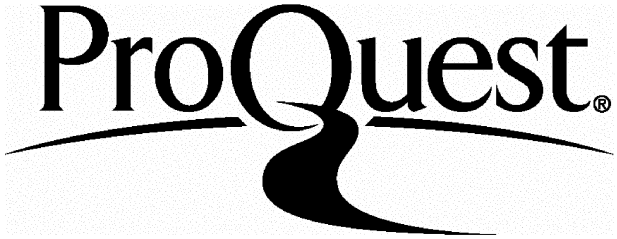
The Clinical Patterns of Frontal Lobe Epilepsy

Thesis for MD

Mark Ralph Andrew Manford
Institute of Neurology
University of London



Abstract

The aims of this study were to define patterns of seizure semiology and see if these can be localised to particular regions, with special emphasis on frontal lobe epilepsies; to establish clinical features differentiating frontal and temporal lobe epilepsies; to assess current classification of frontal lobe epilepsies and to analyse partial epilepsies in a general population. The methods used differ from other studies in this area, especially with respect to breadth of case mix; delineation of clinical syndromes, using statistical techniques and prospective analysis of investigative abnormalities in relation to clinically defined seizure types. Patients were selected from hospital records with evidence of partial seizure onset, on the basis of focal imaging abnormality, interictal or ictal EEG abnormality and clinical seizure pattern. Two hundred and fifty-two patients with 352 seizure types were identified. Clinical seizure manifestations were recorded prospectively and encoded according to sequential occurrence during the seizure. These data were entered into a statistical cluster analysis, which was refined to 14 groupings, each corresponding to a different seizure type. These patterns were displayed in flow charts, allowing assessment of seizure evolution. Interictal EEG spike distribution and ictal EEG onset were related to each seizure type. The 126 lesions identified on neuroimaging were measured by a template technique, and related to each seizure type, using chi-square analysis. Investigations were also related to each other and the clinical seizure associations of pure frontal and pure temporal lesions were assessed. The database of the National General Practice Study of Epilepsy (NGPSE) was also analysed, using a clinical classification, to determine the relative frequency of different partial seizure types in a general population.

Of 14 clinical seizure groupings, 2 had associations with frontal regions and 2 perirolandic associations. Focal clonic and somatosensory seizures were associated with perirolandic lesions and other sensory modalities and experiential phenomena with temporal EEG and imaging abnormalities. Seizures characterised by tonic posturing were strongly associated with lesions of the lateral premotor cortex and frontocentral EEG abnormalities. Seizures characterised by bizarre or frenetic motor activity "motor agitation" were associated with frontal EEG abnormalities and with lesions of the frontopolar or orbitofrontal cortex. These latter seizures were commonly nocturnal and occurred with higher frequency than those in other groups but no other consistent pattern in diurnal variation or seizure frequency emerged. For all seizure types with statistically significant associations with specific lesion sites, there was a substantial minority of cases associated with lesions at different site. A direct comparison of seizures associated with pure frontal and pure temporal lesions confirmed early version, clonic activity and tonic posturing as frontal characteristics but found no consistent differences in characteristics of seizure timing. Seizures with startle sensitivity occurred in 19 cases; MRI suggested lesions in the lateral frontal region or the perisylvian region in this group. The NGPSE data supported a high frequency of seizure types associated with frontal lobe abnormalities in the general population and a good prognosis of all partial seizure categories.

These findings lend some support to the localisation of seizure types attributed to orbitofrontal and temporal lobes by the ILAE but suggests that many regions of the frontal lobes do not have specific associated seizure types, and that many seizure types, although being associated with one cerebral region, may relatively frequently be due to lesions in other sites. The predictive value of clinical seizure type is thus less than described from retrospective and highly selected post-surgical series, on which the classification is based. The hospital and population-based studies suggest that seizure frequency, timing and prognosis are more related to the population under study than the anatomical site of the underlying lesion.

Contents

List of Figures

List of figures (continued)

List of Tables

List of tables, continued

Appendices

Enclosures:

Manford M, Hart YM, Sander JWAS and Shorvon SD. National General Practice Study of Epilepsy (NGPSE): Partial seizure patterns in a general population. Neurology 1992;42:1911-1917.

Manford M and Shorvon SD. Prolonged sensory or visceral symptoms: an underdiagnosed form of non-convulsive (simple partial) status epilepticus. J Neurol. Neurosurg. Psychiatr. 1992;55:714-716.

Introduction

Section 1: Aims and structure of the study

The International League Against Epilepsy (ILAE[1,2]) has proposed a classification of six seizure types arising from different anatomical regions of the frontal lobes (table 1, below). and they suggest common pathological causes for each. Despite this apparently clear-cut anatomical definition of frontal seizures, the National Institutes of Health, Bethesda (NIH) has recognised frontal lobe epilepsy (FLE) as an area of poor understanding and has highlighted it as a priority for epilepsy research[3].

Table 1: Summary of ILAE classification of frontal lobe epilepsy

Region	Typical clinical features according to ILAE classification
Primary motor cortex	Contralateral tonic or clonic movements according to somatotopy, speech arrest and swallowing with frequent generalisation. Ipsilateral leg involved in paracentral seizures
Supplementary motor area	Simple focal tonic seizures with vocalisation, speech arrest, fencing postures, and complex focal motor activity with urinary incontinence
Cingulate	Complex focal motor activity with initial automatisms, sexual features, vegetative signs, changes in mood and affect and urinary incontinence
Frontopolar	Initial loss of contact, adversive and subsequent contraversive movements of head and eyes, axial clonic jerks, falls and autonomic signs with frequent generalised tonic clonic seizures
Orbitofrontal	Complex focal motor seizures with initial automatisms or olfactory hallucinations, autonomic signs and urinary incontinence
Dorsolateral (premotor)	Simple focal tonic with versive movements and aphasia and complex focal motor activity with initial automatisms
Opercular	Mastication, salivation, swallowing and speech arrest with epigastric aura, fear and autonomic phenomena. Partial clonic facial seizures may be ipsilateral and gustatory hallucination is common

The aims of this study are:-

1) To identify clinical seizure types of partial epilepsies with localising value, with special emphasis on frontal lobe epilepsies, using a novel methodology comprising:-

a) the initial delineation of groups sharing clinical symptoms and symptom clusters of epilepsy in the study population, with the assistance of statistical cluster analysis;

b) a prospective analysis of the investigational abnormalities associated with each of the clinically defined seizure types.

2) These methods enable:-

a) the delineation of seizure types associated with frontal lobe abnormalities on EEG and neuroimaging and their value in differentiation from epilepsies associated with abnormalities in other regions, especially temporal lobe epilepsy;

b) the assessment of the intrafrontal localising value of different seizure-types;

c) the cross-correlation of clinical and investigative findings in different seizure types.

3) The characterisation of the evolution of seizure manifestations in different seizure types and the consideration of their possible anatomical and pathophysiological bases.

4) The appraisal of the ILAE classification of frontal lobe epilepsy in the light of seizure groupings identified in the study.

5) In subgroups of patients, the application of new methods of magnetic resonance imaging, including magnetic resonance spectroscopy and three dimensional acquisition of structural MRI data and their assessment.

6) Utilising a clinical classification derived from this study, the analysis of partial seizure types in the National General Practice Study of Epilepsy[4] (NGPSE), to obtain a population-based estimate of the relative incidence of the seizure types reported in the accompanying hospital study, that forms the main part of this thesis.

The methods of this study differ from those generally applied in this area, with respect to:
i) the prospective nature of the analysis; testing the predictive value of clinical seizure patterns, rather than retrospectively defining seizure localisations from cases sharing similar results on investigations or post-surgical remission cases, without reference to control groups;
ii) the breadth of case selection from general neurology as well as specialist epilepsy practice, using several independent criteria without seeking concordance, prior to clinical classification and therefore reducing the inherent bias of case ascertainment;
iii) statistical methods used in delineation of clinical syndromes and in the relationship of clinical types to investigative abnormalities, especially of neuroimaging;
iv) the use of flow charts to describe seizure evolution in detail and consider the mechanisms of ictal symptom generation and their possible pathophysiological significance.
This introduction will examine current knowledge regarding clinical seizure patterns in FLE and discuss the methods of localising seizure origin, with special reference to FLE. Section 2 reviews the background to understanding of focal epilepsy. Section 3 describes current knowledge of the anatomy of the frontal lobes. Section 4 discusses the current understanding of the clinical features of frontal lobe epilepsy and the problems in their interpretation. Sections 5-7 review the value and limitations of investigations commonly used in focal epilepsy, with particular reference to frontal lobe epilepsy. Section 5 assesses the value of electrophysiological investigations; section 6 explores the information provided by imaging in relation to underlying pathology and section 7 reviews neuropsychological assessment. Section 8 discusses the role of surgical treatment in relation to our knowledge of the underlying pathologies in epilepsy and the information that surgery provides about the mechanisms of epileptogenesis.

Section 2: General Background

One of the major steps in the development of modern epileptology was the analysis of seizure manifestations and their relationship to structural pathology especially by Hughlings Jackson in the last century[5]. His findings introduced the concepts of focal

epileptogenesis, opening avenues for epilepsy research and raising the possibility that regional surgery may remove an epileptogenic lesion and relieve the seizure diathesis. A few years later he collaborated with Victor Horsley in successfully exploiting this potential, in the first operation for seizures of the modern era, on a patient with primary motor cortex seizures[6]. Most early surgery was for focal clonic seizures, since it was the type most reliably localisable on purely clinical grounds. The introduction of EEG fifty years ago, allowed an extra dimension of preoperative and intraoperative investigation, enabling the localisation of seizure types that could not be established on clinical criteria alone. The seizure type with the most distinctive EEG signature was found to be temporal lobe epilepsy[7] and most surgery this century has been for TLE. During these phases of development of epilepsy surgery, the pathology underlying an individual's epilepsy could not be determined preoperatively. With the advent of CT scanning, foreign tissue lesions started to be identified in some cases, but the majority of partial epilepsies remained "cryptogenic".

Two recent factors have had a major impact on the approach to presurgical assessment of patients with intractable epilepsy. First, increasing recognition that identification of the nature and extent of the underlying pathology is crucial in determining prognosis of surgery. With the increasing sensitivity of imaging techniques, especially MRI, this has caused a substantial shift in emphasis of investigation. This evolution of approach means that studies of epilepsy localisation and surgery need to be considered in the light of the investigations available when they were performed and many older studies may not be comparable to more recent studies, undertaken in the era of MRI. Second, is the increasing recognition of the importance of extratemporal epilepsy, of which the largest subgroup is probably FLE. Epilepsy of frontal lobe origin is being increasingly recognised and probably represents 20-30% of partial seizures[3,8]. The NIH estimates the number of patients in the USA with frontal lobe epilepsy to be in the region of 569,000, of whom 171,000 continue to have incapacitating seizures, despite optimal drug therapy[3]. Assuming the epidemiology of the disorder is similar in the UK, there are approximately 34,000 patients in this country with chronic frontal lobe epilepsy, for whom surgery might be considered. The total number of operations for epilepsy, mostly of the temporal lobe,

currently stands at less than 150 per year in the UK[9].

The analysis of seizure symptomatology may give clues which are important to our understanding of the underlying mechanisms, and help clarify the role and limitations of surgical treatment. A greater knowledge of the clinically significant pathways of seizure generation, in combination with advances in neuropharmacology, may also in the longer term, be important in the development of other treatment modalities, allowing more specific pharmacological interaction with the pathways involved in specific seizure types.

Central to the validation of current techniques of seizure localisation, is the use of a "gold-standard", supposedly able to identify seizure generating cortex with absolute specificity and selectivity, against which other investigative modalities are assessed. A widely accepted dogma is that if a technique identifies a region, whose resection produces permanent relief from seizures, then it correctly localised the maximally epileptogenic cerebral cortex[10]. Since only a small minority (<1%) of highly selected patients undergo surgery for their epilepsy, alternative means are required to identify epileptogenic cortex in the majority of patients, particularly if non-surgical means of focal treatment of seizures become available. Even in patients who undergo surgery, the range of different outcomes illustrates the variety of interactions between surgery and the seizure generating process (figure 3, page 166) and reflects the incompleteness of current understanding of the mechanisms and pathways of seizure causation and spread, raising doubts concerning its usefulness as the "gold standard". How much epileptogenic cortex need be removed to relieve a patient's epilepsy? If normal cortex is excised, only secondarily involved in seizures, can this too produce a lasting remission? The more extensive the resection the more likely is remission from seizures (the extreme case is hemispherectomy) and the less valuable the localising information from surgery. Since frontal resections are often large, only very general inferences may be made about localisation. The substantial failure rate of surgery, even in the most highly selected patients, raises the question of the applicability of current definitions of sites of focal seizure onset and the relevance of available tools to assess them.

Nevertheless, current bias is toward seizure localisation as part of presurgical assessment. Most series use surgical success as their measure of accuracy of localisation, resulting in

widespread acceptance of surgical relief of seizures as the most accurate means of identifying epileptogenic cortex currently available. Therefore, much of the discussion in this introduction relates to studies of cases that have undergone surgery.

Clinical seizures are, however, the overt manifestations of aberrant neuronal activity, and the orientation of investigation in this thesis is on the identification of patterns of clinical seizure manifestations. These clinical patterns will be analysed prospectively in relation to investigations (interictal EEG, ictal EEG and neuroimaging) to assess the degree to which the location of abnormalities on investigation can be predicted from clinical seizure type. This method avoids the bias introduced by the retrospective analysis of selected patients who have undergone surgical resection and is the crucial difference in methodology between this and previous studies. This approach, starting with the seizure manifestations and working towards localisation, also more accurately reflects the problem facing the clinician with each new patient with partial epilepsy.

Section 3: Anatomy of the frontal lobes

Section 3a: Gross structure

The frontal lobes constitute that part of the cerebral cortex anterior to the Rolandic fissure and superior to the Sylvian fissure (figure 4, page 167) and further subdivisions are usually made on the basis of cytoarchitectonic and proposed functional considerations. The primary motor cortex is just anterior to the Rolandic fissure and is often combined with post-Rolandic primary sensory cortex as "central sensorimotor cortex", because of their close anatomical and functional relationships[11]. Anterior to the motor strip, in Brodmann's areas 6 and 8 (figure 5, page 168) are regions thought to be involved in the higher organisation of motor activity; the premotor cortex (PMC) on the lateral convexity and the supplementary motor area (SMA) on the mesial and superior surfaces[12]. The premotor area contains the frontal eye fields, which are implicated in eye movement and in the dominant hemisphere, Broca's area, involved in the execution of speech. Inferior to the SMA, on the mesial surface and wrapped around the corpus callosum, is the anterior part of the cingulate gyrus, an integral part of the mesiolimbic system[13]. Anteriorly and stretching to the frontal pole, is the agranular frontal cortex (prefrontal cortex), whose

precise functions remain obscure, but where lesions produce pronounced deficits of psychomotor sequencing[13]. On the inferior surface is the orbitofrontal cortex, also closely involved with the mesiolimbic system, especially in relation to autonomic activity[14,15]. Most research has attempted to relate seizure manifestations to these putative functional areas[1].

It is important to consider the detailed structure and connectivity of these regions as these anatomical characteristics may be important determinants of seizure spread and seizure manifestations. Most anatomical research has been conducted in the monkey whose gross cortical anatomy is illustrated in relation to human anatomy in figure 6, page 169. Current opinion[17] is of functional systems that incorporate both sequential, convergent processing and parallel processing components. Sanides[16] postulated two systems (figure 7, page 170), evolving during phylogeny, to form the cerebral cortex. The hippocampal, archicortical moiety evolved through the cingulate cortex, predominantly to occupy the mesial cortex; the SMA in the frontal lobes and the supplementary sensory area in the parietal lobes. It is characterised by the presence of pyramidal cells in layer 5. The olfactory, paleocortical moiety developed through the parainsular area of the central sulcus to form the prefrontal association cortex and the second sensory areas for vision, hearing and somatic sensation. These areas are deficient of pyramidal cells but contain large numbers of granular cells.

Section 3b: Frontal intercortical connections

Figures 8-12, pages 171-173, summarise some major frontal lobe pathways. Within the frontal lobes, connections tend to be between cortical subdivisions arising from the same phylogenetic source, according to Sanides scheme. This also holds for longer interlobar connections; the periarcuate area of the monkey receives input from the first visual, hearing and somatosensory association areas, whereas the prearcuate, prefrontal cortex receives input from the second sensory association areas of these modalities. There is however, considerable integration of the two systems, e.g. reciprocal interconnections between the PMC and SMA. The overall picture is of flow of information from anterior in the frontal lobes to the precentral motor cortex, via two highly interrelated systems. They incorporate

sensory information, projected forwards from the sensory cortex at the higher levels of sensory integration to the most anterior frontal lobes and lower levels of integration closer to the motor output cortices.

There are extensive topographic, interhemispheric projections through the corpus callosum, between the two frontal lobes. Double labelling studies show that these are both from neurons whose axons are exclusively interhemispheric and from neurons whose axons branch, to give a commissural fibre and an ipsilateral projection fibre[17]. Moreover, the cortical columns receiving frontal interhemispheric inputs alternate with those receiving ipsilateral parietal fibres[18]. These variations provide additional potential for interaction between the different regions of the brain in normal function and in the generation of seizure manifestations.

Section 3c: Frontothalamic and frontostriate connections

Subcortical projections to the thalamus and corpus striatum also vary from different parts of the frontal lobes. Different portions clearly project in a topographic fashion to the dorsomedial nucleus of the thalamus[18]. The functional significance of these connections is not clear, but like the prefrontal cortex and unlike the thalamic relay nuclei, this part of the thalamus has multiple bi-directional connections with the corpus striatum and areas of the limbic system, which may theoretically be implicated in seizure spread.

Pathology exclusive to the basal ganglia is not generally associated with epilepsy and it seems unlikely that these structures play a central role in seizure genesis. Nevertheless, they are intimately connected with the cerebral cortex[19,20,21] and may be important in modulating the expression of cortical outflow, and therefore, influence the clinical manifestation of seizure discharges. Basal ganglia lesions may produce movements similar to those seen in some seizures e.g. dystonic posturing and may occasionally cause neuropsychological deficit akin to a "frontal lobe syndrome"[22]. Some older electrophysiological evidence in animal models also suggests a role for the basal ganglia in epilepsy[23], and in humans, early researchers proposed discharges in the basal ganglia in some epileptic subjects when none could be detected at the scalp[24]. On the basis of these findings, lesioning of the basal ganglia was attempted in the treatment of epilepsy -

although with little success[25]. In a rat model, the substantia nigra, which has close relationships with the basal ganglia, has important modulatory influence on the expression of seizures from the highly epileptogenic "substantia tempesta" of the prepyriform cortex[26], but the equivalent site in man is uncertain.

Views of the structure of the basal ganglia and their relation to the cerebral cortex recently have undergone substantial revision. Current opinion suggests that there are anatomically segregated regions within the basal ganglia, each subserving a different loop from cerebral cortex to corpus striatum to globus pallidus to thalamus back to cortex. It is suggested that each loop receives input from several, related cortical regions and then projects back to a more restricted cortical target. Separate loops are postulated to be related to sensorimotor cortex, extraocular movements, dorsolateral prefrontal cortex, lateral orbitofrontal cortex, anterior cingulate cortex and possibly other regions. Outputs to the SMA are particularly prominent. This convergence represents a mechanism whereby cortical regions may interact without direct intercortical spread. Moreover, recent evidence suggests a role for the basal ganglia in limbic function[20]. There are connections at various levels between the limbic and the motor components in the basal ganglia, which suggests possible extracortical sites of interaction, for example in the generation of motor automatisms. In discussing the generation of seizure manifestations, the involvement of subcortical centres must also be considered, particularly in motor seizures, which by definition manifest via descending pathways. Whilst not usually candidates for the origin of seizures, they may also modulate seizure spread via extracortical loops, for example the thalamocortical loop suggested for models of absence epilepsy[27].

Section 4: Clinical seizure localisation

The first clue to a focal seizure is its semiology. Numerous clinical manifestations have been observed in frontal lobe seizures (table 1, page 14). There are considerable problems, however, in localisation of seizures on the basis of some of these characteristics and sometimes it may even be difficult to differentiate epileptic from non-epileptic attacks.

Section 4a: Intrafrontal versus extrafrontal localisation

Focal electrical discharges result in clinical manifestations, at least partly related to the

connectivity of the region involved[28]. The major efferent connections of the primary motor cortex are relatively straightforward, somatotopic outputs to lower motor neurons, whose clinical activity is easily recognised. Seizures arising from this area cause the characteristic clonic motor progression identified by Hughlings Jackson, that bears his name[5]. However, seizures originating from other areas, with more complex connectivity, are less easily predictable. Moreover, where more than one area subserves a particular function, it may be impossible to localise seizure onset on the basis of a given clinical feature. For example, conjugate eye deviation can be elicited by direct stimulation from frontal, occipital and parietal lobes of the brain as well as cerebellum and superior colliculi and there are complex interactions between these regions[29].

Overlap with phenomena usually attributed to seizures arising in other lobes, occurs over a whole spectrum of clinical manifestations e.g. formed and unformed visual hallucinations from documented structural lesions of the anterior mesial frontal cortex[30], which would usually be attributed to more posterior sensory and association areas. A rising epigastric aura is said to be a characteristic feature of temporal lobe seizures, but epigastric sensations are also noted in frontal attacks[31], possibly relating to the close interconnections between these regions in the mesiolimbic system. Similarly, the close relationship between the pre- and post-Rolandic sensorimotor cortices means there is substantial overlap of their clinical seizure manifestations; numbness and tingling in the periphery[7] and tonic posturing[32] have been reported from both regions.

Further to complicate the picture, there is evidence in experimental models, that seizure propagation may occur via non-synaptic mechanisms (reviewed by Yaari and Jensen[33]), perhaps by activating fibres of passage through electrotonic coupling, changes in local electric field or ionic concentrations. This probably occurs most commonly in the hippocampus, where axons are very tightly packed, and is a mechanism by-passing normal synaptic transmission and allowing unpredictable activation of pathways and seizure manifestations. However, the clinical significance of these mechanisms remains uncertain.

Section 4b: Ictal motor activity

Motor activity is a prominent ictal manifestation of frontal lobe epilepsy[8,34,35,36]. This may include clonic movements; tonic seizures without clonic accompaniment[37]; gross or

semi-purposive motor activity and complex motor automatisms[38,39,40]. Head turning is particularly common but Cotte-Rittaud and Courjon demonstrated it may originate from all four lobes of the cerebral cortex[41]. However, in their study it was the initial manifestation in 32 of 37 cases arising from the frontal lobe, but occurred later in the course of the seizure in all of 20 temporal lobe attacks, in which head version was prominent. This suggests that head version is a result of involvement of extratemporal regions, either cortical or subcortical. It may, however, be difficult to differentiate seizure phenomena due to activity in the primary epileptogenic region from that which arises as a result of spread beyond it. For example, it has been demonstrated that propagation of discharges, via the uncinate fasciculus, between the lateral convexity of the frontal lobe and the temporal lobe, may occur in a matter of milliseconds[42]. Clearly, this is too fast for clinical observation to distinguish a primary from a propagated manifestation.

Motor activity is often the most obvious feature of a seizure to an observer. If the seizure onset is with a subjective manifestation e.g. a sensory manifestation, then the identification of this important early localising feature is dependent on the awareness of the patient at the time and his later ability to recall it. Equally, large parts of the cerebral cortex, including much of the frontal lobes, are "silent", producing external manifestations only indirectly, via connections with other regions. Seizures arising in silent areas may erroneously be attributed to more eloquent regions "downstream" e.g. motor phenomena or vocalisation, occurring in seizures with frontopolar or orbitofrontal onset[38,43,44], perhaps reflecting pathological impulse propagation down physiological pathways.

Section 4c: Motor Automatisms

Attempts are made to classify ictal motor activity as simple or complex and make inferences regarding the localisational significance of each. Simple clonic jerks are associated with perirolandic recruitment to a seizure, but the more complex movements are thought to be qualitatively different in frontal and temporal seizures. Tonic postures, bicycling movements of the legs or striking movements of the hands are usually attributed to the frontal lobes[40,45,46,47,48]. Swallowing and orofacial movements are seen frequently, but not exclusively, in temporal lobe seizures[40,49]. Some complex motor automatisms e.g. genital manipulation or gesturing have been noted during seizures originating from both frontal and

temporal lobes[50,51]. However, studies using intracerebral EEG in some patients have suggested that certain automatisms only occur once there has been spread of the discharge to the temporal lobes[46,48] which at first sight is counter-intuitive, since it is the frontal lobes that are especially involved in motor planning.

The differentiation of various forms of motor activity is unclear and a gradation of complexity is probably more appropriate. Nor is it clear the difference between ictal and postictal automatisms and whether this differentiation has any clinical significance. This study will be able to assess the statistical association of different automatic activities with frontal and temporal lobe seizures, and their timing within the progression of the seizure. If the motor pathways of the frontal lobes are not required for the execution of motor automatisms, then the output from temporal lobe may be via subcortical motor centres.

Section 4d: Intrafrontal localisation

Sublocalisation of ictal clinical features within the large volume of the frontal lobes has been attempted by Delgado-Escueta at al[47] and formalised in the ILAE classification[1]. They propose tonic motor manifestations in SMA and dorsolateral frontal regions, associated with speech arrest and autonomic phenomena in the former and sexual automatism and pseudo-absence in the latter. Automatisms appear to be relatively less common in mesial SMA seizures than in dorsolateral frontal seizures in some series[48,52,53], but have been noted frequently by Talairach et al from the cingulum[54,55], on the mesial surface and also from the orbitofrontal cortex[56,57,58], although numbers of cases in all these series combined were less than the current study. Table 1 presents the manifestations attributed to different regions in the ILAE classification, showing the extensive overlap between them.

Delgado-Escueta et al[47] suggest anterior cingulate epilepsy resembles anterior temporal lobe epilepsy with atypical absence and prominent autonomic features, consistent with results of electrical stimulation of the cingulate cortex[54] and its close connectivity in the limbic system[58]. This pattern has also been reported in orbitofrontal attacks[48]. However, studies[47,48] have also emphasised a component of unilateral tonic motor activity seen in many cingulate and orbitofrontal seizures; evidence of substantial overlap of manifestations

attribute to other frontal and even temporal areas.

Section 4e: Vocalisation and speech arrest

Vocalisation is said to be a common feature of frontal lobe seizures[38,59,60], but is also seen in temporal lobe epilepsy[7] and it is not clear whether there are qualitative differences between frontal and temporal vocalisations. Localisation within the frontal lobe is uncertain: there are some reports of successful frontal cortical resections for seizures in which vocalisation was prominent, but these were from frontopolar, supplementary motor or orbitofrontal regions, so providing little localising value[43,54,61]. This may merely reflect the variety of pathways involved in vocalisation; a view supported by electrophysiological evidence, demonstrating the great variety of sites from which vocalisation can be elicited by intracranial stimulation, in man and animals[30,33,35,62].

Equally, Delgado-Escueta et al[47], maintain that speech arrest is characteristic of temporal lobe attacks. This is, however, a very difficult symptom to define in spontaneous seizures, although described by Penfield and Jasper[7] and is easier to elicit by direct cortical stimulation. In order that cessation of speech be due to higher language disorder and not due to an abnormality of the motor component of speech, the patient must be fully aware, have no demonstrable abnormal motor activity or ictal paresis of the mouth. This is very difficult to determine in the brief duration of a seizure but reports have suggested this phenomenon in relation to spontaneous and elicited paroxysmal activity arising from the frontal lobe, including from lateral premotor[34,35], and orbitofrontal cortices[44]. Penfield and Rasmussen[62] demonstrated that both vocalisation and speech arrest could be produced by stimulation of partially overlapping portions of the pericentral region of both dominant and non-dominant hemispheres.

Section 4f: Tempo of ictal activity

Jacksonian focal motor seizures manifest as a sequential activation of the peripheral musculature, over seconds to minutes, presumably reflecting a slow progress of the seizure discharge down the precentral homunculus, facilitating seizure localisation. However, other seizures may spread from a regional onset so rapidly that the attack appears generalised from the start, precluding localisation on clinical grounds alone. This pattern is

seen in akinetic or tonic drop attacks[37,63,64].

Frontal seizures are said to be characterised by sudden onset, short duration and rapid recovery. They are said to occur in clusters, particularly at night[65]. Many of these features can be explained by the predominance of motor activity in frontal seizures. Seizures with a sensory onset will inevitably appear more gradual as the patient reports the sensation before there is spread to an observable motor attack. More posterior seizure types are characterised by frequent auras, which may cluster. This may be the sensory, simple partial seizure equivalent of clustered frontal motor seizures. Finally seizure types with no motor manifestations are only detectable in sleep by special monitoring equipment and their nocturnal frequency is, therefore, undetermined.

Moreover, not all frontal seizures are short and followed by rapid recovery; automatisms and confusional states are frequently seen in seizures arising from a variety of frontal sites [48,52-54]. Epilepsia partialis continua, one of the commonest highly focal, prolonged seizure types, is of perirolandic origin.

This study will be able to address the issue of differences in these characteristics of tempo between frontal and other seizure types.

Section 4g: Non-epileptic seizures and consciousness

A hallmark of generalised tonic clonic seizures has been believed to be loss of consciousness. Although it has long been appreciated that, in absence seizures, loss of contact is dissociated from generalised motor activity[66], it has only recently been recognised that bilateral motor activity can occur with preservation of awareness. So deeply entrenched was the belief that patients had to be unconscious during an epileptic seizure with bilateral movements, that signs of awareness during such attacks were, until recently, interpreted as indicative of non-epileptic seizures, resulting in inappropriate treatment and unnecessary stigmatisation. The pattern of such motor activity; often large amplitude, pseudo-purposeful activity e.g. bicycling of legs, rather than the typical, small amplitude, clonic movements of classical generalised tonic clonic seizures[38,43,67], has contributed to this error[65].

A problem in determining consciousness in epileptic seizures is that when an observer

interacts with a patient during a seizure, he is dependent on intact sensory and motor pathways and internal processing to elicit an appropriate response. Any one of these may be disrupted by a seizure, resulting in apparent "impairment of consciousness". It is difficult to know whether this represents a disruption of a "central consciousness", or merely of its tools of communication[68], or at what level the two merge. Amnesia for the attack may make a patient retrospectively appear to have been "unconscious" even though he was aware at the time[7]. Similarly dysphasia, seen frequently in relation to seizures, alters the ability to comprehend and respond and may erroneously be interpreted as unconsciousness. The definition of consciousness and the dualist and materialist views of its relationship to brain function remain controversial[69,70]. If consciousness does have a discrete anatomical basis, then widely differing regions including frontal[13] and parietal cortices and interhemispheric structures[70] have been proposed as important components of its substrate. In the field of epilepsy, Jasper[71] suggested "loss of consciousness" in temporal seizures was only seen with bilateral spread. However, in 14 patients with stereotactic EEG recordings and stimulations[72], "loss of consciousness" occurred in 24.6% of unilateral temporal discharges with no measured contralateral spread, both in pure neocortical and pure limbic discharges. In frontal attacks, impairment of awareness appears to very variable; in pure motor seizures there is often complete preservation, but loss of awareness is dramatic and devastating in akinetic and tonic drop attacks, where frontal discharges are thought to generalise, almost instantaneously, across the corpus callosum.

Section 4h: Lateralisation of epileptic activity

The clinically significant primary motor cortex innervation of the musculature (except the upper face) is purely contralateral and this is reflected in primary cortex clonic seizures. For other motor seizure phenomena, lateralisation is more difficult to determine. A number of studies have addressed the issue of lateralisation of head turning; estimates of supplementary motor area discharges responsible for contralateral versus ipsilateral head turning range from 33% to 100%[48,60,73,74,75]. This variation may be explained by the bilateral motor representation in the SMA[31,76]. There is little evidence to suggest lateralisation of non-motor epileptic phenomena in the frontal lobes, with the possible

exception of peri-ictal dysphasia, lateralised to the dominant frontal lobe.

Section 4i: Summary

The above examples serve to illustrate the problems in trying to identify seizure patterns specific to the frontal lobes. Even differentiation from non-epileptic seizures may be problematic! Where epilepsy is diagnosed, localisation may be uncertain; frontal lobe epilepsy may present with features more frequently associated with other lobes or present as a generalised epilepsy. Motor manifestations are arguably the most prominent and easily recognisable of all seizure manifestations, and as the major final cortical motor output is from the frontal cortex, seizures arising from other areas may spread into motor regions and appear to be frontal in origin. Bilateral cortical representation of many types of motor activity may make laterality of frontal seizures difficult to determine. Moreover, there appears to be considerable overlap between seizure phenomena arising in different parts of the frontal lobe.

The difficulties may reflect inaccuracies in our methods of localisation of epileptogenic cortex. However, the postulated interconnected, parallel and sequential processing, within the frontal lobes, suggested from anatomical and physiological studies[16,77,78] provide a substrate for blurring the effects of seizure discharges triggered from different regions. If the observable clinical effects of frontal lobe seizures represent merely aberrations of a final common output pathway, with a limited repertoire of clinical manifestations, then it may be impossible, on clinical grounds alone, to recognise the individual signatures of the various "silent" cortical regions converging onto it.

Some differences can be determined, however, in the neuropsychological effects of variously sited frontal lobe lesions[13,79] and in the electrophysiological properties of cells in different frontal regions[77,80] which may also, therefore, manifest in different seizure patterns; if not in different phenomena, then possibly in variations in the order in which they are recruited into the seizure.

In order to define the seizure manifestations that are characteristically frontal, it is vital therefore, not only to illustrate the shared features of FLE, as is done in post-surgical series, but also to show that they are different from epilepsy from other regions. For this reason, patients with frontal lobe abnormalities are compared to others with evidence of

extrafrontal regional involvement, in the same experimental design in this study. This differentiation is also a key problem in clinical practice.

Section 5: Electroencephalographic localisation

EEG is the best established means of investigation of seizure dynamics. The EEG modalities used are: ordinary scalp recording; scalp recording enhanced by the use of special electrodes and intracranial recording. Each of these methods may be used interictally or ictally, the latter is usually combined with video recording of seizure semiology[81,82].

Central to the analysis of EEG is the "inverse problem". This theoretical limitation states that if the brain is considered a uniform volume, from which discharges may arise that are of any magnitude and with any orientation, then there is an infinite number of combinations of discharges that can give rise to any given surface EEG pattern. If these assumptions are correct, it is impossible to define the discharge generators from the surface EEG pattern, although in practice, valuable information can be obtained. In addition to this theoretical limitation, there are a number of physical problems in EEG recording, seen especially in frontal lobe epilepsy.

Section 5a: Scalp EEG

The major problems seen in scalp recordings are: attenuation of signal; artefactual interference; poor spatial resolution and inability to detect deeply sited discharges.

Scalp recordings are inevitably taken at a site distant from the electrical generator. The attenuation that follows means a large volume of cortex must be involved in the discharge, before it will register at the scalp. Moreover, an electric field that is oriented perpendicular to the skull may not be detected at the scalp on a bipolar recording. Therefore, scalp recordings tend be biased in favour of large, transverse electric fields, subjacent to the skull. Much of the frontal cortex lies in deep gyri or on the mesial or orbitofrontal cortical surfaces, where standard electrodes may fail to detect discharges. Increasing the number of electrodes[82] may improve the accuracy of localisation, but is very unlikely to uncover epileptogenic cortex undetected by standard techniques. Occasionally, supra- or

infraorbital surface electrodes will detect orbitofrontal discharges, not seen with standard electrode arrays[83,84].

Special semi-invasive sphenoidal electrodes have established a place in the investigation of temporal lobe epilepsy, but special electrodes for frontal seizures e.g. naso-ethmoidal electrodes for orbitofrontal epilepsy have found less general favour, as up to 40% of patients find them unpleasant, and the same information can almost always be obtained with non-invasive supraorbital electrodes[85].

Some frontal seizures may be without any abnormal surface ictal EEG accompaniment, or else the prominence of motor activity results in artefact that obscures the EEG. This has caused some specific diagnostic problems: first, the absence of EEG change lends support to the inappropriate diagnosis of pseudoseizures; second, there may be uncertainty whether a manifestation is a seizure or another disorder e.g. a primary movement disorder as originally suggested in the "nocturnal paroxysmal dystonia" of Lugaresi[86,87].

In studies of partial epilepsy with various locations, scalp EEG missed up to 50% of resectable cases[88,89,90,91]. Of 113 patients with frontal lobe epilepsy reported from Montreal[47,92], only 12% had focal interictal spiking and focal ictal abnormality was present in only 22% of 302 seizures recorded from 16 patients; the commonest problem being bilateral EEG abnormality from unilateral lesions.

Scalp EEG also has a false positive rate; causing multifocal or widespread epileptogenic cortex to be interpreted as unifocal, potentially indicating operations that would prove unsuccessful[92]. Whilst this problem has also been recognised in FLE[93], it is less frequently a problem than is lack of specificity of the EEG in this region.

It is well recognised that the ictal scalp EEG may present with generalised discharges from the start of the seizure, without giving any clue to the region of onset. This pattern of "secondary bilateral synchrony" occurs especially from mesial frontal and cingulate foci[35,36,57,61,62,94,95,96] and is seen particularly in those seizures that appear to be clinically generalised from the onset. These seizures often cause sudden falls and are particularly devastating for the patient. They frequently result in severe injury, which is both acutely harmful and associated with long term neuropsychological decline. It is a pattern for which investigators may resort relatively frequently to the use of intracranial EEG, in

order to improve localisation. As discussed below, however, these techniques have their own limitations and may not achieve their aim.

Section 5b: Invasive EEG

More invasive methods usually follow one of two conceptually and technically different routes. First, intracerebral, multiple contact electrodes may be placed stereotactically within the brain substance (SEEG). These electrodes typically detect discharges from up to 5-10mm away, resulting in a high spatial resolution but sampling only very small brain volumes. This technique is used to address specific issues of localisation where there is a limited number of alternative hypotheses; e.g. electrodes may be implanted in both mesial temporal lobes, when discharges are known to be mesial temporal but lateralisation is not clear. It is suggested that SEEG, whilst helping in many of the uncertain cases, may make decisions more complex in others[97,98] particularly in the frontal lobes, although in highly selected cases, has given useful localising information, where extracranial EEG was non-specific[92]. It is important to note that most studies of intracranial EEG predate high resolution MRI and the role of intracranial EEG may change when MRI is evaluated fully. In the frontal lobes, targets are more difficult to select after conventional tests. The small volume sampled may result in the ictal onset being missed, unless very large numbers of electrodes are inserted, with their attendant risks. Even if the onset is detected, it may not be clear whether this merely represents one sample part of a much larger epileptogenic zone, as the electrodes may be considerably separated, in order to cover enough of the frontal lobes. Munari et al[99] used SEEG, including the frontal lobes, in 250 patients. They found that even with a relatively large number of electrodes, localisation was considerably less successful than in the temporal lobes. A clearer understanding is required of the clinical seizure types of frontal lobe epilepsy, if intracranial EEG is to be accurately targeted within the large volume of the frontal lobes, in order to answer the questions asked of it. Second, large electrode grids may be placed epidurally or subdurally to sample much larger volumes of cortex with less attenuation and without the interference of artefacts seen on the scalp EEG[100]. In some series this has a higher morbidity than SEEG and may be more difficult to apply to mesial discharges and those located deeply in the sulci, which are

amongst those causing the greatest diagnostic problems[101]. Van Veelen et al[102] found that subdural electrodes were often inadequate to localise deeper placed discharges and some patients required a combination of subdural and intracerebral electrodes.

Another approach is detection of interictal spikes at operation by electrocorticography, which is relatively easier than preoperative implantation. Spikes were focal in only 12% of 72 cases with probable frontal lobe epilepsy recorded by the Montreal group[92].

The increased spatial resolution of intracranial EEG, compared to scalp EEG, means that where it does detect a region, in which there is a consistent localised discharge, that precedes the clinical onset of the patient's habitual seizures, it is generally considered to have a much greater positive predictive value for surgical outcome than scalp EEG[103]. Conversely, where the clinical onset precedes the EEG changes, the value of the investigation is limited.

Section 5c: Special methods of EEG analysis

A number of methods of computer analysis of EEG are being evaluated in an attempt to aid localisation of apparently synchronous discharges using: phase differences; small (millisecond) time differences; dipolar seizure patterns and mutual information analysis[104,105,106]. However, these are still experimental and undergoing evaluation. Some improve the yield of intracranial electrodes, rather than obviate the necessity of their insertion.

These examples illustrate that it is often in those instances where the clinical diagnosis and localisation are least certain, that the EEG is least contributory and additional investigations are required for seizure localisation. Early surgical series, that predate modern imaging, nevertheless suggest that the information from the EEG may have prognostic value[107,108].

Section 6: Localisation by Imaging

Section 6a: Structural scans and their pathological correlates

In some cases partial epilepsy is clearly due to a focal structural lesion e.g. tumour[109], and frequently more minor pathological abnormalities may be found. Sclerosis of the mesial temporal structures is identified in up to 60-70% of temporal lobe specimens resected for surgery[91,110,111], but there is no such uniformity in the lesions underlying frontal lobe

epilepsy. By far the largest series of pathology in frontal lobe epilepsy to date was described by Rasmussen in postoperative patients before the era of modern scanning techniques[7]. Of 250 cases, 63 were due to tumour, 90 had a clear history of major head injury or gunshot wound. Other rarer causes were birth trauma, encephalitis and gliosis, either with an identifiable cause e.g. previous abscess or discovered at operation, with only 29 cases with unknown pathology. This represents a highly selected series and the incidence of clear-cut pathology is generally much lower, although a consistent trend appears to be for the frontal lobes to bear much of the brunt of cranial trauma and minor degrees of dysplasia have been recognised more frequently since this study was undertaken. Where there is a visible abnormality on a brain scan, whose location is consistent with other lines of investigation, the result is considered strong supportive evidence of seizure localisation, and the surgical success rate for seizure remission is greater where a macroscopic lesion is resected, than if epileptogenic cortex with no identifiable lesion is removed[112,113].

In one study computerised tomographic X-ray scans (CT) identified lesions in up to 65% of patients with refractory epilepsy[114]. However, many of these abnormalities were non-specific or non-focal and the number of diagnostically helpful CT scans, identifying focal lesions such as gliomas or hamartomas, is probably about 20%[115,116,117,118,119,120]. The yield from magnetic resonance imaging is higher than from CT and studies in the late 1980's gave yields of around 50%, but detection rates are ever increasing[115,117,121,122,123,124,125,126]. This rate of detection applies even in milder cases of temporal lobe epilepsy, where the seizures are not refractory to medical treatment[126], suggesting the presence of a visible lesion does not necessarily imply more severe epilepsy. MRI has found a particular niche in the detection of mesial temporal sclerosis[121,122]. This subgroup of temporal lobe epilepsy has an especially good surgical prognosis, with claims of detection rates of mesial temporal sclerosis (MTS) approaching 100% with the most recent, specially tailored MRI sequences[123,124,127], 3-D image acquisition and the application of geometric principles of stereology to image analysis[128]. Calcification remains easier to interpret on CT at the moment, unless special MR sequences are used, but other abnormalities are better defined on MRI[125,126,129].

Gross congenital disorders of neuronal migration e.g. lissencephaly, microgyria and pachygyria, have been recognised for many years as associated with mental handicap and as a potent cause of severe epilepsy[130]. These lesions are usually obvious on both CT and MRI[131]. With the increasing sensitivity of MRI, in particular its ability to differentiate grey and white matter on T1 sequences, small neuronal migration defects have been recognised increasingly, in association with focal epilepsy[132,133,134]. These may be isolated abnormalities or part of a more general disorder e.g. tuberose sclerosis. The smaller lesions are certainly better seen on MRI than on CT. Focal epilepsy has been successfully treated by the excision of both isolated tubers and sporadic NMD's in otherwise normal individuals. One case of the latter is reported in the current study. The exact role of microcortical dysgenesis remains unclear, since it may have an appreciable background rate[135] (of the order of 2-5%) in normal individuals and autopsy studies have demonstrated focal, nodular abnormalities in the brains of up to 26% of normal individuals. They appear to be fewer in number than in patients with mild clinical abnormalities e.g. dyslexia[136], and differ in histological characteristics from the more severe forms of dysplasia[135]. There appears to be a particular predilection of these lesions for the frontal lobes in some series[137,138], although in one series of MRI, the lesions of tuberose sclerosis were less reliably identified in the frontal cortex than elsewhere[139]. A golgi study showed dysplastic nodules to contain neurons with abnormal branching patterns radiating a considerable distance through the cortex, suggesting a microanatomical substrate for pathological cortical circuitry[140].

Section 6b: Functional isotope scans

Structural scans provide static images of the brain, which need to be correlated with a dynamic test of abnormal cerebral activity, in order to assess their relevance to the patient's epilepsy. Conventionally the EEG has been used and this remains the most direct measure of epileptic activity, to which other modalities are compared. In recent years, however, functional imaging has been applied; positron emission tomography (PET) or single photon emmission CT (SPECT), mostly utilising markers of cerebral blood flow or glucose metabolism. The analysis of the scans produced is made complex by the very variables the techniques are designed to assess[141]. As well as limited spatial resolution, determined by

the physical processes involved, the images are influenced by a temporal interaction between: (a), the dynamics of radioactive decay of the particle used; (b), the pharmacodynamics of the ligand-tissue interaction and (c), the fluctuations of cerebral activity according to whether cerebral state is ictal, postictal or interictal at the time of the injection.

Penfield[7] noted focal hyperaemia of the cerebrum in seizures during surgery and this has been reflected in PET and SPECT scans, with increased isotope uptake in the ictal region[142,143]. Conversely, most studies show interictal hypometabolism of the epileptic zone[117,144,145]. There is considerable variation[144,146], however, with interictal scans being hypometabolic, isometabolic or hypermetabolic. The patients for whom these scans are used, usually have frequent seizures and are in a constant state of flux between ictal, interictal and postictal states. They also suffer frequent subclinical electrographic discharges. Variations probably relate to these confounding temporal factors. In addition, since the abnormality is either hypometabolic or hypermetabolic, according to ictal state, it is probable that vascular changes are secondary in the epileptic process.

Where abnormalities are seen on MRI or CT, the corresponding regions of abnormal perfusion on PET and SPECT are consistently more diffuse than or discordant with abnormalities on the structural scans[117] and with the extent of the underlying pathological lesion[147] on histological examination.

It is likely that PET scans overestimate the cortex involved in epileptogenesis. Nevertheless, these scans are an extra tool in the preoperative assessment of investigations. Set against this is that the more tests are applied, the more likely it is for one or more to be discordant, so complicating preoperative assessment. In one study, of only 22 patients, PET appeared more sensitive than MRI in detecting of neuronal migration defects[148], but this was prior to the most recent MRI technology. PET and SPECT generally have lateralising rather than highly localising value and may identify abnormalities suggesting multiple epileptogenic regions in some patients, so saving them from unhelpful surgery[115].

Section 6c: Magnetic resonance spectroscopy

The most commonly used MR scanning uses sequences weighted to identify normal and

pathological anatomy. Magnetic resonance spectroscopy (MRS) has been applied to identify concentrations of various atoms or molecules within predetermined blocks of cerebral tissue[149]. These may be markers for functional abnormalities and their spatial anatomical information depends on the size and location of the block analysed: scan output is usually a concentration curve within this volume of cortex, rather than an image of anatomical distribution, because anatomical resolution is lower than with hydrogen, used in MRI, as the concentration of these molecules is lower and cannot give such accurate anatomical information.

Animal studies show that during experimental seizures there is an increase in glucose uptake[150], a fall in phosphate bound to creatinine, with a corresponding increase in unbound phosphate, a rise in lactate and fall in pH, all consistent with increased metabolic activity[151,152]. Similar changes were seen in ictal MRS of human neonates[153]. To what extent abnormalities can be detected in the interictal period is unclear, but the animal studies suggested that the changes in lactate persist beyond the end of measurable EEG abnormality[154].

The molecule N-acetylaspartate (NAA) is believed to be a marker for viable CNS neurons. MRS may be used to compare its concentration to that of a background molecule e.g. choline. In diffusely atrophic cortex, where all elements are similarly depleted, it is believed that the ratio of these molecules will remain unchanged, although overall concentrations will be lowered. However, in some sclerotic lesions, where there is selective neuronal loss, the ratio of NAA to choline will fall. The concentration of NAA was found to be low in resected epileptic temporal lobe tissue in one study[155], presumably representing neuronal dropout. The ratio was not, however, reduced for frontal lobe resections, which may have been because white matter was excluded from temporal but not frontal studies, so diluting the concentration of perikarya in the frontal analyses. One *in vivo* study examined volumes of 19,48 and 63cm^3 of epileptic tissue in three patients and found low NAA to choline ratios, compared with normal controls[156]. However, these patients all had lesions on conventional structural MRI and it is unknown whether this biochemical change is also present in macroscopically normal anatomy. In MTS, the NAA:choline ratio is also altered in the affected hippocampus[157] but again, this is usually in the presence of visible

anatomical abnormality.

Section 6d: Imaging applied to frontal lobe epilepsy

Mesial temporal sclerosis accounts for a significant proportion of temporal lobe epilepsy and other defined pathologies; gliomas, angiomas, hamartomas etc. are also common[109]. Well delineated pathology is less frequent in the frontal lobes[7] and where scanning modalities have been applied specifically to frontal lobe epilepsy, the yield of MRI has been smaller[158]. Swartz et al[159] conducted a comparative study of imaging modalities in 22 patients with probable frontal lobe epilepsy on clinical and electrographic criteria. They compared CT, MRI and PET for each patient and found that PET was the most sensitive test but the abnormalities were rather diffuse and it missed one astrocytoma, detected on MRI. The clinical relevance of these findings is not yet clear in this group of patients. Holmes[160] found that a major limitation of PET was in its ability to differentiate between frontal and temporal epileptic regions - an area in which it would be clinically most useful to have differentiating test. Interictal HMPaO SPECT was also found to be rather non-specific in FLE[161]. Convers et al[162] performed MRI on 100 patients with partial epilepsy and a normal CT scan. They found that in TLE, 36% of patients had imaging abnormalities, but only 5.9% of patients with FLE. They used a 0.5 Tesla magnet whose yield may be lower than newer, more powerful scanners. More recently on a !.5 Tesla machine with volumetric techniques, abnormalities have been found in 80-90% of CT negative cases, and subtle frontal cortical dysplasia appears to be a relatively common pattern[163]. In some cases, visual inspection of the scan does not demonstrate definite pathology, but special analytical techniques e.g. fractal analysis of the grey-white interface may suggest regional abnormalities[164].

6e: Summary

Structural imaging provides a valuable adjunct in seizure localisation, MRI consistently being more sensitive than CT. With modern scans, the yield of focal abnormalities may be up to 80-90%, but the significance of the more subtle abnormalities remains to be established. Functional isotope scans show more diffuse abnormalities of limited use, in planning focal surgery, but may be helpful in selected cases, suggesting multifocal areas of

epileptogenesis. New scan modalities e.g. MRS are still under evaluation.

Section 7: Neuropsychological localisation

Neuropsychological deficit may give supportive evidence of focal neurological dysfunction consistent with other methods of localisation of abnormalities especially in ascertaining lateralisation of speech and memory functions[165,166].

One of the most regular findings of frontal lobe lesions is emotional change, varying from profound apathy and inertia, to lability and euphoria[167]. Another common feature is perseveration, which may be so severe as to make other deficits very difficult to assess. Pribram[11] hypothesised the limbic frontal cortex is particularly involved in attentional behaviour whilst SMA and PMC are implicated in different facets of motor control. The basis of much of this work is in animal models, although many features e.g. attentional deficits are similar in man. Major pathology in the frontal lobes may, however, produce only minor deficits in humans until the lesion is very large[168] and minor lesions are easily missed. Studies show that in humans and animals, large unilateral or bilateral resections from SMA, may cause only minor and transient abnormalities[169,170]. Brown[167] suggested that the SMA is more involved in the initiation of actions whereas the PMC is concerned with the fine control of their execution, under sensory feed back. Even in highly selected patients, with relatively precise frontal lesions, it has, however, been difficult to confirm any major clinical differences between SMA and PMC lesions[171].

There is some evidence that left hemisphere lesions tend to have more effect on speech and right sided lesions cause more emotional deficit[167], although dysphasic abnormalities may be seen in lesions of either hemisphere and equally may be absent after bilateral prefrontal leucotomy. Unilateral lesions anterior to the primary motor cortex, may also cause ipsilateral, contralateral or bilateral motor deficits[171].

Bianchi found characteristic deficits in patients with frontal damage, but there was no difference between those with and those without epilepsy[172]. In many cases of frontal lobe epilepsy no macroscopic lesion has been recognised and the nature of neuropsychological deficits may be even less clear-cut.

Therefore, precise localisation of neuropsychological deficits within the frontal lobes

remains uncertain in most cases. Simple motor deficits suggest more posterior involvement, in the primary motor cortex, whereas more complex abnormalities of motor planning and sequencing in response to multimodal sensory cues, dysphasia and emotional changes, point to more anterior problems, but it is difficult to be more specific. Nevertheless, it remains important to demonstrate any widespread extrafrontal deficits, which may imply broader involvement in pathology or seizure activity, than was suggested by other investigations. These deficits may be secondary to high antiepileptic drug dosages or other factors in some cases, but the degree of localisation of neuropsychological abnormality has been suggested to be an independent factor in the prediction of seizure remission after surgery[101] and the putative functional properties of the frontal lobes and the nature of ictal clinical manifestations, may give some insight into the mechanisms of transient derangement during seizures.

Section 8: Surgical localisation

Section 8a: The background to epilepsy surgery

The last fifty years have seen an evolution in epilepsy surgery, pioneered at the Montreal Neurological Institute by Penfield and his colleagues[7]. Since then numerous series of temporal lobe surgery have been published[10,49,109,110]. The assessment of surgical outcome depends on a variety of factors, including patient selection and timing of the postoperative assessment[10] and is defined differently in different centres. However, applying Engel's[10], (table 2, below) classes 1 and 2 as favourable outcomes, most investigators report successes, for temporal lobe surgery, in the region of 60-80% for appropriately selected patients, with optimal techniques currently available. Frontal lobe epilepsy surgery is more unpredictable; series are much smaller and report successes in the region 20-40%[10,31,95,173,174,175,176]. This leaves 60-80% of those operated, let alone the larger number undergoing extensive and sometimes invasive investigation, without significant benefit.

Table 2. Classification of postoperative seizure outcome from Engel[10]

Class 1: Seizure-free	Completely seizure-free since surgery
	Auras only since surgery
	Some postoperative seizures but seizure-free at least 2 years
	Atypical generalised seizures with drug withdrawal only
Class 2: Rare seizures	Initially seizure-free but now rare seizures
	Rare seizures since surgery
	Initially some seizures but rare for at least 2 years
	Nocturnal seizures only
Class 3: Worthwhile improvement	Prolonged seizure-free intervals for more than half the follow-up period but not less than 2 years
	Other worthwhile seizure reduction
Class 4: No worthwhile improvement	Significant seizure reduction, but less than class 3.
	No appreciable change
	Seizures worse

The fundamental aim of epilepsy surgery is to identify a localised region of cerebral cortex that is both crucial for the development of a patient's seizures and non-essential for normal functioning, such that removal will relieve the seizures without causing significant neurological deficit. For each patient evidence of the suitability of surgery is taken from the clinical seizure description, EEG, imaging and psychological investigations. Resective surgery is most likely to be successful when these are concordant in pointing to a single, well-localised and non-essential region of epileptogenic cortex[177].

The limitations of each of these methods of seizure localisation has been discussed. Most studies of investigations in the pre-surgical assessment of epilepsy patients, compare the yield of one test against another and suffer from the lack of correlation with a yardstick that is of unequivocal relevance to the processes of epileptogenesis; they usually fall back on the

success of surgery itself being used as the standard.

Once epileptogenic cortex has been identified, it remains unclear exactly how it should be approached surgically. The issues are further confounded as the relief of seizures by surgery is measured differently in different centres[10]. There are two easily defined groups (figure 3, page 166): those patients permanently seizure-free after surgery and those for whom surgery was of no help. Between these two extremes are several other groups more difficult to define: those in whom seizures gradually disappear; those whose seizures recur after varying seizure-free intervals and those with partial seizure relief. For these patients the interval after which surgery is assessed, will affect the apparent outcome, as illustrated. Even the seizure-free group is usually taken to include those patients with persistent auras[10]. This may be a pragmatic approach to treatment, and it is not clear whether occasional persistent isolated auras indeed represent continuing epilepsy, but it may imply that surgery had an ameliorating effect on seizure generating cortex, rather than completely removing it. Moreover, the clinical characteristics of postoperative seizures usually resemble those of preoperative seizures in patients who relapse[178]. If the early seizure characteristics represent focal seizure onset in the primary epileptogenic cortex, then how did surgery relieve the seizures, yet leave these behind? The definition of a disease process by its response to treatment also leads to a fundamentally flawed, circular argument and it may be that in some successful cases surgery interferes with the expression of a seizure diathesis rather than eliminating the underlying process.

Section 8b: Surgical approaches to epilepsy

The retrospective, uncontrolled, Mayo Clinic study of 30 macroscopic, epileptogenic lesions, suggested that pure lesionectomy, with minimal clearance of surrounding cortex, can be as successful as more extensive resection[179] and others suggest that resection of a lesion is a more powerful prognostic indicator than resection of the associated cortical EEG abnormality[180]. Seizures were relieved even though the tissue removed was almost exclusively non-neuronal and could not participate directly in the seizure activity. Conversely, in one case of focal epilepsy[181], a postcentral cyst causing mechanical deformity anteriorly was seen on CT scan, but the epileptogenic cortex, as assessed

clinically and intraoperatively by electrocorticography, was in the SMA. Resection of the discharging area was successful in relieving seizures, even though the lesion was left *in situ*. This is, however, rare; many operations guided by EEG and away from a known structural lesion are unsuccessful[182,183]. Penfield and Jasper[7] and Rasmussen[109] found in some cases of limited resection, a second more extensive operation was required, to remove "a fringe of apparently epileptogenic cortex", before the patient eventually became seizure-free. More recently, a study of re-operation after unsuccessful first operations for focal epilepsy showed the best outcome was where there was extension of previously incomplete removal of a macroscopic lesion or non-lesional epileptogenic cortex[184].

In recent years the operation of stereotactic selective amygdalohippocampectomy has been practised in some centres for temporal lobe epilepsy[185], particularly in the dominant hemisphere, when it is feared a more extensive operation may cause substantial neurological deficit. Intracranial EEG in man[186] suggests that temporal lobe seizures usually spread to contralateral structures and generalise via the amygdalohippocampal formation and not directly from temporal neocortex. Consequently, highly restricted pathways via the hippocampus and amygdala may be largely responsible for the early propagation of specific seizures[43]. The selective operation appears to have a similar outcome to more extensive surgery in appropriately selected patients[188]. This mesial temporal location may represent a special case; no single pathway has so far been demonstrated to be responsible for any type of frontal seizure and the more extensive interconnectivity of the frontal lobes make it less likely that any will be discovered. However, an example of surgical seizure treatment by division of fibres, without neuronal resection, can be seen in frontal lobe epilepsy. Where it remains impossible to localise the origin of synchronous discharges arising in the frontal lobes, a therapeutic approach is section of the corpus callosum. This procedure may be effective, not only in preventing the propagation and bilateral manifestation of the seizures, but may also reduce the partial seizures that trigger them[187,188]. It is unknown if this is purely a white matter effect or whether secondary neuronal degeneration after axonal transection may play a role. The clinical improvement may occur even though the procedure does not entirely eliminate the electrical manifestations of secondary bilateral synchrony. Isolation of the hemispheres

after callosotomy may also allow EEG localisation of the primary epileptogenic lesion whose spread is now restricted[189], facilitating regional surgery, not previously possible. In an experimental model, propagation of secondary bilateral synchrony may occur via the thalamus as well as across the corpus callosum[190], possibly explaining persistence of bilateral synchrony after corpus callosum section, but the clinical importance of this in seizure spread in humans, is unclear.

Electrocorticography (ECoG) may be used at operation to delineate the most epileptogenic cortex for removal. However, the correlation between the intensity of residual ECoG spiking after cortical resection and the final outcome of surgery is poor[113,191,192,193]. There are numerous, well described patients, in whom there was significant post-resection spiking, who became seizure-free; spiking of the insula is a particularly poor indicator of outcome after temporal lobectomy[165]. Rasmussen[193] argued that there may be secondary epileptogenic regions that spike on ECoG, whose activity declines after the removal of the primary epileptogenic zone, explaining the reduction in seizure activity seen in some patients in the first few years after operation.

Late recurrence of seizures is being increasingly recognised after epilepsy surgery and their clinical pattern may be identical to that seen preoperatively[10]. In one study of 24 frontal resections, 50% were initially seizure-free but one third of these later relapsed[194]. Thus despite resection of neural tissue and interruption of pathways, producing remission for several years, the same seizures can recur in the absence of the neurons previously thought essential to this clinical pattern. The same arguments of circuits underlying seizures, which may be triggered from multiple sites, may be used to explain this phenomenon. When the primary epileptogenic region is removed, secondary sites may take over the role of activation of the circuit.

In general terms, the choices of operation include: extensive cortical removals; local lesion resection with minimal neuronal removal; removal of discharging cortex, leaving the lesion *in situ*; or even just axonal section to interrupt pathways of seizure propagation, without excision of grey matter. The success of these operations is the accepted standard of

epilepsy localisation. Yet it has major problems: the relationship of the treatment to the underlying seizure mechanism may well be different in each kind of operation; even from one type of operation it is difficult to explain the different outcomes in pathophysiological terms, without casting major doubt on the gold-standard and it applies only to a tiny minority of patients with epilepsy. The use of this method has been particularly unsuccessful in frontal lobe epilepsies, where surgery has the poorest success rate.
The starting-point of seizure analysis is the identification of clinical seizure patterns and the assessment of the reliability with which they can be attributed to specific cortical regions. This project aims to address these issues, especially in relation to epilepsy of the frontal lobes, using techniques that avoid the preconceptions and biases of previous post-surgical series.

Methods

The study was in 2 sections. The largest was an analysis of partial seizure types in a hospital-derived population. The second was an analysis of partial seizure types in a general population, using data from the National General Practice Study of Epilepsy[4].

Hospital Study

Clinical data collection

Patient selection

Patients for the hospital study were selected on the basis of epilepsy with strong evidence of focal onset in one or more of the following modalities, excluding those with characteristics of occipital seizures which are the subject of another study at our institution[195]. Occipital seizures are relatively well defined, with specific clinical symptomatology and relatively infrequently cause problems of classification, in contrast to the major clinical problem of differentiation of frontal and temporal epilepsies.

1) A demonstrable focal epileptogenic structural lesion on CT or MR scan.

2) An ictal EEG recording suggesting focal electrographic seizure onset

3) An interictal EEG showing focal paroxysmal spike activity. Other less specific EEG disturbances e.g. focal slow wave activity were not included.

4) Clinical ictal onset with highly focal activity, according to current concepts[3]. This excluded cases with evidence of partial onset but only poorly localising symptoms e.g. isolated abdominal or cephalic sensations and no other more specific evidence of focal onset on investigation.

These selection methods were designed to include a broad base of patients from general neurology as well as specialist epilepsy practice. Because a proportion of patients may have focal seizure manifestations without any abnormalities on investigation, not to include this group would artificially restrict the study. Its inclusion does, however, risk the selection criteria introducing a bias in the analysis of seizure patterns. In order to offset this risk, it is important to note that those selected according to EEG or imaging criteria were chosen irrespective of associated seizure pattern. In addition those chosen

according to clinical criteria were included irrespective of the site of any lesion or EEG abnormality identified subsequently. Unlike post-surgical series, selection criteria were independent, with concordance deliberately not considered in the **initial selection**, so it could be assessed later in relation to the identified seizure patterns.

Initially all cases identified in each of the categories searched were included in the study. Subsequent searches focused on individuals with focal structural lesions in the frontal regions in order to have the greatest number to enter into statistical analysis of lesion sites.

Patient identification

The CT reports of the Maida Vale branch of the National Hospital are classified according to the nature of pathology involved; those pertaining to cerebral abnormalities were searched for those with frontal or temporal lesions and a history of epilepsy on the request form. The number of CT scans performed at the Queen Square branch of the National Hospital is much greater and it is not feasible to extract those with cerebral lesions and epilepsy, either manually or from the computerised database.

All MR scan reports of the Queen Square Imaging Centre, since its inception in 1983, were searched for patients with focal lesions, other than occipital, and a history of epilepsy.

All patients were identified, who had undergone video-EEG-telemetry (VET) at The National Hospital and in whom a diagnosis of focal epilepsy was made on the basis of electrophysiological or clinical features.

Reports of all routine EEG records of the electrophysiology department over a period of 2 years prior to the start of the study were searched EEG's with focal spikes, other than occipital. Any patient satisfying the above criteria in the previous 2 years was also identified from inpatient and outpatient records of the epilepsy unit of the National Hospital and the Chalfont Centre for Epilepsy.

During the course of the study, colleagues continued to refer to the study, newly identified individuals who conformed to these criteria.

A total of 431 patients were identified. Of these 252 were included in the study. Reasons

for non-inclusion and the numbers involved are shown in table 3 below. For each of the groups identified in the results, the proportions selected according to the different criteria will be included and may be compared to the group as a whole, in order to highlight any possible selection bias. In addition to a witnessed seizure history, minimum investigative requirement for inclusion was an interictal EEG and CT scan or just neuroimaging if it contained strong localising evidence in the form of a foreign tissue lesion.

Table 3: Reasons for non-inclusion in the study

Reason for non-inclusion	Number of patients
Change of address or unable to telephone	112 (26%)
Patient declined to participate	31 (7%)
Patient died	10 (2%)
Total	**153 (35.5%)**

Of the 278 patients successfully contacted, 26 were excluded, mostly because no accurate eye-witness account of their seizures could be obtained. Four cases were excluded because the patient had been seizure-free for more than 2 years and it was felt that time may have eroded the accuracy of the seizure description. Four others were excluded because re-examination of their CT scan or EEG did not support the focal abnormality that had been their original criterion for inclusion.

Patient contact

Initial recruitment of patients was by a postal request. If there was no response, a second letter was sent and finally patients were contacted by telephone to request participation in the study. Forty-four patients (17%) were notified to the study during the course of an admission to hospital and were interviewed at that time. In most cases (88%), I conducted interviews in person, but where this was not possible, for personal reasons, the interview was conducted over the telephone.

Patients were excluded unless an independent, eye-witness account of their seizures could

be obtained. Thus, in all cases an independent description of seizures was available. Where this was from the patient's friend or relative, patients were encouraged to bring this person to the interview. Where this was not possible, I obtained the eye-witness account later by telephone.

In 176 cases an eye-witness account was obtained, in 26 cases only video-telemetry recording was available and in 50 cases both were available.

Patient Interviews

A proforma for a structured interview was designed specifically for the study (appendix 1, page 235). This comprised 2 parts; a section relating to personal and family medical history and previous investigations, and a section devoted to the description of each seizure type for that patient. The details of each seizure were collected in 3 phases. First, a closed questionnaire relating to the frequency and timing of seizures, including diurnal variation and tendency to cluster. Second, an open section in which the patient and then the witness were invited to give a sequential account of seizure manifestations. Finally, a closed section administered as a "checklist" of possible seizure manifestations, to make sure none had been missed.

Some patients reported more than 1 seizure type (table 4 below). Often there was evidence that one type represented an evolution of another seizure type, in which case the seizure was classed as a single type e.g. a patient with frequent auras and relatively infrequent complex partial seizures (CPS) that were always preceded by the same auras. The seizure was then recorded as its fullest expression, which was felt to be of most relevance in the analysis of seizure spread by sequential manifestations. Where a seizure habitually became generalised, this was included in the description of the characteristic seizure, but where secondary generalisation was rare, this was not included. Equally, generalised seizures were only considered separately where there was no evidence of the patient's habitual partial seizure prior to secondary generalisation. Three hundred and fifty-two discrete seizure types were documented in 252 patients.

Table 4: Numbers of seizure types for each patient

Number of discrete seizure types	Number of patients
One seizure type	167 (66%)
Two seizure types	70 (28%)
Three seizure types	15 (6%)
Total	252

Video-telemetry analysis

Video recordings of seizures were analysed and broken down into sequential occurrence of manifestations, corresponding to those in the questionnaire. Non-uniformity of seizures was treated as above, and in most cases was attributable to minor variations of an underlying pattern. Major discrepancies between telemetry and questionnaire data were rare; in one case a witness described posturing only of the right arm, whereas telemetry showed only involvement of the left arm. In such cases, telemetry data were accepted over questionnaire data (see questionnaire validation below).

Clinical Data Recording

The manifestations were divided into groups shown in table 5 below. The individual manifestations and their group definitions were coded in 7 categories, from 0-14, according to whether and when they were first observed to occur in the seizure. The coding provided an ordinal measure of the sequential occurrence of manifestations in relation to other events during the seizure, but was not strictly related to their time of occurrence.

Table 5. Definitions of symptoms and group definitions used in statistical analysis

Manifestation	Description
Physical	Non-specific cephalic or whole body sensations
Abdominal	Nausea, rising epigastric or other abdominal
Experiential	Deja vu, jamais vu, forced thought, flashback or other non-hallucinatory distortions of reality.
Emotion	Fear, depression, elation, anger
Visual hallucination	Formed or unformed hallucinations
Auditory hallucination	Auditory manifestation unrelated to background noise
Olfactory hallucination	Olfactory sensation
Gustatory hallucination	Gustatory sensations
Non-Jacksonian somatosensory	Focal sensations e.g. tingling without clear gradual anatomical progression
Jacksonian somatosensory	Focal sensations with clear gradual anatomical progression.
Focal clonic	Clonic activity without clear gradual anatomical progression
Jacksonian clonic	Clonic activity with clear gradual anatomical progression
Version / posturing	Head turning or maintained postures of the limbs, excluding generalised hypertonia.
Generalised hypertonia	Simultaneous hypertonia of all 4 limbs.
Simple automatisms	Involuntary repetitive movements e.g. tapping, plucking of clothes, bicycling or scissoring of legs.
Behavioural automatisms	Complex acts performed without apparent awareness e.g. undressing or exploratory behaviour.
Oroalimentary automatisms	Swallowing, chewing or other complex oral movements, excluding facial involvement in tonic or clonic movements.
Verbal vocalisations	Apparently involuntary speech
Non-verbal vocalisations	Other involuntary noises e.g. shouting, crying, laughing, singing. Non-specific moans and grunts were excluded.
Vegetative manifestations	Changes in colour, pupils, respiration and pulse.
Objective awareness	The objective responsiveness of the patient to interaction during the seizure.
Subjective awareness	The ability of the patient to recall external events or seizure manifestations, after the end of the seizure.

Questionnaire validation

The questionnaire was very comprehensive; <1% of the manifestations observed in the 352 seizures in the study were not covered by a specific question. The use of the groupings above allowed any very unusual symptoms e.g. bizarre automatisms, to be included in the analysis. A random selection of 13 of patients, in whom both telemetry and witnessed descriptions were available, was analysed for concordance of all objective seizure manifestation variables measured. In each case, the description given by a witness and the telemetry data were encoded separately onto the numerical part of the questionnaire and these were then compared for each patient. Most manifestations included in the questionnaire do not occur in any given seizure but all variables, whether positive or negative, were included in the cluster analysis, hence all were included in the validation. Only 10% of the 780 variables encoded for the ~~25~~ 13 patients differed between the 2 situations (table 6 below) and in nearly half of these, the difference was one of timing than rather than of occurrence. There were manifestations both reported by witnesses and not seen on telemetry and vice-versa; although, there were more instances of the latter. This variability is well within the expected variation of habitual seizures and supports the value of the questionnaire and reliability of the coding method.

Table 6. Differences in seizure variables between telemetry and witnessed seizure accounts

Type of Difference	Number of variables
Manifestation on telemetry but not witnessed	32 (4.1%)
Manifestation witnessed but not on telemetry	12 (1.5%)
Difference in encoding of manifestation = 1*	26 (3.3%)
Difference in encoding of manifestation > 1	8 (1%)
Total	78 (10%)

*Represents a difference in timing of sequential occurrence of one stage, between telemetry and witnessed description.

Statistical analysis of clinical data

Questionnaires were stored in "Dataease" database software on an IBM-compatible personal computer. Files were exported in "Lotus 1-2-3 format" to "SPSS-PC+" and then to "SPSS-X" for analysis. This facilitated checking of exported files for errors and missing values before translation into "ASCII" format for statistical analysis by SPSS.

Cluster analysis

This is a syndromic analysis of seizures rather than of patients. Each seizure type, rather than each patient, was therefore, entered as a separate case in the statistical analysis; patients with more than 1 seizure type were entered more than once. The variables included in the cluster analysis are shown in appendix 2, page 241. Cases of complex partial status epilepticus were excluded from this analysis because analysis of sequence of manifestations was not possible with this type. In some cases variables entered in the analysis were the group categories of manifestations, rather than individual manifestations. If the number of variables in the analysis were too large, this would degrade the data and no groupings would ever be found. A further problem with statistical analysis is the weighting of data to allow for related variables. For example, swallowing and lip smacking automatisms are more closely related to each other than they are to clonic jerks and it would be inappropriate for the analysis to treat all three as equidistant. In order to minimise these problems, categories of variables were analysed, using groupings of related symptoms. The aim of these modifications was to use existing knowledge in order to enhance data entry and make the cluster analysis as clinically meaningful as possible. It is important to appreciate that whilst these modifications may be viewed as seeding the data with preconceived relationships, these are kept to a minimum, are consistent with current literature, and are applied equally to all cases in the analysis. Notwithstanding the groupings, the number of variables used, at 52, was still large. The localising value of some symptoms e.g. olfactory aura is greater than for others e.g. cephalic aura[7]. This would require weighting of data in the analysis but meaningful weights can only be attributed, if there is an outcome measure of the analysis against which to calculate them, which was not available in this study. For this reason the cluster analysis could be seen as

generating general groupings; the aggregation of cases into ever larger clusters was stopped prior to achieving the minimal reasonable number of groups, and final groupings were created by the combination of statistically defined groupings. Because this final definition required some recombination of those derived from the cluster analysis, independent validation was sought (see validation section below).

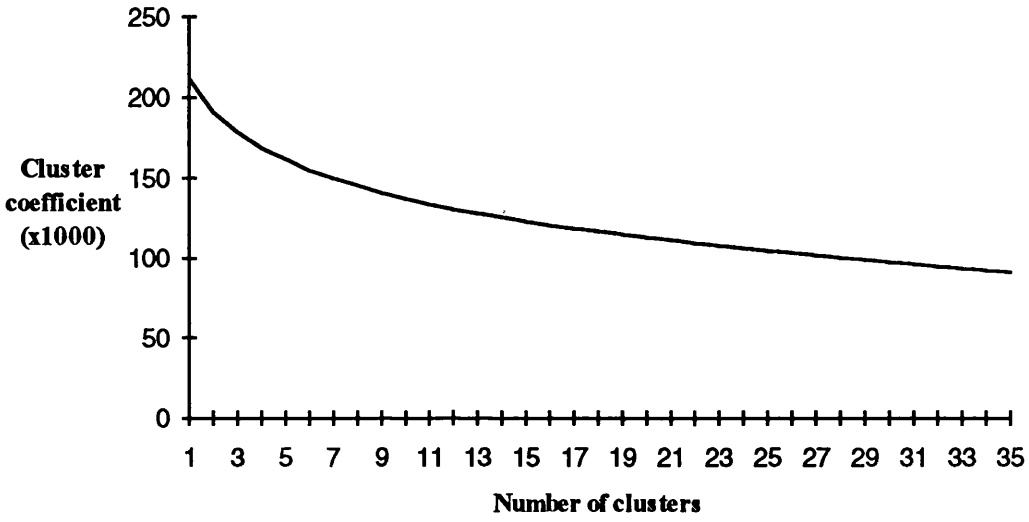
Ward's method was used, utilising squared Euclidean distances for intervariable distance. It is an agglomerative technique; the analysis starts with number of clusters equals number of seizures (346), then combines them into progressively fewer groups until, ultimately all the seizures are combined into a single large group. The coefficient of clustering relates to the distance between the two groups being combined at that stage, representing the magnitude of the differences between them. As the number of groups becomes smaller, progressively more dissimilar groups are combined and the coefficient rises rapidly. Graphical examination showed that the coefficient of clustering started to rise rapidly (seen as increasing gradient on figure 1 below) if the seizures were combined into fewer than 13 clusters, suggesting that the minimum reasonable number of groups was approximately 13.

Accordingly, I selected a level of 25 groups at which to perform manual analysis, combining the groups into a smaller number, finally resulting in 14 groups, each corresponding to an overall seizure type.

The sequence of manifestations for each seizure type and the numbers of seizures following a particular sequence were represented on flow charts. Subgroups of each type were represented by colour coding on the charts.

Figure 1: Cluster coefficient for different numbers of groups

(The higher the coefficient, the more dissimilar the two groups just combined to make one less total number of groups)



Validation of cluster analysis

Individual seizure manifestations were compared between those patients with lesions restricted to the frontal lobes and those with lesions restricted to the temporal lobes. This provided an analysis separate to that derived from the statistical cluster analysis, which identified those clinical manifestations of significant localising value between frontal and temporal lobes, one of the most important clinical differentiations, and supported the choice of variables in the definition of clinical groupings.

Validation of cluster analysis was at 2 levels; internal validation of the statistical technique and external validation of the results. Two methods of internal validation were used: first a random sample of 176 cases (50%) was taken and reclustered according to the same statistical method and compared to the original cluster analysis; second the whole group was clustered using a different technique "Quick-cluster" on SPSS-PC+, specifying the number of clusters as 25. In the first method, 65.5% of cases reclustered to the same groupings and in the second 62%. The number of cases that would recluster to the same groups by chance is a function of the number of groups and their size; for example with two equally sized groups, 50% of cases would necessarily recluster together.

For 25 groups, however, the number would be much smaller and, therefore, a figure of over 60% is highly significant. Previous studies, usually using smaller numbers of groups have quoted acceptable validation figures of 40-70%[196]. For external validation the association of well-defined seizure types into the same groups was assessed; absences without focal features; atypical absences; tonic-clonic seizures without focal features and Jacksonian sensorimotor seizures. These types were defined and segregated by the cluster analysis with an accuracy of 89%. Manual modifications to the cluster analysis were predictable in terms of the varibles included in the analysis. For example; olfactory and gustatory seizures were combined into one group and generalised tonic, tonic-clonic, and clonic seizures were recombined into subgroups of one overall grouping. Jacksonian clonic seizures and isolated jerks were separated into different groups because the cluster analysis had not identified them separately, because of the absence of a seizure duration variable.

Interictal scalp EEG analysis

At least 1 interictal EEG was available for 226 (89%) of patients. Some were assessed from paper records, but the majority on microfilm. The number of patients with different numbers of EEG's is shown in table 7, below.

Table 7. Number of interictal EEG's available for each patient

No. of EEG's	0	1	2	3	4	5	6	7
No. of patients	23 (9%)	106 (42%)	69 (27%)	33 (13%)	15 (6%)	3 (1%)	3 (1%)	1

The number and location of the first 100 spikes were assessed on all available interictal EEG's for each patient. This gave a good sample size and for most patients included all interictal spikes. Other EEG manifestations were not assessed and spikes occurring during overbreathing were excluded, as these may not be representative. This provided a standardised means of assessing interictal abnormality, which though not strictly random, minimised bias. Spikes only were assessed as these are relatively well defined according

to standard criteria[197], whereas other abnormalities e.g. slow waves, are not specifically epileptic and may be influenced by drug treatment and the nature of the underlying pathology. Spikes were classified as focal, regional, unilateral, bilateral, widespread or generalised, according to criteria in table 8 below. EEG's were recorded using the international 10-20 system, on occasion supplemented with additional electrodes, usually placed between standard electrodes, for greater resolution. Assessment of spike distribution in these cases was nevertheless made with reference to standard electrodes, to ensure comparability between cases.

Table 8. Definition of interictal EEG spike distributions

Distribution	Definition
Focal	Maximal at a single electrode with minimal spread
Regional	Maximal at 2-4 neighbouring electrodes
Bilateral	Symmetric, maximal at 1-4 electrodes on both sides
Hemispheric	Maximal at >4 electrodes on one side of the head only
Widespread	Asymmetric, involving many electrodes on both sides
Generalised	Symmetric generalised discharge

Twenty-four (10%) patients' EEG's were re-analysed from 3 to 15 months after initial measurement to obtain intra-observer variation statistics. No EEG reported to have no spikes in the first analysis was found to have spikes in the later analysis or vice-versa. The total number of spikes found differed between analyses by less than 10 in all but one case. The mean difference between the 2 assessments in the proportion of spikes in the most important focal group was 4% (SD 7%), and was similar in other groups. Most importantly, where focal spikes were found, there were no differences in their localisations between assessments. Regional spread was measured in terms of groups of electrodes involved, rather than putative anatomical structures underlying the discharge and there were some minor differences in the electrodes deemed involved in regional or less focal discharges, between the assessments.

Ictal EEG assessment

Ictal scalp EEG's were available in 77 patients; in 74 obtained during video-telemetry recording, enabling correlation with clinical manifestations and in 3 obtained by serendipity during routine EEG recording, without accurate timing of clinical accompaniments. Telemetry recordings were made with 24 channel EEG and computerised recordings, usually utilising the standard 10-20 system, supplemented with superficial or deep sphenoidal electrodes. In a few cases unusual electrode placements were added and abnormalities were again related to standard electrodes to facilitate comparison between cases for the purposes of the study. Where possible, EEG onset was related to clinical onset and the interval between the 2 was noted. The distribution of EEG onsets was described as in table 8 above, the temporal relationship to clinical onset and the pattern of discharge was also recorded, using definitions similar to those described by Quesney and Gloor[198]. In their review, however, they combine the pattern and distribution of EEG abnormality into a single statement regarding accuracy of localisation e.g. "precise focal onset comprises attenuation then fast activity from a narrowly defined area of the scalp". In the analysis of ictal EEG's, these variables were, in the first instance, measured separately, although in discussion, their relative significance in accuracy of localisation will be considered. Evolution of the EEG changes through the seizure and the nature and location of postictal EEG change were also recorded. Where more than one EEG pattern was associated with the same clinical seizure type in a given patient, the number of seizures with each pattern was documented and the most localised and earliest EEG onsets are emphasised. This ensures that each seizure in the study is only represented once, although it may tend to bias slightly the results in favour of patients with fewer recorded seizures, as inevitably, the more are recorded, the more potentially variable may be the EEG pattern observed.

Ictal EEG analyses were compared to detailed reports prepared by a Consultant Neurophysiologist; there were no major discrepancies.

Analysis of neuroimaging

CT Scans

Abnormal CT scans were documented in 51 patients. As a result of the method of case selection, scans were performed at various times on different machines with different parameters and a method of stereotactic lesion mapping was required that took this variation into account. The technique used, was modified from previous methods relating CT to bony landmarks[199,200]. A copy of the brain template was taken from the standard atlas of Talairach and Szikla[201] and measurements were made of its maximum transverse and longitudinal dimensions and of the distance from the superior margin of the petrous temporal bone to the skull vault. The maximum transverse and antero-posterior (A-P) dimensions were measured in the candidate scan, from the slice with the widest and longest sections of brain and multiplication factors obtained to superimpose the scan onto the template. The height of the vault was measured from the lateral scout image, where available, and the vertical multiplication factor likewise calculated, from which the interslice distance for the template was calculated. These separate calculations for each brain, in all 3 dimensions, allowed adjustment for individual variation in brain shape.

On the CT scan, the slices passing through the superior orbit and through the superior petrous temporal bone were identified. From the interslice distance and the number of slices between these 2 bony landmarks, the slice orientation could be judged and the slices mapped onto the template in relation to the same landmarks. Subsequent slices were plotted parallel to these initial slices according to the interslice distances, calculated previously. Slice orientation was checked by eye against that on the scout image, where available.

In the minority of CT scans with no lateral scout image, the interslice distance was estimated from the number of slices between that passing through the superior petrous temporal bone and the highest image available. As the slices approach the top of the skull, their A-P length decreases; the ratio of length of the top slice to the maximum A-P length was used as a measure of the position of the top slice in relation to the top of the skull vault. The slice angle could then be measured as above.

The lesion was mapped onto the equivalent slice of the template for each slice on which it

appeared on the scan. Distances were measured from the most anterior visible brain structure and from the midline on the scan slice and multiplied by the previously calculated factors and drawn onto the template (appendix 3, page 242).

The earliest scan available was used for patients with progressive lesions, as this most likely represented the origins of the patient's earliest seizures. For non-progressive lesions, the clearest scan available was used and in all cases, the maximum extent of the lesion was mapped, including perilesional oedema.

Using the grid references on the template, the lesions could be mapped to different cortical gyri on the corresponding whole brain slices in the stereotaxic atlas. The involvement of different gyri was then related to functional regions, using a standard definitions[202]. Correlation of a similar template technique, utilising Talairach's atlas, with the most recent MRI delineation of anatomy has suggested a residual anatomical variability of only 5-10mm in the position of major sulci[203], confirming the accuracy of the technique. Lesions were coded according to the extent of involvement of each region: Grade 3: >50% involvement of the region or a small lesion entirely within the region (heavily involved); Grade 2: 10-50% involved (partial involvement); Grade 1: 1-10% involved (possible involvement); Grade 0 = uninvolved.

Magnetic resonance imaging

1) Standard images

Standard images were performed using coronal and axial slices with a sagittal scout image on 0.5 Tesla or 1.5 Tesla machines. CNS landmarks were identified and the relationship of the lesion to these analysed utilising the stereotaxic atlas as a guide. In most cases the position of the lesion could be read directly from anatomical structures on the scan. The superior frontal gyrus and its junction with the precentral gyrus are readily identifiable on axial slices and allow localisation of convexity lesions. The corpus callosum, cingulate cortex and supradjacent mesial frontal structures are easily seen on coronal images. Some images from the 0.5 Tesla machine were more difficult to interpret, but the position of each slice could easily be judged by comparison of prominent landmarks e.g. ventricular or corpus callosum morphology, related to the stereotaxic atlas and the site of the lesion

then calculated. Lesions on MRI scans were mapped onto templates from the atlas of Talairach and Szikla[201] to facilitate visual comparison with CT scan lesions (appendix 4, page 243).

2) Special scan techniques

a) Volumetric studies

MRI was performed by Dr Mark Cook and Dr John Stevens on a GE 1.5 Tesla Signa unit (GE Medical Systems, Milwaulkee, USA). Volumetric imaging was performed in the coronal plane, using a spoiled gradient echo technique. Contiguous 1.5mm slices were obtained over the entire head, with a 35/5/1 (TR/TE/NEX) pulse sequence, flip angle 35 degrees, matrix size 256x128. This generated approximately 120 satisfactory images. Imaging time for this sequence 9.5 minutes. In addition, routine sagittal T1 (500/10/2 TR/TE/NEX, axial T2 (2800/90/1 TR/TE/NEX) and proton density weighted (2800/30/1 TR/TE/NEX) series were obtained. All these studies had a 5mm slice thickness and a 2.5mm interslice distance. Spatial presaturation was employed. Field view was of 24cm, matrix size 256x192 for routine studies. Total scanning time was 40 minutes.
The volumetrically acquired images were then reformatted in optimal planes to view abnormal cortical structures. In addition, hippocampal cross-sectional areas were measured on each slice and hippocampal volumes were calculated as described in detail elsewhere[125]. Anatomical structures were extremely well visualised on these scans and the location of foreign tissue lesions was easy to correlate, directly from the scan, with the atlas. In some cases no foreign tissue lesion was seen but there were abnormalities of the cortical ribbon, with simplification of the grey-white interface, probably representing developmental anomalies e.g. neuronal migration defects, milder but akin to those seen in lissencephaly.

b) Magnetic resonance spectroscopy

A pilot study of magnetic resonance spectroscopy was performed on a Siemens 1.5 Tesla machine by Dr Mark Cook and Professor D Gadian. The technique was applied to 10 control subjects and to a group of 9 patients with seizure patterns, attributable to the SMA according to the ILAE classification and no abnormality on CT or ordinary MRI. A

scout image was obtained then a voxel of $8cm^3$ (2*2*2cm) was applied to the medial frontal gyrus, using the anterior border of the paracentral lobule as its posterior margin, thus within the supplementary motor area and this was repeated for the other hemisphere. Spectra were obtained from this region, using a flip sequence of 90-180-180 and relaxation times TE=135ms and TR=1600ms and the water spectra were suppressed. Results were analysed both in terms of absolute signal intensities and ratios of N-acetyl aspartate (NAA)/creatine and NAA/creatine:choline.

Validation of lesion analysis

A random sample of 20 scans (12 MR and 8 CT) was selected and lesion location assessed by inspection by Dr John Stevens, consultant neuroradiologist, who was blinded to the previous assessment. On the 12 MR scans there was complete agreement on the 25 regions graded 3 in each scan, although there was a difference of 4 regions (20%) graded 2 and of 5 regions (40%) with possible involvement (grade 1). A similar pattern was observed in the 8 CT scans, the template method tending to suggest more regions of possible involvement, but with differences in grade 3 lesions of 2 out of 18 regions. It is to be expected that agreement is less on CT than on MR on which anatomical landmarks are more clearly seen and, since the slice angles of CT varied by as much as 70 degrees between cases, anatomical localisation by visual inspection is sometimes very difficult. It was also the policy of this study to be over-inclusive rather than under-inclusive in defining lesion sites in order to maximise the significance of any associations discovered and the primary assessment was always more extensive than the radiologist's validation.

Statistical analyses

Although isolated involvement of the hippocampus was seen relatively frequently, most extrahippocampal lesions involved 2 or more cerebral regions. To assess whether particular characteristics, e.g. seizure duration, were significantly associated with particular clinically defined seizure groups, chi-square analysis was used of the group population against the remainder of the study population. As a large number of analyses was performed, a significance level was set at $P<0.001$, in order to minimise accidental statistcal associations. Chi-squared analysis was used to assess whether involvement of

particular regions was significantly associated with clinically defined seizure types. Yates correction was applied where numbers were small[204].

General population study of partial seizures

Details of the methods of data collection of the NGPSE have been described elsewhere[4,205,206]. My involvement was at the level of data analysis, especially of partial seizure types. In summary, 275 general practitioners notified the coordinating centre of all patients, of over 1 month old, in whom a new diagnosis of definite or possible epileptic seizures was made, during a 3 year prospective recruitment phase. The practices were located around the country in both urban and rural areas, to avoid demographic sources of bias. Patients were followed up by the study at 6 months then at yearly intervals. Follow-up at the time of analysis was from 4 to 7 years. Details of hospital and specialist assessment and results of investigations were also obtained. The study population is thus an unselected cohort of patients with newly diagnosed epileptic seizures, identified at general population level, in whom comprehensive clinical details have been obtained. Considerable emphasis in the design of the study was placed on avoiding the sources of selection bias, in the identification of the study group, and in obtaining comprehensive clinical data from primary and secondary care sources; and the study has been uniquely successful in these regards.

A total of 1195 patients were notified to the study and these were classified by a panel as described previously[4]. Of these, 104 were excluded because of previously diagnosed epilepsy or neonatal seizures and 79 were diagnosed as non-epileptic paroxysmal disorder, most commonly syncope or psychogenic episodes. A further 220 had febrile convulsions, and 197 had possible but not definite epileptic seizures. The remaining 594 patients were classed as having definite epileptic seizures and are included in this analysis. This represents a small increase in the number of definite cases of epileptic seizures in the NGPSE since previous reports[205,206] because of reclassification of some previously uncertain cases, in the light of new data. Seizures were classified into generalised and localisation-related categories, according to the International League Against Epilepsy (ILAE) classification of epilepsies and epileptic syndromes by the study panel[3]. This

study concerns patients with clinical evidence of partial seizure onset, including both those whose seizures remained focal and those with generalisation from a focal origin. Since patients were not all interviewed prospectively, the clinical data could not be as detailed as that obtained in the accompanying hospital-based study. Nevertheless, using a simplified classification employing key features defined in the main study (summarised in table 48, page 230), it was possible to define 6 reproducible categories of clinical seizure onset with intra-observer and inter-observer consistency of 90% and 95% on a sample of 42 cases (16.7%). Four categories were considered classical anatomical regions: frontal; temporal; parietal and central sensorimotor, and 2 "overlap categories": frontotemporal, including seizures with both frontal and temporal features that could not clearly be allocated to one anatomical region, and posterior, with combinations of features attributable to the occipital, parietal or posterior temporal lobes.

Interictal electroencephalograhic (EEG) abnormalities and lesions on computerised tomographic scan (CT) were related to these seizure patterns, to assess concordance between modes of investigation. EEG abnormalities were considered focal only if there was localised spike or sharp wave discharge; isolated slow wave abnormalities were excluded. Only where CT abnormalities were clearly focal; e.g. tumour or focal atrophy were they included. Where CT or EEG crossed anatomical boundaries, they were categorised into that region where the abnormality was maximal. Investigations were considered discordant where there was clear separation of different modalities e.g. a frontal lesion with a temporal seizure pattern, but not a parietal lesion with a posterior seizure pattern. In some cases, the clinical seizure pattern was unlocalised but EEG or CT strongly suggested a focal abnormality. These cases were not included in the clinically defined partial seizures, but are included in the analysis of investigative abnormalities as an important, "clinically unlocalised, localisation-related" subgroup.

Aetiological factors were identified from the history or investigations and classified as definitely significant where there was clear causation; probably significant, where data were suggestive but not conclusive or of uncertain relevance. For example, remote cranial trauma was considered definitely significant where there was clinical or imaging evidence of permanent cerebral damage, probably significant where there was a history of

skull fracture with transient neurological impairment but of uncertain relevance where these factors were absent.

Seizure frequencies were measured for the last available year of follow-up, or for the entire follow-up period if survival was less than 1 year. Patients were classified as seizure-free if there was a minimum of 2 years without seizures at last assessment.

Results

Clinical seizure groupings

Fourteen clinical seizure groupings were identified and form the basis of these results. The sequence of manifestations for each clinical seizure pattern identified in the study is shown in flow charts (figures 14-27, pages 176-189). Seizures sharing similar patterns with minor variation are illustrated by colour coding in the charts. The conventions used are illustrated in the schematic flow chart, figure 13, page 175. The nature of automatisms occurring in each group is shown in table 35, page 192. Additional data for each group concerning: a) average seizure frequency; b) maximum seizure number in 1 day; c) tendency to cluster; d) seizure duration; e) postictal duration; f) frequency of a prodromal phase; g) frequency of secondary generalisation and h) types of vegetative symptoms are presented graphically in appendices 5-12, pages 267-305, to allow easy comparison between groups and the additional distinctive clinical features of each group are summarised in table 13, page 77, at the end of this section.

Group 1; olfactory/gustatory and fear behaviour (figure 14, page 176)

This group contained 31 seizures in 30 patients. Fifteen seizures were characterised by profound fear and epigastric sensation. Most had no specific prior manifestations, but in 4, sensory auras of various types occurred. In all except 1 case, fear led to "fear behaviour"; objective evidence of fear including verbal expressions of fear, appropriate facial expressions and clutching observers for emotional support. In half the seizures this was followed by rapid recovery, but a variety of motor manifestations ensued in the remainder.

Two cases, in which fear was associated with olfactory and gustatory auras are in group 1b, classed with other seizures characterised by similar auras. These auras were also frequently associated with other sensory modalities and with epigastric sensations. The commonest evolutions of these seizures were to absence (44%), then usually to motor activity or sometimes directly to tonic posturing, without obvious preceding absence. One case with prolonged olfactory and gustatory seizures, lasting days, without evolution, is reported in detail in the enclosed paper[207].

A prodrome was common in both subgroups (reported in 13 cases), occurring more frequently than in other groups ($P<0.005$, Yates correction). No specific seizure triggers were identified. Profile of average seizure frequencies was similar to other groups, median 1-4/ month. Other characteristics of seizure timing; seizure duration; postictal recovery time; diurnal variation; tendency to cluster and maximum seizure frequency were similar to other groups and between subgroups, and two cases in subgroup 1a had experienced seizure frequencies in excess of 100/day. Colour change was noted in 19 cases, much more commonly than other groups ($P<0.001$) and 7 of the 15 cases in the study, in which a pupillary change was reported, fell into subgroup 1a ($P<0.001$, Yates correction). Pulse change was noted in 3 cases by the patient or observers. Incontinence was not reported in this group.

Eight cases in subgroup 1a spoke early in the seizure, expressing their fear with varying degrees of coherence; a very high incidence of verbal vocalisation ($P<0.001$, Yates correction) and 1 other gave a cry. By contrast, there were only 2 vocalisations in group 1b; one verbal and 1 non-verbal. Secondary generalisation was similar between the two subgroups and was significantly less likely than in other groups ($P<0.001$, Yates correction), 19 of 31 cases never having experienced generalised convulsive seizures. The incidence and pattern of automatisms were unremarkable (table 35, page 190).

Group 2; absence without specific warning (figure 15, page 177)

Absences without warning or with non-specific physical or abdominal auras accounted for 57 (16%) of seizure types in 54 patients. In 14 seizures, the features were clinically indistinguishable from classical petit mal; no warning, immediate recovery and no focal features. These seizures were also extremely short, 11 of 14 lasted less than 30 seconds. Twelve other cases with no warning had a rapid but not instantaneous recovery and ten of these were also in the subcategory with no aura. There were no other major differences between the subgroups in seizure evolution. Although the commonest progression was to simple automatism, it accounted for only 35% of cases. Immediate progression to version and posturing or behavioural automatisms were also observed relatively frequently. No cases with a physical aura progressed to posturing, but this group was

small. Episodes were reported to be only or predominantly during waking hours in 39 seizures (68%), much more frequently then in other groups (P<0.001), on falling asleep or awakening in 4 and showed no particular diurnal pattern in the remainder. A prodrome was reported in 11 seizures - a similar proportion to the whole study group. Triggering factors for seizures were suggested in 19 (33%), but were generally non-specific, mostly sleep deficit and general stress. There appeared to be a clear susceptibility to startle stimuli in 2 cases.

Distribution of average seizure frequency (median 5-15/ month) and maximum seizure frequency (median 3-5/day) were similar, in all subgroups, to the study group as a whole. Apart from subgroup d -"clinically typical absences" - the pattern of seizure duration did not differ from the rest of the study as a whole. Vegetative symptoms were reported somewhat less frequently from the shorter seizures (7 of 25 cases) but did not differ markedly from the other groups (appendix 12, page 302). Secondary generalisation from absence to tonic or tonic clonic seizures occurred frequently in only 3 cases (5%), somewhat less often than in other groups (P<0.025). Vocalisations and oral automatisms were present with similar frequency in subgroups 2a-2c; vocalisations were generally verbal, with singing in 1 case and laughing in 2 cases.

Group 3; experiential (figure 16, page 178)

Thirty-three seizure types (9.4%) in 30 patients were characterised by initial occurrence of experiential phenomena. The commonest seizure evolution was to absence, seen in 15 cases (45%) of which 8 then recovered rapidly without further manifestations. Evolution directly to tonic posturing occurred in 12 cases (36%), of which 10 developed other motor manifestations.

Non-specific prodromal symptoms were reported in 9 cases (8 in subgroup b). Suggested triggers were non-specific in most cases, although 5 of 12 cases in the whole study noting an exacerbation by alcohol fell into this group. Average and maximum seizure frequencies tended to be less than in other groups and there was less inclination towards seizure clustering. Most seizures (76%) were exclusively or predominantly during waking hours. Seizure duration showed an unremarkable pattern, median 1-2 minutes,

with no difference between subgroups. There was a bimodal distribution of duration of postictal recovery, rapid recovery occurring more frequently after seizures progressing to absence, than those progressing to version/posturing. Vegetative symptoms were common in this group; pupillary alteration reported in 4 cases, second commonest after group 1, and colour change noted in 15 cases (45%). Vocalisations comprising attempted speech were seen at the onset of 5 seizures. Frequency of secondary generalisation was similar to other groups.

Group 4; early visual manifestations (figure 17, page 179)

Sixteen seizure types in 15 patients were characterised by visual symptoms at the onset of the seizure, as tabulated below.

Table 9. Nature of visual manifestations in group 4

Pattern of abnormality	Number of cases
Unformed visual hallucination	4
Formed visual hallucination	6
Micropsia / macropsia	3
Other visual distortion	3

The commonest pattern of observed abnormalities was an absence, associated with oral automatisms and progressing to posturing/version, irrespective of the nature of the visual abnormality. In 2 seizures, however, the tonic movements did not appear to be preceded by an absence phase.

A prodrome was reported in 5 cases and no specific triggers were identified in this group, although some associations with stress and sleep deficit were suggested. Average seizure frequency (median 5-15/month), tendency to cluster and maximum seizure frequency were similar to other groups combined. Seizure duration showed a narrower spread than in other groups, ranging from 30 seconds to 5 minutes, but group size was small. The overall pattern of recovery was unremarkable, but all 5 seizures with recovery in under

30 seconds comprised absences without motor progression and all 4 taking longer than 5 minutes had prominent motor activity or automatisms. Pallor was observed frequently (11 cases) but other vegetative symptoms were uncommon. Secondary generalisation was relatively uncommon in this group, although not significantly different from other groups. Confused speech was noted in 4 seizures, as the patient was going into an absence and in 3 continuing through the absence, taking the form of expletives in one case.

