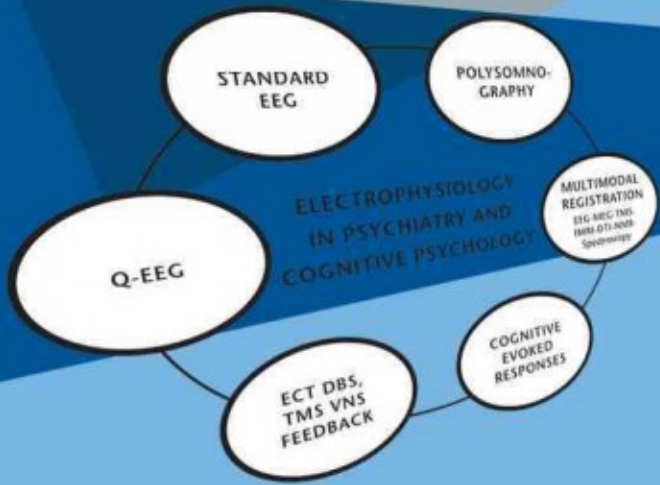
Standard Electroencephalography in Clinical Psychiatry

A practical handbook

Editors: Nash Boutros, Silvana Galderisi, Oliver Pogarell and Silvana Riggio



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A practical handbook

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Preface

Electroencephalography (EEG) is an important, non-invasive functional method for the investigation of electrical activity in the brain. EEG alone, or at times in combination with video EEG monitoring, is a very useful tool in the differential diagnosis of psychiatric and/or neurological presentations. It can also be useful for monitoring and helping to evaluate the clinical or therapeutic course of psychiatric disorders and to guide treatment plans.

The idea of a practical handbook on *Standard Electroencephalography in Clinical Psychiatry* was originally conceived by Dr N. Boutros following many discussions amongst members of the EEG and Clinical Neurosciences Society. These discussions concerned the relative roles of the standard (visually inspected) EEG (EEG) and the quantified EEG (QEEG) in clinical psychiatry. They resulted in the firm conclusion that both techniques are important and that they are complementary. While a number of texts addressing QEEG applications in psychiatry have been published in recent years, the last book addressing EEG in psychiatry was that by John R. Hughes and William P. Wilson [1] from 1983. We therefore started to compile this book, which integrates our combined knowledge and will serve as a comprehensive and practical guide to assist psychiatrists in clinical decision making using EEG.

This book was envisioned as a practical guide to assist psychiatrists in clinical decision making using EEG. It reviews the basics of a normal and abnormal EEG exam, the value and the limitations of EEG testing and its clinical indications. Specific clinical pitfalls and pearls, that are 'red flags', in the EEG assessment are stressed throughout the book.

Despite the fact that we have had the ability to record brain electrical potential since 1924 and that this work was spearheaded by Dr Berger, a psychiatrist, to this day the significance of some EEG changes present in psychiatric patients remains poorly understood. The scalp-recorded visually inspected standard EEG is an under-utilised tool in the assessment of patients with a psychiatric diagnosis: failure to utilise this tool may contribute to a delay in making an accurate diagnosis and initiating appropriate therapy. The EEG is an essential tool in the differential diagnosis of neurological versus psychiatric disorders, especially when performed in correlation with the clinical manifestations and when special techniques such as video monitoring recording are used.

The goals of this book are to provide a brief historical perspective of EEG in psychiatric practice; to provide an understanding of the physiologic bases of the EEG signal and of the basic elements of EEG recording; to review normal and abnormal EEG patterns; and to provide the psychiatrist with a clear understanding of both the value and limitations of EEG testing and its clinical indications in the diagnostic work up as it applies to psychiatric patients.

There is detailed coverage of the role of EEG in:

(1) the evaluation of non epileptic seizures;

(2) the differential diagnosis of the behavioural manifestations of seizures of frontal lobe origin;

(3) the differential diagnosis of nonconvulsive status epilepticus;

(4) the evaluation of childhood psychiatric disorders;

(5) the assessment of the patient with psychosis, mood disorders and catatonia;

(6) the assessment of personality disorders and anxiety disorders;

(7) the differential diagnosis of delirium versus dementia and its differentiation from a primary mood, anxiety or psychotic disorder.

After an historical review, Chapters 2 and 3 provide a synopsis of the physiologic bases of the EEG and its recording and analysis methodology. Chapters 4 and 5 then summarise the most important normal and abnormal EEG patterns. These chapters are not meant to be comprehensive: the interested reader is referred to the many available EEG atlases.

Chapter 6 emphasises the potential of the EEG in the evaluation of behavioural manifestations in order to help reach a clinical diagnosis and develop an appropriate treatment strategy. The following chapters address the application of this technique in specific groups of disorders, starting with developmental disorders, that is ADHD, autism, conduct disorders and learning disabilities even in the absence of seizures. Helpful guidelines are provided for when to use an EEG in the evaluation of these entities.

Chapter 8 discusses possible EEG findings in the evaluation of psychosis, mood disorders and catatonia with particular reference to their prognostic implications and addresses the differential diagnosis with general medical conditions. This is followed by chapters on personality disorders and anxiety disorders and on delirium and dementia.

Chapter 11 describes the effects of psychotropics drugs on the EEG. It includes a discussion of data indicating the usefulness of EEG in the diagnosis of drug-induced CNS side effects or toxicity.

The final chapter highlights the need for training guidelines and certification processes specific to Neuropsychiatric Electrophysiology and the issues involved in developing training programmes and certification.

Throughout the book, the authors provide specific illustrations of the different EEG patterns and review various technical artefacts. These illustrations will enable the reader to have a clear understanding of both the value and limitations of EEG testing and its clinical indications. Helpful clinical vignettes, together with well designed summary tables and flow diagrams, support the application of EEG in the differential diagnosis of psychiatric and neurological illnesses. An overall goal of the volume is to make the point that EEG abnormalities (whether focal or diffuse slowing, abnormal background rhythms, or epileptiform activity) represent important findings that must be taken into consideration when formulating a biopsychosocial understanding of an individual patient.

Reference

1. John, R. Hughes and William P. Wilson (1983) *EEG and Evoked Potentials in Psychiatry and Behavioral Neurology*, Butterworth-Heinemann.

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Historical Review of Electroencephalography in Psychiatry

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Introduction

The very beginning of the field of human electroencephalography (EEG) emerged directly from the field of psychiatry. Its founder, Hans Berger, was a biologically orientated psychiatrist with strong interests in the relationships between mind and body (Figure 1.1) [1]. In 1924, after years of frustrating failed experiments, his overwhelming dedication and persistence finally resulted in the first non-invasive scalp EEG recordings from humans and in 1929 he launched nearly a decade of landmark publications (all in psychiatric journals) that essentially laid down the very foundation of this new field.

Recent decades have seen a substantial resurgence of interest in biological psychiatry and perhaps this will permit greater utilisation of those strengths of EEG already known to exist as well as those that appear to hold substantial promise pending further research. Berger, if he were alive today, would surely be pleased.

The early pre-clinical era

Richard Caton, a Professor of Physiology, was the first to document the existence of electrical potentials emanating from the brains of live animals [2]. The electrical currents

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Figure 1.1 Hans Berger.

of the brain concept was not enthusiastically received because leading authorities of the time simply knew that the brain did not produce a global electrical field.

Following Caton's discovery several exciting developments emerged which not only confirmed his work but also significantly amplified and extended his findings. In one of them Adolf Beck [3,4] was able to show that the visual cortex of the dog produced large electrical potentials when the animal's eyes were rhythmically illuminated. Although Beck could not have known it at the time, his work anticipated the later discovery of 'photic driving' in the human EEG and the subsequent development of 'photic stimulation' for use in activating spike and/or spike wave discharges during clinical EEG studies. Fleischl von Marxow [5] (1890, Vienna) found that the electrical potentials that were recorded could be modified by illuminating the animals eyes and that this phenomenon could be abolished by chloroform. Several early investigators continued to produce evidence that peripheral stimulation of various kinds could produce alterations of the electrical activity detected from the surface of the animal's exposed cortex [1]. Much of this work anticipated today's field of human evoked potentials. As this early period was coming to a close, significant technical improvements in recording amplifiers made it easier to obtain recordings of electrical activity from the outer surface of the animals skull and this more than anything made studies with humans possible.

Early history of human electroencephalography

The early history of human electroencephalography is essentially the history of Hans Berger's work. Berger proceeded over the next decade to publish a landmark series of 23 papers covering many of the fundamental phenomena of the human EEG.

Berger's achievements are far too numerous to document in detail. Amongst his historical achievements is coining the term alpha waves to describe the 10 Hz activity characterising the awake relaxed EEG of adult humans and, of course, he coined the word 'electroencephalogram'.

In less than a decade after Berger's initial publication, the potential use of EEG was being very actively explored in psychiatry and neurology. The strongest correlations between EEG findings and clinical disease involved epilepsy, structural lesions and encephalopathies and this fact essentially moved electroencephalography closer to the discipline of neurology and away from its roots in psychiatry. Although at the same time several minor EEG abnormalities were being found in much higher incidences in samples of psychiatric patients as compared with normals, most of these EEG findings lacked clear psychiatric diagnostic specificity and this operated to reduce interest in EEG amongst many psychiatrists.

The impetus for using EEG in the study of seizure disorders began when Frederic Gibbs became aware of an animal study by Fischer [6] that showed that high-voltage discharges in the brain were produced when the animals were thrown into seizures by administering convulsive drugs. Gibbs and his team soon discovered [7] the diffuse 3/sec. spike and wave and this finding became the EEG signature for petit mal epilepsy. Many other discoveries related to epilepsy soon followed.

Of more specific relevance to psychiatry was the discovery a little over a decade later [8] of the focal anterior temporal EEG spike discharge which became recognised as a diagnostically useful interictal EEG finding in complex partial seizures (previously 'psychomotor epilepsy'). This EEG finding continues to be under-investigated in order to clearly identify its differential diagnostic implications in the practice of psychiatry. This discovery by Frederick and Erna Gibbs and their collaborators was followed by the description, by the same group, of a number of EEG patterns that tend to be more common in psychiatric patients and have come to be collectively known as the 'controversial EEG patterns'. Frederick Gibbs (Figure 1.2) is widely regarded as the true father of clinical electroencephalography.

Second only to seizure disorders, space-occupying lesions provided an avenue through which early EEG could begin to prove its clinical value. The early EEG discoveries in structural lesions were particularly relevant to psychiatrists of that time, and up until the introduction of CT scans EEG referral for suspected tumour was an accepted and valuable part of psychiatric practice. This was understandable because the early literature contained numerous references to the frequent occurrence of psychiatric symptoms in patients found to have brain tumours [9–12], a phenomena which has remained constant up to the present.

Figure 1.2 Frederick Gibbs.

Unlike the field of epilepsy, where EEG had strong clinical roots and where it still remains as a mainstream clinical tool, the assessment of suspected structural lesions has largely moved away from EEG to embrace the more recent imaging techniques, which admittedly are more definitive. Today, practitioners in metropolitan areas would seldom consider EEG as a first referral option for suspected brain tumour. Nonetheless, one should not forget that in some of the more rural locations EEG may be quite a bit more available than the newer and more expensive imaging techniques and it still will detect focal slowing in nearly 90% of tumours of the outer cortex [13].

In one of his later papers, Berger [14] secured EEG tracings from a psychiatric patient undergoing treatment with insulin and was able to demonstrate that EEG slowing accompanied the induced hypoglycaemia. As Niedermeyer [15] later observed, this ushered in the whole wide field of EEG studies of all types of encephalopathies, including delirium.

Historically, the early EEG discoveries occurring with epilepsy, structural lesions and encephalopathies were of considerable clinical value and were often used in assessing what were sometimes life-threatening events. Thus these were the early uses of EEG which had the highest visibility and recognition and because of this EEG came to be increasingly identified with neurology. Gradually, over ensuing years, most (but not all) EEG laboratories became housed within neurology departments or neurology practices.

The neurology discipline appreciates hard EEG data with well-documented and strongly supported diagnostic relevance. Psychiatry must of necessity (at least at the current state of knowledge) be concerned with EEG findings that are associated with a variety of altered behaviours and not necessarily with diagnostic categories defined by current classification systems. The value of EEG findings in psychiatry must be determined from within the field of psychiatry and cannot be evaluated in terms of the clinical conditions deemed important by neurologists.

Electroencephalography in psychiatry today

The interest for electrophysiology in psychiatry is undergoing a renaissance, especially for research purposes; examples are the increasing number of papers on electrophysiological endophenotypes of schizophrenia or multimodal imaging including electrophysiology to unravel neurobiology of psychiatric disorders. Initiatives to promote EEG applications in psychiatry are today found in the mission of scientific societies such as the EEG and Clinical Neuroscience Society (ECNS) and the Psychophysiology Section of the World Psychiatric Association.

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2

Physiologic Basis of the EEG Signal

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Membrane potentials

The EEG is the recording of the spontaneous electrical activity generated by cerebral neurons. Like all other cells in the body, neurons have high concentrations of potassium (K^+) and chloride (Cl^-) ions inside, while high concentrations of sodium (Na^+) and calcium (Ca^{2+}) ions are kept outside. This leads to a voltage difference of about -60 to -70 mV with respect to the outside of the cell membrane. Such a voltage difference is modified by the flux of ions depending on the opening and closing of ion channels induced by electrical or chemical stimuli. A reduction of charge separation across the membrane, due to an influx of positive charged ions into the cell, results in a less negative membrane potential and is termed depolarisation, whereas an increase in charge separation leading to a more negative membrane potential is called hyperpolarisation.

When a critical amount of Na^+ enters the cell and the membrane potential reaches a threshold level, the opening of additional Na^+ channels is facilitated leading to a sudden marked increase of depolarisation. This fast depolarising event corresponds to the rising phase of the action potential, while the falling phase is related to an outflux of K^+ ions which, combined with a decrease of Na^+ influx, induces a repolarisation of the cell. After an action potential, there is a transitory inactivation of Na^+ channels that causes a refractory period during which another action potential cannot be generated.

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Excitatory and inhibitory postsynaptic potentials

The action potential can traverse long axonal distances, reaching the nerve terminal without loss of amplitude. It triggers the release of neurotransmitters across the synaptic cleft, propagating the signal to the next neuron in the circuit. An action potential in the excitatory and inhibitory presynaptic fibre induces an excitatory postsynaptic potential (EPSP) and an inhibitory postsynaptic potential (IPSP), respectively, in the postsynaptic neuron [1]. An EPSP produces a flow of positive charges into the cell (current sink), while an IPSP acts in the opposite way by inducing a flow of positive charges out of the cell (current source).

Both EPSP and IPSP, rather than action potentials, represent the most significant source of scalp-recorded EEG signals [2, 3]. In fact, although action potentials have a higher amplitude, synaptic potentials have a longer duration (tens of milliseconds), which increases the probability to occur with a temporal overlap, and involve a larger membrane surface; these characteristics allow both temporal and spatial summation. Action potentials last too short a time (<2 μs) to contribute to scalp-recorded EEG, except during synchronous events such as sleep transient activity and epileptic discharges.

Nonsynaptic intercellular events contributing to the EEG signal

Recent findings highlighted the possible contribution of nonsynaptic intercellular events such as subthreshold oscillations, after potentials and Ca^{2+} spikes, which also produce long-lasting transmembrane events, to the EEG signal [4]. Moreover, it has been reported that not only neurons but also glia cells can contribute to the mean field measured by EEG, probably with an amplifying effect [5, 6].

Factors determining polarity and other characteristics of the surface EEG waveforms

The main contribution to the electrical signal detected by the electroencephalograph is represented by the summed extracellular electrical field potentials generated by EPSP and IPSP on dendrites and neuronal cell bodies of the cortex [7, 8], in particular those of the vertically orientated pyramidal neurons, with apical dendrites extending upward to more superficial laminae and axons projecting to deeper laminae [9]. The polarity of the surface potentials is related to the location of the synaptic activity within the cortex, since scalp EEG electrodes detect the extracellular electrical fields generated closer to the cortical surface. An EPSP in a dendrite produces electrical negativity in the immediately surrounding area, with the electrical field becoming positive with increasing distance from the source. The reverse occurs with an IPSP, generating an electrical positivity

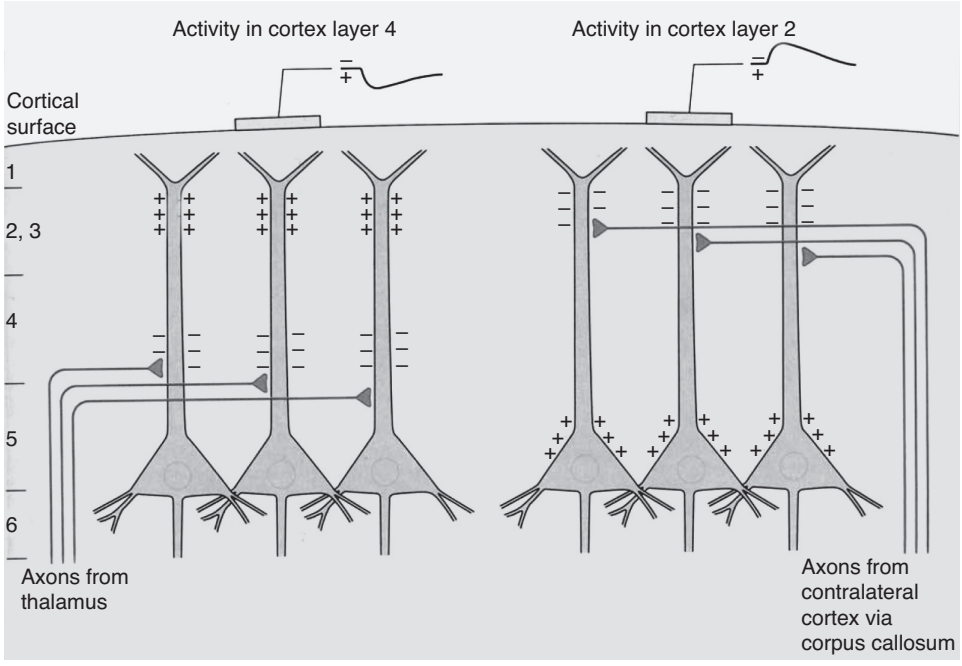

Figure 2.1 Generation of extracellular voltage fields from graded synaptic activity. Relationship between polarity of surface potentials and site of dendritic postsynaptic potentials. (From Kandel *et al.*, Principles of Neural Science, 2000), with permission of the McGraw-Hill Companies.

nearby and a negative field at a distance. So, a deep IPSP and a superficial EPSP will both generate a scalp negativity and vice versa (Figure 2.1).

In both cases, a dipole is created with separation of charge vertically orientated in the cortex. Thus, source areas in the cortical sheet that are parallel to the scalp produce radial fields that are better detectable with scalp electrodes, since they have a maximum field directly above the source and another one with opposite polarity on the opposite side of the head (Figure 2.2). Source areas in the cortex that run down the sulci, oriented orthogonal to the scalp, generate tangential dipoles which are not well seen by scalp EEG since both positive and negative voltage maxima are displaced to either side [10]. Furthermore, substantial impedance to electrical conduction from skin, skull, dura and brain tissue exists between the source of generated electrical potentials and the detecting electrode on the scalp. Weak electrical signals, even those close to the surface, may escape detection. For these reasons spatial and temporal summation of cortical activity is necessary to produce a voltage field recordable from the scalp. The amount of tissue needed to produce an EEG spike has been calculated to be 2 cm × 3 cm [11]. This size of lesion is rather large. Much smaller lesions could have profound effects on cerebral activity but any abnormality produced would escape EEG detection using currently available technology. Advancing the EEG technology to detect spikes emitted from smaller lesions has neither been easily forthcoming nor seriously sought after.

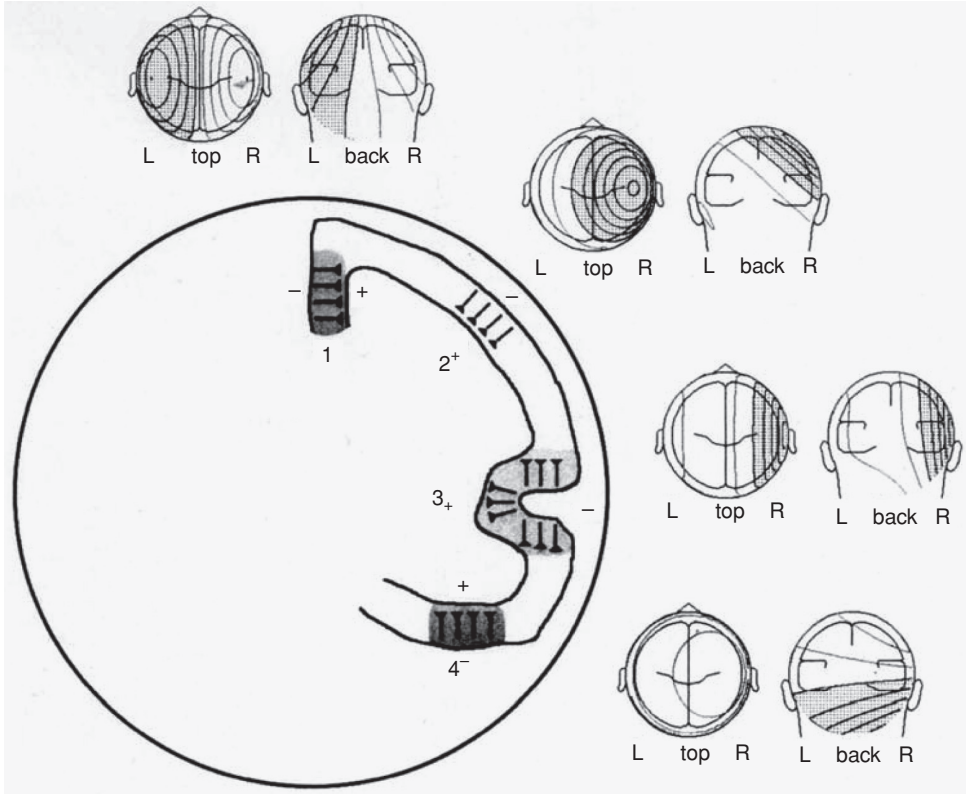

Figure 2.2 Schematic of a brain cross-section, illustrating four representative cortical EEG sources. Sources 2 and 3 produce radial fields which have a maximum field directly above the source and another one with opposite polarity on the opposite side of the head; sources 1 and 4 produce tangential fields which are not well seen by scalp EEG since both positive and negative voltage maxima are displaced to either side. (From Ebersole, Current Practice of Clinical Electroencephalography, 2003), with Permission of Wolters Kluwer.

To summarise, factors influencing size, shape and duration of EEG waves include: the distance of the recording electrode from the current generator, the anatomical orientation of the layer of pyramidal cells generating the signal, and the duration and number of synchronously activated postsynaptic potentials.

Brain structures involved in the genesis of EEG rhythms

The generation of wave-like potential fluctuations on the scalp surface can be explained as follows: synchronised groups of action potentials in afferent fibres that make contact with the superficial dendrites of cortical neurons generate EPSPs summated into major depolarisations, whose amplitude and duration depend on the discharge pattern of the

afferent fibres. If a periodic sequence of the afferent bursts occurs, the recording of the field potentials shows sinusoidal potential fluctuations [12, 13].

Brain structures involved in the genesis of EEG rhythms (defined as regularly recurring waveforms of similar shape and duration) include thalamus and cerebral cortex as well as several generalised modulatory systems arising in the brainstem core, posterior hypothalamus and basal forebrain. Neurons of these structures have intrinsic oscillatory properties [14, 15] that play an important role in shaping the rhythmic behaviour of the network to which they belong, but probably are not sufficient to account for the network rhythmic behaviour. It has been hypothesised that synaptic activities within complex neural networks modulate such intrinsic neuronal properties [16]. The main circuits responsible for the occurrence and modulation of rhythmic behaviour include three types of neurons: thalamic neurons with cortical projections (thalamocortical neurons), thalamic reticular neurons and cortical neurons. According to the facultative pacemaker theory [12], thalamocortical neurons act as pacemakers, by means of a biofeedback mechanism, sending excitatory (glutamatergic) fibres to the cortex and receiving fibres that end on thalamic inhibitory interneurons, as well as excitatory fibres from the mesopontine cholinergic neurons; according to the nucleus reticularis hypothesis [17], thalamic reticular neurons act as pacemakers by releasing the inhibitory neurotransmitter GABA in rhythmic bursts of depolarisations directed to the neurons of the dorsal thalamus and rostral brainstem [18] (Figure 2.3).

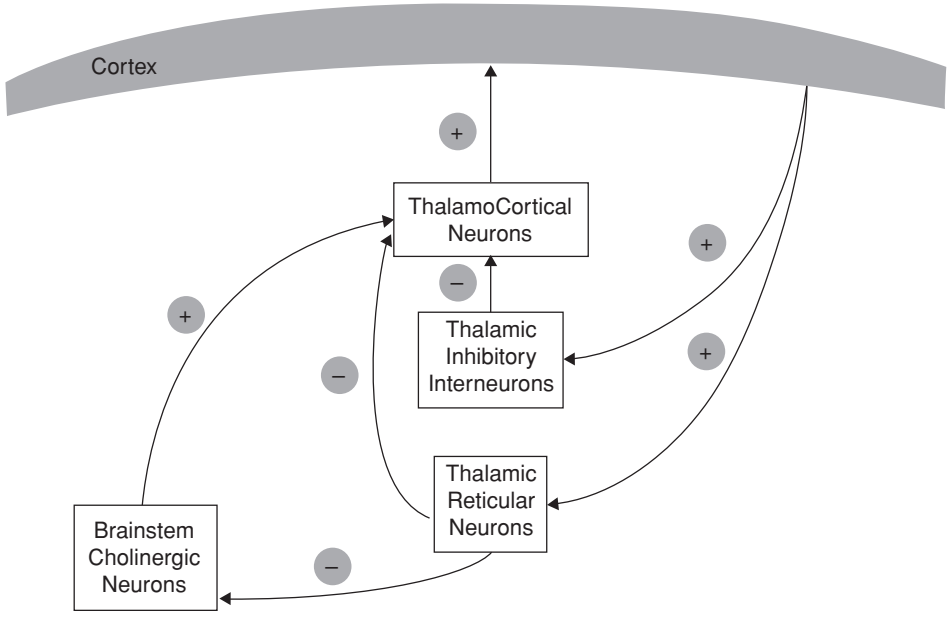

Figure 2.3 Scheme of thalamic neural networks implicated in coherent oscillations and their control by brainstem cholinergic neurons.

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3
EEG Recording and Analysis

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Techniques and technical background

Electroencephalography means detection and recording of brain electric activity generated by the cortex via electrodes applied to the scalp and connected with highly sensitive technical devices. The amplitudes of brain activity and rhythms are within the range of microvolts, which means that powerful amplifiers and filters are needed to detect and distinguish brain activity from other biological signals or technical artefacts [1–3].

EEG machines are needed for recording, amplification, filtering, presentation and storage of brain electric activity. Usually, detection and recording of brain signals take place on the scalp surface via electrodes mounted at specific locations covering the skull, according to the 10-20 Electrode Placement System, an international standardised system [4, 5].

The detection of the very low amplitude EEG signal requires a stable electric conductance between scalp surface and amplifiers, provided by electrodes and electrically shielded wires. Electrode paste, alcohol or other fluids are used to improve the conductivity between skin and electrodes [6–8].

EEG devices

Modern EEG devices are computerised units with online digital recording of the EEG signals, stored in an electronic storage medium for further analyses. This is of

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great advantage compared to former EEG recordings on long 'paper traces'. Digital data allow offline processing (e.g. use of filters for elimination of artefacts, changes of montages, etc.) and facilitate detailed EEG analyses, especially in complex cases [9–13].

Electroencephalographs consist of an electrode board with a set of separate channels (with preamplifiers, filters) connected to electrodes placed on the scalp and receiving the electrical signals via these electrodes. The number of channels (i.e. electrodes) is relevant for the reliability of the EEG signals in terms of localisation; the minimum number of channels (e.g. for screening in emergency departments) is eight to twelve, research laboratories often use more than 64 channels [14–16].

Technical requirements

External disturbance (50 or 60 Hz cycles or other electromagnetic factors) are almost always present, influencing electrodes and signals connected to the amplifier. Therefore, a differential amplifying technique is required so that only differences of amplitudes between two input signals per channel will be amplified, and any unwanted signal similar at both inputs will be rejected or suppressed.

Typically, amplifiers show an amplification factor of at least 10 000. The differential amplification of the two input signals is based on the 'common mode rejection', which means that similar signals are decreased by a certain ratio, depending on the quality of the amplifier.

In order to further decrease unwanted low and high frequency signals (artefacts), EEG devices are additionally equipped with high- and low-pass filters that can be adjusted separately. Common settings are high-pass filters of 0.5 Hz and low-pass filters of 70 Hz to suppress or eliminate activity below 0.5 Hz or above 70 Hz. Notch filters eliminate the 50 or 60 Hz cycle artefacts.

Since nowadays most EEG machines are based on digital signal processing, greater flexibility regarding the filtering (filter settings such as frequencies, characteristics, etc.) is possible. Digital techniques allow the offline modification of signals, for example in terms of screening, re-referencing or artefact elimination.

The EEG machine itself is connected to the electrode board processing the incoming signals as differential amplifier (one per channel): only voltage differences between two electrodes (input 2 minus input 1) will be amplified and processed for output and recording (Figure 3.1). Therefore, similar signals that are in phase at both 'input' electrodes will not be amplified but suppressed or cancelled [17].

One of the input electrodes (usually input 2) serves as the 'reference', the combination of input electrodes for differential amplification depends on the montage used (see Figure 3.4).

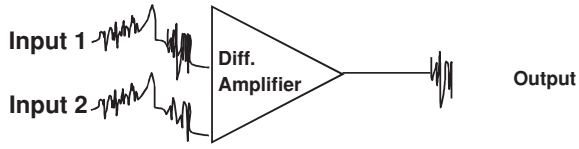

Figure 3.1 Differential amplifier. Schematic illustration of the principles of EEG recording with two input electrodes connected to a differential amplifier, which amplifies the difference between the input signals, and suppresses or decreases unwanted (similar) signals by common mode rejection (Kandel et al., Principles of Neural Science 4/e © 2000. Reproduced with permission of The McGraw-Hill Companies).

In order to decrease the technical artefact load of the recordings, filters are used to narrow the bandwidth of the amplified signals; for standard recordings usual bandpass filters are 0.53 Hz (low) and 70 Hz (high); 'notch' filters allow the rejection of electricity-based 50 Hz (or 60 Hz, where applicable) interferences by the power source [14, 18, 19].Electrodes

Standard electrodes consist of flat metal discs made of silver, gold or tin, connected to a wire (Figure 3.2). Electrodes are attached to the scalp according to a standardised system (10-20 system). Fluid substances (electrode paste, collodion, alcohol, etc.) are used to improve contact with the skin and conductivity, and to keep the impedance skin/electrode below 5 k. Metallic discs or cups are mounted on the scalp to receive electric activity for further processing (filtering, amplifying) with the EEG machine. These electrodes are connected to the EEG amplifier via shielded wire and the electrode board [4, 6].

Electrode placement: International 10-20 System

The position of the electrodes on the scalp follows an international standard placement, the so-called 10-20 International System for electrode placement. 10-20 stands for the

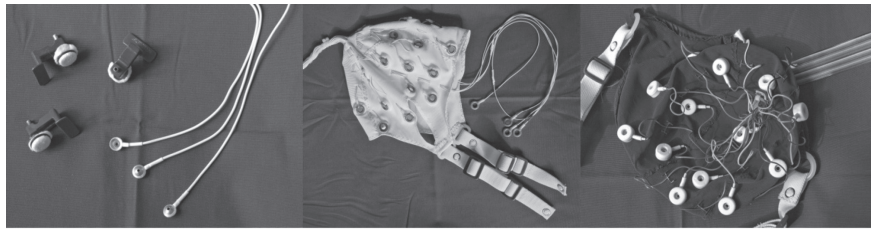

Figure 3.2 Electrodes and caps. Photograph of different types of electrodes and flexible caps, where electrodes are mounted and fixed according to the 10-20 system.

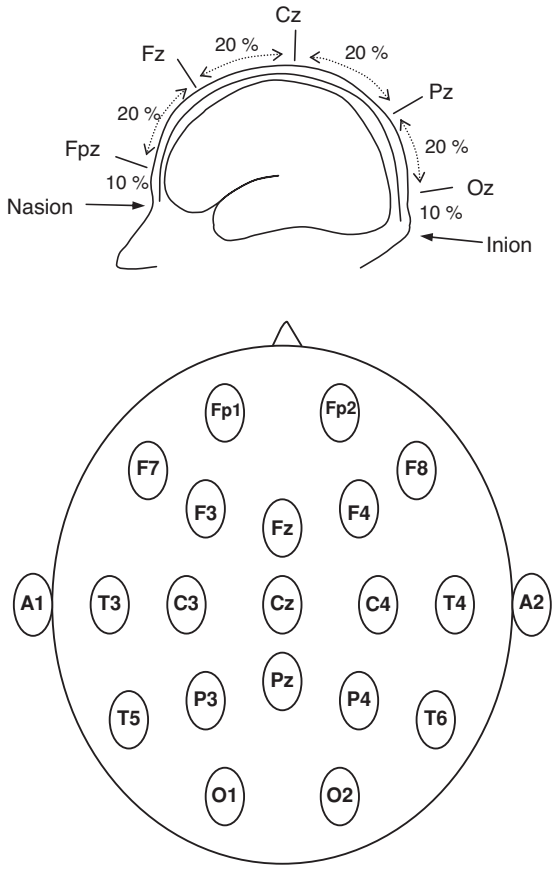

Figure 3.3 10-20 system placement of electrodes with 'landmarks'.

percentage of the distance between neighbouring electrodes relative to the distance between beginning and end of a row, for example the midline between nasion and inion, the circumference above eyebrows and ears, or the coronal electrodes between left and right earlobes (Figure 3.3).

Each electrode has an identifying name with a letter indicating the general area (F – frontal, C – central, P – parietal, T – temporal, O – occipital, A – earlobes) and a figure indicating the location relative to the midline, with higher numbers for more lateral placements. Electrodes over the left hemisphere have odd numbers, those over the right hemisphere have even numbers [5, 10, 20].

Montages

EEG signals reflect the recording and amplification of brain electrical potentials that are different between two electrode sites (differential amplification of the difference

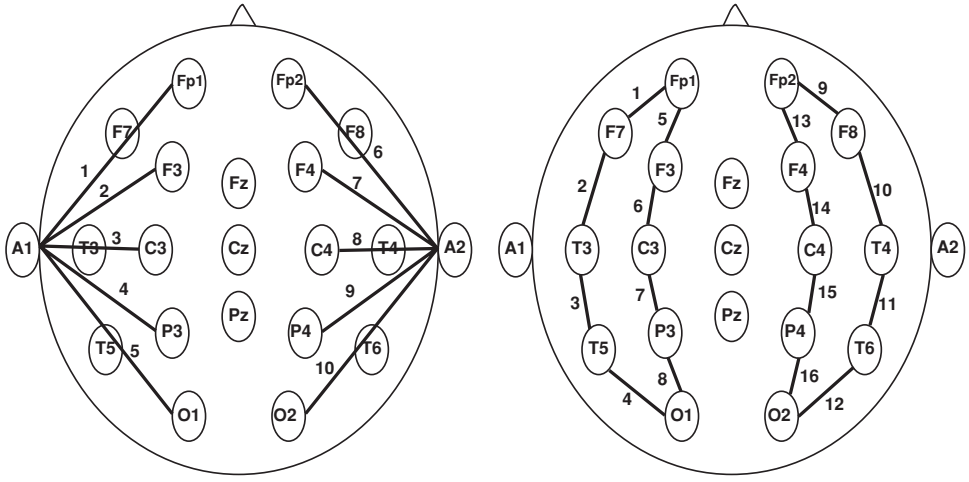

Figure 3.4 Montages. Illustration of a referential montage (left) with the references A1 and A2 for left side and right side electrodes, respectively, and a bipolar montage (right) with the arrangement of neighbouring electrodes in longitudinal chains.

between amplifier inputs 1 and 2). Signals are processed via differential amplification, the differential signals are provided by the amplifiers in output channels.

This means the output signals vary according to the grouping of each pair of electrodes when connecting them with the EEG machine. Therefore, it is of importance to establish a clear and comprehensible schedule for different montages which has to be disclosed beforehand for EEG analysis and interpretation.

Connection and combination of the electrodes are determined by montages with two different kinds of settings, the referential and the bipolar montage (Figure 3.4).

Referential montage means that one electrode is used as common reference (indifferent or reference electrode) for all other electrodes (different or active). The reference electrode is connected to a second input of each amplification channel. At its best, the reference electrode should be free of any brain activity. For this purpose, ear electrodes are often used. However, they too will pick up some brain activity from the temporal lobes [4, 10, 15].

Thus, the referential montage connects each of the ('active') electrodes with the same single reference ('inactive') electrode, ideally away from the scalp, for example on the ear (A1 for all left-sided electrodes and A2 for all right-sided electrodes, alternatively the linked A1/A2 electrodes form a single reference electrode) in order to amplify the 'pure brain signal' of the active electrode without contamination by other brain activities. Other frequently used examples of referential montages are the Cz reference and the common average reference (as technical connection and average of all scalp electrodes).

The bipolar montage is used to investigate differences between 'active' scalp electrodes, whereas the EEG channels receive input from two different active, usually neighbouring, electrodes that are sequentially arranged. The electrodes are connected

with each other and two 'active' neighbouring electrodes are combined for differential amplification. Available sets of electrodes are usually arranged in 'chains', reaching from frontal to occipital regions, parasagittal and temporal, longitudinally or transversally.

For EEG recording and analysis, both types of montage should be used, because they are complementary and have different advantages and disadvantages.

Reference montages are often useful in cases of general alterations excluding the reference electrode. They are less helpful to reliably detect and describe focal abnormalities, especially if the reference electrode is within the focus (for instance ear electrodes and temporal lobe abnormalities).

Reference electrodes within close distance to the scalp (e.g. nose, chin, shoulder) have the disadvantage of picking up a great deal of physical movement, muscle and electrocardiographic artefacts.

Bipolar montages in chains spread over the skull surface provide a good anatomical overview of the distributed brain activity and are more suited for the detection of focal disturbances than bilateral or generalised changes.

EEG recordings

EEG recordings should take place in a quiet, sound attenuated, electrically shielded environment. Subjects are seated in a comfortable reclining chair with eyes closed while being in a wakeful resting state. A routine recording should last for at least 30 minutes, including reactivity tests (eye opening) and activation during at least 4 minutes of deep hyperventilation. Subjects should be observed and monitored during the whole time of recording, while any clinical observations (changes in alertness, vigilance, behaviour, etc.) have to be documented. Artefacts should be identified and eliminated wherever possible [17].

EEG signals

Brain activity consists of rhythmical signals (rhythms) traditionally divided into frequency based categories; the following frequency bands are defined:

Delta band: rhythms below 4/s

Theta band: rhythms between 4/s and <8/s

Alpha band: 8 to <13/s rhythms

Beta band: 13/s to 30/s rhythms

Gamma band: rhythms above 30/s.

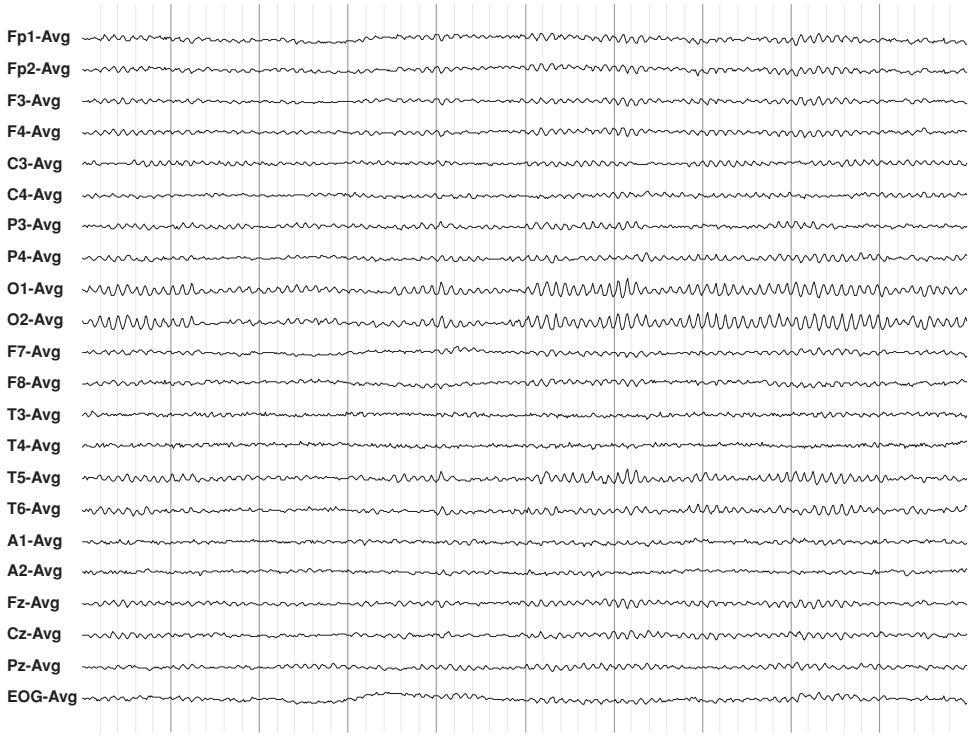

Figure 3.5 Normal EEG with eyes closed in a wakeful resting state.

The presentation of specific EEG rhythms depends on age, wakefulness and other conditions. The dominant or most prominent frequency with a clear suppression upon eye opening is called the background rhythm. In adults (wakeful resting condition) this background rhythm is within the alpha frequency band, usually 8–10/s (Figure 3.5) [1, 7].

General slowing of background activity is suggestive of a global brain dysfunction, but an increase of irregular slow rhythms can also occur in drowsiness and sleep. Faster activity can indicate mental activity, tension or the absence of relaxation (see Chapter 5 for normal rhythms and Chapter 6 for abnormal rhythms).

Interpretation and analysis of the EEG signals – artefacts

A reliable interpretation of EEG recordings is the basis for any clinically relevant report. The most important part in the analysis of the EEG is the clear detection and discrimination of alterations and disturbances that occur in the recording, but do not arise from the brain. These artefacts can be divided into two categories: biological (bioelectrical signals from the subject itself) and technical artefacts (Table 3.1) [20–23].

Table 3.1 A list of biological and technical artefacts

Biological artefacts	Technical (exogenous) artefacts
muscle activity (EMG)	defective electrodes, wires, ground
electrocardiogram (ECG)	loose electrodes
heart beat/pulse	electrostatic disturbances
eye (lid) movements	electromagnetic interference
wet skin (sweating)	50 Hz and 60 Hz power sources
body movements, breathing	
tongue movements	

Artefacts are electrical signals from various sources not related to brain electric activity. These disturbances can be technical or biological (Figure 3.6–3.20).

Technical artefacts comprise influences from the environment, the EEG machine, electrodes, wires, and so on. These signals are often only present in one channel, superimposed on the underlying brain activity, displaying a nonsensical distribution or electric field. They can be induced by the electrical power source (50 or 60 Hz), by abrupt current inductions (EEG switching on or off other electrical devices leading to electrostatic artefacts) or by sudden changes of the conductance or impedance of electrodes (defective or unstable electrodes).

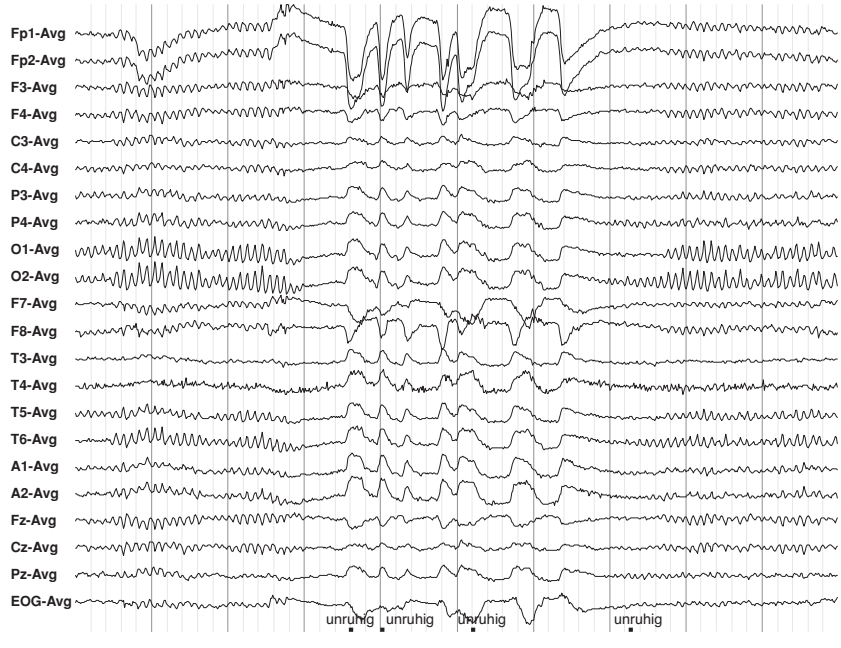

Figure 3.6 Eyes opening. Eye artefacts (vertical eye movements) and blockades of EEG alpha activity (Berger reaction).

