Part I

Background

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Introduction

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In 1997, Dr Pete Engel, President of the International League Against Epilepsy, invited us to establish a commission on psychobiology, and this book represents one of the achievements of the commission's work. The task of the commission was to explore the interface between epilepsy and behaviour disorders, from a biological and social point of view. To these ends a number of subcommissions were established, and their task was to explore the existing knowledge base of the discipline, to suggest research strategies for interventions and to educate both patients and carers about aspects of epilepsy which a number of people consider to have been neglected.

The present book is divided into several parts, covering a spectrum of clinical topics which have been of concern to the commission. Some old chestnuts, for example the interictal psychoses of epilepsy, have not been allocated specific chapters, and a number of other areas, particularly relating to learning disability, cognitive decline, dissociative attacks and vagus nerve stimulation have been included. It is hoped that by expanding upon the literature on some of these less-well-discussed aspects of psychobiology in epilepsy further interest will be stimulated, leading to both intellectual discussion and research endeavours.

We start our text with an introduction to the classification of psychiatric disorders in epilepsy. The point is made that existing classifications used in psychiatry such as the DSM–IV are quite inadequate when it comes to dealing with the subtleties of the behaviour changes of patients with neurological disorders.

We then discuss the biological underpinnings of some behaviour problems, in terms of exploring the limbic system and related structures that are affected by the process of epilepsy and which are also related to behavioural disorders.

The part on clinical aspects explores in particular the problems of learning disability, and introduces the important area of state-dependent learning disabilities: patients with cognitive deficits that can be profoundly reversed by appropriate treatment strategies. Other important areas covered include the ever-controversial topic of aggression, the importance of suicide, and the group of psychoses that occur postictally.

The next part looks further at cognitive problems in patients with epilepsy, examining whether the concept of dementia is relevant, discussing the question as to whether or not there is cognitive decline in patients with various types of epilepsy over time, and also examining the issue of frontal lobe epilepsies. The latter have been well defined from the seizure point of view in recent years, but the behavioural and cognitive associations have yet to be clarified.

We make no apology for including a section on nonepileptic seizures. The fact that many patients who are diagnosed as having epilepsy do not have epilepsy, but have some form of nonepileptic attack disorder (pseudoseizure) is now well recognized. This problem has been around for centuries, and such eminent neurologists as Charcot have spent some considerable time attempting to differentiate between nonepileptic and epileptic seizures. However, this often still proves difficult. We still have inadequate information as to the mechanisms for the development of nonepileptic attack disorder, and these, and the possible biological associations, are taken up in this section.

The final sections deal with treatments and their side effects. Of importance in this section are the references to surgery, not only temporal lobe resection, but also more recent advances such as vagus nerve stimulation. The beneficial and negative psychiatric consequences of these treatments are at the present time being actively explored, and some early work is presented here. However, in the context of psychobiology, our treatment strategies must go beyond medication and surgical interventions, and we include a discussion of psychodynamic principles in relationship to the management of epilepsy, and also a chapter on quality of life.

We, the editors, hope that the book will enliven the debate about the links between epilepsy and behaviour, an area which is often not well discussed, partly because of some worry that any association between psychiatry and epilepsy may stigmatize patients with epilepsy even more than they already are. However, the problems that we have identified are a reality not only in the clinic, but also for patients and carers themselves. It is difficult to define treatment and management strategies if problems are ignored, and so our intention is to enliven this area with these up-to-date reviews on behavioural and cognitive problems in epilepsy, and their social and biological underpinnings.

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Neuropsychiatric disorders in epilepsy – epidemiology and classification

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Introduction

The association between epilepsy and psychiatric disorders has a long and chequered 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 cataloguing, 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 any attention has been paid to the epidemiology of these disorders. Similarly, aside from some early attempts by European physicians, there have been no efforts to develop an operational classification of psychiatric disorders in epilepsy (Schmitz and Trimble, 1992 for a review).

The paucity of epidemiological research at this interface, and the failure to develop an operational international system of classification, is in stark contrast with developments both in epilepsy per se, and in mental health research. The epidemiology of epilepsy has been well studied in many countries and considerable data (both descriptive and analytical) are now available. Indeed, epilepsy has been subject to the gamut of epidemiological research including cross-sectional, case-control and cohort studies (Hauser, 1998). Similarly, operational international systems of classifying epilepsy and its syndromes have been developed both by the Commission on Classification and Terminology of the International League Against Epilepsy (1989), and the World Health Organization (1967), and are used by epileptologists around the world.