Group 5; auditory hallucination (figure 18, page 180)

Two patients (0.8%) had a clear auditory hallucination at the onset of their seizures and their clinical and investigative characteristics are shown in table 10 below.

Table 10. Characteristics of seizures with auditory manifestations

Clinical feature	Case 1	Case 2
Inclusion criterion	Telemetry	MRI
Average frequency	5-15/month	16-30/month
Maximum No. in 1 day	1	20
Tendency to cluster	No pattern	Clusters predominant
Prodrome	Never	Never
Diurnal pattern	Only waking	Mostly waking
Seizure duration	2-5 minutes	1-2 minutes
Postictal duration	5-20 minutes	5-20 minutes
Triggers	None	None
Objective awareness	Sudden loss	Sudden loss
Other seizure types	None	None
Interictal EEG	Normal	Normal
Ictal EEG	Bitemporal	Normal during aura
Scan	Normal CT, MRI N/A	Anterior temporal; dysembryoplastic neuroepithelioma?

Group 6; hypotonic (figure 19, page 181)

Six seizures (1.7%) in 6 patients were akinetic drop attacks, without specific prior warning. The evolution of the seizures varied in this small group, 2 cases developing ictal motor activity after the initial hypotonic collapse and a further case with postictal automatisms. These seizures were uncommon, median frequency 1-6/year, although

tending to cluster in 2 patients and with a maximum ever seizure frequency ranging from 1 to 7 per day. No prodrome or triggers were reported. Seizures were usually short, median seizure duration 10-30 seconds and rapid recovery was seen in 2. Vegetative symptoms, including incontinence were uncommon. All patients with seizures in this category also experienced seizures in other categories.

Group 7; early version or posturing (figure 20, page 182)

Seventy-four seizures (21%) in 69 patients fell into this group, in which version or posturing were either the first manifestation of the seizure or else preceded by non-specific symptoms, for example cephalic sensations. Progression to other motor manifestations occurred in 78%, simple automatisms being the commonest sequel to posturing (40%). By contrast, behavioural automatisms were uncommon (9%). A prodrome was seen only in those patients who also had an aura and occurred with similar frequency to other groups. Prodromal symptoms were typically non-specific fatigue, loss of concentration and irritability, sometimes with associated pallor. Of 18 patients with seizures induced by startle stimuli, 9 fell into this group ($P<0.005$), including all subgroups.

The average seizure frequency was not significantly different from all cases combined and was similar between subgroups. There was a tendency for the maximum frequency of seizures to be higher than in other groups, although this did not reach significance. This high seizure frequency was most apparent in the group with no warning, 3 cases (8%) having experienced over 100 seizures per day. The overall tendency to cluster was no different from the sample as a whole and showed no difference between subgroups. The duration of seizures suggested a bimodal distribution; 29 seizures (39%) under 30 seconds duration, 18 of these in the "no warning" subgroup, representing 46% of that group ($P<0.01$). Postictal duration also showed a bimodal distribution; an accentuation of the pattern seen in the whole study group. Although instantaneous recovery occurred only in those seizures without any warning, recovery in under 30 seconds was seen in many cases in all subgroups.

The frequency and pattern of vegetative symptoms corresponded to those in the whole study group as did the frequency of secondary generalisation. In 9 seizures, awareness was maintained, including 4 of the 8 with instantaneous recovery. In a further 9 cases there was a discrepancy between objective and subjective measures of awareness such that the patient was able to recall events during the seizure despite being reported as "unconscious" by an observer, compared with 26 cases in the study as a whole.

Group 8; focal somatosensory (figure 21, page 183)

A focal sensory onset was reported in 26 seizure types (7.4%) in 26 patients, in 12 of whom there was a typical Jacksonian progression. Of the 20 in which the seizure evolved further, the commonest progression was to tonic posturing and head version (13 cases). Jacksonian clonic motor activity was seen 5 cases, and occurred in both Jacksonian sensory and non-Jacksonian sensory subgroups. A Todd's paresis was observed in 5 of 9 cases that had experienced focal clonic activity at any point in the seizure, irrespective of whether this was obviously Jacksonian and in 1 case with Jacksonian sensory onset that had evolved to tonic activity but not focal clonic activity. Automatisms were uncommon and mostly simple in type (table 35, page 190), exploratory behaviour occurred in only 1 case.

A prodrome was reported in 3 cases. Five cases showed clear sensitivity to startle stimuli, all progressing to tonic activity. Average seizure frequency (median 1-4/month), tendency to cluster, and maximum seizure frequency were similar to the study group as a whole, and without marked variation across subgroups. Diurnal variation was similar to other groups, with 5 patients commonly waking from sleep to experience their aura. Seizure duration appeared to show a bimodal distribution, very brief seizures (<30 secs) occurring in 11 cases (42%). There was no evidence to suggest that any particular pattern of seizure evolution was shorter than the others. In 9 cases, recovery from the seizure took longer than 5 minutes and 6 of these were explained by Todd's paresis; other aspects of recovery were generally rapid. Vegetative symptoms were noted in only 7 cases, less frequently than in other groups ($P<0.005$, Yates correction) and vocalisations were also rare. Secondary generalisation occurred with similar frequency to other groups.

Group 9; focal paresis (figure 22, page 184)

Two patients had seizures characterised by paresis of a body part. Their clinical and investigative features are shown in table 11, below.

Table 11. Characteristics of seizures with focal paresis

Clinical feature	Case 1	Case 2
Inclusion criterion	CT scan	MRI
Average frequency	1/year	5-15/month
Maximum No. in 1 day	1	6
Tendency to cluster	Evenly spread	Predominantly clusters
Prodrome	Never	Never
Diurnal pattern	Waking only	Waking only
Seizure duration	30-60 seconds	<10 seconds
Postictal duration	<10 seconds	<10 seconds
Triggers	None	None
Objective awareness	No loss	No loss
Other seizure types	None	Jacksonian motor and sensory
Interictal EEG	Normal	Not available
Ictal EEG	Not available	Not available
Scan abnormality	Lateral prefrontal to premotor infarction	Widespread atrophy over superolateral convexity

Group 10; complex partial status epilepticus (figure 23, page 185)

Six patients had habitual seizures consistent with complex partial status epilepticus (CPSE). Five patients also experienced other seizure types. In all cases there was a gradual onset of confusion and agitation, in 3 associated with directed aggression. Average frequency was lower than in most categories, median 7-12/year. The duration and lack of clear onset and end to these seizures make clustering, diurnal variation, maximum seizure frequency and postictal phase difficult to assess in this group. Vocalisations were present in all 6 and comprised attempted speech, with verbal abuse, coherent and directed in 3 cases, for which the patient was later amnesic.

Group 11; isolated jerks (figure 24, page 186)

Eight patients had seizures (2.3% of seizures) comprising brief jerks of body parts with immediate recovery. These occurred on waking in 2 cases, being predominantly in waking hours in the other 6, but no other triggers were identified and no prodrome was reported. Average and maximum seizure frequencies were unremarkable, and although there was a tendency to clustering in 5 cases, serial seizures had only ever occurred in 1. Vegetative symptoms were reported in only 2 of these very brief seizures; colour change and urge to micturate in 1 each and a hissing vocalisation was noted at the onset of the seizure comprising a head jerk. All cases except the latter also suffered other seizure types.

Group 12; Jacksonian motor (figure 25, page 187)

Fourteen seizures (4%) in 14 patients were characterised by focal clonic activity with Jacksonian progression. The majority progressed to unilateral clonic activity, usually accompanied by ipsilateral head turning, without affecting the opposite side, and often leading to a Todd's paresis.

A non-specific prodrome was reported in 3 cases. Average seizure frequencies (median 1-4/month), tendency to cluster and secondary generalisation showed a similar distribution to other groups. In 7 seizures, awareness was maintained throughout and 3 of these were the shortest seizures in the group (<30 secs). Postictal duration was >1 minute in 8 cases, in 5 due to Todd's paresis. Speech abnormalities at the onset of the seizure were common and are illustrated in table 12 below.

Table 12. Speech abnormalities in Jacksonian motor seizures

Side of jerking	Dysarthria	Cessation of speech	Expressive dysphasia	Early loss of awareness	Preserved speech
Left 6	3	1	0	2	0
Right 8	4*	1	1	1	1

* One left-handed case with left-handed father.

Vegetative symptoms were observed in 9 cases, including 5 with respiratory abnormalities - clonic jerking interfering with the pattern of respiratory movements - and sphincter disturbance in 3 cases, including 2 with preservation of awareness, during incontinence.

Group 13; generalised motor activity (figure 26, page 190)

Forty seven seizure types in 42 patients comprised bilateral motor activity without prior focal symptoms. Twenty were generalised tonic seizures (subgroup a), 21 tonic-clonic seizures (subgroup b) and 6 bilateral clonic seizures with preservation of awareness (subgroup c). The only progression that was seen after the initial phase was to postictal automatisms, most frequently after generalised tonic seizures. The diurnal pattern tended to favour nocturnal occurrence, compared to the whole study group ($P<0.01$). A prodrome was reported in only 4 cases. Clear-cut startle sensitivity was seen in 3 cases, but other triggers were rarely proposed. The median seizure frequency was <1/month, less than for any other group ($P<0.001$) and seizures only ever occurred very frequently (>5/day) in the tonic seizure category. Similarly, maximum seizure frequency and inclination for seizures to cluster, tended to be less than in the study group as a whole, but were similar across subgroups. Although seizure duration did not differ from the whole study group, there was considerable variation across subgroups; median 30-60 seconds for tonic seizures and 2-5 minutes for subgroups b and c. Rapid recovery was seen after 5 (25%) of tonic seizures but never after generalised tonic clonic seizures. Incontinence was commonest in this group, occurring in 17 seizures ($P<0.001$) but other vegetative symptoms were rarely reported. Vocalisations usually comprised a shout at seizure onset in subgroups a and b, although one patient appeared to giggle briefly at the onset of hypertonia. In subgroup c, vocalisations mostly comprised speech with varying degrees of clarity, from individual words to coherent sentences, spoken during the period of bilateral clonic activity. Automatisms were mostly of the simple type, with behavioural automatisms seen most frequently after tonic seizures.

Group 14; motor agitation (figure 27, page 191)

Thirty seizures (8.5%) in 29 patients were dominated by early motor agitation. Most had no warning or a non-specific abdominal or other physical aura, but in 3 cases there was a vague prior gustatory sensation and in one an occasional olfactory sensation in association with an abdominal aura. In most cases the seizure evolved directly into simple repetitive activities but in 6 cases (20%), this was preceded by tonic posturing or head turning. Simple repetitive motor activity become more frenetic until the patient appeared in a state of general motor agitation, sometimes evolving extremely rapidly. The pattern of this activity could be bizarre; thrashing or bicycling movements or throwing themselves against the bed. Half the cases recovered rapidly; there was no difference between subgroups in this regard, and the others went on to a variety of other motor manifestations. A prodrome was reported in 7 cases from all subgroups. There were no consistently reported seizure triggers. Twelve (40%) cases were exclusively or predominantly nocturnal ($P<0.001$, Yates correction). Seizure duration showed a smaller scatter than in most groups with 73% seizures lasting 30 seconds to 2 minutes and all between 10 seconds and 5 minutes. Although average seizure frequency differed little from the study group as a whole, there was a somewhat stronger tendency to clustering (60% of cases versus 38% in other groups combined) and maximum seizure frequency was generally higher than in other groups ($P<0.005$, Yates correction). The distribution of postictal recovery times appeared shorter than other groups, although this was difficult to judge with so many nocturnal cases, where the patient often returned to sleep immediately after the seizure. Prominent vocalisations were common and often bizarre; piercing cries in 6; laughing and crying in 2; singing in 5 and "Donald-Duck speech" in 1 case. Vegetative symptoms were common, especially colour change, in 14 cases (47%), which unlike other groups, was facial flushing more often than pallor. Secondary generalisation was relatively uncommon, but not markedly different from other groups.

Table 13. Summary of distinctive features of seizure types (in addition to those seizure manifestations defining clinical groups)

Group	Distinctive features
1: fear behaviour and olfactory/gustatory	Frequent prodrome; frequent vegetative changes, especially pupillary; verbal vocalisation; rare secondary generalisation
2: absence	Predominantly waking; frequent behavioural automatisms
3: experiential	None
4: visual	None
5: auditory	Two cases only
6: hypotonic	Brief duration; generally infrequent (only 6 cases)
7: version/posturing	A subgroup with frequent, brief seizures, no aura, rapid recovery and retained awareness, but not true of the whole group.
8: somatosensory	Often evolve to simple motor activity but rare behavioural automatisms.
9: focal paresis	Two cases only.
10: CPSE	Generally low frequency, usually associated with other seizure types.
11: isolated jerks	Rapid recovery by definition; usually associated with other seizure types.
12: Jacksonian clonic	Rare vegetative symptoms or automatisms; Todd's paresis common.
13: generalised motor	Low frequency; common incontinence; other vegetative symptoms uncommon
14: motor agitation	High frequency; mainly nocturnal; bizarre vocalisation; frequent vegetative symptoms (often facial flushing rather than pallor)

Combinations of seizure types

Tables 37 and 38, page 192 show the combinations of seizure types experienced by 70 patients with 2 and 15 patients with 3 seizure types. The most striking association, in 13 cases, was between groups 2 and 13; absences without focal onset and generalised motor seizures (table 14 below), mostly of tonic clonic type ($P<<0.001$). Interictal EEG showed spikes in 9 of 12 cases in which it was available; 4 bifrontal; 2 unilateral frontal; 1 bitemporal; 2 centrotemporal. Widespread or generalised spikes were seen in only 1 case. Imaging was abnormal in 4; 2 temporal (associated with frontal spikes in 1) and 2 frontoparietal lesions.

Table 14. Associations of absences and generalised motor seizures

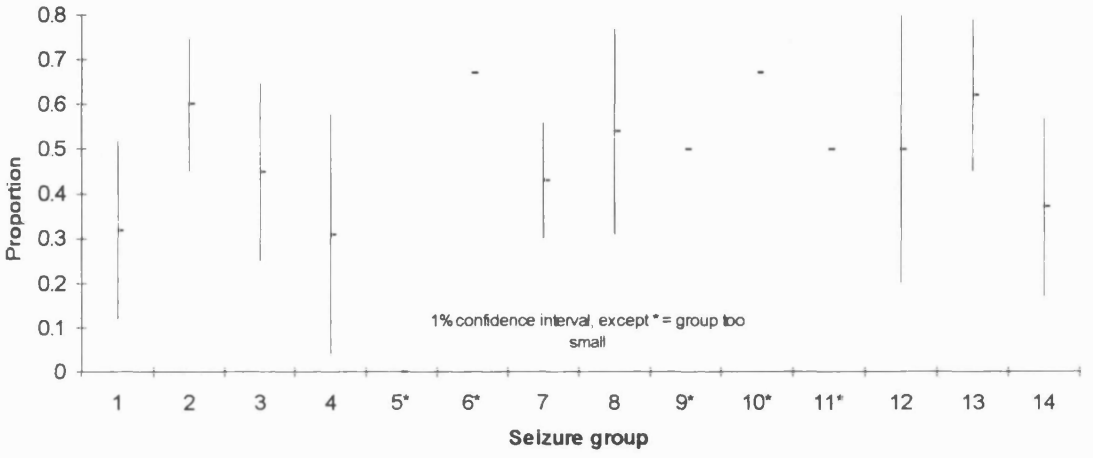
Seizure types	Group 13a, generalised tonic	Group 13b, generalised tonic-clonic	Group 13c, bilateral clonic
Group 2, absence	4	8	1

Generalised hypotonia was always a second seizure type. Of 6 cases, 4 had other generalised seizure types; absence in 3, generalised tonic and tonic-clonic in 1 each. (Numbers were too small for statistical analysis.) Three of 4 with abnormal interictal EEG's had widespread or generalised disturbances. Two cases were lesional; one medial prefrontal/SMA AVM and one anterior temporal infarction.

In several groups, patients were encountered whose seizures varied in their initial manifestation, sufficiently to be considered separate seizure types, but had similar subsequent evolution, and therefore, were in different subgroups of the same overall category. For example, 6 patients had seizures that fell into 2 very distinct patterns of limb posturing. There was a suggestion that patients with a generalised seizure pattern tended to have more seizure types but this was probably an artefact of selection bias, as clinical selection criteria were mostly for seizures with a more focal pattern of onset and generalised tonic or tonic clonic seizures were patients' second or third seizure type in 26

cases (63%). There was little suggestion that any other seizure type was particularly associated with more varieties of seizure pattern (figure 2, below), although confidence intervals were wide in smaller groups.

Figure 2. Proportions of seizures in each group associated with another seizure type



Epilepsy with startle provoked seizures

During the course of this study, it became apparent that a significant proportion of patients had suffered epilepsy in response to startle stimuli (ESPS). These seizures came from several of the categories described above (table 36, page 191) and they are, therefore, described separately. Their detailed clinical, EEG and imaging characteristics are described in table 39, page 193. As only one variable of 52 in the cluster analysis, the presence of startle sensitivity did not result in a discrete group, among seizures that in other respects had various clinical characteristics.

General clinical characteristics

Nineteen patients were identified with ESPS with onset of startle sensitivity usually in childhood or adolescence, although in adult life in a minority. Startle sensitivity usually evolved in the context of pre-existing epilepsy, that had often been present for some time before; in one case epilepsy started at the age of 1 but startle sensitivity only supervened

in association with an exacerbation of her epilepsy at the age of 25. Similarly startle sensitivity disappeared after a few years in many cases and it was, therefore a transient phenomenon in the course of the patient's epilepsy history.

A congenital cause was postulated for 9 cases on the basis of neurological signs since birth, or else from the nature of the imaging abnormalities. In one case, severe meningitis in the first few months of life was thought to be the cause and in another epilepsy with startle sensitivity followed treatment for a pineal tumour at the age of 10.

Focal neurological signs were present in 7 individuals, with unilateral motor signs in 6 (reflex changes only in 2) and pseudobulbar palsy in 1. Mild to moderate mental retardation was present in 4 (3 with other focal neurological signs) and intelligence in others was distributed across the normal range; 2 had university degrees.

Seizure characteristics

Seizures tended to have a high frequency and maximum seizure frequency was more than 10/day in over half (all had experienced more than 1 in a day). Seizures were usually of brief duration.

In 16 cases the seizures evolved into tonic motor activity, which was focal in 14. Five had a focal somatosensory onset prior to tonic posturing, but in the others there were no earlier specific symptoms. Three patients had very different seizure patterns; absence with no focal features; generalised tonic clonic with no focal features and complex absence with giggling then behavioural automatisms. All except one patient reported seizures at times not precipitated by startle and 4 patients had a second seizure type that was not startle-induced.

All patients were sensitive to noise, but other modalities were more variable. Six could have a seizure triggered by somatosensory stimuli e.g. an unexpected tap on the shoulder or by catching a paretic foot against the pavement. Visual stimuli such as unexpected, sudden movement in the visual field was reported to be effective in 3, but in all cases in which these stimuli were effective, they were less reproducible in their effect than noise. No patient reported a seizure in response to taste or smell.

Interictal EEG results

General data

Interictal EEG' s were available in 229 patients (90%) representing 317 different seizures (90%). The number of EEG's available in each group is shown in table 40, page 195, with the principal features of their results. It was significantly more likely not to discover any spikes in cases where there was only 1 EEG available ($P<0.001$). There were no significant differences between groups in the number of cases for which EEG's were available or in the mean number of EEG's per case. It is difficult to interpret the frequency of EEG spikes in each group since the proportion for which EEG abnormality was a selection criterion varies and needs to be taken into account. The number of focal spikes per patient was generally small with median number for each group usually between 10 and 20. Table 40, page 195 illustrates the distribution of interictal EEG characteristics in each group and the principal patterns of spike abnormality.

Data by clinical groups

Details of interictal spike data for cases in each group are presented in figures 28-39, pages 196-207. For each seizure associated with interictal EEG spikes, the spikes are colour-coded according to pattern of distribution and the details of spike location and number with each location written onto the case. A summary of the major interictal EEG findings for each group is in table 15, page 85, at the end of this section.

Group 1; olfactory/gustatory or fear behaviour (figure 28 page 196)

Interictal EEG's were available in all cases of group 1. No interictal spikes were identified in 16 cases, in 9 of which only 1 EEG was seen. Where spikes were focal, almost all were at temporal electrodes, although in 1 case the abnormalities were predominantly restricted to the anterior frontal electrodes. Regional and bilateral spikes were mostly frontotemporal in distribution and widespread or generalised spikes were uncommon - seen in only 2 cases.

Group 2; absence (figure 29, page 197)

There was no evidence to suggest the number or distribution of EEG spikes differed across clinically defined subgroups. Focal spikes were generally in 3 patterns; temporal and sphenoidal; medial frontocentral and frontopolar with associated involvement of the transfrontal chain. Bilateral spikes occurred most frequently in association with focal frontal (8 seizures) rather than temporal spikes (1 seizure). Generalised and widespread spikes were relatively uncommon, although in one case the EEG pattern was exclusively of generalised discharges.

Group 3; experiential (figure 30, page 199)

Focal spikes were infrequent in most cases (median 8 spikes) and were restricted to the temporal or frontal electrodes in 7 and 3 patients respectively. The predominantly frontal or temporal EEG patterns did not correspond to any clinical subdivisions and "frontal" spikes were usually at F7 or F8, where they may reflect temporal lobe activity. Two cases with focal frontal spikes represented different clinical seizure patterns from the same patient. Most cases also had regional or bilateral spikes with a frontotemporal distribution. One patient, with 2 clinical patterns of absence, and a history of unilateral orbitofrontal trauma had predominantly bilateral frontopolar and generalised spikes.

Group 4; visual (figure 31, page 200)

In only 1 case were there more than 10 focal spikes - restricted to the temporal region and associated with hippocampal volume loss on quantitative MRI. This patient with two seizure types; micropsia and visual distortion in early life and prolonged olfactory hallucination in later life has been described in detail, in the accompanying paper[207]. In the other case with frequent spikes, their distribution was more widespread, predominantly in the pericentral region, and MRI demonstrated a small anterior parietal lesion with increased signal intensity. Other EEG's tended to have a frontotemporal distribution of spikes but numbers of spikes in these cases were very small (figure 31).

Group 5; auditory

No spikes were present in either case.

Group 6; hypotonic (figure 32, page 200)

There were only 4 patients with interictal EEG abnormalities and only one of these had more than 10 spikes. In no case, however, were spikes predominantly focal and 3 of 4 cases exhibited mainly bilateral or generalised spikes.

Group 7; version/posturing (figure 33, page 201)

Where focal abnormalities were identified, these were almost always frontal (19 cases), with central spikes in 4 cases and a single temporal spike recorded as the only focal spike in 1 case. There was no evidence to suggest that spike frequency was different in the subgroup with higher seizure frequency or that spike localisation differed between clinically defined subgroups. Where regional spikes were recorded, these almost always included frontal electrodes and most bilateral spikes were bifrontal or transcentral in distribution with occasional temporal or parietal spikes noted. Widespread or generalised spikes were noted in 14 cases (37%). Focal spikes within the frontal lobes tended to involve the medial and lateral rather than frontopolar electrodes, but where spikes were regional or bilateral, frontopolar electrodes were also usually involved.

Group 8; somatosensory (figure 34, page 203)

Focal abnormalities were very varied in this group, the most striking case showing consistent spiking at one medial frontal electrode but a more temporal distribution of focal spikes was commoner. Bilateral frontopolar spikes were seen in 4 cases (36%). One of these, with a history of surgery to an optic nerve glioma suffered 3 seizure types; focal sensory; akinetic drops and brief hand-rubbing automatisms and had a wide field of interictal spikes from frontopolar to bicentral with frequent generalisation, suggesting a wide epileptogenic zone.

Epileptiform spikes were somewhat commoner in cases with non-Jacksonian seizures (50% versus 25%). There were no discernible, consistent differences in the pattern or distribution of spikes between subgroups and the proportion of patients with interictal spikes was similar irrespective of whether their habitual seizures progressed beyond the sensory stage, but numbers were small.

Group 9; focal paresis

No interictal EEG was available in either case.

Group 10; complex partial status epilepticus (figure 35, page 204)

Spikes were very few in this small group, with no characteristic pattern of distribution.

Group 11; isolated jerks (figure 36, page 204)

There were EEG spikes in 3 cases (37.5%), the second lowest proportion of any seizure type, but they were very frequent in two. They showed a consistent pattern of frontocentral discharges; the patient with focal spiking at F3 having jerks of only his right arm; case 3 with bicentral spikes experiencing bilateral jerks and the other case, with less frequent frontocentral spikes, experienced isolated jerks of either arm alone.

Group 12; Jacksonian motor (figure 37, page 205)

Only 3 cases with Jacksonian motor seizures had spikes on interictal EEG, the lowest proportion of any group, and EEG was an inclusion criterion in only 1 case. It was impossible to discern a distinct pattern in this small number of cases, but in those case with spikes, they were frontocentral or centrotemporal rather than temporal in distribution.

Group 13; generalised motor (figure 38, page 205)

EEG's were available in only 2 cases of subgroup c (bilateral clonic seizures with preserved awareness); neither had interictal spikes. Therefore, the spikes observed relate only to generalised tonic and generalised tonic clonic seizures. Focal spikes were present in 18 cases, of which 11 were frontal, 3 temporal, 2 central and 2 with mixed pattern. It was rare to see spikes exclusively at one electrode and multifocal spikes from several electrodes in one or both frontal regions was a common pattern. Regional spikes also showed frontal preponderance, although tending to appear at various electrode combinations. Bilateral and generalised spikes were common, seen in 15 and 9 cases (50%

and 30%), again having a frontal preponderance. There were no differences in interictal EEG characteristics between tonic and tonic-clonic subgroups.

Group 14; motor agitation (figure 39, page 207)

Focal spikes were observed in 14 cases and of 6 cases with greater than 10 focal spikes, these were at frontal electrodes in 4 and at temporal and central sites in the other 2. In one case focal activity predominated at the supraorbital electrode, but this electrode was rarely used in other cases. Regional and bilateral spikes reflected the distribution of focal spikes of the same case, although with a tendency to frontotemporal overlap. In one case there were frequent peri-central spikes, but generally bilateral spikes were uncommon and spikes with a diffuse unilateral or bilateral distribution were seen in only one case.

Table 15. Summary of interictal spike distribution for different seizure groups.

Group	Predominant interictal EEG spike distribution
1: fear behaviour and olfactory/gustatory	Temporal
2: absence	Variable
3: experiential	Mainly temporal
4: visual	Mainly temporal
5: auditory	Normal (2 cases only)
6: hypotonic	Rare spikes
7: version/posturing	Frontocentral
8: somatosensory	Variable
9: focal paresis	No EEG available (2 cases only)
10: CPSE	Rare spikes
11: isolated jerks	Frontocentral
12: Jacksonian clonic	Few EEG's available
13: generalised motor	Mainly frontal
14: motor agitation	Mainly frontal

Interictal EEG in epilepsy with startle provoked seizures

Interictal scalp EEG showed focal spikes in 8 of the 19 cases, but varied considerably from case to case, between frontal, central and temporal regions (table 39, page 193).

Ictal EEG results by clinical group

Ictal EEG results were available for 79 (22.4%) of seizures, in 79 patients (31%). The proportions recorded from different groups varied from none in groups 6, 9 and 13 to 63% in group 14 (detailed in table 41, page 208). The median number of seizures recorded was 3 there was a tendency for the cases with larger numbers of seizures recorded to have more than 1 associated EEG pattern. Where there was more than one pattern, the most specific pattern was usually the one occurring earliest in relation to clinical onset. Detailed results are presented in table 42, pages 209-212.

Group 1; olfactory/gustatory and fear behaviour

Abnormalities were documented in 8 of 10 cases undergoing recording and were focal or regional in 5; invariably at the temporal electrodes or lateral frontal electrode. The EEG pattern was of rhythmical slow activity, varying from 3-7 Hz in 2 cases and focal attenuation in the temporal region in 2 cases.

Group 2; absence

In group 2 (absences), 5 seizures (9%) were recorded. Ictal EEG abnormalities were identified in all cases but varied in location, including bifrontal, mesial frontal and focal temporal abnormalities. In this small sample there was no evidence to support a difference in clinical pattern between these types, for example oroalimentary automatism was present in both frontal and temporal EEG patterns.

Group 3; experiential

Of 8 seizures recorded, a localised abnormality was identified in 5; in 4 restricted to the temporal lobe and in the other bilateral frontotemporal in distribution.

Group 4; visual

Of 4 seizures recorded, regional EEG abnormalities were found before clinical onset in 3. In case 55, a formed visual hallucination was associated with a frontotemporal EEG abnormality and normal CT scan; in case 16 visual distortion was associated with frontotemporal EEG abnormality and a mesial temporal AVM and in case 292, micropsia was associated with a frontal EEG abnormality and hippocampal atrophy on MRI.

Group 5; auditory

In both cases in group 5, ictal recording was undertaken. In one, with auditory hallucination, disordered speech and secondary generalisation, following an encephalitic illness, EEG abnormalities prior to clinical onset were seen in left and right temporal lobes on different occasions. In the other case, who only experienced auras during recording, no scalp EEG abnormality was identified.

Group 6; hypotonic

No ictal recordings were available for this group.

Group 7; version/posturing

Of 21 cases with ictal recordings, one third were masked by artefact throughout each seizure and in two-thirds an abnormality was identified. This was unlocalised in 5 cases and localised in 9; invariably to the frontal or central region. In 3 seizures, however, the discharge appeared symmetric about the midline and could not be lateralised. In contrast to the other seizure types in the study, the commonest EEG seizure manifestations were spikes or fast activity.

Group 8; somatosensory

In one of 4 cases, in which an ictal recording was obtained, there was an identifiable seizure discharge, in the paracentral region, contralateral to the clinically affected limb.

Group 9; focal paresis

No ictal recordings were available for these two patients.

Group 10; complex partial status epilepticus

In three of six cases, a recording was obtained during a seizure, but in none did this include the onset of the episode. Generalised slow wave abnormalities were observed in each case.

Group 11; isolated jerks

In the case with isolated jerking of the head, the movement was immediately preceded by a generalised slow wave. No others were recorded in this group.

Group 12; Jacksonian motor

In one case captured fortuitously on routine EEG recording, there was an evolving seizure discharge in the paracentral region, contralateral to the clinically affected side. In the other recorded case, there was continuous paracentral spiking and it was difficult to discern any change in EEG pattern in association with the clinical seizure onset.

Group 13; generalised motor

No ictal recordings were available in this group.

Group 14; motor agitation

Ictal electrographic discharges were seen frequently in this group and were localised in 10 cases and in 7 were frontal or bifrontal, with frequent involvement of frontopolar electrodes. Of the other 3, discharges were frontotemporal in 2 and temporal in 1. The clinical seizure pattern in these did not clearly differ from the frontal cases.

Ictal EEG in epilepsy with startle-provoked seizures

An ictal surface recording was available in only 8 patients (42%) and, as is commonly the case in patients whose seizures are characterised by early motor activity, was obscured by

artefact in 7. The remaining case showed clear 12-16Hz activity at the left medial frontal electrode, contralateral to head turning and to the predominant side of posturing, at the onset of the seizure.

Table 16. Summary of ictal electrographic recordings for each group

Group	Ictal EEG summary
1: fear behaviour and olfactory/gustatory	Temporal
2: absence	Few recorded
3: experiential	Temporal
4: visual	Mainly frontotemporal (few recorded)
5: auditory	Two cases only; 1 temporal
6: hypotonic	None recorded
7: version/posturing	Frontocentral fast activity/spikes
8: somatosensory	One abnormal only; pericentral
9: focal paresis	None recorded
10: CPSE	Generalised slow waves, no onsets recorded
11: isolated jerks	Only one recorded; generalised slow wave
12: Jacksonian clonic	Only one recorded; pericentral
13: generalised motor	None recorded
14: motor agitation	Frontal predominance

Analysis of cases with lesions on neuroimaging

General data

In 126 patients (50%), with 163 seizure types (46%), there was an abnormality on neuroimaging considered to be of aetiological significance. The distribution of lesions between the lobes and the intrafrontal distribution of those restricted to the frontal lobes are shown in tables 43 and 44, pages to 213-217. All lesions, except pure hippocampal atrophy, and their associated seizure types are illustrated on templates in appendix 4, pages 243-266. Temporal lesions were pure hippocampal atrophy (32 cases), and primarily extrahippocampal tissue lesions in 26 cases, which were either so extensive or else anatomically situated to cause direct hippocampal involvement in 5 cases. Because of the size of the frontal lobes and in accordance with the current ILAE classification, they were subdivided into more divisions than, parietal or temporal lobes. Nevertheless, in neither the frontal group alone nor in all seizures combined, was there any relationship between the number of seizure types experienced and the size of the lesion. Nor was involvement of any particular region associated with a larger number of seizure types.

Pure frontal versus pure temporal lesions

A direct comparison of 61 seizures with lesions restricted to the frontal lobes, irrespective of subdivision and 58 seizures restricted to the temporal lobes was performed, both in terms of clinical seizure types defined by previous analysis and individual manifestations (table 45, page 218 and figures 40-45, pages 219-221).
The age of onset of epilepsy in patients with pure frontal and pure temporal lesions was similar, median ages 15 and 14 and means (standard deviations) 20.9 (16.9) and 15.6 (11.4). There was a suggestion of a more unimodal distribution in the temporal group and this may reflect the dominance of a single pathology, MTS.
Seizures characterised by absence were strongly associated with temporal lobe lesions ($P<0.001$) but the association of experiential seizures with temporal lobe lesions did not quite reach significance ($P=0.005$) and there were weaker tendencies for seizures in groups 1 and 4 (profound fear/olfactory/gustatory and visual hallucinations) to be associated with temporal rather than frontal lesions. Seizures characterised by fear

behaviour were associated with hippocampal but not extra-hippocampal temporal lesions. There was a suggestion that seizures characterised absences with no aura were more common in association with hippocampal lesions, whereas a physical or abdominal aura was commoner with extrahippocampal lesions. Numbers were too small to draw clear conclusions (table 17 below).

Table 17. Seizure types associated with hippocampal and extrahippocampal lesions

Seizure category	Hippocampal	Extra-hippocampal
1a; fear/fear behaviour	4	0
1b; olfactory/gustatory	2	4
2a,d; absence with no warning	9	3
2b,c; absence with non-specific warning	2	5
3; experiential	9	5
4; visual	3	3

Groups 1-4 all contained predominantly temporal lesions and the numbers of frontal lesions in these groups were small. Of the 6 cases with absences and pure frontal lesions, 4 were small; 2 including medial prefrontal; 1 SMA and 1 orbitofrontal. Of 3 pure frontal lesions associated with experiential phenomena, all had medial frontal involvement including the anterior cingulate, which in one case, extended to frontopolar and orbitofrontal regions. Four further cases had frontoparietal involvement and experiential phenomena; 2 including the cingulate region and 2 the lateral parietal suprasylvian region. There was a tendency for extratemporal lesions associated with experiential phenomena to progress directly into motor activity (6 of 7 cases), commonly version or posturing. By contrast, of 13 cases with temporal lobe lesions, only 5 had relatively early motor activity without an obvious preceding absence phase, 4 had no

motor activity at any stage during the seizure, and in those that did develop motor activity, this was usually of the form of automatisms.

Two patients with visual manifestations and a frontal lesion had formed and unformed hallucinations, indistinguishable from those with temporal lesions. Although head turning in group 4 occurred in a similar proportion of lesional cases in both temporal and extratemporal groups, both cases in whom there was no prior absence phase fell into the extratemporal category.

In these categories where temporal lesions predominated, there was a suggestion that interictal spikes, where present, co-localised with the structural lesion, whether frontal or temporal (see inter-relationships of investigations, page). Ictal EEG had been recorded in only one patient with an extratemporal lesion and a clinical seizure pattern in categories 1-4 (case 329) - a negative selection effect of the presence of structural lesions - and had an absence seizure with a mesial frontal lesion and bifrontal ictal discharge.

Only 1 case with a pure hippocampal lesion had a seizure pattern with early posturing. The interictal EEG in this case showed widespread spiking, ipsilateral to the sclerosis, ranging from P3 to Fp1, including some spikes regionalised to Fp1-F3-Fz.

Seizures with early posturing or version were associated with frontal lobe lesions $P<<0.001$) and seizures with general motor agitation were also strongly associated with pure frontal rather than temporal regions ($P<<0.001$). Their anatomical distributions are described in the section on intrafrontal localisation below.

Individual seizure manifestations

Most seizure manifestations occurred with similar frequency in frontal and temporal groups, and although some rarer symptoms appeared to have possible associations, e.g. olfactory and gustatory hallucinations, with temporal lesions, numbers were too small to analyse statistically (table 45). The manifestations that significantly differentiated frontal from temporal were largely the main determining symptoms of groups 1-4, 7 and 14, as described above.

Oral automatisms and experiential symptoms were significantly associated with temporal lobe lesions $P=0.001$. Although clonic movements and head turning *per se* were not

strongly associated with one or other lobe, if they occurred early in the seizure there was a significant association with frontal lobe lesions ($P<0.001$). A similar, but weaker, association was seen for early tonic movements ($P<0.01$) but not for tonic movements as a whole.

No measures of seizure frequency, duration or postictal duration showed any significant difference between frontal and temporal lobe seizures, although only seizures with a frontal lobe lesion had ever occurred at a frequency greater than 50 per day. Sensitivity to startle stimuli was seen in 4 cases with pure frontal lesions and in no pure temporal cases.

Intrafrontal localisation

Only 16 seizures were associated with a lesion restricted to a single intrafrontal region, as suggested by the ILAE, and no conclusions could be drawn from this small sample. An alternative approach was adopted: a statistical analysis of involvement of different cortical regions in the pathology underlying the clinically defined seizure patterns. This allowed the analysis of lesions covering more than 1 region of cerebral cortex and all 163 lesional seizures were included in this analysis.

The strongest association was seen between orbitofrontal lesions and seizures characterised by motor agitation (group 14). Of 14 lesional patients with involvement of the orbitofrontal cortex, 7 had a seizure type falling into this category ($P<<0.001$). Frontopolar involvement nearly as strong an association ($P<0.001$) and many lesions of the orbitofrontal cortex extended to the frontopolar region. Inclusion of the frontopolar cortex, without orbitofrontal involvement, was however, seen relatively frequently with more caudal lesions and tended to be associated with other seizure types, such that only 7 of 22 cases with frontopolar involvement fell into group 14. The 6 cases with motor agitation involving neither orbitofrontal nor frontopolar cortices, showed no consistent pattern: hippocampal; extrahippocampal temporal; perisylvian, SMA, anterior cingulate and lateral prefrontal/premotor in 1 case each. Orbitofrontal and frontopolar involvement were seen in 2 each of 6 non-focal tonic and 7 tonic-clonic seizures with structural lesions.

Lateral cortical lesions frequently extended from premotor through prerolandic to parietal cortex, and there were, therefore, shared features across this region. The lateral premotor cortex was the only region whose involvement was significantly associated with seizures characterised by early posturing ($P<0.001$), involved in 18 of 29 seizures. In those cases where the premotor cortex was not involved, the lesion was perirolandic in 3, mesial prefrontal or SMA in 4, frontopolar or orbitofrontal in 2 and widespread in the rostral frontal cortex in 2.

Both prerolandic and parietal cortices were significantly associated with seizures with somatosensory onset ($P<0.001$), irrespective of whether this had a typical Jacksonian progression. Only 1 case did not include either of these regions; a large lesion spreading across anterior frontal and temporal regions. The statistical association of this seizure type with the premotor cortex was weaker than with either precentral or parietal cortex. There was no suggestion that the size of the lesion correlated with the tendency of the seizure to progress and in 3 cases pure sensory seizures and pure motor seizures were seen at different times from the same pericentral lesion.

In 7 of 9 Jacksonian motor seizures associated with a structural lesion, there was involvement of the primary motor cortex in the lesion ($P<0.001$) and in the other 2 cases, the prefrontal and parietal cortices were involved. Only the prerolandic cortex was significantly associated with this seizure type.

The prefrontal region did not appear to be associated with specific seizure types. Its intermediate position in the frontal lobes meant that lesions tended to extend either into the frontopolar region, or posteriorly into the premotor and motor regions, which were associated with more specific seizure types. There were no associations between lesional involvement of the supplementary motor area and specific seizure types.

The cingulate region was the only extratemporal region to be involved frequently with experiential seizures of group 3 (6 cases) but this was not statistically significant as lesions associated with 19 other seizure types also included the cingulate region and no other association of the cingulate cortex was seen.

Analysis of all lesions involving the temporal lobe showed similar associations to those in the comparison of pure temporal to pure frontal lesions: strong association with absences

($P<0.001$) and weaker associations with groups 1, 3 and 4. The proportions of extrahippocampal and hippocampal lesions in each group showed no clear differences, but numbers were small.

Table 18. Summary of location of imaging abnormalities for each clinical group

Group	Predominant imaging appearance
1: fear behaviour and olfactory/gustatory	Predominantly temporal
2: absence	Strong temporal predominance
3: experiential	Predominantly temporal with some cingulate and some perisylvian involvement
4: visual	Predominantly temporal
5: auditory	Temporal (1 of 2 cases abnormal)
6: hypotonic	No pattern
7: version/posturing	Strong association with lateral premotor cortex
8: somatosensory	Strong association with parietal and perirolandic cortex
9: focal paresis	Two cases; lateral premotor and caudal superolateral frontal
10: CPSE	Variable
11: isolated jerks	Only 1 lesional case (lateral premotor/perirolandic)
12: Jacksonian clonic	Strong perirolandic association
13: generalised motor	Variable
14: motor agitation	Strong orbitofrontal/frontopolar association

Lesion types

The spectrum of lesion types in this study was large and further subdivision of cases by scan appearance renders groups too small for analysis. Some general observations can, however, be made. The major determinant of seizure type appeared to be lesion location rather than lesion type; where seizure types were associated with particular regions, this was irrespective of the pathological appearance on neuroimaging. For example, orbitofrontal lesions characterised by seizures with motor agitation (group 14), included post-traumatic atrophy, glioma and dysplasia (proven at resection). Post-traumatic atrophy was the commonest cause, reflecting the susceptibility of this region to trauma.

Dysplasia discovered with high resolution, reformatted MRI, frequently occupied the lateral prefrontal region (table 44), sometimes extending to the primary motor region and was responsible for several cases of seizures characterised by posturing and version. The similarity of scan appearance and distribution of these lesions was striking and suggests common factors in their aetiology. Of note was that many (53%) of 19 cases with dysplastic cortical appearance were bilateral, even though EEG and clinical manifestations may have suggested a lateralised onset of the epilepsy. Another congenital lesion; porencephalic cyst, with similar lateral distribution was responsible for other seizures in this category.

High resolution structural MRI

Forty-nine patients with normal CT or MRI underwent high resolution imaging, which was abnormal in 45 (92%). Twenty-three cases of hippocampal atrophy, 14 cases with dysplastic appearance and 8 previously undiscovered foreign tissue lesions. This represents some selection bias since some cases, especially those with hippocampal abnormalities were included in the study because of their structural lesion, but of 26 patients scanned after inclusion in the study for other reasons, 22 (85%) had abnormal appearances.

Magnetic resonance spectroscopy

In the group selected for spectroscopy, satisfying ILAE criteria for SMA seizures, there was a tendency for the SMA to have lower NAA/Cho+Cr ratios (figure 46, page 222) but this was not significant and there was considerable overlap with normal controls. Subsequent high resolution MRI revealed abnormal appearances in 7 of 9 cases, 5 with lateral frontal cortical dysplasia, one case with hippocampal atrophy and one with widespread dysplasia.

Imaging in epilepsy with startle-provoked seizures

CT scan was available in 5 of 6 with focal neurological signs and showed extensive abnormalities. In three cases of congenital lesions this appeared to be a large porencephalic cyst (figure 47, page 223) extending over frontoparietal regions and in the patient with previous meningitis/abscess, there was infarction in the prefrontal/premotor regions. In the 2 cases whose only clinical signs were reflex changes and in clinically normal individuals, the CT scan was normal, except in one who had mild hemiatrophy. High resolution MR scans were performed in 7 patients with normal CT scans and in the patient with mild hemiatrophy on CT. Abnormalities were seen in 6 of these and appeared to fall into two overlapping patterns.

In four cases there was perisylvian atrophy associated with thickening of the cortical mantle. This was predominantly anterior and unilateral in 3 cases (figure 48, page 223), with maximal involvement of the frontal component of the perisylvian region. In the other it was bilateral, with waisting of the perisylvian region. The latter was observed in the patient with pseudobulbar palsy and closely resembles the pattern of congenital Foix-Marie-Chavany syndrome seen in pathological specimens[208].

The second pattern, in 2 cases, was of a lateral frontal cortical migration defect. In the first case (figure 49, page 224) following contiguous slices showed these islands of grey matter to be discontinuous from the overlying cortex, which appeared normal. Resection of the abnormal region and adjacent cortex resulted in seizure remission which has lasted over a year to date, the patient previously suffering seizures several times a day. Pathological examination confirmed the presence of dysplastic neurons.

In the second case, there was a similar but more severe appearance on MR scan, this time with associated thickening of the lateral frontal and medial frontal cortex. There was no pathological verification in this case, but the probable ectopic grey matter was again entirely separate from the overlying cortex in serial sections.

The anatomical localisation of those cases with pathological lesions remains difficult because of the wide extent of atrophy in some cases, the difficulty in defining the limits of cortical thickening and the involvement of the perisylvian region, which is at the junction of 3 lobes. In the unilateral perisylvian cases, and those with porencephalic cysts, the maximal involvement appeared to be frontoparietal. In the case of Foix-Marie-Chavany syndrome, opercular involvement was extensive and probably included all 3 lobes. In 4 cases, the lesion was restricted to one lobe and this was frontal in each. No case had an obvious temporal lobe lesion.

Inter-relationships of investigations

Relation of interictal EEG to imaging

Table 46, page 225 shows the relationship between location of interictal spikes and lesions on neuroradiological imaging. The mean number of EEG's was similar to those without neuroradiological abnormality; 1.69 against 1.64. Absence of interictal spikes was common with lesions in any region, occurring in 47% of cases who underwent EEG examination. Highly concordant spikes were uncommon, occurring in only 9%, similar in both frontal and temporal groups. In the temporal lesional group, the commonest pattern was of overlapping abnormalities, with EEG spikes occurring over a relatively wide area of scalp from relatively restricted lesions; 26% of temporal abnormalities versus 9% of other groups combined. In the frontal lesional group, bilateral spikes were commoner than a focal or overlapping EEG abnormality. Bilateral spikes in the frontal group tended to be bilateral simultaneous in contrast to the bilateral independent spikes, usually seen in the temporal group.

Spikes purely contralateral to the identified lesion e.g. left temporal spikes with right hippocampal atrophy, were moderately frequent (10%), as were other patterns of clearly discordant spikes (11%) and occurred with similar frequency in both frontal and temporal

groups. In 7 of 11 cases with discordant spikes, the number of spikes observed was very few (<5). In two patients spikes were contralateral to a parafalcine lesion. Examination of the 15 seizure patterns shared by the 11 patients with discordant interictal EEG and imaging showed an unexpectedly high proportion of absences and general motor seizures without specific features - occurring in 11 of 15 seizures - significantly higher than in the study group as a whole (P<0.001, Yates correction). With this high proportion of clinically unlocalised seizures it was impossible to say if ~~they~~ their seizure pattern was more typical of lesion site or interictal EEG abnormality in these discordant cases. In 1 patient with EEG contralateral to the lesion site, an absence evolved into focal clonic activity of limbs contralateral to the scan lesion and ipsilateral to the EEG. In another case in which an absence progressed to adversion, head turning was contralateral to the lesion and ipsilateral to the EEG spikes. There was no obvious association between probable pathology on scan appearance and discordance with the EEG.

Relation of interictal EEG, ictal EEG and imaging

Table 47, page 226, shows the relationships between interictal EEG, ictal EEG and structural lesions, where present for those patients who had undergone ictal EEG recordings. Of 18 cases with both ictal EEG and imaging abnormalities, frank discordance was seen in only 2, although widespread unilateral or bilateral abnormalities from a focal lesion was relatively common.

Cases with normal interictal EEG and abnormal ictal EEG and imaging

Of 31 seizures with a normal interictal EEG, 11 (35%) had a regional or focal ictal EEG abnormality; 2 temporal, 1 frontotemporal and 8 frontal or frontocentral. A structural lesion was present in 6 of these, 2 temporal and 4 frontal and the ictal EEG was concordant or overlapped the structural lesion in all cases. There appeared to be no difference in the clinical seizure patterns of those seizures in which an abnormality was identified on ictal recording and those in whom it was not. Of 9 cases with ictal recordings and frontal/frontocentral dysplastic appearance on MRI, 8 had an onset with artefact or widespread abnormality, whereas of 5 patients with acquired pathology of the

same region, 4 had a concordant focal or regional onset, despite similar clinical patterns with early motor components.

Ictal patterns in cases with abnormal interictal EEG

Of 46 seizures associated with interictal spikes and ictal EEG recordings, ictal EEG appeared to be more specific in its localisation in 12 cases (26%), less specific in 17 (37%) and of equal specificity in the remainder (37%). There was no suggestion that cases with interictal spikes in any particular region tended to show more specific ictal abnormalities, although numbers were small.

Ictal EEG versus imaging abnormality

Among thirty-five patients who had undergone ictal recording and had a demonstrable lesion on imaging, discordance between investigations was rare; 2 patients had ictal EEG's lateralised opposite to the lesion, one with a paracentral glioma and the other with hippocampal atrophy and 1 had a frontal scalp electrographic onset from an ipsilateral mesial temporal glioma. In the first 2 instances, the interictal EEG was concordant with the scan and in the latter, was normal.

Cases with abnormalities of ictal EEG, interictal EEG and imaging

There were 15 cases in which all 3 investigations were lateralised. In 1 the interictal EEG lateralised opposite to the lesion, in which ictal EEG was ipsilateral to the lesion with a diffuse distribution. A much commoner pattern than discordance was for a scan lesion to be associated with non-specific EEG abnormalities; normal; widespread; unilateral or bilateral or to be masked by movement artefact.

Summary of inter-relationships of investigations

Frank discordance of investigations was uncommon in any group and where discordance was seen, there were too few cases to determine which investigation was most consistent with the clinical pattern. A commoner pattern was for EEG to be less specifically localising, either ictally or interictally, than neuroimaging. Bilateral EEG abnormalities in the presence of a unilateral lesion was seen commonly and the converse also seen, but more rarely. There appeared to be little difference between frontal and temporal regions

with respect to sensitivity of different EEG modalities, interictal being positive in the presence of normal ictal EEG and vice-versa, with similar frequency, in both regions.

Laterality of somatic manifestations and investigations

Lateralisation of different clinical manifestations

Seventeen cases experienced both focal clonic and focal sensory manifestations and these colateralised in every one. In 20 of 22 cases with both focal clonic jerks and head turning, the manifestations colateralised. In one case with a paracentral lesion contralateral to the clonic activity there was bilateral head turning, and in the other, not associated with investigative abnormality, version was contralateral to clonic activity. In 9 of 12 cases with version and focal sensory manifestations, there was colaterality and the remaining 3 were discordant. One of these had a large lesion in one hemisphere, another bilateral interictal EEG spikes and the third normal investigations.

Relation of clinical to imaging laterality

Of 21 lesional cases with focal clonic activity, there was colaterality with imaging in 12 (57%), in 11 of whom clonic jerks were an early seizure manifestation; discordance in 6 and focal jerking arising from bilateral lesions in 3. Of the 6 discordant cases, 5 had clonic activity late in the seizure; 3 of these had hippocampal atrophy, and 2 well localised lesions, maximal in the SMA with possible extension into mesial prefrontal and cingulate regions. In the case with early clonic activity, this affected the mouth and spread to the limbs and was associated with an ipsilateral lateral premotor AVM.

An interictal EEG showed no spikes in 4 of the 6 discordant patients, in whom it was recorded and bitemporal spikes in one case of hippocampal atrophy. Ictal EEG was recorded in 2 cases and colateralised with the scan in 1 and showed bilateral spikes in the other.

Of 54 lesional cases with version during the seizure, there was contraversion in 32 (60%), in 20 (62.5%) of whom version was an early manifestation; bilateral version in 6 cases (11%), all from unilateral lesions; ipsiversion in 11 (20%) and unilateral version from a bilateral lesion in 5 cases (9%). Of cases with bilateral lesions, an interictal EEG was

available in 4 and had spikes in 3; contralateral to version, ipsilateral to version and bilateral in 1 case each. Of cases with turning ipsilateral to a lesion, in 9 (81%) version was a late seizure manifestation. Ten of these ipsiversive cases had interictal EEG's, with either no spikes or bilateral spikes in all. Eight had ictal EEG recordings which colateralised with the lesion in 4, was contralateral to the lesion in 1 and non-specific in 3. Of 16 lesional cases with focal sensory manifestations, the manifestation colateralised with the lesion in 10 (62.5%) and was a unilateral manifestation of a bilateral lesion in the other 6. In one of these the interictal EEG colateralised with the clinical manifestation but in the other cases was bilateral or normal. Sensory manifestations purely ipsilateral to a lesion never occurred.

Relation of clinical laterality to interictal EEG

Seventeen cases had focal clonic activity and EEG spikes; 11 colateralising; 4 with bilateral EEG and 2 discordant. In one of the discordant cases, ictal EEG was available and agreed with clinical lateralisation and in the other an identified lesion was again concordant with clinical data rather than interictal EEG.

Of 10 cases with sensory manifestations, 5 colateralised with the EEG and 5 had bilateral EEG spikes, none was discordant.

Of 60 cases with version, this was contralateral to EEG spikes in 27 (45%); associated with bilateral EEG abnormalities in 21 (35%); bilateral version in 6 (10%) - associated with unilateral spikes in 5 - and ipsilateral to EEG spikes in 6 (10%). In 3 (50%) of ipsiversive cases, head turning was an early manifestation and in the 2 lesional cases, EEG colateralised with the lesion. Of 32 cases with unilateral spikes and purely unilateral head turning, version was contralateral to the spikes in 27 (82%) and ipsilateral in 18%.

Relation of clinical laterality to ictal EEG

Nine cases seizures with focal clonic activity were recorded and in 7 laterality was concordant. In both discordant cases, clonic activity was a late manifestation and in one, EEG abnormality colateralised with pathologically documented Ammon's horn sclerosis. Imaging in the other also pointed to a temporal lobe lesion.

Of 27 cases with version, 8 (30%) had turning contralateral to EEG side of onset; 7 (27%) ipsilateral; 4 (15%) bilateral version with a unilateral EEG; and 8 (30%) unilateral version with bilateral EEG changes. Of those with ipsiversion, 2 were lesional, both extrahippocampal, in the anterior temporal lobe, one with a frontotemporal EEG onset, the other widespread over the hemisphere. In 4 of 5 non-lesional, ipsiversive cases, EEG onset was over the frontal electrodes and in the remaining case widespread over the hemisphere. Head turning was an early manifestation in 2 (28%) ipsiversive and 3 (38%) contraversive cases.

In both cases with focal sensory onset, the ictal EEG colateralised with the clinical picture.

Summary of laterality issues

Focal clonic and focal somatosensory activity colocalised and where a unilateral lesion was present, focal sensory activity localised to it in every case. Focal clonic activity, occurring early in the seizure, colocalised with unilateral lesions, in all but 1 case. The relationship of these manifestations to interictal spikes was generally concordant, but with some cases having bilateral spikes. Discordance with ictal EEG onset was seen in 2 cases with focal clonic activity as a late seizure manifestation. The relationship of head-turning to other clinical manifestations or to investigational abnormality was less consistent, but where there was a unilateral lesion, contraversion appeared somewhat commoner than ipsiversion.

Partial Seizure results of the National General Practice Study

1) Clinical patterns

Of the 594 cases with definite seizures, 252 were classified as localisation-related on the basis of focal clinical manifestations, focal EEG or imaging abnormalities, or a clinical history suggesting focal cerebral pathology. 187 suffered partial seizures and of these, 142 had sufficiently characteristic clinical patterns to allow clinical localisation, leaving 45 patients with evidence of partial seizure onset, which was too vague for seizure localisation e.g. isolated head turning or vague epigastric sensations. A further 18 patients suffered secondarily generalised seizures with a localisable partial onset but no partial seizures; a total of 160 patients with localisable seizure onset who form the basis of this analysis. Forty-seven patients had historical, EEG or imaging evidence of focal cerebral pathology but only generalised seizures. A total of ninety-two cases, therefore, were placed in the "clinically unlocalised group", although having other evidence pointing to partial onset. Of the 160 clinically localisable cases; 36 were classified as frontal onset; 52 as central onset; 9 as frontotemporal onset; 10 each as parietal and posterior onset and 43 as temporal onset. There were no differences in the age or sex ratios of the patients in each group.

Of the patients in the frontal lobe seizure group, 12 had seizures with early posturing, and the remainder (24) experienced combinations of simple automatisms, motor agitation, head version, tonic and clonic features. Temporal lobe seizures manifested as predominant olfactory and/or gustatory hallucination (7 cases); experiential phenomena (9 cases); abdominal manifestation with orofacial automatisms (10 cases); auditory hallucination (1 case) and combinations of the above in 16 patients. Parietal seizures manifested as localised paraesthesiae (4 cases), numbness or pain (3 cases each). The frontotemporal group included combinations of autonomic manifestation, complex motor activity and abdominal features (4 cases); oroalimentary and complex motor activity (4 cases) and vertigo followed by complex motor activity (1 case). Posterior seizures included 2 with unformed visual hallucinations, and 4 each with formed visual and polymodal hallucinations.

2) Investigative abnormalities

Of the 160 patients with clinically localised seizures, 149 (93%) attended hospital, 107 (67%) underwent EEG, 86 (54%) CT and 38 (24%) had neither test. Table 49, page 231 shows the number of patients in each group to undergo investigation and their results. Table 50, page 232 shows the relationship of clinical seizure pattern to investigative abnormality for those patients with focal abnormalities. Patients in the "clinically unlocalised group" with focal investigative abnormalities are included.

An EEG was available in 8 of 12 patients with frontal lobe lesions on CT scan. In one of these the EEG was discordant; co-localising with the clinical pattern to the temporal region and in the others EEG was not localising. EEG's were present in 3 of the 6 patients with focal central lesions and were non-specific in 2, the third showing temporal spikes. In 7 patients, the EEG showed frontoparietal spikes, in 5 of whom a diagnosis of Benign Epilepsy of Childhood with Centrotemporal Spikes (BECT) was strongly suspected, on the basis of electroclinical pattern, although patients had not all undergone imaging or sleep EEG studies. In all 3 patients with temporal lobe lesions, EEG's were non-specific. In 2 of the 10 cases with parietal or other posterior cortical lesions, the EEG lateralised opposite to CT and clinical pattern and was non-localising in the other 6, in whom it was performed.

3) Aetiologies (table 51)

Overall, 32% had a clear cause and 9.4% a probable cause for their seizures. Figures were similar for different seizure patterns except in the temporal group, where there were fewer identifiable causes (14%).

4) Seizure frequency (table 52)

Data of seizure frequency were available in 89.4% of patients. The pattern of seizure recurrence and frequency did not show any significant difference between the six clinical seizure locations; 45% experienced only one seizure or became seizure-free and 27.5% suffered only rare seizures. Frequent seizures were seen in only 11 cases (6.9%). Four were due to cerebral tumour, 1 each subarachnoid haemorrhage and hypertensive vascular

disease, and 5 were of unknown aetiology. Of the 27 patients who died during the follow-up period, 3 each (11.1%) had frequent or moderately frequent seizures, compared with 8 each (6%) of survivors.

Discussion

Methodological considerations

Patient selection

The lack of a single criterion to identify the origin of seizures leads to fundamental difficulties in their definition and in selection of patients for study[10]. An important feature of this study is the broad criteria with which patients were selected, since any one criterion is likely to exaggerate bias. The relative importance of different selection methods in the different groups identified can be assessed from table 34 (page 174), illustrating inclusion criteria.

These methods differ significantly from those of most previous investigators who attempt to resolve the problems of case selection by the adoption of a "gold-standard", representing the single best, currently available, measure of seizure origin. They report series of patients seizure-free after similar cortical resections and conclude that the clinical features they share are characteristic of the resected region. This approach is inherently flawed; it is necessarily retrospective and using either no controls or historical controls, leaves many questions unanswered. There is substantial selection bias in that the criteria for selection for surgery usually include considerations of seizure pattern, thus predetermining the results. In what way do those patients who are not surgical candidates differ from those who are and do they have different seizure patterns? If their seizure patterns are the same, of what value is the seizure pattern in defining the region of onset of epilepsy by this method? In addition, those patients with apparently similar electroclinical characteristics, yet not rendered seizure-free by the same resective surgery are rarely reported in detail. Yet these form an important group of false positives that must be included in the assessment of any predictive test of post-surgical outcome and any more general consideration of localisation of seizure patterns. This is particularly relevant in frontal lobe epilepsies where resective surgery is successful in only 20-40%[173]. Ideally, in order to judge the value of clinical or investigative features as criteria for surgical treatment, it must be studied prospectively on an intention-to-treat basis, including those patients for whom surgery was successful, those for whom it failed and

those who ultimately did not undergo surgery. Moreover, frontal lobe resections are generally large[173] and if successful the only conclusion that may be drawn is that a region somewhere within the resective area was crucial in epileptogenesis and further localisation is impossible.

The definition of epileptic seizures by the tiny proportion who undergo presurgical assessment also represents a major bias in current thinking. Finally, a successful outcome includes those patients who continue to have epileptic auras after surgery, which is a useful, pragmatic approach in the evaluation of patients. The persistence however, after otherwise successful surgery, of symptoms which may be associated with the primary epileptogenic region[209], suggests that surgery may have interfered with the expression of seizure activity, by interfering with spread, rather than eliminating the underlying diathesis. Whilst empirically useful, therefore, one must be cautious in interpreting the pathophysiological mechanisms of surgical treatment.

Rather than ascertaining the features of groups with similar, successful resections, this study has a different approach to the problem of clinical seizure manifestations and their localising value. A standard protocol was used for recording clinical features, in which a preliminary statistical cluster analysis was performed, in order to minimise observer bias in the delineation of clinical patterns. Only then was the localising evidence for each pattern analysed, to establish which seizures share similar investigational abnormalities, pointing to similar cortical localisation. This enabled the predictive value of clinical seizure manifestations to be ascertained for different seizure types.

Effects of case selection

Because selection of patients was on clinical, EEG or imaging criteria, without seeking *a priori* concordance between them, the bias inherent in selecting on the basis of only one criterion was offset and any bias can be assessed by considering the inclusion criterion of each case in the seizure categories defined. Since only patients with concordant investigations tend to undergo operation, this contrasts with the analysis of post-surgical

series. In addition this enables the issue of concordance to be assessed as part of the study, which is not possible in post-surgical series.

For example selection from VET records includes many in whom surgery is being considered and, therefore, may have more refractory epilepsy and more concordant results on other criteria. By contrast, individuals with foreign tissue lesions are sometimes not considered to require VET and, therefore, there is a negative selection bias against VET cases. The inclusion of both these groups, to some extent, offsets the possible bias introduced by either one alone.

Interictal EEG's were present in the majority of cases (90%) and the main bias introduced in this regard by the selection method, was that some patients were accepted without interictal EEG, but only if there was a structural lesion, on neuroimaging, arguably the strongest localising evidence in this study. The lower number of recordings for some patients also reduced detection rate of interictal spikes.

Selection from more general neurology practice, using various criteria is likely to include individuals with less refractory epilepsy than post-surgical cases seen in a specialist epilepsy centre. These patients include a spectrum of hospital-based cases, including some epilepsy clinic patients and therefore, vary from very severe to an intermediate grade of severity. In order to assess the relevance of this study to epilepsy in the general population, a derived classification was applied to a community-based cohort of the National General Practice Study of Epilepsy. It is important to consider these less refractory patients as the mechanisms of their epilepsy may differ from those seen in post-surgical series and may be more representative than highly selected cases from specialist centres.

Finally, this study recognised the problems with current investigative techniques and included cases whose clinical patterns were thought likely to be focal (excluding occipital). Importantly, abnormalities were found in some of these some cases on re-investigation, especially on MRI and these, therefore, represent a truly prospective group, selected on clinical basis and subsequently found to have structural lesions underlying their epilepsy. All those cases with dysplasia on MRI fall into this category. Since a primary aim of this study is to assess the predictive value of clinical seizure patterns in

frontal lobe epilepsy, the breadth of this case ascertainment is crucial in order that important subgroups are not missed.

Data analysis

Clinical seizure data was collected prospectively by a standardised technique, by one investigator, rather than retrospectively, as is the case from post surgical series. Cases were then classified according to the thing they all have in common; one or more clinical seizure patterns, independent of investigational findings, and only then was this classification related to other measures of seizure localisation; imaging; interictal EEG and ictal EEG. In this way the analysis is closer to a prospective, predictive analysis of clinical patterns than in other studies.

Many patients have more than one seizure type and another important feature of this study is the differential consideration of patients and seizures. Ictal EEG is a seizure-specific investigation and need only be analysed in terms of the clinical seizure pattern it accompanies. Imaging and interictal EEG are patient-related investigations and the same abnormalities in these modalities are associated with all the patient's seizure types. Irrespective of the cause, there is no *a priori* justification in considering one habitual seizure type more representative of the underlying cause than another on grounds of e.g. seizure frequency. Any localisational scheme must explain all the seizure types arising from a given lesion in order to be of practical value and have pathophysiological significance. For this reason all patients' habitual seizure patterns were analysed against imaging and interictal EEG, rather than selecting one type, which would have ignored important data.

The decision whether a patient's seizures represent variations on a theme or separate seizure types is difficult. In this study, differences in the initial manifestations were taken to represent different seizure types and differences in later manifestations as variations, perhaps due to differences in seizure spread. The fullest, habitual expression of each seizure was used as likely to give the most information regarding spread. Two factors further complicate this analysis. First, the effect of long-standing epilepsy on seizure evolution: patients may initially have an aura or a partial seizure onset and subsequently

develop seizures with rapid generalisation and, therefore, no clinically apparent partial onset. Second, treatment changes may modify seizure expression. Whilst the commonest effect is to prevent secondary generalisation, which would therefore, leave the initial ictal events (crucial to this classification) unchanged, sometimes treatment may abolish the aura or other early manifestations. Both factors are partially countered by the inclusion of cases according to EEG and imaging as well as clinical criteria and by the analysis of all the seizure types for which there is a good witnessed history, including those from the past. The sands of time inevitably erode the memory, and retrospective accounts were excluded unless the description was full, leading to a historical bias. Nevertheless, the accuracy of the retrospective accounts in this study is supported by the high detection rate of startle sensitivity as a transient phenomenon in the past, compared to other clinical studies. Since alterations in drug treatment are also made on admission for telemetry, a possible bias may arise here. It is arguable which is more representative of a patient's habitual seizures; a good witnessed account or the recording made under artificial circumstances with drug withdrawal. The high concordance between the 2 accounts in those cases in which they were compared, suggests this is not a major source of bias. This analysis of seizures rather than cases led to double representation of a few cases, whose seizures appeared clinically different but were ultimately classified into the same overall category, partly because of the use of group variables in the cluster analysis. For example one patient had two forms of tonic posturing; one a brief collapse always precipitated by startle stimuli and the other a more prolonged posture, never precipitated by startle, which would be difficult to call the same clinical type. This double representation, therefore represents clinically significant variants, occurs in only 4.5% of cases and is more than offset by the advantages of analysis of all the seizure types in each case that are probably attributable to the same pathology. With the exception of these significant variants, each seizure was considered a single data point in this study, in contrast to other studies where seizures of the same clinical type from the same patient were considered as separate events, biasing the data in favour of those with more recorded seizures[59,210].

Whilst the emphasis of this study is on the delineation of clinical seizure patterns and their relationship to investigative abnormalities, the possibility of unforeseen bias in this classification technique needs to be taken into account. Moreover, whilst classification is desirable to enhance understanding, there is a continuum of manifestations in different seizures and their allocation to different categories may mask similarities. For these reasons further analyses were performed; relating the three investigative techniques to each other; assessing concordance independent of clinical classification and relating clinical manifestations to lesion site, from raw clinical data, prior to seizure classification by cluster analysis.

Although some forms of TLE are considered highly characteristic, a very major issue in clinical practice is the differentiation of some cases of FLE from TLE . We analysed cases of TLE , included according to similar criteria; some with strong localising evidence, foreign tissue lesions on neuroimaging, or MRI evidence of mesial temporal sclerosis - increasingly recognised as a reliable marker of TLE[127,128]. These acted as a control group for the frontal cases, in order to identify genuine differences between frontal and temporal epilepsy. Patients with classical epileptic syndromes e.g. Jacksonian clonic seizures or experiential seizures were also identifiable groups to enable external validation of the cluster analysis technique. The large number of patients included in this study allowed statistical analysis of groups against each other, to ascertain differences that are significant, and are likely to be clinically and possibly pathophysiologically important, rather than reporting unconnected case series.

Cluster analysis

Cluster analysis[196] is a non-parametric multivariate statistical technique, that may be applied to non-metric data and occasionally has been used to define symptom complexes in illness, especially in psychology[211,212]. The most widely used variants are average linkage, centroid and Ward's analyses. Critical issues are the selection of the clustering technique; the choice of variables to be entered into the analysis and the method of calculation of inter-variable distance. The output of the analysis is in two major forms; a cluster membership table and a clustering coefficient series. The former shows the group

membership of each case for the different numbers of clusters specified. In this case the number of groupings was felt probably to lie between 10 and 30 and the group membership of each case was tabulated in the output of the analysis for each number of groups. The cluster coefficient shows the numerical distance between the clusters combined at each stage of the analysis and is a measure of the proximity of cases, which may be used as a guide to the number of clusters likely to give the most meaningful results (figure 1, page 55).

The choice of clustering paradigm is empirical[196] and there are, as yet no reliable theoretical guidelines. Variables entered into the analysis were only those relating to the clinical manifestations of the seizure itself. It was felt that these were more likely to be fundamental properties of the seizure-generating region and its connectivity, whereas other considerations of e.g. seizure frequency, duration and tendency to secondary generalisation might rather be functions of the severity of the underlying pathology and could have corrupted the statistical analysis. These variables were considered subsequently in manual analysis of the results. Variables were coded according to their relative time of occurrence in the seizure. This is of probable clinical value in terms of consideration of seizure spread and makes more meaningful comparisons between seizures of different durations than using absolute timings. Moreover, it is of more relevance to the nature of cluster analysis, which uses the relative positions of variables rather than their absolute values. In addition for those cases in whom telemetry recordings were not available, the sequence of manifestations could be determined but not the precise timing of manifestations in the seizure.

The number of potential seizure manifestations is so legion that were each to be entered as an independent variable into the statistical analysis, no groupings would ever be found. A further problem with statistical analysis is the weighting of data to allow for related variables. For example, swallowing and lip smacking automatisms are more closely related to each other than they are to clonic jerks and it would be inappropriate for the analysis to treat all three as equidistant. In order to minimise these problems, categories of variables have been analysed, using groupings of related symptoms. The aim of these modifications was to use existing knowledge in order to enhance data entry and make the

cluster analysis as clinically meaningful as possible. It is important to appreciate that whilst these modifications may be viewed as seeding the data with preconceived relationships, these are kept to a minimum, are consistent with current literature, and are applied equally to all cases in the analysis. The use of group variables reduces the number of variables entered into the statistical analysis, making patterns easier to discern and the cases were then analysed according to individual manifestations within the groups. Notwithstanding the groupings, the number of variables used, at 52, was still large. The localising value of some symptoms e.g. olfactory aura is greater than for others e.g. cephalic aura[7]. This too would require weighting of data in the analysis but meaningful weights can only be attributed, if there is an outcome measure of the analysis against which to calculate them, which was not available in this study. For these reasons the cluster analysis could be seen as generating general groupings, the aggregation of cases into ever larger clusters was stopped prior to achieving the minimal reasonable number of groups (figure 1), and final groupings were refined by hand. This stage of the analysis may have introduced bias and some independent cross-checking was required. Internal validation showed a high degree of reproducibility, compared to previous studies utilising cluster analysis, using different samples and techniques of analysis. The acid test of cluster analysis is whether the clusters produced have any clinical relevance. External validation showed consistent identification of well recognised, clinically meaningful groupings e.g. absences with no focal features; focal clonic seizures; focal sensory seizures; seizures with olfaction and gustation, experiential seizures and differentiating generalised tonic from focal tonic or generalised tonic-clonic seizures. Because of the nature of the variables entered into the analysis, there was predictable combination of some seizure types e.g. isolated jerks and focal clonic seizures were combined because no seizure duration variable was included and non-Jacksonian and Jacksonian sensory seizures were initially separated because of presence of a "Jacksonian progression variable", but these were subsequently combined. It could be argued that this validation of data entry and analysis was tailored to the grouping of well known seizure types and this accuracy cannot necessarily be extrapolated to the other less well known types, which are central to this study. Against this however was the consistent identification in the

analysis of at least one less well recognised seizure type; motor agitation, with significant investigative associations, which could not be predicted at the start of analysis. In addition an independent analysis was performed, comparing the features of cases with strong localising evidence, in the form of lesions on imaging, restricted to the frontal or temporal lobes. This differentiation is one of the most important in clinical practice and it supported the cluster analysis classification, in identifying those clinical characteristics with most distinguishing power between frontal and temporal lesions, from the raw clinical data independent of the cluster analysis technique.

A criticism of previous statistical analyses applied to seizure symptomatology, is that they take individual symptoms in isolation, whereas seizures are made up of numerous manifestations, whose relative timing may be of particular importance in terms of seizure spread. This cluster analysis, whilst emphasising early symptoms not only allows the simultaneous analysis of many clinical seizure variables, but with appropriate encoding of symptoms, their sequential occurrence may be analysed in a standardised fashion. The presentation in flow diagrams highlights the components of seizure progression as well as their initial manifestations.

Imaging studies

The relation of the epilepsy to the site of a tissue lesion is a matter of debate, since as Hughlings Jackson originally pointed out[5] non-neural tissue cannot propagate seizure discharges. Nevertheless, the frequent association of structural lesions with epilepsy leaves no doubt that they are frequently responsible. Lueders[213] has proposed a scheme in which different aspects of the epileptogenic zone are highlighted by different investigations (figure 50, page 229); lesion site by structural imaging; interictal and ictal electrographic distribution; cortical region responsible for clinical seizure expression and region of neuropsychological deficit. He argued that these regions usually overlap but are not necessarily fully concordant. Whilst this approach emphasises the requirement for concordance between investigations in patient management, it is based on concepts prevalent prior to the introduction of modern imaging techniques. With the most recent MRI techniques, lesions can be identified in 80-90% of CT scan negative cases[163] and it is

to be hoped that this will further increase in the near future. Taking this fact with the strong evidence that resection of a lesion, whether foreign tissue, or mesial temporal sclerosis, offers the best chance of surgical cure, suggests that concepts should now move from phenomenological considerations to an aetiological framework[214] figure 50, page 229. Whilst the mechanism whereby a major cortical lesion causes epilepsy is unknown, it cannot be doubted that it is the cause, and therefore, the localisation of the underlying problem is the site of the lesion, even if its expression is at a remote site. Problems occur if it is difficult to define the anatomical extent of the lesion, e.g. NMD's or if there are distant effects e.g. expanding foreign tissue lesions that may cause raised intracranial pressure effects and distant epileptogenesis or if current techniques cannot identify the lesion e.g. subtle dysplasias. Recent studies have shown, however, that to ignore the site of the cause and surgically treat the remote, apparent site of the effect is an approach doomed to failure, whereas the converse is much more likely to succeed and that where the lesion is identified, the major predictor of operative success is the extent of removal[179,184,215], such that reoperation to extend the site of resection in incompletely removed lesions may be a successful strategy. There are, therefore, both conceptual and pragmatic attractions of this approach, and with the accuracy of post-operative MRI, the model is currently undergoing testing in several centres.

In this study, half the cases had an identified structural lesion, which was mapped accurately to cortical regions, using a template technique and these were analysed in relation to clinically defined seizure patterns. Although some patients were selected on the basis of their structural abnormality, and not all cortical regions were equally represented, the classification of cases was initially clinical, without reference to imaging abnormality and only once this classification was completed, were the lesions associated with each seizure type considered. This is, therefore, a prospective analysis of the lesions underlying each clinical type. In case the clinical classification had introduced bias, a direct statistical comparison of lesions involving only frontal or only temporal lobes was included, in relation to individual seizure symptoms and the results of this analysis supported the clinical classification. The maximal extent of lesions, including surrounding

oedema, was taken as the potential source of the epilepsy. Since it cannot be assumed that the epilepsy arises from any particular site within the lesion, highly focal onsets may be "diluted" if the structural lesion is large. This problem has been partly circumvented by the use of statistical analysis of the lesion sites underlying seizure types. Moreover, the number of regions involved in a lesion was included as a variable, to ascertain whether the size of the lesion is a determining factor in the clinical seizure type, or the number of associated seizure types.

Theoretical explanations for varying seizure types from a given lesion include: different manifestations may represent different epileptogenic regions of the same lesion and this may apply for instance to the 2 patients with frontoparietal lesions who had distinct Jacksonian motor and Jacksonian sensory seizures; or that different manifestations represent different modes of spread of seizure activity. The results in this study, however, suggest no correlation between the size of identifiable lesions and the number of seizure types, and are against the first explanation.

The relationship of lesion type to seizure type has not been explored in the past in detail. It may be difficult to disentangle the effects of anatomical location and histology, since they are related in some cases, e.g. post-traumatic epilepsy and the frontopolar region or sclerosis in the mesial temporal region. In this study the location appeared to be a more important determinant than lesion type, but in group 7 (version/posturing) a large proportion of lesions were congenital, with a similar location and it is difficult to know which was more important. One might speculate that functional connectivity of a region is more likely to determine seizure manifestations than histology and this is supported by the evidence of seizure types from well defined functional areas e.g. primary sensory and motor cortices, irrespective the pathology affecting them[7].

Interictal EEG analysis

The analysis of interictal EEG used the method of spike counting. Although epilepsy may be associated with other EEG abnormalities, they are more subjective and observer dependent in their interpretation. In addition, slow wave abnormalities are a recognised consequence of structural lesions, irrespective of associated epilepsy[216], and therefore, their assessment would be biased towards those patients selected on the basis of cerebral lesions. Intra-observer validation of the technique showed a high degree of consistency. The reporting of sites of EEG abnormality was in relation to electrode placements. Since precise anatomical correlates cannot be determined from scalp EEG, this gives a clearer picture of the EEG results, than reporting sites in terms of underlying cortex, which is applying additional interpretation to the raw data, although this has been done in summarising the results. The number of EEG spikes is also an important variable, that is commonly not reported, as the larger the number of spikes and the more consistent their localisation, the more reliable the results.

Sampling error is a potential problem in uncovering epileptiform abnormalities in interictal EEG's and the proportion of cases with interictal spikes who had only one EEG was significantly less than those who had more than one. The mean number of EEG's was very similar across all groups; consequently inter group comparison remained possible. In addition by considering seizure types, rather than individual cases, the EEG's could be pooled between cases to give a measure of frequency and consistency of abnormalities.

The potential number of different categories of EEG abnormality (taking into account all the possible combinations of frequency, location and spread of spikes) was such that statistical analysis would have resulted in unrealistically small groups, and therefore, a purely descriptive approach was adopted.

Ictal EEG analysis

Ictal EEG was analysed in a minority of cases and all EEG patterns identified in relation to each seizure were reported. This illustrates the variability of EEG patterns in relation to clinically similar seizures but leads to a statistical quirk, in that the more EEG's

recorded, the more likely it is for there to be more than 1 ictal EEG pattern and, therefore, apparently the less reliable the EEG. Sometimes this was due to variations in the timing EEG onset, in which case the earliest EEG onset in relation to clinical onset was considered most representative and this usually showed the most focal abnormalities.

Previous investigators have suggested that fast EEG (>12Hz) activity is more suggestive of a nearby seizure onset than slow (<8Hz) activity[198]. The distribution and pattern of EEG onset were examined separately in this study, with a suggestion that seizures arising in frontocentral regions were far more likely to be characterised by fast activity than those from other regions. Whether these seizure generating regions were closest to the scalp electrodes or whether these site and pattern variables may be inter-related is unclear in this study.

Ictal EEG onset was related to seizures types in the clinical classification to see if consistent patterns could be determined. The location of ictal EEG onset was also related to the site of structural lesions and to interictal EEG spikes in the subgroups that had undergone combinations of investigations in order to assess concordance, avoiding any potential bias introduced by the clinical classification.

Concordance of Investigations

In a study of successful post surgical cases, concordance between investigations cannot be assessed, since concordance is a primary consideration in selection for surgery. In this study efforts were made to minimise selection bias, with selection made independently on various criteria. It is reasonable, therefore, to measure concordance between investigational modalities, independent of the clinical classification. In addition, because the clinical classification was made without reference to any investigations, it is possible tentatively to combine the investigative evidence from interictal EEG, ictal EEG and imaging to give an overall picture of the likely localisation of cases, where no one investigation alone shows a statistically significant association of seizure type with cerebral region.

Strengths and weaknesses of the methods - summary

The key feature of this study is the initial definition of clinical seizure types, allowing the assessment of their strength at predicting abnormalities on investigations, by comparison with other seizure types which acted as controls. Other important features are: the large number of cases, especially the large proportion with identified structural lesions; the selection of cases according to various independent criteria in order to reduce bias; the standardised collection and recording of clinical data by one observer and the analysis of all seizure types of each patient in relation to the investigative abnormalities. The clinical classification technique is also supported by a statistical analysis of pure frontal against pure temporal seizures, from raw data without reference to results of the cluster analysis. In addition concordance issues are explored, which cannot be done in post-surgical series that are highly preselected on the basis of concordance.

Its main weakness is the relatively small proportion of seizures that were recorded by VET. The absence of ictal EEG recordings is the more important aspect, since the validation data suggest that the clinical data was highly concordant with VET, where both were available. In addition, because of sampling error, a minimum of 2 interictal EEG's per patient would have been desirable. The definition of seizure types is a difficult issue in relation to natural history and treatment effects as described above, but the emphasis on early seizure manifestations adopted, provides the best approach to the problem. Although imaging techniques were not standardised for all patients, there was a sufficiently large number of lesional cases for these to be analysed separately and obtain meaningful results, but a potential criticism is that these were a selected sample that may not be typical. I have argued, however, that identification of a lesion is more a function of the sensitivity of the test used than any property of the epilepsy and this is supported by the 85% of those scanned with MRI, initially thought to have no lesion, in whom one was subsequently found. Ideally, a totally objective method for the delineation of clinical seizure types would have been used, but the complexity of seizure manifestations and the

variation in their significance in seizure localisation did not allow complete reliance on the cluster analysis.

Interpretation of ictal symptomatology

It is important to appreciate the relationships between the nature of seizure symptoms and the recording and measurement of data. At its simplest, the interpretation of ictal motor activity relies on accurate description of seizure progression by a reliable witness or on VET and provided seizures are consistent, data are reliable. By contrast, the analysis of subjective symptoms is complex, their reporting relies on the account of the patient, who by definition is not at his best at the time of the seizure, such that even if there are subjective manifestations at the onset of a seizure, subsequent events may obscure their memory. The duration of seizures with a predominantly subjective component is also difficult to assess and their nocturnal occurrence is impossible to measure without overnight EEG recording. Thus whilst it is possible to say if motor seizures occur during the night but not during the day, a false impression may be obtained of the diurnal variation of purely subjective seizures and this may contribute to an apparent difference between seizure types that has no pathophysiological basis.

Other more subtle symptoms may be masked by motor phenomena which dominate the clinical picture; changes in colour or pupils are unlikely to be detected in a patient with vigorous motor activity, particularly if the seizure is nocturnal, either by an observer or on VET. This may lead to a bias in recording these phenomena in favour of seizures with initial subjective symptoms or a period of absence.

Especially difficult are the inter-related analysis of speech and awareness during a seizure, as these depend on skilled interaction between an observer and the patient in order to distinguish speech disorder from confusional state and language disorder from oral motor dysfunction. Even then a receptive problem during the seizure may result in apparent speech disorder unless motor responses to speech are also tested. Even if a patient is aware during a seizure they may suffer postictal amnesia and not recall events to which they made appropriate responses at the time[7,59,217]. In this study, most seizure histories were obtained from untrained observers and whilst it was generally clear whether patients

preserved or completely lost awareness during the seizure, some subtle alterations were difficult to detect. Some patients, however, gave clear reports of events during seizures when those around them had thought them unaware and these are documented.

Discussion of clinical seizure groups

Group 1: fear behaviour and olfactory/gustatory

Table 19: Summary of results of investigations of group 1:

Number of cases in group	31
Main interictal EEG spikes, No. of cases	Temporal 11, frontal 1
Main ictal EEG associations, No. of cases	Temporal 8
Main imaging associations, No. of cases	Temporal 10, frontal 2

The data from this group suggested 2 subgroups with overlapping clinical features: subgroup 1a, characterised by fear behaviour, sometimes had olfactory or gustatory hallucinations, key features of subgroup 1b and both subgroups had frequent abdominal sensations and autonomic manifestations and rarely underwent secondary generalisation. The clinical inter-relationships were supported by the results of investigation with a strong temporal lobe emphasis of imaging and EEG in both subgroups.

The degree of complexity of fear behaviour has never been elicited by cortical stimulation, without an afterdischarge, although components; fear; vegetative changes and vocalisation have been produced separately[7]. As the majority appear to have situationally appropriate early vocalisations, patients are probably still partially aware at this stage of the seizure, suggesting this is a behavioural response to the seizure, which may therefore, not require spread of seizure discharges to become manifest. Such manifestations have been observed in TLE[7] and in spontaneous seizures recorded by SEEG, originating in the orbitofrontal region, although the latter are difficult to interpret, since there was always rapid spread to other regions[218].

Subgroup 1b was characterised by olfactory and gustatory hallucination, often in association with other sensory modalities, with a variety of clinical seizure progressions.

Interictal and ictal EEG and imaging abnormalities all pointed to the temporal lobe, in both subgroups, although no one investigation reached statistical significance. These findings are consistent with the cortical representation of olfaction and gustation; predominantly in the temporal lobes and many cases had polymodal sensory symptoms - all five modalities being represented - suggestive of the polymodal sensory representations of the parietotemporal region. Similar polymodal seizures are well described from this region[7]. There was only a weak suggestion, however, that the latter group were more likely to be associated with extrahippocampal lesions but numbers were small. One case had an unequivocal frontal lesion associated with gustatory symptoms, a recognised but uncommon association[30], but no frontal lesions were associated with olfactory manifestations, which are probably more specific to the temporal lobes[219].
Group 1 represents one type of non-frontal seizures that occurred with extremely high seizure frequency, and are associated with rapid recovery, contradicting the belief that these characteristics of timing are likely distinctive of FLE.

Group 2: absences

Table 20: Summary of results of investigations of group 2:

Number of cases in group	57
Main interictal EEG spikes, No. of cases	Frontal 12, temporal 7, mixed 15
Main ictal EEG associations, No. of cases	Frontal 3, temporal 2
Main imaging associations, No. of cases	Temporal 16, frontal 6

Absences without specific warning usually progressed to simple or behavioural automatisms rather than to simpler clonic or tonic movements or head turning. The pattern of EEG abnormality varied, with focal spikes seen over both frontal and temporal regions in different cases, consistent with previous descriptions of absence in association with both frontal and temporal lobe epilepsies[7,49,95]. Imaging, however, suggested a predominant association with the temporal lobe abnormalities, although an important minority had lesions in the frontal lobes. Ictal recordings were made in only a few cases

but these too were variable in distribution and where both EEG and imaging abnormalities were present, they generally colocalised.

Absences were associated with a high frequency of oroalimentary automatisms and there was also a close association between the finding of temporal lesions and the occurrence of oroalimentary automatisms across all seizure types. The ratio of temporal to extratemporal lesions in the absence group was the same, however, irrespective of the presence of oroalimentary automatism, suggesting that temporal lobe lesions are associated with absences *per se* and not just with the automatisms that frequently accompanied them.

The anatomical basis of absence is unclear. In primary generalised epilepsy loss of awareness is associated with widespread seizure discharges[66], and a similar pattern of discharge has been noted in some cases with a focal lesion, especially from the anterior and mesial frontal lobes[220], but absence has been said to be typical of temporal rather than extratemporal seizures[43].

Group 3: experiential phenomena

Table 21: Summary of results of investigations of group 3:

Number of cases in group	33
Main interictal EEG spikes, No. of cases	Temporal 7, frontotemporal 5
Main ictal EEG association, No. of cases	Temporal 4, frontal 1
Main imaging association, No. of cases	Temporal 14, mesial frontoparietal 4

Experiential phenomena were closely associated with temporal lobe lesions in common with previous studies[7,221] and this was supported by the ictal EEG data, in which all localisable EEG onsets were temporal and by the interictal data, although spike numbers were small. The tendency of temporal cases, in this group, to become absent before manifesting motor activity in contrast to those with frontal lesions, may again reflect the relative closeness of the frontal lobe lesions to the motor cortices. The prominence of cingulate involvement in the extratemporal cases of this group is consistent with

manifestations associated with cingulate seizures in the past[222] and is of interest since the cingulate cortex is the frontal cortical region phylogenetically most closely related to the hippocampal formation according to Sanides scheme[16]. In monkeys there are direct interconnections between the cingulate gyrus and the hippocampus and extensively overlapping efferents from both cingulate and para-hippocampal gyrus to the perisylvian and prefrontal regions[11].

Group 4: visual manifestations

Table 22: Summary of results of investigations of group 4:

Number of cases in group	16
Main interictal EEG spikes, No. of cases	Frontal 1, temporal 2, mixed 4
Main ictal EEG association, No. of cases	Frontotemporal 2, frontal 1, hemispheric 1
Main imaging association, no. of cases	Temporal 6, frontal 2

Seizures characterised by visual manifestations occurred in temporal and extratemporal lesional cases. Although it was impossible clearly to differentiate these by the nature of the visual manifestation, there was, once again, a suggestion that those cases with frontal lesions tended to evolve more rapidly to motor activity. The control of vision and stability of the visual image depend on close integration of eye movements with visual image and one can postulate that seizures with prominent eye movements may cause visual distortion if the appropriate feedback signals to the receptive and association cortices do not occur. It is important to note, however, that the cases in this group are separate from those in which witnessed eye deviation was associated with a degree of visual distortion, in which the visual manifestation was interpreted as secondary and the nature of the visual manifestations in group 4, apparently unrelated to external stimuli, suggest that the manifestations in the frontal lobe cases in this group were genuine visual hallucinations. The 2 pure frontal lesions with this seizure pattern were small; one restricted to the orbitofrontal cortex and the other in the SMA. Previous studies have demonstrated visual manifestations in seizures arising from the frontal region, including a

localised orbitofrontal abscess, a subfrontal anterior communicating artery aneurysm, and a parasagittal meningioma[30]. The orbitofrontal cortex has prominent connections with the temporal lobe, via the uncinate fasciculus[223], and single unit recordings in the SMA have suggested it is an additional frontal area with polysensory convergence en route to motor output[224,225].

Group 5: auditory hallucination

Table 23: Summary of results of investigations of group 5:

Number of cases in group	2
Main interictal EEG spikes, No. of cases	None, 2
Main ictal EEG association, No. of cases	Temporal 1
Main imaging association, no. of cases	Temporal 1

Both had evidence of temporal origin of the seizure, which is typical of auditory hallucinations[7]. In the case with ictal EEG abnormality, telemetry suggested onset in different temporal lobes on different occasions. Whilst undetected spread of seizures with apparent scalp onset contralateral to the lesion is well recognised in TLE[198], the cause of the epilepsy in this case was previous encephalitis, which may produce bilateral pathology. Both cases, therefore, had probable extrahippocampal involvement, which is typical of seizures with auditory manifestations[7], but in the lesional case, the abnormality was small and sited adjacent to the uncinate gyrus and distant from the superior temporal gyrus, more usually associated with the auditory system.

Group 6: generalised hypotonia

Table 24: Summary of results of investigations of group 6:

Number of cases in group	6
Main interictal EEG spikes, No. of cases	Widespread 4
Main ictal EEG association, No. of cases	Not available
Main imaging association, No. of cases	Frontal 1, temporal 1

It is not possible to localise these cases because of the small numbers involved. There appeared to be an association of hypotonia with other pseudo-generalised seizure types and in this group interictal EEG spikes tended to be widespread, supporting the possibility that this seizure type may reflect widespread epileptogenic abnormalities or rapid seizure spread. This is the pattern seen in other studies where drop attacks are associated with secondary bilateral synchrony on ictal EEG recording, often with primary mesial frontal involvement[35,36,57,61,63,100-102] and drop attacks have been seen with mesial frontal lesions[226] but are less generally associated with temporal lobe abnormalities.

Group 7: early version/posturing

Table 25: Summary of results of investigations of group 7:

Number of cases in group	74
Main interictal EEG spikes, No. of cases	Frontal 19, central 4
Main ictal EEG association, No. of cases	Frontocentral high frequency, 7
Main imaging association, No. of cases	Lateral frontal 18, frontoparietal 4

Seizures characterised by early version or posturing usually progressed to other simple motor phenomena; generalised tonic; clonic or simple automatisms. More complex behavioural automatisms were uncommon and there was no difference in the pattern of investigative abnormalities in this small subgroup. This seizure type is one generally

thought to be associated with the frontal lobes[7,38,41,43,44,47,53,59] and the investigative findings strongly support this; interictal EEG and ictal EEG consistently involving frontal electrodes and rarely temporal electrodes. Only 1 case in group 7 had a pure temporal lesion and there was a strong statistical association with lesions of the lateral premotor region. This seizure pattern has been associated more frequently with the SMA but clear differences between the lateral premotor and SMA regions have been difficult to define[53]. For example Penfield and Jasper[7] described adversion elicited from the SMA, but only with high currents from the lateral cortex, whereas Morris et al[76] suggested SMA seizures only caused adversion when there is secondary generalisation on intracranial EEG. In the current study, version and tonic activity were so closely linked, they were classed together. This reflects the findings of Chauvel et al, on SEEG, that spontaneous seizures restricted to either SMA or lateral premotor cortex are rare, and are likely therefore, to share similar clinical features[227]. In addition, although the SMA and lateral premotor regions have different connectivity and different physiological functions have been postulated for each[77], there is considerable overlap in connectivity and substantial interconnections between them[15].

The delineation of lesions from CT scans, although not MRI scans, can be difficult close to the superior convexity, because of adjacent bone. Since the SMA stretches over the superior convexity to the superolateral frontal lobe, a possible criticism is that its involvement may have been missed in some cases. This problem was anticipated by giving a low positive score to cerebral regions with *possible* involvement in lesions and this, therefore, should not have been a major factor.

There were no consistent differences between subgroups of group 7, in terms of investigative findings, suggesting that the presence of an abdominal or other physical aura does not affect the localisation of the seizure if there are no more specific features prior to the version/posturing. This is consistent with the "temporal lobe auras", previously reported from the anterolaterodorsal region[53] and the association of abdominal sensations with posturing reported by Penfield and Jasper[7], although they attributed this pattern to the SMA. Quesney et al[53] found focal somatosensory auras were typical of SMA seizures, but in the current study, the clinical classification would have placed these

seizures into a different group (No. 8, see below), and they are, therefore, not directly compared here. Where ictal EEG abnormalities were recorded in group 7, they were noteworthy for the predominance of high frequency discharges. This pattern is said[195] to be characteristic of a discharge close to the electrode and again would be more consistent with a laterally placed discharge than one in the mesial SMA, which would usually only manifest as slow waves on scalp EEG and frequently be missed altogether.

Magnetic resonance spectroscopy was performed for a block of SMA in patients with this seizure type and there was no significant change in NAA/choline ratios. It is not yet clear whether these ratios should be expected to change in the absence of visible abnormality on structural imaging, but this result represents another negative in the SMA for this seizure type in this study group.

Although a subgroup had very short seizures with rapid recovery, often with very high frequency, previously described as typical of this seizure type, this was not true of the group as a whole, whereas the relationship to frontal lobe abnormality on investigation was across all durations of seizure. This again suggests that it is the early occurrence of version or posturing that is the frontal lobe feature, irrespective of seizure duration, and therefore, duration alone cannot be used as a guide as to the origin of the seizure[65].

Most patients in this group also experienced daytime and nocturnal seizures, suggesting that the overall diurnal variation of seizures did not differ from other groups although a subgroup may have exclusively nocturnal attacks, as suggested by Tinuper et al[87].

Group 8: focal somatosensory

Table 26: Summary of results of investigations of group 8:

Number of cases in group	26
Main interictal EEG spikes, No. of cases	Temporal 3, frontal 2, central 4,
Main ictal EEG association, No. of cases	Pericentral 1
Main imaging association, No. of cases	Pericentral 7, lateral frontal 4

Focal somatosensory seizures sometimes did not progress at all, but in 16 of 17 cases that did progress, this was directly into simple motor activity, most commonly version or posturing. Tonic postural changes during parietal discharges have been well described[32] and whilst the association of Jacksonian sensory seizures with the parietal cortex is accepted, the situation with non-Jacksonian seizures is less clear-cut[7,53]. The sensory manifestations must be interpreted with caution, since they are often rapidly overtaken by motor phenomena and associated loss of consciousness and one cannot exclude the possibility that a parietal march does occur but that spread of the discharge with associated motor activity and loss of consciousness obscure it, or else that the spread within the parietal cortex is so rapid that a clinical progression is not perceived. The latter is supported by the frequent occurrence of widespread ictal EEG discharges in association with parietal lesions[228].

A number of potential mechanisms for the occurrence of sensory manifestations and tonic posturing may be considered. If the seizure is initiated in the somatosensory cortex, it may be propagated, either to motor cortical regions, to subcortical regions (e.g. basal ganglia) or directly to the periphery, since it has been demonstrated that the parietal region contributes to the corticospinal tracts[229]. An alternative possibility is that the sensory manifestation is the non-specific initial feature of a motor seizure or reflects the patient's initial perception of focal tonic activity in the periphery, in which case the initiation of the seizure may be anterior to the motor strip as suggested in SMA seizures[53]. The evidence from this study is that where lesions are present, they are perirolandic, with strongest association with parietal cortex, although some lesions were large and extended to the premotor area. There was no evidence to support the association of SMA involvement in this seizure type, irrespective of whether the seizure was obviously Jacksonian. One case with no demonstrable lesion had previous surgery to the orbitofrontal region, an area from which somatosensory manifestations have been documented previously[30]. Other cases also had bilateral anterior interictal spikes, but as noted, widespread distribution is common with parietal lesions. Only one case had ictal EEG recording and this too pointed to a central onset.

Group 9: focal paresis

Table 27: Summary of results of investigations of group 9:

Number of cases in group	2
Main interictal EEG association, No. of cases	Not available
Main ictal EEG association, No. of cases	Not available
Main imaging association, No. of cases	Lateral frontal 1, superior frontal convexity 1

Focal paresis is a rare seizure manifestation, seen in 2 cases in this study. Of note, in one case there was a Jacksonian progression of the paresis suggesting involvement of the perirolandic region and the lesion lay slightly anterior to this in the premotor area. The other case, in addition suffered Jacksonian motor and Jacksonian sensory seizures and was also lesional with congenital atrophy over a wide distribution, affecting the superior frontal gyrus on both sides and especially extending onto the lateral convexity contralateral to the side of the paretic and Jacksonian seizures. These findings are consistent with previous studies that attribute paretic seizures to the dorsolateral frontal or to the parietal regions[7,230]. This ictal phenomenon may represent one of the uncommon negative manifestations of epilepsy, and since the cortical control of movement via the pyramidal pathway, involves both activation of agonists and suppression of antagonists via inhibitory effects on spinal interneurons[231], one may speculate that focal paresis selectively involves inhibitory pathways.

Group 10: Complex partial status epilepticus

Table 28: Summary of results of investigations of group 10:

Number of cases in group	6
Main interictal EEG spikes, No. of cases	Frontal 2, frontotemporal 1 (rare spikes)
Main ictal EEG association, No. of cases	Widespread 3, onset not recorded
Main imaging association, No. of cases	Frontal 1, temporal 1

Complex partial status epilepticus was recorded relatively infrequently. Patients who suffer CPSE, usually have infrequent attacks and the onset is difficult to define. For these reasons, witnessed accounts may be unsatisfactory and would have lead to exclusion of these cases. They illustrate, however, the possibility for CPSE to arise from both frontal and temporal lesions. The high frequency of coordinated aggressive behaviour with directed verbal abuse and in one case, physical violence, differs from most reports of a non-specific confusional state. Aggression has been reported in some seizures, especially of amygdala origin[232].

