

Neurophysiological investigation of epilepsy

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Routine EEG recording

Since its discovery in the late 1920's, the electroencephalogram (EEG) has developed into an array of digitally based techniques, integrated with video and other investigative modalities that retain a central role in diagnosis and management of patients with seizure disorders. In contrast to the technological advances, relatively little progress has been made in understanding the cerebral generators of EEG signals, in part because of their anatomical complexity. Much of what appears on scalp EEG recordings represents the summation of synchronised excitatory or inhibitory post-synaptic potentials in apical dendrites of neurones in superficial neocortex, while deep generators may produce little or no change at the surface.

EEG is not always used appropriately in epilepsy care; evidence based guidance on its role is limited by a paucity of high quality data and methodological deficiencies in published studies (1). Furthermore, the limitations of scalp EEG may not be fully appreciated by non-specialists, and EEGs can be misinterpreted if there is insufficient knowledge of the range of normal and non-specific phenomena – this being a common reason for over-diagnosis of epilepsy (2).

In general, sensitivity of routine inter-ictal EEG for detecting epilepsy and its specificity for distinguishing epilepsy from other paroxysmal disorders are both limited. Published figures for diagnostic sensitivity of EEG range between 25 to 55%; up to about half of patients with epileptic disorders may have one normal interictal EEG, and around 10% of patients with epilepsy never show epileptiform discharges (3). Hence, a normal or negative EEG cannot be used to rule out the clinical diagnosis of an epileptic seizure.

Importantly, demonstration of epileptiform abnormalities in the EEG does not in itself equate to epilepsy or indicate that the patient has a seizure disorder. Non-epileptic individuals show epileptiform abnormalities in the EEG in a number of circumstances. A large study of standard EEG in healthy mostly male adults with no declared history of seizures, showed epileptiform discharge in 0.5% of the subjects (4). A slightly higher incidence of 2-4% is found in healthy children and in non-epileptic patients seen in hospital EEG clinics. The incidence rises substantially to 10-30% in patients with cerebral pathologies such as tumours, previous head injury, cranial surgery or congenital brain injury (5), and patients with pure psychogenic type non-epileptic seizures have a higher incidence of epileptiform EEGs than normal subjects (6). Thus, great caution is necessary when

assessing the significance of epileptiform activity in such circumstances, particularly if the history offers little or no indication that the patient has epilepsy on clinical grounds.

- a. *An EEG should be performed to support a diagnosis of epilepsy in patients in whom the clinical history suggests that the event was likely to be epileptic*
- b. *EEG cannot be used to exclude a diagnosis of epilepsy in a patient in whom the clinical history suggests an event of non-epileptic origin*
- c. *The EEG cannot and should not be used in isolation to make a diagnosis of epilepsy*

(adapted from NICE guidelines, ref 1)

Epileptiform phenomena

EEG features classified as epileptiform are spike discharges, spike or polyspike wave complexes, and sharp waves. Some types of epileptiform phenomena are strongly correlated with clinical epilepsy; others are weakly linked to active epilepsy, or have limited association with seizure disorders. Three per second spike wave discharge in childhood absence epilepsy and the hypsarrhythmic pattern of West's syndrome are examples of epileptiform phenomena that are closely correlated with an epileptic disorder. The EEG of normal subjects can show a range of spikey features, particularly during sleep. Physiological and pathological but non-epileptogenic variants include wicket spikes, 14 and 6 Hz spikes, rhythmic mid-temporal theta, and sub-clinical rhythmic epileptiform discharge in adults (SREDA). Mostly, these are not associated with epilepsy, but non-epileptogenic variants are a potential source of confusion and EEG misinterpretation.

