Activation Procedures

14

Oriano Mecarelli

14.1 Hyperventilation

HyperVentilation (HV)–or overbreathing (synonym)–is the first described EEG activation procedure, always used in clinical EEG laboratories; it is recommended as part of the standard EEG recording by the most prestigious international guidelines [1, 2]. The procedure is easy to perform and very safe [3, 4] and, in most cases, is able to induce the appearance of interictal or ictal epileptiform discharges [5]. Gibbs and colleagues already described in 1935 that HV was able to determine the appearance of a 3 Hz SW discharge, associated with absence seizure [6].

This method consists of seriated acts of deep and regular breathing, performed for a minimum of 3 min at a rate of about 18–20 breaths per minute, with the EEG recording lasting at least 1–2 min after cessation of overbreathing [1, 2]. In special cases, it is necessary to continue the recording even for longer periods after stopping HV. A recent large-scale study [5] showed that HV prolonged for 5 min increased the diagnostic yield of HV (16% of seizures and 30% of interictal EEG abnormalities triggered by HV occurred after 3 min of HV) and that 99% of patients who are able to hyperventilate for 3 min can complete a 5 min HV, without additional adverse events.

Adult subjects generally ensure a good cooperation in HV execution, even though the technician should give very precise and comprehensible instructions and supervise carefully that the procedure is carried out appropriately. The EEG technician should, therefore, ask the subject to breathe faster than normal (with deep inhalation, prolonged and intense exhalation, with semi-open mouth), and he should always write down an assessment of the quality of patient's efforts, throughout the HV procedure.

HV can be normally carried out in children older than 5–6 years; younger children generally indeed perform HV discontinuously and irregularly and the manoeuvre could therefore be useless or even counterproductive. It should also be remembered that, in very young children, EEG changes similar to those obtained with HV are observed during prolonged crying. Finally, the technician should inform the subject that, during the HV test, he sometimes might experience symptoms, such as tingling limbs, dizziness and blurred vision, but these should not prevent the continuation of the test, being these mostly negligible and transitory.

HV is contraindicated in severe cardiac or pulmonary diseases, recent stroke or myocardial infarction, intracerebral or subarachnoid haemorrhage, hyperviscosity state, sickle cell anaemia, uncontrolled hypertension, severe carotid stenosis and Moyamoya disease [7]. Contraindication should however be evaluated in each case, and chronic cardiovascular and respiratory diseases in older patients do not always exclude the possibility of HV execution.

14.1.1 Normal EEG Changes Induced by HV

The characteristic EEG response to HV, most evident in children and young subjects, consists in a slowing of posterior dominant background rhythm and in a fluctuating, bilaterally synchronous, slow activity. The slowings induced by HV are dominant posteriorly in children and anteriorly in adolescents and young subjects (Fig. 14.1), the incidence and magnitude of these slowings depending on the efforts during the test and on age. The age of subjects is an important factor for the magnitude of HV response, since the most evident EEG slowings are observed between 8 and 12 years. Approximately 10% of young adults and 70% of children show a physiological response to HV [7], with a remarkable interindividual variability. After HV interruption, EEG generally returns to basal conditions in <30 up to 60 s; sometimes, especially in children, the tracing does not revert to baseline, because the subject continues actually to hyperventilate, even if discontinuously. Very often, in children, HV causes the appearance of

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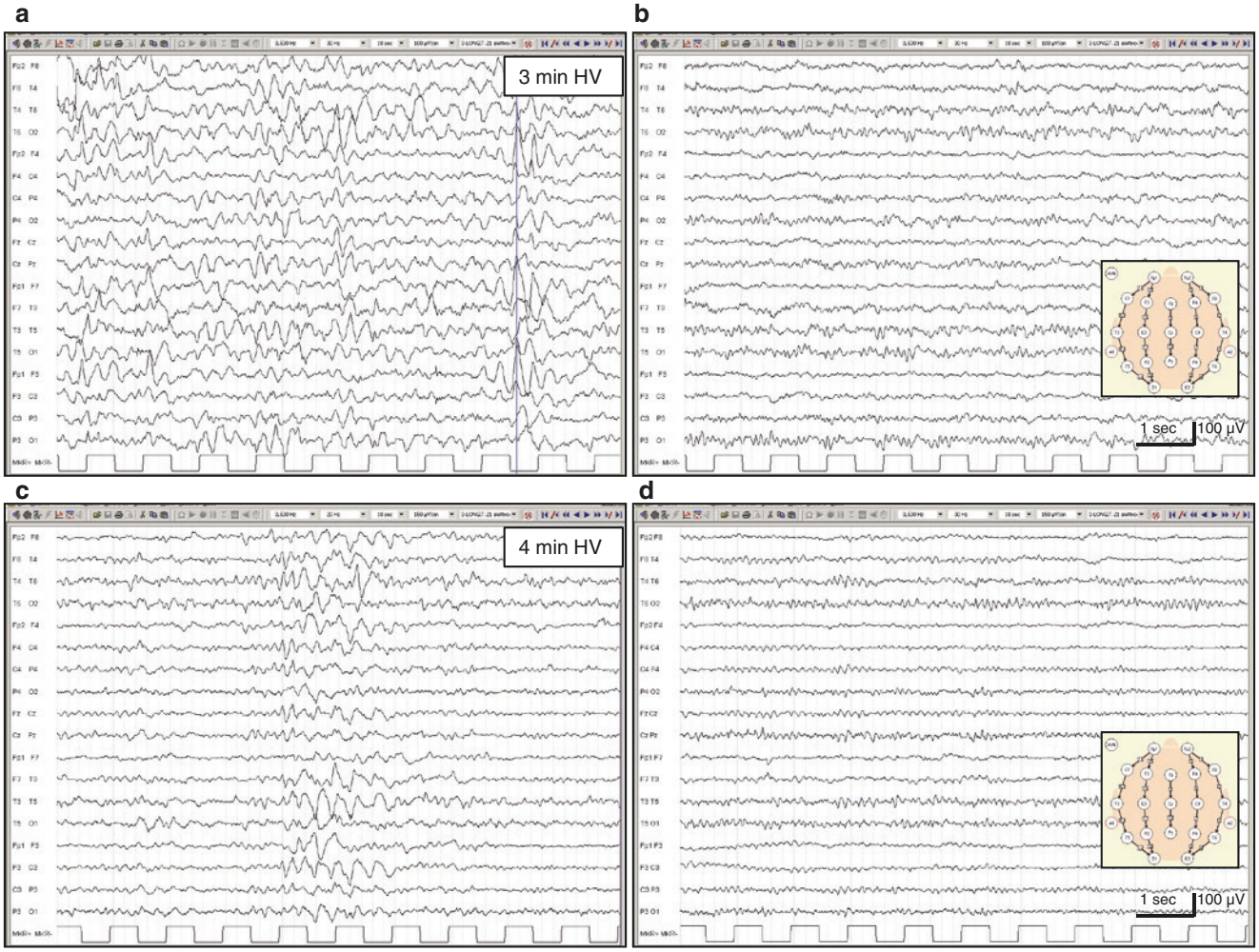