Group 11: isolated jerks

Table 29: Summary of results of investigations of group 11:

Number of cases in group	8
Main interictal EEG spikes, No. of cases	Frontocentral 2
Main ictal EEG association, No. of cases	Generalised 1
Main imaging association, No. of cases	Frontal 1

Isolated jerks were a second seizure type in all but one case and would not always appear to be merely aborted Jacksonian motor seizures, since the two types occurred together in only one patient. In the one case in which a structural lesion was identified, however, this was a dysplastic region involving both precentral and premotor regions, suggesting a similar localisation. Where there were spikes on interictal EEG, these were pericentral; in the one case with purely unilateral arm jerks, the strictly focal contralateral spikes at F3, close to the motor homunculus, supports the involvement of this region. The unilateral jerk may, therefore be an alternative expression of motor cortex ictal activity.
Where myoclonus and more prolonged somatomotor seizures, either clonic or tonic, coexist, SEEG suggests the former is a fragment of the latter[227]. Previous investigators have suggested a similar localisation for epileptic myoclonus[233] and shown stimulus sensitivity to be an important feature of this condition in many cases. In this study, no history of stimulus sensitivity was obtained, but patients were not examined during a

period of epileptic activity and their seizures were not termed myoclonic, since this diagnosis denotes a specific electrophysiologic and electromyographic entity and such measurements were not made.

Group 12: Jacksonian clonic

Table 30: Summary of results of investigations of group 12:

Number of cases in group	14
Main interictal EEG spikes, No. of cases	Frontocentral 2
Main ictal EEG association, No. of cases	Frontocentral 1
Main imaging association, No. of cases	Frontal 4, Parietal 1, Pericentral 1

Focal Jacksonian clonic seizures usually evolved to full unilateral clonic seizures, before generalising and were often associated with turning of the head. This seizure type is classically associated with the prerolandic cortex[227] and this was reconfirmed in this study. Only 2 cases did not appear to involve this region and both involved immediately adjacent cortex; the perirolandic cortex is increasingly considered sensorimotor in function with both prerolandic and postrolandic components contributing to motor and sensory function[7]. Only one third of pyramidal tract neurons originate from area 4, the remainder coming from parietal and premotor cortex[229]. This may partly explain the close association of this seizure type with lesions extending across these three areas. The absence of more complex behavioural automatisms in this subgroup may be because the initiation of the seizure is downstream of the regions involved in motor planning, at a level more closely involved with activation of specific muscle groups. The frequency of postictal Todd's paresis illustrates the intimate relationship between the perirolandic region and muscle activity.

Group 13: Seizures with generalised motor activity

Table 31: Summary of results of investigations of group 13:

Number of cases in group	47
Main interictal EEG spikes, No. of cases	Frontal 11, temporal 3, central 2
Main ictal EEG association, No. of cases	Frontal 7, frontotemporal 2
Main imaging association, No. of cases	Frontal 9, temporal 5

Generalised tonic and tonic-clonic seizures were not associated with particular lesion sites. This differs from some studies which suggested that this is more characteristic of frontal, especially mesial frontal lesions[189,190]. A possible explanation of the difference is that if there was significant asymmetry of the initial tonic posture than it was classed as version/posturing; 16 cases classed as tonic posturing in group 7 went on to generalised hypertonia and these were characteristically frontal. There was a tendency for generalised motor seizures to be associated with widespread interictal EEG abnormalities, perhaps reflecting either rapid spread of discharges or a large or multifocal epileptogenic region, although in those with identified lesions, the lesions were no larger than in cases with clinically localised seizure onset.

Of note was the finding that of 3 cases with identified lesions and seizures characterised by bilateral clonic activity with preserved awareness, 2 were frontal parasagittal meningiomas, the only such lesions in the study. The mechanism for this may the simultaneous activation of bilateral motor centres without spread to other regions, although, as higher motor centres have a degree of bilateral representation, bilateral discharges may not be a requirement for the generation of bilateral motor activity[59].

Group 14: motor agitation

Table 32: Summary of results of investigations of group 14:

Number of cases in group	30
Main interictal EEG spikes, No. of cases	Frontal 4, central 2
Main ictal EEG association, No. of cases	Frontal 7, frontotemporal 2
Main imaging association, No. of cases	Orbitofrontal, frontopolar 7

Of all the groups, this one had the timing characteristics attributed by many authors to frontal lobe epilepsy; high seizure frequency, a high incidence of nocturnal attacks, and a tendency to short duration and rapid recovery[222]. Imaging positive cases showed a strong association with orbitofrontal and frontopolar regions, consistent with previous studies[55,61,222]. Most of the ictal EEG abnormalities were recorded in scan negative cases, and these too were consistent with a frontal abnormality in all but one case. Interictal EEG was often normal, but where localised spikes were identified, they were mostly frontal, again supporting this localisation. This group has, therefore, strong localising evidence to the frontal lobes in the majority of cases and most likely to the frontopolar/orbitofrontal region.

An aura of olfaction/gustation was recognised in some cases and has been described before from the orbitofrontal region[218]. Despite these initial sensations, the cluster analysis separated these cases from those in group 1 and allocated them to the group with general motor agitation. The different investigative findings of these two groups highlight the importance of considering the seizure sequence and not just the first symptom and also illustrate the power of cluster analysis as a method for analysing the whole seizure and making divisions that may not be intuitively obvious. Two cases with gustatory symptoms had documented frontal lobe lesions; one associated with a frontal lobe ictal EEG abnormality. The case with vague olfactory symptoms had bitemporal interictal EEG spikes but ictal EEG was masked by artefact from the outset. It is recognised that lesions of the orbitofrontal region can impair olfactory and gustatory discrimination and it

is not, therefore necessary to invoke seizure spread as a mechanism underlying this manifestation. Alternatively the prominent uncinate fasciculus may mediate extremely rapid spread of epileptic discharges in some cases, from this area to the temporal lobe, which is more characteristically associated with olfaction and gustation[7,219] and this transmission has been documented in both directions by SEEG in spontaneous seizures[218].

The associated characteristics have been described in relation to frontopolar seizures; bizarre vocalisation and autonomic changes[55,61,218,222]. Motor agitation can be produced by stimulation of this region of cortex in animals[234] and its importance in autonomic control in various systems, including cardiovascular, respiratory, urinary and thermoregulatory is supported by anatomical and physiological studies[235]. Abdominal aura, as seen in this study has also been claimed to be a frequent accompaniment of seizures of this region[218].

Summary of major associations of clinical seizure types

There were 4 patterns localisable outside the temporal lobes. Jacksonian motor seizures were associated with perirolandic lesions and, where EEG abnormalities were present, these were consistent. Somatosensory seizures were associated with lesions more posterior in the perirolandic/parietal area. Seizures characterised by version/posturing were associated with lateral premotor lesions (18 of 29 lesional cases) and with frontal EEG abnormalities. The pattern of ictal EEG abnormalities in this group was of fast activity, supporting the involvement of superficial cortex and at variance with other studies, which suggest a primary role for the mesial SMA in this type. Seizures with frenetic motor agitation were strongly associated with lesions of the orbitofrontal (8 of 13 lesional cases) and frontopolar cortices and with consistent frontal EEG abnormalities. This seizure type was the only one to be characterised by brief, predominantly nocturnal seizures, with rapid recovery, said to be typical of FLE in other studies. Other subjective seizures, including olfactory, fear, visual, experiential and auditory were more associated with temporal lobe abnormalities on investigation, although no one group achieved significance at a level of 0.001. Absences were significantly associated with temporal lobe

lesions but with various abnormalities on interictal and ictal EEG. In all groups, except somatosensory and focal motor seizures, there were substantial minorities that did not conform to the statistically significant associations on neuroimaging and EEG associations of the majority of cases in that group and yet were clinically indistinguishable. *Though these relationships are statistically significant, they are, therefore not absolute and the predictive value of the seizure pattern is limited for many seizure types.*

Epilepsy with startle-provoked seizures

This syndrome is characterised by seizures precipitated by stimuli of various modalities, most commonly noise, but only in a specific context. The same stimulus that triggers a seizure if unexpected, will have no effect if the patient is warned. ESPS has been reported intermittently over the last 40 years, especially by Gastaut, Bancaud and their groups[227,236,237,238,239,240]. Patients described previously have usually suffered severe epilepsy, associated with moderate to severe handicaps. Although some of the current series were similarly affected (table 39), others were clinically normal, with normal intelligence. This latter group affords the opportunity of trying to localise the region responsible for startle sensitivity without the confounding factors of widespread damage often associated with fixed neurological deficit.

Epilepsy with startle provoked seizures appears to be commoner than suggested by the relative scarcity of previous reports and this is probably because it is a transient phenomenon in the individual's seizure history. Although typically starting in childhood it may not occur until adult life, and may still be associated with MRI abnormality suggesting congenital aetiology, even in the absence of fixed clinical deficit. Seizures are most effectively triggered by noise and other modalities appear to be less consistent, but this may merely reflect the relative potency of noise to cause startle in normal individuals. The seizure type was consistent with that in other series; most commonly of tonic posturing, although atonic seizures have been reported especially in association with Trisomy 21 and this may represent a special case[241]. Scalp EEG showed various abnormalities interictally and a normal EEG is well recognised. Even during the seizure, all that may be seen is a vertex spike, which is relatively non-specific and followed by

muscle artefact because of the prominent motor component to the seizure. Intracranial EEG is often required to localise the discharge but has only been reported in one large series[223]. This pointed to discharges originating in either the mesial frontal lobe alone or both mesial and lateral frontal lobes. Our MR cases, in 4 of whom there were no neurological signs and who, therefore, represent a selected subgroup, suggested that the brunt of structural pathology was lateral cortical.

One possibility that may account for this difference is that these seizures may arise from more than one region, or as has been suggested by Chauvel et al[227] from SEEG, that seizures rarely remain restricted to either lateral or mesial premotor regions, producing overlap in their manifestations.

Teleologically, one may ask what mechanisms may underlie ESPS. It appears to represent a pathological response to sensory stimuli in various modalities, but only if presented in a certain context, related to some feature of the patient's attentional state. The lateral premotor cortex, rather than the SMA is thought to be especially involved in the sensory guidance of movement, a function perhaps related to the sensorimotor startle response[242].

In contrast to stimulus-sensitive myoclonus, ordinary sensory evoked potentials have not shown any consistent abnormality[243], although performed in patients with fixed deficits and are, therefore, difficult to interpret. Late component evoked potentials would be of especial interest in view of the importance of attentional factors in the response. There is, therefore, no current measure of startle sensitivity in these patients except the generation of seizures. Startle sensitivity may be transient in a patient's epilepsy history and hence partially dissociable from the continuing seizure diathesis.

Polymodal sensory inputs are to be found in the perisylvian region; the prearcuate cortex in the lateral frontal region[78] and have also recently been described in the SMA. Limbic connections, which may be the substrate of the attentional component, are important in all these regions. Mountacastle's group described perisylvian neurons in the monkey that fired in response to sensory stimuli only if certain attentional conditions were met[244]. It may be that the junction of polymodal sensory cortex and limbic inputs provides the startle sensitivity that feeds forwards to a pathological motor response at a remote site.

This abnormality would appear to be a combination of "hard" and "soft" wiring, since the underlying defect is usually congenital and yet the effect transient in the patient's history. The clinical, electrophysiological and imaging features support a cortical origin to this phenomenon in contrast to idiopathic startle disease, where no definite cortical abnormalities have been identified and elctrophysiological tests point to an exacerbation of the physiological startle response, mediated from brainstem level[245,246]. The major difference between the syndromes are summarised below.

Table 33 : Features differentiating hyperekplexia from ESPS

Feature	ESPS	Hyperekplexia
Motor development	Normal or Spasticity	Infantile hypertonia (non-spastic)
Mental development	Normal or impaired	Normal
Family history	Normal	May be positive
Automatic obedience	Never	Sometimes
Seizure stimuli	Often independent of startle	Startle only
Seizure pattern	Usually focal tonic	Exaggerated startle
Interictal EEG	Variable	Normal
Ictal extracranial EEG	Occasional focal abnormality	Vertex spike
Startle latencies	Non-brainstem	Brainstem origin
Imaging	Usually cortical abnormality	May have brainstem abnormality

Association of seizure types

In this study there were 13 cases with an association of absences without specific warning and generalised motor seizures - pseudo generalised epilepsy. Possibly these seizures may have appeared generalised because the patient could not recall early subjective focal events after the obtundation of a generalised motor seizure or the amnesic effects of an absence seizure. It is interesting, however, that this was the only significant association of

seizure types to emerge in this study and suggests that absences and generalised motor seizures are linked, not just in the generalised epilepsies, which may give a clue to the pathophysiology of both primary and secondarily generalised epilepsies. There were no obvious shared investigative features in this group of 13 patients; in particular interictal EEG's, where positive, were not generalised, although bifrontal in 4. Unfortunately ictal EEG was not available in these cases. The associations of these generalised seizure types with each other poses questions regarding the nature of secondary generalisation; the relationships of secondary generalised seizures to primary generalised epilepsy syndromes which share similar associations of seizure types and the mechanisms underlying generalised epileptic manifestations.

The nature of secondary generalised seizures - speculations

Seizures with generalised features and no focal clues, (including absences, tonic, tonic-clonic and atonic seizures) were the only seizure types in only 14 (8%) of the 168 patients selected on criteria other than clinical seizure pattern. In the substantial majority of patients, therefore, any investigative evidence of partial seizure origin was likely to be associated with focal features in at least one of their seizure types. This is a higher proportion than in most studies, partly related to the selection criteria but suggests a high degree of accuracy of clinical assessment, probably related to the detailed prospective collection of clinical data.

The concept of the generalised seizure in relation to localised pathology needs careful evaluation, since it relates to principles derived from consideration of primary generalised epilepsies. These are electroclinical entities with a constitutional element, and in the case of juvenile myoclonic epilepsy a possible specific location of the genetic abnormality. Other epilepsies are characterised as generalised for example Lennox-Gastaut syndrome in which the seizures appear generalised, the EEG appears generalised and the pathology generalised or multifocal, for instance tuberose sclerosis. When applied to these syndromes the term "generalised" means a generalised electrographic syndrome with symmetrical motor accompaniment or else absence. The concept of secondary

generalisation from a partial seizure can be understood in these terms; the seizure evolves from a partial pattern to the electrographic or clinical features of a generalised epilepsy. If that evolution is sufficiently rapid, then the seizure may be interpreted as generalised from the outset and its regional onset not appreciated, unless there is postictal focal neurological deficit e.g. dysphasia or paresis. The major clinical features of generalised seizures are symmetrical motor activity either positive; tonic, clonic or myoclonic, or negative; loss of tone or movement, and loss of awareness. The resulting forms of seizures in adults are generalised tonic, generalised tonic-clonic, myoclonic, hypotonic and absence. That these seizure types are associated in patients with evidence of partial onset, raises questions regarding the nature of the association and whether there is any anatomically localisable component in primary generalised epilepsies that share the same combinations of seizure types.

The substrate for generalised motor seizures is present in unilateral form in partial seizures; unilateral clonic and unilateral tonic seizures and paretic seizures for hypotonic attacks. If progression is slow, the seizure appears to start as a focal motor attack and may progress to a generalised attack. Ictal EEG studies by other groups have suggested that rapid generalisation is due to rapid propagation of discharges between hemispheres[187-190] and that these may present as pseudo generalised discharges as is often the picture seen with mesial hemisphere lesions. In this study, there were 6 cases with clear preservation of awareness associated with bilateral clonic seizures and those that were lesional, were all prefrontal with 2 parasagittal meningiomas. It is therefore, possible to dissociate bilateral clonic activity from loss of awareness in the presence of a lesion situated in an ideal position to cause bilateral motor activity, without generalised disturbance. Direct brain recordings from some patients with generalised convulsions have suggested origin in the prefrontal regions[247] consistent with these findings.

In patients with primary generalised absence there is a generalised discharge, but there is evidence for variable functional deficit, both between patients and in one individual at different stages of the spike-wave discharge. Evoked potential recordings show clear responses suggesting some primary sensory cortex function[248]; careful neuropsychological demonstrates very variable levels of amnesia after "absence"

attacks[249], suggesting some retention of integrative function and the maintenance of postural tone during the absence is also against a universal cerebral dysfunction, or even of temporary generalised disconnection and in favour of focal elements. The intuitively appealing idea that loss of awareness is a manifestation of a widespread cerebral dysfunction is, however, not supported by reports from stereotaxic EEG that it may occur in association with discharges restricted to a single hippocampus[72] or to the frontal pole[59] and that the onset of generalised discharge does not coincide with the onset of altered awareness in petit mal[250]. Perhaps it is better to consider absence seizures in terms of what they are not. Foremost there is an absence of motor activity and of 6 frontal lesional cases with absences in this study, none involved the primary motor cortex, although distributions were otherwise variable. Moreover, by definition, there are no focal sensory features, or if sensory manifestations occur, they are masked by subsequent loss of awareness and amnesia. Possibilities for the origin of these seizure types are, therefore, remote from primary motor and sensory regions; association, limbic and prefrontal are prime candidates. Absence like episodes can be produced by stimulation of temporal or prefrontal cerebral regions, but it is the latter that are associated with generalised discharges and these may be indistinguishable from those of classical petit mal. Unilateral carotid amytal blocks discharges bilaterally[251] in PGE suggesting that synchronisation may be mediated partly at cortical level. Moreover, spontaneous petit mal is characterised by discharges that phase-reverse at the mesial frontal electrodes and in some cases of petit mal histopathological examination has yielded microdysplasia of the frontal cortex[252].

There may, therefore, be focal elements to primary generalised seizures, identical electroclinical manifestations may be elicited from focal cortical lesions. In a generalised convulsive seizure the primary motor cortex is activated, dominating the clinical picture and preventing the expression of more complex motor seizure manifestations originating upstream. In selected cases this may occur in the absence of loss of awareness, and equally absences may occur from prefrontal seizures without motor activity, suggesting an anatomical double dissociation of these "generalised" manifestations and complex relationships between the clinical manifestations of partial and generalised seizures.

Analysis of localisation of individual symptoms

The analysis of individual symptoms showed that the major symptoms defining the seizure types in the clinical classification had most localising significance, supporting the clinical classification. Since these were not always the first symptoms of the seizure, and there may have been earlier less specific symptoms e.g. cephalic sensations, this highlights the importance of looking at the whole seizure and not merely analysing the first symptom and supports the use of cluster analysis, and flowcharts, which were designed to compare whole seizures albeit with emphasis on earlier symptoms.

Sensory symptoms

Apart from focal somatosensory symptoms, associated with the parietal and pericentral cortices, most subjective symptoms were associated with the temporal lobe. These seizures may be very difficult to classify, not least because of the frequent occurrence of more than one symptom of localising significance in the same seizure. As they all appear to be associated with the temporal lobes, however, this fact may have masked any errors in classification. A recent study of epileptic auras had very similar results[209], despite a slightly different classification of experiential symptoms, supporting the idea that further resolution, although of undoubted conceptual interest, is of limited importance for surgical localisation. The main differences in results from that study, were that they suggested a specificity for abdominal and general physical sensations. In the current study these were found not to have localising value, supporting the categorisation of seizure types on the basis of other features irrespective of the presence of abdominal sensations. Subgroups with these sensations were considered, however, and in none did these manifestations appear to confer different investigational characteristics on the subgroup, although numbers were small. For example fear behaviour, with a high incidence of abdominal aura was associated with temporal lobe lesions, whereas motor agitation, also with a high incidence of abdominal aura, was associated with frontal lobe abnormalities. Even analysing specific rising epigastric sensations separate from other abdominal manifestations did not yield any difference. This is consistent with the wide variety of sites from which such sensations have been documented[7,53]. Although Palmini et al

found an association with general physical sensations and frontal lobe epilepsy, this was only in the retrospective group and not in the prospective group which is more comparable to the current study[209].

Apart from the group of abdominal and general body sensations, the aura was highly specific in its localising value. This is consistent with previous findings supporting the high value placed on the presence of certain auras in seizure localisation[209,253]. At the time of the aura, the patient already knows that he is about to have a seizure and yet over 50% of auras are not detectable on scalp EEG[253]. Even intracranial EEG frequently misses the aura[253], presumably through sampling error of the small volume of tissue that can be analysed by intracranial electrode placement. This suggests that the aura represents a time at the onset of the seizure, when the seizure can be detected by the patient but is so localised that it cannot be detected at the scalp and does not spread far enough to be detected by nearby intracranial electrodes. Moreover, in order to be able to report the aura the patient has recall for early events in the seizure and by definition is conscious. This contrasts with motor symptoms which are objective manifestations during which the patient does not have to be aware, and therefore, are inherently less reliable, as there is necessarily more doubt about the very first symptoms of the seizure. By comparing seizures from frontal lobes with a temporal lobe control group, this study points out not only that certain specific auras are associated with the temporal lobes, but that their absence is likely to point to the frontal lobes in this context. This suggests that the absence of a specific temporal lobe aura often implies origin outside the temporal lobes and is not just due to failure of the patient to recall an aura because of the effects of subsequent events on recall and helps in differentiating temporal from extratemporal seizures, when there are no other specific features of TLE.

Motor symptoms

Even if not the very first symptom, motor symptoms had the most powerful localising significance, only when occurring early in the seizure, especially when falling into highly characteristic patterns of motor activity. This is consistent with previous findings in relation to localisation of head turning, where they were found only to represent frontal lobe discharges if at seizure onset[41]. The most specific motor pattern is generally recognised to be Jacksonian clonic, and the paracentral lobule was involved in all lesional cases in this study. This is probably because seizure activity in this region has direct access to the peripheral musculature, without having to go through other cortical or subcortical regions and there is a very obvious topography of this relationship which is reflected in clinical seizure evolution if there is slow seizure spread[7]. When analysing seizures with non-Jacksonian motor onset, other characteristic patterns of motor activation must be sought and one is forced to ask from how far back along the sensorimotor pathways in the cerebral cortex they originate and the route via which this activity is manifested. Frenetic motor activity and version/posturing seem to be relatively specific to different regions of the frontal lobes but their route of expression is unclear. SPECT has suggested early activation of the contralateral basal ganglia in TLE associated with head turning and intracranial EEG has shown conflicting results; sometimes preferential spread of temporal discharges to the frontal lobes[28,254,255], prior to contralateral temporal involvement and sometimes vice-versa. Wieser[256] applied cluster analysis and other multivariate techniques to the spread of seizure discharges in psychomotor seizures and also found varying patterns of spread.

Early lesion studies showed that the primary motor cortex was essential for the expression of motor activity induced by SMA stimulation[229], suggesting it is an important final common pathway, although whether this is via a cortico-cortical connection or basal ganglia loop is not certain.

The nature of lesional analysis and pathophysiological correlates

It is important to note that the associations of different seizure manifestations with different structural lesions was a statistical rather than an absolute one in most cases. This has implications both for pre-surgical assessment and understanding of the generation of these manifestations. Only somatosensory and Jacksonian motor manifestations were almost invariably associated with particular cortical regions and this may be because these regions have functions restricted to one system with an intimate relation to peripheral effector organs. The next most highly correlated manifestation was frenetic motor activity associated with the frontopolar/orbitofrontal regions. This seizure pattern was seen in half of all cases with such lesions and equally 8 of 13 lesional cases in which this was a seizure pattern included this region. Although statistically a highly significant association, there was therefore, a large proportion of cases in which lesions in the appropriate areas were not associated with this seizure pattern and in which distant lesions produced this pattern, that need to be explained. There are several considerations. First, the statistical method was used to overcome the problem of large lesions which form the majority of epileptogenic lesions within the frontal lobes. In some cases the epilepsy may have been generated at a distant site in a large lesion, even though orbitofrontal and frontopolar cortices were involved. Second, some lesions may be a marker of more widespread abnormalities and this may be particularly true of 1) congenital dysplastic lesions whose scan appearance may be the macroscopic representation of diffuse abnormalities of connectivity e.g. tubers in tuberose sclerosis; 2) post-traumatic lesions, where contre-coup and shearing injuries may be more widespread than is apparent from the scan; 3) space occupying lesions which may cause distant epileptogenesis via pressure effects. Third is variable functional anatomy; speech localisation may cross hemispheres after cerebral damage early in life and it is unknown to what extent other functions may redistribute after the early insults that are responsible for much epilepsy and how this may be reflected in altered pathophysiological expression during seizures. In one recent case, redistribution of somatosensory evoked potentials and motor stimulation sites was demonstrated with intracranial electrodes[257]. Fourth is the functional heterogeneity of association cortex, which means that different seizure patterns

may be generated from the same regions according to which systems are involved. This can be demonstrated over very small distances by variations in connectivity and single cell recording properties, such that even very small lesions may involve subregions with possibly very different functions. Contrast this with the primary sensory and motor cortices, which appear to be more strictly dedicated to an individual function, with a specific relationship to peripheral organs and whose seizures are clinically the most easily localised. (Our better understanding of the functions of the paracentral lobule relates directly to these considerations.) Fifth, a related phenomenon, that of parallel and distributed processing, in which different brain regions subserve similar functions or different aspects of the same function, such that seizure activity in either may produce a similar manifestation, for example the widely separated regions involved in the control of eye movements[29]. Sixth, the possible effects of interference with corollary discharge mechanisms: corollary discharges were hypothesised to explain the differential effects on sensation of passive and active movements. For example, if the eyes are abducted actively the world appears to stay still, whereas if they are abducted passively, the world appears to move. A functional disconnection of corollary discharge pathways during the seizure could lead to ictal sensations, even though sensory cortex is not directly involved in the discharge.

All these potential mechanisms may be responsible for the anatomical diversity of the generation of symptoms without even invoking the spread of seizure discharges which undoubtedly occurs very early in some seizures. This spread may take only milliseconds[42,254], yet the clinical assessment of seizures is over seconds to minutes. The ultimate resolution of the clinical method, therefore, can never match the potential speed of seizure spread and its aim must be restricted, therefore to the identification of typical seizure syndromes, and the acceptance that many seizures may remain unlocalisable by this technique.

For example, in a significant minority of cases, sensory stimuli were associated with frontal lobe lesions. If the origin of the epilepsy is considered to be genuinely frontal then a number of explanations can be hypothesised. First, the discharge is silent until it has spread to posterior sensory cortex, via frontofugal pathways that are well

described[15,258,259]; second that the activity of frontal neurons with polymodal sensory input is registered as a sensory manifestation and third the possibility of corollary discharge effects, as described above.

Flow of seizure manifestations

The interactions of different seizure manifestations on our ability to measure what is really going on during the seizure complicates interpretation of the seizure but the flow charts allow some tentative suggestions regarding trends that appeared. All seizure types relatively frequently evolved into simple clonic or tonic motor activity and there was divergence of cases at a relatively early stage of nearly all seizure types. Those starting with visual, experiential, olfactory/gustatory manifestations usually developed an absence first, suggesting that the path to such motor activity is not direct. This is supported by the finding that those in group 2, characterised by absence without focal onset, had the lowest incidence of evolving to tonic or clonic activity (22%) at any stage of the seizure. Seizures that did not start with or develop simpler forms of motor activity, more frequently evolved into complex behavioural automatisms and consequently these automatisms were associated with temporal lobe seizures. In the somatosensory group, nearly all cases that progressed, developed tonic or clonic motor activity and in contrast to other subjective onsets, this was without intervening absence in all cases. In this study these seizures appeared to be mostly parietal in onset and this evolution may be because of the intimate relationship between somatosensory and somatomotor cortex. In the monkey, the somatosensory cortex appears to be the only sensory modality to project directly to the premotor region posterior to the arcuate sulcus, other modalities projecting anteriorly to the prearcuate, prefrontal region[15]. Similarly hippocampal efferents, via the fornix, do not project near to motor cortices. An alternative explanation in other studies[7,209], is that the frontal cortex itself may give rise to the somatosensory aura before motor activity ensues, or that the sensation is the first appreciation of the onset of motor activity[53] but this is not supported by the current data.

The only case that developed behavioural automatisms in the somatosensory group did not have intervening simpler motor activity, in contrast to the 19 in which the converse

was true. The nature of behavioural automatisms is uncertain; hypotheses include the involuntary activation of a learned behaviour motor plan and the response of a confused individual to the seizure[217]. Against the former is that such automatisms have never been elicited by direct electrical stimulation of the brain with implanted electrodes, without an afterdischarge. Fear behaviour may be an example of the latter mechanism, but in the absence of a highly specific stimulus such as fear, it is difficult to see why individuals should perform complex, stereotyped activities such as bed-making in so a reproducible fashion after each seizure. In the majority of patients with automatisms there is complete loss of awareness during the automatisms, although in a minority of patients, including in this study, there is vague recall of the automatism, suggesting that loss of awareness is usual, but not an absolute requisite.

There appears to be a paradox in that complex motor activity and behavioural automatisms are more associated with temporal lobe than with frontal lobe which is said to be involved in motor planning[13]. One possibility is that these manifestations are due to activation of subcortical motor centres and early hypermetabolism of the basal ganglia has been documented in TLE associated with head turning by SPECT in humans and in other epilepsies by early depth recordings[24]. It is unlikely, however, that these complex behaviours occur entirely without cortical involvement and some PET and intracranial EEG studies[254,255] suggest direct intercortical spread, which would be consistent with the patterns of seizure evolution discussed above, with seizure manifestations feeding forward from sensory to motor along recognised intercortical pathways.

A possible mechanism for automatisms is that they are a release phenomenon of the frontal lobes and consistent with this is the finding that automatisms are associated with temporal rather than frontal discharges[46,48]. The current data suggest an inverse relationship between behavioural automatisms and simpler motor activity. If a seizure discharge involves the primary motor cortex at an early stage, then it is unlikely that the regions upstream will be able to coordinate the musculature into a complex behavioural automatisms and seizures with simpler motor activity rarely exhibited automatisms. If the seizure activity starts in the temporal lobes and rapidly spreads to the motor cortex, then a motor seizure will ensue, for the same reasons. Whereas if the seizure is restricted to the

temporal lobes, producing an absence episode and the frontal lobes remain uninvolved in direct seizure activity, complex behavioural automatisms may be expressed by a release phenomenon.

Although flow from sensory to motor manifestations was seen frequently, the converse was not the case. In some patients there was pain associated with tonic posturing or visual distortion associated with ictal eye movements, which were probably direct effects of peripheral seizure activity rather than intracranial spread of discharges. There are several potential explanations for the absence of flow of manifestations in this direction. First, is that in the presence of ictal involuntary motor activity, a conscious patient may not appreciate any associated sensations, unless they are very marked e.g. pain or involve another system e.g. vision. Second, the involvement of both sensory and motor cortices reflects a wide area of cortical involvement and is likely to be associated with loss of awareness; if the sensory manifestation is not first, it may not be appreciated. Third the main fibre pathways are from sensory to motor and this may reflect the dominant route of spread of discharges, as has been suggested by EEG and PET studies[260,261]. These hypotheses cannot be tested using purely clinical methods, in view of the other confounding possibilities and as others have suggested propagation via unusual pathways[262] in some seizures, this further complicates the analysis.

Absence is denoted by loss of awareness, associated with paucity, if not arrest, of motor activity. By definition, therefore, it is unlikely to occur in seizures of those areas which are intimately associated with motor activity and this is supported by the strong association in this study with temporal lobe auras and abnormalities on investigation. Absence following from motor activity was not seen in this study.

Special imaging

The pilot study of magnetic resonance spectroscopy (MRS) failed to show any significant abnormality of the SMA. This investigation was, however, conducted on the basis of the clinical impression of SMA seizure type, prior to cluster analysis, and subsequent analysis

of the seizure type allocated 7 of the 9 patients, who underwent MRS, to group 7 and 2 to group 14, suggesting they may not have been entirely homogeneous. This could mask a genuine association but the patients allocated to group 14 did not have the highest NAA:Cho/Cr ratios of the patients, suggesting this is not a major factor. It remains unclear whether an abnormality in the ratio is to be expected in the absence of a neuron-depleting lesion visible on structural imaging, so the negative result cannot be interpreted as signifying no abnormality in the SMA. High resolution structural imaging, however, illustrated dysplastic appearances in the lateral frontal cortex of 6 of 7 patients with group 7 seizures. Repeat MRS with a voxel over this region would be of interest to answer this question.

High resolution magnetic resonance imaging had a very high (85%) detection rate of abnormality in selected, previously scan-negative patients in this study. Both unsuspected foreign tissue lesions and appearances of NMD were identified, with anatomical distribution and seizure correlates that appeared consistent with more gross lesions, identified with other investigations.

The specific association of the appearance of congenital abnormalities in the lateral frontal area with seizures of tonic posturing is of interest. Lesions are rarely discovered underlying these seizures and EEG usually points to the SMA[7,53,227]. Also of note is the high incidence of bilateral scan abnormalities, even with seizures that appear clinically lateralised, with consistent unilateral head turning and consistently unilateral EEG abnormalities. This finding may explain the especially poor success rate of these cases at surgery[175] and is consistent with the concept of secondary seizure generators, masked by the primary generator preoperatively, but expressing a seizure diathesis postoperatively[10].

Inter-relationships of investigations

Patients were selected on the basis of abnormalities on an individual investigation, without reference to other investigations. This provides an opportunity to assess concordance between investigations, which is not possible from post-surgical series since concordance is a criterion for selection for surgery. The relationships of the different modalities of

investigation to each other and to the seizure pattern showed a high degree of concordance, in view of the relatively unselected nature of this population.

Laterality

The laterality of most clinical manifestations is impossible to establish. The most reliable are focal clonic and focal sensory and even the primary motor cortex representation of the upper face is bilateral. In no case in this series was the somatosensory manifestation of a seizure ipsilateral to a unilateral structural lesion and in only one of 12 cases with early clonic activity was this ipsilateral to the lesion, supporting the reliability of these manifestations. Similarly, in all cases early clonic activity, with lateralised ictal EEG abnormality, this colateralised with the clinical pattern. In all 17 patients with focal sensory and focal clonic symptoms, either in the same seizure or in different seizures, the lateralisation was the same. By contrast, clonic activity later in the seizure could occur on either side in relation to investigational abnormality. Where there was discrepancy between ictal or interictal EEG and side of focal jerking this was usually a bilateral EEG rather than a strictly discordant EEG.

Estimates of the proportion of ictal head turning that is contralateral to the epileptic process, vary from 33-100%[48,60,73-75]. This study was in the middle of that range and perhaps the relative frequency of bilateral pathology, especially NMD's in this study, explains the very variable results observed by others, before high resolution MRI facilitated detection of subtle bilateral pathologies. The relationship between head turning and EEG is thus complex, since both may relatively frequently be bilateral and the relationship cannot be considered entirely predictable from this data, although of 33 cases with unilateral interictal spikes and unilateral head version, turning was contralateral in 27 (82%). In the smaller number of lateralised ictal onsets, turning was ipsilateral nearly as often as contralateral, irrespective of whether head turning was early or late in the course of the seizure.

Localisation and discordance of investigations

Interictal EEG abnormality tended to be more widespread than that seen on imaging. Although discordant patterns were relatively common, they were often in patients with very few interictal spikes, which would be considered of low localising significance. The overall figure of 21% discordance is similar to that seen in the accompanying population-based study from the NGPSE, and may reflect the broad selection criteria of these cases. Nearly half of discordant cases had spikes precisely contralateral to the lesion, a well recognised feature especially of mesial temporal sclerosis[92,263].

In several cases with no interictal spikes, ictal EEG showed a specific abnormality. This is unlikely to be due to sampling error on the interictal EEG, since in these cases there were always long periods of interictal EEG available. There was no suggestion that ictal EEG recording was of less value in frontal lobe than temporal cases as has been suggested in some studies[10,92,102], but this may be partly attributable to telemetry results being a selection criterion for some cases. The low rate of major discordance between the location of identifiable ictal onset and structural imaging suggests that electrographic onset is generally in the region of the lesion and supports the value of the ictal EEG, in those cases in which a localised abnormality is identified, irrespective of whether frontal or temporal. Where discordance did occur, with all 3 investigations abnormal, there was no obvious pattern of which investigation was "odd one out" and no clear clue as to which fitted best with the clinical seizure pattern, but numbers were small.

The frequent association of "generalised" seizure types with the discordant cases, perhaps suggests a wide epileptogenic region with different investigations highlighting different components, leading to apparent discordance of investigations. Alternatively, these lesions may be associated with rapid propagation of ictal and interictal activity to distant sites and a similar rapid propagation leading to early generalisation of the seizure. Either explanation would support the general impression that such cases would have a poor post-surgical prognosis.

Relationship of results to the ILAE classification of frontal lobe epilepsies

The results of this study illustrate that classical syndromes can be defined from certain regions of the frontal lobes. The ILAE[1] classification describes frontal lobe epilepsies as comprising generally short seizures, with little or no postictal confusion. The data from this study supports subgroups of seizures that are short in both temporal and frontal groups and that within any one clinical type, the short seizures have the same investigative associations as the longer seizures. Criteria of duration cannot, therefore, be considered useful in localisation and emphasis must be placed on the qualitative, symptomatic content of the seizure. The close association of the primary motor cortex with Jacksonian seizures was reaffirmed in this study. Two other characteristic patterns emerged. The close association of seizures characterised by version and posturing with lesions of the lateral premotor region supports the definition of the dorsolateral group of the ILAE. Conversely, no specific features of SMA seizures could be identified with statistical significance, although it too was involved in a proportion of focal tonic seizures. Orbitofrontal seizures were strongly associated with frenetic motor activity and olfactory/gustatory hallucination were seen in some cases, consistent with the ILAE description of seizures from this area. No separate features of frontopolar involvement could be identified. No typical features of cingulate involvement could be identified with statistical significance although where frontal epilepsy was associated with experiential phenomena, the cingulate was always involved, and this seizure type was also associated with autonomic changes, as suggested in the ILAE classification. In common with the ILAE classification, no clear pattern was associated with prefrontal cortex. The operculum is a very different region to characterise on neuroimaging and lesions often appear to overlap more than 1 lobe. No distinctive features clinical features of the prefrontal region emerged from this study.

This study, therefore, supported the classification of the ILAE in relation to a number but not all seizure groups. In a study such as this, it may be argued that had more individuals been analysed, then more distinctions between different regions would have been made. A word of caution need be expressed, however, as in even the best characterised groups, a significant minority of lesions lay outside the expected region. The importance of the

prospective analysis in this study, in contrast to postsurgical series, needs to be stressed in this regard. Possible mechanisms for these frequent exceptions have been discussed in detail. Moreover, in the frontal lobes, lesions rarely sit neatly in one anatomical subdivision, unlike in MTS, and consequently the concept of strict parcellation of seizures within the frontal lobes is potentially misleading. Underlying these problems of clinical classification is the functional heterogeneity of association cortex, resulting in varying manifestations from the same region and similar manifestations from different regions and that seizure discharges may sometimes propagate over a time scale considerably faster than that over which clinical manifestations occur. The clinical method can, therefore, only expect to detect classical syndromes of accurate localising significance in a minority of cases.

Discussion of partial seizure types of the National General Practice Study

This is the only population-based, prospective study of epileptic seizures to date, which has addressed the question of seizure localisation. This design would be expected to confer a different emphasis from previous studies, which have relied on retrospective diagnosis from EEG or specialist records, or if prospective, have been hospital based[264,265,266,267,268,269,270]. In this partial seizure group, 93% attended hospital. Many of these, however, particularly the elderly with known cerebrovascular disease, were managed by general physicians, without recourse to specialist investigations and other patients attended a variety of specialities (e.g. paediatrics, geriatrics, psychiatry) and would not be detected in a study selecting patients from neurological or EEG department records. In hospital practice, moreover, patients' seizures may not be recorded as a separate diagnosis, for instance if secondary to acute cerebrovascular disease. A major feature of the study design was the measures taken to avoid selection bias at all levels. Clinical criteria formed the basis of seizure localisation in this study. This is consistent both with the methodology of the cluster analysis of symptomatology in the accompanying study and with the emphasis of the ILAE classification on clinical seizure patterns.

Partial seizures were identified clinically in 31% of patients with definite epileptic seizures, compared to 15-38% in other studies[264-268]. Of the 594 patients referred to the NGPSE, seizures without unequivocal focal or generalised features were seen in 190 cases and localisation-related epilepsies without clear focal onset in a further 92 cases. Our estimates of partial seizure localisation are, therefore, a minimum, based on the best categorised cases. Of partial and secondary generalised seizures with a localisable clinical onset, the proportion conforming to a likely frontal location was high (22.5%) with a further 38% with frontoparietal or frontotemporal seizure patterns. Whilst the results of the accompanying hospital-based analysis suggest that the power of clinical classification to predict anatomical localisation of investigative results may be limited, this study used clinical categories corresponding to those seizure types with the strongest anatomical associations and suggest that even if the minimum number is accepted, FLE is relatively

common in a general epilepsy population. This contrasts with current opinion, suggesting that frontal seizures are relatively uncommon[43].

For this analysis, we selected only those patients with clearly focal manifestations, excluding 92 (36.5%) with localisation-related seizures but clinically unlocalisable seizure onset. A number of sources of potential error exist; frontal motor phenomena are the most striking, objective seizure phenomena, and may mask more subtle, earlier manifestations, arising from other cortical sites, in some cases. Conversely, in the current study, frontal lesions, demonstrated on imaging, presented with generalised seizures, a feature sometimes said to be associated more commonly with frontal than extrafrontal lesions[271], although not supported by the accompanying hospital-based study. Moreover, the prominent motor effects of frontal seizures may also mimic generalised seizures, again leading to an underestimation of frontal seizures. It is likely, therefore, that a population-based study will, to some extent, underestimate all partial seizure categories, rather than imposing a specific bias against one type. This study strongly suggests that extratemporal epilepsy is a common form of localisation-related epilepsy in a general population and that the largest subgroups have frontal or perirolandic seizure patterns.

The aetiology of seizures was recognised less frequently in patients in the temporal group than in the other groups. It is increasingly recognised that as much as 70% of TLE may be due to mesial temporal sclerosis[162], a pathology generally undetectable by CT scanning, which may account for the low rate of detection and diagnosis in this group. With modern imaging techniques, especially magnetic resonance imaging (MRI), the rate of detection of significant pathology is much greater[126,127]. The current study was undertaken before these MRI techniques were available and the proportion with mesial temporal sclerosis is, therefore, unknown.

The seizure frequency at last follow-up was similar in all groups; 47.5% were seizure-free at 2 years and only 11 (6.9%) had frequent seizures. There was no evidence that chance of remission was any more likely in any of the groups. Most hospital-based studies suggest that frontal lobe attacks tend to occur frequently, in clusters and are particularly difficult to treat[14,38,44,48,60,65,272]. Our findings do not confirm this, and the hospital

studies may show a selection bias to a particularly refractory subgroup, rather than reflect frontal lobe epilepsy as a whole. Indeed, the response to treatment was generally excellent in all the partial seizure patterns, with many patients becoming seizure-free, again in contrast to reports from hospital-based studies. This general population was, as expected, less refractory than the accompanying hospital-based population, but shares the similarity of seizure frequency across different seizure types and different localisations and does not support the use of seizure frequency characteristics to differentiate seizure types and localisations. These studies suggest that the temporal characteristics of seizure frequency and diurnal variation are similar across clinical localisations in the general population and in a hospital based population (although very different between the 2 populations), and therefore, are more a function of the population studied than the clinical seizure localisation.

We also looked at the results of EEG and CT in this unselected population and at the relation of clinical features to focal findings on CT and EEG. Our findings need to be interpreted with caution, since not all patients underwent investigation.
It is, however, intuitively likely that those selected for investigation would yield a higher incidence of abnormalities than the population as a whole and this is supported by the finding that CT was performed in 54% of patients with newly diagnosed focal seizures compared with 26% of patients with newly diagnosed generalised seizures.
Most studies[114-118] report rates of focal CT abnormality in partial epilepsy of 10-30%, but they have examined patients with chronic refractory seizures. In the current study, the overall yield of CT abnormalities was 35% of those with partial seizures who underwent CT. The high proportion of abnormalities probably represents patient selection. Also, our data are drawn from the general population presenting with a recent onset of seizures, a proportion of which represented obvious, *de novo* structural lesions, that time would select out from studies of chronic refractory epilepsy.

The criteria for focal EEG abnormality were rigorous and comparable to the accompanying study, with slow wave, or other less specific abnormalities excluded, unless

accompanied by spikes or sharp waves. The yield of focal abnormalities on interictal EEG in patients with clinically localised seizure onset was 18%, and was similar in all groups. However, a further 15 clinically generalised seizures were identified as localisation-related on the basis of focal temporal EEG abnormalities.

Focal spike discharges and CT both gave a localisation strongly at variance with the clinical picture in approximately 20% of cases. This supports the finding in the accompanying hospital-based study that even with the best categorised seizures, the ability of the clinical pattern to predict abnormalities on investigation is limited and significant numbers of exceptions to the clinical localisations may be found in most clinical categories.

General Summary

The major aim of this study was to ascertain the localising significance of different clinical seizure patterns, especially in relation to frontal lobe epilepsy. The methods used enabled: 1) the delineation of clinical patterns of epilepsy of frontal lobe origin and their differentiation from other epilepsies, especially temporal lobe epilepsy; 2) the assessment of the intrafrontal localising value of the different seizure-types identified; 3) the cross-correlation of clinical and investigative findings in different seizure types and 4) the assessment of these findings in relation to the current ILAE classification of localisation-related epilepsies. A derived classification was then applied to the database of the NGPSE, to determine the relative frequency of different seizure types in a general population.

The methods used in this study differed radically from others especially in regard to the breadth of case ascertainment, which was from a more representative epilepsy population than post-surgical series and in that a clinical classification was first established by statistical cluster analysis and only then prospectively related to investigational abnormalities, rather than a retrospective analysis of preselected post-surgical cases. This technique also allowed different groups to act as each others' controls, to enable the identification of clinical features of value in differentiating between them, unlike previous series which have generally reported series of similar patients.

Hospital records were searched for patients with evidence of partial seizure onset, excluding those suggesting occipital onset. Selection criteria, included focal imaging abnormality, focal ictal or interictal EEG abnormality and focal ictal symptomatology. Each criterion was treated independently in order to keep selection as broad as possible and to allow subsequent assessment of concordance of investigations. Two hundred and fifty-two patients were interviewed and 352 seizure types were identified. 126 patients had lesions on neuroimaging and 79 seizures were recorded with ictal scalp EEG.

Patients and witnesses were interviewed prospectively in all cases and clinical seizure manifestations were recorded and encoded according to their relative time of occurrence during the seizure. These data were then entered into a statistical cluster analysis, using Ward's technique and 25 groupings of seizure symptomatology were obtained. Some of these were then combined to produce a final number of 14 groupings, each corresponding to a different clinical seizure type. These patterns were displayed in the form of flow charts, allowing assessment of seizure evolution.

Available interictal EEG's were analysed in 90% of patients and spike locations were recorded. Ictal EEG onsets were also analysed, according to region of onset, pattern of onset and timing in relation to clinical onset for 79 seizures. Abnormalities on neuroimaging were identified in 126 patients (50%) and these were mapped by a template technique and their precise locations assessed with reference to a stereotaxic atlas. The identified seizure groups were then analysed in relation to abnormalities identified on these investigations, including chi-square analysis of lesion site versus seizure type. Thus the relationship of clincal seizure pattern investigative abnormalities could be measured, and in the case of lesion site on neuroimaging, could be statistically quantified.

The occurrence of symptoms in 61 seizures associated with pure frontal and 58 seizures associated with pure temporal lesions was also analysed from the raw clinical data, without reference to statistically derived clusters, in order to provide an additional analysis independent of the clinical classification by cluster analysis. This analysis allowed identification of features differentiating frontal and temporal epilepsy, one of the most important clinical problems and supported the identification of clinical features of most differentiating value in the cluster analysis, suggesting the clinical classification technique had not introduced substantial bias.

Of 14 clinical seizure types, there were 2 seizure types assocviated with the perirolandic region and 2 with frontal lobe regions. Seizures characterised by clonic motor activity

were associated with lesions of the perirolandic cortex and lateral premotor cortex ($P<0.001$), and with frontocentral EEG abnormalities.

Seizures characterised by somatosensory onset were associated with lesions of a similar distribution but with a more parietal predominance ($P<0.001$).

Seizures characterised by tonic posturing or version were strongly associated with lesions of the lateral premotor cortex ($P<0.001$) and with an ictal onset of fast or spike activity in the frontal region, supporting a superficial origin.

Seizures characterised by bizarre or frenetic motor activity, "motor agitation", were associated with frontal EEG abnormalities and with lesions of the frontopolar or orbitofrontal cortex ($P<0.001$). These latter seizures were commonly nocturnal and occurred with higher frequency than those in other groups but no other consistent pattern in diurnal variation or seizure frequency emerged from the study; probably reflecting its broad case mix from specialist epilepsy and non-specialist neurology practice.

Seizures characterised by absence without prior focal symptoms were strongly associated with temporal lesions ($P<0.001$) but with variable EEG manifestations

Seizures with other early forms of sensory manifestation; visual; auditory; olfactory and gustatory, or with experiential phenomena or intense fear, were also associated with temporal lobe abnormalities on interictal EEG, ictal EEG and neuroimaging, although no single group reached statistical significance.

Although these statistical associations of seizure type were strong, in each grouping there was an important minority associated with different patterns of investigations, that were clinically indistinguishable.

Analysis of individual seizure manifestations between pure frontal and pure temporal lesional cases supported the findings of the groupings derived from cluster analysis. Early version or posturing and early clonic activity were significantly associated with frontal lesions but there were no significant overall differences between frontal and temporal cases with respect to diurnal variation, seizure frequency or tendency to cluster.

In patients exhibiting more than one seizure type, there was a statistically significant association between absences and non-specific generalised tonic clonic seizures,

suggesting a "pseudo-generalised epilepsy", but numbers were too small to identify clear investigational associations of this group.

The flow of seizure manifestations, illustrated by flow charts, showed considerable variation within groups with early divergence of initially similar seizures. Complex behavioural automatisms were more frequently associated with seizures with onset with sensory phenomena, other than somatosensory, or with absence, whereas those with early motor activity more frequently evolved into simple repetitive automatisms.

Seizures with startle sensitivity occurred in 19 patients, at some point during their epilepsy history, more commonly than previously recognised and appeared to be especially associated with seizures with early focal or generalised tonic motor activity. MRI suggested lesions in the lateral frontal region or the perisylvian region in this group.

Imaging generally gave the most anatomically specific localising information; of 102 cases with imaging and interictal EEG, there was close concordance in 9%, frank discordance in 11% and relatively diffuse EEG in relation to imaging in 33%. Interictal EEG showed no spikes in the other 46%. Ictal EEG and imaging were discordant in only 2 cases but ictal EEG showed no abnormality or non-specific features very commonly, in relation to both frontal and temporal lesions.

Of 160 seizures with focal symptomatology in the NGPSE, seizures with hemiclonic or Jacksonian sensory manifestations occurred in 32.5%, other motor patterns in 22.5%, other somatosensory in 6.3%, olfactory, gustatory, auditory or experiential in 27%, polymodal or complex sensory in 6.3%, and a frontotemporal overlap group 5.6%. The prognosis of these clinically defined groups was similar, and much better than in hospital-based series. Although the clinical pattern was associated with consistent interictal EEG and CT findings in 80%, there was a significant minority with different associations on investigation - very similar to the hospital-based study.

These findings lend some support to the localisation of seizure types attributed to the orbitofrontal and temporal lobes by the ILAE but suggests that many regions of the

frontal lobes may not have specific associated seizure types, especially the prefrontal cortex. In addition in this study, seizures with tonic posturing, traditionally associated with the SMA, were strongly linked to the lateral premotor cortex. This prospective analysis of clinical seizure types also shows that a significant number do not conform to the classical patterns and in this respect differs from retrospective and more highly selected post-surgical series, on which the classification is based. It suggests that the clinical pattern of highly specific patterns e.g. Jacksonian motor and somatosensory seizures (both closely anatomically linked to peripheral end-organs) is of strong localisng significance but that other patterns are of more limited value. A number of mechanisms may underlie this variability of seizure expression including the heterogeneity of function within cortical regions, especially association cortex, and variations in spread of seizure discharges. The results suggest that frank discordance between surface EEG, either ictal or interictal and imaging is relatively uncommon, but non-specific EEG findings are much more frequent and do not differ greatly between frontal and temporal groups in this relatively unselected series. Although uncommon, the localising value of a highly focal ictal or interictal EEG is, therefore, generally high in this series in relation to both frontal and temporal lesions.

The population-based study suggested that clinical patterns suggestive of extratemporal epilepsy are common in the general population, although the relatively subtle manifestations of some patterns of TLE may lead to slight underestimation of their relative frequency. It suggested that prognosis is similar for extratemporal and temporal lobe epilepsy in the general population and that discordance between clinical and CT or EEG localisation occurs at a similar frequencey to the hospital-based population. Thus the classification derived from a hospital population appears to have value in the classification of partial epilepsy in the general population. Taking these 2 studies together, factors of timing, such as seizure frequency, tendency to cluster and diurnal variation, appear to be similar across most clinical seizure localisations and their main determinant is the nature of the population under study.

Acknowledgements

I should like to thank Dr Simon Shorvon and Dr David Fish for their help and criticism, throughout the design, execution and writing of this study. I also thank Dr Stevens for his ideas regarding analysis of neuroimaging and for performing the validation assessment and he and Dr Mark Cook for performing the additional magnetic resonance studies. I should like to thank Catherine Scott for her help in organising the analysis of video-telemetry and Dr Tony Johnson of the MRC biostatistics unit for his advice regarding statistical analysis. Thanks also to Dr Yvonne Hart and Dr Ley Sander for their help with the General Practice Study. Special thanks to my wife Catherine for her indulgence during the long gestation of this study and for her help with the illustrations.

Figure 3. Schematic representation of possible seizure outcomes after epilepsy surgery

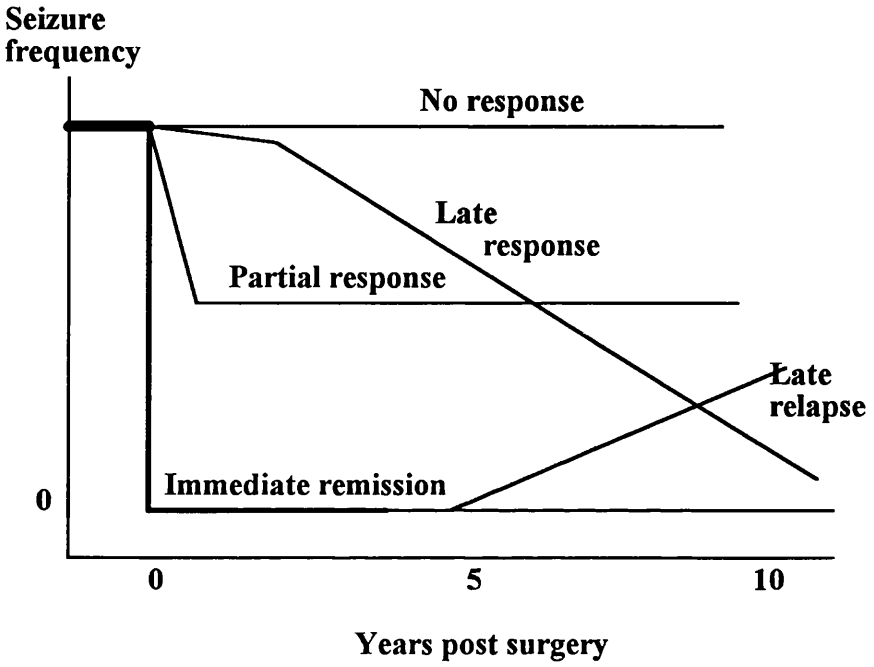


Figure 4. Gross anatomy of the human cerebral cortex (from Gray's Anatomy[199], with permission)

A: Mesial surface; B: Lateral surface; C: Orbital surface

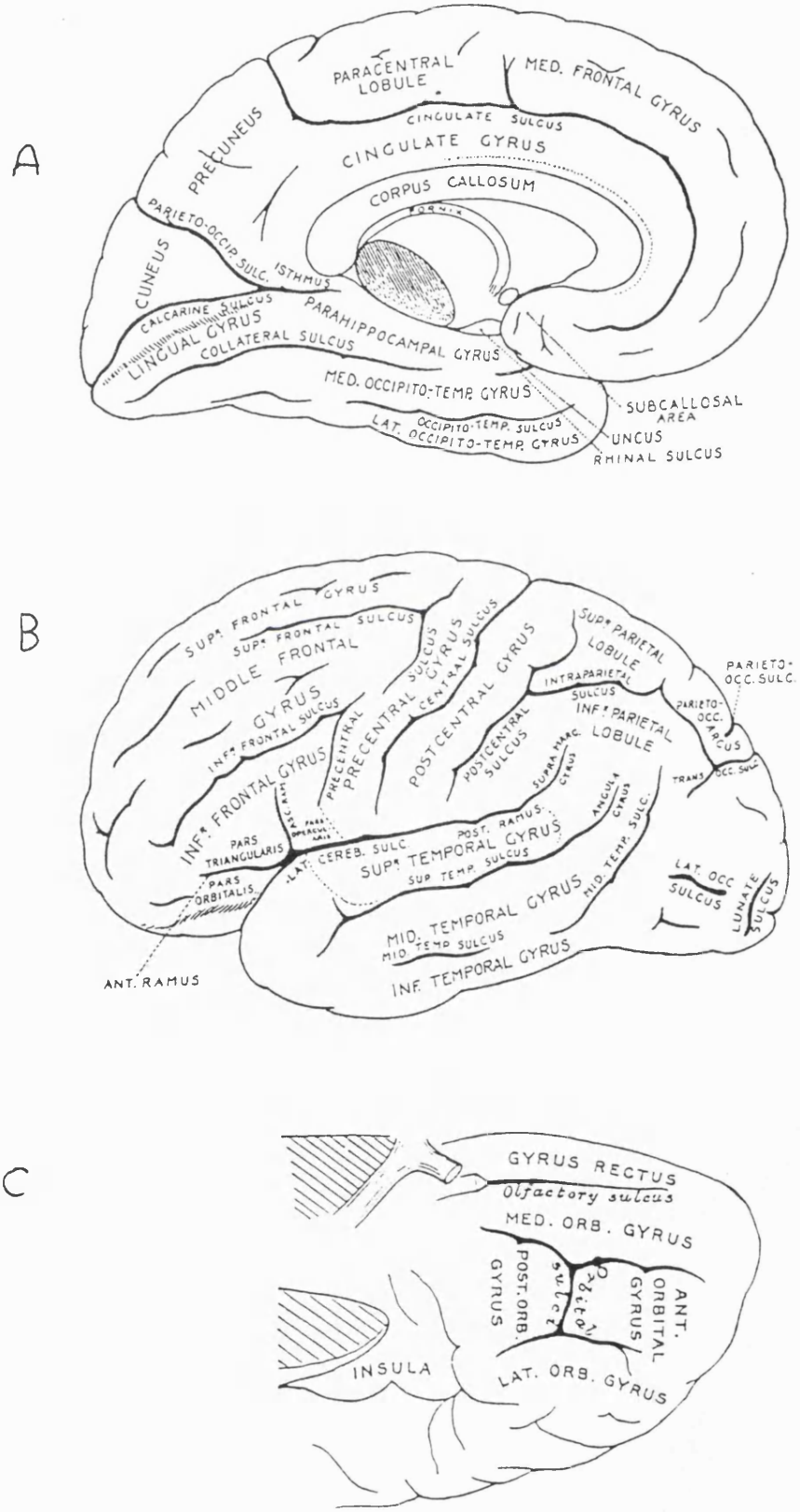
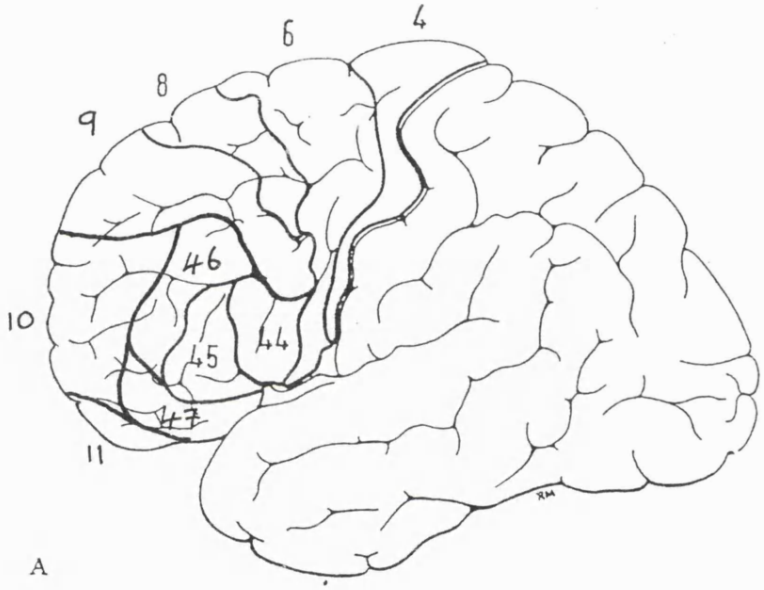
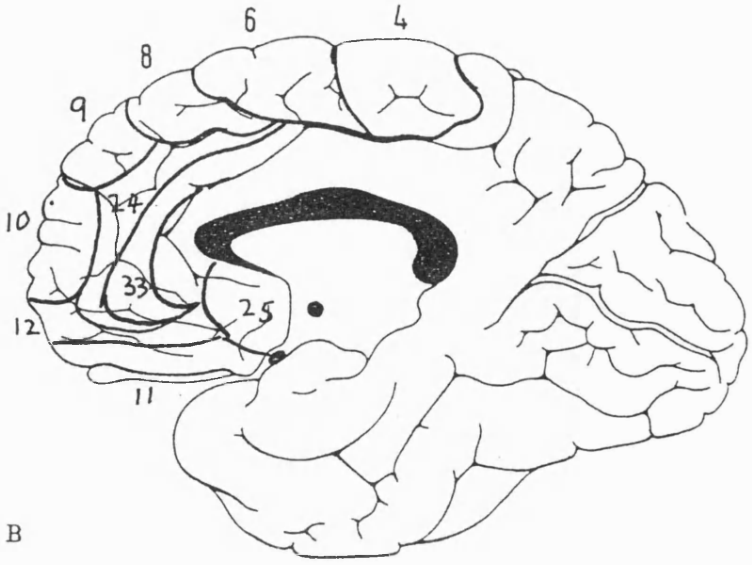


Figure 5. Brodmanns areas of a) lateral and b) mesial frontal lobes in man. (Adapted from Gray's Anatomy[202] with permission.)





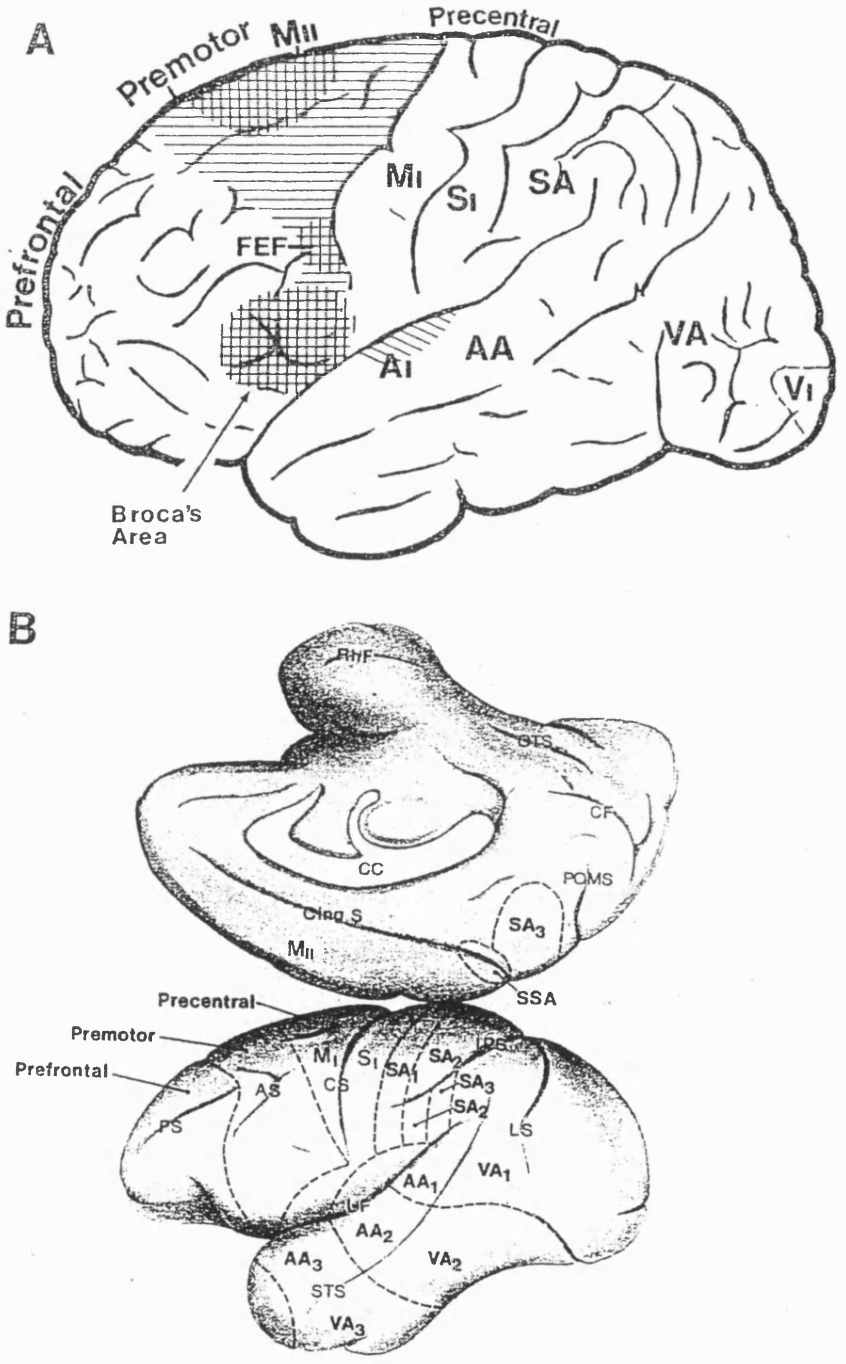


Figure 6: Functional areas of a) human and b) monkey cerebral cortex (from Pandya and Barnes[272], with permission)

A1, primary auditory cortex; AA, auditory association area; FEF, frontal eye fields; M1, motor cortex; MII, Supplementary motor area; SA/SA1-3, somatosensory association areas; SI, primary somatosensory area; VA/VA1-3 Visual association areas; V1, primary visual area. AS, arcuate sulcus; CC, corpus callosum; CF, calcarine fissure; Cing. S, cingulate sulcus; CS, central sulcus; IOS, infereior occipital sulcus; IPS, intraparietal sulcus; LF, lateral fissure; LS, lunate sulcus; OTS, occipitotemporal sulcus; POMS, medial parieto-occipital sulcus; PS, principal sulcus; RhF; rhinal fissure; STS, superior temporal sulcus.

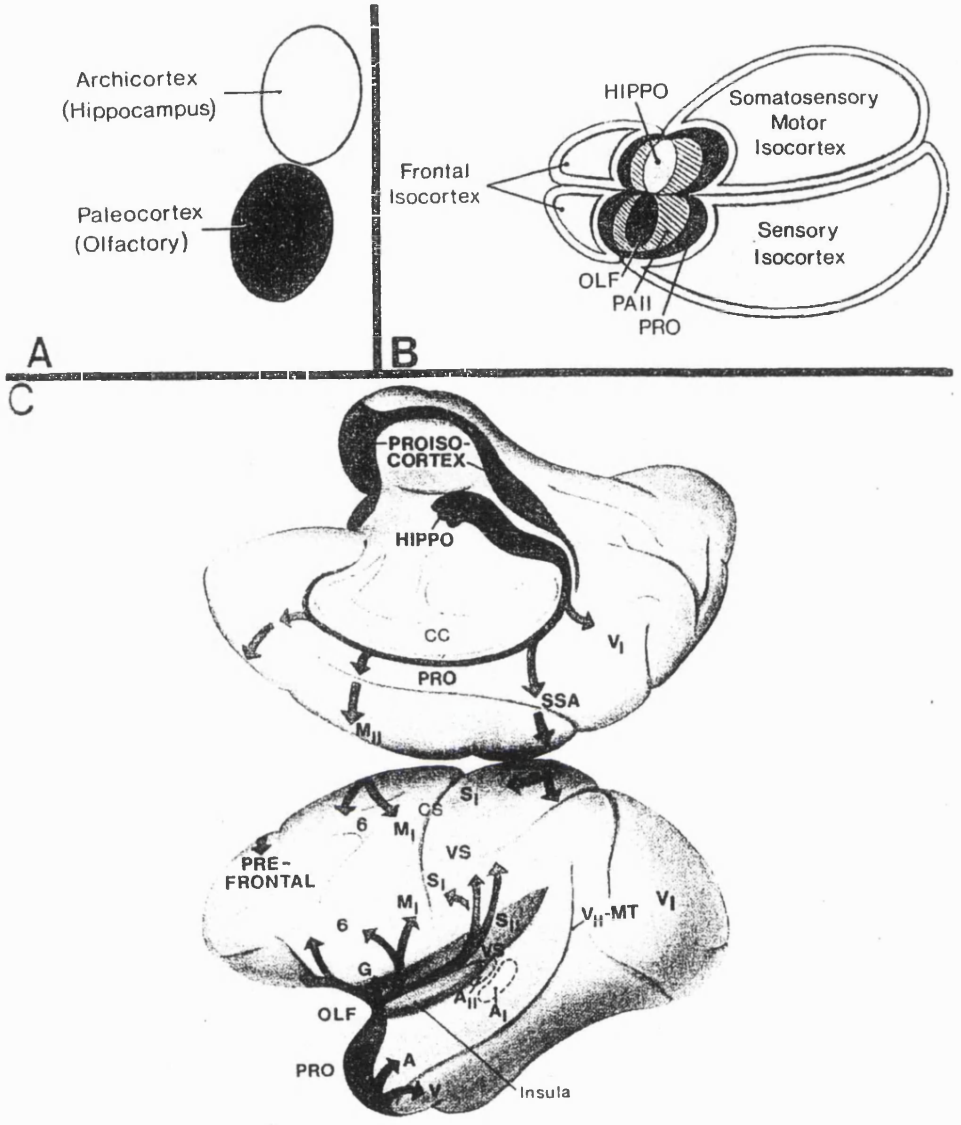


Figure 7: Schematic diagram shoowing the progressive development of the cortical areas from two primordial moieties (archicortical and paleocortical) through successive steps: periallocortex (PAII to proisocortex (PRO) culminating in pre- and postrolandic sensory, motor and association areas. (From Pandya and Barnes[172], with permission.)

Abbreviations: A, auditory; AI, primary auditory; AII, secondary auditory; G, gustatory; MI, primary motor; MII; supplementary motor; MT, middle temporal visual area; OLF, olfactory; PRO, proisocortex; SI, primary somatosensory; SII, second somatosensory; SSA, supplementary sensory area; V, visual areas; VI, primary visual; VII, visual area MT in the superior temporal sulcus; VS, vestibular area.

Figure 8: Location of sensory inputs from visual, auditory, and somatosensory cortices to the frontal lobes. (From Pandya and Barnes[172], with permission.)

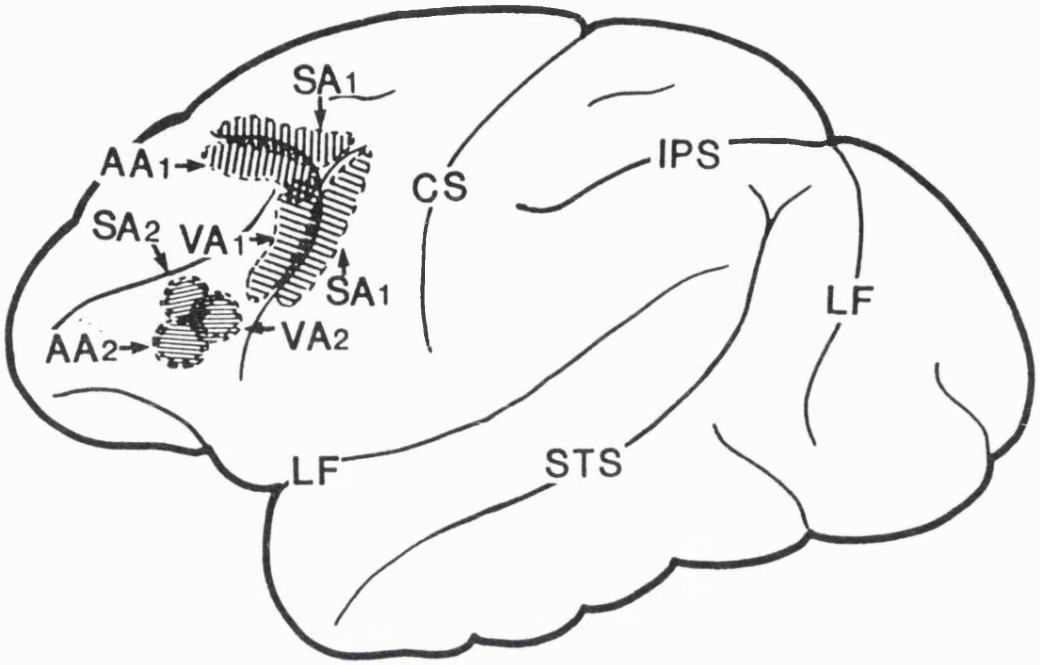


Figure 9: Long association efferent connections of the premotor and prefrontal cortex. (From Pandya and Barnes[172], with permission.)

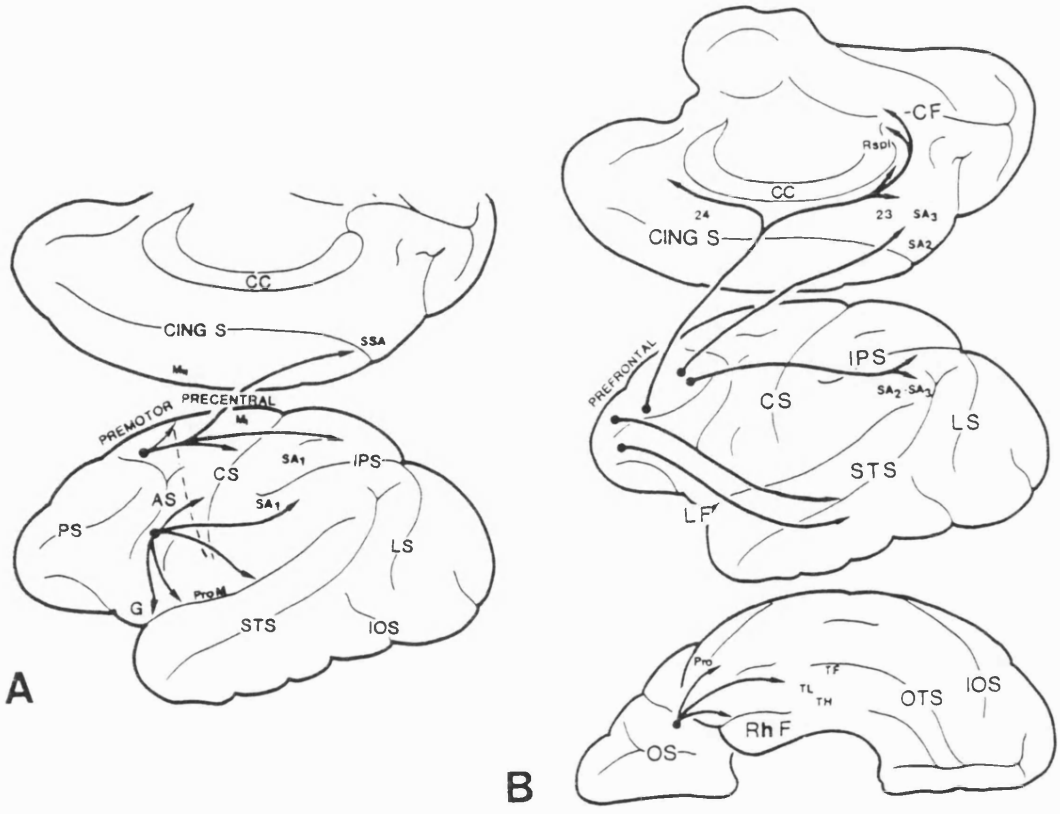


Figure 10: Intrinsic connections of a) dorsal and b) ventral trends of the prefrontal region. (From Pandya and Barnes[172], with permission.)

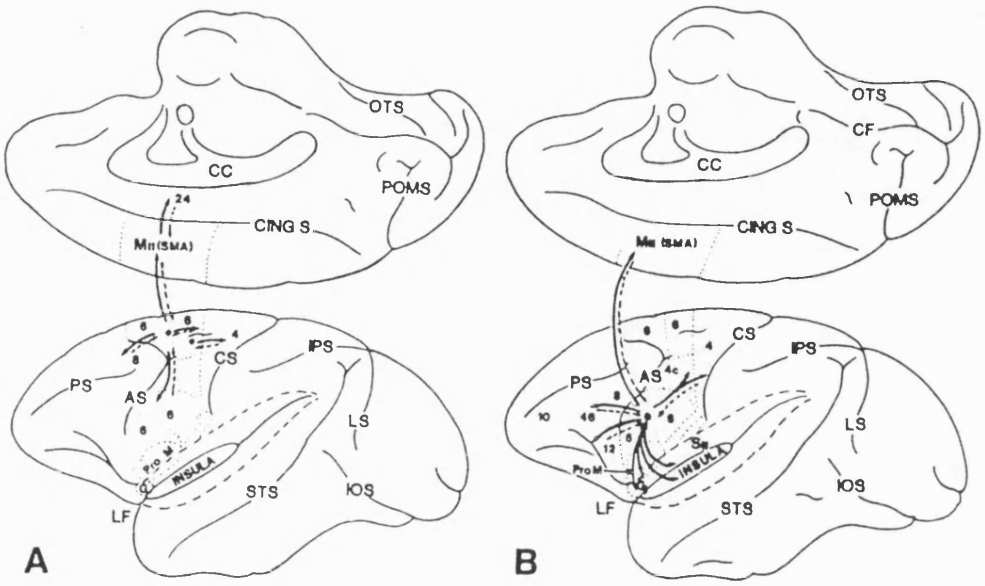


Figure 11: Diagram showing the interconnections bewteen dorsal and ventral trends - for example found at proisocortical, prefrontal and premotor areas. (From Pandya and Barnes[172], with permission.)

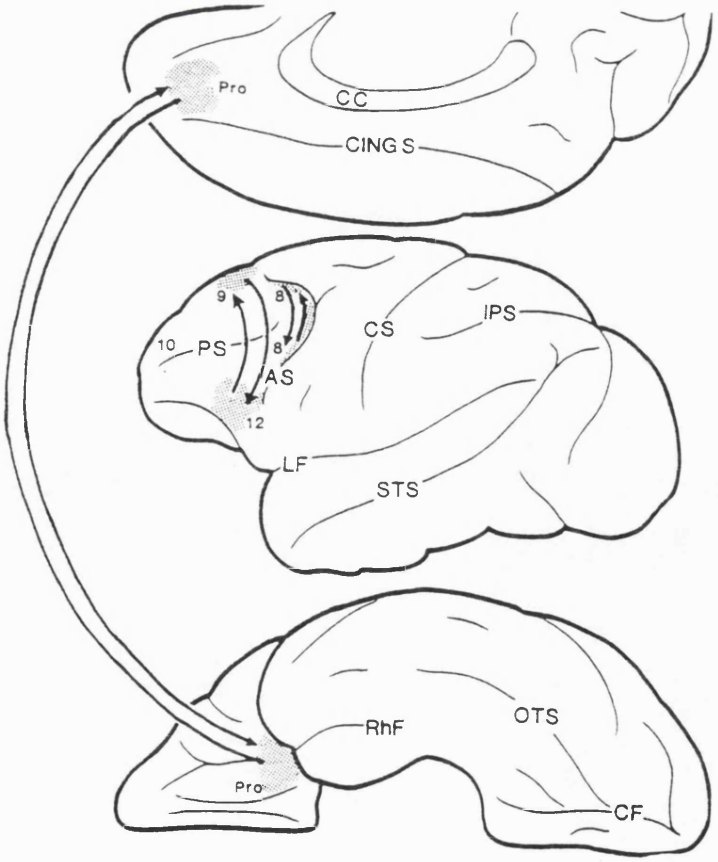


Figure 12: A) Diagram summarising limbic afferents to the frontal lobes;
B) Diagram summarising connections of the parahippocampal region
(From Pandya and Barnes[172], with permission.)

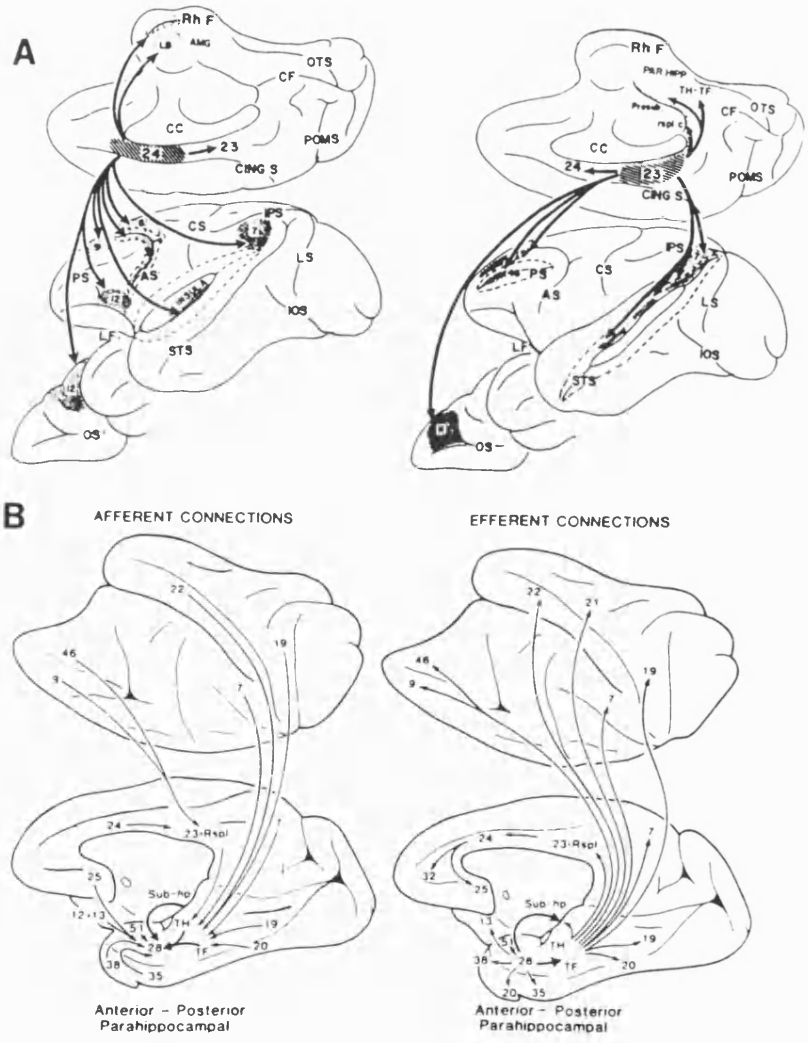
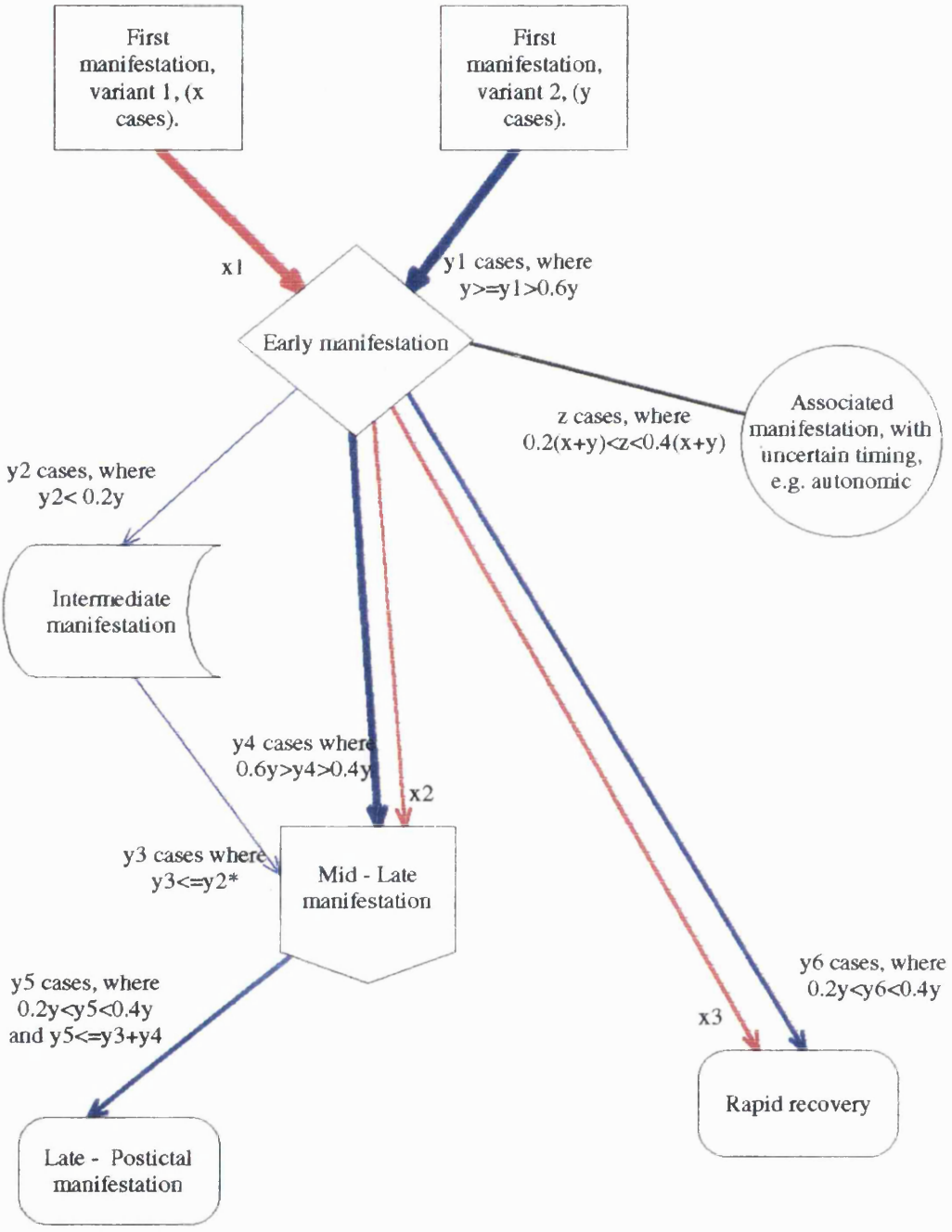


Table 34. Inclusion criteria for cases in each group.

Group	Clinical	Imaging	Interictal EEG	Ictal EEG	Total
1	8	10	7	6	31
2	20	27	9	1	57
3	4	16	11	2	33
4	3	9	1	3	16
5	0	1	0	1	2
6	2	2	2	0	6
7	34	16	15	9	74
8	13	8	2	3	26
9	0	2	0	0	2
10	3	2	1	0	6
11	2	0	5	1	8
12	6	6	1	1	14
13	19	13	15	0	47
14	13	8	2	7	30
Total	**127 (36%)**	**120 (34%)**	**71 (20%)**	**34 (10%)**	**352**

Figure 13

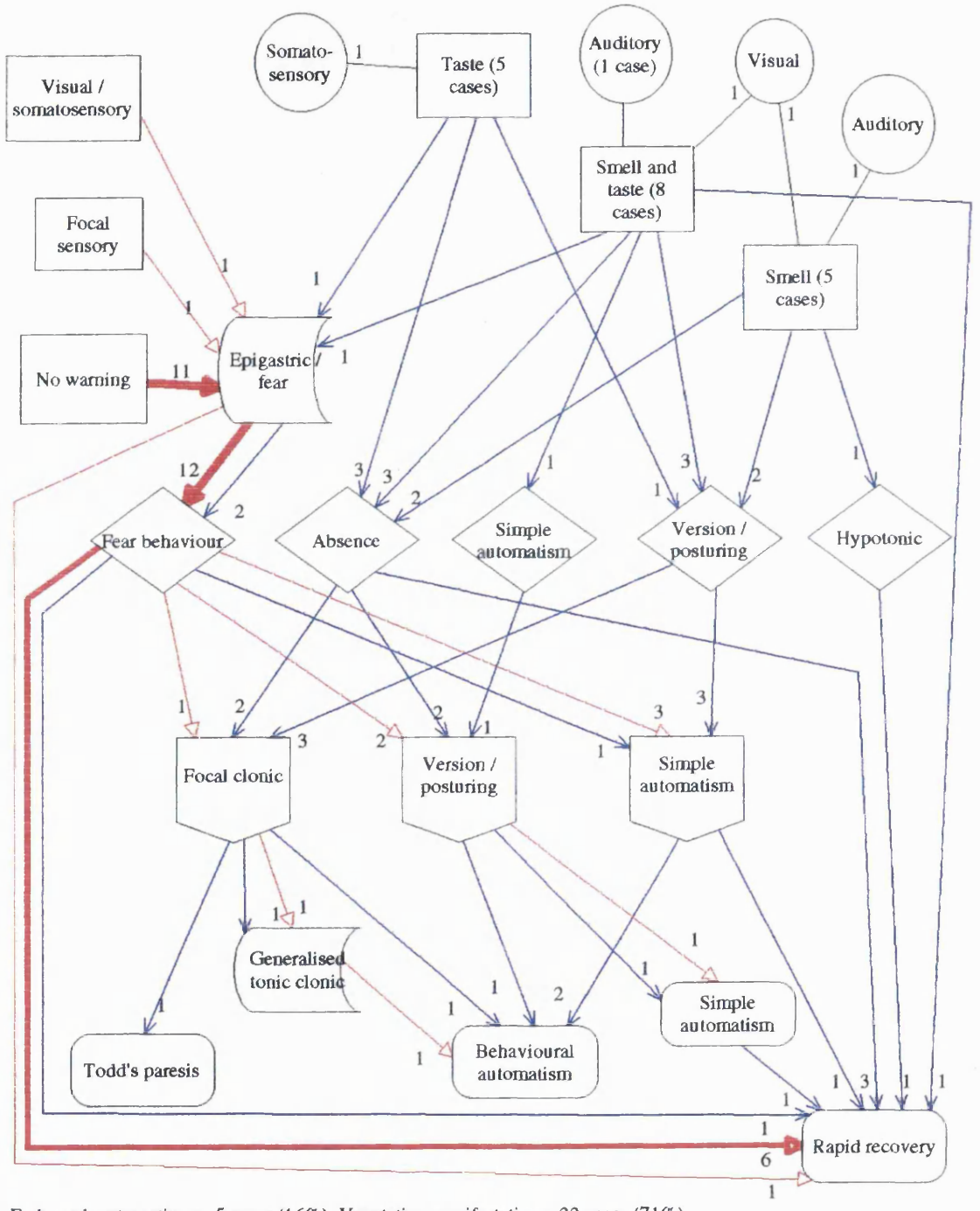
Chart 1: Flow diagram scheme



* Where there is gradual recovery after a manifestation, the cases are no longer marked, hence the total number of cases leaving a box may be smaller than that entering it.

