Seizure 1996; 5: 7–33

Electrophysiological aspects of interictal and ictal activity in human partial epilepsy*

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Key words: partial epilepsy; interictal epileptiform discharges; dipole localization; spectral analysis; stereoencephalography; epilepsy surgery.

INTRODUCTION

Considerable attention has been paid in recent times to cellular and synaptic mechanisms involved in epileptogenesis. A number of in vivo and in vitro animal models are now available to study basic mechanisms of epileptogenesis and to select and evaluate antiepileptic compounds which could be potentially effective in human epilepsy. Although this approach has been useful for practical purposes, conceptual implications of epileptogenesis and neurophysiology in general, there is still a gap in the understanding of human epilepsy in the light of basic mechanisms of epileptogenesis. This appears to be particularly true for partial epilepsy since animal models are usually generated by environmental factors which are not common causes of partial epilepsy in humans and cellular aspects of human epileptogenesis have only been studied in very particular circumstances[1–3].

The chronic implantation of intracranial electrodes in epileptic patients being assessed for surgery allows the study of ictal and interictal electrical activity from regions which are usually inaccessible to scalp recordings. Apart from their primary purpose in the localization of epileptic foci, the study of human intracranial recordings can provide an insight into some electrophysiological aspects of human epileptogenesis and provide a bridge between the reductionist approach of cellular animal studies and the non-invasive approach of more standard electrophysiological studies in humans. A particularly important problem in human partial epilepsy is the identification and delimitation of the epileptogenic zone (that region of tissue the removal or transection of which is both necessary and sufficient to abolish seizures) and the identification of propagation pathways of epileptiform activity. This has important practical implications in the surgical treatment of epilepsies and the evaluation of alternative techniques recently developed for the non-invasive localization of epileptic foci [magnetoencephalogram (MEG), positron emission tomography (PET), quantitative electroencephalogram (EEG)], in addition to more theoretical implications in the classification of epilepsies and in the understanding of human epileptogenesis.

In the present work, ictal and interictal intracranial recordings from human patients with partial epilepsy have been studied in order to estimate:

(a) the extent and topography of the epileptogenic zone;

(b) the mechanisms involved in the propagation of ictal and interictal discharges;

(c) the topological relationships between interictal and early ictal activity;

(d) the potential value of MEG and non-invasive EEG in the localization of epileptogenic foci in surgical assessment.

Results are discussed with reference to neurophysiological mechanisms involved in human partial epilepsy and their relevance to epilepsy surgery and compared with previous reports on animal models.

Interictal activity

The interpretation of intracranial recordings usually concentrates on the onset and propagation of ictal events (for reviews, see for instance Wieser, 1988[4] or Spencer, 1988[5]). However, interictal paroxysmal events (spikes and sharp

* This paper was the winning entry in the Gowers Prize 1994 (Young Physician) competition.

1059-1311/96/010007 + 27 $12.00/0

waves) are recorded from both deep and superficial structures. The analysis of scalp interictal activity has been suggested as an alternative to intracranial recordings, largely on the assumption that synchronized neural activity remains localized during interictal paroxysms. Accordingly, the electric and magnetic fields generated at the scalp by interictal epileptic activity have been analysed by a number of authors in order to localize epileptogenic foci[6–10]. The models often assume that cellular currents produced by synchronized neuronal activity (primary or impressed currents) generate an electromagnetic field which in turn induces secondary currents in the surrounding conducting medium (volume currents). In principle, both impressed and volume currents can contribute to the scalp electric and magnetic fields EEG and MEG). Several algorithms have been developed to localize the impressed currents from scalp EEG or MEG measurements. Most methods model the impressed current as a current dipole or a restricted number of dipoles[11–13].

Source localization by means of scalp EEG modelling has now been used for over 15 years, but has never become a standard clinical tool. One reason is that volume currents resulting from inhomogeneities in medium conductivity or differences between the assumed geometrical head model and the real head shape can smear or displace source localization. It can be demonstrated that, in a spherical conductor, the component of the external magnetic field normal to the surface does not contain contributions from volume currents (Sarvas, 1987). This has motivated several investigators to evaluate interictal MEG recordings as a non-invasive alternative to deep recording for localizing epileptogenic foci during preoperative assessment. Various publications have claimed that scalp MEG can be successfully used for this purpose[6,7,10,14]. Nevertheless, Cohen *et al.*[15] found that EEG and MEG achieved similar accuracy in localizing current dipoles generated by intracranial electrodes implanted in patients[15]. This finding has triggered a lively discussion among MEG researchers[16].

Surprisingly, although theoretical physical models of interictal activity have been thoroughly discussed, the neurophysiological mechanisms involved in interictal phenomena in humans and their relations to ictal events are little understood. Moreover, a neurophysiological understanding of interictal activity would be highly useful to the clinician, not only because of the potential relevance of scalp EEG and MEG activities in non-invasive surgical assessment, but more generally as most electroencephalographic studies carried out on patients with epilepsy are based on interictal recordings.

In the present study I have analysed human interictal activity recorded simultaneously by surface electrodes and deep electrodes situated in or near mesial temporal structures and sometimes in the frontal lobe. Three main aspects of interictal activity are addressed: (a) the degree of confinement of neural activity during interictal paroxysms, (b) the degree to which instantaneous volume conduction (electromagnetic propagation) and neural conduction contribute to the propagation of interictal activity, and (c) the topographical relationship between interictal and early ictal activity. I will discuss the complexities of interictal events, their influence in the localizing capabilities of scalp recordings, and comment on the most appropriate mathematical models for the source.

Ictal activity

A successful outcome of resective epilepsy surgery depends on the localization of nervous tissue which is structurally and functionally abnormal. Recent developments of medical imaging provide powerful means to localize structural lesions. However, the need for identification of functional abnormalities still requires electroencephalographic recordings and sometimes intracerebral, stereoelectroencephalographic (SEEG) recordings of seizure onset. The success of these surgical procedures depends on the identification of an 'epileptogenic zone' which is defined as that region of tissue the removal (or transection) of which is both necessary and sufficient to abolish seizures[17]. Various dysfunctional regions may be distinguished in partial epilepsy: (1) the irritative zone, or area of interictal epileptiform activity, (2) the ictal onset zone, the site of the first electrophysiological changes at seizure onset, and (3) the ictal symptomatogenic zone from which clinical ictal phenomena arise. The concept of an epileptogenic zone is purely theoretical at present, since no agreed criteria exist to identify it preoperatively. It is assumed, however, that the epileptogenic zone includes the ictal onset zone and that the location of the latter is therefore an important consideration in planing a proposed resection. Where the site of seizure onset cannot be confidently predicted from the scalp EEG or other evidence, it may be necessary to locate it directly by intracranial recordings, and sometimes

with intracerebral electrodes implanted into candidate sites of the ictal onset zone. When recorded by intracranial electrodes, seizure onset in partial epilepsy may be characterized by various focal electroencephalographic changes: high frequency (multiunit) activity, bursts of irregular sharp and slow waves, spike-wave activity, electrodecremental event and rhythmic sinusoidal activity. Such focal patterns can be seen for several seconds before secondary ictal generalization. SEEG patterns at seizure onset have been found to correlate with specific pathology[18,19] and it has been suggested that the different morphologies of SEEG seizure onset have different degrees of localizing value[18,20] or may be related to the topography of the epileptogenic zone[21,22]. Nevertheless, whether specific patterns characterize the electrical activity of different ictal onset of epileptogenic zones is unknown, and the usual practice is to assume that the ictal onset zone corresponds to the site where the first focal electrical changes are detected, irrespective of their morphology, provided that these take place before any clinical manifestations. However, focal electrical changes at seizure onset may be subtle and difficult to identify by eye. For instance, high-frequency activity (HF) at seizure onset can be difficult to detect due to its low amplitude relative to other components. Furthermore, seizure onset in partial epilepsy is often associated with widespread or generalized changes, and these too may be subtle. In particular, a widespread reduction in the amplitude of electrical background activity (electrodecremental event, EDE) may be recorded for several seconds before or at the onset of focal ictal changes. It can be difficult to distinguish by visual inspection a significant electrodecremental event from the spontaneous fluctuations of amplitude which occur in the interictal record. These subtle early electrical changes often take place within a specific frequency band and can best be identified by restricting the signal to the frequency band of interest, either through signal filtering or through appropriate manipulations of the Fourier transform. Conventional EEG and EEG spectral analysis have been found to be of similar sensitivity and mutually complementary in detecting focal abnormalities of the background activity in patients with focal brain lesions[23]. Binnie *et al.*[24] found spectral analysis to be more sensitive when combined with a non-linear pattern recognition method. However, signal analysis has seldom been used in the detection and quantification of subtle electrical changes at seizure onset in the SEEG. Gotman *et al.*[25] have recently proposed a method for displaying changes in amplitude and average frequency to characterize seizure onset, and Darcey and Williamson[26] described a statistical technique to identify seizure onset based on the preictal/ictal ratio of the EEG power, particularly in the 8–30 Hz frequency band, and found good correspondence between automatic and conventional visual analysis, but the validity of either method as measured by surgical outcome was not reported.

In the present study I have combined visual assessment of raw EEG traces and changes in several variables of the power spectrum at seizure onset. The several spectral features used (see methods) were evaluated as means of detecting subtle electroencephalographic changes, particularly electrodecremental events and low-amplitude high-frequency activity. The presence and topography of different electrical patterns recorded early during seizures (i.e. before secondary generalization of ictal discharges) by intracerebral and subdural electrodes has been correlated with surgical outcome in 15 patients with partial epilepsy of suspected temporal origin.

METHODS

Interictal activity

Intracranial and scalp EEG recordings of interictal events from 12 patients under telemetric presurgical assessment for epilepsy surgery have been studied. Patient ages were between 22 and 45 years (mean, 29.7).

Patient selection

All patients suffered from partial epilepsy refractory to medical treatment, had complex partial seizures, and were not considered candidates for hemispherectomy, callosotomy or for 'lesionectomy' (on grounds of lack of a discrete lesion on neuroimaging at a site concordant with clinical, interictal EEG and neuropsychological findings). At our centre, 74% of patients referred for epilepsy surgery fall in this category and undergo telemetry with intracranial foramen ovale (FO) electrodes. Failure to demonstrate a probable temporal ictal onset zone or non-convergence between different sources of evidence concerning the likely source of seizures leads to further investigation by stereoelectroencephalography

(SEEG). For a more detailed account of considerations which presently lead to selection for intracranial recordings, see Binnie *et al.*[27].

Recording protocols

(a) Patients with scalp and foramen ovale (FO) electrodes (six patients): a flexible bundle of six electrodes was inserted bilaterally through the FO under fluoroscopic control[28]. Each electrode consisted of a 0.1 mm stainless steel isolated wire with a 5 mm recording contact. The centres of contacts from contiguous electrodes were located 15 mm apart along the bundle. Electrodes in the same bundle are labelled from 1 (the most superficial contact) to 6 (the deepest contact). Postinsertion radiography was performed to confirm that the FO electrode was lying between the mesial aspect of the temporal lobe and the brainstem. A full set of standard EEG electrodes was attached to the scalp according to the Maudsley System, which provides a more comprehensive coverage of the temporal regions than does the standard International 10/20 System[29]. Telemetry which included simultaneous FO and scalp recordings was started less than 36 hours after FO electrode implantation and continued for 1–2 weeks.

(b) Patients with subdural and intracerebral electrodes (six patients): bilateral frontal trephine holes were made to implant subdural seven-electrode bundles along the orbital frontal, lateral frontal, anterior temporal, mid-temporal and posterior temporal surfaces of both cerebral hemispheres under radiographic control. Each subdural bundle had a 0.4 mm diameter and comprised seven electrodes consisting of 0.1 mm stainless steel insulated wire. Contacts from contiguous electrodes were 5 mm long and their centres were situated 15 mm apart within the bundle. Each intracerebral bundle was 0.4 mm thick and contained six electrodes of similar physical characteristics. Contacts from the three distal electrodes (numbered 6, 5 and 4) were 2.5 mm long and their centres were located 5 mm apart along the bundle. Contacts from the three proximal electrodes (numbered 3, 2, and 1) were 5 mm long and their centres were situated 10 mm apart along the bundle. Intracerebral electrodes were bilaterally implanted under CT control in amygdala, anterior and posterior hippocampus, and occasionally in the mesial frontal regions. For details see Van Veelen *et al.*[30] and Agbi and Polkey[31]. Telemetric recording from intracerebral and subdural electrodes commenced 3–7 days following implantation and continued for up to 3 weeks. Scalp EEG was recorded in one patient simultaneously with intracerebral and subdural recordings in order to estimate the signal attenuation produced by the skull and scalp.