Fig. 14.1 Physiological EEG changes induced by HyperVentilation (HV). Sequences of delta slowings, dominant posteriorly, after 3-min HV, in a 7-year-old child (**a**); basal reverting of EEG recording 30 s after HV end (**b**). Burst of delta waves dominant anteriorly after 4 min of HV in an 18-year-old subject (**c**), with EEG return to basal condition after 20-s HV end (**d**)

a slow (2–5 Hz) high-amplitude hypersynchronous activity, even with paroxysmal morphology (*HV-Induced High-Amplitude Rhythmic Slowing, HIHARS*), which generally promptly disappears at the interruption of the test (within 30–60 s) (Fig. 14.2). Children with HIHARS sometimes present altered responsiveness and automatisms during the test, but these symptoms are not correlated with epileptic typical discharges [8–10]. Other relevant factors in determining the EEG slowings are the blood glucose level (hypoglycaemia can induce delta waves during HV, particularly if it is less than 80 mg/dL) and the upright position, as compared to the reclining position [11].

Diffuse intermittent rhythmic delta activity during HV may be also observed in young adults with recurrent vasovagal syncope. These distinctive EEG changes, a common finding in syncope patients, should not therefore be confused with any abnormal slow pattern or epileptiform activity [12] (Fig. 14.3).

14.1.2 Abnormal EEG Changes Induced by HV

The EEG changes elicited - or increased - by the HV can be represented by focal and/or diffuse slowings and by epileptiform abnormalities (Figs. 14.4 and 14.5). Classically, HV is considered to be the more effective activation test in the majority of cases (80–90%) of untreated generalised epilepsy with absences of childhood. In these cases, HV induces the appearance of typical diffuse SSW discharges at 3 Hz, related or not to clinical seizures [5, 7, 10, 11]. Furthermore, HV may activate atypical SSW discharges in approximately 50% of patients with symptomatic generalised epilepsy who are able to perform the procedure correctly. Focal epileptic seizures can also be triggered by a correctly performed HV, even though in significantly lower percentages (seizures originating from the temporal lobe are more easily activated by HV compared to the frontal ones) [13]. Beyond the facilitation of electroclinical discharges,

