilepsy represent the most accurate procedure for assessing the cognitive impact of AEDs (Aldenkamp 2001). These studies are not clouded by the effect of concurrent or previous AED use and permit the accurate collection of nondrug baseline data that is required for determining whether a particular treatment affects cognitive processing (i.e. to isolate drug-induced impairments from those due to other sources such as the seizures). Data from such studies can be supplemented with information from studies using add-on or polytherapy designs. In these studies, the use of two AEDs makes identifying the components of the treatment that are responsible for the observed effects more complex. In many cases, however, patients with epilepsy require dual AED therapy before adequate seizure control is obtained; therefore, data from add-on studies does warrant consideration. Also, data from healthy volunteers should be treated with caution. In general, the power of such studies is limited by small sample sizes, and drug-exposure periods are typically brief. It is possible that chronic treatment results in entirely different types of cognitive impairment that cannot be observed during short-term treatment. For example, such differences in side effect profile between acute and long-term administration have been found with PHT. Finally, the differing cerebral substrate in patients with epilepsy and healthy volunteers suggests that cognitive responses to AEDs may be different in these populations. Nonetheless, volunteer studies may provide an early insight into the cognitive effects of an AED and therefore provide a foundation for further studies in patients with epilepsy (see Vermeulen and Aldenkamp 1995 for a discussion of methodological aspects of cognitive drug trials in epilepsy).

Results

Phenobarbital (PB)

The main anticonvulsant mechanism of action is the increase of the duration (not the frequency) of the GABA-activated chloride ion channel opening (Twyman et al. 1989), hence potentiating GABA-mediated inhibitory neurotransmission. PB can also activate the GABAa receptor in the absence of GABA, which is sometimes considered to be a mechanism leading to its sedative properties.

One study is available allowing the evaluation of the cognitive effects of PB relative to a nondrug condition (MacLeod et al. 1978). This study shows relatively serious memory impairment (short-term memory recall) in 19 patients with epilepsy.

Comparisons with other AEDs are available from four studies (Vining et al. 1987; Calandre et al. 1990; Meador et al. 1990; Gallassi et al. 1992), all with patients with epilepsy. One of these shows more impairment for PHB than for phenytoin (PHT) or carbamazepine (CBZ) on visuomotor and memory tests (Gallassi et al. 1992) and two other studies show convincing and clinically highly relevant impairments of intelligence scores after long-term PHB treatment in comparison with valproate (VPA) (Vining et al. 1987; Calandre et al. 1990). Only the study by Meador et al. (1990) does not show differences between PHB and PHT or CBZ.

Phenytoin (PHT)

The main anticonvulsant mechanism of action is use-dependent (voltage and frequency dependent) sodium channel blocking (Schwarz and Grigat 1989). It binds to the fast inactivated state of the channel, reducing high frequency neuronal firing. PHT has a stronger effect on the sodium channel than CBZ, delaying recovery longer than CBZ. PHT may also have mild effects on the excitatory glutamate system and on the inhibitory GABA system.

For PHT five studies are available (Smith and Lowrey 1975; Thompson et al. 1980; 1981; Meador et al. 1991; 1993) comparing PHT with a nondrug condition. These studies all reveal PHT-induced cognitive impairment in the areas of attention, memory, and especially mental speed. The magnitude of the reported effects is moderate to large. A caveat is, however, in order as all these studies were carried out in normal volunteers, which opens up the

possibility that these effects represent short-term outcomes of the drug.

The results of head-to-head comparisons with other AEDs are somewhat more confusing. Using an ingenious long-term treatment and withdrawal design, Gallassi and coworkers (Gallassi et al. 1992) found more cognitive impairments than with CBZ. On the other hand, no differences with CBZ, VPA, and even with PHB have also been reported (Meador et al. 1990; 1991; 1993; Forsythe et al. 1991).

Ethosuccimide (ESX)

ESX modifies the properties of voltage-dependent calcium channels, reducing the T-type currents and thereby preventing synchronized firing. The reduction is most prominent at negative membrane potentials and less prominent at more positive membrane potentials. Most effect is assumed to take place in thalamocortical relay neurones. ESX was introduced in 1960 and mainly used for the treatment of generalized absence seizures. No controlled studies are available to evaluate the cognitive effects of ESX.

Carbamazepine (CBZ)

The main anticonvulsant mechanism of action is similar to that of PHT with a less "slowing" effect in the recovery state than obtained for PHT. The mechanism of action is also voltage and frequency dependent.

For CBZ two studies, one in normal volunteers (Thompson et al. 1980) and one in patients with epilepsy (Aldenkamp et al. 1993) report "no cognitive impairment" compared to a nondrug condition. This is challenged by Meador and coworkers (1991; 1993) who report impairments of memory, attention, and mental speed, largely the areas that may also be affected by phenytoin.

When evaluating the comparisons of CBZ with other AEDs there are the conflicting results of the Italian study by Gallassi and coworkers, which showed a more favorable profile compared with PHT and PHB (Gallassi et al. 1992), and the US-based study by Meador and coworkers (Meador et al. 1990; 1991; 1993), which showed no differences compared with PHT and PHB.

Valproate (VPA)

VPA, a fatty acid, is believed to possess multiple mechanisms of action. A number of studies have demonstrated an effect on sodium channels, which is different from that of PHT and CBZ. An effect on T-type calcium channels has also been demonstrated. Recent studies have demonstrated that a predominant effect concerns the interaction with the GABAergic neurotransmitter system. More precisely, VPA elevates brain GABA levels and potentiates GABA responses, possibly by enhancing GABA synthesis and inhibiting degradation. Furthermore, VPA may augment GABA release and block the reuptake of GABA into glia cells. VPA is one of the most effective drugs against generalized absence seizures.

For VPA, three studies (Thompson and Trimble 1981; Craig and Tallis 1994; Prevey et al. 1996) allowed the interpretation of absolute effects and showed mild to moderate impairment of psychomotor and mental speed. The comparison with other drugs showed lower performance of memory and visuomotor function compared to CBZ (Gallassi et al. 1992) and a favorable profile compared to PHB on tests for intelligence (Vining et al. 1987; Calandre et al. 1990). One study did not show a difference with PHT (Forsythe et al. 1991).

Oxcarbazepine (OXC)

OXC is essentially a prodrug, a keto homolog of CBZ, structurally very similar to CBZ, but with a different metabolic profile. In humans, the keto group is rapidly and quantitatively reduced to form a monohydroxy derivative that is the main active anticonvulsant agent during OXC therapy. Metabolism of OXC does not result in the formation of 10,11-epoxy-carbamazepine, which is sometimes considered to be the main metabolite causing side effects. The mechanism of action is similar to CBZ. However, OXC is also considered to reduce presynaptic glutamate release, possibly by reduction of high-threshold calcium currents.

The effects of OXC on cognitive function have been evaluated in one study in healthy volunteers and in four studies in patients with epilepsy. A double-blind, placebo-controlled, crossover study was conducted in 12 healthy volunteers (Curran and Java 1993). The effects of two doses of OXC (300 mg/day and 600 mg/day) and placebo on cognitive function and psychomotor performance were assessed. The treatment duration for each condition was 2 weeks. Cognitive function tests were administered before treatment initiation and 4 hours after the morning doses on days 1, 8, and 15. In this study, OXC

improved performance on a focused attention task, increased manual writing speed, and had no effect on long-term memory processes.

In patients with epilepsy, four monotherapy comparative studies are available to evaluate the effects of OXC on cognitive functions in adult patients with newly diagnosed epilepsy. The first study (Laaksonen et al. 1985) was a double-blind, active-control study evaluating the effects of CBZ and OXC on memory and attention in 41 patients with newly diagnosed epilepsy. The treatment duration was 1 year. Cognitive function and intelligence tests were administered before treatment initiation and after 1 year of treatment. The results indicated no deterioration of memory or attention with either CBZ or OXC. The second study was an active-control study that evaluated the effects of CBZ, VPA, and OXC on intelligence, learning and memory, attention, psychomotor speed, verbal span, and visuospatial construction in 32 patients with newly diagnosed epilepsy (Sabers et al. 1995). The treatment duration was 4 months. Cognitive function and intelligence tests were administered before treatment initiation and after 4 months of treatment. The results indicated no deterioration of cognitive function in any treatment group. Significant improvements in learning and memory tests were found for the CBZ- and OXC-treated patients. Improvements were also found in attention and psychomotor speed tests for the VPA-treated patients and partly for the CBZ-treated patients.

The third study was a double-blind, randomized, active-control study that evaluated the effects of PHT and OXC on memory, attention, and psychomotor speed in 29 patients with newly diagnosed epilepsy (Äikiä et al. 1992). The treatment duration was 1 year. Cognitive function tests were administered before treatment initiation and after 6 and 12 months of treatment. The results indicated no significant differential cognitive effects between PHT and OXC during the first year of treatment in patients with newly diagnosed epilepsy who achieved adequate seizure control.

In the fourth study (McKee et al. 1994), three groups of 12 patients taking either CBZ, VPA, or PHT took a single 600 mg dose of OXC followed 7 days later by 3 weeks of treatment with OXC 300 mg thrice daily and matched placebo in random order. Seven untreated patients, acting as controls, were prescribed the single OXC dose and 3 weeks of active treatment only. There were no important changes in cognitive function test results during administration of OXC compared with placebo.

In summary, the results of these studies indicate that OXC does not affect cognitive function in healthy volunteers and adult patients with newly diagnosed epilepsy. The effects of OXC on cognitive function have recently been studied in children and adolescents and also showed a favorable profile (Donati et al. 2006; 2007).

Topiramate (TPM)

TPM is a sulfamate-substituted monosaccharide that has clearly multiple mechanisms of action (White, 1997). TPM blocks neuronal sodium channels in a voltage- and frequency-dependent manner, it inhibits calcium channels, it promotes the action of GABA at the GABAa receptor complex, and it elevates GABA brain concentrations by about 60% at 3 and 6 hours after a single dose; this increase was maintained with 4 weeks of TPM administration (Petroff et al. 1996). TPM is a carbonic anhydrase-inhibiting drug.

During the initial add-on clinical trials, central nervous system-related "cognitive" subjective complaints were frequently reported, including mental slowing, attentional deficits, speech problems, and memory difficulties (Privitera et al. 1996). It should be mentioned, however, that higher target doses and faster titration schedules were used than are now common in clinical practice (see Faught et al. 1996 for a discussion of dose and titration speed). Recent studies with TPM-treated patients have confirmed high levels of adverse cognitive effects based on subjective complaints (Ketter et al. 1999; Tatum et al. 2001). A follow-up study (Bootsma et al. 2004) showed long-term retention of 30% for a 4-year follow-up. For about half of the 70% of patients who discontinued treatment, side effects were the major reason, with cognitive side effects being most frequently mentioned.

Only a few studies have psychometrically measured cognitive changes using neuropsychological tests. A study by Martin et al. in six normal volunteers (Martin et al. 1999) used an acute dose of 2.8 mg/kg (~200 mg/day) followed by a titration to 5.7 mg/kg (~400 mg/day) in 4 weeks, resulting in weekly dose escalations of about 100 mg. The rate at which TPM was escalated in this study was very similar to the dose escalation used in the initial TPM adjunctive therapy trials (Privitera et al. 1996), in which escalating the

TPM dose to 200 or 400 mg/day over 2–3 weeks was associated with somnolence, psychomotor slowing, speech disorders, and concentration and memory difficulties (Bootsma et al. 2004). Martin et al. (1999) showed neuropsychometric changes commensurate with these CNS effects. The cognitive effects of the acute starting dose of 200 mg/day were impairments of verbal function (word finding and verbal fluency) of approximately 2 standard deviations (which represents very serious impairment) and of sustained attention. Titration to 400 mg/day in 4 weeks resulted in impairments of verbal memory and mental speed of >2 standard deviations.

Five studies involving patients with epilepsy are available. In a study by Meador (1997) with 155 patients with epilepsy, the effects of the gradual introduction of TPM as add-on (a 50 mg starting dose, followed by increments of 50 mg per week over 8 weeks) were compared with those of more rapid dose escalation (initial dose of 100 mg, followed by two consecutive weekly increments of 100 and 200 mg). In a test battery of 23 variables representing selective attention, word fluency, and visuomotor speed, the subjects who were on a slow-titration schedule and treated with one background AED displayed TPM-associated score changes of more than one-third but less than one standard deviation.

A study by Aldenkamp et al. (2000) was specifically designed to compare cognitive effects of TPM and VPA added to therapeutic dosages of CBZ in 59 patients with epilepsy. In this study, a slow titration rate was used with a starting dose of 25 mg/day TPM, and weekly increments of 25 mg. Moreover, the average achieved dose (approximately 250 mg) was relatively low. Neuropsychometric testing was conducted 8 weeks after the last dosage increase (20 weeks after the start of TPM therapy). The study therefore used optimal conditions (i.e. slow titration, relatively low dose, and a longer treatment period), allowing for patient habituation to the effects of TPM therapy. Nonetheless, cognitive impairment was found for verbal memory function both during titration and at end point.

In a study by Burton and Harden (1997), attention was assessed weekly in 10 subjects receiving TPM over a 3-month period. In one subject the exact dose was not known, but four of the nine remaining subjects showed significant correlations between TPM dosage and forward digit span measured weekly, such that higher dosage was associated with poorer attention.

In a retrospective study by Thompson et al. (2000), the neuropsychological test scores of 18 patients obtained before and after the introduction of treatment with TPM (median dose 300 mg) were compared with changes in test performance of 18 patients who had undergone repeat neuropsychological assessments at the same time intervals. In those patients taking TPM, a significant deterioration in many domains was found. The largest changes were for verbal IQ, verbal fluency, and verbal learning.

In an open, prospective study, 41 patients with intractable epilepsy initially received either TPM or tiagabine (TGB) as add-on treatment. Of these, 21 patients were assessed at baseline, after a 3-month titration phase, and after a 3-month maintenance phase. The patients were assessed on various aspects of cognitive functioning such as attention, memory, language, and self-report mood and quality of life. The TPM group performed worse on measures of verbal fluency and working memory and reported more depression than the TGB group. They also felt that they were suffering from more adverse effects due to the TPM medication. However, TPM patients did report an increase in mental flexibility between titration and maintenance phase (Fritz et al. 2005).

In summary, there is clear clinical evidence for TPM-induced cognitive impairment. Not all studies are comparable because of the confusion about dose and titration speed (see Aldenkamp 2000 for a discussion). Moreover, the complete lack of controlled studies is remarkable.

Lamotrigine (LTG)

LTG is a phenyltriazine with weak antifolate activity. The main anticonvulsant mechanism of action is to block voltage-dependent sodium channels that result in voltage- and frequency-dependent inhibition of the channel. This suggests that the mechanism of action is similar to that of PHT and CBZ. However, much attention has focused recently on the fact that this mechanism in LTG treatment results in preventing presynaptic excitatory neurotransmitter release. It is still in debate to what extent the mechanisms of action are different from CBZ (Leach et al. 1995).

A large number of cognitive studies are available for LTG (see Aldenkamp and Baker 2001 for an overview). Five volunteer studies have been conducted with LTG. Doses of 120 mg and 240 mg did

not produce a significant change in cognitive function compared with baseline when administered to 12 normal volunteers in an acute study of 1 day (Cohen et al. 1985). Similarly, five volunteers received LTG (acute dose 3.5 mg/kg and then titrated to a maximum of 7.1 mg/kg) in a single-blind manner and were assessed for change in cognitive function after 2 and 4 weeks (Martin et al. 1999). There was no significant change in any of the neurocognitive measures relative to baseline performance.

LTG and CBZ have been compared in 12 healthy male volunteers and associations were made between the observed cognitive effects and plasma concentrations of these drugs (Hamilton et al. 1993). The effects of these drugs were examined by means of adaptive tracking, which assesses eye-hand coordination and effects of attention, and eye movement tests. LTG treatment was not significantly different from placebo, but increased CBZ saliva concentrations were significantly associated with impaired adaptive tracking and smooth and saccadic eye movements.

The long-term effects of LTG and CBZ were compared in 23 volunteers in a 10-week crossover study (Meador et al. 2000). The neuropsychological battery in this study consisted of 19 instruments yielding 40 variables, including both subjective and objective measures. LTG showed better performance or fewer side effects in 17 (42%) of the variables, while no statistically significant differences were seen in the remaining variables.

Finally, a study by Aldenkamp et al. (2002) in 30 volunteers (12 days of treatment, using a daily dose of 50 mg of LTG) showed evidence for a selective positive effect of LTG on cognitive activation, relative to both placebo and VPA. Although the results of these volunteer studies provide us with preliminary insight into the impact of LTG on cognition, the generalizability of the results from these studies to patients with epilepsy receiving long-term AED treatment is limited.

The effects of LTG on cognitive function have been compared with those of CBZ in patients with newly diagnosed epilepsy. Patients completed tests of verbal learning and memory, attention, and mental flexibility at baseline and then periodically for up to 48 weeks. Significant differences favoring LTG over CBZ were observed with semantic processing, verbal learning, and attention (Gillham et al. 2000). The authors concluded that LTG may have a favorable long-term effect on cognitive function when compared with CBZ.

Other studies have reported positive cognitive effects of LTG used as adjunctive therapy. Two independent double-blind, randomized, crossover studies have examined the cognitive effects of LTG used as add-on therapy (Smith et al. 1993; Banks and Beran 1991). Both studies included patients with a history of partial seizures (at least once weekly during the preceding 3 months) who had received no more than two other AEDs or VPA monotherapy. Both studies also used two treatment periods (12 and 18 weeks), which were separated by a washout period (4 and 6 weeks). Despite the similarity in trial design and patients, there is some inconsistency between the findings of these two studies. One study showed a marginal reduction in general "cerebral efficiency" (an indirect measure of cognitive function) following LTG treatment (Banks and Beran 1991). Conversely, significant improvements were reported in the second study (Smith et al. 1993). In an uncontrolled add-on study (Aldenkamp et al. 1997) using CBZ as baseline drug, no deterioration on any of the cognitive tests was found after introducing LTG (200 mg).

LTG therapy in seven patients with epilepsy and mental retardation has been reported to lead to both positive and negative psychotropic effects (Ettinger et al. 1998). These findings were based on the observations of parents and supervising staff. Positive effects included reduced irritability and increased compliance with simple instructions, while negative effects included behavioral deterioration with temper tantrums, restlessness, and hyperactivity. Similarly, a second study in 67 patients with mental retardation showed that following adjunctive treatment with LTG, social functioning was stable or improved in 90% of patients (Earl et al. 2000).

In addition to clinical studies that have assessed the impact of LTG on cognitive function, further evidence can be obtained from examining the effect of LTG on electroencephalographic (EEG) parameters. Overt EEG discharges can occur without any visible clinical correlate in many patients with epilepsy. These epileptiform episodes may be associated with transient deterioration in cognitive function (see Chapter 5; Aarts et al. 1984; Aldenkamp et al. 2001). Data from several studies indicate that LTG may reduce spontaneous epileptiform discharges, which may partially explain the favorable cognitive profile of LTG. In five patients displaying spontaneous EEG discharges, a single dose of LTG (120 mg or 240 mg in addition to existing medication) resulted in

a substantial reduction in spontaneous interictal discharges within a 24-hour period (Binnie et al. 1986).

The long-term effects of LTG on paroxysmal abnormalities have also been monitored with a computer-based analysis system (Marciani et al. 1996). Twenty-one patients with intractable epilepsy (20 of whom were receiving multiple AED therapy) were evaluated before and after LTG treatment for EEG ictal events and number of spikes in a 10-minute period. Before LTG treatment, patients typically showed discharges characterized by diffuse spike-wave complexes. However, following a 4-month treatment period with LTG, ictal discharges disappeared and diffuse slow wave activity was seen with no adverse effect on background activity. Nineteen of the 21 patients also showed a reduction in seizure frequency.

The effect of LTG add-on therapy in 11 patients with refractory partial seizures with or without secondary generalization has also been reported (Marciani et al. 1998). LTG was added to existing therapy consisting of CBZ with at least one additional AED. EEG recordings were made at rest with eyes closed, during an attentive task (blocking reaction induced by several episodes of eyes open lasting 8–9 seconds), during cognitive tasks, and while performing mental arithmetic. In addition, a battery of neuropsychological tests was carried out. Before LTG treatment, EEG data revealed a decrease in fast activity at rest and a reduction in alpha and beta bands during attentive and cognitive tasks. LTG treatment resulted in a selective increase in alpha reactivity and beta power during the attentive tasks with no other detectable changes. During cortical activation, subtle changes were observed that were taken as indicative of a slight improvement in attention. Neuropsychological evaluation revealed that following 3 months of LTG therapy, no deterioration in cognitive function had occurred.

LTG also shows a promising cognitive profile in elderly patients suffering from age-associated memory impairment (Mervaala et al. 1995). A neuropsychological test battery in combination with auditory event-related potentials (ERPs) was used to measure the impact of LTG on cognitive function. LTG treatment caused a reduction in amplitude of the P_{300} component of the ERP and a corresponding improvement in immediate and delayed visual memory and delayed logical memory. LTG may therefore improve simple memory functions in a memory-impaired elderly population.

Levetiracetam (LEV)

LEV is a new AED, structurally and mechanistically dissimilar to other AEDs. It is believed to bind to a specific, as yet undetermined, site on the synaptic plasma membrane. Moreover LEV seems to reduce the GABA turnover in the striatum by reducing GABA synthesis and increasing GABA metabolism.

With regards to its impact on cognitive function, we only have data from a small pilot study that does not allow definite conclusions (Neyens et al. 1995). An international (UK/The Netherlands) cognitive study is at present being carried out. In this study a first-line add-on design is being used, comparing the cognitive effects of LEV with CBZ and VPA.

Tiagabine (TGB)

Tiagabine (TGB) is a γ-aminobutyric acid (GABA) uptake inhibitor that is structurally related to the prototypic GABA uptake blocker nipecotic acid, but has an improved ability to cross the blood–brain barrier. TGB temporarily prolongs the presence of GABA in the synaptic cleft by delayed clearance. Three cognitive studies are available.

Dodrill et al. (1997) included 162 patients who received the following treatments: placebo (N=57), 16 mg/day TGB (N=34), 32 mg/day TGB (N=45), or 56 mg/day TGB (N=26) at a fixed dose for 12 weeks after a 4-week dose titration period. Eight cognitive tests and three measures of mood and adjustment were administered during the baseline period and again during the double-blind period near the end of treatment (or at the time of dropout). The results showed no cognitive effects of monotherapy with TGB at a low or high dose, but there was some evidence for mood effects of add-on treatment with TGB at higher dosing, possibly related to titration speed.