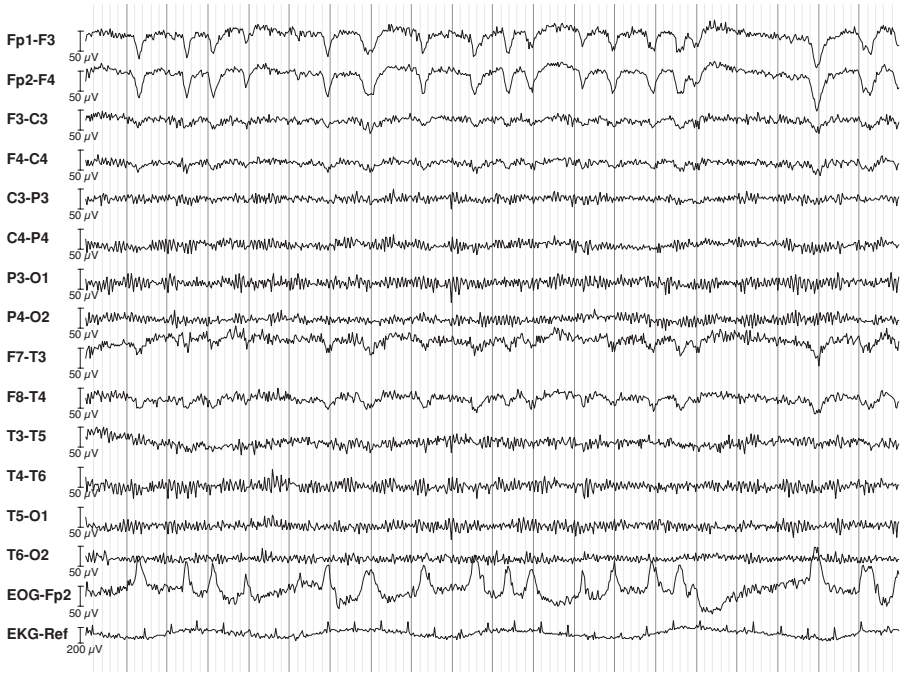

Figure 3.7 Eye movements. Artefacts due to eye movements (especially in frontal electrodes).

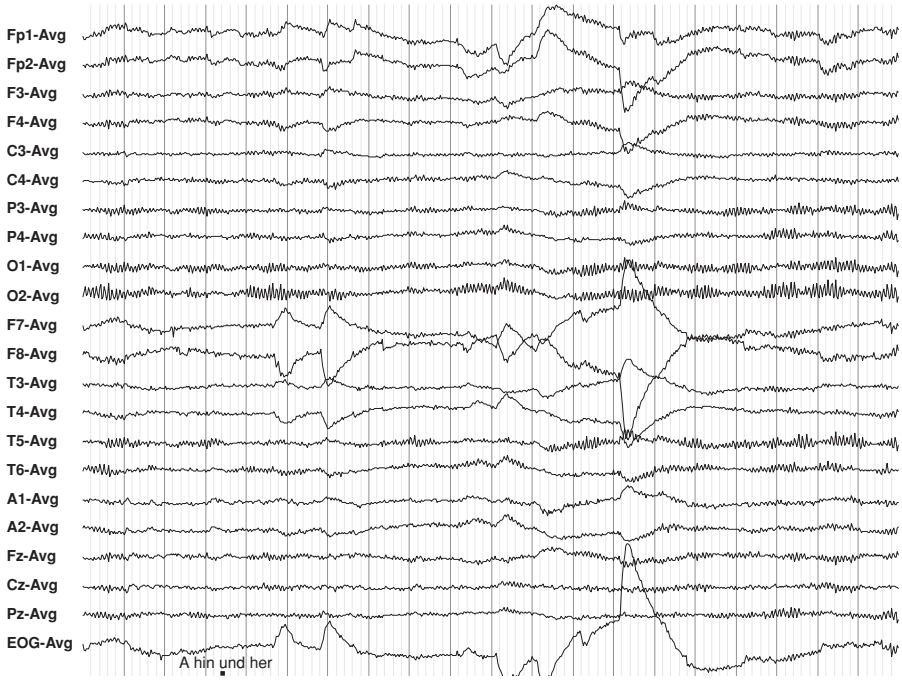

Figure 3.8 Lateral eye movements.

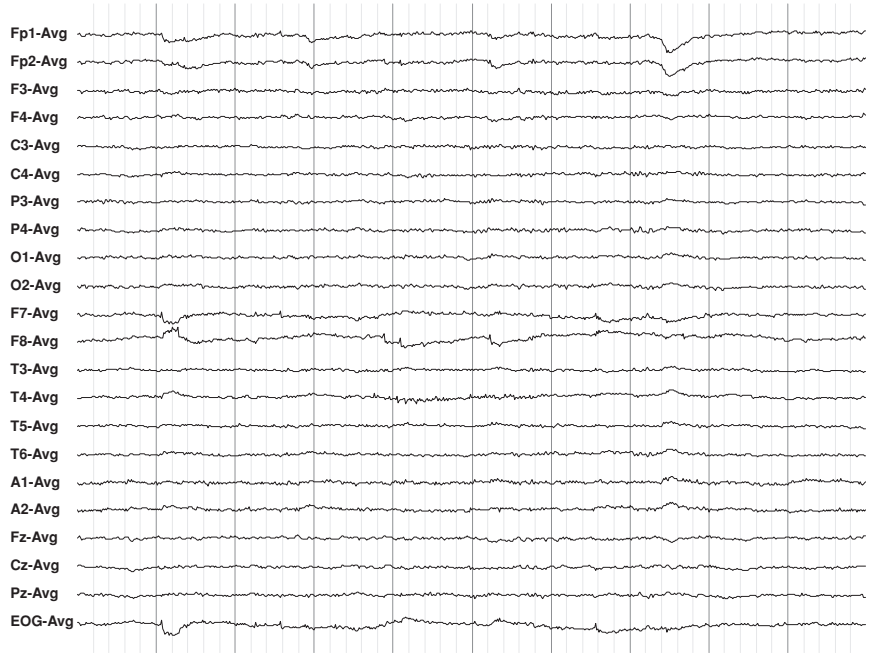

Figure 3.9 Slight lateral eye movements and rectus lateralis spikes.

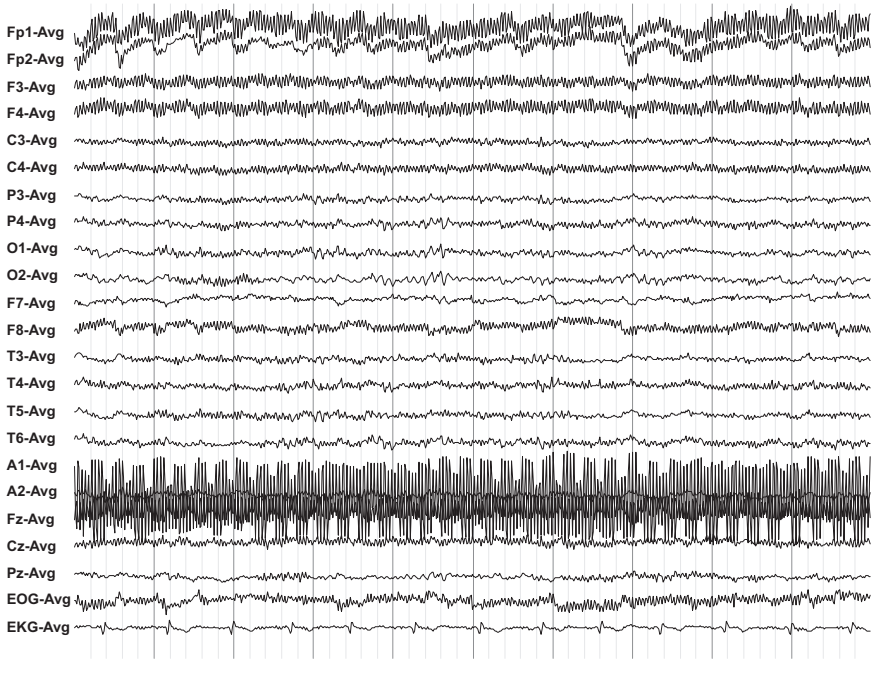

Figure 3.10 Power source artefact. Fifty Hz cycle artefact (power source) of various electrodes, leading to impairments of the entire recording.

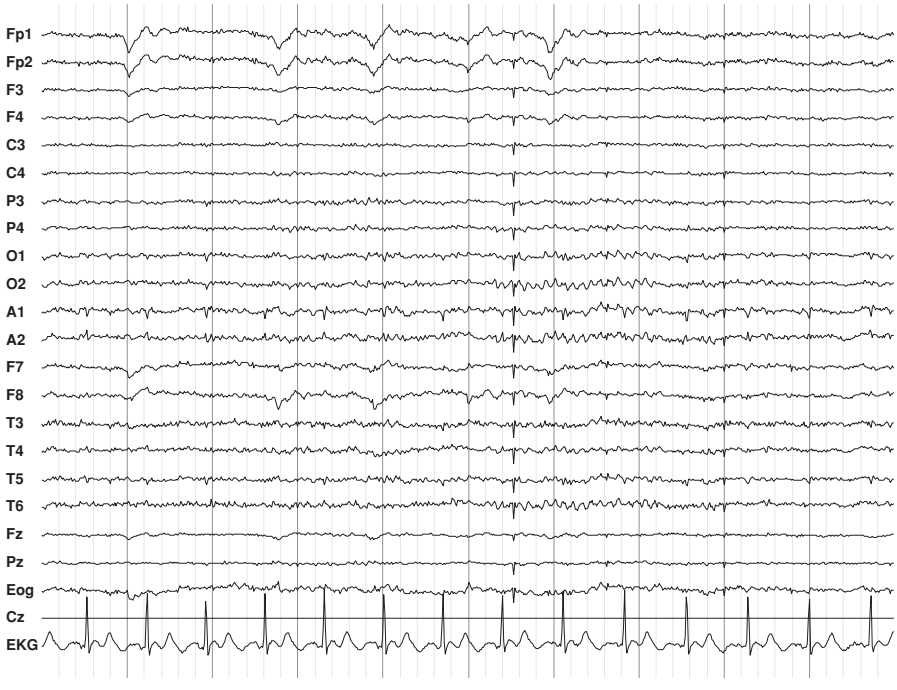

Figure 3.11 Single electric artefact (switching on the room light in the EEG chamber).

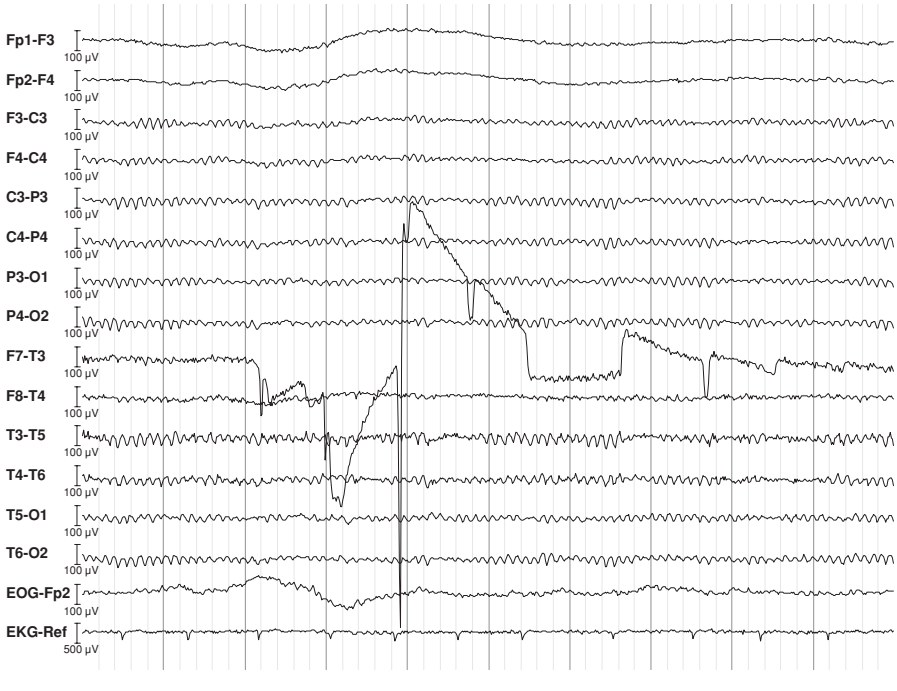

Figure 3.12 Electrode artefact of electrode F7.

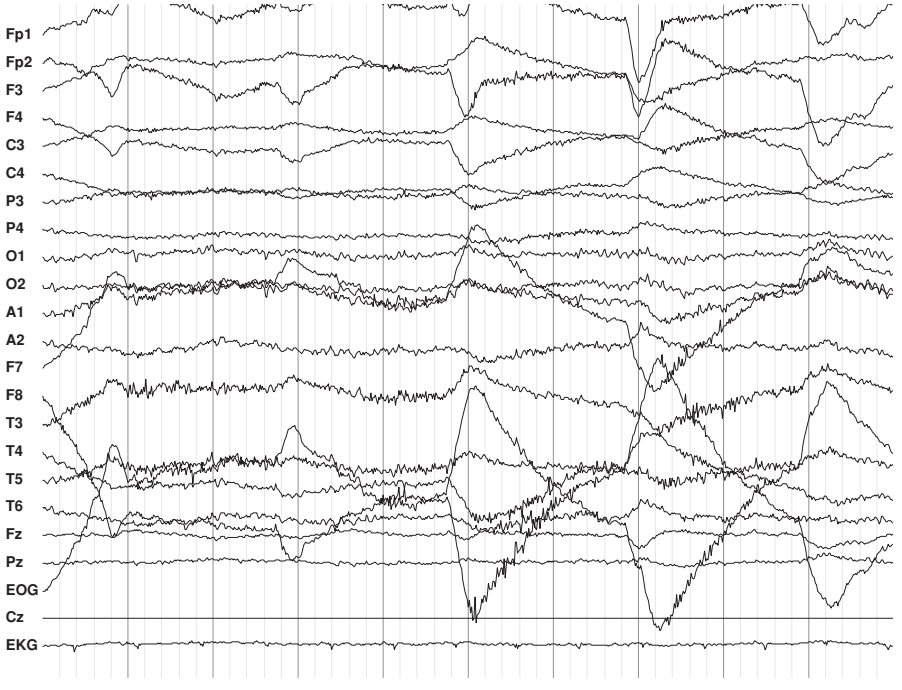

Figure 3.13 Artefacts due to head movements of the subject.

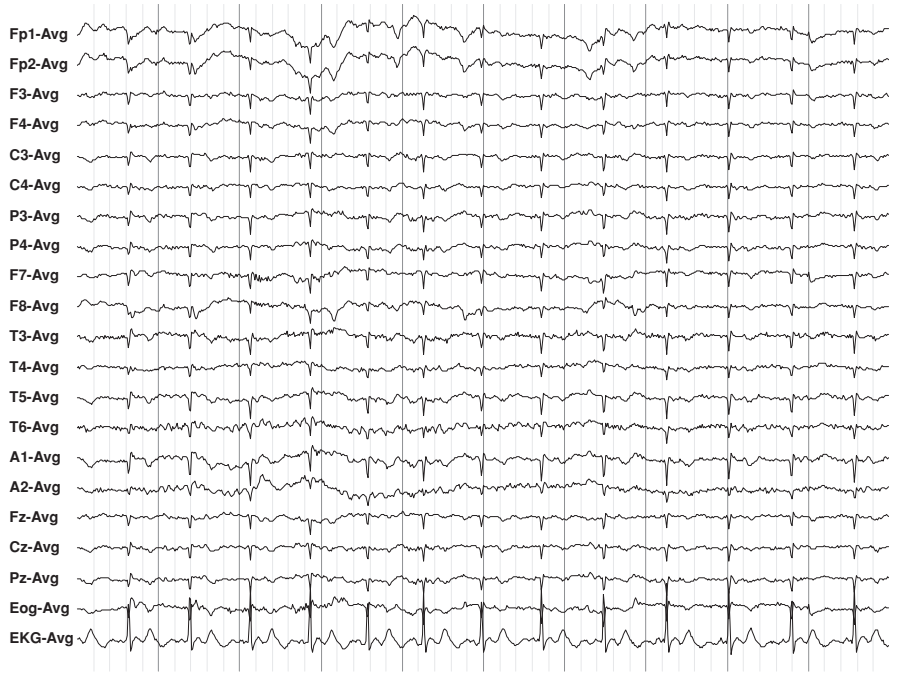

Figure 3.14 ECG artefacts.

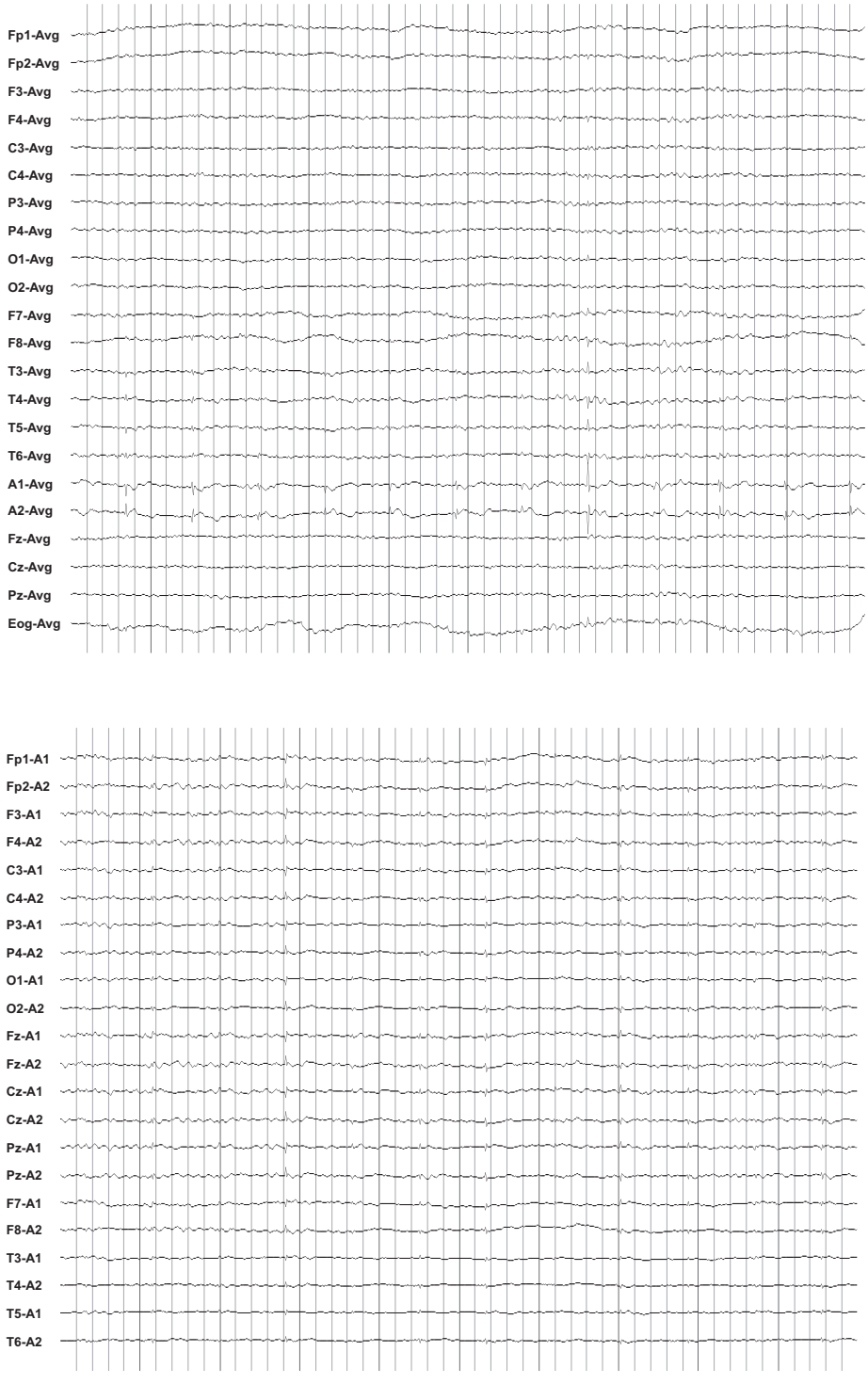

Figure 3.15 Rhythmical artefact in single channels, due to a cardial pacemaker.

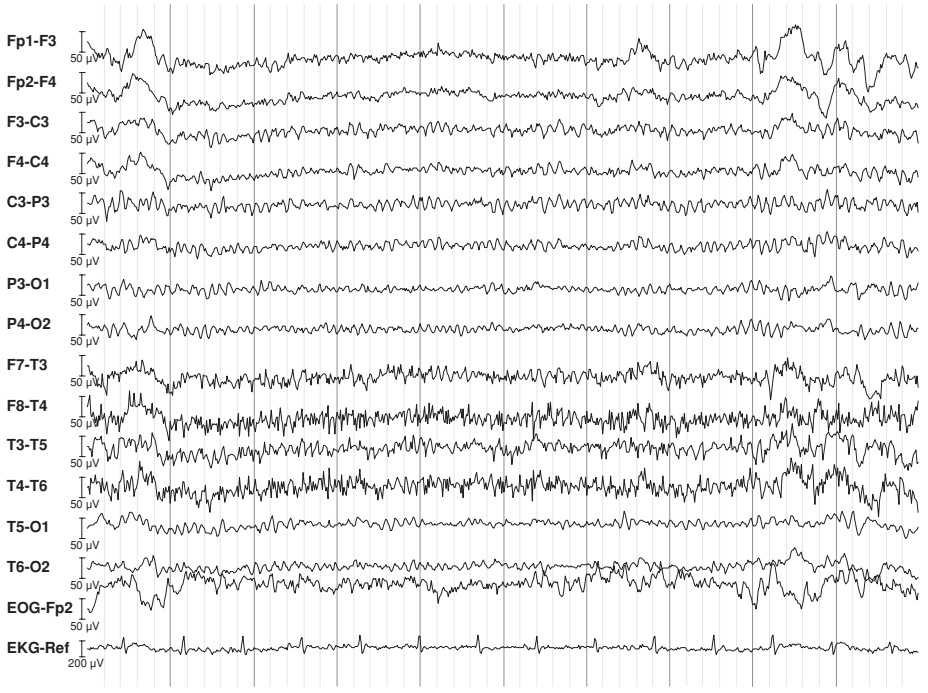

Figure 3.16 Muscle activity in temporal electrodes.

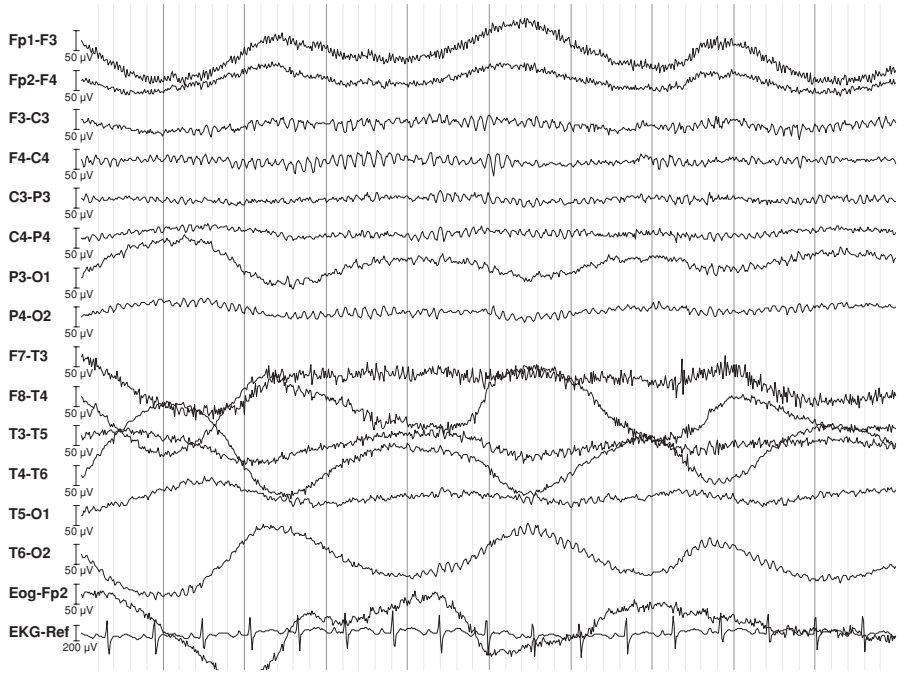

Figure 3.17 High amplitude slow artefacts, caused by wet skin (sweating).

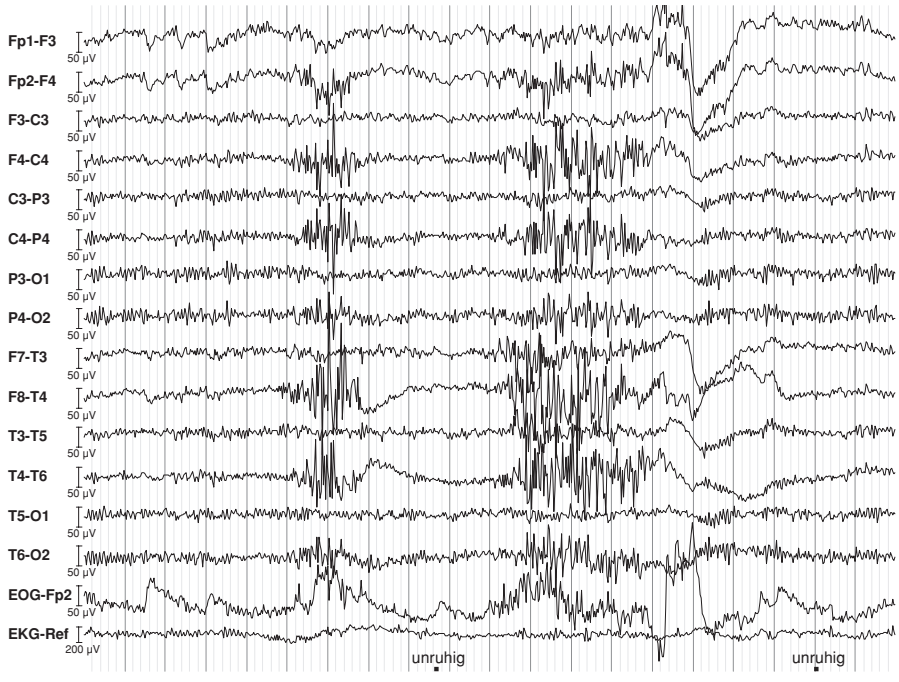

Figure 3.18 Muscle artefact from swallowing.

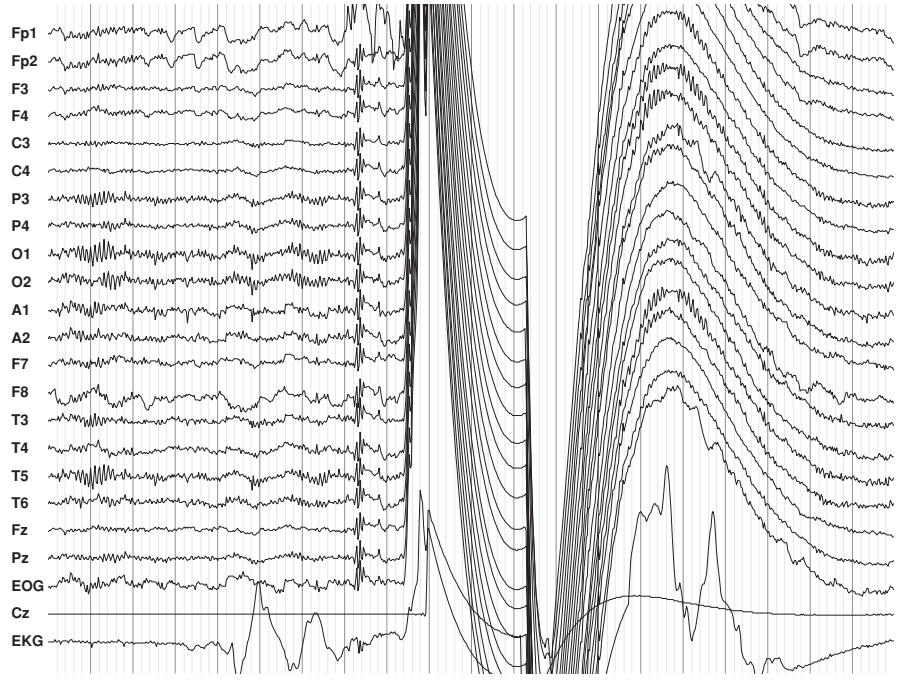

Figure 3.19 Artefact due to defective reference electrode (Cz).

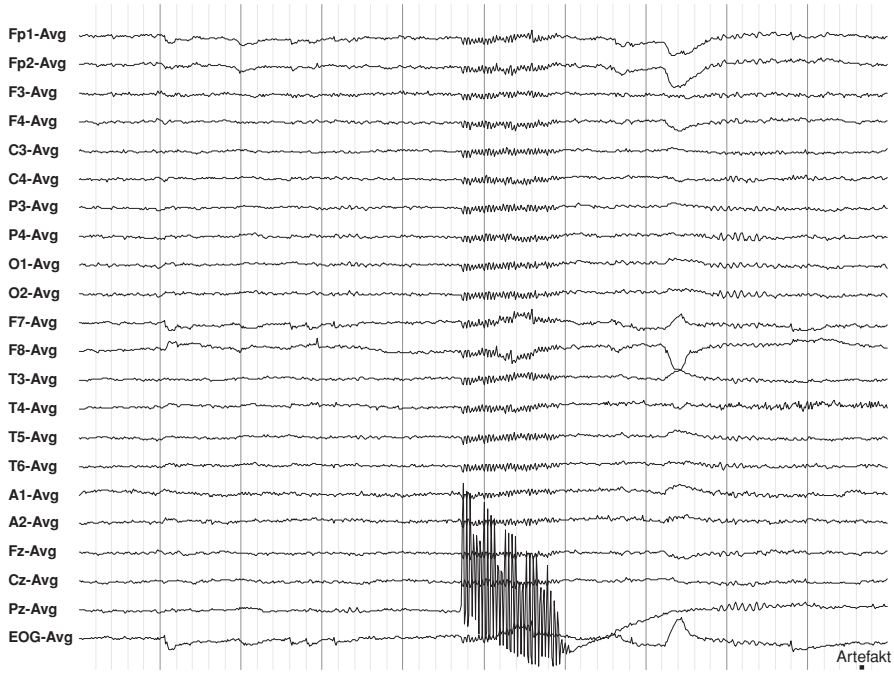

Figure 3.20 Technical artefact of electrode Pz.

Biological artefacts are related to the patient and comprise biological signals from different sources (eyes, tongue, heart, arteries/pulse, skin/sweating, muscles).

Characteristic for biological artefacts are a sudden onset and/or termination, a crescendo/decrescendo pattern as well as various other frequencies, occurring simultaneously in different regions [4, 6].

50 Hz (60 Hz) artefacts

Artefacts can originate in the power source (50 or 60 Hz), especially if there are problems with the grounding of the technical devices or of the subjects, or if the electrodes show a high resistance (which should be kept below 5 kΩ throughout the recording). This kind of artefact shows regular 50 or 60 Hz deflections of uniform appearance. A notch filter can help to minimise these artefacts, but ideally they should be avoided by thorough preparation of the devices and the subjects before recording is started.

Electrode artefacts

If electrodes are defective, sudden mostly positive deflections can occur in all channels the respective electrodes are linked with. These electrodes should be removed and replaced.

Eye movements

Electrically, the eye can be regarded as a strong electric dipole with a positive corneal surface and a retinal negativity. Compared to EEG signals, this dipole has a larger voltage; therefore, all eye movements will lead to marked disturbances of the electric fields on the surface of the scalp, especially in frontal regions. According to Bell's phenomenon, every blink (when the lids close) will lead to an upward movement of the eyes with a sudden increase of positivity (positive charge of the cornea) in frontal electrode positions, which means that Fp1 and Fp2 electrodes will become more positive than the surrounding electrodes, leading to marked deflections of the EEG signals. When the eyes go down again, a relative negativity causes a reverse deflection. In case of vertical eye movements the disturbances of the EEG signals are in phase on both sides (Fp1 and Fp2).

Lateral (side to side) eye movements lead to deflections, especially of the lateral frontal electrodes F7 and F8. Movements to the right (the positive corneal pole goes to the right side, the negative retinal pole is more on the left side) lead to a positivity around electrode F8 but to a relative negativity around F7, thus the deflections are separate and out of phase in this case (see Figures 3.6–3.9).

Tongue movements

The tongue can be characterised as an electric dipole with positivity at the base and negativity at the tip of the tongue. Rhythmic tongue movements will lead to frontal slowing in particular.

Muscle activity

Muscle activity can be caused by any movement like chewing, swallowing or an increased tension, influencing especially temporal and frontal electrodes.

Activity from muscles under the scalp (e.g. M. frontalis, M. temporalis, M. occipitalis) or even from remote areas (face, neck, throat) can interfere with EEG recordings. Muscle artefacts are sometimes short and focal with single deflections of spike-like appearance.

Swallowing leads to a characteristic generalised 'muscle activity pattern' of less than 1 s duration.

Muscle activity can also be long lasting and widespread, diffusely affecting all channels and, especially in tense, anxious or stressed subjects, these artefacts can lead to severe disturbances affecting the entire brain activity.

Sweating

Wet skin under the electrodes impairs conductance and resistance of the electrodes.

Subsequently, sweating leads to an increase in subdelta frequencies of various amplitudes. Sometimes, perspiration can lessen the skin contact with the electrodes. As a result, very slow artefacts of the involved channels (slow irregular deflections) can occur, masking the brain activity.

Electrocardiogram and vascular artefacts

Heart and blood vessels are responsible for a different kind of artefact.

The electrocardiogram can be recorded from anywhere on the surface of the body. The heart serves as an electric dipole with a positivity at the apex, which is usually connected (via volume conduction) to left temporal electrodes (positivity), whereas right temporal electrodes are influenced by the negative pole. Especially earlobe electrodes, A1 and A2, can be influenced by the 'heart vector' projecting to the head. This 'ECG artefact' appears in phase with the QRS complexes showing the same regularity. This artefact can easily be recognised if ECG and EEG are recorded simultaneously (one channel for ECG).

Another artefact is associated with the pulse: if an electrode is placed above or near a pulsating vessel, each beat can produce slight movements or changes in resistance leading to pulse synchronised (slow) deflections and rhythmic slowing with a temporal correlation to the electrocardiogram.

Typical presentations of various artefacts are pictured in Figures 3.6–3.20, showing EEG recordings (10 sec epochs each).

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4

Normal EEG Patterns and Waveforms

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Introduction

The classification of EEG rhythms is based on their frequency range; however, in the definition and description of different rhythms other parameters such as amplitude, shape, topographic distribution and reactivity are taken into account. To give significance to the observed waveforms, these parameters must be integrated with information on factors influencing the EEG rhythms, such as age of the subject, state of alertness or sleep, use of psychotropic drugs (as an example, a rhythm of 7 Hz or less is considered abnormal in awake adults, while it is normal in children or in adults who are asleep). Moreover, EEG activities can be affected by activation procedures such as hyperventilation and intermittent photic stimulation. A schematic representation of the EEG rhythms' characteristics is provided in Figure 4.1.

In the present chapter, normal EEG patterns in the waking adult, in infancy and childhood and in normal ageing, as well as unusual EEG patterns, activation procedures and sleep patterns will be described.

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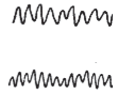
		Frequency range	Amplitude	Main scalp area	Subject condition
Delta		0.1-3.5 Hz	50-350	Variable	Drowsiness and deep sleep; hyperventilation; infancy and childhood.
Theta		4-7.5 Hz	10-150 μV	Variable	Drowsiness and deep sleep; hyperventilation; infancy and childhood. Small amount in awake adults.
Alpha		8-13 Hz	20-100 μV	Posterior (occipital-parietal)	Relaxed wakefulness with eyes closed.
Beta		above 13 Hz	10-30 μV	Frontal or diffuse	Increase during cognitive efforts as well as during drowsiness and light sleep.
Mu		7-12 Hz	10-50 μV	Central	Relaxed wakefulness with both eyes open and closed. Blocked by movements of the contralateral body parts.
Lambda		sharp transients of 200-300 msec duration	below 50 μV	Occipital	Visual exploration.

Figure 4.1 Schematic representation of EEG rhythms.

Normal EEG patterns in the waking adult

Alpha rhythm

The frequency range of the alpha rhythm is defined from 8 to 13 Hz; however, in normal conditions it is usually from 9 to 11 Hz, with a distribution curve centring around 10 Hz. An alpha frequency of 8 Hz should raise suspicion for abnormal slowing since it occurs in <1% of normal adults [1]. Alpha frequency is related to cerebral blood flow, becoming slower when there is a reduction of cerebral perfusion; it may also vary in relationship to the menstrual cycle, showing a slight increase during the follicular phase [2].

Amplitude, morphology, topographic distribution, abundance and reactivity of the alpha rhythm are summarised in Box 4.1.

Box 4.1 Characteristics of alpha activity [3, 4]

• Amplitude	From 20 to 100 μV (high inter- and intra-individual variability). Negative correlation with frequency.
• Morphology	Rounded or sinusoidal waves; less often, sharp morphology due to an admixture of beta waves. Typical spindle shape due to amplitude fluctuation in a regular fashion.
• Topography	Posterior predominance. An anterior distribution can be observed in some cases.
• Abundance (% time in which it is present under stable conditions)	High interindividual variability, genetically determined [5]. From almost continuous alpha rhythm, to the presence of alpha rhythm for less than 25% (alpha rare).
• Reactivity	Maximum expression with eyes closed during relaxed wakefulness. Attenuated or blocked by eyes opening, it reappears when closing the eyes (Figure 4.2). Also attenuated by auditory, tactile and other sensory stimuli, as well as by sustained attention (e.g. mental arithmetic) and during drowsiness (Figure 4.3).

An alpha amplitude asymmetry can be observed in approx. 60% of healthy individuals, with the right side tending to be of higher voltage (without consistent correlation with handedness); amplitude asymmetry achieves clinical significance only when the difference in amplitude between the two hemispheres is more than 50% [1]. On the contrary, the frequency of alpha rhythm is very similar in the two hemispheres: a

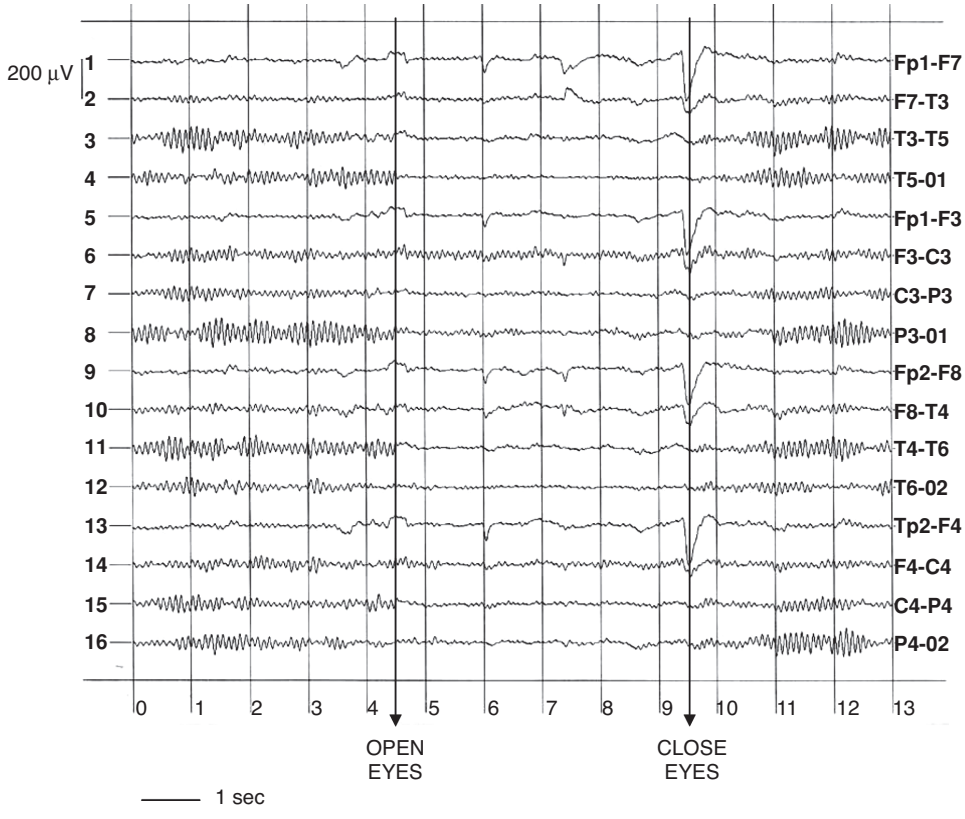


Figure 4.2 Alpha rhythm prevalent over the posterior regions, which attenuates with eyes opening and reappears when eyes are closed. Note the persistence of a 10 Hz rhythm (mu rhythm) over the left central lead (C3) and, with a lower amplitude, over the contralateral lead (C4) during eyes opening.

persistent difference of 1 Hz between the two sides is considered abnormal indicating a dysfunction on the side on which the frequency is slower [3].

Neural generators of alpha rhythm, as well as sources of other EEG rhythms, are investigated by means of relatively new technologies, including: (a) magnetoencephalography (MEG), which records small magnetic fields produced by electrical activity of neurons in the brain: its spatial resolution is not superior to that of EEG but, since it is sensitive to different sources, it can provide useful insights in neural generators when used as an adjunct to EEG measurements; (b) low resolution electromagnetic tomography (LORETA, [6]), which calculates, from the recorded scalp distribution of voltages, the three-dimensional distribution of cortical current source density (i.e. the distribution of neuronal active generators), referred to the digitised version of the Talairach human brain atlas; (c) the simultaneous acquisition of EEG and functional magnetic resonance imaging (fMRI), a technique which can measure neuronal activity indirectly by assessing

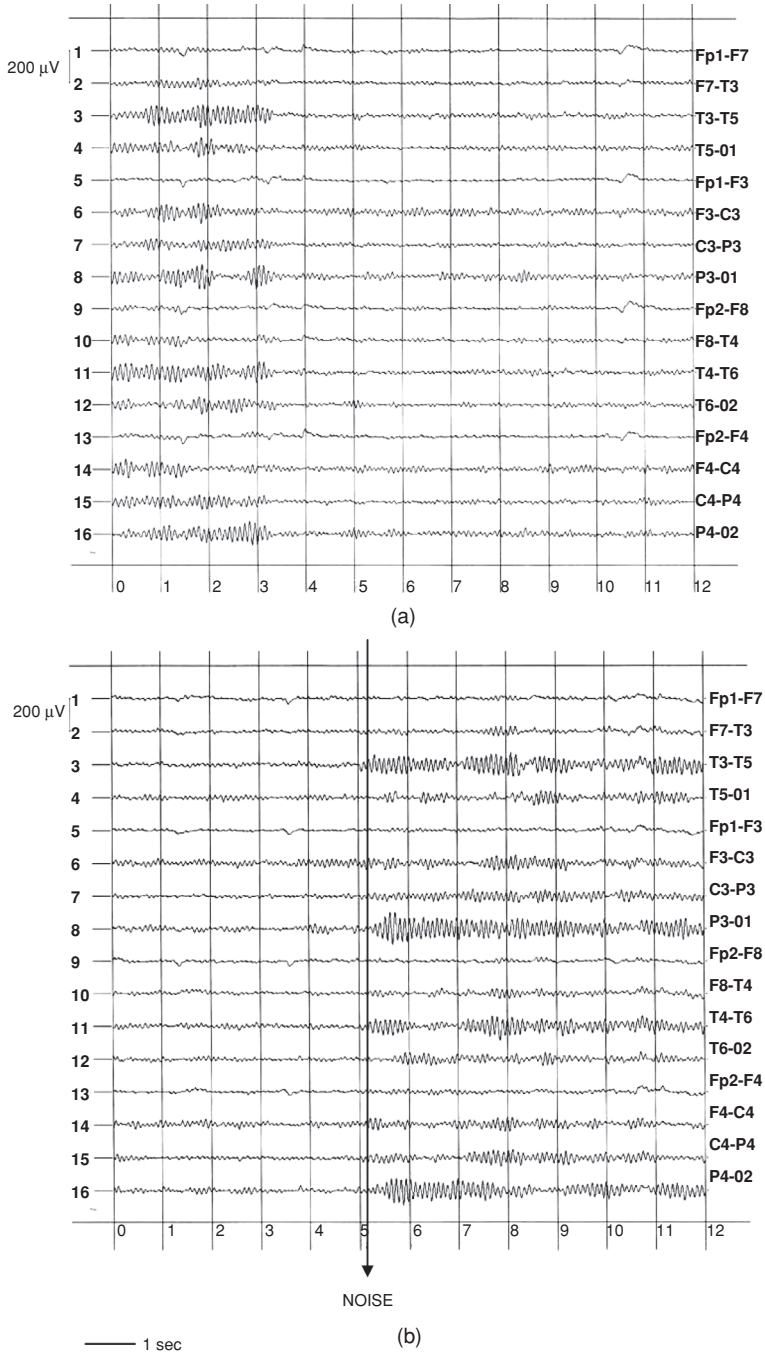


Figure 4.3 (a) Alpha attenuation during drowsiness. (b) An alerting stimulus (noise) during drowsiness induces the return of a sustained alpha rhythm; this phenomenon is called 'paradoxical effect', since normally (i.e. during relaxed wakefulness) alertness induces alpha attenuation (Markand [3]).

the difference between the concentration of the oxygenated haemoglobin in the arterial blood and the deoxygenated haemoglobin in the venous outflow.

MEG investigations reported that the sources of alpha rhythm mainly cluster in the region of the calcarine sulcus [7] and around the parieto-occipital sulcus [8, 9]. These sources have been confirmed by LORETA findings [10, 11].