Diagnostic yield

A number of factors influence whether patients with epilepsy will show interictal epileptiform discharge (ED) in a routine EEG. Children do so more often than older subjects, and certain epilepsy syndromes or seizure types are more likely to show ED. The location of an epileptogenic region is relevant: a majority of patients with temporal lobe epilepsy show ED, whereas epileptic foci in mesial or basal cortical regions remote from scalp electrodes are less likely to demonstrate spikes, unless additional recording electrodes are used. Patients with frequent (1 per month) seizures are more likely to have ED than those with rare (1 per year) attacks (7). The timing of EEG recording may be important: investigation within 24 hours of a seizure revealed ED in 51%, compared with 34% who had later EEG (8). Some patients show discharges mainly during sleep, or there may be circadian variation as in the idiopathic generalized epilepsies.

A routine EEG recording typically takes 20-30 minutes, and should include standard activation procedures of hyperventilation (up to 3 minutes) and photic stimulation, using published protocols (9), or specific triggers in rare types of reflex epilepsies (reading and musicogenic epilepsy etc). It is good practice to warn patients of the small risk of seizure induction and obtain consent to activation procedures. Breath counting is a reliable and effective means to test transient cognitive impairment during generalized spike wave discharges induced by hyperventilation (10). Most centers use the International 10-20 system of scalp

electrode placement, but additional electrodes are often useful, especially those that record from the anterior temporal lobe region (superficial sphenoidal electrodes). The yield of routine EEG can be increased by repeat recordings (up to a total of 4 in adults), or by use of sleep studies, achieved by recording natural sleep or through use of hypnotics to induce sleep. The combination of wake and sleep records gives a yield of 80% in patients with clinically confirmed epilepsy. Whether sleep deprivation is of additional value for induction of ED is difficult to determine from reported studies, although there is some evidence that it specifically activates ED in idiopathic generalized epilepsies (11). A recent evaluation of different EEG protocols in young people (<35 years) with possible epilepsy found that sleep deprived EEG (SD-EEG) provided significantly better yield of than routine EEG or drug-induced sleep EEG, and the authors suggested that SD-EEG is the most cost-effective protocol for investigation of new epilepsy (12).

Prolonged interictal sampling using long term monitoring also increases yield by about 20%, and is now widely available through 24 hour ambulatory multi-channel digital EEG recording.

What are the roles of EEG in diagnosis of epilepsy?

EEG is performed in patients with possible or known seizure disorders to assist accurate diagnosis and provide information about epilepsy type. EEG findings contribute to the multi-axial diagnosis of epilepsy, by establishing whether the seizure disorder is focal or generalized, idiopathic or symptomatic, or part of a specific epilepsy syndrome. In a newly presenting case of suspected epilepsy, the physician will ask:

- Does the patient have a partial or generalised seizure disorder?
- Is there evidence of photosensitivity, if the subject is likely to have idiopathic generalised epilepsy?
- Are there EEG features indicative of an epileptic syndrome?

Although conceptual division of partial and generalized seizures/epilepsy types is fundamental in epilepsy characterization, there is overlap in both clinical and electrographic manifestations of focal and generalized seizure disorders. Rapid propagation or generalization of epileptiform activity related to a symptomatic focus can mimic idiopathic generalized epilepsy (13); localised discharges and regional accentuation of generalized spike wave discharge are widely recognized in idiopathic generalized epileptic syndromes (14). In some individuals, there may be co-existence of a partial and a generalized seizure disorder (15). In most instances, the clinician will be reasonably certain about seizure type based on accounts provided by the patient and witness, but when history is unclear – as with an un-witnessed “blackout or brief impairment of awareness, EEG can help to distinguish between a complex partial seizure with focal ED, and an absence type seizure with generalized ED.

Syndromic findings

Relatively specific EEG abnormalities are found in certain epilepsy syndromes, many of which present in childhood or adolescence. In some individuals, the true epilepsy syndrome may not be apparent at initial assessment, necessitating regular electro-clinical appraisal. For example, juvenile myoclonic epilepsy would be the likely diagnosis in an intellectually normal teenager presenting with myoclonic jerks; if that patient went on to develop refractory epilepsy and cognitive decline, the syndromic diagnosis would be revised to a progressive myoclonic epilepsy.