Figure14

Group 1: Seizure with olfactory or gustatory hallucination (subgroup1b, or profound fear behaviour, without smell/ taste (subgroup 1a)



Early oral automatisms; 5 cases (16%) Vegetative manifestations; 22 cases (71%)

Early vocalisations; 11 cases (35%) Abdominal symptoms; 21 cases (68%)

Figure 15

Group 2: seizures with absence without specific warning

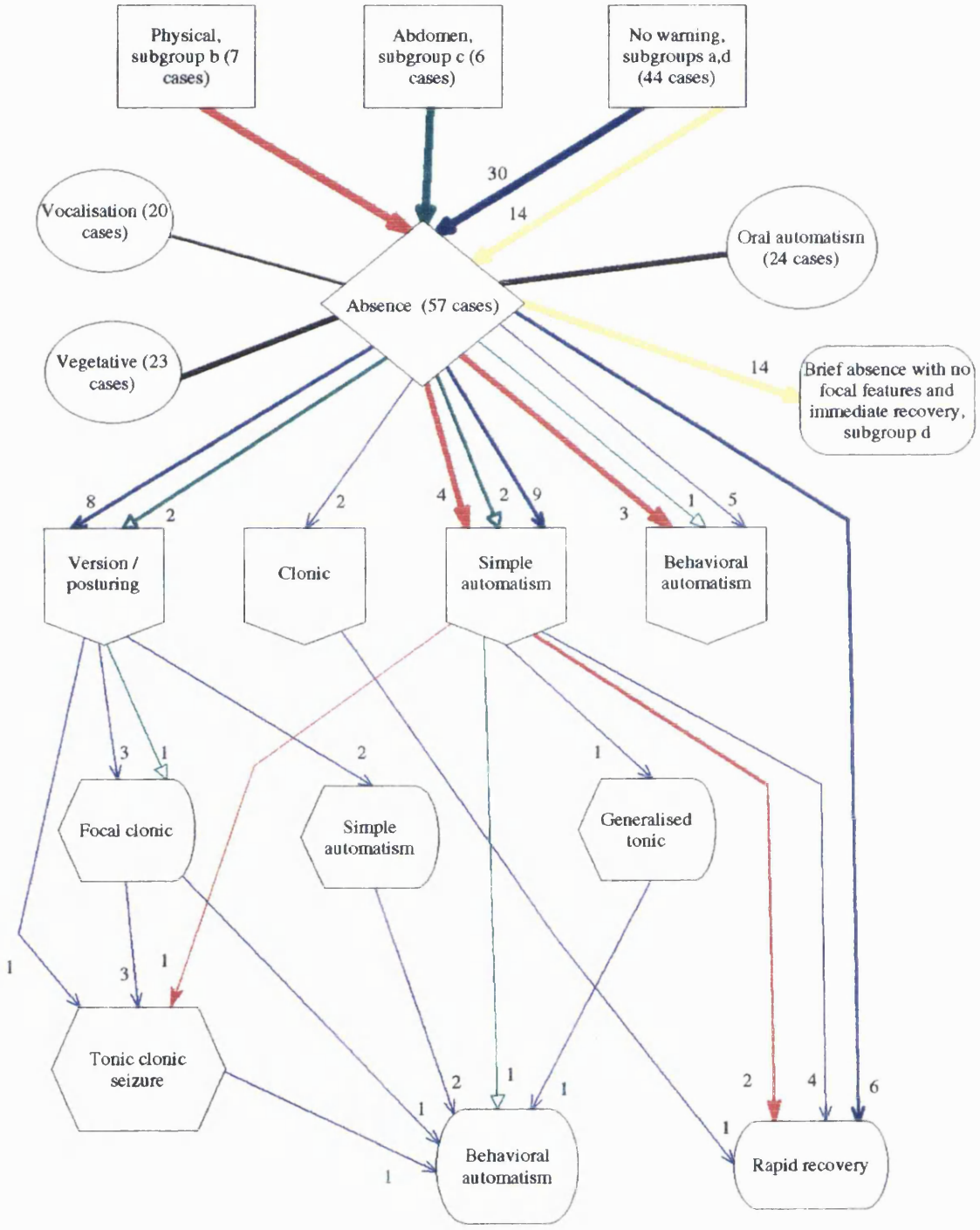


Figure 16

Group 3: seizures characterised by early experiential phenomena

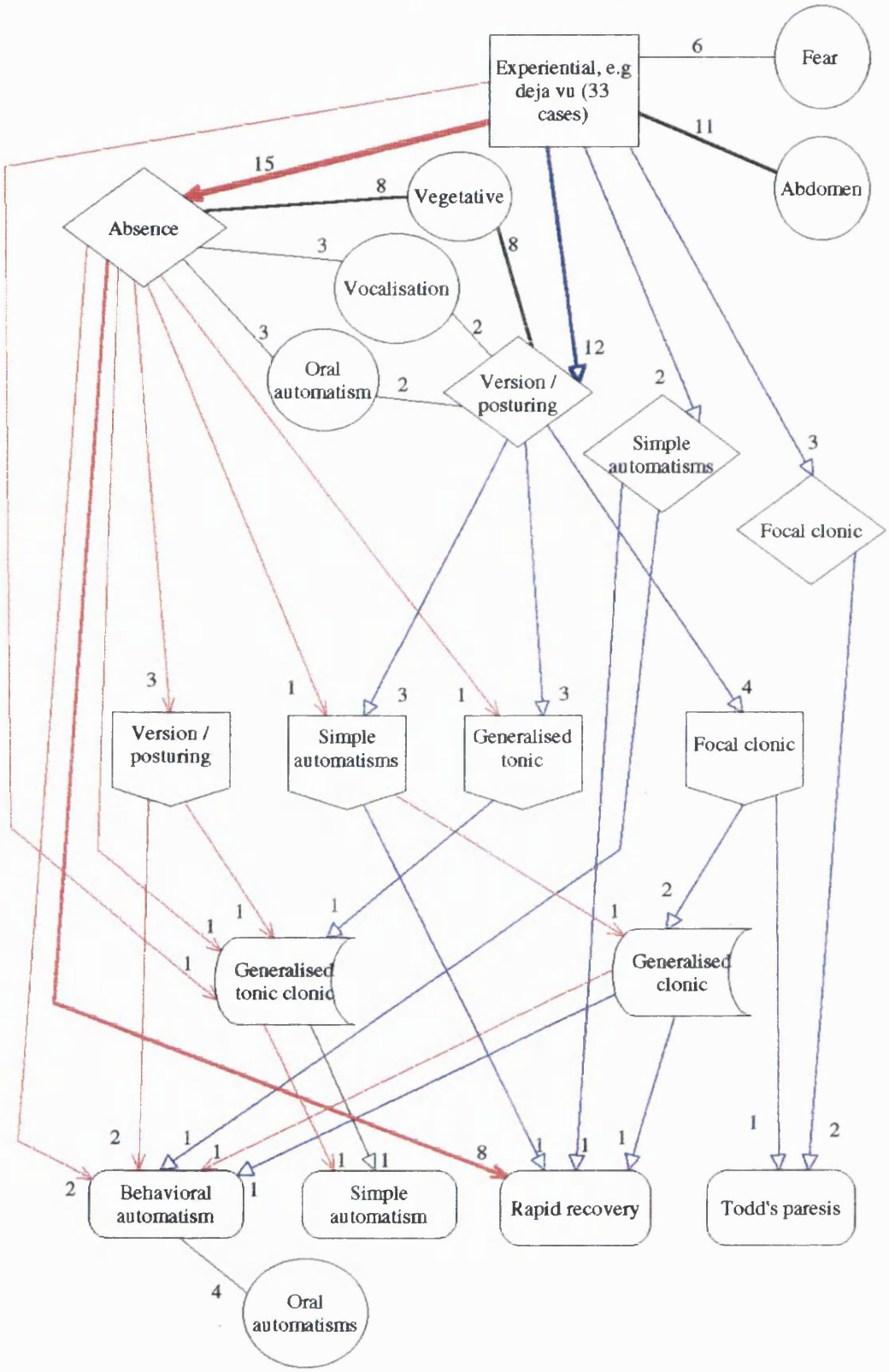


Figure 17

Group 4: seizures with early visual manifestation

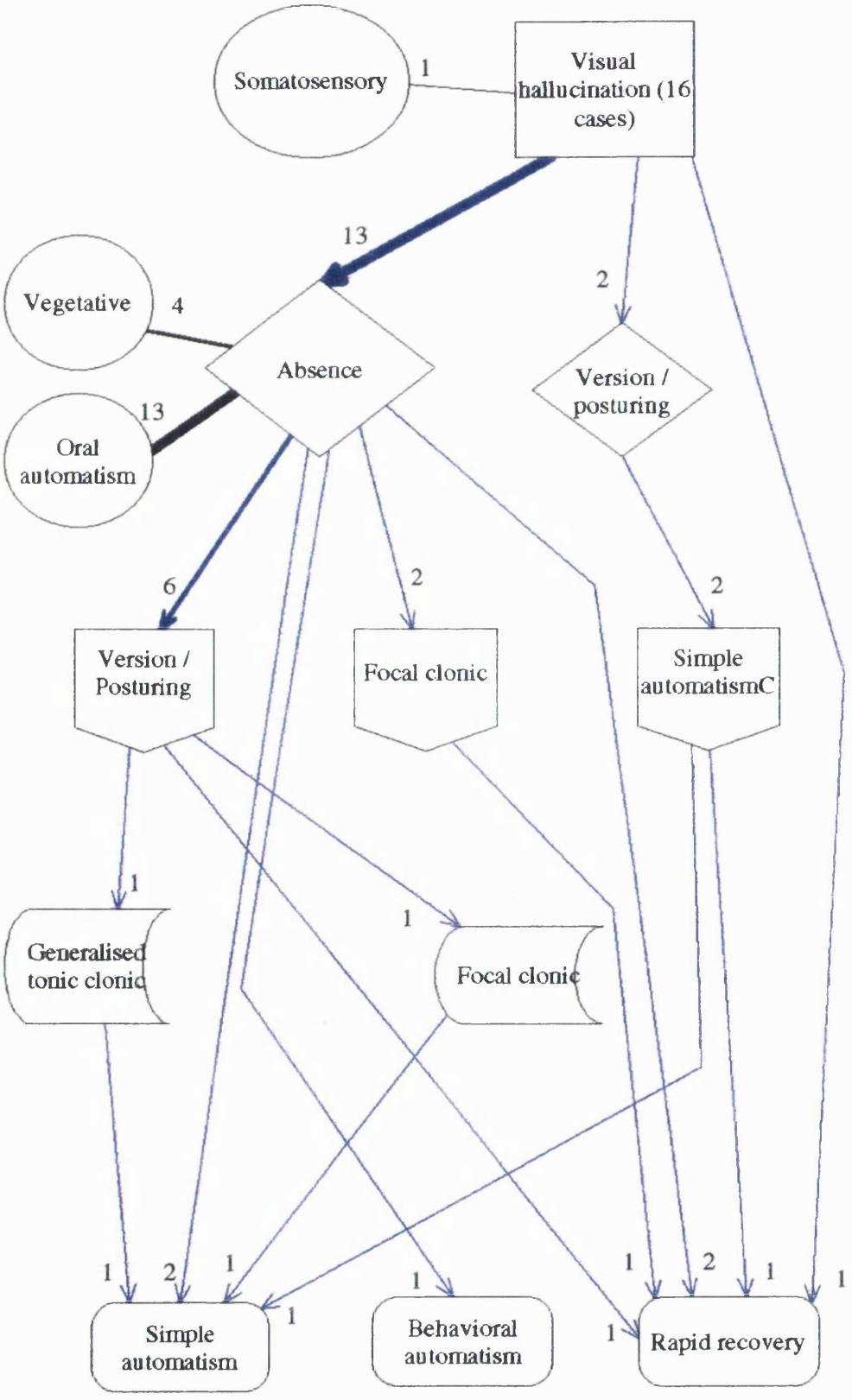


Figure 18

Group 5: seizures with early auditory hallucination

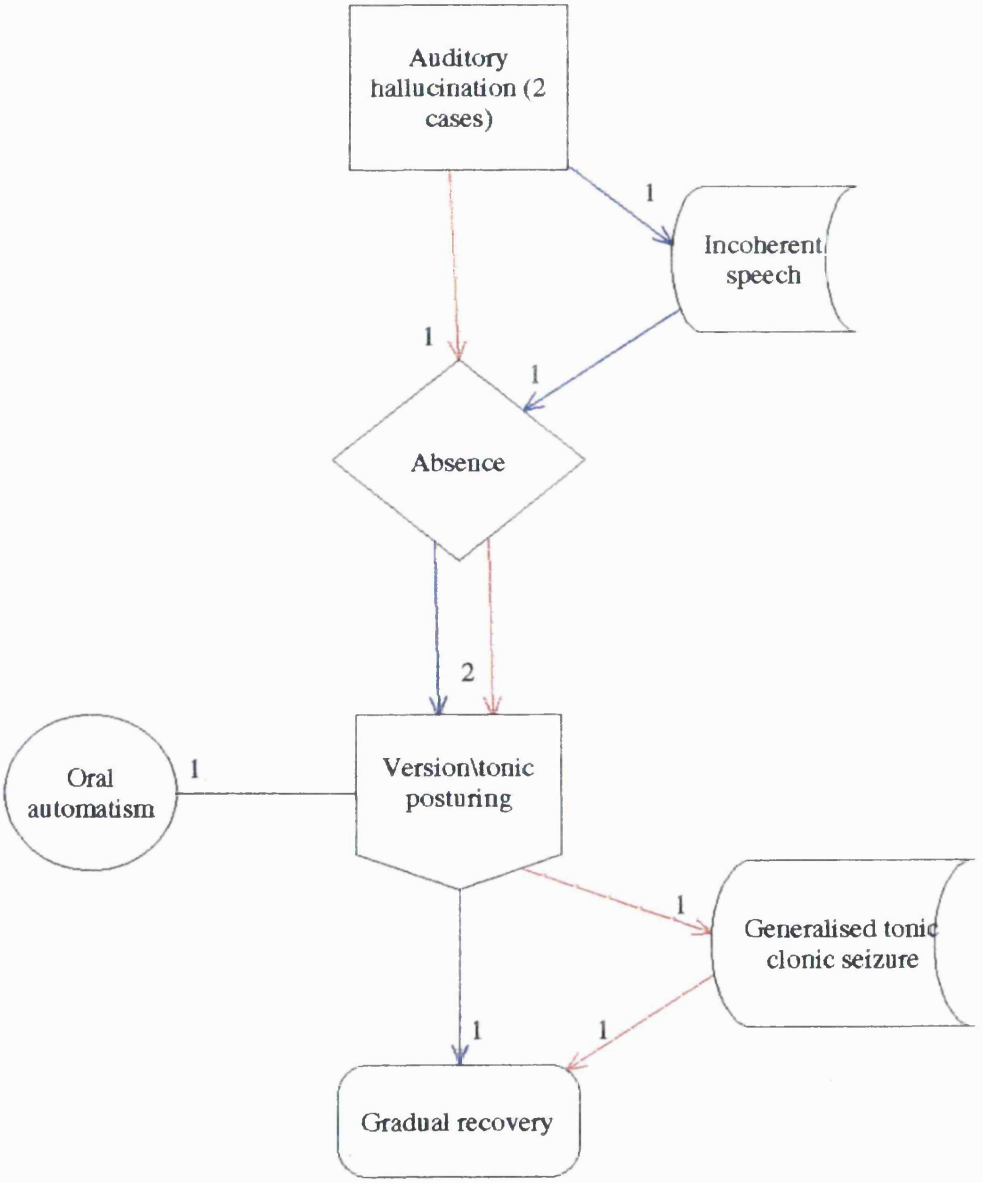


Figure 19

Group 6: hypotonic drop attacks

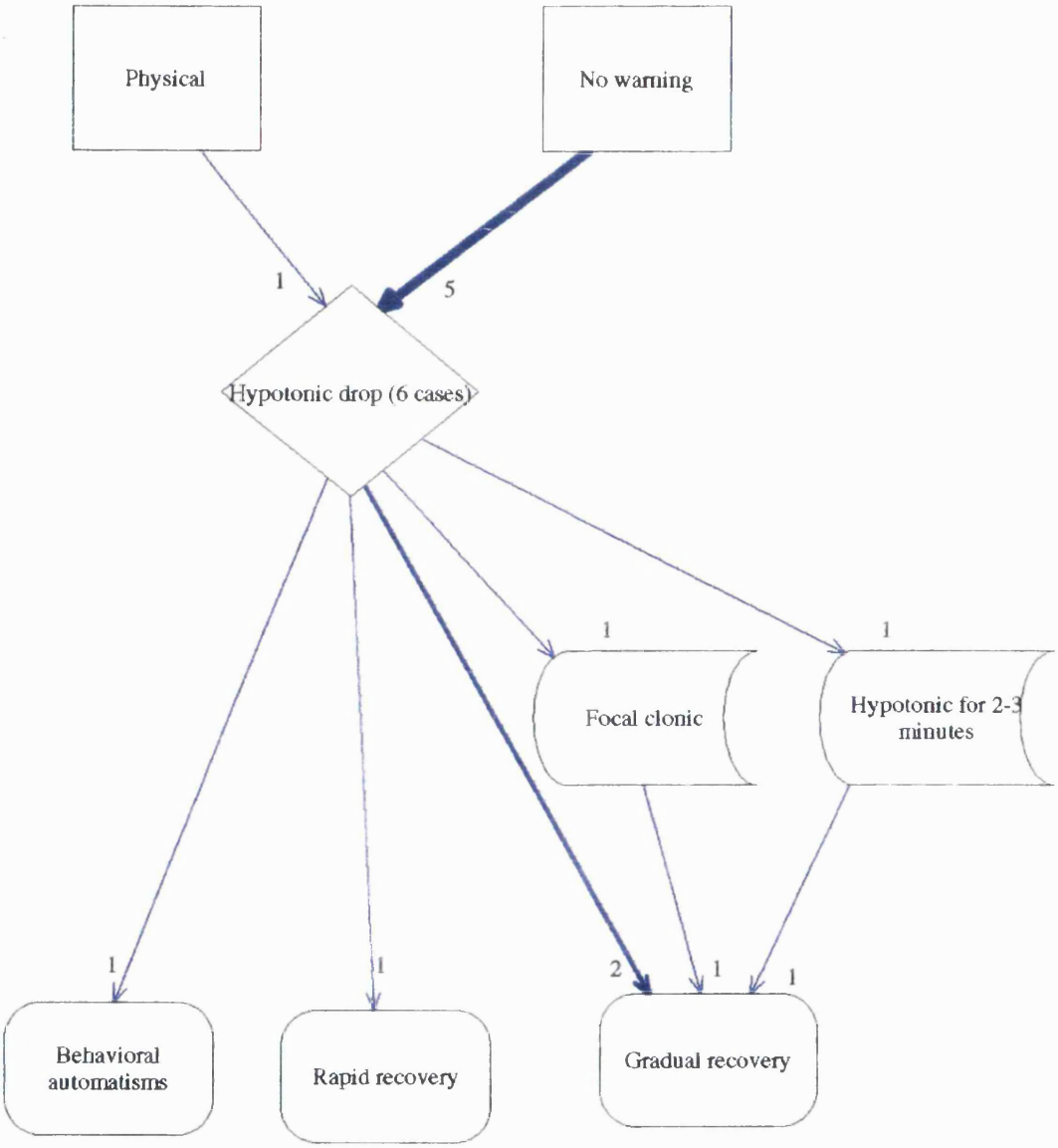


Figure 20

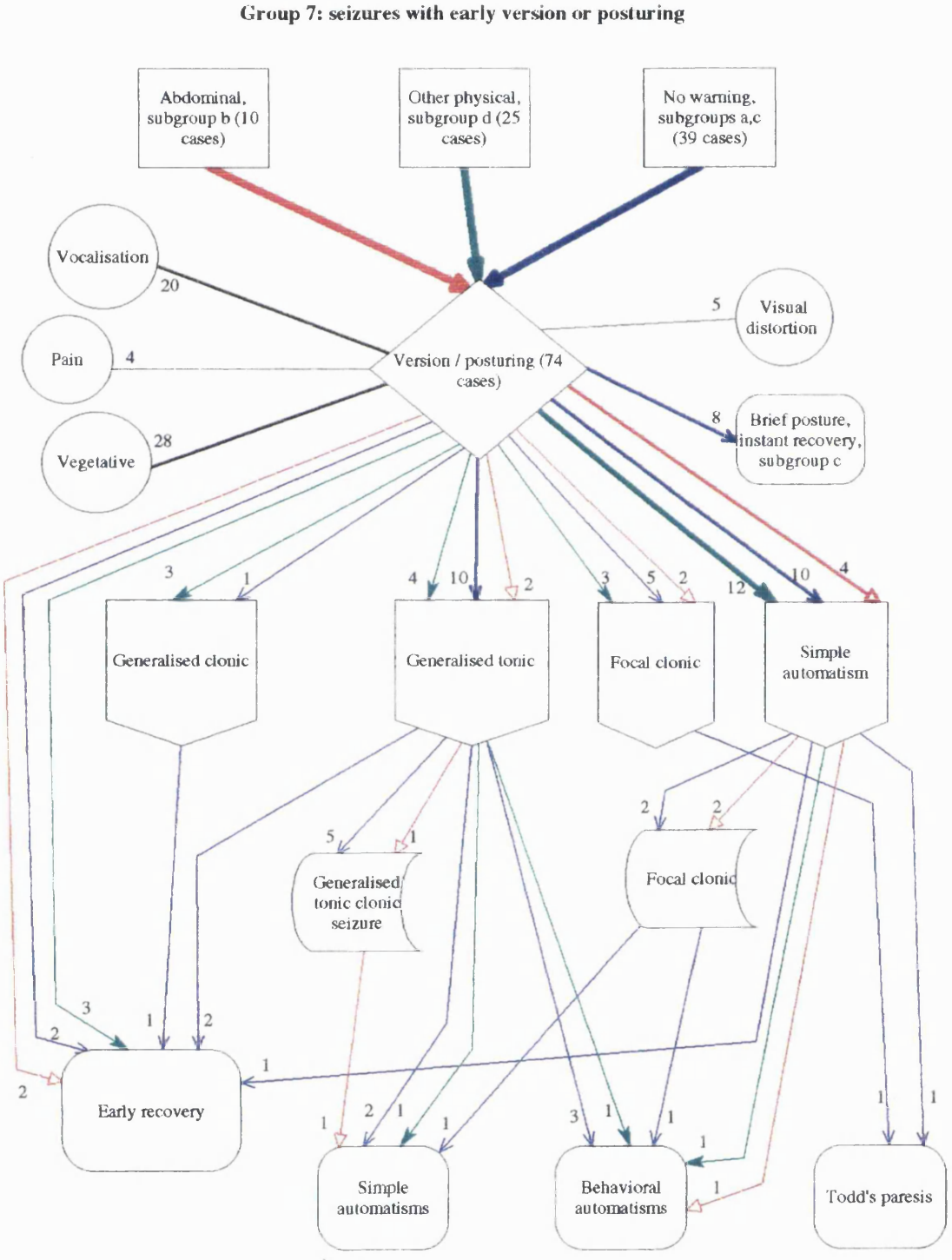

Group 7: seizures with early version or posturing
Abdominal, subgroup b (10 cases)
Other physical, subgroup d (25 cases)
No warning, subgroups a,c (39 cases)
Vocalisation
20
Pain
4
Vegetative
28
Version / posturing (74 cases)
5
Visual distortion
8
Brief posture, instant recovery, subgroup c
Generalised clonic
Generalised tonic
Focal clonic
Simple automatism
Generalised tonic clonic seizure
Focal clonic
Early recovery
Simple automatisms
Behavioral automatisms
Todd's paresis

Figure 21

Group 8: seizures with focal sensory onset

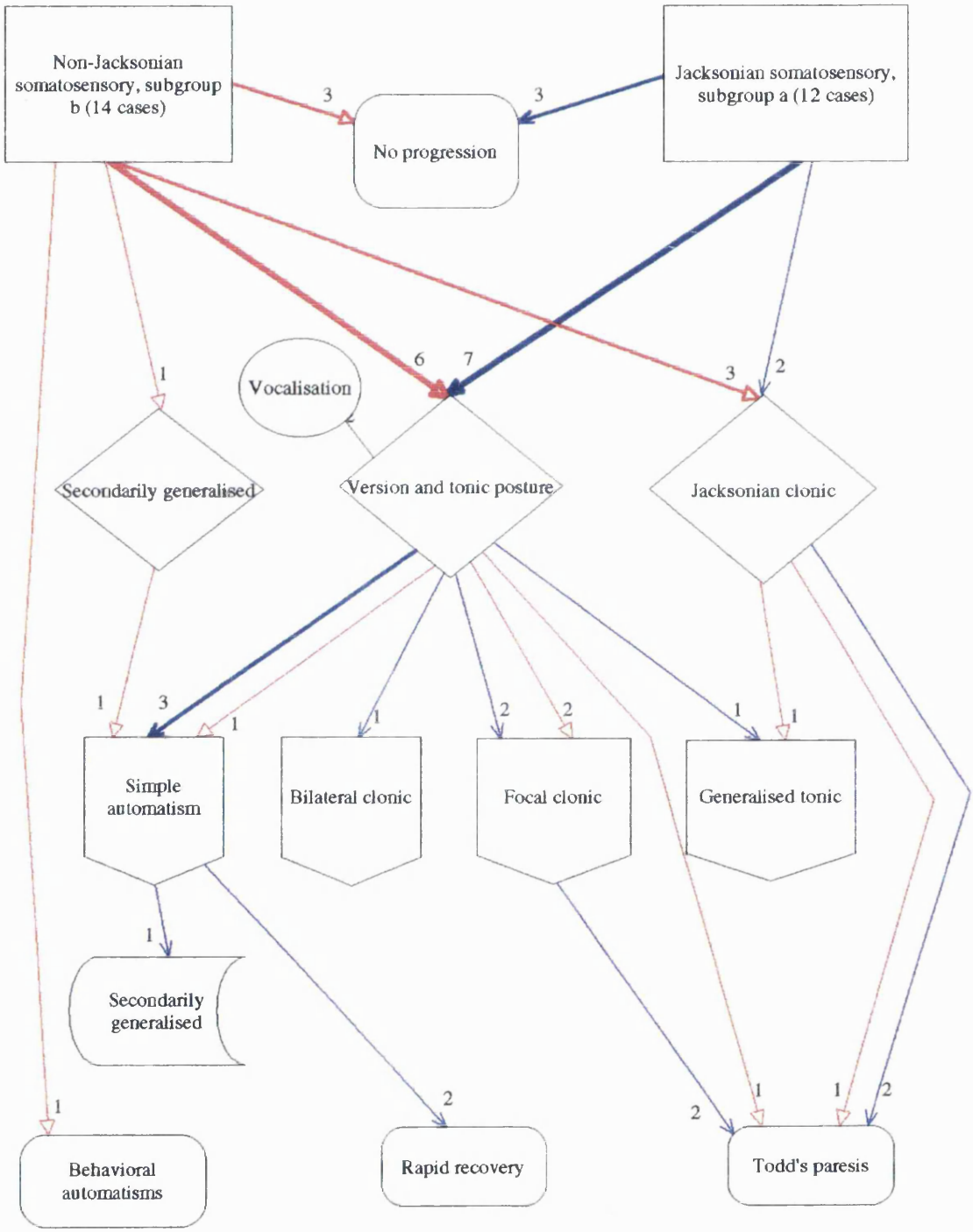


Figure 22

Group 9: seizures characerised by focal paresis

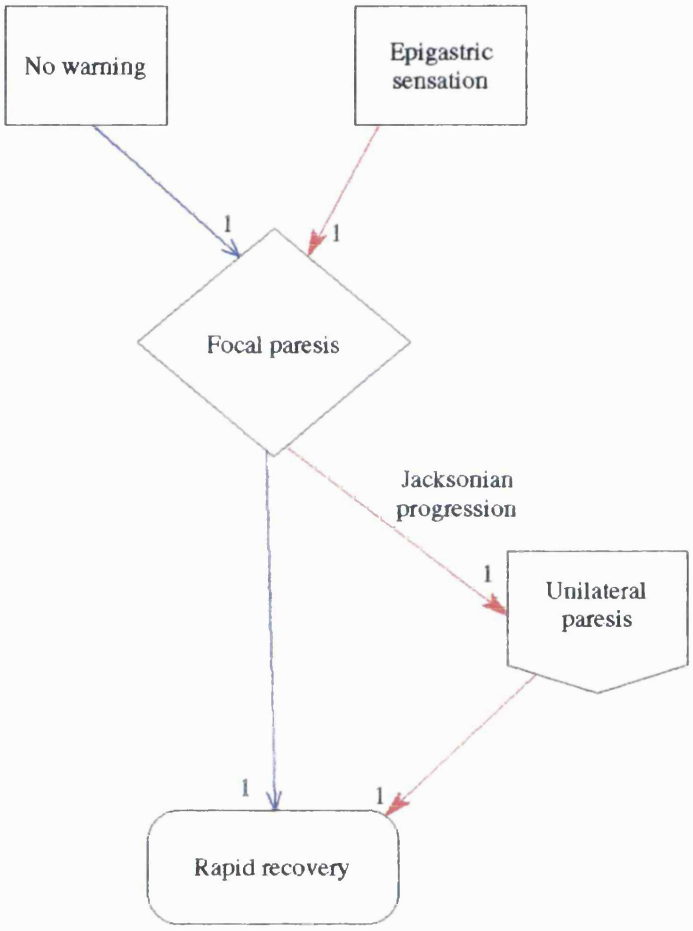


Figure 23

Group 10: habitual complex partial status epilepticus

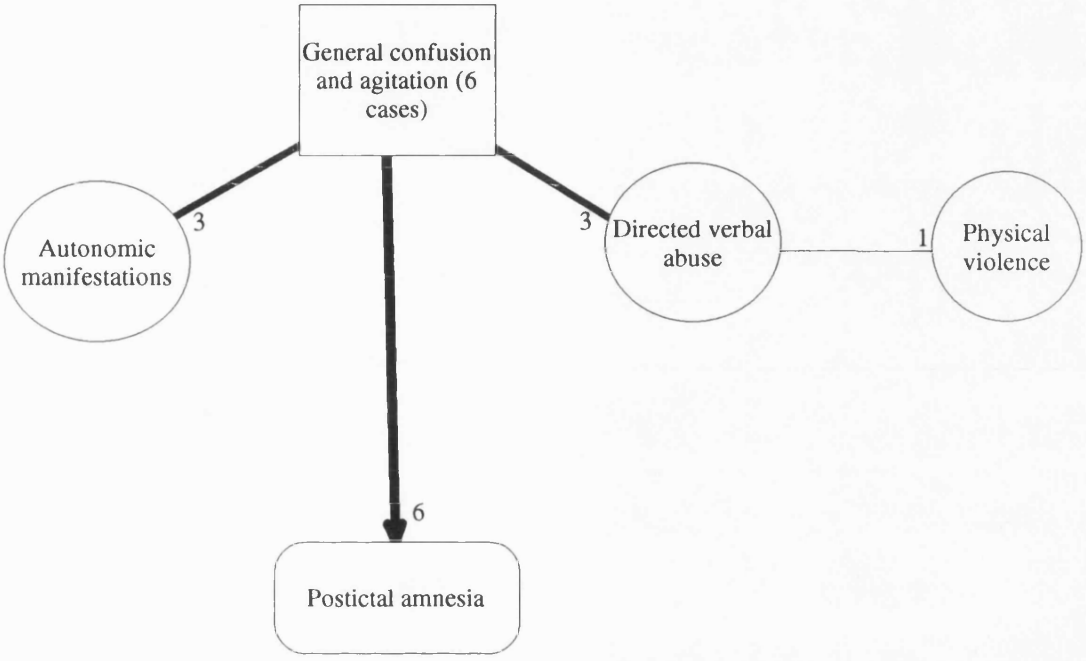


Figure 24

Group 11: seizures consisting of brief isolated jerks

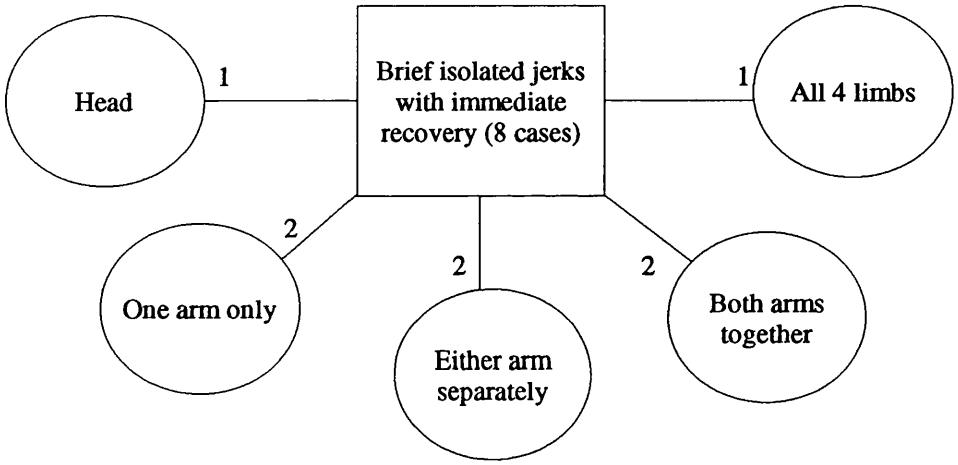


Figure 25

Group12: seizures characterised by Jacksonian motor onset

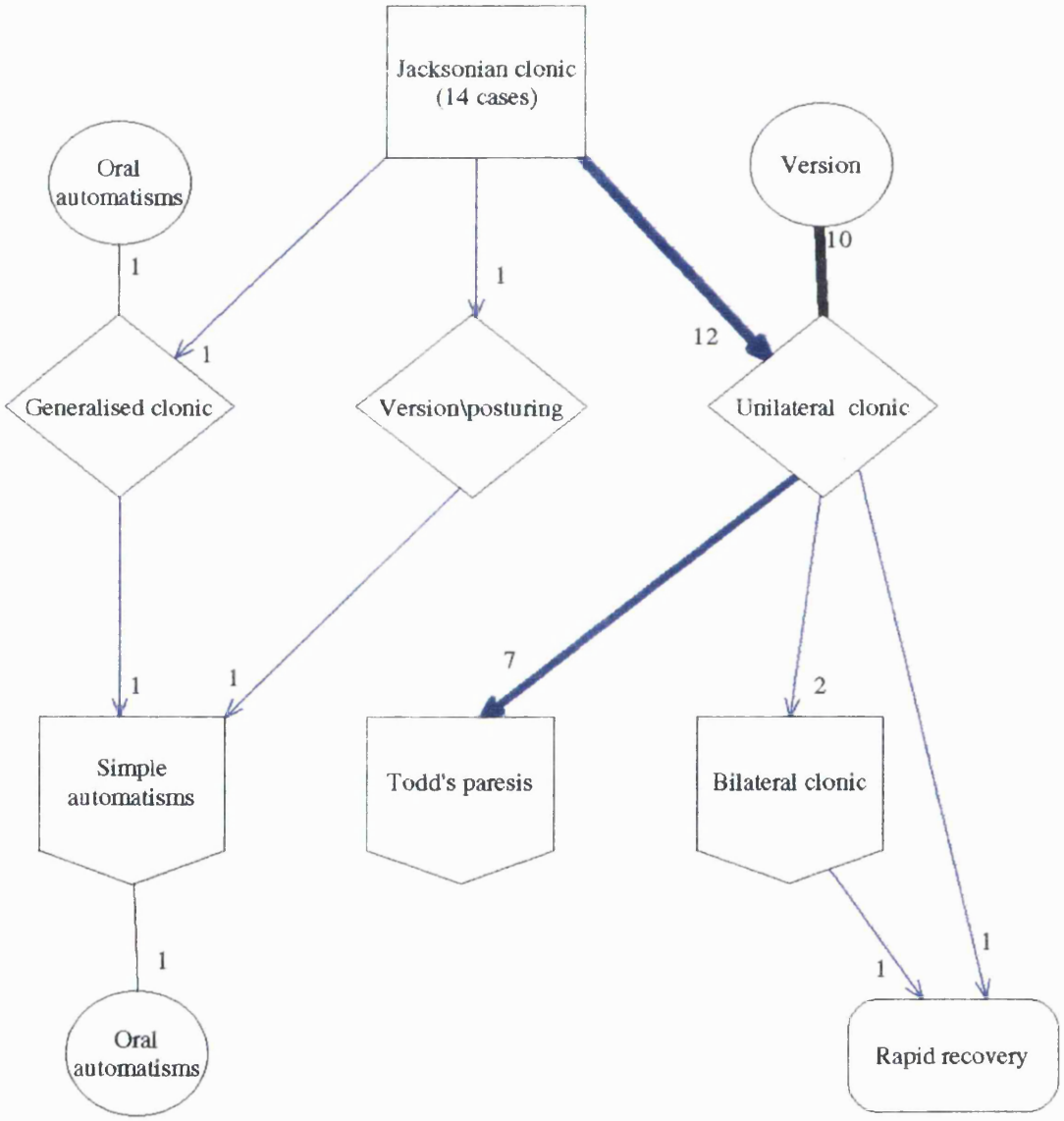


Figure 26

Group 13: seizures characterised by generalised motor activity without specific warning

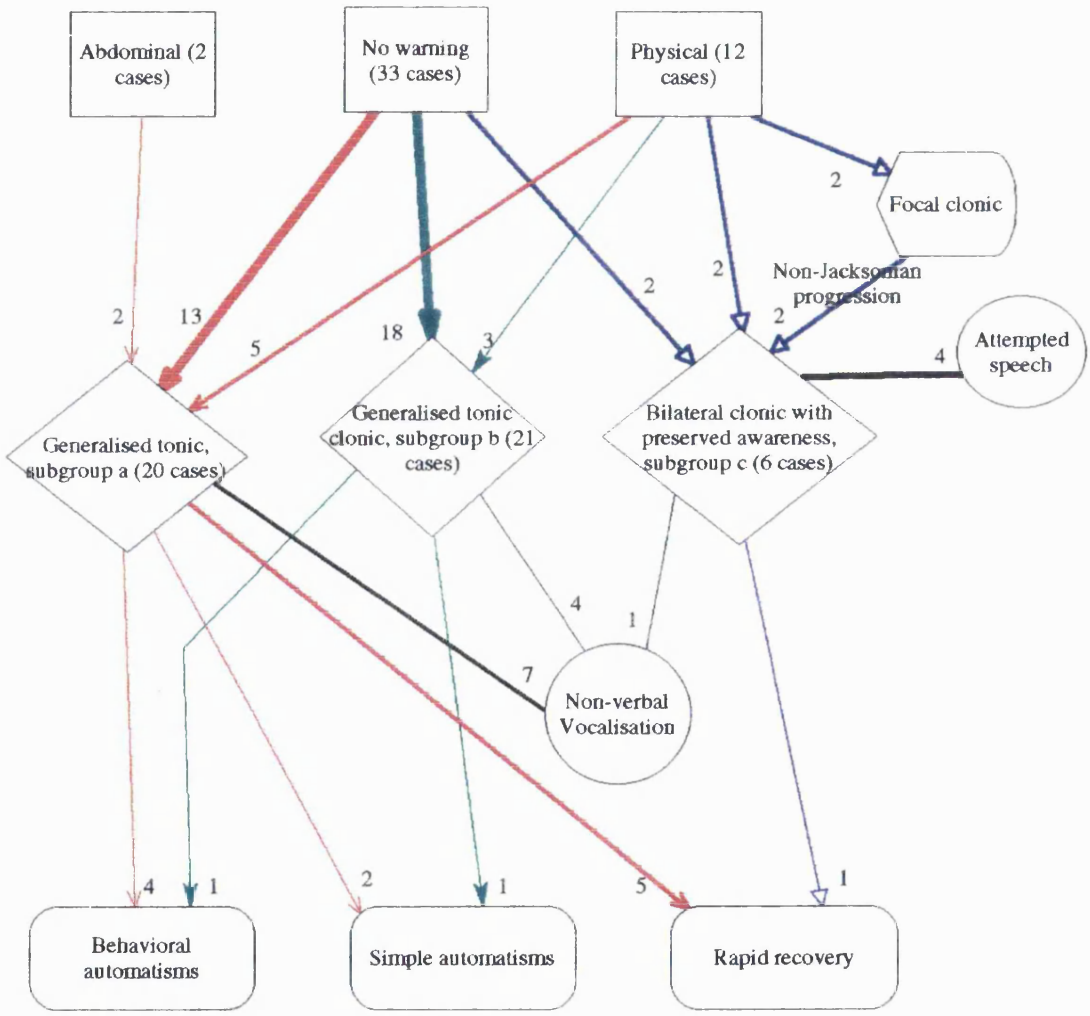


Figure 27

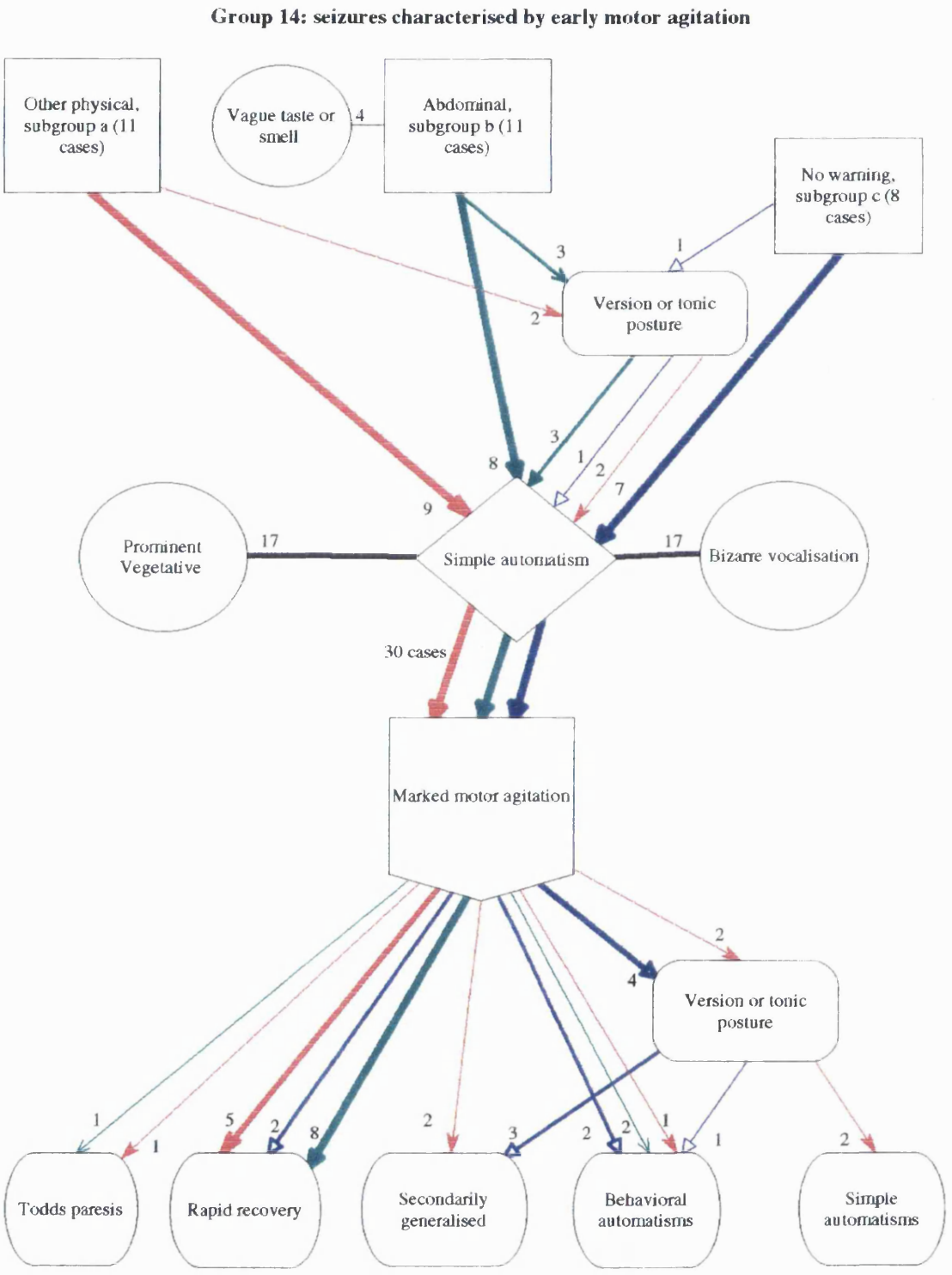

Group 14: seizures characterised by early motor agitation
Other physical, subgroup a (11 cases)
Vague taste or smell
4
Abdominal, subgroup b (11 cases)
No warning, subgroup c (8 cases)
3
1
2
Version or tonic posture
3
8
1
2
7
9
Prominent Vegetative
17
Simple automatism
17
Bizarre vocalisation
30 cases
Marked motor agitation
2
4
Version or tonic posture
1
1
5
2
8
2
3
2
2
1
1
2
Todds paresis
Rapid recovery
Secondarily generalised
Behavioral automatisms
Simple automatisms

Table 35. Simple, behavioural and oral automatisms associated with different seizure types.

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Simple automatisms														
Bicycling	0	0	4	1	0	0	4	0	0	0	0	0	0	7
Scissoring	2	1	0	0	0	0	8	1	0	0	0	0	0	8
Striking	1	2	0	0	1	0	4	0	0	0	0	0	4	11
Kicking	4	0	0	1	1	0	11	2	0	0	0	1	5	17
Rotation	3	0	1	0	0	0	5	1	0	0	0	0	0	3
Head shaking	0	0	0	0	0	0	0	0	0	0	0	0	0	8
Rocking	1	0	2	0	0	0	1	0	0	0	0	0	0	6
Fumbling	1	4	1	1	0	0	3	1	0	3	0	1	2	4
Plucking	5	9	6	4	0	0	14	3	0	2	0	0	8	5
Bimanual	4	2	2	2	1	0	3	0	0	0	0	0	2	10
Rubbing	1	2	2	0	0	1	0	0	0	1	0	0	1	2
Other	0	4	1	1	0	0	2	0	0	0	0	0	0	0
Total cases*	10	19	8	6	1	1	30	4	0	4	0	2	8	30
Behavioral automatisms														
Exploratory	5	8	6	1	0	0	7	1	0	0	0	0	5	5
Tidying	2	0	0	0	0	1	0	0	0	0	0	0	1	1
Bed-making	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Undressing	0	2	1	0	0	0	1	0	0	0	0	0	1	0
Washing	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Other	0	2	1	0	0	0	0	0	0	0	0	0	0	0
Total cases*	5	6	7	1	0	1	7	1	0	0	0	0	5	6
Oral automatisms	10	24	8	6	0	0	17	1	0	2	0	2	3	5

*Some cases had more than one type of automatism

Table 36. Suggested seizure triggers in each group

Group	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
No. of cases	31	57	33	16	2	6	74	26	2	6	8	14	47	30	352
None	21	38	16	11	2	6	50	18	2	5	6	7	31	21	234
Sleep deficit	4	7	9	3	0	0	3	1	0	0	0	3	3	2	35
Startle	0	2	0	0	0	0	9	5	0	0	0	0	3	0	19
Exertion	0	2	1	0	0	0	1	0	0	0	0	1	1	1	7
Relaxation	1	2	0	0	0	0	1	1	0	0	0	0	0	1	6
Stress	8	9	11	1	0	0	9	3	0	1	0	2	4	5	53
Alcohol	0	2	5	0	0	0	3	0	0	0	0	0	2	0	12
Hunger	0	0	2	1	0	0	1	0	0	0	0	0	0	1	5
Food	0	1	1	0	0	0	1	0	0	0	0	0	0	1	4
Heat	0	1	0	0	0	0	0	0	0	0	0	1	1	1	4
Menstruation	1	0	2	1	0	0	2	1	0	0	0	0	1	1	9

Table 37 . Combinations of 2 commonest types in patients with 2 or 3 different seizure types

Group	1	2	3	4	6	7	8	9	10	11	12	13	14
1	1	0	0	1	0	3	0	0	1	0	0	2	1
2	-	4	3	0	3	5	2	0	1	1	0	10	1
3	-	-	5	0	0	1	0	0	0	0	0	1	1
4	-	-	-	1	1	1	0	0	0	0	0	0	0
6	-	-	-	-	0	1	0	0	0	0	0	1	0
7	-	-	-	-	-	5	2	0	0	1	2	5	2
8	-	-	-	-	-	-	0	0	0	1	2	2	1
9	-	-	-	-	-	-	-	0	0	0	1	0	0
10	-	-	-	-	-	-	-	-	0	0	0	1	1
11	-	-	-	-	-	-	-	-	-	0	1	1	0
12	-	-	-	-	-	-	-	-	-	-	0	0	0
13	-	-	-	-	-	-	-	-	-	-	-	2	2
14	-	-	-	-	-	-	-	-	-	-	-	-	1

Table 38. Associations of seizure types in patients with 3 different seizure types

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Commonest seizure type	1	2	2	2	6	7	7	8	8	10	10	12	13	14	14
Second seizure type	1	2	3	7	13	7	13	2	7	1	14	9	13	8	11
Rarest seizure type	8	13	13	13	13	6	13	6	7	11	13	8	11	2	8

Table 39. Clinical and investigative features of cases with epilepsy with startle-provoked seizures

Case	Age at interview	Age of onset of epilepsy	Age of onset of startle response	Aetiology	Intelligence	Clinical signs	Interictal EEG spikes	CT/MR scan features	High resolution MR appearance
1	42	11	Uncertain	Congenital	Low average	Pseudobulbar palsy	None	Normal	Bilateral opercular microgyria
2	14	7	7	Abscess age 5 months	Mild retardation	Left hemiparesis	Rare right parietotemporal	Right frontal atrophy	N/A
3	20	1	3.5	Congenital	Mild retardation	Left hemiparesis	None	Right frontoparietal porencephalic cyst	N/A
4	58	14	14	Unknown	High average	None	Occasional bifrontal	Normal	Normal
5	18	7	13	Unknown	Average	None	Bifrontal	Normal	N/A
6	55	44	44	Possible congenital	Average	Bilateral optic atrophy from congenital rubella	None	Normal	N/A
7	20	2 mths	uncertain	Congenital	Mild retardation	None	Widespread	Normal	Right perisylvian atrophy and dysplasia
8	31	1	25	Congenital	Mild retardation	None	Bifrontal	Normal	Right frontal migration defect
9	50	20	33	Unknown	Average	None	Rare centrotemporal	Normal	N/A

Table 39, continued

Case	Age at interview	Age of onset of epilepsy	Age of onset of startle response	Aetiology	Intelligence	Clinical signs	Interictal EEG spikes	CT/MR scan features	High resolution MR appearance
10	20	8	8	Congenital	Average	Left hemiparesis	None	Right frontocentral porencephalic cyst	N/A
11	7	3.5	7	Congenital	Moderate retardation	Right hemiparesis	N/A	N/A	Left frontoparietal porencephalic cyst
12	34	6.5	Uncertain	Congenital	Low average	Left Babinski response	Normal	None	Right lateral frontal cortical thickening
13	29	19	23	Unknown	Low average	Normal	Normal	Normal	N/A
14	45	7	17	Unknown	Average	Normal	Bifrontal	Normal	N/A
15	13	11	11	Congenital	Low average	Normal	Normal	Mild hemiatrophy	Mild hemiatrophy with marked perisylvian atrophy
16	31	12	12	Congenital	Low average	Left hemiparesis	Normal	Right frontoparietal porencephalic cyst	N/A
17	24	16	18	Pinealoma age 10	Mild retardation	Bitemporal visual field defect	Bifrontal	Generalised atrophy	N/A
18	31	2.5	Uncertain	Congenital	High average	None	Rare right frontotemporal	Normal	Right lateral frontal migration defect
19	53	13	22	Unknown	Average	None	Bitemporal	Normal	N/A

Table 40. General interictal EEG data for each group

Group	Seizures with EEG (%)	Mean EEG's per case	EEG as case inclusion criterion	Cases with spikes (%)	Median spike number	Cases with >10 focal frontal spikes	Cases with >10 focal temporal spikes	Cases with >10 bifrontal spikes	Cases with >10 widespread spikes
1	31 (100)	2.0	6	15 (50)	18	0	7	0	2
2	51 (89)	11.5	9	35 (69)	18	4	0	5	0
3	30 (90)	1.6	11	17(57)	10	2	3	1	0
4	13 (81)	1.8	1	7 (54)	4	0	1	0	0
5	2 (100)	3.5	0	1 (50)	4	0	0	0	0
6	6 (100)	1.8	2	4 (67)	9	1	0	1	1
7	67 (90)	1.7	15	39 (58)	15	8	0	2	6
8	22 (85)	1.8	1	11 (50)	13	2	1	1	1
9	1 (50)	1	0	0	0	0	0	0	0
10	6 (100)	1.4	1	3 (50)	3	0	0	0	0
11	8 (100)	1.5	1	3 (38)	100	1	0	0	0
12	10 (71)	2.5	1	3 (30)	30	0	0	1	0
13	41 (87)	1.8	15	28 (68)	14	3	1	5	3
14	29 (97)	2.2	2	18 (64)	18	4	1	0	0

Figure 28a

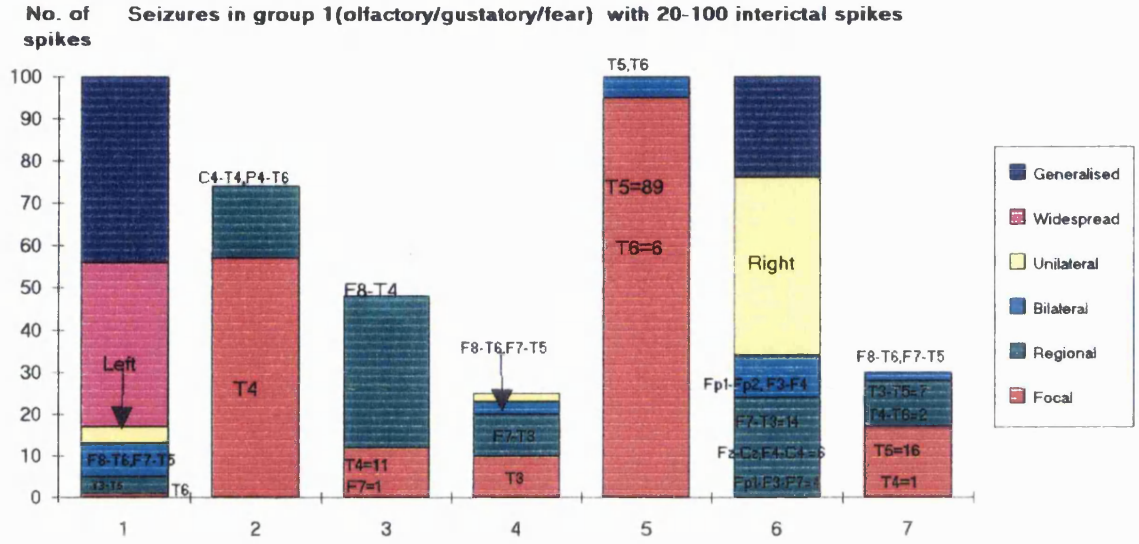


Figure 28b

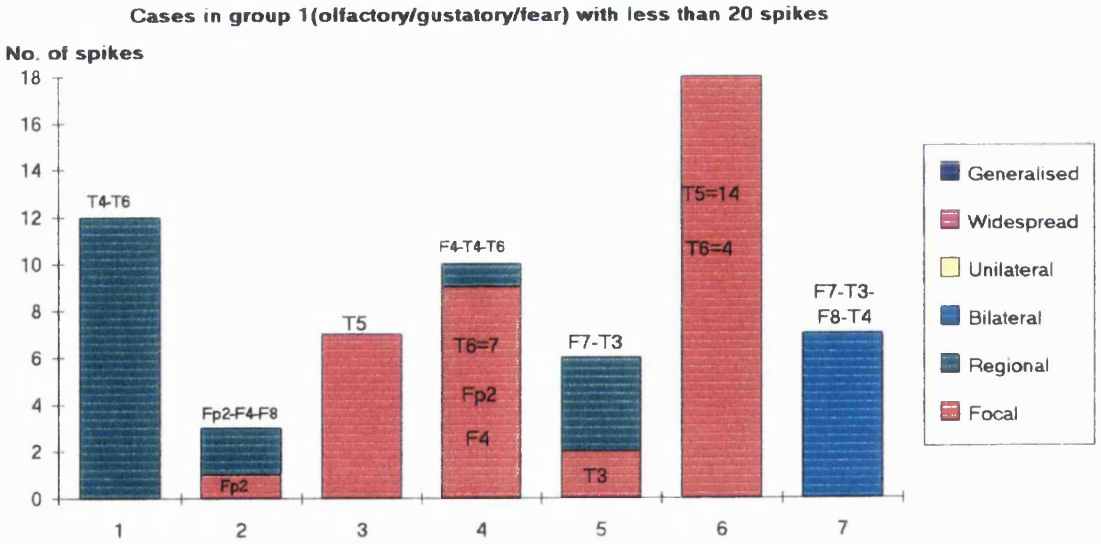


Figure 29a

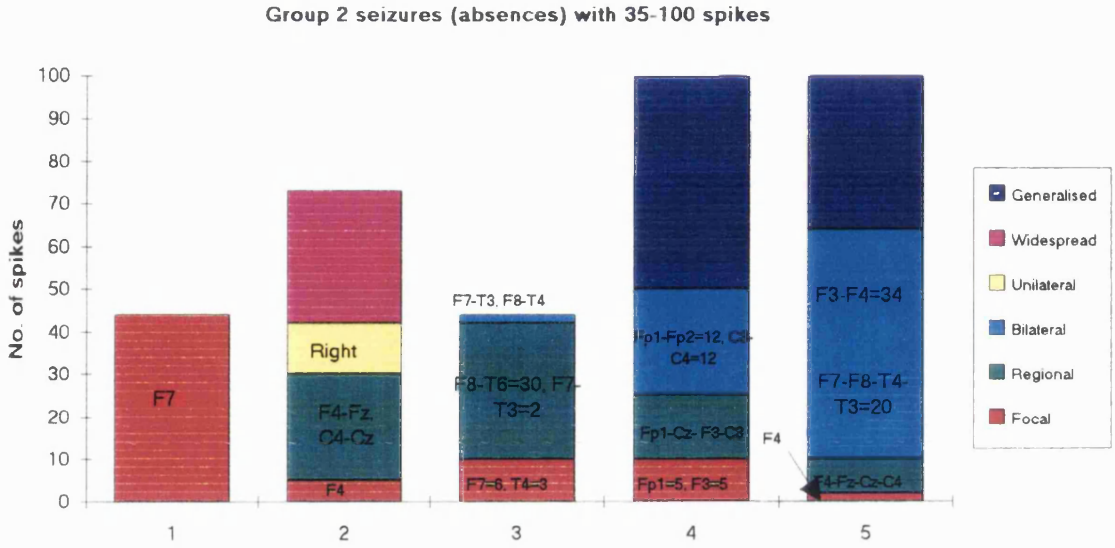


Figure 29b

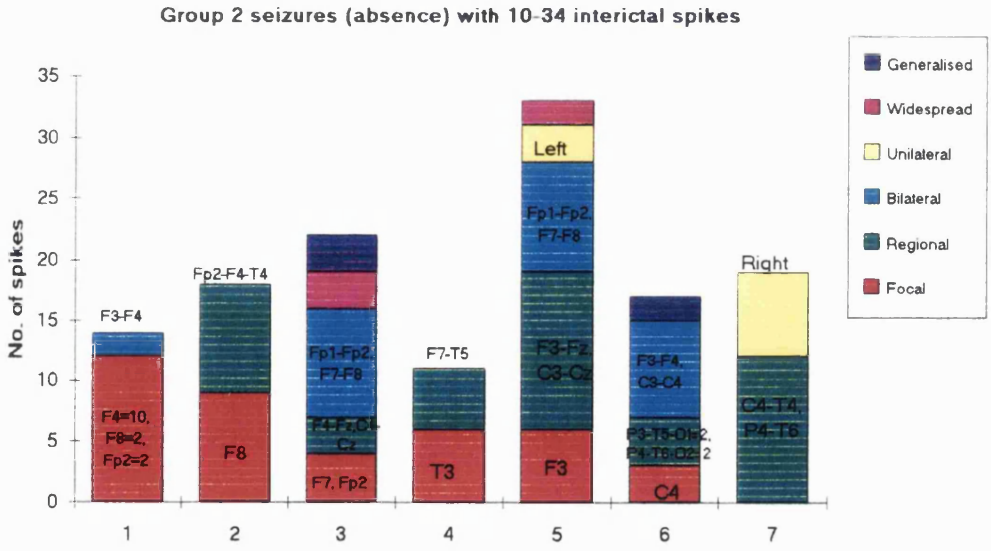


Figure 29c

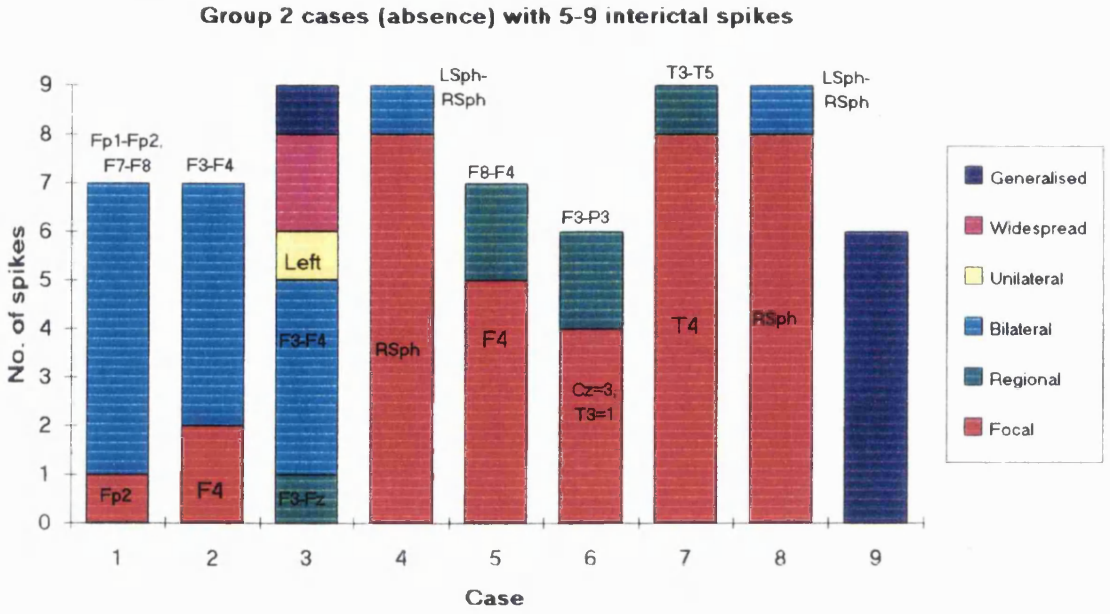


Figure 29d

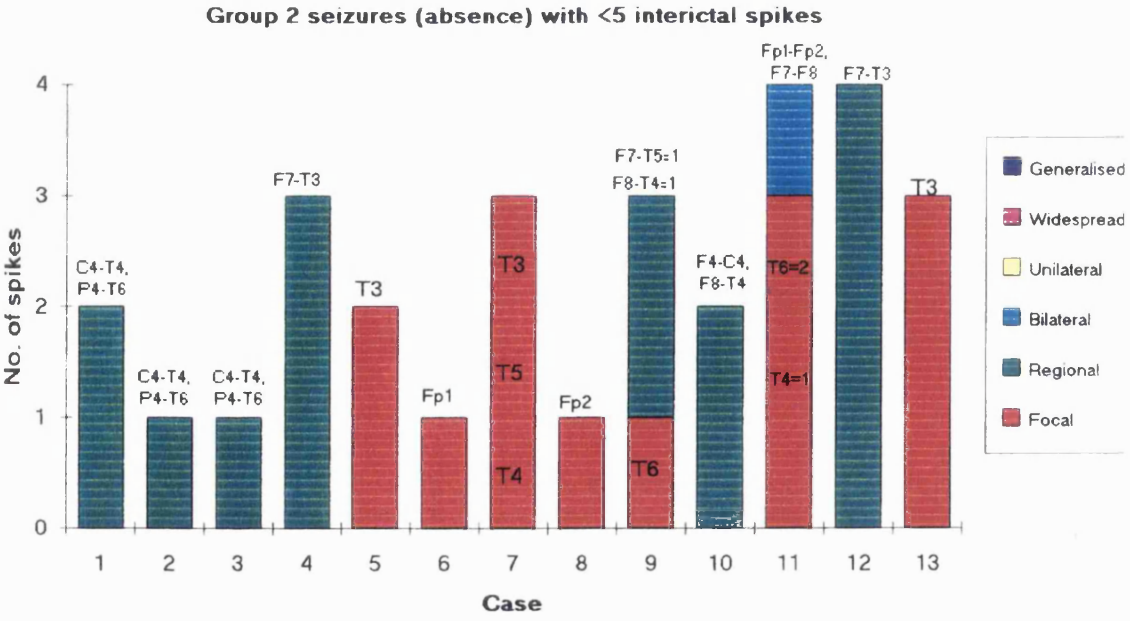


Figure 30a

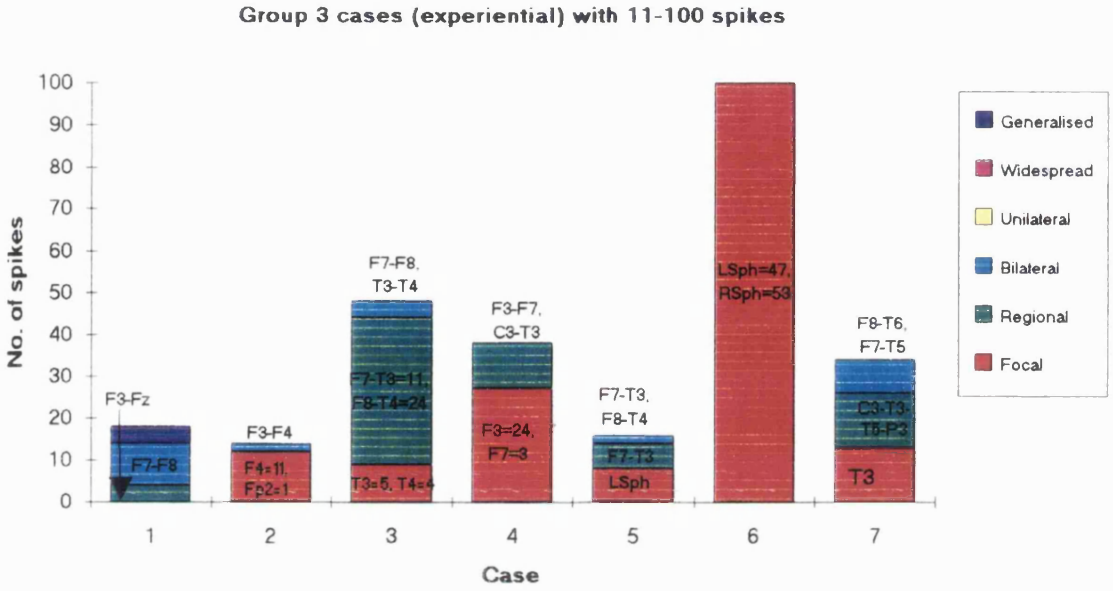


Figure 30b

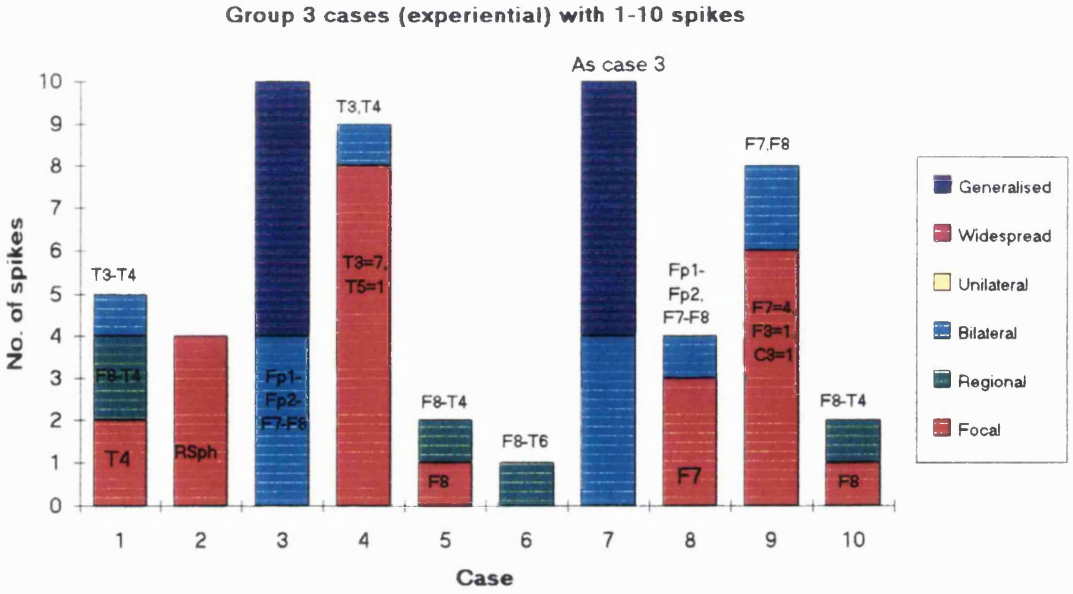


Figure 31

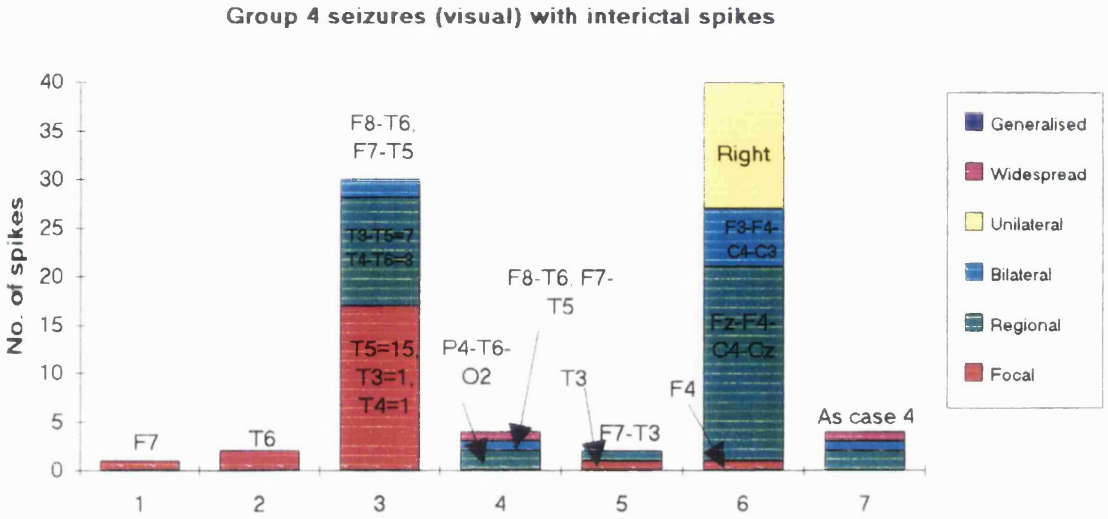


Figure 32

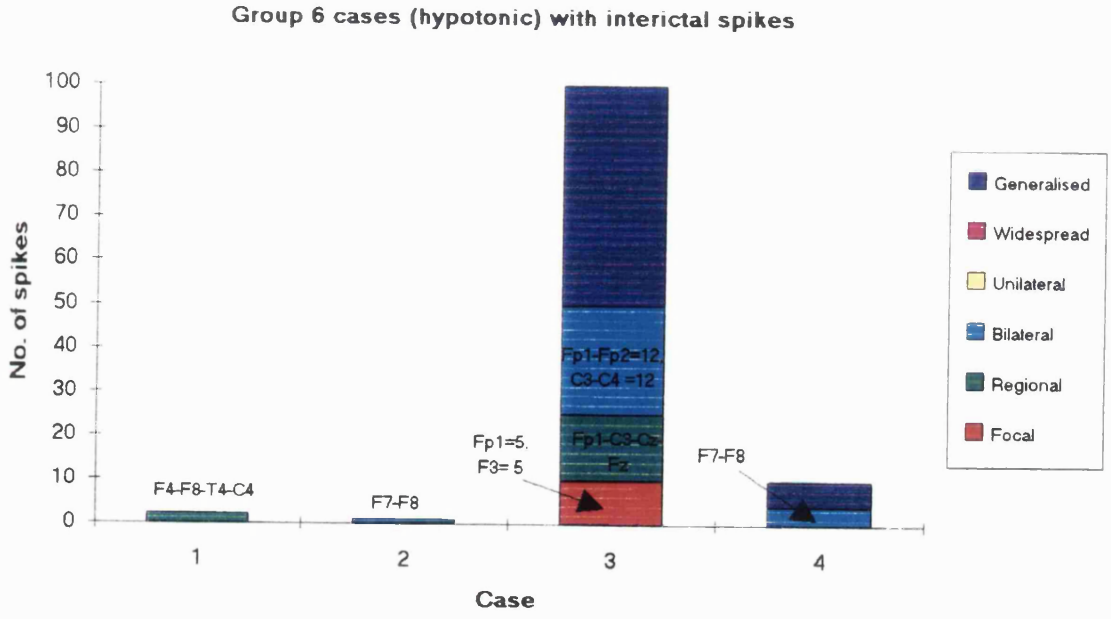


Figure 33a

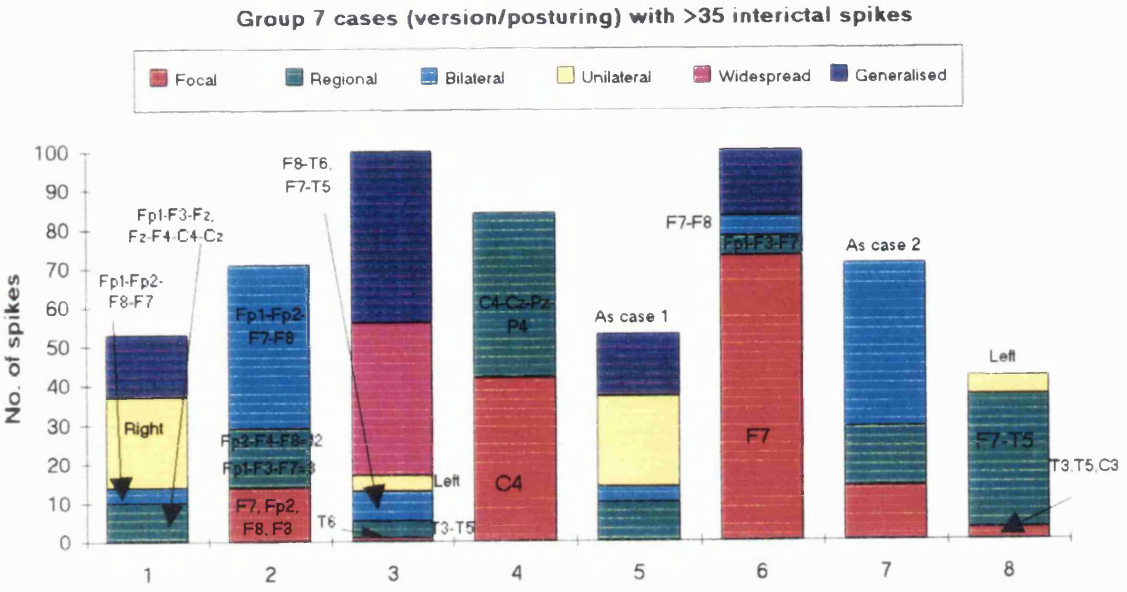


Figure 33b

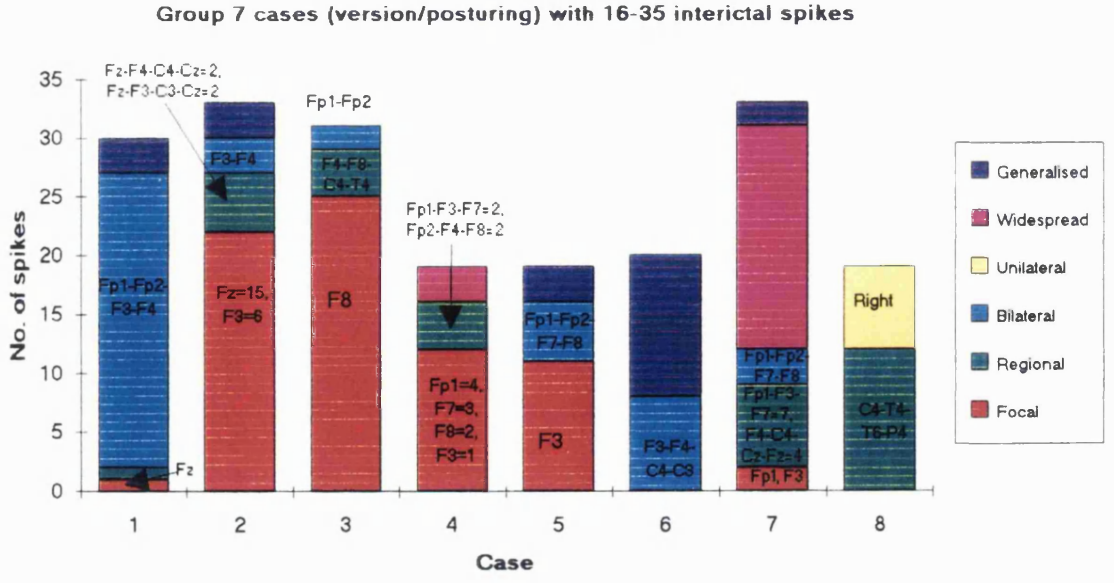


Figure 33c

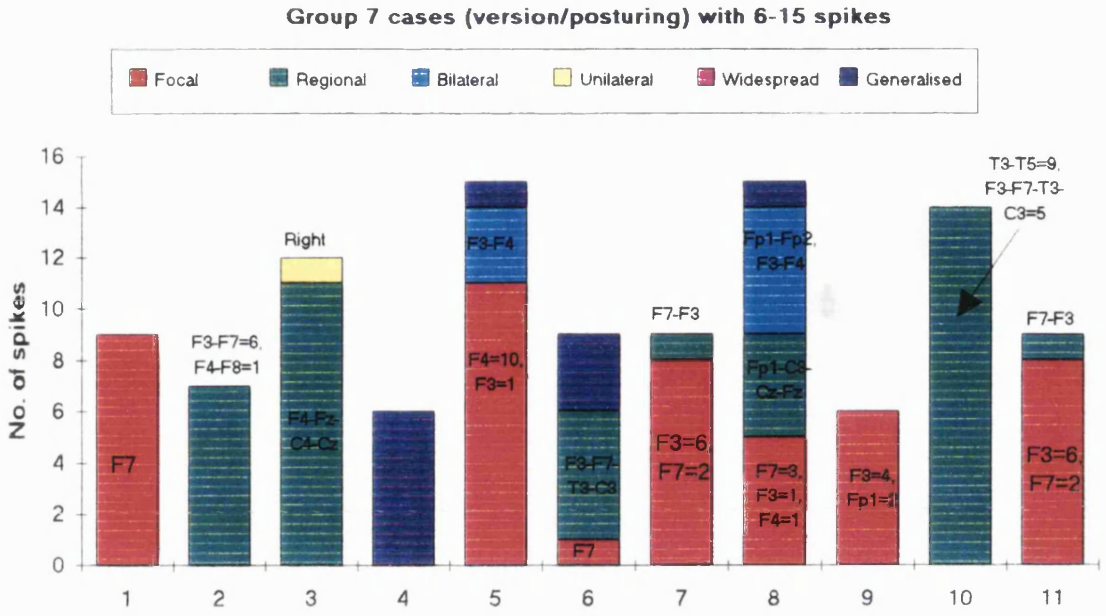


Figure 33d

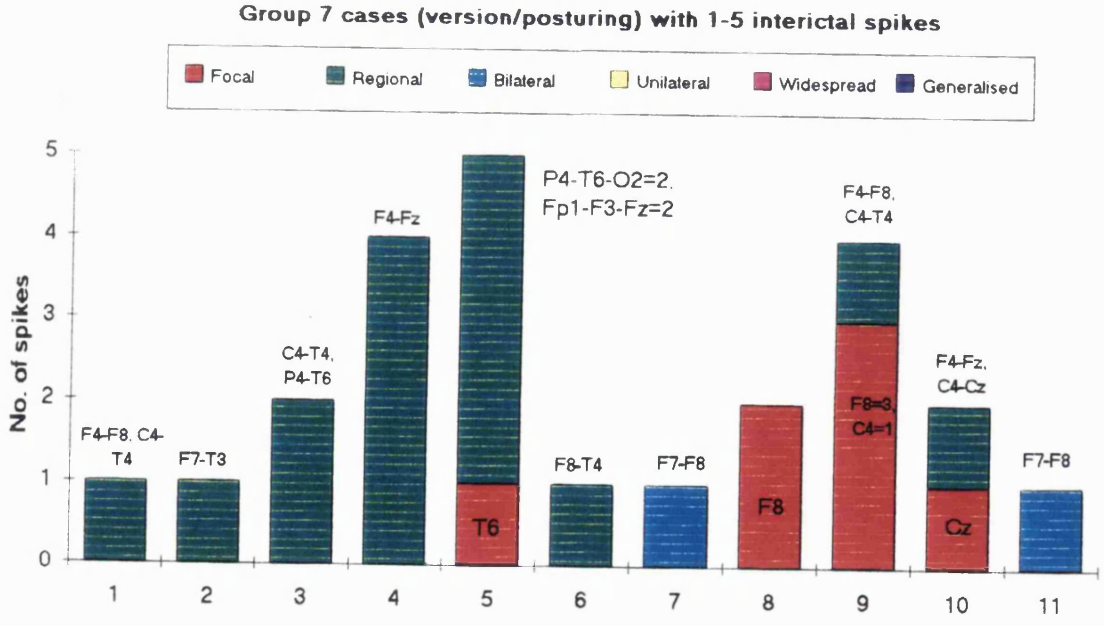


Figure 34a

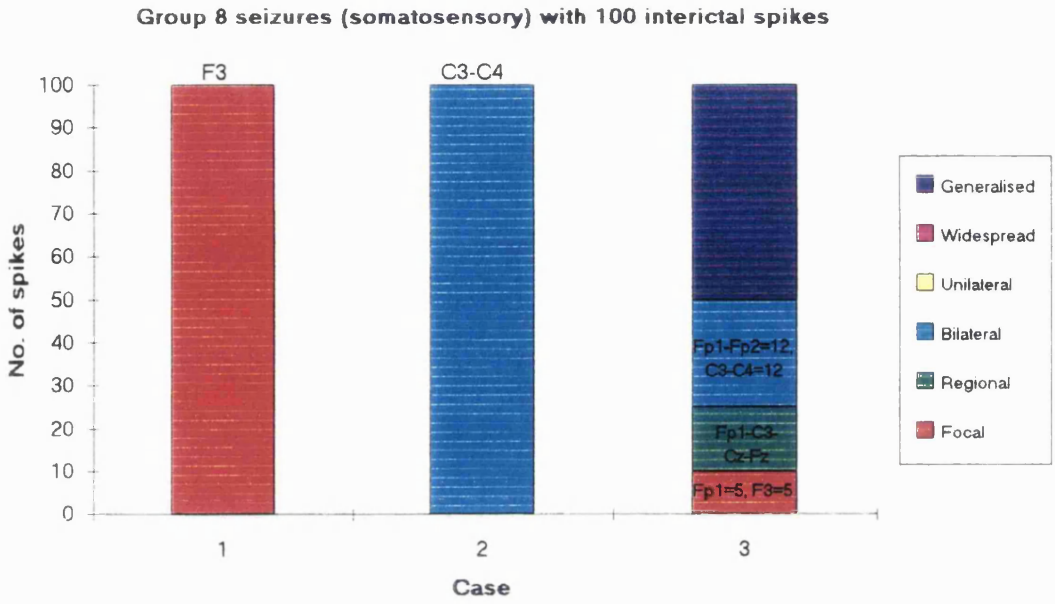


Figure 34b

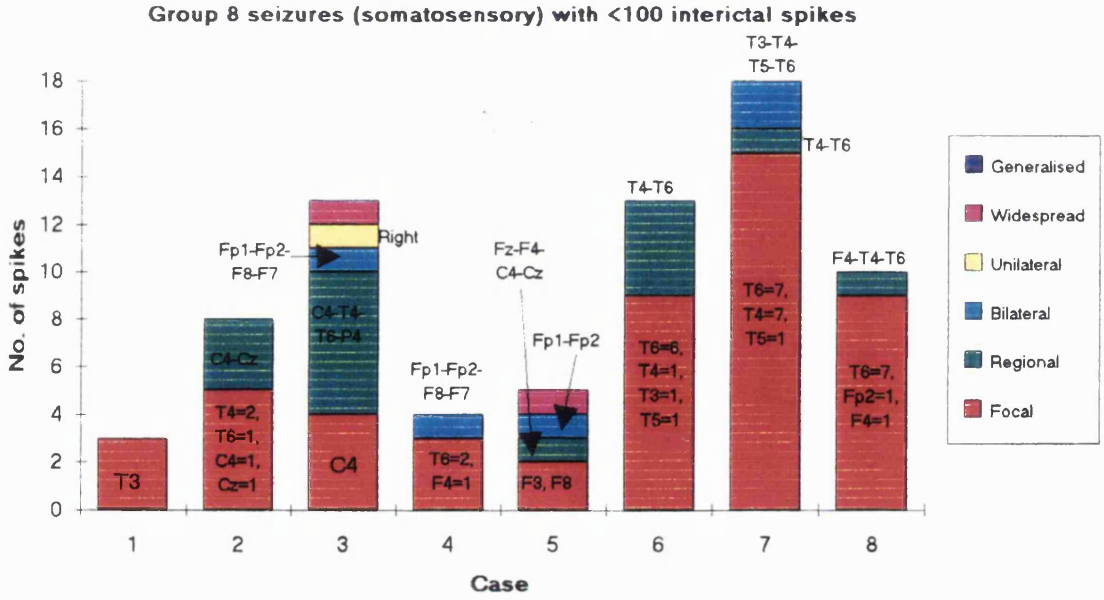


Figure 35

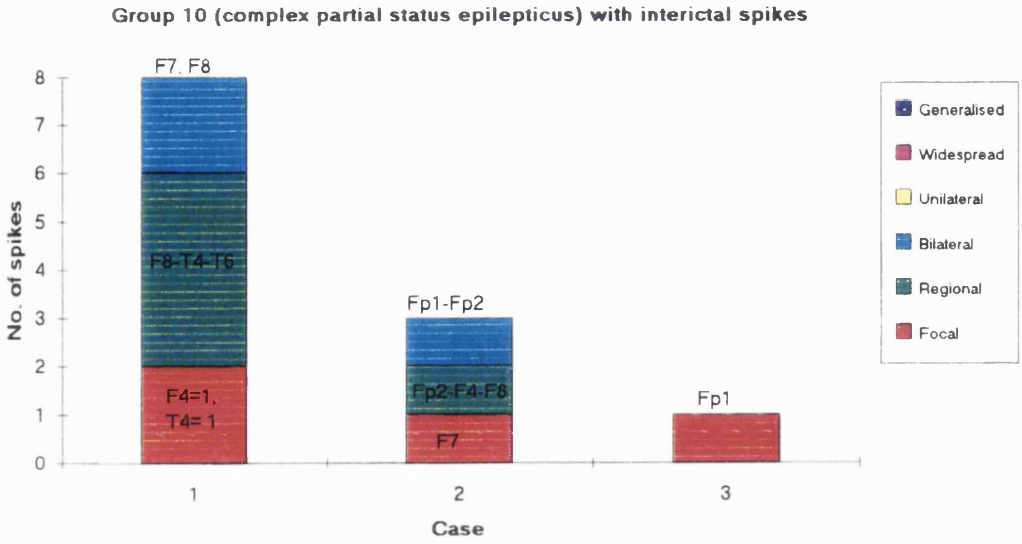


Figure 36

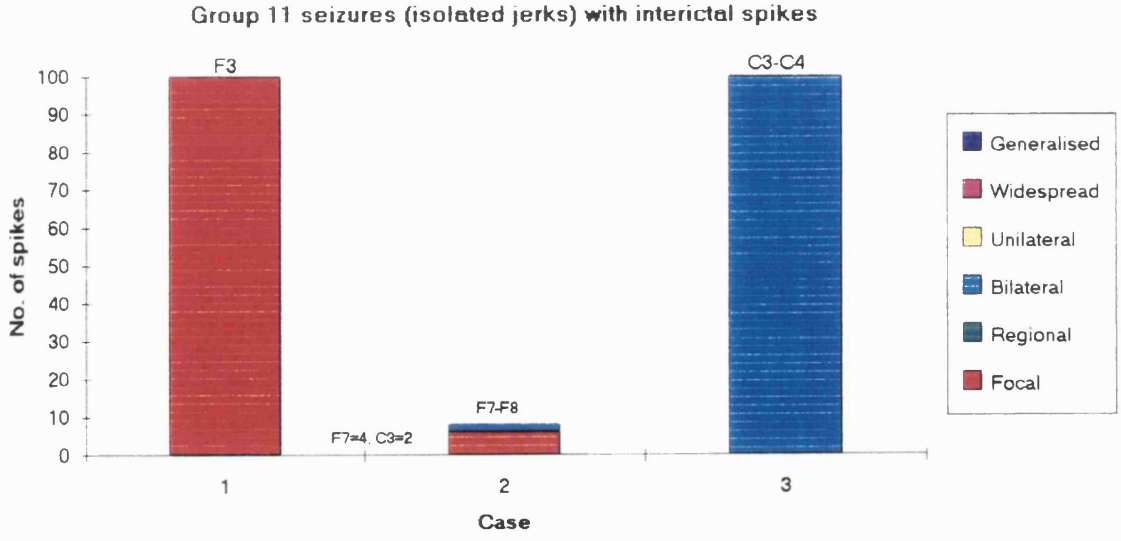


Figure 37

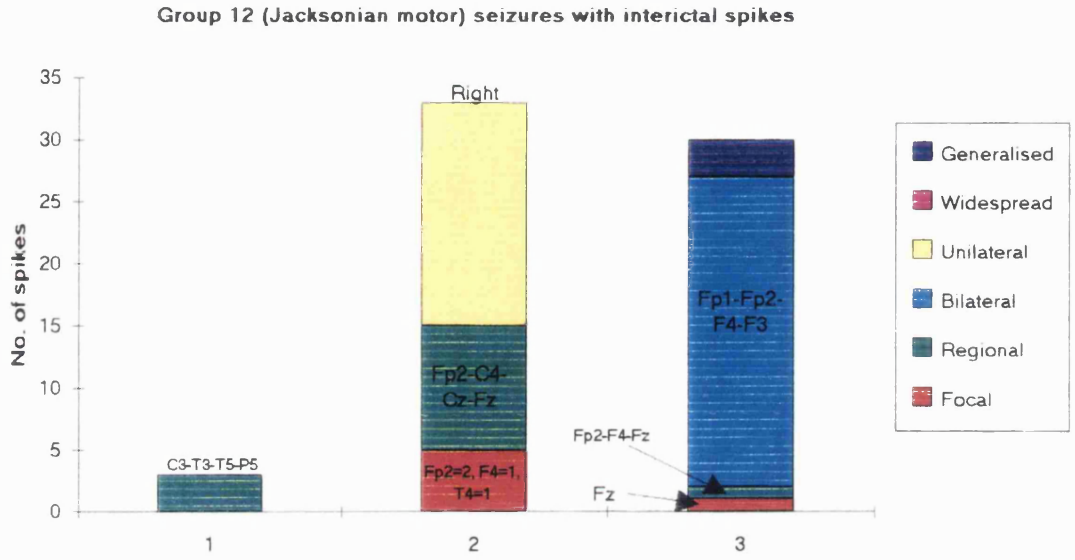


Figure 38a

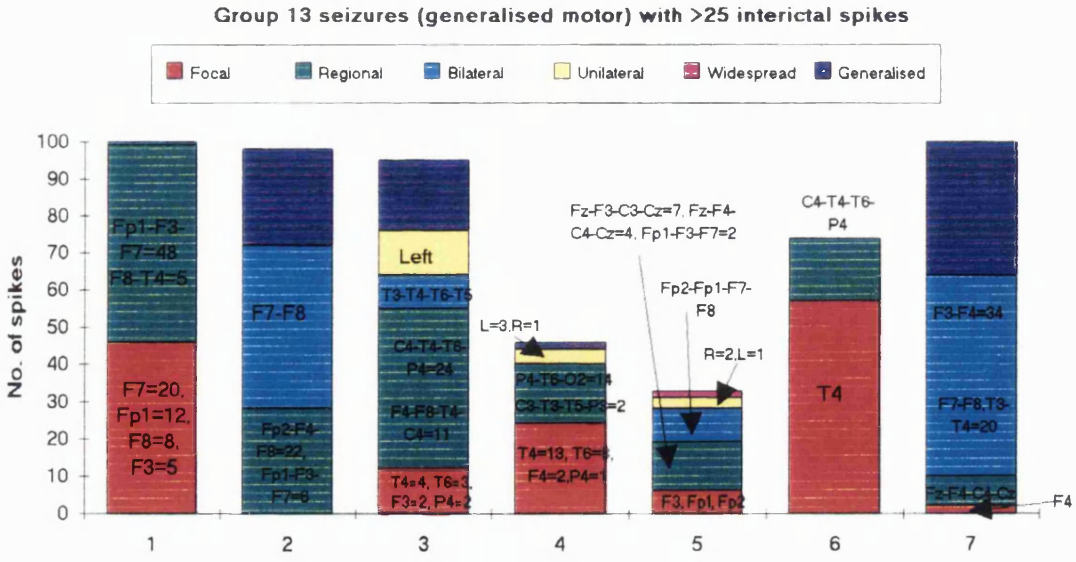


Figure 38b

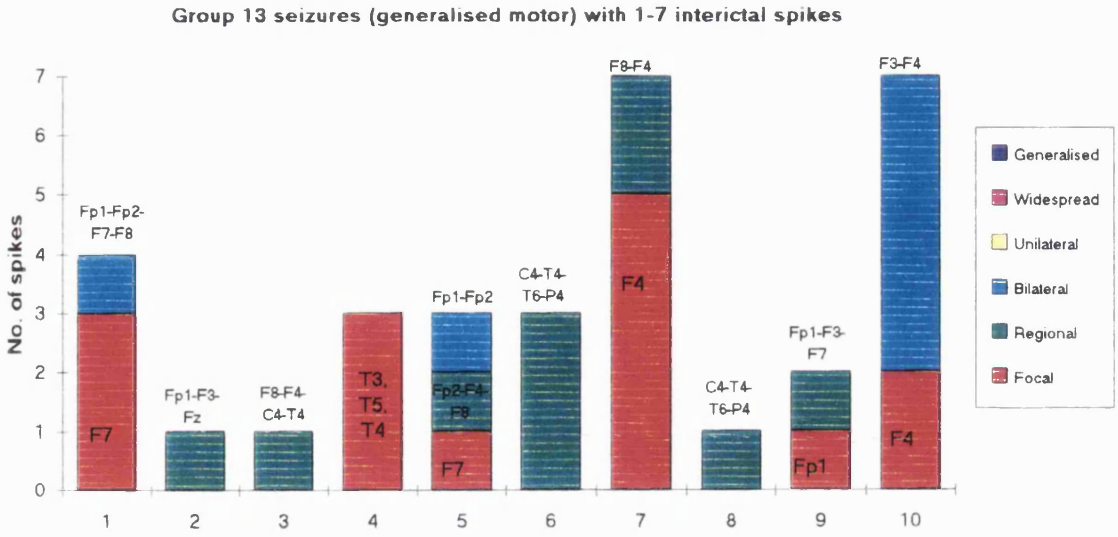


Figure 38c

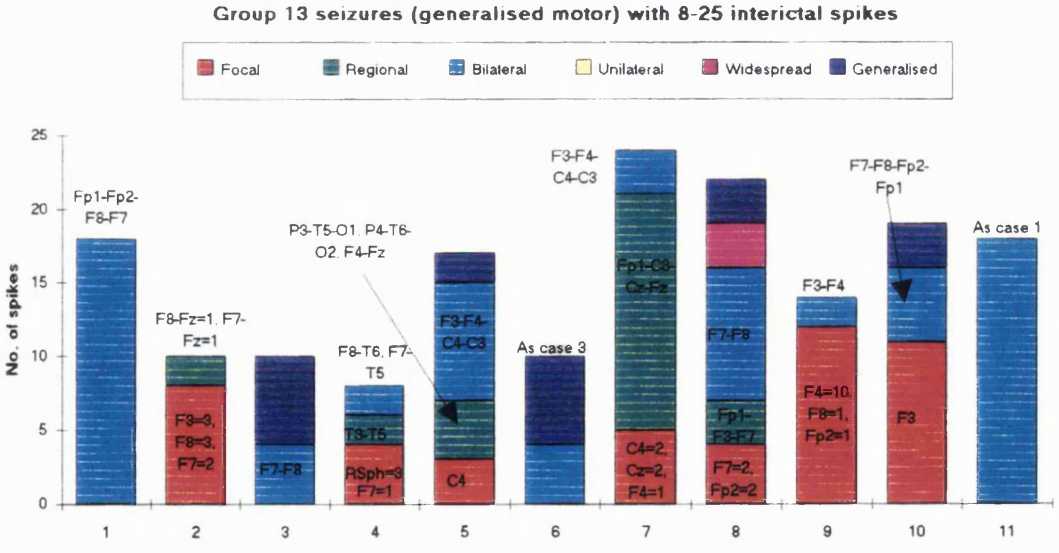


Figure 39a

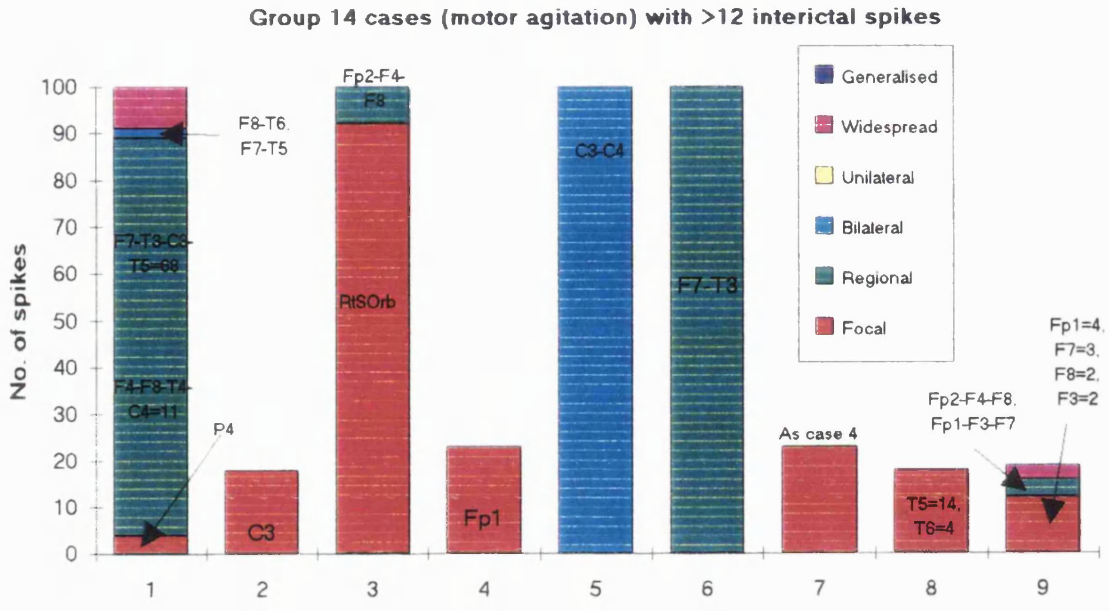


Figure 39b

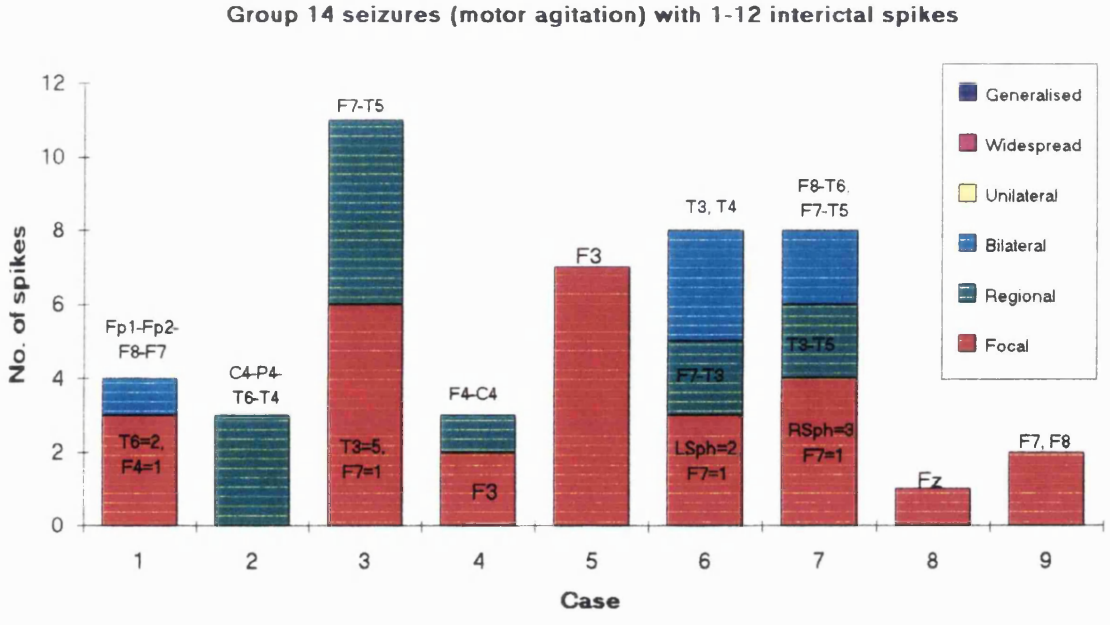


Table 41. General ictal EEG data and ictal EEG specificity in each group

Group	Total seizures recorded (% of group)	Seizures with abnormal EEG in first 20 seconds	Median No. of seizures recorded	Seizures masked by artefact	Median No. of seizures recorded	Seizures with unchanged EEG	Median No. of seizures recorded	Seizures with both abnormal and unhelpful EEG	Median No. of seizures recorded
1	10 (32)	5	2	1	1	1	2	3	3
2	5 (9)	4	2	0	0	0	0	1	2
3	8 (24)	3	4	1	1	2	4	2	3.5
4	4 (25)	3	1	0	0	0	0	1	2
5	2 (100)	1	2	0	0	1	5	0	0
7	21 (28)	14	3	7	3	0	0	0	0
8	4 (15)	1	3	2	5.5	1	1	0	0
10	3 (50)	0	1	0	0	0	0	3*	0
11	1 (12.5)	1	2	0	0	0	0	0	0
12	2 (14)	1	3	1	4	0	0	0	0
14	19 (63)	13	5	5	2	0	0	1	5
Total	**79 (22.4)**	**46 (58)**		**17 (22)**		**5 (6.3)**		**11 (14)**	

* No recording available at onset of complex partial status epilepticus

Table 42. Patterns of abnormal ictal EEG in relation to seizure type: Groups 1 (olfactory/gustatory and fear behaviour) and 2 (absence)

Group	Case	No. of seizures	EEG - Clinical interval (>0 = EEG before clinical)	Focal EEG onset	Regional EEG onset	Bilateral EEG onset	Unilateral EEG onset	Widespread EEG onset	Generalised EEG onset	EEG pattern
1 a	270	2	30		F8-T4					4 Hz
1a	270	1	-5				Left			3-5 Hz
1a	270	1	-5					Yes		3-5 Hz
1a	102	1	15		T4-T6					Attenuation
1a	102	2	-5					Yes		Attenuation
1a	240	1	-5				Right			3-4 Hz
1a	115	1	-5		F8-T4					6-7 Hz
1c	17	3	1	T5						4-5 Hz
1c	98	3	1	Rt Sph						3-4 Hz
1c	33	1	5				Left			4-6 Hz
1c	63	2	15				Right			3-4 Hz
2a	297	1	9	Rt Sph						3 Hz
2a	297	1	10		C4-T4-T6-P4					3 Hz
2a	329	1	-15			Fp1-Fp2-F8-F7				4-5 Hz
2a	325	1	0			F3-F4-C4-C3				Irregular spike/wave
2b	170	4	15		F7-F3-Fz					12-16 Hz
2c	239	2	30	Rt Sph						4-6 Hz

Table 42 continued. Ictal EEG in groups 3 (experiential), 4 (visual) and 5 (auditory)

Group	Case	No. of seizures	EEG - Clinical interval (>0 = EEG before clinical)	Focal EEG onset	Regional EEG onset	Bilateral EEG onset	Unilateral EEG onset	Widespread EEG onset	Generalised EEG onset	EEG pattern
3a	92	2	0	Rt Sph						5 Hz
3a	97	4	20		Rt Sph-T4					6 increasing to 11 Hz
3a	253	7	-10			F7-T3/F8-T4				3-4 Hz
3b	296	1	10	Lt Sph						3 Hz
3b	296	1	3				Left			Attenuation
3b	26	1	1	Lt Sph						5-6 Hz
3b	26	2	-10				Left			5-6 Hz
4b	55	1	5		F7-T3					3-5 Hz
4b	16	1	5		F8-T4					4-6 Hz
4b	292	3	5		Fp2-F4-F8					4 Hz
4b	38	1	0				Right			Attenuation
5	15	1	2	Lt Sph						Slow
5	15	1	5	Rt Sph						Slow

Table 42 continued. Ictal EEG in groups 7 (version/posturing), 8 (focal somatosensory) and 10 (complex partial status epilepticus)

Group	Case	No. of seizures	EEG - Clinical interval (>0 = EEG before clinical)	Focal EEG onset	Regional EEG onset	Bilateral EEG onset	Unilateral EEG onset	Widespread EEG onset	Generalised EEG onset	EEG pattern
7a	324	3	0.5		Fz-F3-C3-Cz					Spikes
7a	93	15	1					Yes		Slow
7a	19	1	10					Yes		4-6 Hz
7a	322	1	-15				Right			Spike/wave, 3-5 Hz
7b	22	1	-2					Yes		2 Hz
7c	358	3	4	F3						12-16 Hz
7c	158	5	10		C3-Cz					4-5 Hz
7c	62	1	2			F3-F4-C4-C3				Spikes 3-5 Hz
7d	72	1	5	Fz						Spikes 4-5 Hz
7d	72	4	2		F8-F4-Fz					Spikes 4-5 Hz
7d	357	5	5		Fp2-F4-F8					16 Hz
7d	40	6	-15			Fp1-Fp2-F8-F7				1 Hz
7d	336	4	0			Fp1-Fp2-F8-F7				Spikes/fast; 16 Hz
7d	85	7	-10		C4-Cz					3-4 Hz
7d	11	1	0.5						Yes	Single slow wave
8a	350	3	5		F4-C4-P4					20 Hz
10	27	1	N/A					Yes		2-3 Hz
10	196	2	N/A					Yes		2-5 Hz
10	347	1	N/A					Yes		2-5 Hz

Table 42 continued. Ictal EEG in groups 11 (isolated jerks), 12 (Jacksonian motor) and 14 (motor agitation)

Group	Case	No. of seizures	EEG - Clinical interval (>0 = EEG before clinical)	Focal EEG onset	Regional EEG onset	Bilateral EEG onset	Unilateral EEG onset	Widespread EEG onset	Generalised EEG onset	EEG pattern
11	14	2	0.5						Yes	Single slow wave
12	323	3	0	C4						5 Hz
14a	13	2	10	T4						4-6 Hz
14a	13	4	60		F8-T6					4-6 Hz
14a	12	2	15		F4-F8-T4-C4					1-2 Hz
14a	334	2	5		Fp2-F4-Fz					2-4 Hz
14a	334	5	5			Fp1-Fp2				2-4 Hz
14a	73	3	5		Fp1-F3-F7					4 Hz
14a	73	2	10				Left			4 Hz
14a	20	8	5				Left			3-5 Hz
14a	128	2	10				Right			3 Hz
14a	306	6	3						Yes	2-3 Hz
14b	335	5	2	F7						14-16 Hz
14b	286	2	60		F8-F4-Fz					4-5 Hz
14b	126	1	-20				Left			3 Hz
14b	113	1	-20					Yes		3-4 Hz
14c	337	6	20	Fp1						Spikes 3-4 Hz
14c	337	6	0		Fp1-Fp2-F8-F7					3-4 Hz
14c	108	2	10		F7-T5					8 Hz
14c	339	5	-5		F4-Fp2					4- 6 Hz

Table 43. Distribution of lesions in abnormal scans

Group	Frontal	Temporal	Parietal	Fronto-parietal	Fronto-temporal	Temporo-parietal	Fronto-temporo-parietal	Total
1	2	10	0	1	0	0	1	14
2	6	18	1	2	1	1	0	29
3	3	13	1	3	0	0	0	20
4	2	6	0	1	1	0	1	11
5	0	1	0	0	0	0	0	1
6	1	1	0	0	0	0	0	2
7	18	1	0	4	1	0	3	27
8	4	0	0	7	1	0	3	15
9	1	0	0	0	0	0	1	2
10	1	1	0	0	0	0	0	2
11	1	0	0	0	0	0	0	1
12	4	0	1	1	0	0	3	9
13	9	5	0	2	0	0	1	17
14	9	2	1	0	1	0	0	13
Total	61	58	4	21	5	1	13	163

Table 44. Regional frontal involvement in pure frontal lesions in seizure groups 1 (olfactory/gustatory and fear behaviour); 2(absence); 3 (experiential); 4 (visual) and 6 (hypotonic)

Seizure category	Case number	Number of regions involved	Lesion type	Fronto -polar	Orbito-frontal	Lateral Prefrontal	Medial Prefrontal	SMA	Lateral premotor	Primary motor	Anterior cingulate
1a	95	3	AVM	3	0	0	3	0	0	0	3
1b	3	3	Post-traumatic atrophy	0	0	2	0	1	3	2	0
2a	155	4	Meningioma	0	0	3	2	2	2	0	0
2a	329	1	Glioma	0	0	0	3	1	0	0	1
2a	132	2	AVM	0	0	1	3	3	1	0	0
2a	257	1	Glioma	0	3	0	0	0	0	0	0
2a	154	2	Calcification (cause ?)	0	0	0	0	3	3	0	0
2a	167	5	Post-trauma	3	1	3	3	0	3	0	3
3a	238	3	Gliosis	2	3	0	0	0	0	0	2
3b	309	3	Glioma	0	0	0	3	2	0	1	2
3b	9	2	AVM	0	0	2	3	1	0	0	3
4	342	1	AVM	0	3	0	0	0	0	0	0
4	264	1	Meningioma	0	0	0	0	3	0	0	0
6	214	2	AVM	0	0	1	3	3	1	0	0

0=uninvolved; 1=possibly involved (1-10%);

2=partial involvement (11-50%); 3=heavy involvement (>50% or a small lesion restricted to that region)

Table 44 continued. Regional frontal involvement in pure frontal lesions in seizure group 7 (version/posturing)

Seizure category	Case number	Number of regions involved	Lesion type	Fronto -polar	Orbito-frontal	Lateral Prefrontal	Medial Prefrontal	SMA	Lateral premotor	Primary motor	Anterior cingulate
7a	93	3	Dysplasia	0	0	2	0	0	3	2	0
7a	60	1	Dysplasia	3	0	1	0	0	0	0	0
7a	105	2	Dysplasia	0	0	1	0	3	3	1	1
7a	344	7	Post-traumatic atrophy	3	1	3	3	3	3	0	3
7a	133	7	Post-abscess scarring	3	2	2	3	3	1	1	3
7a	330	1	Glioma	0	0	0	3	1	0	0	1
7a	324	2	Post-abscess scarring	0	0	0	0	3	2	0	0
7a	202	2	Dysplasia	0	0	1	0	3	3	1	1
7b	314	1	Dysplasia	0	0	2	1	0	3	0	0
7b	57	4	AVM	3	2	2	1	0	0	0	3
7b	201	1	Cyst, congenital?	0	0	0	0	0	3	0	0
7c	100	1	Cyst, congenital?	0	0	0	0	0	3	0	0
7d	153	3	meningioma	0	0	2	3	3	0	0	0
7d	278	2	Post-traumatic atrophy	3	0	1	3	0	0	0	0
7d	72	2	Glioma	0	0	0	0	1	2	3	0
7d	311	2	AVM	0	0	1	0	0	3	2	0
7d	263	2	Glioma	0	0	2	3	1	1	0	1
7d	85	2	Dysplasia	0	0	0	0	0	3	0	0

0=uninvolved, 1=possibly involved, 2=partial involvement, 3=heavy involvement

Table 44 continued. Regional frontal involvement in pure frontal lesions in seizure groups 8 (focal somatosensory); 9 (focal paresis); 10 (complex partial status epilepticus); 11 (isolated jerks); and 12 (Jacksonian motor)

Seizure category	Case number	Number of regions involved	Lesion type	Fronto -polar	Orbito-frontal	Lateral Prefrontal	Medial Prefrontal	SMA	Lateral premotor	Primary motor	Anterior cingulate
8a	295	3	AVM	0	0	3	0	1	3	2	0
8a	75	3	Dysplasia	1	0	3	0	0	3	3	0
8b	287	3	Dysplasia	0	0	3	1	1	3	3	0
8b	83	3	Dysplasia	0	0	2	1	1	3	3	0
9	142	2	Infarct	0	0	3	0	0	2	0	0
10	347	2	Post-traumatic atrophy	2	3	0	0	0	0	0	0
11	194	3	Dysplasia	1	0	3	0	0	3	3	0
12	323	3	Glioma	0	0	0	0	3	2	2	3
12	52	3	Dysplasia	0	0	0	0	2	3	2	0
12	312	1	AVM	0	0	0	0	0	3	1	0
12	294	3	AVM	0	0	3	0	1	3	2	0

0=uninvolved, 1=possibly involved, 2=partial involvement, 3=heavy involvement

Table 44 continued. Regional frontal involvement in pure frontal lesions in seizure groups 13 (generalised motor) and 14 (motor agitation)

Seizure category	Case number	Number of regions involved	Lesion type	Fronto -polar	Orbito-frontal	Lateral Prefrontal	Medial Prefrontal	SMA	Lateral premotor	Primary motor	Anterior cingulate
13a	227	1	Dysplasia	3	0	1	0	0	0	0	0
13a	23	3	Post-abscess scarring	3	2	0	0	0	0	0	2
13a	5	2	Glioma or AVM ?	0	0	0	0	0	0	0	3
13b	222	5	Post-traumatic atrophy	3	1	3	3	0	3	0	3
13b	349	2	Post-traumatic atrophy	2	3	0	0	0	0	0	0
13b	308	2	Dysplasia	0	0	0	0	0	3	3	0
13c	169	3	Meningioma	0	0	2	3	3	0	1	0
13c	171	4	Meningioma	3	0	3	3	0	1	0	3
13c	111	4	Glioma	0	0	3	3	0	3	1	2
14a	313	2	Post-traumatic atrophy	0	3	0	0	0	0	0	2
14a	187	1	Dysplasia	3	0	1	0	0	0	0	0
14a	128	5	Post-traumatic atrophy	3	2	3	3	1	0	0	2
14b	285	3	AVM	0	0	2	0	2	3	0	0
14b	254	1	Glioma	0	0	0	3	0	0	0	0
14b	261	5	Dysplasia	2	3	0	3	2	0	0	3
14c	104	1	AVM or Glioma ?	0	0	0	1	0	0	0	3
14c	343	7	Post-truamatic atrophy	3	1	3	3	3	3	0	3
14c	348	2	Post-traumatic atrophy	2	3	0	0	0	0	0	0

0=uninvolved, 1=possibly involved, 2=partial involvement, 3=heavy involvement

Table 45. Comparison of seizure manifestations between cases with pure frontal and pure temporal lesions (61 frontal and 58 temporal seizures).