Studies recording simultaneously EEG and fMRI found that increased alpha power was correlated with decreased fMRI signal in multiple regions of occipital, superior temporal, inferior frontal and cingulated cortex, and with increased signal in the thalamus and insula [12, 13], suggesting that alpha rhythm is an index of cortical inactivity that may be generated in part by the thalamus. A similar pattern of correlation was found in a study by Moosmann *et al.* [14], while other authors [15, 16] did not confirm these findings.

Low-voltage record

The low-voltage record is characterised by irregular mixtures of low amplitude activities mostly from 5 to 30 Hz, without a dominant frequency, with an amplitude lower than 20 μV over all head regions (Figure 4.4a). Its incidence is around 7–9% [3], but it is much rarer in children [4]. In normal subjects, low-voltage records are modified by some physiological stimuli: an alpha rhythm may appear immediately after eye closure as well as during hyperventilation (Figure 4.4b) [3]. Low-voltage record does not represent an abnormal pattern, unless the frequency spectrum shows abnormal local or diffuse slowing, asymmetries or paroxysmal events. According to Niedermeyer [4], this pattern is determined by a genetic predisposition which manifests itself after childhood.

Beta rhythm

Beta activity includes all frequencies above 13 Hz. Three different beta activities can be distinguished by visual inspection: a more commonly observed beta within the 18–25 Hz bandwidth, a less frequent beta ranging from 14 to 16 Hz and a rare beta with a frequency above 35 Hz [17]. Based on its topographic distribution, four types of beta activity are described, as reported in Box 4.2.

LORETA findings showed differences in source localisation between low (14–18 Hz) and high (24–28) beta [11]: an activation of posterior areas for low beta, interpreted by the authors as the high tail of the frequency range traditionally classified as alpha rhythm, and a frontal activation for both low and high beta, close to the motor cortex.

Absence of beta activity is not abnormal. On the other hand asymmetrical beta or the absence on one side or one location would be indicative of an abnormality where beta is not being produced.

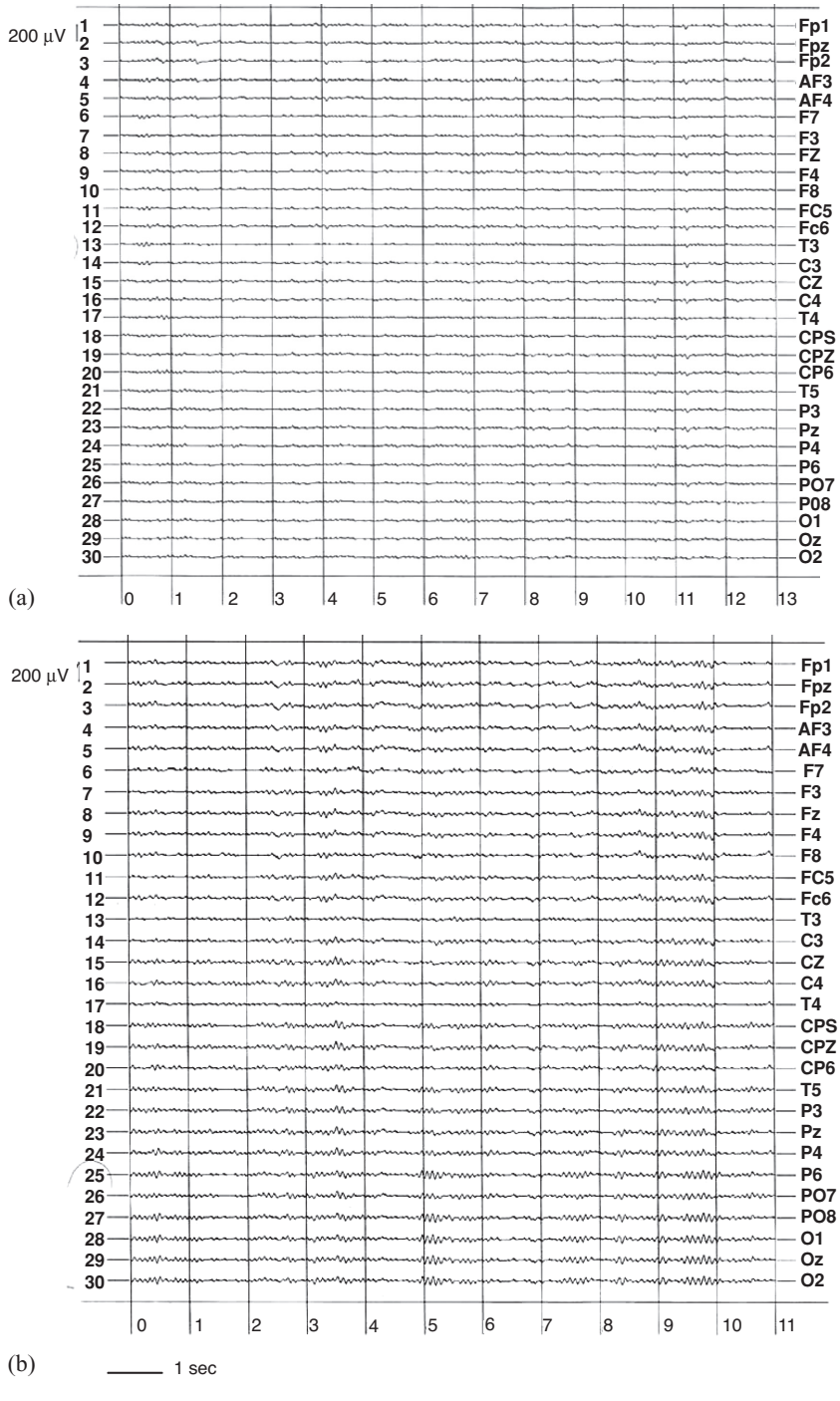


Figure 4.4 (a) Low voltage record before hyperventilation; (b) an induction of alpha rhythm is observed two minutes after hyperventilation.

Box 4.2 Classification of beta activity based on its topographic distribution [1, 17]

• Central beta	May show the same reactivity of mu rhythm (attenuation with movements of the contralateral body parts).
• Posterior beta	Often represents the fast variant of alpha rhythm, showing the same reactivity of alpha.
• Diffuse beta (Figure 4.4a) and frontal beta (Figure 4.5)	No relationships with other physiological rhythms. Increase during mental arithmetic and other cognitive efforts, as well as during drowsiness and light sleep, especially in children.

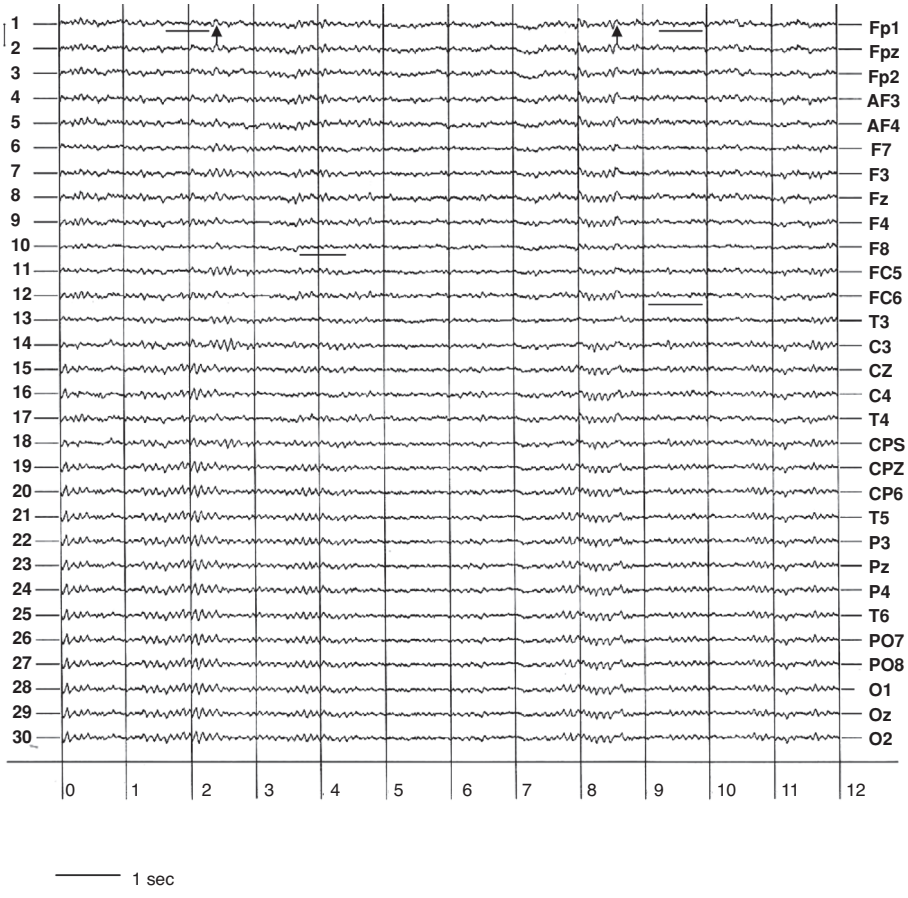


Figure 4.5 Beta (some examples underlined) intermixed with theta activity (arrows) over the frontocentral regions.

Mu rhythm

The mu rhythm is related in frequency and amplitude to the alpha rhythm but has different topography and reactivity. Its frequency ranges from 7 to 12 Hz, although more often a frequency of 10 Hz is observed, while a frequency of less than 8 Hz is suggestive of mild abnormality [4]. Its morphology, topographic distribution and reactivity are summarised in Box 4.3.

Box 4.3 Characteristics of mu rhythm [1, 4]

- Morphology: Arch-shaped waves.
- Topography: Precentral and postcentral regions, with maximum amplitude over C3 and C4 leads.
- Reactivity: Not modified by eyes opening (Figure 4.2).
  Transiently blocked by voluntary, passive or reflexive movements of the contralateral body parts; this effect precedes the onset of muscular contraction and also occurs with imagined movement in subjects with amputated limbs.

The mu rhythm can be asymmetrical and asynchronous and can even be seen only on one side in the absence of any organic brain disease [18]. Early studies showed a high degree of variability in its prevalence (from 0 to 34%), probably related to the difficulty in identifying the mu rhythm with visual inspection in some cases [19]; studies carried out with computerised EEG reported a prevalence of 50–60% [20, 21].

MEG recordings revealed that the mu rhythm is generated in distinct brain regions to the alpha rhythm; in particular, two main frequency components have been recorded by MEG: one around 10 Hz and the other around 20 Hz; for the latter, source locations centre on average 5 mm more anterior than the 10 Hz frequency, suggesting the existence of separate precentral (20 Hz) and postcentral (10 Hz) rhythms [9].

Theta activity

Theta activity includes EEG waveforms with a frequency between 4 and 7.5 Hz of varying amplitude and morphologies. In the normal awake EEG of adults there is a small amount of theta, never organised in a rhythmic activity (Figures 4.5 and 4.6). Intermittent 6 to 7 Hz theta of less than 15 μV has been reported in 35% of normal young adults during relaxed wakefulness [1]. Theta activity is much more represented in infancy and childhood as well as during drowsiness and sleep. It is increased during the performance of mental tasks [22] and hyperventilation.

A few studies investigated theta-range MEG activity; a 5–7 Hz MEG signal has been recorded from the frontal cortex during mental calculation and intensive thinking [4].

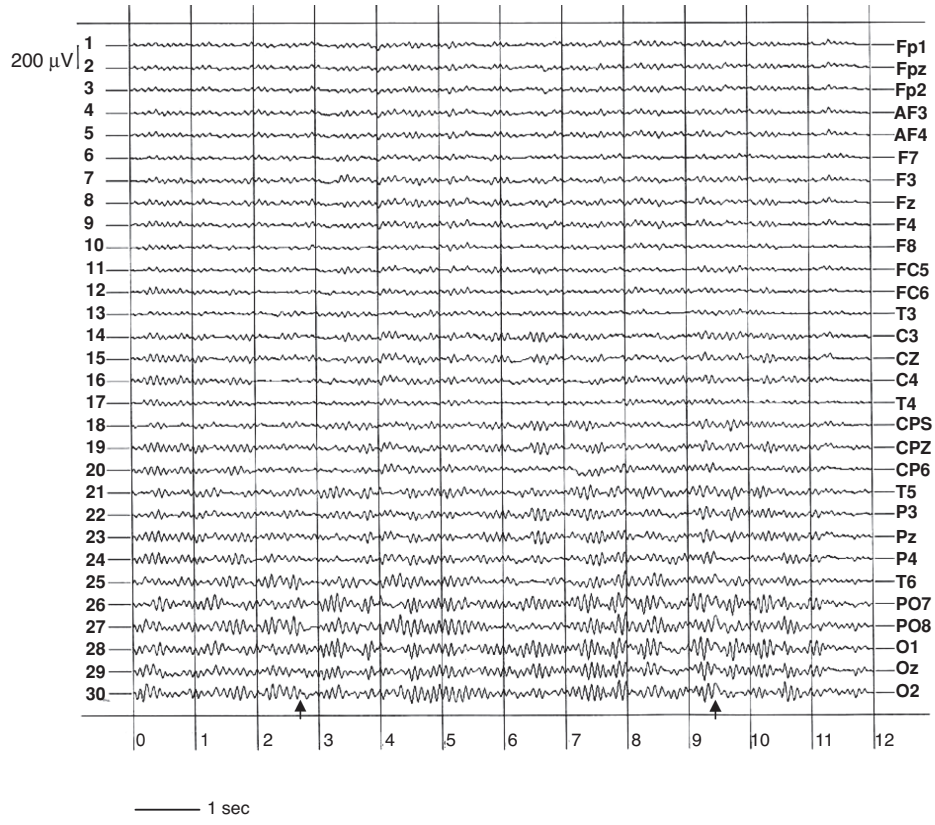


Figure 4.6 Theta waves (arrows) intermixed with the background activity.

In the 6–8 Hz range, LORETA findings showed activation in posterior, temporal and frontal areas [11]. The authors hypothesise that the posterior activation may represent the low frequency extreme of the posterior alpha range, while the theta activity source in the temporal regions may be due to the participation of hippocampus in the generation of theta activity.

Lambda waves

Lambda waves are sharp transients, with an amplitude generally below 50 μV, occurring over the occipital region of the head of waking subjects during visual exploration (IFSECN, [23]). Sometimes they are asymmetric, with higher amplitudes than the rest of posterior dominant rhythm. In these cases, to distinguish them from interictal epileptiform discharges, it is useful to place a plain white sheet of paper in front of the individual: this will eliminate the visual input and therefore will block the normal lambda waves but will not affect the epileptiform discharge [1].

Delta activity

Delta activity includes waveforms with a frequency lower than 4 Hz. Delta waves are considered abnormal findings in the awake EEG of adults. Normally they are seen at the onset of drowsiness, in deep sleep, in response to hyperventilation or induced by psychotropic drugs in adults (Figure 4.7), as well as in infants and children.

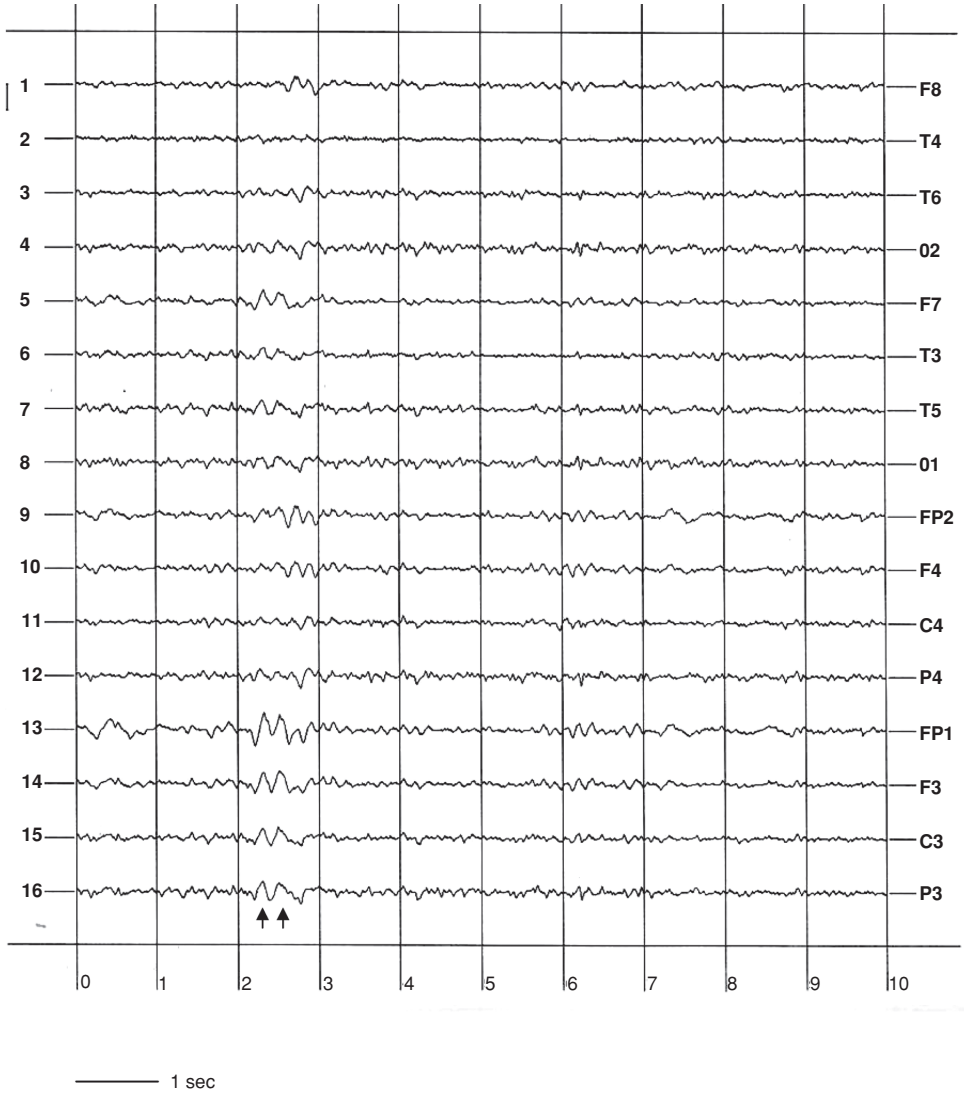


Figure 4.7 Delta waves (arrows) induced by the administration of 12.5 mg of clozapine (3rd hour).

Both delta and theta activities are related to cerebral blood flow, increasing when the cerebral perfusion is reduced; this is not true for the physiological slow waves of sleep and childhood [24].

Gamma activity

The frequency range of gamma band is between 30 and 70 Hz, usually centred around 40 Hz. The gamma oscillations have been classified into induced, evoked, emitted and spontaneous [25, 26]. Probing of gamma activity has proven of great interest in the field of quantified EEG. The resolution of EEG does not allow the naked eye to examine this frequency range in a clinically useful manner.

Physiological modifications induced by activation procedures

The most commonly used activating procedures are hyperventilation, intermittent photic stimulation and sleep deprivation. The former is carried out by asking the subject to hyperventilate for 3–5 minutes; this causes the subject to exhale excessive amounts of CO_2 and become hypocapnic. The hypocapnia causes mild cerebral vessel vasoconstriction and, hence, mild cerebral hypoxia. The intermittent photic stimulation is performed by alternating flashes varying from 1 to 35 Hz by means of a stroboscopic stimulator placed 1 metre from the subject's eyes [2]. Sleep deprivation consists in keeping the subject awake all or part of the night before recording an EEG. Activation procedures are aimed at inducing epileptic and non-epileptic pathological patterns, but they also can induce physiological modifications of the EEG, as summarised in Box 4.4.

Box 4.4 Physiological modifications of the EEG which can be Induced by activation procedures [4]

• Hyperventilation	– Bilateral increase of slow waves (Figure 4.8) resolving within 2 minutes after hyperventilation. – Induction of alpha rhythm in subjects with low-voltage EEG.
• Intermittent photic stimulation	Photic driving: production of rhythmic potentials time-locked to the frequency of stimulation, prevalent over the occipital leads.
• Sleep deprivation	Periods of drowsiness or sleep.

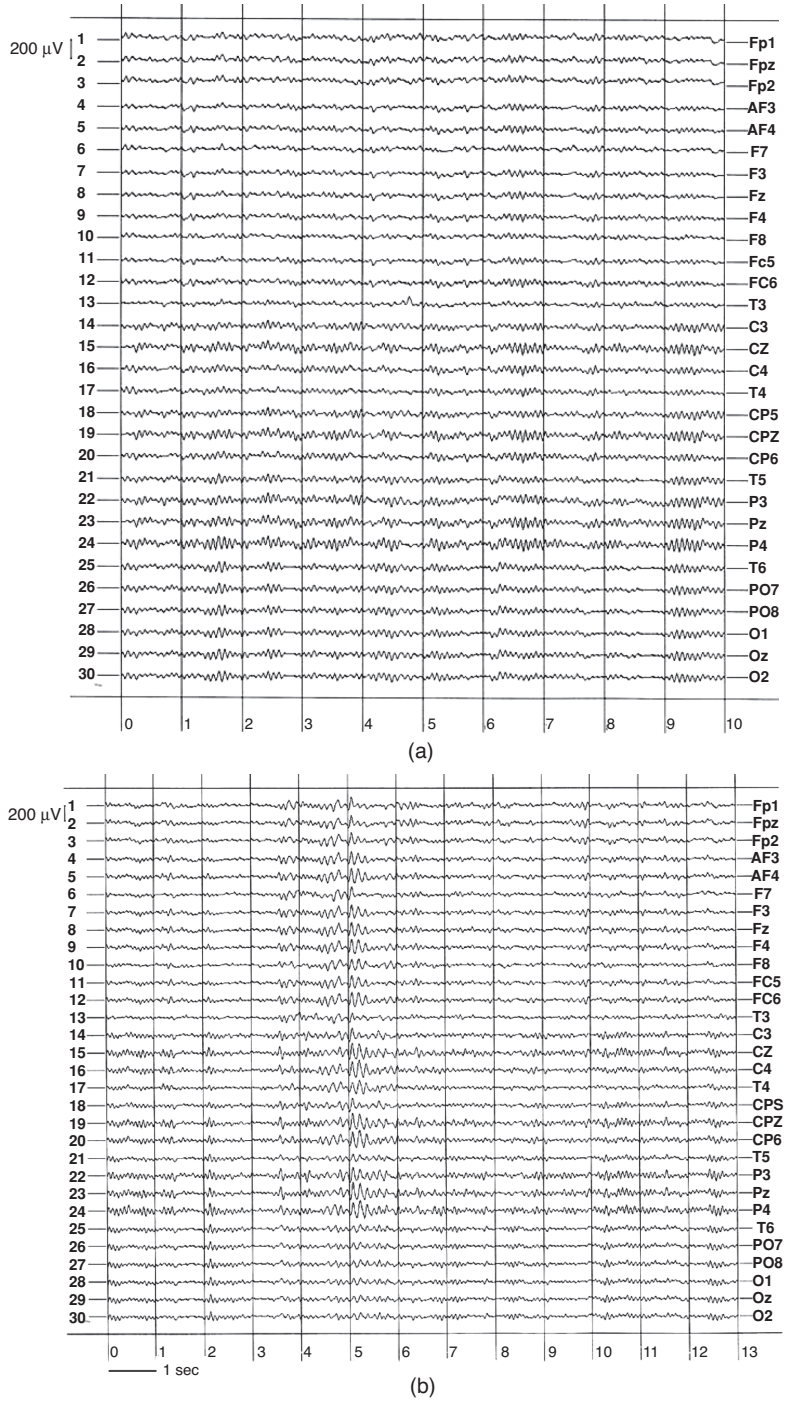


Figure 4.8 Physiological response to hyperventilation (HP). (a) EEG recorded before starting HP; (b) EEG recorded 3 minutes after starting HP: bilateral increase of slow waves.

Normal EEG patterns in infancy and childhood

A description of EEG patterns during infancy and childhood is reported in Box 4.5, while a schematic representation of EEG waveforms during these periods is reported in Figure 4.9.

Box 4.5 EEG patterns during infancy and childhood [1, 4]

• 7 months–3 years	Increase of frequency and reactivity of the precursor of alpha. Variable amount of slow waves over all scalp regions.
• 3–5 years	Alpha range frequency (8 Hz) over the posterior regions from the age of 3 years. Slow waves intermixed with the posterior alpha.
• 7–9 years	Further increase of alpha frequency (9 Hz). Posterior slow activities still present. Very pronounced slow response induced by hyperventilation.
• 10 to 20 years	Mean frequency of alpha gradually reaches 10 Hz. Posterior slow activities gradually reduces (10–15%). Slow response to hyperventilation is less pronounced than in children.

EEG patterns in normal ageing

A shift toward slower frequencies of alpha activity with a reduction of 1 Hz every 10 years after the age of 50 years has been reported in healthy elderly subjects since early investigations [27, 28]. Subsequent studies that controlled for subtle neurological alterations reported values of mean alpha frequency ranging from 9 to 10 Hz in healthy elderly subject [29, 30]. However, the frequency of the alpha rhythm remains always above 8 Hz even at or over the age of 100 years [30].

Other changes of alpha activity in elderly subjects compared to young adults include a slight reduction in amplitude, a reduced percentage of time in which alpha is present and a reduced reactivity [3], while no increase of amplitude asymmetry occurs in normal ageing.

The presence of focal slow waves has been reported in healthy elderly subjects, mainly in the temporal regions [31] (Figure 4.10). However, the allowable quantity of these slow waves in a normal EEG is not defined; moreover, Torres *et al.* [30] found the same prevalence of temporal delta waves in healthy elderly subjects and in patients with stroke. Klass and Brenner [32] proposed the following list of characteristics describing what they suggested to call 'benign temporal delta transients of the elderly': (a) occurrence after 60

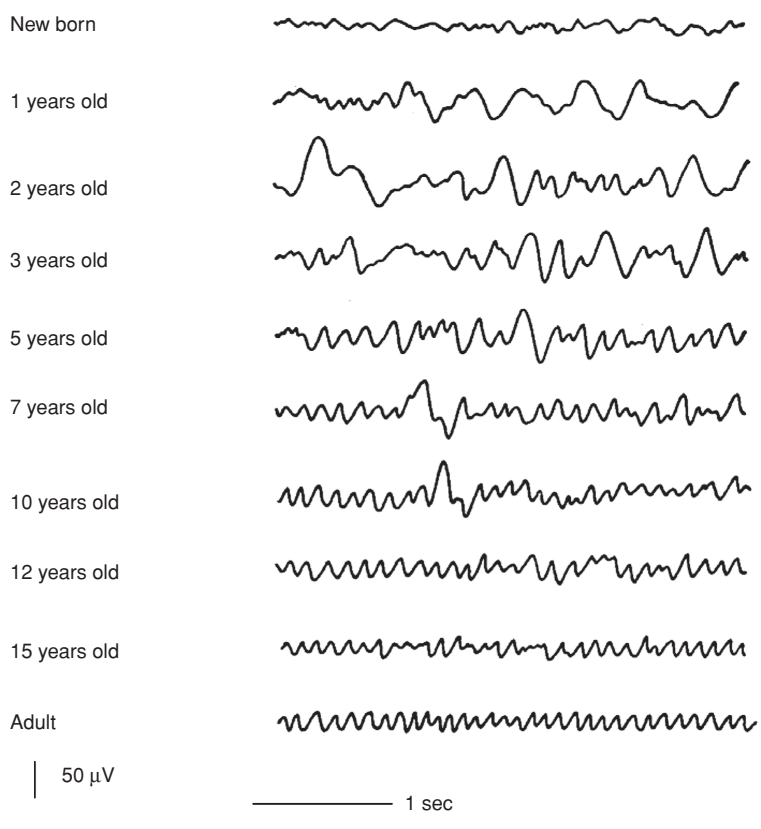


Figure 4.9 EEG waveforms during maturation of the EEG.

years of age; (b) presence confined over the temporal regions; (c) higher prevalence on the left side; (d) absence of background abnormalities and of abnormal asymmetries of the alpha rhythm; (e) rounded morphology; (f) voltage usually <60–70 μV; (g) reactivity consisting of an attenuation during mental alerting and eyes opening and increase with drowsiness and hyperventilation; (h) occurrence sporadically as single waves or in pairs, not in longer rhythmic trains; (i) present only for a very small proportion (up to about 1%) of the recording.

A reduced slow response to hyperventilation has been reported in normal elderly subjects with respect to young adults [32].

Unusual EEG patterns

(A) Non-controversial EEG patterns. These patterns are widely accepted as normal variants with no clinical correlates. They refer to rhythmic or epileptiform waveforms that are rare or unusual but without known clinical significance.

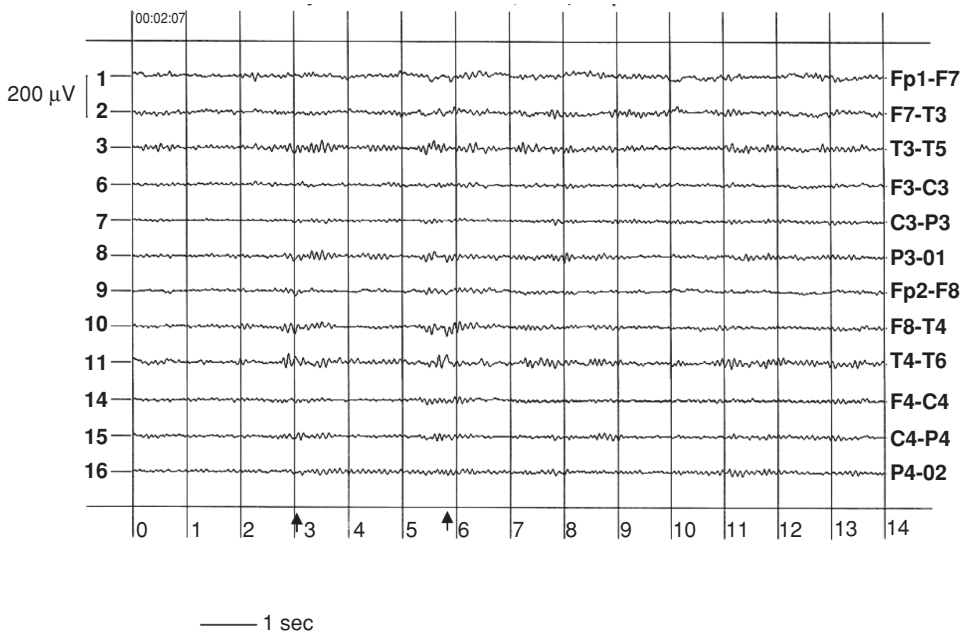


Figure 4.10 Focal slow waves in the theta range over the mid-temporal regions (arrows) in a healthy 66 years old woman.

Rhythmic patterns most frequently fall within the theta, alpha and beta frequency ranges [33]. This group of EEG patterns include: slow and fast alpha variants, midline theta activity, subclinical rhythmic EEG discharges of adults and posterior temporal fast activity in children (Figure 4.11). Their characteristics are summarised in Box 4.6.

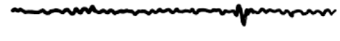
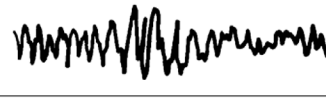
(B) Controversial EEG patterns. This group of EEG patterns include the rhythmic mid-temporal discharges, positive bursts of 14 and 6 Hz, small sharp spikes or SSS of sleep, wicket spikes and 6/second spike and waves discharges. Their description is provided in Box 4.7.

These five EEG patterns share the following characteristics: they tend to be more represented in psychiatric populations, in general they do not indicate a seizure disorder, and the clinical correlates tend to be vague as in neurovegetative symptoms (e.g. headaches, abdominal pain). The reason for the controversial label reflects a large body of literature that suggests some clinical correlates and a separate body of literature that supports them to be normal variants. These patterns have two names representing the controversy. Those who believe that they are not normal variants use the names that we report outside the brackets, for example 'Rhythmic mid-temporal discharges or RMTS', while those who believe they are normal variants use different names reported in brackets in this paragraph, for example 'theta bursts of drowsiness or psychomotor variant'.

(a) - **Non-controversial EEG patterns**

Slow alpha variant	
Midline theta activity	
Subclinical rhythmic EEG discharges of adults (SREDA)	

(b) - **Controversial EEG patterns**

Rhythmic mid-temporal discharges (theta bursts of drowsiness or psychomotor variant)	
Positive bursts of 14 and 6 Hz (ctenoids)	
Small sharp spikes or SSS of sleep (benign epileptiform transients of sleep or BETS)	
Wicket spikes	
6/second spike and wave discharges (phantom spike and wave)	

1 sec

Figure 4.11 Schematic representation of main unusual EEG patterns. (a) Non-controversial EEG patterns; (b) Controversial EEG patterns.

Rhythmic mid-temporal discharges or RMTS (theta bursts of drowsiness or psychomotor variant), are generally considered benign and do not correlate with psychomotor seizures [38]; however, Hughes and Olson [39] present a different view point and Boutros *et al.* [40] reported a correlation between this pattern and somatisation.

Box 4.6 Non-controversial unusual EEG patterns (normal variants) [18, 34, 35]

• Slow and fast alpha variants	Physiological variants of the alpha rhythm, which sometime coexist in the same subject. Their frequency has a harmonic relationship to the alpha rhythm of the subject (frequency range: 4–5 for the slow alpha variant, 14–20 Hz for the fast alpha variant. Both variants have topographic distribution and reactivity similar to the alpha rhythm and may show a dicrotic morphology.
• Midline theta activity	Sinusoidal or arciform 4 to 7 Hz rhythm maximal over the vertex region. It appears during wakefulness and drowsiness but not during sleep and is attenuated by eyes opening, somatosensory stimuli, alerting and limb movement. In its first description, it was reported in patients with temporal lobe epilepsy, but later it has been observed in heterogeneous populations without epilepsy.
• Subclinical rhythmic EEG discharges of adults (SREDA)	Theta waveforms in the range of 5–7 Hz, diffuse or prevalent over the temporoparietal regions, lasting from a few seconds to a few minutes, occurring in subjects older than 50 years during wakefulness or drowsiness. No association with epilepsy.
• Posterior temporal fast activity in children [36]	Fast activity of 20–26 Hz observed in children between 1 and 3 years, over the temporal regions. Blocked by passive eye closure.

Positive bursts of 14 and 6 Hz (or ctenoids) are generally thought to be clinically insignificant [35]. However, this conclusion is seriously challenged by a number of reviews [41, 42]. Despite these reviews being old, their assumptions have never been empirically challenged. Bosaeus and Sellden [43] demonstrated how children with this pattern who were thought to be 'normal' at initial evaluation were found to exhibit neurobehaviuoral symptoms upon closer scrutiny. More recently, Boutros *et al.* [44] reported an association between this pattern and attention-deficit hyperactivity disorder. It is likely that the difficulty in identifying this pattern, as well as its closeness in shape and frequency to sleep spindles, have contributed to the controversy. The use of a combined referential and bipolar montage commonly called Queens Square helps increase the likelihood of detecting the pattern confidently as it reliably

localises it to the posterior temporal region versus a more central region for sleep spindles.

Box 4.7 Controversial EEG patterns [18,34]

• Rhythmic mid-temporal discharges (temporal theta bursts of drowsiness or psychomotor variant) [37]	Bursts of rhythmic theta waves lasting often longer than 10 sec, with variable morphologies, but more often sharply contoured, occurring predominantly over the midtemporal leads during relaxed wakefulness and drowsiness.
• Positive bursts of 14 and 6 Hz (ctenoids)	Bursts of rhythmic arciform waves lasting 0.5–1 sec, usually unilateral or bilaterally asynchronous. The two frequencies are intertwined, with the 14 Hz frequency more prevalent. Prevalent in children and adolescents.
• Small sharp spikes or SSS of sleep (benign epileptiform transients of sleep)	Monophasic or diphasic spikes of low voltage (<50 μV) and brief duration (<50 ms), over the anterior and midtemporal regions during non-REM sleep. Not associated with focal slowing, not occurring in runs.
• Wicket spikes	Bursts of arciform waves or single spike-like waves with a frequency between 6 and 11 Hz and an amplitude ranging from 60 to 200 μV, observed over the temporal regions bilaterally or independently, during drowsiness and light sleep, predominantly in adults. Distinguished from pathological spike discharges for the similar morphology of waves in the same burst; as well as the absence of after coming slow-wave components.
• 6/second spike and waves discharges (phantom spike and wave)	Bursts of 6 Hz spike and wave complexes, usually of low amplitude, lasting 1–2 s.

The pattern of small sharp spikes or SSS of sleep (benign epileptiform transients of sleep or BETS), although described in epileptic patients, is often observed in healthy individuals and seems unrelated to the diagnosis of epilepsy [35].

Wicket spikes are considered an epileptiform normal variant, although they have also been reported in patients with epilepsy [45].

The 6/second spike and waves discharges (phantom spike and wave) represent a benign variant when they have a low amplitude and appear during drowsiness, while they are associated with seizures when they are of high amplitude, occur with less than 6 Hz frequency or during wakefulness [18]. Hughes [46] described the two forms: WHAM (Wake, High amplitude, Anterior, Male) and FOLD (Females, Occipital, Low amplitude, occurring more during Drowsiness); WHAM is more frequently associated with seizures than the FOLD, which is more associated with behavioural aberrations. Hughes and Fino [47] provided strong evidence for the pathological nature of the discharge.

As already observed by Boutros *et al.* [48], the finding of unusual EEG patterns in normal subjects may often be related to the lack of rigorous inclusion and exclusion criteria for selection of healthy subjects, with the consequent risk to include in 'normal' samples subjects with previous head trauma, alcohol and drug abuse or dependence, endocrine or metabolic disorder, psychiatric disorders or family history of psychiatric disorders, that is, all conditions that may underlie the observed unusual EEG patterns. Further research in these conditions might improve our understanding of the meaning of unusual EEG patterns. Several studies investigating clinical EEG in psychiatric populations reported the presence of the controversial waveform (see Shelley *et al.* [49] for a review of the literature). Small sharp spikes, 6/second spike and waves and positive bursts of 14 and 6 Hz have been reported in 20–40% of patients with mood disorders [50–53], as well as in 33% of patients with schizoaffective disorder and in 30% of patients with schizophreniform disorder [53]. Small sharp spikes have been reported also in patients with schizophrenia [50]. A higher prevalence of positive bursts of 14 and 6 Hz and small sharp spikes has been reported in patients with eating disorders with respect to normal controls and to unselected psychiatric patients [54]. All in all, it is apparent that much additional research to explore these controversial patterns in psychiatric populations is warranted.

Normal sleep EEG patterns

Sleep is generally divided in two basically different types: rapid eye movement (REM) sleep and nonrapid eye movement (NREM) sleep. NREM is subdivided in 4 stages, characterised by different EEG patterns: stage 1 (drowsiness), stage 2 (light sleep), stage 3 (deep sleep) and stage 4 (very deep sleep) [55]. NREM and REM sleep alternate in cycles lasting 90–100 min, with a total of four to six cycles/night. EEG waveforms of different EEG stages are reported in Figure 4.12.

Stage 1 (drowsiness)

Early drowsiness is characterised by 'alpha dropout', consisting in a gradual attenuation of the alpha rhythm that becomes slower, less prominent and discontinuous (Figure 4.3a) and, with deepening of drowsiness, is progressively replaced by a 2–7 Hz low-voltage activity. These modifications may be poorly defined in subjects with low-voltage records

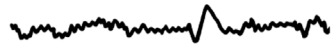
		Sleep stage
Vertex waves		Stages 1 (deep drowsiness) and 2
POSTS		From stage 1 (deep drowsiness) to stage 3
K complexes		Stages 2 and 3
Sleep spindles		Stages 2 and 3 (less frequent in stage 4)
Polymorphic delta activity		Stage 2 (less than 20% of the recording); stage 3 (20-50%); stage 4 (more than 50%).
Background desynchronization		REM sleep

Figure 4.12 Schematic representation of EEG waveforms of sleep.

[4]. An increase of alpha amplitude over the anterior regions has also been described during early drowsiness [22].

Deep drowsiness is characterised by the appearance of vertex waves, which appear in this stage but may persist in stage 2. They are compounded potentials of 200 ms duration, with a positive spike followed by a large negative wave, bilateral and symmetric, with maximum negativity at the vertex electrode (Cz), which can appear isolated or in runs and may be induced by auditory stimuli [2].

Another feature of deep drowsiness is represented by positive occipital sharp transients of sleep (POSTS): positive, bisynchronous sharp waves of 50–100 μV, which may show voltage asymmetries; they appear over the occipital regions, either isolated or in repetitive bursts. POSTS may persist during light and deep sleep [4].

Stage 2 (light sleep)

This stage is characterised by a progressive slowing of background activity, with frequencies ranging from 0.75 to 4 Hz, as well as by the occurrence of sleep spindles and K-complexes.

Sleep spindles consist in short bursts of waxing and waning (fusiform) rhythmic activity with an amplitude ranging from 20 to 100 μV, maximal over the vertex region. According to Gibbs and Gibbs [56] a frequency of 14 Hz characterises spindles during the beginning of light sleep, while 10–12 Hz spindles appear later with deepening sleep and are more pronounced over frontal areas.

K-complexes are high-amplitude (>100 μV) diphasic waves with an initial sharp transient followed by a high amplitude slow wave, often associated with a sleep spindle. They are observed over the frontocentral regions, with a maximum at the midline. K-complexes occur spontaneously, but may also be evoked by sudden auditory stimuli [4]. K-complexes show a great interindividual variability: Pavia and Rosa [57] described six different morphologies, mainly on the basis of the aspect of the negative component.

As already mentioned, both vertex waves and POSTS may persist during light sleep.

Stage 3 (deep sleep)

During deep sleep, polymorphic slow activities in the range of delta occupy from 20 to 50% of the recording; rhythmical activities in the frequency range between 5 and 9 HZ are also observed [18].

Sleep spindles with a frequency between 10 and 12 Hz can still be found; typical K-complexes can be elicited by arousing stimuli [4].

An 'alpha sleep pattern' characterised by a 7–11 Hz activity prevalent over the anterior regions and intermixed with delta waves has been described in several healthy subjects during this stage of sleep [58, 59].

Stage 4 (very deep sleep)

During this stage, polymorphic slow activities in the range of delta occupy more than 50% of the recording [18]. Sleep spindles are less frequently observed with respect to the previous stage [60].

REM sleep

REM sleep is characterised by the occurrence of repetitive bursts of mainly horizontal rapid eye movements, muscle atonia and EEG desynchronisation characterised by a faster (within the theta and beta ranges) and lower voltage activity resembling that of light drowsiness replacing the slow waves of stages 3 and 4 [4].

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5
Abnormal Patterns

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Introduction

Distinctive features of the EEG can range from subtle/minor changes to obvious and severe anomalies; therefore, an EEG report should contain some kind of grading. Since the term 'borderline result' is of no help to clinicians, a clear distinction of normal and abnormal EEG patterns and EEG results is mandatory [1, 2].

Extensive education and experience is required in order to reliably detect even subtle changes in EEG patterns. This chapter comprises a presentation of the most important abnormal patterns of standard EEG, also useful in the diagnosis (or exclusion) of psychiatric disorders. It has to be noted that even normal EEG recordings can show numerous 'irregularities' in wave forms and rhythms; therefore, any abnormal pattern has to be detected and identified in view of a wide range of normal results (Figure 5.1). Special clinical conditions of the subjects such as drowsiness or sleepiness, fasting state, low relaxation or restlessness (which is a particular problem in psychiatric patients) complicate the differentiation of artefacts and a distinction from expected irregularities regarding the above conditions [3, 4].

The detection of abnormal patterns requires the exclusion of artefacts. The second step is the characterisation and classification of the pattern and the description of the distribution regarding general or focal, diffuse or random appearance. The most important abnormalities are diffuse slowing of background activity, continuous or intermittent slowing with irregular theta or delta activity and sharp paroxysmal activity (epileptiform patterns), which can also occur generalised or focally. Since diffuse slowing is also an indication of reduced alertness, drowsiness or sleepiness, it is necessary to monitor the

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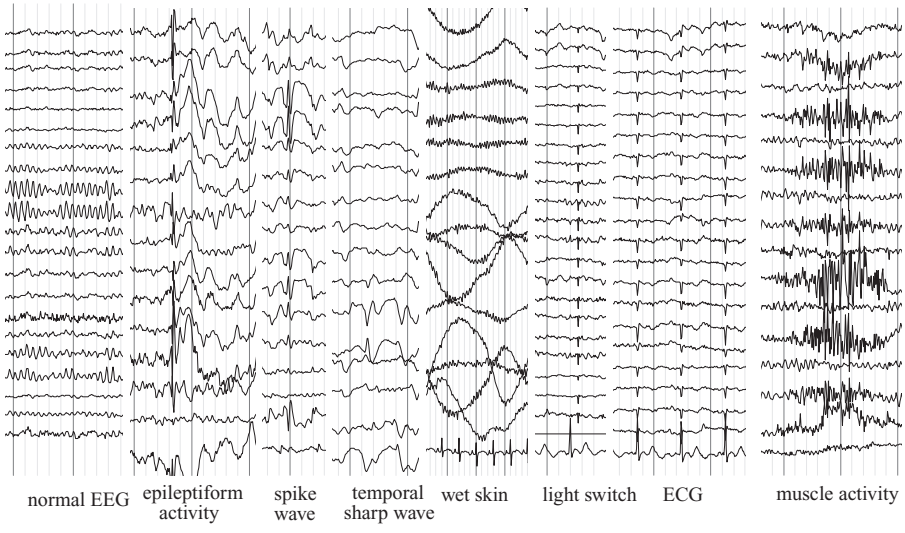


Figure 5.1 The first step of EEG analysis and interpretation includes the separation of brain signals and artefacts.

subjects and record their clinical and vigilance state. This also applies to the detection of artefacts, requiring close observation and monitoring of the subjects [1, 5–7].