Epilepsy syndromes presenting in neonatal periods and infancy include benign idiopathic neonatal seizures, in which the EEG shows trace pointu alternans in 75%; early myoclonic epilepsy & infantile epileptic encephalopathy (Ohtahara syndrome) with burst suppression in the EEG; West syndrome in which infantile spasms are associated with hypsarrhythmia, and Dravet syndrome or severe myoclonic epilepsy of infancy in which generalised spike wave and photosensitivity are reported.

Idiopathic generalised epilepsies (IGE):

EEG features in IGE comprise generalised spike or polyspike and slow wave discharges at 3-5 Hz, normal background cortical rhythms, and a relatively high occurrence of photosensitivity (16). In *childhood absence epilepsy*, the characteristic finding is bilateral synchronous 3 Hz spike wave, usually lasting between 5 and 10 seconds, and accompanying typical absence seizures. The discharge is often slightly faster than 3 Hz at onset, and tends to slow down towards the end of the seizure. Interictal EEG is normal, but may show runs of occipital rhythmic delta (15-40% of cases), which can persist in some children after remission of absences. Photosensitivity is uncommon (less than 10%), and may be a marker of poorer prognosis. Patients with *juvenile absence epilepsy* are more likely to show polyspike discharge or spike wave frequency above 3 Hz, and occipital rhythmic delta is not seen. In *juvenile myoclonic epilepsy*, the interictal and ictal EEG characteristic is brief bursts of polyspike (but sometimes single spike) and wave discharge. Photosensitivity is relatively common in JME (40-50%), and seizures can be induced by other reflex mechanisms including reading or praxis induction. Prominent polyspike wave discharge is also seen in *eyelid myoclonia with absence epilepsy*. *Generalised tonic clonic seizures on awakening* have no distinct EEG features.

A retrospective evaluation of EEG features in IGE found only one-third showed typical features on the first EEG (17). Whilst serial EEG records were necessary to elucidate syndromic diagnosis, appropriate treatment could be initiated in a majority of cases on clinical grounds at presentation. Absence epilepsy was the syndrome most likely to show diagnostic EEG abnormalities at initial investigation.

IGE beginning in adult life is now an established entity (18). Most cases have either generalised tonic-clonic seizures with or without myoclonus, and electro-clinical manifestations are similar to those in IGE presenting at more classical ages.

Photosensitive epilepsy: Photosensitivity occurs in about 5% of all epilepsies, usually IGE, but also in progressive myoclonic epilepsies and very occasional cases of partial epilepsy (19). Photosensitivity has age related expression, with three-

quarters of cases having the first photic induced fit between the ages of 8 – 20 years (20), and photosensitivity is twice as common in females. Longitudinal follow up studies have revealed persistence of photoparoxysmal responses and hence seizure risk in the majority of cases of photosensitive epilepsy, without age limit. Photoparoxysmal EEG abnormalities can occur as an acute symptomatic phenomenon on abrupt withdrawal of alcohol or certain drugs, but are not then associated with long term risk of epilepsy.

Benign childhood epilepsy syndromes: in *benign childhood epilepsy with centro-temporal spikes*, the EEG hallmark is focal sharp wave discharges in central and temporal regions, either bilateral or unilateral, and potentiated by sleep. Occasional patients show focal discharges in other brain regions or generalised spike wave activity. Background cerebral rhythms are normal. Interictal EEGs can show large amounts of ED, although frequent epileptic seizures occur in only around one-quarter of cases, and the EEG trait may manifest without clinical expression. *Benign childhood occipital epilepsy* (BCOE) has more variable EEG features; paroxysms of occipital spike wave on eye closure (fixation off sensitivity) are characteristic of the early onset form or Panayiotopoulos syndrome. Otherwise, multifocal discharges, rolandic spikes and generalised spike wave are common, and the finding of frequent multifocal discharges in a routine EEG should alert to BCOE in a child who has occasional seizures or paroxysmal autonomic symptoms.

Landau-Kleffner syndrome (acquired aphasia and epilepsy) & Electrical Status Epilepticus in sleep: these disorders, which may be related, are characterised by continuous spike wave discharge occupying 85% or more of the sleep record. The wake EEG shows variable findings.