In the add-on polytherapy study by Kälviäinen et al. (1996), 37 patients with partial epilepsy were included. The study protocol consisted of a randomized, double-blind, placebo-controlled, parallel-group add-on study and an open-label extension study. During the 3-month double-blind phase at low doses (30 mg/day), TGB treatment did not cause any cognitive changes as compared with placebo. TGB treatment also did not cause deterioration in cognitive performance during longer follow-up with successful treatment on higher doses after 6 to 12 months (mean 65.7 mg/day, range 30–80 mg/day)

and after 18 to 24 months (mean dose 67.6 mg/day, range 24–80 mg/day).

Finally, Sveinbjornsdottir et al. (1994) carried out an open trial of 22 adult patients with refractory partial epilepsy followed by a double-blind, placebo-controlled, crossover trial in 12 subjects. Nineteen patients completed the initial open titration and fixed-dose phase of the study and 11 patients completed the double-blind phase. The median daily TGB dose was 32 mg during the open fixed-dose period and 24 mg during the double-blind period. Neuropsychological evaluation did not show any significant effect on cognitive function in the open or double-blind phase.

Gabapentin (GBP)

GBP is a cyclic GABA analogue, originally designed as a GABA agonist (Macdonald and Kelly, 1995). Further research has clearly shown a specific effect of GBP on GABAergic neurotransmitter systems, especially influencing GABA turnover. Investigations using nuclear magnetic resonance imaging spectroscopy have confirmed that GBP elevates GABA concentrations, specifically in the occipital cortex of patients with epilepsy (Petroff et al. 1996).

Two volunteer studies and one clinical study are available to interpret the cognitive effects.

Martin et al. (1999) used an acute dose and rapid titration in six volunteers and did not find cognitive effects of GBP. Meador et al. (1999) compared the cognitive effects of GBP and CBZ in 35 healthy subjects by using a double-blind, randomized, crossover design with two 5-week treatment periods. During each treatment condition, subjects received either GBP 2400 mg/day or CBZ (mean 731 mg/day). Subjects were tested at the end of each AED treatment period and in four drug-free conditions (two pretreatment baselines and two post-treatment washout periods [1 month after each AED]). The neuropsychological test battery included 17 measures yielding 31 total variables. Significantly better performance on eight variables was found for GBP, but on no variables for CBZ. Comparison of CBZ and GBP with the nondrug average revealed significant statistical differences for 15 (48%) of 31 variables.

Leach et al. (1997) studied GBP in 21 patients in an add-on polytherapy study after 4 weeks of adjunctive therapy and found no change in psychomotor and memory tests. Drowsiness was more often found in higher dosing (2400 mg). Mortimore et al. (1998) did not find a difference between continued polytherapy and an add-on with GBP in measures of quality of life.

Zonisamide (ZNS)

ZNS has multiple mechanisms of action: blockade of voltage-gated sodium channels, reducing sustained repetitive firing, blocking T-type calcium channels, and inhibiting ligand binding to the GABAa receptor. ZNS is also a carbonic anydrase-inhibiting drug.

Clinical anecdotal information shows a cognitive side effect profile very similar to TPM but no controlled studies are available. Also no information is available about ongoing studies.

Rufinamide (RUF)

Rufinamide is a structurally novel compound which limits the frequency of sodium-dependent neuronal action potentials. One study is available to assess the cognitive effects (Aldenkamp and Alpherts 2006). The study used a multicenter, multinational, double-blind, randomized, placebo-controlled parallel study design with four different doses of rufinamide (based on prior studies): 200 mg/day, 400 mg/day, 800 mg/day, and 1600 mg/day as add-on to the existing medication. Cognitive assessments were performed at baseline (before starting rufinamide treatment) and at endpoint (after 3 months of treatment). The most important finding was that for none of the cognitive tests was a statistically significant worsening found for any of the doses of rufinamide when the period after 12 weeks of treatment was compared with the baseline before introducing rufinamide. Also none of the comparisons between dose and placebo showed a statistically significant difference.

Conclusion

A general conclusion that may be derived from most of the meta-analyses that have considered the association between AEDs and cognitive function (Vermeulen and Aldenkamp 1995) is that polypharmacy shows a relatively severe impact on cognitive function when compared with monotherapy, irrespective of the type of AEDs included. Two drugs that individually have mild cognitive effects may induce serious cognitive impairment when used together, possibly because of potentiation of tolerability problems (Trimble 1987).

Possibly the most remarkable finding is that, although the severity of cognitive side effects is generally considered to be mild to moderate for most AEDs (Vermeulen and Aldenkamp 1995), all commonly used AEDs have some impact on cognitive function. Such a mild impact may be amplified in specific conditions and may become substantial in some patients when crucial functions are involved, such as learning in children (Aldenkamp et al. 1995) or driving capacities in adults (often requiring millisecond precision), or when functions are impaired that are already vulnerable, such as memory function in the elderly (Trimble 1987). Moreover, the cognitive side effects represent the long-term outcome of AED therapy; therefore, the effects may increase with prolonged therapy, which contributes to the impact on daily life functioning in refractory epilepsies (American Academy of Pediatrics 1985).

Definite evidence for drug-induced cognitive impairment has been established for phenobarbitone (memory impairment), phenytoin (mental slowing), and topiramate (mental slowing and dysphasia). Treatment with these drugs should consider these side effects and patients should be monitored on a regular basis. Mild effects (mostly psychomotor slowing) were found for carbamazepine, oxcarbazepine, valproate, and lamotrigine (with mild cognitive activating effects). The effects for ethosuximide, tiagabine, gabapentin, levetiracetam, and zonisamide are inconclusive.

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Chapter 16

Psychiatric illness and psychotropic medication use in epilepsy

Jane V. Perr and Alan B. Ettinger

Introduction

Since antiquity, medical practitioners have noted an association between epilepsy and psychiatric illness (Reynolds and Trimble 2009). This complex relationship is well-described in preceding chapters and the first edition of this book. In this discussion, we now focus upon treatment considerations.

Because of a fear of lowering the seizure threshold or inducing clinically significant interactions with antiepileptic drugs (AEDs) by using psychotropic medications, many clinicians fail to adequately treat psychiatric illness in people with epilepsy (PWE). Yet, the excessively high risk of suicide in PWE compared with the general population highlights in stark terms one example of the enormous cost of inadequate treatment (Bell and Sander 2009).

The paucity of controlled studies investigating the use of psychiatric medications in this population only compounds the fears of clinicians. Premarketing trials of psychotropic medications regularly exclude populations of medically ill individuals, including PWE. Postmarketing observations pool data from varied patient populations in which confounding variables that might independently lead to increased seizures are not properly identified, thereby skewing any interpretation of the data. Seizures as an outcome of medication overdose do not necessarily provide useful information regarding the potential of medications to lower the seizure threshold prescribed at therapeutic doses. There are some clinically significant interactions between AEDs themselves and between AEDs and psychotropic medications. Nonetheless, there appears to be little justification for the extreme hesitation many clinicians feel about using many of the available psychotropic medications in the context of epilepsy. Although AEDs can have numerous negative psychotropic effects, many of them have also become established treatments for affective disorders or have been used off-label to treat a variety of psychiatric symptoms like aggression, anxiety, irritability, and impulsivity and therefore must be considered in any discussion of psychotropic medications.

In this chapter, we touch upon evidence for underlying shared pathogenic mechanisms in epilepsy and psychiatric disorders, as it has direct implications for the safety and efficacy of psychotropic medications in the context of epilepsy. Then these medications will be discussed in the context of the psychiatric illnesses for which they are used as treatments. Because they are the most common and their complex relationship with epilepsy the most studied, affective disorders, anxiety disorders, psychoses, and, finally, attention-deficit hyperactivity disorder (ADHD) will be discussed. We will examine the potential impact of psychotropic medications on the seizure threshold, their efficacy in PWE, their adverse drug reactions (ADRs), and drug–drug interactions (DDIs). Because of the paucity of controlled studies involving PWE, decisions regarding psychotropic regimens are often made by analogy to treatment response data from the more researched general population.

Depression

From a treatment perspective, it is necessary to first differentiate primary depression from the iatrogenic depressive effects of the AED regimen. Benzodiazepines (Grabowska-Grzyb et al. 2006), phenytoin (Ettinger 2006), primidone (Lopez-Gomez et al. 2005) and other barbiturates (Ettinger 2006), levetiracetam (Mula and Sander 2007), and topiramate (Mula and Trimble 2003; Mula et al. 2009a) have been associated with causing depression and

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dysphoria. Depending on the time course for the appearance of the depressive symptoms and the necessity to maintain the current regimen, a change in dose or change in AED would be merited before considering antidepressants (ADs). Among the AEDs, lamotrigine has been FDA-approved for maintenance treatment of bipolar I disorder and has demonstrated significant mood-enhancing properties in PWE (Kalogjera-Sackellares and Sackellares 2002; Ettinger et al. 2007; Fakhoury et al. 2007; Weisler, Calabrese et al. 2008; Labiner, Ettinger et al. 2009). Although there are no double-blind, randomized trials examining the efficacy of AEDs in treating depression in PWE, limited clinical data suggest the possible utility of lamotrigine in treating comorbid depression. Since the 1980s, numerous studies have demonstrated the efficacy of clonazepam for depression (as monotherapy or adjunctively with ADs), for the acute treatment of unipolar and bipolar depression and in preventing relapses and recurrences. However, clinicians tend to avoid using benzodiazepines in epilepsy because of tolerance and concern about potential withdrawal effects. In one 10-year study, 80% of patients with depression for whom clonazepam had been discontinued experienced recurrences compared to the 26.7% who had continued it (Morishita 2009). While oxcarbazepine (Mazza et al. 2007) appears to have mood-enhancing properties as well, there is significantly less supporting clinical data. Limited case series (Harden et al. 2000) and extrapolation from the psychiatric literature in primary depression suggest that the vagus nerve stimulator may have positive psychotropic effects (Rush et al. 2000).

AEDs can affect the metabolism of co-prescribed medications that affect mood, through inhibition or induction of CYP450 isoenzymes, altering their blood levels.

Since some AEDs can contribute to depression (see Chapters 13 and 14), before considering the addition of an AD, if possible, a change in the AED regimen or co-prescribed substrate medication should be attempted first (Besag 2000). In patients on an AED the discontinuation of an enzyme inhibiting AED will cause a reversal of the inhibition of a substrate's metabolism, causing a reduction in its blood levels, while the removal of an inducing AED will cause a gradual reversal of the induction of a substrate's metabolism and the subsequent increase in its blood levels (Armstrong et al. 2003).

Seizure induction

The unfortunate elevation of anecdote over science (Dailey and Naritoku 1996) has caused many clinicians to avoid prescribing ADs for fear of lowering the seizure threshold and has delayed further scientific inquiry into the role serotonin (5-HT) and norepinephrine (NE) deficiencies play in epileptogenesis (Jobe and Browning 2005). (For a general review of the role of 5-HT and epilepsy, see Bagdy et al. 2007.) Early studies implicating ADs as causing seizures are problematic. Pisani and colleagues (Pisani et al. 1999) presented several reasons for the variability of their results and the inherent difficulties in meaningfully comparing them. The assumption that any occurrence of a seizure or increase in seizure frequency had to be causally related to the concurrent use of psychotropic medications in therapeutic doses failed to consider other potential etiologies, such as AEDs themselves (Greenwood 2000; Somerville 2002; Gayatri and Livingston 2006), the inherent risk psychiatric illness confers, and, finally, the relationship of dosage to convulsant liability and those factors which increase AD blood levels, such as potential DDIs and patient-status as a "poor metabolizer" (Dailey and Naritoku 1996).

Many animal studies have demonstrated dose-dependent anticonvulsant properties of ADs, for example: desipramine (Yan et al. 1998); imipramine (Macedo et al. 2004; Smolders et al. 2008); doxepin (Sun et al. 2009); fluoxetine (Yan et al. 1994; Browning et al. 1997; Wada et al. 1999); citalopram (Smolders et al. 2008); mirtazapine (Yilmaz et al. 2007), and milnacipran (Borowicz et al. 2009), among others. Some ADs have shown contradictory results, particularly fluoxetine (Zienowicz et al. 2005; Freitas et al. 2006; Mostert et al. 2008). It has been postulated that at higher doses and in overdoses, other mechanisms, such as local anesthetic, antimuscarinic, and antihistaminic properties (Dailey and Naritoku 1996) reverse the anticonvulsant action seen at lower doses. Antagonism of histamine$_1$ (H_1) receptors has been potentially implicated in lowered seizure thresholds (Scherkl et al. 1991; Jobe and Browning 2005; Ago et al. 2006), as have increases in hippocampal glutamate (Glu), facilitated by higher/toxic doses of monoamines (Clinckers et al. 2004).

Selective serotonin reuptake inhibitor (SSRI)-induced hyponatremia, possibly through a drug-induced Syndrome of Inappropriate Antidiuretic

Hormone Hypersecretion (SIADH), is another potential epileptogenic mechanism (Degner et al. 2004; Flores et al. 2004; Maramattom 2006).

Clinical studies confirm the anticonvulsant properties of ADs. In one notable open-label, add-on trial of fluoxetine as an adjunctive AED (Favale et al. 1995), 35% (6/17) of patients experienced a complete cessation of their daily seizures, while the remaining 65% experienced a reduction in seizure frequency of 30%. In an extended account of this study, Albano et al. also discussed a similar study using citalopram (Favale et al. 2003; Albano et al. 2006), demonstrating again a significant decrease in seizure frequency (mean reduction of 64%) in nondepressed patients with refractory epilepsy.

By reviewing the FDA data from the Summary of Basis Reports, Alper et al. (2007) convincingly showed that psychiatric conditions by themselves confer a risk for seizure development, an effect in the past erroneously attributed to the psychotropic medications treating them. Popli et al. (1995) identified psychotropic medications as the etiological agent for less than 0.1% of inpatients' seizures during a 30-month period in a psychiatric hospital. Another study (Gross et al. 2000) reported that only 23% of their patient group experienced an increase in seizure frequency, while the remainder either had improvements (33%) or no change (44%) in seizure control. In a study of sertraline (Kanner et al. 2000), 6% experienced an increase in seizure frequency. A definitive causal relationship could only be demonstrated for one patient, while no patients experienced an increase of seizure frequency on paroxetine.

The association of TCAs (tricyclic and related antidepressants) with seizure induction has largely been fostered by reports of seizures with overdoses and toxic blood levels. Other than clomipramine, the associated rate of seizures with TCAs at therapeutic dosages (and blood levels) has been estimated to be 0.1%, which is close to the rate of unprovoked seizures in the general population (0.061%) (Levenson 2008). Clomipramine has been associated with a dose-dependent rate of 0.7% (Mylan Pharmaceuticals 2007a) and therefore is typically not used in PWE, though not contraindicated. In a study by Alper et al., clomipramine as a treatment for obsessive-compulsive disorder (OCD) was associated with an increased seizure incidence relative to placebo of 4.08 (Alper et al. 2007), likely involving higher doses than those typically needed to treat depression. According to its premarketing information, maprotiline was associated with an incidence of seizures of "less than 1/10 of 1%" (Mylan Pharmaceuticals 2007b), yet it is also not typically used in PWE. Although no figures are provided in the professional information for amoxapine (Watson Laboratories 2007), it is advised that "extreme caution" be exercised in prescribing amoxapine to PWE. Monoamine oxidase inhibitors (MAOIs) do not confer a risk of seizure induction (Trimble 1978); however, their use has become third-line because of the risk of hypertensive crises precipitated by ingesting foods rich in tyramine (Kanner and Gidal 2008). A dopamine-norepinephrine reuptake inhibitor, bupropion, has also been associated with an increased risk of seizures, depending upon dose and formulation. With the IR formulation, the rate is 0.4% with doses up to 300–450 mg/day, while the rate drops to 0.1% with the SR formulation at doses of 300 mg/day, as it avoids high peak concentrations (Dunner et al. 1998; Fava et al. 2005). Perhaps reflecting medico-legal concerns, bupropion is generally avoided in treating depression in PWE unless there are no other options. SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with a risk of *de novo* seizures of $\leq$0.1% (Trimble and Hensiek 2002).

Efficacy

The SSRIs and SNRIs have largely supplanted the use of the older antidepressants, the TCAs and MAOIs, because of their more favorable side effect profile and relative safety, both in overdose and in the presence of other medical illnesses like cardiovascular disease. There have been a few trials examining the efficacy of SSRIs in the treatment of depression in PWE but no randomized controlled trials (RCTs) and experience with the SNRIs has been even more limited.

Kanner et al. (2000) demonstrated the efficacy of sertraline in treating depressive disorders in PWE, finding that 54% experienced a complete remission, including those with iatrogenic depressions secondary to necessary AEDs. For those who needed but did not respond to higher doses, switching to paroxetine brought about a remission.

Citalopram has also been shown to be effective in treating interictal depressive disorders, with a response rate of 65% at 8 weeks (Hovorka et al. 2000), leading to marked or moderate improvement in 67% and complete remission in 18% (Specchio et al.

2004). Kühn et al. found that citalopram, mirtazapine, and reboxetine were all effective in treating major depressive disorder (MDD) over a 2-year inpatient course in patients with temporal lobe epilepsy (TLE), with response rates at weeks 20–30 of 36.4%, 51.9%, and 53.3% and remission rates at weeks 20–30 of 21.2%, 14.8%, and 20.0%, respectively (Kühn et al. 2003).

Blumer presented a series of case histories of PWE diagnosed with the epilepsy-specific disorder, interictal dysphoric disorder (IDD) (see Chapter 9), who were successfully treated with low dose TCAs and, if necessary, combined with SSRIs (generally a variety of TCAs and paroxetine or fluoxetine), without apparently causing an increase in seizure frequency, serious ADRs, or DDIs (Blumer 1997; Blumer et al. 2004). Barry and Jones questioned whether Blumer's IDD might represent a "subsyndromal depressive disorder," presenting as residual symptoms in the course of partially treated idiopathic depressions, which can over time increase the risk of relapses into diagnosable depressive syndromes. They noted that combining antidepressants with different mechanisms has long been a common strategy for treating refractory depression (Barry and Jones 2005), its success, in Blumer's cases, deriving from the synergistic effect of combining serotonergic and noradrenergic ADs.

A similar advantage might be expected from using SNRIs, dual mechanism agents; however, there is controversy over the degree to which they have sufficient noradrenergic effect to truly be considered SNRIs (Gillman 2007) and whether they actually confer advantages over SSRIs (Burke 2004). In their study, Papakostas and colleagues reviewed the combined results of 97 trials of these drugs in depression, and found that the newer SNRIs conferred a "modest" advantage over SSRIs, with response rates of 63.6% over 59.3% (Papakostas et al. 2007). An earlier study by Nelson et al. suggested that efficacy was enhanced or time to remission was reduced by combining fluoxetine and desipramine (Nelson et al. 2004). While citing the value of being able to independently adjust the contribution of serotonergic and noradrenergic effects by using combinations of SSRIs and TCAs rather than one dual action agent, Gillman called attention to the need for expertise in attempting this, given the ability of SSRIs to dramatically raise blood levels of TCAs through their inhibition of CYP450 isoenzymes (Gillman 2007).

Because of the limited experience with SNRIs such as venlafaxine and duloxetine, SSRIs are presently first-line treatments for depression in PWE with TCAs as third-line after SNRIs. If TCAs are used, they should be started at low doses and increased gradually, with periodic serum levels as guides to the titration and to identify "slow metabolizers" (Kanner and Gidal 2008). Of the SSRIs, sertraline, paroxetine, citalopram, and escitalopram have been studied the most in patients with epilepsy.

Adverse drug reactions

The side effect profile for TCAs and MAOIs led to their relative abandonment in favor of using SSRIs. As discussed earlier, use of MAOIs is complicated by the potential for a hypertensive crisis if tyramine-rich foods are ingested. The dietary restrictions affect compliance and the potential lethality of these blood pressure elevations in a population with significant suicidal ideation makes their use daunting. Though lethality in overdose is typically cited as a reason for avoiding TCAs, there is some controversy concerning this as well. Gillman found that the toxicity of nortriptyline is considerably less than other TCAs and than venlafaxine. Deaths from overdoses of nortriptyline were similar to those from SSRI overdoses (5.5 deaths per million scripts) and less than from venlafaxine (13.2 deaths per million scripts) (Gillman 2007).

As a class, TCAs are more poorly tolerated because of side effects resulting from the antagonism of a variety of receptors in addition to their therapeutic effects. Muscarinic blockade leads to anticholinergic side effects like dry mouth, constipation, urinary hesitation/retention, exacerbation of narrow-angle glaucoma, blurred vision, tachycardia, memory impairment, and confusion. The blockade of α_1-adrenoreceptors leads to postural hypotension, dizziness, reflex tachycardia, and potentiation of the antihypertensive agents that act at that receptor. Antagonism of the H_1 receptor can cause both weight gain and sedation. Blockade of NE reuptake is responsible for tremors, tachycardia, blockade of the hypertensive effects of certain peripherally acting antiadrenergic agents, and augmentation of the pressor effects of sympathomimetic amines. Blockade of 5-HT reuptake can lead to gastrointestinal complaints, sexual dysfunction, and a state of excessive 5-HT, the "serotonin syndrome," characterized by changes in mental status, agitation, myoclonus, hyper-reflexia, fever, shivering, diaphoresis, ataxia, and diarrhea (Richelson 2003; Schatzberg 2007).

The SSRIs have captured the market for AD treatment in part because of their more tolerable side effect profile and presumed safety in overdose. They clearly can cause the side effects associated with the blockade of 5-HT reuptake discussed above. Because of their significantly lower muscarinic and α-adrenergic blockade, they cause fewer of the anticholinergic or cardiovascular side effects detailed above. Paroxetine, however, does have significant affinity for muscarinic receptors, 0.93, midway between imipramine at 1.1 and desipramine at 0.5 (Richelson 2003) and therefore can be expected with dose increases to cause more anticholinergic side effects. The most serious side effects in one study for SSRIs were agitation, hyponatremia, increased liver enzymes, and serotonin syndrome (Degner et al. 2004), while the most "bothersome" side effects were weight gain, gastrointestinal symptoms, insomnia, and sexual dysfunction. In a study of geriatric patients, though SSRIs were associated with lower rates of discontinuation, between 17% and 21% found the side effects "intolerable" (Wilson and Mottram 2004). Venlafaxine has been associated with dose-related increases in blood pressure in the IR form, anxiety, insomnia, nausea, dizziness, dry mouth, somnolence, and sexual dysfunction, while duloxetine has been associated with nausea, dry mouth, fatigue, insomnia, dizziness, and constipation (Schatzberg 2007).