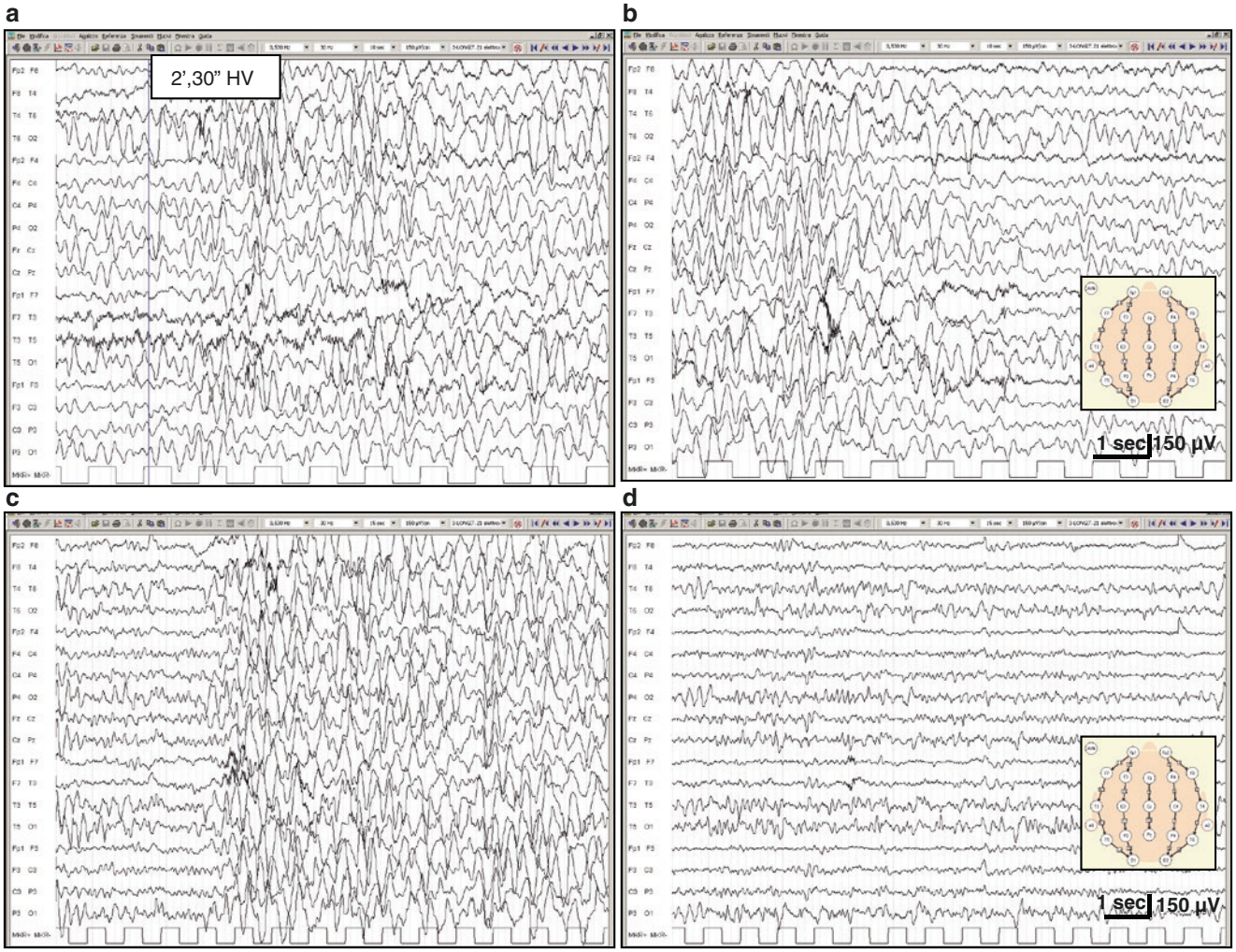

Fig. 14.2 Two examples of hyperventilation-induced high-amplitude rhythmic slowing, in a 6-year-old (**a**, **b**) and 7-year-old child, respectively (**c**, **d**). In (**b**) a gradual reappearance of normal background activity 40 s after the HV stop is observed, while in **d** the EEG normalisation is earlier, 30 s after the end of the activation procedure

HV may also increase interictal epileptic abnormalities already present in the baseline tracing, or allow identification of previously unreported epileptic foci [3, 4]. Focal epilepsies are relatively resistant to HV activation in adolescent and adults and, in these cases, a 5 min HV is recommended [7]. However, some studies report contrasting views regarding the utility and effectiveness of HV in this type of epilepsy. The existing literature describes a yield of 6–11% in focal epilepsies and a recent population-based study found that the yield of activation-related epileptiform abnormalities accounted for 7.9% on the first EEG, higher in children and in generalised seizure types [14].

HV can be avoided if abundant epileptiform activity on the pre-HV baseline EEG is already present. The technician should consider that, during the HV, an epileptic seizure (generalised or focal) might occur. In this event, he will try to continue the recording and to test the level of consciousness of the subject. The ideal solution in these cases is always to start a video-EEG registration, if available in the laboratory.

For the clinical interpretation of HV-induced slow EEG changes, a few simple guidelines should be followed. HV-induced slowings should be considered abnormal when the slowings are significantly asymmetrical (2:1 ratio) or with superimposed spikes and when the slowings persist for several minutes after the command to stop hyperventilation.

In children with Moyamoya disease it was reported, about 5 min after HV cessation, a "re-buildup" of slow waves, in correspondence with a decrease of cerebral blood flow. In this view, HV should be avoided in patients with Moyamoya syndrome [15].

Finally, HV is very effective (as other suggestive manoeuvres) to activate Psychogenic Non-Epileptic Seizures (PNES). According to Abubakr et al. [16], more than one-third of patients with PNES may have events precipitated by