Progressive myoclonic epilepsies (PME): the individual disorders manifest as PME share neurophysiological features – generalised spike wave discharge, photosensitivity, “giant” SEPs, facilitation of MEPs by afferent stimulation, and abnormalities of background cerebral activity, typically an excess of slow activity. The background abnormalities are usually progressive, with marked changes occurring in syndromes with dementia or significant cognitive decline, such as Lafora body disease. Relatively specific findings include vertex sharp waves in sialidosis, occipital spikes in Lafora body, and giant VEPs in Batten’s disease (late infantile neurolipofuscinosis).

Partial epilepsy syndromes: *mesial temporal lobe epilepsy* with unilateral hippocampal sclerosis (21) shows anterior/mid temporal interictal spikes, which are ipsilateral or predominant over the pathological temporal lobe in 60% of cases, and a typical rhythmic 5-7 Hz ictal discharge accompanying seizures in 80%. There may also be post-ictal ipsilateral slow activity and potentiation of spikes, both of which are reliable lateralising findings.

Several familial partial epilepsies have now been described. There is variation in phenotypic and EEG expression between families; overall, familial partial seizure disorders tend to be more benign than lesional partial epilepsy. In *familial temporal lobe epilepsy*, focal temporal spikes are seen in only around 20% of clinically

affected cases. EEG findings are a defining feature of *familial partial epilepsy with variable foci*, which manifests as temporal and extratemporal seizures; the EEG focus is usually congruent with seizure type in individual cases. In *autosomal dominant frontal lobe epilepsy*, interictal EEG is often normal, and ictal EEG unhelpful or non-localising.

Routine interictal EEG & management of epilepsy

An important question for a patient presenting with a first unprovoked epileptic seizure is risk of seizure recurrence. Here, EEG is helpful, since risk is higher when the initial EEG shows unequivocal ED. If so, treatment should be offered after the first tonic-clonic seizure. In a systematic review (22), the pooled risk of recurrence at 2 years was 27% if the EEG was normal, 37% if there was non-specific abnormality, and 58% if epileptiform activity was present.

Inter-ictal EEG does not provide a reliable index of severity or control in seizure disorders. Reduction in the amount of epileptiform activity shows only a weak association with reduced seizure frequency, and antiepileptic drugs (AEDs) have either little or variable effect on discharge frequency. Hence routine EEG has limited value for assessment of treatment effect, except IGE when persistent epileptiform activity or a photoparoxysmal response usually indicates sub-optimal therapy in patients taking sodium valproate or lamotrigine. In general, “treating the EEG” i.e. to abolish spikes, is unnecessary, although there is emerging evidence that suppression of interictal discharges which cause transient cognitive impairment can improve school performance in some children.

A common reason for EEG referral is prediction of likelihood of seizure relapse in the patient who has been seizure free for a number of years and wishes to come off medication. However, the usefulness of EEG recording is uncertain. Relative risk of relapse if the EEG is abnormal ranges from 0.8 to 6.47 in published studies (23). Some of these studies include both children and adults, or a range of seizure types and epilepsy syndromes, and it is unclear which aspects of EEG may be important – viz. demonstration of non-specific abnormality versus ED, prior or persisting abnormality, or de novo appearance of ED during the course of or following drug withdrawal. Overall, EEG appears to be more helpful in prediction of seizure relapse in children, and otherwise for identification of epilepsies that carry relatively high risk of relapse, such as photosensitive epilepsy, juvenile myoclonic epilepsy or symptomatic seizure disorders.

Cognitive deterioration : confusional states or acute/sub-acute cognitive decline in epilepsy might be the result of a marked increase in ED; frequent subtle/clinically unrecognised seizures; a metabolic or toxic encephalopathy; or non-convulsive status. EEG plays an important role in differentiating these causes. However, electrographic confirmation of acute encephalopathy or non-convulsive status in severe symptomatic epilepsies can be very challenging, because these disorders often show substantial overlap of interictal and ictal EEG patterns.