Drug–drug interactions

The most usual DDIs are pharmacokinetic, generally involving changes in metabolism through effects on the CYP450 enzyme system, or pharmacodynamic, the additive, synergistic, or antagonistic actions of two drugs. Most psychotropic medications and AEDs are substrates of (metabolized by) isoenzymes in the CYP450 system and some can affect the action of these isoenzymes through either their induction or inhibition, as alluded to earlier. Table 16.1 summarizes substrates, inhibitors, and inducers of the most pertinent isoenzyme families. At their usual therapeutic doses, TCAs and SNRIs have a minimal effect on the action of the CYP450 isoenzymes; however, they can as substrates be impacted by other medications which inhibit or induce the enzymes responsible for their metabolism. Because TCAs have a more narrow therapeutic index (Nemeroff et al. 2007), changes in their blood levels can have more clinically significant effects, either with diminishing efficacy or increasing toxicity. In their study, Billups and coworkers demonstrated that elevated or toxic levels of TCAs were associated with increasing TCA dose (doses $\geq$150 mg/day), female gender, and concurrent use of either fluoxetine or paroxetine, both potent CYP2D6 inhibitors, while concurrent use of other SSRIs (sertraline and citalopram specifically) and buproprion, all weaker CYP2D6 inhibitors, were not factors (Billups et al. 2009).

The enzyme-inhibiting AED valproate can cause clinically significant elevations in various TCAs by as much as 50–60% (Fleming and Chetty 2005; Kanner and Gidal 2008). Enzyme-inducing AEDs, like carbazamepine, phenytoin, phenobarbital, and primidone, can lead to decreases in effective blood levels (Spina and Perucca 2002). Increasing the dose of a TCA to accommodate for this metabolic effect would be most safely done by checking the antidepressant blood levels. If an enzyme-inducing AED is removed from a regimen, a previously well-tolerated dose may become toxic from decreased metabolism, suggesting the importance of blood levels or downward adjustments in the TCA dose prior to AED discontinuation (Armstrong et al. 2003).

SSRIs can have clinically significant effects on the action of the CYP450 isoenzymes and can alter blood levels of AEDs and other psychotropic medications. Fluvoxamine, a potent inhibitor of CYP2C9, and CYP2C19, can cause significant elevations in phenytoin (Mamiya et al. 2001) and in both olanzapine (Weigmann et al. 2001) and clozapine (Koponen et al. 1996; Peritogiannis et al. 2005), through potent inhibition of CYP 1A2. Better studied in PWE, sertraline is a weak inhibitor of CYP 450, 1A2, 2C9, and 2C19 and a moderate inhibitor of 2D6 and 3A4 but there are few reported significant interactions (Spina et al. 2003). One case report detailed a 3-fold increase in valproate blood levels leading to toxicity with the addition of 100 mg of sertraline (Spina and Perucca 2002), while two cases of toxic elevations of lamotrigine, through inhibition of its glucuronidation, have been reported (Kaufman and Gerner 1998). However, Reimers and colleagues found that only fluoxetine significantly altered blood levels of lamotrigine and could not replicate the findings regarding sertraline (Reimers et al. 2005).

Sertraline has demonstrated a dose-dependent inhibition of the metabolism of CYP2D6 substrates, with doses of 50, 100, and 150 mg leading to a 20%, 30%, and 64% increase in the area under the curve

Table 16.1 Pharmacologic inhibitors and inducers of psychotropic metabolism by the CYP system[1]

CYP	Substrates			Antidepressant inhibitors	Other inhibitors		Inducers
1A2	Amitriptyline Clomipramine Clozapine Cyclobenzaprine Duloxetine Estinyl estradiol Fluvoxamine	Haloperidol Imipramine Mexiletine Mirtazapine Olanzapine Ondansetron Pentazocine	Tacrine Tizanidine Verapamil Warfarin Zileuton Zolmitriptan	Fluvoxamine Paroxetine*	Amiodarone Cimetidine Fluoroquinolones Methoxsalen Mibefradil Ticlopidine		Inhaled smoke Insulin Modafinil Nafcillin Omeprazole Phenobarbital Rifampicin
2B6	Bupropion Cyclophosphamide	Efavirenz Ifosfamide	Methadone		Thiotepa Ticlopidine		Phenobarbital Rifampicin
2C8	Amodiaquine Cerivastatin	Paclitaxel Repaglinide	Torsemide		Gemfibrozil Glitazones	Montelukast	Rifampicin
2C9	Amitriptyline Celecoxib Diclofenac Fluoxetine Fluvastatin Glipizide Glyburide	Meloxicam Nateglinide Phenytoin Piroxicam Irbesartan Losartan	Rosiglitazone Tamoxifen Tolbutamide Torsemide Sertraline Warfarin	Fluoxetine* Fluvoxamine	Amiodarone Fluconazole Fluvastatin Isoniazid Lovastatin Phenylbutazone Probenecid	Sulfamethoxazole Sulfaphenazole Teniposide Ticlopidine Trimethoprim Zafirlukast	Phenobarbital Rifampicin Secobarbital
2C19	Amitriptyline Carisoprodol Citalopram Clomipramine Cyclophosphamide Diazepam	Escitalopram Fluoxetine Hexobarbital Imipramine Indomethacin	Lansoprazole Mephenytoin Phenytoin Primidone Sertraline	Fluoxetine* Fluvoxamine	Chloramphenicol Cimetidine Felbamate Indomethacin Ketoconazole Lansoprazole	Modafinil Omeprazole Oxcarbazepine Ticlopidine Topiramate	Carbamazepine Norethindrone Prednisone Rifampicin

Table 16.1 (*cont.*)

CYP	Substrates			Antidepressant inhibitors	Other inhibitors		Inducers
2D6	Amitriptyline Amphetamine Aripiprazole Atomoxetine Carvedilol Chlorpheniramine Chlorpromazine Citalopram Clomipramine Desipramine Duloxetine Encainide	Escitalopram Flecainide Fluoxetine Fluvoxamine Haloperidol Metoclopramide Metoprolol Mexiletine Mirtazapine Nortriptyline Olanzapine Ondansetron	Paroxetine Perphenazine Phanothiazines Propafenone Risperidone Sertraline Tamoxifen Thioridazine Timolol Tramadol TCAs Venlafaxine	Bupropion Citalopram* Duloxetine Fluoxetine Fluvoxamine Paroxetine	Amiodarone Celecoxib Chlorpheniramine Chlorpromazine Cimetidine Clemastine Clomipramine Cocaine Diphenhydramine Doxepin Doxorubicin Halofantrine	Haloperidol Hydroxyzine Levomepromazine Methadone Mibefradil Moclobemide Quinidine Ritonavir Terbinafine Thioridazine Ticlopidine Tripelennamine	Dexamethasone Rifampicin
2E1	Chlorzoxazone Dapsone Enflurane Halothane	Isoflurane Isoniazid Sevoflurane Venlafaxine			Disulfiram		Isoniazid
3A4/5/7	Alfentanil Alprazolam Amitriptyline Amlodipine Aripiprazole Astemizole Atorvastatin Benzodiazepines Buspirone Cafergot Carbamazepine	Ergotamine Escitalopram Ethinyl estradiol Ethosuximide Etoposide Felodipine Fentanyl Finasteride Fluconazole Fluoxetine Haloperidol	Omeprazole Ondansetron Paclitaxel Paroxetine Pimozide Progesterone Quetiapine Reboxetine Risperidone Salmeterol Sertraline	Fluvoxamine Nefazodone	Amiodarone Aprepitant Chloramphenicol Cimetidine Ciprofloxacin Clarithromycin Diethyl-dithiocarbamate Diltiazem Erythromycin Fluconazole	HIV protease inhibitors Itraconazole Ketoconazole Macrolide antibiotics Mibefradil Mifepristone Nefazodone Norfloxacin Verapamil	Barbiturates Carbamazepine Efavirenz Glucocorticoids Modafinil Nevirapine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampicin

Table 16.1 (*cont.*)

CYP	Substrates			Antidepressant inhibitors	Other inhibitors	Inducers
3A4/5/7	Cerivastatin Chlorpheniramine Cisapride Citalopram Clarithromycin Clomipramine Clozapine Cocaine Cyclosporine Dapsone Diazepam Dihydropyridine calcium channel blockers Diltiazem Docetaxel Doxycycline Eplerenone	HIV protease inhibitors Hydrocortisone Ifosfamide Imatinib mesylate Imipramine Irinotecan Isradipine Itraconazole Lidocaine Loratadine Lovastatin Methadone Midazolam Mirtazapine Nefazodone	Sildenafil Simvastatin Sirolimus Tacrolimus Tamoxifen Telithromycin Testosterone Trazodone Triazolam Venlafaxine Verapamil Vincristine Zaleplon Ziprasidone Zolpidem		Gestodene	Troglitazone

*Weaker inhibitor; however, higher doses may affect the CYP sufficiently to cause drug–drug interaction.
CYP – cytochrome P450; TCAs – tricyclic antidepressants.
[1]Reprinted with permission from Ereshevsky, L. (discussant) and D. M. Sloan (interviewer) (2009). "Q & A: drug–drug interactions with the use of psychotropic medications." *CNS Spectr* (Suppl 8), p. 4.

(AUC), respectively, compared to a 500% increase with fluoxetine and paroxetine (Nemeroff et al. 2007). Because of its extensive half-life and potential for potent interactions, fluoxetine is not generally the first-line SSRI used with PWE. Paroxetine similarly inhibits CYP2D6 but has a much shorter half-life than fluoxetine (Brosen et al. 1993; Ashton 2000; Spina et al. 2002). Citalopram (Baettig et al. 1993; Ashton 2000; Brosen and Naranjo 2001; Moller et al. 2001; Kuhn et al. 2003; Specchio et al. 2004) and its less studied single *S*-isomer, escitalopram, appear to cause few pharmacokinetic DDIs. Venlafaxine does not appear to have significant effects on CYP450 isoenzymes (Ereshefsky 1996). (For helpful reviews, see Patsalos and Perucca 2003a; 2003b; Spina et al. 2003; Perucca 2005; Kanner and Gidal 2008. For a regularly updated CYP450 chart of interactions on the internet, see Flockhart 2007.)

Pharmacodynamic interactions between AEDs and ADs are also important to consider, particularly when they share undesirable ADRs like sedation and weight gain. Valproate, gabapentin, vigabatrin, and, to a lesser extent, carbamazepine have been associated with weight gain (Greenwood 2000), as have TCAs, paroxetine, fluvoxamine, and, to lesser extents, sertraline, fluoxetine, citalopram, and escitalopram. Because both carbamazepine and oxcarbazepine can cause hyponatremia (Gates 2000), care should be taken when combined with SSRIs.

Anxiety disorders

Because anxiety disorders occur comorbidly with depression, as well as independently, and are treated with many of the same psychotropic medications, they will be discussed here. Numerous studies document the tendency for greater psychopathology and more severe symptoms, poorer response to treatment, longer time to remission and more chronicity, poorer overall functioning, and higher prevalence of suicide (Keller et al. 2005) when the two disorders are comorbid in nonepileptic patients (Coryell et al. 1988; Joffe et al. 1993). Studies have demonstrated that appropriate treatment with ADs can improve symptoms of both (Brown et al. 1996; Mohamed et al. 2006). PWE demonstrate a higher prevalence of anxiety (20.5% vs. 13.9%) than in the general population (Mensah et al. 2007) and its presence is an independent factor influencing the health-related quality of life (HRQOL), along with depression (Johnson et al. 2004), though the two are often comorbid. As with depression, anxiety occurs in relationship to ictal events. Distinguishing panic disorder (PD) from epilepsy, especially TLE, can be particularly challenging with misdiagnosis leading to inappropriate treatment in both directions (Weilburg et al. 1987; Bernik et al. 2002; Sazgar et al. 2003; Saegusa et al. 2004; Deutsch et al. 2009). Often undiagnosed, OCD occurs more frequently in individuals with TLE than in the general population (Monaco et al. 2005) and may even develop *de novo* after the onset of epilepsy (Kettl and Marks 1986). Certain AEDs have been associated with the development of anxiety such as primidone (Lopez-Gomez et al. 2008), felbamate, and topiramate (Vazquez and Devinsky 2003). (For a review of anxiety in PWE, see Beyenburg et al. 2005.)

Aside from psychological and psychosocial factors predisposing to their development (de Souza and Salgado 2006), anxiety disorders likely share underlying neurobiological mechanisms with epilepsy in a bidirectional relationship (Kanner 2009). Animal models, preclinical studies, and drug trials implicate the central NE and 5-HT systems, as well as those of γ-aminobutyric acid (GABA) and possibly Glu. Klein's demonstration in 1964 that imipramine could completely eliminate panic attacks in agoraphobic patients confirmed the role of the noradrenergic systems (Sullivan et al. 1999). Since that time it has been convincingly shown, by the efficacy of other TCAs and SSRIs, that serotonergic deficits are also involved. While 5-HT_{1A} receptor agonists are anxiolytic (Kim and Gorman 2005), 5-HT_{2A} receptor antagonists are anxiolytic. As well, antidepressants decrease the density of these receptors with chronic administration. The relative balance between 5-HT and NE systems serves a regulatory function that when disturbed leads to mood and anxiety disorders. Serotonergic neurones in the dorsal raphe can inhibit the locus coeruleus, whereas its noradrenergic neurones can excite the serotonergic soma in the dorsal raphe. By restoring serotonergic tone via this mechanism, SSRIs may decrease the discharges from the locus coeruleus, which are excitatory to the amygdala, a part of the brain intimately involved in anxiety. SSRIs may also cause allosteric changes in GABAa receptors that facilitate its binding, possibly through their effect on the synthesis of neurosteroids like allopregnanolone (Czlonkowska et al. 2003). Through their impact on the *N*-methyl D-aspartate (NMDA) receptor, SSRIs may also modulate the glutamatergic

system, as anxiety may also represent an imbalance between inhibitory GABA systems and the excitatory Glu systems (Kent et al. 2002). Benzodiazepines (BZDs) achieve their therapeutic action through binding to the GABAa receptor with α_2-subunits (only 15% of all diazepam-sensitive GABAa receptors), whereas their anticonvulsant effect, memory impairment, and sedation require binding with α_1-subunits (Mohler et al. 2002), suggesting again the close relationship between epilepsy and anxiety. An AED with significant anxiolytic properties, pregabalin inhibits the release of excitatory neurotransmitters like glutamate by modifying calcium ion channels of excited presynaptic neurones (Garner et al. 2009).

Efficacy

The treatment of anxiety disorders has been studied less than depressive disorders in PWE. SSRIs, particularly sertraline, citalopram, and escitalopram, are the first-line treatments for all the anxiety disorders, followed by the SNRIs. Venlafaxine has received FDA approval for treatment of generalized anxiety disorder (GAD) but there is less experience with this population. As there have been no RCTs examining the efficacy of these medications in PWE, choices are guided by analogy to the general population and by considering safety and tolerability. (For a review, see Hoffman and Mathew 2008.) TCAs are very effective in treating anxiety disorders but, as for depression, remain third-line treatments. At least one meta-analysis suggested that continuation of AD treatment prevented relapses in those who responded acutely to treatment and that particular anxiety disorders may respond differently to ADs. The researchers found that GAD was the most responsive and PD and OCD the least, with higher relative risks of relapse and numbers needed to treat. They theorized that this difference might in part be accounted for by the degree of comorbidity with MDD (Donovan et al. 2010).

Although BZDs have the reputation of efficacy in treating GAD and PD, in clinical practice they often serve as adjunctive agents with SSRIs/SNRIs, providing rapid relief while the latter's delayed effects take place. Mounting concerns about potential problems with long-term use, such as abuse and dependence, traffic accidents, non-accidental falls, cognitive impairment, and associated costs for the treatment of these sequelae (Fang et al. 2009) have diminished the enthusiasm with which they were recommended for anxiety disorders in general. Although not uncontested (Martin et al. 2007), diazepam, alprazolam, and lorazepam have shown efficacy in treating GAD but were outperformed by ADs when there was comorbid depression (Davidson 2009). FDA-approved to treat PD, clonazepam remains a popular choice for its treatment, especially in the initial treatment in combination with an SSRI (Susman and Klee 2005).

All BZDs share similar pharmacological properties (anxiolysis, sedation, sleep induction, muscle relaxation, and anticonvulsant effects), while their differences reside in their half-lives, distributions, receptor affinities, and potency. Short half-life BZDs like alprazolam are more likely to lead to withdrawal reactions and the development of dependence (Fang et al. 2009). Diazepam, lorazepam, and clonazepam remain valuable options for the treatment of status epilepticus, seizure clusters, and refractory seizures (Trimble 2002; Riss et al. 2008); however, because of their potential to cause tolerance, dependence, rebound phenomena, and withdrawal, along with significant sedation and cognitive/memory impairment, their use as long-term AEDs is controversial. They can cause paradoxical disinhibition and can cause severe seizure exacerbation and mental status changes if not withdrawn slowly enough (Ettinger 2006). The 1,5-benzodiazepine, clobazam, has been shown to be effective as an anti-anxiety medication and also may be less prone to produce tolerance and, therefore, a better AED.

Buspirone is a partial 5-HT_{1A} agonist whose therapeutic effect appears to be secondary to its inhibition of postsynaptic 5-HT_2 receptors. It has primarily been used to treat GAD and has shown minimal effectiveness in PD and only possible value in post-traumatic stress disorder (PTSD). However, its main drawback is its delayed onset of therapeutic effect (2–3 weeks) (Argyropoulos et al. 2000). It is rarely used as a monotherapy, but is a useful adjunctive treatment for GAD, PD, and social phobia (Pollack 2009). In one study, its impact on the seizure threshold appeared to be dose-dependent (Macêdo et al. 2004); however, in doses up to 90 mg (above the standard 60 mg maximum) in the treatment of an autistic adult, it did not appear to increase the seizure frequency of pre-existing epilepsy (Brahm et al. 2008) and in rats

not only blocked pilocarpine-induced seizures but as a pretreatment increased the activity of hippocampal superoxide dismutase and catalase, both antioxidant enzymes (de Freitas et al. 2009).

Certain AEDS also are reputed to have anxiolytic properties and may be particularly advantageous in treating anxiety in PWE; however, limited RCTs have been done. Indicated for use in treating refractory GAD in Europe though not the US (Pollack 2009), pregabalin has shown efficacy in GAD in double-blind, randomized placebo-controlled trials (Pohl et al. 2005; Montgomery et al. 2008) and in comparison against alprazolam (Rickels et al. 2005) and venlafaxine (Montgomery et al. 2006). It has proved efficacious in a double-blind RCT for social anxiety (Pande et al. 2004). Unlike the SSRIs/SNRIs and like BZDs, pregabalin provided rapid relief for both psychic and somatic symptoms. In the Pohl et al. study (2005), pregabalin also showed efficacy over placebo with comorbid depressive symptoms. It has also been successfully used to treat anxiety in the context of schizophrenia (Schonfeldt-Lecuona et al. 2009). Three randomized, double-blind, placebo-controlled studies demonstrated no efficacy for tiagabine, a selective GABA reuptake inhibitor, in treating GAD (Pollack et al. 2008). One case report highlighted the efficacy of carbamazepine for moderate OCD, poorly treated by clomipramine, fluoxetine alone and in combination with risperidone and whose onset succeeded epilepsy (da Rocha et al. 2009). Though its mechanism is not completely understood, gabapentin may possess anxiolytic properties in treating social phobia (Pande et al. 2004), PD (Pande et al. 2000), and in adjunctively accelerating the response of OCD to fluoxetine (Onder et al. 2008). Topiramate has been studied as an add-on treatment (275 mg on average) to SSRIs/SNRIs for refractory OCD with 83% (10/12) experiencing a positive response, with improved social functioning and resumption of work (Rubio et al. 2006). In an open-label study of its use in PTSD, it decreased the symptoms of re-experiencing, avoidance, and hyperarousal by 49% from baseline, "intrusions" by 94%, and nightmares by 79% (Berlant 2004). In a randomized, double-blind, placebo-controlled trial, it failed to show efficacy as an adjunctive agent, possibly because of a high dropout rate (Lindley et al. 2007). However, because of the dearth of effective agents to treat PTSD and sufficient promising reports, another randomized, double-blind, placebo-controlled trial has been registered and will be conducted in Brazil (Mello et al. 2009). (For a review see Mula et al. 2007.)

Adverse drug reactions

The ADRs of the ADs have been discussed in the section on depression and those of the BZDs have been discussed above. Buspirone has mild side effects, primarily dizziness, headaches, nausea, and nervousness (Clark and Agras 1991). Pregabalin is generally well-tolerated, even in the elderly (Montgomery et al. 2008), with dose-dependent ADRs of somnolence, dizziness, dry mouth, and nausea. Tolerance to these developed within 2 weeks, except for reported weight gain (Rickels et al. 2005). Gabapentin has been associated with dizziness, dry mouth, headache, nausea, somnolence, insomnia, and facial edema (Pande et al. 1999, 2000), and weight gain (Greenwood 2000). In studies in PTSD, ADRs that led to discontinuation of topiramate were all neuropsychiatric, such as impaired cognition, paresthesias, headache, sedation, ataxia (Lindley et al. 2007), and intolerable overstimulation (Berlant 2004). Topiramate has also been demonstrated to cause dose-dependent weight loss, which has been exploited as a positive effect (Kirov and Tredget 2005). It has also been linked with causing depression during rapid titration in susceptible individuals (Mula et al. 2009a), word-finding difficulties, psychomotor slowing even with a slower titration, and the development of psychosis (Ettinger 2006).

Drug–drug interactions

SSRIs/SNRIs are discussed in the section on depression while BZDs have been discussed briefly above. Pharmacodynamic interactions of BZDs with other AEDs can amplify their propensity to cause sedation and cognitive/memory impairment. Enzyme-inducing AEDs (phenytoin, phenobarbital, primidone, and carbamazepine) can increase their clearance, while valproate has increased blood levels of lorazepam through inhibition of its glucuronidation (Tanaka 1999). Topiramate (Bourgeois 1996), gabapentin (Pande et al. 2000), and pregabalin (Rickels et al. 2005) have little effect on the CYP450 isoenzymes (see Table 16.1).