Detection of artefacts

Artefacts can be divided into technical and biological signals superimposed on brain electric activity. Technical artefacts include electrical disturbances related to the EEG device, alternate current artefacts (50 or 60 Hz artefacts) and intermittent irregularities due to defective electrodes. So-called biological artefacts are biological signals from the subject, not originating from the brain and leading to disturbances of the brain signals. Examples are eye movements, muscle activities (especially in patients with abnormal involuntary facial movements, chewing or low relaxation), influences from tongue movements and sweating (humid skin alters the conductance). Often reported, too, are prominent disturbances by heart actions with the volume conduction of the electrocardiogram influencing temporal ear or mastoid electrodes in particular. A more detailed description and categorisation of artefacts and EEG examples are given in Chapter 4 [2, 4].

Abnormal patterns

The depression of normal EEG rhythms

One of the most frequent abnormalities – and often difficult to distinguish from alterations caused by artefacts – is the depression of normal rhythms.

Some characteristics favouring the brain as origin of the depression of EEG signals are:

- The depression of brain activity is usually detected in more than one electrode.
- A depression is not the only finding in an abnormal EEGs.
- The difference between depressed and non-depressed EEG signals should be at least 50% of its amplitude (a normal EEG shows an asymmetry in EEG amplitudes with lower amplitudes over the left hemisphere; therefore, right-sided depression could be more significant).
- The depression rarely occurs on its own, but often in combination with other abnormalities. The presence of additional slowing adds to the assessment of the underlying pathological condition.

Often, a depression is caused by increased amounts of fluid under the electrodes, for instance because of intracranial haematomas or hydromas. Where epi- or subdural haematomas are clinically significant (which is usually the case when EEG recordings are required), slow waves can occur due to disturbances of the underlying neurons.

Early signs of tumours can also lead to a focal depression of brain activity, followed by slowing.

A depression of spindles is often associated with diencephalon pathology, leading to impaired rhythms, especially in different states of vigilance [5].

It has to be noted that differences in amplitudes can also be caused by an original increase in brain activity and that regions with lower amplitudes (depression) are not necessarily a pathological finding. In cases of craniotomy, increased amplitudes can occur (especially with fast rhythms) and here regions with high amplitudes indicate pathological findings. Therefore, a medical history of brain trauma or cranial surgery is an important piece of information and should be documented, as well as any other abnormality (scalp scars, etc.) observed during EEG recording [2, 4].

EEG slowing and slow waves

Slowing or slow waves are defined as waves slower than expected, particularly waves in theta frequency bands (4–7/sec) or delta frequency bands (<4/sec).

For the correct identification of slowing it is important to perform EEG recordings during waking states without drowsiness, because any change in vigilance and sleepiness will automatically lead to an increased amount of slow waves. The slowing of the frequency reflects a decrease in responsiveness or excitability of the underlying neurons; thus, the occurrence of slow waves is not necessarily a specific finding. Slow waves are aetiologically non-specific findings and can be associated with a neuronal dysfunction

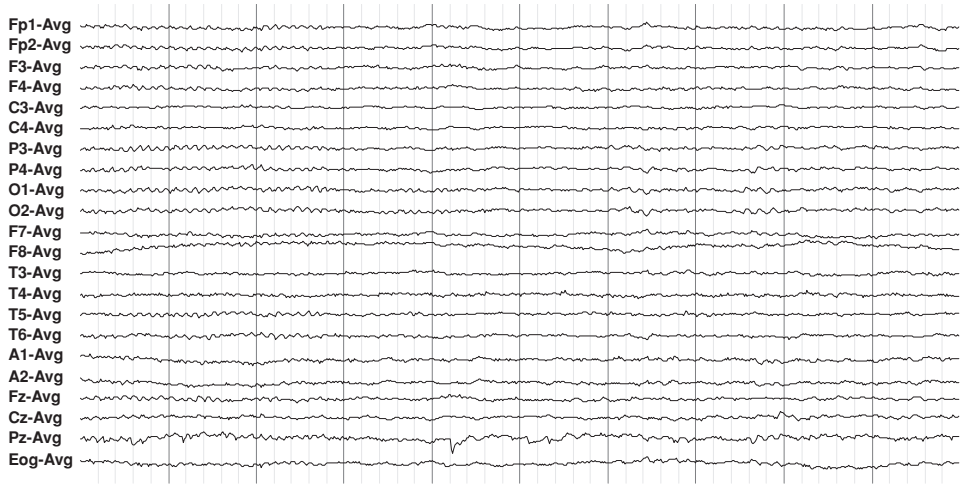


Figure 5.2 Increase of diffuse slow activity in drowsiness.

if other explanations (normal conditions such as reduced vigilance, drowsiness) do not apply (Figure 5.2) [1].

Diffuse slow waves

Diffuse slow waves are usually seen in metabolic, toxic or infectious alterations of the entire brain. A decrease of background frequency is suggestive of diffuse and generalised disturbances, while symmetrical diffuse slowing can indicate a projected disturbance from midline subcortical regions [8, 9].

Focal slowing

Continuous slowing within the delta frequency bands is strongly suggestive of brain occupying lesions (tumours, abscesses), frontal intermittent rhythmical delta activity (FIRDA) or specific wave forms that are often associated with disturbances within the brain stem or mesencephalon (subcortical), due to tumours, metabolic, infectious, degenerative or vascular disorders (Figure 5.3) [4, 6].

Temporal slowing

Temporal slowing is the most common unspecific EEG finding, often seen in neural degeneration (cortical dementia), anoxic conditions or head injuries [8, 9].

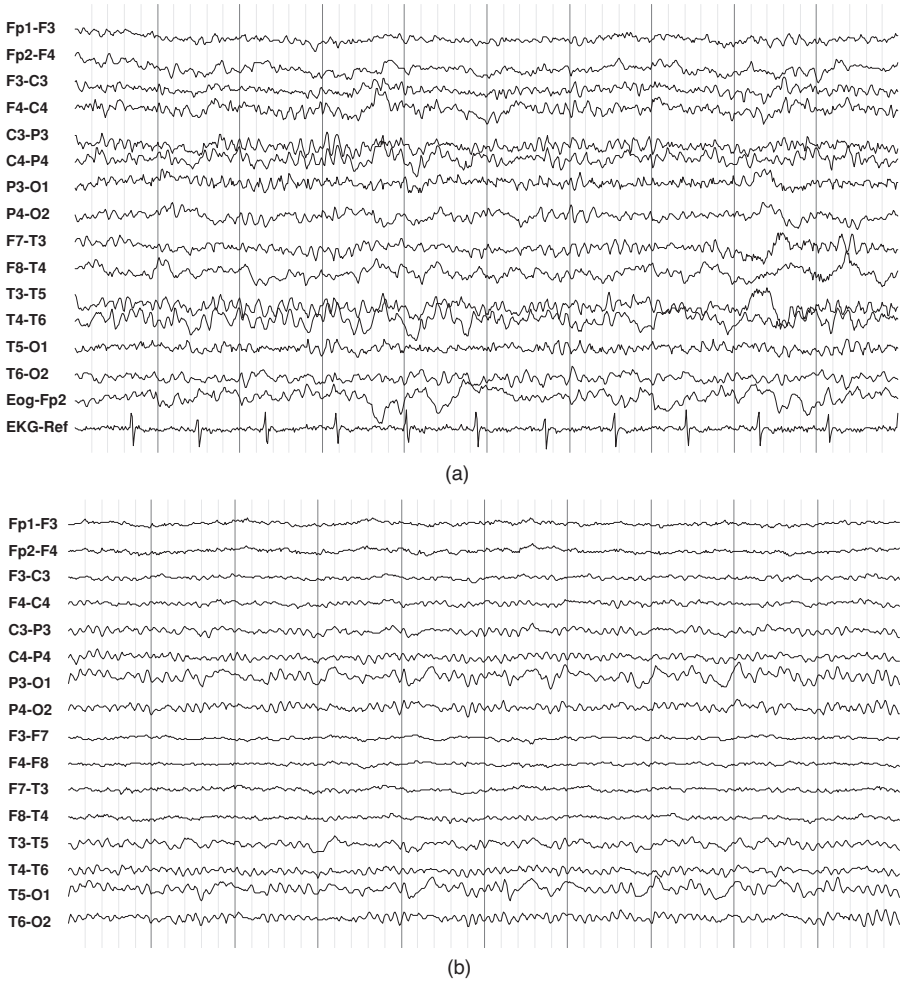


Figure 5.3 (a) Right frontotemporal slowing in a patient with intracerebral haemorrhage. (b) Left temporoparietal slowing in a patient with an acute migraine attack.

Parietal and occipital slow activity

In parietal slowing, underlying structural (space occupying) lesions should be considered. Occipital slow activity can be a non-specific finding. In combination with bi-temporal slowing, however, it can be indicative of vertebral basilar malperfusion [3, 4].

Epileptiform activity

Epileptiform activity or potentials are amongst the waveforms frequently detected in patients with epilepsy. However, in rare cases epileptiform activity can also be present in

subjects who will never develop epileptic seizures in their lifetime. Clear epileptiform potentials are comparatively easy to recognise for the experienced EEG reader, but difficult to describe without the context of the EEG background activity, the clinical parameters and the condition of the subject during recording [2, 7, 10, 11].

There are no clear-cut characteristics such as amplitudes or duration supporting an explicit or unequivocal identification of these EEG wave forms. The identification of epileptiform potentials depends on quantification rather then qualification. Important potentials and criteria are:

– *Sharp waves*: these wave forms are clearly 'outside' the regular background activity being suppressed or interrupted by the occurrence of sharp waves. The mean duration of sharp waves ranges between 70 and 200 ms.

– *Spikes*: spikes usually have a duration of between 20 and 70 ms. They are often bi- or triphasic with an asymmetric configuration, a steep increase and a shallow decrease. The main component of spikes is negative, the background activity is interrupted.

On the whole, spikes and sharp waves are followed by slow potentials/slow waves, which are the electrophysiological correlate of inhibitory processes after the occurrence of excitatory spikes or sharp waves.

The difference between spikes and sharp waves is the duration of the potentials, reflecting the distance of the neuronal origin of the potentials from the surface recording.

Epileptiform activity (spikes, sharp waves, spike wave complexes) should present with a logical field, which means the distribution of the electrodes on the scalp should be in line with the presence of cerebral generators. This characteristic is important in order to distinguish them from artefacts.

Epileptiform potentials

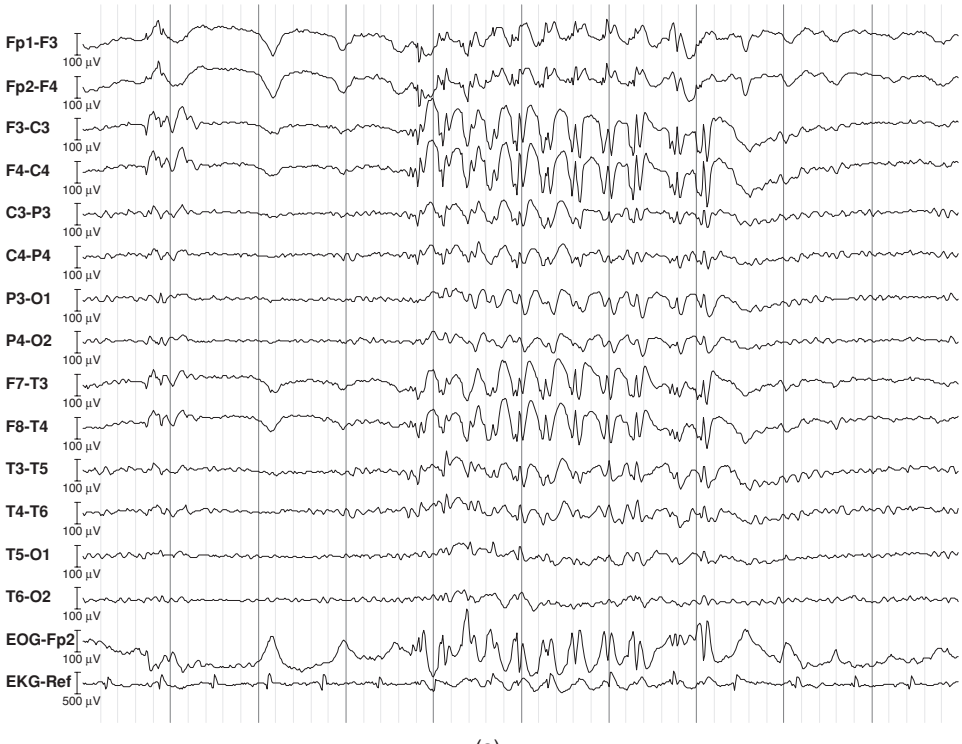
The most prominent epileptiform potential or wave form is the generalised 3/sec spike wave complex, which is an ordinary combination of spikes and slow waves in a frequency of 3–4 or 5 Hz with a maximum over frontal regions.

Atypical spike wave complexes have a frequency range of 3–6/sec and show irregular spikes or poly spike waves (Figure 5.4).

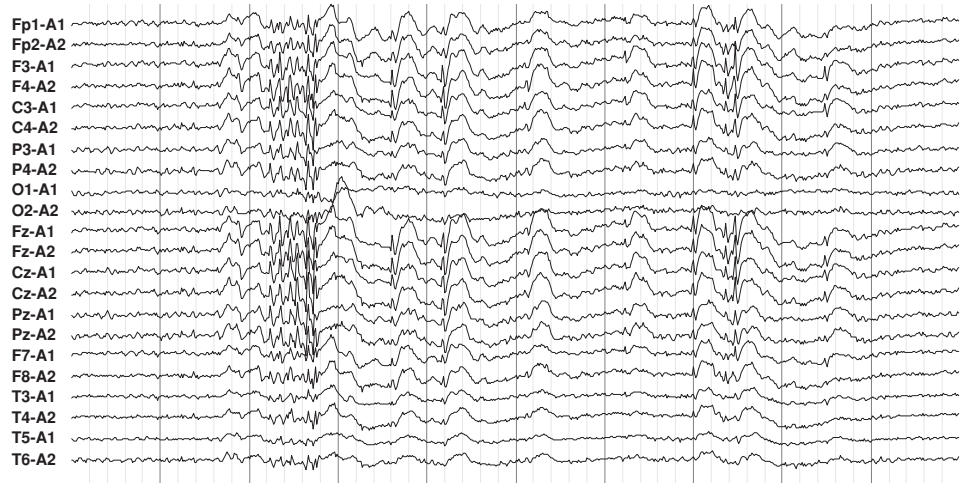
Slow spike wave complexes have a frequency below 2.5 Hz.

Photoparoxysmal activity can be a further indicator of increased cerebral excitability. Generalised photoparoxysmal spike wave complexes can be induced by photic stimulation, often in frequencies of between 14 and 20 Hz. In about 10% of cases, photic sensitivity is most prominent in patients with primary generalised epilepsy.

Polyspikes include a series of spikes within alpha or beta frequencies and often occur during sleep in patients with secondary generalised epilepsy [2–4].



(a)



(b)

Figure 5.4 (a) Epileptiform activity: generalised 3/s spike and wave complexes. (b) Epileptiform activity: generalised polyspike/wave complexes in a female patient with myoclonic epilepsy.

Reliability, validity and relevance of epileptiform potentials

Clear epileptiform activity is strongly suggestive of epilepsy, but is not overall specific. In rare cases, epileptiform activity can be detected in clinically inconspicuous subjects. For the diagnostic work up of patients with seizures the exact localisation of epileptiform activity is important. Sharp waves with temporal or frontal predominance are clearly related to the clinical presence of epilepsy in about 80–90% [6].

Generalised epileptiform activity is suggestive of generalised epilepsy.

Nevertheless, the diagnosis of epilepsy or the presence of epileptic seizures is mainly based on clinical assessments, observations and medical history taking. The EEG can contribute to the diagnosis of epilepsy, but cannot exclude it [3].

Epileptiform activity in the EEG helps to distinguish between focal and generalised epileptiform syndromes. The presence of 3/sec spike wave complexes (generalised) is suggestive of the clinical diagnosis of absence epilepsy, whereas the recording of irregular generalised (poly) spike wave complexes favours the diagnosis of myoclonic epilepsy. Focal discharges support the diagnosis of focal (temporal, frontal, parietal, occipital) epileptic syndromes. Nevertheless, the EEG can only contribute to a correct (clinical) diagnosis. Negative EEG results make the diagnosis of epilepsy less likely, but cannot exclude it [4, 6].

The clinical relevance of EEG recordings in terms of the occurrence of epileptiform activity can be increased by an extended duration of the recordings. In addition, activation techniques such as sleep recordings, photic stimulation or hyperventilation can trigger epileptiform activity during recordings [2, 3].

In summary, the EEG and its characteristic waveforms provide statistical relationships with possible underlying clinical conditions, but not a 100% electro clinical correlation [11–13].

Sharp paroxysmal activity

These patterns are suggestive of increased excitability of the brain and are often associated with the presence of epileptic seizures.

There are different wave forms in neonates, children and adults. The most characteristic wave forms are spikes and sharp waves in combination with slow deflections and wave complexes, reflecting inhibitory processes. These potentials must not be misinterpreted and a clear distinction has to be made between normal patterns (such as vertex sharp transience during drowsiness), occipital lambda and central new rhythms that can appear in sharp configurations. Sharp paroxysmal activity is marked by wave forms in interictal periods. During clinical seizures, there are different activity or seizure patterns, usually consisting of focal or generalised rhythmic activity [11, 14].

Controversial and other periodic patterns

Controversial patterns with a 'sharp' configuration are most likely not associated with epilepsy, but with neuropsychiatric and behavioural syndromes and require special attention [2, 4]:

– 7 and 14 Hz positive spikes

– rhythmic mid-temporal discharges (RMTD)/psychomotor variant

– 6 Hz spike wave complexes

– small sharp spikes (SSS) or benigne epileptiform transience of sleep (BETS)

– wicket (temporal) spikes.

Other periodic patterns include

– triphasic waves suggestive of metabolic (hepatic, renal) alterations

– periodic sharp wave complexes, for example in transmissible spongiform encephalopathies (Figure 5.5)

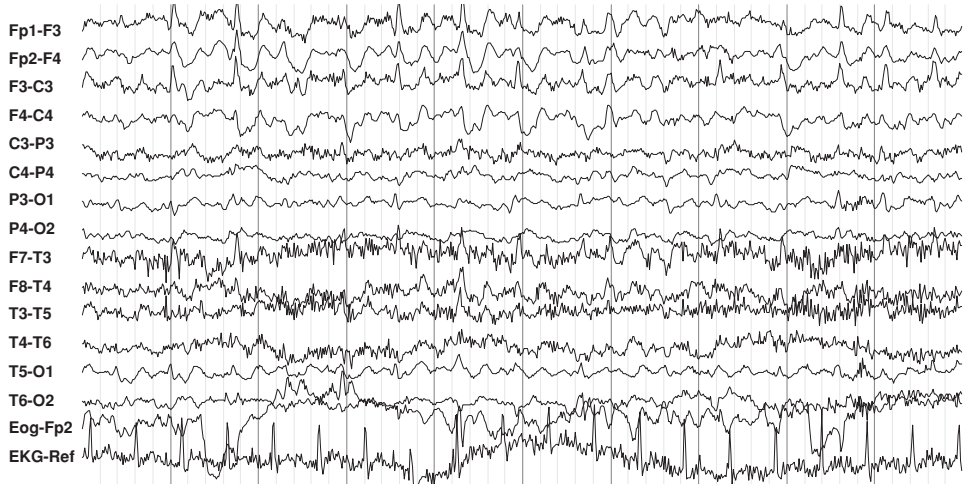


Figure 5.5 Patient with Creutzfeldt–Jakob disease: frontal periodic sharp wave complexes (PSWC).

– periodic temporal sharp waves, for example in herpes simplex encephalitis

– extreme spindles (to be distinguished from patients with benzodiazepine use)

– mitten pattern

– frontal arousal rhythms.

Focal alterations

Imaging techniques are the method of choice in cases of focal brain lesions. However, the EEG is still a complementary tool since it provides information on the brain's functional integrity. This is of particular importance in conditions where functional alterations are not exclusively associated with structural abnormalities, which is the case in many psychiatric disorders or in epilepsy [12, 13, 15, 16].

Here, the separation of focal versus generalised or diffused alterations can have diagnostic and therapeutic consequences. For instance, focal epilepsy (with a presentation of focal or regional epileptiform activity) usually requires a different set of treatments than generalised epilepsy (paroxysmal generalised epileptiform activity), including treatment options such as neurosurgery [10, 14].

Focal non-epileptiform abnormalities

In case of focal or circumscribed brain lesions, focal slowing is the most frequent EEG abnormality. Continuous irregular or arrhythmic theta/delta slowing in a circumscribed region strongly suggests an underlying structural brain lesion.

Slowing reflects unspecific brain dysfunction, either due to loss of neuronal activity and impaired metabolism or due to abnormal neuronal input on the regional cortical networks. Differences in wave amplitudes often reflect the distance of the lesion from the scalp surface or are the result of clear cortical grey matter lesions [2, 8].

Intermittent focal slowing is less specific, only indicating an unspecific dysfunction of underlying brain regions.

Intermittent rhythmical delta activity, especially in frontal regions (so-called FIRDA), is suggestive of more centrally located subcortical (diencephalic) midline orientated alterations (Figure 5.6) [3].

Asymmetries

Background activity often shows an asymmetry with lower amplitudes in the left hemisphere. Therefore, only amplitude differences above 50% are to be considered significant.

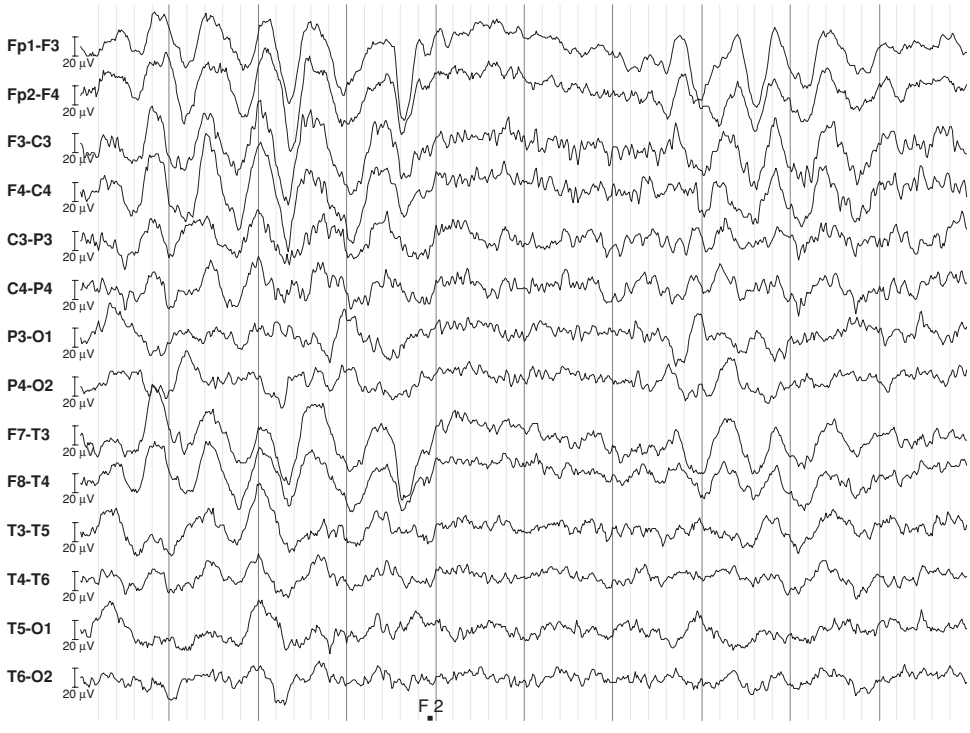


Figure 5.6 Intermittent rhythmical delta activity – FIRDA suggestive of dysfunction of deep subcortical midline regions.

Amplitude asymmetries point at lateralised brain dysfunctions, especially of parietal or occipital cortical regions, but can also be induced by intracranial haematomas leading to a possible unilateral attenuation of brain electric signals. Although asymmetries are unspecific, the dysfunction is usually on the side of the lower amplitude, except for cases of skull defects. The skull is a strong filter for high frequencies; therefore, any bone lesion facilitates the appearance of fast or sharp activity [2, 3, 8].

Periodic lateralised epileptiform discharges (PLED)

These complex, regional, 1/sec repetitive patterns often occur in acute encephalopathies with a latency of 1–2 days after lesion. PLEDs include high-amplitude slow waves plus sharp waves and spikes, show a widespread unilateral (or bilateral) distribution and are indicative of severe brain disorders (e.g. due to tumours, encephalitis or ischaemia). Following hypoxic states, PLEDs often occur bilaterally. In patients presenting with PLEDs there is a high mortality (Figure 5.7) [3, 4].

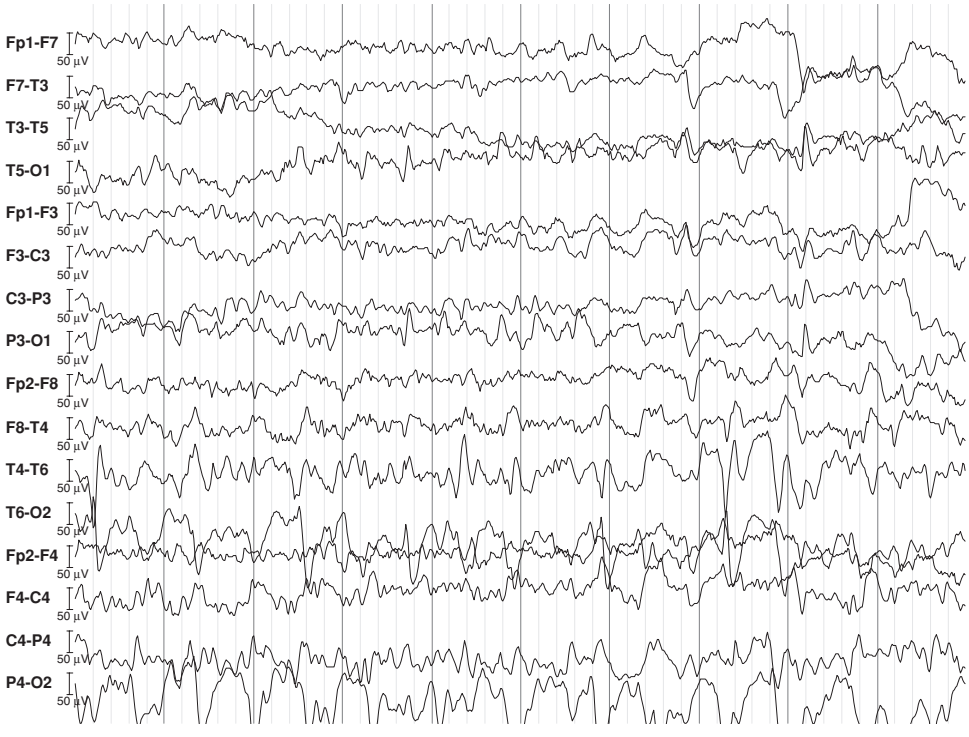


Figure 5.7 Comatose patient with a brain tumour, right sided PLED.

Clinical conditions associated with abnormal EEG patterns

Brain tumours

Tumours can be associated with a continuous focal slowing (theta delta band), while the distribution depends on the location of the tumour and its distance from the surface. In patients with elevated intracranial pressure or midline shifts due to tumours, intermittent or continuous bilateral slowing can occur. Also, tumours in deep brain structures can evoke intermittent rhythmic delta activity, epileptiform activity is also possible (Figure 5.8).

Still, none of the findings are specific enough and normal EEG recordings cannot exclude brain tumours [3, 4, 6].

Ischaemia

EEG abnormalities due to brain ischaemia have a high sensitivity but a low specificity. Brain ischaemia leads to dysfunctions associated with reduced EEG amplitudes and

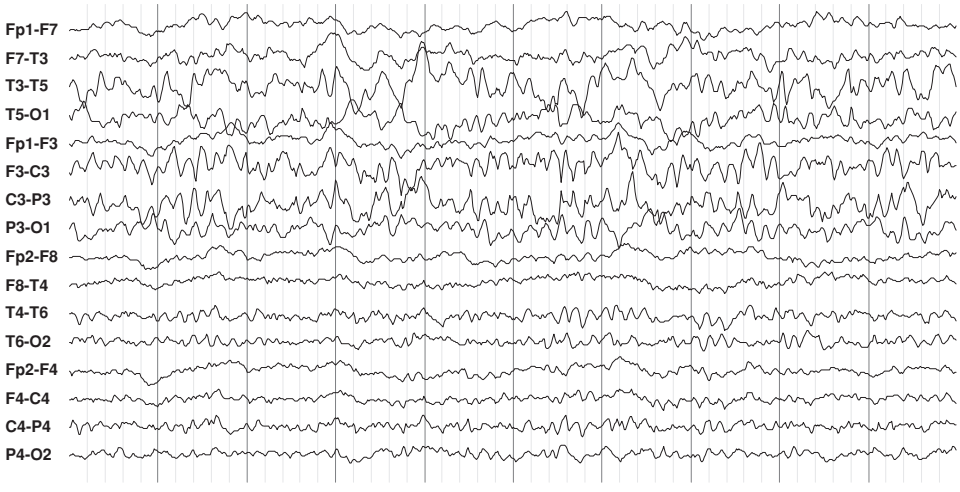


Figure 5.8 Focal slowing right hemisphere and epileptiform activity in a patient with astrocytoma.

later with focal continuous slowing. In the early stages, EEG abnormalities can be the first indicator providing higher sensitivity than structural imaging techniques. Ischaemic thalamic lesions can lead to bitemporal or general slowing. Severe and widespread brain infarction can be followed by periodic lateralised epileptiform discharges (PLEDs) indicating a poor prognosis.

Intracranial brain haemorrhage shows similar EEG abnormalities to ischaemia, in particular focal slowing with or without attenuation of normal EEG activity. In patients with subarachnoid haemorrhage EEG recordings can show normal results despite severe clinical impairments [4, 6].

Trauma

Nowadays, imaging is the preferred technique in order to diagnose and investigate traumatic brain lesions, and the EEG is less important for diagnosis and assessment of brain traumatic conditions. However, since post-traumatic epilepsy might occur, an EEG can be helpful to detect epileptiform potentials originating from the surroundings of the traumatic lesions [4, 6].

Infections

In patients with encephalitis, such as herpes simplex infections, the detection of focal (temporal) slowing or focal epileptiform potentials can be most helpful, leading to the immediate treatment with antiviral agents. In the case of normal EEG recordings, the

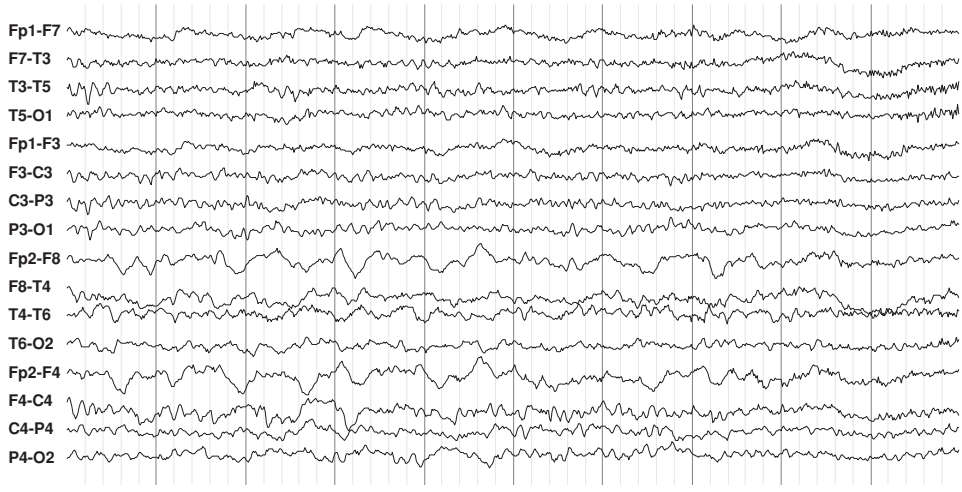


Figure 5.9 Right frontal slowing in a patient with right frontopolar brain abscess.

diagnosis of herpes simplex encephalitis is unlikely. Patients with focal abscesses often present with focal irregular theta/delta activity (see tumours, above) (Figure 5.9) [3, 6].

Diffuse encephalopathies

Diffuse encephalopathies are usually caused by general medical conditions such as metabolic alterations, the influence of drugs, diffuse hypoxia and infections, leading to a disturbance of cerebral haemostasis. Furthermore, neurodegenerative disorders (especially cortical dementias) can affect diffuse and widespread brain regions [2, 3].

Metabolic disorders

Metabolic alterations can lead to generalised neuronal dysfunction and consequently to encephalopathy with associated EEG alterations. The clinical characteristic of metabolic encephalopathies is a fluctuating disturbance of consciousness. The key EEG characteristic is a diffuse background slowing with a wide spectrum of changes, ranging from subtle signs of dysfunction to severe and generalised abnormalities indicating diffuse cortical dysfunction. In rare cases triphasic waves can occur as a special wave form; however, none of the changes or alterations are specific.

The slowing of background activity usually begins with an increase in theta activity, followed by intermittent generalised theta slowing or bilateral synchronous delta wave groups, sometimes with a frontal maximum (frontal intermittent rhythmic delta activity). A characteristic of these abnormalities is that they can be blocked by eye opening. Along with a growing severity of the diffuse encephalopathy, an increase of slow activity occurs with continuous slowing from theta to delta frequencies, usually with a frontal maximum.

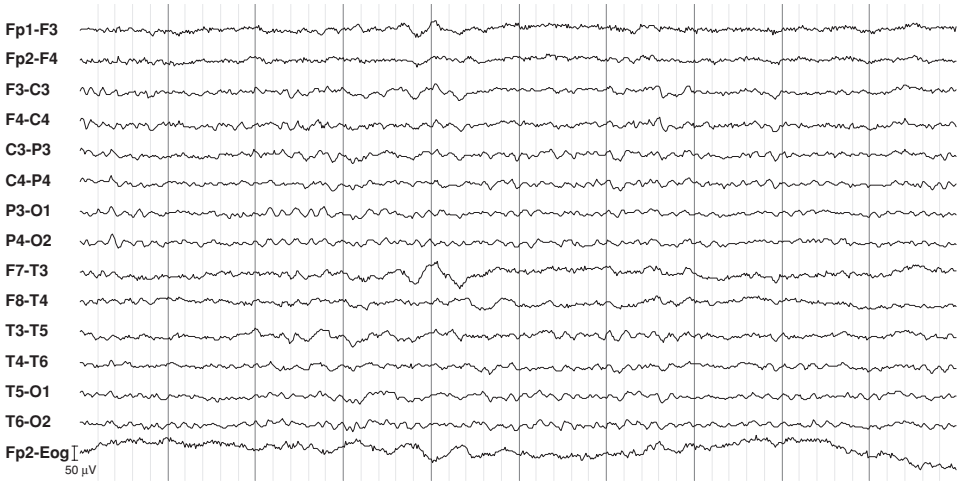


Figure 5.10 Diffuse slowing of background activity in a patient with hepatic encephalopathy (severe ammonaemia, somnolence).

Typical for metabolic encephalopathies is a preserved reactivity to external stimuli (eye opening). In case of additional (EEG hypoxic) regional lesions, focal changes and/or epileptiform potentials can occur [17].

Often there is a discrepancy between marked abnormalities in the EEG, with a severe slowing in view of only moderate impairments of cognition or consciousness.

Hepatic disorders

In hepatic disorders with an impairment of the detoxification capacity of the liver and an increasing ammonaemia, there is an association of the severity of EEG abnormalities with the degree of consciousness impairments (Figure 5.10). Together with developing ammonaemia, there is an increasing slowing from theta to delta frequencies, sometimes transient triphasic waves can be found. They are high amplitude rhythmic sharp waves with triphasic configuration and a major positive component. These patterns occur in metabolic encephalopathies but they are not specific and can also be detected in severe dementia, spongiform encephalopathies or extensive focal lesions [18, 19].

Renal failure

In patients with kidney diseases and renal failure there are similar abnormalities, a diffuse background slowing, sometimes with paroxysmal bursts of spike waves and triphasic waves. If dementia develops in the course of dialysis treatment, bilateral paroxysmal slow waves can occur [2, 17].

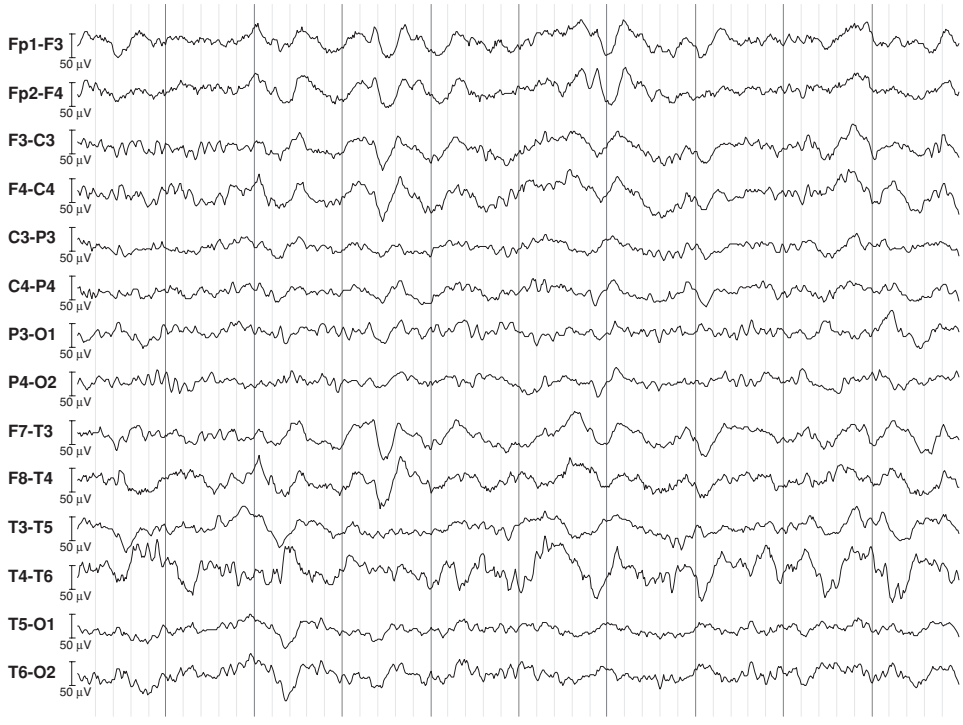


Figure 5.11 Patient with severe hypoglycaemia; diffuse slowing.

Alterations of glucose metabolism

The brain is very sensitive to disturbances of the glucose haemostasis. Hypoglycaemia leads to severe EEG changes, initially with slowing (especially under hyperventilation), then increasing towards generalised slowing, which happens especially in connection with a rapid decline of glucose levels (Figure 5.11). In the case of additional vascular lesions, regional or focal changes can occur. Furthermore, epileptic seizures are frequent in hypoglycaemia with epileptiform activity visible in EEG recordings. Sometimes, the abnormalities are sustained for days or weeks despite of the normalisation of glucose levels [3, 4].

Calcium

With both low or increased levels of blood calcium, generalised EEG slowing can occur. In hypercalcaemia bursts of delta activity are possible. Hypercalcaemia is epileptogenic with the occurrence of paroxysmal epileptiform potentials [3, 4].

Effects of psychotropic drugs on EEG are discussed in Chapter 12.

Neurodegenerative disorders, dementias

Progressive neurodegenerative disorders, especially with cortical involvement, lead to increasing alterations of the EEG signals during the course of the disease. The most important EEG sign is slowing, often together with a diffuse background slowing and a reduction of the frequency of the background rhythm below 8/sec. During the course of the disorder, EEG abnormalities often begin with subtle changes; therefore, the use of baseline EEG recordings for comparison can be helpful. Sometimes, in severe cases and in the course of time, triphasic waves can occur. In transmittable spongiform encephalopathies (Creutzfeldt–Jakob disease) periodic sharp wave complexes can be a characteristic attribute of the EEG. EEG abnormalities in dementia are dealt with in Chapter 11 [8, 9].

Coma

In comatose patients, depending on the underlying disease, EEGs are often severely abnormal with suppression patterns, periodic activity, loss of reactivity and a decrease or flattening of amplitudes. Brain death is defined as the complete absence of brain electric activity with a total suppression of any EEG.

Abnormal rhythmical patterns in comatose patients with alpha, delta or theta frequencies of diffuse distribution or frontal or occipital maximum, irresponsive to external stimuli (paradoxically, the EEG appears to be normal), can occur after severe brain

Table 5.1 Abnormal clinical conditions and associated EEG patterns.

Metabolic, toxic and infectious alterations	Vascular lesions	Space occupying lesions
- Decrease of background frequency	- Ischaemia (carotid artery): frontal and temporal slow waves	- Abscesses: focal (localised) slow waves above the area with the abscess
- Diffuse slow waves	- Vertebral basilar artery: temporal and occipital slow waves	- Tumours: focal slow (delta) activity and more rhythmical activity, related to the depth of the lesion.
- Frontal intermittent rhythmic delta activity (FIRDA)	- Haemorrhage: focal slow waves, often with paroxysmal activity	
- Hepatic coma, uraemia: triphasic waves	- Haematoma: focal slow waves.	
- Transmissible spongiform encephalopathies: periodic sharp wave complexes (PSWC).		

damage and are often associated with a poor prognosis. These patterns require special attention and must not be misclassified as normal [3, 17].

A synopsis of various EEG patterns and abnormalities in major clinical conditions is provided in Table 5.1.

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6

The Role of EEG in the Diagnostic Work Up in Psychiatry: Nonconvulsive Status Epilepticus, Frontal Lobe Seizures, Non-Epileptic Seizures

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Nonconvulsive status

Introduction

Nonconvulsive status epilepticus (NCSE), once thought to be a relatively rare aetiology of altered mental status or abnormal behaviour, has been increasingly described in the neurology and epilepsy literature. To this day it represents a diagnostic challenge for both fields.

- Nonconvulsive status epilepticus (NCSE), like convulsive status epilepticus (CSE), is a state of continuous or intermittent seizure activity without a return to baseline lasting more than 30 minutes. It differs from convulsive status in that its presentation is primarily non motor and the outcome is not thought to be as grave [1].

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Table 6.1 Clinical presentations of patients in nonconvulsive status epilepticus.

- Mild cognitive disturbances (impaired attention, difficulty in sequential planning of complex motor tasks)
- Prolonged confusional states
- Mood disturbance
- Psychotic states
- Speech disturbance, for example, verbal perseveration, reduced verbal fluency, muteness, speech arrest or aphasia
- Bizarre behaviour that is uncharacteristic or deviates from baseline, for example, laughing, dancing and singing inappropriately
- Repetitive motor activity
- Autonomic disturbances (belching, borborigmi, flatulence)
- Sensory and psychic phenomena
- Coma.

- The hallmark of NCS is a change in behaviour or mental status that is associated with diagnostic EEG changes.

Clinical characteristics

- The clinical manifestations of NCS are characterised by a change in behaviour which can vary from minimal confusion, to bizarre behavioural manifestations, to psychotic or affective states, all the way to coma and they are associated with diagnostic EEG changes [Table 6.1].

- Motor activity is usually normal; however, decreased response time, clumsiness, twitching of facial muscles (in particular of the eyelids and automatisms such as licking, chewing or picking), apraxia and focal jerks have been described [1]. Automatisms in the form of gross movements such as positioning, raising, flexion or extension of the extremities, head deviation, have been seldom seen [1].

- Automatisms have been thought to be longer in duration and more complex in nature in complex partial nonconvulsive status (CPSE) than in absence nonconvulsive status [2].

- NCSE is possibly one of the most frequently missed diagnosis in patients with a change in mental status. This occurs in part because of the broad range of clinical presentations, in part because of limited awareness to this condition in part because of co-morbidities and at times because of lack of ready available EEG which is essential in establishing the diagnosis. The diagnosis becomes even more challenging when confronted with a patient who presents with cognitive impairment at baseline, for example, mental

retardation or dementia, or who carries a prior history of a psychiatric disorder. A multidisciplinary approach is essential in order to improve the recognition, diagnosis and ultimately outcome of NCS and an EEG is the goal standard.

Classification

There are two main types of NCSE: absence status, which is a primary generalised process, and complex partial status (CPSE), which is focal in origin. Both absence and complex partial status are characterised by a change in mental status. Onset can be sudden or gradual [2]. The episodes can vary in duration and intensity. In both types of NCS abnormal motor activity is either not present or minimal. Some of the described overlap in clinical presentations may be the result of misdiagnosis. In addition, rapid generalisation of CPSE during EEG recording is at times the most likely explanation of misdiagnosing cases of CPSE as absence status. This is compounded by the relative limited awareness of this entity [4].

Epidemiology

- Determining the incidence on NCS is an interesting challenge. The hallmark of NCSE is a change in behaviour or mental status that is associated with diagnostic EEG changes. Unfortunately an EEG is not usually readily available in most institutions, making this diagnosis particularly challenging. To this day the true incidence of NCSE as well as its morbidity and mortality are ill defined. Some authors have reported a high morbidity and mortality in NCSE and suggested that aggressive therapy be used [5].

Other series suggest that NCS is a relatively benign condition [6].