Although FO electrodes are subdural electrodes in the sense that they are immersed in the subdural space, they supposedly record from deep (mesial temporal) structures. Therefore I will group FO and intracerebral electrodes as 'deep electrodes' in order to simplify terminology in this dissertion. I will generically designate scalp electrodes in patients with FO insertions and subdural electrodes in patients with intracerebral electrodes as 'surface electrodes', since they lie over the convexity of the neocortex.

Recording system and analysis

Cable telemetry of 32 or 64 channels was used for data acquisition (Telefactor Beekeeper system). Data were digitalized at 200 Hz and band filtered (high pass cutoff frequency at 0.3 Hz and low pass cutoff frequency at 100 Hz). The system input range was 2 millivolts and data were digitalized with a 12 bit analogue-to-digital converter, i.e. an amplitude resolution of 0.488 μV. All data were recorded as common reference. Pz was used as common reference during display of data from patients with FO electrodes. For data display from intracerebral electrodes the selection of the reference varied, but was usually a remote scalp reference. Sections of 10–20 minutes of interictal recordings from each patient were transcribed onto hard disk and paper. The topography and waveform of interictal events occurring within the transcribed sections were studied visually by the author (a total of 651 events) and 45 spikes and sharp waves were selected for computer analysis. Although most patients showed more than one type of interictal events regarding waveform and spatial distribution, all events selected for computer analysis fulfilled two criteria: (a) they appeared as sharp spikes or spikes in at least one of the recording sites, i.e. events consisting solely of a paroxysmal burst of slow activity, with no spike component in any recording channel, were discarded, (b) they occurred relatively frequently with consistent waveform and topography within each patient.

Selected channels were expanded in time and amplitude for display (Fig. 1). Cursors running through the data were used to measure latency and amplitude differences between channels. Statistical dispersion is given as standard deviation in all cases. Approximate surface amplitudes produced by dipole currents located in mesial

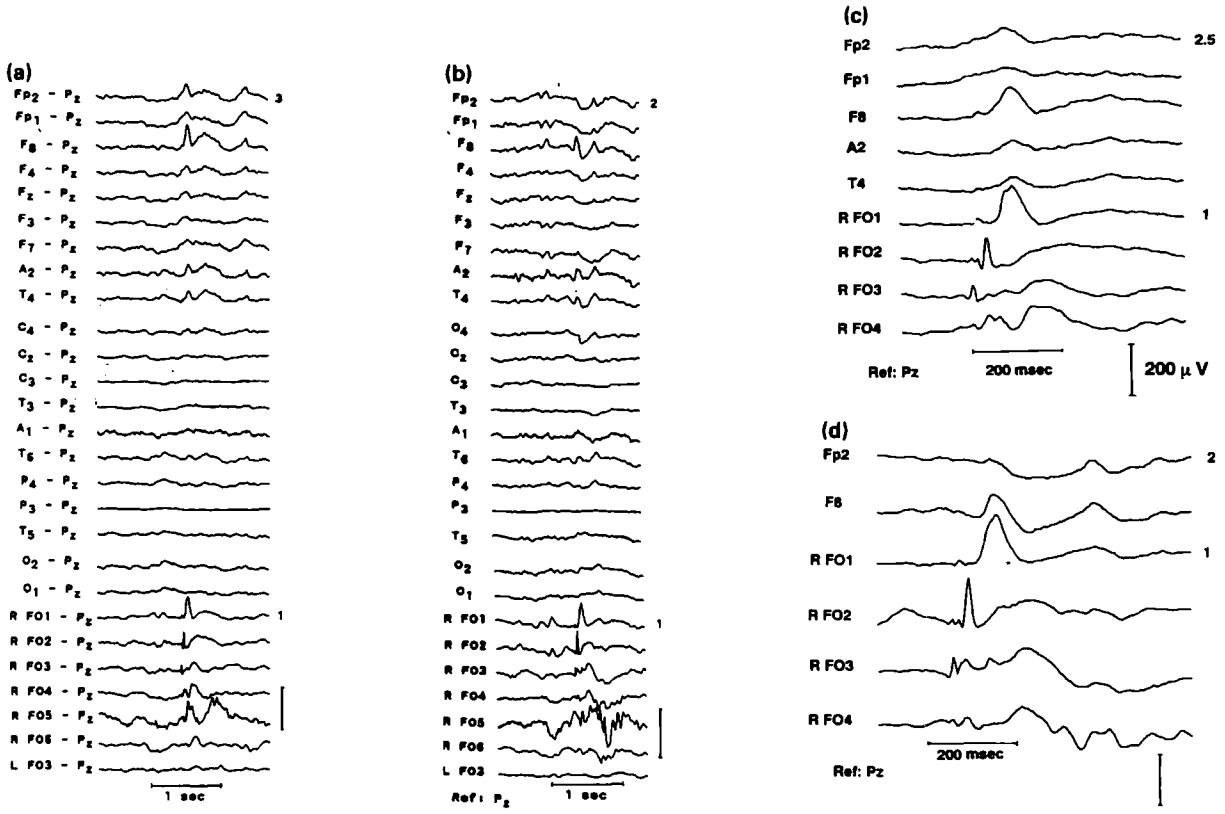


Fig. 1: Propagation of interictal activity along the mesial aspect of the right temporal lobe in patient 7. A and B, Scalp and FO recordings of two examples recorded in the same patient. C and D, Same events on expanded time scale. The events increase in amplitude and in duration as they propagate, presumably recruiting more neuronal activity for longer time. On the scalp the signal is recorded with largest amplitude at F8 but also at Fp2, A2, and T4. The spike at RFO2 takes place 40 ms after the initial spike at RFO3. Note the striking similarities between recordings at F8 and RFO1. Both electrodes record mainly a high amplitude sharp wave in the alpha range (9 Hz) with a 105 ms delay with respect to the initial RFO3 spike. Electrodes RFO1 and F8 are about 4 cm apart and show nearly the same trace, regardless of different amplitudes probably due to bone attenuation. On the contrary, RFO2 and RFO3 are 1 and 2.5 cm apart from FO1 and all three show different waveforms. Note that the main deflections on RFO2, RFO1 and F8 are preceded by small amplitude deflections. RFO2 spike is preceded by a low amplitude rhythm which starts simultaneous to RFO3 spike. RFO1 and scalp main deflections are preceded by a low amplitude notch which takes place 15–20 ms after RFO3 spike. Numbers to the right of traces indicate the relative display gain for the corresponding channels and the ones below. Calibration marks correspond to 400 μV in A and B, and 200 μV in C and D, in the channels with relative gain of 1.

temporal structures have been estimated for an unbounded homogeneous medium (formulae 12 and 13, Sarvas[32]), with conductivities for grey and white matters given by Barber and Brown[33].

Ictal activity

Seventy-eight intracranial ictal EEG recordings have been studied from 15 patients undergoing SEEG studies as part of a presurgical assessment for epilepsy surgery. Patient ages were from 11 to 55 years (mean, 29.3).

Patient selection

All patients had satisfied criteria for FO recordings, as stated above. However after ictal recordings with FO electrodes the site of seizure onset remained in doubt, due either to an inconclusive result of the FO studies or because of non-concordance of evidence from different sources concerning localization. At our centre, 12% of patients referred for epilepsy surgery fall in this category. For a more detailed account of considerations which presently lead to selection for SEEG, see Binnie *et al.*[27]

Recording protocols

Bilateral frontal trephine holes were made to implant subdural and intracerebral electrode bundles as described above regarding methods for interictal activity.

Recording system and analysis

Methods of recording and display were as for interictal SEEG studies (see above). Sections of several minutes of ictal and preictal recordings (including at least 1 minute preictally) for each seizure were transcribed onto hard disk files and paper. Data saved with each EEG sample included the time of the day when the sample was taken.

For each seizure file, the Fast Fourier Transform (FFT) was then calculated for each channel for consecutive 1.28 second epochs (256 samples) on an IBM compatible personal computer with software developed in QuickBASIC. These parameters provided a frequency resolution of 0.78 Hz within each epoch. FFT calculations and storage took about 1 second per epoch per channel on a 386 20 MHz microprocessor. FFTs from each seizure file were saved onto optical disks. Specific variables were then extracted from the FFT for each seizure and channel, and the time course of these variables was displayed from at least 1 minute before ictal onset as assessed by visual inspection of the traces and/or clinical signs. Epochs within which values of the displayed variable differed by more than 0.6 standard deviations from the average of preictal epochs (usually the first 75 epochs) were identified on the display with an underlying dot (as shown in figures). Cursors running through the data allowed the identification of the time when the first sample of each epoch was taken, and therefore allowed correlation between the time course of the extracted variables and the raw EEG data with a precision of ±600 milliseconds.

Variables systematically extracted from the FFT included:

(a) the total amplitude of the signal within specific frequency bands, calculated as the integration (summation) of all frequency components within the given frequency band. The frequency bands used were: 2–4 Hz, 4–8 Hz, 8–12 Hz, 12–20 Hz, 20–30 Hz, 30–40 Hz, 40–49 Hz, 51–60 Hz, 60–70 Hz, 70–80 Hz, 80–90 Hz and 90–100 Hz.

(b) Activity, mobility and complexity[34] within the following frequency bands: 2–100 Hz and 2–40 Hz. Activity was calculated as the spectral moment of order 0 and represents the amplitude variance in the time domain or the integration of the power spectrum in the frequency domain. Its square root is an estimate of the RMS amplitude of the signal and therefore has an interpretation equivalent to that of the total amplitude within the same band. Mobility was calculated as the square root of the ratio between spectral moments of order 2 and 0, and represents the mean frequency of the power spectrum. Mobility gives an indication of how much the frequency components of the signal depart from 0 and has physical dimensions of frequency. Complexity was calculated as the ratio of the square root of the ratio between spectral moments of order 4 and 2, and the mobility. Complexity is a dimensionless parameter whose minimum value of 1 corresponds to a pure sine wave. Higher values reflect the deviation of the waveform from a single sine wave and indicate the presence of a scatter of frequencies due, for instance, to whitening of the spectrum.

RESULTS

Analysis of interictal activity

Types of interictal activity according to spatio-temporal distribution

Consistent patterns of interictal activity were classified according to the morphology and spatio-temporal distribution of interictal events across deep and surface recordings. Five distinct types of interictal activity emerged and have been described in detail elsewhere[35]. In summary, interictal events were classified in: (a) events recorded only by deep electrodes [deep only (DO), Figs 2 and 3] observed in 11 patients, (b) events recorded in depth and surface with no latency differences [synchronous (Synch), Figs 2 and 4] observed in 11 patients, (c) events which showed latency differences of 10–50 ms between different recording sites [short latency (SL), Fig. 3] present in nine patients, (d) events which showed latency differences larger than 50 ms between different recording sites [long latency (LL), Figs 1 and 5] present in six patients, (e) events recorded only by subdural or scalp electrodes [surface only (SO), Fig. 6] observed in two patients. More than one type was usually present in any one patient.

Complex mixtures of the types described above were often found within the same interictal event. For instance, different ranges of latency differences were often found between deep and surface recordings, among deep recordings or among surface traces (Figs 5 and 6). A more detailed account of the different types of spatio-temporal relations present in each patient and the topography of ictal onset has been published elsewhere[35].

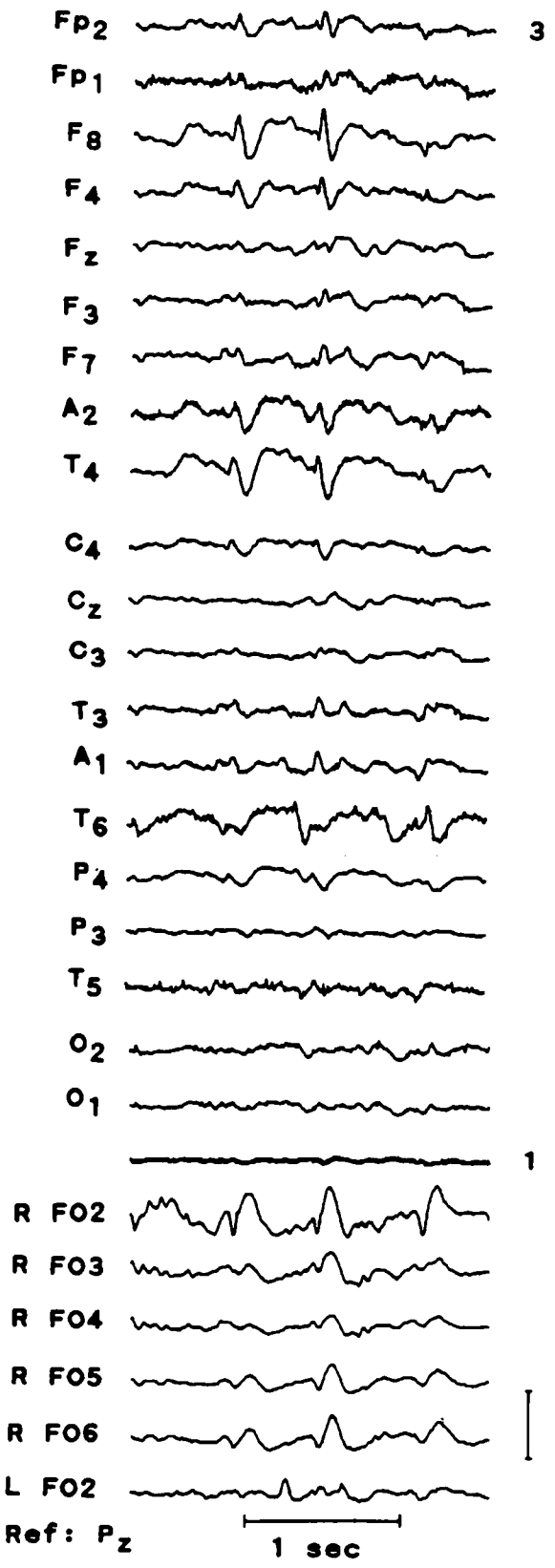


Fig. 2: Examples of DO and Synch interictal activity in Patient 3. Three spikes are successively recorded in the right FO contacts. The first two are associated with a clear spike and wave on the scalp and there are no time delays between FO and scalp spikes (Synch). The third spike is not associated with a clear scalp correlate (DO). Note that the first and third spikes show completely different scalp activity even though their spatial and temporal distribution in the FO electrodes are nearly identical. The calibration mark corresponds to 800 μV in channels of relative gain of 1.