Bipolar disorder

While much attention has been placed upon the association of depression with epilepsy, relatively little focus has been directed toward investigating rates of bipolar disorder in epilepsy. While there are similarities in the presentations of both bipolar disorder (BD) and epilepsy, such as their episodic nature and their responsiveness to AEDs, an association between the two has been difficult to establish (Amann and Grunze 2005). Noting that "classic bipolar disorder is extremely rare in epilepsy," Schmitz went on to suggest that there might be an "antagonistic" relationship between the two or perhaps confounding variables decreasing its diagnosis, such as the alteration of its presentation by AEDs or the symptomatic overlap with epilepsy-specific dysthymic disorders (Schmitz 2005). Given that individuals with BD spend the majority of their symptomatic time in major depressive episodes (MDE) or subsyndromal depression (Judd and Akiskal 2003; Kupka et al. 2007; De Dios et al. 2009), it is possible that some depressive episodes in epilepsy patients could represent in fact bipolar depression.

In their community-based study of the prevalence of bipolar symptoms using the Mood Disorder Questionnaire (MDQ) in patients with epilepsy, migraine, asthma, and diabetes as well as a control group, Ettinger and colleagues (2005) found that bipolar symptoms were evident in 12.2% of PWE. This was 1.6 to 2.2 times more frequent than in the other disease groups and 6.6 times more likely than in the control group. Of the epilepsy group that had a positive result on the MDQ, 47.9% had been diagnosed previously with BD, while 26.3% had been diagnosed with MDD and the remainder were diagnosed with neither. Factors predictive of positive MDQ results were younger age, male sex, and a family history of BD. The authors cautioned, however, that this study demonstrated bipolar symptoms and not necessarily formal BD. Indeed, in a subsequent study of 110 patients at a tertiary epilepsy center (Lau et al. 2010), Ettinger and colleagues found that only one out of the 10 MDQ+ patients met the formal DSM-based criteria for BD on structured psychiatric interview. Notably, some MDQ+ patients did score positively on a recently developed survey for symptoms found in the controversial IDD, suggesting that mood instability symptoms in epilepsy may have more to do with IDD than formal BD. Supporting this notion is the success Blumer and others have had in treating these mood instability symptoms with TCAs alone or with SSRIs (Blumer 1997; Blumer et al. 2004) without provoking a manic crisis or inducing increased mood cycling.

Mula et al. (2008) also studied the occurrence of BD in a sample of PWE drawn from highly selected tertiary settings. When they excluded patients who either met the criteria for IDD or whose bipolar symptoms were clearly related to AEDs or were ictal events from the group diagnosed with BD by DSM-IV and the MDQ+ group, the prevalence of "pure" BD was only 1.4% and 2%, respectively, in line with estimations in the general population. Bipolar symptoms are associated with lower quality-of-life measures, as are depression and anxiety (Mula et al. 2009b). Both studies also highlight the challenges in accurately diagnosing BD in PWE and in the general population.

The cost of misdiagnosis in the general population can be enormous. It is less clear how to understand the impact in PWE, given the overlap of bipolar symptoms with IDD, its successful treatment with ADs, and the possibility that chronic use of AEDs may alter the presentation of BD in PWE. As many anticonvulsants are also mood stabilizers, they may protect to some degree against the deleterious effects of an AD for a patient with BD. Still, Kanner reported that the second most frequent ADR with the use of sertraline for depressed PWE in his study was hypomania (7%). Of those 7 patients, 6 had family histories of depression (Kanner et al. 2000). Some have argued that patients who have demonstrated AD-induced hypomania or mania should be considered to have a "bipolar spectrum disorder," as that occurrence appears to predict a bipolar course with 100% specificity (Akiskal et al. 2000; Phelps et al. 2008). As this has not been studied in PWE, it is difficult to know whether the same relationship holds true.

Treatment issues

Post decried the "myth of evidence-based medicine" for BD, citing the paucity of informative studies and the complexities of treatment, requiring efficacy for the different polarities of illness and for every aspect of treatment, including "initiation, continuation, relapse prevention, and approaches to residual comorbidities, cognitive dysfunction, and treatment

resistance" (Post 2009). According to the reviews conducted by the Oregon Evidence-based Practice Center's Drug Effectiveness Review Project (DERP), funded by a consortium of state Medicaid agencies after the Neurontin lawsuit in 2004, current evidence best supports the use of carbamazepine, valproate, and lamotrigine for "maintaining remission" for *bipolar I with recent mania or mixed episodes* with only "modest" support for the efficacy of these same three AEDs in "achieving and maintaining remission" with *bipolar I with a recent depressive episode or bipolar II*. The rates of these three AEDs in achieving and maintaining remission were similar to those of lithium with *bipolar I*. Carbamazepine and valproate achieved similar response rates to lithium in treating *acute mania* while lamotrigine was more efficacious with *depressive episodes*. Finally, with all three AEDs, there was still considerable medication discontinuation and recurrence (Carey et al. 2008).

While lithium has undisputed efficacy in treating bipolar I and in reducing suicidality (Tondo et al. 1998; Baldessarini and Tondo 2000) and has been safely used in the context of epilepsy (Barry et al. 2008), it is a second-line agent in PWE, used in low dose adjunctively. Using appropriate AEDs can minimize the number of medications used and avoids additive ADRs with AEDs like weight gain, tremor, and cognitive impairment (Kanner and Gidal 2008).

The use of lithium has been associated with encephalopathy, especially with concurrent carbamazepine use (Prueter and Norra 2005). Carbamazepine and divalproex have been shown to be equally as protective as lithium against suicidality in at least one study, with a 16-fold increase after their discontinuation. This underscores the importance of careful monitoring of medication compliance and a potential for increased suicidality with AED discontinuation (Yerevanian et al. 2007).

Recent analyses of five randomized, double-blind, placebo-controlled clinical studies suggested that, though beneficial for relapse prevention and well tolerated, lamotrigine was only modestly efficacious in the acute treatment of bipolar I and II depression. Acknowledging the magnitude of the placebo response, the authors speculated that a study comparing lamotrigine to another active agent might be necessary to demonstrate a statistical effect (Calabrese et al. 2008; Geddes et al. 2009). More recent studies have suggested that valproate may be effective in acute bipolar depression (Smith et al. 2009) and that divalproex-ER deserves further study for bipolar II depression (Wang et al. 2009). Redmond and coworkers (2006) reported on a series of 55 patients with BD who were treated over a 3-year period with lamotrigine with either divalproex (39) or lithium (16), noting 67% and 62% of each group respectively were either rated as "much improved" or "very much improved" from the preceding phase. When the preceding phase was depression, 67% of the group taking lamotrigine and divalproex achieved this level of improvement, compared to 44% with lithium; with mania, 44% of the group taking lamotrigine and lithium improved significantly compared to 33% with divalproex. Finally, recent studies suggest that atypical antipsychotic agents (APDs) may be effective in treating BD. Olanzapine, quetiapine, risperidone, and ziprasidone may be helpful in treating acute mania alone or with AEDs (Scherk et al. 2007; McElroy et al. 2010; Novick et al. 2009). Quetiapine and olanzapine have shown some efficacy in treating acute depressive episodes and preventing depressive relapses while olanzapine and aripiprazole have demonstrated some efficacy in preventing manic relapses (Beynon et al. 2009; Malhi et al. 2009). Further studies of their effectiveness in treating BD are clearly needed, especially as serious side effects complicate their use, such as inducing the metabolic syndrome, causing sedation, extrapyramidal side effects, and possibly tardive dyskinesia (Malhi et al. 2009). Issues about their use in PWE will be discussed further in the next section. (For a review of treatment for bipolar depression, see Goodwin et al. 2008.)

Psychoses

Although few studies have demonstrated a bidirectional relationship, psychoses and epilepsy, as diseases, share a well-known "affinity" (Sachdev 2007). At the same time, there can be an "antagonism" between psychotic symptoms and seizures, exemplified by the use of convulsive therapy to treat refractory psychosis, forced normalization, and alternative psychoses (Wolf and Trimble 1985). Research in schizophrenia has suggested that dopaminergic hyperactivity of subcortical D_2 receptors, the target of most effective antipsychotic medications, primarily causes the positive symptoms of psychosis and may be secondary to dysfunctional glutamatergic regulation via NMDA receptor hypofunction (Laruelle et al. 2005).

However one conceptualizes the etiology of psychoses, it has a clear association with epilepsy (Chapter 2). In their recent population-based study, Qin et al. found an increased risk of schizophrenia (2.48 times) and schizophrenia-like psychosis (2.93 times) in people with a history of epilepsy as compared to the general population. Furthermore they demonstrated that a personal history of epilepsy was a more potent factor increasing that risk for those who lacked a family history of psychosis, while a family history of epilepsy was only influential in increasing the risk for those without a family history of psychosis. Unlike other studies, the impact of a history of TLE slightly but not significantly increased the risk. They postulated that epilepsy and psychotic disorders likely share common underlying pathogenetic mechanisms (Qin et al. 2005). In another recent study, having epilepsy conferred an 8-fold risk of developing psychosis compared to other chronic medical illnesses (van der Feltz-Cornelis et al. 2008), while in another, only a history of psychosis, among a variety of psychiatric conditions, was independently associated with new-onset epilepsy in older individuals (>65 years), supporting the bidirectional relationship discussed in Chapter 2 (Ettinger et al. 2010).

As with the other psychiatric disorders we have reviewed, psychotic symptoms in PWE are classified by their relationship to the ictus. As peri-ictal psychiatric symptoms and postictal psychosis (PIP) are considered in detail in Chapters 7 and 8, they will not be reviewed here. Researchers have postulated that interictal psychosis (IIP) is related to PIP (Umbricht et al. 1995) and that a proportion of patients with PIP will go on to develop IIP and chronic IIP. All are associated with serious morbidity and mortality, including increased suicidality (Tarulli et al. 2001). Before commencing treatment with APDs, AED-related psychosis needs to be considered, as adjustment of the AED regimen may be efficacious. Certain AEDs have been associated with psychoses, most notably: ethosuximide (Mula and Monaco 2009); zonisamide (Miyamoto et al. 2000); tiagabine (Weintraub et al. 2007); vigabatrin (Trimble et al. 2000); topiramate (Kanner et al. 2003); and levetiracetam (Kossoff et al. 2001; Krishnamoorthy et al. 2002). Mula et al. offered as etiological possibilities the forced normalization phenomenon with more powerful AEDs (Mula and Trimble 2003; Mula et al. 2007), dosing schedules with too rapid titration as well as too high doses, the refractory nature of the populations studied, and their pre-existing vulnerability to psychosis (Mula and Monaco 2009). Abrupt discontinuation of AEDs, including BZDs (Ettinger 2006), can also lead to psychoses (Kanner 2000). In these circumstances, a brief course of a low dose APD may be necessary.

Seizure induction

Non-clozapine APDs work chiefly by antagonizing the D_2 striatal receptors. Animal studies have convincingly shown that D_1 agonists/D_2 antagonists are proconvulsant, while D_2 agonists/D_1 antagonists are anticonvulsant (al-Tajir et al. 1990; Barone et al. 1991; Starr 1996; Clinckers et al. 2004). As one would expect from this, APDs are proconvulsant, some even theorizing that their ability to excite specific neuronal circuits may be critical for their therapeutic effect (Denney and Stevens 1995). Clozapine is thought by some to be a partial D_1 agonist, possibly contributing to its increased convulsant liability and its enhanced efficacy (Laruelle et al. 2005).

First generation agents (FGAs), the "conventional" APDs, and second generation agents (SGAs), the "atypical" APDs, can cause electroencephalogram (EEG) abnormalities, with the greatest risk seen with clozapine, followed by olanzapine and with the least risk with quetiapine and molindone (Centorrino et al. 2002). In their study of the FDA Summary Basis of Approval Reports, Alper et al. found that clozapine had an incidence of seizures of 3.5% compared to 0.9% for olanzapine, 0.8% for quetiapine, and 0.3% for risperidone (Alper et al. 2007). Other reports note no difference in the incidence of seizures observed in patients taking quetiapine (0.4%) or placebo (0.5%) (Torta and Monaco 2002). The risk for seizures with clozapine is dose-related, with an incidence equivalent to the other SGAs, around 1%, in low dose use ($\leq$300 mg/day) but increased to 4.4% with higher doses ($\geq$600 mg/day). However, in a small series, 50% of PWE experienced a reduction in their seizures, while the frequency for the remainder was unchanged (Langosch and Trimble 2002). The FGAs with the lowest risk of seizure induction include haloperidol, molindone, fluphenazine, perphenazine, and trifluoperazine. The highest risk of seizure induction appears to be associated with clozapine, followed by chlorpromazine and loxepine (Kanner and Gidal 2008).

APDs should be started at low doses and raised slowly. Depot formulations should not be used, as

they cannot be quickly withdrawn in the case of increased seizure activity (Haddad and Dursun 2008).

Efficacy

There are few RCTs assessing the efficacy of APDs in the treatment of psychosis of epilepsy (POE), as most studies pertain to individuals with schizophrenia. According to the conclusion of the "Cochrane Review of Interventions for psychotic symptoms concomitant with epilepsy," there was "no reliable, objective evidence" for the efficacy of APDs for POE (Farooq and Sherin 2008). Currently, SGAs are the first-line treatment, though select FGAs are still used. Various authors who treat PWE have their preferred choices: olanzapine (2.5–25 mg/day), risperidone (0.5–6 mg/day), and molindone (50–200 mg/day) (Alper et al. 2002); low dose risperidone or haloperidol (Kanner 2004); ziprasidone, quetiapine, and aripiprazole (Nadkarni et al. 2007); and finally, risperidone (2–6 mg/day), olanzapine (5–15 mg/day), and quetiapine (25–600 mg/day) (Elliott et al. 2009). While treatment with APDs may be brief with PIP, IIP, especially in its chronic form, may require a lengthier treatment (Kanner 2000). Some have found that interictal psychoses generally respond better to APDs than schizophrenia and require lower doses (Tadokoro et al. 2007).

For treatment of refractory psychosis, as in the general population, clozapine is the first-line recommendation. As the most potent APD, it is also the most proconvulsant and yet has been safely and effectively used in PWE (Langosch and Trimble 2002). Supplementation with antiepileptic drugs such as valproic acid may be indicated to reduce the chance of seizures and to suppress EEG-documented clozapine-induced generalized discharges. For elderly PWE, lower doses of risperidone, olanzapine, and quetiapine are recommended (Zaccara and Cornaggia 2002). Finally, noting the presence of psychotic symptoms in IDD, Blumer et al. recommended using a TCA (imipramine or amitriptyline, 100–150 mg at bedtime), an SSRI (usually paroxetine 20 mg in am or BID), and, if necessary, an APD (risperidone up to 2 mg BID) for IIP, conceptualized as a "severe form of IDD with predominant inhibition and decreased seizure activity" (Blumer et al. 2000). As there are only case series documenting the efficacy of this approach, RCTs would be important in delineating the specific clinical presentations for which this would be the optimal treatment.

Adverse drug reactions

The FGAs are used less frequently because of their less tolerable side effect profile, although recent studies have questioned the accuracy of this perception (Jones et al. 2006; Swartz et al. 2008; see Table 16.2 for a summary). FGAs have a greater liability for increasing prolactin levels and for causing "emotional blunting" (Kanner and Gidal 2008), sedation, and extrapyramidal side effects (EPS), namely acute dystonia, parkinsonism, akathisia, tardive dyskinesia (TD), and tardive dystonia. While SGAs have less liability for these troublesome ADRs, their degree of freedom from them and efficacies are not uniform, so choice must be individualized for each patient (Leucht et al. 2009). Correll and colleagues determined that the weighted mean annual incidence for TD with SGAs was 0.8%, compared to 5% for FGAs. They also noted that even low dose treatment with FGAs could lead to higher risks for TD than with SGAs. However, at higher doses, SGAs, especially risperidone, were associated with higher rates of EPS and the use of anticholinergic medications, both risk factors for TD (Correll et al. 2004). The recent CATIE study appears to contradict these findings (Swartz et al. 2008); however, both the brevity of the study and the choice of a moderate maximum dosage for the representative FGA may have skewed the results in its favor (Casey 2006). Among the SGAs, risperidone is most likely to cause EPS, while clozapine and quetiapine are the least (Edwards and Smith 2009). According to the *APA Practice Guideline for the Treatment of Patients with Schizophrenia* (Second Edition), screening tests for TD, like Abnormal Involuntary Movement Scale (AIMS), should be done biannually with FGAs and annually with SGAs (Lehman et al. 2004).

The most serious ADR for the SGAs is the propensity to cause weight gain, dyslipidemias, and other components of the metabolic syndrome, affecting compliance and increasing the risks for type II diabetes and cardiovascular complications. Clozapine and olanzapine have the greatest liability, while aripiprazole and ziprasidone have the least (Edwards and Smith 2009; Novick et al. 2009). In one 24-week study, olanzapine caused a marked reduction and risperidone a smaller but significant reduction in glucose tolerance from baseline compared to quetiapine, likely related to insulin insensitivity. It also caused a marked increase in total cholesterol, LDL, and triglyceride levels while risperidone caused none

Table 16.2 Selected side effects of commonly used antipsychotic medications[a]

Medication	Extrapyramidal side effects/tardive dyskinesia	Prolactin elevation	Weight gain	Glucose abnormalities	Lipid abnormalities	QT_C prolongation	Sedation	Hypotension	Anticholinergic side effects
Thioridazine	+	++	+	+?	+?	+++	++	++	++
Perphenazine	++	++	+	+?	+?	0	+	+	0
Haloperidol	+++	+++	+	0	0	0	++	0	0
Clozapine[b]	0[c]	0	+++	+++	+++	0	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	0
Olanzapine	0[c]	0	+++	+++	+++	0	+	+	++
Quetiapine[d]	0[c]	0	++	++	++	0	++	++	0
Ziprasidone	0[c]	+	0	0	0	++	0	0	0
Aripiprazole[e]	0[c]	0	0	0	0	0	+	0	0

[a]0 – no risk or rarely causes side effects at therapeutic dose, + – mild or occasionally causes side effects at therapeutic dose, ++ – sometimes causes side effects at therapeutic dose, +++ – frequently causes side effects at therapeutic dose, ? – data too limited to rate with confidence.
[b]Also causes agranulocytosis, seizures, and myocarditis.
[c]Possible exception of akathisia.
[d]Also carries warning about potential development of cataracts.
[e]Also causes nausea and headache.

and quetiapine caused smaller but significant increases only in total cholesterol and LDL (Newcomer et al. 2009). As the weight gain often occurs within the first 6 months of treatment, a baseline evaluation of metabolic status is indicated (weight, height, waist circumference; personal history of high BMI, diabetes, or hyperlipidemia; family history of diabetes mellitus; hemoglobin A1c (HbA1c), fasting blood glucose, lipid panel; EKG). While in more vulnerable individuals, monitoring of fasting blood glucose and lipid panel every 6 months is suggested (de Leon et al. 2009), the APA Practice Guidelines recommend a fasting blood glucose or HbA1c at 4 months after initiating a new treatment and then annually thereafter, with lipid panels at least every 5 years. Clinical findings, preexisting illness, family history, and simultaneously prescribed medications may indicate the need for more frequent monitoring (Lehman et al. 2004). (For reviews see Nasrallah 2003; Meyer and Stahl 2009.)

Hyperprolactinemia caused by the FGAs and some SGAs can cause sexual dysfunction, menstrual abnormalities, infertility, and in the long-term, osteopenia in both sexes. Risperidone is associated with marked elevations in prolactin, even above those caused by haloperidol, while aripiprazole causes lesser elevations (Henderson and Doraiswamy 2008), olanzapine causes modest elevations, and clozapine none (Melkersson 2005). However, as suggested by the APA Guidelines, a prolactin level should be ordered on the basis of the clinical history regarding "changes in libido, menstrual changes, or galactorrhea in women; changes in libido or in erectile or ejactulatory function in men" (Lehman et al. 2004). In populations that are not able to provide accurate histories, an annual prolactin level is a prudent practice (de Leon et al. 2009), with elevations prompting an evaluation.

Among the SGAs, clozapine and quetiapine are reputed to cause the most sedation. Zisprasidone can sometimes cause QTc prolongation at therapeutic doses (Leucht et al. 2009), as can thioridazine (Mathews and Muzina 2007). In view of the possibility of seizure-related prolonged QTc, as demonstrated in a recent study (Brotherstone et al. 2009), this potential should be kept in mind.

Because of its serious ADRs, clozapine has been relegated to the treatment of refractory schizophrenia, usually defined as failed trials with one or more FGAs and two SGAs, and an episode that presents with suicidal behavior (Kane et al. 2003). Side effects include: agranulocytosis, requiring regular monitoring; rarely, myocarditis and cardiomyopathy; marked weight gain with increased risk of hyperglycemia, hyperlipidemias, and type II diabetes; orthostatic hypotension and tachycardia; fever; and sedation, constipation, hypersalivation, and urinary incontinence. There is an extremely low risk of EPS, TD (Sabaawi et al. 2006), or hyperprolactinemia (Melkersson 2005).

Drug–drug interactions

In terms of pharmacodynamic interactions, it would be important to avoid using as much as possible APDs and AEDs which have additive ADRs. Clearly, carbamazepine and clozapine should not be prescribed together because of the additive risk of agranulocytosis. APDs associated with weight gain or sedation would be a poor match for AEDs that bear that same liability. As AEDs also cause bone mineral density loss (Sheth et al. 2008), the benefit of using an APD for extended periods with the potential to cause hyperprolactinemia must be weighed carefully.