Despite suggestions that neuronal damage may occur in NCS [7], controversy still exists regarding the need for aggressive therapy since there are reports of complete recovery and other of associated cognitive or neurological deficit.

The limiting factor in better assessing the true morbidity and mortality of NCSE is due to the variety of clinical symptoms, potential misinterpretation of EEG patterns, grouping of patients with different co-morbidities, the lack of prior cognitive function or neuropsychological assessment for comparison.

- The Epilepsy Foundation Research workgroup amalgamated the data from the literature and reported an estimated incidence of 6–18/100 000 cases/year [8] Privitera *et al.* reported in a prospective study of 198 patients with altered consciousness but no clinical convulsions who were referred for emergency EEG, that 37% of these patients showed EEG and clinical evidence of NCSE [9].

DeLorenzo *et al.* found that NCSE was present in 14% of patients after control of GCSE [10]. Towne *et al.* reported on a prospective study of 236 patients with coma who had no clinical evidence of seizures that 8% met criteria for NCS on EEG [4]; NCS has been reported in all age groups from the very young to the very old and in both sexes without a clear predominance in either sex [4].

- Depending on the different series anywhere from 10 to 100% of patients who present with NCS do not have a past history of seizure disorder [1, 11].

- NCSE has been reported in all age groups and in both sexes.

- Though absence status has been mostly reported in children it can present *de novo* in later life [12, 13]. It has been described that 10% of adults with absence seizures will have at least one episode of absence status [14].

- Different precipitating factors including infection, alcohol intoxication/withdrawal, drug toxicity, metabolic abnormalities, pregnancy, CNS disturbances and ECT treatment have been implicated in NCS [4–14], and can be identified in 15–70% of cases emphasising the importance of assessment in the evaluation of these patients [15].

EEG in NCSE

- At the present time, there are no clear criteria to guide the decision of when an EEG should be requested. That said, when NCS is suspected on clinical grounds alone, an EEG is indicated to confirm the diagnosis and direct management.

- In absence nonconvulsive status, the EEG can be characterised by continuous or nearly continuous generalised, rhythmic, bilaterally synchronous, spike-and-wave discharges at three per second intervals with a maximum over the bifrontal region. Variation in the EEG pattern can occur including 2–3 per second spike-wave complexes as well as bursts of rhythmic slow, rhythmic or arrhythmic spike wave or polyspike activity [16, 17].

- In CPSE, various forms of less synchronous seizure activity, rhythmical slowing, rhythmic spikes, rhythmic sharp and slow waves, have been described [16,17]). Despite the fact that several EEG patterns have been described to be suggestive of both types of NCS, a clear pathognomonic pattern has not been defined. When (and if) an EEG is performed at the onset of the seizure, a clear focus may be identified that may be critical in differentiation CPSE from absence nonconvulsive status. If secondary generalisation is present, either because of rapid spread or because the EEG

is performed when a patient has been in CPSE for a long period of time, then there is the risk of misclassification [1]. These findings are important prior to deciding treatment options in that these options are different in the different type of NCSE.

Conclusion

Nonconvulsive status epilepticus is not as rare as once thought and should be considered in any patient presenting with a change in mental status of uncertain aetiology. The clinician must be aware of the different clinical characteristics of this disorder as well as similarities and differences from psychiatric disorders and other neurological disorders. A past seizure history is not necessary for the diagnosis, nor is there necessarily associated motor activity. An EEG is essential in order to confirm the diagnosis, and should be performed as soon as possible in that early recognition and treatment may improve outcome. The EEG can help making the differential diagnosis between absence nonconvulsive status versus CPSE so that, when indicated, the proper long-term anti-epileptic drug therapy can be started. Treatment begins with correcting the underlying aetiologies and using benzodiazepines. There is usually a good response to an intravenous benzodiazepine, but the response can be delayed in which case other anticonvulsants have been used as adjuncts. It appears that overall the prognosis is generally good for both absence nonconvulsive status and CPS, although the literature is unclear regarding neurocognitive outcomes and its possible relation to the duration of the status. More studies are needed in order to be able to obtain guidelines which can assist us in the management and decision making of this difficult condition and ultimately improve outcomes.

Nonconvulsive status, once considered a rare disorder, should be ruled out in any patient who presents with altered mental status of undetermined aetiology. An EEG is required to confirm the diagnosis.

Psychogenic non-epileptic seizures

Introduction

- Psychogenic non-epileptic seizures (PNES) are characterised by a change in behaviour and/or motor activity. When EEG changes are present are usually secondary to muscle, movement or electrodes artefacts. No associated epileptiform activity have been associated with PNES.

- PNES seizures can be divided into two major categories; those in which motor abnormalities predominate the clinical presentation, thus mimicking convulsive seizures, and those which are characterised by a change in mental status without associated motor activity, thus mimicking complex partial or absence seizures [18, 19].

- It can be extremely difficult to differentiate PNES from neurogenic seizures. Misdiagnosis can result in patient mismanagement with the potential for iatrogenic harm [20–22].

- A detailed history, pattern recognition of the events, scalp and or video EEG monitoring are essential measures in the differential diagnosis of this potentially serious condition.

Epidemiology

- It has been estimated that the prevalence of PNES ranges between 2 and 33 over 100,000 [23] while the prevalence of epilepsy is between 4 and 6 per 1000 [24].

- 5–20% of patients followed in epilepsy clinics actually have been described to have a psychogenic cause of their events [25, 26].

- Different series have reported that 5 to 58% of patients with PNES had a coexistent neurogenic seizure disorder [25, 26].

- A female predominance has been reported, with women comprising 70–80% of patients with PNES [25, 26]. If the female predominance is indeed real, or a product of cultural factors, has not been established.

- The incidence of PNES seizures declines after the age of 35 and is rare after the age of 50 [19].

- An association between sexual abuse and the development of PNES has been described, with 10% to 25% of patients with NES having a history of abuse [27].

Clinical characteristics of PNES versus neurogenic seizures

- PNES seizures can present with multiple clinical manifestations. They can be associated with motor abnormalities or they can be characterised by a change in mental status without associated motor activity, thus mimicking absence seizures, complex partial or simple partial seizures.

- PNES tend to occur in clusters with multiple events of multiple patterns in the day. They are usually more gradual in onset than neurogenic seizures and they last longer. Pelvic thrusting movements, asynchronous and/or thrashing movements of the extremities can be present. A post ictal period is usually missing and recollection of the event is usually present.

- During one of these events the eyes can often turn away from the observer even if the observer moves from one side of the patient to the other. Urinary or faecal incontinence is uncommon, though can be present. The same is true for self-injury and tongue lacerations [26]. Directed violence can also be present differently from neurogenic seizures where directed violence is not seen [26].

- Neurogenic seizures tend to be isolated events, last in general less than 90 seconds and are stereotypic in origin. An aura can be present or absent. They tend to have in-phase, synchronous tonic-clonic movement of the extremities. When the seizures is generalised the patient cannot recall the episode. Pupils that dilate and become unresponsive to light are suggestive of neurogenic seizures. In neurogenic seizures eyes will often deviate to one side and remain fixed in that position regardless of the patient's position or the observer's location. Since incontinence does not consistently occur in neurogenic seizures the presence or absence is not helpful in distinguishing the two. Directed violence is extremely rare in this type of seizure [28].

- The above characteristics can be at times helpful in the differentiation of PNES versus neurogenic seizures. In view of the fact that a wide variety of clinical presentations exists, an accurate history and possible EEG correlate are essential in reaching a final diagnosis and prior to determining a treatment plan.

Manoeuvres

- It has been described that patients with psychogenic seizures are particularly responsive to suggestion. Several manoeuvres and or placebo inductions have been at times used as a helpful tool in the diagnosis of PNES versus neurogenic seizures, though some of these manoeuvres have been controversial [Table 6.2].

The simple tests described in Table 6.2 will often result in avoidance or resistance from a patient having a PNES while they should not elicit any response from a patient having a neurogenic seizure. Verbal suggestions combined with saline injection have been described for a long time, though a lot of controversy surrounds this practice.

Table 6.2 Manoeuvres in PNES.

• Non-noxious sensory stimulation (such as placing a cotton swab in the nose)
• Noxious stimulation (such as a sternal rub, firm pressure on a digit, or an anhydrous ammonia capsule under the patient's nose)
• Passive eye opening
• Geotrophic eye testing
• Dropping the patient's arm over their face
• Corneal stimulation.

Table 6.3 Neurogenic vs. motor NES.

	Neurogenic	NES
serum pH	acidosis	normal
serum bicarbonate	decreased	normal
serum prolactin	elevated	normal
EEG	abnormal during event	unchanged during event
response to saline infusion test	no effect	often positive
induction by suggestion	unusual	common

Laboratory tests can be helpful in the differential diagnosis of these two conditions [Table 6.3]. Additional value can be added when a correlation is made with EEG monitoring.

EEG findings

- An EEG is the ultimate test in the diagnosis of PNES versus neurogenic seizures.
- In PNES when EEG changes are present they are usually secondary to muscle, movement or electrodes artefacts. No associated epileptiform activity has been associated with PNES.
- Scalp EEG recording and or video EEG monitoring, especially in the presence of a clinical event, can be diagnostic in the differential diagnosis of PNES versus neurogenic seizures.
- It is important to remember that a normal interictal EEG is not always helpful in ruling out a neurogenic seizure disorder since 29 to 55% of first-time interictal EEGs in seizure patients are normal [29]. Simple partial seizures and complex partial seizures can be difficult to capture on surface EEG recordings. In this case the expertise of an experienced epileptologist is warranted. A multidisciplinary approach is essential in order to reach an accurate diagnosis.
- Misdiagnosis can potentially result in the inappropriate use of anticonvulsants. Most important of all, misdiagnosis can result in delay in obtaining proper psychiatric treatment.
- When the diagnosis is entertained, patients should be referred to a specialised centre as management of PNES can begin only after the diagnosis is established. Correlation of historical, clinical, laboratory and EEG information are essential in order to reach an accurate diagnosis.
- Video EEG monitoring is the gold standard in the evaluation of PNES.

Frontal lobe seizures

Introduction

- Over the last 30 years our understanding of the functional anatomy of the frontal lobe has improved and so has our understanding of the clinical syndromes of frontal lobe origin. Nonetheless, seizures of frontal lobe origin can present a challenge for both the neurologist and the psychiatrist. Despite the fact that frontal lobe seizures have been described in approximately in 20% of patients admitted to an epilepsy unit its diagnosis is often challenging. At times seizure of frontal lobe origin can be confused with nonconvulsive status, PNES and other psychiatric disorders and the reverse is also true.

- Factors that can limit the study of seizures of frontal lobe origin are:

  its anatomical size

  its limited access to scalp EEG recording

  its extensive networking with other parts of the brain

  the variety of clinical manifestations.

The frontal lobes are the largest cortical region. They comprise about 40% of the cerebral cortex making its deep recesses inaccessible to standard scalp EEG recording. The challenge of frontal lobe seizures also lies on the diversity of the clinical manifestations, which can often be bizarre in origin. Also, ictal signs and symptoms are often not related to the area of primary epileptogenesis but to the electrical spread of the discharge to the ipsilateral, controlateral or deep structures. Subsequently, the clinical presentations can at times be confused with seizures of temporal lobe origin, with primary generalised seizures and/or with psychogenic nonepileptic events or other psychiatric disorders. The advent of video monitoring and intracranial recording allows for a correlation between the clinical presentations and the EEG changes which have improved our ability to detect seizures of frontal lobe origin (FLE) [30].

Clinical characteristics

Clinical manifestations in FLE can vary and can be characterised by a corollary of symptoms. In general, seizures of frontal lobe origin are brief . They usually last less than 1 minute. They may occur in clusters. They often present with a nocturnal predominance and or are exclusively nocturnal [Table 6.4]. Seizure presentation depends on the area

Table 6.4 Frontal lobe seizures.

- Stereotypic
- Usually brief
- Auras are usually non-specific
- Frequent
- Often occur in clusters
- Can be nocturnal
- RMA (useful when present)
- Automatisms may be repetitive
- Postictal confusion is not a major feature.

of the frontal lobe involved and whether the event remains focal or spreads. Although focal motor activity, adversive head and eye deviation and tonic postural episodes are the most commonly described features, a wide variety of clinical manifestations have been described, including somatosensory symptoms, autonomic dysfunctions, speech arrest, forced vocalisation, pesudoabsence, visual hallucinations, illusions or visceral symptoms. Simple motor automatisms and complex motor automatism in the form of alternating bizarre motor activity or repetitive motor activity may also occur in seizures of frontal lobe origin [30,31] [Table 6.5]. Seizures originating in the supplementary motor area are usually brief, lasting 10–15 s. They can present with bilateral symmetric tonic posturing and the patient can be conscious throughout the seizures [29, 30].

Of is of note that some of the clinical manifestations, especially motor automatisms or prolonged absence, can at times be misdiagnosed as PNES or other psychiatric disorders.

Table 6.5 Clinical characteristics of FLE.

- Tapping
- Kicking
- Rubbing
- Pelvic trusting
- Thrashing
- Picking
- Alternating movements
- Running
- Scratching
- Genital manipulation
- Speech disturbance (area 44)
- Speech arrest
- Forced vocalisation (moaning, grunting)
- Repetition of words, vowels, syllables (in SMA)
- Behavioural disturbances (RMA)
- Autonomic dysfunction
- Dizziness
- Light-headedness
- Rearranging of the clothing.

Key features which may help to differentiate seizures of frontal lobe origin from PNES are: presence or absence of stereotipicity, duration, frequency and timing of the events, the presence versus absence of a specific aura, the presence of simple and or complex automatism with or without repetitive motor activity and lack of postictal confusion [30].

EEG characteristics

Scalp EEG can be an helpful first tool in the diagnosis of frontal seizures, though one should be aware that some series have reported that only 14–15% of patients with frontal lobe seizures will present localised frontal lobe discharges [30]. Also it has been reported that when an EEG is performed in the outpatient setting it detects inter-ictal epileptiform abnormalities in only 29–55% of patients, in any type of focal epilepsy. Also several series have reported no EEG changes even during ictal recording in 33–36% of patients [29].

When the dorsolateral cortex is involved, paroxysmal discharges can be easily detected while discharges from the mesial (interhemispheric) cortex, the orbitofrontal region and the cingulum often shows no surface EEG correlates even during ictal activity or may be volume conducted over a wide region bifrontally, sometimes with a frontal maximum, like in discharges arising from the mesial frontal cortex. Callosal connections at times can result in bifrontal paroxysmal activity and a large portion of the prefrontal region give no symptoms on electrical stimulation. It is important to be aware of the fact that a normal or nonspecific EEG, even during clinical seizure activity, can be compatible with the diagnosis of frontal lobe seizures [30].

Over the years, work with expanded EEG channels, including supraorbital or nasoethmoidal electrodes, computerised EEG analysis and intracerebral recording of the frontal lobe have helped us to better understand the complexity of the different type of seizures and to correlate clinical manifestations with the anatomical localisation.

Video EEG monitoring is used to help correlate clinical seizures characteristics with EEG changes. Some of the invasive techniques like subdural recording and intracerebral depth recordings have been an essential tool in identifying the foci responsible for the seizure, allowing for an improvement in the diagnosis and guiding in the surgical resection when necessary.

Summary

- Frontal lobe epilepsy is a common disorder, though at times difficult to diagnose. Despite the fact that we have reached a better understanding of the variety of clinical manifestations, rapid generalisation and limited expression in scalp recording still represents an obstacle to the diagnosis. The clinical symptoms of FLE can be confusing and misdiagnosis can occur with other type of events including PNES and/or other psychiatric illness.

- Stereotypic bizarre behaviour should alert the clinician to the possibility of FLE.

- Attention to clinical presentation and the use of adjunctive diagnostic modalities, for example, scalp and intracranial recording and or neuroimaging, has greatly improved our ability to diagnose FLE and to direct management.

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7

EEG in Childhood Psychiatric Disorders

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Introduction

Recent advances in the understanding of the electrophysiological correlates of many childhood or adolescent-onset psychiatric disorders offer promising future opportunities to target effective treatments based on precise markers [1–4]. However, quantitative EEG findings do not yet translate to diagnostic or treatment applications specific to behaviour disturbance or psychiatric disorder. It is already clear that translational research in neurodevelopment, genetics, imaging and electroneurophysiology will profoundly alter the diagnostic precision and management of paediatric neuropsychiatric disorders, such as obsessive compulsive disorder, Tourette disorder or depression. But for the present, we will focus discussion on those childhood psychiatric disorders most commonly associated with, or confounded by, standard EEG abnormalities: attention deficit/hyperactivity disorder and autism spectrum disorders. The prevalence of hyperactivity, inattention or impulsivity in seizure disorders or childhood requires inclusion of a discussion of these symptoms and their correlates in childhood epilepsy.

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Attention deficit disorder

Introduction

Attention deficit/hyperactivity disorder (ADHD) remains the most common childhood school-related behavioural problem. Despite an extensive body of research, it also remains one of the more controversial neuropsychiatric disorders both regarding its diagnosis and treatment. The diagnostic criteria and process are inherently complex and influenced by external adult informants, as well as multiple and variable ratings instruments. There are also significant co-morbidities. Presentation is heterogeneous and dynamically variable with developmental stage.

The current Diagnostic and Statistical Manual (DSM-IV-TR) nomenclature for diagnosis of ADHD describes the syndrome in terms of either partial or full expression: ADHD Predominantly Inattentive Type, ADHD Predominantly Hyperactive-Impulsive Type and ADHD Combined Type. Such distinctions are useful in delineating correlated neurological disorders presenting with hyperactive, impulsive or inattentive symptoms. Further, different subtypes of ADHD may predominate during distinct periods of child and adolescent development, aiding differential diagnosis. Pre-school children with ADHD most often present with the hyperactive-impulsive (HI) form of the disorder; whereas in contrast, older adolescents will largely manifest a predominantly Inattentive subtype with only residual restlessness. A child must meet six out of nine inattentive symptoms for diagnosis of the inattentive type, and/or six of the hyperactive-impulsive symptoms for the HI type. Six symptoms from each list must be present for diagnosis of the combined type. The range of potential symptom combinations within each type, as well as across individuals, highlights the heterogeneity in clinical presentation for diagnostic assessment. Although the DSM-IV remains the most commonly referenced diagnostic system for ADHD in the US, it must be noted that the ICD-10 system most commonly used in Europe and elsewhere in diagnosis of hyperkinetic disorder confronts similar issues of complexity and heterogeneity, although the symptom list has been described as more restrictive than what is published in the DSM-IV.

Two important points need to be emphasised prior to discussing the role of the routine EEG in the diagnosis and management of ADD and ADHD. The assessment approach to the child with possible ADHD must involve careful symptom assessment, setting assessment for each symptom, standardised behaviour rating scales and a thorough developmental history, which includes details of any prenatal substance exposures. Any patient being considered for the diagnosis of ADD or ADHD should receive a full neurological history and examination, with additional neurological work up (EEG or imaging) if the history and exam give any indication of abnormality [5, 6]. The second important point to be emphasised is the differential diagnosis.

Once the possibility of ADHD arises, a differential diagnostic list needs to be developed. The list of developmental, neurological and psychiatric differential diagnoses of ADHD to be considered in the evaluation of the disorder is extensive. Post-traumatic and post-infectious encephalopathies, foetal alcohol syndrome (FAS), chronic lead

poisoning, untreated phenylketonurea, pervasive developmental disorders, absence seizures and, rarely, hyperthyroidism, number amongst the disorders to be differentiated from ADHD. Additionally, other psychiatric disorders such as bipolar disorder, anxiety disorders, depression, oppositional-defiant disorder or conduct disorder must be considered on the differential diagnostic list. Given the non-invasive and relatively inexpensive nature of the EEG test, full consideration of its possible usefulness in helping the clinicians arrive at an accurate diagnosis should be considered. In this chapter we review available literature examining the routine EEG evaluation of children, adolescents or adults with ADHD, with an emphasis on appreciating the need to exclude underlying seizure activity in the diagnostic process.

The problem of co-morbidity, not only with learning disability, but also with other disruptive, anxiety and mood disorders is a major confound of this literature. It is generally accepted that a diagnosis of ADHD carries a significant risk for coexisting disorders, particularly in clinic-referred populations of children. Co-occurrence and symptom overlap similarly confound the ability to report independent correlations between seizure disorders and specific ADHD co-morbidities such as oppositional defiant disorder, conduct disorder or bipolar disorder, although symptom correlates between seizure, aggression, impulsivity or mood disturbance have been widely observed and well documented [7–9]. There is continuing diagnostic controversy regarding the differential diagnoses of ADHD and bipolar disorder in children. The identification of bipolar disorder in youth, the extent of diagnostic continuity with adult bipolar disorder and associations or overlap with ADHD remain open to continuing research and debate.

EEG abnormalities in ADHD

A significant number of studies found variable rates of EEG abnormalities in children with ADHD. Phillips *et al.* [10] reported on routine EEG screening in children hospitalised over an 18-month period for behavioural problems. Eighty-six children were admitted for conduct disorder or conduct disorder plus ADHD ($N = 75$; breakdown not provided) and ADHD alone ($N = 11$). They reported that 91% of the records were either normal or showed 'normal variant patterns'. The specific 'normal variant' patterns exhibited were not provided. Eight (9%) records showed definite abnormalities showing background slowing or paroxysmal discharges. They concluded that EEG screening may be of limited value in childhood behavioural problems without clinical evidence of neurological disorders. Also in 1993, Frank reported significantly higher rates of abnormalities [11]. They reported that 31% of a sample of 7–12 year old children diagnosed with ADHD had abnormal routine EEG (21 out of 64). Of the 21 children with abnormal EEGs, 84% had spikes or spike-wave discharges. The others had slowing of the background in excess of what is expected for the age.

The Phillips *et al.* [10] report differs from conclusions reached in subsequent studies (Hughes *et al.* [12]). This group examined the EEGs of 176 children with ADHD.

They reported an overall rate of 'definite' noncontroversial epileptiform activity of 30.1%, mainly focal (usually occipital or temporal). Less often the epileptic activity was generalised, with bilaterally synchronous spike and wave complexes seen in 11 children. In the entire group, only 27.8% were completely normal and an additional 18.8% had positive spikes as the only abnormality. They concluded that ADHD is a condition often with organic changes in the form of EEG abnormalities; at times these abnormalities are of epileptiform character. Such activity could contribute to a deficit in attention or a plethora of movements [12]. Another report soon appeared following the Hughes *et al.* [12] report from an independent group. Millichap [13] reported on the EEG findings from 100 consecutive children with ADHD. They reported an incidence of 7% of 'definite abnormalities' suggestive of epilepsy and an additional 19% moderately abnormal dysrhythmias not diagnostic of epilepsy. Based on their findings, they suggested six specific indications for when to obtain an EEG in a child presenting with ADHD. These indications were: (1) the presence of personal or family history of seizures; (2) inattentive episodes characterised by excessive 'daydreaming', and/or periodic confused states; (3) co-morbid episodic, unprovoked temper or rage attacks; (4) frequently recurrent headaches; (5) a history of head trauma, encephalitis or meningitis preceding the onset of ADHD; and (6) abnormalities on neurological examination.

Wojna *et al.* [14] confirmed that approximately one third of children with ADHD had abnormal routine EEG with a sizeable proportion exhibiting epileptiform activity. The same finding was supported by Gustafsson *et al.* [15] when they found 10 out of 28 ADHD children with EEG to have EEG abnormalities.

More recently, Holtman *et al.* [16] examined the EEGs of 483 ADHD outpatients between 2 and 16 years of age (diagnosis based on DSM-IV). Rolandic spikes were detected in the EEGs of 27 children (5.6%); 22 boys and 5 girls. Seizure rate during follow-up tended to be larger in children with Rolandic spikes. ADHD children with Rolandic spikes were brought for evaluation at an earlier age than ADHD children with normal EEGs. These children were also noted to exhibit more hyperactive-impulsive symptoms. Aydin *et al.* [17] found an overall rate of abnormalities (both slowing and epileptiform) of 9.1% of 49 children with ADHD diagnosis. Three children had focal or multifocal spikes (6.1%) and three had slow wave abnormalities.

Finally, Hemmer *et al.* [18] reported 15.4% of 234 children (179 males/9.1 $\pm$ 3.6 years of age and 55 females/9.6 $\pm$ 3.9 years of age) to have epileptiform abnormalities. They did not include any of the controversial EEG waveforms like the 14 and 6 positive spikes, thus explaining (at least in part) the lower rate of abnormalities. They also reported that the risk for seizures with incidence of 0.6% in subjects with normal pre-Ritalin EEGs and 10% in subjects with pre-Ritalin epileptiform EEGs.

While the standard practice in the USA does not recognise the importance of the routine EEG in the work up of children presenting with ADHD, this is not the case in Europe. Schmidt *et al.* [19] discusses this issue. The EEGs of 124 children with ADHD before and during treatment with methylphenidate were analysed retrospectively. They did not see evidence of increased abnormalities due to the therapy. They concluded that

an EEG during therapy with methylphenidate is not necessary but before commencing a planned methylphenidate therapy an EEG should be performed.

Boutros *et al.* [20] reported an association between ADHD and the 14 and 6 positive spikes in children and adolescents. This EEG pattern is controversial but has been linked to a variety of behavioural abnormalities including episodic somatic symptoms and hyperactivity, as well as emotional instability. As alluded to in different parts of this text, this pattern and its clinical correlates is in need of further investigation.

Case example

Timothy was first referred for evaluation of aggression and hyperactivity at age two years. He was adopted at birth. Prenatal exposures included tobacco, 2nd trimester pyelonephritis and gonorrhoea. He was difficult to console as an infant, and prone to intense tantrums. Despite achieving normal language and motor milestones and normal early paediatric and neurological screenings, he continued to be hyperactive, aggressive and destructive at home. Toilet training was complicated by retention encopresis. He was described as chronically irritable, oppositional and dangerously impulsive: for instance, jumping from the top of the stairs or darting from parents in public. He had failed to improve on stimulant or alpha agonist medication, or through parent behavioural guidance.

Timothy's medical history was significant only for recurrent otitis media with tube placement. He received pre-primary special education for two years, and was referred to regular kindergarten, as his behaviour calmed on a combination of guanfacine and risperidone.

However, by age 6, his teacher complained of intermittent deterioration in his printing, occasionally odd verbal utterances, and wandering away from the class group on field trips. Academic testing at this time revealed age appropriate reading skills, but delayed basic concepts achievement and very low (1st centile) math skills. The psychiatrist had observed difficulties with daily regulation, transitions and time concepts. He was referred again for neurological assessment to rule out subclinical seizures and an EEG was ordered.

Initial EEG was significant for central temporal sharp waves with some appearance of a Rolandic dipole, more prominent in the temporal region, suggesting an irritative process. MRI of the head revealed a small arachnoid cyst in the left middle cranial fossa and a larger right middle cranial fossa cyst in the parasylvian region. He was titrated on oxcarbazepine to 300 mg b.i.d., and continued risperidone 0.25 mg b.i.d., with tapered discontinuation of guanfacine. Academic performance improved and behaviour calmed markedly, although oppositionality and defiance continued, and ultimately responded moderately well to parent management strategies. Repeat EEG demonstrated continuing left central sharp waves and single spike transients, more prominent in stage I and II sleep. Anticonvulsant therapy was continued.

Discussion

Pre-school onset hyperactivity and impulsivity with normal milestone achievement present a particularly challenging diagnostic differential. Pre-school children with ADHD have reportedly greater incidence of chronic illness, service use and Emergency Room visits, as well as higher rates of parent-reported aggression, difficulty with pre-academic achievement, and co-morbid psychiatric disorders (Greenhill *et al.* [21]). Timothy's behavioural history was consistent with reported ADHD presentation in this age group, although the possibility of seizure or other CNS pathology was appropriately revisited as more subtle cognitive disturbances became evident with increased developmental demand at school age. Careful attention must be paid continuously to all areas of development for deviance from expected progress, as well as failure to respond to known targeted interventions for ADHD, such as parent management training or stimulant therapy. Prenatal risk factors remain salient: in this case, it is likely that Timothy's biological mother had been infected prenatally with both gonorrhoea and HSV, suggesting a possible viral aetiology for arachnoid cyst development. The nearly exclusive dependence upon parent report in diagnosis in this age group limits historical assessment, and prompts consideration of more routine screening of severe pre-school or atypical onset ADHD.

Recommendations

The essential question of the impact of discovering epileptic activity in a child presenting with ADHD remains not completely answered. Nonetheless, whether the yield from an EEG is 6 or 30%, the information seems important for better formulating diagnosis and treatment. This is particularly true in view of the non-invasive and inexpensive nature

Box 7.1 Indications for EEG in the child with ADHD [13]

1. Personal or family history of seizure.
2. Inattentive episodes of excessive daydreaming and/or periodic confusion.
3. Episodic, unprovoked temper or rage attacks.
4. Frequent, recurrent headaches.
5. History of head trauma, encephalitis or meningitis preceding the onset of ADHD.
6. Abnormal neurological exam.

of the EEG, as well as in the potential for expected attentional improvement associated with anticonvulsant treatment of seizure.

Based on the cumulative EEG findings in children and adolescents, noting particularly the strength of larger, more recent study populations [1–4], and bearing in mind that EEG is a non-invasive test, it seems reasonable to recommend a routine EEG particularly if stimulant or other psychotropic therapy will be recommended.

Box 7.2 ADHD neurological diagnostic pearls

- Obtain a full neurological history and examination.
- Follow up any clinical neurological abnormality with EEG and/or imaging.
- Generate a developmentally appropriate neurological and psychiatric differential.
- Consider the possible presence of co-occurring disorders.

ADHD and epilepsy

Co-morbidity of epilepsy and ADHD is common and has a substantial impact on functioning, treatment and prognosis. ADHD has been associated with childhood epilepsy; prevalence rates have ranged from 8 to 77% depending on the sample studied and the criteria used for diagnosis [22]. Dunn *et al.* [22] assessed 175 children with at least a six-months history of epilepsy (90 males and 85 females ranging in age from 9 to 14 years) for evidence of ADHD. Based on the Child Symptom Inventory-4 (CSI) or the Adolescent Symptom Inventory (ASI), 66 children met criteria for one of the subtypes of ADHD (37%). Sex, seizure type and focus of seizure discvharge were not predictors of symptoms of ADHD. The population of ADHD children with epilepsy differ from other ADHD populations in two main respects: an equal male: female ratio, and a higher proportion with predominantly inattentive type [22].

The problem of ADHD and epilepsy may not be as simple as a co-morbidity issue. Behavioural problems suggestive of ADHD could actually be pre-seizure or nocturnal seizure manifestations. Seizure syndrome, frequency and severity represent important additional variables [9]. In children with known epilepsy, behavioural problems have been associated with certain antiepileptic drugs, such as benzodiazepines, phenytoin or topiramate.

Because it is not known when behavioural problems begin in children with epilepsy, Austin and colleagues [10] sought to describe the rates of behavioural problems in epileptic children in the months preceding the onset of recognisable epileptic attacks.

They also attempted to compare the behavioural problems of these children to the behavioural problems reported in their siblings. They conducted computer-assisted structured interviews with mothers of 224 children with a first recognised seizure and 135 of their healthy siblings, to measure child and siblings behavioural problems. Behavioural problems were assessed using the Child Behaviour Checklist. They reported higher than expected rates of behavioural problems in the 6 months before the first recognised seizure, with 32% exhibiting significant behavioural symptoms. Children with seizures had significantly higher internalisation, attention, thought and somatic complaints than the siblings group.

Hesdorffer and his colleagues [23] further examined the relationship between epilepsy and ADD/ADHD in children with new onset seizures. All newly diagnosed unprovoked seizures amongst Icelandic children between the ages of 3 and 16 years of age were examined to ascertain prevalence of ADD/ADHD. Children with seizures were matched to the next two same-sex birth from the population registry of Iceland. The Diagnostic Interview Schedule (DIS-C) for Children was used to make DSM-IV diagnoses. They reported that a history of ADHD was 2.5-fold more common among children with newly diagnosed seizures than among control subjects. The association was restricted to ADHD predominantly inattentive type (odds ratio, 3.7) and not ADHD predominantly hyperactive-impulsive type (odds ratio, 1.8) or ADHD combined type (odds ratio, 2.5). Seizure type, aetiology, sex or seizure frequency at diagnosis did not affect findings. They concluded that ADD/ADHD occurs more often than expected before unprovoked seizures, suggesting a common antecedent for both conditions.

Case example

Susan is a 7-1/2 year old female and fraternal twin who presented for treatment of a several year history of behaviour and academic problems, which had been intensifying over the previous 18 months. She had been diagnosed with ADHD at age 5, and responded previously to a long acting preparation of methylphenidate.

Susan had been engaging in destructive and dangerous behaviour at home, particularly associated with wandering the house at night. She would eat in the kitchen, had painted on walls, had set fires and was found to be hiding knives. She had longstanding difficulties with sleep initiation and middle insomnia, dating as far back as the age of 3. More recently, her father remarked that she was 'calling out' in her sleep, several nights per week, although she would neither remember the incidents nor wake up during the episodes. She was described as highly disruptive at school, constantly out of her seat, off-task, talking to peers, not completing work. There were reports of difficulty understanding, concentrating and remembering. She was in frequent conflict with peers, and felt that she was disliked.

Susan was a fraternal twin, born prematurely at 27 weeks with a presumed prenatal infectious exposure, weighing 2 lbs. 7 oz. She required mechanical ventilation for 1

week, and 2 months of oxygen therapy. Developmental milestones were reported as met appropriately. However, school history indicated a need for special education supports in speech, occupational therapy and physical therapy in kindergarten. Bowel training was completed at age 5 years, but Susan resumed episodes of incontinence or encopresis at age 6-1/2 years, during a period of intense family discord. She had a history of elevated serum lead level (to 13), which was managed expectantly, without active treatment.

Susan's mental status exam at initial evaluation was remarkable for a high degree of inattention and distractibility, as well as poor eye contact, verbal perseveration when answering questions, and an odd tangentiality with frequent derailments in her attempts to answer abstract questions. There were clear reading difficulties, as well as motor clumsiness. She was initially diagnosed with ADHD, learning disorder, conduct disorder, adjustment disorder (parental divorce) and borderline intellectual functioning. She improved behaviourally during a period of parental reconciliation with psychotherapy and stimulant treatment. She slept nights after starting nightly doses of clonidine, although she continued to cry out in her sleep. Psychological testing at school revealed WISC-IV FSIQ score of 70, with a marked discrepancy between verbal comprehension and perceptual reasoning.

Eight months after entering treatment, Susan had a seizure: she was found standing with her head and eyes deviated to the right, and nonresponsive. Routine EEG obtained in follow up reported a sharply contoured wave coming from the bifrontal region and left central region, although no seizure was seen on the study. The same wave pattern was observed during sleep on 24-hour ambulatory tracing.

Discussion

Although concern regarding the degree to which daytime stress would have influenced Susan's night-time behaviour, the frequent calling out in her sleep, depending on the content or quality of the cry, may have provided a clue to the possibility of nocturnal seizure, although the study does not confirm ictal activity.

Recommendations

The observation of a clinical seizure, preceded by the unusual nocturnal and daytime behavioural history in the above case, suggest the importance of close continuing behavioural observation and consideration of an anticonvulsant trial, with follow-up EEG monitoring. Both seizure and ADHD may be treated concurrently and safely, although stimulant treatment is advised only in the context of well controlled seizure disorder. Clinicians must be alert and suspicious of the possibility of seizure in atypical presentations of behavioural disturbance labelled ADHD, and must be prepared to pursue more careful diagnostic assessment, including behaviour logs, rating scales and EEG.

Box 7.3 Clinical pearls: ADHD in children with epilepsy

- Children with both epilepsy and ADHD are as likely to be female as male.
- Children with epilepsy and ADHD are more likely to present with the inattentive type of disorder.
- Behavioural problems in children with epilepsy and ADHD may be associated with certain antiepileptic drugs.
- Behavioural problems may be notable in the months preceding the first recognised seizure.

Autistic spectrum disorders

Introduction

Pervasive developmental disorders (PPD) or autistic spectrum disorders (ASD) encompass a heterogeneous group of individuals with early childhood onset of deficits in social interaction and language development, a restricted repertoire of interests and activities, as well as a wide range of cognitive difficulties. The DSM-IV divides the pervasive developmental disorders into five behaviourally defined categories: autistic disorder, Asperger disorder, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (NOS).

Two of the above disorders are distinguished by a marked loss of skills: Rett disorder and childhood disintegrative disorder. Although the regressive pattern in CDD is suggestive of a possible genetic aetiology, the aetiology remains unconfirmed, unlike the recognised association of mutation in MECP2 in Rett disorder. Despite the relatively rare prevalence and weaker direct relationships to autistic disorder per se, inclusion of both on the spectrum has remained important, perhaps influencing critical research directions in understanding all of the autistic spectrum disorders, as well as those epilepsy syndromes with associated autistic features.

Asperger syndrome remains a diagnosis of continuing disagreement, as multiple definitions of the syndrome exist, in addition to those in the DSM-IV and ICD-10, with limited agreement to each other. Further, distinctions between Asperger Disorder and multiple other diagnoses, such as schizotypal personality disorder, right hemisphere or nonverbal learning disability and semantic pragmatic language disorder remain unclear. Studies of PDD-NOS remain limited, although efforts to characterise the disorder as a distinct entity, rather than a diagnosis of exclusion, have increased in recent years.

In a significant minority (20–40%) of children diagnosed with autism, parents report deterioration in the child's language skills, non-verbal communication and play skills after approximately age 2 years. This has been described clinically and in the literature as 'late onset autism' or 'autistic regression.' A typical history in late onset autism might involve the report of a child with normal development for as long as 12 to 18 months prior to the onset of typical autistic features. These children, in contrast to those with childhood disintegrative disorder, would have some, albeit minimal and not necessarily normal, speech skills at the time of regression. Behaviour often worsens and cognitive decline may also be observed. At least some of these children are entirely healthy prior to the onset of the disorder.

Behaviour may be more characteristic of Kanner's core autistic features in 'late autistic regression'. The rigid need for sameness and specific communication findings such as delayed echolalia are more prominent, in contrast to generalised decline in language seen in CDD or the auditory verbal agnosia of Landau-Kleffner syndrome. Diagnostic reliance on retrospective reporting from parents and others often makes this diagnosis difficult to distinguish from developmental stagnation or arrest. Children with late onset autism are likely a heterogeneous group, generating interest in potential for lines of continuity or overlap with other seizure-associated regression syndromes and childhood disintegrative disorder.

Childhood disintegrative disorder refers to a rare (approx. 1.7/100,000) subgroup of children on the PPD spectrum who, prior to regression, were developing normally, including speaking in sentences, for an extended developmental period after 2 years of age and with a mean age of onset at 3.4 years [24]. In some of these children, onset of deterioration may be as late as mid-childhood. Regression in language, play, social skills, adaptive behaviour, bowel and bladder control and motor skills has reportedly occurred over periods of a few days to a few months. Childhood disintegrative disorder is not distinguished from other autistic disorders or regression syndromes in the presence or absence of seizure on the EEG, but perhaps more by virtue of clinical presentation and progression or history – the observation of global milestone regression in addition to language and behavioural features. Up to 77% may have epileptiform EEGs.

Epilepsy in ASD

Epilepsy is defined as the occurrence of two unprovoked seizures in an individual. Approximately one-third of children with ASD develop epilepsy. Canitano *et al.* [25] examined 46 consecutive children with autism (34 boys and 12 girls, mean age 7.8 +/−2.7 years). Thirty-five percent of the children had epilepsy. Also recently, Hrdlicka *et al.* [26] examined 66 autistic children. They found 22.1% of children to have epilepsy. On the other hand, Hughes and Melyn [27] reported that 46% of 59 children with autism had clinical seizures. Tuchman and Rapin [28] found 11% (66) of 585 children on the autistic spectrum to have epilepsy as defined above.

In a recent review by Curatolo *et al.* [29], they noted that the incidence of autism in patients with tuberous sclerosis is higher than the incidence of cardiac and renal abnormalities. They suggested that no single factor (early refractory seizures or location of tubers) can account for the behavioural symptoms. They suggested that early identification of autism in this group may lead to better outcome.

West syndrome is a very early onset epilepsy syndrome which may be associated with tuberous sclerosis (TS). It is characterised by hypsarrythmia, learning problems and infantile spasms, with psychiatric disorders manifesting in up to a third. Autistic regression has been observed amongst those with behavioural disorder, and more than half of those with West syndrome associated with TS have reportedly remained autistic [30].

Bolton *et al.* [31] examined the neuroepileptic determinants of ASD in tuberous sclerosis patients. They reported that an ASD diagnosis was associated with the presence of tubers in the temporal but not other lobes of the brain. The presence of tubers in the temporal lobes appeared to be a necessary but not sufficient risk factor for the development of ASD. Further, the location of tuber in specific temporal lobe regions (i.e. right side or superior temporal gyrus) was not a significant factor in determining which individual will develop ASD. The presence of temporal lobe discharges on the EEG, onset of seizures before 3 years of age and history of infantile spasms all seemed to contribute to the development of ASD. These results underscore the fact that children with tuberous sclerosis where the tubers are located at the temporal lobes, have abnormal temporal lobe activity on the EEG, and have history of infantile spasms are at very high risk for developing ASD.

Autistic features have been reported in associated with other common infantile epilepsy syndromes; such as Dravet syndrome, a severe myoclonic epilepsy of infancy, and Lennox-Gastaut syndrome, a disorder of multiple seizure types, with its onset between the ages of 1 and 9 years. As described in West syndrome above, these disorders are typified by the emergence of changes in learning, interpersonal development, language or motor skills around the time of seizure emergence in most cases, with later clinical improvements dependent upon seizure control, which in cases (i.e. Lennox-Gastaut) may prove difficult to achieve.

Landau-Kleffner syndrome (LKS), otherwise referred to as acquired epileptic aphasia, is increasingly distinguished in the literature from other regression presentations by the more distinct regression in language associated with verbal agnosia, and characteristic generalised spike and wave EEG, with or without electrical status epilepticus of slow wave sleep (ESES; see below). The language regression characteristically occurs in concert with an epileptiform EEG and/or clinical seizures. In the majority of children with LKS, clinical seizures occur; however, onset may follow regression by a year or more. Some authors have reported a higher correlation between autistic regression and the absence of clinical seizure at presentation in this syndrome [32]. The seizures associated with LKS have been reportedly more readily controlled with AEDs and often remitted by adolescence. Shinnar's prospective study of 177 children with language regression supported other reports of lasting language impairment in the vast majority of their

study group at adolescence, despite improvements observed in over half of the children studied.

DeLong and Nohria [33] obtained both complete neurological assessment and psychiatric family history from 40 children with ASD, Neurological evaluation included EEG, MRI, karyotyping and positron emission tomography as indicated. Twenty patients had positive neurological findings, 18 of which had negative psychiatric family histories. Fourteen of the 20 patients without neurological findings had family histories of affective disorders. These patients tended to be of higher function. These findings highlight the importance of early work up to identify the subgroup to which the patient belongs, as there seems to be significant treatment and prognostic implications.

EEG abnormalities in ASD

A significant proportion of ASD children have abnormal EEGs, even those who never had seizures. These abnormalities can range from mild slow wave abnormalities to frank epileptiform discharges. It is very important to point out very early in this discussion that these epileptiform discharges may only be detected during sleep and at times may require prolonged monitoring. Gillberg and Schaumann [34] described two cases of infantile autism without clinical seizures where EEG abnormalities were not discovered until relatively late in the course of the psychiatric disorder. Anticonvulsant medications led to the complete disappearance of psychotic symptoms and to simultaneous disappearance of the pathological EEG changes.

Reinhold *et al.* [35] found abnormal EEGs in 27% of 316 children evaluated for ASD. Of these abnormalities 65% (55 children) were epileptiform and slowing in 15% (13 patients). The focality of the epileptiform activity was in the temporal regions in 30%, 28% in the central region, 23% in the frontal regions and 8% in the occipital area. Also recently, Canitano *et al.* [25] examined 46 consecutive children with autism (34 boys and 12 girls, mean age 7.8 +/−2.7 years). Twenty-two percent had epileptiform abnormalities without having history of seizures. On the other hand, Hughes and Melyn [27] found abnormal EEGs in 75% of 59 children with autism. Twenty percent of patients with spike discharges did not have clinical attacks.

Hrdlicka *et al.* [26] examined 66 autistic children. They reported the EEGs to be abnormal in 55.6% with non-epileptiform abnormalities in 17.5% and epileptiform in 38.1%.

Hashimoto *et al.* [36] examined the EEGs (during sleep) of 86 autistic children. Forty-three percent (37 cases) had epileptic discharges. Of these 37 patients 27 (73%) had localised spikes, eight had multiple spike foci, and one with generalised and one with both focal and generalised spikes. Forty-seven epileptic discharging foci were identified in the 36 patients with focal abnormalities. Thirty-six (76.6%) of these foci were in the frontal region, one in the temporal, seven in the centroparietal and three in the occipital regions. Twenty (55.6%) of the frontal spikes were at mid-line (11 at FZ and 9

at CZ), 8 on the left side, and 8 on the right side. The dipole of midline spikes was in the deep midline frontal region. These results strongly suggest that frontal dysfunction is important in the development of autistic symptoms.