Manifestation	Frontal	Temporal	Association
Clustering	23	18	None
Diurnal variation	See figure 40		None
Average frequency	See figure 41		None
Maximum frequency	See figure 42		None
Seizure duration	See figure 43		None
Postictal duration	See figure 44		None
Secondary generalisation	See figure 45		None
Prodrome	16	12	None
Frequent purely subjective seizures	**14**	**29**	**Temporal (P=0.001)**
Abdominal symptom	11	20	None
Rising epigastric	3	6	None
Cephalic or general body sensation	17	12	None
Olfactory or gustatory sensation	1	6	None
Visual symptoms	2	6	None
Somatosensory symptoms	4	10	None
Vegetative symptoms	31	31	None
Incontinence	10	4	None
Pallor	13	12	None
Facial flushing	9	10	None
Experiential symptoms	**9**	**22**	**Temporal (P=0.001)**
Fear	9	7	None
Generalised hypertonia	19	12	None
Clonic movements	35	17	Frontal ? (P<0.005)
Early clonic movements	**21**	**4**	**Frontal (P<0.001)**
Tonic movements	23	16	None
Early tonic movements	20	7	Frontal ? (P<0.01)
Head turning	28	19	None
Early head turning	**26**	**6**	**Frontal (P<0.001)**
Oral automatisms	**9**	**23**	**Temporal (P<0.001)**
Simple automatisms	28	31	None
Complex automatisms	10	18	None
Non-verbal vocalisation	12	6	None
Verbal vocalisation	10	10	None

Figure 40. Comparison of diurnal variation of seizures associated with pure temporal and pure frontal lesions

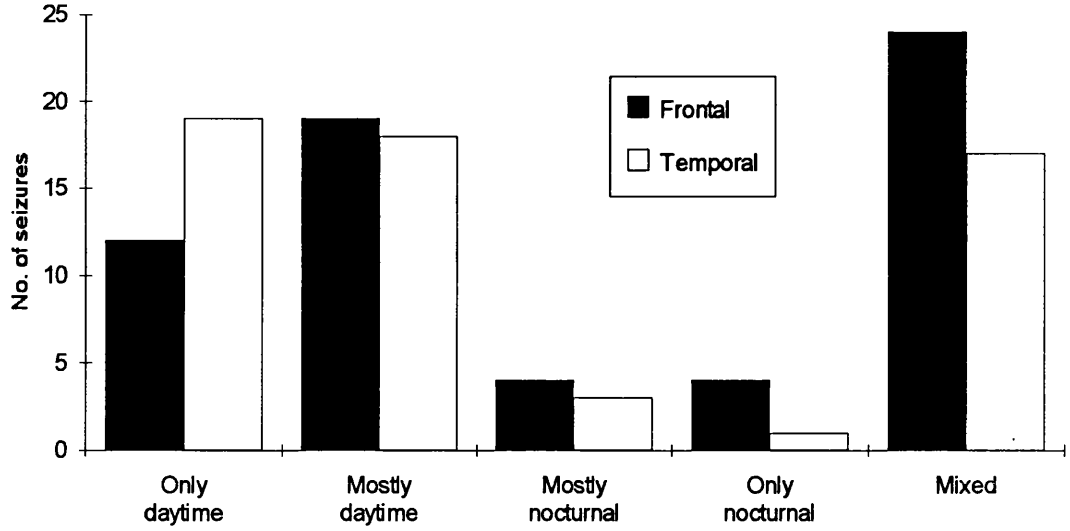


Figure 41. Comparison of average seizure frequency of seizures associated with pure temporal and pure frontal lesions

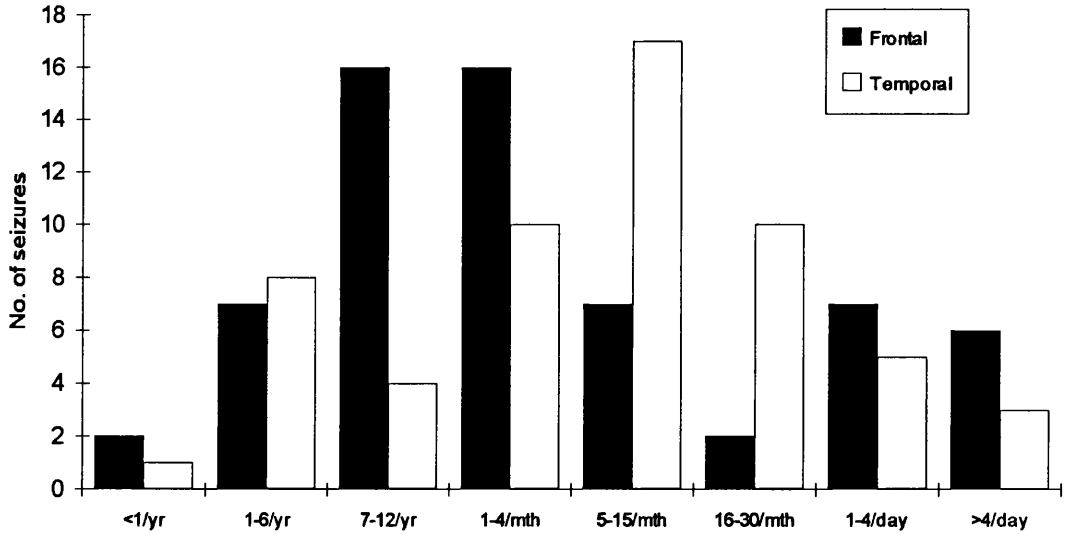


Figure 42. Comparison of maximum seizure frequency of seizures associated with pure temporal and pure frontal lesions

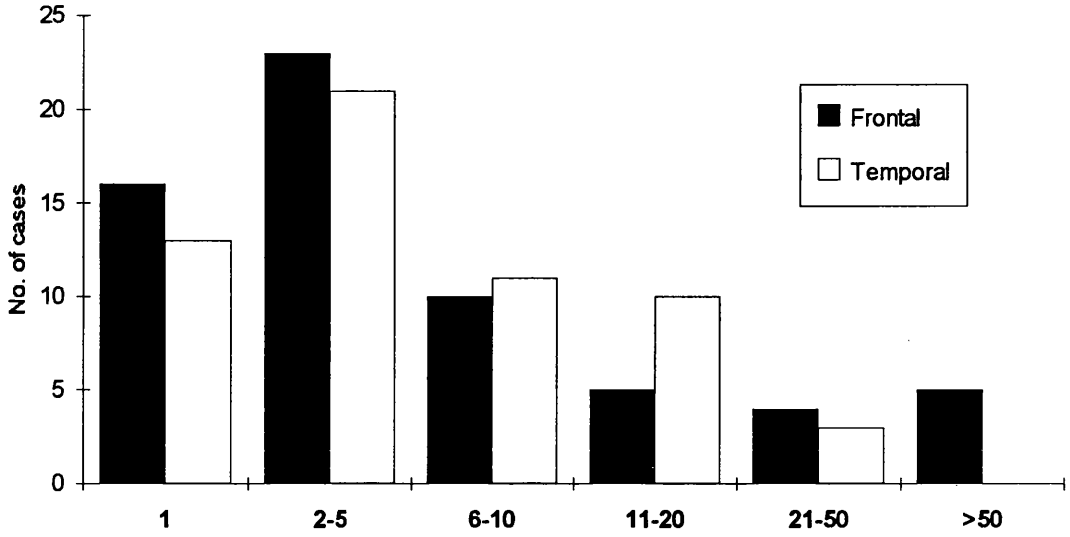


Figure 43. Comparison of seizure duration of seizures associated with pure temporal and pure frontal lesions

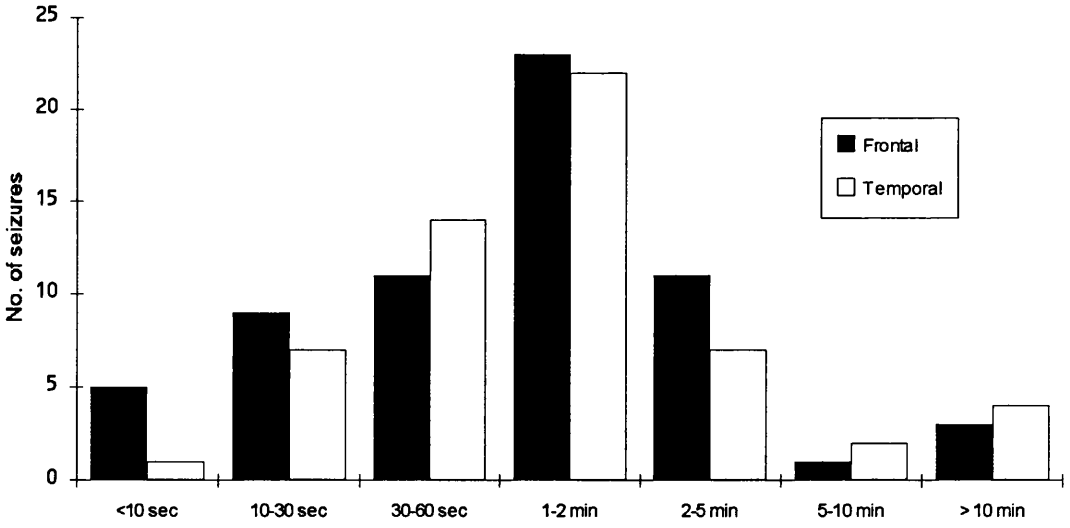


Figure 44. Comparison of postictal duration of seizures associated with pure temporal and pure frontal lesions

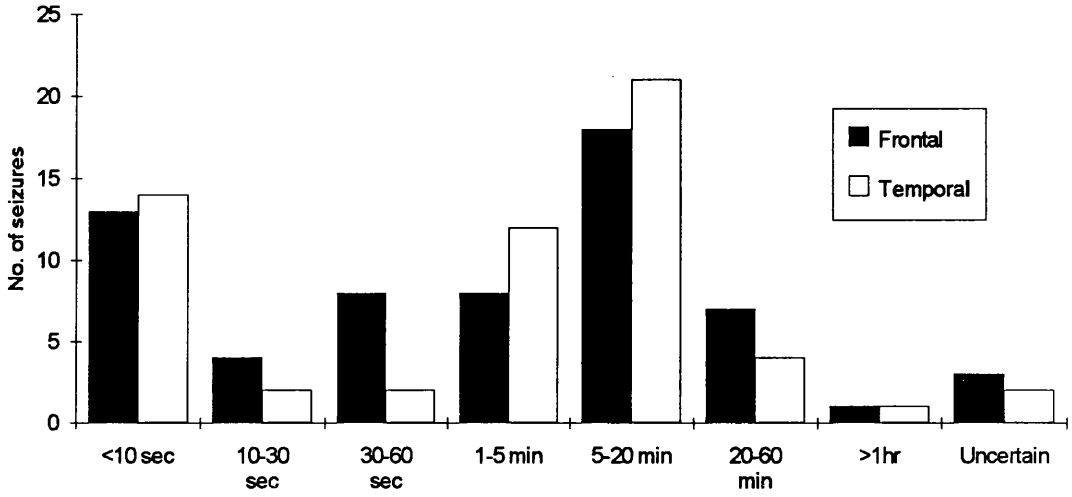


Figure 45. Comparison of frequency of secondary generalisation of seizures associated with pure temporal and pure frontal lesions

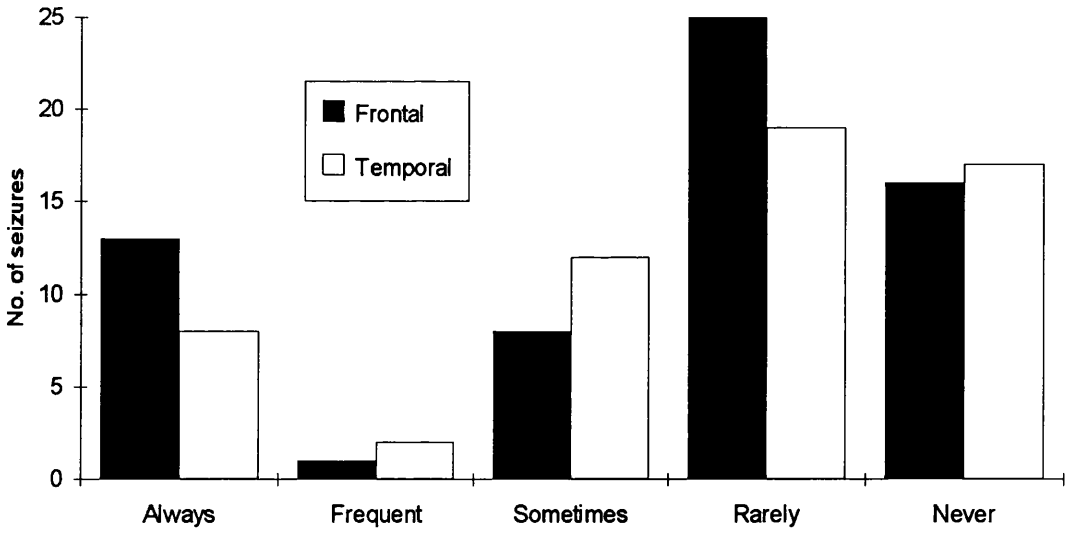
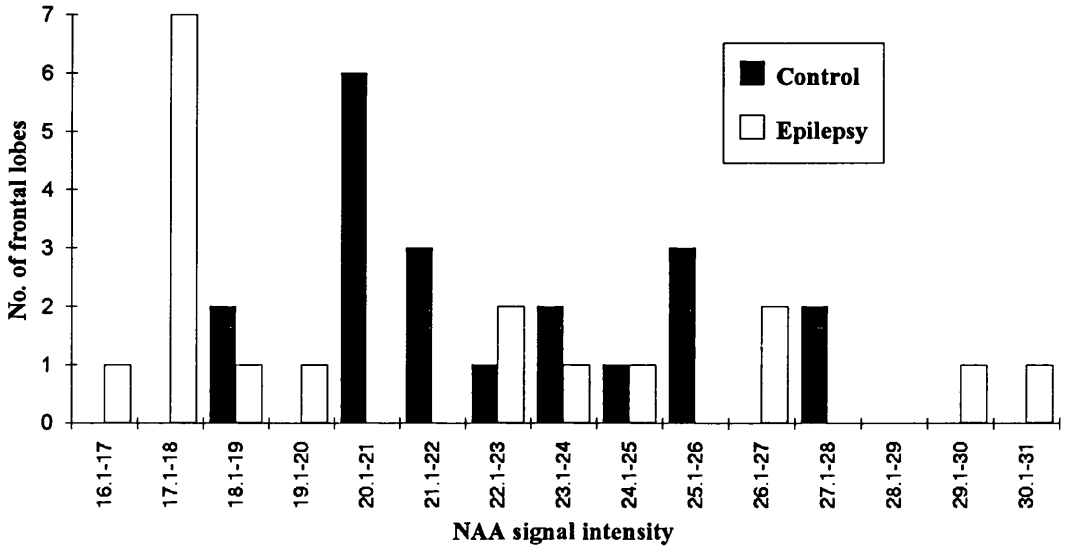


Figure 46. Magnetic resonance spectroscopy of in $8cm^3$ of SMA of 10 controls and 9 patients with normal CT scans and suggested clinical diagnosis of SMA seizures.

a) N-acetylaspartate (NAA) alone



b) Ratio of NAA to Choline (Cho) plus Creatine (Cr); NAA/Cho+Cr

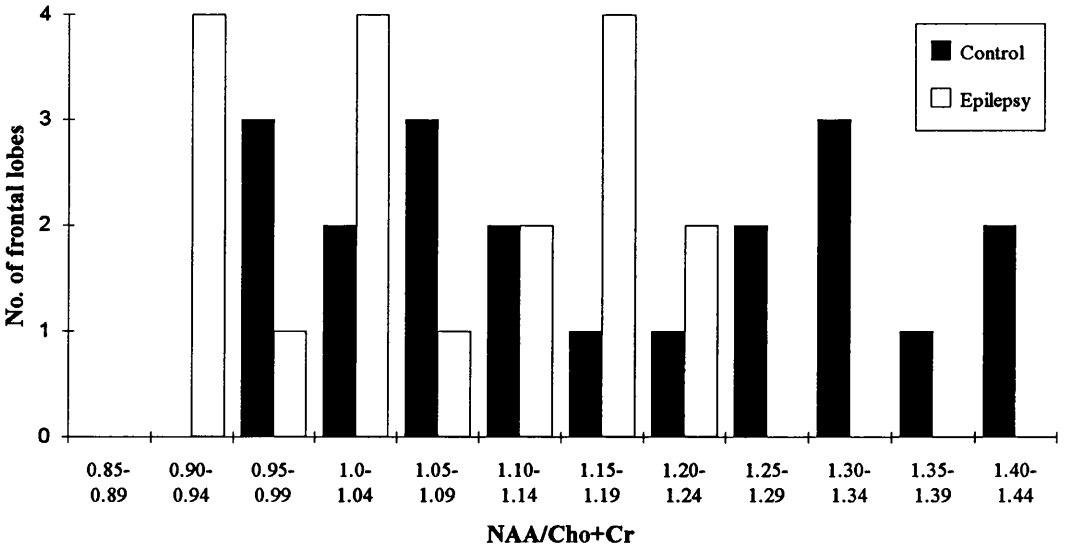


Figure 47 Porencephalic cyst in a patient with epilepsy with startle provoked seizures (ESPS) a few times per year, a mild hemiparesis and normal intellectual function.

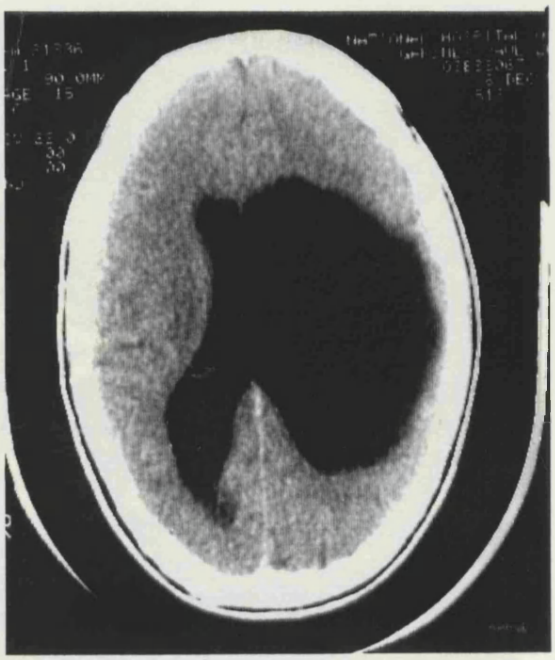
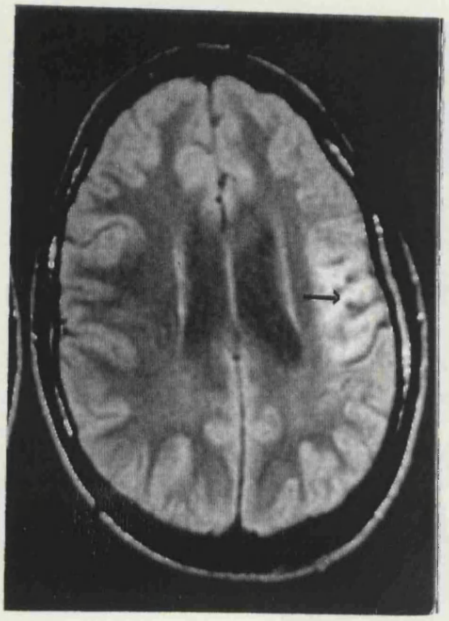


Figure 48. Perisylvian atrophy in startle-provoked seizures with daily seizures

a) unilateral **b) bilateral (Foix-Marie-Chavany syndrome)**



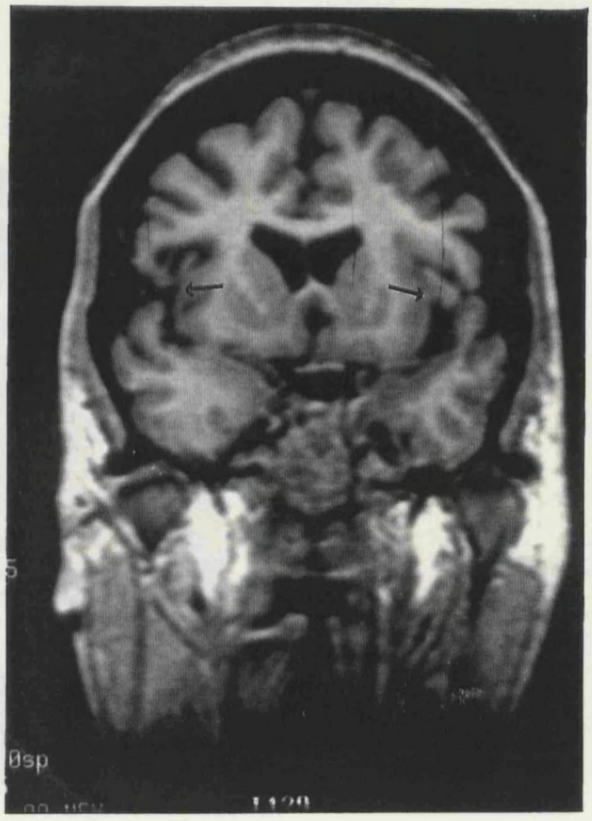
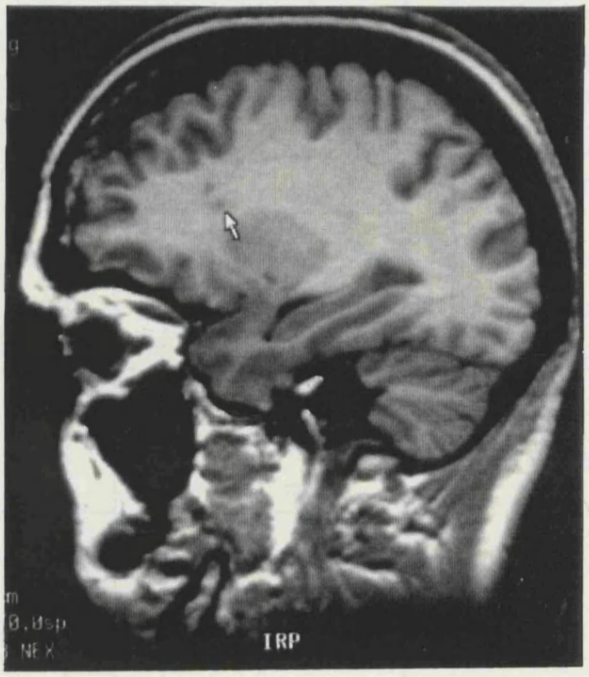


Figure 49 Lateral frontal dysplasia in patients with ESPS and many seizures daily.

a) in a pharmacist with normal IQ and no neurological signs; parasagittal view



b) in a patient with low IQ but no neurological signs; coronal view

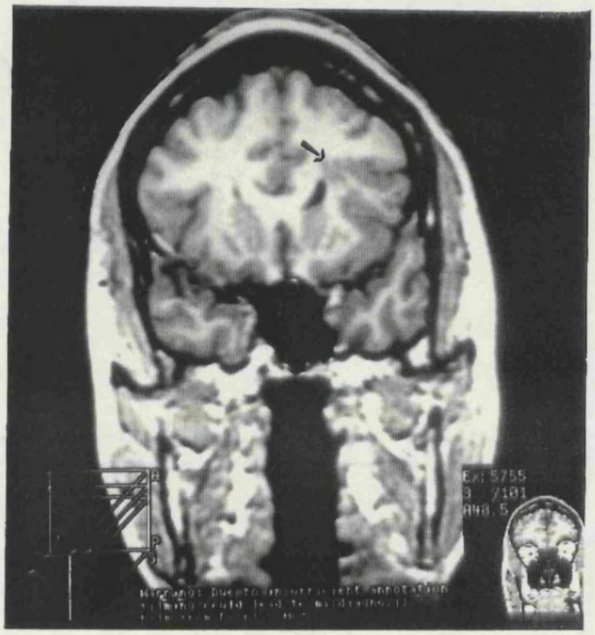


Table 46. Comparison of imaging and interictal spike localisation

Scan lesion site	Concordant EEG	Overlapping EEG	Discordant ipsilateral EEG	Bilateral EEG	Contralateral EEG	No spikes	No EEG available	Total	Comments
Frontal	4	3	2	8	3	14	9	43	
Bifrontal	0	0	0	1	0	1	0	5	Unilateral spikes in 3.
Temporal	3	10	3	7	1	14	3	41	
Frontotemporal	1	0	0	0	0	1	1	3	
Parietal	0	0	0	0	0	3	0	3	
Frontoparietal	1	1	0	1	0	10	3	16	
Parietotemporal	0	0	1	0	0	0	0	1	
Tri-lobar	0	2	0	0	1	3	3	9	Fronto-parieto-temporal lesions
Total	**9**	**16**	**6**	**17**	**5**	**46**	**19**	**121**	

Concordant: >80% spikes restricted to electrodes overlying structural lesion.

Overlapping: > 80% regional spikes including electrodes overlying structural lesion.

Discordant: > 80% regional spikes involving electrodes excluding those overlying structural lesion.

Bilateral EEG: > 80% regional spikes including electrodes overlying structural lesion and those symmetrically opposite, either independently or simultaneously.

Contralateral EEG: > 80% of spikes contralateral to electrodes overlying structural lesion.

Table 47. Comparison of interictal EEG, ictal EEG and imaging

Case	Interictal EEG	Ictal EEG	Scan location	Scan appearance	Seizure type
72	Bifrontal	Right frontocentral	Left frontocentral	Glioma	7d
339	Bifrontal	Right frontal	None		15
336	Bifrontal	Bifrontal	None		7d
62	Bifrontal	Bilateral frontocentral	None		7a
325	Bifrontal	Widespread unilateral	None		2a
30	Bilateral frontocentral	Normal	None		8b
324	Bilateral frontocentral	Left frontal	Left frontocentral	Previous abscess	7a
334	Bilateral frontocentral	Right frontal	None		14a
126	Bilateral frontotemporal	Widespread left side	Left mesial temporal	Atrophy	14b
63	Bilateral frontotemporal	Widespread left side	Left mesial temporal	Hamartoma	1c
239	Bilateral frontotemporal	Right temporal	Right mesial temporal	Atrophy	2c
113	Bitemporal	Artefact	None		14b
108	Bitemporal	Left frontotemporal	Left mesial temporal	AVM	15c
296	Bitemporal	Left temporal	Left mesial temporal	Atrophy	3b
158*	**Right centroparietal**	**Left central**	**None**		**7d**
270	Right centrotemporal	Right frontotemporal	Right mesial temporal	Atrophy	1a
12	Right centrotemporal	Right frontocentral	None		14a
337	Left frontal	Left frontal	None		14c
335	Left frontal	Left frontal	None		14b
93**	**Left frontal**	**Widespread**	**Bilateral frontal**	**Dysplasia**	**7a**
358	Left frontal	Left frontal	None		7c
18	Right frontal	Widespread	None		7b
64	Left frontal	Artefact	None		3b
52**	**Right frontocentral**	**Artefact**	**Right frontal**	**Dysplasia**	**12**
22	Left frontocentral	Widespread	None		7b
20	Left frontotemporal	Widespread left side	None		14a
32*	**Right frontotemporal**	**Normal**	**Right pericentral**	**Atrophy**	**3b**
314**	**Right frontotemporal**	**Artefact**	**Right frontal**	**Dysplasia**	**7b**

*** : discordance between investigations**

****: dysplastic lesion on imaging**

Table 47 continued. Comparison of interictal EEG, ictal EEG and imaging

Case	Interictal EEG	Ictal EEG	Scan location	Scan appearance	Seizure type
128*	**Left frontotemporal**	**Diffuse right sided**	**Right frontal**	**Atrophy**	**14a**
16	Left frontotemporal	Left frontotemporal	Left temporal	Angioma	4b
92	Right frontotemporal	Right temporal	Right mesial temporal	Atrophy	3a
333	Right frontotemporal	Normal	Right mesial temporal	Atrophy	3a
250	Left frontotemporal	Normal	None		7d
98	Right frontotemporal	Right temporal	Right mesial temporal	Atrophy	1c
13	Right frontotemporal	Right temporal	None		14a
17	Left temporal	Left temporal	None		1c
15	Left temporal	Bitemporal	None		5
253	Left temporal	Bitemporal	Left mesial temporal	Atrophy	3a
297*	**Left temporal**	**Right temporal**	**Left mesial temporal**	**Atrophy**	**2a**
26	Left temporal	Left temporal	None		3b
38	Right temporal	Widespread right side	None		4b
115	Right temporal	Right frontotemporal	Right mesial temporal	Atrophy	1a
292*	**Widespread**	**Right frontal**	**Right mesial temporal**	**Glioma**	**4b**
357	Widespread	Right frontal	None		7d
287**	**Widepsread**	**Artefact**	**Bifrontal**	**Dysplasia**	**8b**
73	Normal	Left frontal	None		14a
170	Normal	Left frontocentral	None		2b
11**	**Normal**	**Generalised**	**Bilateral Perisylvian**	**Dysplasia**	**7d**
19	Normal	Widespread	None		7a
51**	**Normal**	**Artefact**	**Widespread**	**Dysplasia**	**14a**
103	Normal	Artefact	None		7a
74	Normal	Artefact	None		7a
97	Normal	Right temporal	Right mesial temporal	Atrophy	3a
42	Normal	None	Left mesial temporal	AVM	5
40	Normal	Bifrontal	None		7d
55	Normal	Left frontotemporal	None		4b

*** : discordance between investigations**

****: dysplastic lesion on imaging**

Table 47 continued. Comparison of interictal EEG, ictal EEG and imaging

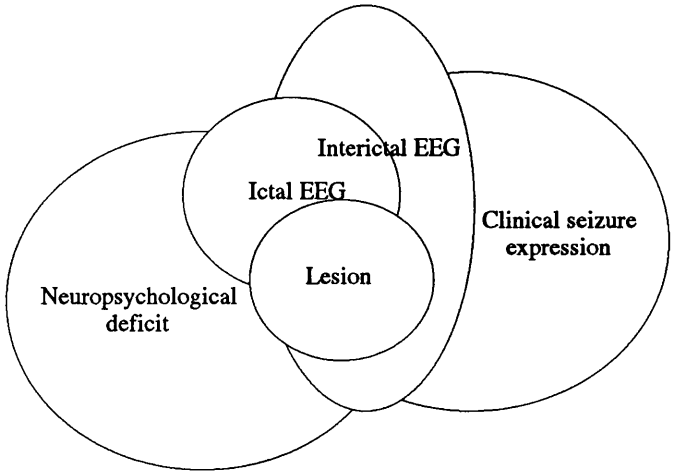
Case	Interictal EEG	Ictal EEG	Scan location	Scan appearance	Seizure type
240	Normal	Widespread right side	Right mesial temporal	Atrophy	1a
248	Normal	Artefact	None		7b
249	Normal	Artefact	Perisylvian	Atrophy	14c
286	Normal	Right frontal	None		14b
85	Normal	Bilateral frontocentral	Frontal	Dyplasia	7d
33**	**Normal**	**Widespread left**	**Left temporal**	**Glioma**	**1c**
31	Normal	Artefact	None		7b
282	Normal	Artefact	None		1a
83**	**Normal**	**Artefact**	**Right frontocentral**	**Dysplasia**	**8b**
129**	**Normal**	**Artefact**	**Left frontoparietal**	**Dysplasia**	**7a**
101	Normal	Artefact	Right frontotemporal	Atrophy	14b
102	Normal	Temporal	Right mesial temporal	Atrophy	1a
299	Normal	Artefact	None		14b
14	Normal	Generalised	None		11
306	Normal	Widespread	None		14a
321	Normal	Widespread	None		1a
322	Normal	Normal	None		7a
323	Normal	Central	Right frontocentral	Glioma	12
350	Normal	Frontocentral	None		8a
345	Normal	Artefact	None		14a
329	Normal	Bifrontal	Left mesial frontal	Glioma	2a

*** : discordance between investigations**

****: dysplastic lesion on imaging**

Figure 50. Comparison of zonal and aetiological concepts of epileptogenesis

Zone concept of epilepsy pathophysiology



Aetiological concept of epilepsy pathophysiology

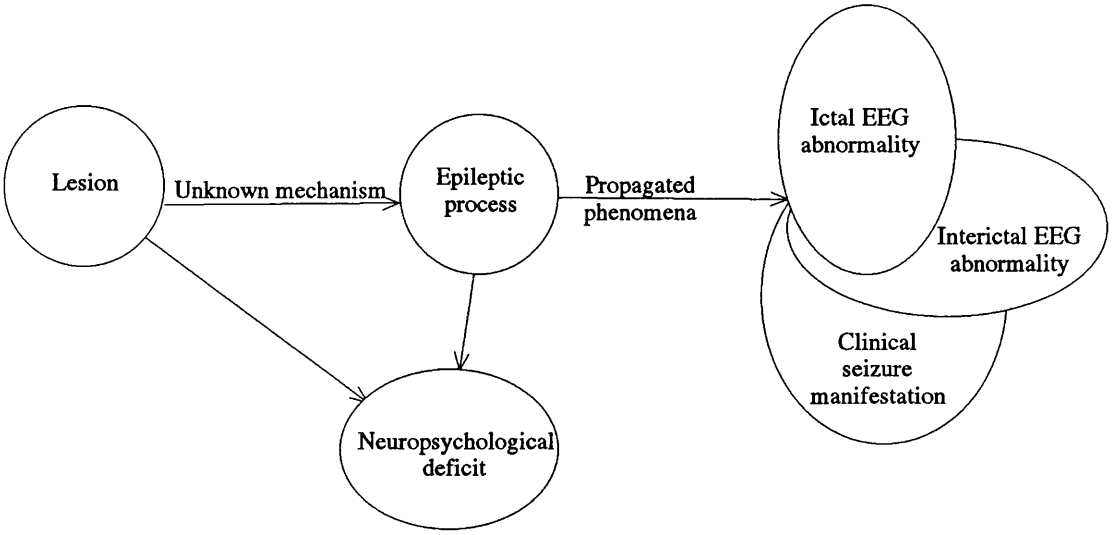


Table 48: Criteria for clinical classification of partial seizures in the NGPSE

Frontal	1) Seizures with focal, tonic or clonic motor activity or posturing and sometimes non-specific somatosensory manifestations, but no other experiential manifestations. 2) Seizures comprising purely dystonic posturing. 3) Seizures with prominent motor automatisms of the limbs, but no orofacial automatisms or experiential phenomena.
Central	1) Focal clonic seizures with preservation of awareness 2) Focal simple clonic seizures, with either isolated motor activity or mixed sensorimotor effects, with Jacksonian progression.
Temporal	1) Seizures with prominent experiential phenomena, gustatory or olfactory hallucination. 2) Seizures with arrest, absence and oroalimentary automatisms.
Frontotemporal	1) Seizures with combinations of manual and oro-alimenary automatisms. 2) Seizures with epigastric sensations, autonomic manifestations and prominent motor activity.
Parietal	Seizures with exclusively somatosensory manifestations, with or without Jacksonian progression.
Posterior	1) Seizures with polymodal sensory manifestations. 2) Seizures with unformed visual, or complex visual, auditory or somatosensory hallucinations
Unlocalised	1) Seizures with semiological evidence of partial onset with features not attributable to a single cerebral region e.g. vague epigastric or cephalic sensations or isolated head turning. 2) Patients with historical or investigative evidence of partial seizure onset, but seizures apearing clinically generalised from the outset.

Table 49: EEG and CT results in partial seizures in the NGPSE

Clinical seizure type	EEG performed	Focal EEG abnormality	Discordant EEG abnormality	CT performed	Focal CT lesion	Discordant CT abnormality
Frontal	23 (64%)	4 (17%)	1	15 (42%)	7 (47%)	2
Central	23 (44%)	7 (30%)	1	22 (42%)	9 (41%)	1
Frontotemporal	6 (66%)	2 (33%)	0	6 (66%)	0	0
Temporal	38 (89%)	4 (11%)	0	30 (70%)	3 (10%)	2
Parietal	7 (70%)	2 (28%)	1	6 (60%)	4 (67%)	0
Posterior	10 (100%)	1 (10%)	1	7 (70%)	5 (72%)	1
Total	**107 (67%)**	**20 (19%)**	**4 (20%)**	**86(54%)**	**28 (33%)**	**6 (21%)**

Table 50. Abnormalities of investigation related to clinical seizure pattern in the NGPSE

		Clinical Localisation						
	Location of abnormality	**Frontal**	**Central**	**Fronto-temporal**	**Temporal**	**Parietal**	**Posterior**	**Unlocalised**
EEG	**Frontal**	1	1	0	0	0	0	1
	Central	2	5	0	0	0	0	0
	Frontotemporal	0	0	1	0	0	0	2
	Temporal	1	1	1	4	0	0	15
	Parietal	0	0	0	0	1*	0	0
	Posterior	0	0	0	0	1	1*	2
CT	**Frontal**	4	2	0	2	0	0	4
	Central	1	5	0	0	0	0	0
	Frontotemporal	0	0	0	0	0	0	0
	Temporal	0	0	1	1	0	1	0
	Parietal	0	1	0	0	2	1	0
	Posterior	2	1	0	0	0	2,1*	1

*Investigation lateralised opposite to clinical localisation

Table 51: Partial seizure aetiologies in the NGPSE

Aetiology	Frontal	Central	Frontotemporal	Temporal	Parietal	Posterior	Total
Vascular	4	16	2	2	2	2	28 (18%)
Primary tumour	3	4	0	3	1	3	14 (9%)
Secondary tumour	3	2	0	0	1	0	6 (4%)
Infection	0	1	0	0	0	1	2 (1%)
Acute trauma	1	2	0	0	0	0	3 (2%)
Remote trauma	4	1	1	0	0	0	6 (4%)
Congenital	2	2	1	0	0	0	5 (3%)
Other	1	0	0	0	0	0	1 (1%)
Unknown	**18 (50%)**	**24 (46%)**	**5 (55%)**	**37 (86%)**	**6 (60%)**	**4 (40%)**	**95 (59%)**

Table 52: Seizure frequency of different clinical seizure types in the NGPSE

Clinical type	Single seizure	Seizure-free	<4/year	4-12/ year	>12/ year	Unknown
Frontal	1	15	11	4	3	2
Central	3	23	15	1	2	8
Fronto-temporal	0	4	1	2	0	2
Temporal	1	20	14	2	3	3
Parietal	0	5	1	1	2	1
Posterior	0	5	2	1	1	1
Total	**4 (2.5%)**	**72 (45%)**	**44 (28%)**	**11 (7%)**	**11 (7%)**	**17 (11%)**

Appendices

Appendix 1. Study clinical questionnaire: a) General medical history

Study No: ___

Date of Birth: _____ Age: __ Inclusion criterion: __

Aetiology of epilepsy:-

Family history of 1) epilepsy: _____

2) Neurological disease: ___ 3: Psychiatric disorder: ___

4) Other medical disorder: ___

Specify disorder: _____

Perinatal history:-

Maternal illness in pregnancy: ___ Gestation: _____

Delivery: _____ Neonatal hypoxia: ___ Other illness: ___

Specify disorder: _____

Febrile seizures: _____ Development: _____

Head injury: ___ Neurological illness: _____

Other (specify): _____

Psychiatric illness: ___ Medical illness: ___

Specify disorder: _____

Seizure types:-

Number of seizure types: _

Individual seizure characteristics on forms: "BFIT"; "CFIT"; "DFIT".

Examination:-

Neurological: _____ Specify: _____

General: _____ Specify: _____

Surgical treatment: ___ Type of operation: _____

Describe: _____

_____

Lesion: _____

Site: _____ Side: _____

Specify others: _____

_____

Appendix 1 continued. Study questionnaire: b) Characteristics of each seizure

Study No: ___

For commonest seizure type:-

Age of onset: _____ Change in frequency: _____ Age ceased: _____

Average frequency: _____ Diurnal pattern: _____

Clustering: _____ Maximum No. in one day: ___

History of 1) Status epilepticus: ___

2) Serial seizures with recovery of consciousness: ___

3) Seizure free period: ___ Age of onset: _____ Duration (months): ___

Medication when seizure free: _____

Seizure provoking factors

Sleep: ___ Sleep deficit: ___ Hunger: ___ Food: ___ Alcohol: ___

Stress: ___ Startle: ___ Exertion: ___ Relaxation: ___

Menstruation: ___ Photosensitvity: ___ Other: ___

Specify: _____

Current Seizure Charateristics

Prodrome

Present: _____ Duration: _____

Symptoms of prodrome Altered self perception: ___ Altered mood: ___

Headache: ___ Other: ___ Specify: _____

Aura

Preceding seizure: _____ Without seizure: _____

Duration: _____

Sequence of first ten symptoms of aura and seizure and duration of each

A: _____

B: _____

C: _____

D: _____

E: _____

F: _____

G: _____

H: _____

I: _____

J: _____

Comments: _____

_____

_____

Objective account of seizure:- Observer: _____

A: _____

B: _____

C: _____

D: _____

E: _____

F: _____

G: _____

H: _____

I: _____

J: _____

Comments: _____

_____

_____

Specific symptoms

Physical

Nausea: ___ Rising epigastric: ___ Other abdominal: ___

Cardiac oppression: ___ Breathing difficulty: ___ Other chest: ___

Light headedness: ___ Headache: ___ Migraine: ___ Other head: ___

Other symptoms: _____

Duration: _____

Psychic

Dreaminess: ___ Illusion of altered time: ___ Derealization: ___

Recollection/flashback: ___ Familiarity: ___ Unfamiliarity: ___

Deja vu: ___ Jamais vu: ___ Deja vecu: ___ Jamais vecu: ___

Deja entendu: ___ Jamais entendu: ___ Depersonalizaton: ___

Forced thought: ___ Stereotyped phenomenon: ___ Other symptoms: ___

Specify symptoms: _____

Duration: _____

Emotion

Sadness: ___ Anger: ___ Happiness: ___ Anxiety: ___ Fear: ___

Lability: ___ Sexual arousal: ___ Other: ___

Specify others: _____

Duration: _____

Sensory

Visual hallucination: _____ Stereotyped: ___

Visual field site: _____

Disordered visual perception: ___ Duration: _____

Specify abnormality: _____

Auditory hallucination: _____ Stereotyped: ___

Disordered hearing: _____ Duration: _____

Specify abnormality: _____

Olfactory hallucination: _____ Stereotyped: ___

Duration: _____

Gustatory hallucination: _____ Stereotyped: ___

Duration: _____

Somatosensory: _____ Site: _____ Side: _____

Specify others: _____

Duration: _____

Awareness

Degree of impairment: _____

Tempo of impairment: _____ Duration: _____

Motor

General motor effects: _____ Duration: _____

Eyelid fluttering: _____ Blinking: _____ Eye version: _____

Head version: _____ Trunk version: _____ Duration: _____

Tonic movements: _____ Dystonic movements: _____

Single jerks: _____ Repeated jerks: _____

Duration of movements: _____

Other movements: _____

Simple motor automatisms

Fencing: ___ Bilateral karate: ___ Bicycling: ___ Bimanual: ___

Bilateral leg extension/kicking: ___ Back arching: ___

Pelvic movements: ___ Striking: _____ Walking: ___ Running: ___

Plucking: _____ Threading: _____

Duration: _____ Other: ___

Specify: _____

Complex behavioural motor automatisms

Exploratory: ____ Undressing: ____ Bed-making: ____

Situational: ___ Duration: _____

Other: ___ Specify: _____

Oro-alimentary automatisms

Lipsmacking: ___ Lip-pursing: ___ Tongue movements: ___

Swallowing: ___ Dyskinetic: ___ Other: ___ Duration: _____

Specify others: _____

Sexual automatisms

Gestures: _____ Genital manipulations: _____

Speech

Speech abnormality: _____ Duration: _____

Onset of speech abnormality: _____

Vocalisations

Non-verbal: _____ Duration: _____ Situational: ___

Specify others: _____

Verbal: _____ Content: _____ Situational: ___

Specify others: _____

Duration: _____

Behavioural change

Mimicry: ___ Staring: ___ Arrest: ___ Fear: ___ Other: ___

Specify others: _____

Duration: _____

Vegetative symptoms

Pupils: _____ Respiration: _____ Pulse: _____

Colour: _____ Sphincters: _____

Secondary generalisation: _____

Total duration: _____ Specify other: _____

Postictal state

Sleep:	___	Duration:	_____
Confusion:	___	Duration:	_____
Amnesia:	_____	Duration:	_____
Speech:	_____	Duration:	_____
Motor deficit:	_____	Duration:	_____
Visual deficit:	_____	Duration:	_____
Headache:	_____	Duration:	_____
Other:	___	Duration:	_____

Specify: _____

Appendix 2. Variables entered into cluster analysis

Presence of a prodrome

Abdominal sensation

Cephalic sensation

Chest sensation

Other physical sensation

Psychic sensation

Fear

Other emotion

Visual hallucination

Visual distortion

Auditory hallucination

Olfactory hallucination

Gustatory hallucination

Somatosensory hallucination

General hypertonia

General motor arrest

Generalised clonic activity

Generalised hypotonia

Eye version

Head version

Body turning

Version group

Focal clonic activity

Focal paresis

Jacksonian clonic progression

Asymmetric tonic posture e.g. fencing

Bicycling of legs

Kicking

General motor agitation

Simple automatism group

Exploratory behaviour

Bed making

Complex automatism group

Oroalimentary automatism

Speech arrest

Speech distortion

Shout

Bizarre vocalisation e.g. giggling

Non-verbal vocalisation group

Coherent verbal vocalisation

Incoherent verbal vocalisation

Speech arrest

Pupillary change

Colour change

Respiratory change

Pulse change

Autonomic group

Incontinence

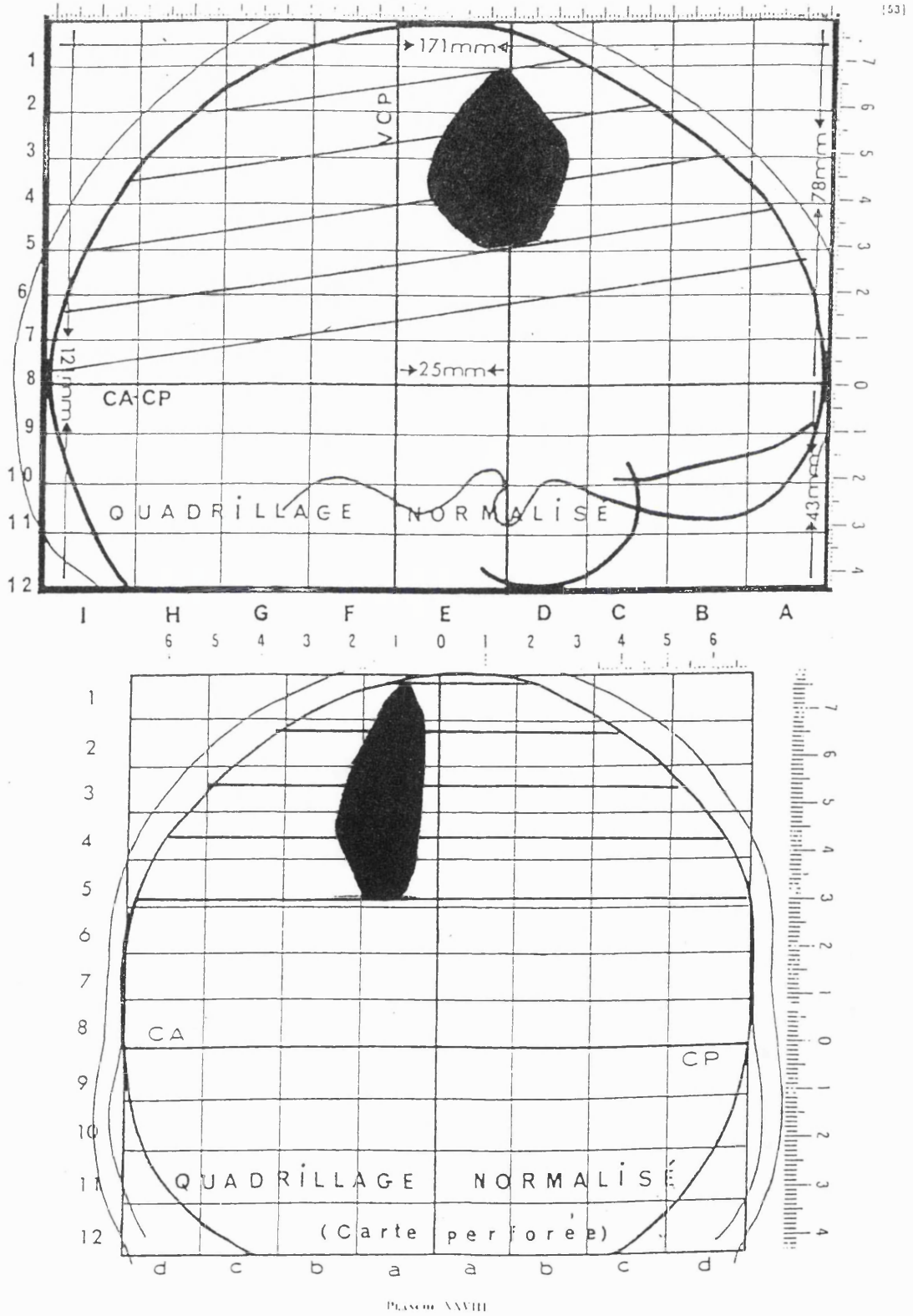
Tongue biting

Postictal confusion

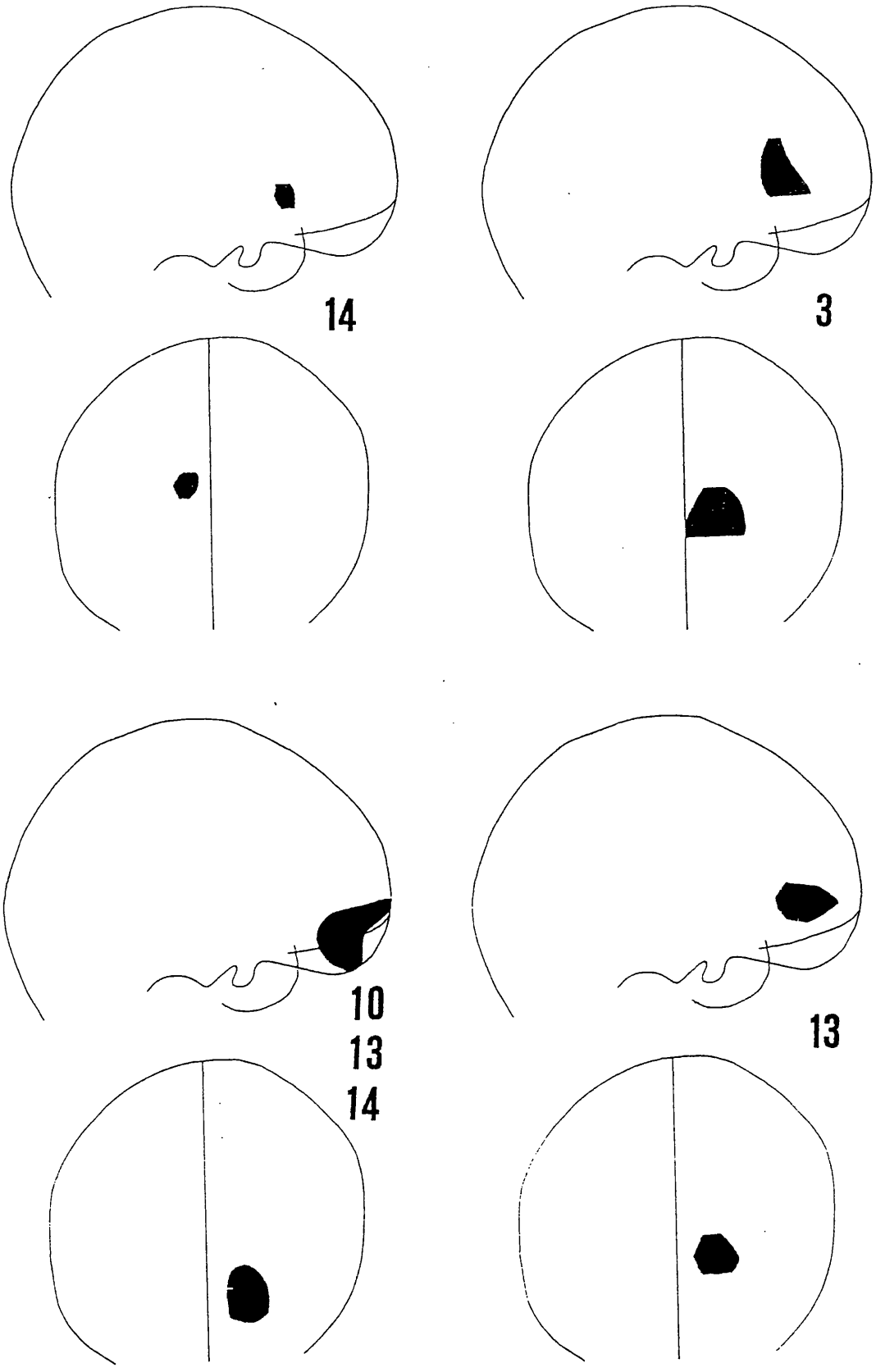
Postictal dysphasia

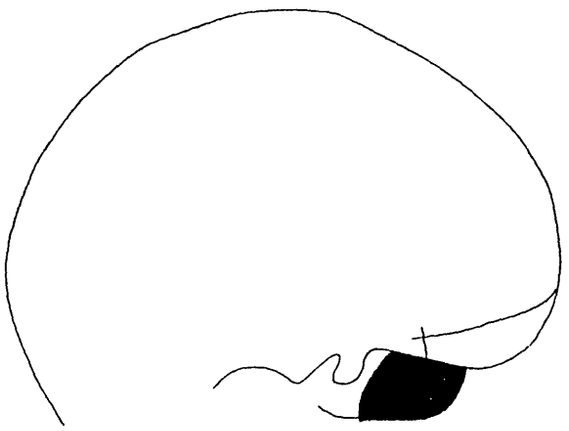
Postictal motor deficit

Appendix 3. Standard template for projection of lesions from neuroimaging

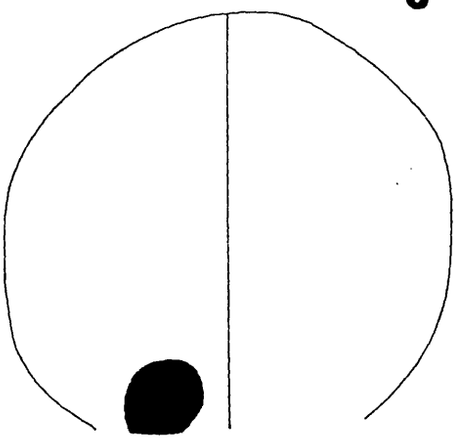


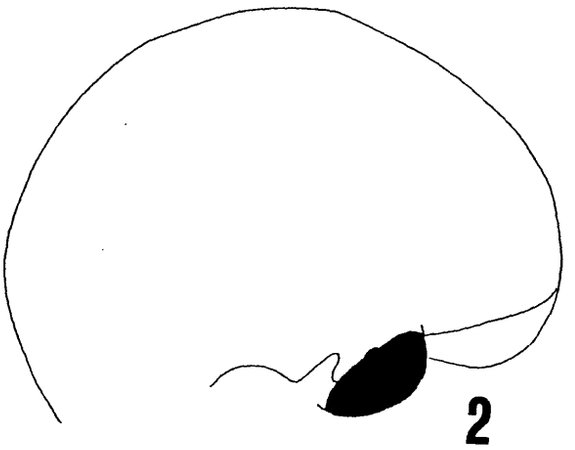
Appendix 4. Lesions plotted onto brain templates and associated seizure types by group number. (Excludes pure hippocampal lesions)