Amplitude distributions in depth and on surface

Interictal spikes showed average maximal amplitudes of $595 \pm 263\,\mu V$ when recorded by intracerebral electrodes, $590 \pm 338\,\mu V$ by FO electrodes, $514 \pm 304\,\mu V$ by subdural electrodes and $186 \pm 84\,\mu V$ on the scalp. In any one event recorded at both surface and depth contacts, the ratio of subdural to depth amplitudes was 0.86 ± 0.27 and the ratio of scalp to FO amplitudes was 0.35 ± 0.17. One patient was studied simultaneously with depth, subdural and scalp electrodes over the temporal regions. Interictal spikes of the same polarity and frequency characteristics (apart from superimposed muscle activity) were recorded by subdural and scalp electrodes in this patient, and the ratio of scalp to subdural amplitudes was 0.22.

Laterality correlations between surface and depth within the same event

Of all events recorded by surface electrodes, the majority (87.6%) were unilaterally recorded by surface electrodes and ipsilateral deep electrode(s), regardless of whether the FO or intracerebral recording protocol was used. In only 0.87% of all events was the surface activity recorded exclusively contralateral to deep activity. In 3.14% of events activity was unilateral in deep electrodes and bilateral on the surface. In 3.9% of the events, activity was recorded bilaterally in deep electrodes and unilaterally on the surface and in 4.3% of events activity was recorded bilaterally by deep and surface electrodes.

Dipolar distribution in the depth

Patient 1 frequently showed phase reversals between two consecutive intracerebral channels, which suggested the existence of a single dipole generator adjacent to the intracerebral electrodes, i.e. interictal spikes recorded with opposite polarity by two continuous intracerebral contacts

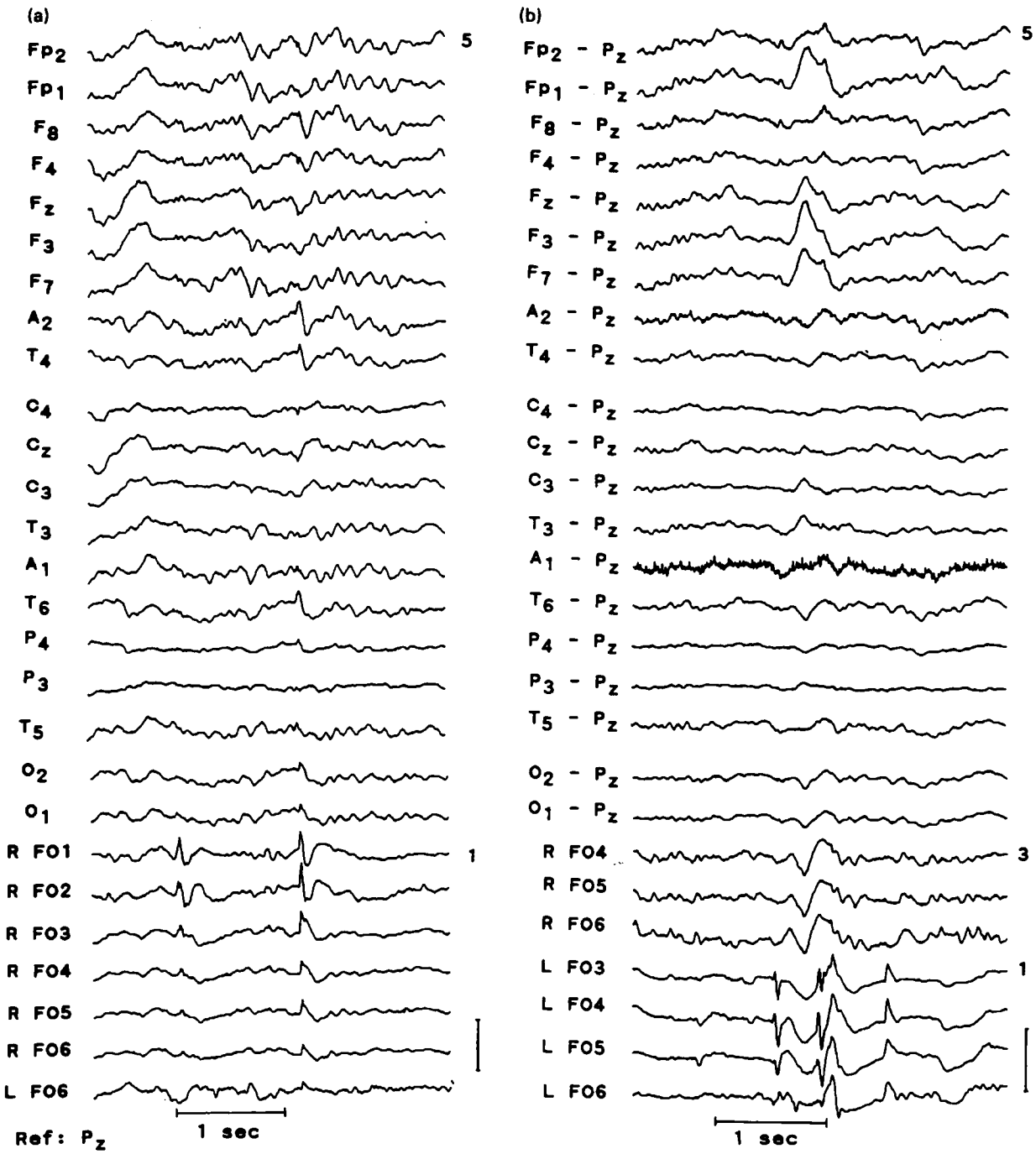


Fig. 3: Two types of interictal activity in Patient 6. A, Example of DO and SL interictal activity: spikes on the scalp (A2, T4 and T6) show 15–20 ms delays with respect to RFO1 and RFO2. Note there is a first spike involving RFO1 and RFO2, associated with no obvious scalp epileptiform activity, and with amplitude in the same range as the second, SL spike. B, Type LL interictal activity: spikes in deep contacts are followed by ipsilateral frontal slow waves. Note that surface recordings show a small notch nearly simultaneous to spikes in the FO electrodes. Careful latency analysis however showed 20 ms delays between FO spikes and scalp notches. Note that FO spikes in the same range of amplitudes can be associated with no deflection, a small deflection or a proper spike on the scalp. Calibration marks correspond to 1 000 μV in channels of relative gain of 1.

and decreasing in amplitude with distance. Subdural electrodes never recorded interictal activity associated with these events. These spikes showed largest amplitude at the left anterior hippocampus contact 5, with typical peak amplitudes of around 500 μV with respect to a remote scalp reference. They were recorded with opposite polarity and half the amplitude (about 250 μV) at contact 6, situated 2.5 mm inferior to contact 5.

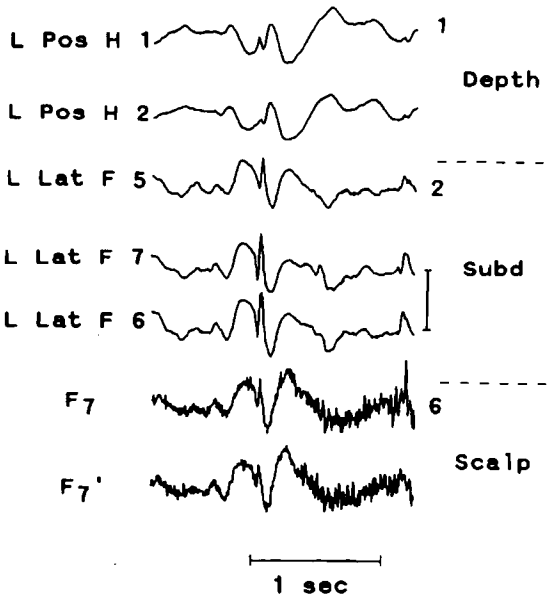


Fig. 4: Example of Synch interictal activity (Patient 2). Synchronous events in scalp, subdural and depth recordings. All channels which record the event show the same components although with different amplitude and/or polarity. The calibration mark corresponds to 1 000 μV in channels of relative gain of 2.

Correlation between interictal and ictal foci

The relationships in topographies of ictal onset foci and interictal foci (sites where interictal spikes were recorded) were studied. In all patients where a single ictal onset zone was found in the depth (five patients with intracerebral electrodes and two with FO electrodes) the electrodes which recorded the onset of ictal activity also recorded frequent interictal spikes. However, in all seven patients there were also frequent independent interictal spikes in at least one deep electrode contralateral to the site of seizure onset. Surface interictal events could be associated with any of the deep interictal foci, regardless of their capacity to trigger seizures. In three patients, surface interictal spikes which were recorded independently on either side had associated activity recorded at the ipsilateral deep electrodes. In three patients only the deep interictal spikes which were observed at the site of seizure onset were associated with interictal activity on the surface. However, in one patient, interictal events recorded by surface electrodes were associated with spikes recorded only by deep electrodes contralateral to the ictal onset zone, even though frequent interictal spikes were recorded independently by deep electrodes at the ictal onset zone.

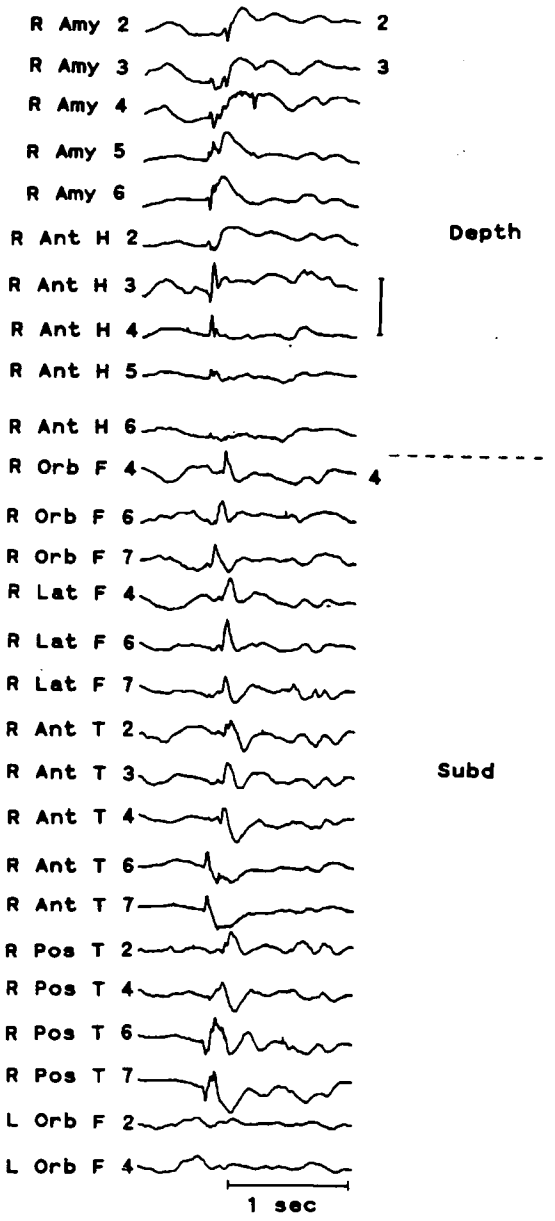


Fig. 5: Neocortical propagation of interictal activity (Patient 11). Polymorphic spikes recorded in right amygdala and anterior hippocampus show synchronous onset. Negative spikes are recorded by anterior temporal subdural electrodes, simultaneous to positive spikes in posterior temporal regions, with no significant delay with respect to deep spikes. However, delays of over 200 ms are present in spikes/sharp waves recorded in the lateral and orbital aspects of the frontal lobe and in the superior contacts of the anterior and posterior temporal electrodes, which are possibly lying over parietal regions. Note how a wave of activity propagates along the orbito frontal contacts and the anterior temporal contacts 4 to 2, providing evidence for intraneocortical propagation of epileptiform activity. All waves of delayed activity are preceded by small amplitude notches of variable delays. Note that spikes recorded by depth electrodes show shorter duration and higher frequency components than activity recorded by subdural electrodes. The calibration mark corresponds to 800 μV in channels of relative gain of 3.