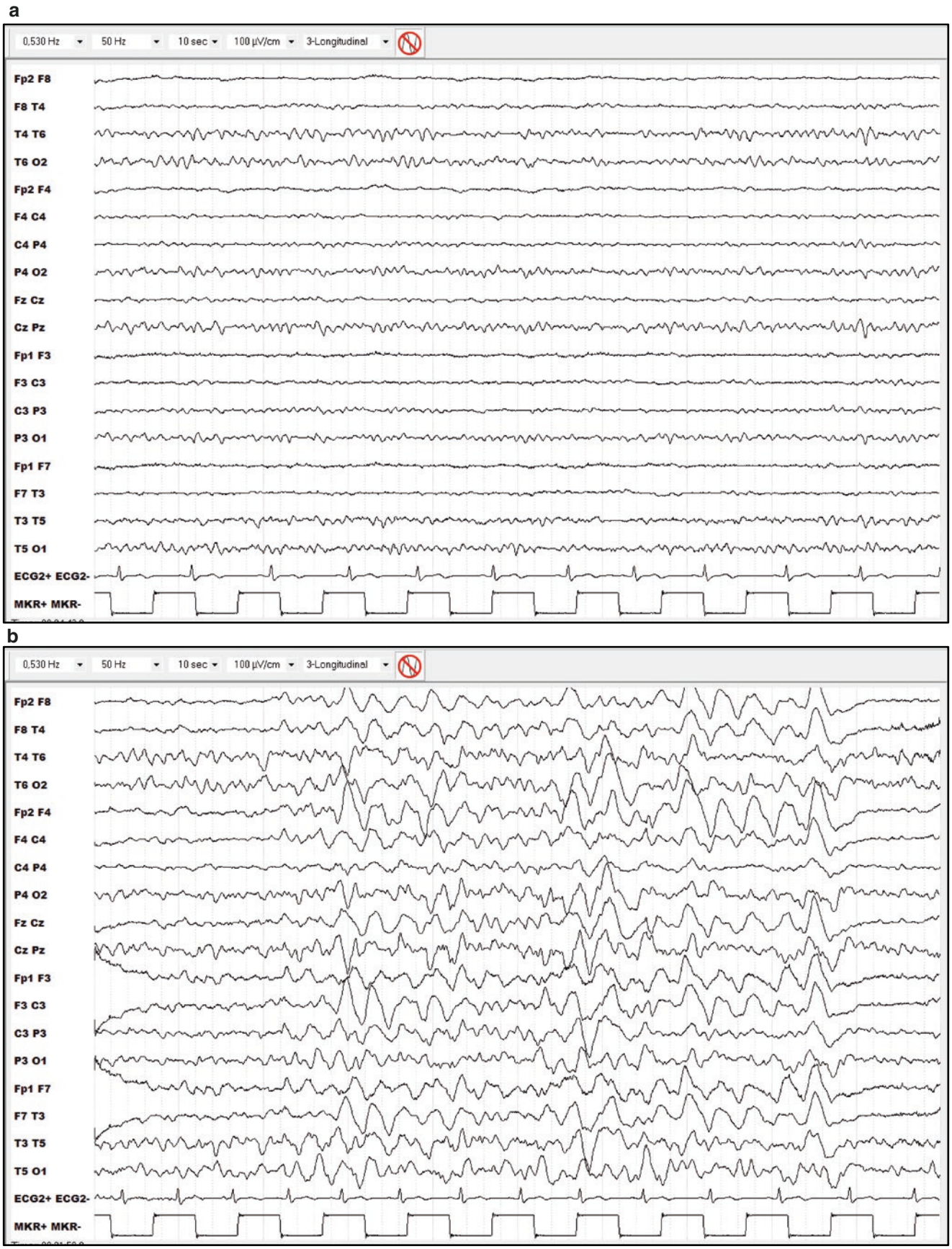

Fig. 14.3 Normal basal EEG (**a**) and slow diffuse hypersynchrony after 3-min hyperventilation (**b**) in an 18-year-old subject with recurrent neurally mediated syncopes