Chronic cognitive decline in epilepsy may be due to a progressive neurological condition underlying the seizure disorder, or an independent neurodegenerative process. EEG demonstration of deterioration in background cortical activity can help to identify an organic brain syndrome, but is unlikely to discriminate as to cause. Epileptic encephalopathy is an emerging concept, notably in childhood seizure syndromes. The encephalopathy and progressive disturbance in cerebral function is viewed as being directly related to electrographic epileptiform abnormalities, but the required EEG features for a diagnosis of epileptic encephalopathy have not yet been widely agreed or defined.

Long-term EEG monitoring

Long-term monitoring (LTM) in epilepsy is available in all age groups from neonates to the elderly (24-6), and applicable in hospital and community settings. There is now substantial evidence that LTM has a crucial role in the assessment of seizure disorders, as indicated by a recent ILAE Commission report (27).

The clinical applications of EEG monitoring are:

- Differential diagnosis of paroxysmal neurological attacks
- Differentiation between nocturnal epilepsy and parasomnias
- Diagnosis of psychogenic non-epileptic seizures
- Characterisation of seizure type & the electro-clinical correlates of epileptic seizures
- Quantification of ED or seizure frequency
- Evaluation of candidates for epilepsy surgery
- Identification of sleep related epileptiform discharge/electrical status in children
- Electro-clinical characterisation of neonatal seizures
- Monitoring of status epilepticus (convulsive, non-convulsive, electrographic)

LTM methods comprise ambulatory and video-EEG telemetry. Ambulatory EEG is more suited to clinical problems which do not require concurrent synchronised video to document clinical features (although it can be combined with hand-held camcorder), or for monitoring in an out-patient setting or specific environment. In-patient video EEG telemetry is expensive and labour intensive, and often a limited resource. Specialised telemetry units have the advantage of ward based staff, experienced in identification of subtle clinical events and able to care for patients during seizures. Methods to increase the likelihood of paroxysmal events include reduction in dose of anti-epileptic medication, sleep deprivation and provocation techniques, such as saline injections. However, the latter can result in false positives, and there are ethical issues if the patient is deliberately misled.

Optimal duration of LTM study depends on the clinical problem, and frequency of attacks. Patients are unlikely to benefit from monitoring if paroxysmal events occur less than once per week. Duration of out-patient LTM is to some extent limited by technical issues – the need to replace data storage media and batteries every 24-48 hours, and the potential for faulty recording due to poor electrode contact.

Ictal EEG

Certain seizure types have specific ictal EEG patterns, such as 3 per second

generalised spike wave discharge in a typical absence seizure, the evolving temporal theta rhythm (5-7 Hz) in mesial temporal lobe epilepsy, high frequency discharge in tonic seizures, and irregular slow spike and wave (<2.5 Hz) in an atypical absence attack. Ictal changes can however be obscured by artefact from movement or muscle, and scalp EEG may be unchanged or unhelpful in simple partial seizures, some frontal lobe epilepsies and *epilepsia partialis continua*, mostly because the epileptogenic focus is small and anatomically circumscribed or distant from recording electrodes on the scalp. In partial epilepsies, the most important ictal EEG changes for seizure localisation occur within the first 30 seconds after the seizure onset. Broadly speaking, localised and lateralised changes are more likely to be found in temporal lobe epilepsy than in extratemporal seizures, and epileptiform or high frequency discharge tends to be seen in neocortical epilepsy, particularly when the focus is relatively superficial (28-9). Frontal lobe epilepsy often shows generalised or widespread high frequency activity/ slow rhythms / attenuation, as a result of rapid propagation or secondary generalisation.

The EEG and status epilepticus

EEG is essential for correct diagnosis and management of status epilepticus (SE) in convulsive and non-convulsive forms. The different electro-clinical types of SE show common EEG features, manifest as waxing and waning rhythmic or patterns or epileptiform discharges (30).