Impressive developments have also taken place in the field of mental health epidemiology. Efforts by the World Health Organization's Division of Mental Health, and other pioneering organizations around the world, have led to a significant understanding of the epidemiology of psychiatric disorders. This has led to the development of universally accepted classificatory systems in psychiatry, such as the *Diagnostic and Statistical Manual* now in its fourth edition (DSM–IV; American

Psychiatric Association, 1994), and the mental disorders component of the *International Classification of Diseases*, now in its tenth edition (ICD–10; World Health Organization, 1992).

The commonly held conviction among epileptologists and neuropsychiatrists is that psychiatric comorbidity is not only common in epilepsy, but that distinct and unique forms of psychopathology are prevalent (Krishnamoorthy 2000, 2001). In the past three decades attention has been directed towards discrete forms of psychopathology in epilepsy such as the temporal lobe personality, interictal and postictal psychosis, and interictal dysphoric disorder (Bear and Fedio, 1977; Blumer 1995, 2000). This combined with the observation of similarities in behaviour during seizures and in psychopathological states has strengthened the notion of an affinity between epilepsy and psychiatric disorder. Yet, the evidence that psychiatric disorders are overrepresented in epilepsy is far from convincing, with conflicting results in different studies.

In this chapter the epidemiology of psychiatric comorbidity in adult, non-learning-disabled patients with epilepsy will be reviewed. There is a considerable literature on children and the learning disabled that is being addressed elsewhere in this book (Chapters 5 and 6). Some ideas on how psychiatric disorders in epilepsy may be classified, and the work of the subcommission on classification of the International League Against Epilepsy – the Commission on Epilepsy and Psychobiology – in this regard, will also be discussed.

Epidemiology

A majority of studies in this area has been hospital- and institution-based. While the contribution of these studies to the current understanding of psychopathology in epilepsy has been invaluable, the strong selection bias in these studies does make the extrapolation of their findings to the majority of patients with epilepsy, who live in the community, difficult.

There have been some population-based studies of psychiatric comorbidity that are summarized here. Most studies have been cross-sectional and some have compared cases with controls. By and large, save one or two exceptions, these studies have generated crude estimates of prevalence, rather than more specific epidemiological indices.

Population-based studies of psychiatric comorbidity in epilepsy

One of the earliest investigations to be carried out was that of Pond and Bidwell (1959/60), who surveyed patients from 14 doctor's 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. The main criticism levelled against this study is its use of a social worker rather than a trained mental

health professional, and a lack of standardized techniques to assess patients with epilepsy for psychiatric comorbidity. The strength of this study, however, lies in its recognizing, four decades ago, the importance of an epidemiological approach.

Gudmundsson (1966) personally surveyed 987 patients with epilepsy living in Iceland and reported that 512 (52%) had personality changes of various kinds. Of these 271 (27.5%) were described as ixoid, 73 (7.4%) as ixothymic and 168 (17.0%) as neurotic. More men were ixoid and more women neurotic. While Gudmundsson, unlike Pond, personally examined every subject, the clinical terminology and classification used have few parallels today, and no attempts were made to reduce bias. However, the high proportion of subjects with behavioural changes in this community-based population is striking and worthy of note.

Edeh and Toone (1987) conducted a survey in doctor's surgeries in south London. They interviewed 88 adult patients with epilepsy drawn from doctor's surgeries in the area, using the Clinical Interview Schedule, and reported that 48% emerged as psychiatric cases. They also found that while patients with temporal lobe epilepsy (TLE) and focal non-TLE did not differ in terms of psychiatric morbidity, both groups were significantly more impaired than patients with primary generalized epilepsy. The techniques of ascertainment used in this study are commendable. Subjects with epilepsy underwent both CT scans and EEG tests, in confirmation of their diagnosis. The study also used a validated instrument for common mental disorder, the CIS-R (Lewis et al., 1992). In criticism, however, it must be said that the study failed to examine matched population-based controls, psychopathology specific to epilepsy was not examined, and while cases with psychosis were identified, no validated diagnostic instrument for psychosis was administered, the CIS-R being a validated instrument for common mental disorder alone.

Cockerell et al. (1996) conducted a nation-wide survey in the UK of acute psychological disorders (APD) in patients with epilepsy using the British Neurological Surveillance Unit. Sixty-four incident cases were ascertained over a period of one year. Thirty-one were considered to have APD due to ictal or postictal activity and 33 were interictal. In 30% of cases the APD was reported by the referring physician to be secondary to the prescription of an antiepileptic drug (AED). The drugs most commonly implicated were carbamazepine, lamotrigine and vigabatrin. The broad psychiatric categories diagnosed included delirium (25%), schizophreniform (31%), affective (30%), delusional (5%) and other disorders (9%). The findings of this study are of interest as it gives us crude incidence figures of acute psychiatric disorder in epilepsy and highlights the importance of antiepileptic drugs in precipitating comorbid psychiatric illness in epilepsy. However, as the study used a reporting system, rather than a population-based cohort, the results cannot be used to generate population-based incidence figures, or be generalized.