Tuchman and Rapin [28] examined the EEGs (containing sleep) of 392 children on the autistic spectrum. The EEGs were epileptiform in 59% amongst epileptic children but only 8% of 335 non-epileptic children. When historical clinical deterioration is evident (as was the case in 155 non-epileptic children) the rate of epileptiform EEG abnormalities was significantly higher (14%) as compared to the rate in children without obvious deterioration (6%). In this study, approximately half of the epileptic discharges were centrotemporal. A smaller percentage of epileptiform activity was in the peri-sylvian region and this occurred mainly in non-epileptic children with clinical deterioration. A rather important point made in this paper is that the average child was first evaluated neurologically 4 years following the onset of deterioration. This point highlights the need for studies conducted at much earlier stage of the illness.

A rather interesting study was conducted by Chez *et al.* [37], where they examined the rate of EEG abnormalities of age-matched siblings of autistic children who had abnormal sleep-EEGs. They report fewer abnormalities in these children and conclude that genetic factors alone do not explain the higher frequency of EEG abnormalities reported in ASDs.

Lewine *et al.* [38] utilised the magnetoencephalogram (MEG) to compare patients with LKS and ASD. They made sure all subjects achieved phase III sleep during the recording. They included six children with LKS, and 50 children with ASD (with evidence of deterioration between 20 and 36 months). Sixteen of the subjects met criteria for autism and 34 for PDD-NOS. Five of the six LKS children had complex partial seizures but only 15 of the ASD children had a seizure disorder. The MEG of all LKS children had primary or secondary epileptiform involvement of the left intra-perisylvian region (all but one had involvement of the right perisylvian region as well). In all LKS cases there were no independent foci outside the sylvian regions. MEG identified epileptiform activity in 41 of the 50 ASD patients (82%). In contrast, simultaneous EEG revealed epileptiform activity in only 68%. When epileptiform activity was present, the same intra-perisylvian areas like in LKS were involved in 85% of cases. Whereas primary activity outside of the sylvian regions were not seen in any LKS children, 75% of the ASD children with epileptiform activity demonstrated additional non-sylvian zones of independent epileptiform activity. Despite the multifocal nature of the epileptiform activity in the ASDs, neurosurgical intervention aimed at control has led to the reduction of autistic features and improvement in language skills in 12 of 18 cases.

A well-designed study was conducted by Rossi and colleagues [39] where 106 autistic patients without any evidence of congenital or acquired encephalopathies were examined. They reported a prevalence of 18.9% of EEG abnormalities in children without epilepsy. Epileptiform activity was focal and multifocal. In 45% of cases this activity was typically of benign childhood partial epilepsy with centrotemporal spikes.

In a recent effort to develop guidelines for screening EEGs in ASD, Kagan-Kushnir *et al.* [40] conducted a comprehensive review of available literature. They concluded

that seizures are common occurring in 20–30% based on the majority of studies. Subclinical EEG abnormalities (i.e. no epilepsy) were found in 6.1–31%. Evidence for the effectiveness of anticonvulsants and corticosteroids in reducing seizures and/or autistic symptoms is based primarily on case series, with only one published randomised trial. They concluded that, as of now, there is insufficient evidence to recommend against the use of screening EEGs in autistic patients. They also conclude that given the high frequency of seizure disorders in this population that a high index of clinical suspicion should be maintained for subtle symptoms of seizures.

Electrical status epilepticus in slow-wave sleep (ESES)

ESES is an epileptic syndrome that occurs in childhood and may or may not be accompanied by seizures. Regression of language and behaviour are also seen in this condition which may need to be differentiated from ASD, and is frequently associated with the LKS [41]. In ESES behavioural correlates may range from a severe global deterioration compatible with the diagnosis of disintegrative disorder or autistic disorder to minimal or absent behavioural correlates [42].

Response in ASD to anticonvulsant treatment

Hollander *et al.* [43] conducted a retrospective pilot study to determine whether divalproex sodium was effective in treating core dimensions and associated features of autism. They included 14 patients with either autism, Asperger's syndrome or PPD-NOS. Subjects were included irrespective of history of seizures or EEG abnormalities. Ten of the 14 patients who completed the trial (71%) were rated as responsive to treatment (mean dose 768 mg/day and range of 125–2500 mg/day). The medication was generally well tolerated. Improvement was noted in core symptoms of autism as well as the associated features of affective instability, impulsivity and aggression. Of note is that all patients with abnormal EEGs were rated as responders.

A recent review by Tharp [44] concluded that there is no justification for use of anticonvulsant medications or surgery in children with PPD without seizures; that is there is no evidence that treatments to eliminate EEG spikes will have a therapeutic effect on the behavioural abnormalities of PPD and autism.

Case example

Patrick was admitted to a children's in-patient psychiatric unit for safe observation at the age of 21 months of age due to extreme hyperactivity, aggression (especially biting) sleep dysregulation and dangerous impulsivity, which his single mother reportedly could

not contain. He would have intense, prolonged tantrums with aggression toward his mother. He was the only child of healthy, unmarried parents, and the family history was devoid of members with psychiatric or developmental disorders.

The pregnancy and delivery had been uneventful. A single episode of note in mother's memory was a prolonged screaming episode of what had seemed like several hours after the child received his initial DPT immunisations at age 6 months. Developmental milestones were reportedly on schedule, including language, which consisted of an approximately 60 word vocabulary in single words to short declarative sentences. Gestures, relatedness and play were as expected for his age at the time. Growth was symmetric and consistent above the 75th centile. There had been no accidents or serious illness. Neurological exam was without focal or global abnormality. The extreme hyperactivity calmed with parent coaching manoeuvres and clonidine therapy and the patient was discharged for close joint Neurology/Psychiatry outpatient follow-up in his home community.

Patrick and his parents presented to the outpatient speciality unit for consultation at age 39 months. Mother reported that Patrick's hyperactivity and impulsivity had steadily calmed and that he had been able to discontinue medication through his local neurologist shortly after discharge. However, he had become increasingly withdrawn and passive, engaging in perseverative patterns of spinning circular objects or tapping on toys, rather than playing meaningfully with them. Eye contact was now unreliable to poor, and his local neurologist had become concerned about a possible autistic regression. Mother was most distressed that the child's expressive vocabulary, which had reached approximately 300 words in the last quarter of his third year, had declined dramatically – he was speaking less, initiated little, was less interactive and responsive. Paediatric neurology consultants performed an EEG, which demonstrated a multimodal Landau-Kleffner spike-and-wave pattern. Subsequent specialty speech and language assessment suggested verbal agnosia. By age 4 years, Patrick was no longer speaking, walking, independently playing or self-feeding, requiring a stroller and helmet for safety due to global regression. Further follow-up was lost due to discharge from psychiatric service.

Discussion

Patrick's early manifestation of extreme hyperactivity and irritability, which was observed to recede with the onset of language and later global regression, has been reported elsewhere [8]. Patrick exhibited prominent autistic features, behaviourally absent the rigid need for sameness, which receded into a more predominantly passive and globally impaired presentation.

Careful observation is required to differentiate inattention from cognitive or communication disturbance during the pre-school years, and both cognitive/developmental assessment and EEG evaluation can be hampered during this period before the child's co-operation can be assured. Patrick's case illustrates the diagnostic necessity in separating language arrest, emerging vocal stereotypies or characteristic language disturbances in

autism, and language regression potentially associated with a new onset aphasia or verbal agnosia. Importantly, language regression immediately narrowed this child's differential diagnosis by immediately excluding developmental delay or developmental language disorder, once the regression was corroborated and characterised through formal testing.

Although some recent authors have described LKS specifically in terms of language regression in the course of the classic seizure syndrome, and have assigned language plus global regression to the category of disintegrative disorders. Earlier descriptions more inclusively grouped children with the LKS EEG, language and later global regression under LKS. Clearly, the finding of Patrick's characteristic EEG narrowed the differential in his autistic regression to a Landau-Kleffner pattern of autistic regression without clinical seizure. The subsequent global regression raises the question of the DSM diagnosis of childhood disintegrative disorder (ICD 10 diagnosis – disintegrative disorder).

Patrick's case nicely illustrates the possibility of viewing the autistic regressions (late autistic regression, LKS, CDD) as potentially distinct phenotypes with the potential for overlap or continuity. Although this case data is incomplete with regard to overnight EEG and the possibility of ESES associated with the known multifocal spike and waves, we are reminded to include consideration of ESES in the autistic regression differential for a presentation like Patrick's.

Intriguingly, the literature associates onset of regressions with reports of a range of stresses, both biological and psychosocial [32]. One could not readily correlate Patrick's neurodevelopment course with an immunisation-associated onset, but we are reminded of the observed, yet not fully understood phenomenon and the potential establishment of future genetic or immunological correlates associated with the full range of ASDs [45].

Patrick's neurologists discussed steroid therapy, although it was ultimately not pursued, and he continued AED therapy as of last contact. To date, the EEG findings do not specifically influence prognosis, to the extent that the clinical features such as age at onset or observed developmental course might. Response of clinical seizures or epileptiform findings on EEG to AED therapy continues to be most closely associated with at least some language and cognitive recovery.

Conclusions and recommendations

At present the aetiologic yield of work up for children presenting with autistic spectrum symptomatology is not well characterised. Moreover, the cost effectiveness of such work up has not been determined. Of course, if intervention at some stage can prevent a life-long disorder, even a low yield may be well justified not only on economic bases but also for the suffering of patients and their families that may be avoided.

Shevell *et al.* [46] examined the diagnostic yield in 50 consecutive children referred from the community to a paediatric neurology clinic at a university setting. They concluded that the yield for identifying a specific aetiology to be rather low. Only

one child proved to have Landau-Kleffner syndrome (LKS). They still concluded that strong consideration should be given to genetic testing and EEG studies. They felt that a full metabolic and neuroimaging work up for screening are not justified based on current knowledge. On the other hand, Steiner *et al.* [47] applied a protocol of clinical and laboratory evaluations to 103 outpatients with PDD. The protocol included chromosomal analysis, screening for inborn errors of metabolism, EEG, SPECT and MRI. Eighty-four subjects were included and fell into three clinical categories: autism, atypical autism or Asperger syndrome. Imaging and EEG abnormalities occurred in similar proportions amongst the three groups. Genetic factors were more prevalent in the two autism groups.

While a relatively old study, the findings and predictions made by Gillberg *et al.* [48] are important and worth highlighting. They subjected 20 high functioning children with autism (17) and Asperger syndrome (3) to a battery of neurobiological tests including CAT scans, auditory brain stem evoked responses, EEG, chromosomal cultures, CSF, blood and urine analyses, as well as a thorough physical examination. Fifteen of the 20 children had 'definite abnormalities' on at least one of these examinations. They concluded that 'number of non-organic autism' cases even amongst children with relatively higher intelligence, dwindles rapidly as our neurobiological assessment methods become increasingly sophisticated.

Box 7.4 Clinical pearls: epilepsy and autistic spectrum disorders

- Rates of epileptiform EEGs may be higher in children with a history of clinical deterioration.
- Children with ASD and epileptiform EEG may benefit in both core features and associated behavioural symptoms from a trial of anticonvulsant medication.
- ESES must be considered in the differential of any child with symptoms of autistic regression.
- Future classifications of ASD will likely incorporate expanded phenotypes, overlap syndromes and increasingly identifiable neurological, metabolic and genetic abnormalities.

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8

EEG in Psychoses, Mood Disorders and Catatonia

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Introduction

The great excitement induced by the first recording of the human EEG by the German psychiatrist Hans Berger in the field of psychiatry resulted in a large number of EEG investigations in large groups of psychiatric patients. All this work occurred over a span of about three decades from the 1940s to the 1970s. Three major findings emerged and remain undisputed today.

Electroencephalography in psychiatry is underused and underestimated. The use of EEG in psychiatric disorders is indispensable for the exclusion of disorders with a clear structural or functional organic background, but can also contribute to diagnosis and differential diagnosis of psychiatric syndromes and disorders. Approximately 64–68% of EEGs in psychiatric patients can provide evidence of abnormal electrical activity [1]. The following sections of this chapter and Chapter 9 will deal with the different psychiatric conditions where EEG abnormalities are detected.

Standard Electroencephalography in Clinical Psychiatry: A Practical Handbook, First Edition
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Box 8.1 Early EEG findings in adult psychiatric patients

- There is an increased prevalence of EEG abnormalities in psychiatric populations as compared to any other control group, with the exception of neurological patients.
- The increased rate of abnormalities is not a non-specific increase in all psychiatric groups and varies based on diagnosis and severity.
- Identified abnormalities do not correlate well with the diagnostic system they had at the time or the diagnostic system we have today.

EEG in psychoses

> Although the psychotic individual cannot be recognised by his EEG, nevertheless, as a group the psychotics have a significantly larger percentage of abnormalities in their EEGs than do normals. [2]

Psychoses are abnormal conditions of the mind with a loss of contact with reality. Major symptoms are hallucinations, delusions or thought disorders. These symptoms are unspecific and, apart from schizophrenia or severe mood disorders, can be caused by various psychiatric or general medical conditions:

– substance abuse and intoxication, psychoactive drugs, or withdrawal of drugs or alcohol

– brain tumours or damage

– sleep deprivation

– epilepsy (especially temporal lobe epilepsy)

– neurodegeneration

– general or CNS infectious or inflammatory disorders

– metabolic disorders or malnutrition.

Hallucinations and delusions can also be present in confusional states and delirium; however, the key features here are confusion and alterations of consciousness; these conditions will be the object of Chapter 9.

Regarding electroencephalography, there are no specific changes, neither regarding the presentation of signs and symptoms nor the underlying aetiology.

In acute psychoses (with or without confusion and alterations of consciousness) a prompt and comprehensive diagnostic procedure is essential in order to exclude or distinguish general medical conditions from psychiatric disorders. Apart from careful clinical examination and medical history taking, electroencephalography can contribute to a differential diagnosis and can be most helpful in the evaluation, especially of patients with acute psychosis in which other auxiliary tests, such as imaging, might be unavailable due to lack of co-operation of the patients or show normal results.

In patients in which psychotic symptoms are thought to be due to epilepsy with single seizures or a series of seizures (including non-convulsive status epilepticus), EEG is usually the only diagnostic test allowing a reliable diagnosis as a basis for adequate and immediate therapeutic consequences.

EEG in schizophrenia

Schizophrenia is a relatively common disorder, with a lifetime prevalence of about 1%, onset in the early adult life and a severe disabling course in the majority of cases. Key symptoms and disturbances include positive symptoms (delusions and hallucinations), which might be bizarre, negative symptoms (flattening of affect, alogia, anhedonia and apathy), cognitive deficits (involving attention, memory and executive functions), disorganised speech and behaviour, as well as catatonic symptoms (such as negativism, catalepsy and stereotypies). The clinical presentation of schizophrenia varies widely amongst patients and DSM-IV-R classification in subtypes is based on the prevailing symptoms in the clinical picture: paranoid (positive symptoms), catatonic (catatonic symptoms), disorganised (disorganisation), with a large proportion of patients, however, failing to fit any of the above subtypes and falling into the 'undifferentiated' one. These subtypes lack temporal stability and more recently a deficit schizophrenia subtype was proposed characterised by the prevalence of primary and enduring negative symptoms. The onset of schizophrenia varies greatly from an insidious to a very acute onset with dramatic change in behaviour, affectivity and thought processes. In these cases, particularly when catatonic symptoms prevail, a complete work up for differential diagnosis with acute encephalopathy, epilepsy (including non-convulsive status epilepticus) or other central nervous system pathology is necessary.

The number of EEG studies in schizophrenia has substantially declined over time, with only a few papers published in the last 10 years, while EEG quantitative methods have re-gained interest in psychiatry. However:

- A high percentage of patients with schizophrenia shows EEG abnormalities whose correlates are still not understood [3, 4].
- EEG abnormalities predict conversion to psychosis in subjects at risk [5].

- The use of EEG in cohort studies of first-episode patients indicated that EEG abnormalities might predict a worse outcome [6, 7].

Pros and cons about the use of EEG in patients with schizophrenia

- EEG is not useful to diagnose schizophrenia and findings are not specific for this disorder.

- Schizophrenia is associated with epilepsy in many cases and obtaining an EEG in recent-onset cases before and shortly after treatment might help identifying those patients with co-morbid epileptic conditions and guide the choice of the antipsychotic drug and concomitant medications.

EEG findings in schizophrenia

In the early 1950s, before the introduction of antipsychotic drugs, five controlled studies (reviewed in [8]) reported a higher frequency of EEG deviations in never-treated patients with schizophrenia, as compared with healthy subjects (23–44% in patients vs. 7–20% in controls). Subsequent EEG studies confirmed a high frequency of these deviations (for reviews: [1, 8, 9]), and extended the findings reporting the occurrence of EEG abnormalities in patients with chronic schizophrenia, with overall reported frequency of EEG abnormalities ranging from 20 to 60%.

Box 8.2 EEG findings in patients with schizophrenia

- EEG deviant patterns most frequently found in patients with schizophrenia include:
  - choppiness: low amplitude, disorganised fast activity, with reduced or absent alpha and sometimes excess of slow activity (Figure 8.1a)
  - slowing of background activity (Figure 8.1b)
  - high amplitude beta waves (Figure 8.1c).
- EEG abnormalities most frequently found in patients with schizophrenia include:
  - dysrhythmia (Figure 8.2a)
  - spike and spike-and-waves (Figure 8.2b)
  - generalised slowing (Figure 8.2c).

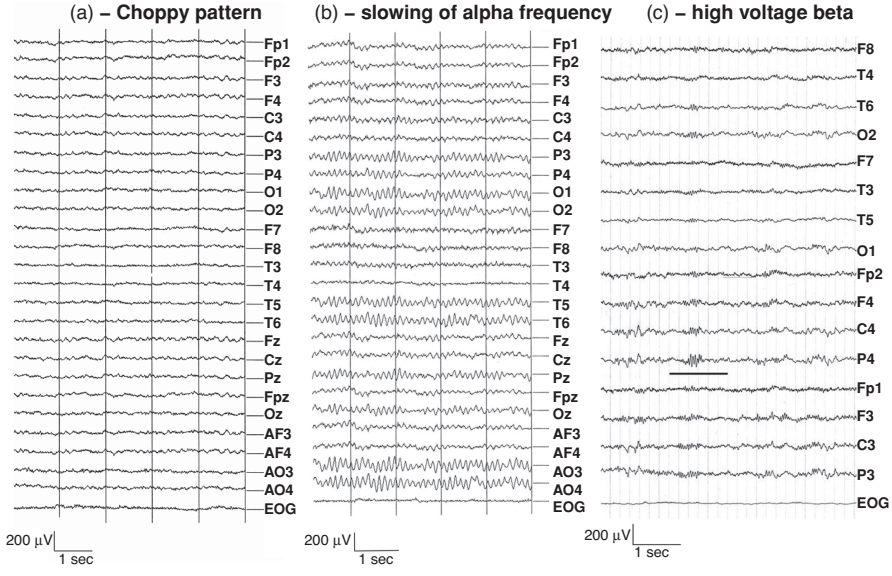

Figure 8.1 Common EEG deviations observed in patients with schizophrenia. (a) MC, m, 27 yrs, undifferentiated schizophrenia, choppy pattern (low-amplitude disorganised fast activity, absent alpha, low amplitude theta). (b) SC, m, 20 yrs, paranoid schizophrenia, alpha slowing. (c) GP, m, 32 yrs, chronic paranoid schizophrenia, high voltage beta with maximum in right parietal (marked by a solid line), an excess of diffuse slow activity is observed as well as sporadic sharp waves over bilateral centro-parietal leads. In all cases, no history of ECT or other shock therapies, 14 days of drug wash-out. Eyes closed EEG.

EEG findings and diagnostic boundaries of schizophrenia

- The introduction of DSM-III changed the diagnostic boundaries of schizophrenia.
- EEG abnormalities reported in patients with schizophrenia before the DSM-III probably included those found in affective psychoses.
- The presence of EEG abnormalities predicted a change in diagnosis with re-assignment to an affective disorder when applying more restrictive criteria for schizophrenia [10].
- The slowing of alpha frequency was more severe in patients with schizophrenia than in those with affective disorders, amongst those who did not change diagnosis when using more restrictive criteria [10].
- A more recent study using DSM-IV criteria for diagnosis found epileptiform variants (six per second phantom spike and wave, fourteen and six per second cycle

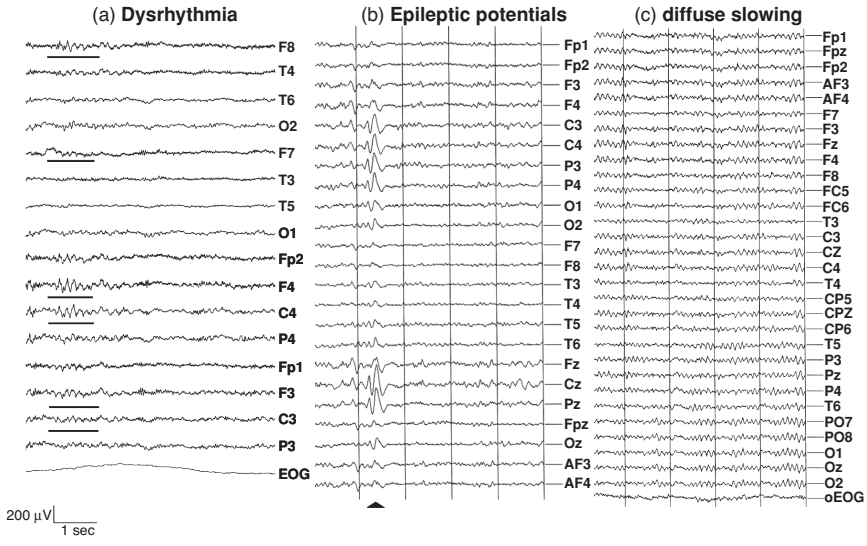

Figure 8.2 Common EEG abnormalities reported in patients with schizophrenia. (a) GP, male, 32 years, paranoid schizophrenia, dysrhythmia (paroxysmal 6 Hz sharp waves, marked by solid lines). (b) IF, female, 24 years, disorganised schizophrenia, sharp-and slow wave (marked be an arrow head). (c) FM, male, 47 years, paranoid schizophrenia, diffuse slowing. Eyes closed EEG. For all patients 14 days of drug wash-out.

positive spikes and small sharp spikes) in affective disorders with psychotic features and schizoaffective disorder but not in schizophrenia [11].

Investigated EEG abnormalities in early studies were different from those highlighted by more recent studies (e.g. epileptiform variants were investigated in recent studies only), which makes findings difficult to compare; the most recent studies often did not include a healthy comparison group and normative ranges of the EEG features were poorly defined [3, 12].

However, the overall picture seems to indicate that patients with schizophrenia might present a lower rate of epileptiform abnormalities or variants than those with an affective psychosis, while having a more severe alpha frequency slowing.

EEG findings and familiarity for schizophrenia

- The association of EEG abnormalities with familiarity for schizophrenia remains controversial [10, 13].

- The studies which examined this issue did not distinguish between slowing and epileptic abnormalities and did not characterise the clinical picture of patients as to the presence of affective or negative symptoms.

EEG findings and outcome

Several pre-DSM-III studies noticed a hypersynchronous EEG pattern (Figure 8.3) in chronic patients with unfavourable response to treatment [9,10]. The issue has been the object of later investigations using quantitative EEG which reported that an increase of the slow alpha in the baseline EEG is associated with poor prognosis (for a review: [14]).

Apart from the slowing of alpha, the association between EEG abnormalities and outcome remains controversial [6,7,11]:

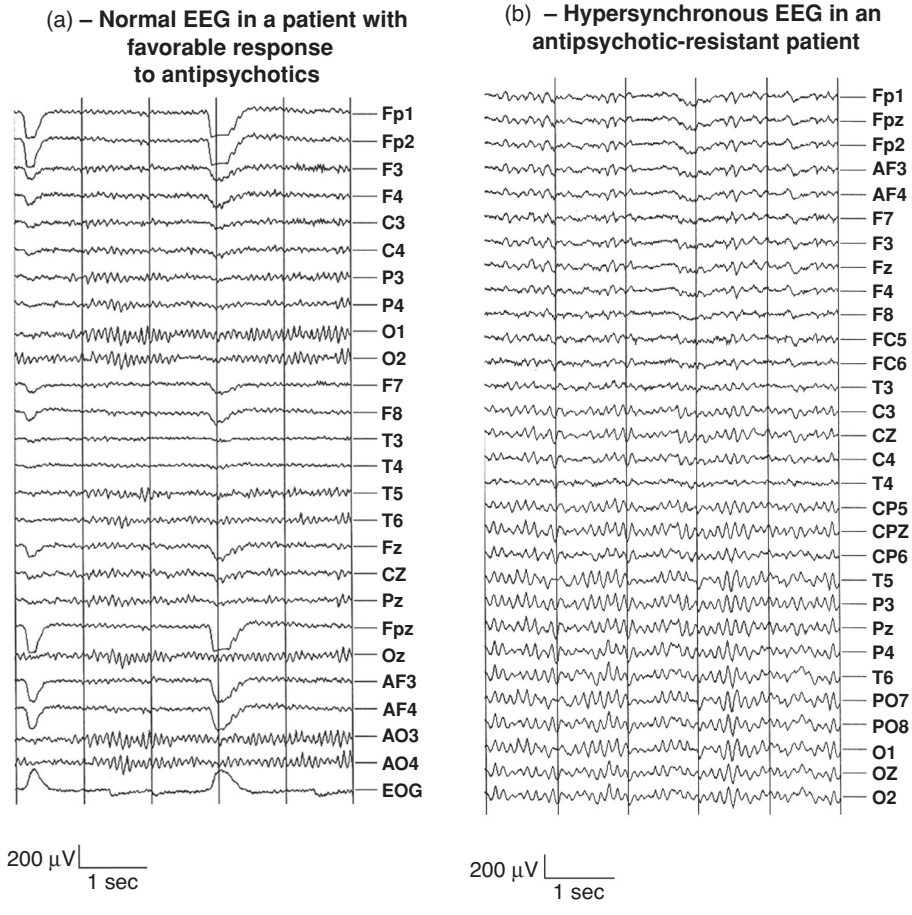

Figure 8.3 EEG and response to antipsychotic drugs. (a) AP, female, 36 years, paranoid schizophrenia, normal EEG and favourable response to antipsychotics. (b) SC, 26 years, paranoid schizophrenia, hypersynchronous EEG and poor response to antipsychotic treatment. Eyes closed EEG. For both patients 14 days of drug wash-out.

- In a subgroup of patients with affective symptomatology, early in the course of the illness, a good outcome was predicted by normal EEGs and no slowing of the alpha frequency.
- In patients without affective symptomatology a better outcome was predicted by the presence of EEG abnormalities.
- Schizophrenia is a heterogeneous disorder in which subgroups of patients showing more abnormalities might have better outcome (similar conclusions were drawn on the basis of structural brain imaging studies, see [15–17]).

Box 8.3 EEG abnormalities and outcome in patients with first-episode schizophrenia

- First-episode patients with persistent psychosis were found to have abnormal EEG as compared to remitted patients [6]. The two groups did not differ for severity of negative, positive or affective symptomatology.
- In patients with a first episode of schizophrenia EEG abnormalities predicted a negative outcome [6, 7]:
  - these data need to be replicated
  - no attempt to differentiate which kind of abnormalities predicted a poor outcome (epileptic potentials or abnormal slowing).

Schizophrenia and epilepsy

Schizophrenia and schizophrenia-like-disorders are 6 to 12 times more frequent in subjects with epilepsy than in the general population [18–20].

Unlike idiopathic forms, schizophrenia and schizophrenia-like psychoses occurring in epilepsy have atypical characteristics such as lack of negative symptoms and interpersonal disability [18–20].

- EEG is indicated to diagnose this kind of co-morbidity.
- Antipsychotic treatment has to take into account if patient has co-morbid epilepsy.

EEG in psychoses due to general medical conditions

The DSM-IV Organic Mental Disorders Task Force proposed that the term organic be discarded and a new group of 'secondary' conditions be added [33]. This new

group of secondary conditions includes psychoses due to a general medical condition (GMC).

Psychoses due to GMC are psychiatric disorders with a well-established aetiology. They are often associated with changes of consciousness, with disorientation or confusion. Changes in the level of consciousness are generally associated with abnormalities in the EEG, independent of aetiology or pathogenesis; this will be dealt with in Chapter 11. Also, the age of the patient has to be taken into account; however, this is only of minor relevance. The slowing of EEG background activity with age is minimal. If there is a clear slowing in the EEG of the elderly, it is probably due to age related pathological processes.

One of the first steps in the diagnostic procedure is to distinguish global from focal aetiology. Brain imaging by computed tomography or magnetic resonance imaging is the method of choice in order to rule out structural alterations. However, since they are difficult to perform in agitated, restless and confused patients, these techniques are not reliable.

In such cases electroencephalography can help to provide a diagnostic overview. Furthermore, EEG is a method reflecting brain functional activity, which is sometimes superior to computer tomography or MRI, especially in early stages of focal processes like tumours or ischaemia, where EEG (even though it is not specific) can suggest a focal pathology (focal brain, functional alterations).

In diffuse encephalopathies (due to metabolic disorders, intoxication, withdrawal syndromes), structural imaging is usually without pathological findings, whereas the EEG can provide evidence for encephalopathy and even give some information on the severity of the brain dysfunction.

EEG findings in focal encephalopathies

Patients with focal brain lesions due to cerebral vascular disorders, tumours or encephalitis do not necessarily present with motor or sensory symptoms. Cognitive alterations can be the leading clinical feature. Lesions of deep subcortical (midline) structures especially can lead to severe amnesia. Here, the EEG can help to identify circumscribed brain functional alterations. For instance, in cases of subcortical (diencephalic) alterations intermittent rhythmic delta activity can occur.

EEG findings in diffuse encephalopathies

Diffuse encephalopathies are often caused by general medical conditions, such as intoxication, metabolic abnormalities, psychoactive drugs or withdrawal syndromes.

EEGs in metabolic encephalopathies usually show diffuse slowing of background activity and/or irregular polymorphic delta/theta activity. The increase of slow activity correlates with the severity of the encephalopathy. Periodic patterns or triphasic waves can occur, especially in patients with metabolic (hepatic) encephalopathies.

Case vignette

AL, male, 48 years, was seen at the outpatient unit of our University Psychiatric Department for his first episode of a psychotic disorder. The doctor who had visited him reported intact cognitive functions (Mini Mental State score of 30), no focal neurological findings and referred him to our psychiatric department. He had been admitted for the sudden onset, 3 months before, of grossly disorganised behaviour, tangentiality, mild incoherence, ambivalent affect, impairment of personal and social functioning. He was a respected police inspector happily married and father of two children. He had a negative history for psychiatric disorders. At the onset, he stole a bicycle from the basement of his next door neighbour, who for several years had given him a copy of the key to the basement to have in case of loss. When his wife found the bike, she asked him why and he appeared embarrassed and as he was talking to imaginary people he answered '..do not tell her ... it is not a theft I have the key ...'. In a few hours he developed an odd behaviour with psychomotor agitation and lack of insight concerning these abnormal behaviours. In the following 3 months he did not want to go to work, spent most of the time doing nothing, his wife had to prompt him to take care of his personal hygiene and to dress. He had an odd language and sometimes was incoherent and could not be understood. He had incongruous emotional reactions (he could laugh talking about his troubles with the family) and showed apathy most of the time. When

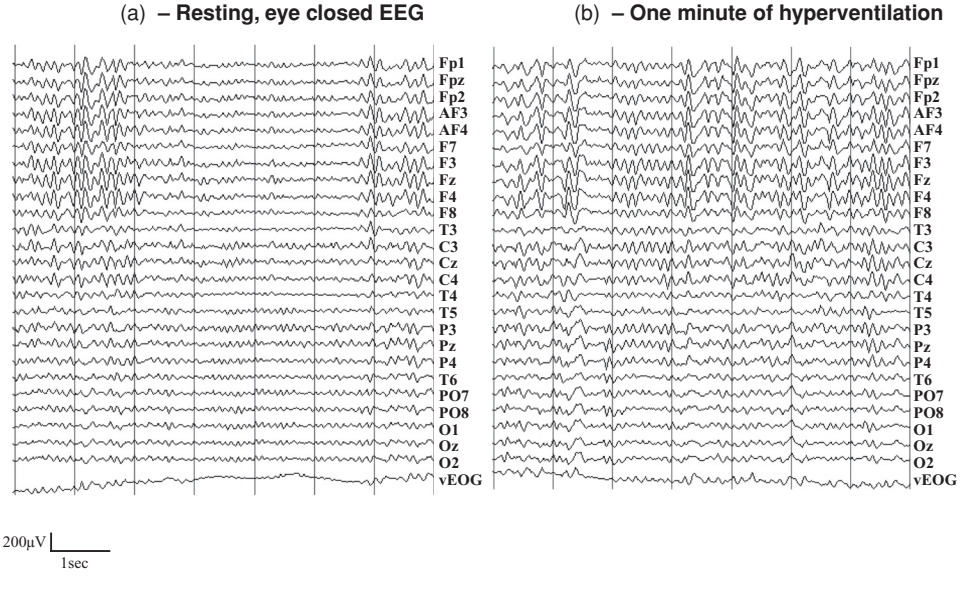

Figure 8.4 EEG in the assessment of a recent-onset schizophreniform disorder. AL, male, 48 years, first-episode, schizophreniform disorder. Eyes closed EEG. Before (a) and after 1 min of hyperventilation (b). Frontal bilateral polyphasic sharp waves, with increased frequency after hyperventilation. MRI showed severe frontal atrophy.

he was first seen in our department the unusual late onset and the absence of delusions in his clinical picture were considered atypical features. He did not show cognitive impairment (MMS = 30) and an EEG to exclude CNS pathology was recorded. Frontal bilateral polyphasic sharp waves were observed (Figure 8.4) and these results prompted neuroradiologic assessment. The MRI revealed atrophy of the frontal lobe, involving the bilateral orbitofrontal regions. A diagnosis of frontal lobe dementia was made.

EEG in mood disorders

Mood disorders like depression and bipolar disorder are amongst the most frequent psychiatric diseases in Western societies. Approximately 15% of the population are suffering from major depression once in their lifetime and about 1 to 1.5% are diagnosed with bipolar disorder. Several of the following symptoms can generally be found in patients with depression: depressed mood, anhedonia, loss or markedly diminished interest or pleasure in activities, unintentional weight loss and appetite loss, sleep disturbances, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished concentration, thoughts of death, recurrent suicidal intention. Patients suffering from bipolar disorder are seriously affected by recurrent episodes of mania and depression (bipolar I) or hypomania and depression (bipolar II). In manic or hypomanic episodes typical symptoms are inflated self-esteem, decreased need of sleep, increased talkativeness, accelerated threads, increased psychomotor agitation and sexual appetence, distractibility and huffiness. Moreover, the spectrum of mood disorders includes cyclothymia, bipolar disorder not otherwise specified, as well as mixed states.

Abnormal EEG-findings can be detected in about 20–40% of patients suffering from mood disorders [21–23]. Using quantitative EEG analyses, several studies have shown an increase in alpha- and/or theta-power in patients with depression [24–26]. In unipolar depression interhemispheric asymmetry and hypocoherence in anterior regions have been described; in bipolar patients there was an increase in beta-activity and a decrease in alpha-activity. Treatment studies using low-resolution electromagnetic tomography (LORETA) have demonstrated that an increase in brain-electric activity of the anterior cingulate gyrus was associated with a positive response to treatment [27, 28].

Furthermore, patients with unipolar or bipolar depression frequently show alterations of vigilance regulation and abnormalities of sleeping EEG-recordings with a shortened REM latency, an increase in REM density and a reduction in sleep stages 3 and 4 [29]. Acute mania can be associated with reduced vigilance states and an increase in posterior slow rhythms [30].

Early EEG studies revealed a frequent increase of small sharp spikes (SSS), 6/sec spike and wave complexes and positive spikes (especially in patients with suicidal ideation) in patients with mood disorders [10, 31].

Nevertheless, there are no specific alterations in patients with mood disorders and EEG recordings are particularly important in order to exclude known brain structural or functional abnormalities as the underlying cause of mood disorders [32].

EEG findings in catatonia

Catatonia was first described by Karl Ludwig Kahlbaum (1828–1899) and was associated with schizophrenia by Kraepelin (1855–1925) and Bleuler (1857–1939). Kahlbaum described a wide range of motor abnormalities, some are classic but infrequent (e.g. echopraxia, waxy flexibility), while others are common in psychiatric patients (e.g. agitation, withdrawal), amongst other signs including immobility, mutism, negativism, staring, stereotypy, verbigeration, echolalia, posturing, catalepsy, rigidity and refusal to eat or drink. In DSM-III-R, this syndrome was incorporated into psychiatric nosology as a subtype of schizophrenia. However, Kahlbaum and modern investigators have observed that catatonia occurs most frequently in affective disorders. In DSM-IV, therefore, catatonia is listed as a modifier of major depression and bipolar disorder, these lack specific diagnostic codes. DSM-IV also recognises catatonic schizophrenia and catatonia secondary to a GMC.

From the above it could be concluded that catatonia is a neuropsychiatric syndrome, most commonly due to mood disorders (bipolar depression, mania and MDD), that may present a difficult diagnostic dilemma. Catatonic disorder due to general medical conditions must be considered in every patient with catatonic signs, laboratory work should vary based on clinical factors and brain imaging is encouraged, since strokes, haematomas and space-occupying lesions (SOL) can all present with new onset catatonia. The clinical EEG can be useful in attempting to sort out possible aetiologies for a particular patient presentation.

Case reports of EEG in catatonia

Gomez *et al.* [34] reported a case of an illegal alien brought to the Emergency Room in a catatonic stupor; his condition worsened after administration of a neuroleptic and it was learned later that he had a history of epilepsy.

Arias *et al.* [35] reported a case of a 22-year-old woman admitted with a picture of catatonic posturing, stupor, fever, rigidity and seizures. She also had dysautonomic symptoms (tachycardia and hypertension). CT, MRI and CSF were normal. EEG revealed diffuse slow waves and right frontotemporal paroxysmal activity. CK was found to be elevated. Early in her presentation she did not respond to neuroleptics, anticholinergics nor antidepressants. Despite her EEG abnormalities, a course of ECT was begun and she began to improve during the 19 treatments she received. This case is illustrative of the possibility of an organic factor contributing to a functional presentation. The presence of the EEG abnormalities did not preclude the consideration of ECT and stressed that ECT is the most effective treatment option in situation of malignant catatonia.

Another illustrative case was reported by Swartz *et al.* [36] where a 68-year-old man with a history of depression developed a catatonia-like syndrome. Catatonic symptoms resolved with the administration of lorazepam. A subsequent EEG revealed a continuing

non-convulsive status epilepticus (NCSE). Presumably, lorazepam suppressed seizure in areas where it had caused clouding of consciousness, but did not suppress all seizure activity. When lorazepam was stopped, the catatonia-like delirium returned. In this case valproic acid was effective in stopping both catatonic and EEG convulsive activity. This case illustrates the fact that reduction of signs of catatonia with benzodiazepine does not necessarily confirm a diagnosis of functional catatonia. The idea that catatonia can represent a NCSE is not new.

Lim *et al.* [37] reported three cases of ictal catatonia. These three patients responded dramatically to intravenous phenytoin. The EEG showed continuous bilateral pseudoperiodic sharp waves and spike discharges in one, spike and wave complexes were prominent on the right frontocentral region in another, and the EEG of the third patient was dominated by periodic lateralised epileptiform discharges during the catatonic state.

Primavera *et al.* [38] stated that although ictal catatonia as a manifestation of non-convulsive status epilepticus has been described, reference to the occurrence of seizures in patients with acute catatonic syndrome remains anecdotal.

The case reported by De Entrambasaguas *et al.* [39], was that of a 24-year-old man presenting with a generalised tonic-clonic seizure of focal onset. Within the following 48 hours he developed agitation and paranoid ideations, which evolved into a severe catatonic syndrome. CT and MRI scans as well as CSF, urine and blood chemistry were all negative. EEG showed theta and delta waves originating in the right frontal region which later generalised. He remained in the ICU with severe catatonic stupor for 3 months, during which time he was receiving a course of ECT. In this case 27 sessions were necessary to resolve the catatonic syndrome.

Kanemoto and colleagues [40] described a case presenting with catatonia as a manifestation of absence status epilepticus following benzodiazepine withdrawal. This elderly patient had long psychiatric history and developed acute catatonia upon benzodiazepine withdrawal. EEG recording revealed a continuous state of 3/second spike and wave (absence status). The case suggests that new onset catatonia in an elderly person should be considered secondary until proven otherwise.

Earlier, Louis and Pflaster [41] reported a case of a 24-year-old woman whose initial examination was notable for a fixed stare, no response to voice or command, tonic head posturing, gaze preference, constant stereotypic chewing movements, and profuse foamy salivation. She responded dramatically to parenteral administration of benzodiazepine. Based on the clinical examination and presentation, the patient was diagnosed as being in a non-convulsive status epilepticus. EEG, however, was perfectly normal, strongly suggesting a functional diagnosis. This case fully illustrates that reliance on the clinical exam alone without the help of ancillary tests (particularly EEG) in attempting to differentiate these conditions is not reliable.

An important differential diagnostic problem is differentiating lethal or thermal catatonia from neuroleptic malignant syndrome (NMS). A detailed case where this differentiation was particularly difficult was reported by Revuelta *et al.* [42]. They described an 18-year-old woman with history of infantile psychosis. She developed a catatonic syndrome which was made worse by neuroleptics. Following her mother's hospitalisation

she developed anorexia, insomnia and agitation. Catatonic symptoms were accompanied by fever and elevated hepatic transaminases. Benzodiazepine was not effective. CT scan, EEG, blood bacterial cultures and CSF were all normal. Rehydration and bromocriptine (30 mg/day) improved the autonomic symptoms and alertness but not the hyperpyrexia or catatonic symptoms. Carbamazepine (600 mg/day) helped her regain speech and mobility but anorexia and rigidity persisted. ECT was judged to be necessary and only after two treatments the remaining symptoms cleared up. This is a difficult case to interpret and it is possible that this patient was already recovering at the time ECT was instituted. The main point of the case, for our purposes, is to highlight the fact that in NMS the EEG is normal unless patient has gone into an encephalopathic state. On the other hand, the presence of epileptic activity (particularly a NCSE) has not been reported in association with the NMS. Catatonia has been reported in association with many conditions including bacterial meningoencephalitis [43], lupus [44], hyperparathyroidism [45] and acute intermittent porphyria [46].

In rare occasions the EEG can point to a specific aetiology. This is the case with subacute sclerosing panencephalitis (SSPE). In one of the earlier reports of a neurological condition presenting in a psychiatric form, Koehler and Jakumeit [47] reported a case of SSPE presenting as catatonia. They described a 20-year-old female who presented with what appeared to be hysterical blindness. The condition soon progressed into catatonia. The EEG exhibited the specific pattern indicative of this disorder (Figure 8.5).

Case series and literature reviews

Suzuki *et al.* [48] reported three case of epileptic seizures superimposed on psychiatric catatonic stupor, none of them had personal or family history of neurological disease and catatonia persisted after resolution of epileptic seizure with phenytoin. They concluded that because catatonia can be caused by epileptic seizures, EEG in patients presenting with catatonic stupor is indicated not only to rule out status epilepticus but also to detect epileptic seizures superimposed on catatonic stupor.

Rosebush and Mazurek [49] reported five patients who became catatonic (age range 53–88 years) following benzodiazepine withdrawal, illustrating that catatonia can develop in the wake of benzodiazepine withdrawal and that the elderly are particularly vulnerable.

Twenty-nine patients with acute catatonic syndrome were reviewed to identify those with seizure after the onset of catatonia. The patients were divided into four diagnostic groups: affective (15), schizophrenic (8), toxic (2), and organic (4). Seizures occurred in four patients (13.8%): two with dystonic seizures had viral encephalitis and schizophrenia, one with complex partial seizures had viral encephalitis, and one patient with absence status had NMS. These results indicate the value of the EEG in detection of epileptic activity in patients with acute catatonia and to provide differential diagnosis between pseudo-seizure and neuroleptic-induced acute dystonia.

As early as 1942, it was noted that the rate of abnormal EEG associated with a catatonic presentation is significant [50].

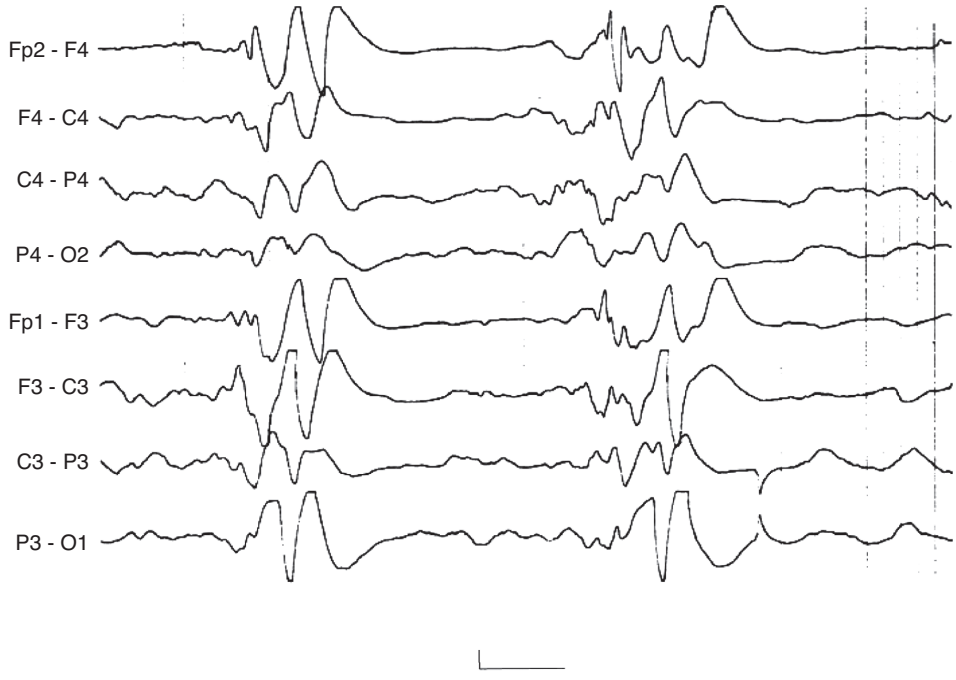

Figure 8.5 EEG tracing from a patient with SSPE presenting with a catatonic picture (Reproduced with the permission of Elsevier Health).