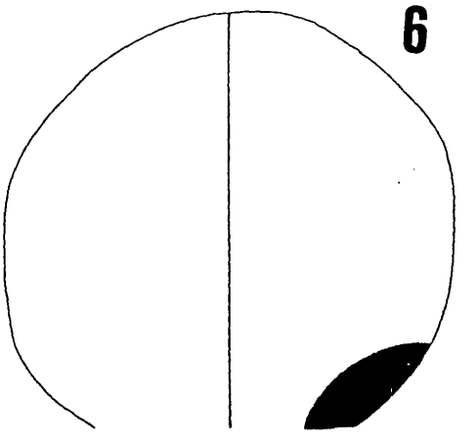


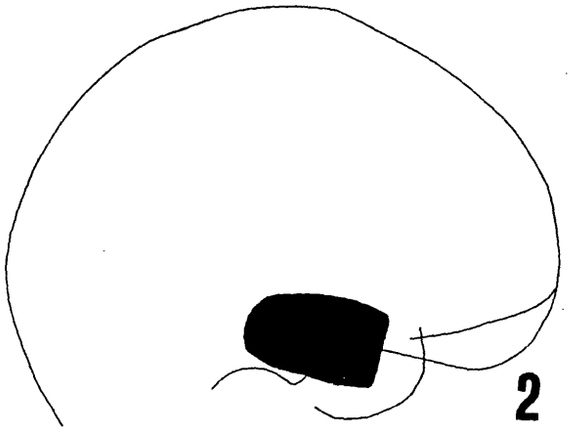
3



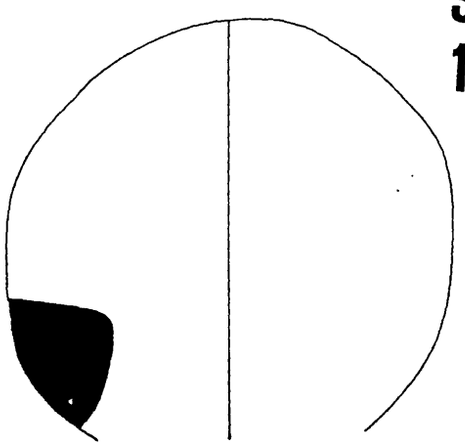


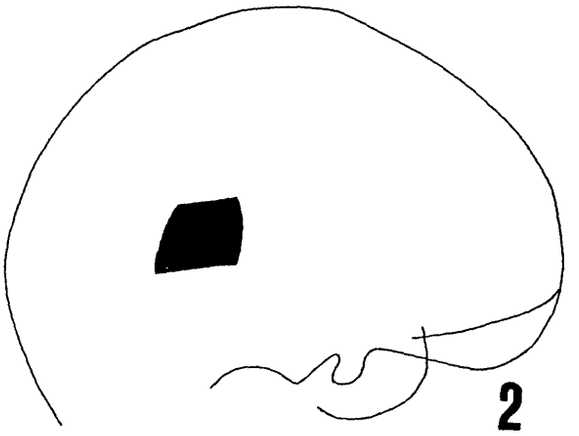
2
6



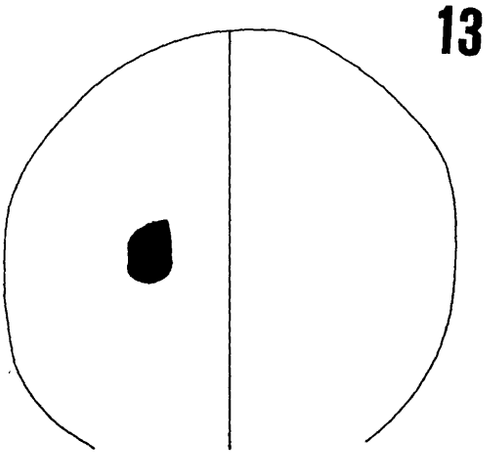


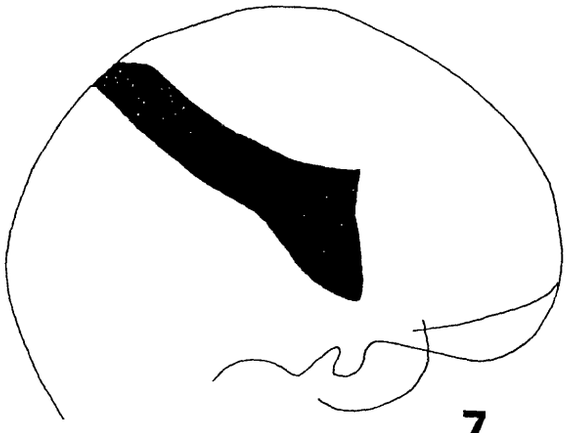
2
3
13





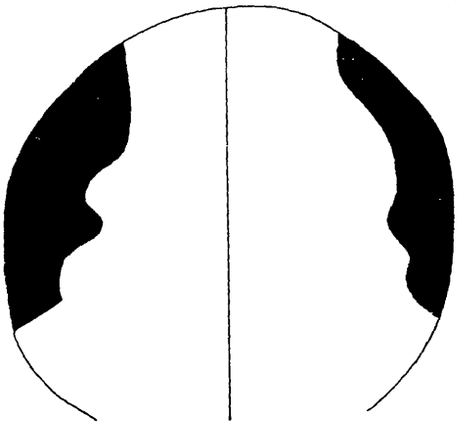
2
13

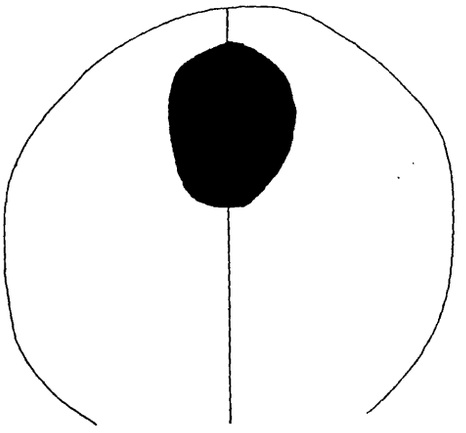


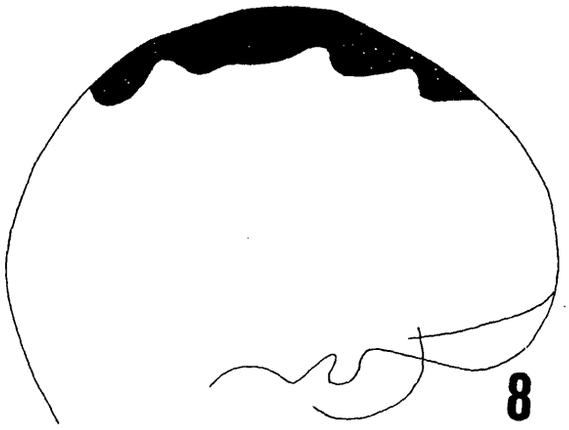


7

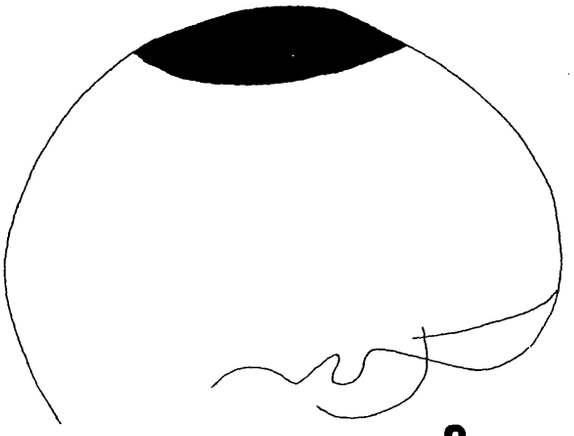
12



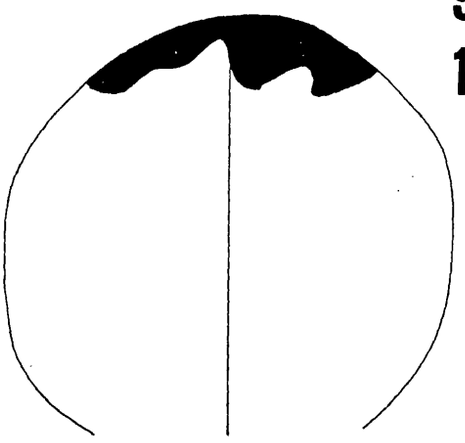


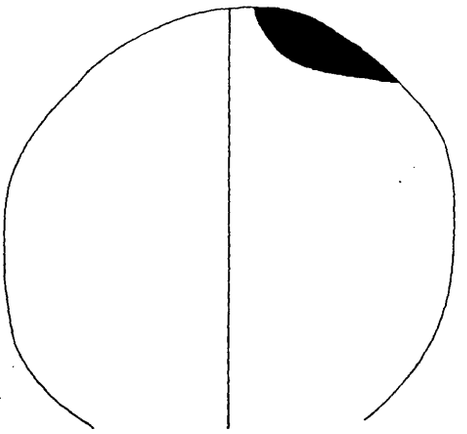


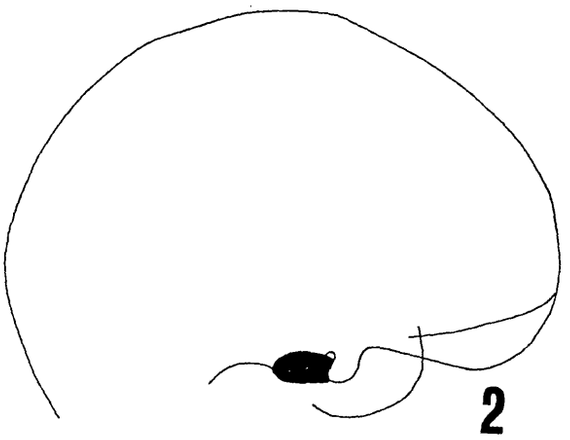
8
9
12



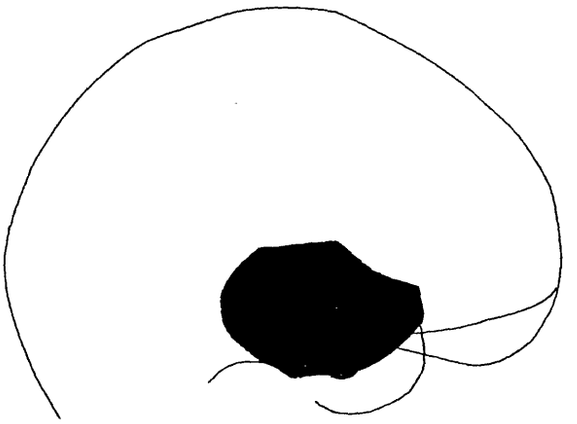
8





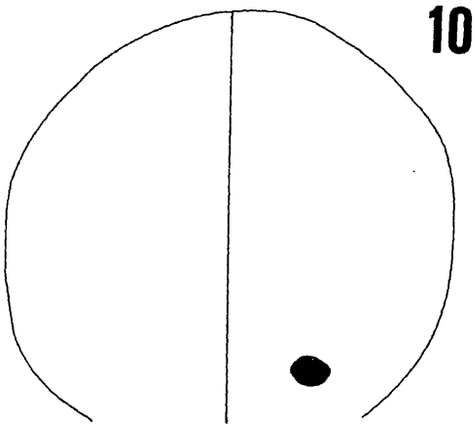


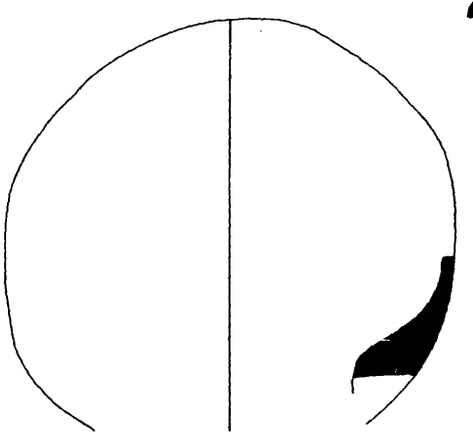
2

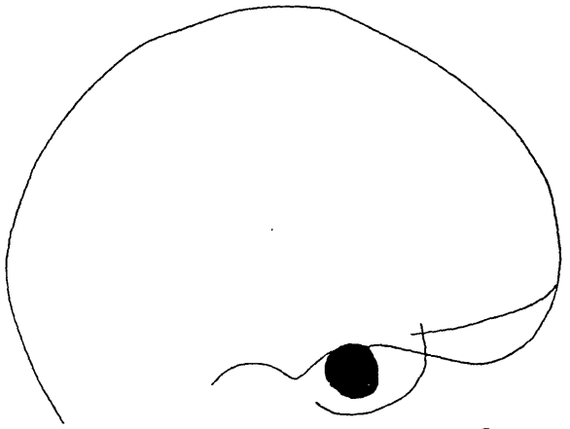


2

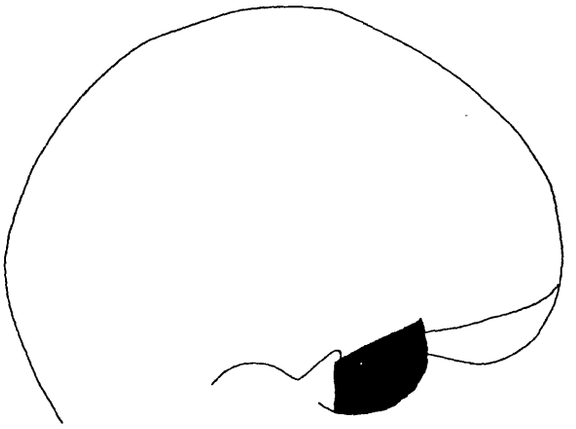
10



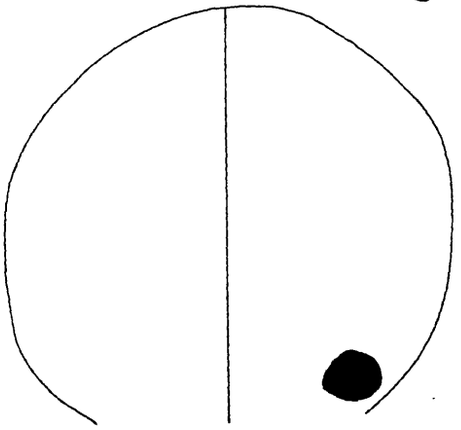


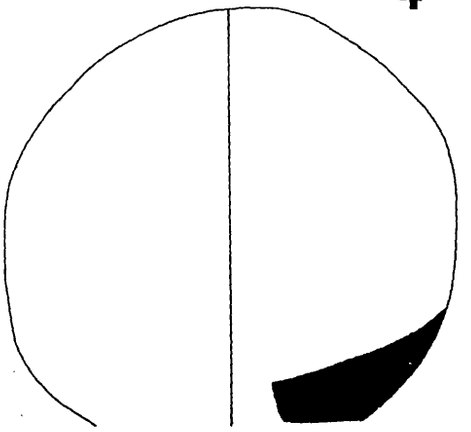


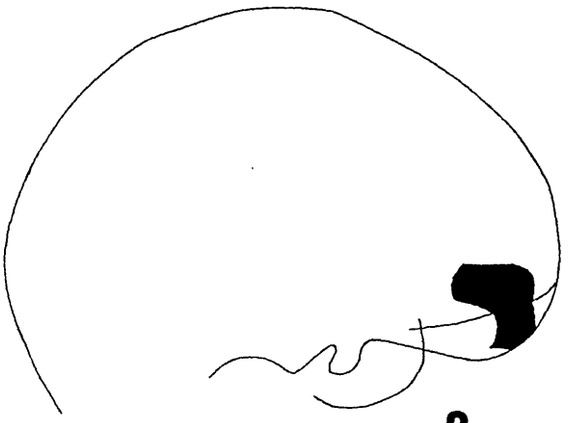
3



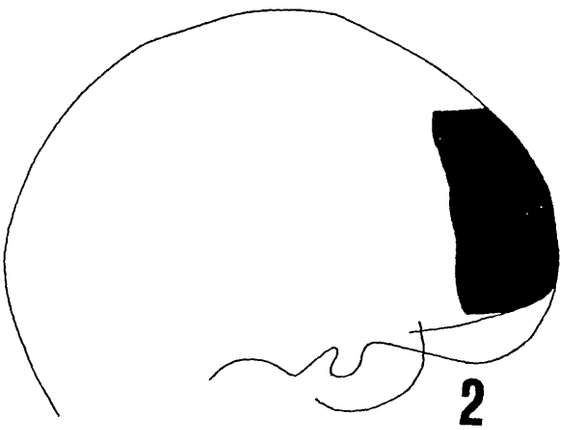
4



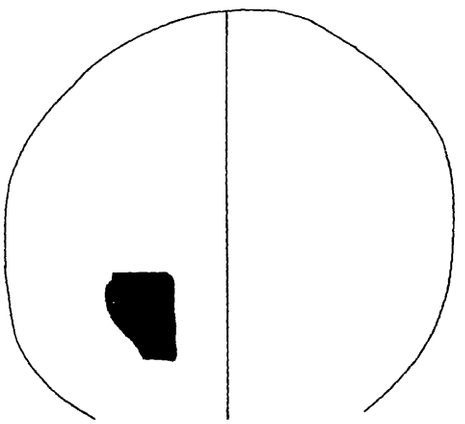


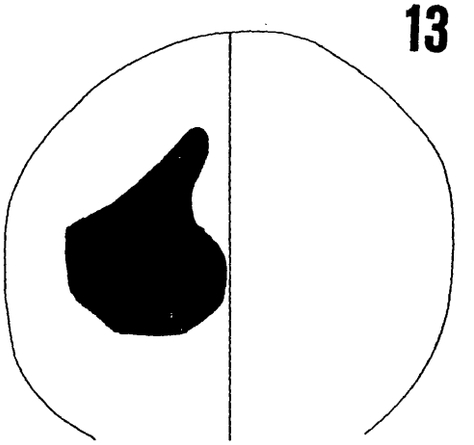


2

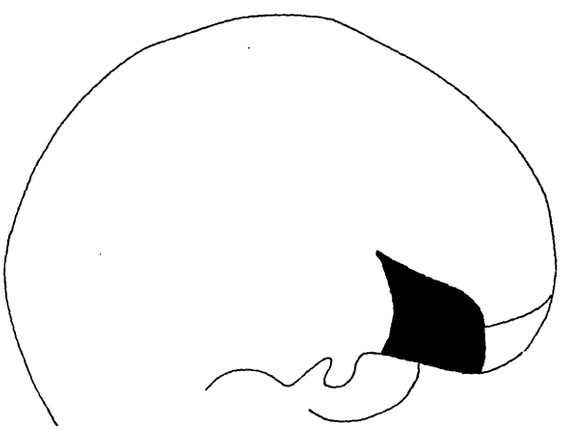


2

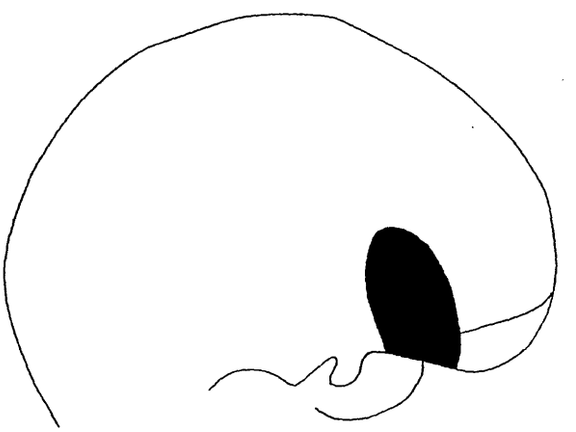




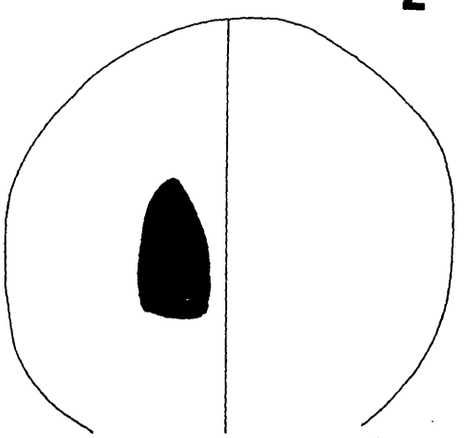
13

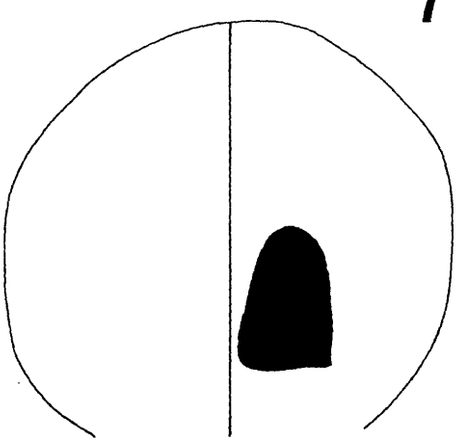


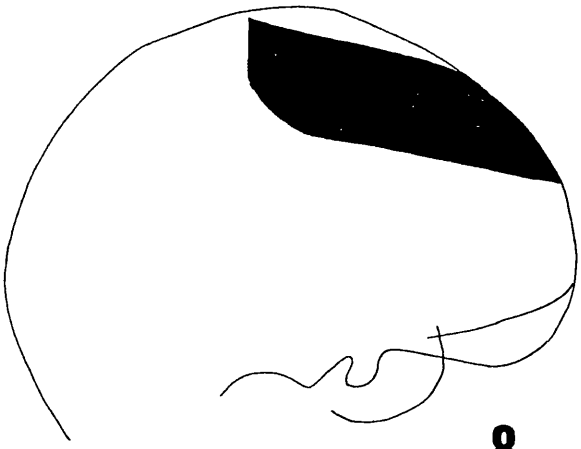
2



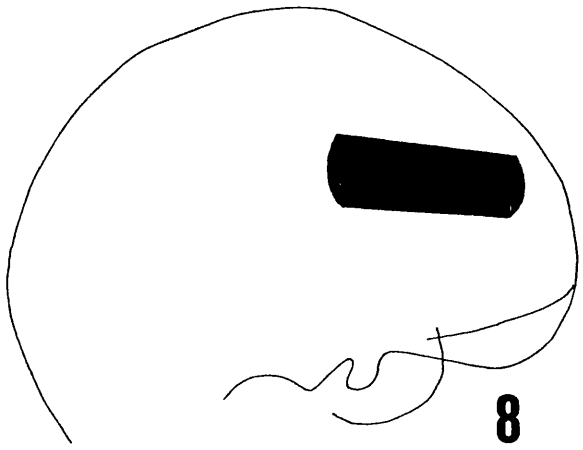
7



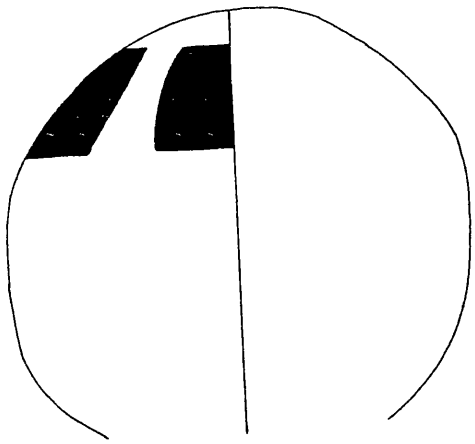




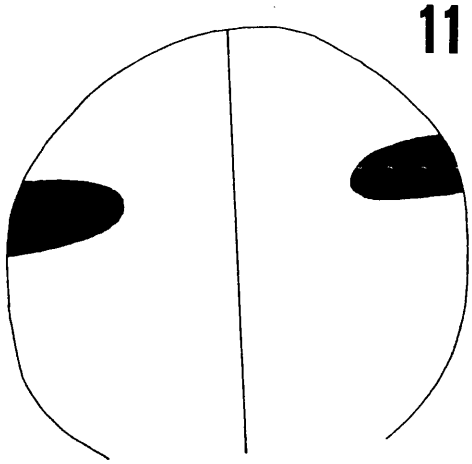
8

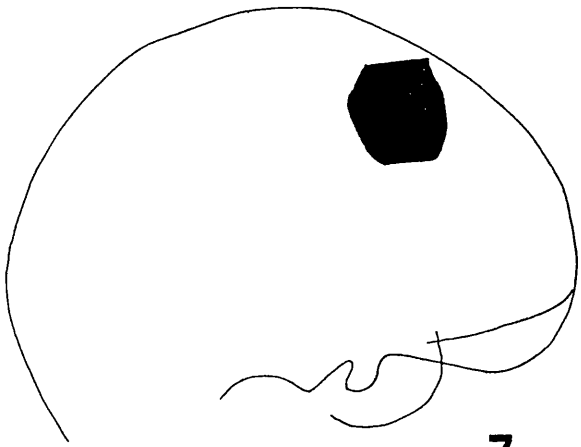


8

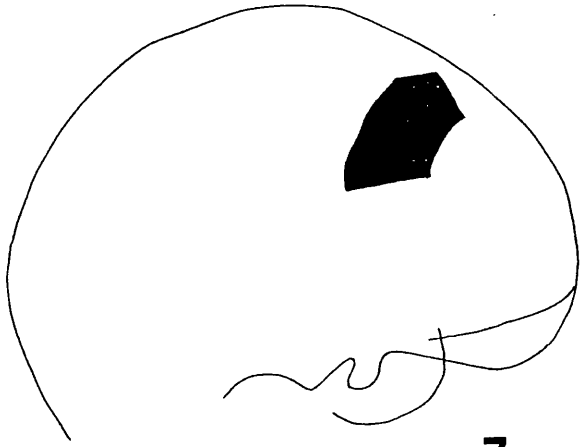


11

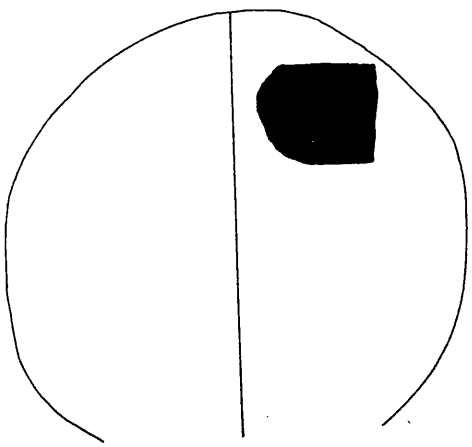


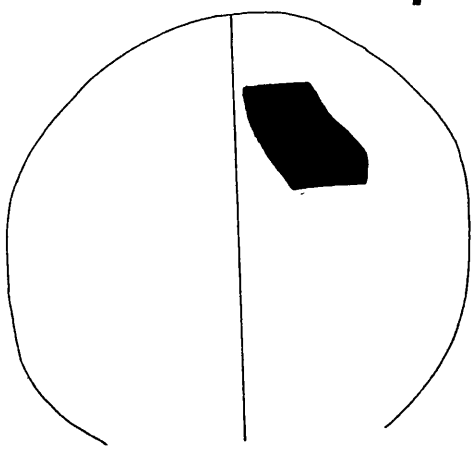


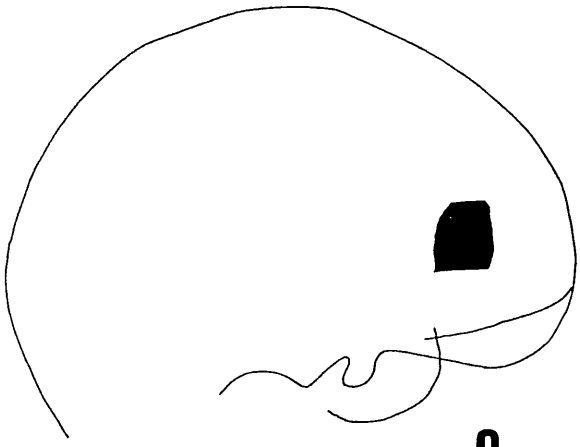
7



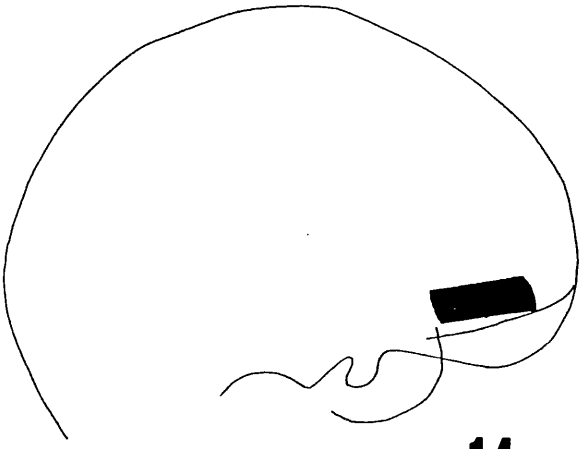
7



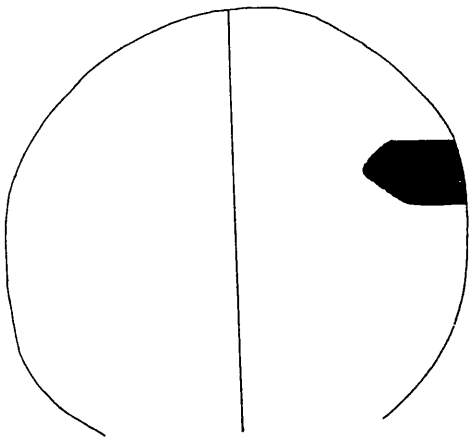


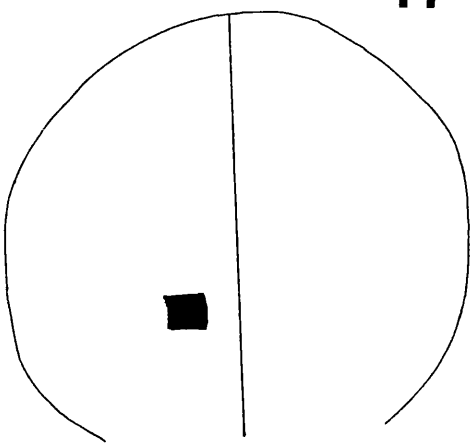


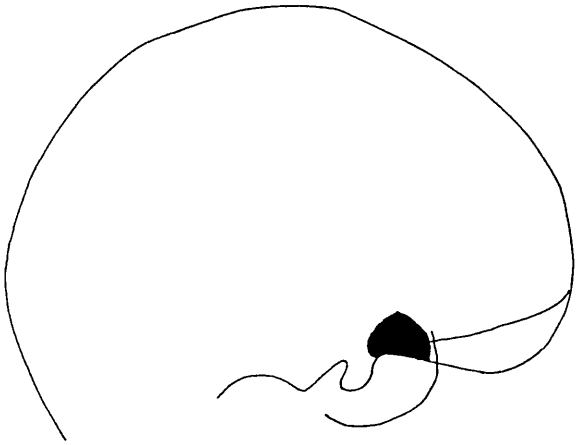
9



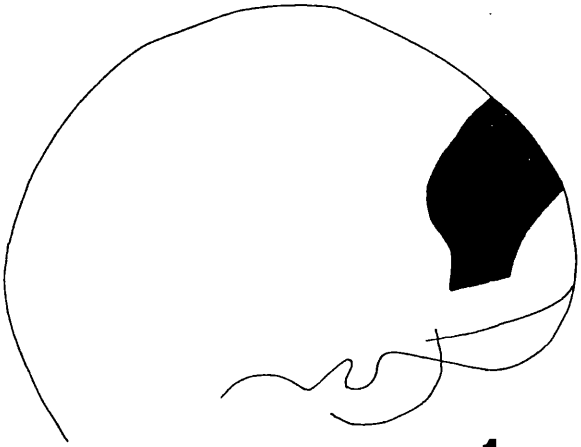
14



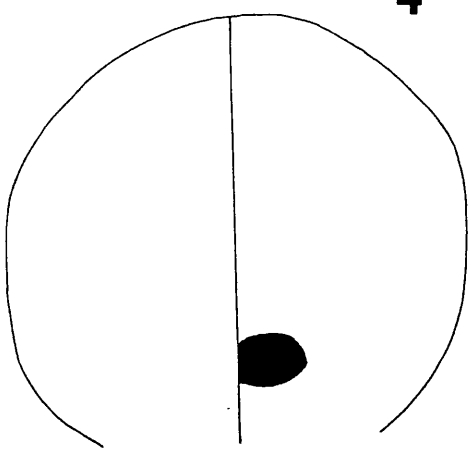


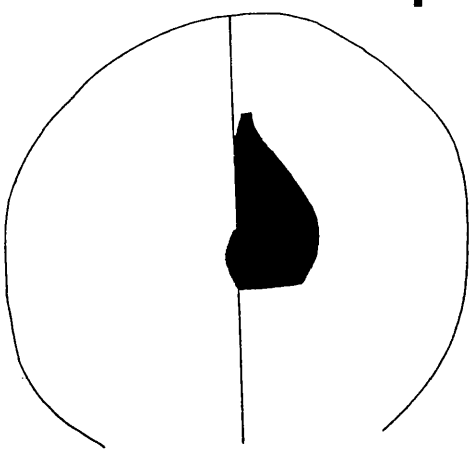


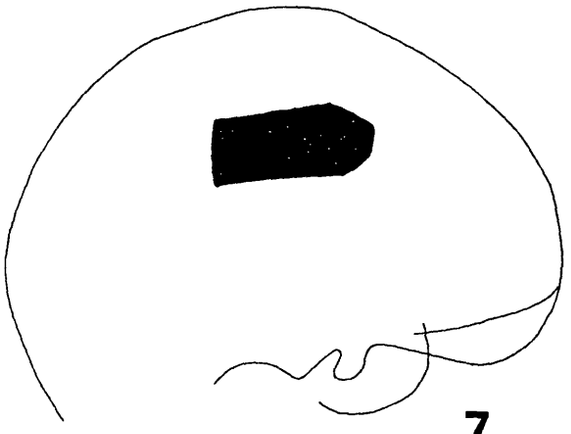
4



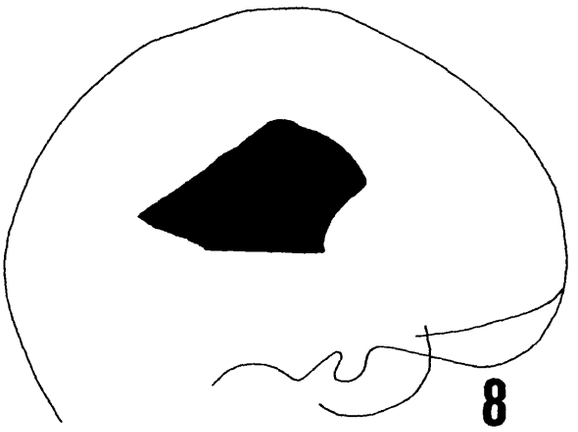
1





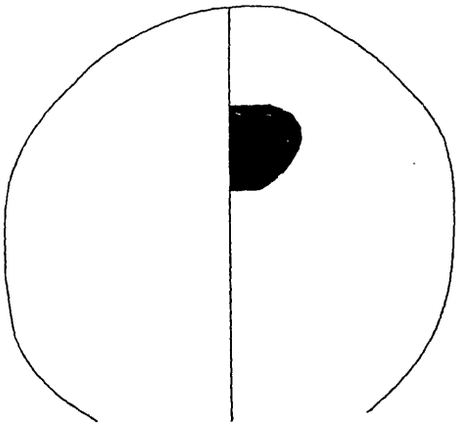


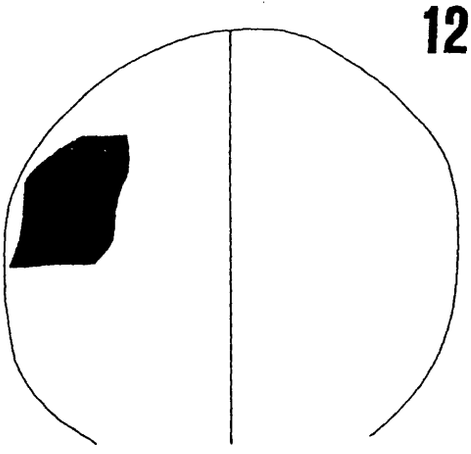
7

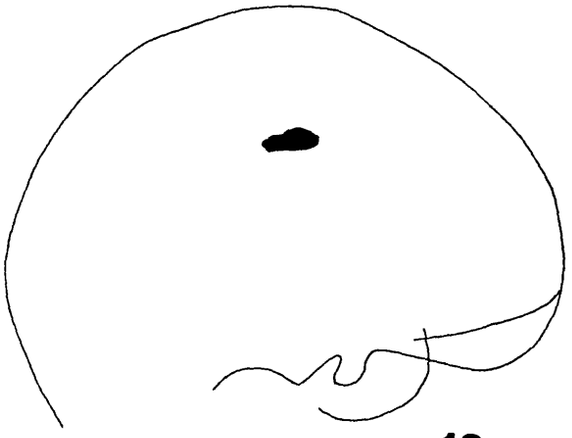


8

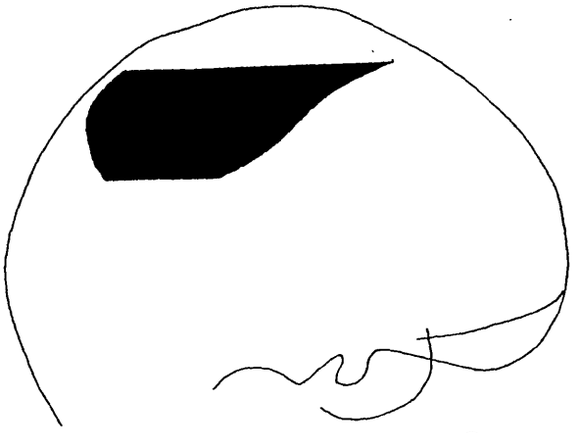
12



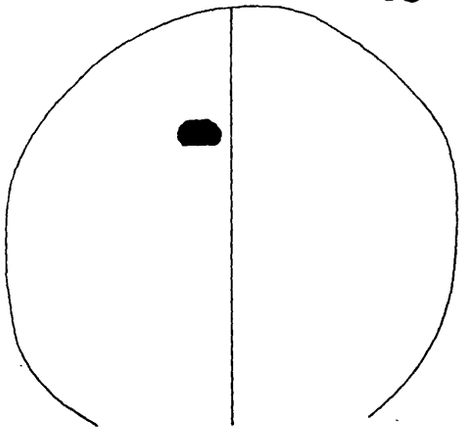


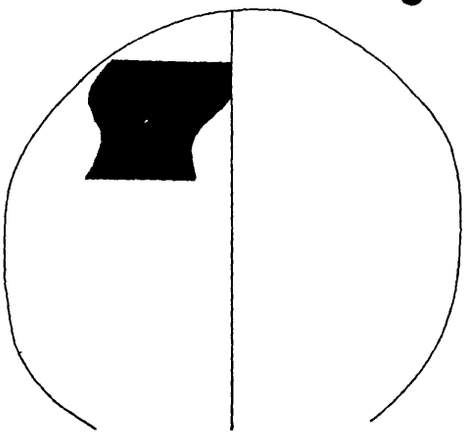


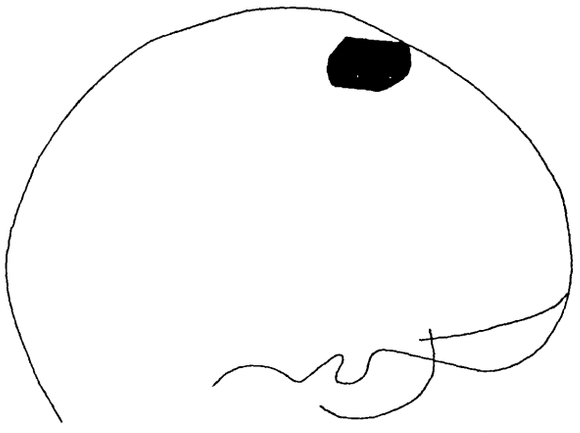
13



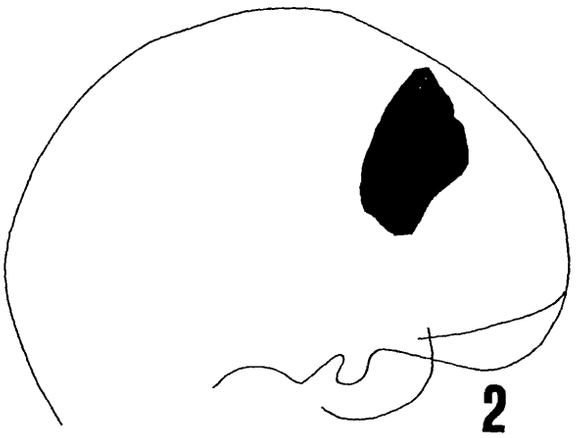
8





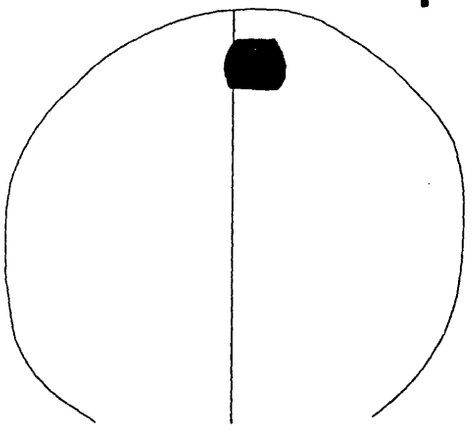


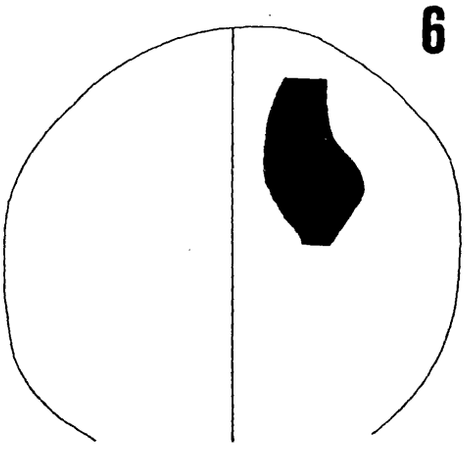
4

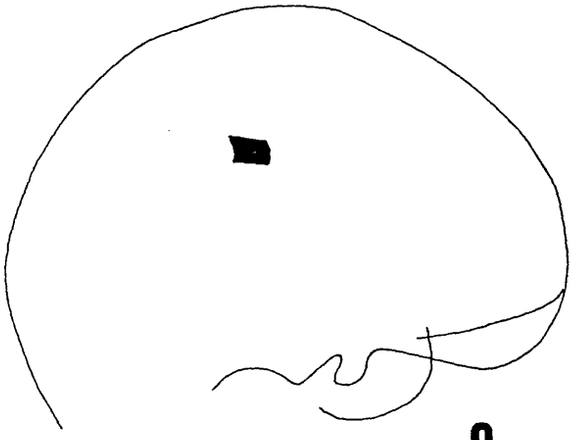


2

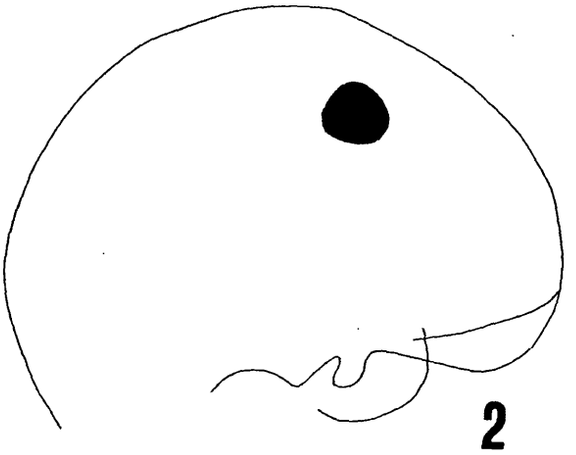
6





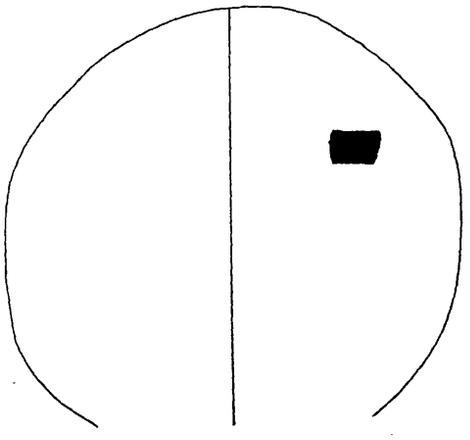


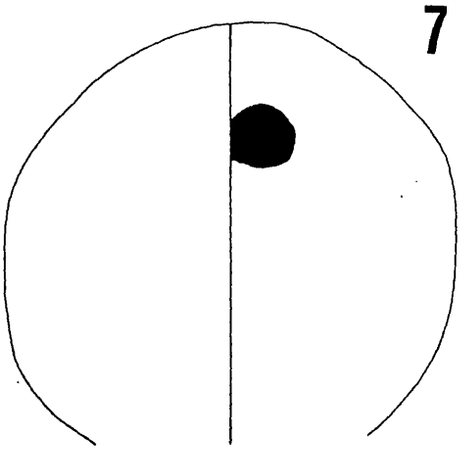
8

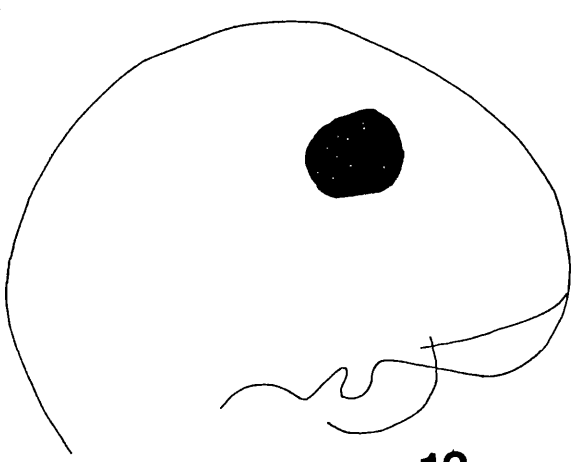


2

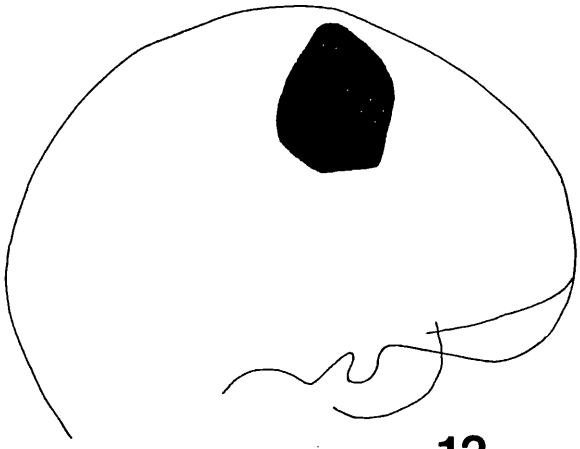
7



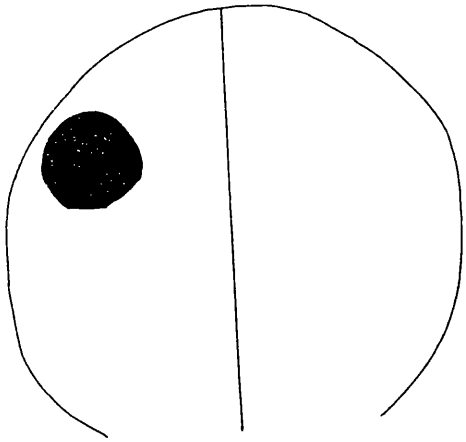


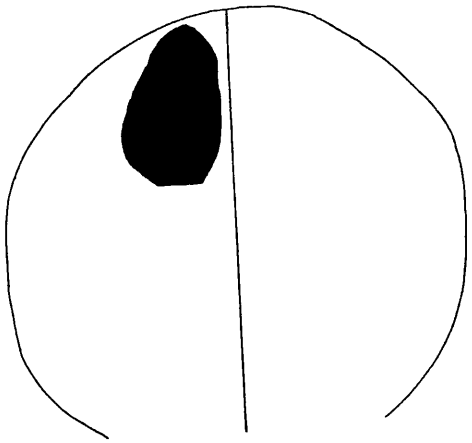


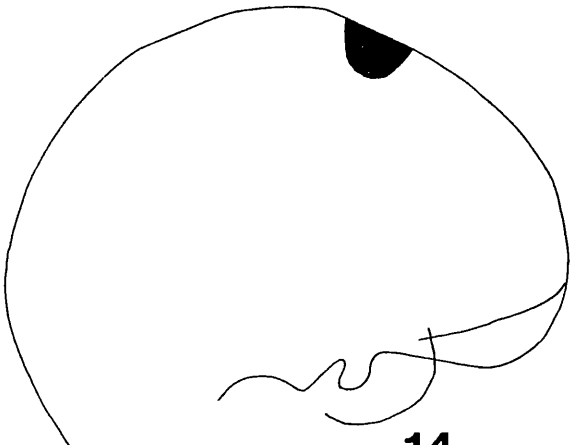
12



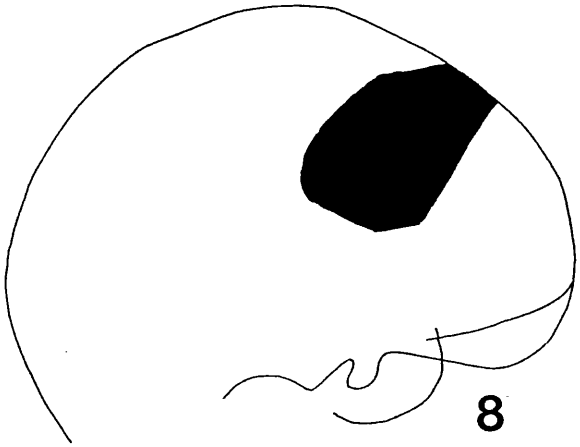
12





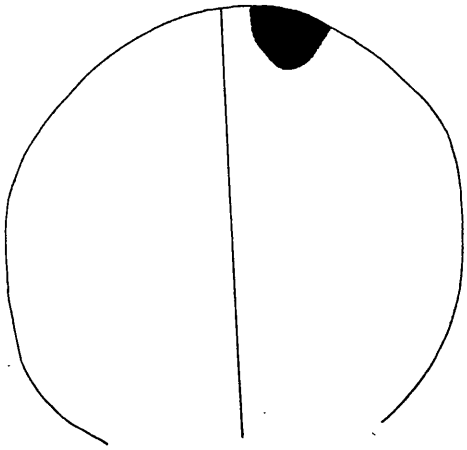


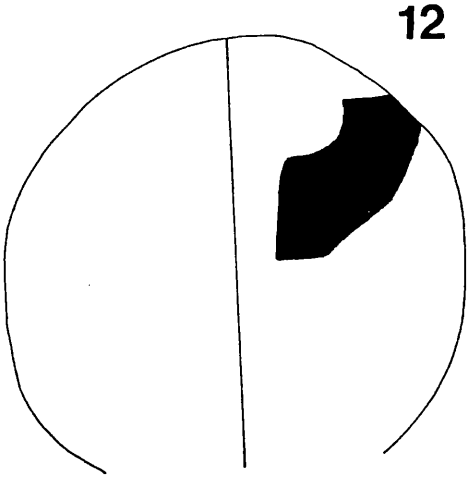
14

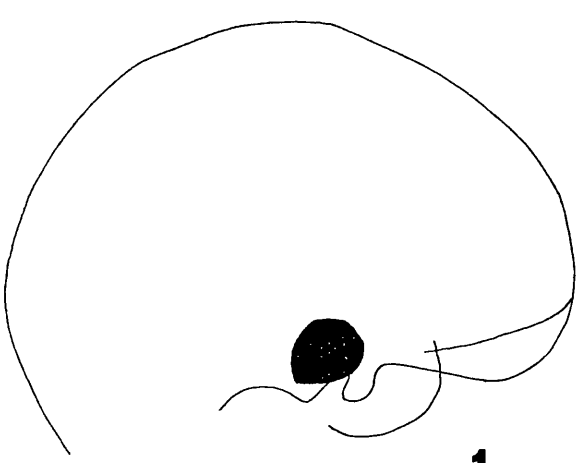


8

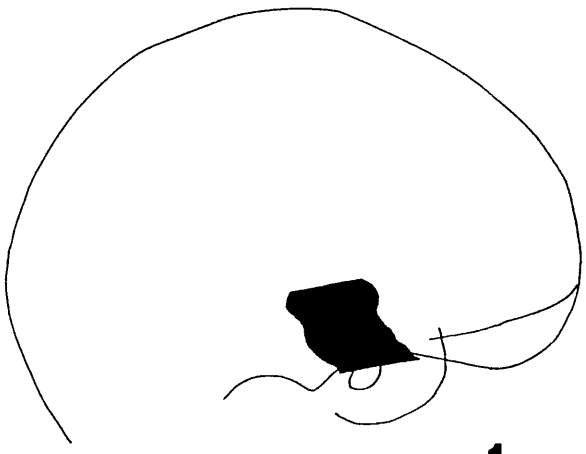
12



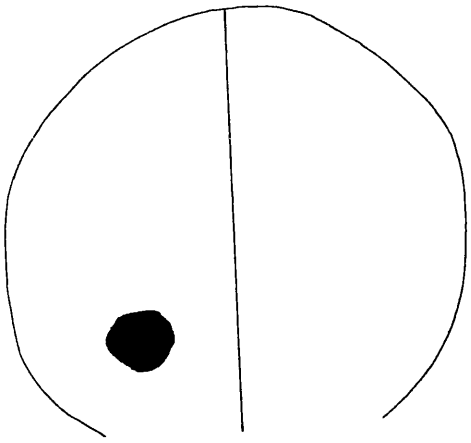


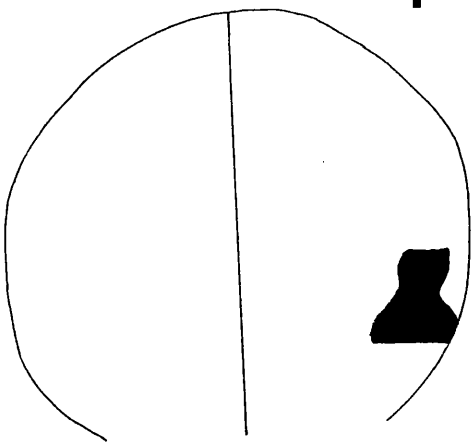


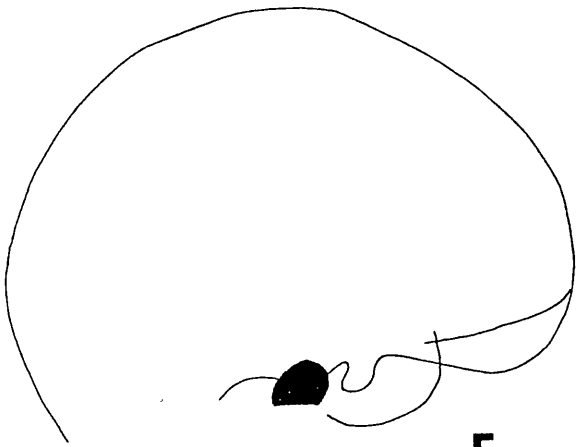
1



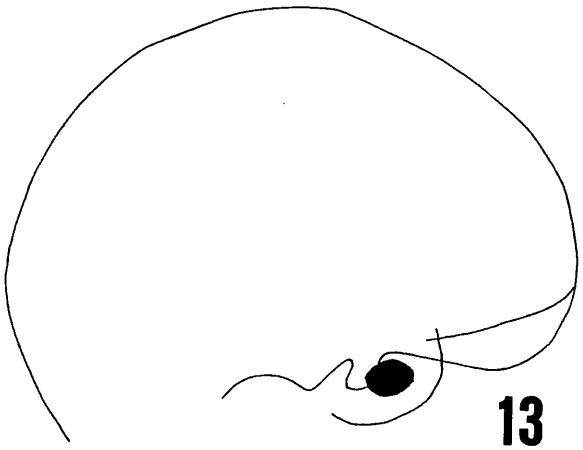
1





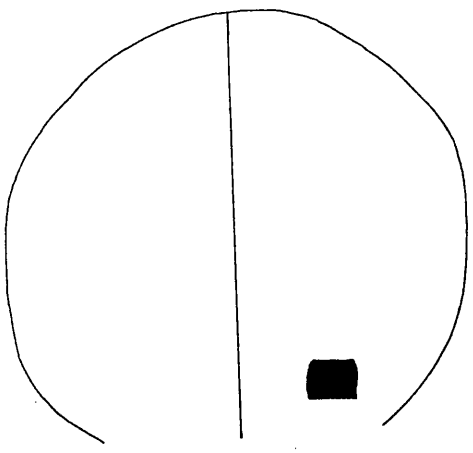


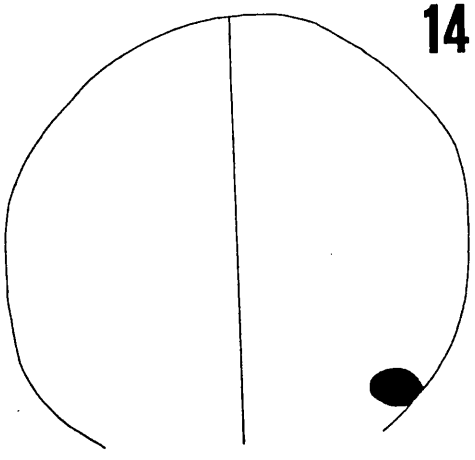
5

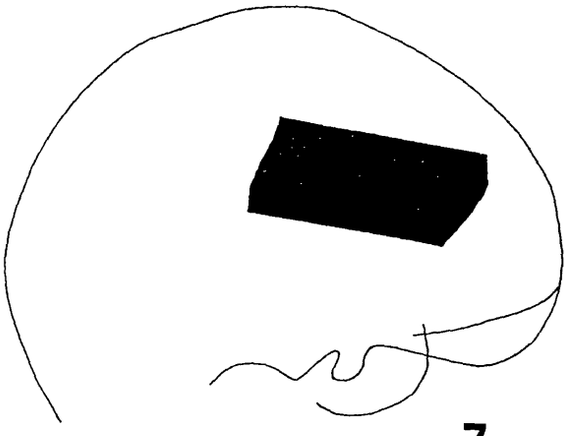


13

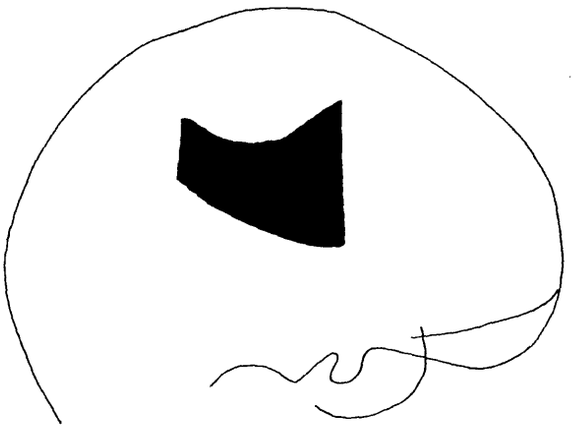
14



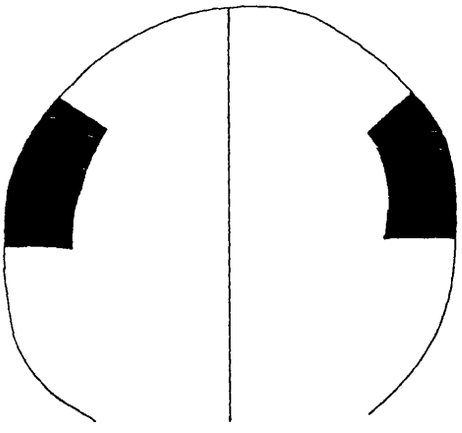


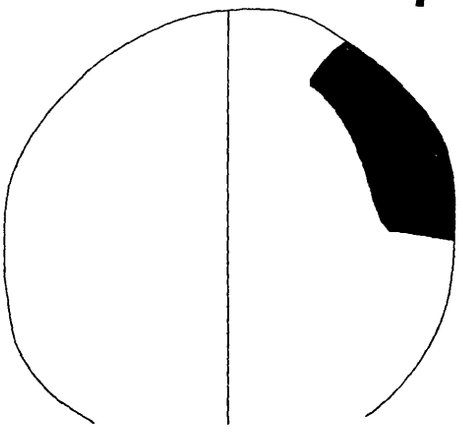


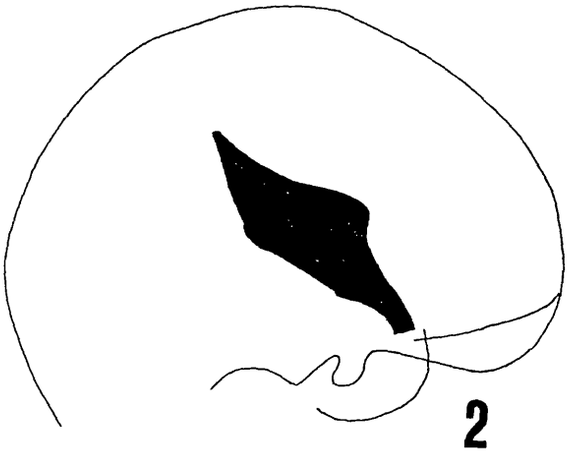
7



7

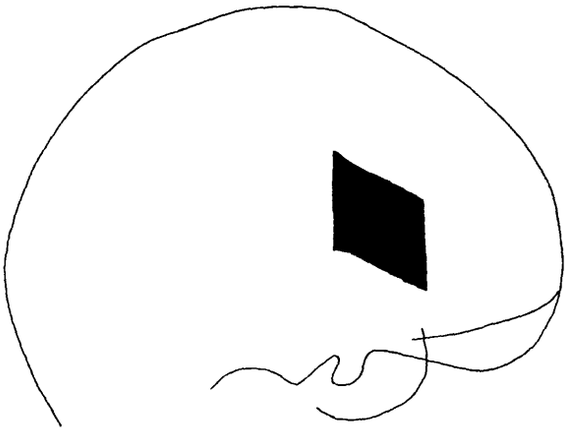




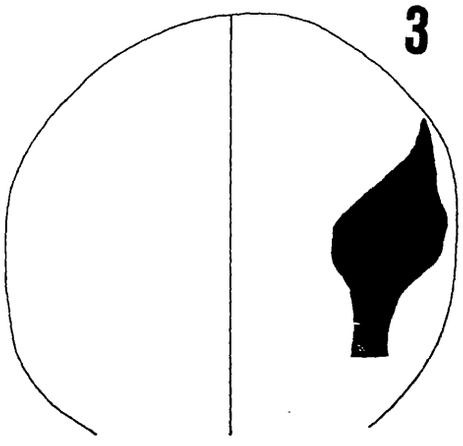


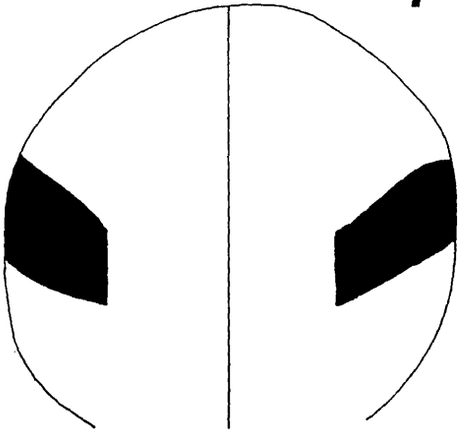
2

3

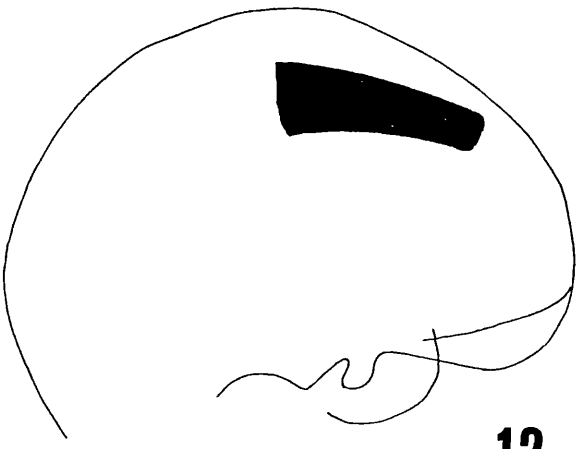


7

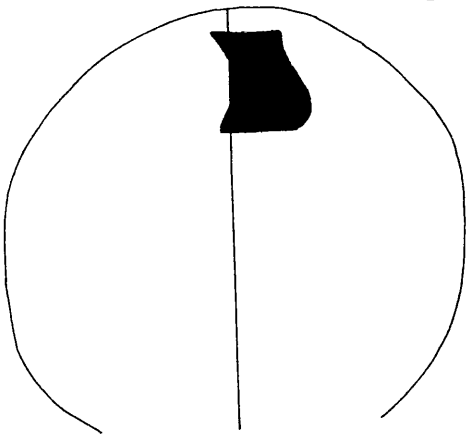


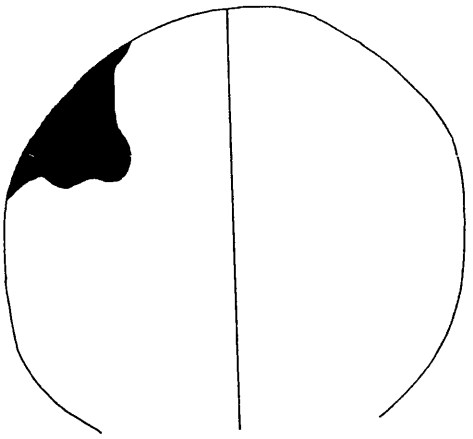


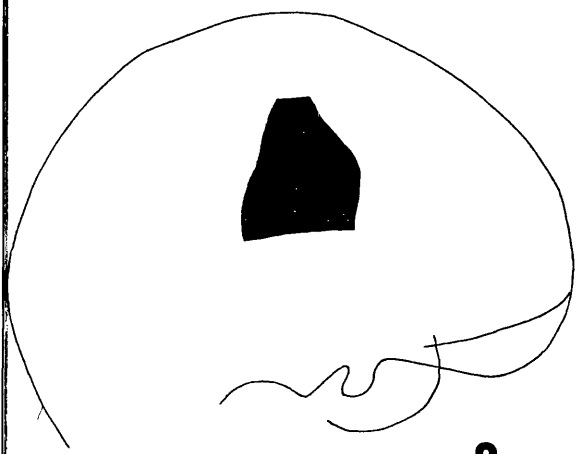
14



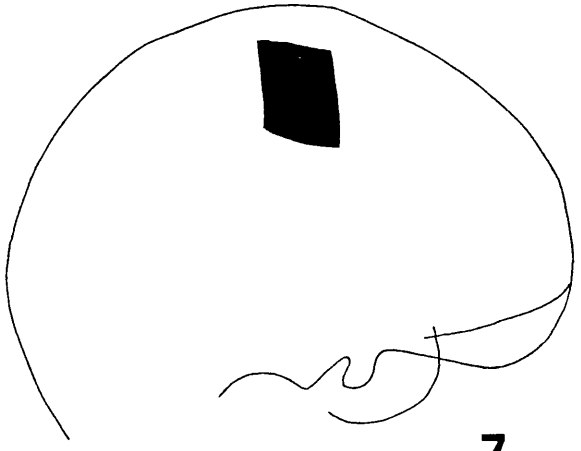
12



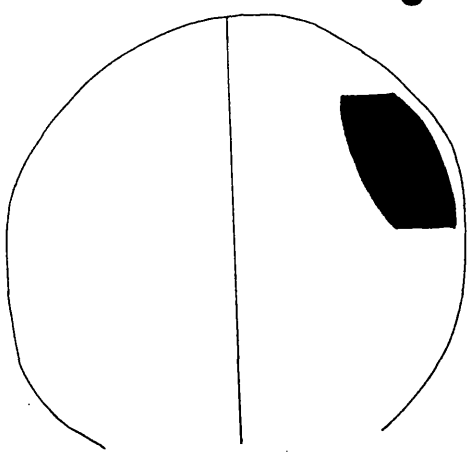


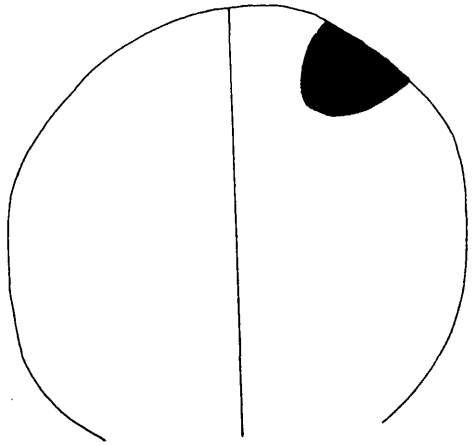


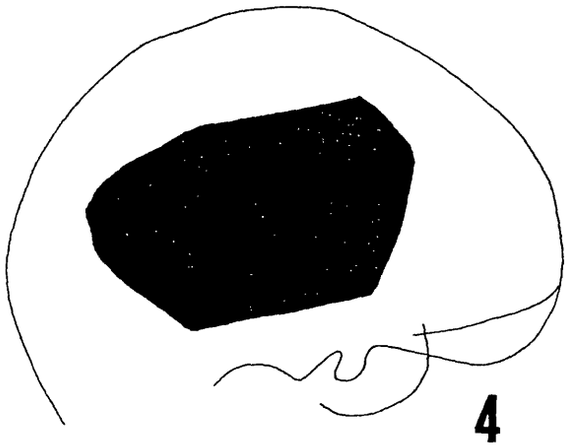
8



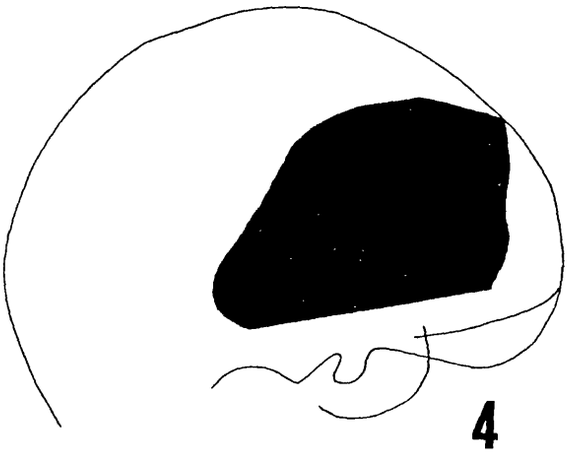
7





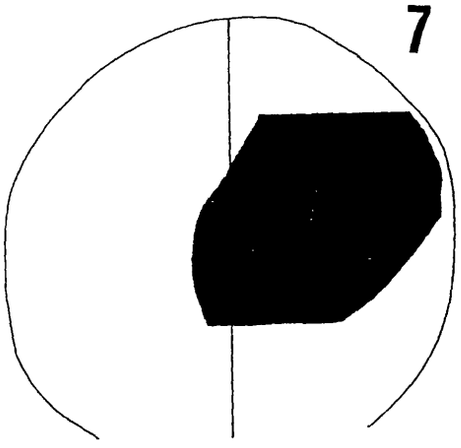


4

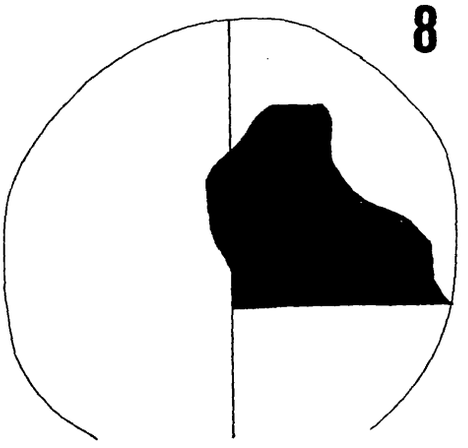


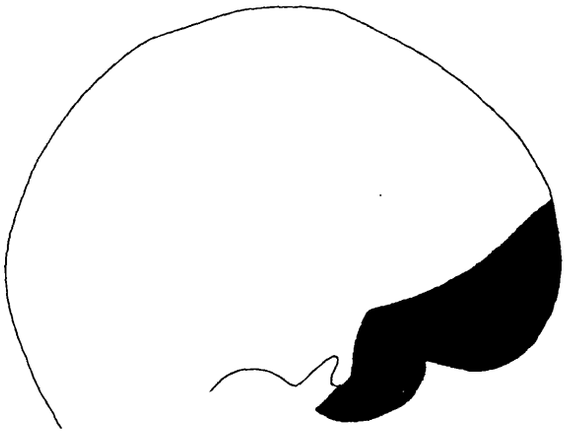
4

7

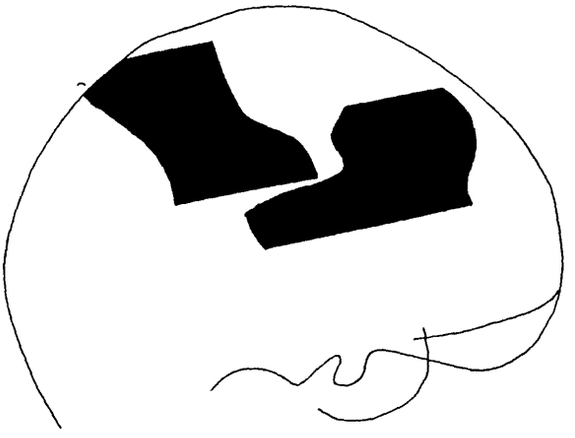


8

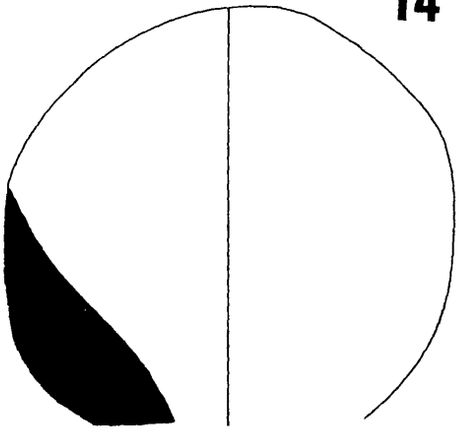


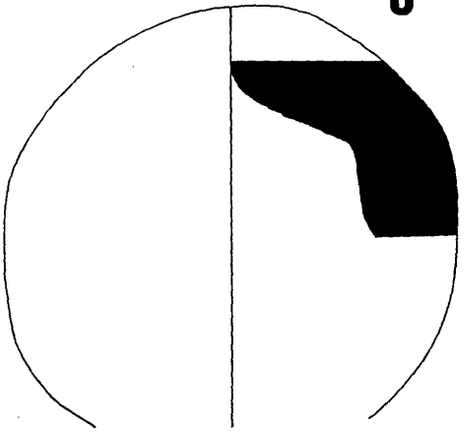


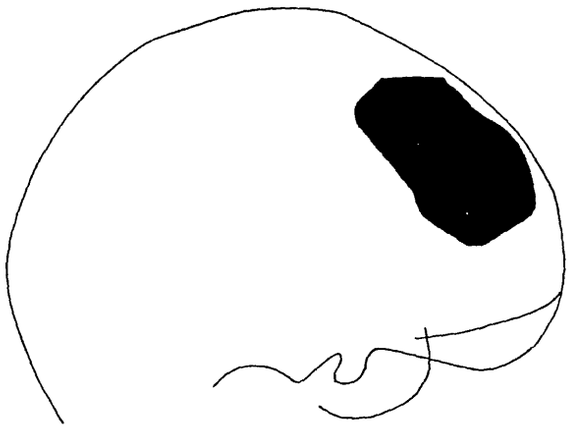
14



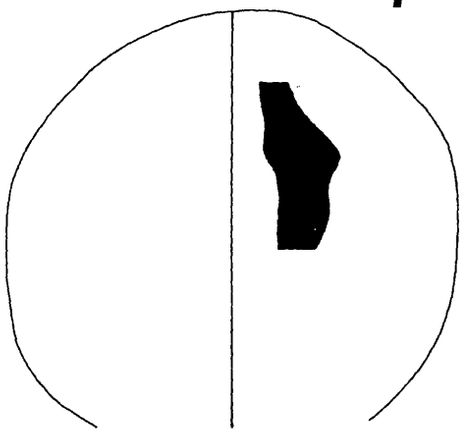
8

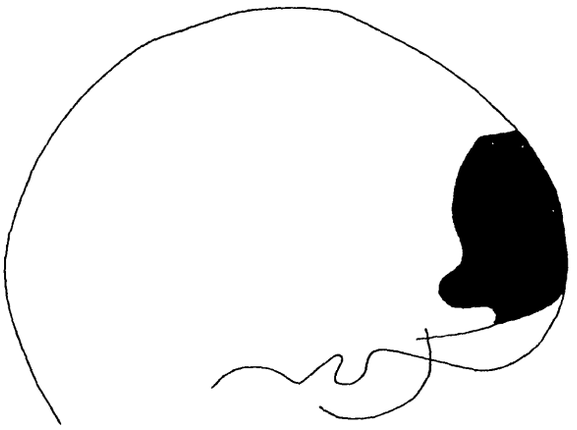




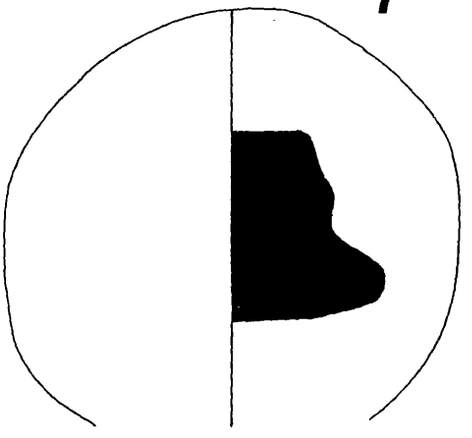


7

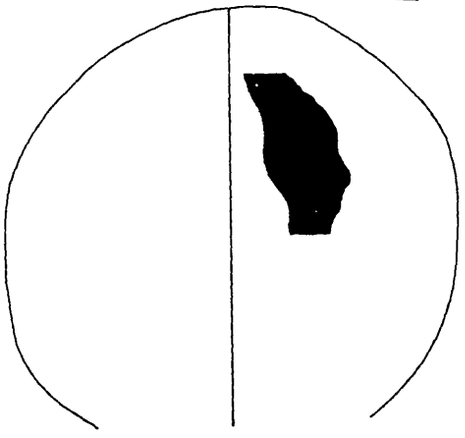


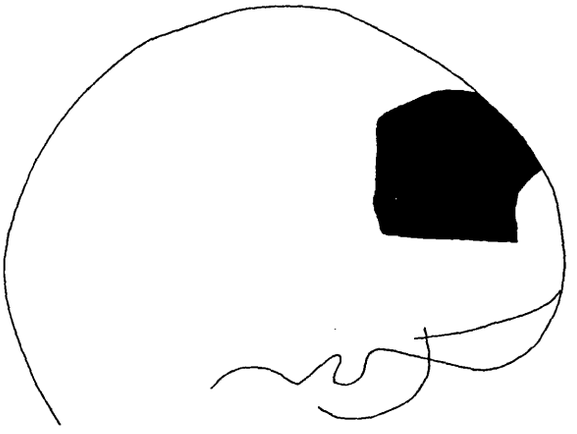


7

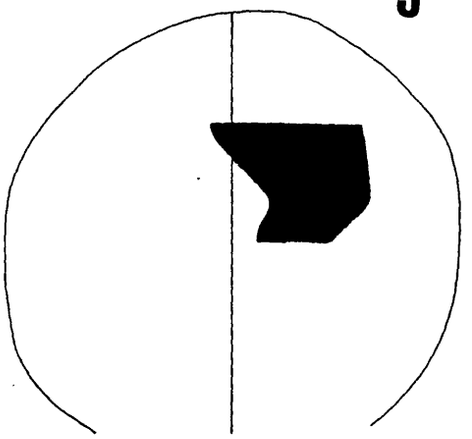


2

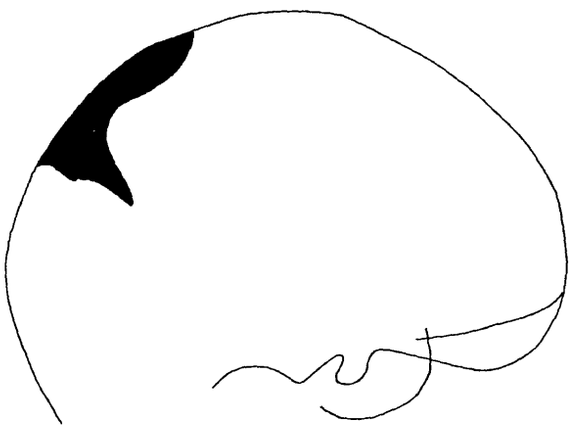




3

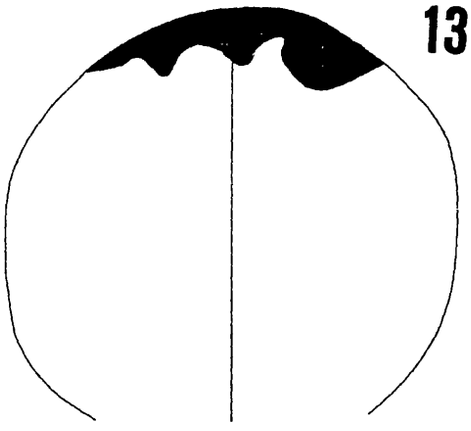


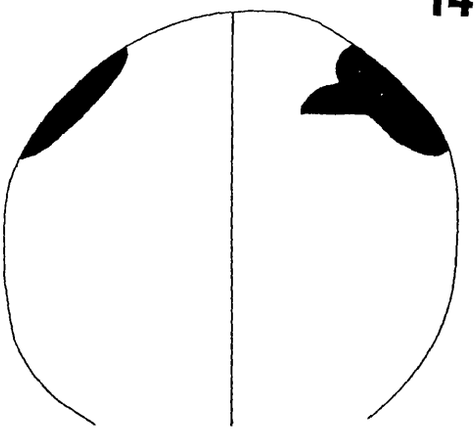
2

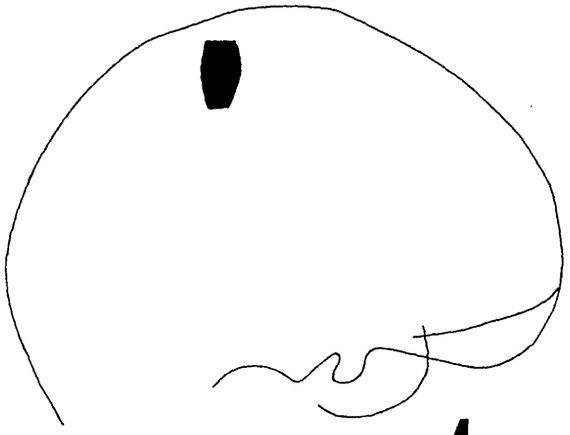


14

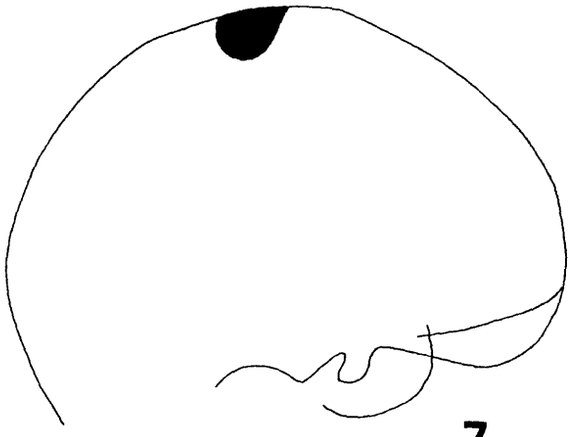
13



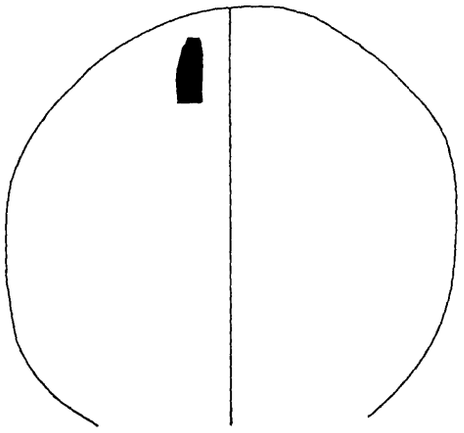


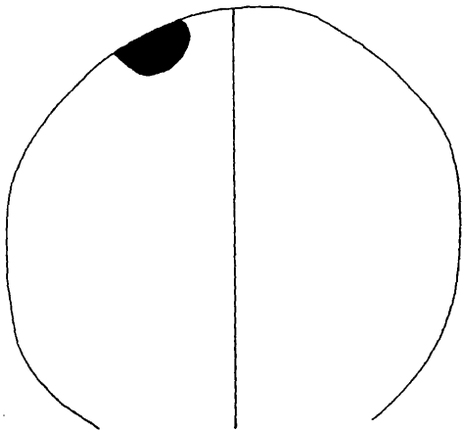


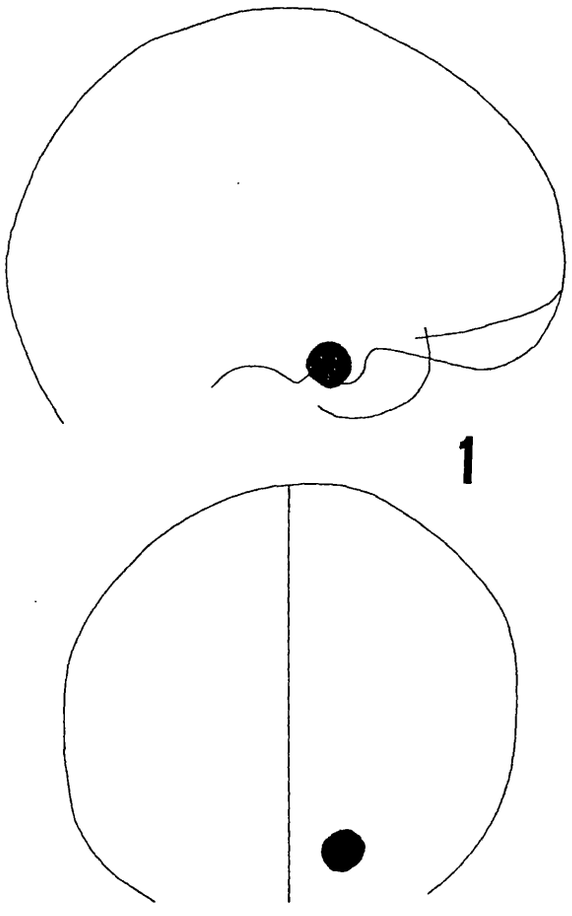
4



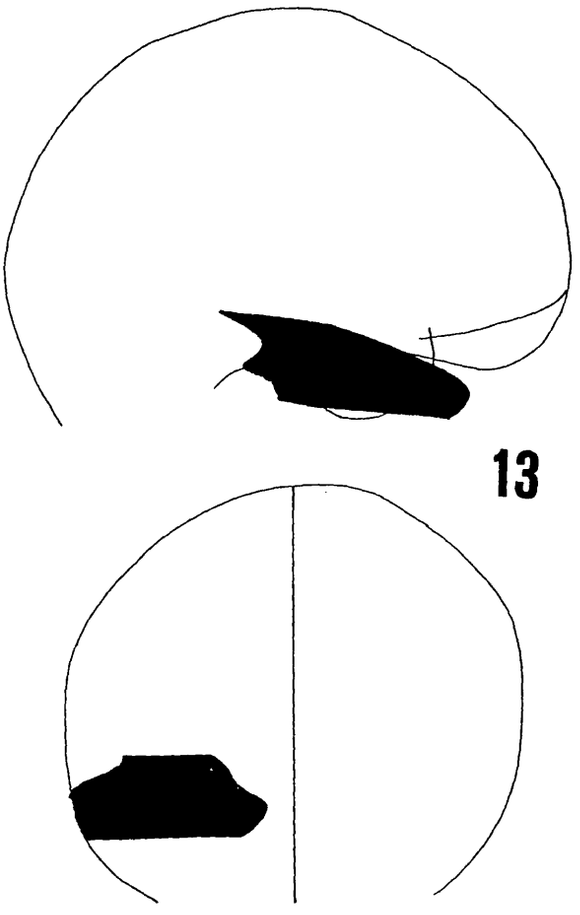
7



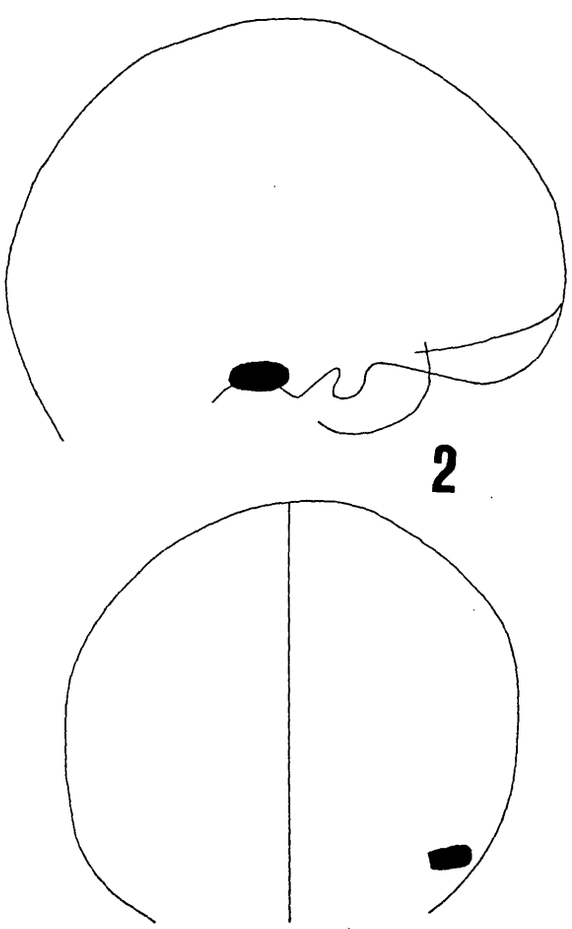




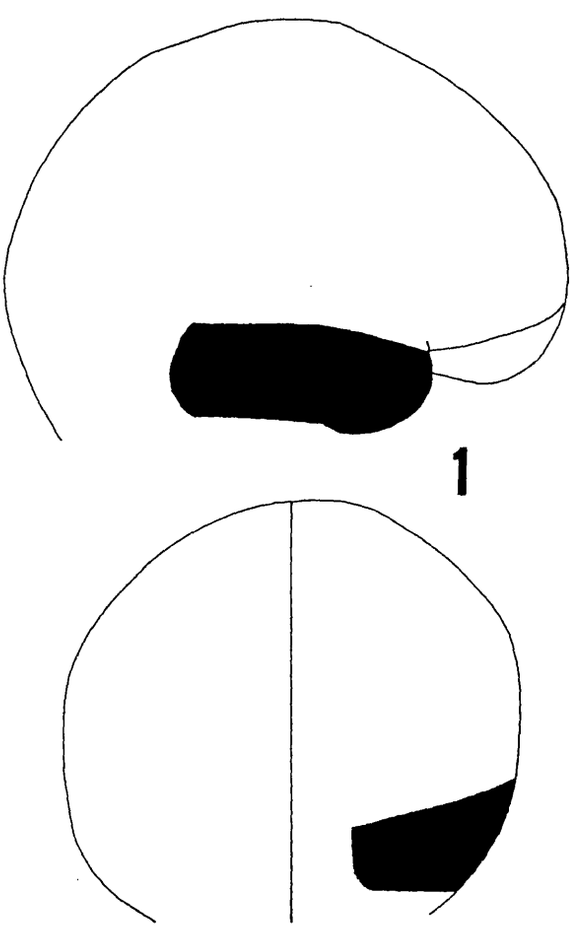
1



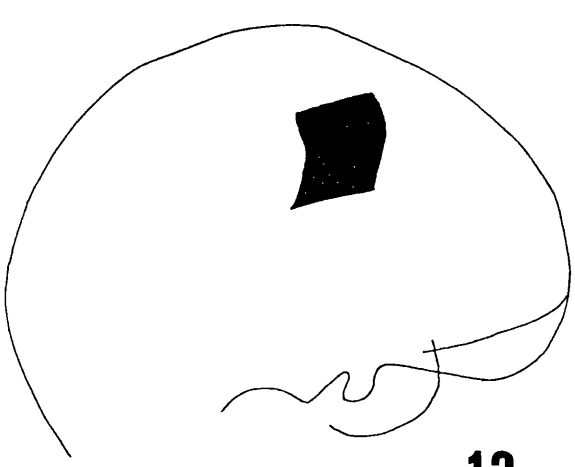
13



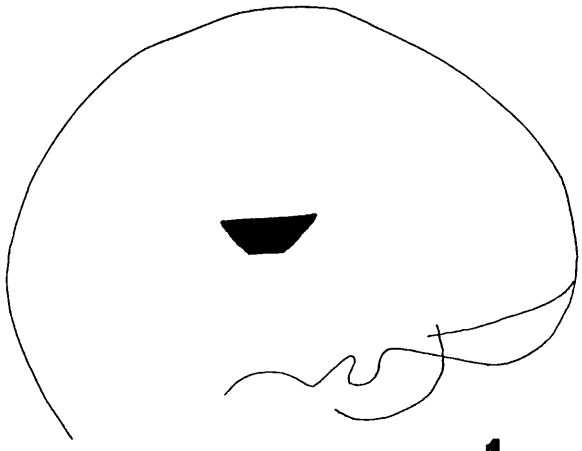
2



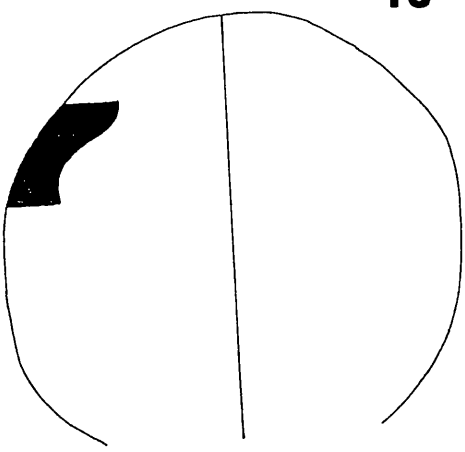
1

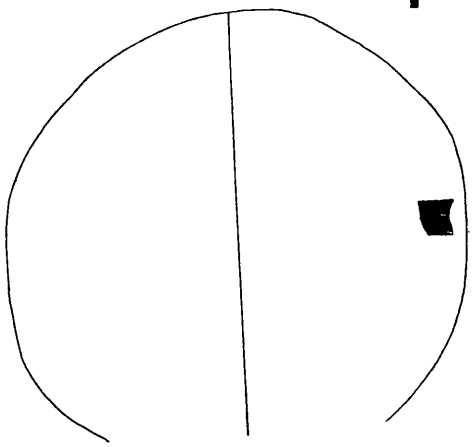


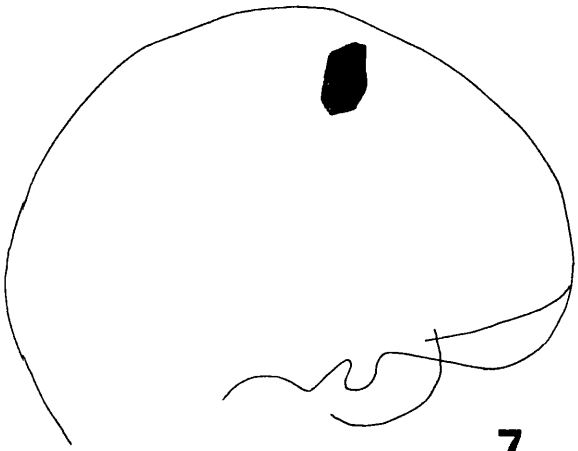
13



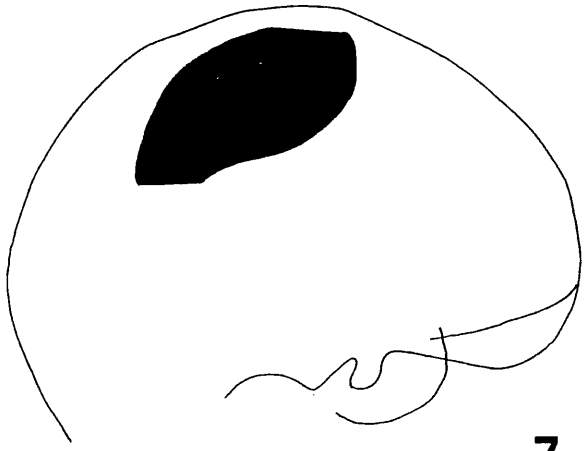
1



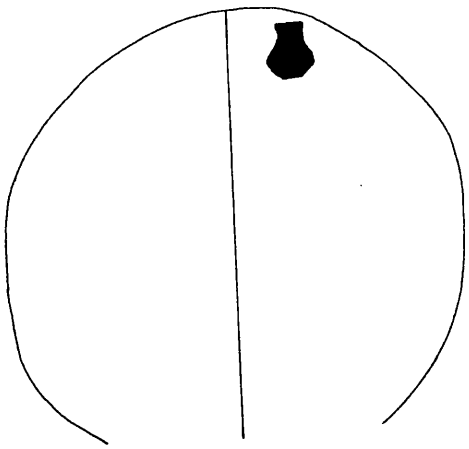


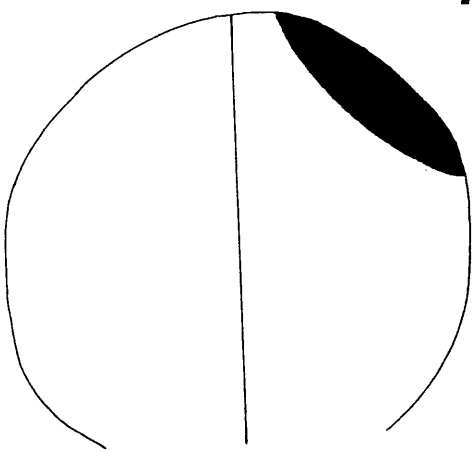


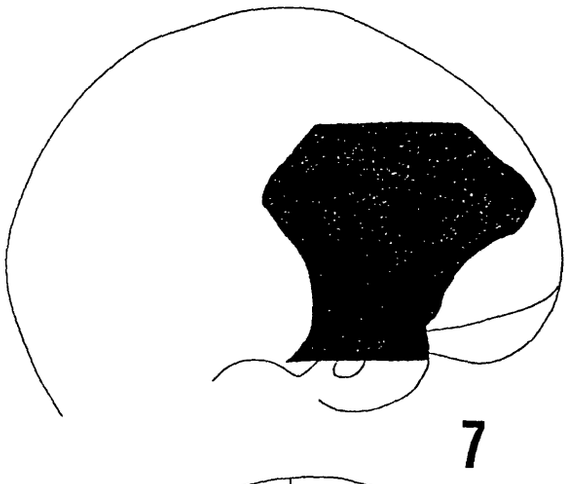
7



7

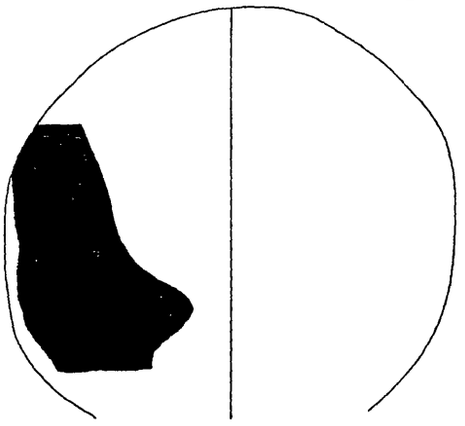


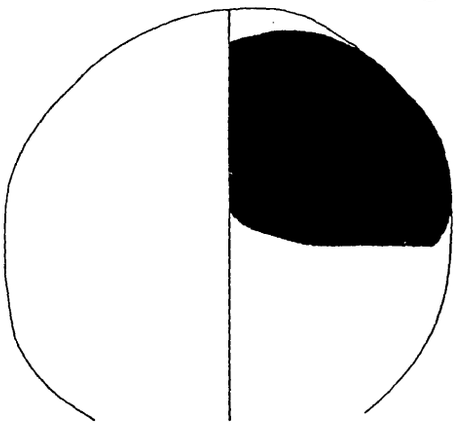


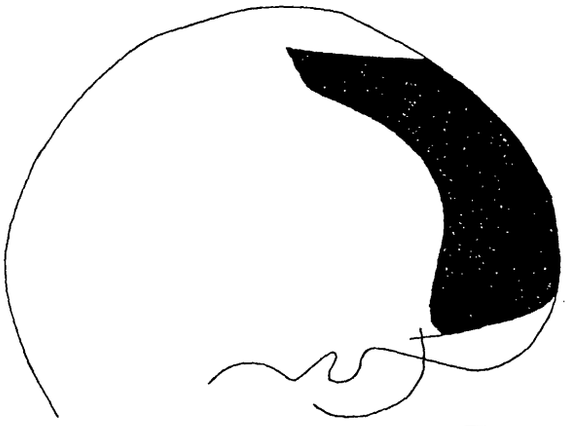


7

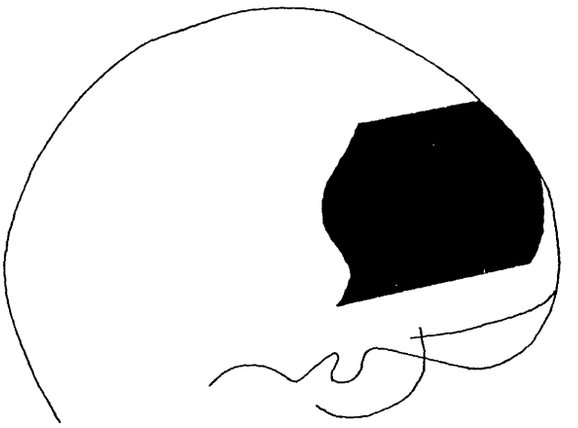
8



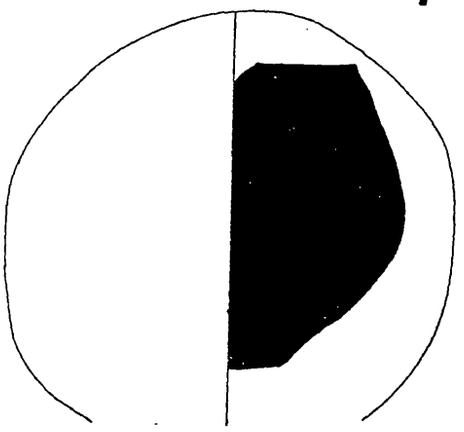


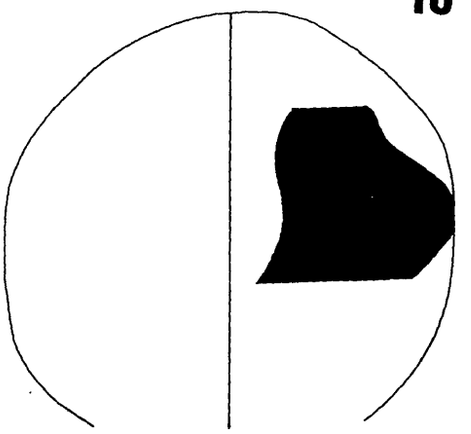


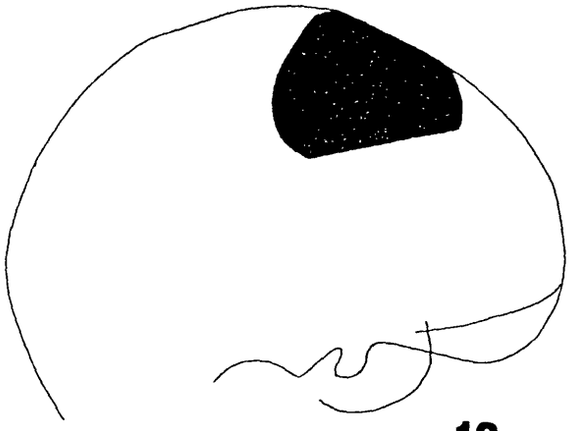
7



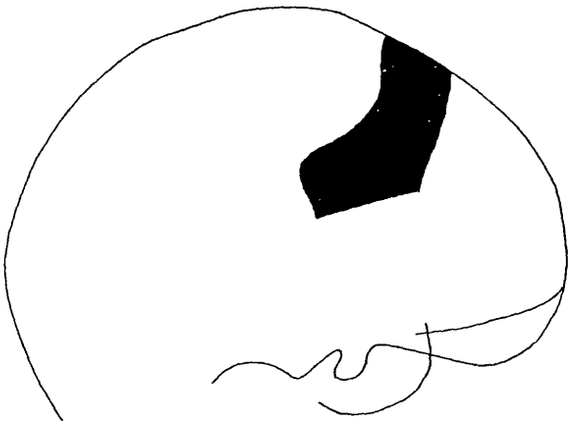
13



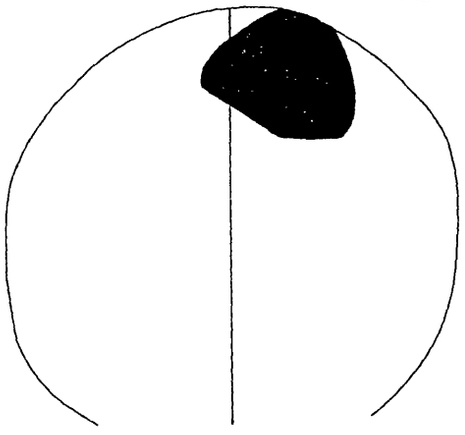


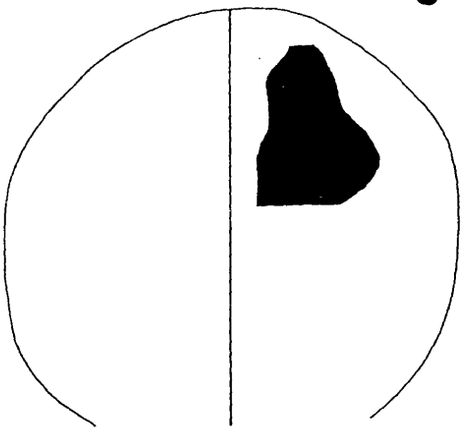


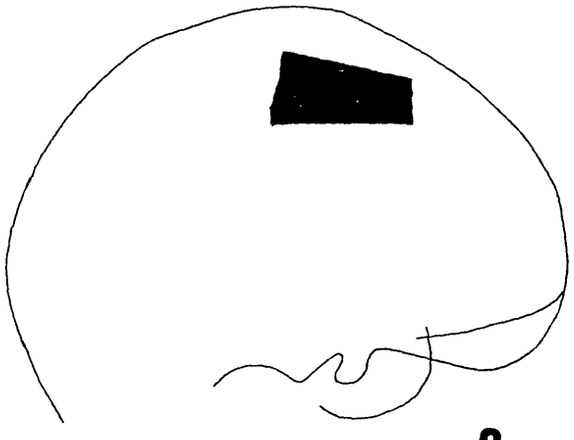
13



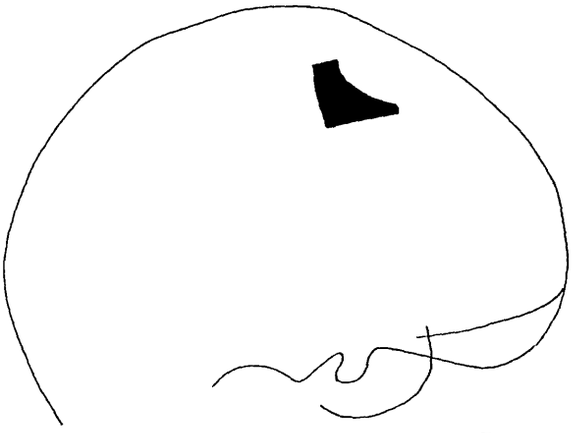
3



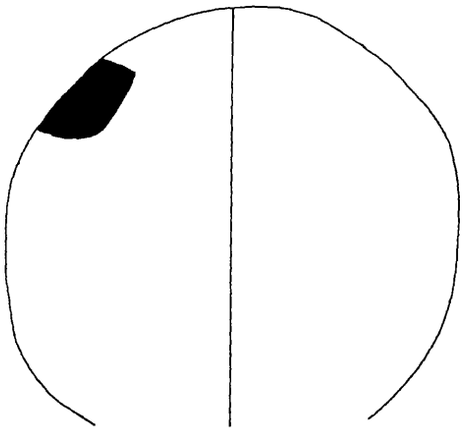


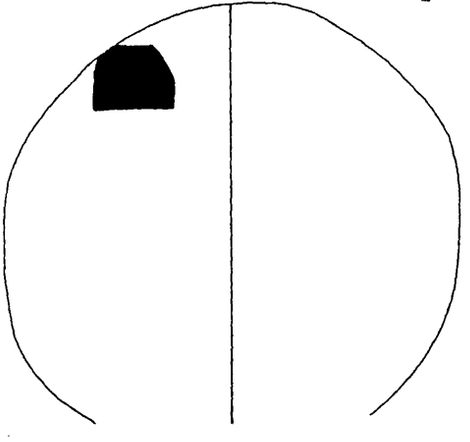


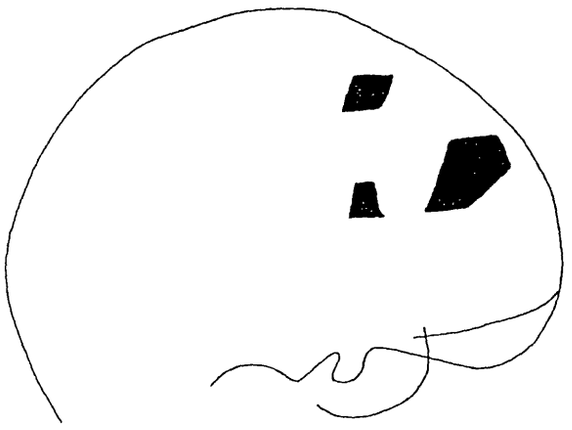
8



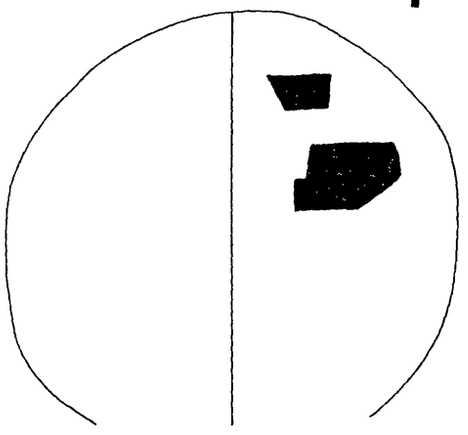
7

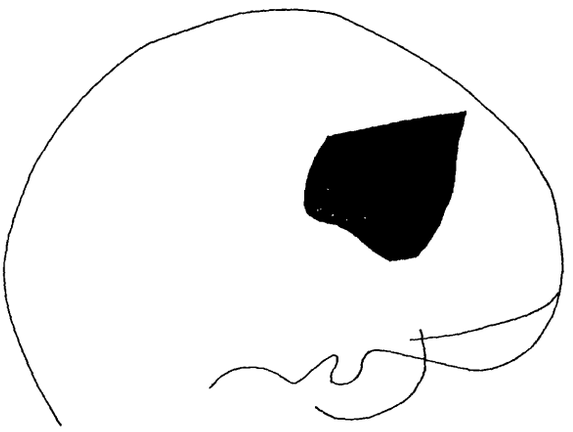




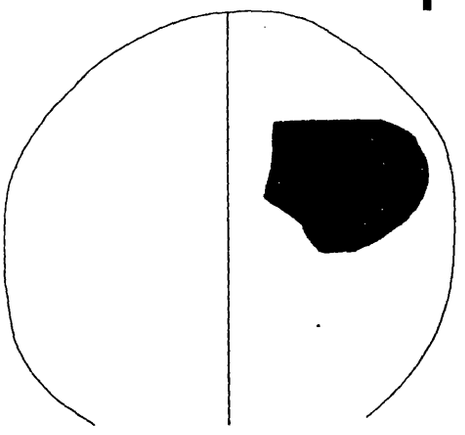


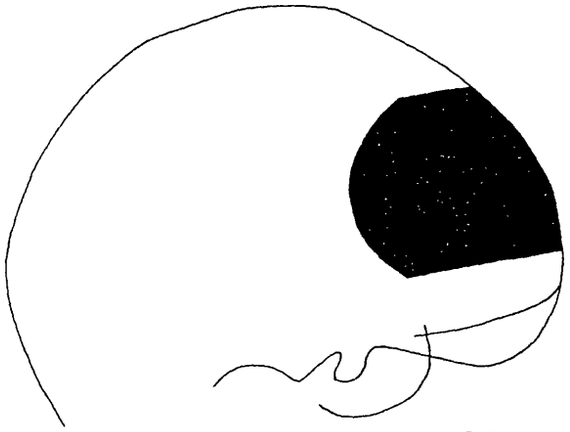
1



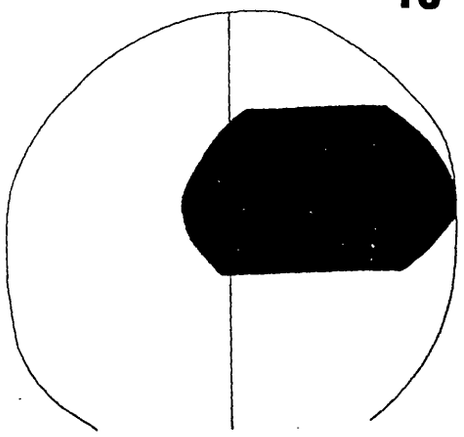


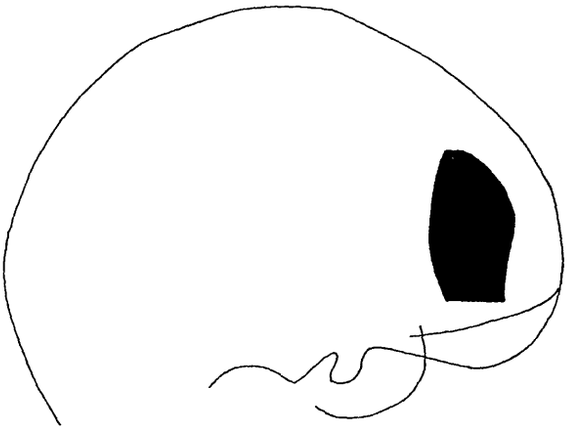
1



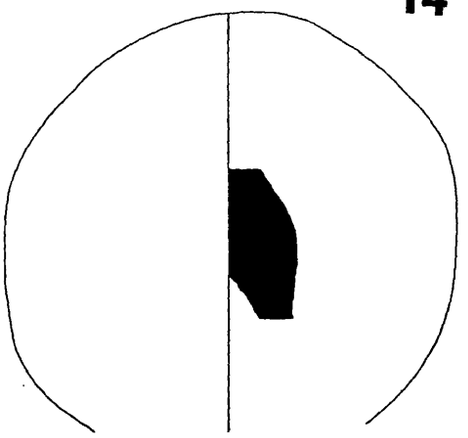


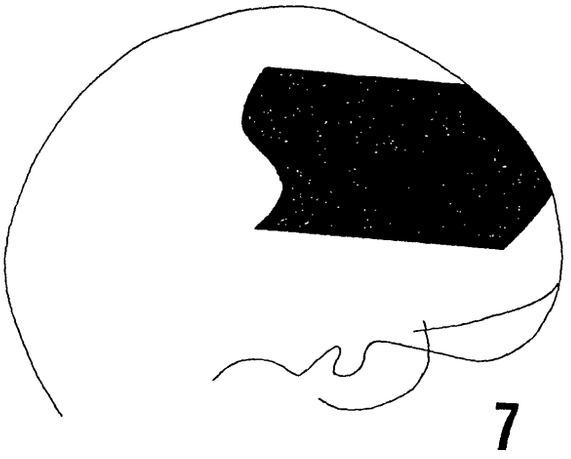
13



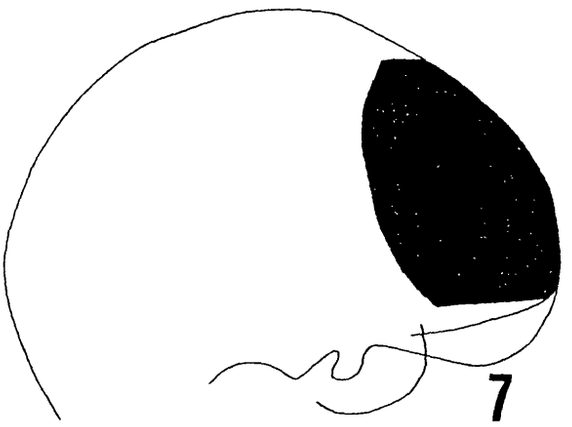


14



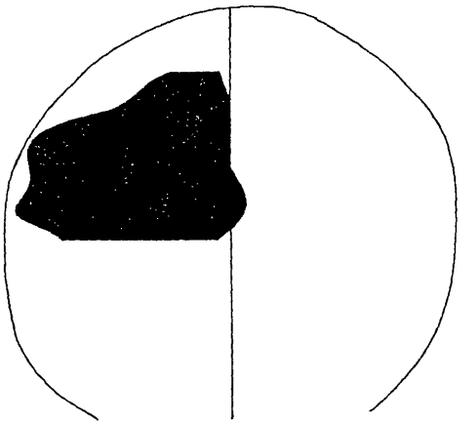


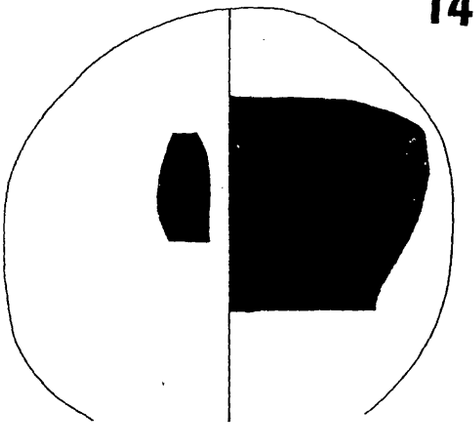
7



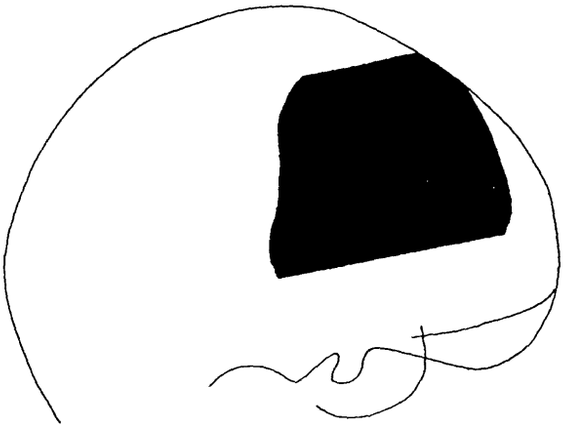
7

14

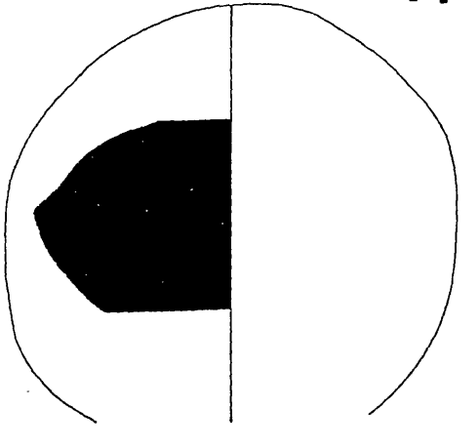


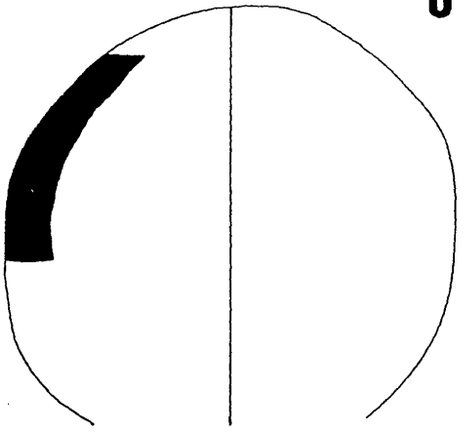


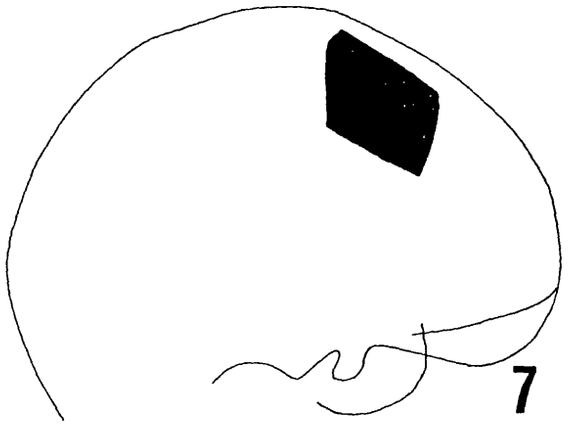
14



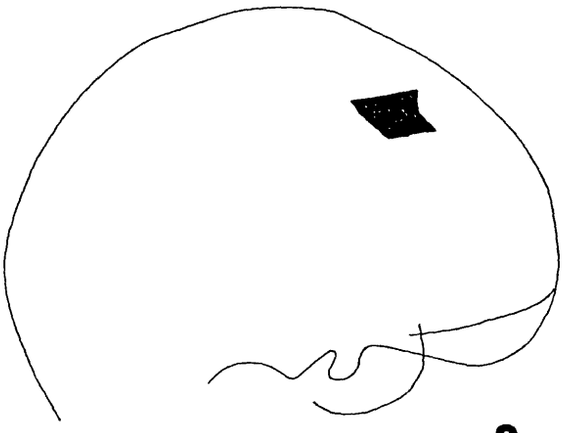
8





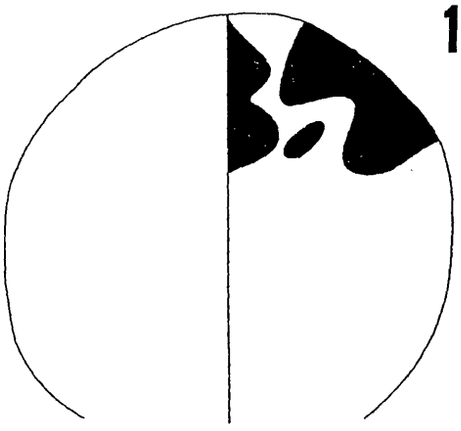


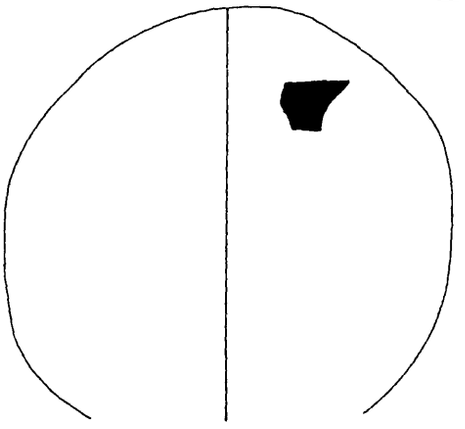
7

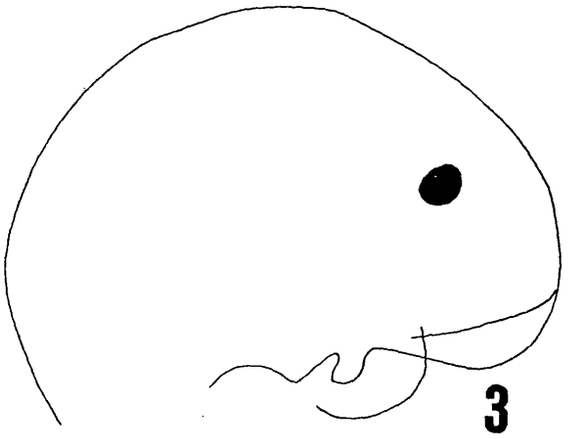


2

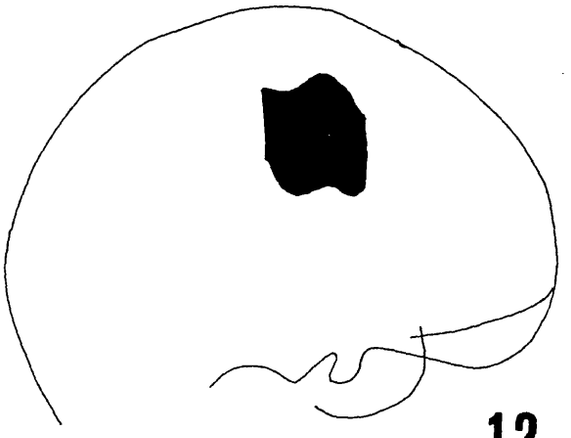
13





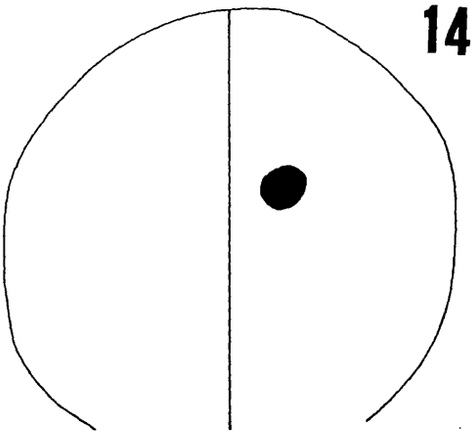


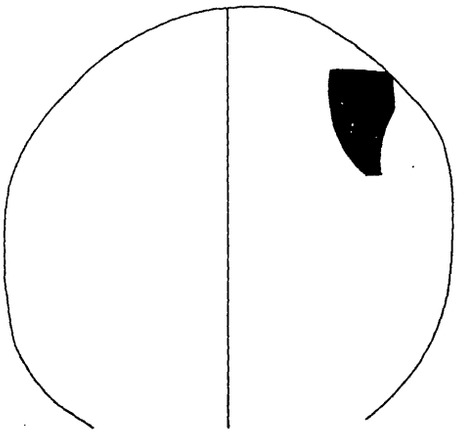
3



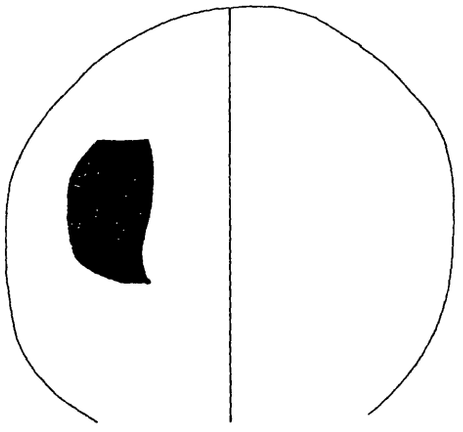
12

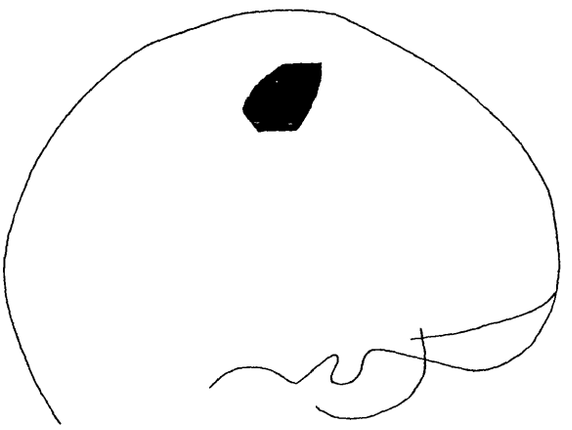
14



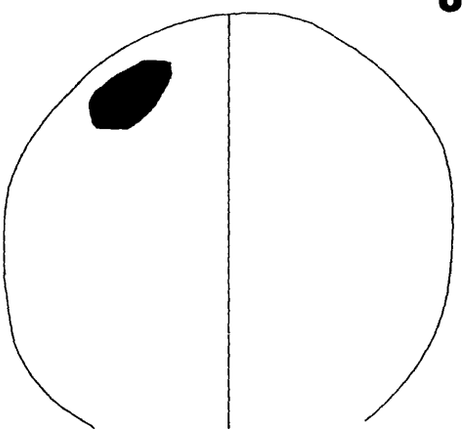


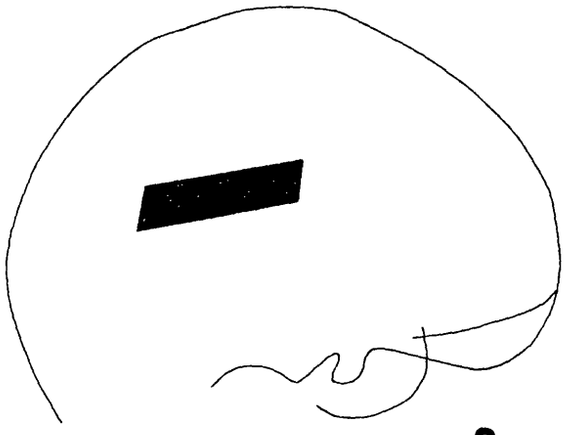
12



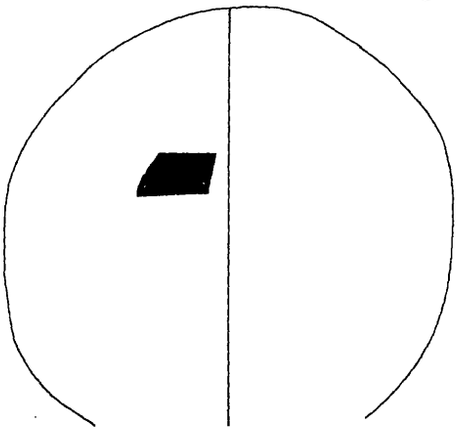


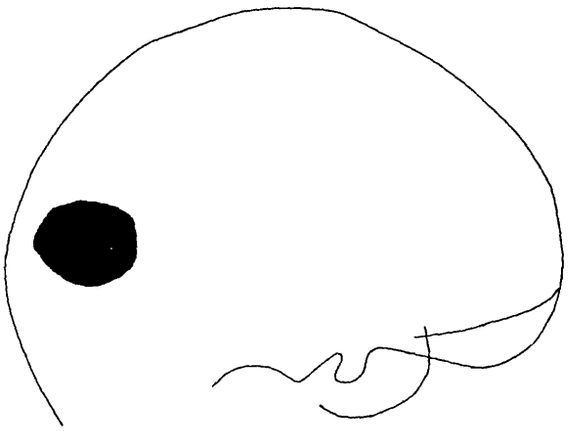
8



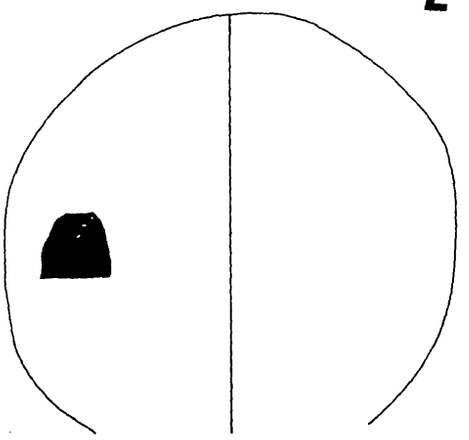


3



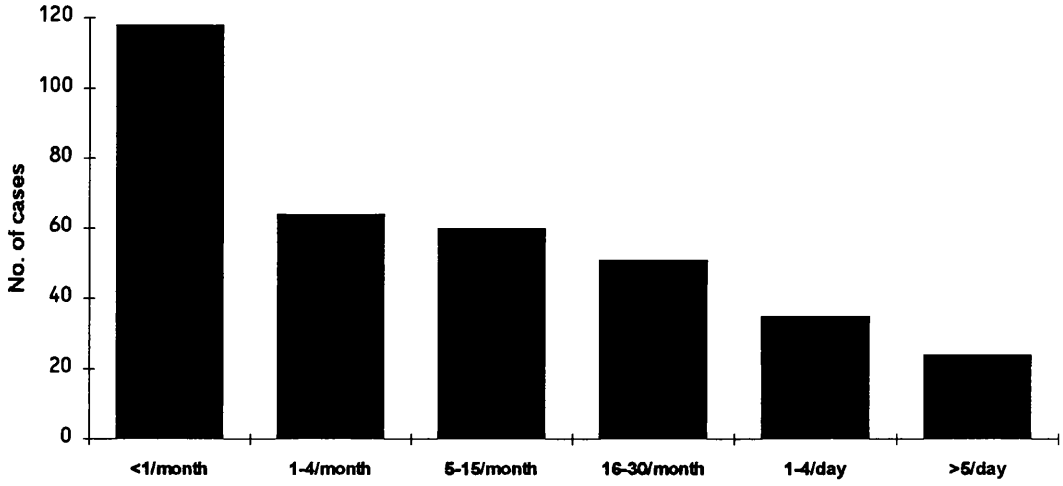


2

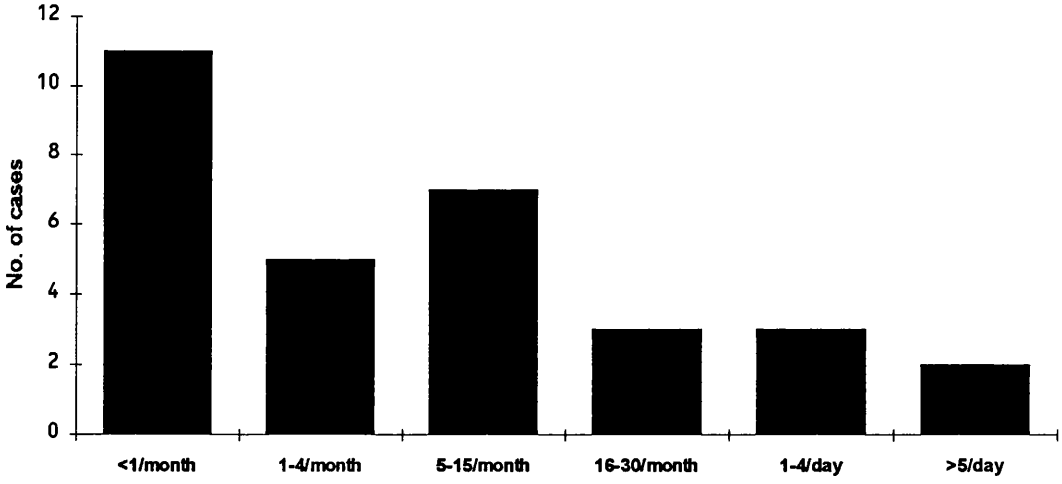


Appendix 5. Average seizure frequency for each group

a) Average seizure frequency for all seizures combined

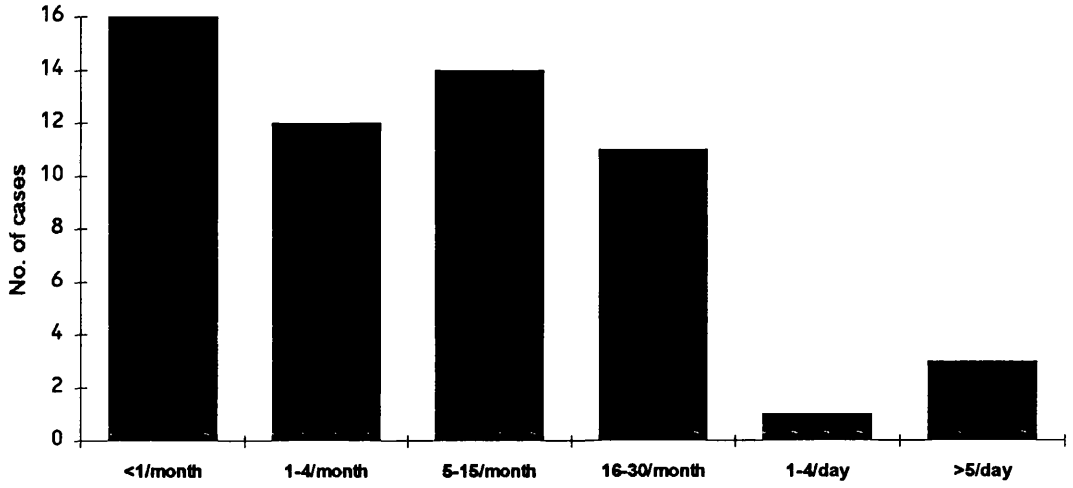


b) Average seizure frequency for group 1; olfactory/gustatory and fear behaviour

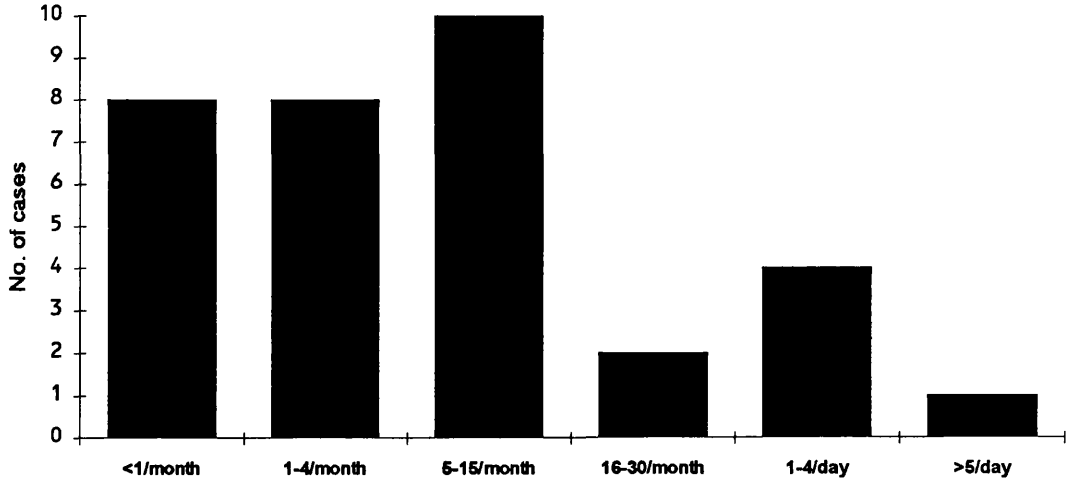


Appendix 5, continued

c) Average seizure frequency for group 2; absences

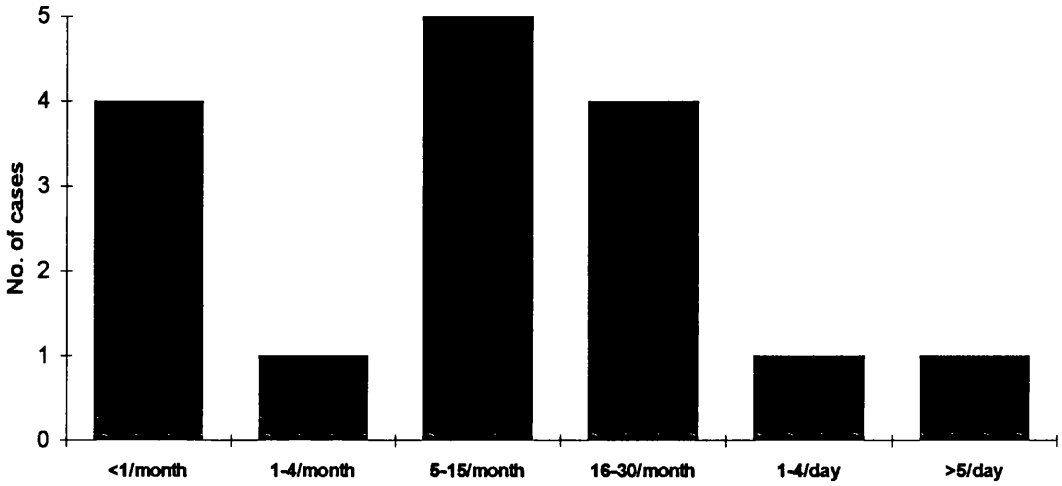


d) Average seizure frequency for group 3; experiential

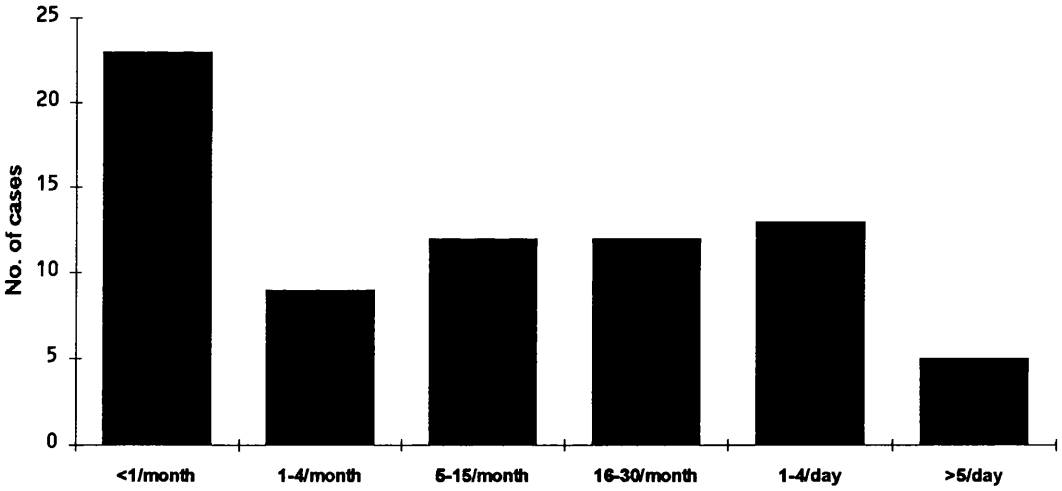


Appendix 5, continued

e) Average seizure frequency for group 4; visual

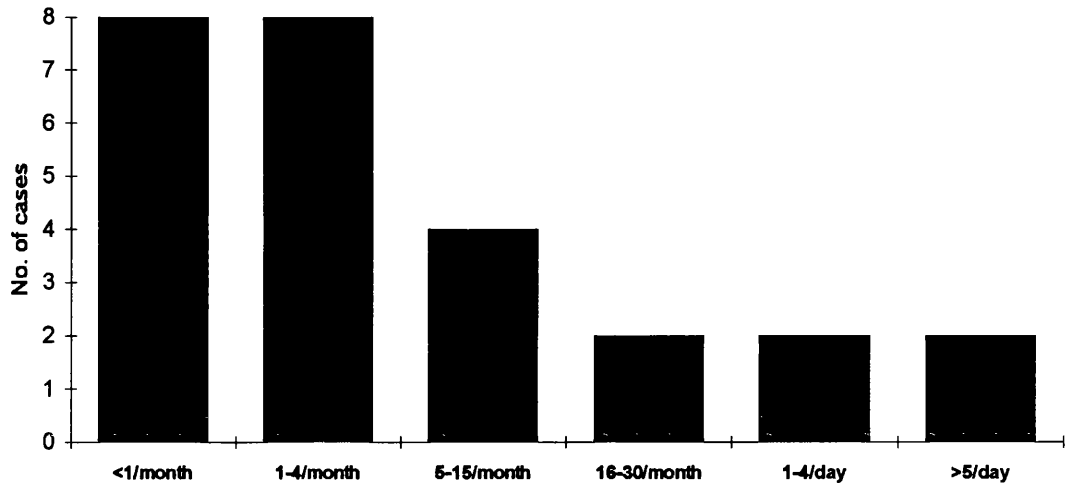


f) Average seizure frequency for group 7; version/posturing

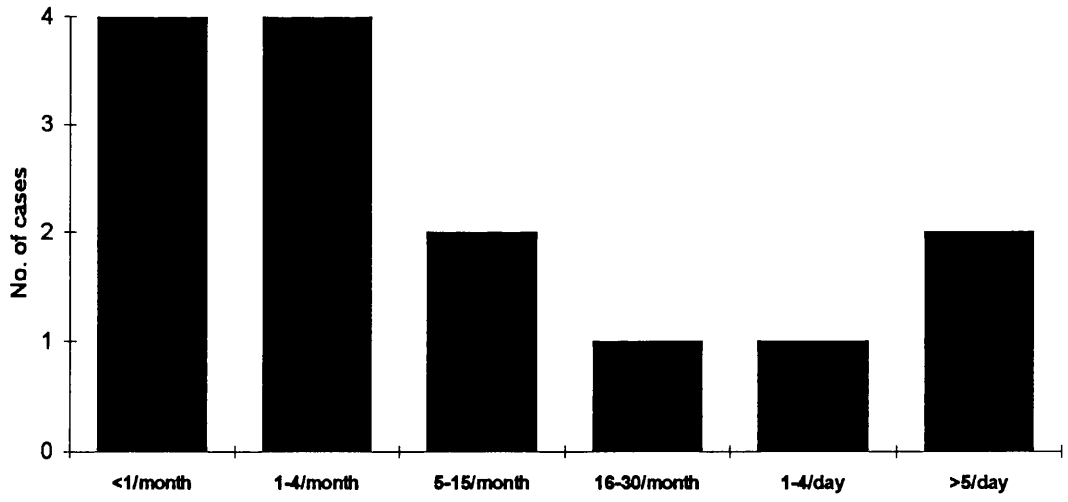


Appendix 5, continued

g) Average seizure frequency for group 8; focal somatosensory

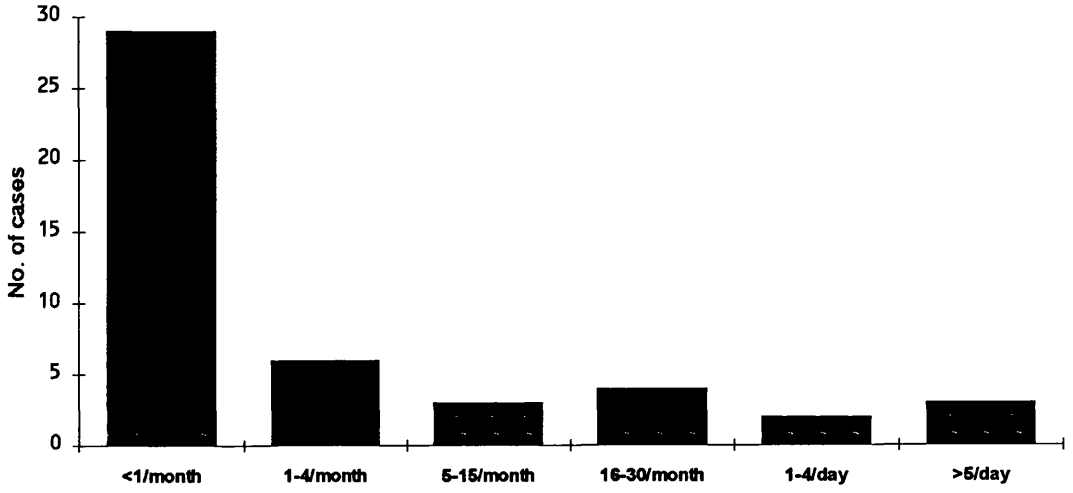


h) Average seizure frequency for group 12; Jacksonian motor

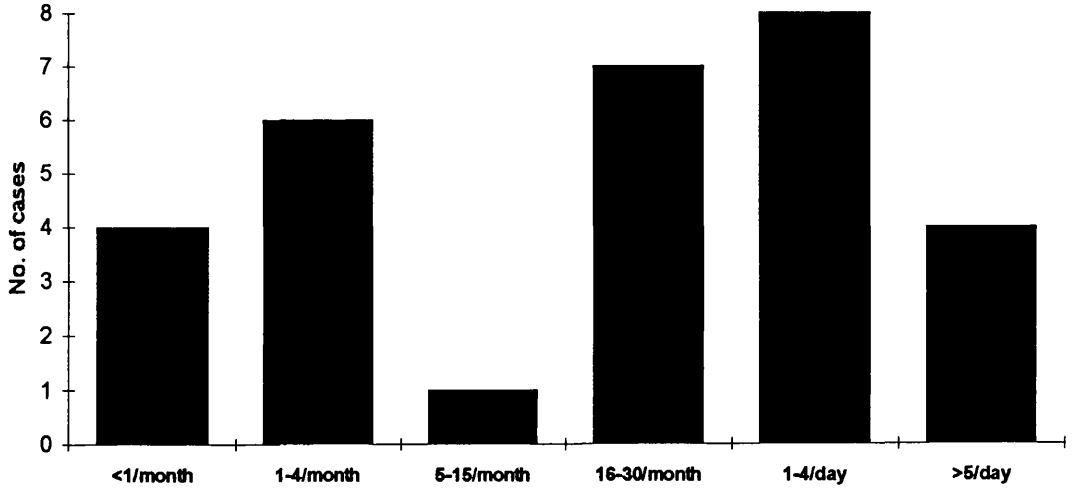


Appendix 5, continued

i) Average seizure frequency for group 13; generalised motor

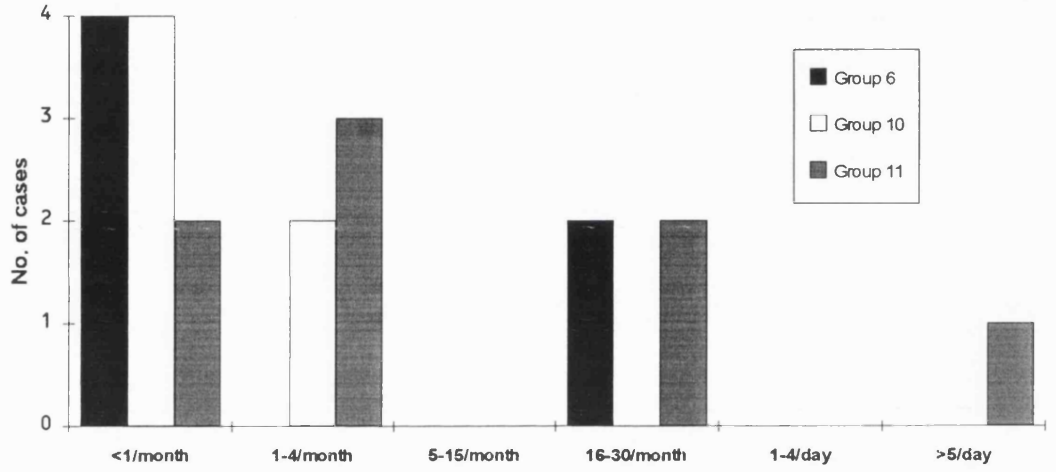


j) Average seizure frequency for group 14; motor agitation



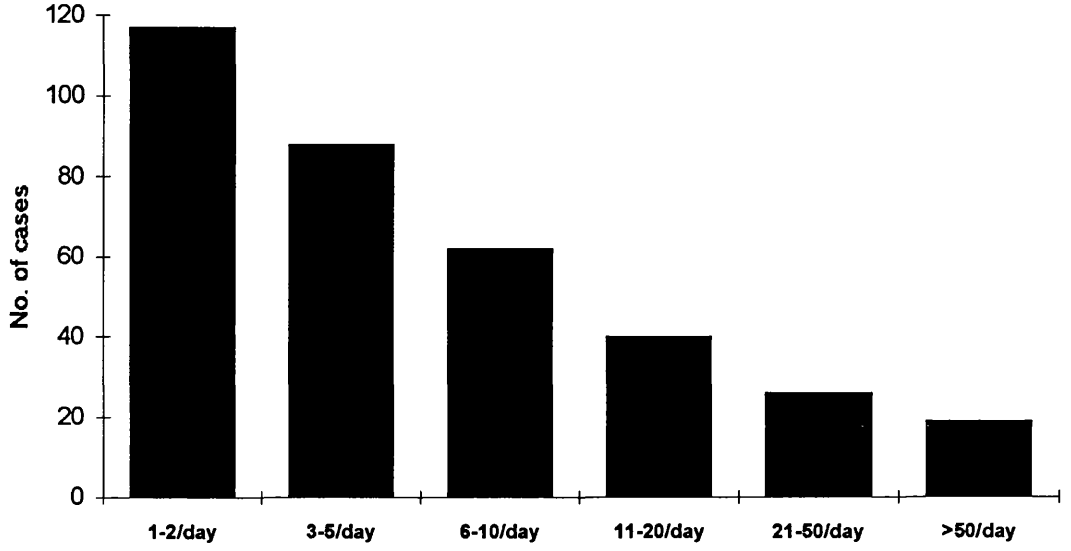
Appendix 5, continued

k) Average seizure frequency for groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks).