Jalava and Sillanpaa (1996) examined a prospective population-based cohort (mean follow-up of 35 years) of patients with epilepsy since childhood, for comorbid somatic, psychosomatic and psychiatric disorders. In comparison with random controls, patients with epilepsy had a fourfold risk of psychiatric disorders or combinations of somatic, psychosomatic and/or psychiatric disorders. Thus patients with childhood-onset epilepsy demonstrated a higher risk for psychiatric or psychosomatic disorders and this appeared to be related to epilepsy and not AED administration.

This is perhaps the only cohort study of psychiatric comorbidity in epilepsy and the findings have great relevance. The results clearly indicate that subjects with epilepsy are at higher risk of developing comorbid psychiatric illness, when compared with population-based controls, and indicate the need for greater provision for psychiatric treatment in primary care settings for epilepsy. However, as individual cases were not ascertained in any systematic way, it is possible that the findings do not represent the true extent of comorbidity, with subtle nevertheless disabling forms of psychopathology, or those not requiring medical attention or admission, being missed. This is of relevance, as subtle forms of psychopathology that often do not meet conventional diagnostic criteria may be overrepresented in epilepsy.

Bredkjaer et al. (1998) conducted a record-linkage study in Denmark between a sample of people with epilepsy from the National Patient Register and from the Danish Psychiatric Register. They found that the incidence of nonorganic nonaffective psychoses including personality disorders that were broadly within the schizophrenia spectrum 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 the absence of long-term prospective data, this study based on national registers provides evidence that disorders in the schizophrenia spectrum are clearly overrepresented in epilepsy. The study enabled the calculation of more sophisticated epidemiological indices, such as standardized incidence ratio, that have not been estimated in previous studies. However, the methodological limitations of reliance upon a case-register, i.e. the lack of standardization of ascertainment methods, both for epilepsy and psychoses, and the exclusion of more subtle cases, or those not requiring admission, do apply here.

Stefansson et al. (1998) conducted a case-control study comparing the prevalence of nonorganic psychiatric disorders among patients with epilepsy and controls with other somatic diseases, both groups being of normal intelligence. The two groups were drawn from a disability register of the State Social Security Institute in Iceland. In this way, 241 index cases meeting inclusion criteria were

identified, and the ratio between subject (epilepsy) and control (somatic illness) cases was 1:2. Psychiatric diagnosis was present among 35% of cases as compared with 30% of controls, the difference not being statistically significant. Psychiatric disorders were, however, significantly more common in men with epilepsy, but not in women, the difference being due to a significantly higher rate of psychosis, particularly schizophrenia or paranoid states, among men.

Some large hospital-based studies

Currie et al. (1971) surveyed 666 patients recorded to have features of temporal lobe epilepsy in the hospital diagnostic index and the records of the neurology, neurosurgery and EEG departments. They found 375 (56%) to be normal, 127 (19%) to be anxious, 71 (11%) to be depressed, 47 (7%) to be aggressive, 41 (6%) to be obsessive and 38 (6%) to have a severe disturbance of affect.

Smith et al. (1986) studied 622 patients in the USA in a nation-wide cooperative study spanning 10 Veterans Administration Medical centres, using a battery of neuropsychological testing procedures. The majority of patients was not on anticonvulsant drugs at the time of initial testing, and the few who were had subtherapeutic levels on measurement. They found that patients with epilepsy scored significantly and consistently below the level of the 74 control subjects on all but three behavioural measures. Differences reaching statistical significance were found on tests of motor function (finger tapping, pegboard, colour naming), cognitive-attention (digit symbol, discrimination reaction time, word fluency) and subtests of the Profile of Mood States (tension, depression, vigour and confusion). These they felt provided a profile of behavioural characteristics of unmedicated patients with epilepsy.

Gureje (1991) evaluated 204 unselected patients with epilepsy attending a neurological clinic using the Clinical Interview Schedule (Goldberg, 1972); 37% emerged as psychiatric cases. Of these 53% had a neurosis, 29% had a psychosis and 7% were diagnosed to have a personality disorder.

Mendez et al. (1993) conducted a retrospective investigation of neurology clinic attenders. They found that interictal schizophrenic disorders occurred in 149 (9.25%) of 1611 patients with epilepsy as compared to only 23 (1.06%) of 2167 patients with migraine. They went on in the latter part of the study to compare 62 epilepsy and schizophrenia patients with 62 patients who had epilepsy alone on 6 seizure variables, and 62 patients with schizophrenia alone on 10 psychosis variables.