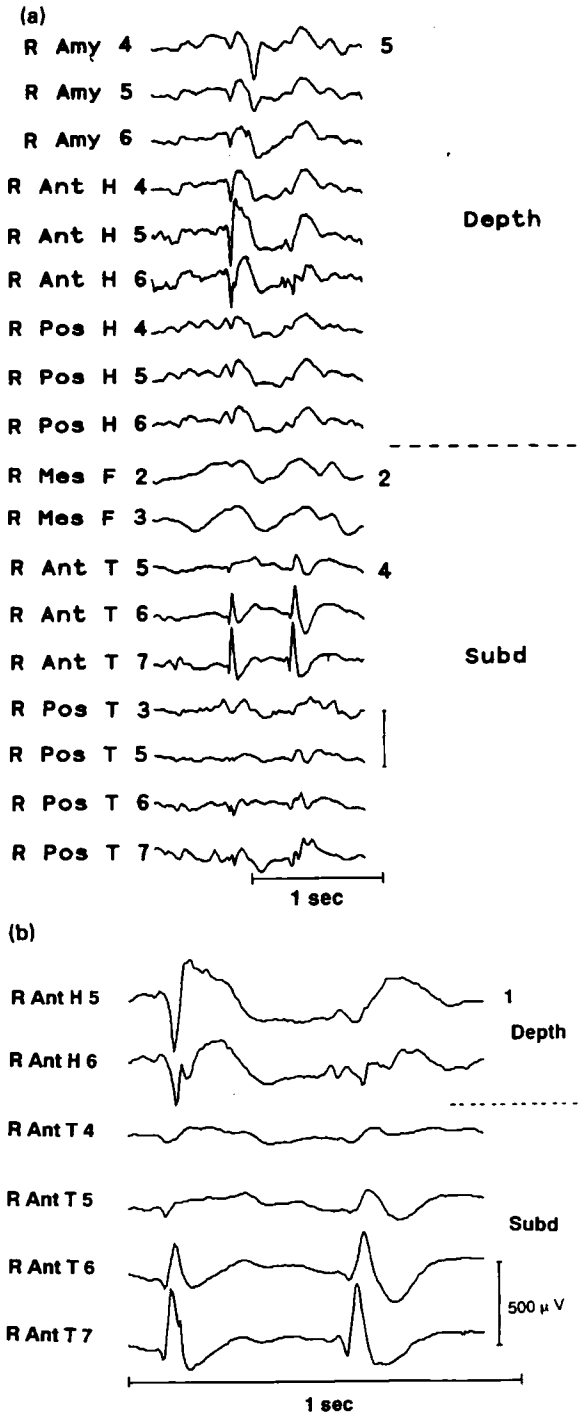


Fig. 6: Example of LL and SO interictal discharges (Patient 8). A, Two spikes are consecutively recorded by the right anterior temporal subdural electrodes. The calibration mark corresponds to 500 μV in channels of relative gain of 4. B, Same event expanded in time: the first spike is recorded at the right anterior hippocampus and shows no significant delays among channels at our sampling rates. However, the second spike propagates along the right anterior temporal electrodes which are situated 2.5 mm apart from each other and is not clearly recorded in the depth. Note how amplitude and sharpness decrease as the spike propagates along the subdural electrodes, perhaps reflecting gradual synchronicity loss.

Analysis of ictal activity

Technical results

Displays of the time course of the total amplitude (or activity) of the EEG within the frequency band 2–40 Hz were found particularly useful to detect electrodecremental events (Figs 7 and 8). Increments in the amplitude of the signal in frequency bands above 20 Hz were particularly useful to detect bursts of low-amplitude high-frequency activity (Figs 8 and 9). In agreement with previous authors[36–38], there was a large variability in the value of EEG spectral variables during the interictal-preictal state. Changes in power spectrum at seizure onset were often within a range occasionally seen preictally, but were of relatively long duration. Accordingly, changes were considered of significance if the variable in question differed more than 0.6 standard deviations from the average of preictal epochs for more than three consecutive epochs. Assuming that consecutive epochs are independent and follow a normal distribution, the probability of this criterium occurring by chance is 0.0057 (one-tailed) or 0.011 (two-tailed).

Outcome

The surgical procedure performed, surgical outcome, pathology and early and initial ictal events for each patient are shown in Table 1. Surgical outcome is coded according to the scale described by Engel[39]. In summary, grades 1, 2 and 3 define different degrees of worthwhile improvement after surgery. Grade 4 indicates no worthwhile improvement after surgery. Five types of early and initial electrical patterns were recognized which in principle could be bilateral or local (see below).

Early ictal events

Ictal electrical changes recorded prior to secondary generalization of ictal discharges have been generically designated as 'early ictal events'. Early electrical ictal changes could in principle be local (restricted to one electrode, one bundle or one lobe) or bilateral (including generalized). Five types of early ictal events were recognized: (a) electrodecremental events, consisting of a diminution in the amplitude of the EEG (Figs 7 and 8). Electrodecremental events are associated with a reduction in the amplitude of the power

spectrum, particularly below 40 Hz, with increments in mobility, with no significant changes in complexity or with decrements in complexity if coincident monorhythmic low-amplitude high-frequency activity is present (Figs 7 and 8).
(b) Onset of low-amplitude high-frequency activity, consisting of amplitude increase in some frequency band above 20 Hz (Figs 8 and 9). High frequency activity could be fairly sinusoidal, with most of its power in a narrow frequency band (<5 Hz), or fairly irregular (multiunit activity), with most of its power in a wider frequency band (5–20 Hz). High frequency activity is accompanied by increments in mobility and variable changes in complexity.
(c) A brief burst of irregular sharp waves intermixed with slow activity in the theta or upper delta range (Fig. 8 B). This type of irregular activity was associated with increments in mobility and no clear changes in complexity.
(d) Regular spikes, spike-wave or sharp-wave activity, associated with increments in activity and no significant changes in mobility or complexity.
(e) Rhythmic ictal transformation, consisting of a gradual or sudden onset of rhythmic sharp waves, usually with frequency below 20 Hz. Typically, the rhythmic activity remains local for several seconds and then gradually increases in amplitude and decreases in frequency as it spreads to neighbouring regions. When the onset of rhythmic activity is sudden, it is often preceded by a high amplitude slow wave (Fig. 9C). Rhythmic ictal transformation is associated with increments in mobility and decrements in complexity.

Electrodecremental events and high frequency activity could initially be local or bilateral. Irregular sharp and slow activity, regular spike-and-wave activity, and rhythmic ictal transformations were always initially local (Table 1). Table 2 shows the proportion of patients who showed each type of early electrical events and the proportion of patients with favourable outcome within each group. Under favourable outcome were included patients within groups 1, 2, or 3A of the outcome scale described by Engel[39].

Ictal onset

All early electrical events described above, except rhythmic ictal transformation, could be observed as the first electrical change at seizure onset in one or more patients. Table 3 shows the proportion of patients who showed each type of early events as the first electrical change at seizure onset and the proportion of patients with favourable outcome in each group. Local irregular sharp waves often intermixed with slow activity was the most common first electrical change (seven patients). This could be the only first electrical change (five patients) or could be associated with simultaneous local high frequency activity of similar topography (two patients). Bilateral electrodecremental events were the second most common first ictal change (five patients). This was followed by local high frequency activity (three patients), either on its own (one patient) or in combination with simultaneous local irregular activity of similar topography (two patients). Local clear spikes or spike-wave activity were relatively uncommon as a first ictal electrical change (two patients). Rhythmic ictal transformation was never found as an initial electrical change at seizure onset.

Two patients out of the 15 did not undergo operation. These two patients showed a bilateral electrodecremental event as the first ictal change. Out of the 13 operated patients, all three who showed local high frequency activity as the first ictal change enjoyed a favourable outcome. Six out of seven patients with irregular activity as the first ictal change had a favourable outcome (two of them also showing simultaneous high frequency activity). Two out of three patients with bilateral electrodecremental events as the first ictal electrical change showed a favourable outcome. Only one patient out of two, who showed typical spike or spike-wave activity as the first electrical change enjoyed a favourable outcome.

Congruence of early electrical changes

Early electrical changes usually lasted for several seconds prior to secondary generalization of ictal discharges and more than one type of early events were often present in any one seizure. These might have similar (congruent) of differing (incongruent) topographies. Table 4 shows the incidence of topographical congruence between different types of early ictal events and the correlation between congruence and surgical outcome. Local electrodecremental events were always incongruent with other local changes. The topography of local high frequency activity was always congruent with other local changes, except for local electrodecremental events. Irregular sharp and slow activity was congruent with other local changes, except for local electrodecremental events and on one occasion with spike-and-wave activity. When the presence of congruence or