Pharmacokinetic interactions can occur, especially when an enzyme-inducing AED (carbamazepine, phenobarbital, phenytoin, and primidone) is co-prescribed with certain APDs, such as clozapine, haloperidol, olanzapine, quetiapine, risperidone, ziprasidone, and mesoridazine, requiring larger doses for therapeutic effect. The addition of such an AED to a stabilized regimen with these APDs can lead to a sudden loss of efficacy and potentially serious psychiatric symptoms (Perucca 2005). In one study, phenytoin increased the clearance of quetiapine by 5-fold (Wong et al. 2001). If an enzyme-inducing AED is withdrawn, the decrease in clearance of these substrate APDs can lead to more serious ADRs (Kanner and Gidal 2008). Valproate has inconsistent effects on co-prescribed clozapine and risperidone (Fleming and Chetty 2005). In at least one study, valproate had negligible effects on the metabolism of olanzapine (Spina, D'Arrigo et al. 2009). While minimally increasing the level of olanzapine, lamotrigine did not affect the plasma levels of risperidone and clozapine or their metabolites (Spina et al. 2006). Older phenothiazine FGAs, like chlorpromazine and thioridazine, are inhibitors, with reports of causing phenytoin intoxication (Spina and Perucca 2002) and decreased clearance of valproate (Fleming and Chetty 2005). At therapeutic doses, the SGAs are only weak inhibitors of CYP isoenzymes and do not affect AED metabolism (Spina and Perucca 2002), with the

possible exception of risperidone and carbamazepine. In a small study, Mula and Monaco detected small increases in carbamazepine levels at 24 hours and 2 weeks after the addition of 1 mg risperidone, though the combination was well-tolerated. They postulated that risperidone may have inhibited CYP3A4 as well as CYP2D6 and that both may be involved in carbamazepine metabolism, a phenomenon possibly more clinically significant with higher doses of risperidone (Mula and Monaco 2002) (see Table 16.1).

Attention-deficit hyperactivity disorder

Attention-deficit hyperactivity disorder (ADHD) and epilepsy share a bidirectional relationship (Kanner 2009), suggested by the association between a history of ADHD, particularly the inattentive type (Dunn et al. 2003), and the subsequent development of epilepsy (Hesdorffer et al. 2004; Jones et al. 2007), and the increased prevalence of ADHD in children with epilepsy (CWE), estimated to be as high as 20% compared to 3–5% in their unaffected cohort (Gross-Tsur et al. 1997). Chronic seizures, nonconvulsive epileptiform EEG discharges, and AEDs can also cause cognitive and attentional impairment (Torres et al. 2008), as can certain types of seizures, especially TLE, in both adults (Bocquillon et al. 2009; Zhang et al. 2009) and children (Rzezak et al. 2007). Although the focus of this chapter is adults with epilepsy, ADHD is generally diagnosed in children and adolescents and most studies involve those groups. A majority of children with ADHD retain significant attentional deficits into adulthood (Greenhill et al. 2002); however, current DSM-IV criteria include symptoms that are not age-appropriate and fail to capture significant aspects of adult ADHD, such as difficulties with "temper, affective lability, emotional over-reactivity, and disorganization" (Wender et al. 2010). Hopefully, changes in DSM-V will reflect the course of ADHD, the differences in the developmental expression of its symptoms, and the need for its treatment across the life span of many individuals.

A significant number of children with ADHD have abnormalities on EEG without overt seizures. In one study, only 27.8% had completely normal EEGs, while the remainder showed various abnormalities, ranging from positive spikes, possibly a "normal variant" (34.1%), to focal discharges (23.9%), slow waves (18.8%), frontal arousal rhythm (12.5%), extreme spindles (6.8%), and bilateral spike-and-waves (6.3%), the latter mostly seen rarely. Hughes and his colleagues hypothesized that focal discharges might lead to "transient cognitive impairments" seen in PWE, caused by interictal subclinical epileptiform discharges and improved by changes in the AED regimen (Hughes et al. 2000; Schubert 2005). As the incidences of both the positive spike and frontal arousal rhythm in this group were significantly greater than those found in comparative groups in their EEG laboratory, 19.7% and 0.22% respectively, they concluded that these patterns could be related to ADHD (Hughes et al. 2000). Richer and coworkers (2002) found a lower incidence of EEG abnormalities in their retrospective study of school children with ADHD; however, they noted that the incidence was still double that seen in a cohort of normal children. In a previously quoted study, ADHD was prevalent in the histories of children with newly diagnosed epilepsy, at a higher rate (45.8% vs. 6.9%) before than after seizure onset (Jones et al. 2007). Although their study failed to demonstrate any correlation between the presence of EEG abnormalities in ADHD and the development of unprovoked seizures, 71.4% with the inattentive type had EEG abnormalities, compared to 50% for each of the other types (Hesdorffer et al. 2004).

In a study of children with a first recognized seizure, close investigation revealed that a third had had unrecognized previous seizures. Using the Child Behavior Checklist (CBCL) but not DSM diagnoses, this subgroup demonstrated a marked increase in total behavioral problems (34.2% vs 19.6%) and specifically attention problems (15.8% vs. 8.1%) compared to the children with no previous seizures (Austin et al. 2001). A recent study confirmed that 35.9% had prior unrecognized seizures and performed significantly worse on neuropsychological tests measuring "attention/executive/construction" (Fastenau et al. 2009).

Prior to considering any ADHD-specific treatment in PWE/CWE, it is crucial to both optimize seizure control and to evaluate the AED regimen for cognitive and attentional effects. As "cognitive/coordination" ADRs among all others are most strongly associated with lower scores on quality of life (QOL) measures (Perucca et al. 2009), the withdrawal of AEDs associated with cognitive impairment or a reduction in dose or polypharmacy can mitigate the impact. Barbiturates and BZDs are most often associated with cognitive impairment, while carbamazepine, valproate (Shehata et al. 2009), and phenytoin cause less, with no

consistent differences among them. Gabapentin's risk appears to be greatest in children (Loring et al. 2007). In agreement with animal studies (Lamberty et al. 2000), Cramer and colleagues demonstrated that levetiracetam was free of negative cognitive impact (Cramer et al. 2000); however, in other studies, it has been linked to behavioral side effects like irritability (Weintraub et al. 2007). Lamotrigine has caused less cognitive ADRs than topiramate, both as a monotherapy or used adjunctively (Blum et al. 2006) and may be a first-line AED for children with ADHD (Schubert 2005; Parisi et al. 2009). There are few reports of a negative effect on attention and behavior with oxcarbazepine, tiagabine, or zonisamide (Schubert 2005).

Seizure induction

Psychostimulants like methylphenidate (Ritalin among others) and dextroamphetamine are the primary treatment for ADHD. *The Physician's Desk Reference* noted for Ritalin that it "may lower seizure threshold, especially with prior history of seizures or with prior EEG abnormalities; d/c if seizures occur" (PDR 2010b), and similarly for dextroamphetamine (PDR 2010a). Of note, prior to 1950, dextroamphetamine was used as an adjunctive AED in petit mal and was associated, in a study in the 1980s, with achieving seizure control in two previously refractory patients (Schubert 2005). Its use has not been studied extensively in CWE/PWE with ADHD.

Hemmer and her group (2001) examined the seizure risk with stimulant use, both methylphenidate and dextroamphetamine, in nonepileptic children with ADHD. While 84.6% of their group had normal or nonepileptiform EEGs, a high proportion, consistent with other studies, had epileptiform abnormalities (15.4%), of which 40% were rolandic spikes. Four patients experienced seizures, all in the group receiving methylphenidate; however, only one had had an initially normal EEG. The other three all had epileptiform EEGs, one consistent with primary generalized epilepsy and the other two with "benign rolandic epilepsy." As there was a long delay between treatment initiation and seizure in the latter two, they concluded that the stimulant was either not strongly "provocative" or that only chronic exposure was sufficient to contribute to the expression of seizures. Seizures occurred in 2% (4/205) of the methylphenidate-exposed group, with a 0.6% incidence with a normal EEG and 16.7% incidence with rolandic spikes. They concluded that the data suggested that stimulants would not provoke seizures in the absence of an underlying diathesis; however, because the comparative group with abnormal EEGs who did not take methylphenidate was quite small (6), a causative role could not be assigned to the methylphenidate. They noted as well that "about 1% of unselected children will have at least one febrile seizure by age 14 and 0.4–0.8% will have epilepsy by age 11" (Hemmer et al. 2001). In the studies discussed above, at the time of their first seizure, approximately a third of the children had previously undetected seizures and had behavioral profiles possibly consistent with a diagnosis of ADHD (Austin et al. 2001; Fastenau et al. 2009). These findings cast doubts on the absolute certainty that this nonepileptic group never had seizures and increase the likelihood, as the authors concluded, that the occurrence of seizures was not causally related to methylphenidate use.

Studies with PWE and ADHD mostly involve CWE treated with methylphenidate. Most of the studies' subjects did not experience increases in the frequency of seizures (McBride et al. 1986; Feldman et al. 1989); significant changes in their AED levels (Feldman et al. 1989); or significant alterations in their EEGs (Feldman et al. 1989). In one study, the seizure-free children remained so when taking methylphenidate; however, of the five CWE, the frequency increased in three, remained the same in one, and decreased in one patient. Although they felt this could have been related to normal variations in seizure frequency as the treatment portion was only 2 months long, the authors recommended "caution" in using methylphenidate only with children whose epilepsy is not "well-controlled" (Gross-Tsur et al. 1997). Seventeen percent of their patients experienced insomnia and 41% loss of appetite but it is not known whether there was overlap between these children and those with increased seizures. Sleep deprivation is a well-known risk factor for deterioration in seizure control (Tan and Appleton 2005) and at least one author noted that a significant weight loss can negatively affect serum carbamazepine levels (Gonzalez-Heydrich et al. 2006). Gucuyener and his colleagues (2003) observed an improvement in EEGs with methylphenidate treatment in their two groups, children with ADHD and clinical seizures and those with ADHD and EEG abnormalities only. Of the latter, none had seizures, 29% experienced a normalization of their EEG, and the number experiencing active epileptiform activity was almost halved. Four times

as many CWE had normal EEGs after treatment and the proportion with active epileptiform activity was reduced from 35% to 19%. Over the year of the study, only 8% (5/57) had an increase in their seizure frequency but details regarding these particular children and any possible relationship to the side effects discussed above are not provided. They recommended "close monitoring" of CWE and ADHD but deemed methylphenidate safe (Gucuyener et al. 2003). Torres et al. recommended "cautious" use of both methylphenidate and dextroamphetamine with CWE with ADHD (Torres et al. 2008), while others have endorsed methylphenidate as an option for CWE with moderate or severe ADHD and "well-controlled" seizures (Parisi et al. 2009). *The Practice Parameter for Use of Stimulant Medications in the Treatment of Children, Adolescents, and Adults* recommended stabilization on AEDs prior to treatment with stimulants (Greenhill et al. 2002). Finally, relative contraindications to ADHD treatment at one hospital included "untreated epilepsy, unstable epilepsy with daily seizures and severe, degenerative forms of epilepsy with constant epileptiform activity on EEG" (Gonzalez-Heydrich et al. 2006).

The effect of stimulant use on seizure frequency in adult PWE and comorbid ADHD has not been studied. In a 3-month study, methylphenidate was prescribed to eight adult PWE to determine whether it could improve cognition and decrease fatigue and sedation associated with AED treatment. One patient, out of the six who were seizure-free at baseline, experienced two seizures during the final month of treatment. Of the two who had been actively experiencing seizures, one became seizure-free and the other experienced no change in frequency (Moore et al. 2002).

Atomoxetine is a non-stimulant, potent, specific norepinephrine reuptake inhibitor which is a second-line treatment for ADHD. In a study presented in abstract only, one of 17 children treated with atomoxetine experienced an increase in seizures without a change in serum AED levels (Hernandez and Barragan 2005). In their meta-analyses, Wernicke and his colleagues (2007) examined 31 clinical trials, only 6 including adults and all excluding anyone with a past seizure history except for febrile ones, and the database of postmarketing events. The overall crude seizure incidence in pediatric and adult trials was 0.2% and 0.1%, respectively, rates which were not significantly different from placebo or methylphenidate. Of the 500 postmarketing spontaneous ADR reports, 43% involved patients with contributing factors such as pre-existing epilepsy and 2% had no clear contributing factor (Wernicke et al. 2007). However, as discussed in the Introduction, there are serious methodological difficulties in deriving evidence of a causal risk between a medication and increased risk of seizures in PWE from these kind of data.

Clearly, controlled studies of sufficient size and length of time need to be conducted to conclusively determine the safety of these treatments for children and adults with epilepsy and ADHD. It is especially important to establish whether these medications are as safe with more active epilepsy as they appear to be with "well-controlled" epilepsy. In addition, as individuals with ADHD and focal epilepsy may respond differently from those with generalized epilepsy, studies need to be designed to elucidate that (Kaufmann et al. 2009).

Efficacy

There are few studies examining the efficacy of ADHD treatments in CWE and even fewer in adults. All small studies quoted above, investigating their safety, also reported improvements on a variety of ADHD scales for methylphenidate and atomoxetine (Hernandez and Barragan 2005), while less robust responses have been reported with dextroamphetamine (Torres et al. 2008). The only study addressing stimulant treatment in adults with epilepsy did not examine its use for ADHD. However, in keeping with earlier comments about the relationship of the cognitive ADRs of AEDs to lower QOL scores, the addition of methylphenidate at doses between 7.5 and 25 mg daily led to improved indicators on the QOLIE-89, most significantly in the "attention/concentration" domain (Moore et al. 2002), a possible indicator of its potential use for ADHD symptoms. At this time, given the paucity of evidence, we would recommend with caution methylphenidate and, as second-line, atomoxetine for moderate to severe ADHD in the context of "well-controlled epilepsy" (Parisi et al. 2009). (For a review of treatments of ADHD in the nonepileptic population, see Biederman et al. 2004).

Adverse drug reactions

The most common ADRs from methylphenidate, reported in the studies of CWE cited previously, were loss of appetite, initial insomnia, stomach pains, nausea, headache, and motor tics (Gucuyener et al. 2003), with all lasting less than 2 weeks except for loss

of appetite (Gross-Tsur et al. 1997). A study failed to demonstrate however that methylphenidate either caused or exacerbated pre-existing tics compared to placebo (Law and Schachar 1999). Dextroamphetamine, though studied less, is likely to have similar side effects. In CWE, atomoxetine caused sedation, loss of appetite, and nausea (Hernandez and Barragan 2005). In the general population, atomoxetine has rarely caused severe hepatotoxicity. Atomoxetine has not been associated with insomnia or abuse potential. However, more recently, it has been linked with increased suicidal ideation (Ashton et al. 2006) and patients should be monitored for depression, suicidality, and irritability (Torres et al. 2008). In adults with epilepsy, methylphenidate caused "jitteriness" which was eliminated by a reduction in dose (Moore et al. 2002). The most significant ADRs for all three drugs entail the potential cardiovascular complications. Because all three can cause increases in pulse and blood pressure, generally mild but perhaps of more significance in adults, vital signs should be monitored at baseline and regularly throughout treatment.

More controversial and concerning is the possible link between stimulants and sudden cardiac death. In postmarketing surveillance, 8 youths treated with methylphenidate and 18 youths treated with amphetamines experienced "nonfatal cerebrovascular adverse events" over a 4-year period. During this same period, 7 children and 1 adult taking methylphenidate and 12 children and 5 adults taking amphetamine suffered sudden cardiac death. Many of these cases involved "pre-existing, though sometimes undetected cardiovascular problems or risks or were using multiple drugs simultaneously" (Newcorn and Donnelly 2009). While they also represent a very small fraction of the total number of people prescribed these medications and are below the estimated rate for sudden cardiac death in the general population, it cannot be assumed that there is no causative relationship between stimulant use and these outcomes. To diminish whatever risk there is, however small, the current recommendations include obtaining a thorough history of cardiovascular function in all prospective patients and of cardiovascular risks in their biological family; and a thorough examination and consultation with a cardiologist if there is any indication of cardiac disease in the patient or family. The decision to obtain a pretreatment ECG should be made on the basis of the history and physical examination (Newcorn and Donnelly 2009).

Drug–drug interactions

As noted in several of the small studies previously quoted, there are limited pharmacokinetic interactions between methylphenidate, the most studied, and most AEDs. No studies have demonstrated interactions between atomoxetine and AEDs, while there have been reports of methylphenidate inhibiting the metabolism of phenytoin, primidone, and phenobarbital (Torres et al. 2008). Though not seen in larger studies (Gross-Tsur 1999), there have been case reports of carbamazepine reducing methylphenidate levels drastically (Behar et al. 1998; Schaller and Behar 1999). No pharmacodynamic interactions with AEDs have been identified; however, the rare association of atomoxetine with liver failure should be considered in the context of AEDs, like valproate and felbamate, which have been associated with hepatotoxicity. Regular monitoring of liver function tests may be prudent, especially with any clinical evidence of liver toxicity (Torres et al. 2008).

Conclusion

Epilepsy and psychiatric illness are intrinsically linked, likely sharing underlying diatheses. The presence of psychiatric illness is a more powerful determinant of overall global outcome for PWE than any seizure variable and can increase the already-heightened risk of suicidality many-fold. Not only are many psychotropic medications safe in the context of epilepsy but, given these facts, necessary. Not only are they generally effective in the context of epilepsy but they may improve seizure control as well.

Myths and misinformation have for too long hindered optimal treatment, aided and abetted by the prevalent lack of collegiality and collaboration between neurology and psychiatry. Writing in 2003, Kanner wondered why neurologists and psychiatrists in general communicate poorly with each other and, as well, have inadequate training in each other's field, despite sharing a professional board and overlapping areas of interest (Kanner 2003). In their discussion of conflicts between consultants of different disciplines, Caplan and colleagues discussed the disagreement between a psychiatrist and neurologist concerning a patient with epilepsy, making the point that most conflict arises on the borderland between two specialties' "territories" and their differing notions of the boundary's location (Caplan et al. 2008). The advances in neuroscience over the last two decades have refuted the truth of the old

dichotomies of organic versus functional and mind versus brain, ushering in the possibility of more integrated approaches to CNS disease that incorporate the particular contributions of each discipline (Price et al. 2000). As Kanner noted, the neurologist's reliance on psychiatric screening instruments might contribute, for instance, to the misdiagnosis of a bipolar depression and potentially harmful treatment with an AD (Kanner 2003), while many psychiatrists would be uncomfortable treating a depressed patient with epilepsy.

Changes in healthcare systems have conspired with the forces keeping these two specialties apart. Hurried appointment times and infrequent follow-up appointments might prevent a neurologist from obtaining sufficient data to conclude that a psychiatric problem exists. However, because of inadequate training and the inequities of insurance coverage and healthcare financing, an insufficient number of psychiatrists might be available, even in a hospital setting, to assist in the care of his or her patient. Ironically, *The Guidelines for Essential Services, Personnel and Facilities in Specialized Epilepsy Centers in the United States* stipulates psychiatric consultation as one of the essential services provided in Third Level (Medical Center for Epilepsy and Medical–Surgical Center for Epilepsy) and Fourth Level (Center for Epilepsy) Care (Gumnit and Walczak 2001). In one study, the most significant independent predictors that medical patients would seek mental health treatment were the frequency of appointments with their healthcare providers, perceived need, prior use, and, most importantly, a referral from their healthcare provider (Ledoux et al. 2009). One of the factors possibly contributing to the high relative risk of suicide in PWE in one case–control study was inadequate neurological follow-up, not only in the number of contacts but in the failure of specialists to appreciate the importance, in the context of epilepsy, of psychiatric symptoms as targets for treatment (Nilsson et al. 2002).

Patients may also contribute to the failure to address psychiatric comorbidity, both through lack of insight into their own problems and reluctance to seek treatment. In their 16-country study of perceived stigma, a potential barrier to treatment, Alonso and coworkers found that depression and anxiety were associated with a 2-fold increase in the likelihood of experiencing stigma, a greater than 3-fold likelihood with comorbid anxiety and depression, and a much lower likelihood with chronic physical illness (1.3 for a single condition and 1.4 for multiple ones) alone (Alonso et al. 2008). As well, untreated psychiatric illness can contribute to non-compliance with treatment and failure to appear for follow-up.

The most studied comorbid psychiatric illness, depression, was most effectively treated in the context of primary care through "collaborative care." Compared to primary care as usual, a 2-fold increase in compliance with ADs in the first 6 months was followed by improvements in functionality and relief of depression which lasted for 2–5 years. A stepped-care model would involve a psychiatrist directly intervening only at higher levels of adverse outcome or complexity of disease. Any increase in spending was offset by overall medical savings (Katon and Seelig 2008). While not studied in epilepsy or for other psychiatric illnesses, the collaborative care model gives a framework by which psychiatric illness might be better recognized and treated in PWE (Jones et al. 2005), as long as an adequate diagnostic assessment and monitoring of response, adverse reactions, and potential complications to treatment were available in the levels not including direct psychiatric input. For centuries epilepsy has occupied the borderland between neurology and psychiatry, requiring for optimal treatment the therapies and expertise that have been the province of each, and in doing so, can be the "bridge between the two" (Reynolds and Trimble 2009).

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Chapter 17

Psychiatric effects of surgery for temporal lobe epilepsy

Steffi Koch-Stoecker

Introduction

The cessation of epilepsy by surgical intervention – although it may be an end in itself – primarily aims at a reduction of injuries and embarrassment, in order to enable patients to do what they formerly were precluded from doing. It offers possibilities to live a more fulfilled and self-confident life. But "if the disasters and injuries are somehow self-imposed, if the embarrassment arises mainly from peculiarities of character, if the sense of stigmatization is a deeply held conviction ... removing the epilepsy will not necessarily alter these conditions" (Taylor et al. 1997). Those patients – although seizure-free – may stay in their disabled situation.

Results of epilepsy surgery (ES) – even if successful from a neurological point of view – may be far from satisfying for those patients who are not able to use new postsurgical opportunities to improve their quality of life.

Today, in many epilepsy surgery centers psychiatric comorbidity is – at least partly – included in prognostic considerations. The early strategy of contraindications for patients with psychoses, in fear of postoperative worsening, following very high rates of psychoses in the study of Jensen and Larsen (1979) has now been overcome due to increased knowledge of the postoperative development of those with psychotic syndromes. The strategy to consider an exclusion of patients with predictable severe barriers to surgical success is reasonable; however, the question is who those persons are, or more precisely, which psychiatric disorder type leads to which postoperative psychiatric complications?

In epilepsy generally, as well as for the evaluation of surgical outcome, aspects of quality of life have been increasingly appreciated, parallel to the psychiatric disorders in a narrow sense. An early push in this direction originates from the widely accepted system of outcome classification by Engel et al. (1993). They stated that "some degree of consideration for the impact of residual seizures on quality of life is necessary" and differentiated between the two outcome categories, Class III: "Worthwhile improvement" and Class IV: "No worthwhile improvement." With that differentiation, Engel et al. explicitly went beyond the level of pure seizure-counting and introduced aspects of quality and subjective value: the same postoperative seizure frequency may be a worthwhile success for one patient but a negligible seizure reduction for another one. Evaluators are forced to take into account the individual experiential conditions of patients postoperatively. There is no plausible reason not to apply such a "worthwhile" category also with respect to seizure-free patients meaning that even optimal surgical success may not result in worthwhile improvement of life conditions. This non-worthwhile seizure-freedom definitely relates to the group of patients who have psychopathology.