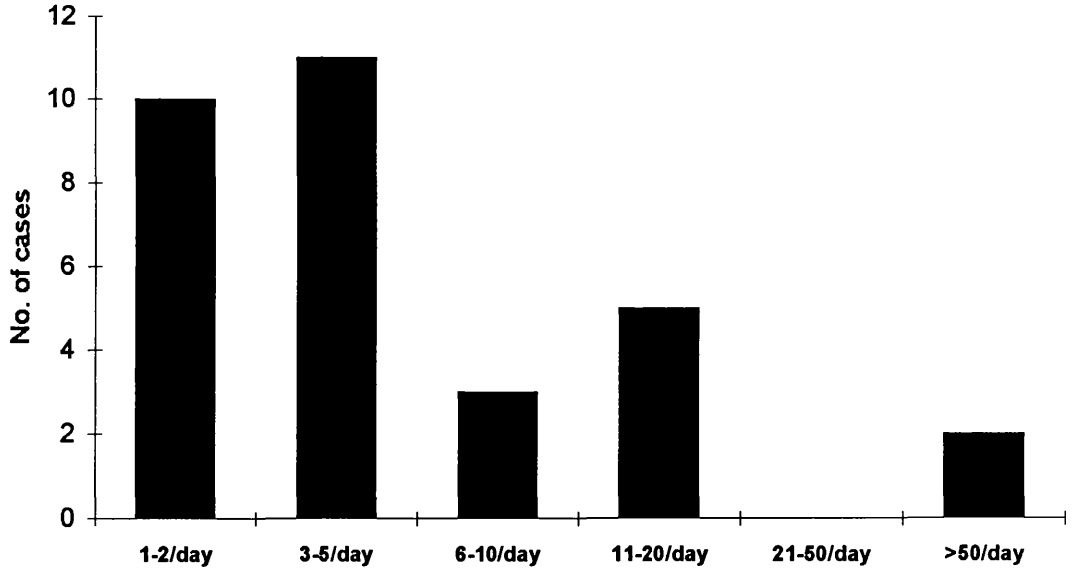


Appendix 6. Maximum seizure frequency distribution for each group

a) Maximum seizure frequency for all cases combined

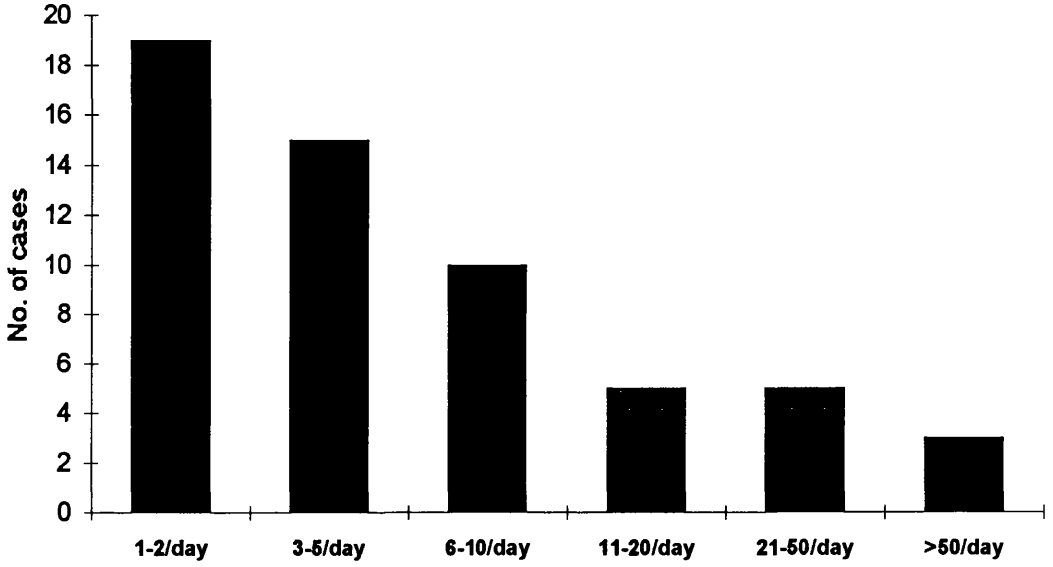


b) Maximum seizure frequency in group 1; olfactory/gustatory and fear behaviour

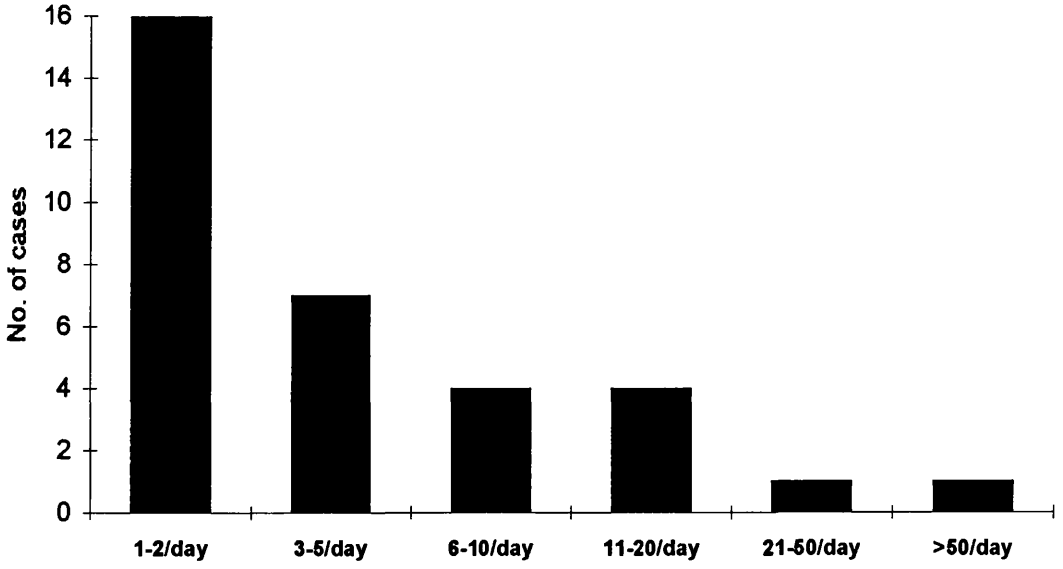


Appendix 6, continued

c) Maximum seizure frequency in group 2; absences

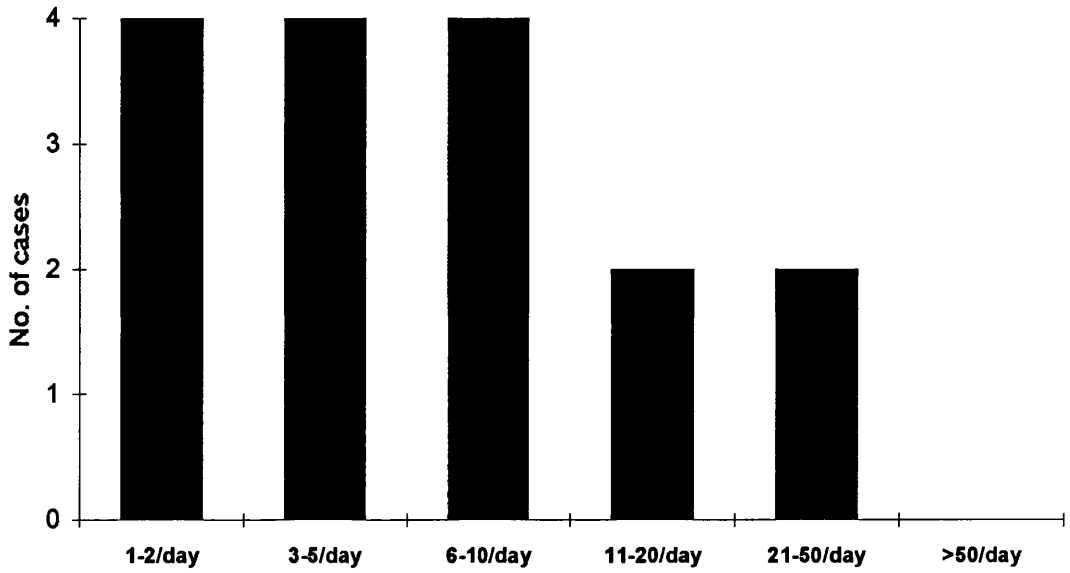


d) Maximum seizure frequency in group 3; experiential

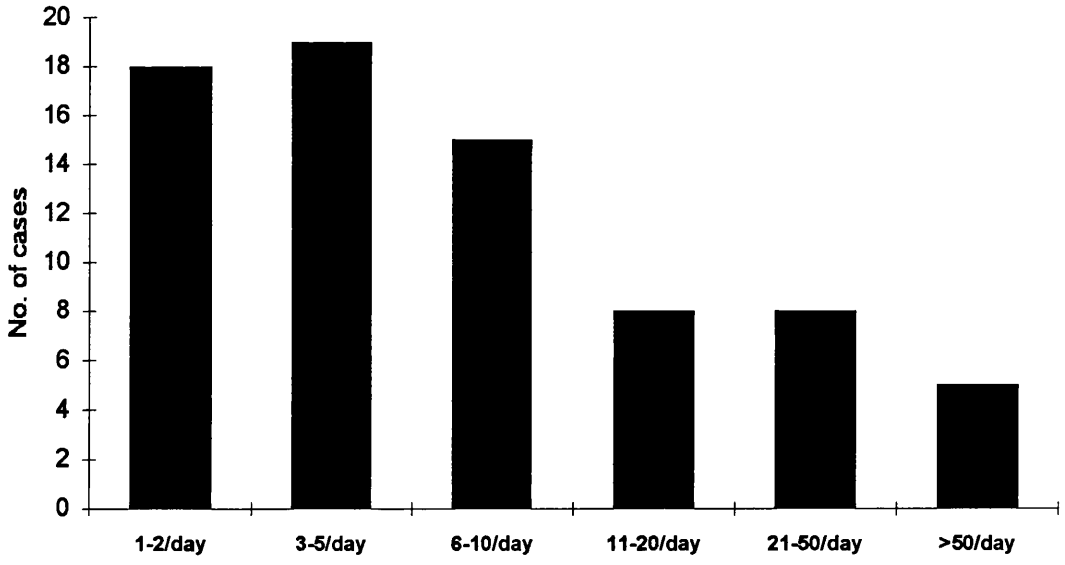


Appendix 6, continued

e) Maximum seizure frequency in group 4; visual

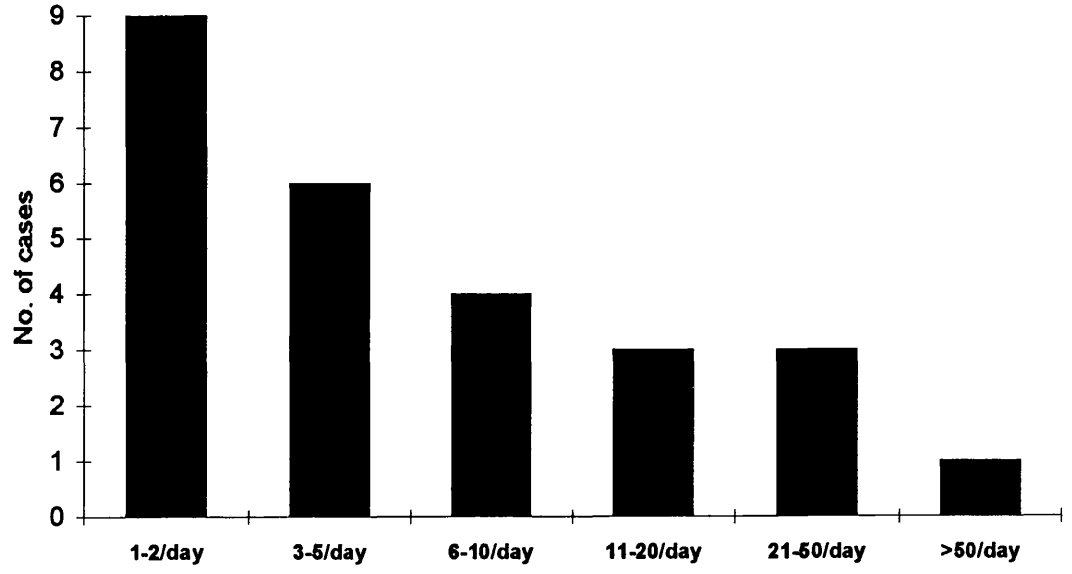


f) Maximum seizure frequency in group 7; version/posturing

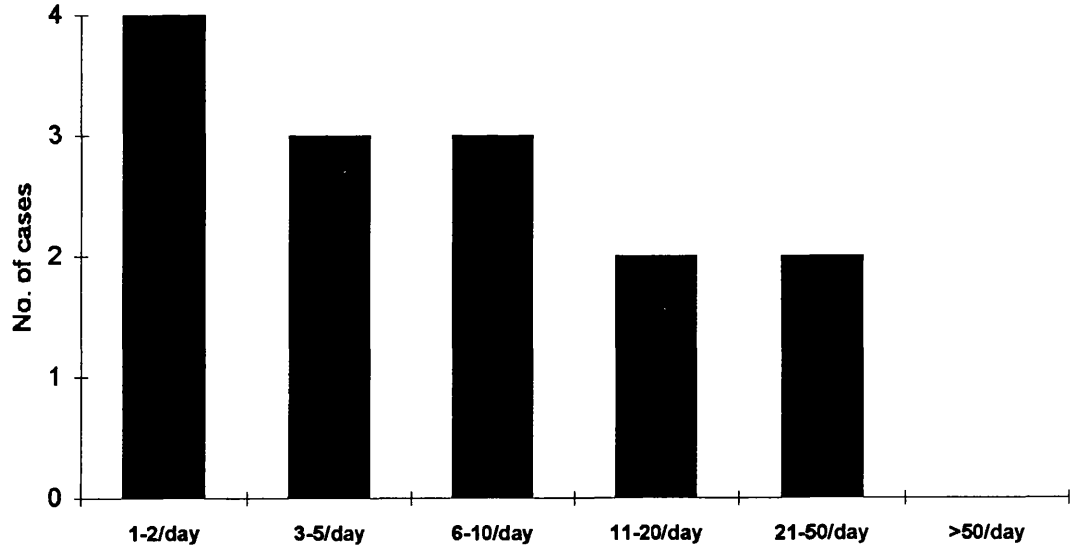


Appendix 6, continued

g) Maximum seizure frequency in group 8; focal somatosensory

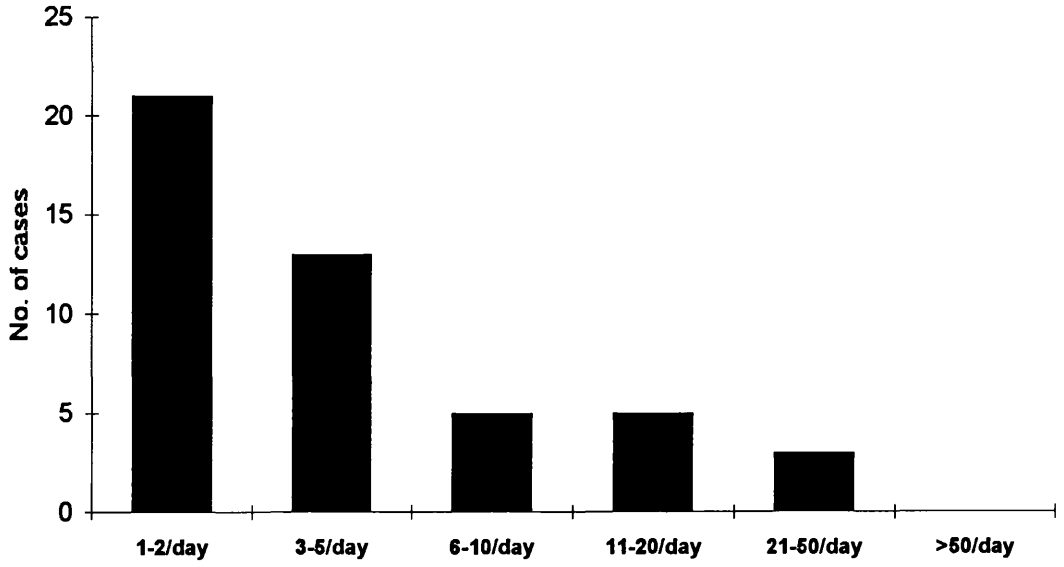


h) Maximum seizure frequency in group 12; Jacksonian motor

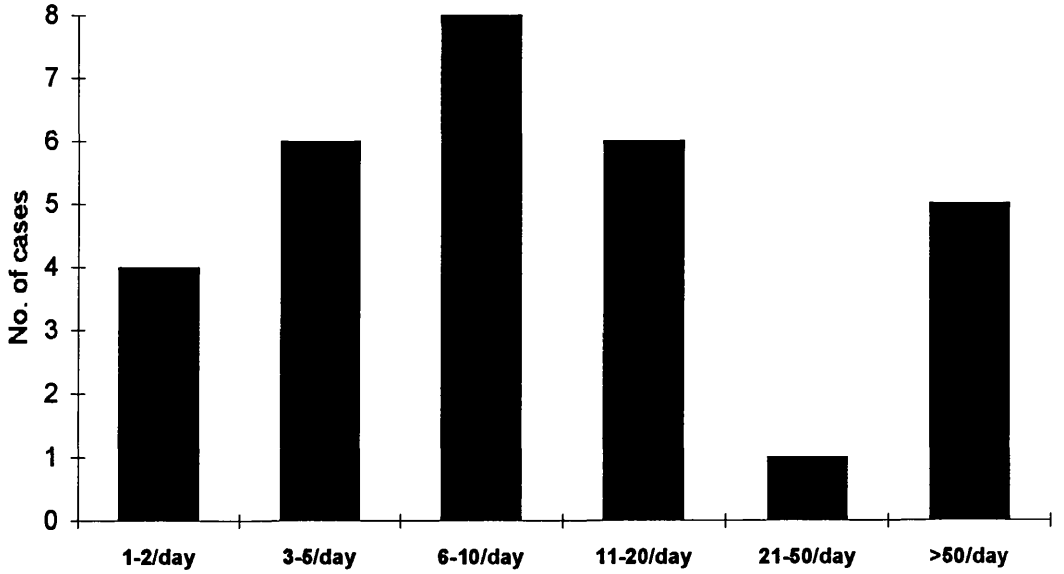


Appendix 6, continued

i) Maximum seizure frequency in group 13; generalised motor

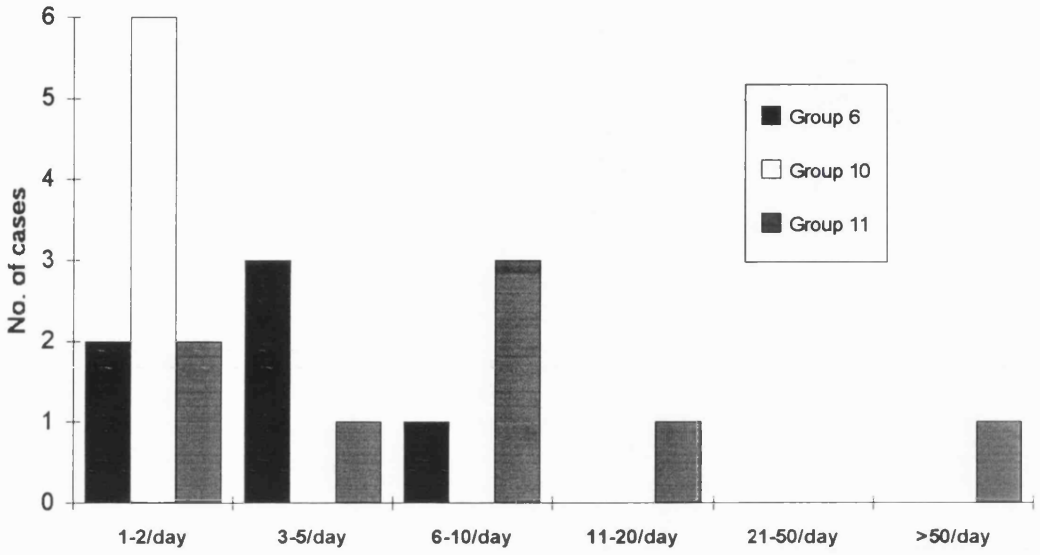


j) Maximum seizure frequency in group 14; motor agitation



Appendix 6, continued

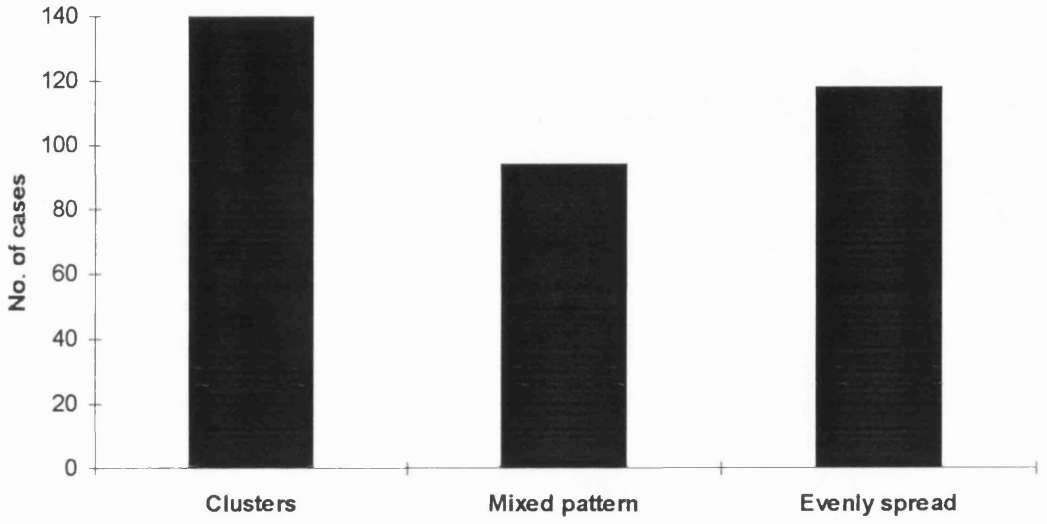
k) Maximum seizure frequencies in groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks).



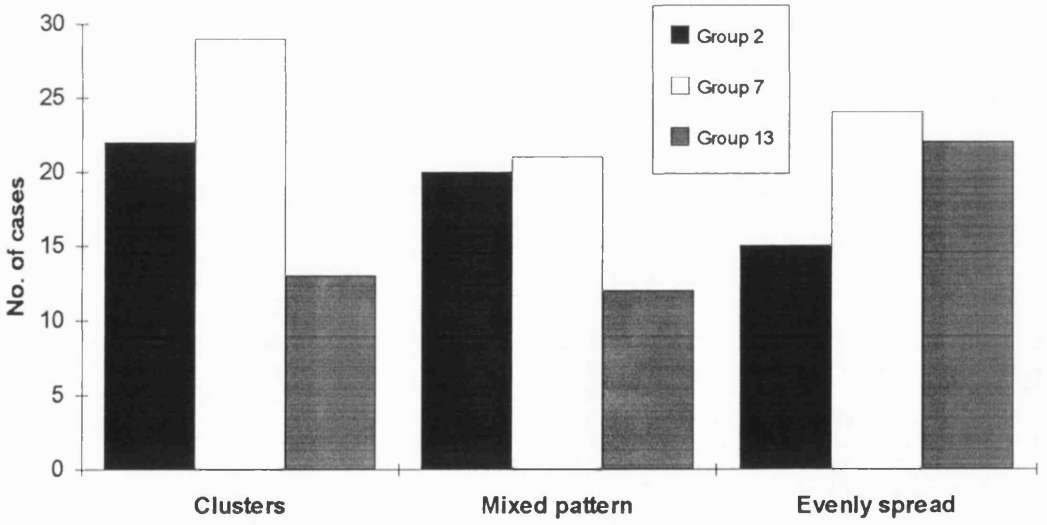
Appendix 7. Tendency for seizures to cluster in each group

(Clustering = 75% of seizures in less than 25% of the time)

a) Tendency for seizures to cluster; all cases combined.

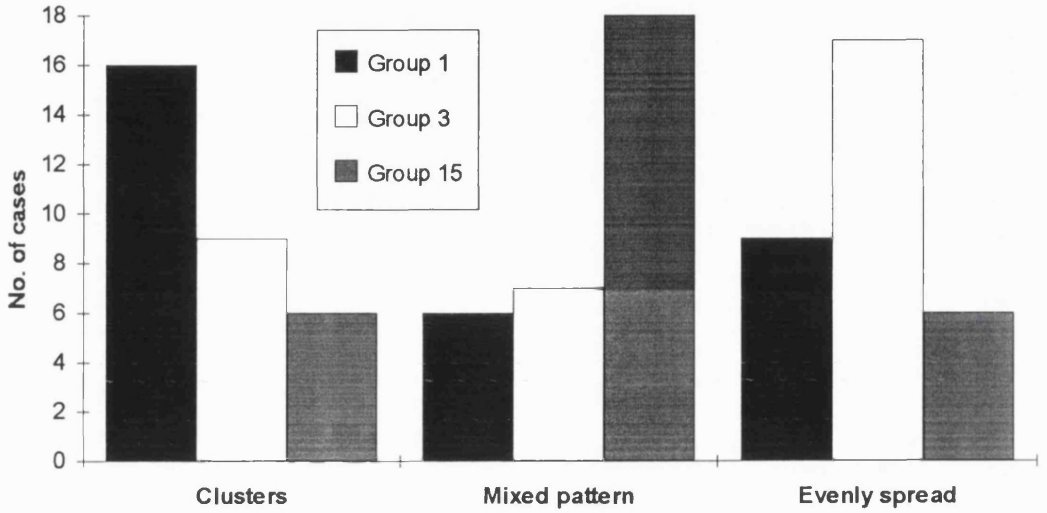


b) Tendency for seizures to cluster in groups 2 (absences); 7 (version/posturing) and 13 (generalised motor)

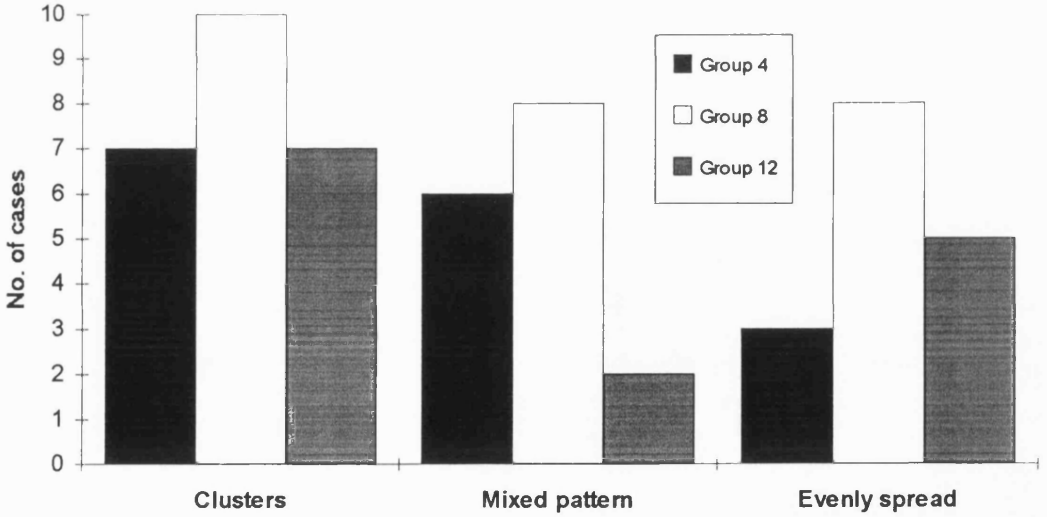


Appendix 7, continued

c) Tendency for seizures to cluster in groups 1 (olfactory/gustatory and fear behaviour); 3 (experiential) and 14 (motor agitation).

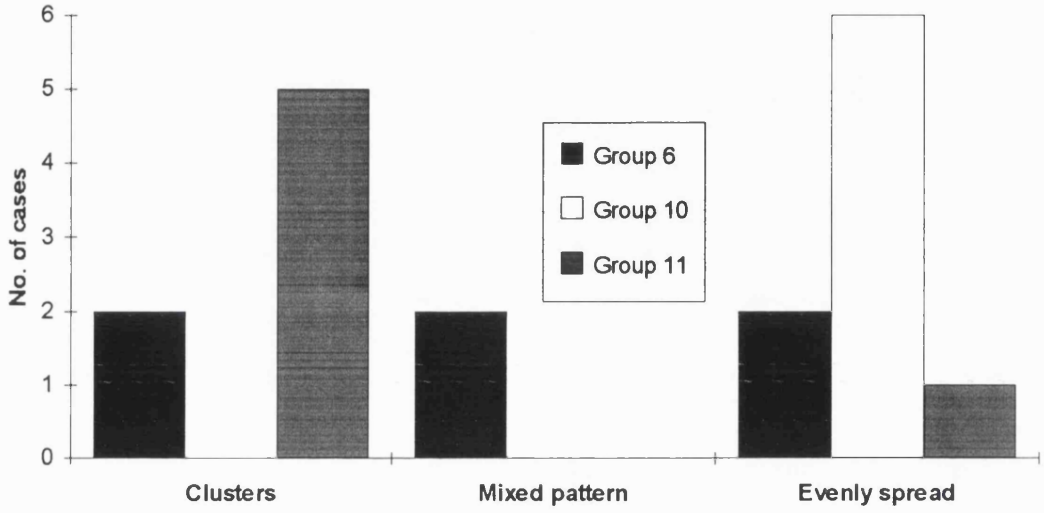


d) Tendency for seizures to cluster in groups 4 (visual); 8 (focal sensory) and 12 (Jacksonian motor).



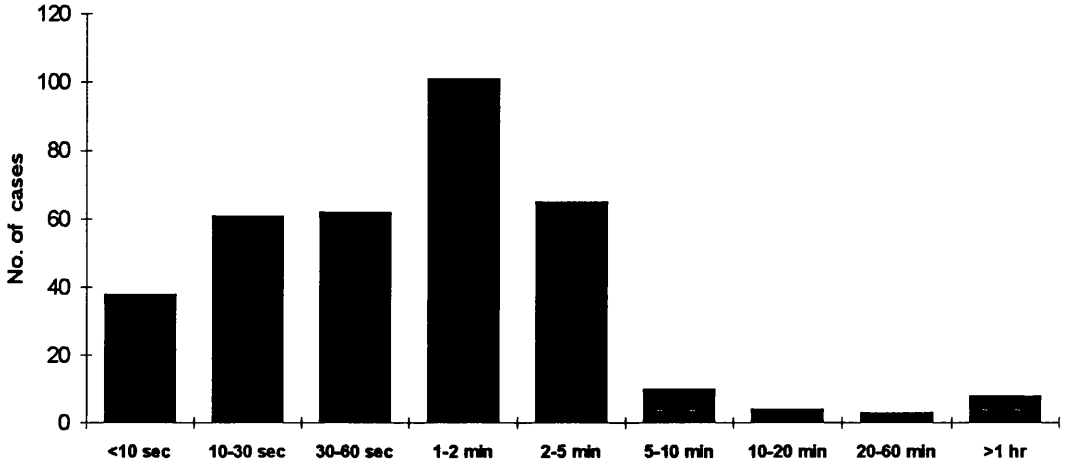
Appendix 7, continued

e) Tendency for seizures to cluster in groups 6 (hypotonic); 10 (complex partial status epilepticus and 11 (isolated jerks)

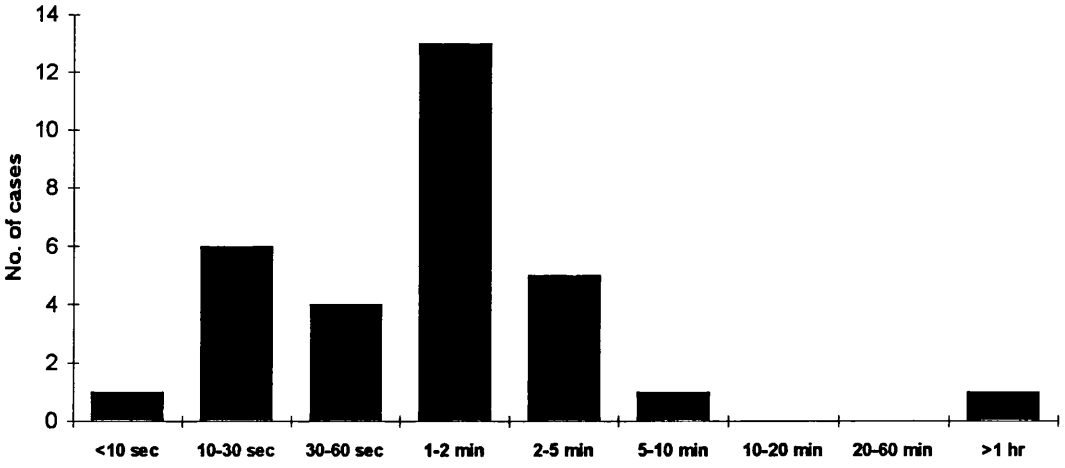


Appendix 8. Seizure durations for each group

a) Seizure duration for all seizures combined

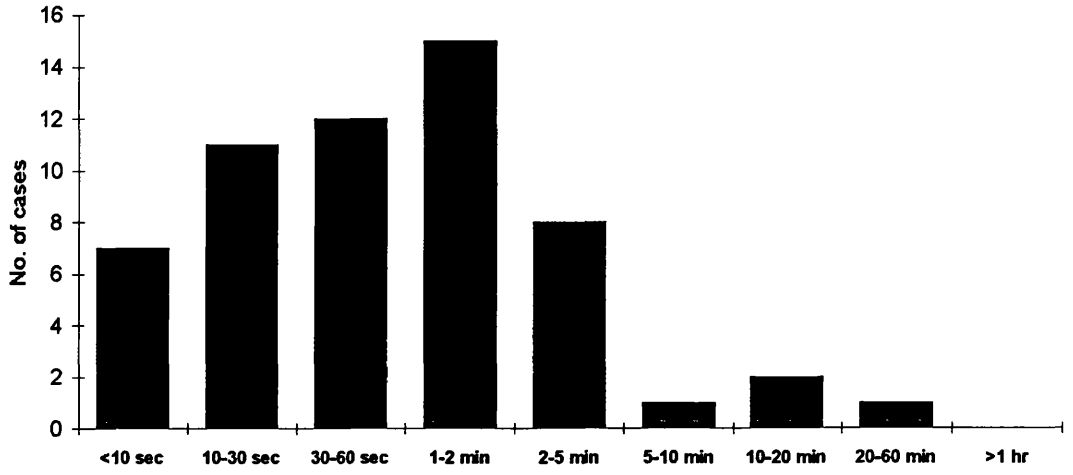


b) Seizure duration in group 1; olfactory/gustatory and fear behaviour

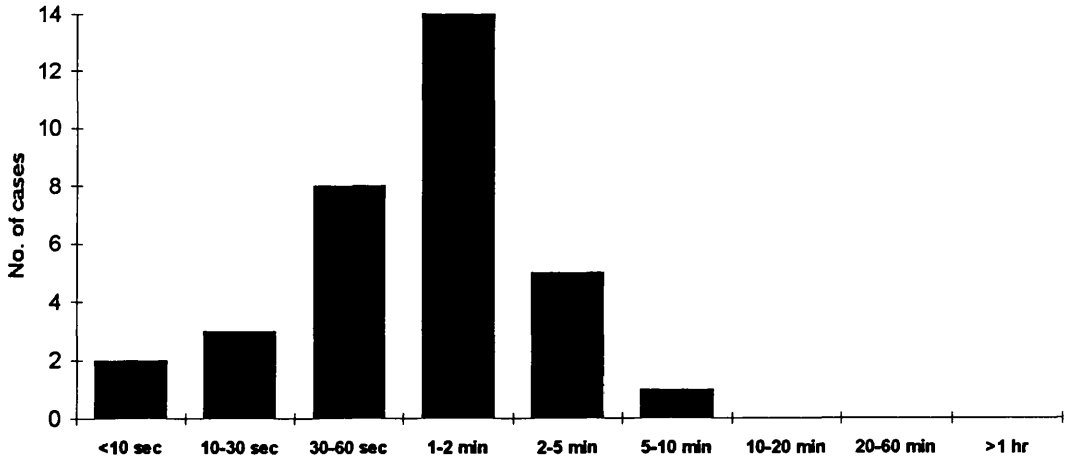


Appendix 8, continued

c) Seizure duration in group 2; absences

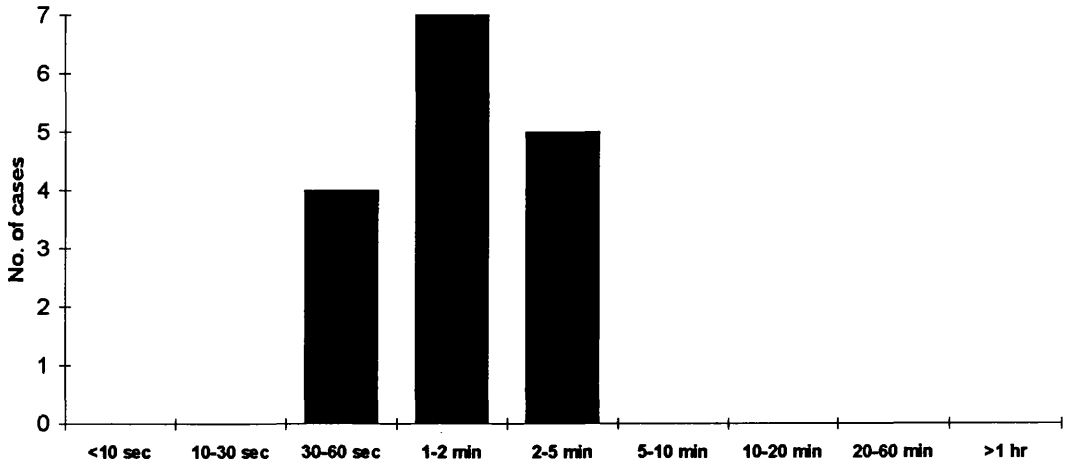


d) Seizure duration in group 3; experiential

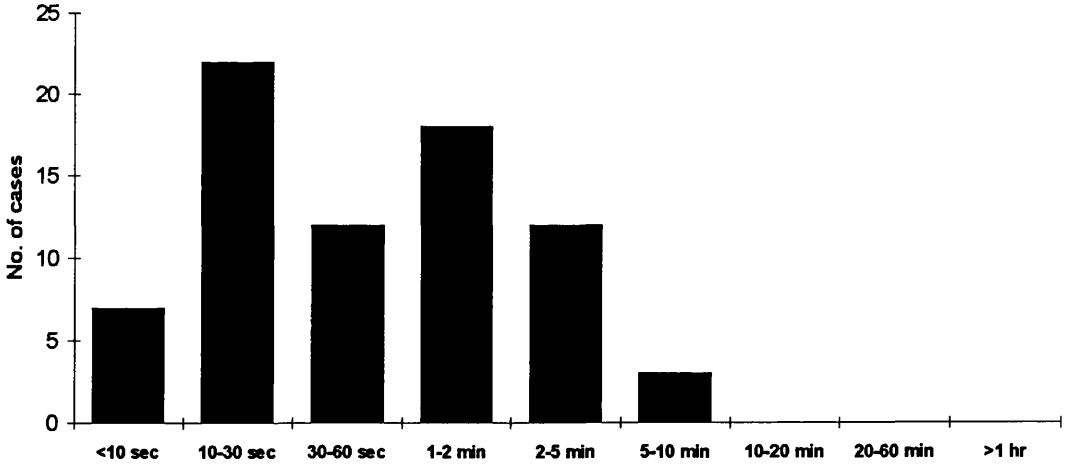


Appendix 8, continued

e) Seizure duration in group 4; visual

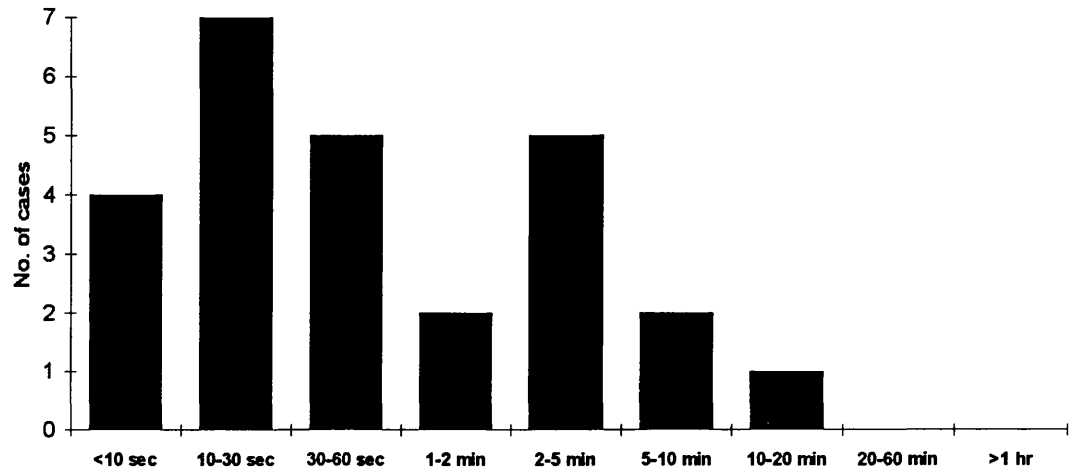


f) Seizure duration in group 7; version/posturing

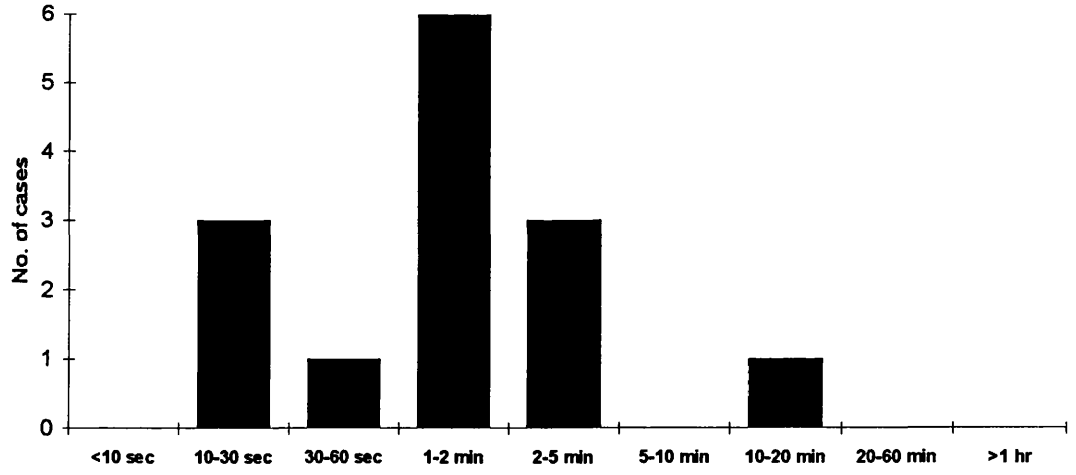


Appendix 8, continued

g) Seizure duration in group 8; focal sensory

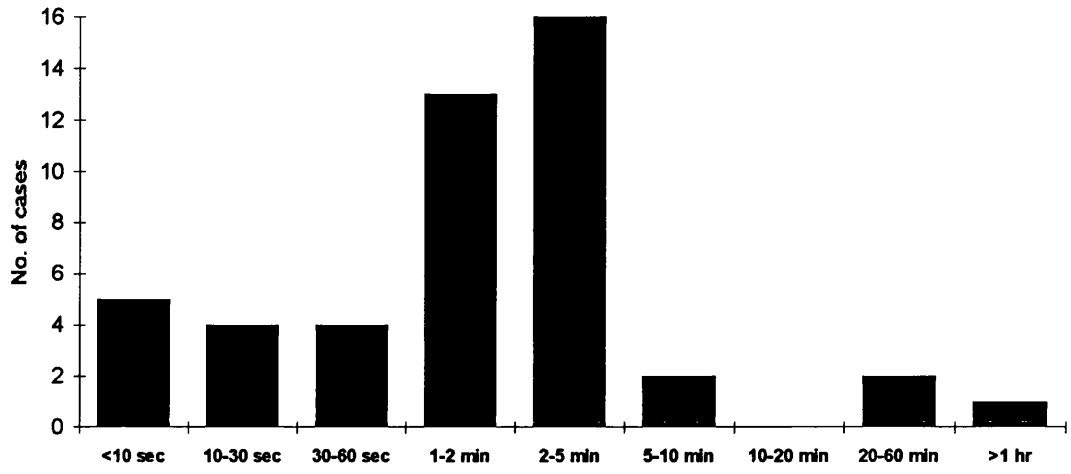


h) Seizure duration in group 12; Jacksonian motor

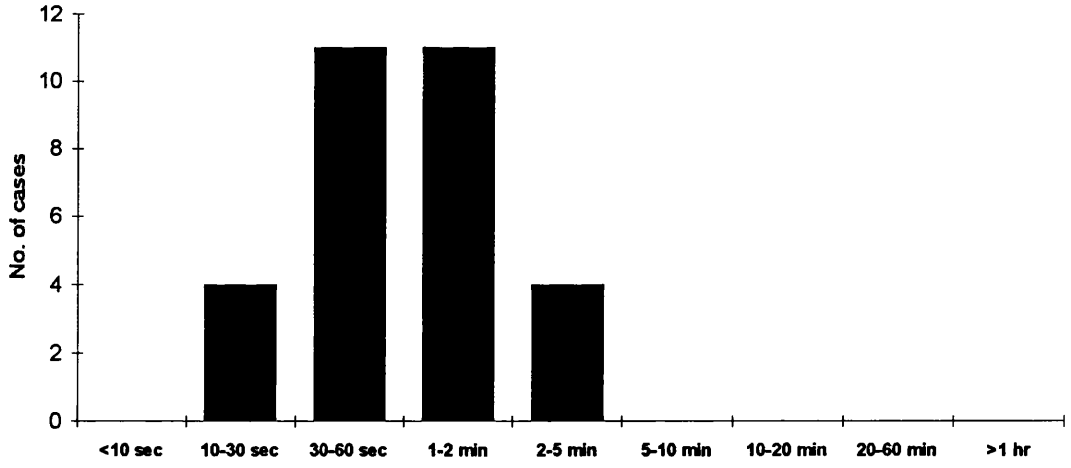


Appendix 8, continued

i) Seizure duration in group 13; generalised motor

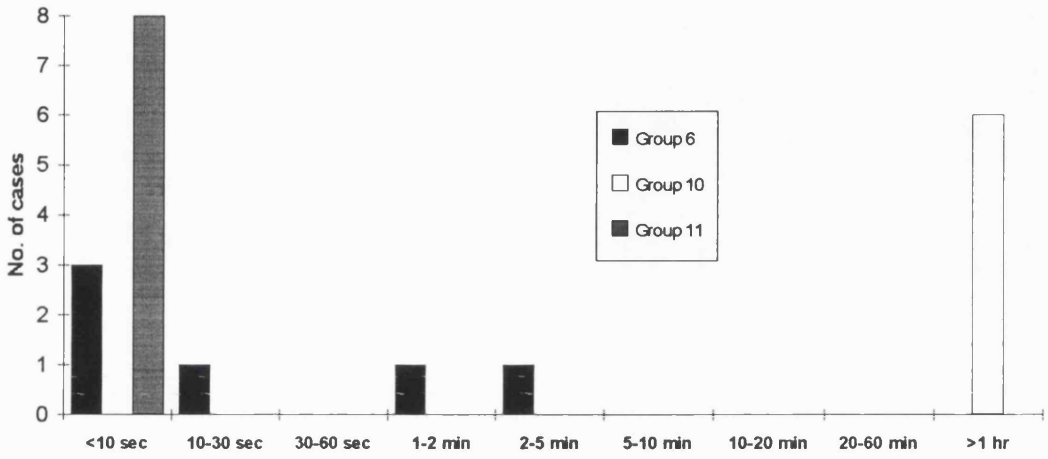


j) Seizure duration in group 14; motor agitation



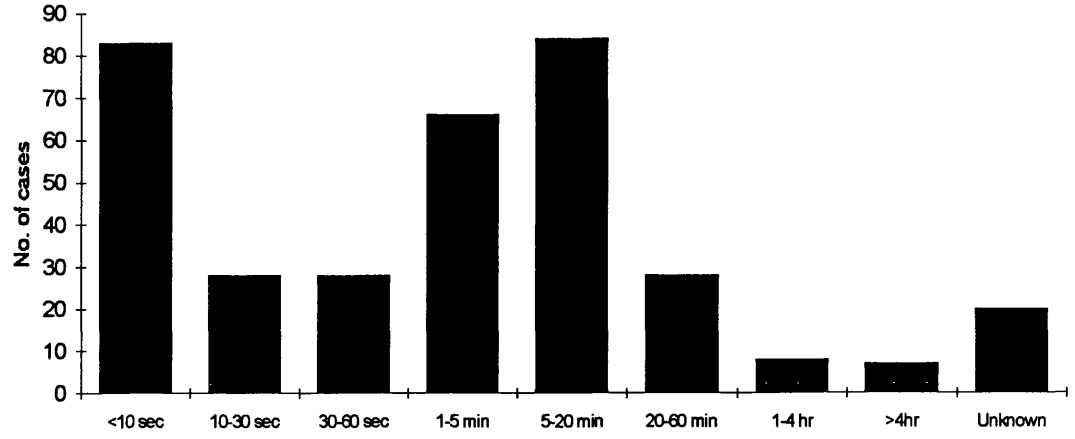
Appendix 8, continued

k) Seizure duration in groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks)

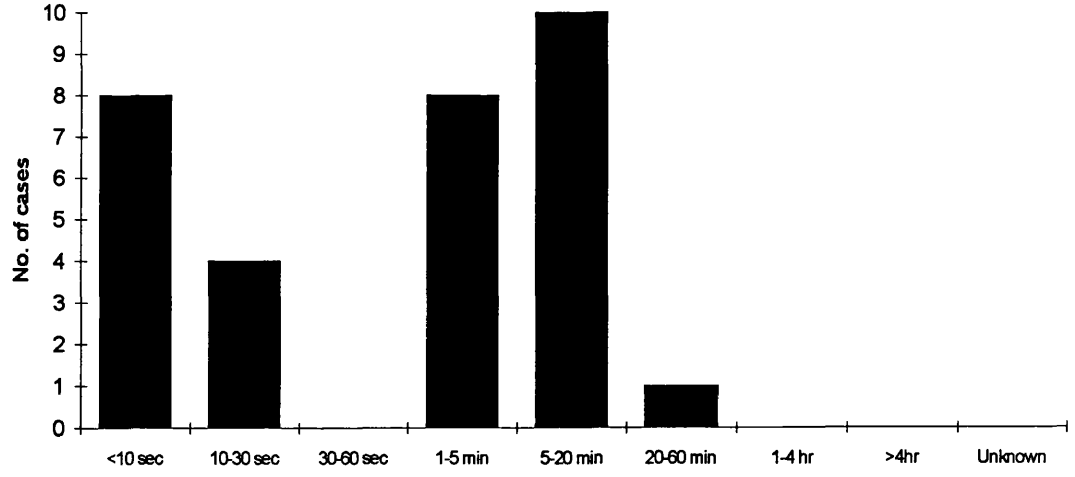


Appendix 9. Postictal duration of seizures in each group

a) Postictal durations of all seizures combined

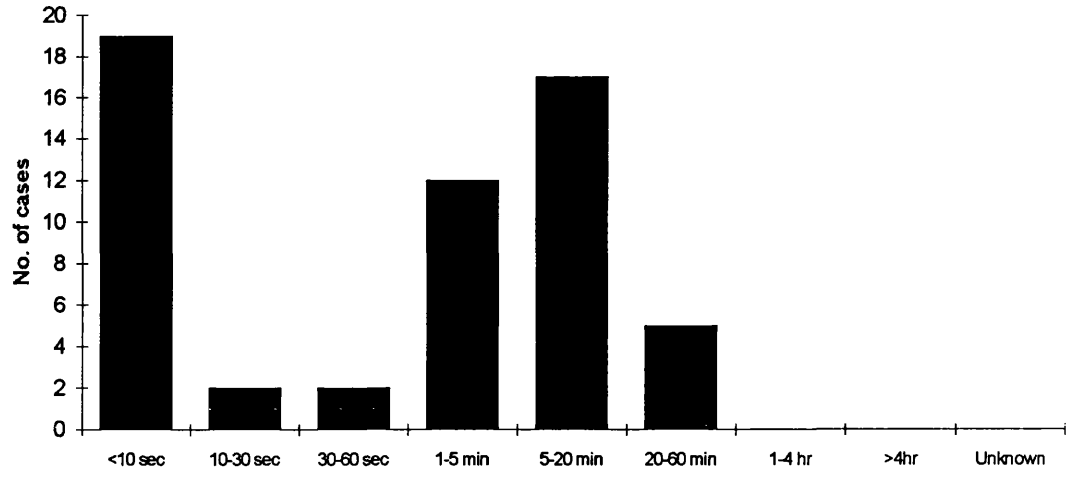


b) Postictal duration of seizures in group 1 (olfactory/gustatory, fear behaviour)

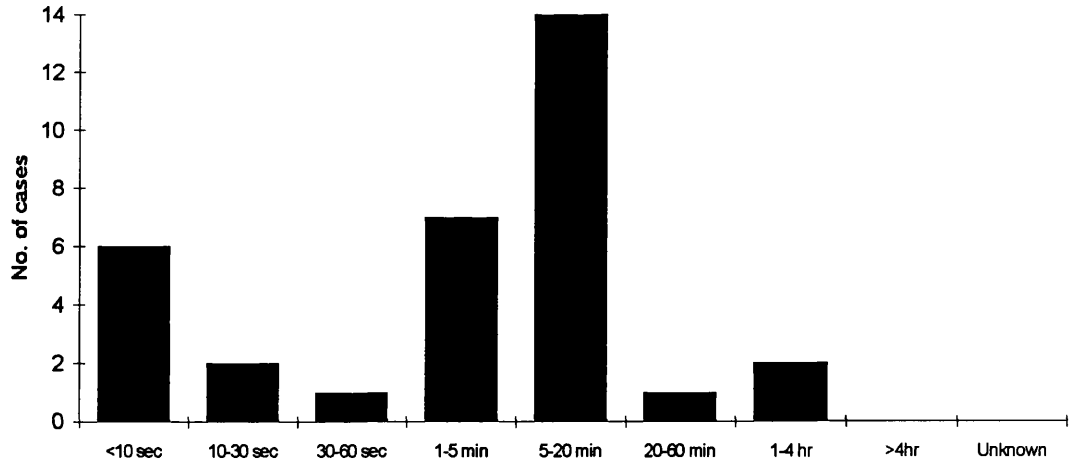


Appendix 9, continued

c) Postictal duration of seizures in group 2 (absence)

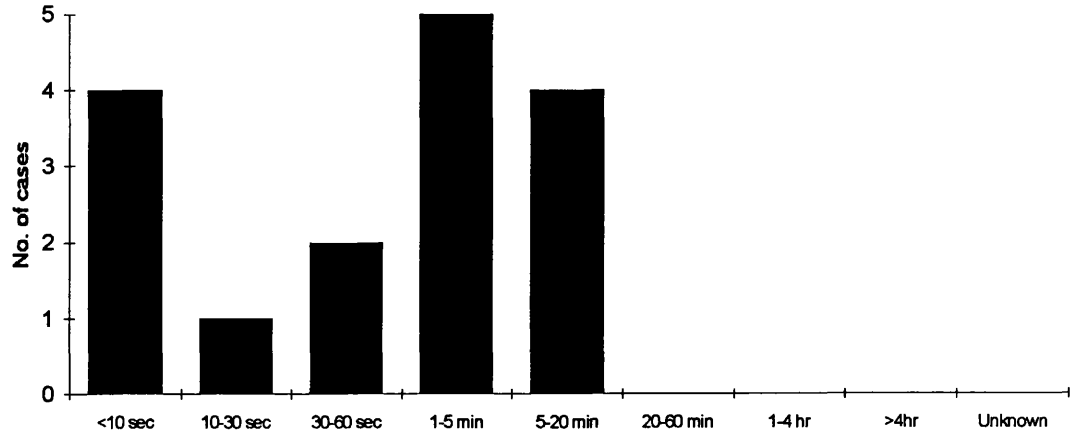


d) Postictal duration of seizures in group 3 (experiential)

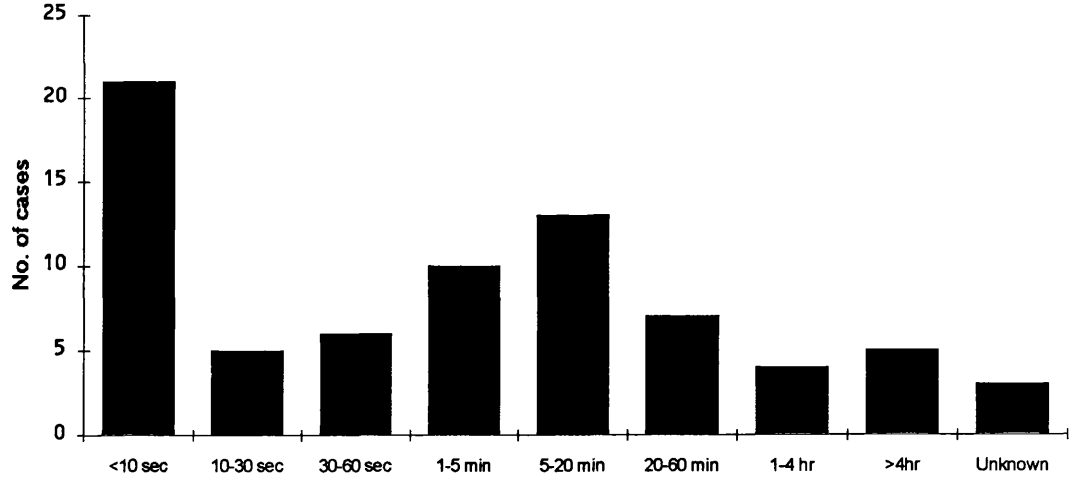


Appendix 9, continued

e) Postictal duration of seizures in group 4 (visual)

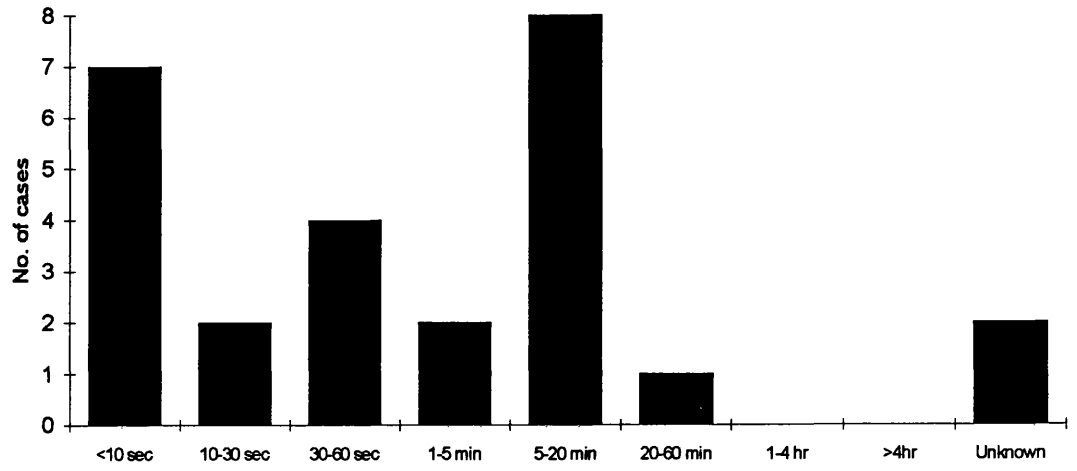


f) Postictal duration of seizures in group 7 (version/posturing)

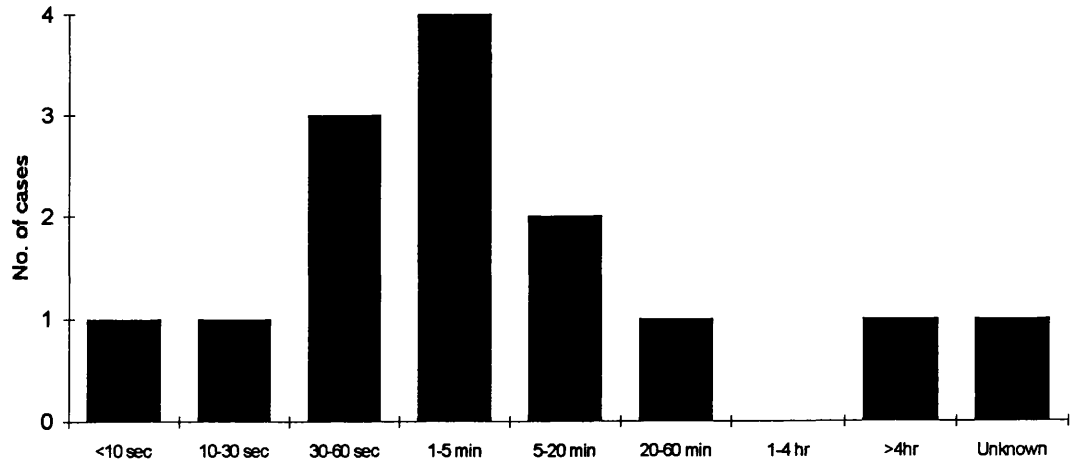


Appendix 9, continued

g) Postictal duration of seizures in group 8 (focal somatosensory)

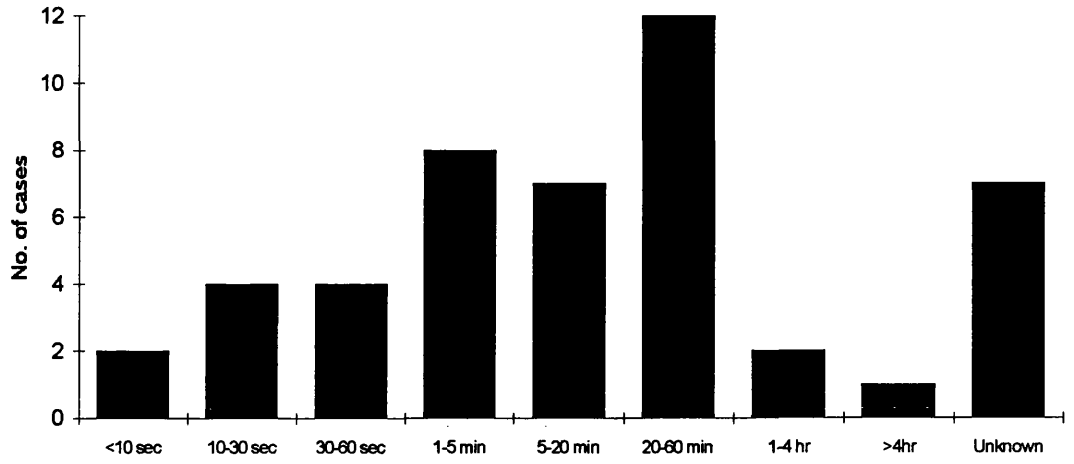


h) Postictal duration of seizures in group 12 (Jacksonian motor)

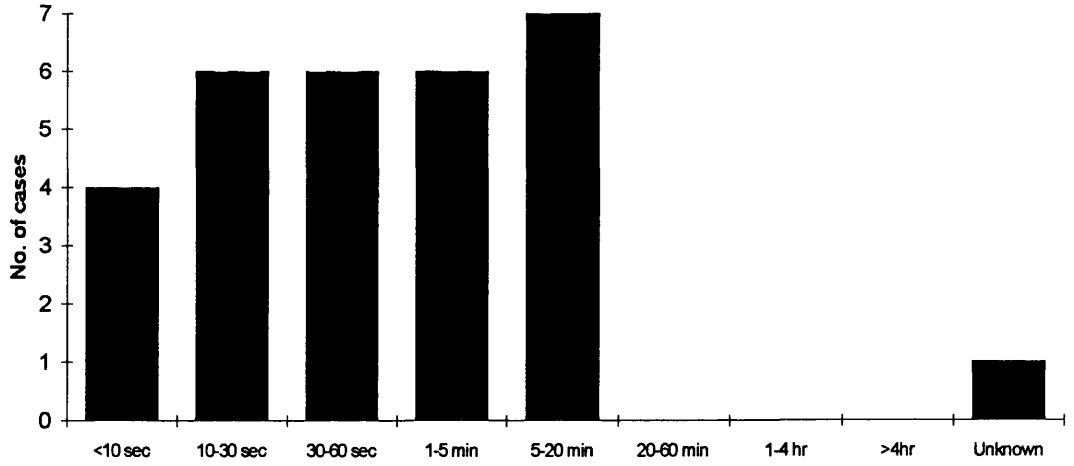


Appendix 9, continued

i) Postictal duration of seizures in group 13 (generalised motor)

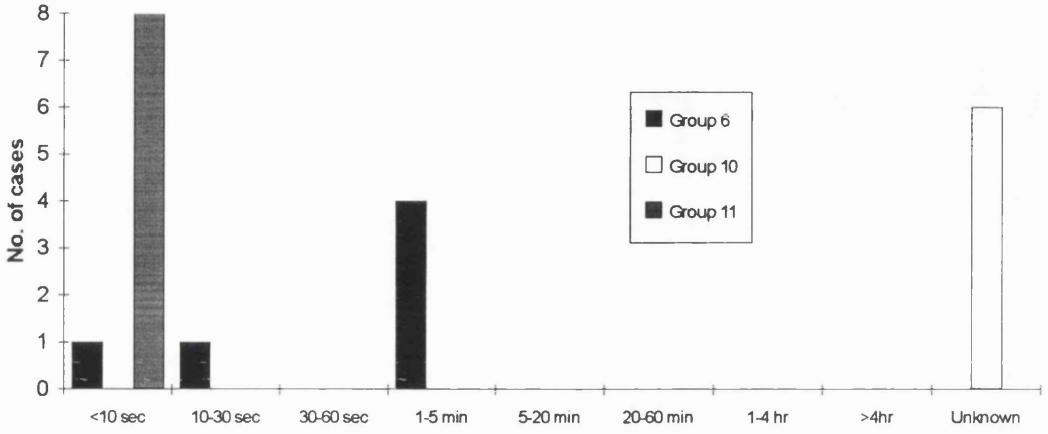


j) Postictal duration of seizures in group 14 (motor agitation)



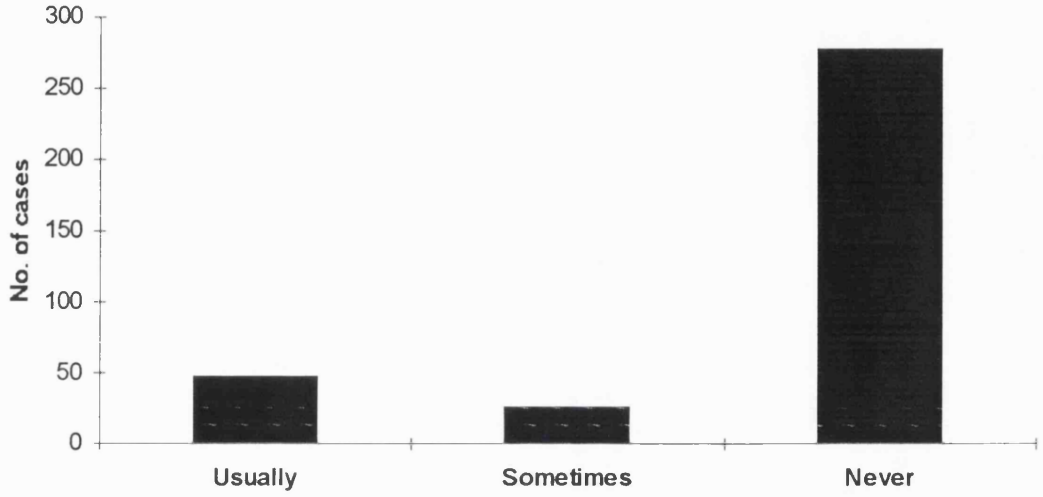
Appendix 9, continued

k) Postictal duration for seizures in groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks)

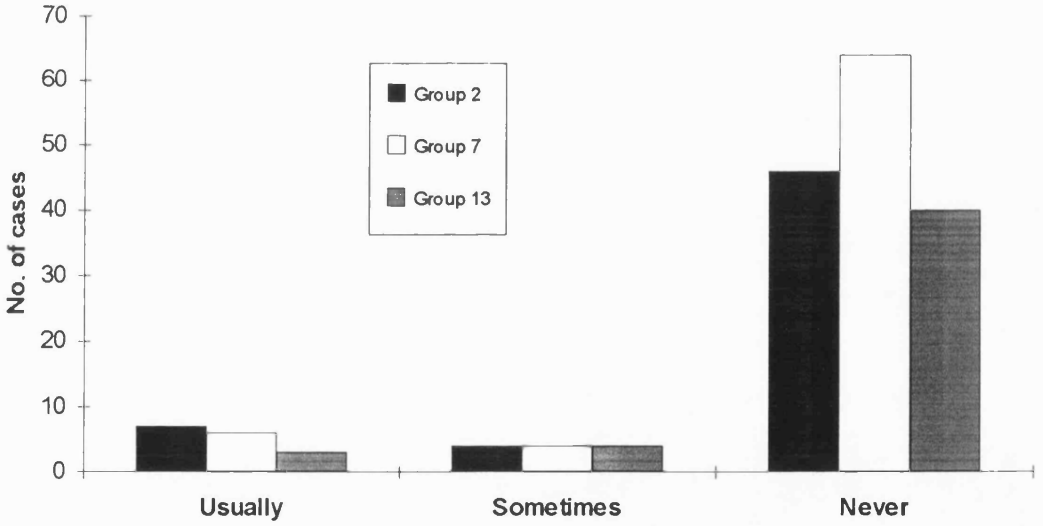


Appendix 10. Frequency of a prodrome in each group

a) Frequency of a prodrome in all cases combined

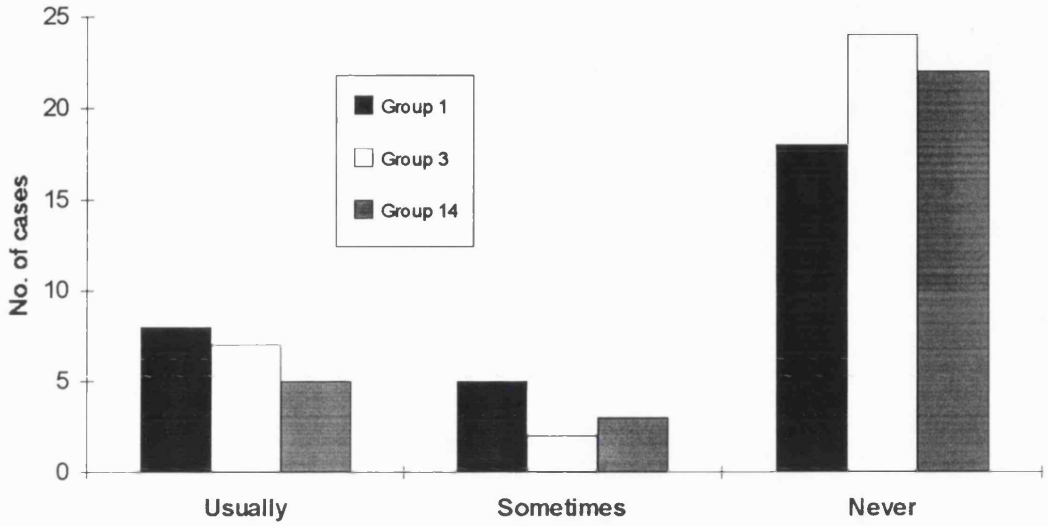


b) Frequency of a prodrome in groups 2 (absence); 7 (version/posturing) and 13 (general motor)

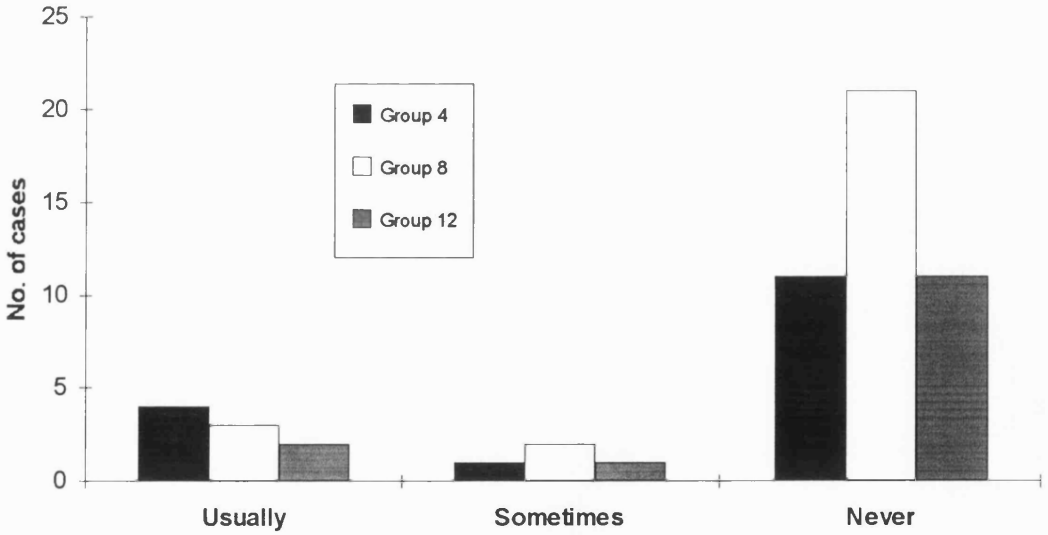


Appendix 10, continued

c) Frequency of a prodrome in groups 1 (olfactory/gustatory and fear behaviour); 3 (experiential) and 14 (motor agitation)

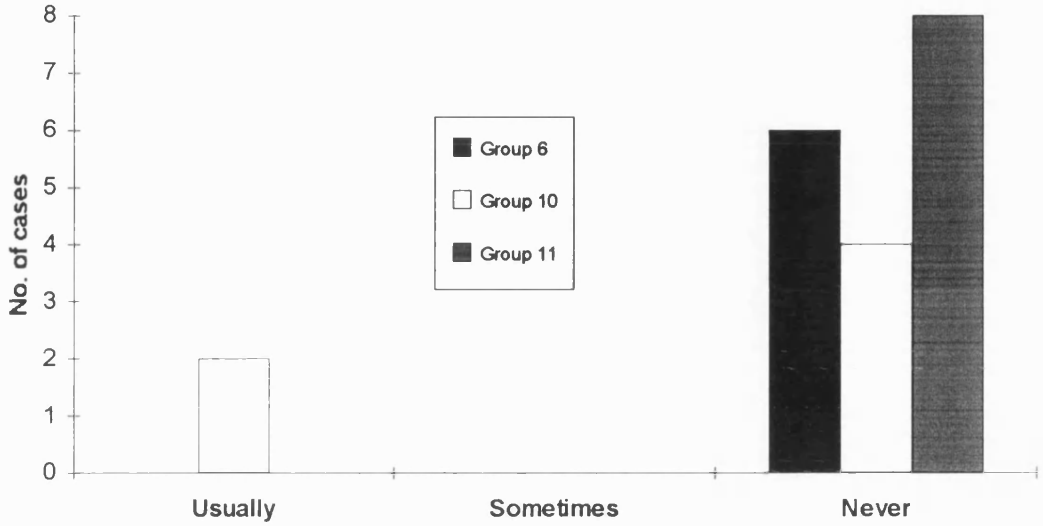


d) Frequency of a prodrome in groups 4 (visual); 8 (focal somatosensory) and 12 (Jacksonian motor)



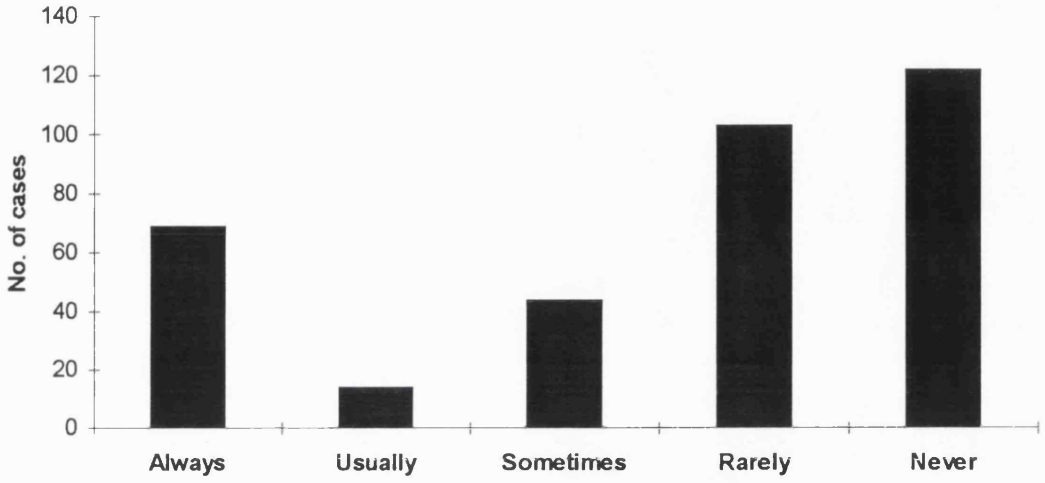
Appendix 10, continued

e) Frequency of a prodrome in groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks)

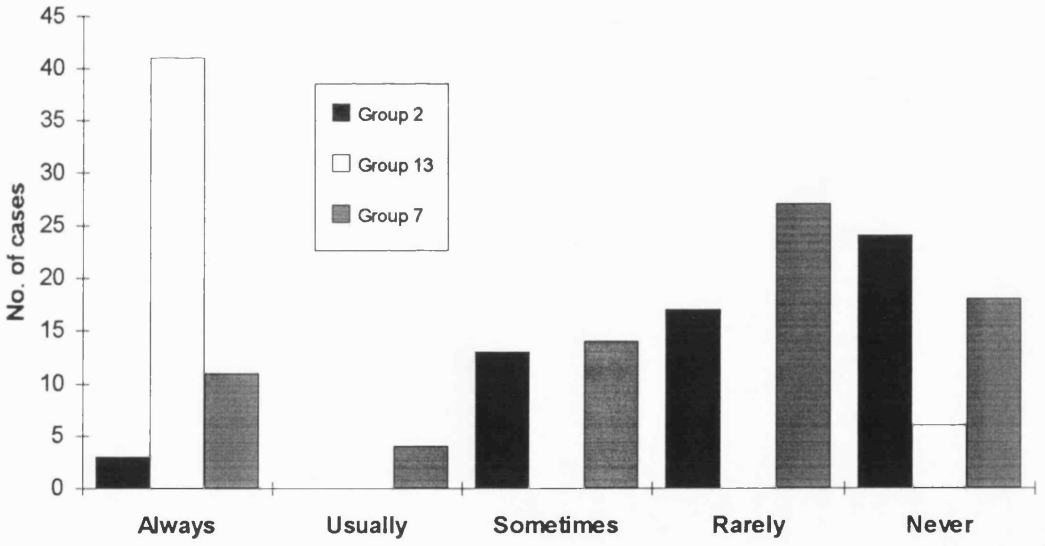


Appendix 11. Frequency of secondary generalisation in each group

a) Frequency of secondary generalisation of all seizures

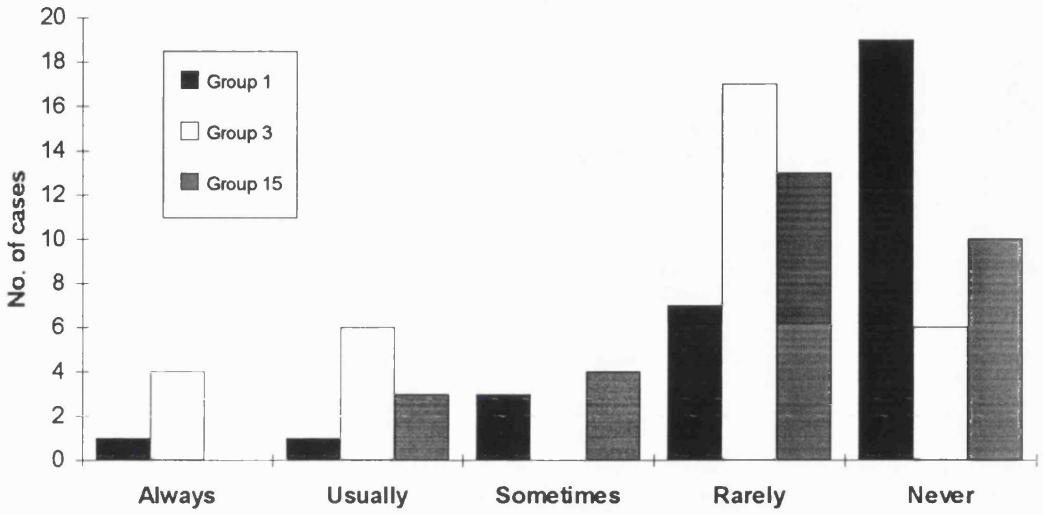


b) Frequency of secondary generalisation of groups 2 (absence); 7 (version/posturing) and 13 (generalised motor)

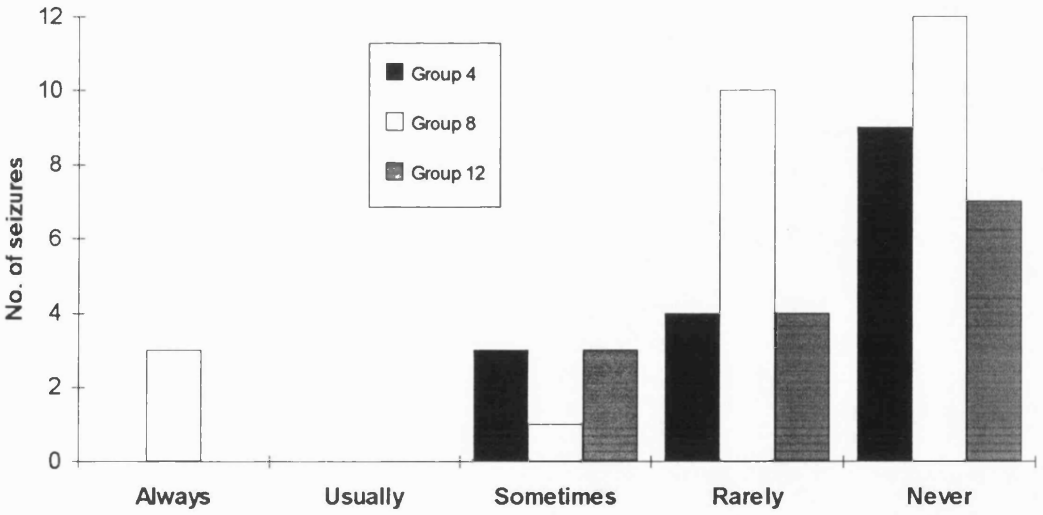


Appendix 11, continued

c) Frequency of secondary generalisation of groups 1 (olfactory/gustatory/fear behaviour); 3 (experiential) and 14 (motor agitation).