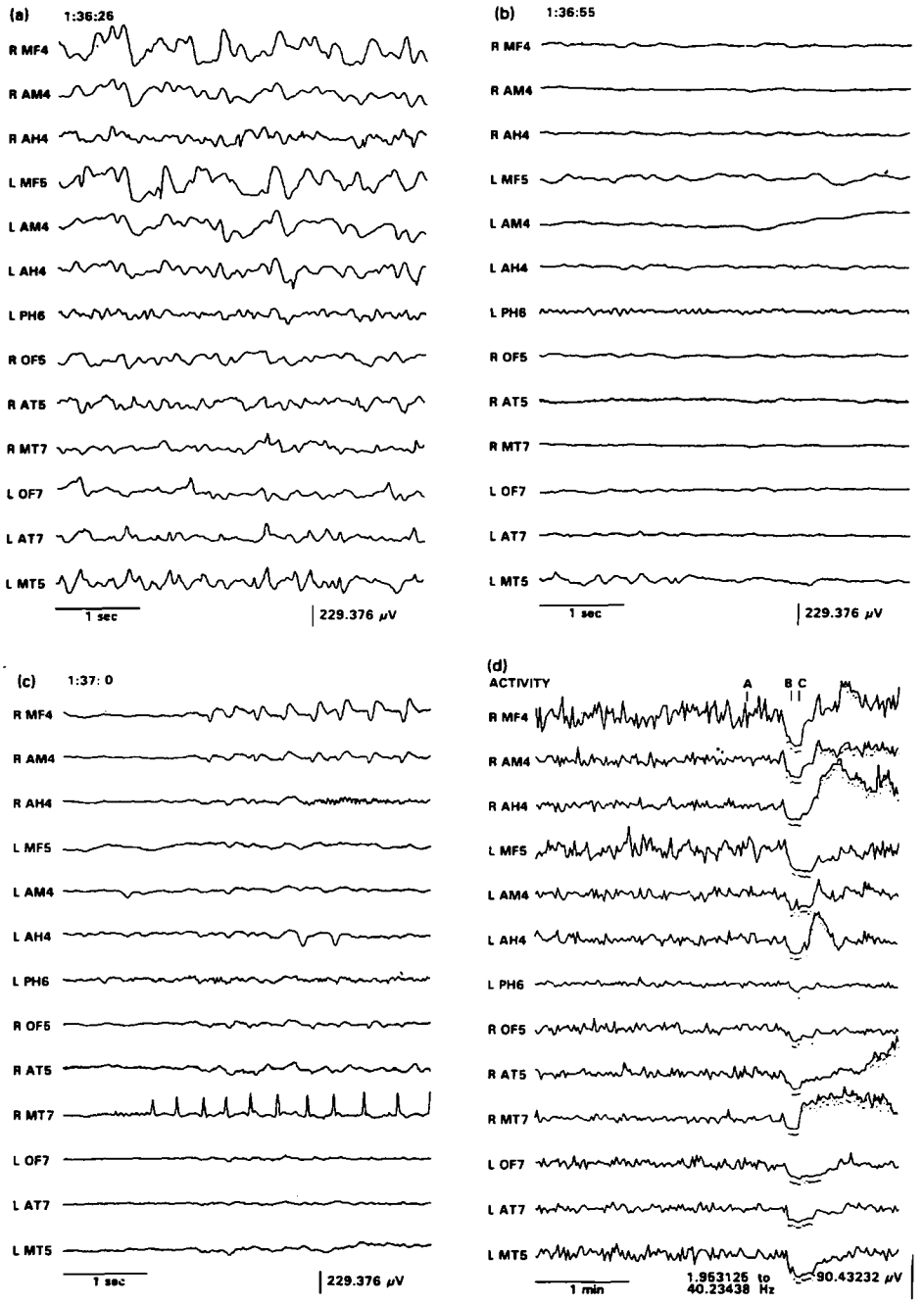
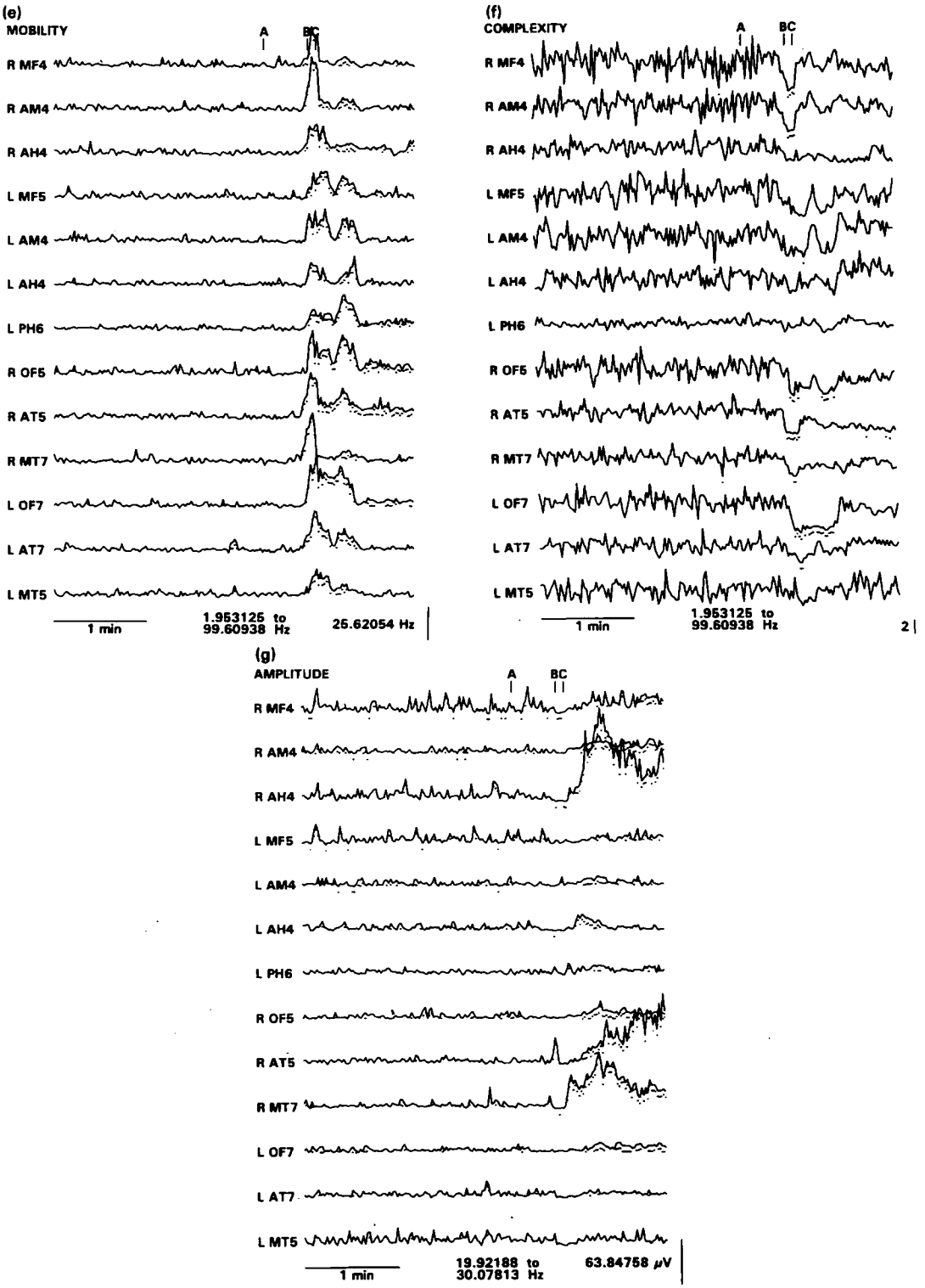


Fig. 7: Example of a seizure in which the first ictal manifestation is a generalized electrodecremental event (patient MS). A, A sample of preictal EEG record. B, EEG during the initial electrodecremental event. C, Rhythmic transformation and sharp waves at the right mid-temporal electrode 7, followed by secondary generalization. D, Time course of the square root of the activity (equivalent to the RMS value of the signal amplitude) between 2 and 40 Hz from about 2.5 minutes before the onset of the electrodecremental event to about one minute into the seizure. E and F, Time course of the mobility and complexity between 2 and 100 Hz. G, Time course of the total amplitude within 20 and 30 Hz, showing a brief burst of low-amplitude high-frequency activity at the right anterior temporal electrode 5 coincident with the electrodecremental event seen in the activity graph (D). Note that activity, mobility, complexity and amplitude displays (D, E, F, G) show over 4 minutes in one figure, so that small but long-lasting changes at seizure onset become more evident. A, B, and C pointers which appear on the top of the graphs for activity, mobility, complexity and amplitude indicate the time slice where the EEG records shown in A, B and C took place.



Epochs with values for activity, mobility, complexity or amplitude exceeding 0.6 standard deviations from the average of baseline (the first 75 epochs) have been marked with an underneath dot in the corresponding figure. Four or more consecutive marked epochs is considered a significant change associated with a seizure. Note that seizure onset is associated with a reduction in activity (electrodecremental event) and complexity and increments in mobility. R, Right; L, Left; MF, mesial frontal; AM, amygdala; AH, anterior hippocampus; PH, posterior hippocampus; OF, orbito frontal; AT, anterior temporal; MT, mid temporal.

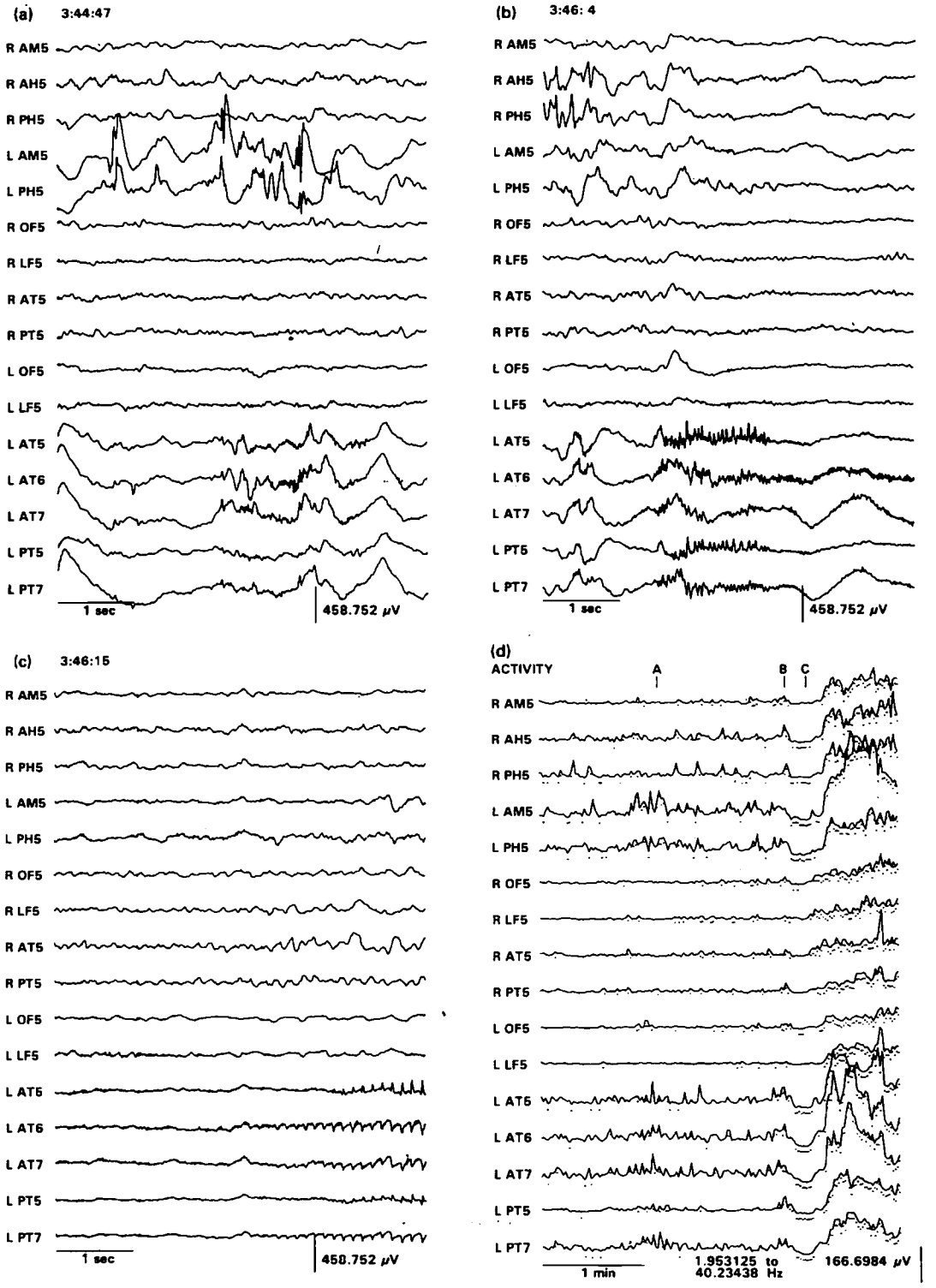
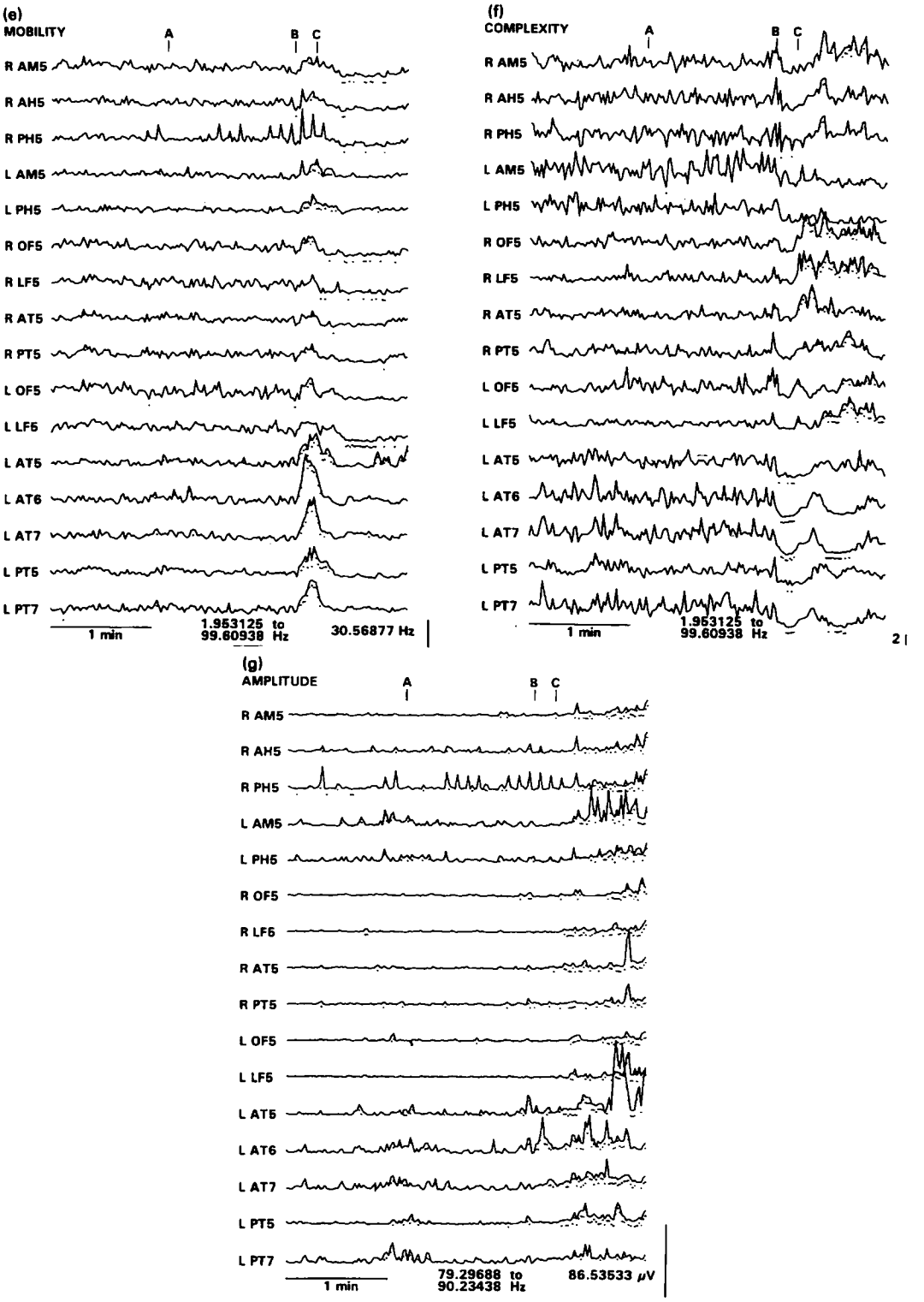