The epilepsy and schizophrenia group was found to have a later age of onset of epilepsy with more complex partial seizures, more patients with auras and fewer patients with generalized epilepsy. Except for increased suicidal behaviour, patients with epilepsy did not differ from controls on psychosis variables; however, psychotic symptoms often emerged with increased seizure activity. They felt that the

data supported a distinct association of schizophrenic disorders with epilepsy, particularly with seizures emanating from the temporal limbic system.

Manchanda et al. (1996) studied 300 consecutive patients refractive to treatment, admitted for evaluation of their candidature for epilepsy surgery over a 6-year period. Of these, 231 had a temporal lobe focus, 43 had a nontemporal lobe focus and 26 had generalized and multifocal seizure onset; 142 (47.3%) emerged as psychiatric cases based on DSM–III–R criteria. A principal Axis I diagnosis was made in 88 (29.3%). Anxiety disorders (10.7%) and schizophrenia (4.3%) were the most common Axis I diagnoses. Dependent and avoidant personality traits were frequent (18%) although patients rarely fulfilled criteria for a personality disorder.

Are psychiatric disorders commoner in epilepsy?

This question needs to be addressed from a public health perspective. Were psychiatric disorders to be commoner in patients with epilepsy, specific mental health resources would need to be created in the community for this patient group. On the other hand were there no excess in psychiatric comorbidity, when patients with epilepsy were compared with other illness groups, matched for age, sex and disability, and normal controls, such resources would not be required. Here we shall examine the evidence, to see if depression and psychosis are commoner in epilepsy.

A majority of studies has shown depression to be common in epilepsy. Many of these have employed the Minnesota Multiphasic Personality Inventory (MMPI). Whitman et al. (1984) used a MMPI sequential diagnostic system (Goldberg, 1972) to reanalyse 87 published profiles of patients with epilepsy, other neurological disorders and chronic physical illnesses, encompassing a total of 2786 patients. This included 10 studies of epilepsy encompassing a total of 809 subjects. They found that patients with epilepsy were at higher risk of psychopathology than normal controls. However, no difference was found between people with epilepsy and those with other chronic disorders, or between people with TLE and those with generalized epilepsy. A similar investigation was also reported by Dodrill and Batzel (1986), who found that patients with epilepsy demonstrated more psychopathology than normal controls and patients with other neurological disorders, but that there were no differences in rates of psychopathology between TLE and other forms of epilepsy.

Investigations using other instruments such as the Present State Examination have also shown a higher prevalence of depression in epilepsy (Standage and Fenton, 1975). However, other investigations have failed to demonstrate an increased prevalence of depression in epilepsy. For a review of these studies and a discussion of the phenomenology of depression in epilepsy see Lambert and Robertson (1999).

Of all the different psychiatric disorders in epilepsy, it is psychosis for which there is considerable evidence of overrepresentation. The prevalence of psychosis in epilepsy is reported to be in the order of 4% (see Manchanda et al., 1996 for example), sometimes rising as high as 10%. Psychotic disorders are 10 times more common in epilepsy than in the general population, and this is borne out in well-designed population-based cohort and case-control studies, reviewed here. For a detailed review of studies of psychosis and of the nature and phenomenology of the epileptic psychosis, see Trimble (1991).

Another reason for the difficulty in answering this question is the selection bias in most studies mentioned above. In this chapter we have deliberately concentrated on population-based studies. Reviewing these (Table 2.1) it is apparent that there is a considerable degree of psychiatric comorbidity in epilepsy, even in well-designed cohort studies (see Jalava and Sillanpaa, 1996 for example). However, while the evidence for a higher prevalence of psychotic disorders stands out, both in cohort studies (Bredjkaer et al., 1998) and nested case-control studies (Stefannson et al., 1998), the evidence for other psychiatric disorders, while present (see Jalava and Sillanpaa, 1996 for example), is contradictory and not as compelling.

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. The first is that the existing systems of classification in psychiatry, the current being the ICD–10 and DSM–IV, in its fourth edition, have made adequate provision for 'organic' conditions like epilepsy, and further subsystems of classification would only add to their complexity. The second, 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, in press).

One recurrent theme in reviewing the literature about psychiatric disorders in epilepsy is that the failure to identify an excess of psychopathology is due more to the instruments used (generic to mental disorder and not specific to mental disorders in epilepsy), rather than a true finding. It was this that led Bear and Fedio (1977) to develop their own instrument, and conduct a study of psychopathology in patients with temporal lobe epilepsy. The traits that they 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.

The study by Bear and Fedio (1977) showed that while the MMPI failed to identify differences between patients with TLE and other patient groups, the differences were all too apparent when the responses to the instrument they developed were