Abenson [51] found that minor EEG abnormalities in patients with catatonic schizophrenia are not uncommon (24%). In this report the author reviewed the EEGs of 210 chronic schizophrenics, 78 diagnosed with catatonic schizophrenia. Strict EEG criteria were used to evaluate abnormalities, and patients were off neuroleptic medications for at least 3 months. Excluding one pattern that was not clearly abnormal (choppy EEG, low voltage, fast activity with no visible alpha rhythm) the rate of abnormality was 12.6%. This rate is comparable to the rate of EEG abnormalities in schizophrenia patients in general [8].

Gjessing *et al.* [52] attempted to correlate the state of catatonic stupor to the EEG in patients with periodic catatonia. They observed that alpha frequency was increased while amplitude was decreased in three patients with acute catatonia. Rosebush *et al.* [53], on the other hand, found most psychiatric inpatients presenting with catatonia to have normal EEGs. Carrol *et al.* [54] and Carrol and Boutros [55] reviewed the then existing world literature regarding the various aetiologies of 'catatonic disorder due to general medical conditions' (CDGMC) and provided four detailed case reports of such cases. In these four patients, general medical conditions associated with CDGMC included dystonia, HIV encephalopathy, encephalitis and renal failure. It should be noted though that the majority of patients had multifactorial aetiologies.

Carrol and Boutros [55] further explored the nature of EEG abnormalities and their clinical correlates in psychiatric patients with CDGMC, bipolar disorder with catatonia and catatonic schizophrenia. From amongst 82 episodes of catatonia (obtained from 67 patients), a total of 42 EEG recordings were available from 26 catatonic episodes. EEGs that did not coincide with a catatonic episode were not included in this study. There were 15 male and 11 female patients. In 50% of the patients a significant general medical condition was diagnosed: non-convulsive status epilepticus (3), metabolic encephalopathy (1), dementia (1), Huntington disease (1), neuroleptic malignant syndrome (4), frontal lobe syndrome (1), hypothermia (1) and CNS tumour (1). Sixteen of the 26 EEGs were abnormal: diffuse slowing (12), focal slowing (3), bilateral spikes (1). Patients receiving second or third EEGs were more likely to show abnormal patterns. Four of six patients showed diffuse slowing on the second EEG, and two of four had focal slowing on the third EEG. The presence of EEG abnormalities was seen more frequently in patients over 40 and patients with more than one medical condition. Psychiatric diagnosis, psychiatric family history and gender were not associated with the presence of EEG abnormalities.

Fink and Taylor [56] suggested that the commonality in response to anti-convulsants (barbiturates and benzodiazepines) and ECT, indicates that catatonia, malignant catatonia, NMS, toxic serotonin syndrome, delirious mania, catatonic excitement and oneirophrenia are best evaluated as a diverse manifestation of one syndrome for clinical and neuroscience research.

Box 8.4 Conclusions

Available literature suggests that a patient presenting with catatonia may have an acute neurological process or catatonia can be a representation of a purely functional disorder. The inescapable conclusion though, is that obtaining an EEG in a person presenting with acute catatonia could be extremely informative to the differential diagnostic process.

- It seems, at least from the bulk of the literature, that once an organic aetiology is ruled out, the routine EEG tends to be normal [53, 57].
- Advanced EEG analysis (i.e. spectral or coherence analysis) studies are sparse but are likely to yield important information about the pathophysiology of catatonia in functional disorders.
- Predicting EEG (or structural/neurological) abnormalities based on the presentation could be misleading [58] and clinicians should err on the side of safety (again given the relative low cost of the EEG). A major question remains is this true even when the patient has had a number of prior presentations with functional catatonia?

EEG and hallucination

Hallucinations can accompany many psychiatric disorders and can be a localizing sign. Warning signs for possible structural pathology include the presence of any form of hallucination other than auditory. Warning signs with auditory hallucinations include sounds experienced being of a simple form, unilateral, stereotyped and the presence of insight into the nature of the experience. When lateralised auditory hallucinations are of a complex nature, they most likely point to the opposite superior temporal gyrus [59]. Further support for the value of auditory hallucination as a localising sign came from the observation that LSD-induced hallucinations significantly decreased following temporal (anterior) lobectomy in epileptic patients. An EEG would be one investigation modality to rule out neurological causes for the hallucination when one is suspected.

Interictal hallucinosis in epilepsy has been poorly studied but is probably more common than appreciated [60]. Occipital lobe epilepsy can be associated and could also present with visual hallucinations [61].

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9

Standard EEG in Personality and Anxiety Disorders

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Introduction

In this chapter we review the data on selected conditions where EEG abnormalities are common. EEG abnormalities are reported in association with other personality and anxiety disorders, but at lesser frequencies, and the implications for these conditions are far less clear than in the conditions reviewed in this chapter. The interested reader is referred to the excellent listing of the relevant literature by John R. Hughes [1].

EEG in aggression and impulse dyscontrol

Introduction

Psychopathic, antisocial and violent behaviour largely remain understudied. The thorough understanding of the biological mechanisms contributing to habitual aggression is fundamental if effective preventive, diagnostic and rehabilitative programmes are to be developed. Electrophysiological techniques can be very helpful in advancing our knowledge of this area.

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EEG abnormalities associated with aggression and impulse dyscontrol

The prevalence of abnormal EEGs in clinical populations characterised by violence or aggressive acts vary widely amongst studies ranging from as low as 6.6% in patients with rage attacks and episodic violent behaviour [2] to as high as 53% in patients diagnosed with antisocial personality disorder [3]. Bach-Y-Rita *et al*. [4] reported the EEGs of 79 patients diagnosed with 'episodic dyscontrol'. Thirty-seven of them were abnormal (47%). Twenty of the 37 abnormal records showed spikes in the temporal region. They classified patients that were included in the study into four categories; (1) patients already diagnosed with temporal lobe epilepsy; (2) patients with epilepsy-like episodes; (3) patients with 'diffuse violence' with violent outbursts at varied targets. These subjects constituted the largest group and exhibited a significantly increased level of anxiety. The fourth group was that with 'pathological intoxication'. This categorisation may be of some clinical value in guiding the work up of such subjects.

Bennett and his colleagues [5] examined the EEGs of 48 children between the ages of 5.2 and 12.9 years who were hospitalised for aggressive, explosive or conduct disorders. They reported a prevalence of 58.3% abnormalities.

EEG and antisocial personality disorder (APD)

As early as the mid 1940s it was recognised that criminals had a higher prevalence of EEG abnormalities. Amongst psychiatric populations the group of 'psychopaths' had the largest incidence of either borderline or frank abnormalities (48%) which consisted mainly of diffuse background slowing (unmedicated patients) and/or paroxysmal activity with or without spike components [6]. When they divided the group into aggressive ($N = 66$) and non-aggressive ($N = 38$) they found 65% of aggressive patients and only 32% of non-aggressive subjects to exhibit abnormal EEGs. In this paper they also reported a significant relationship between history of head injury and presence of EEG abnormalities. *They concluded that the more aggressive the patient the more likely the EEG to be abnormal*. Wong *et al*. [7] retrospectively examined the EEGs and CT scans of 372 male patients in a maximum-security mental hospital. They reported that 20% of the EEGs were abnormal in the most violent patients as compared to 2.4% for the least violent patients, with majority of abnormalities localised to the temporal lobes.

Blake *et al*. [8] performed detailed neurological evaluations of 31 individuals awaiting trial or sentencing for murder. Neurological examination revealed evidence of 'frontal' dysfunction in 20 (64.5%). There were symptoms or some other evidence of temporal lobe dysfunction in 9 (29%). *Most importantly is that neuropsychological testing revealed abnormalities in all subjects tested*. There were EEG abnormalities in 8 of the 20 subjects who had EEGs. EEG abnormalities consisted mainly of bilateral sharp waves with slowing.

Habitual vs. sporadic aggression

It has also been shown that amongst groups of prisoners convicted of murder, the highest incidence of EEG abnormalities (74%) occurred in individuals whose crimes were apparently motiveless or had minimal motives [9, 10]. EEGs, medication status, nature of the offence as well as personality characterisation were examined in 265 consecutive admissions to a special hospital for offenders [11]. The EEGs were classified into: (a) normal (monorhythmic); (b) low voltage fast; (c) choppy (i.e. dysrhythmic with excess theta); and (d) dysrhythmic with paroxysmal features. The prevalence of abnormalities was not different between medicated and non-medicated subjects, strongly suggesting that abnormalities in this population are not secondary to medication effects. The close to 50% prevalence of EEG abnormalities in association with violence seems to be culturally independent. Okasha *et al*. [12] reported a prevalence of 43% of EEG abnormalities in a group of Egyptian murderers.

Specific EEG abnormalities

Convit *et al*. [13] demonstrated that violence was very significantly related to the hemispheric asymmetry in EEG for the frontotemporal regions. They provided evidence that with increased levels of violence a greater level of delta power in the left compared with the right hemispheres can be found. A relationship between left hemisphere focal EEG abnormalities and increased violent tendencies was further supported by Pillmann *et al*. [14] who examined the EEGs of 222 offenders referred for psychiatric evaluation.

Posterior temporal lobe focal slow wave abnormality has been described to be more prevalent in populations that had higher propensity for violent or aggressive acts [15]. Hill [16] reported a 12% ($N = 194$ non-epileptic psychopaths) posterior temporal lobe slowing in association with psychopathic personalities as compared to 2% in healthy control subjects. They also noted that this abnormality tended to decrease with increasing age suggesting a maturational nature of the abnormality. Aird and Gastaut [17] similarly noticed that children with this abnormality tend to mature out of it. Fenton *et al*. [15] doubted that all violent subjects with posterior temporal slowing will outgrow the abnormality or the violence.

EEG and institutional aggression (including aggression in schizophrenia)

Violence is also a problem in psychiatric institutions. With de-institutionalisation, the problem is inherited by inner city communities where most of these patients tend to segregate. Barber *et al*. [18] examined the clinical characteristics of 15 patients with repetitively assaultive behaviour. These patients constituted 3.3% of the average

daily census but accounted for 48.6% of all assaultive incidents during a one-year period.

Sayed *et al*. [19] reported the EEG abnormalities in a group of 32 murderers who were deemed 'insane' as compared to a group of non-patient controls. They found an overall incidence of abnormalities not far different from what has been reported in other studies (65.6%), which was approximately four times the incidence of EEG abnormalities in the control group. They found a higher prevalence of EEG abnormalities in the subgroup diagnosed as 'schizophrenics' with 73.4% as compared to the non-psychotic psychopathic group (50%). Three murderers with 'psychotic depression' all had abnormal EEGs. Again, the most frequently encountered abnormality was diffuse slowing of the background rhythm (66%) with paroxysmal abnormalities only in 4 subjects (19%).

Epilepsy and violence

The interrelationship between violence and epilepsy is both controversial and complex. For a more expanded discussion of the medical-legal aspects of epilepsy and aggression and the status of epilepsy as a defence in murder trials the interested reader is referred to the chapter by J. R. Hughes [20]. In this chapter and due to limited space, we do not attempt to provide a comprehensive account for the possible link between the two phenomena. The overall impression is that violence is somewhat increased in epileptic populations as compared to the general population. The estimates of this increase vary considerably, but is not likely to be very high, particularly when mental subnormality is excluded. Aggressive behaviours in epileptics were found to be associated with the male gender, early onset of seizures and history of long standing behavioural problems [21].

Treatment implications

The main function of the EEG is to provide evidence for cerebral abnormalities that may be sufficient to suggest treatment consideration (e.g. presence of epileptic discharges), or to suggest the need for further work up (e.g. the presence of focal or diffuse slowing).

Whether the appearance of an abnormal EEG predicts a favourable therapeutic response to anticonvulsant medications is currently unknown. Monroe [22] showed that anticonvulsants can block electroencephalographic epileptiform discharges and can lead to dramatic clinical improvement in individuals exhibiting repeated and frequent aggressive behaviour. An earlier study by Boelhouwer *et al*. [23] found adolescents or young adults exhibiting the 14 and 6 positive spikes to respond favourably to the combination of anticonvulsants and antipsychotic medications. With a maximum of 8 week trials comparing thioridazine, diphenylhydantoin or combination of the two against placebo, they reported that the PS spike group responded best to the combination of drugs. These investigators then assessed the EEGs for the presence of the posterior temporal lobe slowing. They noted that patients with both abnormalities did least well

on any treatment while patients with posterior temporal slowing alone did best on the anticonvulsant as sole treatment. Tunks and Dermer [24] reported a detailed case where other than deafness, there were no obvious neurological abnormalities in a female with episodic aggression who responded extremely well to carbamazepine therapy. Neppe [25] provided evidence that the addition of carbamazepine to the treatment of schizophrenia patients, who also exhibit temporal lobe abnormalities on the EEG and without a history of a seizure disorder, can be clinically useful. Earlier, Hakola and Laulumaa [26] noted a reduction of aggressive episodes when carbamazepine was added to the neuroleptic regime of eight highly aggressive women with schizophrenia who also had EEG abnormalities. A detailed case report of a response of a severely aggressive patient with schizophrenia who responded well to carbamazepine adjuvant therapy was reported by Yassa and Dupont [27]. Mattes [28] examined the clinical response to propranolol versus carbamazepine in a group of 80 patients with rage outbursts. Fifty-one of the subjects were randomised while patients with history of epilepsy ($N = 11$) were assigned to the carbamazepine arm and patients with known allergy to one of the medications were assigned to the other study medication. Twenty of the 80 subjects had abnormal EEGs including nine of the 11 with epilepsy. The diagnosis of attention deficit disorder predicted a preferential response to propranolol while diagnosis of intermittent explosive disorder predicted a favourable response to carbamazepine.

On the other hand, other studies suggest that anticonvulsant therapy may have a beneficial effect on aggressive tendencies irrespective of the presence or absence of EEG abnormalities [29]. Until definitive studies are performed, patients should be given the benefit of the doubt and a trial of anticonvulsant should be performed when an EEG proves to be abnormal, particularly focally and paroxysmally.

Box 9.1 Conclusions

The above reviewed literature supports the following conclusions:

(1) EEG abnormalities are prevalent in populations that exhibit habitual aggressive behaviour. The presentation with episodic aggression is a definite indication for launching an EEG work up (see below under 'Panic attacks' for what constitutes an adequate EEG work up).

(2) Such abnormalities could have significant treatment implications. Large multicentre studies examining the clinical correlates, particularly treatment responses, of patients with various abnormalities are yet to be conducted.

(3) History of head injury, increased and habitual aggressiveness (particularly against strangers) all correlate with increased EEG abnormalities and are very likely to have additional evidence of neurological dysfunctions from MRIs or neuropsychological testing.

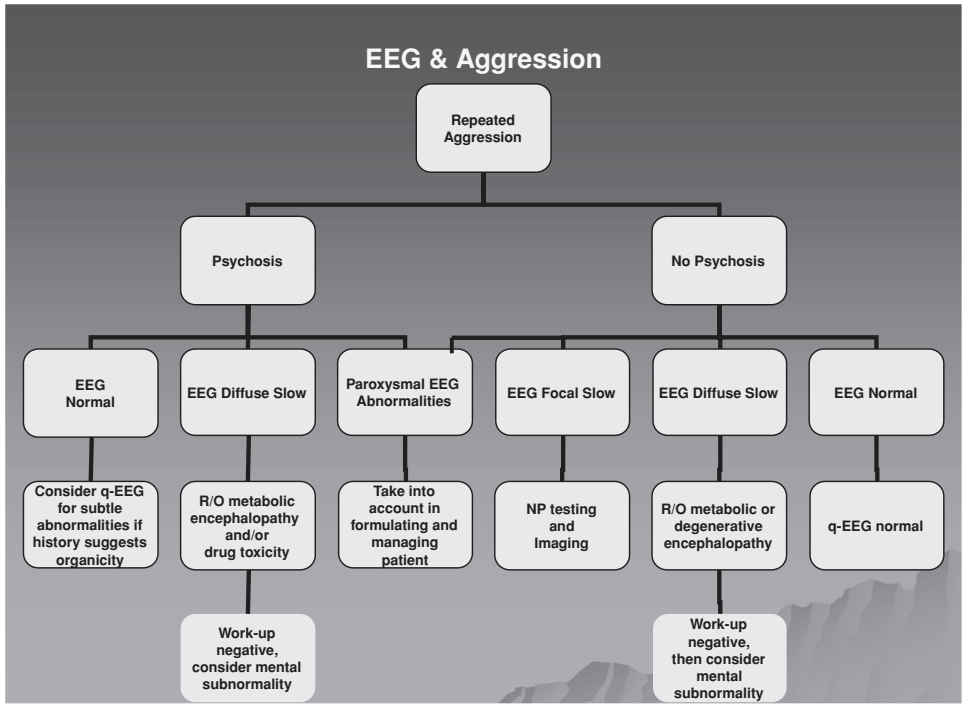

Figure 9.1 Flow chart for EEG work-up for individuals with aggressive or violent episodes. Please note that an individual with or without psychosis can still harbour epileptic discharges. The work-up must be driven by the clinical picture and suggestions of the electroencephalographer.

Figure 9.1 is a flow chart for EEG work-up for individuals with aggressive or violent episodes.

Panic attacks

Introduction

Panic disorder (PD) is a common anxiety disorder. According to Kessler *et al*. [30], PD affects around 4.7% of the adult population. Panic attacks can be disabling and may lead to agoraphobia with devastating psychosocial and economic consequences. The identification of the aetiology of these attacks is important for the proper management of the disorder. DSM-IV describes a typical attack as a discrete period of intense fear or discomfort, in which at least four of the following symptoms develop abruptly and reach a peak within 10 minutes: palpitation, sweating, trembling or shaking, sensations of shortness of breath, feeling of choking, chest pain or discomfort, nausea or abdominal stress, feeling dizzy (or light-headed, unsteady or faint), derealisation

(feelings of unreality), depersonalisation (being detached from oneself), fear of losing control or going crazy, fear of dying, paresthesias, chills or hot flashes. Many of these symptoms have been reported by patients with well-documented complex partial seizures.

Epilepsy and panic symptoms

Panic symptoms carry a significant resemblance to symptoms induced by temporolimbic epileptic activity, particularly those originating from the sylvian fissure. Fear, derealisation, tachycardia, diaphoresis and abdominal discomfort are characteristic symptoms of simple partial seizures with psychiatric and autonomic symptomatology. Evidence from population surveys suggests that panic disorder is significantly more prevalent in epileptic patients than the general public [31]. These authors did not find a similar relationship between epilepsy and agoraphobia, social phobia or generalised anxiety. However, the relationship between PD and epilepsy remains controversial [32–34].

Actually, the differentiation between PD and CPS could be diagnostically challenging as patients with documented CPS of temporal lobe origin may have concomitant non-ictal episodic emotional symptoms, including phobia, true panic attacks and anxiety. Careful diagnostic evaluation and correlation with video electroencephalography is important in distinguishing seizure activity from panic disorder [35]. Panic attacks can occur in epileptic patients [36]. These attacks could lead to over-medication for seizures if their nature is not precisely defined. Again EEG monitoring during multiple attacks is indispensable in rendering such an evaluation.

It should be emphasised that it is well documented that a single negative EEG does not rule out epilepsy even in patients with well-documented seizures. Moreover, the necessity for obtaining sleep during the recording cannot be over-emphasised. Finally, it is possible that EEG abnormalities can only be detected during panic episodes, requiring more prolonged ambulatory EEG monitoring.

EEG in non-epileptic panic disorder patients

EEG abnormalities, such as paroxysmal epileptiform discharges and asymmetric increases in slow wave activity, are not infrequent in panic disorder patients who have no evidence of epilepsy (and can be up to 12 times higher in patients than in healthy controls [37].

In subjects with PA the following abnormalities were also reported: focal paroxysms of sharp wave activity coinciding with spontaneous onset of panic attack symptoms [38] and slow wave abnormalities [39].

The appearance in the literature of several cases of PD with EEG abnormalities indicates the need for detailed work up of every panic disorder patient [40].

Case vignette

LMM was a 47-year-old female, mother of three children, who was seen in the outpatient unit of the University of Naples, Department of Mental Health. She had been treated for panic disorder with agoraphobia, without experiencing a significant clinical improvement, over the preceding year. The first episode was described by the patient as a sudden onset of '... a feeling of emptiness in the stomach and then something rising up from the stomach to the throat', palpitations, chills and fear. Several other attacks occurred and she developed agoraphobia (she could not be alone at home nor could drive or go out shopping). The attacks were similar to the first one, but some of them were characterised by '... sensation of lump in the throat ', choking, derealisation and occasionally '... sensation of something rising up to the nose and a bad smell like garlic'. She was treated by a neurologist with fluoxetine (20 mg/day) and ketazolam (30 mg/day),for two months, without a significant clinical improvement. Fluoxetine was then changed to clomipramine (starting dose of 25 mg × 2/day), but she discontinued treatment within the first few weeks for lack of improvement. In the following months, her panic attacks increased in frequency (up to 3/day) and intensity and her agoraphobia worsened. She was also treated with psychotherapy for several months but with almost no improvement.

When she was first assessed in our department, the unusual clinical presentation, with feelings of a bad smell in some occasions, and the lack of improvement on antidepressants (floxetine and clomipramine) and BDZ (ketazolam) were thought to require a differential diagnosis with temporal lobe epilepsy. EEG showed bi-temporal slow waves in the theta range (Figure 9.2). A Tc-99m-single photon emission tomography of the brain was then obtained and a left hemisphere hypoperfusion was found. Carbamazepine (up to 1200 mg/day) was started and after 1 month clonazepam (up to 3 mg/day) was added with remission of the panic attacks in 3 months and of agoraphobia in 5 months. A 2 year follow-up showed long-lasting remission of the symptoms, and good compliance with the therapy.

Treatment implications

The literature reviewed above and the case vignette provide presumptive evidence that the subgroup of panic disorder patients who exhibit EEG abnormalities may be a distinct subgroup with different treatment responses. Treatment of the subgroup of panic disorder patients with demonstrable EEG abnormalities has not been well examined.

It remains to be seen in larger well-controlled studies if anticonvulsant treatment should be the first line of treatment in abnormal EEG/panic disorder subjects. Also awaiting well-designed studies is the demonstration of (or lack of) responsivity of such patients to psychotherapy.

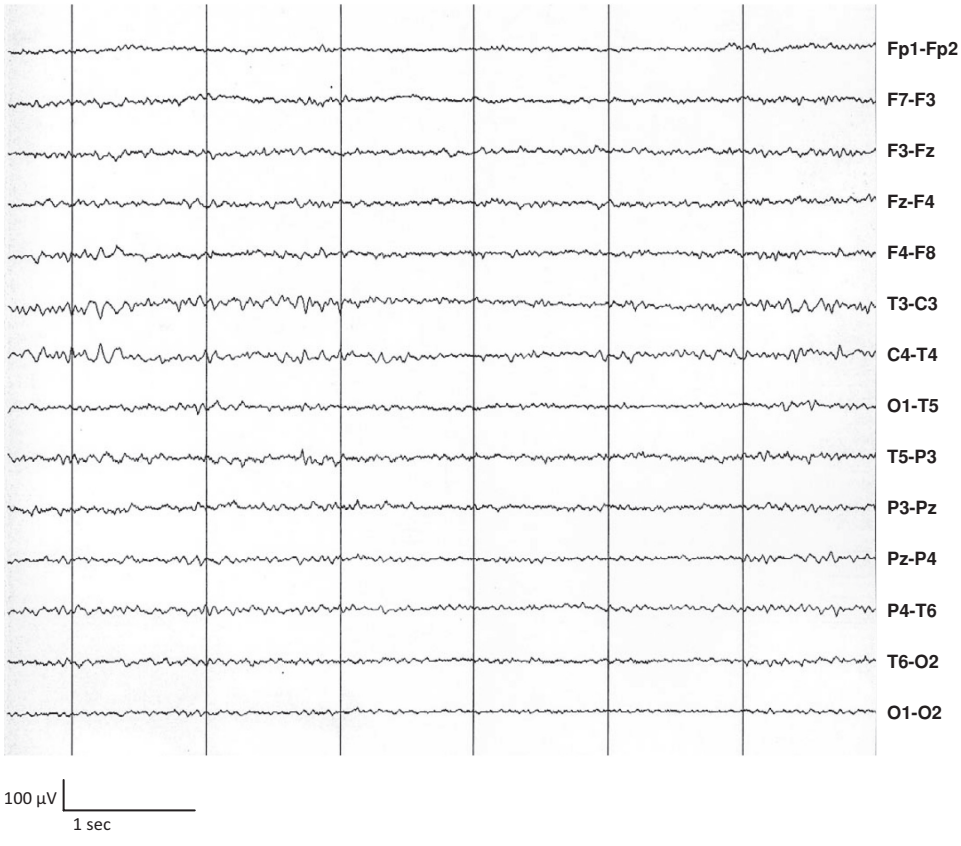

Figure 9.2 EEG in a patient with atypical panic attacks. LMM had a typical clinical presentation, with bad smell feeling in some attacks, and no improvement with antidepressants and benzodiazepines. LMM improved with carbamazepine and clonazepam.

Box 9.2 Conclusions

The literature reviewed above supports a number of conclusions:

- A sizeable proportion, approximately 25–30% of panic attack patients have demonstrable EEG abnormalities indicative of a process other than an idiopathic panic disorder. It follows that the presentation with panic symptoms is a definite indication for obtaining EEG work up.

(*continued*)

- It is possible that these patients may be responsive to anticonvulsant treatment [41]. In the absence of large well-designed studies, patients with panic attacks and abnormal EEGs should have a trial of anticonvulsant therapy.

- An adequate EEG work up should begin by obtaining the EEG during full wakefulness, performing hyperventilation for a minimum of 3 minutes (but could be extended to 5), and photic stimulation. Subject should be allowed to fall asleep at least into stage one but preferably stage two without allowing deeper stages of sleep. If sleep could not be obtained, the record must be considered inadequate for the evaluation of paroxysmal activity. If the initial recording is normal, a repeat following sleep deprivation would increase the yield.

- It must be born in mind that current day technology is not capable of ruling out epileptic or paroxysmal activity at or even close to a 100% certainty.

- If the repeat EEG is also normal and the panic attacks are relatively frequent (at least daily), particularly if unresponsive to first line of treatment (usually an SSRI), then an ambulatory EEG to record during the attacks could be useful.

- The roles of magnetoencephalography and more invasive electrodes (like sphenoidal placements) are yet to be explored.

Borderline personality disorder

Introduction

Borderline personality disorder (BPD) patients constitute a large burden on the resources of mental health services. The thorough understanding of the neurobiology of borderline personality disorder is essential for the development of effective preventive, therapeutic and rehabilitative approaches. While BPD is one of the most investigated personality disorders, the neurobiological bases of this devastating disorder remain largely unknown. Evidence for an organic basis for BPD has been forthcoming since the 1980s [42, 43]. A number of electrophysiological studies linked BPD to complex partial seizures (CPS) [44]. Andrulonis *et al*. found 27% of adolescent BPD patients had evidence of brain dysfunction or current epilepsy [42]. They also found history of head trauma, encephalitis or past seizures in 11%. Several episodic or paroxysmal symptoms are common between BPD and temporal lobe epilepsy: impulsivity, transient psychosis and intermittent experience of depersonalisation and derealisation [45]. Carbamazepine has been shown to be effective in decreasing paroxysmal symptoms [46]. Indeed, a number of case reports

have described complex partial seizures in patients previously diagnosed as BPD [47,48]. For a more recent review, the interested reader is referred to Boutros *et al*. [49].

Box 9.3 EEG abnormalities in borderline patients and treatment implications

- Most common abnormality is diffuse EEG slowing. A neuropsychology testing would be recommended and unless the cause of the slowing is correctable, this patient is unlikely to be suitable for dynamic psychotherapy.
- Epileptic discharges. The possibility of complex partial seizures should be considered. A trial of antiepileptic drugs should be considered if standard treatment is not effective.
- Focal slowing: a neuropsychology testing could help plan a cognitive remediation programme.

Box 9.4 Clinical red flags that should alert the clinician to a possible neurological or other general medical conditions contributing to the presentation

These red flags apply to all clinical presentation of any psychiatric condition and none of them, in isolation, are pathognomonic of a structural or neurological conditions:

- Unusual age of onset.
- Any focal or lateralised symptoms (unilateral hallucinations).
- Focal neurological abnormalities.
- Presence of any difficulty with orientation or memory (in general MMS should be normal).
- Complete lack of family history of the disorder being considered.
- Clinicians should have a high index of suspicion for suspecting underlying medical conditions and low threshold for initiating appropriate work ups.

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10
EEG in Delirium and Dementia

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Introduction: Epidemiology of delirium and dementia

Delirium, an illness characterised by an acute impairment in attention, is estimated to cost the US at least $38 billion dollars per year [1]. The prevalence of delirium ranges from about 10 to 30% in hospitalised patients [2,3] to as high as 70–90% in the intensive care unit setting, in surgical patients, frail elderly patients and terminally ill patients [4–6].

One major challenge in the diagnosis and treatment of delirium is that its aetiology is frequently multifactorial. Possible causes include infections, metabolic-endocrine, structural, toxic, withdrawal, nutritional and/or nonconvulsive status epilepticus (NCS). (See Table 10.1 for detailed examples.)

The potential for medication toxicity needs to be considered especially in geriatric patients, patients on polypharmacy or patients with hepatic or renal dysfunction. Drug toxicity accounts for approximately 30% of all causes of delirium [7].

A detailed history is the most important first step in the diagnosis of delirium.

Unlike the acute changes seen in delirium, the cognitive decline in dementia usually occurs over months to years. It can be characterised primarily by a dysfunction in memory, language, apraxia as seen in the early phase of Alzheimer's disease, or in other domains depending on the underlying aetiology.

The prognosis of the different types of dementia is different based on the mechanisms of action. Over 5.3 million people in the US are diagnosed with Alzheimer's disease,

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Table 10.1 Common types of delirium.

Type	Common examples
Infection	• Pneumonia • Urinary tract infection • Sepsis • Meningitis/encephalitis • Hyperthermia, hypothermia
Metabolic and endocrine	• Electrolyte disturbances (hyponatraemia or hypernatraemia, hypoglycaemia or hyperglycaemia) • Hepatic or renal failure • Endocrinopathies (hypothyroidism and hyperthyroidism) • Myxoedema coma • Hypoxia, anoxia
Structural/CNS causes	• Space occupying lesions • Complications from neurosurgical procedures. • Seizures especially nonconvulsive status epilepticus
Drug toxicity/withdrawal	• Drug of abuse (e.g. alcohol, heroin, hallucinogens) • Prescription drugs (sedatives/narcotic, anticholinergics) • Withdrawal states (e.g. alcohol, benzodiazepines) • Polypharmacy • Medication side effects (lithium, valproic acid, carbamazepine, dilantin toxicity, serotonergic agents) • Others
Iatrogenic/environmental	• Surgery (orthopaedic and cardiac procedures)
Nutritional	• Wernicke encephalopathy • B12, folate deficiencies

the most common form of dementia [8]. It is now the sixth leading cause of death [8] and is associated with higher rates of respiratory illness leading to death [9]. The cost of Alzheimer's disease in the US has now reached $148 billion each year for both direct and indirect costs to caretakers [8].

Dementia is categorised into three major subtypes: cortical, subcortical and mixed. Cortical dementias can present with disturbances of memory, language, apraxia, agnosia, impaired capacity for abstract thoughts and/or behavioural disturbances. Alzheimer's disease, the most common type of cortical dementia, accounts for about 70% of all dementias [10]. Vascular dementia, including multi-infarct and Binswanger's disease, accounts for about 13% of all dementias [10]. Other subtypes of cortical dementias include frontotemporal dementia, (2.8–4.0%) [11]. Normal pressure hydrocephalus accounts for about 1.5–5.4% of dementias [12, 13] and Creutzfeldt–Jakob disease for less than 1% [11].

Subcortical dementias are characterised mostly by apathy, forgetfulness and slowness in thought process and speech. The most common type of subcortical dementia is Lewy body dementia, which represents about 6.1–22.4% of all dementias [11]. Other types

Table 10.2 Dementias classified by cause.

Cause	Examples
Neurodegenerative	• Alzheimer's disease • Parkinson's disease • Huntington disease • Pick's disease • Lewy body dementia
Vascular	• Multi-infarct dementia • Subcortical small vessel
Infectious	• Creutzfeld–Jakob disease • HIV dementia • Progressive multifocal encephalopathy
Normal pressure hydrocephalus	• Normal pressure hydrocephalus
Nutritional/alcoholic	• Wernicke–Korsakoff • B12, thiamine, folate deficiency
Metabolic	• Hepatic disease • Thyroid disease • Renal disease
Traumatic brain injury	• Head injury

include Parkinson's dementia, progressive supranuclear palsy (PSP), Huntington disease and HIV dementia.

Mixed dementias contain features of both cortical and subcortical dementia. Table 10.2 lists the various causes of dementia with examples.

Clinical diagnosis in delirium

The diagnosis of delirium can be missed by the general medicine and surgical services in about 40–60% of cases referred to the psychiatric consultation-liaison service [14]. One main factor which contributes to the difficulty in the diagnosis is the variety of clinical presentations. Clinical manifestations of delirium are characterised by an inability to maintain attention and/or to focus on a task, sleep wake cycle reversal, behavioural changes and/or new onset disorientation. Impaired attention interferes with patients' ability to register. As a consequence, patients cannot store and/or retrieve information even though they do not suffer from a dementing process.

At times the clinician may misinterpret the cognitive changes as refusal to cooperate with the interview or the exam. Patients with delirium can present with psychotic, manic or depressive symptoms, which can be mistaken for a primary psychotic or mood disorder. Hypoactive delirium, which accounts for almost half of delirium cases, is often associated with misdiagnosis of depression on initial psychiatric consultation [14].

Rapid onset, brief duration, fluctuating course and altered level consciousness can be helpful characteristics in the differentiation of delirium versus dementia, though at times

they can coexist. Also, signs of delirium may persist for 12 months or longer, especially in patients with underlying dementia, making the diagnosis difficult [15].

A thorough history, including medical and psychiatric co-morbidities, drug history, pharmacotherapy and corroborative information from family, friends and caretakers, is essential in order to maximise the clinical diagnosis and treatment plan.

Serial interviews, careful documentation of patients' mental status and a multidisciplinary approach may also help clinicians track these fluctuations in mental status. Often psychiatry or neurology services are consulted when the initial work up has been negative. Work up should include complete blood count, electrolytes (including measurements of renal function and hepatic functions), thyroid function tests, vitamin B12 and folate. When necessary, urine toxicology, neuroimaging, lumbar puncture and EEG should also be considered.

Making the diagnosis of delirium in patients with baseline cognitive impairment can be especially challenging. This is not a trivial issue given that the presence of a cognitive disorder is a risk factor for delirium; about 25% of patients with delirium have dementia [14, 16].

Given the fluctuating course of delirium and the high mortality of untreated delirium, there should be a low threshold to pursue the delirium work up in all patients, particularly in those who suffer from dementia.

Early diagnosis is essential in order to initiate the needed treatment of the underlying cause. Most patients return to their baseline after the cause of the delirium is corrected. The prediction of the course of delirium, especially in patients with underlying neurological compromise, however, remains a major clinical challenge. Some studies suggest that delirium may accelerate long-term cognitive decline in patients with Alzheimer's disease [17]. Future strategies may need to focus on the prevention of delirium in this high risk population.

EEG work up in delirium

EEG is a tool which can be helpful in the work up of delirium [2]. Certain EEG changes can be helpful for clinicians diagnosing patients who present with otherwise unexplained changes in mental status.

Slowing on EEG during sleep, drowsiness or hyperventilation is a normal pattern, whereas slowing of the posterior alpha rhythm during wakefulness suggests a diffuse cerebral disturbance which may be secondary to delirium. Diffuse slowing [18] and the loss of reactivity to eye opening and closing [19] can become more pronounced with an increasing degree of encephalopathy. At times, slowing can be intermittent and/or periodic, like in frontal intermittent rhythmic delta activity (FIRDA) [20]. These changes usually correlate with the level of consciousness regardless of the underlying aetiology. One major exception is seen in the case of patients in whom the delirium is secondary to alcohol or drug withdrawal in which case low voltage fast activity predominates [21].

Non-toxic levels of psychotropics do not routinely cause significant slowing on EEG recordings. Therefore, in psychiatric patients with an acute change in mental status and diffuse slowing on EEG, these findings should trigger a delirium work up and not necessarily attributed to psychotropics [22, 23].

Certain EEG patterns may also point towards specific underlying causes such as toxic encephalopathy, herpes encephalitis, lithium or other drug toxicity, or seizures disorders. Table 10.3 describes different patterns commonly seen in patients with delirium [20]. Although a normal EEG does not necessarily exclude delirium, abnormal EEG can confirm the diagnosis of delirium and rule out a psychiatric illness, such as a mood, anxiety or psychotic disorder, as the primary cause of the change in mental status.

If the initial work up for delirium is negative, one important cause that should be ruled out is nonconvulsive status epilepticus (NCS). This is characterised by a change in mental status of varying degrees and no motor activity or limited motor activity with associated diagnostic EEG changes. There are two major types of NCS: absence status and complex partial status. In absence status, a type of primary generalised seizure, the EEG is usually characterised by continuous or nearly continuous generalised, rhythmic, bilaterally synchronous 3 per second spike wave discharges with a maximum over the frontal regions. At times, 2–3 per second spike wave complexes as well of bursts of rhythmic activity or arrhythmic spike wave, or polyspike activity can also be present [24]. In complex partial seizure, the EEG can be characterised by rhythmic slowing, rhythmic sharp and slow waves or rhythmic spikes [24]. For further discussion on NCS please see Chapter 7.

In addition to the diagnosis of NCS, EEG can be especially useful for diagnostic work up of delirium of other causes, most notably metabolic, endocrine, infectious and toxic causes.

Metabolic disturbances are often due to electrolyte disturbances and end organ failure. Electrolyte abnormalities are quite common, especially in the elderly and/or medically ill. Hyponatraemia and hypocalcaemia can lead to diffuse slowing EEG and epileptiform activity [25].

Metabolic causes of delirium

Hepatic encephalopathy can be characterised clinically by different degrees of alteration of consciousness and on EEG by different degrees of slowing. The posterior alpha rhythm can be preserved during the early stage of the disease [20]. There is some indication that the level of ammonia often parallels the degree of slowing [26].

Triphasic waves have been considered an indicative finding in hepatic encephalopathy [27]. These waves are in the range of 1.5–3 seconds. They start up with a sharp transient configuration which at times takes the form of a clear spike. There is no correlation between the clinical presentation and the EEG findings. A normalisation of the record has been described during the sleep phase. Triphasic waves occur about 20% more

Table 10.3 Common EEG findings in delirium.

Cause	EEG findings
Infection	
• acute bacterial meningitis/encephalitis	• mild to severe diffuse slowing of the background • paroxysmal epileptiform activity
• herpes simplex encephalitis	• disorganisation of the background rhythm with excessive intermixed delta activity and high amplitude periodic complexes • changes can be focal or lateralised with predominance over the temporal region. • focal sharp, sharp and slow complexes and or spike activity can be present over the temporal region • periodic lateralised epileptiform discharges
Metabolic and endocrine	
• hypoglycaemia	• different degrees of slowing at times combined with epileptiform activity
• hyperglycaemia/ advanced diabetic coma	• intermixed slowing of the background, excessive fast and spike activity
• hepatic encephalopathy	• triphasic waves • in later stages, excessive slowing with predominant theta and delta frequencies.
• acute uraemia	• slowing of the posterior basic rhythm and excessive intermixed theta bursts • bursts of bilaterally synchronous slow and sharp activity or frank spikes
• chronic uraemia	• diffuse slowing • sleep changes: ✓ generalised spike-wave like bursts ✓ bursts of high voltage vertex sharp activity during sleep ✓ lack of spindles in stage 2 sleep ✓ paroxysmal high voltage slow bursts with awakening
• hypocalcemia/hyponatremia	• diffuse slowing
• hyperthyroidism	• increase alpha frequency and fast activities
• hypothyroidism/ myxedematous coma	• low voltage slow activity • poor or absent alpha blocking response
Drug toxicity	
• barbiturate withdrawal	• transient generalised paroxysmal activities and spikes especially with photic stimulation
• lithium toxicity	• slowing of alpha rhythm and paroxysmal generalised slowing, occasionally accompanied by spikes

frequently in hepatic encephalopathy than other types of metabolic encephalopathy [28, 29] but can also be present in uraemic or septic encephalopathy. Triphasic waves are not helpful in the differential diagnosis of different metabolic encephalopathy but they are a poor prognostic indicator of survival. Different authors found that there is an equal incidence of epileptiform discharges and clinical seizures in both hepatic and renal encephalopathy [20].

In a study of preoperative theta/delta waves seen in patients with hepatic encephalopathy, theta/delta waves were significantly improved after patients underwent liver transplantation [30].

EEG findings in renal failure depend on the stage of the disease. EEG changes are seen in about two-thirds of cases of acute renal failure. Common findings on EEG include slowing of the posterior basic rhythm with occasional intermixed theta and delta waves. At times, bursts of bilaterally synchronous slow and sharp activity can be present in about 25% of cases of patients with uraemia and EEG changes may correlate with the level of fluctuation in blood urea nitrogen level [31–34].

EEG changes such as the lack of spindles in stage 2 sleep (14/sec waves), high voltage vertex sharp activity, paradoxical response to awakening and sensitivity to photic stimuli, have been described by different authors in association with chronic renal failure [32,33].

EEG findings in hypoglycaemia can be characterised by different degrees of slowing at times combined with epileptiform activity. The degree of the abnormalities can vary, based on individual propensity and co-morbidities [35].

In hyperglycaemia, intermixed slowing of the background and excessive fast and spike activity have been described in association with glucose levels above 400 mg/100 mL [36]. Epileptic manifestations of focal origin have also been described in non-ketotic hyperglycaemia [37].

In diabetic acidosis, disorganisation of the background and diffuse slowing can occur, although it usually reverses upon metabolic correction [31]. In diabetic coma, EEG changes are consistent with those of coma, including disorganisation of alpha rhythm and shift towards generalised theta or delta activity [26]. On the other hand, generally, well-controlled, compensated diabetic patients do not show abnormalities on EEG [26].

Clinical manifestations, glucose level and EEG changes do not necessarily parallel each other, and clinical manifestations can depend mainly on the rapid fall of the blood sugar level, rather than on absolute values [20].

Thyroid disease is a common condition seen in psychiatric patients. In hyperthyroidism, an increase in alpha frequency and fast activity has been reported by different authors [20, 38]. In hypothyroidism, low voltage slow activity and poor or absent alpha blocking response have been reported [39].

Hypothermia accompanying myxoedema can also result in very low amplitude and slow activity [26]. Hashimoto's encephalopathy is characterised by behavioural disturbance, seizure and focal neurological symptoms; EEG changes include diffusely abnormal slowing with or without focal slow wave findings [40]. EEG changes in hypothyroidism may also show generalised periodic sharp waves similar to those in Creutzfeldt–Jakob disease, but these changes usually resolve with thyroid replacement therapy [41]. EEG

changes in adrenocortical sufficiency include diffuse slowing and an increased sensitivity to hyperventilation [42].

In acute porphyria, EEG changes are usually not present unless there are CNS manifestations. In these cases, delta frequencies, asymmetrical slowing and spike or sharp wave activity have been described. Epileptiform activity has also been described in up to 20% of acute porphyria cases, which can be associated with clinical seizures [20].

Infectious encephalitis and/or meningitis can be associated with various degrees of arrhythmic or rhythmic delta slowing and possible epileptiform activity. The degree of slowing varies based on the amount of cerebral involvement, the level of consciousness, the severity of the infection, and other metabolic or systemic factors [26, 43]. In cases when the white matter is involved, diffuse polymorphic arrhythmic delta activity can be present. Paroxysmal bilaterally synchronous slow wave activity can instead be present when the subcortical grey matter is involved [44].

Herpes simplex encephalitis is caused by herpes simplex virus type 2 in adults with a subtype of encephalitis having a mortality of 70% in untreated patients and 17% in treated patients. EEG findings in herpes simplex encephalitis are first characterised by disorganisation of the background rhythm, excessive intermixed delta activity and high amplitude periodic complexes, which at times can be focal or lateralised with predominance over the temporal region. Later on, focal sharp, sharp and slow complexes and/or spike activity can also be present over the temporal region [45, 46]. These complexes can evolve into a periodic pattern, with the sharp waves having a stereotyped appearance and recurring every 1–3 seconds. These patterns can occur between 2 and 5 days after the onset of the illness, but on occasion it has been observed up to 24 to 30 days after the onset of the illness [45]. The time course of the EEG changes is usually seen within 2nd–15th day of illness with rapid resolution after treatment [46]. The rate of resolution distinguishes herpes simplex encephalitis from other CNS disorders with similar appearing periodic complexes such as Creutzfeldt–Jacob disease and subacute sclerosing encephalitis [46].