Fig. 8: Example of a seizure (patient JG) which starts with a 1 second burst of irregular sharp waves in the left anterior and posterior temporal regions, shortly followed by a bilateral electrodecremental event and by local low amplitude high frequency activity with most power in the 80–90 Hz frequency band. A, Preictal EEG showing spike and wave activity in the left amygdala and posterior hippocampus associated with slow waves and short bursts of low-amplitude high-frequency activity at the left anterior temporal electrodes. B, Seizure onset showing a 1 second burst of irregular sharp waves at the left anterior and posterior temporal subdural electrodes followed by a bilateral electrodecremental event and local high-frequency activity, particularly at left anterior temporal electrode 6, with fundamental frequency at 82 Hz. C, Onset of local regular sharp waves and spike activity at the left anterior and posterior temporal subdural electrodes. D, Time course of the square root of the activity



between 2 and 40 Hz showing an electrodecremental event affecting mainly right and left deep structures and left anterior and posterior temporal regions. E and F, Time course of mobility and complexity between 2 and 100 Hz showing that the electrodecremental event is associated with significant increases in mobility and reductions in complexity. G, Time course of the integrated total amplitude between 80 and 90 Hz showing a sustained increase of power in this band at the left anterior temporal electrode 6, taking place during the electrodecremental event. Note that changes are more pronounced in the channels which recorded the initial burst of irregular sharp waves. Captions, epoch marking and time pointers as in Fig. 9. LF, lateral frontal; PT, posterior temporal.

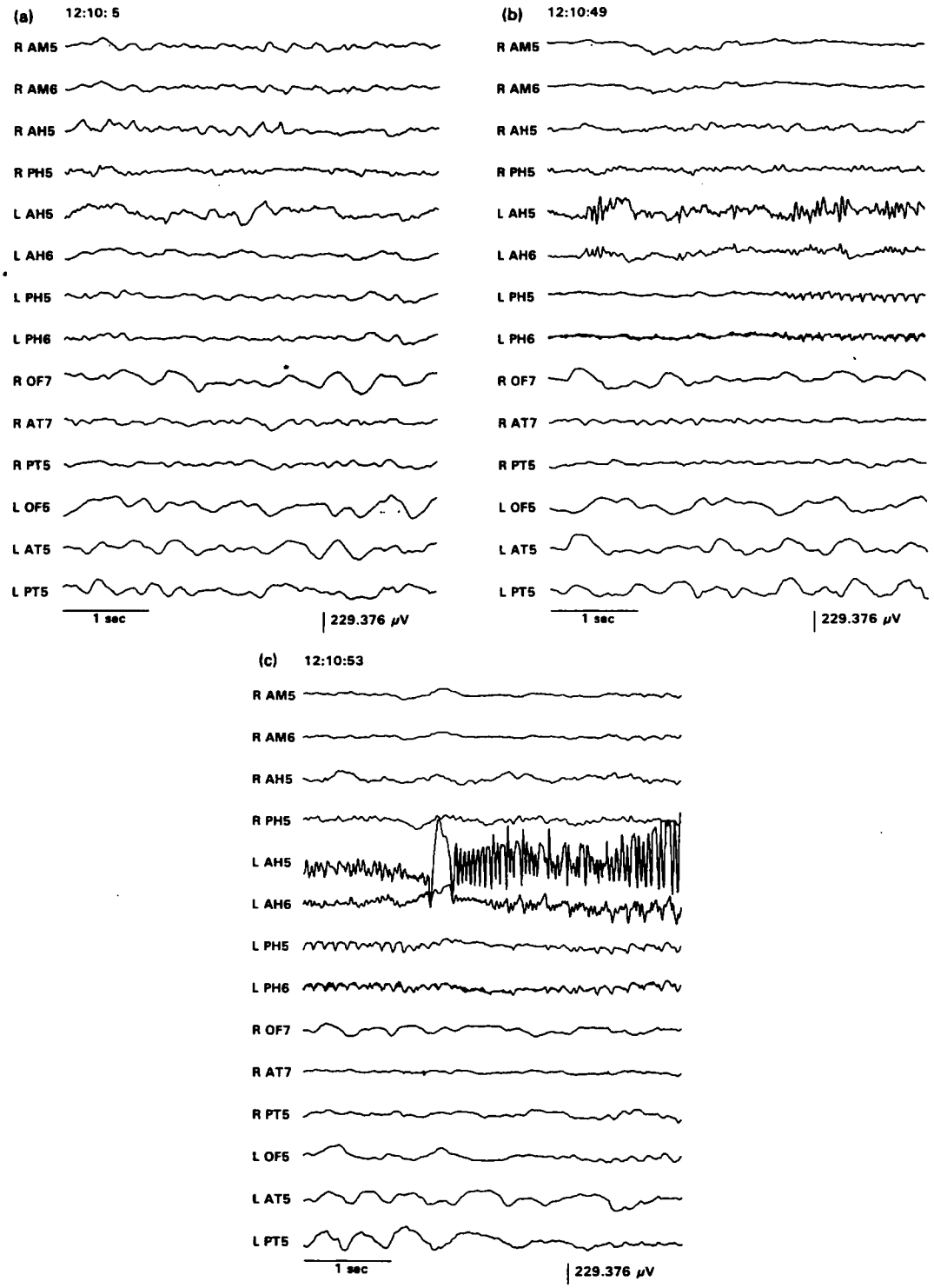


Fig. 9: Example of seizure (patient CS) starting with low amplitude, high frequency activity in the left posterior hippocampus (electrode 6). A, An example of preictal EEG. B, Early stages of a seizure showing low-amplitude high-frequency activity at the left posterior hippocampus 6 and regular small spikes at the left posterior hippocampus 5. C, Later stages of the seizure showing a halt in spike activity and a sudden rhythmic ictal transformation at the left anterior hippocampus 5. D, Time course of the square root of the activity of the signal between 2 and 40 Hz. E, Time course of the total amplitude between 60 and 70 Hz. The onset of high frequency activity in the left posterior temporal electrodes takes place about 30 seconds before the rhythmic ictal transformation at the left anterior temporal electrodes (E). Note that despite the absence of a generalized electrodecremental event there is a mild local electrodecremental event in the right amygdala 5 at the time of the onset of the rhythmic ictal transformation (D). Captions, epoch marking and time pointers as in Figs 9 and 10.

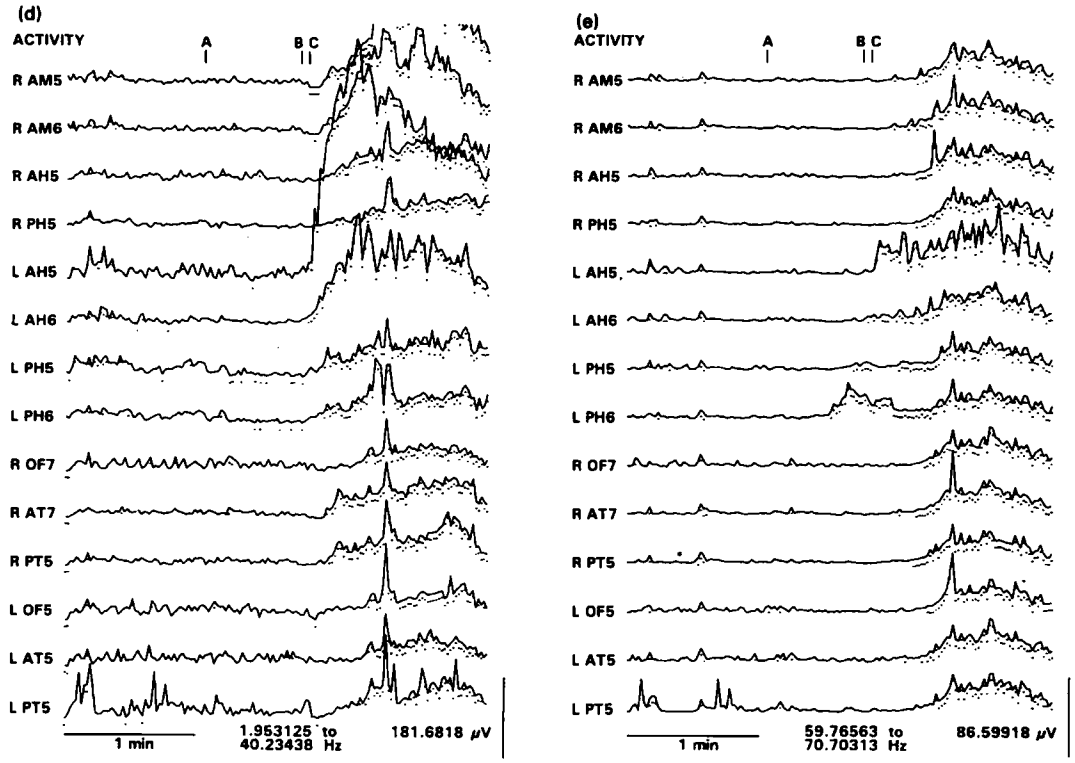


Fig. 9: (*Continued.*)

Table 1: Early ictal events, surgical procedure, surgical outcome and pathology for each patient. EDE, Electrodecremental event; HF, high frequency activity; Irr.sh/sl, irregular sharp and slow waves; RT, rhythmic ictal transformation; S-W, regular spike and wave or sharp wave activity; Outc, outcome; Path, pathology; Proc, surgical procedure; B, bilateral; L, local; P, present; NP, not present; NS, non-specific; MTS, mesial temporal sclerosis; CD, cortical dysplasia; RTL, right temporal lobectomy; LTL, left temporal lobectomy; RAH, right amygdalohyppocampectomy; LAH, left amygdalo-hippocampectomy; SRTR, Spencer's right temporal resection; RFR, right frontal resection; *, marker for the initial ictal events in each patient. Note that EDE and HF could be bilateral or local whereas irr.sh/sl, RT and S-W were always local when present. In patients where more than one seizure types were found, the type on which surgical decisions were based is described

Patient	EDE	HF	Irr.sh/sl	RT	SW	Outc	Path	Proc
LB	B	B	P*	NP	NP	3A	NS	RTL
AC	B	L	P*	P	NP	1A	MTS	LAH
SE	B*	B	NP	P	NP	4A	NS	RTL
JF	L*	NP	NP	P	NP	—	—	NONE
CF	NP	NP	P*	P	P	4A	NS	SRTR
JG	B	L*	P*	P	NP	1A	CD	LTL
RG	B	L*	P*	P	NP	3A	MTS	RTL
GK	B	L	P*	P	NP	3A	MTS	LAH
TM	B*	NP	NP	NP	P	—	—	NONE
AM	B*	L	P	P	NP	3A	NS	LTL
DN	NP	NP	P	P	P*	1A	MTS	RAH
AR	L	NP	NP	P	P*	4 *	MTS	RTL
MS	B*	L	NP	P	P	2A	NS	RTL
CS	L	L*	NP	P	NP	3A	NS	LTL
KW	NP	NP	P*	NP	P	1A	CD	RFR

Table 2: Incidence of the different types of early ictal events and number of operated patients who showed a favourable outcome (groups 1, 2, or 3A). The shortest follow-up was 1 year

Event type	Total patients	No. patients operated	No. patients with favourable outcome
Electro-decremental event	12	10	8
Bilateral	9	8	7
Local	3	2	1
HF activity	9	9	8
Bilateral	2	2	1
Local	7	7	7
Irregular sharp/slow activity	9	9	8
Spike, spike-wave	6	5	3
Rhythmic ictal transformation	12	11	8
Total patients	15	13	10

Table 3: Incidence of the different types of first ictal events and number of patients operated who showed a favourable outcome (groups 1, 2, and 3A). The shortest follow-up was 1 year

Event type at onset	Total patients	No. patients operated	No. patients with favourable outcome
Electro-decremental event (bil.)	5	3	2
Local HF activity	1	1	1
Local irregular sharp/slow activity	5	5	4
Local irreg. sharp/slow plus HF activity	2	2	2
Local spikes, spike-wave activity	2	2	1
Total patients	15	13	10

noncongruence was grouped together for all possible pairs of early ictal events (Table 4B), a favourable outcome was present more frequently when local changes were congruent (22/23) than when they were incongruent (3/7).