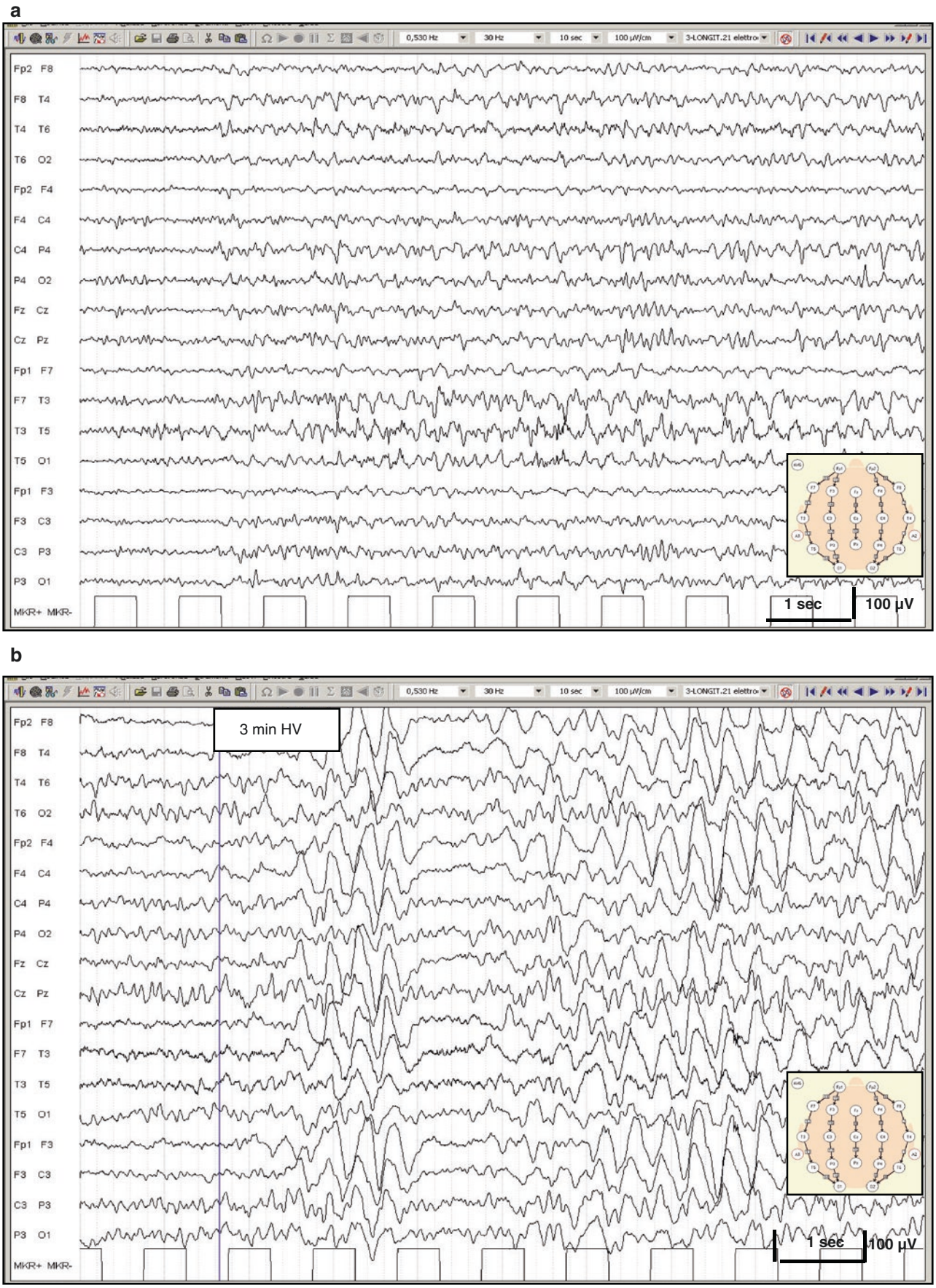

Fig. 14.4 (**a**) Focal hyperventilation-induced slowings in the left anterior temporal region in a 48-year-old patient with a brain tumour. (**b**) Diffuse and rhythmic high-amplitude delta activity dominant anteriorly, in a 26-year-old patient with generalised genetic epilepsy on antiepileptic treatment

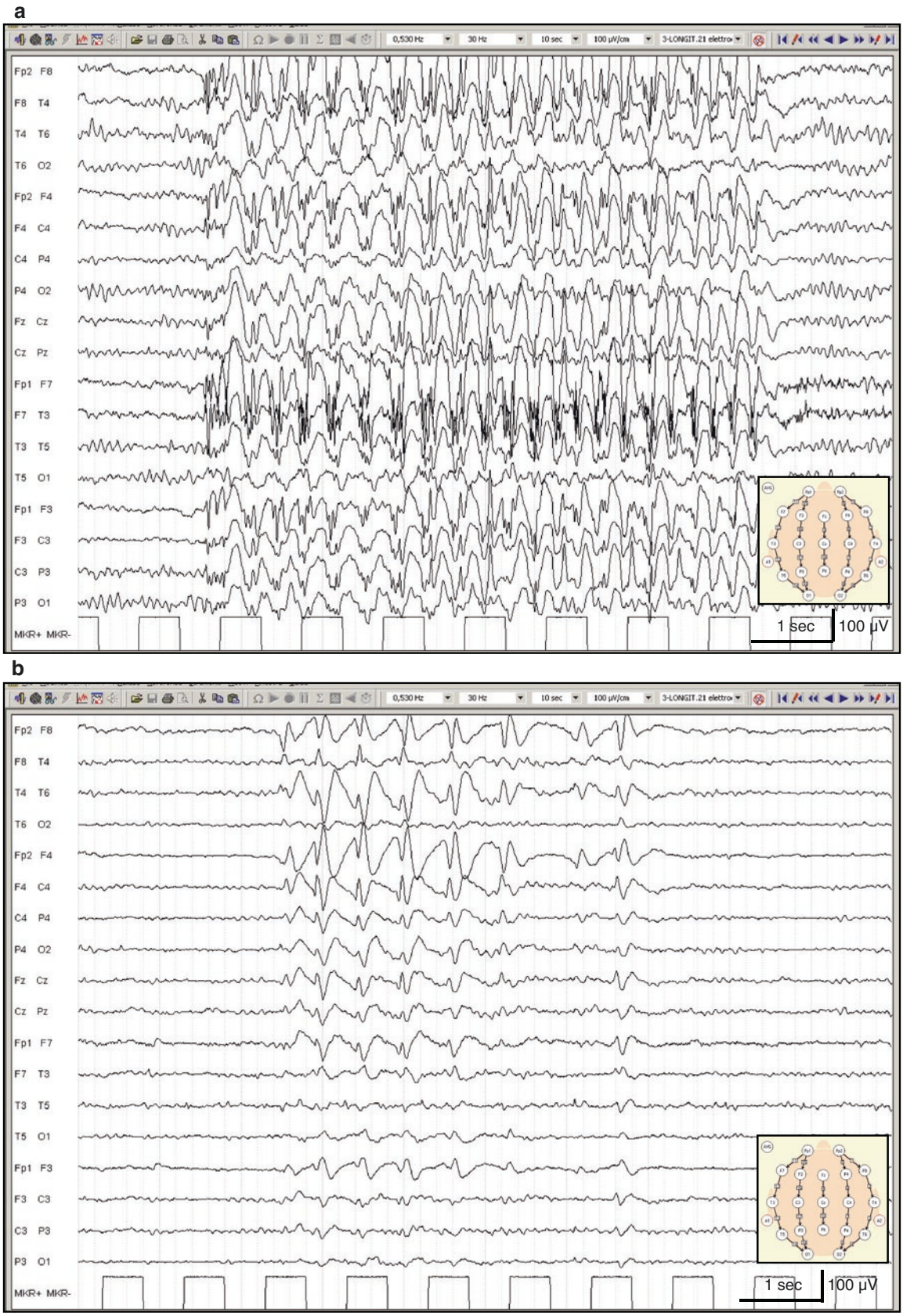

Fig. 14.5 Epileptic hyperventilation-induced abnormalities. (**a**) Generalised discharge of spike- and polyspike-and-wave complexes at 3 Hz in a 16-year-old adolescent 150 sec after the beginning of the procedure; typical discharge is correlated with absence seizure. (**b**) Interictal hyperventilation-induced focal discharge of sharp wave-and-slow wave complexes in a 36-year-old adult with right frontotemporal post-traumatic lesion and focal epilepsy