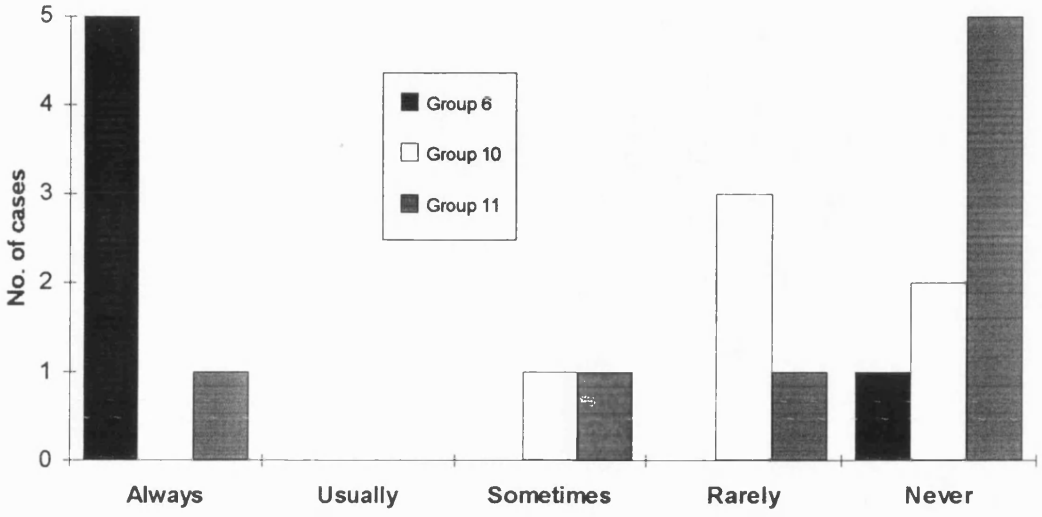


d) Frequency of secondary generalisation of groups 4 (visual); 8 (focal somatosensory) and 12 (Jacksonian motor)



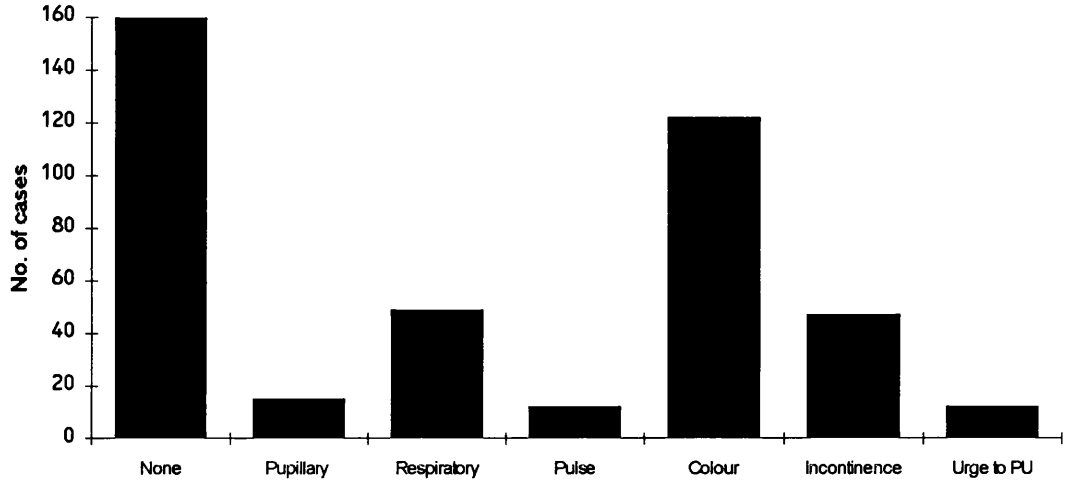
Appendix 11, continued

e) Frequency of secondary generalisation of groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks)

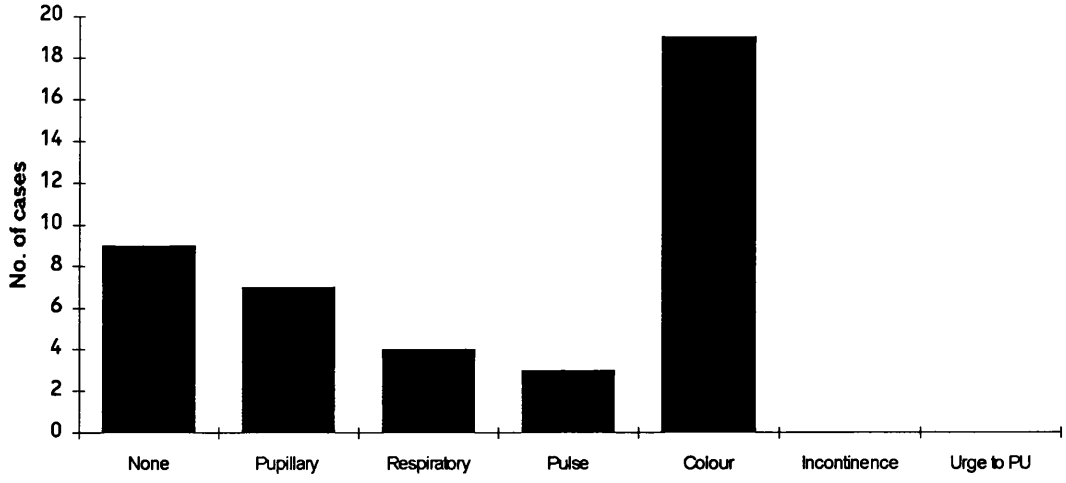


Appendix 12. Frequency of vegetative symptoms in each group

a) Frequency of vegetative symptoms in all seizures

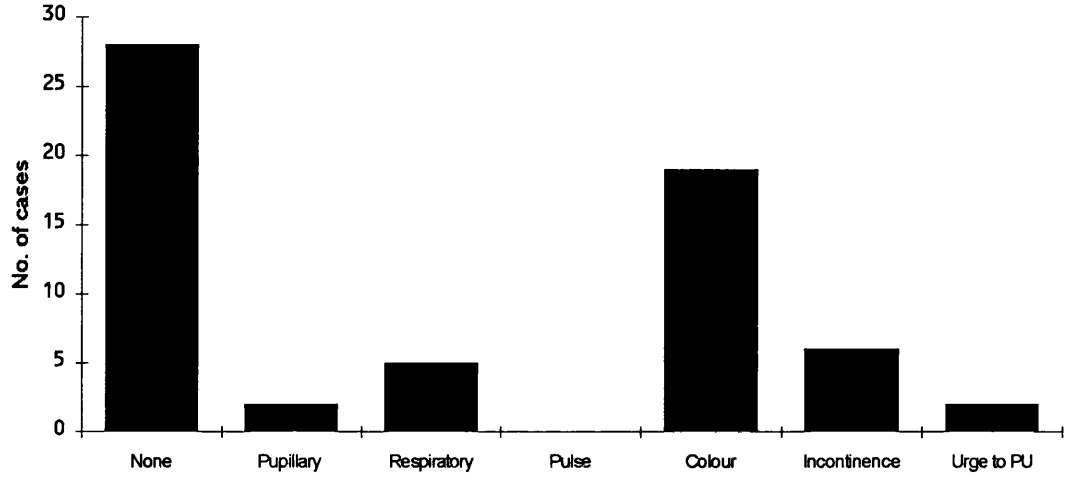


b) Frequency of vegetative symptoms in group 1 (olfactory/gustatory and fear behaviour)

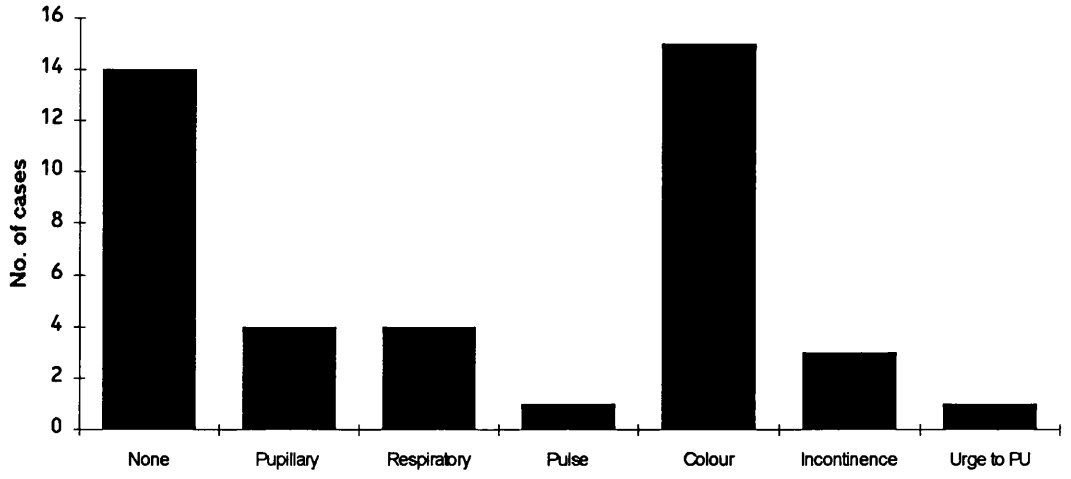


Appendix 12, continued

c) Frequency of vegetative symptoms in group 2 (absence)

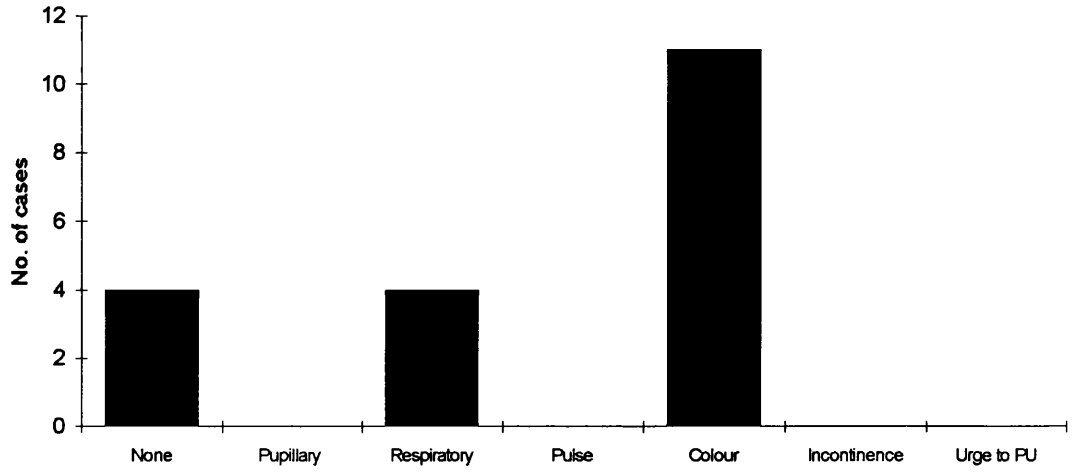


d) Frequency of vegetative symptoms in group 3 (experiential)

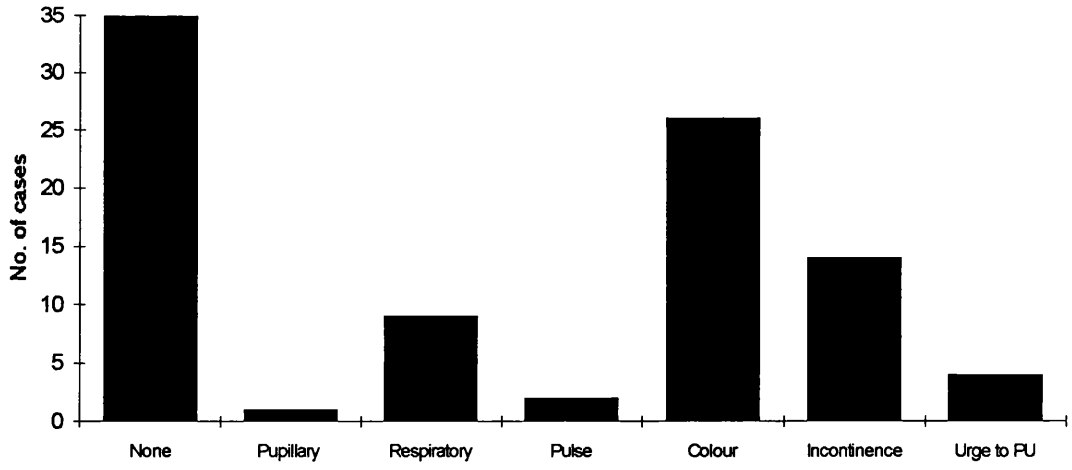


Appendix 12, continued

e) Frequency of vegetative symptoms in group 4 (visual)

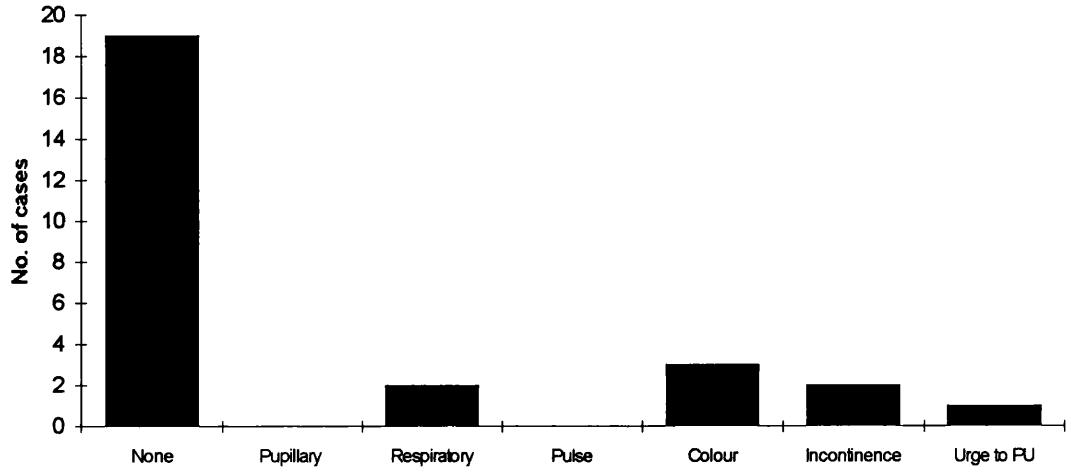


f) Frequency of vegetative symptoms in group 7 (version/posturing)

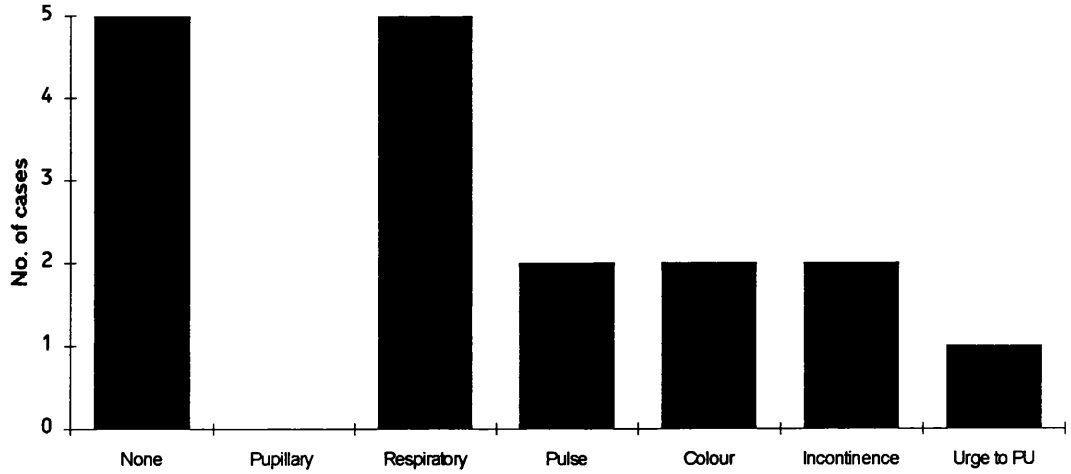


Appendix 12, continued

g) Frequency of vegetative symptoms in group 8 (focal somatosensory)

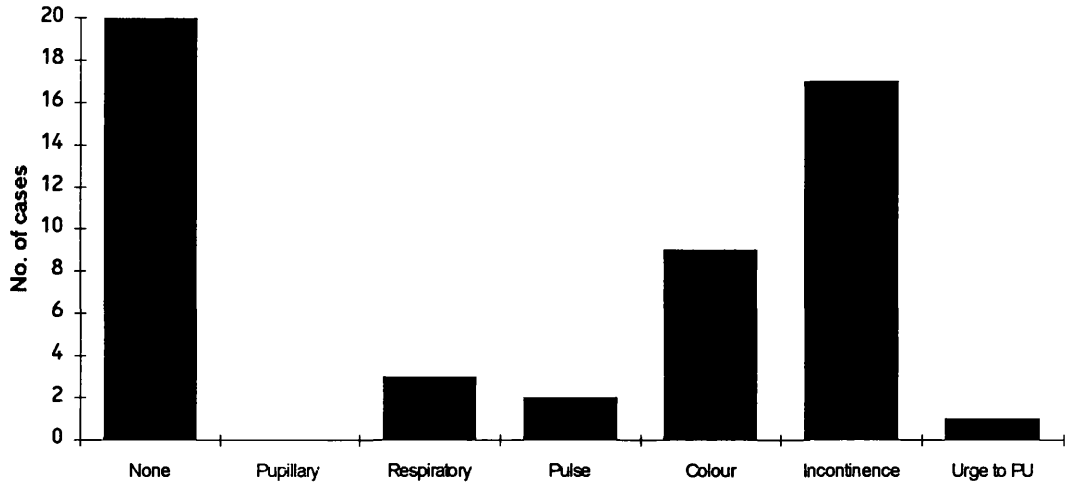


h) Frequency of vegetative symptoms in group 12 (Jacksonian motor)

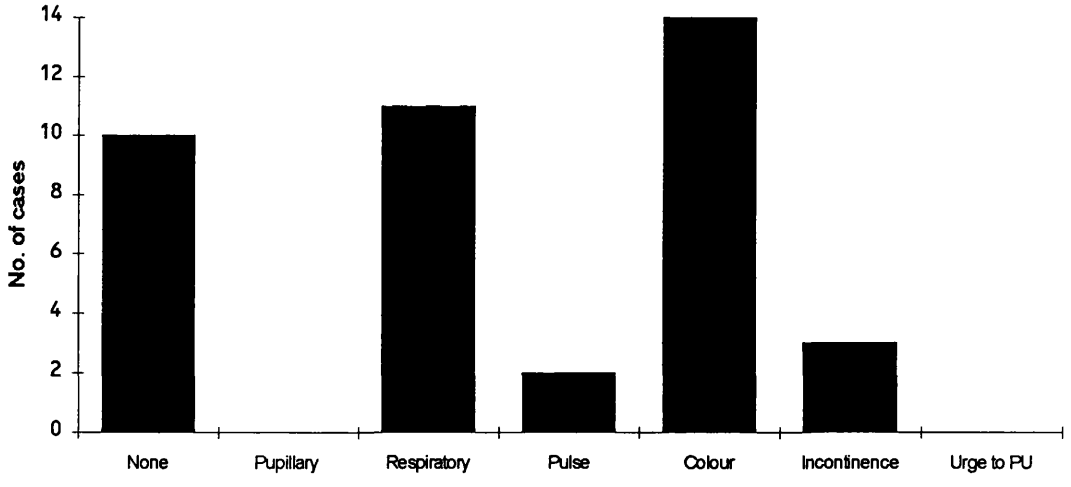


Appendix 12 continued

i) Frequency of vegetative symptoms in group 13 (generalised motor)

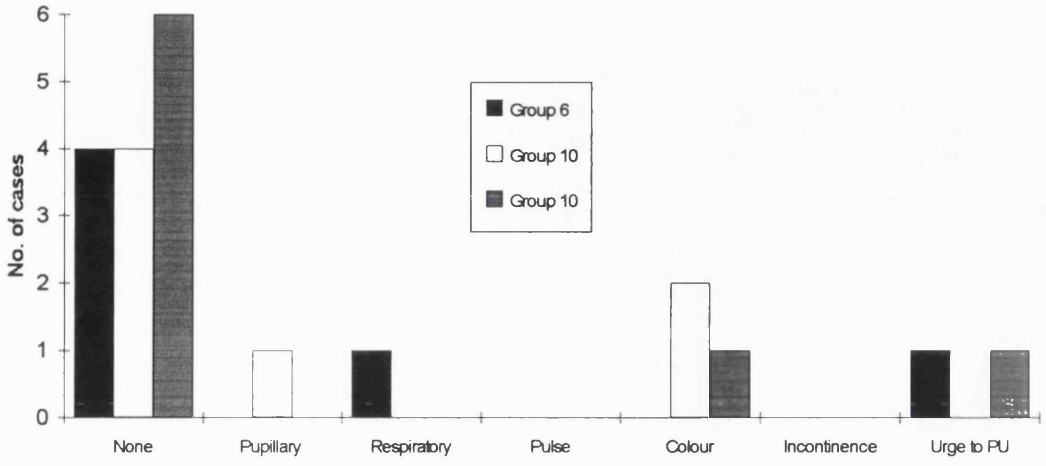


j) Frequency of vegetative symptoms in group 14 (motor agitation)



Appendix 12, continued

k) Frequency of vegetative symptoms in groups 6 (hypotonic); 10 (complex partial status epilepticus) and 11 (isolated jerks)



References

1. ILAE Commission on classification and terminology. Proposal for classification of epilepsies and epileptic syndromes. Epilepsia 1985;26:268-78.

2. Commision on Classification and Terminology of The International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-399.

3. National Institute of Neurological Disorders and Stroke ongoing program announcement. Frontal lobe epilepsies. NIH guide for grants and contracts 18, February 3, 1989.

4. National General Practice Study of Epilepsy and Epileptic Seizures (NGPSE): Objectives and study methodology of the largest reported prospective cohort study of epilepsy. Neuroepidemiol 1989:8:221-227.

5. Taylor A Ed. Selected writings of John Hughlings Jackson. 1958. Staples Press London.

6. Horsley V. Brain surgery. Brit Med J 1886;2:670-75.

7. Penfield W and Jasper H. Epilepsy and functional anatomy of the human brain. Boston Little Brown & Co, 1954.

8. Bhatia R and Kollevold T. A follow-up study of 91 patients operated on for focal epilepsy. Epilepsia 1976;17:61-66.

9. Binnie C, Chadwick D and Shorvon S Eds. Surgical treatment for epilepsy. A report commissioned by the British branch of The International League Against Epilepsy. ILAE 1991.

10. Engel J Jr. Outcome with respect to epileptic seizures. In Engel J Jr. Ed. Surgical treatment of the epilepsies. Raven Press New York, 1987, pp 553-571.

11. Pribram K. The sudivisions of the frontal cortex revisited. In Perecman E Ed. The frontal lobes revisited. IRBN Press 1987, pp11-40.

12. Penfield W and Rasmussen T. The cerebral cortex of man. New York MacMillan 1952.

13. Luria A. The frontal lobes and the regulation of behaviour. In Pribram K and Luria A Eds. Psychophysiology of the frontal lobes Academic Press 1973, pp 3-26.

14. Kaada B. Respiratory and vascular responses in monkeys from temporal pole, insula, orbital surface and the cingulate gyrus. J Neurophysiol 1949;12:347-56.

15. Maclean P. The midline frontal cortex and the evolution of crying and laughter. In Thefrontal lobes revisited. Ed Perecman E. IRBN Press NY, 1987, pp121-140.

16. Sanides F. Functional architecture of motor and sensory cortices in the light of a new concept of neocortex development. In Noback C and Montana W Eds. Advances in primatology (Vol 1 pp 137-208). New York Apple-Century-Crofts,1971.

17. Swartz M and Goldman-Rakic P. Single cortical neurons have axon collaterals to ipsilateral and contralateral cortex in fetal and adult primates. Nature 1982;229:154-55.

18. Goldman-Rakic P. The frontal lobes: uncharted provinces of the brain. TINS 1984;7:425-29.

19. Alexander G, DeLong M and Strick P. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 1986;9:357-81.

20. Nauta H. The relationship of the basal ganglia to the limbic system. Handbook of Clin Neurol 1986;49:19-31.

21. Albin R, Young A and Penney J (1989). The functional anatomy of basal ganglia disorders. TINS 1989;12:366-75.

22. Laplane D, Levasseur M, Pillon B, Dubois B and Baulac M. Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron tomography study. Brain 1989;112:699-725.

23. Spiegel E, Wycis H, Baird H and Szekeley E. Functional state of the basal ganglia in extrapyramidal and convulsive disorders. Arch Neurol 1956;75:167-74.

24. Wycis H, Baird H and Spiegel E. Long range results following pallidotomy and pallidoamygdalotomy in certain types of convulsive disorder. Confin Neurol 1966;27:114-20.

25. Fine A, Meldrum B, and Patel S. Modulation of experimentally induced epilepsy by intracerebral grafts of fetal GABAergic neurons. Neuropsychologia 1990;28:627-34.

26. Gale K, Browning R. Anatomical and neurochemical substrates of clonic and tonic seizures. In Mechanisms of epileptogenesis; the transition to seizure. Ed Dichter M. Plenum Press, NY 1988, pp 111-152.

27. Pollen D. Intracellular studies of cortical neurons, during thalamic induced spike and wave. Electroenceph. Clin Neurophysiol. 1964;17: 154-163.

28. Spencer S. Cortical and intercortical seizure spread. In Meldrum B, Ferrendelli J and Wieser H. Eds. Current problems in epilepsy 6: anatomy of epileptogenesis. John Libbey & Co. 1989, pp 139-54.

29. Robinson D. Eye movement control in primates. Science 1968;161:1219-24.

30. Schneider R, Crosby E, Bagchi B and Calhoun H. Temporal or occipital hallucinations triggered from frontal lobe lesions. Neurol 172-179.

31. Rasmussen T. Surgical therapy of frontal lobe epilepsy. Epilepsia 1963;4:181-98.

32. Geier S, Bancaud J, Talairach J, Bonis A, Hossard-Bouchaud H and Enjelvin M. Ictal tonic postural changes and automatisms of the upper limb during epileptic parietal lobe discharges. Epilepsia 1977;18:517-24.

33. Yaari Y and Jensen M. Non-synaptic mechanisms and interictal-ictal transitions in the mammalian hippocampus. In Dichter M Ed. Mechanisms of epileptogenesis: the transition to seizure pp183-98, NY Plenum, 1988.

34. Penfield W and Welch K. The supplementary motor area of the cerebral cortex. Arch Neurol Psychiat 1951;66:289-317.

35. Juergens U. Reinforcing concomitants of electrically elicited vocalisation. Exp Brain Res 1976;26:203-214.

36. Rasmussen T. Characteristics of a pure culture of frontal lobe epilepsy. Epilepsia 1983;24:482-493.

37. Tuekel K and Jasper H. The electroencephalogram in parasagittal lesions. Electroencephalography and Clinical Neurophysiol 1952;4:481-94.

38. Waterman K, Purves S, Kosaka B, Strauss E and Wada J. An epileptic syndrome caused by mesial frontal lobe seizure foci. Neurol 1987;37:577-82.

39. Geier S, Bancaud J, Talairach J, Bonis A, Enjelvin M and Hossard-Bouchaud H. Automatisms during frontal lobe seizures. Brain 1976;99:447-58.

40. Delgado-Escueta A, Bascal F and Treiman D. Complex partial seizures on closed-circuit television and EEG: a study of 691 attacks in 79 patients. Ann Neurol 1981;11:292-300.

41. Cotte-Rittaud M and Courjon J. Semiological value of adversive epilepsy. J Electrophysiol Clin Neurophysiol 1962;14:138 (abstract).

42. Kendrick J and Gibbs F. Interrelations of mesial temporal and orbital frontal ares of man revealed by strychnine spikes. Arch. Neurol. Psychiat. 1958;77:518-24.

43. Williamson P, Spencer D, Spencer S, Novelly R and Mattson R. Complex partial seizures of frontal lobe origin. Ann Neurol 1985;18:497-504.

44. Fegerstein L and Roger A. Frontal epileptogenic foci and their clinical correlation. J Electrophysiol Neurophysiol 1961;13:905-13.

45. Wada J and Purves S. Oral and bimanual-bipedal activity as manifestations of frontal lobe epilepsy. Epilepsia 1984;25:668.

46. Marchini M, Munari C, Parietti L, Broglin D, Giallonardo A and Bancaud J. Contribution of the direct clinical observation to the ictal semiology knowledge: Stereo-EEG and videotape study of 57 frontal lobe seizures. Boll Lega Ital Epilessia 1989; 66-67:115-23.

47. Delgado-Escueta A, Swartz B, Maldonado M, Walsh G, Rand R and Halgren E. Complex partial seizures of frontal lobe origin. In Wieser H and Elger C. Eds. Presurgical evaluation of epileptics. Springer Verlag,1987, pp 267-99.

48. Quesney L, Krieger C, Leitner C, Gloor P and Olivier A. Frontal lobe epilepsy: clinical and electrographic presentation. In Porter R et al Eds XVth International Symposium of the Epilepsies. Raven Press NY,1984, pp 503-508.

49. Delgado-Escueta A and Walsh G. Type 1 complex partial seizures of hippocampal origin: excellent results of anterior temporal lobectomy. Neurol 1985;35:143-54.

50. Spencer S, Spencer D, Williamson P and Mattson R. Sexual automatisms in complex partial seizures. Neurol 1983;33:527-33.

51. Freemon F and Nevis A. Temporal lobe sexual seizures. Neurol 1969;19:87-90.

52. Ajmone-Marsan C. and Ralston B. The epileptic seizure: its functional morphology and diagnostic significance. Thomas Springfield, Illinois 1957.

53. Quesney L, Constain M, Fish D and Rasmussen T. The clinical differentiation of seizures arising in the parasagittal and dorsolateral frontal convexities. Arch Neurol 1990;47:677-79.

54. Talairach J, Bancaud J, Geier S, et al. The cingulate gyrus and human behaviour. Electrencephalography and Clinical Neurophysiology 1973;34:45-52.

55. Ludwig B, Ajmone Marsan C and Van Buren J. Cerebral seizures of probable orbitofrontal origin. Epilepsia 1975;16:141-58.

56. Ludwig B, Ajmone Marsan C and Van Buren J. Depth and direct cortical recording in seizure disorders of extratemporal origin. Neurol 1976;26:1085-99.

57. Geier S, Bancaud J, Talairach J, Bonis A, Szikla G and Enjelvin M. Clinical note: clinical and tele-stereo-EEG findings in a patient with psychomotor seizures. Epilepsia 1975;16:19-25.

58. Baleydier C and Maugiere F. The dualtiy of the cingulate gyrus in the monkey. Neuroanatomical study and functional hypothesis. Brain 1980;103:525-54.

59. Geier S, Bancaud J, Talairach J, Bonis A, Szikla G and Enjelvin M (1977). The seizures of frontal lobe epilepsy: a study of clinical manifestations. Neurol 1977;27:951-58.

60. Quesney L (1986). Seizures of frontal lobe origin. In Meldrum B and Pedley T Eds. Recent Advances in Epilepsy 1986;3:81-110.

61. Tharp B. Orbitofrontal seizures. An unique electroencephalographic and clinical syndrome. Epilepsia 1972;13:627-42.

62. Penfield W and Rasmussen T. Vocalization and arrest of speech. Arch Neurol Psychiat 1949;61:21-27.

63. Farwell J and Stuntz J. Frontoparietal astrocytoma causing absence seizures and bilaterally synchronous epileptiform discharges.Epilepsia 1984;25:695-98.

64. Gastaut H, Roger J, Ouahchi S, Timsit M and Broughton R. An electroclinical study of seizures of tonic expression. Epilepsia 1963;4:15-44.

65. Kanner A, Morris H, Lueders H et al. Supplementary motor seizures mimicking pseudoseizures. Neurol 1990;40:1404-1407.

66. Penry J, Porter R and Dreyfuss F. Simultaneous recording of absence seizures with video tape and electroencephalography. Brain 1975;98:427-40.

67. Wiliamson P, Spencer D, Spencer S, Novelly R and Mattson R. Complex partial status epilepticus: a depth electrode study. Ann Neurol 1985;18:647-54.

68. Gloor P. Consciousness as a neurological concept in epileptology: a critical review. Epilepsia 1986;27(Suppl.2):S14-S26.

69. Sperry R. Consciousness, personal identity and the divided brain. Neuropsychologia 1984;22:661-73.

70. Dimond S. Neuro psychology: a textbook of systems and psychological functions of the human brain, pp 417-43. London, Butterworths, 1980.

71. Jasper H. Some physiological mechanisms involved in epileptic automatisms. Epilepsia 1964;5:1-20.

72. Gloor P and Olivier A. Loss of consciousness in temporal lobe seizures: observations obtained with sterotactic electrical recordings and stimulations. In Canger R, Angeleri F and Penry J Eds. Advances in Epileptology 11th Symposium pp 349-53. New York Raven Press, 1980.

73. Robillard A, Saint-Hillaire J, Mercier M and Bouvier G. The lateraliszing and localizing value of adversion in epilepsy. Neurol 1983;33:1241-42.

74. Talairach J and Bancaud J. The supplementary motor area in man. (Anatomo-functional findings by stereoencephalography in epilepsy.) Int J Neurol 1966;5:330-47.

75. Wyllie E, Lueders H, Morris H, Lesser R and Dinner D. The lateralizing significance of versive head and eye movements during epileptic seizures. Neurol 1986;36:606-11.

76. Morris H, Dinner D, Lueders H, Wyllie E, Kramer R. Supplementary motor seizures: clinical and electrographic findings. Neurol 1988;38:1075-1082.

77. Goldberg G. Supplementary motor area sructure and function: review and hypotheses. Behav Brain Sci 1985;8:567-616.

78. Jones E and Powell T. An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. Brain 1970;93:793-820.

79. Freund H-J . Differential effects of cortical lesions in humans. Ciba Foundation Symposium 1987;132:269-81, Wiley Chichester.

80. Tanji J. Neuronal activity in the primate non-primary cortex is different from that in the primary cortex. Ciba Foundation Symposium 1987;32:142-150.Wiley Chichester.

81. Morris H and Lueders H. In Eds Gotman J, Ives J and Gloor P. Long-term monitoring in epilepsy (EEG Suppl. No. 37)1985; pp 3-26.

82. Morris H, Lueders H, Lesser R Dinner D and Klem G. The value of closely spaced electrodes in the localization of epileptiform foci: a study of 26 patients with complex partial seizures. Electroencephalography and Clinical Neurophysiology 1986;63:107-11.

83. Tinuper P and Cerullo A. Scalp EEG and frontal epilepsy. Boll Lega Ital Epilessia 1989;66-67:107-109.

84. Quesney L. Extracranial EEG evaluation. In Engel J Jr. Ed. Surgical treatment of the epilepsies. Raven Press New York, 1987, pp 129-66.

85. Lehtinen L and Bergstrom L. Nasoethmoidal electrodes for recording the activity of the inferior surface of the frontal lobes. Electroenceph. Clin. Neurophysiol. 1970;29:303-305.

86. Lugaresi E and Cirignotta F. Hypnogenic paroxysmal dystonia: epileptic seizure or a new syndrome? Sleep 1981;4:129-38.

87. Tinuper P, Cerullo A, Cirignotta F, Cortelli P, Lugaresi E and Montagna P. Nocturnal paroxysmal dystonia with short-lasting attacks: three cases with evidence for an epileptic frontal lobe origin of seizures. Epilepsia 1990;31:549-56.

88. Spencer S, Spencer D, Williamson P and Mattson R. The localizing value of depth electroencephalography in 32 patients with refractory epilepsy. Ann Neurol 1982;12:248-53.

89. Engel J Jr., Rausch R, Lieb J, Kuhl D and Crandall P. Correlation of criteria used for localizing epileptic foci in patients considered for surgical therapy of epilepsy. Ann Neurol 1981;9:215-24.

90. Spencer S. Depth electroencephalography in selection of refractory epilepsy for surgery. Ann Neurol 1981;9:207-14.

91. Lieb J, Engel J, Gevins A and Crandall P. Surface and deep EEG correlates of surgical outcome in temporal lobe epilepsy. Epilepsia 1981;22:515-38.

92. Quesney L. Preoperative electroencephalographic investigation in frontal lobe epilepsy: electroencephalographic and electrocorticographic recordings. Can J Neurol Sci 1991;18:559-563.

93. Quesney L, Fish D, Olivier A, Gloor P and Andermann F. Presurgical evaluation of children and young adolescents with intractable partial seizures using chronic intracerebral and epidural electrodes. J Epilepsy in press.

94. Mazars G. Criteria for identifying cingulate epilepsies. Epilepsia 1970;11:41-47.

95. Pedley T, Tharp B and Herman K. Clinical and electroencephalographic characteristics of midline parasagittal foci. Ann Neurol 1981;9:142-49.

96. Ambrosetto G, Pazzaglia P and Tassinari C. Sudden epileptic falls: Malignant evolution of frontal lobe epilepsy. Boll Lega Ital Epilessia 1989;66-67:137-138.

97. Laws E, Niedermeyer E and Walker A. Diagnostic significance of scalp and depth EEG findings in patients with temporal and frontal lobe epilepsy. Johns Hopkins J 1970;126:146-53.

98. Ludwig B, Ajmone Marsan C and Van Buren J. Depth and direct cortical recording in seizure disorders of extratemporal origin. Neurol 1976;26:1085-99.

99. Munari C, Giallonardo A, Brunet P, Broglin D, and Bancaud J. Stereotactic investigations in frontal lobe epilepsies. Acta Neurochirurgica Suppl 1989;46:9-12.

100. Wyler A, Walker G, Richey E and Hermann B. Chronic subdural strip electrode recordings for difficult epileptic problems. J Epilepsy 1988;1:71-78.

101. Wyler A (1987). Electrocorticography. In Wieser H and Elger C Eds. Presurgical evaluation of epileptics. Springer-Verlag pp 183-191.

102. Van-Veelen C, Debets R, Van Huffelen A, Van-Emde-Boas W, Binnie C, Storm-van-Leeuwen W, Velis D and Van-Dieren A (1990). Combined use of subdural and intracerebral electrodes in preoperative evaluation of epilepsy. Neurosurgery 26:93-101.

103. Wieser H. Stereo-electroencephalography. In Wieser H and Elger C Eds. Presurgical evaluation of epileptics. Springer Verlag, Berlin, 1987,pp 192-204.

104. Darcy T (1988). Initiation and spread of seizures in man: analytical methods for monitoring seizures. In Richter M Ed. Mechanisms of epileptogenesis: the transition to seizure. NY Plenum 1988, pp 39-56

105. Gotman J. Measurement of small time differences between EEG channels: method and application to epileptic seizure propagation. Electroenceph. clin. Neurophysiol. 1983;56:501-14.

106. Sutherling W, Risinger M, Crandall P et al. Focal functional anatomy of dorsolateral frontocentral seizures. Neurol 1990;40:87-98.

107. Dodrill C, Wilkus R, Ojemann G et al. Multidisciplinary prediction of seizure relief from cortical resection surgery. Ann Neurol 1986;20:2-12.

108. Dodrill C, van Belle G and Wilus R. Stability of predictors of outcome of surgical treatment for epilepsy. J Epilepsy1990;3:29-35.

109. Rasmussen T. Surgical treatment of complex partial seizures: results lessons and problems. Epilepsia 1983;24 Suppl. 1:65-76.

110. King D, Flanigin H, Gallagher B, et al. Temporal lobectomy for partial complex seizures: evaluation, results and one year follow-up. Neurol 1986;36:334-39.

111. Falconer M. Surgical treatment of drug-resistant epilepsy due to mesial temporal sclerosis. Arch Neurol 1968;19:353-61.

112. Falconer M. A follow-up study of surgery in temporal lobe epilepsy. J Neurol Neurosurg Psychiat 1963;26:154-65.

113. Bengzon A, Rasmussen T, Gloor P, Dussault J and Stephens M. Prognostic factors in surgical treatment of temporal lobe epilepsy. Neurol 1968;18:717-31.

114. Kyoi K, Utsumi S, Sakaki T, Tada T and Miyamoto S. Relationship between CT findings and electrical focus in epileptic patients. Jpn. J. Psychiat. Neurol. 1989;43:337-47.

115. Duncan R, Patterson J, Hadley D et al. CT, MR and SPECT imaging in temporal lobe epilepsy. J Neurol. Neurosurg. Psychiat. 1990;53:11-15.

116. Schorner W, Meencke H and Felix R. Temporal lobe epilepsy: comparison of CT and MR imaging. Am J Roentgenol. 1987;149:1231-39.

117. Theodore W, Dorwart R, Holmes M, Porter R and DiChiro G. Neuroimaging in refractory partial seizures: comparison of PET, CT and MRI. Neurol 1986;36:750-59.

118. Cordes M, Christe W Henkes H et al. Focal epilepsy: HM-PAO SPECT compared with CT, MR and EEG. J Comput Assist Tomogr 1990;14:402-9.

119. Spencer D, Spencer S, Mattson R et al. Intracerebral masses in patients with intractable partial epilepsy. Neurol 1984;34:432-36.

120. Rich K, Goldring S and Gado M. Computed tomography in chronic seizure disorder caused by glioma. Arch Neurol 1985;42:26-27.

121. Heinz E, Crain B, Radtke R et al . Magnetic resonance imaging in patients with temporal lobe seizures: correlation of results with pathologic findings.

122. Kuzniecky R, de la Sayette V and Ethier R. Magnetic resonance imaging: pathological correlations. Ann Neurol 1987;22:341-7.

123. Brocks B, King D, el Gamma T at al. Magnetic resonance imaging in patients with intractable partial epileptic seizures. Am J Roentgenol 1990;154:577-833.

124. Matsuda K, Yagi K, Miharo T, Tottori T, Watanabe Y and Seino M. MRI lesion and epileptogenic focus in temporal lobe epilesy. Jpn J Psychiat. Neurol. 1989;43:393-400.

125. Riela A, Penry J, Laster D and Schwartzke G. Magnetic resonance imaging and complex partial seizures. Electroencephalog. Clin. Neurophysiol. 1987;39(3) Suppl. 161-73.

126. Franceschi M, Triulzi F, Ferini-Strambi L et el. Focal cerebral lesions found by magnetic resonance imaging in cryptogenic non-refractory temporal lobe epilepsy patients. Epilepsia 1989;30:540-46.

127. Jackson G, Berkovic S, Tress B, Kalnins R, Fabinyi G, Bladin P. Hippocampal sclerosis can be relably detected by magnetic resonance imaging. Neurology 1990;40:1869-1875.

128. Cook M, Fish D, Shorvon S, Straughan K, Stevens J. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 1992;115:1001-1016.

129. Schorner W, Meencke H and Felix R. Temporal lobe epilepsy: comparison of CT and MR imaging. Am J Roentgenol. 1987;149:1231-39.

130. Barth P. Disorders of neuronal migration. Can J Neurol Sci 1987;14:1-16.

131. Byrd S, Osborn R, Bohan T and Naidich T. The CT and MR evaluation of migrational disorders of the brain. Part I. Lissencephaly and pachgyria. Pediatr-Radiol 1989;19:151-56.

132. Byrd S, Osborn R, Bohan T and Naidich T. The CT and MR evaluation of migrational disorders of the brain. Part II. Schizencephaly, heterotopia and polymicrogyria. Pediatr-Radiol 1989;19:219-22.

133. Wilms G, Marchal G, Decrop E, Van Hecke P, Baert A and Caesar P. Computed tomography and magnetic resonance imaging in anomalies of neuronal migration. J Radiol 1989;70:1-6.

134. Smith A, Weinstein M, Quencer R et al. Association of heterotopic grey matter with seizures: MR imaging. Radiol 1988;168:195-98.

135.Meencke H. Pathology of the childhood epilepsies. Cleveland Clinic J Med 1989;56(suppl. 1):511-520.

136. Kaufmann W and Galaburda A. Cerebrocortical microdysgenesis in neurologically normal subjects: a histopathological study. Neurol 1989;39:238-44.

137. Kuzniecky R, Berkovic S, Andermann F, Melanson D, Olivier A and Robitaille Y. Focal cortical myoclonus and rolandic cortical dysplasia: clarification by magnetic resonance imaging. Ann Neurol 1988;23:317-25.

138. 134. Morel F and Wildi J. Dysgenesie nodulaire de l'ecorce frontale. Rev Neurologique 1952;87:251-70.

139. Tamaki K, Okuno T, Ito M, Asato R, Konishi J amd Mikawa H. Magnetic resonance imaging in relation to EEG epileptic foci in tuberous sclerosis. Brain Dev. 1990;12:316-20.

140. Della Giustina E, Goffonet A, Landrieu P and Lyon G. A Golgi study of the brain in Zellweger's cerebro-hepato-renal disease. Acta Neuropathol 1981;55:23-28.

141. Henry T, Engel J Jr and Mazziotta J (1989). PET studues of functional cerebral anatomy in human epilepsy.

142. Engel J Jr, Kuhl D and Phelps M. Patterns of local human cerebral glucose metabolism during epileptic seizures. Science 1982;214:64-66.

143. Stefan H, Bauer J, Feistel H et al. Regional cerebral blood flow during focal seizures of temporal and frontocentral onset. Ann Neurol 1990;27:162-66.

144. Fish D, Lewis T, Brooks D, Zilkha E, Wise R and Kendall B. Regional cerebral blood flow of patients with focal epilepsy studied using xenon enhanced CT brain scanning. J Neurol Neurosurg Psychiat 1987;50:1584-88.

145. Hosokawa S, Kato M, Otsuka M, Kuwabara Y, Ichiya Y and Goto I. Positron Emission Tomography in epilepsy: correlative study. Jpn J Psychiat Neurol 1989;43:349-53.

146. Duncan R, Patterson J, Hadley D, Wyper D, McGeorge A and Bone I. Tc99m HM-PAO single photon emission computed tomography in temporal lobe epilepsy. Acta Neurol Scand 1990;81:287-93.

147. Engel J Jr, Brown W, Kuhl D, Phelps M, Mazziotta J and Crandall P. Pathological findings underlying temporal lobe hypometabolism in partial epilepsy. Ann Neurol 1982;12:518-28.

148. Falconer J, Wada J, Martin W and Li D. PET, CT and MRI imaging of neuronal migration anomalies in epileptic patients. Can J Neurosci 1990;17:35-39.

149. Sauter R, Loeffler W, Brulin H and Frahm J. The human brain: localised H-1 magnetic resonance spectroscopy at 1.0T. Radiology 1990;176:221-24.

150. Koga K, Miura I. A measurement of cerebral glucose uptake rate by 31P MRS. Biochem Biophys Res Commun 1990;157:1258-63.

151. Prichard J, Alger J, Behar K, Petroff O and Schulman R . Cerebral metabolic studies in vivo by 31P NMR. Proc Natl Acad Sci (USA) 1983;80:2748-51.

152. Petroff O, Prichard J, Ogino T, Avison M, Alger J and Schulman R. Combined 1H and 31P nuclear magnetic resonance studies of bicuculline induced-seizures in vivo. Ann Neurol 1986;20:185-93.

153. Younkin D, Delivoria-Papdopoulos M, Maris J, Donlon E, Clancy R and Chance B (1986). Cerebral metabolic effects of neonatal seizures measured with in vivo 31P NMR spectroscopy..

154. Prichard J, Petroff O, Ogino T and Schulman R. Cerebral lactate elevation by electroshock: a 1H magnetic resonance study. Ann NY Acad Sci 1987;508:54-63.

155. Petroff O, Spencer D, Alger J and Prichard J. High-field proton magnetic resonance spectroscopy of human cerebrum obtained during surgery for epilepsy. Neurol 1989;139:1197-1202.

156. Matthews P, Andermann F and Arnold D. A proton magnetic resonance spectroscopy study of focal epilepsy in humans. Neurol 1990;40:985-99.

157.Connelly A, Gadian D, Jackson G et al. MRI and MR Spectroscopy of medial temporal lobes in intractable partial epilepsy: evidence of regional and bilateral abnormalities. Epilepsia 1992;33(suppl.3):70 (abstract).

158. Furune S, Negoro T, Maehara M et al. Magnetic resonance imaging in complex partial seizures. Jpn J Psychiat Neurol 1989;43:361-67.

159. Swartz B, Halgren E, Delgado-Escueta A et al. Neuroimaging in patients with seizures of probable frontal origin. Epilepsia 1989;30:547-48.

160. Holmes M, Kelly K and Theodore W. Complex partial seizures. Correlation of clinical and metabolic features. Arch Neurol 1989;45:1191-93.

161. Sanabria E, Munsch C, Remy C and Chauvel P. Single photon emission tomography in frontal epilepsy: Comparative study using two different tracers. Boll Lega Ital Epilessia 1988;62-63:425-429.

162. Convers P, Bierme T, Ryvlin P, Revol M, Fischer C, Froment J and Mauguiere F. Brain magnetic resonance imaging (MRI) in drug-resistant partial epilepsy. A study of 100 patients with normal CT scans. Rev Neurol 1990;146:330-37.

163. Cook MJ, Manford M, Fish DR, Shorvon SD, Straughan K, Stevens JM. Volumetric MRI in CT negative frontal lobe epilepsy. European Neurological Society 1992 J Neurol 1992;239(suppl.2):S71. (abstract).

164. Free S, Straughan K, Cook M, Fish D, Shorvon S, Stevens J. Application of image analysis techniques to MRI in frontal lobe epilepsy. Epilepsia 1992;33(suppl. 3):52 (abstract).

165. Wyllie E, Lueders H, Murphy D et al. Intracarotid amobarbital (Wada) test for language dominance: correlation with results of cortical stimulation. Epilepsia 1990;31:156-61.

166. Wada J. A new method for determination of the side of cerebral speech dominance: a preliminary report on the intracarotid injection of sodium amytal in man. Igaku to Seibutsugaku (Japanese) 1949;14:221-2.

167. Brown J. Frontal lobe syndromes. Handbook of clinical neurology 1985;1:23-41.

168. Penfield W and Evans J. The frontal lobe in man: a clinical study of maximal removals. Brain 1955;58:115-133.

169. Travis A. Neurological deficiencies following supplementary motor area lesions in Macaca mulatta. Brain 1955;83:174-98.

170. Laplane D, Talairach J, Meininger V, Bancaud J and Orgogozo J. Clinical consequences following corticectomies invoving the supplementary motor area in man. J Neurol Sci 1977;34:301-14.

171. Halsband U and Freund H-J. Premotor cortex and conditional learning in man. Brain 1990;113:207-22.

172. Bianchi A and Severi S. Validity of some neuropsychological tests in the study of frontal epilepsy. Boll Lega Ital Epilessia 1989;66-67:131-134.

173. Wyllie E, Lueders H, Morris H et al. Clinical outcome after complete or partial cortical resction for intractable eplepsy. Neurol 1987;37:1634-41.

174. Sironi V, Ravagnati L and De Santis A. Frontal lobe epilepsy: Depth EEG study and surgical results. Boll Lega Ital Epilessia 1989;66-67:155-56.

175. Rasmussen T. Tailoring of cortical excisions for frontal lobe epilepsy. Can J Neurol Sci. 1991;18:606-610.

176. Bonis A. Long term results of cortical excisions based on stereotactic investigations in severe, drug resistant epilepsies. Acta Neurochirurgica 1980;(Suppl.30):55-66.

177. Andermann F. Identification of candidates for surgical treatment of epilepsy. In Engel J Jr. Ed. Surgical treatment of the epilepsies New York Raven Press, 1987, pp 51-70.

178. Wingkun E, Awad I, Lueders H, Awad C. Natural history of recurrent seizures after resective surgery for epilepsy. Epilepsia 1991;32:851-856.

179. Cascino G, Jack C, Parisi J et al. MRI in the presurgical evaluation of patients with frontal lobe epilepsy and children with temporal lobe epilepsy: pathologic correlation and prognostic importance. Epilepsy Res 1992;11:51-59.

180. Awad I, Rosenfeld J, Ahl J, Hahn J, Lueders H. Intractable epilepsy and structural lesions of the brain: mapping, resection strategies and seizure outcome. Epilepsia 1991;32:179-186.

181. Green J, Angevine J, White J, Edes A and Smith R. Significance of the supplementary motor area in partial seizures and in cerebral localization. Neurosurg 1980;6:66-75.

182. Fish D, Anderman F, Olivier A. Surgical strategies in patients with complex partial seizures and small posterior temporal or extratemporal lesions. Presented to the American Epilepsy Society December 1989.

183. Clark D, Olivier A, Fish D, Andermann A. The problem of focus/lesion incongruence (abstract). Epilepsia 1992;33(Suppl. 3):99.

184. Wyler A, Hermann B and Richey E. Results of reoperation for failed epilepsy surgery. J Neurosurg 1989;71:815-819.

185. Yasargil M and Wieser H. Selective microsurgical resections. In Wieser H and Elger C Eds. Presurgical evaluation of epileptics. Springer Verlag, Berlin, 1987, pp 352-60.

186. Spencer S, Williamson P, Spencer D and Mattson R. Human hippocampal seizure spread studied by depth and subdural recording: the hippocampal commissure. Epilepsia 1987;28:479-89.

177. Wilson D, Reeves A and Gazzaniga M. "Central" commissurotomy for intractable generalised epilepsy: series 2. Neurol 1982;32:687-97.

188. Spencer S, Spencer D, Wiliamson P, Sass K, Novelly R and Mattson R. Corpus callosotomy for epilepsy. I. Seizure effects. Neurol 1988;38:19-24.

189. Purves S, Wada J, Woodhurst W, Moyes P, Strauss E, Kosaka B and Li D. Results of anterior corpus callosum section in 24 patients with medically intractable seizures. Neurol 1988;38:1194-1201.

190. Ralston B. Cingulate epilepsy and secondary bilateral synchrony. Electroenceph. clin. Neurophysiol 1961;13:591-98.

191. Ajmone Marsan C and Baldwin M. Electrocorticography. In Eds. Baldwin M and Bailey P, Temporal Lobe Epilepsy. Sprinfield Illinois, 1958. pp 368-95.

192. Gloor P. Contributions of electroencephalography and electrocorticography to the neurosurgical treatment of the epilepsies. In Purpura D, Penry J and Walter R Eds, Neurosurgical management of the epilepsies. NY Raven Press, 1975. pp 59-105.

193. Wyllie E, Lueders H, Morris H et al. Clinical outcome after complete or partial cortical resection for intractable epilepsy. Neurol 1987;37:1634-41.

194. Collichio G, Bozzini V and Pallini R.Presurgical evaluation in the epilepsies with suspected frontal origin. Boll Lega Ital Epilessia 1989;66-67:159-60.

195. Sveinsbjorndottir S, Duncan J, Smith S. Clinical and electrographic features of parietal and occipital epilepsy J Neurol 1992;239(suppl.2):S57 (abstract).

196. Hair J, Anderson R, Tatham R. Multivariate data analysis. Cluster analysis pp293-348. Macmillan NY 1987.

197. Maulsby RL. Some guidlines for assessment of spikes and sharp waves in EEG tracings. Am J EEG Technol 1971;11:3.

198. Quesney L, Gloor P. Localisation of epileptic foci. In Long-term monitoring in epilepsy Eds. Gotman J, Ives I, Gloor P, Elsevier Amsterdam 1985;165-199.

199. Cail W, Morris J. Localisation of intracranial lesions from CT scans. Surg Neurol 1979;11:35-37.

200. Greitz T, Bergstrom M. Stereotactic procedures in computed tomography. Chapter 126.

201. Talairach J, Szikla G, Tournoux P et al. Atlas d'anatomie stereotaxique du telencephale. Masson et Cie Paris 1967.

202. Williams P and Warwick R Eds. Gray's Anatomy 36th Edition pp981-1021. Churchill-Livingstone Edinburgh.

203. Evans A.3-D reconstruction and MRI. NATO advanced research workshop on magnetic resonance techniques and epilepsy, Institute of Neurology, London 1992.

204. Kirkwood BR. Essentials of medical statistics. Blackwell Scientific Publications, Oxford, 1988. pp89.

205. Sander J, Hart Y, Johnson A, Shorvon S. National General Practice Study of Epilepsy: newly diagnosed seizures in a general population. Lancet 1990;336:1267-71.

206. Hart Y, Sander J, Johnson A, Shorvon S. National General Practice Study of Epilepsy: recurrence after a first seizure. Lancet 1990;336:1272-1274.

207. Manford M and Shorvon SD. Prolonged sensory and visceral symptoms; an under-recognised form of focal (non-convulsive) status epilepticus. J Neurol Neurosurg Psychiat. 1992;55:714-716.

208. P Scott Becker Dixon A, Troncoso J. Bilateral opercular microgyria. Ann Neurol 1989;25:90-92.

209. Palmini A, Gloor P. The localising value of auras in partial seizures: a prospective and retrospective study. Neurol 1992;42:801-808.

210. Swartz B, Walsh G, Delgado-Escueta A, Zolo P. Surface ictal electroencephalographic patterns in frontal vs temporal lobe epilepsy. Can J Neurosci 1991;18:649-662.

211. Fish J, Rourke B. Identification of subtypes of learning-disabled children at three age levels: apsychological multivariate approach. J Clin Neuropsychol 1979;1:289-310.

212. Mezzich J. Evaluating clustering methods for psychiatric diagnosis. Biological Psychiatry 1978;13:265-281.

213. Lueders H, Awad I. Conceptual considerations. In Epilepsy surgery. Ed. Lueders H. Raven Press NY 1991 pp51-62.

214. Manford M, Hart YM, Sander JWAS, Shorvon SD. The classification of the ILAE applied to epilepsy in a general population: data from the National General Practice Study of Epilepsy. Arch Neurol 1992;49:801-808.

215. Palmini A, Andermann F, Olivier A, Tampieri D, Robitaille Y. Focal neuronal migration disorders and intractable partial epilepsy: results of surgicl treatment. Ann Neurol 1991;30:750-757.

216. Hughes J, Zak S. EEG and clinical changes in patients with chronic seizures associated with slowly growing brain tumours. Arch Neurol 1987;44:540-543.

217. Palmini A, Gloor P, Jones-Gotman M. Pure amnestic seizures in temporal lobe epilepsy. Definition, clinical symptomatology and functional anatomical observations. Brain 1992;115:749-770.

218. Munari C, Bancaud J, Electroclinical symptomatology of partial seizures of orbital frontal origin. Adv Neurol 1992;57:257-266.

219. Daly D. Uncinate fits. Neurology 1958;8:250-260.

220. Quesney L. Preoperative electroencephalographic investigation in frontal lobe epilepsy: electroencephalographic and electrocorticographic recordings. Can J neurosci 1991;18:559-563.

221. Gloor P, Olivier A, Quesney L, Andermann F, Horowitz S. The role of the limbic system in the experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982;12:129-144.

222. Wada J. Predominantly nocturnal recurrence of intensely affective vocal and facial expression associated with powerful bimanual, bipedal and axial activity as ictal manifestations of frontal lobe epilepsy. Adv in Epileptol 1989;17:261-267.

223. Leichnetz G, Astruc J. Efferent connections of the orbitofrontal cortex in the marmoset *(Sanguinus oedipus)* Brain res 1975;84:169-180.

224. Tanji J, Kurata K. Neuronal activity in the cortical supplementary motor area related with distal and proximal forelimb movements. Neurosci Letters 1979;12:201-206.

225. Wiesendanger M, Hummelsheim H, Bianchetti M et al. Input and output organization of the supplementary motor area. In "Motor areas of the cerebral cortex". Ciba Foundation symposium 1987;132:40-62.

226. Ethelberg S. On "cataplexy" in a case of frontal lobe tumour. Acta Psych 1950;24:421-27

227. Chauvel P, Trottier S, Vignal J, Bancaud J. Somatomotor seizures of frontal lobe origin. Adv Neurol 1992;57:185-232.

228. Quesney L, Gloor P. Localisation of epileptic foci. Electroencephalogr. Clini Neurophysiol 1985;(suppl.37):165-200.

229. Ghez C. Voluntary movement. In Principles of Neural Science Eds Kandel and Schwartz J. Elesevier Amsterdam 1985 pp487-501.

230. Lueders H, Lesser R, Dinner D et al. A negative motor response elicited by electrical stimulation of the human frontal cortex. Adv Neurol 1992;57:149-158.

231. Jankowska E, Padel Y, Tanaka R. Disynaptic inhibition of spinal motoneurons from the motor cortex in the monkey. J Physiol 1976; 258:467-487.

232. Delgado-Escueta A, Mattson R. The nature of aggression during epileptic seizures. N Engl J Med 1981;305:711-716.

233. Hallett M, Chadwick D, Marsden CD. Cortical reflex myoclonus. Neurol 1979;29:1107-25.

234. J de Bruin. Social behaviour and the prefrontal cortex. Progress in Brain Research 1990;85:485-496.

235. Neafsey E. Prefrontal control of the autonomic nervous system: anatomical and physiological observations. Progress in Brain Research 1990;85:147-164.

236. Alajouanine T and Gastaut H. La syncinesie-sursaut et l'epilepsie-sursant a declanchement sensoriel ou sensitif inopine. Rev Neurol (Paris) 1955;93:29-40.

237. Bancaud J, Talairach J and Bonis A. Physiopathogenie des epilepsies-sursaut: a propos d'une epilepsie de l'aire motrice supplementaire. Rev Neurol (Paris) 1967;117:441-453.

238. Bancaud J, Talairach J, Lamarche M, Bonis A and Trottier S. Hypotheses neuro-physiopathologiques sur l'epilepsie-sursaut chez l'homme. Rev Neurol (Paris) 1975;131:559-71.

239. Gastaut H and Tassinari C. Triggering mechanisms in epilepsy: the electroclinical point of view. Epilepsia 1966;7:86-138.

240. Kolbinger H, Zierz S, Elger C, Penin H. Startle-induced seizures and their relationship to epilepsy: three case reports. J Epilepsy 1990;3:23-27.

241. Guerrini R, Genton P, Bureau M, Dravet C, Roger R. Reflex seizures are frequent in patients with Down's syndrome and epilepsy. Epilepsia 1990;31:406-417.

242. Weinrich M and Wise S. The premotor cortex of the monkey. J Neurosci 1982;2:1329-1345.

243. Paty J, Deliac-Nevarte M, Fontan D, Loiseau P. Les potentiels evoques dans l'epilepsie sursaut. Rev EEG Neurophysiol 1978;8:316-371.

244.Mountcastle V (1981). The influence of attentive fixation on the excitability of light-sensitive neurons in the posterior parietal cortex. J Neurosci 1981;1:1218-35.

245. Brown P, Rothwell J, Thompson P, Britton T, Day B, Marsden C. New observations on the normal startle reflex in man. Brain 1991;1891-1902.

246. Brown P, Rothwell J, Thompson P, Britton T, Day B, Marsden C. The hyperekplexias and their relationship to the normal startle reflex. Brain 1991;1903-192

247. Goldring S. The role of the prefrontal cortex in grand mal convulsion. Arch Neurol 1972;26:109-119.

248. Chatrian G, Lettich E, Miller L, Green J, Kupfer C. Pattern-sensitive epilepsy. Part 2: Clinical changes, tests of responsiveness and motor output, alterations of evoked potentials and therapeutic meausures. Epilepsia I970;11:151-162.

249. Andermann F, Robb J. Absence status, a reappraisal, following review of thirty-eight patients. Epilepsia 1972;13:177-187.

250. Goldie L, Green J. Spike and wave discharges and alterations of conscious awareness. Nature 1961;191:200-201.

251. Gloor P. Generalised cortico-reticular epilepsies. Some considerations on the pathophysiology of generalised bilaterally synchronous spike and wave discharge. Epilepsia 1968;9:249-263.

252. Meencke H, Janz D. The significance of microdysgenesia in primary generalised epilepsy: an answer to the considerations of Lyon and Gastaut. Epilepsia 1985;26:368-371.

253. Sperling M, O'Connor M. Auras and subclinical seizures: characteristics and prognostic significance. Ann Neurol 1990;28:230-328.

254. Lieb J, Dashieff R, Engel J. Role of the frontal lobes in the propagation of mesial temporal seizures. Epilepsia 1991;32: 822-827.

255. Bossi L, Munari C, Stoffels C. et al. Somatomotor manifestations in temporal lobe seizures. Epilepsia 1984;25:70-76.

256. Wieser H. Ictally active pathways in psychomotor seizures: a stereo-EEG study. Adv Epilpeptol: XIIth Epilepsy International Symposium. Ed Dam M, Gram L, Penry J. Raven Press NY 1981, pp305-312.

257. Hedstrom E, Ekholm S, Hagberg I, Malmgren K, Rydenhag B, Silfvenius H. Rearrangement of of motor and sensory cortical areas following early cortical lesions. Epilepsia 1992;33(Suppl. 3):56 (abstract).

258. Pandya D, Dye P, Butters N. Efferent corticocortical projections of the prefrontal cortex in the monkey. Brain Res 1971;31:35-46.

259. Juergens U. The efferent and afferent connectionx of the supplementary motor area. Brain Res 1984;300:63-81.

260. Mars N, Lopes da Silva F. Propagation of seizure activity in kindled dogs. Electroenceph Clin Neurophysiol 1983;56:194-209.

261. Collins R. Kindling of neuroanatomical pathways during recurrent focal penicillin seizures. Brain Res. 1978;503-517.

262. Brazier M. Spread of seizure discharge in epilepsy: anatomical and electrophysiological considerations. Exp Neurol 1972;36:263-272.

263. Gloor P Preoperative electroencephalographic investigation in temporal lobe epilepsy: extracranial and intracranial recordings. Can J Neurosci 1991;18:554-558.

264. Loiseau J, Loiseau P, Guyot M, Duche B, Darigues J-F, Aublet B. Survey of seizure disorders in the French Southwest. I. Incidence of epileptic syndromes. Epilepsia 1990;31:391-96.

265. Shi-chuo Li, Schoenberg B, Chung-cheng Wang, Xue-ming Cheng, Bolis C. Epidemiology of epilepy in urban areas of the People's Republic of China. Epilepsia 1985;26:391-394.

266. Hauser W, Kurland L. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975;16:1-66.

267 Gastaut H, Gastaut J, Goncalves e Silva G, Fernandez Sanchez G. Relative frequency of different types of epilepsy: a study employing the classification of the International League Against Epilepsy. Epilepsia 1975;16:457-461.

268. Granieri E, Rosati G, Tola R et al. A descriptive study of epilepsy in the district of Copparo. Epilepsia 1983;24:502-514.

269. Gudmundsson G. Epilepsy in Iceland. Acta Neurol Scand 1966; 43 Suppl. 25.

270. Juul-Jensen P, Foldspang A. Natural history of epileptic seizures. Epilepsia 1983;24:297-312.

271 Jensen I. Temporal lobe epilepsy. Etiological factors and surgical results. Acta Neurol Scand 1976;53:103-118

272. Quesney L, Constain M, Fish D, Rasmussen T. Frontal lobe epilepsy: a field of recent emphasis. Am J EEG Technol 1990;30:177-93.

273. Pandya D and Barnes C. Architecture and connections of the frontal lobes. In The frontal lobes revisited Ed. Perecman E. IRBN Press 1987 pp41-72.

National General Practice Study of Epilepsy (NGPSE):

Partial seizure patterns in a general population

M. Manford, MRCP; Y.M. Hart, MRCP; J.W.A.S. Sander, MD; and S.D. Shorvon, FRCP
(for the NGPSE)

Article abstract—The National General Practice Study of Epilepsy (NGPSE) is a prospective community-based study of newly diagnosed epileptic seizures. Of 594 patients with definite epileptic seizures, 160 (26.9%) had seizures with a clinically localizable onset: 36 (22.5%) frontal, 52 (32.5%) central sensorimotor, 43 (27%) temporal, nine (5.6%) frontotemporal, and 10 each (6.3%) parietal and other posterior cortex. There was no difference among these groups in seizure frequency or remission rate; 46.5% were seizure free and 6.9% had severe epilepsy. Etiology was identifiable in 41% and focal CT and EEG abnormalities in 33% and 19%, with results discordant with the clinical seizure localization in 21% and 20%. Temporal lobe epilepsy may be underreported, as it may be more difficult to localize clinically. Extratemporal seizures are extremely common in the general population, especially frontal and central sensorimotor, in relation to cerebrovascular disease. Prognoses are similar for partial epilepsies with different clinical patterns and regions of onset and are much better than suggested in hospital-based studies. The clinical, EEG, and CT localizations may frequently be discordant in this nonrefractory group.

NEUROLOGY 1992;42:1911-1917

Partial epilepsies are common and are the seizure category most likely to be refractory to current therapy; therefore, they are of prime clinical importance. Conventionally, they are classified according to proposed site of onset, and in the past much emphasis was placed on those arising from the temporal lobes.[1-3] However, in recent years the significance of extratemporal seizures has been increasingly appreciated. In particular, it has been recognized that frontal lobe seizures[4-11] may be responsible for a substantial proportion of partial seizures and may be a subgroup that is particularly difficult to treat.[9] Most studies, however, are conducted from referral centers and it is not clear to what extent this may reflect their practice and patterns of referral. The National General Practice Study of Epilepsy (NGPSE) is the largest reported prospective, population-based study of epilepsy[12-14] and provides an ideal opportunity to analyze the relative frequency of different seizure patterns in the general population, to describe their clinical details and response to treatment, and to evaluate EEG and CT and correlate these with clinical features.

Methods. Details of the methods of the study have been described elsewhere.[12-14] In summary, 275 general practitioners during a 3-year prospective recruitment phase notified the coordinating center of all patients over 1 month old in whom a new diagnosis of definite or possible epileptic seizures had been made. The practices were located around the country in both urban and rural areas, to avoid demographic sources of bias. Patients were followed up by the study at 6 months, then at yearly intervals. Follow-up to date is from 4 to 7 years. Details of hospital and specialist assessment and results of investigations were also obtained. The study population is thus an unselected cohort of patients with newly diagnosed epileptic seizures, identified at general population level, in whom comprehensive clinical details have been obtained. Considerable emphasis in the design of the study was placed on avoiding the sources of selection bias, in the identification of the study group, and in obtaining comprehensive clinical data from primary and secondary care sources. The study has been uniquely successful in these regards.

A total of 1,195 patients was reported to the coordinating center and these were classified by a panel, as described previously.[12] Of these, 104 were excluded because of previously diagnosed epilepsy or neonatal seizures and 79 were diagnosed as having nonepileptic paroxysmal disorder, most commonly syncope or psychogenic episodes. A further 220 had febrile convulsions, and 198 had possible but not definite epileptic seizures. The remaining 594 patients were classed as having definite epileptic seizures and are included in this analysis. This represents a small increase in the number of definite cases of epileptic seizures in the NGPSE since previous reports[13,14] because of reclassification of some previ-

From the National General Practice Study of Epilepsy, Chalfont Centre for Epilepsy, Buckinghamshire, England.

Received December 30, 1991. Accepted for publication in final form March 12, 1992.

Address correspondence and reprint requests to Dr. M. Manford, NGPSE, Chalfont Centre for Epilepsy, Chalfont St. Peter, Gerrards Cross, Buckinghamshire, England, SL9 0RJ.

Table 1. Features of seizures attributable to different regions

Clinical pattern	No. (%)	Male (%)	Age mean (SD)	Definite etiology (%)	Probable etiology (%)	Seizure frequency A	B	C	D	E	F
Frontal	36 (22.5)	67	38 (27)	10 (28)	8 (22)	1	15	11	4	3	2
Central	52 (32.5)	52	41 (29)	21 (40)	5 (10)	3	23	15	1	2	8
Frontotemporal	9 (5.6)	33	46 (26)	1 (11)	4 (33)	0	4	1	2	0	2
Temporal	43 (27)	49	40 (20)	4 (9)	2 (5)	1	20	14	2	3	3
Parietal	10 (6.3)	20	43 (19)	4 (40)	0	0	5	1	1	2	1
Posterior	10 (6.3)	50	42 (18)	4 (40)	2 (20)	0	5	2	1	1	1
Total (%)	160	51	40.6	44 (27.5)	21 (13)	4 (2.5)	72 (45)	44 (27.5)	11 (6.9)	11 (6.9)	17 (10.6)

A Single seizure.
B Seizure-free (minimum, 2 yr).
C Rare seizures (<4/yr).
D Moderate frequency (5-12/yr).
E Frequent seizures (>12/yr).
F Unknown frequency.

Table 2. Abnormalities of investigations related to clinical patterns

Investigation	Clinical seizure pattern: Frontal	Central	Fronto-temporal	Temporal	Parietal	Posterior	Unlocalized
EEG							
Frontal	1	1	0	0	0	0	1
Central	2	5	0	0	0	0	0
Frontotemporal	0	0	1	0	0	0	2
Temporal	1	1	1	4	0	0	15
Parietal	0	0	0	0	1*	0	0
Posterior	0	0	0	0	1	1*	2
CT							
Frontal	4	2	0	2	0	0	4
Central	1	5	0	0	0	0	0
Frontotemporal	0	0	0	0	0	0	0
Temporal	0	0	1	1	0	1	0
Parietal	0	1	0	0	2	1	0
Posterior	2	1	0	0	0	2, 1*	1

* Investigation lateralized opposite to clinical localization.

ously uncertain cases in the light of new data. Seizures were classified by the study panel[12] into generalized and localization-related categories, according to the International League Against Epilepsy (ILAE) classification of epilepsies and epileptic syndromes.[15] This study concerns patients with clinical evidence of partial seizure onset, including both those whose seizures remained focal and those with generalization from a focal origin. These partial seizures were subdivided into six categories of regional onset, according to clinical manifestations, using criteria simplified from the ILAE classification of epileptic syndromes[15] and standard textbook descriptions[16] (appendix). Four were classical anatomic categories—frontal, temporal, parietal, and central sensorimotor—and two were "overlap categories": frontotemporal, including seizures with both frontal and temporal features that could not clearly be allocated to one anatomic region, and posterior, with combinations of features attributable to the occipital, parietal, or posterior temporal lobes. A random sample of 42 cases (16.7%) was reassessed by the same author and by another study member; an interobserver consistency of 95% and an intraobserver consistency of 90% were obtained.

Interictal EEG abnormalities and lesions on CT were related to these seizure patterns, to assess concordance between modes of investigation. EEG abnormalities were considered focal only if there was localized spike or sharp wave discharge; isolated slow wave abnormalities were excluded. Only where CT abnormalities were clearly focal, eg, tumor or focal atrophy, were they included. Where CT or EEG crossed anatomic boundaries, they were categorized into that region where the abnormality was maximal. Investigations were considered discordant where there was clear separation of different modalities, eg, a frontal lesion with a temporal seizure pattern, but not a parietal lesion with a posterior seizure pattern. In some cases, the clinical seizure pattern was unlocalized but EEG or CT strongly suggested a focal abnormality. These cases were not included in the clinically defined partial seizures, but are included in the analysis of investigative abnormalities as an important, "clinically unlocalized, localization-related" subgroup.

Etiologic factors were identified from the history or investigations and classified either as definitely signifi-

CT			EEG		
Performed (%)	Focal lesion (%)	Discordant (%)	Performed (%)	Focal abnormality (%)	Discordant (%)
15 (42)	7 (47)	2	23 (64)	4 (17)	1
22 (42)	9 (41)	1	23 (44)	7 (30)	1
6 (66)	0	0	6 (66)	2 (33)	0
30 (70)	3 (10)	2	38 (89)	4 (11)	0
6 (60)	4 (67)	0	7 (70)	2 (28)	1
7 (70)	5 (72)	1	10 (100)	1 (10)	1
86 (54)	28 (33)	6 (21)	107 (67)	20 (19)	4 (20)

cant, where there was clear causation, or as probably significant, where data were suggestive but not conclusive or of uncertain relevance. For example, remote cranial trauma was considered definitely significant where there was clinical or imaging evidence of permanent cerebral damage, but was considered probably significant where there was a history of skull fracture with transient neurologic impairment but of uncertain relevance where these factors were absent.

Seizure frequencies were measured for the latest available year of follow-up or for the entire follow-up period if survival was less than 1 year. Patients were classified as seizure free if there was a minimum of 2 years without seizures at latest assessment.

Results. *Clinical patterns.* The ILAE classification of the epilepsies and epileptic syndromes[15] was applied to the 594 patients with definite seizures (table 1). Two hundred fifty-two were classified as localization-related seizures on the basis of focal clinical manifestations, focal EEG or imaging abnormalities, or a clinical history suggesting focal cerebral pathology. This number differs slightly from the original patient categorization,[13] which was made before the syndromic classification of the ILAE.[15] One hundred eighty-seven suffered partial seizures and, of these, 142 had sufficiently characteristic clinical patterns to allow clinical localization, leaving 45 patients with evidence of partial seizure onset, which was too vague for seizure localization—eg, isolated head-turning or vague epigastric sensations. Many of these may have represented temporal lobe epilepsy, which is more difficult to localize clinically. A further 18 patients suffered secondarily generalized seizures with a localizable partial onset but no partial seizures, yielding a total of 160 patients with localizable seizure onset who form the basis of this analysis. Forty-seven patients had historical, EEG, or imaging evidence of focal cerebral pathology but only generalized seizures. A total of 92 patients, therefore, was placed in the "clinically unlocalized group," although having other evidence pointing to partial onset. In table 1 are the clinical characterizations of the 160 localizable patients: in 36 the evidence pointed to likely frontal onset, in 52 to central onset, in nine to frontotemporal onset, in 10 each to parietal and posterior onset, and in 43 to temporal onset. There were no differences in the age or sex ratios of the patients in each group.

Of the patients in the frontal lobe seizure group, 12 had seizures with prominent posturing, strongly suggestive of prominent supplementary motor area involvement, and the remainder (24) experienced combinations of complex motor activity, head version, and tonic and clonic features suggestive of other primary sites of frontal involvement. Temporal lobe seizures manifested as predominant olfactory or gustatory hallucination or both (seven patients), experiential phenomena (nine patients), abdominal manifestation or orofacial automatisms or both (10 patients), auditory hallucination (one patient), and combinations of the above in 16 patients. Parietal seizures manifested as localized paresthesias (four patients) or numbness or pain (three patients each). The frontotemporal group included combinations of autonomic manifestation, complex motor activity, and abdominal features (four patients), oroalimentary and complex motor activity (four patients), and vertigo followed by complex motor activity (one patient). Posterior seizures included two with unformed visual hallucinations and four each with formed visual and polymodal hallucinations.

Investigative abnormalities. Of the 160 patients with clinically localized seizures, 149 (93%) attended the hospital, 107 (67%) underwent EEG, 86 (54%) underwent CT, and 38 (24%) had neither test. Table 1 shows the number of patients in each group to undergo investigation and their results. Table 2 shows the relationship of clinical seizure pattern to investigative abnormality for those patients with focal abnormalities. Patients in the "clinically unlocalized group" with focal investigative abnormalities are included.

An EEG was available in eight of 12 patients with frontal lobe lesions on CT. In one of these, the EEG was discordant, colocalizing with the clinical pattern to the temporal region, and, in the others, EEG was not localizing. EEGs were present in three of the six patients with focal central lesions and were nonspecific in two, the third showing temporal spikes.

In seven patients, the EEG showed frontoparietal spikes, in five of whom a diagnosis of benign epilepsy of childhood with centrotemporal spikes was strongly suspected, on the basis of electroclinical pattern, although patients had not all undergone imaging or sleep EEG studies. In all three patients with temporal lobe lesions, EEGs were nonspecific. In two of the 10 cases with parietal or other posterior cortical lesions, the EEG lateralized opposite to CT and clinical pattern and was nonlocalizing in the other six in whom it was performed.

Etiologies (table 3). Overall, 32% of patients had a clear cause and 9.4% a probable cause for their

Table 3. Identified etiologic factors in seizures with different clinical patterns

Etiology	Seizure type					
	Frontal	Central	Fronto-temporal	Temporal	Parietal	Posterior
Vascular	4	16	2	2	2	2
Primary tumor	3	4	0	3	1	3
Secondary tumor	3	2	0	0	1	0
Infection	0	1	0	0	0	1
Acute trauma	1	2	0	0	0	0
Remote trauma	4	1	1	0	0	0
Congenital	2	2	1	0	0	0
Other	1	0	0	0	0	0
Unknown (%)	18 (50)	24 (46)	5 (55)	37 (86)	6 (60)	4 (40)

seizures. Figures were similar for different seizure patterns except in the temporal group (14%), in which there were fewer identifiable causes.

Mortality. Twenty-seven patients (16.9%), 11 female, died during the 3 to 7 years of follow-up; 18 clearly succumbed to the disease that also caused their seizures. The mean age of nonsurvivors (64.2) at presentation was higher than that of survivors (35.2). There were 11 deaths in the frontal group (30.6%), 11 in the central group (21.2%), three in the temporal group (7.0%), and one each in the parietal and posterior groups during the period of follow-up. The mortality was higher in the frontal and central groups than in the temporal group. The proportion of identifiable seizure etiologies in nonsurvivors was 85%, higher than in survivors, even controlling for the relative preponderance of frontal and central cases. Cerebral tumors and cerebrovascular disease were identified in 11 cases each.

Seizure frequency. Data of seizure frequency were available in 89.4% of patients (table 1). The pattern of seizure recurrence and frequency did not show any significant difference between the six clinical seizure locations; 45% experienced only one seizure or became seizure free and 27.5% suffered only rare seizures. Frequent seizures were seen in only 11 patients (6.9%). Four were due to cerebral tumor, one each to subarachnoid hemorrhage and hypertensive vascular disease, and five were of unknown etiology. Of the 27 patients who died during the follow-up period, three each (11.1%) had frequent or moderately frequent seizures, compared with eight each (6%) of survivors.

Discussion. We are aware of no other population-based prospective study of epileptic seizures to date that has addressed the question of seizure localization. This design would be expected to confer a different emphasis from previous studies, which have relied on retrospective diagnoses from EEG or specialist records, or, if prospective, have been hospital based.[17-23] In this partial seizure group, 93% attended the hospital. Many of these, however, particularly the elderly with known cerebrovascular disease, were managed by general physicians, without recourse to specialist investigations; other patients were managed by a variety of specialists (eg, pediatrics, geriatrics, psychiatry) and would not have been detected in a study selecting patients from neurologic or EEG department records. In hospital practice, moreover, patients' seizures may not be recorded as a separate diagnosis—for instance, if secondary to acute cerebrovascular disease. A major feature of the study design was the measures taken to avoid selection bias at all levels.

Clinical criteria formed the basis of seizure localization in this study. This is consistent with the emphasis of the ILAE classification on clinical seizure pattern and is most appropriate for epileptic seizures in the general population, with a low mean seizure frequency, although in tertiary referral practice, clinical analysis may be supplemented by other investigations.

Partial seizures were identified clinically in 31% of patients with definite epileptic seizures, compared with 15 to 38% in other studies.[17-21] Of partial and secondary generalized seizures with a localizable clinical onset, the proportion conforming to a frontal location was high: 22.5% consistent with pure frontal onset and a further 38% with frontoparietal or frontotemporal discharges. This contrasts with current opinion, suggesting that frontal seizures are relatively uncommon.[5] For this analysis, we selected only those patients with clearly focal manifestations, excluding 92 (36.5%) with localization-related seizures but clinically unlocalizable seizure onset. A number of sources of potential error exist; frontal motor phenomena are the most striking objective seizure phenomena and may mask more subtle, earlier manifestations, arising from other cortical sites, in some cases. Perhaps more importantly, temporal lobe epilepsy may present with subtle symptoms that are unlocalizable in this scheme leading to underrepresentation of this group. Conversely, in the current study, frontal lesions, demonstrated on imaging, presented with generalized seizures, a feature well known to be associated more commonly with frontal than extrafrontal lesions.[24] Moreover, the prominent motor effects of frontal seizures may also mimic generalized seizures, again leading to an underestimation of frontal seizures.

Of the 594 patients referred to the NGPSE, seizures without unequivocal focal or generalized features were seen in 190 and localization-related epilepsies without clear focal onset in a further 92 patients.

There was a trend for frontal lobe seizures to occur in younger, male patients but this did not approach significance. In Rasmussen's large series of refractory frontal epilepsy,[25] there was a high incidence of previous trauma, for which young men are at the highest risk. Although a history of significant trauma was elicited in only nine cases of the current series, five were frontal, three frontoparietal, and one frontotemporal. The etiology of seizures was recognized less frequently in patients in the temporal group than in the other groups. It is increasingly recognized that a substantial proportion of temporal lobe epilepsy may be due to mesial temporal sclerosis,[26] a pathology generally undetectable by CT, which may account for the low rate of detection and diagnosis in this group. With modern imaging techniques, especially MRI, the rate of detection of significant pathology is much greater.[27-29] The current study was undertaken before these MRI techniques were available and the proportion with mesial temporal sclerosis is, therefore, unknown.

The seizure frequency at latest follow-up was similar in all groups. Overall, 47.5% were seizure free at 2 years and only 11 (6.9%) had frequent seizures. In the six nonsurvivors with moderately frequent or very frequent seizures, the cause of death was also the cause of their seizures. This suggests there may be a group who develop severe seizures as part of their final illness, leaving an even smaller proportion of the general population with severe chronic epilepsy.

There was no evidence that chance of remission was any more likely in any of the groups. Hospital-based studies suggest that frontal lobe attacks tend to occur frequently, in clusters, and are particularly difficult to treat.[5-11,30] Our findings do not confirm this, and the hospital studies may show a selection bias to a particularly refractory subgroup rather than reflect frontal lobe epilepsy as a whole. Indeed, the response to treatment was generally excellent in all the partial seizure patterns, with many patients becoming seizure free—again in contrast to reports from hospital-based studies.

We also looked at the results of EEG and CT in this unselected population and at the relation of clinical features to focal findings on CT and EEG. Our findings need to be interpreted with caution since not all patients underwent investigation.

It is, however, intuitively likely that those selected for investigation would yield a higher incidence of abnormalities than the population as a whole, and this is supported by the finding that CT was performed in 54% of patients with newly diagnosed focal seizures, compared with 26% of patients with newly diagnosed generalized seizures.

Most studies[31-35] report rates of focal CT abnormality in partial epilepsy of 20 to 30%, but they have examined patients with chronic refractory seizures. In the current study, the overall yield of CT abnormalities was 35% of those with partial seizures who underwent CT. The high proportion of abnormalities probably represents patient selection. Also, our data are drawn from the general population presenting with a recent onset of seizures, a proportion of which represented obvious, de novo structural lesions that time would select out from studies of chronic refractory epilepsy.

The higher mortality in the frontal and central groups than in the temporal group is probably due to the higher proportion of identifiable pathology. Although mortality was lower in the parietal and posterior groups, in which major structural pathology was also frequently diagnosed, this may be a chance effect of smaller group size. The criteria for focal EEG abnormality were rigorous, with slow wave or other less specific abnormalities excluded, unless accompanied by spikes or sharp waves. (Temporal slow waves were frequently described in the absence of other abnormalities in a large number of patients in all groups.) The yield of focal abnormalities on interictal EEG in patients with clinically localized seizure onset was 18%, and was similar in all groups. However, a further 15 clinically generalized seizures were identified as localization related on the basis of focal temporal EEG abnormalities. Focal spike discharges gave a localization strongly at variance with the clinical picture in 20% of cases. Although of a community-based rather than a hospital-based patient group, our results are consistent with the limitations of the role of interictal scalp EEG in partial seizures. Most studies of scalp EEG localization have examined its value in refractory epilepsy, in which, compared against depth EEG, even ictal scalp EEG may miss up to 50% of focal epilepsies, particularly if there is secondary bilateral synchrony,[36-42] which is commonly seen in mesial frontal epilepsies. False-positive EEG results are also reported, especially from the frontal lobes.[43]

The high rate of discordance between the localization of clinical pattern and investigative abnormality may be giving important information regarding seizure mechanisms. The frontal lobe seizure pattern elicited from posterior cerebral tumors in two cases of this series (table 2) may represent the spread of discharges from an area that is either clinically silent or whose manifestations are purely subjective and masked by subsequent loss of consciousness and amnesia. Rapid seizure spread has been demonstrated experimentally with intracerebral recording in humans.[44,45] Occipitofrontal pathways are well described in humans[46] and are a likely substrate for seizure spread in this example. This study suggests that discordance among CT, EEG, and clinical seizure patterns may be a feature of epilepsy at all levels of severity and may not

be restricted to refractory cases seen in specialist centers, although it is clearly particularly relevant for those patients for whom epilepsy surgery is considered.

Appendix. Clinical criteria for seizure localization

Frontal	1. Seizures with focal, tonic or clonic motor activity, or posturing and sometimes nonspecific somatosensory manifestations, but no other experiential manifestations 2. Seizures constituting purely dystonic posturing 3. Seizures with prominent motor automatisms of the limbs, but no orofacial automatisms or experiential phenomena
Central	1. Focal clonic seizures with preservation of awareness 2. Focal simple clonic seizures, with either isolated motor activity or mixed sensorimotor effects, with jacksonian progression
Temporal	1. Seizures with prominent experiential phenomena, gustatory or olfactory hallucination 2. Seizures with arrest, absence, and oroalimentary automatisms
Frontotemporal	1. Seizures with combinations of manual and oroalimentary automatisms 2. Seizures with epigastric sensations, autonomic manifestations, and prominent motor activity
Parietal	1. Seizures with exclusively somatosensory manifestations, with or without jacksonian progression
Posterior	1. Seizures with polymodal sensory manifestations 2. Seizures with unformed visual, or complex visual, auditory, or somatosensory hallucinations
Unlocalized	1. Seizures with semiologic evidence of partial onset with features not attributable to a single cerebral region, eg, vague epigastric or cephalic sensations or isolated head-turning 2. Patients with historical or investigative evidence of partial seizure onset, but seizures appearing clinically generalized from the outset

Acknowledgments

We thank Action Research for grants in support of the NGPSE, Dr. David Goodridge of the NGPSE panel and Dr. A.L. Johnson of the NGPSE and MRC Biostatistics Unit for their support in the study, and the participating general practitioners,[12] without whom the study would not be possible.

References

1. Falconer M. Surgical treatment of drug-resistant epilepsy due to mesial temporal sclerosis. Arch Neurol 1968;19:353-361.
2. Jensen I. Temporal lobe epilepsy: etiological factors and surgical results. Acta Neurol Scand 1976;53:103-118.
3. Delgado-Escueta AV, Walsh GO. Type I complex partial seizures of hippocampal origin: excellent results of anterior temporal lobectomy. Neurology 1985;35:143-154.
4. Penfield W, Jasper H. Epilepsy and functional anatomy of the human brain. Boston: Little, Brown, 1954:350-388.
5. Williamson P, Spencer D, Spencer S, Novelly R, Mattson R. Complex partial seizures of frontal lobe origin. Ann Neurol 1985;18:497-504.
6. Fegerstein L, Roger A. Frontal epileptogenic foci and their clinical correlation. J Electrophysiol Neurophysiol 1961;13:905-913.
7. Waterman K, Purves SJ, Kosaka B, Strauss E, Wada JA. An epileptic syndrome caused by mesial frontal lobe seizure foci. Neurology 1987;37:577-582.
8. Delgado-Escueta A, Swartz B, Maldonado M, Walsh G, Rand R, Halgren E. Complex partial seizures of frontal lobe origin. In: Wieser H, Elger C eds. Presurgical evaluation of epileptics. Berlin: Springer-Verlag, 1987:267-299.
9. Quesney L, Krieger C, Leitner C, Gloor P, Olivier A. Frontal lobe epilepsy: clinical and electrographic presentation. In: Porter R, Mattson R, Ward A, Dam M, eds. Fifteenth international symposium of the epilepsies. New York: Raven Press, 1984:503-508.
10. Quesney L, Constain M, Fish D, Rasmussen T. Frontal lobe epilepsy: a field of recent emphasis. Am J EEG Technol 1990;30:177-193.
11. Quesney L. Seizures of frontal lobe origin. In: Meldrum B, Pedley T, eds. Recent advances in epilepsy, vol 3. Edinburgh: Churchill Livingstone, 1986:81-110.
12. National General Practice Study of Epilepsy and Epileptic Seizures (NGPSE): objectives and study methodology of the largest reported prospective cohort study of epilepsy. Neuroepidemiology 1989;8:221-227.
13. Sander J, Hart Y, Johnson A, Shorvon S. National General Practice Study of Epilepsy: newly diagnosed seizures in a general population. Lancet 1990;336:1267-1271.
14. Hart Y, Sander J, Johnson A, Shorvon S. National General Practice Study of Epilepsy: recurrence after a first seizure. Lancet 1990;336:1272-1274.
15. Commission on classification and terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389-399.
16. DeLorenzo R. The epilepsies. In: Bradley W, Daroff R, Fenichel G, Marsden CD, eds. Neurology in clinical practice. Boston: Butterworth-Heinemann, 1990:1443-1477.
17. Loiseau J, Loiseau P, Guyot M, Duche B, Darigues J-F, Aublet B. Survey of seizure disorders in the French southwest. I. Incidence of epileptic syndromes. Epilepsia 1990;31:391-396.
18. Shi-chuo Li, Schoenberg B, Chung-cheng Wang, Xue-ming Cheng, Bolis C. Epidemiology of epilepsy in urban areas of the People's Republic of China. Epilepsia 1985;26:391-394.
19. Hauser W, Kurland L. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975;16:1-66.
20. Gastaut H, Gastaut J, Goncalves e Silva G, Fernandez Sanchez G. Relative frequency of different types of epilepsy: a study employing the classification of the International League Against Epilepsy. Epilepsia 1975;16:457-461.
21. Granieri E, Rosati G, Tola R, et al. A descriptive study of epilepsy in the district of Copparo. Epilepsia 1983;24:502-514.
22. Gudmundsson G. Epilepsy in Iceland. Acta Neurol Scand 1966;43(suppl 25):1-125.
23. Juul-Jensen P, Foldspang A. Natural history of epileptic seizures. Epilepsia 1983;24:297-312.
24. Ketz E. Brain tumours and epilepsy. In: Vinken P, Bruyn G, eds. Handbook of neurology. Amsterdam: Elsevier,

1974;16:254-269.
25. Rasmussen T. Surgical therapy of frontal lobe epilepsy. Epilepsia 1963;4:181-198.
26. Convers P, Bierme T, Ryvlin P, et al. Brain magnetic resonance imaging (MRI) in drug-resistant partial epilepsy: a study of 100 patients with normal CT scans. Rev Neurol (Paris) 1990;146:330-337.
27. Franceschi M, Triulzi F, Ferini-Strambi L, et al. Focal cerebral lesions found by magnetic resonance imaging in cryptogenic nonrefractory temporal lobe epilepsy patients. Epilepsia 1989;30:540-546.
28. Cook M, Fish D, Shorvon S, Stevens J. The application of volumetric imaging to epilepsy surgery [abstract]. Br J Neurosurg (in press).
29. Jackson GD, Berkovic SF, Tress BM, Kalnins RM, Fabinyi GCA, Bladin PF. Hippocampal sclerosis can be reliably detected by magnetic resonance imaging. Neurology 1990;40:1869-1875.
30. Kanner AM, Morris HH, Lüders H, et al. Supplementary motor seizures mimicking pseudoseizures: some clinical differences. Neurology 1990;40:1404-1407.
31. Theodore WH, Dorwart R, Holmes M, Porter RJ, DiChiro G. Neuroimaging in refractory partial seizures: comparison of PET, CT, and MRI. Neurology 1986;36:750-759.
32. Schorner W, Meencke H, Felix R. Temporal lobe epilepsy: comparison of CT and MR imaging. AJR Am J Roentgenol 1987;149:1231-1239.
33. Kyoi K, Utsumi S, Sakaki T, Tada T, Miyamoto S. Relationship between CT findings and electrical focus in epileptic patients. Jpn J Psychiatry Neurol 1989;43:337-347.
34. Duncan R, Patterson J, Hadley D, et al. CT, MR and SPECT imaging in temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 1990;53:11-15.
35. Cordes M, Christe W, Henkes H, et al. Focal epilepsy: HM-PAO SPECT compared with CT, MR and EEG. J Comput Assist Tomogr 1990;14:402-409.
36. Spencer S, Spencer D, Williamson P, Mattson R. The localizing value of depth electroencephalography in 32 patients with refractory epilepsy. Ann Neurol 1982;12:248-253.
37. Engel J Jr, Rausch R, Lieb J, Kuhl D, Crandall P. Correlation of criteria used for localizing epileptic foci in patients considered for surgical therapy of epilepsy. Ann Neurol 1981;9:215-224.
38. Spencer S. Depth electroencephalography in selection of refractory epilepsy for surgery. Ann Neurol 1981;9:207-214.
39. Lieb J, Engel J, Gevins A, Crandall P. Surface and deep EEG correlates of surgical outcome in temporal lobe epilepsy. Epilepsia 1981;515-538.
40. Laws E, Niedermeyer E, Walker A. Diagnostic significance of scalp and depth EEG findings in patients with temporal and frontal lobe epilepsy. Johns Hopkins J 1970;126:146-153.
41. Tharp B. Orbitofrontal seizures: a unique electroencephalographic and clinical syndrome. Epilepsia 1972;13:627-642.
42. Rasmussen T. Characteristics of a pure culture of frontal lobe epilepsy. Epilepsia 1983;24:482-493.
43. Quesney L. Extracranial EEG evaluation. In: Engel J Jr, ed. Surgical treatment of the epilepsies. New York: Raven Press, 1987:129-166.
44. Kendrick J, Gibbs F. Interrelations of mesial temporal and orbital frontal areas of man revealed by strychnine spikes. Arch Neurol Psychiat 1958;77:518-524.
45. Spencer S. Cortical and intercortical seizure spread. In: Meldrum B, Ferrendelli J, Wieser H, eds. Current problems in epilepsy 6: anatomy of epileptogenesis. London: John Libbey, 1989:139-154.
46. Williams P, Warwick R, Dyson M, Bannister L, eds. Gray's anatomy. 37th ed. Edinburgh: Churchill Livingstone, 1989:1071.

Reprinted from NEUROLOGY, Volume 42, Number 10, October 1992

Journal of Neurology, Neurosurgery, and Psychiatry 1992;55:714–716

SHORT REPORT

Prolonged sensory or visceral symptoms: an under-diagnosed form of non-convulsive focal (simple partial) status epilepticus

M Manford, S D Shorvon

Abstract

Four patients had prolonged, sensory, simple partial seizures (SPS), lasting up to several days, without associated behavioural impairment. In three patients, the SPS often occurred as a prolonged "aura" before a more overt seizure. Descriptions included: "butterflies", rising epigastric sensation; "a thought in the stomach", and an olfactory sensation. Seizure localisation was frontal in one case, temporal in two cases and uncertain in one case. These sensations may represent an under-reported form of continuous, focal seizure activity, which arises from various cerebral regions.

(*J Neurol Neurosurg Psychiatry* 1992;55:714–716)

The epileptic aura is generally considered to be a short-lived phenomenon, representing the early stages of build up of abnormal, synchronous electrical activity. This usually develops further into a more obvious seizure or else halts abruptly, with reversion to the interictal state. We present four cases of prolonged, sensory SPS, without invariable ictal progression, presenting to us over the course of one year.

Case reports

Case 1: "Butterfly sensation"

This was a twenty three year old, right handed male motor mechanic. Complex partial seizures (CPS) first occurred when he was six years old, in association with fever and a head injury but they did not become regular until he was 10. They were frequently preceded, for up to two days, by a butterfly sensation, often felt in the abdomen but not specifically localised, which sometimes persisted after the seizure. Attacks were recorded with video-EEG-telemetry, before and after stereotactic EEG electrode insertion. They started with dizziness and pallor, followed by a single loud scream, abduction of his legs, bilateral upper limb posturing, then rocking movements and complex motor activity, for example, bicycling movements. After their recurrence, CPS occurred in clusters lasting up to one week, with a cluster often followed by a generalised tonic-clonic seizure (GTCS).

Ictal scalp EEG recording showed a 20 second build up of high amplitude sharp and slow waves, negative in the right frontocentral leads. Postictally the continuation of the butterfly sensation was characterised by a period of frontocentral, electrographic status epilepticus (figure). During this episode there was no objective behavioural abnormality.

Intracranial ictal EEG revealed a build up of spike and wave at the deepest medial frontal electrode, which spread to the rest of the frontal lobe, to the temporal neocortex and to the hippocampus. There were frequent, widespread, interictal spikes that were not clearly correlated with the butterfly sensation. He did not, however, experience such a prolonged feeling as during scalp recording.

He had right frontal lobectomy with intraoperative electrocorticography. The resected tissue showed histological evidence of a neuronal maturation defect. One year later, he had suffered a single cluster of seizures, and no further prolonged auras.

Case 2: "Thought in the stomach".

Case 2, a twenty five year old, right handed male motor mechanic had a normal neonatal and early childhood history. At five years of age he suffered a GTCS without obvious precipitant. He was treated with phenobarbitone, and had no further attacks until the age of eleven years, when he started to experience CPS. These started with an aura of a "thought in his stomach", lasting up to one minute. A brief speech arrest with blankness, was followed by hand rubbing automatisms, dysphasia and amnesia, lasting a few minutes. He was seizure free from 16–20 years of age, but seizures then recurred in the same pattern. When he was 24 years old, his medication was changed and his overt seizures ceased. However, at roughly monthly intervals (the same frequency as his seizures one year previously) he experiences the same sensation of a "thought in his stomach". This fluctuates over several days, not disappearing and not reaching the severity he associates with an impending attack. During this time he remains fully alert and able to carry out his normal work and duties.

Interictal EEG consistently showed mild sharp and slow wave abnormalities over the right anterior temporal region. CT and MRI were normal. We have not obtained an EEG during an aura.

Case 3: Epigastric sensation

This was a 36 year old right handed, male housing officer with a normal perinatal and

Institute of Neurology, National Hospitals for Neurology and Neurosurgery and The National Society for Epilepsy Research Group, Chalfont
M Manford
S D Shorvon

Correspondence to:
Dr Manford, Institute of Neurology, Queen Square, London WC1N 3BG, UK

Received 23 August 1991 and in revised form 11 November 1991. Accepted 20 November 1991

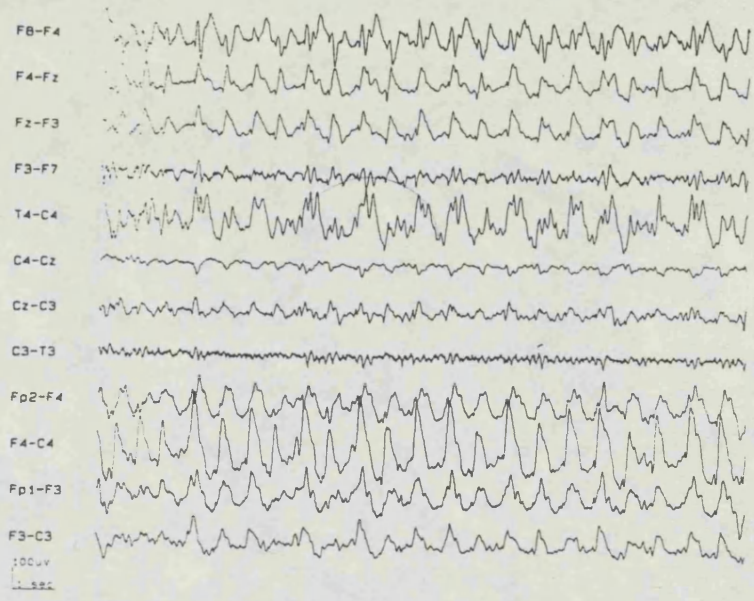


Figure 1 Case 1: Standard 10–20 scalp EEG during a prolonged epigastric sensation, showing rhythmical slow activity, predominantly in the right frontocentral leads.

early childhood history. Seizures started at the age of 18 and have been present once a week for the past 13 years. On the day he is due to have a seizure, he awakes with an epigastric sensation, which persists for hours and a few seconds before an attack, it rapidly rises to his chest. He shouts "Oh God" and is unaware for several seconds. There follows up to one minute of manual automatisms. Recovery occurs within two minutes, with no dysphasia. Sometimes the epigastric sensation persists after the seizure when he knows he will have a further seizure that day.

CT scan was normal but MRI, with planes orientated parallel to the long hippocampal axis, showed substantial loss of right hippocampal substance. Interictal EEG on a normal day showed diffuse delta and sharper components anteriorly with a left-sided preponderance. Video telemetry was performed: there was no EEG abnormality during an aura or a seizure, but postictally there was diffuse right sided slow activity.

Case 4: Olfactory sensation

A right handed 55 year old male electronics engineer had experienced occasional micropsia, with the illusion of progressive diminution of the size of objects since the age of four years. This lasted for two minutes, with no alteration of consciousness and was associated with a pleasurable sensation. Since 1984 he has suffered frequent, strong, olfactory hallucinations of a variable nature, but usually a chemical odour, resembling paint or hot oil. These would persist for several days with numerous exacerbations lasting up to 30 minutes. There have not been any more overt seizures and his work and concentration remain unimpaired.

Interictal EEG consistently showed a left-sided spike focus between the anterior and midtemporal regions, which did not change in association with the hallucinations. CT scan was normal but volumetric MRI showed reduction in volume of the anterior portion of the left hippocampus. Initial treatment with carbamazepine made no impact on his attacks, and subsequently phenytoin was only transiently effective.

Discussion

An aura represents a focal epileptic discharge, manifesting as a sensory SPS, which may progress to a more overt seizure. The first three cases clearly satisfy the International League Against Epilepsy criteria for an aura;[1] a stereotyped sensation, without impairment of consciousness, temporally closely related to seizures. The fourth is also epileptic in view of clinical features, EEG and MRI findings and response to anticonvulsants. They are, however, unusual in that the phenomena may persist for a considerable period without development of an overt seizure. This can be classified as "simple partial status epilepticus", non-convulsive as distinct from epilepsia partialis continua (EPC) or other motor seizure phenomena.

For case 1, the sensation was clearly associated with electrical seizure activity on surface but not on intracranial EEG. Up to half of auras may be missed on intracranial recording, probably because of the small volume of tissue sampled.[2,3] The diagnosis of an aura is clinical; not affected by the absence of localising EEG abnormality, either ictal (cases 3, 4) or interictal (case 2).[3,4]

Evidence for a frontal focus is strong in case 1, and cases 3 and 4 strongly suggest temporal lobe epilepsy. These results present evidence that prolonged, sensory SPS is not a property of a single cerebral region.

Psychomotor complex partial and focal motor status epilepticus are well accepted entities, but despite series amounting to thousands of cases with careful analysis of seizure semiology,[3,5,9] we have found few reports of sensory status epilepticus. Hughlings-Jackson[10] described a case in which: "sometimes when the attacks are about, she has a sensation of smell or of taste at the back of her throat, but

not in connection with her seizures". Penfield and Jasper[11] described a patient with a previous parietal injury who suffered continual tingling of the left foot for a week and recently, Sowa and Pituck[12] reported a case with weeks of continuous visual hallucination, accompanied by EEG abnormality and with no functional impairment. Our four patients were taken from our current clinical practice and we have seen others with a past history of a similar phenomenon, suggesting that this pattern of epilepsy may be more frequent than previously recognised. These patients with a prolonged, continuous SPS are distinct from others who experience frequent, brief auras before an overt seizure.

These symptoms represent continuous, highly localised seizure activity, manifesting as sensory or visceral symptoms, without spread to areas that would result in behavioural impairment. The subtlety of these symptoms, that they last longer than is usual for epileptic phenomena and that they are rarely accompanied by EEG change, probably explain why they are less frequently recognised than other forms of focal status epilepticus, for example, EPC or psychomotor. This may mean that a group of patients has undetected, mildly symptomatic, prolonged seizure activity; case 4 had symptoms from early childhood, but a diagnosis was only made in middle age.

Apart from patient 1, who also had severe complex partial seizures, all these patients were in employment and continuing to function normally in their social setting. This may therefore be a relatively benign form of prolonged seizure activity. If, as has been suggested, continuous, focal discharges are harmful to neurons in the long term,[13] then early identification and treatment of this group may prevent the development of a more intractable seizure disorder, and associated neuropsychological deterioration.

1 Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1981;**22**:489–501.
2 Sperling MR, Lieb JP, Engel J Jr, Crandall PH. Prognostic significance of independent auras in temporal lobe seizures. *Epilepsia* 1989;**30**:322–31.
3 Sperling MR, O'Connor MJ. Auras and subclinical seizures: Characteristics and prognostic significance. *Ann Neurol* 1990;**28**:320–8.
4 Janati A, Nowack WJ, Dorsey S, Chesser MZ. Correlative study of interictal encephalogram and aura in complex partial seizures. *Epilepsia* 1990;**31**:41–6.
5 Gowers WR. *Epilepsy and other chronic convulsive diseases: their causes, symptoms and treatment.* London: Churchill 1901.
6 Lennox WG, Cobb S. Aura in epilepsy; a statistical review of 1,359 cases. *Arch Neurol Psychiat* 1933;**30**:374–87.
7 Gupta AK, Jeavons PM, Hughes RC, Covanis A. Aura in temporal lobe epilepsy: clinical and electroencephalographic correlation. *J Neurol Neurosurg Psychiat* 1983;**46**:1079–83.
8 Taylor DC, Lochery M. Temporal lobe epilepsy: origin and significance of simple and complex auras. *J Neurol Neurosurg Psychiat* 1987;**50**:673–81.
9 Kanemoto K, Janz D. The temporal sequence of aura-sensations in patients with complex focal seizures with particular attention to ictal aphasia. *J Neurol Neurosurg Psychiat* 1989;**52**:2–56.
10 Selected writings of John Hughlings-Jackson vol 1. A Taylor, ed. London: Staples Press, 1958:385–405.
11 Penfield W, Jasper H. *Epilepsy and the functional anatomy of the human brain.* Boston: Little and Brown, 1954:395.
12 Sowa MV, Pituck S. Prolonged spontaneous complex visual hallucinations and illusions as ictal phenomena. *Epilepsia* 1989;**30**:524–6.
13 Rodin EA, Schmaltz S, Twitty G. Intellectual functions of patients with childhood onset epilepsy. *Dev Med Child Neurol* 1986;**28**:25–33.