Infectious causes of delirium

Subacute infectious disease can also cause distinctive EEG abnormalities. Creutzfeldt–Jacob disease (CJD, also known as subacute spongiform encephalopathy), can be classified as subacute infection dementia of infectious aetiology. Further details about CJD are in the dementia section (see below).

HIV is another example of a subacute infectious disease which can result in long-term cognitive impairment and/or dementia. Subacute encephalitis occurs in about 90% of AIDS cases [47]. EEG changes in patients with AIDS can be characterised by focal or generalised paroxysmal slowing, which at times can be associated with epileptiform discharges. EEG changes can be seen in association with the primary disease or in the presence of opportunistic infection [48].

Subacute sclerosing panencephalitis is a complication of measles virus infection, usually in children and adolescents. It is characterised by slowing of the background and high voltage (300–1500 mV) sharp and slow waves or polyphasic complexes lasting about 0.5 to 2 s, which often occur every 1–15 s [26]. These complexes can be present at any stage of the disease, they can vary in different stages of the disease process and can vary from patient to patient.

EEG abnormalities in neurosyphilis are seen in about 54% of the patients [26]. This increases to about 60–70% when paralysis is also present and to over 70% with dementia [26]. Common findings include an excess of diffuse slow wave abnormalities with a maximum over the frontal regions. Slowing can sometimes improve with penicillin [26]. At times, slowing can be focal and associated with epileptiform discharges [43].

Drug toxicity is another common cause of delirium. In particular, lithium toxicity should always be considered in a patient on lithium therapy who begins to experience lethargy, confusion, ataxia and/or myoclonus. EEG findings are usually characterised by excessive slowing of alpha rhythm and paroxysmal generalised slowing. Occasional spike activity, triphasic wave or focal slowing can be present, though focal slowing in this case is not correlated with a focal organic brain lesion. EEG changes might be correlated with clinical manifestations, although the EEG abnormalities usually last from days to months after the normalisation of serum level of lithium.

Clinical diagnosis and EEG work up in dementia

EEG is a valuable tool in the work up of dementia since it can distinguish dementia from delirium or a primary psychiatric diagnosis such as a mood, anxiety or psychotic disorder. Psychiatrists are frequently consulted on patients with behavioural disturbances, especially in the geriatric population, and are requested to comment on the possible origin of their symptoms. One major diagnostic challenge is the determination of whether a primary psychiatric disorder, a dementia, or both are contributing to these clinical manifestations. EEG can be part of a multidisciplinary approach to address this question. It can detect underlying co-morbidities that may play a role in the presentation, improve the diagnostic accuracy in patients with cognitive disturbance, provide prognostic information in certain cases of dementia, and guide clinicians in treatment planning. Clinical correlation is necessary as the timing of the process and associated symptoms are usually essential in distinguishing dementia from delirium. The accuracy of the EEG interpretation depends on the experience of the reader but, most importantly, on the history provided, so findings can be placed in the context of the clinical presentation.

The EEG in dementia is initially characterised by slowing of the background rhythm with a frequency less than 8 Hz. This pattern can sometimes be associated with decreased beta activity and intermixed excessive theta and delta activity, which varies in quantity depending on the severity. As the disease progresses, the background rhythm becomes more disorganised and, at times, even disappears. The cerebral mechanisms for most of these slowing patterns are unknown.

Table 10.4 Subtypes of dementia.

Cortical	Subcortical	Mixed (both cortical and subcortical features)
• Alzheimer's disease • Frontotemporal dementia	• HIV dementia • Parkinson's disease	• Vascular dementia • Mixed dementia (vascular associated with Alzheimer's)
• Creutzfeldt–Jakob disease • Normal pressure hydrocephalus	• Huntington disease • Progressive supranuclear palsy • Wilson's disease	

Dementias are categorised into cortical, subcortical and mixed presentations (see Table 10.4). EEGs tend to be relatively normal in patients with subcortical dementia, whereas they are abnormal in patients with cortical dementia [49]. Mixed dementias can also have abnormal features on EEG, similar to those of cortical dementias.

In the early stages of Alzheimer's disease, the EEG is characterised by a decrease in alpha and beta activity. In later stages, alpha activity can be minimal or non-existent [20, 26] while theta and delta activity increases and become more diffuse [20, 26]. Generalised bursts of slow activity can be usually seen found anteriorly. Not surprisingly, the severity of EEG abnormalities is associated with worse cognitive impairment [20]. Longitudinal analyses in AD patients found a trend towards increased theta and delta activity, but these do not occur in all patients as their disease progresses [20]. Some data indicate that the abnormal EEG during the early stage of disease predicted more severe decline. Many studies have investigated the use of EEG to distinguish AD from other types of dementias, but no consistent pattern has been identified [20].

Vascular dementia is the second most common dementia. Clinical manifestations are related to the area of interest in the brain and by the severity of the insult. EEG abnormalities in vascular dementia tend to correlate with the location of the infarcts and to be more sensitive to those lesions which are superficial and larger [20].

Frontotemporal dementia, previously known as Pick's disease, has two main categories. The first type is characterised predominantly by behavioural disturbance, which includes impaired interpersonal conduct, emotional blunting and limited insight. The second type is characterised by new onset progressive language disturbance in the context of accompanying behavioural changes [50, 51]. These behavioural symptoms are attributed to atrophy of the frontal and temporal lobes. Classically, few to no EEG changes are usually seen in frontotemporal dementia [20].

Creutzfeldt–Jakob disease (CJD) is characterised by rapidly progressive dementia [52]. Early symptoms include memory loss and behavioural changes. In later stages, there is significant cognitive loss, involuntary movement, muscle weakness and eventually coma and death. CJD is fatal, and about 85% of cases occur sporadically without any known genetic factor or known mode of transmission. Onset of the disease is about 60 years old, and about 90% of patients die within a year of diagnosis [52].

EEG is especially useful for the diagnosis of CJD. One of the most important classic findings of CJD is the distinctive periodic discharges. In the early stages of CJD, the EEG changes include disorganisation of the background activity with an increase in slow waves, which can be either focal or generalised. With progression of disease, periodic sharp-wave complexes or triphasic or biphasic waves are present every second. They can occur intermittently and, at times, predominate over one region. Discharges are usually diffuse and symmetrical, but early in the disease they can be asymmetrical and at times lateralised. EEG can also help to differentiate between CJD and AD, especially when myoclonus is present clinically. Though the EEG can present with disorganisation of the background in both conditions, the characteristic periodic discharges of CJD can help differentiate them. As with all psychiatric diagnoses, the clinical history and exam along with neuroimaging and neuropathology are necessary to confirm the diagnosis [53].

Parkinson's disease is characterised clinically by resting tremor, bradykinesia and rigidity. Other neuropsychiatric complications, including mood disturbances (most notably depression) and cognitive decline, are also quite common. Dementia can also occur in later stages of the disease in about 10–15% of patients [54]. Only non-specific changes such as slowing of background and increased of delta and theta activity have been observed in Parkinson's disease [20]. Progressive supranuclear palsy (PSP) is one of several Parkinson plus disorders. Namely, it is a movement disorder with Parkinsonian features that does not fit the clinical presentation of Parkinson's disease [51]. The key clinical feature of PSP is a vertical supranuclear palsy and prominent postural instability usually manifested as falls [51]. EEG findings in PSP are mostly non-specific, commonly including excessive theta activity and changes in sleep architecture [20].

The key clinical features of dementia of Lewy body (DLB) are Parkinsonian features, fluctuations of mental status between near normal cognition to that of marked confusion or decreased alertness and visual hallucinations [51]. Sleep disturbance from dysregulation of REM sleep cycles and wakefulness also occur frequently. Autonomic dysfunction is characterised by orthostatic hypotension, impotence, urinary incontinence and constipation. Many studies have investigated whether EEG can be used to distinguish AD from LBD but no specific EEG changes have associated with either [20].

Huntington disease is a neurodegenerative disorder that usually starts in adulthood. Patients usually suffer from chorea, dementia and personality changes. The cognitive dysfunction is usually a frontal-subcortical pattern, namely impairment in problem-solving, judgement and attention. Common psychiatric disturbances include impulsivity, affective instability, depression and psychosis. The inheritance pattern of this disease is autosomal dominant transmission of the trinucleotide CAG repeat expansion on chromosome 4. The subsequent overproduction of the *huntingtin* protein product leads to the formation of intranuclear inclusions and disrupts cellular function [51]. The EEG in Huntington disease is abnormal, with findings including poorly developed alpha rhythm, low voltage and either slow or fast activity [20, 26].

In normal pressure hydrocephalus (NPH), EEG can be normal or can present slightly excessive theta activity in milder cases to diffuse delta activity in severe cases [26]. EEG abnormalities can improve significantly after shunting [20].

Conclusion

In summary, the EEG can be a helpful tool in the diagnosis of delirium and dementia and in the differentiation of these entities from a primary mood, anxiety or psychotic disorder. An EEG should be considered in cases in which the differential diagnosis represents a challenge to the clinician as it can be an invaluable, non-invasive and relatively easy test to perform.

CL was a 55-year-old man in good health who one morning, instead of going to work, went into his home office where he was found by his wife pacing back and forth. When she asked him what he was doing, he stated that he was waiting for the aliens to pick him up. She immediately called an ambulance which took him to the Emergency Department (ED). On arrival, the patient was noted to be agitated: He was alert to person, but not to place or time. His mental status was waxing and waning throughout the interview. At times he was aware of 'not feeling well'; at other times he was pacing, asking to be left alone because, 'I am waiting for the aliens to pick me up'. He denied mood symptoms or other psychotic symptoms.

Past medical history and past psychiatric history were negative. He was on no medications.

Social history: He was married. Had no children. Lived with his wife. Worked as a CEO of a company.

Laboratory: complete blood count, electrolytes, blood sugar, renal function and CBC were all within normal limits. A urine toxicology screen for drugs of abuse was negative.

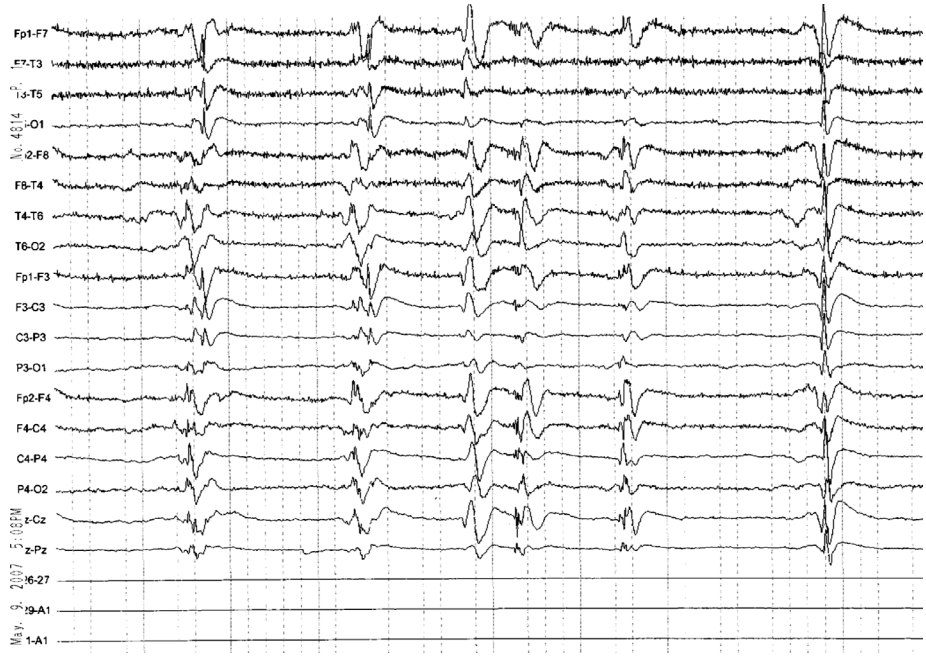

Figure 10.1

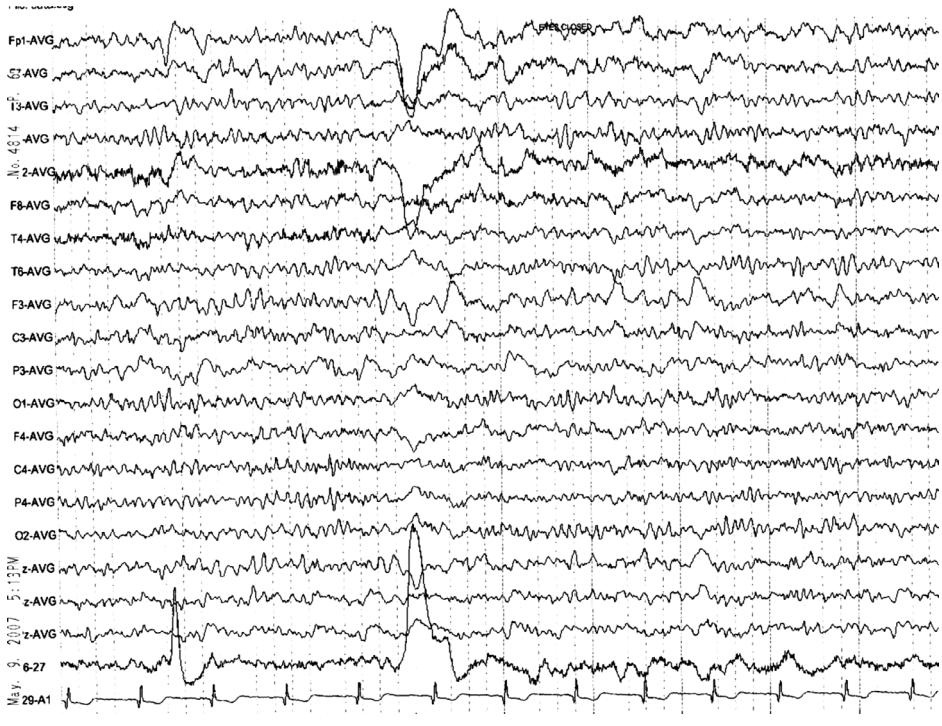

Figure 10.2

Head computed tomography (CT) was normal.

Because of waxing and waning mental status and disorientation to place and time, a diagnosis of delirium was made: in view of normal laboratory test results and a normal CT scan, nonconvulsive status epilepticus was suspected so an EEG was obtained (see Figure 10.1). The EEG showed intermittent bursts of spike and slow activity with a maximum over the temporal regions which improved with 2 mg of intravenous lorazepam (see Figure 10.2), with clinical resolution of his symptoms. The diagnosis of nonconvulsive status was confirmed. Interestingly, further diagnostic testing, including cerebral spinal fluid analysis, failed to identify an aetiology. A decision was made to initiate therapy with carbamazepine with no recurrence of events.

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11

Effects of Psychotropic Drugs on EEG

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Introduction

Since the discovery of the EEG, it was observed that drugs affecting behaviour also modify the EEG [1]. Several controlled studies have demonstrated specific EEG changes for different classes of psychotropic drugs, such as antidepressants or anxiolytics (for a review [2]). There is accumulating evidence indicating the usefulness of the EEG for the diagnosis of drug-induced CNS toxicity and epileptic conditions [3, 4].

The role of EEG assessment of drug-induced CNS toxicity in psychiatric patients

All drugs used in psychiatry might induce CNS toxic effects, particularly when polypharmacy is required for management of patients.

Toxic effects can occur at therapeutic doses when concomitant medical conditions interfere with drug metabolism and/or cause a potentiation of CNS toxicity, for example in elderly subjects treated with lithium a delirium due to encephalopathy can be precipitated by renal failure, dehydration following diuretics or adjunctive neuroleptic therapy.

In these cases, patients with schizophrenia or bipolar disorder might present only a slight deterioration of their clinical picture (e.g. agitation, misidentifications) which might not be easily distinguished from relapse of their psychiatric disorders. An EEG

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investigation may be useful to ascertain whether the clinical deterioration is related to an emergent condition: a concomitant encephalopathic process will be documented by diffuse slowing or the presence of triphasic waves and an epileptic condition by spike and spike-and-wave potentials [4, 5]. EEG can help in the differential diagnosis of delirium due to encephalopathy or non-convulsive status epilepticus (NCSE) (see [6], for examples).

CNS depression occurring with drug overdosing has no specific EEG signature and is associated with generalised slowing, progressive delta increase and isoelectricity if the depression progresses to coma. Patterns such as burst suppression mostly seen with barbiturates are considered to be less specific then believed in the past.

Antipsychotic drugs

Antipsychotic drugs are widely used in the treatment of patients with schizophrenia-spectrum disorders, affective disorders or dementia and are associated to an increased risk of epileptic disorders (see [2], for a review).

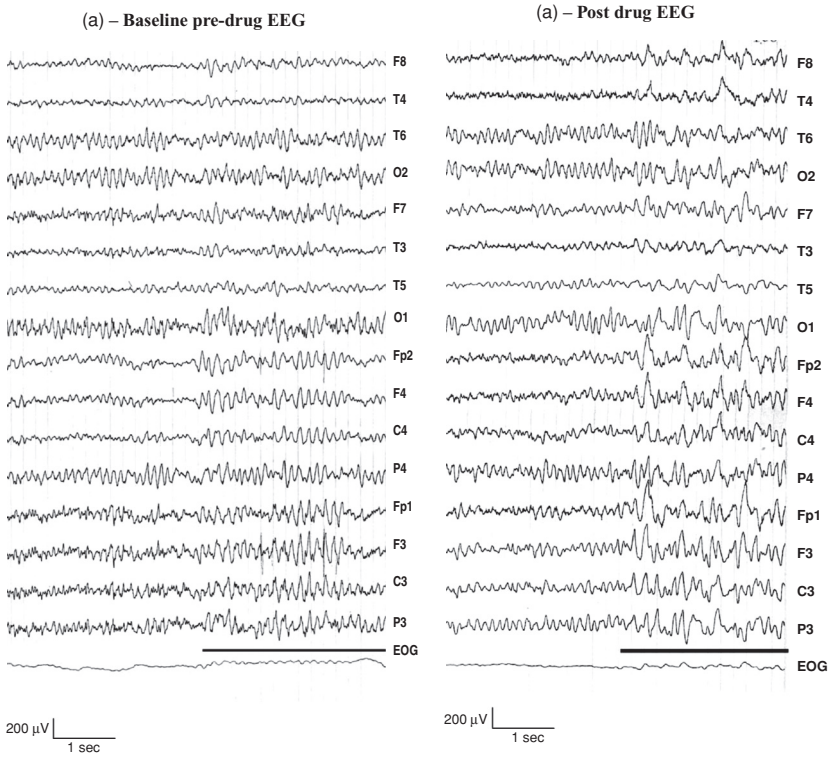

Figure 11.1 Haloperidol induced EEG abnormalities. RG, male, 31 years, chronic undifferentiated schizophrenia, baseline EEG (a) after 14 days of drug wash-out; post-drug EEG (b) 3 hours after a single dose of haloperidol. Example of paroxysmal theta at baseline (a, marked by a solid line) and paroxysmal high voltage sharp-and-slow-waves induced by haloperidol (b, marked by a solid line).

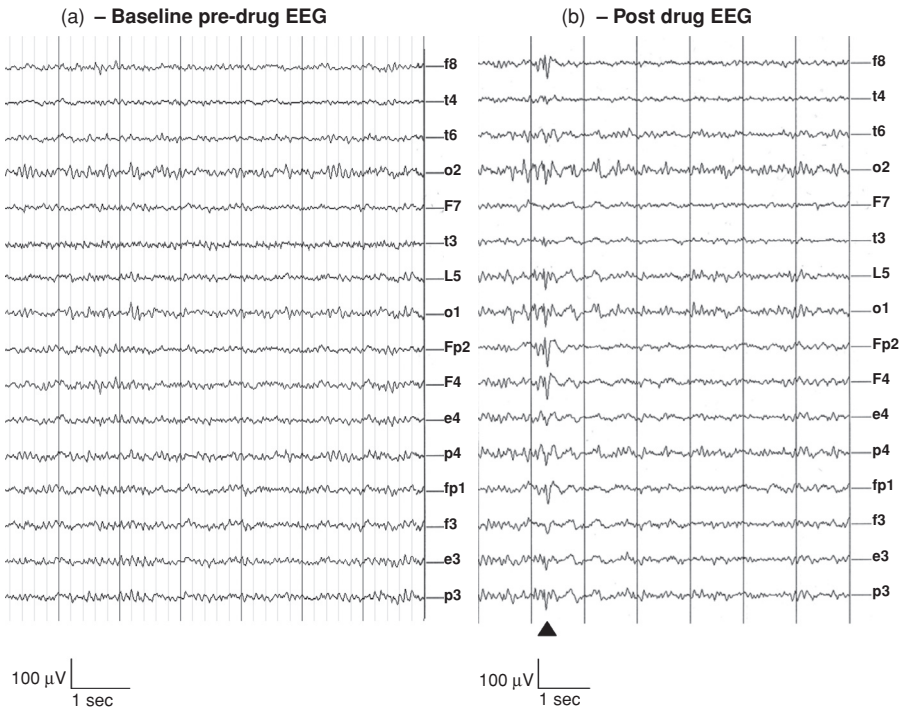

Figure 11.2 Clozapine induced EEG abnormalities. SN, female, 17 years old, first episode schizophrenia, drug-naïve, baseline EEG (a); post-drug EEG (b) 6 hrs after a single dose of clozapine. Example of paroxysmal high voltage sharp-and-slow-wave induced by clozapine (b, marked by an arrow head).

Amongst the first-generation antipsychotic (FGA) drugs, the low-potency compounds, such as chlorpromazine, are associated with the greatest risk of seizures and high-potency drugs, such as haloperidol, with the lowest. For high-potency FGA, the presence of epileptic abnormalities at baseline predicts the increase of epileptic potentials in post-drug EEG (Figure 11.1a and b).

For second-generation antipsychotic (SGA) drugs, only clozapine has been adequately studied and has been found to bear a high risk of epileptic seizures, while newer SGAs have not been studied to the same extent for their epileptic potential [7–9]. Clozapine induces a generalised slowing of EEG, which might be dose-dependent and epileptiform abnormalities (Figure 11.2a and b). Olanzapine has been associated to generalised slowing (Figure 11.3a and b), and occasional epileptiform activities, particularly with toxic effects, while risperidone and quetiapine seem to be associated with less frequent EEG abnormalities, comparable to those observed with high-potency FGA drugs:

- the choice of the antipsychotic drug should take EEG findings into account in patients with increased risk for epilepsy;

- adjunctive benzodiazepine treatment should also be considered in vulnerable subjects.

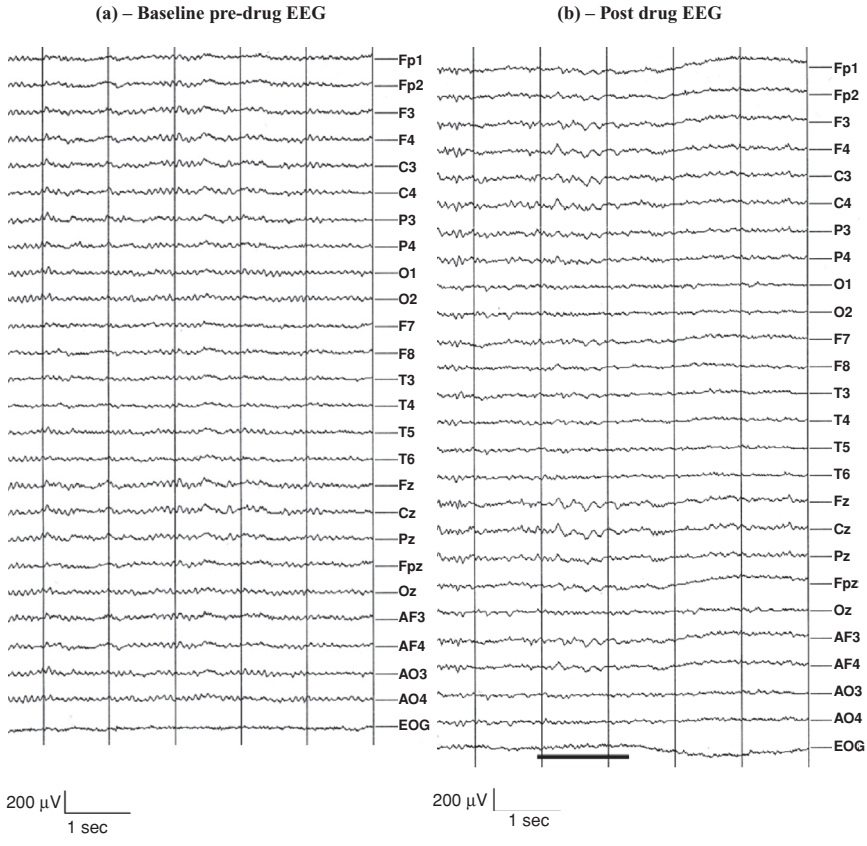

Figure 11.3 Olanzapine induced EEG abnormalities. FI, female, 24 years, disorganised schizophrenia, baseline EEG (a) after 14 days of drug wash-out; post-drug EEG (b) 6 hrs after a single dose of olanzapine. Example of slowing (delta activity) induced by olanzapine (b, marked by a solid line).

Lithium

Lithium is largely utilised for the long-term treatment of patients with bipolar disorders and its profile of multiple organs potential toxicity requires monitoring of the serum levels (therapeutic range: 0.6–1.2 mEq/l); however, CNS adverse effects, including NCSE, can occur at therapeutic serum levels [3, 10, 11].

Box 11.1 EEG and lithium toxicity

- Lithium can induce EEG abnormalities which correlate better than plasma levels with CNS toxicity. EEG signs of CNS toxicity during lithium therapy include:
  - slowing of alpha rhythm
  - paroxysmal delta and theta waves

- myoclonus occurring at therapeutic doses is associated with slowing of alpha frequency and paroxysmal theta.

- Lithium-antipsychotic combination might lower the threshold for toxicity in vulnerable individuals:
  - when baseline EEG abnormalities are present, start lithium at low doses and monitor EEG.
- EEG is useful in the differential diagnosis of lithium-induced delirium:
  - when NCSE is present, EEG shows epileptic abnormalities, clearing with BDZ administration
  - when a lithium-induced toxic encephalopathy is present EEG shows triphasic waves or slowing not improving with BDZ.

Other mood stabilisers

Antiepileptics are used as primary or adjunctive drugs in the treatment of affective, schizoaffective, anxiety and impulse control disorders. Some of them are associated with untoward CNS effects particularly when polypharmacy is required for management of refractory psychiatric disorders. They can produce CNS side effects when given in

Box 11.2 EEG and mood stabilisers

- Carbamazepine is the only antiepileptic drug which might increase or induce generalised paroxysmal activity and leave unchanged interictal spikes. During intoxication carbamazepine induces generalised slowing.
- Oxcarbazepine seems to normalise EEG: so far generalised epileptiform activity has been observed only in refractory subjects.
- Valproate induces slowing and reduces generalised and photosensitive spikes in epileptic patients:
  - EEG demonstrates bilateral high voltage slow waves during valproate-induced encephalopathy (often mediated by hyperammonaemia).
- Lamotrigine reduces epileptic potentials and does not slow background activity:
  - lamotrigine can induce NCSE and exacerbate myoclonic epilepsy.

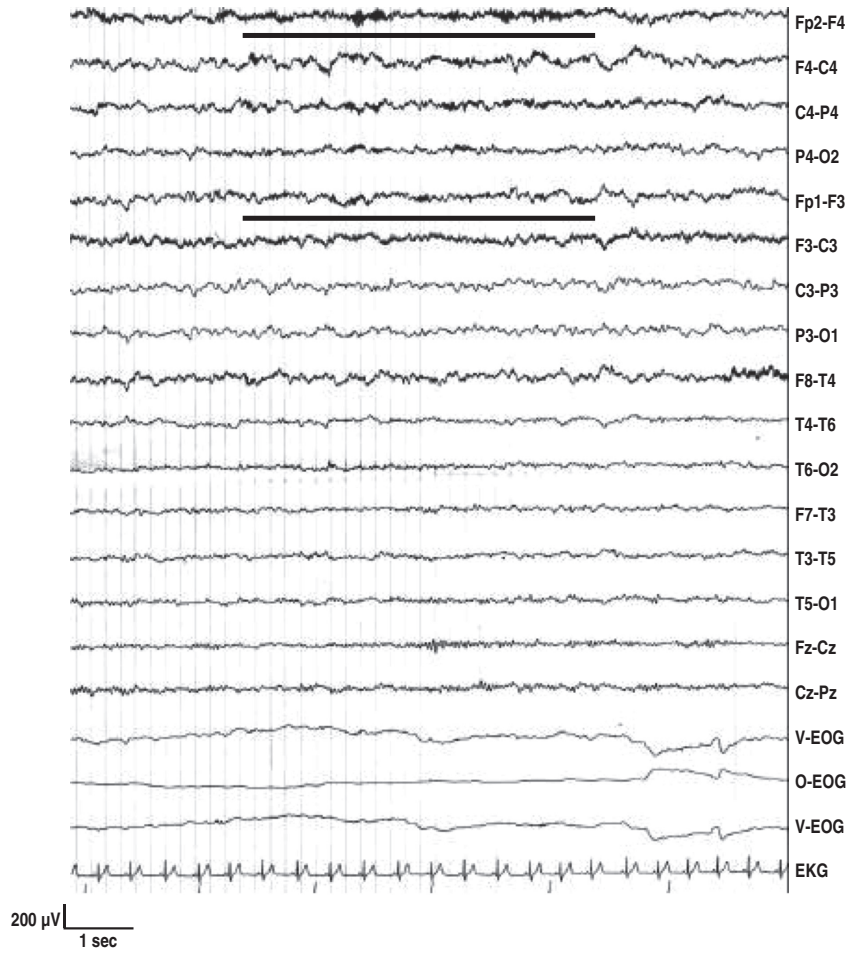

Figure 11.4 Benzodiazepine induced anterior beta. RG, male, 45 years, chronic residual schizophrenia. Anterior beta (25 Hz) induced by chlordemethyldiazepam (2 mg, per os), marked by solid lines.

combination with other drugs or when there are other medical conditions (hyponatraemia or hyperammonaemia) (for a review: [12–14]).

Anxiolytics

Benzodiazepines and barbiturates induce a diffuse increase of beta activity, most prominent over the anterior leads, and a decrease of alpha activity (Figure 11.4) [1, 12].

- Asymmetry of drug-induced beta indicates dysfunction in the side where beta is not expressed.

Antidepressants

Most antidepressant drugs, especially tricyclic but also selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs), might induce epileptic conditions, including myoclonus and NCSE, both in overdose and at therapeutic doses in vulnerable individuals. EEG changes associated with these side effects include generalised polyspikes and spike-and-slow waves discharges [4]. As a class they reduce alpha activity and increase slow and beta activity [2]. These changes do not index drug toxicity but are related to their pharmacodynamic properties.

Recreational drugs

Recreational drugs do not generally produce marked EEG alterations, except when causing toxic effects [5, 12]. Nonetheless, they cause EEG changes that are best characterised by quantitative EEG analyses [2, 5]. In acute overdose associated with coma, the EEG shows generalised slowing with many of the substances.

Box 11.3 EEG and recreational drugs

1. Hallucinogenic drugs, such as LSD, produce EEG changes similar to the choppy pattern seen in schizophrenia; those with anticholinergic activity also increase delta.

2. Morphine and similar drugs produce increase of high voltage delta.

3. Methadone in high doses can induce spikes and waves.

4. Cocaine and crack cocaine produce EEG slowing during acute intoxication.

5. Alcohol-induced delirium is associated with an excess of fast activity unlike delirium of different aetiology that is associated with generalised slowing.

6. Cannabis effects on EEG are best seen with quantitative methods and include an increase of alpha activity particularly over frontal regions (so-called alpha hyperfrontality) and a reduction of alpha frequency.

7. Chronic abuse of inhalation substances, such as glue or gasoline, might be associated to marked slowing of EEG when complicated by neurological or neurocognitive symptoms.

Case vignette

A patient of 54 years was admitted to the compulsory treatment unit of a University Psychiatric Department for psychomotor agitation. The patient had been treated for years for schizophrenia undifferentiated type (20 years before the present episode with electroconvulsive treatment (ECT) and more recently with haloperidol, last dosage 1 mg/day). She had type II diabetes treated with oral medications and insulin. At admission she appeared sedated and the doctor who had visited her at home and decided for the compulsory treatment had administered haloperidol 0.5 mg orally and chlordemethyl-diazepam 2.5 mg i.m. A few minutes after admission she presented with what seemed to be a kind of upper limbs stereotypies (she hit her chin with the left and right fist alternatively) and in 15 minutes she further deteriorated with mutism and incontinence. She had a negative history of seizure disorders and was doing well on medication for her diabetes. Blood sugar was 120 mg/dl, emergency toxicological analyses were negative, blood pressure was 120/80 mmHg and pulse frequency 80/min. The EEG showed diffuse depression of background activity with low-voltage polyrhythmic delta and superimposed disorganised fast activity, excluding a non-convulsive status epilepticus (Figure 11.5). She was transferred to the emergency department with a diagnosis of possible drug-induced toxic encephalopathy and given supportive therapy. CT scan was

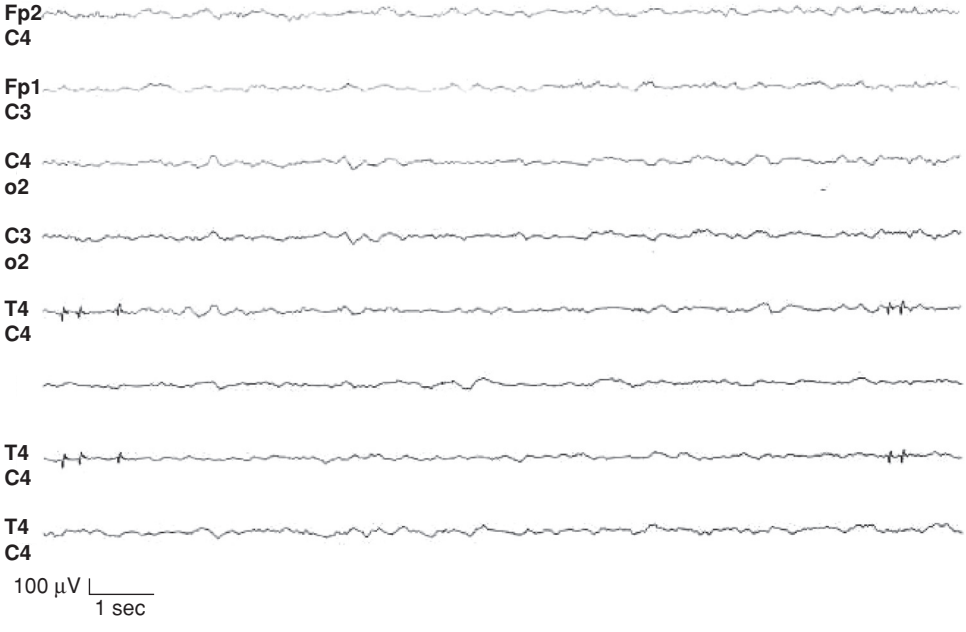

Figure 11.5 Drug-induced toxic encephalopathy. RDA, female, 54 years, chronic undifferentiated schizophrenia. Diffuse depression of background activity with low-voltage polyrhythmic delta and superimposed disorganised fast activity. She had taken unknown doses of haloperidol and oral medications for diabetes.

normal. She recovered completely in three days. Her mother informed us in the following days that she had probably taken three times her dose of haloperidol and oral medication for diabetes.

The above case demonstrates the fact that when the effects of a psychotropic drug become obvious to the naked eye, there is a good chance that the effect has approached or caused toxicity [15].

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12

Certification and Training in EEG and Clinical Neurophysiology

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The focus of this book has been on the standard visually interpreted EEG. As was clearly demonstrated in many chapters, the standard EEG has a very definite role in the diagnostic work up of psychiatric patients. This statement could not be made, at least not as forcefully, for other electrophysiological modalities like quantified EEG (QEEG), evoked responses including event-related potentials (EP/ERPs), or polysomnography. When these other modalities can be used to rule out medical or neurological causes for the psychiatric symptoms, then they also can be used similar to the standard EEG (e.g. ruling out sleep apnoea in a depressed patient). Hence, outside the ruling out of non-psychiatric causes for psychiatric symptoms, psychiatric electrophysiology remains a strictly research field. This probably contributes to the lack of mandatory training in electrophysiology for many psychiatrists.

Psychiatry trainees in the USA get NO exposure to any of the methodologies and the state of training in electrophysiology is summarised later.

Clinical neurophysiology board certification

In USA four board certifications exist but none has a clear emphasis on psychiatric disorders.

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- Added Qualification in Clinical Neurophysiology: This is the official board of the American Board of Medical Specialties (ABMS) and the American Board of Psychiatry and Neurology (ABPN). It administers a written examination covering clinical EEG, standard evoked responses like brain stem, visual and somatosensory responses. No ERPS (e.g. P300 or MMN). Also covers EMG, NCV and intraoperative monitoring of EEG and EPs.

- American Board of Clinical Neurophysiology (ABCN). Associated with the American Clinical Neurophysiology Society (ACNS). The examination includes four sections: written (passing is required before oral can be taken), oral I: clinical EEG, oral II: evoked potentials, practical: actual EEG records discussion. Same scope as for Added Qualification but light on the EMG/NCV.

For both Added Qualification and ABCN, in order to qualify for the examination, candidates have to meet the following requirements: MDs, a 12 months approved clinical neurophysiology fellowship; approved fellowships are ALL based in neurology departments and require a board eligible neurologist or neurosurgeon for admission. Hence *both are practically not available for psychiatrists.*

- American Board of EEG and Neurophysiology (ABEN). MDs or PhDs with documented training. Open to non-neurologists as well as physicians not holding a US medical degree. Scope is similar to ABCN but with some additional emphasis on abnormalities seen in psychiatric populations. This is the least sought after board and is almost inactive. This is not surprising in view of the existence of two main stream clinical neurophysiology (CN) boards (i.e. the ABCN and the Added Qualification) where neurologists, child neurologists and neurosurgeons can get qualified. On the other hand, the ABEN failed to reorganise itself to wholly represent the growing psychiatric electrophysiology discipline, which is depicted in Figure 12.1.

- Biofeedback Certification Institute of America (BCIA). Open to many professionals including registered nurses (RNs) and masters of social work (MSWs), PhDs, and MDs) with required training; heavy emphasis on Q-EEG and neurofeedback. Certification is open to professionals from clinical health care areas including, but not limited to, psychology, nursing (includes all licensed RNs), counselling, and therapy who hold a degree from a regionally accredited academic institution, that is an Accredited Institution of Postsecondary Education as determined by the American Council on Education.

In Europe the situation is not better than in the USA.

- In Switzerland, training in electrophysiology for medical doctors is provided by postgraduate schools of specialisation in clinical neurophysiology or in neurophysiopathology. However, the degree obtained from these schools is not mandatory for EEG

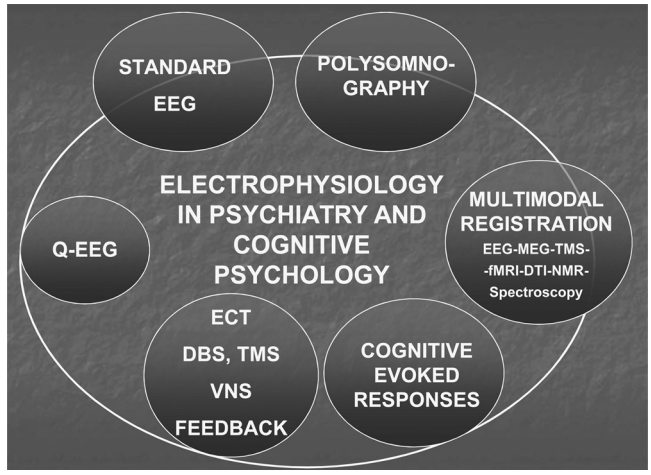

Figure 12.1 An overall view of the scope of the field of psychiatric electrophysiology. Areas outside the main circle represents other disciplines that use the same methodology. The best two examples are pulmonology/sleep disorders medicine using polysomnography for evaluation of breathing disorders of sleep and neurology using EEG to evaluate neurological syndromes.

recording and interpretation; as a matter of fact other medical doctors experienced in the field can take this responsibility.

- In Italy, training in clinical neurophysiology is clearly defined only for the postgraduate schools of specialisation in neurophysiopathology. The status of this speciality is very uncertain at the present time, and the possibility that training schools in neurophysiopathology disappear to become part of the neurology training schools is being discussed. So far, the medical doctor with this specialisation must have acquired knowledge in the field of physiology and pathology of the nervous system, with special reference to instrumental diagnostic of nervous and muscle pathology and to techniques relevant to the ascertainment of cerebral death and to the pathophysiology of vigilance and consciousness. The majority of Italian psychiatrists never receive a training in electrophysiology and therefore are unfamiliar with EEG and its clinical applications in psychiatry. Neurologists are in many, but not in all, cases trained in EEG procedures and clinical applications. The standardisation of recording procedures is not yet satisfactory. No specific degree, obtained from any school of medicine, is mandatory for EEG recording and interpretation. Different medical doctors, if experienced in the field, can take the responsibility of recording and interpretation of clinical neurophysiology tests. No clear recommendations are available about the practice of recording and interpreting neurophysiological data.

- In Germany, training in electrophysiology for medical doctors is commonly provided by neurological or psychiatric hospitals. The qualification to perform the education

of medical doctors is awarded to medical doctors in person. It is accredited by the German Society for Clinical Neurophysiology and Functional Imaging. The training comprises theoretical teaching, performing EEG recordings and the evaluation and interpretation of a specific number of EEGs. Medical doctors completing this curriculum receive an official EEG certificate provided by the German Society for Clinical Neurophysiology, which is generally required for leading positions in departments of psychiatry or neurology but not mandatory for reimbursement by the health insurance for electrophysiological recordings. Within the specialisation in psychiatry the educational institute providing the training must certify the EEG education. During this education, trainees are required to analyse and interpret at least 150 EEG recordings. However, a specific content of the EEG education is not regulated. Although many German psychiatrists do not receive a comprehensive training in electrophysiology, most of them have access to EEG facilities and are at least familiar with the major clinical applications of EEG in psychiatry (e.g. exclusion of organic/epileptiform disorders). Most neurologists are adequately trained in EEG procedures and clinical applications, while for psychiatrists the standardisation of recording procedures is far from satisfactory.

- In Turkey, the situation is quite different for neurology and psychiatry. In fact, in neurology, standardisation and training is pretty well established and all neurologists are automatically certified if they spend some time in their EEG units during residency training. In psychiatry none of the components are well established.

Contrary to the current trend to reduce the EEG education, the core curriculum of psychiatrists should include training in electrophysiology, at least covering the basic aspects described in this book. We would also advocate the creation of a subspecialty of clinical electrophysiology within psychiatry, based on the availability of:

- a defined body of knowledge (this textbook is a definite step in this direction);

- training programmes including education on the proper use of EEG in diagnosis and management of patients with psychiatric disorders and the acquisition of basic skills in qualitative and quantitative EEG and event-related potentials recording and interpretation;

- examination and certification process, to be carried out by an International Board for NeuroBehavioral Electrophysiology (IBNBE) to be created. It might be an umbrella organisation, including several existing associations which share interest for electrophysiology and neuroimaging in Psychiatry and behavioural neuroscience, promoting standardisation, qualifications and training requirements amongst different countries.

The training proposed by IBNBE should be designed for psychiatrists and neurologists with documented psychiatric training. It should be emphasised that in the USA,

neurology training does not include any official exposure to psychiatry. Many neurology residents do elect to spend some time usually 4–8 weeks in psychiatric settings.

As can be seen from the above figure, areas of overlap exist that could represent potential grounds for conflicts of interests in territorial disagreements. The current field of sleep disorders medicine is heavily focused on evaluating and treating sleep disordered breathing. Where psychiatric interest in sleep studies is focused is in the ability of sleep EEGs to differentiate between psychiatric disorders (e.g. delusional depression vs. schizophrenia), and identify neuropsychiatric disorders (e.g. nocturnal panic attacks). The psychiatric questions remain largely in the research arena while the sleep medicine issues are all widely accepted clinically. Another, and even perhaps more contentious area of overlap is with clinical neurophysiology and the standard EEG (which is the focus of this entire text. Indeed if the two disciplines of neurology and psychiatry fully recognise the significant overlap of the fields (both being related to brain disorders), then such conflict may not have grounds as current clinical neurophysiology labs would provide the service and be nourishing environments for research in both neurophysiology and psychiatric electrophysiology. As of the writing of this text, this scenario does not seem very likely. Indeed, as of now, psychiatrists in the USA are not eligible to sit for either of the two mainstream CN boards. This obvious overlap need not create major conflict as psychiatric electrophysiology labs would provide clinical services only for patients presenting with psychiatric complaints. A parallel board should also be developed for PhDs with significant training in psychiatry.

MD training should include: a two-year fellowship (PGY-IV and V) aimed to develop a sufficient understanding of basic neurophysiology; proficiency in clinical EEG of individuals with psychiatric problems (age down to 3 Y/O); proficiency in recording and analysing quantified EEG of individuals with psychiatric problems (age down to 3 Y/O), with a sufficient understanding of the complexity of the data analysis and statistical procedures involved; proficiency in recording and interpreting sleep EEG studies for the purpose of psychiatric differential diagnosis or treatment prediction and monitoring; proficiency in recording and interpreting evoked potentials studies for the purpose of psychiatric differential diagnosis or treatment prediction and monitoring; significant exposure to therapeutic techniques like ECT, TMS, VNS, DBS and neurofeedback. This exposure should be sufficient to enable an individual physician to get involved or obtain additional training to start a programme in one of these areas.

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