Table 14.1 HyperVentilation (HV): modality of execution and synthesis of EEG changes

Hyperventilation	Methods and activated EEG pattern
Patient	Sitting or reclining position; relaxed environment
Modality of execution (breath)	Deep inhalation and prolonged and intense exhalation, with semi-open mouth; 18–20 breaths per minute
Duration procedure	3–5 min
Normal EEG changes	Slowing alpha rhythm Diffuse slowings (>in posterior regions in children; >in anterior regions in young): – Variable entity (depending on the age, individual characteristics, etc.) – EEG return to baseline within <30 up to 60 s
Abnormal EEG changes	Focal and/or diffuse slowings not justified by age and of considerable entity Relevant asymmetries EEG return to baseline very late Epileptiform abnormalities (interictal or ictal): >Generalised (>SW discharges at 3 Hz), more rarely focal

HV. In these cases, the absence of EEG abnormalities is essential to clarify the non-epileptic origin of the behavioural manifestations [17].

Table 14.1 synthetizes the modality of execution of HV and the various EEG changes induced by this activation procedure.

14.1.3 Pathophysiological Changes Induced by HV

In healthy individuals, the primary effect of HV is a decrease in carbon dioxide (CO_2) in the alveolar area. CO_2 is present in small quantities in the air we breathe, but it is also produced by metabolic activity and eliminated through the lungs. When blood CO_2 increases (e.g. as in the case of physical activity), the brainstem breath centres induce an increase in lung ventilation to eliminate the CO_2 excess. This mechanism can be stimulated voluntarily increasing the frequency of breaths/minute. In this case, blood pCO_2 reduces from the normal values of 40 mmHg to 20–30 mmHg (hypocapnia); furthermore, the CO_2 reacts with the fluids to form carbonic acid, with a consequent increase in the pH of 0.20 units (alkalosis). Achenbach-Ng et al. [18] have studied the changes in blood gases and EEG in healthy adult subjects before, during and after HV. The mean pCO_2 reduced to 18 mmHg from the baseline during HV and recovered in 7 min. The mean pO_2 increased to 7 mmHg during HV and reduced to 25 mmHg below baseline 5 min after the end of HV. The changes of EEG median power frequency showed

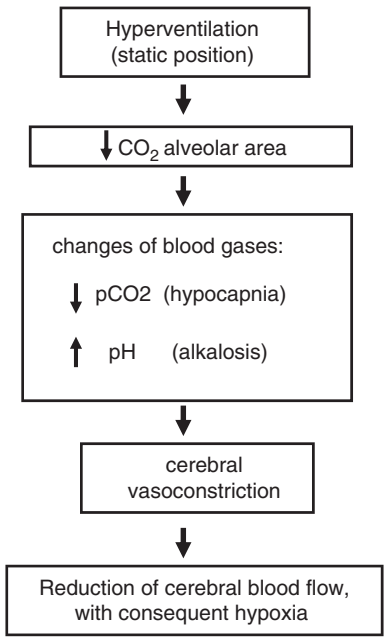

Fig. 14.6 Hyperventilation-induced metabolic and vascular changes, according to the theory of cerebral hypoxia

marked variability; on average, the median frequency dropped 1 Hz during HV and returned to baseline within 2 min of normal breath resumption. The changes in pCO_2 and blood pH determine a cerebral vasoconstriction, with a consequent reduction of blood flow (minimum 30%) and hypoxia while, at the peripheral level, there is a vasodilatation with decreased blood pressure, less blood return to the brain, slower elimination of brain CO_2 and restoration of normal carbon dioxide pressure (Fig. 14.6). Studies performed by transcranial Doppler [19, 20] have confirmed a reduction of up to 50–60% of cerebral blood flow during HV in the middle cerebral artery (Fig. 14.7). According with these studies, the decrease of the pCO_2 and the reduction of cerebral blood flow during HV are the fundamental factors inducing EEG slowings. It should be added that the decrease of cerebral flow does not only provoke the reduction of the concentration of O_2, but also induce a decrease in the glycaemic rate, both mechanisms responsible of the EEG activation. In addition to the blood flow decrease, hypoxia is also determined for the Bohr effect, the phenomenon whereby oxyhemoglobin increases in alkalosis conditions its affinity for O_2, which is then exchanged with higher difficulty to the tissues. Hypoxia can then lead to a greater nerve cell anaerobic glycolysis, as it results from the increase of the lactate/pyruvate ratio and, therefore, from the tissue acidity.

The theory of cerebral hypoxia is still the most accredited as the fundamental cause of the appearance of EEG abnormalities during forced HV, but it is not free from criticism and it is not universally accepted.