Engel et al. (1993) emphasized the lack of quantitative measures to distinguish between Class III and Class IV. Of course, although quality of life research has developed some approaches to comprehend quality with quantitative methods, an appraisal of individual worthwhile success regularly requires a lengthy case reconstruction in a way psychiatrists and psychotherapists tend to do. It comprises both assessment of surgical effects and psychotherapeutic support for the patient. In psychiatry the different maladaptive ways of processing critical life events and of coping with failure are represented in the concept of personality disorders. It is our experience that some basic predictors for subjective surgical success beyond the number of postoperative seizures can be found if personality disorders

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

are considered. A recent study in support of this showed that high neuroticism and reported disrupted family dynamics lead to difficulties adjusting to seizure freedom (Wilson et al. 2009).

During the last years another aspect has entered the discussion of psychiatric disorder in epilepsy surgery, namely if the pre-existence of a psychiatric disorder may even compromise surgical success in terms of seizure outcome. It relates to the increasing knowledge about common pathomechanisms of epilepsy and psychiatric disorders.

How, then, do psychiatric disorders influence outcome of epilepsy surgery?

In short, there are three main aspects, all of which should be covered in the psychiatric evaluation of surgical candidates:

1. assessment of psychiatric disorders and their development after surgery
2. the role of personality disorders in hampering surgical success
3. the question whether or not bad seizure outcome is predicted by pre-existing psychiatric disorders.

In the following, all three aspects will be discussed. What do we know about the occurrence of psychiatric disorders before and after epilepsy surgery, how can the analysis of individual personality traits be used to explain individual peculiarities as well as subjectively missing postoperative success, and finally, does psychiatric morbidity reduce the probability of seizure freedom after surgery?

Presented data refer to surgical candidates with temporal lobe epilepsies only.

Psychiatric disorders in the context of temporal lobe resections

In order to achieve relevant information about psychiatric diagnoses in the context of epilepsy surgery it is imperative to collect psychiatric data preoperatively and set them in relation with postoperative changes. Moreover, in order to ensure the comparability of results, it would be sensible for different epilepsy centers to attempt an agreement about the diagnostic methods to be used. Those two basic demands were already formulated in the 1960s (Ferguson and Rayport 1965), but are still not sufficiently fulfilled. What is lacking is the integration of psychiatrists into the epilepsy surgery units, who routinely conduct a psychiatric assessment for all surgical candidates prospectively.

Instead, the currently available literature contains numerous retrospective analyses, in which psychiatric disorders have been reconstructed by the use of incomplete patients' notes, without proper diagnoses and without distinct case histories. The reliability of results is doubtful; these retrospective studies are susceptible to underestimations and false classifications of psychiatric disorders, and also a consensus about assessment strategies is lacking.

Further, several studies solely used psychological questionnaires. Although well constructed and standardized for specific disorders, these questionnaires often are not validated for specific topics of patients with epilepsy, and in any case cannot substitute for clinical psychiatric assessments.

In the following these limitations of some of the presented data are to be kept in mind.

Total psychiatric morbidity in patients with temporal lobe surgery

Results on total psychiatric comorbidity differ depending on the ways patients are referred to the centers, on the strategies of evaluation, and on the absence or presence of a psychiatric assessment, the latter leading to higher frequencies of psychiatric diagnoses. There are two noteworthy trends.

First, comorbidity in surgical candidates is surprisingly high, ranging between 27% and more than 80% (Table 17.1). The most plausible, but yet not well-confirmed, explanatory hypothesis of these findings lies in the fact that mesiotemporal structures which are disturbed in temporal lobe epilepsy (TLE) are central to experiencing and processing emotions.

Second, the total amount of psychopathology diminishes only slightly after surgery: stable patients usually stay stable, some deteriorate, and some – especially if seizure-free – improve (see below for more details). As for the prognosis of a poor psychiatric outcome, the presence of preoperative psychiatric disorders, bilateral independent spike discharges, and the size of surgical resections are predictive (Anhoury et al. 2000). Also the existence of severe personality disorders seems to be a potent indicator of bad psychiatric outcome (Koch-Stoecker 2001; 2002).

Psychoses

The term "psychosis" designates – globally spoken – severe psychiatric syndromes, characterized by thoughts, feelings, and actions that are incomprehensible for a

Table 17.1 Total psychiatric comorbidity in surgical candidates

Jensen and Larsen 1979	>80%
Polkey 1983	43%
Naylor et al. 1994	43%
Manchanda et al. 1996	47%
Ring et al. 1998	52%
Blumer et al. 1998	57%
Glosser et al. 2000	51% (psychiatric syndromes only, Axis I DSM–III–R)
Anhoury et al. 2000	44%
Inoue 2001	27%
Cankurtaran et al. 2005	27%
Koch-Stoecker, in preparation	47% (psychiatric syndromes) 69% (psychiatric syndromes plus personality disorders)

neutral observer. Diagnoses are often based on spectacular symptoms such as delusions and hallucinations without any further diagnostic differentiation. Given this weak assessment basis, Savard (1991) found in a meta-analysis of diverse studies preoperative rates of psychoses between 7% and 16%, and postoperative ones between 10% and 28%.

The importance of an exact classification of psychoses in the context of epilepsy is emphasized by Trimble and Schmitz (1997). They distinguish between ictal, postictal, peri-ictal, interictal, and alternative psychoses. Except for interictal psychoses, which require antipsychotic treatment, all other psychoses in epilepsy require a regulation of the antiepileptic drugs as the first therapeutic intervention. Thus, clear diagnoses can save patients from referrals to psychiatric hospitals and from antipsychotic medication, but are also relevant for epilepsy surgery.

Postictal psychoses

Poor diagnostic differentiation between the psychoses, especially between postictal and interictal ones, can have severe consequences for surgical candidates.

Table 17.2 Postictal psychoses

Incidence in TLE
4% (Kanemoto et al. 1996)
Incidence in surgical candidates
18% (Umbricht et al. 1995)
13% (Kanemoto et al. 1998)
6% (Koch-Stoecker 2001)
Psychiatric outcome
Psychoses
None (Koch-Stoecker 1997)
Temporary mood disorders
60% (Kanemoto et al. 1998)
50% (Koch-Stoecker 2001)
Seizure outcome (class I)
3%; further 33% after second resection (Koch-Stoecker 2001)

Thus, without exact psychiatric classification, the already-mentioned tendency to exclude psychotic patients from surgery could mislead surgeons into regarding postictal psychoses as a contraindication for epilepsy surgery. "Mislead" because patients with postictal psychoses can profit from surgery in two ways. If the resection is successful, they lose their seizures. However, in addition they will lose their directly seizure-related psychosis. For these reasons Fenwick (Fenwick 1994) has even suggested that postictal psychoses should be regarded as a psychiatric indication for epilepsy surgery.

The occurrence of postictal psychoses was quoted at 4% in a large study group of more than 800 patients with TLE (Kanemoto et al. 1996), but the incidence in surgical candidates is higher (between 6% and 18%, cf. Table 17.2). Despite the optimistic view of being a psychiatric indication, there are some caveats concerning the postoperative course of patients with postictal psychoses.

The neurological condition of these patients is complicated. Bitemporal (Savard et al. 1991) and extratemporal EEG discharges, clusters of seizures (Umbricht et al. 1995), and nocturnal GTCS (Kanemoto et al. 1996) occur frequently in this group. Whether this complicated epileptological precondition results in a seizure prognosis less favorable than in other patient groups needs further evaluation. With respect to the

psychiatric course after surgery, the odds of having a postoperative depression are increased (Kanemoto et al. 1998).

Results on incidence and postsurgical course are shown in Table 17.2.

Chronic interictal psychoses

Because of the widespread reservation about operating on chronic psychotic patients, due to the argument that the psychoses would continue to persist anyhow and surgery would therefore not be profitable, the number of severe psychotic patients evaluated has been small in epilepsy surgery centers. However, the argument of the positive effects of a seizure reduction in psychotic patients is relevant, and Fenwick (1988) has argued that psychotic patients without seizures could be much "better off" than patients with psychosis plus seizures. Moreover there are reports of permanent remittances of psychoses after surgery (Jensen and Larsen 1979), and enduring deteriorations have been rarely reported (Taylor 1972). Marchetti et al. (2003) studied six cases, with postoperative improvement in the mental conditions except for one patient. Altogether only one patient has been reported who, although seizure-free, showed a worsening in psychotic symptoms (Reutens et al. 1997).

Nevertheless, surgical interventions in chronic psychotic patients are complicated. First, the comorbidity of psychosis and TLE may be evidence for an extended limbic dysfunction. Second, we know that these patients are highly vulnerable and tend to experience acute exacerbations of their psychosis during stressful life events, like surgery. It is therefore imperative to provide special perioperative care and tailored postoperative rehabilitation settings for them in order to prevent acute crises (Krahn et al. 1996; Taylor 1987). It is recommended that preoperative education of chronic psychotic patients and their carers includes information about the restricted aims of surgery. They must understand that their epilepsy and their psychosis are two different disorders, and that psychosis will most probably continue after surgery, even if in a milder way.

With these special preparatory conditions, worthwhile results can be achieved. In our experience, chronic psychotic patients who were operated on suffered from acute psychotic exacerbations after surgery in most cases, but in the long run the psychoses became milder in some of them, going along with seizure reduction. This is in accord with results of Kanemoto et al. (2001) who found improvements of chronic psychoses in one-third of operated psychotic patients, and no worsening. However, the probability of seizure freedom for psychotic patients is unclear and needs further studies.

Postoperative psychoses

There is a continuing discussion as to whether or not typical *de novo* psychoses are induced by epilepsy surgery. According to one position, postoperative psychoses primarily occur as so-called *de novo* postictal psychoses (Savard et al. 1998) in patients with persistent seizures, and thus are only indirectly connected with the surgical event. Another position is that surgery only has the function of a trigger that releases a manifest psychosis, which was already latent and might have found its preoperative expression in paranoid personality traits (Koch-Stoecker 2002; Ferguson et al. 1993). However, there are still good arguments for the diagnostic entity "*de novo* psychosis" as etiologically linked to the surgical intervention itself. Mace and Trimble (Mace and Trimble 1991) consider them to be an effect related to a nondominant hemisphere hypofunction, because they predominantly occur after right/nondominant resections. They further argue that the sudden inhibition of seizure activity through surgery may induce mechanisms parallel to those of "forced normalization" (cf. Krishnamoorthy and Trimble 1998).

There is no doubt about the occurrence of postoperative psychoses, but again the data concerning etiology and predictors as well as clinical features have to be interpreted with caution, because of methodological reasons (retrospective analyses, missing reliable preoperative information, problems of classification).

Regarding the frequencies, Savard (Savard 1991) found in a meta-analysis a spectrum between 0.5% and 21%, and Trimble (Trimble 1992) between 3.8% and 35.7%, with a mean of 7.6%. If only studies of the last decade are considered, five de novo psychoses are reported out of altogether 253 patients, which means a 2% rate (Anhoury et al. 2000; Kanemoto et al. 2001; Cankurtaran et al. 2005). Concerning pathology, it has been suggested in several studies that gangliogliomas predispose to postoperative psychoses (Andermann et al. 1999; Bruton 1988), but this finding is equivocal. Nondominant temporal foci are frequent (Koch-Stoecker 2001; Mace and Trimble 1991) in

contrast to an excess of left-sided, dominant lesions noted for chronic psychoses in epilepsy without surgery (Flor-Henry 1969). In a recent case-control study some other preoperative neurological characteristics were found. Patients with de novo psychoses had smaller contralateral amygdalas, bilateral EEG dysfunctions, and pathologies other than mesial temporal sclerosis in the excised lobe (Shaw et al. 2004).

Concerning preoperative psychopathology, in our studies we found that all patients with new postoperative psychoses had personality disorders before surgery (Koch-Stoecker 2001; Koch-Stoecker 2002), which indicates that surgery may be the critical event overwhelming the psychotic threshold in patients with already preoperatively weakened personality structures as Ferguson predicted in 1993 (Ferguson et al. 1993).

Postoperative psychoses often start with symptoms of mood and sleep disturbance and then continue with delusions, which are frequently initiated by a seizure-relapse. The psychotic contents mainly relate to two themes (Ferguson and Rayport 1965): (1) psychotic processing of the surgical context, such as suspecting microchip implantation by surgery or laser influence in the brain; and (2) psychotic processing of anticipated new psychosocial demands, such as suspecting neighbors of controlling influences or negatively commenting on patients' actions.

The long-term course in some cases depends on patients' compliance to take prescribed medications, in others on further treatment of epilepsy (e.g. reoperation). Many patients respond to antipsychotic medication, but in others there is a necessity for repeated treatment in psychiatric hospitals.

The findings on postoperative psychoses are summarized in Table 17.3.

Table 17.3 Postoperative "*de novo*" psychoses

Frequency
0.5–21% meta-analysis (Savard et al. 1991); 3.8–35.7% meta-analysis (Trimble 1992); collection of cases from newer studies (cf. text): 2%
Morphology
Gangliogliomas preferred (Andermann et al. 1999, Bruton 1988)
Laterality
Nondominant epileptic focus (Kanemoto et al. 2001; Mace and Trimble 1991)
Preoperative psychopathology
100% personality disorders (Koch-Stoecker 2001)
Symptoms
Starting with depressive symptoms, sleep disorders, going on with delusions (frequently after first seizure relapse)
Psychotic contents
Attempted coping with surgery itself or with new psychosocial demands (Ferguson and Rayport 1965)
Long-term development
Variable: some chronic, some free of psychosis after second resection, some remitting with antipsychotic treatment

Affective disorders and anxiety

As is the case for psychoses, it is also true for affective disorders that the usual psychiatric diagnostic categories do not offer adequate classification for epilepsy patients. Typical constellations of symptoms allowing the diagnosis of a "major" depressive episode are rare; dysthymic, dysphoric, or "organic" depressive states are rather frequent (see also Chapters 9 and 10).

Blumer et al. (1998) found that those interictal dysphoric mood disorders – present in 57% of their patients – faded away after surgery in 20% of patients; 36% stayed stable with their dysphoric disorder, and 44% worsened after surgery, some with a remission after antidepressant treatment. In Blumer's group there were also about 40% of the psychiatrically intact group, predominantly those who continued to have seizures, who developed dysphoric episodes after surgery.

Congruently, high rates of postoperative emotional irritation and lability with sudden mood changes, uncertainty concerning the future, reduced stress tolerance etc. during the first months after epilepsy surgery have been found as typical early postoperative complications in more than 40% of all resected patients (Fraser 1988; Ring et al. 1998). A recent study found younger age, preoperative anxiety, and operation on the right side as potential risk factors for early postoperative complications (Moss et al. 2009). In the series of Ring et al. (1998), the early postoperative symptoms of anxiety strongly diminished after 3 months.

However, an exact differentiation between the interwoven symptoms of irritability, anxiety, and

mood fluctuation during the early postoperative weeks is not easy, or may even be impossible. This time period deserves to be better evaluated from the psychopathological perspective.

Besides these early mood changes, circumscribed episodes of de novo depression occur after epilepsy surgery. As early as in 1957 Hill et al. (1957) described their occurrence, being independent of seizure outcome, with a remission within the first 18 months after surgery. Because of their temporary character, Trimble (1992) designates them as "complications of surgery." Their frequency is about 8–10% of surgically treated patients (Naylor et al. 1994; Glosser et al. 2000; Koch-Stoecker 2001). They occur more often after nonlesional resections or mesiotemporal scleroses (Bruton 1988), in nondominant resected patients (Fenwick et al. 1993; Quigg et al. 2003), and in preoperatively aggressive patients, who lose their aggressiveness after surgery and tend to switch into depressions (Hill et al. 1957; Taylor 1987). There are hints from one paper of dominant resections as risk factors for postoperative depression and, as mentioned above, a higher risk for those patients with postictal psychoses before surgery (Kanemoto et al. 1998).

Malmgren et al. (2002) presented a different approach to postoperative affective symptoms. They studied pre- and postoperative psychopathologies and were able to classify definitely more "organic" affective disorders than episodes of depression. Especially the category of an "astheno-emotional" affective disorder seemed suitable to describe epilepsy-related organic symptoms.

The occurrence of postoperative depression was found to be independent of seizure outcome (Hill et al. 1957), except for preoperatively psychiatrically intact patients in whom depression seems to be linked to seizure recurrence (Blumer et al. 1998). High irritability after surgery and marital conflicts are described as potential catalysts (Wrench et al. 2009).

The enduring remittance of depressive symptoms depends on complete seizure relief (Hermann and Wyler 1989; Blumer et al. 1998). Depression and anxiety in patients with refractory epilepsy significantly improve in the long run after epilepsy surgery, especially in those who are seizure-free.

For an overview on postoperative depression see Table 17.4.

In our studies there are hints of a laterality effect of postoperative symptoms in preoperatively depressed patients. A dominant resection frequently leads to somatoform symptoms as surrogates of depression (headache, backache, etc.), while nondominant resected patients show typical episodes of depression postoperatively. But there is also contradictory evidence that, instead, right temporal resection contributes to the development of somatoform disorders (Naga et al. 2004).

Mania seldom occurs in patients with TLE (Wolf 1982). However, with respect to postsurgical outcome there are some reports of manic syndromes. Krahn et al. (1996) described hypomanic states immediately after surgery and Kanemoto et al. (1998) reported about 10% of the resected patients showing (hypo-)manic episodes directly after surgery. A case–control study (Carran et al. 2003) revealed the following risk factors for manic symptoms after surgery: EEG dysfunctions contralateral to the resected side, secondary generalized seizures, and right temporal resections, again, all factors showing a more widespread cerebral pathology which transcends the resected focus. It may

Table 17.4 Episodes of postoperative depression

Duration
Remission within 18 months (Hill et al. 1957)
Etiological hypothesis
Process of scarring (Trimble 1992)
Frequency
8–10% of resected patients (Bruton 1988; Naylor et al. 1994; Koch-Stoecker 2001)
Morphology
Mesiotemporal sclerosis or nonlesional resections (Bruton 1988)
Laterality
Nondominant resections (Fenwick et al. 1993; Koch-Stoecker 2001); dominant resections (Kanemoto et al. 1998)
Psychiatric predictors
Aggressivity leads to postoperative depression (Taylor 1987); postictal psychoses leads to postoperative depression (Kanemoto et al. 1998)
Seizure outcome
Independent occurrence (Hill et al. 1957; Koch-Stoecker 2001)

well be that the incidence of manic disorders is usually underestimated because of two different reasons: (1) the differentiation between optimistic happiness after successful resection and symptomatic euphoria is difficult in some cases; and (2) manic symptoms may have already vanished and may not be remembered at the time of the first postoperative evaluation, which in many centers takes place at 3 or 6 months after surgery.

Anxiety disorders or at least symptoms of anxiety are very common in epilepsy patients, but their classification raises many problems. A differentiation between fear of seizures, fear as a symptom of seizures, avoidant behaviors due to stigmatization, fear as a symptom of depression, and others is complicated, and most studies lack a clear diagnostic classification. Accordingly, preoperative estimations of anxiety disorders in candidates for surgery vary between 10% (Manchanda et al. 1996) and 44% (Bladin 1992).

More than 2 years after surgery Koch-Weser et al. (1988) even found higher rates of anxiety than before surgery.

Nonepileptic attacks (nonepileptic seizures)

Most centers have been reluctant to operate on patients with epileptic seizures which occur in association with nonepileptic attacks. Even if the epilepsy is cured by surgery, there is a high probability of the dissociative attacks continuing. The recommendation is that only after nonepileptic attacks are at least in an ongoing psychotherapeutic treatment should surgery be considered (Henry and Drury 1897). The argument used in chronic psychoses that patients are better off when one of two disorders is cured does not apply to nonepileptic seizure disorders. Often the two types of seizures cannot be disentangled by the patient. Thus the reduced number of epileptic seizures with ongoing nonepileptic seizures is no qualitative improvement after surgery.

Concerning postoperative nonepileptic attack disorders (NEADs), there are some reports in the early surveys of the psychiatric effects of epilepsy surgery (Ferguson and Rayport 1965; Taylor 1972). Later studies revealed that NEADs were found in just fewer than 10% of cases within a timeframe of 10 years after epilepsy surgery (Glosser et al. 1999). They started within the first months after surgery, affected predominantly women, lateralization of resection was right temporal, and the seizure-onset was frequently after adolescence. Ney et al. (1998), in another study, found 5% postoperative NEADs, with left lateralization, a high rate of preoperative psychopathology, low IQ, and high frequency of perioperative complications. In a third study, a 3.5% rate of nonepileptic seizures in operated patients was reported (Davies et al. 2000), postoperative "interictal dysphoric disorder" and operative complications being risk factors. In our study we had 4% postoperative dissociative attacks, all of them right temporal resections, and all of them with preoperative borderline personality disorders (Koch-Stoecker 2001).

Table 17.5 Postoperative nonepileptic attacks

Frequency
10% (Glosser et al. 1999); 5% (Ney et al. 1998); 4% (Koch-Stoecker 2001), 3.5% (Davies et al. 2000).
Preferred incidence
Gender
Women (Glosser et al. 1999; Koch-Stoecker 2001)
Laterality
Right (Glosser et al. 1999; Koch-Stoecker 2001); left (Ney et al. 1998)
Onset time
After adolescence (Glosser et al. 1999)
Preoperative psychopathology
High (Ney et al. 1998)
Borderline personality disorders (Koch-Stoecker 2001)
IQ
Low (Ney et al. 1998)
Peri- and postoperative complications
High operative complication rate (Ney et al. 1998; Davies et al. 2000)
Postoperative dysphoric states (Davies et al. 2000)

See Table 17.5 for a summary.

While Glosser et al. (1999) interpret the incidence of nonepileptic attacks as some kind of somatoform disorder, we would regard them as phenomena of dissociation, which enable the patient to shut down conscious experience temporarily, especially in distinct situations of unbearable, overwhelming emotions. The mechanisms of dissociative states are

perhaps comparable to the functional loss of consciousness with epileptic seizure activity.