DISCUSSION

Interictal activity

Latency differences

The largest proportion of interictal activity is recorded only by deep electrodes. Often deep events with similar amplitudes, or even waveforms, occur both with and without significant accompanying surface signals (Figs 2 and 3). Therefore, events recorded only by deep electrodes must represent neuronal activity which does not propagate significantly through neural pathways to the gyri.

More direct evidence of neuronal propagation of interictal activity from deep structures to the neocortex in humans is provided by time delays between deep and surface recordings. Delays of as much as 220 ms between deep interictal spikes and surface activity have been measured. The shortest delays (SL) are associated with surface spikes, whereas longer latency differences (LL) are associated with surface sharp or slow waves, often preceded by low amplitude rhythmic activity or a small deflection. Since the main waveform is usually the same in deep and surface SL activity, delays in the range of 10–50 ms could in principle be explained by: (a) the filtering behaviour of the tissues due to their passive electrical properties (resistance, capacitance) in the presence of a single source closer to deep electrodes and (b) different channels recording different electromagnetic sources that correspond to neural populations which share a generic form of activation in response to a common epileptogenic event. The filtering behaviour of the

Table 4: Topographical congruence between the different types of early ictal events and surgical outcome. Events were considered congruent if they took place within the same electrode bundle. A, Incidence and congruence of different pairs of early ictal events. Denominators represent the number of patients in which each particular pair of ictal events was seen in the same seizures. Numerators represent the number of patients in which the topography of both events in that pair was congruent. Bilateral/generalized events are congruent with all events and therefore only the incidence of a particular pair is shown. B, Surgical outcome of patients who presented particular pairs of localized early ictal events. Denominators show the number of patients who presented each particular pair with congruent or non-congruent topography. Numerators show the number of patients with favourable outcome (groups 1, 2, or 3A) within each combination

	Electrodec. event		HF activity		Irreg. sharp/ slow waves	Spikes
(A)						
	Bil.	Loc.	Bil.	Loc.		
HF activ.	8	0/1	—	—	—	—
Irreg. sh/sl	6	0	1	5/5	—	—
Spike & wave	2	0/1	0	1/1	2/3	—
Rhythm. trans.	7	0/3	1	7/7	7/7	1/3
(B)						
	Local electrodec.		Local HF activity		Irreg. sharp/ slow waves	Spikes
HF activ.						
congruent	0		—		—	—
noncongruent	1/1		—		—	—
Irreg. sh/sl						
congruent	0		5/5		—	—
noncongruent	0		0		—	—
Spike and wave						
congruent	0		1/1		2/2	—
noncongruent	0/1		0		0/1	—
Rhythmic transf.						
congruent	0		7/7		6/7	1/1
noncongruent	1/2		0		0	1/2

tissues seems to be negligible at the frequencies of interest. It has been shown that the cerebral white matter behaves predominantly in a resistive manner up to 20 kHz[40] and the dielectric permittivity and electrical conductivity of fresh and fixed bone are independent of frequency up to 100 kHz[41]. Alternatively, different cortical regions could nearly simultaneously be activated by fast conductive fibres from a deep source, presumably close to or within mesial temporal structures but perhaps from other subcortical or limbic structures. In any one SL interictal spike, all channels which record the event often show a similar pattern consisting of a negative or positive spike followed by a slow wave of opposite polarity, each component showing different duration and sharpness, presumably reflecting differences in cell synchronization.

Long latency interictal activity provides clear evidence for neural propagation of activity from deep sources to the neocortex. Sharp or slow waves are recorded 50–220 ms after a deep spike. Neither the waveform nor the large delay, nor the fact that delayed activity often has larger amplitude than early spikes (Fig. 1), can be explained by tissue filtering. However, deep interictal spikes often occur with low amplitude deflections or rhythmic activity recorded on the surface preceding the main sharp wave (Figs 1, 3 and 5). These initial low amplitude deflections show SL and LL delays, which suggest that they could represent a volley of activity that triggers local phenomena responsible for the generation of late sharp waves (Figs 1 and 5).

In seven patients, a proportion of interictal spikes showed no delays between deep and surface electrodes (Synch). The lack of delays could in principle be explained by a single source. However, amplitude inconsistencies between deep and surface recordings exist (see below).

Alternatively, as with SL events, Synch activity could also represent a generic mechanism of cortical activation by fast conducting fibres driven by deep sources or by a structure from which activity has not been recorded.

SO interictal activity (recorded only on the surface) may represent events only involving neocortex, or those in which deep activity, if present, has not been detected in depth recordings.

Amplitude distribution

Even when latency differences are compatible with a single deep source, amplitude inconsistencies exist. There is no clear proportionality between amplitude distributions in depth and surface within the same patient. Nearly identical interictal events in the depth can accompany completely different events on the surface (Figs 2 and 3) and vice versa (Fig. 6). The spatial distribution of voltage in deep recordings is usually not clearly dipolar and the topography of interictal paroxysms is quite localized in the depth, often recordable over no more than 1 or 2 cm, yet showing a relatively wide distribution and high amplitude on the surface (Fig. 2). In addition, depth and subdural interictal spikes show the same range of amplitudes. These features of spatial distribution suggest that neural populations located as far as several centimetres apart can be simultaneously active during interictal activity, a situation which could severely hamper spatial discrimination in dipole source localization.

In addition, phase reversals in deep recordings compatible with the existence of deep dipoles are rare. In our series some interictal activity in only one patient showed dipolar distribution in the depth, with voltages of about 750 μV between two hippocampal electrodes situated 2.5 mm apart. Assuming grey matter resistivity of 2.84 ohm · m[33] and assuming that the measured voltages were generated by a dipole located in the hippocampus between both electrodes, e.g. 1 mm from contact 5, the current dipole in the depth would have to be of the order of 2 nA · m. The largest voltages generated at the subdural space or on the scalp (situated approximately 4 and 5 cm from mesial temporal structures) by a 2 nA · m current dipole would be of the order of 0.7 and 0.45 μV, respectively (assuming white matter resistivity = 6.82 ohm · m[33]). Similarly, assuming the magnetic permeability of human tissues to be of the same order as the magnetic permeability of free space, the largest magnetic fields generated over the scalp by a current dipole of 2 nA · m situated in mesial temporal structures would be 88 fT. Therefore, EEG amplitudes measured on the surface are three orders of magnitude larger than predicted by a single dipole situated in mesial temporal structures, with strength compatible with amplitudes generated in the depth. Similarly, measured MEG scalp spikes (about 1 pT) are one order of magnitude bigger than predicted by the assumption of a deep source.

Inconsistencies between the amplitude of deep epileptiform activity, the strength of deep dipoles calculated from scalp measurements and the amplitude of scalp signals produced by deep implanted dipoles

Several studies with deep implanted electrodes and simultaneous subcortical, cortical and scalp recordings have shown that potential differences due to deep dipoles are attenuated by over 1:5 000 on the scalp and are undetectable in the EEG unless dipole voltages are much higher than those ever found in brain tissue. It was concluded that volume conduction inside the brain is very small[42,43]. Recent work has shown that deep implanted dipoles require highly supra-physiological current intensities in order to generate relatively small signals on the scalp. For instance, current dipoles of the order of 320 nA · m (the maximum allowed by safety regulations in the Massachusetts Institute of Technology) were required to produce 15 μV deflections on the scalp[44]. This means that for amplitudes of epileptiform activity reported in the present study (intracranial voltage gradients in the range of 750 μV/2.5 mm, with equivalent currents of about 2 nA · m, and scalp amplitudes of 186 μV), the ratio of deep-to-superficial electrical activity recorded on the scalp during an interictal event would be of the order of 1:2 000. Furthermore, the strength of hippocampal dipoles calculated from scalp MEG or EEG measurements, being of the order of 300–600 nA · m, is well above currents required to generate the amplitudes of deep signals measured in this study. Dipoles of this strength would generate voltage gradients of about 80 mV across sites situated 2.5 mm apart across the dipole, which are about two orders of magnitude larger than the amplitude of spikes ever recorded in the brain. These estimations suggest that signals spreading by volume conduction from deep

sources are hardly recordable on the scalp. This implies that scalp EEG and MEG signals arise from generators closer to the scalp than the estimated deep dipoles. Few authors who use modelling to locate equivalent dipoles give estimates of their values. However, the amplitude of scalp measurements used for modelling imply dipole magnitudes far in excess of the signal strength observed in depth signals, e.g. a 100 μV spike widely distributed over the anterior temporal region would require a mesial temporal dipole moment of about 100–600 nA · m.

Anatomico-physiological basis of neural propagation

The existence of mutual interconnections between amygdala and hippocampus and widespread projections from both structures to the neocortices have been well established (for reviews see Lopes da Silva[45] and Pandya and Yeterian[46]). They provide an anatomical substrate to the interictal propagation of activity from deep sources to neocortex or in the opposite direction. In particular, Amaral and Price[47] have described extensive projections from the amygdala to the pole of the temporal lobe, the superior temporal gyrus and the medial and orbital surfaces of the frontal lobe. This is consistent with the finding that mesial temporal spikes are often associated with lateral frontal, orbito frontal and anterior temporal spikes or sharp waves at subdural electrodes (Figs 5 and 6) and with anterior temporal spikes on the scalp (Figs 1, 2 and 3), see also Hughes[48]. Unfortunately little is known about the diameter of fibres projecting from mesial temporal structures to the neocortex and whether their conduction velocity could account for the neocortical activation by mesial temporal structures with the latency differences described (more than 3 m/second for LL delays and 1.2–3 m/second for SL). However, very fast conducting rates have been observed in the central nervous system. For instance, the first cortical components of somatosensory evoked responses appear with 20 ms delay after medial nerve stimulation[49]. Assuming a peripheral conduction velocity of about 60 m/second for the fastest afferent fibres (12 μm diameter A fibres[50]), peripheral conduction probably takes at least 10 ms, leaving 10 ms for central conduction to occur from the cervical spinal cord to somatosensory cortex. Similarly, large areas of the neocortex could be synchronized in a few milliseconds by mesial temporal structures, or archi- and neo-cortex could be activated simultaneously by a limbic or a subcortical pacemaker, perhaps thalamic. In any case, at the usual sampling rates, short or absent delays are compatible with activation of temporal and frontal neocortex through fast conducting fibres from deep sources. However, even for the slowest axonal conduction, delays over 70 ms require a multisynaptic pathway, presumably with intracortical and/or subcortical relays. Neocortical events which show long delays are often preceded by a low amplitude deflection or rhythmic activity which starts with a deep spike (Figs 1, 3B and 5). This low amplitude activity could represent an initial neocortical afferent volley that is responsible for the generation of local changes which will in turn give way to a propagated sharp/slow wave under appropriate conditions.

Neural synchronicity

An interesting finding is that deep recordings often show sharper and shorter spikes than surface recordings. Synchronization could be lost as the wave travels, probably due to statistical differences in synaptic delays or fibre conduction velocities. Moreover, deep spikes can be associated with surface spikes, sharp waves or slow activity, down to the delta range. Usually the slowest activities showed the longest delays and more widespread spatial distribution. These findings are consistent with the suggestion that sharper epileptiform activity and fast spikes are more common when recording from close to the neural generator of epileptiform activity[51].

Neural vs. electromagnetic propagation

Our results regarding latency and spatial distributions suggest that interictal activity is a complex phenomenon in which relatively large areas of neo, and archi-cortex can be simultaneously or consecutively activated through three mechanisms: (a) by fast association fibres directly, (b) by fast association fibres that trigger local phenomena which might in turn give way to sharp/slow waves or spikes and (c) propagation along the cortex. In addition, there must be a generic mechanism by which widespread areas of the cortex generate certain patterns in response to epileptiform events. Specific factors such as

neurone network anatomy, dynamics or previous state could condition the cortex to generate spike-and-wave, sharp or slow waves as a response. The simultaneous activation of large areas of the neocortex in a generic form can simulate electrical activity distributed over a wide solid angle, similar to that generated by a deep single electrical source. In this context, the distinction between electromagnetic and neuronal propagation of the signal can be difficult because the existence of multiple solutions to the inverse problem complicates modelling in the presence of multiple sources. For instance it can be shown that the deeper the source the wider the surface area where it is detected[52]. Therefore, it could be difficult to distinguish scalp electromagnetic fields generated by an extended neocortical source from those generated by a single deep source on the basis of the spatial distribution of external electromagnetic fields. The magnitude of the dipole moment should also be considered, and must be compatible with physiological neuronal currents (with voltage gradients smaller than 1000 μv/2.5 mm). Hence, when deep and surface sources are active simultaneously, as seems to be the case in Synch and SL types, the active sources nearest the recording sites could mask or cancel activity from deep sources, which additionally shows very small signal to noise ratio. Averaging would probably not improve the signal to noise ratio of deep sources significantly, since simultaneous signals from superficial sources, several hundred times larger, are also time locked to the average. Under these circumstances, modelling of neuronal activity as a single dipole or as a small number of dipoles seems to be inadequate. In a situation where the contribution of volume currents from deep sources to scalp EEG is minimal and most of the surface EEG or MEG is due to the activated neocortex underlying the recording site, MEG would not provide major advantages over EEG recordings for deep source characterization, apart from being insensitive to radial currents and the lack of patient reference. Nevertheless, a number of reports have localized scalp epileptiform MEG activity to single deep structures. However, since a deep temporal epileptogenic zone commonly produces, mainly propagated, interictal EEG and MEG discharges over the ipsilateral temporal neocortex which can be represented by an equivalent dipole within the temporal lobe, evidence of the presence of such a zone (whether from depth recording, neuroimaging or clinical outcome of lobectomy) does not amount, as several authors have claimed, to validation of dipole modelling.