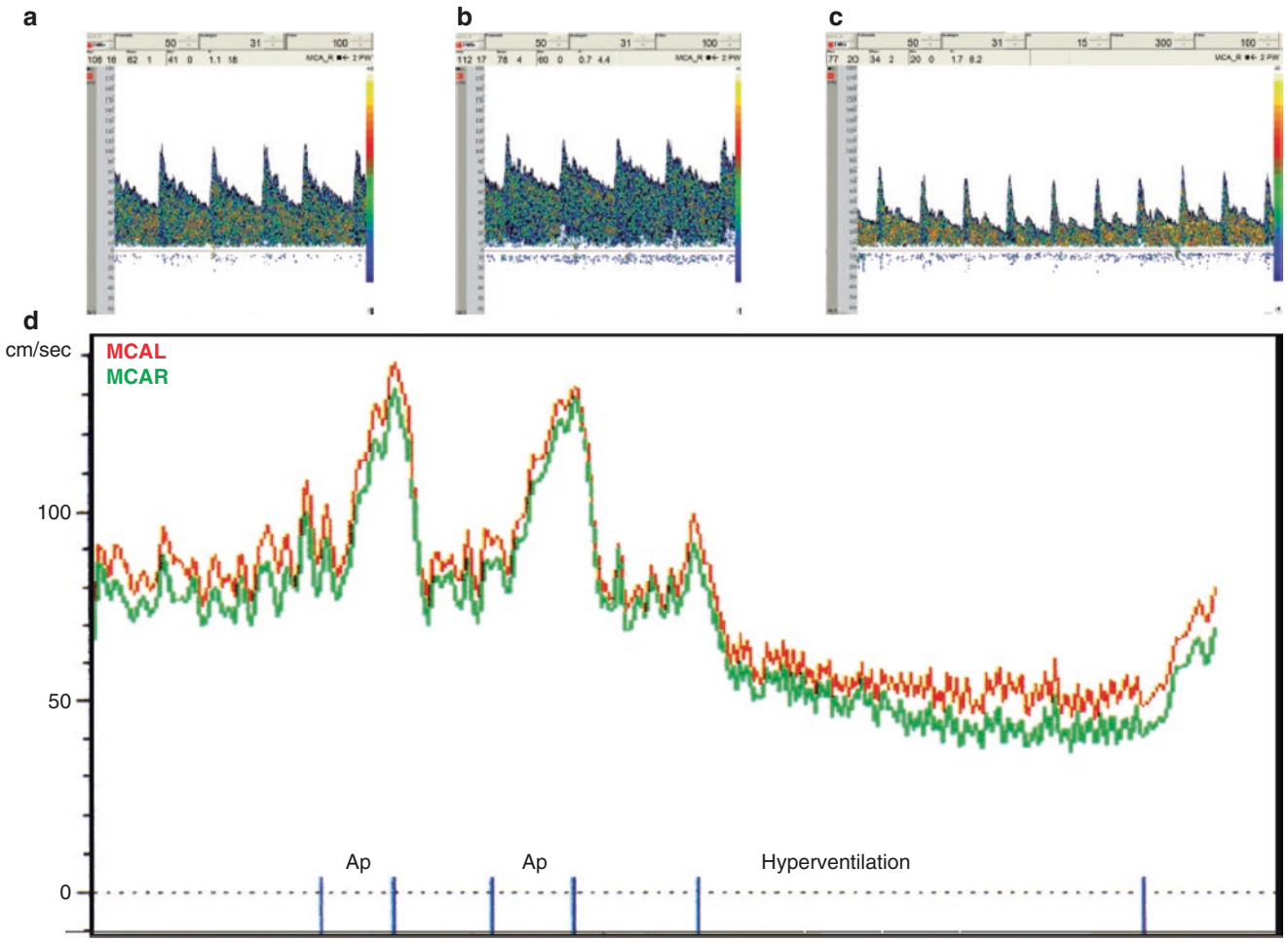

Fig. 14.7 Transcranial Doppler showing variations of cerebral blood flow velocities in the middle cerebral artery during apnea (Ap, **a**, **b**) and hyperventilation (**c**). Apnea induces vasodilation with increase of blood flow velocities. Hyperventilation induces vasoconstriction with the reduction of blood flow velocities. In **d** the throughout middle cerebral artery monitoring during two apnea trials (Ap) and a hyperventilation is shown. Note the green and red lines indicating blood flow mean flow velocities changes (cm/sec) in the left middle cerebral artery (MCAL) and in the right middle cerebral artery (MCAR).

Van der Worp et al. [21] compared, in healthy subjects, EEG changes and mean cerebral artery flow during hypocapnia (induced by voluntary hyperventilation) and during progressive normobaric hypoxia. The slow activity increase was less pronounced during hypoxia in comparison with HV-induced hypocapnia, while the blood flow velocities were reduced in the case of hyperventilation and increased in hypoxia. Consequently, according to these authors, EEG changes observed during hyperventilation must be attributed to factors other than to cerebral hypoxia. In this regard, it should be furthermore noted that during HV cerebral O_2 consumption not only is not reduced (as we would expect considering vasoconstriction), but it rather tends to increase; oxidative phosphorylation processes are adequate, as shown by normal ATP and phosphocreatine values and, therefore, there should be no need to activate the anaerobic glycolysis; increase in the lactate/pyruvate ratio may be the consequence of the stimulation of the phosphofructokinase due to blood alkalosis, rather than the increased use of anaerobic glycolysis. In normal adult subjects, HV-induced cerebral hypoxia is generally unable to determine appreciable changes in electrical activity, probably for the rapid establishment of physiological compensatory mechanisms. On the other hand, in children and adolescents, there are usually changes in the electrocortical patterns, more relevant when the subject is young, even in the absence of specific pathologies. This is probably related to a more pronounced lowering of the pCO_2, to a more rapid and vigorous decrease in cerebral flow (due to the immaturity of the vascular response to CO_2) and to a different sensitivity of the CNS itself to CO_2, depending on age.