In *convulsive status epilepticus*, EEG is used diagnostically to confirm that the patient has status and not pseudostatus, in which ictal EEG is normal, and to differentiate causes of altered mental status – on-going seizure activity, drug-induced coma, or other encephalopathy (31). In refractory convulsive status, EEG monitoring to control and guide treatment is essential once general anaesthesia (GA) has been induced, as clinical manifestations of continuing seizure activity may be subtle or absent. A typical end-point for GA treatment is EEG burst suppression; cessation of seizure activity or ED may be sufficient, but is less easy to define. EEG can contribute prognostic information: continuing electrographic status is associated with worse outcome in convulsive status (32), and some studies have shown that periodic epileptiform discharges are associated with poorer outcome independent of aetiology of status (33).

Non-convulsive status epilepticus (NCSE) covers a range of conditions, which have variable clinical features and aetiological bases: generalised absence status, *de novo* absence status, simple partial status epilepticus, complex partial status, electrographic status with subtle clinical manifestations, and electrical status epilepticus in sleep (34). EEG patterns described in NCSE include continuous spike wave discharge, discrete localised electrographic seizures, diffuse slow activity with or without spikes, and periodic/repetitive ED. Electrographic diagnosis is relatively easy in generalised absence status, when the prolonged state of altered consciousness is accompanied by generalised 3Hz spike-wave discharge. EEG confirmation is usually straightforward in persistent electrographic status after control of convulsive status, and in children with ESES. More problematic are cases of simple partial status, in which the EEG can be unchanged or non-specific;

or in acute cerebral damage due to anoxia, infection or trauma, when EEG abnormalities may be due to the primary pathology (35).

Role of neurophysiology in evaluation of patients for epilepsy surgery:

Interictal and ictal EEG are pivotal in pre-surgical assessment, in conjunction with neuroimaging and neuropsychological evaluation, but the importance of neurophysiological investigation depends in part on the surgical procedure. It is high in resective surgery (lesionectomy, lobectomy) and multiple sub-pial transection, moderate in hemispherectomy, and low in functional procedures (callosotomy, vagal nerve stimulation) except to exclude the option of resection.

Neurophysiological assessment in pre-surgical evaluation is aimed at:

- ensuring that the individual has epileptic seizures (4-10% of patients in surgical programmes have co-morbid psychogenic non-epileptic seizures)
- characterisation of electro-clinical seizure features, and show concordance with other data (MRI, functional imaging, psychometry)
- demonstration of epileptogenicity in the presumed pathological substrate of refractory epilepsy
- identification of possible other epileptogenic foci
- assessment of cortical function when pathology is in or close to eloquent cortex

Whilst most epilepsy surgery candidates can be adequately investigated by scalp interictal and ictal EEG, some require invasive neurophysiological studies. The proportion who do in a given epilepsy surgery centre depends on complexity of case mix, availability of non-invasive localising investigations such as SPECT, PET, MEG, and fMRI-EEG. Invasive EEG utilises depth electrodes (rigid or flexible multi-contact wires inserted under stereotactic MRI guidance, most appropriate for deep lying foci, and with the disadvantage of sampling only small areas of brain), and sub-dural electrodes (strips or grids, inserted via a craniotomy or burr hole, and recording from larger superficial cortical regions). Cortical stimulation can be performed with either type of electrode. Electrode selection and placement is determined by location of the epileptogenic zone. The usual indications for invasive EEG are dual or possibly multiple potential epileptogenic pathologies, bilateral hippocampal sclerosis, and focal lesions in eloquent cortex. Invasive EEG is also undertaken when underlying structural pathology is not evident on neuroimaging, but a plausible hypothesis as to location of the epileptogenic region has been generated by other investigations.

Specialised neurophysiological techniques

A number of techniques have been developed to optimise selection of candidates for epilepsy surgery, and to enhance understanding of the anatomical-pathophysiological basis of epilepsy. These include analytical methods to study seizure propagation (small time differences in EEG signals, cross-correlation, chaos theory); source localisation of the generators of epileptic foci using EEG, magnetoencephalography and combined functional MRI/EEG; DC recording; measurement of cortical excitability through magnetic brain stimulation (36); and

anticipation/prediction of seizures using linear and non-linear analysis of EEG signals (37). These techniques are of considerable theoretical interest, but at present, their application is largely confined to specific areas of research.

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