Relations between topographies of ictal and interictal events

It is particularly important that surface interictal epileptiform activity can be driven by structures which do not trigger seizures. Moreover in one out of five patients who showed focal ictal onsets during telemetry with intracerebral electrodes, only those interictal deep spikes which were contralateral to the ictal onset zone could be detected on the surface. This obviously poses a difficult physiological problem to solve, regardless of discussions about the ideal mathematical model for the source, since not all structures which seem to be active interictally are able to trigger seizures. This can be a neurophysiological substrate to the common clinical finding that the analysis of interictal activity may be misleading in lateralizing the seizure onset in partial epilepsy[53].

Ictal electrical events in complex partial seizures can remain confined to a limited number of deep contacts for a few seconds before activity is recorded on the surface (see discussion on ictal activity). The propagation of ictal activity has been extensively studied since depth recordings became available (for review see Wieser[4]). It has been reported that the spread of seizures of mesial temporal origin takes place along preferential anatomical pathways, most often to fronto-orbital areas, posterior cingulate gyrus and contralateral hippocampus. Apart from the latter, these projections seem to largely coincide with those followed by interictal discharges. However, the reason why ictal activity can remain relatively confined for seconds whereas interictal activity can spread within milliseconds, causing a less sustained phenomenon and much less symptomatology, is not known but it poses an important fundamental question about the genesis and propagation of epileptiform activity.

Clinical relevance

This work corroborates the traditional interpretation of EEG as being generated by cellular activity taking place near the electrode which records discharges, and emphasises the importance of ictal recordings. However, propagation of activity is likely to follow certain neural pathways. For instance, most activity from deep sources seem to propagate to the ipsilateral neocortex. If topographic patterns of propagation are consistent within and between subjects, information about deep epileptogenic foci could in principle be obtained from detailed mapping of

their neocortical projection areas by means of scalp EEG and/or MEG, not by a simplistic dipole model but by empirical observations. In this respect, the association of definite interictal patterns with surgical outcome would be of paramount clinical importance and the combined use of scalp EEG and MEG could prove very helpful in this task[54]. Since large areas of the neocortex can be simultaneously active during interictal events, the characterization of electromagnetic sources as a convoluted strip of dipoles, perhaps superimposed on neocortical grey matter identified on radiological images, seems to be a more appropriate mathematical model than isolated dipoles or clusters of dipoles. Whether the topography of such neocortical dipole arrays is reliably predictive of the location of a deep pacemaker has yet to be established.

Ictal activity

SEEG changes associated with seizure onset in partial epilepsy are complex and appear not always to be confined to a restricted region. In the interictal state, most spectral power of the EEG is contained below 12 Hz. A number of electrical changes are seen during the onset of ictal activity, often involving a widespread decrease in the amplitude, particularly of low frequencies, and/or the focal recruitment of higher frequencies.

It appears that a generalized electrodecremental event is one of the most common early or initial ictal manifestations (Tables 2 and 3). Widespread long-lasting DC electrical changes, apparently due to a sustained inward current across the neurone membrane, have been described in association with seizures induced by repetitive electrical stimulation of hippocampal afferents in the rat[55]. However, the significance of generalized electrodecremental events at seizure onset in human partial epilepsy remains uncertain. It might be supposed that where the first detected ictal electrical change is generalized, seizure onset is either diffuse or occurs at a site which has not been implanted, and that surgical outcome will consequently be poor. However, the presence of a generalized electrodecremental event does not imply a poor outcome, even when this constitutes the first ictal change observed (Table 3) despite the use of computer algorithms to identify earlier, focal changes. Since fast commissural propagation of ictal changes seems unlikely[56-58], the absence of poor outcome associated with generalized ictal changes at onset may suggest that generalized electrodecremental events are not part of the ictal process itself, but reflect generalized cerebral changes which allow particularly susceptible regions to develop paroxysmal behaviour that gradually recruits neighbouring regions. This interpretation implies that partial seizures can be the result of two processes: (a) generalized cerebral changes associated with subtle generalized electrical changes, and (b) focal onset of an epileptogenic process in regions particularly prone to show paroxysmal behaviour in response to these generalized cerebral changes. Focal changes could then propagate and potentially recruit the whole brain (secondarily generalized seizure). This is an interesting interpretation, since it can explain the relatively frequent finding that clinical features of seizures change significantly after surgery in some patients: removal of the region which was most prone to suffer paroxysmal behaviour under the appropriate generalized changes could allow other susceptible regions to become active, regions whose potentially epileptogenic nature was previously latent due to their involvement in the propagated paroxysmal behaviour originating in the region which has now been removed.

A brief burst of irregular sharp waves (Fig. 8), often superimposed with slow activity, also appears to be a fairly common early ictal event (nine patients, Table 1) and a very frequent first detected ictal change, with (two patients) or without (five patients) concomitant high frequency activity (Table 4). In the present series this type of activity appears to be associated with a good outcome (Tables 2 and 3).

On the contrary, classical focal spikes or spike-and-wave activity, similar to interictal discharges but more frequent and regular, constitute a relatively rare early ictal event. They were found only in two patients as the first initial ictal change, one of them showing poor surgical outcome (Table 3). Indeed, in most cases interictal spike-and-wave discharges actually halt before the first electrical ictal changes take place. This suggests that ictal onset is not secondary to an exacerbation of interictal activity due, for instance, to a decrease of the inhibition preventing the propagation of interictal discharges. It appears that ictal onset involves mechanisms which may be different from those of the onset and propagation of interictal discharges. For instance, local early ictal changes often take seconds to propagate whereas neuronal propagation of interictal discharges usually takes less than 220 ms (see above discussion on interictal activity). However, once ictal activity generalizes, spike-and-wave activity is readily seen.

It appears that the best surgical results are obtained when the topography of most of the changes seen at onset is congruent. In this respect, localized high frequency activity was found always congruent with the topography of coexisting focal events, except localized electrodecremental events, and the existence of localized high frequency activity was associated with a good outcome (Table 4). This has also been suggested by previous authors regarding frontal lobe epilepsy[59]. It therefore seems that localized high frequency activity is the most likely electroencephalographic correlate of the ictal onset zone. On the contrary, in the present series, localized electrodecremental events were always non-congruent with other focal signs but were not particularly associated with a poor prognosis (Tables 2 and 4). Thus localized electrodecremental events appear to be of no localizing value.

The relationship between high-frequency activity and electrodecremental events is probably complex but can be observed in simultaneous single unit and SEEG recordings from human epileptic seizures[2]. At seizure onset, high frequency firing is seen in neurones situated in regions where high frequency SEEG activity is recorded. A simultaneous drop in neurone firing rate can be recorded from contralateral regions which show electrodecremental SEEG patterns. It therefore appears from single unit recordings that electrodecremental events are due to a genuine decrease in neurone firing rate rather than to desynchronization. Accordingly, I have not always found an absolute increase in amplitude within a specific frequency band during electrodecremental events. Electrodecremental events are associated with decrements in the amplitude of low frequencies and with either no significant changes in complexity or decrements in complexity, which presumably indicate the appearance of low amplitude monorhythmic fast activity. The absence of increments in complexity during electrodecremental events further suggests that these are due to decreased neuronal firing rather than to desynchronization.

If surgical removal of sites of localized high frequency seizure onset is indeed associated with a favourable prognosis, the use of automatic methods for early detection of low amplitude, high frequency activity at seizure onset could be of considerable clinical importance. Different types of high frequency activity can be recorded (see results), with variable values of peak frequency and frequency scatter. How these parameters affect surgical prognosis is uncertain but the problem deserves further study in a larger population of patients. In this respect, frequency analysis through FFT algorithms show high frequency discrimination at the expense of relatively low time resolution and long computing time. If higher time resolution or shorter computing time are required for clinical applications, alternative methods such as narrow band digital filtering or complex demodulation could be used.

CONCLUSION

Interictal activity

Correlations between the amplitudes of deep and surface recordings, together with previous reports on the amplitude of scalp signals produced by artificially implanted dipoles suggest that the ratio of deep to surface activity recorded during interictal epileptiform activity on the scalp is around 1:2 000. This implies that most such activity recorded on the scalp does not arise from volume conduction from deep structures but is generated in the underlying neocortex. In addition, time delays of up to 220 ms recorded between interictal paroxysms at different recording sites show that interictal epileptiform activity can propagate neuronally within 220 ms to relatively remote cortex. Large areas of archi- and neo-cortex can then be simultaneously or sequentially active via three possible mechanisms: (a) by fast association fibres directly, (b) by fast association fibres that trigger local phenomena which in turn give rise to sharp/slow waves or spikes, and (c) propagation along the neocortex. The low ratio of deep-to-surface signal on the scalp and the simultaneous activation of large neocortical areas can yield spurious equivalent dipoles localized to deep structures. In addition, frequent interictal spike activities can take place independently in areas other than the ictal onset zone and their interictal propagation to the surface is independent of their capacity to trigger seizures. It is concluded that: (a) the deep-to-surface ratios of electromagnetic fields from deep sources is extremely low on the scalp; (b) single dipoles or a limited number of dipoles are not adequate models for interictal activity for surgical assessment; (c) the correct localization of the onset of interictal activity does not necessarily imply the onset of seizures in the region or in the same hemisphere. It is suggested that, until volume conduction and neurophysiological propagation can be distinguished, semi-empirical correlations between symptomatology, surgical

outcome and detailed presurgical modelling of the neocortical projection patterns by combined MEG, EEG and MRI could be more fruitful than source localization with unrealistic source models.

Ictal activity

Regarding ictal activity it is concluded that: (a) most patients (12/15) showed early electrodecremental events, generalized or local, mainly involving frequencies below 40 Hz, (b) generalized electrodecremental events at onset did not imply poor outcome, (c) localized high frequency activity, between 20 and 80 Hz, was associated with a good outcome, (d) topological congruency of early ictal events is associated with a favourable outcome.

Comparison of interictal and ictal activities

It appears that interictal and ictal discharges are different expressions of a given specific or non-specific pathology. The traditional view that interictal discharges correspond to an epileptiform phenomenon which does not propagate far or widely enough to provoke a clinical seizure appears too simplistic. Seizures differ fundamentally from interictal events in their basic mechanisms and in the substrate of neuronal populations. Even though regions which appear to originate seizures also show frequent interictal discharges, interictal activity is also readily seen in regions which do not seem to originate ictal events. Both interictal and ictal discharges seem to propagate to relatively remote cortex by differing mechanisms. Interictal discharges can propagate at relatively high conduction velocities, within milliseconds, presumably via cortical association fibres but also intracortically, often following established neural pathways. Interictal discharges therefore appear to propagate via synaptic and axonal mechanisms. On the contrary, the onset of ictal activity is often associated with subtle widespread electrical events which might correspond to the electrical expression of widespread metabolic or biochemical changes. Within the context of these widespread changes, initial focal ictal discharges typically remain localized during several seconds and gradually spread to neighbouring regions. It appears that what propagates during ictal phenomena is the **capacity to produce discharges** rather than the discharges themselves (Fig. 8C). This interpretation would again be compatible with the propagation of some underlying metabolic or biochemical phenomenon which might interfere with membrane threshold and enable neuron aggregates to generate discharges. Whether ephaptic interactions or changes in extracellular ionic concentrations are involved in the propagation of seizures is still to be determined, but animal studies have shown that changes in extracellular ions, particularly potassium and calcium, can provoke 'seizure-like' discharges in hippocampal slices[60–63]. The assumption that synaptic and non-synaptic mechanisms are involved in the propagation of human seizures also explains that the clinical patterns of seizures often changes after surgery (see discussion on ictal activity) and that computer analysis of phase spectrum which has often been used to identify the leading regions during ictal events has only been partially successful[64]. Identification of chemical changes during seizures might be a way forward in the understanding of human epileptogenesis. Whether MRI spectroscopy or microdialysis probes inserted with intracerebral electrodes can play a role in this task remains unknown. In any case a multidisciplinary approach seems to be an essential factor for a global understanding of human epilepsy.

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