Personality disorders – a gateway to an individual understanding of patients

After a period of 20 years of neglect, a growing scientific interest has again been directed to personality disorders during the last decades. One reason is the increasing knowledge about the neurobiological basis of behavior, including questions of how personality traits are represented in brain functioning. Issues of the demarcation of personality disorders from manifest psychiatric syndromes at one end and from normal variants of behavior patterns at the other have been discussed, as well as the etiological components and the predictive value of personality disorders for psychiatric disorders in later life.

According to current psychiatric theory, personality disorders represent enduring patterns of thoughts, emotions, and actions which differ considerably from expectations of sociocultural surroundings and lead to impairment and suffering. They usually become manifest during adolescence. Constitutional, biographic, and experience-related conditions are discussed as etiological factors.

With respect to TLE, the debate about the "epileptic personality" has been more harmful than helpful. There is much evidence that epilepsy patients, especially those with a mesiotemporal seizure focus, show behavior disturbances, which could be partly seizure-related due to limbic system hyperactivity and interictal inhibitory mechanisms, partly linked to the brain lesion itself, and partly due to the effects of antiepileptic drugs, etc. (Engel et al. 1991; Blumer 1999).

Our own main studies on personality disorders in the surgical context revealed their negative impact on outcome: first, 60% of our patients with temporal lobe resections had personality disorders; second, about one-third of all patients with severe personality disorders suffered from postoperative psychiatric deteriorations; third, we had no new psychoses after surgery without pre-existing personality disorder (paranoid features in most cases) and we had no new dissociative attacks after surgery without pre-existing personality disorders (all borderline type) (Koch-Stoecker 2001). Finally all patients in need of psychiatric inpatient treatment after surgery had a diagnosis of a personality disorder (Koch-Stoecker 2002). About 10% of all personality disorders were classified as "organic" ones, due to the neurological disease.

These results have implications for preoperative patient information. On the one hand education about risks of postoperative psychiatric complications must be part of an informed consent; on the other hand an analysis of the individual development that brought about the personality disorder permits us to gain an insight into the complex structure of the internal affairs of patients and provides hooks for psychotherapeutic interventions.

How could the development of personality disorders and their neuronal basis be explained?

Temporal lobe epilepsy itself may be relevant for the impairment of successful personality development. It provokes intermittent neuronal overexcitations within limbic structures, with the result of a disturbance in processing adequate emotional reactions. It may perhaps lead to sudden unexplained experiences of fear. The seizure-induced "kindling" process then evokes a generalization of fear reactions, and facilitates avoidant behavior as a means of fear reduction. This process finally may cause the development of an avoidant personality. The same behavior strategy could develop as a reaction to punishment-induced fear, or it could be a consequence of feelings of inferiority in social communication due to severe memory deficits, etc. In any of these cases, the avoidant behavior is the person's attempt to choose the subjectively most adaptive of all available reactions to cope with fear. For that reason the persons themselves will not understand that their behavior is judged as inconvenient or even as a psychiatric disorder.

Beyond the problem of maladaptive behavior itself, personality disorders involve a reduced stress tolerance and a heightened psychic vulnerability, possibly as an additional result of the limitations due to dysfunctional neuronal connections. Thus it becomes evident that so-called "stressful life events" processing capacities are easily overwhelmed and the cognitive/emotional system breaks down resulting in psychotic decompensation.

For epilepsy patients with personality disorders, the context of surgery itself is a stressful event. In addition, and supporting the escalating process, the surgical

disconnection of temporal structures alters the activity of other parts of the brain. This process may exacerbate behavior changes. Thus the postoperative period is a double delicate time-span, involving changes in the cerebral mechanisms of excitation and inhibition.

Such a model of interaction of psychosocial and neurobiological factors could be paradigmatic for the development of all psychoses: maladaptive schemata of action and behavior, acquired by constitutional and/or experiential faults, are preconditions, which emerge as personality disorders. Under emotional stress they become dysfunctional and end up as psychoses.

Treatment options are rare, because psychotherapeutic interventions in patients with personality disorders are arduous and must proceed slowly.

Included are:

1. Analysis and validation of the maladaptive strategies within the individual social and neuronal network.
2. Continuous instruction about the possibility and the benefit of change by the use of different, more adaptive behavior strategies.
3. Support and coaching during the attempts of an implementation of new behavior, altering neuronal pathways by use and extinguishing unsuitable old ones.

Psychiatric disorders as predictors of postoperative seizure outcome

The question of whether there is a link between presurgical psychiatric morbidity and seizure outcome has been touched upon several times in the above paragraphs. For many years this topic has not been at the center of psychiatric research around epilepsy surgery. It seemed rather incidental that in 1994 Naylor et al. (1994) provided some information that there was a nonsignificant tendency for a failure to become seizure-free in patients with preoperative psychopathology. In 2000, again as an incidental result in a study focusing on psychiatric outcome, Anhoury et al. (2000) described "weak evidence" that patients with a past psychiatric history and new postoperative psychiatric symptoms were less likely to achieve 90% seizure reduction. Our own results also supported the predictive value of psychopathology on seizure outcome (Koch-Stoecker 2001).

In 2009, the first three papers were published which directly focused on the predictive value of preoperative psychopathology on seizure outcome.

Guarnieri et al. (2009) found a significantly worse seizure outcome for patients with anxiety and with personality disorders when comparing the classes Engel 1A with 1B or higher.

Kanner et al. (2009) found that lifetime psychiatric history independently predicted a failure to reach Engel's outcome classes 1A, 1A+1B, and 1A+1B+1C. Kanner concluded: "Patients with psychiatric disorders could have epileptogenic areas that are more diffusely distributed." And with respect to the surgery decision he stated that ". . .a lifetime psychiatric history is a red flag for a more severe seizure disorder."

In a third study the predictive value of preoperative depressive symptoms (measured by the Beck Depression Inventory) on seizure outcome was confirmed (Metternich et al. 2009).

These studies go beyond the psychiatric question about how to prevent bad psychiatric outcome after epilepsy surgery. The results demonstrate that psychiatric disorders and epilepsy belong together so strongly that we have to assert that psychiatric topics are no longer a luxury add-on but an essential component of a thorough approach to the field of epilepsy surgery. It underlines the necessity that neurologists and psychiatrists start talking to each other (Kanner 2003; Koch-Stoecker and Kanemoto 2008).

A proposal for psychiatric assessment strategies

It is neither necessary, nor economic, nor possible to carry out extensive life chart analyses for every patient prior to surgery. Instead, it is mandatory to have a diagnostic screening for everybody and then decide who needs acute psychiatric treatment or a detailed examination of organic, biographic, and situational aspects of personality structure in order to discover the individual traps.

Psychiatric syndromes like depression or psychoses should be treated adequately before surgery; patients with nonepileptic seizures should be in an effective psychotherapeutic treatment setting before surgery is conducted.

If severe maladaptive personality traits are discovered, information about possible dangers in the context of surgery is necessary, and, if possible, a process of psychotherapeutic counselling should be started, which is often long-lasting. Unfortunately, most healthcare providers are reluctant to take care of these patients.

Specific recommendations for diagnostic screening

For an overview about the patient's general physical and mental symptom-load we use the SCL-90 R (Derogatis et al. 1973). It is a helpful instrument not only for a broad screening, but is also helpful to visualize pre-postoperative symptom changes in various domains and to reflect these changes with the patient.

For the assessment of depressive symptoms we use the Beck Depression Inventory (Beck et al. 1961). Another very short option to screen for depressive symptoms in epilepsy patients is the six-item Neurological Disorder Depression Inventory for Epilepsy (NDDI-E) (Gilliam et al. 2006).

For an overview of potential personality disorders the Structured Clinical Interview for DSM IV, Axis II Personality Disorders (SCID-II) questionnaire is useful (First et al. 1994). Yet, it is not sufficient to make valid diagnoses. In any case, even if not administered to make personality diagnoses, this instrument should be followed by an offer of a personal interview, because the questions touch substantial personal areas and behavior features which may require some therapeutic support after answering.

Conclusions

A high prevalence of psychiatric disorders, transcending the rates of the normal population in all diagnostic domains, is found in the group of epilepsy patients presenting for surgery. The quality of those psychiatric disorders is atypical in many cases, modulated by epilepsy-related organic processes.

At the same time the existence of psychiatric comorbidities in epilepsy surgery candidates has a strong impact on surgery outcome. On the one hand psychiatric disorders can hamper the utilization of seizure reduction or seizure freedom, with the effect that an amelioration of quality of life does not evolve. On the other hand comorbid psychiatric disorders reduce the probability of postoperative seizure freedom. In both cases epilepsy-correlated personality disorders are in the focus of negative effects.

Preoperatively it is essential to conduct a psychiatric screening and to start psychiatric treatment (medication or counselling), if necessary.

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Chapter 18

Brain mechanisms of impaired consciousness in epilepsy

Andrea Eugenio Cavanna and Fizzah Ali

Epilepsy and the renaissance of consciousness

From intricately interwoven philosophical theories to its proclaimed symbiosis with religion, the mysterious concept of consciousness presents humankind with a dilemma. The past decade has witnessed a metamorphosis of interest, since neuroscientific curiosity and empirical scrutiny have flourished in place of theoretical debate (Zeman 2001).

Scientific understanding of consciousness has been hampered to some degree by notorious ambiguities linked with the multifaceted term. The clinical relevance of consciousness, however, is indisputable; spanning from neurodegenerative dementias to coma and vegetative states and from sleep disorders to epilepsy (Cavanna and Monaco 2009). The connection between epilepsy and consciousness is longstanding. Current classification recognizes the dichotomy between "partial" seizures (involving focal brain regions or confined to one hemisphere) and "generalized" seizures (involving diffuse brain regions throughout both hemispheres) (Engel 2001). Transient impairments of consciousness have long been considered a trademark of generalized seizure activity (Zappulla 1997). However, epileptic seizures as a whole represent a spectrum of disorders of underlying dynamic and reversible brain dysfunction that generate selective impairment of consciousness, ranging from minor impairment of attention to total behavioral unresponsiveness. Furthermore, International League Against Epilepsy criteria have previously dictated impairment of consciousness to be a major definitional criterion in the differentiation between "simple" and "complex" partial seizures (Commission on Classification and Terminology of the International League Against Epilepsy 1981). Whatever degree of impairment, the sudden departure of consciousness that typifies epilepsy has major negative consequences attached, including social sanctions (stigma, driving restrictions), economic burden (occupation-related), and personal injury (burns and falls).

Epilepsy provides an ideal model to scrutinize abnormal changes in neural activity alongside associated alterations in the conscious state in order to delineate brain mechanisms and localize implicated anatomical structures of impaired consciousness (Monaco et al. 2005; Cavanna 2008; Blumenfeld 2009). This chapter commences with clarification of definitional issues encompassing the concept of consciousness; an outline of a widely endorsed bi-dimensional model for the study of the neural correlates of conscious states in relation to ictal phenomenology ensues. A review of current insights into the brain mechanisms underlying alterations in consciousness according to epileptic seizure type concludes.

Definitional issues

Denoted to be both the most obvious and most mysterious quality of the human mind, consciousness holds an ambiguous place in a world dependent on communication through definition (Dennett 1987). Consciousness, quintessentially subjective, evades unequivocal definition; attempts at generating a unanimously accepted definition have yielded varying results over time and from various domains whether that of clinical medicine, neurosciences, psychology, or philosophy (Markowitsch 1995). The distinction between consciousness and self-consciousness has been previously emphasized, with the former relating to "wakefulness," "experience," and the "possession of various mental states," and the latter to encompass such states as "self-recognition," "self-knowledge," and "awareness of awareness" (Zeman 2001).

The Neuropsychiatry of Epilepsy, ed. Michael R. Trimble and Bettina Schmitz. Published by Cambridge University Press.

From a clinical perspective, consciousness has been considered akin to the waking state, and the capacity to perceive, interact, and communicate with the environment and with other individuals (Dennett 1987; Markowitsch 1995; Zeman 2001). Thus, clinical medicine employs terminology such as *clouding* and *dwindling* to represent reduced levels of awareness. More specifically, in epileptological terms consciousness has been determined to be the patient's responsiveness during the ictal state. It is pertinent to observe, however, that such a definition fails to account for impaired responsiveness as a result of alternative causes (e.g. ictal aphasia, forced attention, and other transient disturbances of sensory processes and memory) (Zappulla 1997; Monaco et al. 2005) and further fails to express variations in the subjective contents of ictal consciousness (Cavanna 2008; Johanson et al. 2008). The latter criticism is fundamental to current understanding of consciousness; consciousness is not simply a unitary phenomenon but is multi-compartmental. Particular distinction between the quantitative features (*level*) of consciousness and qualitative features (*content*) of consciousness is supported by an array of neurophysiological and neuroimaging studies (Cavanna and Monaco 2009; Blumenfeld 2009; Cavanna et al. 2009).

Level and contents of consciousness

Despite difficulties in formulating a universally acceptable and all-encompassing definition, the underlying neural correlates of consciousness can be divided into those structures necessary for the maintenance of the level of conscious states and those required for the generation of the content of conscious experiences (Plum and Posner 1980; Baars et al. 2003; Blumenfeld and Taylor 2003; Blumenfeld 2009).

The level of consciousness is the degree of wakefulness, arousal, or vigilance, and ranges along a continuum extending from alertness progressing to drowsiness and terminating with coma. Assessment of the behavioral constituents of awareness, including motor and verbal responsiveness to external stimuli, as in the Glasgow Coma Scale, allows clinical quantification of the level of consciousness (Plum and Posner 1980). In order to demonstrate the multi-compartmental nature of consciousness the level of consciousness may be further subdivided into three mechanistically linked processes: those that maintain the (1) alert state, (2) attention, and (3) awareness of self and environment. The three processes are dependent on interactions between numerous parallel neurotransmitter systems originating from the upper brainstem and diencephalon, higher order frontal and parietal association cortex, and, more controversially, the basal ganglia and cerebellum (Zeman 2001; Dreher and Grafman 2002).

The integrity of ascending ponto-meso-diencephalic reticular pathways and widespread thalamocortical projections is elementary to the neurobiological basis of awareness (Moruzzi and Magoun 1949). Furthermore, the reverberating activity of thalamocortical neural loops has been hypothetically implicated (Crick 1994; Llinas et al. 1998). Circumscribed lesions involving the reticular formation and/or thalamic intralaminar nuclei have been associated with bilateral cortical impairment, thereby restricting the level of consciousness to coma and a persistent vegetative state (Giacino 1997; Laureys et al. 2004). Functional imaging reports have provided further converging evidence: the spread of ictal discharge to subcortical structures generates abnormal or disrupted activity in the thalamocortical networks and correlates with complete loss of consciousness (Lee et al. 2002). Positron emission tomography studies of normal subjects during slow wave sleep (Maquet 2000), drug-induced anesthesia (Alkire et al. 2000), and hypnotic states (Rainville et al. 2002) demonstrate a pattern of selective thalamic hypometabolism. Subsequently the upper brainstem-diencephalic activating system has been established as a neuroanatomical foundation of conscious awareness (Ortinski and Meador 2004).

The content of consciousness encompasses subjective experiences such as emotions, sensations, memories, and intentions and is a product of the interaction between exogenous factors derived from the environment plus endogenous factors such as internal attention, with associated visceromotor reactions (Coslett 1997; Critchley 2005). Consequently, the intensity and emotional salience associated with such subjective experiences tends to vary vastly, ranging from the phenomena of peripheral consciousness to intense experiences, according to modulation by temporo-limbic activity (Johanson et al. 2003). Early experiments illustrated the role of the temporal cortex in eliciting significant changes in the contents of consciousness (Jasper 1998). Likewise the importance of the medial temporal lobe structures for the conscious recall of past events has been demonstrated (Gloor et al. 1982).

Specific cortical lesions have demonstrated the capacity of the contents of consciousness to vary independently of the level of consciousness (Frith et al. 1999). Pathological conditions such as limbic status epilepticus are an exception whereby high levels of arousal can be associated with diminished contents of consciousness (Monaco et al. 2005). Clinical neurologists frequently allude to the level of consciousness in the phenomenological description of the ictal state; phrases such as "loss" or "impairment" of consciousness embody ictal unresponsiveness in the clinical setting (Gloor 1986). In comparison, the subjective dimension of ictal consciousness is something of a clinical recluse. One of the numerous challenges of the subject of consciousness is reconciling the qualitative and quantitative aspects through a unified model. Therefore, over recent years an integrated bi-dimensional model of consciousness has been proposed, allowing the comprehensive assessment of the ictal conscious state in different types of epileptic seizures in accordance with the two key component phenomena (Monaco et al. 2005).

When either content or level of consciousness is disturbed, loss of consciousness ensues. The most dramatic alteration of consciousness is its temporary extinction in the generalized seizure, characterized by complete unresponsiveness and absence of ictal subjective experience. Complex partial seizures produce a more variable picture; seizures originating from the temporal lobe, for example, generate intense subjective experiences as a result of perceptive and affective features affecting the contents of ictal consciousness. The level of general awareness is typically preserved in simple partial seizures, with the contents of consciousness selectively affected by a blend of visual, auditory, somatosensory, and mnemonic experiences (Monaco et al. 2005; Cavanna 2008, Cavanna et al. 2008; Johanson et al. 2008).

Ictal consciousness: from clinical assessment to brain activity

Graphically uniting the subjective and objective dimensions of consciousness in a bi-dimensional plot has aided in further delineating ictal consciousness experiences and providing possible representative conscious states of subjects undergoing particular seizure types (Figure 18.1) (Monaco et al. 2005; Cavanna 2008).

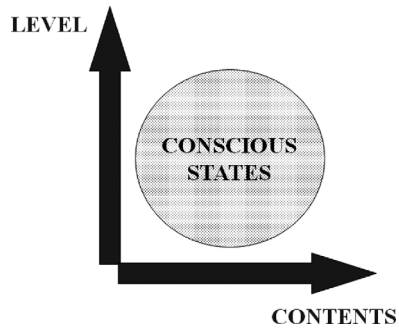

Figure 18.1. Biaxial diagram showing the two dimensions of consciousness (level and contents) which can be altered during epileptic seizures.

Table 18.1 Items 0–10 of the Ictal Consciousness Inventory (ICI) dealing with the level of ictal consciousness

During the seizure were you. . .
1. Aware of what was happening to you?
2. Aware of your surroundings?
3. Aware of the time passing by?
4. Aware of the presence of anyone around you?
5. Able to understand other people's words?
6. Able to reply to other people's words (e.g. *What's wrong with you?*)?
7. Able to obey other people's commands (e.g. *Sit down!*)?
8. Able to control the direction of your gaze?
9. Able to focus your attention?
10. Able to take any initiative?

Further assessment of the ictal conscious state, however, had previously been stunted by the lack of standardized tools available for quantitative bi-dimensional analysis. Use of alternative methods had additionally contributed to generating poor inter-rater and intra-rater reliability. The Ictal Consciousness Inventory (ICI) is a recently developed and validated self-report scale that allows standardized quantification of (1) the level of general awareness/responsiveness and (2) the vividness of ictal subjective phenomena. The first 10 items (Table 18.1) of the scale assess general awareness: querying general awareness of time, place, and the presence of others; comprehension of others' spoken words; verbal and nonverbal responsiveness; gaze control; and forced attention and voluntary initiative. The second set of items (Table 18.2) assesses content of consciousness including: dreamy states; derealization with regard to

Table 18.2 Items 11–20 of the Ictal Consciousness Inventory (ICI), dealing with the contents of ictal consciousness

During the seizure did you. . .
11. Feel like you were in a dream?
12. Feel like you were in an unusually familiar place?
13. Feel that things around you were unknown?
14. Feel that everything was in slow motion or sped up?
15. Feel the presence of another person who was not there?
16. See or hear things that were not real?
17. See people/objects changing shape?
18. Experience flashbacks or memories of past events (as though you were reliving the past)?
19. Experience unpleasant emotions (e.g. fear, sadness, anger)?
20. Experience pleasant emotions (e.g. joy, happiness, pleasure)?

time and space; illusions and hallucinations; and déjà vu and unpleasant and pleasant ictal emotions. Each item is rated on a 0–2 Likert type scale and the scale yields two subscores for each dimension of consciousness each ranging from 0 to 20 (Cavanna et al. 2008). Despite the intrinsic limitations of self-report instruments and the inherent limitations with the study of epileptic seizures, including compliance and ictal amnesia, the ICI represents a reliable and user-friendly instrument for the assessment of the ictal conscious state within the framework of the bi-dimensional model.

The ICI reveals the nature of impairment in consciousness, allowing differentiation between those seizure types generating principally deficit in the level of awareness (generalized seizures, including absence or tonic–clonic) and those modifying the contents of consciousness (focal seizures). Although the distribution of brain electrical activity and consequent phenomenology of the ictal consciousness state varies, studies suggest that all three seizure types disrupt a core network of anatomical structures fundamental for preservation of the normal consciousness state. Anomalous neuronal excitation or anomalous neuronal inhibition is generated, thereby disrupting the function of (1) the upper brainstem and medial thalamus, (2) the medial prefrontal cortex, cingulate cortex, and precuneus, and (3) lateral and orbital frontal cortex, and lateral parietal cortex, subsequently impairing consciousness.

The term "consciousness system" has been given to a network of cortical and subcortical structures involved in the formation of consciousness (Blumenfeld and Taylor 2003). Studies of impaired consciousness states, including sleep (Maquet 2000), drug-induced anesthesia (Alkire et al. 2000), coma, and vegetative state (Laureys et al. 2004), have demonstrated the involvement of regions of the upper brainstem (midbrain and upper pons), medial thalamus, cingulate gyrus, medial prefrontal cortex, and precuneus, as well as lateral frontal and parietal association cortex. Additionally the significance of midline and intralaminar thalamic nuclei as well as hypothalamus has also been noted (Blumenfeld 2009). The following section will focus on the selective involvement of the "consciousness system" by different seizure types.

Consciousness in generalized seizures

Generalized tonic–clonic seizures (GTCS) occur as a result of widespread bi-hemispheric abnormal neuronal discharges. GTCS are characterized by complete unresponsiveness and convulsions. The tonic phase of these seizures comprises sustained axial muscle contraction, upward eye deviation, and pupillary dilatation, in association with 10–20 seconds of high-frequency electroencephalographic (EEG) activity. The ensuing clonic portion refers to rhythmic limb contraction with EEG demonstrating poly-spike-and-wave discharges (Blumenfeld 2009). The tonic–clonic phase with its associated dramatic impairment of consciousness, as a result of the involvement of widespread brain regions, persists for up to a few minutes. A period of lethargy and unresponsiveness of variable duration, from minutes to hours, proceeds. GTCS can be primarily generalized with no obvious focal onset, alternatively discharges originating from a single focus may propagate to form secondarily generalized seizures (i.e. secondary generalization of partial seizures).

Animal studies based on electrophysiological, blood flow, and metabolic mapping of GTCS have produced contradictory findings. Initial neuroimaging studies indicated homogenous involvement of the brain in its entirety (Engel et al. 1982), whilst some experimental studies demonstrate more regional changes (Cavanna et al. 2009; Blumenfeld 2009). In humans, secondary GTCS generate focal

postictal deficits, reflecting impaired function in the regions of seizure onset (Blumenfeld et al. 2003). In addition, more recent single photon emission CT (SPECT) studies of cerebral blood flow in secondary GTCS have demonstrated focal involvement of the brain, frequently in the region of seizure onset (Lee et al. 1987; Shin et al. 2002; Blumenfeld 2003; Blumenfeld et al. 2009). Altogether, these findings indicate that secondary GTCS and arguably primary GTCS do not implicate the whole brain homogenously but alternatively are more likely to involve particular areas.

Ictal–interictal SPECT has been used to investigate the neuroanatomical correlates of GTCS in humans. These investigations revealed cerebral blood flow increases during the seizure in specific focal brain regions; namely in the thalamus and upper brainstem as well as lateral frontal and parietal cortex. In contrast, decreases in cerebral blood flow were seen during the seizure period in the cingulate gyrus. Reduced cerebral blood flow continued postictally in the anterior and posterior cingulate gyrus and was additionally accompanied by diminished blood flow in the lateral frontal and parietal cortex.

The study of the postictal phase after spontaneous secondarily GTCS seizures further demonstrated the potential role of inhibitory cerebellar outputs in seizure termination, and in postictal decline in consciousness. Increases in cerebral blood flow are correlated with increased flow in the thalamus and with a massive decrease in blood flow in frontal and parietal cortex (Norden and Blumenfeld 2002; Blumenfeld 2009; Cavanna and Monaco 2009). The bilateral frontal and parietal association cortex are associated with greatest increases in cerebral blood flow during GTCS and are implicated in the profound and long-lasting impairment of consciousness associated with this seizure type. There is relative sparing of the intervening regions of the primary sensory and motor cortices. Sparing of the motor cortex adds support to the idea that the motor manifestations of GTCS may be mediated by brainstem circuitry. In some secondary GTCS following propagation from temporal lobe foci (Bell et al. 1997) and in the rare event of seizures limited to the bilateral sensorimotor areas, individuals can exhibit generalized tonic–clonic seizures and total preservation of consciousness (Nogueira et al. 2008).

Absence seizures are typified by sudden onset of blank staring and unresponsiveness of short duration, usually 5–10 seconds. They occur most commonly in children. Interruption of voluntary behavior may occur, including slowing or interruption of speech, and cessation of activities such as chewing or walking; in other instances simple behaviors including repetitive tapping or counting may be unimpaired. Clonic movements of the eyes or mouth including eyelid fluttering, or varying degrees of atonic, clonic, tonic, or myotonic activity including mild myoclonic jerks may also feature. Recovery is sudden with previous activity resuming and no significant postictal deficit (Cavanna and Monaco 2009).

The motor manifestations of absence seizures are relatively mild such that these seizures may be considered to be the most fundamental and transparent form of impaired consciousness in epilepsy. As a result of total reduction in both the level of general awareness and contents of consciousness, absence seizures are devoid of subjective experiences. The underlying ictal EEG pattern for typical absence seizures is characteristically bilateral and frontal predominant 3–4 Hz large amplitude spike-and-wave discharges (Weir 1965). The sudden onset and rapid generalization of discharge over the entire EEG suggests the involvement of a central neuroanatomical structure projecting extensively to the cerebral cortex. The thalamus has been proposed as a potential candidate, since simultaneous thalamic and cortical recordings in humans during absence seizures exhibited unambiguous thalamic participation during the seizure (Williams 1953). The evidence for the thalamic involvement was confirmed by PET studies (Prevett et al. 1995).

Thalamic circuits can generate hypersynchronized oscillations at 3 Hz, resembling the typical frequency occurring during absence seizures. However, the role of the thalamus alone does not sufficiently explain seizure generation; reports also cite the cortex as a key player in spike-and-wave seizures. Thalamic injections of high doses of GABAa antagonists such as penicillin resulted in 3–4 Hz oscillations with absence of spike-and-wave discharges, suggesting that the hypersynchronized oscillations induced by such drugs are not adequate in explaining seizures (Gloor et al. 1977). Conversely, injection of the same drugs to the cortex produced seizure activity with spike-and-wave patterns (Steriade and Contreras 1998). The evidence reviewed above suggests that absence seizures can be generated intracortically; however, the thalamus seems to be necessary. Principally this is indicated through lesional studies: spike-and-wave

discharges fade following thalamic lesions or by otherwise inactivating the thalamus (Vergnes and Marescaux 1992). Thus, both human and animal studies suggest the role of corticothalamic network oscillations in generating absence seizures, whereby the thalamus acts as the generator of the 3 Hz oscillation and the cortex generator of the spike-and-wave patterns.

Although generalized on EEG recording, studies in animal models have revealed that spike-and-wave seizures may involve certain corticothalamic loops more intensely, sparing other brain regions (Meeren et al. 2002). Involvement of specific neuroanatomical regions may hold crucial indicators toward explaining why these seizures cause reasonably selective impairment of consciousness. Human imaging studies have yielded highly controversial findings. Some investigations have shown global increases in cerebral blood flow, whilst others have demonstrated no change or alternatively increased or decreased blood flow in either focal or generalized patterns (Blumenfeld 2009; Cavanna and Monaco 2009). An amount of this variability may be attributable to technical limitations of the methods used as well as the intrinsic variability of absence seizures themselves, including fluctuation in EEG amplitude, duration, and rhythmicity (Blumenfeld and Taylor 2003).

The last decade has yielded the advantages of investigation through coupled functional MRI (fMRI) with simultaneous EEG recordings. Preliminary EEG-fMRI investigations have verified generalized spike-and-wave seizures to selectively involve particular networks, whilst sparing others. These studies have demonstrated bilateral thalamic activation, and cortical signal decrease in the anterior and posterior midline regions, and lateral frontal and parietal association areas (Hamandi et al. 2006; Salek-Haddadi et al. 2003; Aghakhani et al. 2004; Gotman et al. 2005). In accordance with these findings, various authors have convincingly criticized the notion that loss of consciousness in absence seizures occurs as a result of involvement of the entire brain in the seizure discharge (Blumenfeld and Taylor 2003). Alternatively it has been hypothesized that impaired consciousness in absence seizures occurs as a result of disruption of normal information processing in specific brain regions due to focal involvement of the bilateral fronto-parietal association cortex and related subcortical structures (Blumenfeld 2009; Cavanna and Monaco 2009).

Consciousness in complex partial seizures

Partial epileptic seizures are of focal origin; abnormal discharges may remain localized to the specific source or can secondarily generalize. Partial epileptic seizures can be further classified into simple partial seizures whereby consciousness is retained, or alternatively complex partial seizures which are defined by a loss of consciousness. Clinical manifestations of such seizures are dependent on the area of the cortex in which the seizure originates, extent of seizure propagation, and seizure duration.

The temporal lobe is the area of onset in approximately 80% of patients with partial seizures (Cascino 2001). Mesial temporal lobe sclerosis is a frequent neuropathological finding in patients with complex partial seizures of the temporal lobe (Williamson et al. 1993). These seizures commence with focal premonitory phenomena such as fear, rising abdominal sensation, or lip-smacking automatisms (epileptic aura) (Alvarez-Silva et al. 2006). Since the initial observations of Hughlings Jackson, it is well understood that local epileptic activity arising from the temporal lobe can create subjective experiential phenomena. Hughlings Jackson is credited with the first systematic study of conscious contents and wrote of "psychical states which are much more elaborate than crude sensations" (Hogan and Kaiboriboon 2003). These clinical manifestations of temporal lobe epilepsy are still poorly understood; however, it has been established that their repertoire ranges between affective, mnemonic, and composite perceptual phenomena. The affective components of experiential phenomena, otherwise referred to as "epileptic qualia" (Monaco et al. 2005), include both pleasant (joy, excitement, euphoria) and unpleasant (sadness, fear, guilt) subjective feelings, as well as symptoms of depersonalization (altered sense of self) and derealization (altered experience of the external world). Other cognitive and psychosensory subjective experiences may feature, including forced thought, abnormal familiarity, or unfamiliarity feelings (*déjà vu* and *jamais vu*), and dream-like states (Bancaud et al. 1994; Hogan and Kaiboriboon 2003). Auditory distortions, metamorphopsias including visual distortions such as micropsia and macropsia, and olfactory and gustatory hallucinations complete the catalog of the more common sensory experiences. Automatisms (stereotyped behavioral patterns) including oral activities

such as lip smacking, chewing, and swallowing, as well as postural changes can accompany or follow the experiential phenomena. In complex partial seizures, consciousness is initially spared, but the individual progressively and variably loses contact with the environment, and fixed staring and unresponsiveness may be exhibited. Complex partial seizures usually last between 15 seconds and 3 minutes; however, impaired consciousness is typically most profound late in the seizure. It may persist for several minutes after seizure termination; postictal behavior often continues to demonstrate impairment of consciousness with confusion and event amnesia.

Although experiential phenomena were originally described following stimulation of the temporal neocortex, subsequent studies have suggested that they can be elicited during medial temporal lobe stimulation, discharges, and seizures. In particular, activation of the limbic components of the medial temporal lobe, especially the amygdala, have been proposed to be responsible for the affective component of experiential phenomena (Cavanna and Monaco 2009; Monaco et al. 2005). However, the sheer diversity of the experiential repertoire manifesting during temporal lobe seizures suggests recruitment of widespread neural networks beyond the temporal lobe. Specific alterations of experience can also occur as isolated phenomena in simple partial seizures with experiential symptoms. These ictal manifestations have been an informative source of evidence on regional brain function and raise theoretical questions, in particular that of whether they represent a direct manifestation of ictal activity or are rather the result of disinhibition of connected neural systems by the ictal activity.

Scalp EEG recordings of complex partial seizures originating in the temporal lobe demonstrate 5–7 Hz rhythmic temporal lobe activity with some bilateral slowing (Williamson et al. 1993). Electrophysiological studies have indicated the requirement for bilateral temporal lobe involvement for loss of consciousness (general level of awareness) in complex partial seizures (Bancaud et al. 1994). However, this is a source of perplexity: although bilateral temporal lobe dysfunction may generate amnesia, the mechanisms by which this would also affect the level of consciousness remains to be clearly determined, as impairment of consciousness is deemed to occur only in disorders involving diffuse bilateral cortical areas, or the brainstem diencephalic activating systems.

In order to demystify the connection between loss of consciousness and complex partial seizures, Norden and Blumenfeld have suggested a "network inhibition hypothesis" (Norden and Blumenfeld 2002). The neuroanatomical structures important for consciousness have been stated to include the frontal and association parietal cortex, cingulate gyrus, precuneus, and activating systems located in the basal forebrain, thalamus, hypothalamus, midbrain, and upper pons. According to the network inhibition hypothesis, medial temporal lobe seizures propagate to midline subcortical structures (medial diencephalon and ponto-mesencephalic reticular formation) and interrupt their normal activating function, in turn spawning widespread inhibition of non-seizing regions of the frontal and parietal association cortex. Fronto-parietal network inhibition may ultimately be responsible for the impaired level of consciousness in the late ictal and immediate postictal phase.

In order to gain wholly reliable support for the network inhibition hypothesis complete investigation of underlying seizure physiology is required; however, the results of numerous studies provide support for this model. Functional imaging findings with ictal SPECT highlight the importance of medial temporal and midline subcortical connections in limbic complex partial seizures (Lee et al. 2002). Further investigations with SPECT have shown complex partial seizures with impairment of consciousness to exhibit extratemporal changes, namely increases in cerebral blood flow in the upper brainstem and medial thalamus, and decreases in the fronto-parietal association cortex and the anterior and posterior interhemispheric regions. In contrast, those partial seizures remaining confined to the temporal lobes were found to be associated with preservation of consciousness and more focal changes limited to the temporal lobes (Blumenfeld 2009; Cavanna and Monaco 2009). Abnormal activity in the midline subcortical structures in association with depressed function of the fronto-parietal association cortex may therefore be responsible for loss of consciousness during temporal lobe seizures.

An ictal-interictal investigation of 24 subjects with surgically confirmed mesial temporal lobe epilepsy tested this model through analysis of cerebral blood flow changes whilst performing continuous video-EEG monitoring (Blumenfeld et al. 2004a). Seizures associated with loss of consciousness (complex partial seizures) were associated with

Table 18.3 Ictal alterations in the level and contents of consciousness and associated patterns of brain activity according to the different seizure types

Seizure type	Alterations of consciousness		Brain activity		
	Level	Contents	Br/ Thal	PreF/ Cing/Pr	FP[a]
GTCS	↓	↓	↑	↓	↑–↓
ABS	↓	↓	↑	↓	↑↓–↓
CPS[b]	↓↑	↑	↑	↓	↓

[a]In generalized tonic–clonic and absence seizures, fronto-parietal activity can show an initial increase followed by a decrease.
[b]Experiential phenomena reported during partial/focal seizures are usually associated with increased activity within the temporal lobe.
ABS – absence seizures; Br – upper brainstem; Cing – cingulate cortex; CPS – complex partial seizures; FP – fronto-parietal association cortex; GTCS – generalized tonic–clonic seizures; PreF – medial prefrontal cortex; Thal – medial thalamus.

widespread changes: increases in cerebral blood flow in the temporal lobe and in midbrain subcortical structures (including mediodorsal thalamus and upper brainstem), alongside decreases in the frontal and parietal association cortex bilaterally (including lateral prefrontal, anterior cingulate, orbitofrontal, and lateral parietal cortex). Simple partial seizures characterized by sparing of consciousness, in contrast, were accompanied by more focal changes limited to the temporal lobes without concurrent alterations in the fronto-parietal or midline subcortical structures.

Ictal EEG recordings obtained during temporal lobe seizures with impaired responsiveness demonstrate marked slowing in bilateral frontal and parietal association cortices, noted to be particularly prominent in the late ictal phase and extending into the early postictal period (Blumenfeld et al. 2004b). The strong correlation between increases in blood flow in midline subcortical structures and decreases in the frontal and parietal cortex further suggests that impaired function in the frontal and parietal cortex during complex partial seizures may be related to seizure spread to subcortical structures. Such findings substantiate the hypothesis that loss of consciousness during temporal lobe seizures may be a consequence of abnormal activity in the midline cortical structures (upper brainstem – diencephalic activating systems) that disseminates into diffuse inhibition of the fronto-parietal cortex.

Table 18.3 summarizes the putative alterations in the level and contents of the ictal conscious state and associated patterns of brain activity in the main seizure types associated with impaired consciousness.

Epilepsy and the brain "default mode"

Almost a decade has come to pass since brain functional imaging studies first highlighted that cerebral blood flow and metabolism may differ across various cortical regions during the conscious resting state, being greater in the medial parietal, medial occipital, and mid-dorsolateral prefrontal areas (Gur et al. 1995; Binder et al. 1999). Preliminary reports revealed signal decreases involving the fronto-parietal areas, including the precuneus, during the performance of goal-directed actions (for example visual tasks) in comparison with passive stimulus viewing or eye closure. Such findings suggest the presence of processes that sustain a "basal" consciousness state, whilst being attenuated during the performance of non-self-directed cognitive tasks (Shulman et al. 1997; Mazoyer et al. 2001). A landmark study by Raichle and colleagues (2001) used the oxygen extraction fraction, a measure that corresponds to the change in the proportion of oxygen delivered to oxygen utilized, to demonstrate that despite alterations in cerebral blood flow and oxygen consumption, a metabolic equilibrium is reached in terms of neuronal activity when normal participants are in a resting state (lying awake in the scanner with eyes closed). During this baseline state, high metabolic activity was noted in a neural network encompassing the precuneus and posteromedial parietal region, along with lateral parietal, ventromedial prefrontal, mid-dorsolateral prefrontal, and anterior temporal cortices. Of note, the tonic level of activity of this network decreases when subjects are engaged in goal-directed cognitive processing or perceptual tasks (otherwise called "task-induced deactivations", TIDs). Therefore, it appears that when obliged to perform an active task, the brain defers baseline processes thereby producing deactivations in the areas that subserve those processes (Mitchell et al. 2003). The high baseline metabolic rate together with the predilection for TIDs indicates the existence of an organized baseline state of neural activity, referred to as the "default mode of brain function" (Gusnard et al. 2001).

Amongst this higher-order associative network, the precuneus and surrounding areas within the

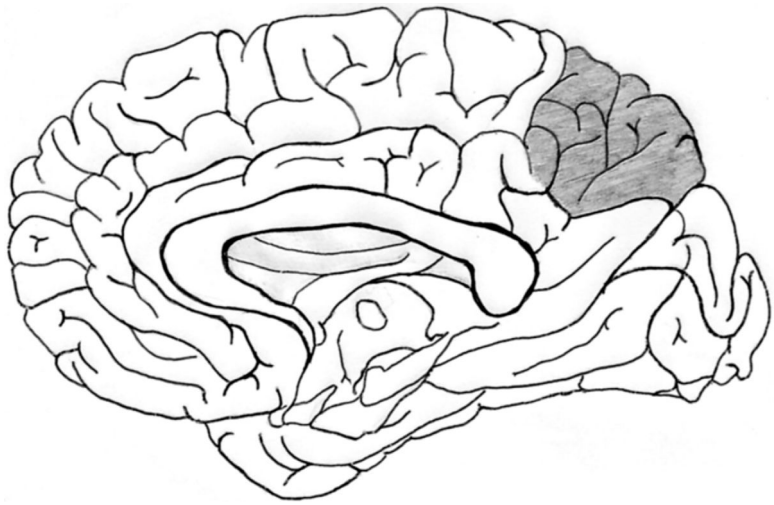

Figure 18.2. Medial view of the human brain. The precuneus (shaded gray area), hidden in the posteromedial parietal cortex, plays a pivotal role in the default mode network subserving consciousness.

posteromedial aspect of the parietal lobe are of particular interest, as they demonstrate the greatest resting metabolic rate, consuming approximately 3% more glucose than any other region of the human cerebral cortex (Cavanna and Trimble 2006). Figure 18.2 shows the location of the precuneus within the posteromedial parietal cortex.

The precise behavioral correlates of this default-mode network activity have proven difficult to appropriately delineate. One hypothesis puts forward the view that when an individual is awake and alert yet not actively engaged in any particular cognitive task, the precuneus and interconnected posterior cingulate and medial prefrontal cortices are engaged in continuous information gathering and representation of the self and the external environment. The successful performance of a task, however, demands a focus of attention and self-referred information processing is curtailed (Gusnard and Raichle 2001). Moreover converging functional imaging studies evidence the precuneus to play a role in the internal mentation processes of self-consciousness (Lou et al. 1999), and an interaction between the precuneus and prefrontal cortex has been suggested in states of consciousness defined by a high level of reflective self-awareness (Kjaer and Lou 2000). Alzheimer's disease, attention-deficit hyperactivity disorder, schizophrenia, and other neuropsychiatric conditions characterized by reduced self-awareness have also been noted to be associated with considerable deactivations in the "default mode" areas (Cavanna 2007; Greicius 2008; Broyd et al. 2009).

Epilepsy is another neuropsychiatric condition characterized by impaired consciousness in which selective hypometabolism in the precuneus and related "default mode" areas has been reported (Gotman et al. 2005; Hamandi et al. 2006). Both generalized seizures and complex partial seizures have been noted to generate impairment in consciousness through the same specific brain networks which overlap considerably with the "default mode" networks, of which the precuneus is one of the key regions (Cavanna and Trimble 2006; Cavanna 2007; Cavanna and Monaco 2009). A recent neuroimaging study applied fMRI and diffusion tensor imaging (DTI) to examine the functional and structural connectivity of the default mode network in 20 patients with mesial temporal lobe epilepsy (mTLE) and 20 gender- and age-matched healthy controls (Liao et al. in press). By measuring the temporal correlation coefficient derived from fMRI signal and the axonal path length and connection density derived from DTI tractography, the authors found that both functional and structural connectivity were significantly decreased between the precuneus/posterior cingulate cortex and the bilateral mesial temporal lobes in the patients compared to the controls. In addition, functional connectivity was found to be correlated with structural connectivity in two pairwise regions, namely between the posteromedial parietal cortex and the bilateral mesial temporal lobes. These results suggest that the decreased functional connectivity within the default mode network in mTLE may be a consequence of the decreased connection density underpinning the degeneration of structural connectivity. The observed

alterations in functional connectivity between the posteromedial parietal cortex and the limbic brain in patients with temporal lobe epilepsy open new avenues for research exploring the possible association between seizure-induced alterations of consciousness and other alterations of cognition or even behavior in this patient population (Broyd et al. 2009).

Conclusion

The concept of consciousness is central to epileptology, despite the methodological difficulties concerning its application to multifaceted ictal phenomenology. Both the level of general awareness and the subjective contents of consciousness can be altered to some degree during epileptic seizures. Moreover, the differences in ictal semiology between patients with epilepsy can offer unique avenues for the understanding of the so far elusive "neural correlates of consciousness." Generalized seizures (tonic–clonic seizures, absence seizures) are characterized by complete loss of consciousness, i.e. unresponsiveness in the absence of any ictal experience, whilst complex partial seizures (especially seizures with medial temporal lobe focus) are associated with variable degrees of responsiveness and specific alterations in the subjective ictal experiences.

Converging findings from neurophysiological investigations and functional neuroimaging studies suggest that the involvement of bilateral thalamus and upper brainstem leads to a selective disruption of fronto-parietal associative networks, resulting in impaired consciousness during generalized and complex partial seizures. In particular, ictal impairment of the general level of awareness seems related to the transient disruption of fronto-parietal and midline (precuneus/posterior cingulate cortex) associative networks, which subserve the conscious resting state according to the "default mode" of brain function. Important challenges and tasks for future research will be to explore the behavioral correlates of the default mode network and to provide an integrative account of how they relate to epilepsy-induced alterations of consciousness.

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