With regard to the cerebral structures responsible for EEG changes onset during forced HV, it seems that hypocapnia inhibits the mesencephalic reticular ascending system, causing the diffuse EEG slowings, due to the predominance of non-specific thalamic projection system [22]. It was also hypothesised that, due to a specific reduction of blood flow at

the diencephalic level, an increase in the activity of the non-specific thalamic nuclei could be determined, resulting in cortical hyperexcitability. It should also be highlighted that a potential link between thalamocortical networks, HV and absence epileptic seizures exists. In particular, it has been shown that the non-specific thalamic projecting system appears to be critically involved in both SW discharges and HV-triggered cortical activity patterns [10].

Finally, pathophysiological modifications induced by HV (hypocapnia and alkalosis) cannot be compared to those occurring as a result of elevated breathing during physical exercise (hyperpnea). Compensatory hyperpnea during physical exercise is associated with the increased metabolic demands and high CO_2 elimination is matched by high CO_2 production. In this case, blood pCO_2 is relatively stable and pH does not significantly change. Furthermore, muscle activity determines the production of lactic acid that contributes to the blood pH lowering. As a matter of fact, during physical activity, even though hyperpnea is determined, an accentuation of the SW discharges at 3 Hz in children with absence epilepsy has not been observed [23] and, therefore, sport practice should not be discouraged.

14.2 Intermittent Photic Stimulation

According to a revised glossary [24], the Intermittent Photic Stimulation (IPS) or Photic Stimulation (PS, synonymous) is an EEG activation procedure consisting of the presentation of intermittent flashes of light to the eyes. The first pioneering studies on the effects of visual stimuli on human EEG were carried out in 1934 by Adrian and Matthews [25]; subsequently, the stimulation method was developed by Walter et al. [26] and it became routinary used in standard EEG from the 1950s [7, 27, 28]. Since IPS is performed with different methods all over the world, several publications have been recently designed in an attempt to standardise the technical procedure and the interpretation of results [29, 30].

14.2.1 Methodology

IPS should be performed in a room with dimmed lighting, because the sensitivity to photostimulation increases in ambient conditions of reduced illumination. Several factors have been considered as the cause of this phenomenon: adaptation to the dark, pupils dilatation, higher contrast between the flash and the dim light of the environment, etc. The procedure should be performed before the HV, or at least 3 min after stopping HV, when both HV-related EEG and metabolic changes have resolved [2], with a patient in a sitting position. In order to have the patient more relaxed, the EEG recording with IPS should be performed with the subject lying on a bed. However, IPS should always be carried out while the patient is awake after a normal night sleep.

The equipment required to perform IPS consists of a preferably circular lamp (about 13 cm in diameter), placed at least 30 cm from the patient's face with an angle of 13°. The subject should be sitting comfortably, with the head slightly reclined, and he should fix on the centre of the lamp. The flash intensity should be at least 0.7 Joule (preferably 1 Joule).

The test is more effective when executed on the subject with the eyes closed, apparently paradoxical phenomenon for the interposition of the eyelids between the light source and the eyes. In reality, this situation seems to facilitate the appearance of the paroxysmal response to IPS, since the eyelids act as light diffusers and behave like selective filters for the wavelengths of the visible light spectrum, which gives rise to the perception of red. Not surprisingly, considering the different susceptibility of photosensitive epileptic patients to different colours, red is the most incriminating colour (at wavelengths of 660–720 nm) than blue or white, at the same overall intensity.

Normally, IPS should be however performed in three eye conditions, with separate trains of flashes of 5 s duration each during eye closure, eyes closed and eyes open, and with a 5 s rest time between each flashes train. If there is not enough time, it is preferable to apply each flash frequency for 7 s, after the closure of eyes on command.

According to the most recent recommendations [30], the IPS must be carried out as follows: stimulation sequence including in ascending order the frequencies of 1—2—8—10—15—18—20—25—40—50—60 Hz. When the patient is not sensitive, all the frequencies stimulations are done and the IPS can be stopped when 60 Hz is reached (the global duration of IPS procedure is 330 s). If there is a Photo Paroxysmal Response (PPR) to a specific frequency (*lower threshold*), the authors recommend skipping the remaining frequencies of the ascending series, starting again with IPS at higher 60 Hz frequency and going down (60—50—40—25—…) until a PPR again occurs (*upper threshold*). In this case, the duration of the IPS will be obviously shorter in time. The lower and the upper thresholds should be determined to prevent seizure occurrence and, when they have been identified, further stimulations should not be attempted.

In our EEG laboratory, to shorten the IPS recording time, flash frequencies described earlier are applied for 5 s with eyes open and for another 5 s after closing the eyes, with an interstimulus interval of 7 s. Therefore, if all the photic stimulation trains are executed in an increasing direction and the photoparoxysmal response does not appear, IPS should last a total of 180 s.

Table 14.2 Methodology for Intermittent Photic Stimulation (IPS)

IPS	Methods
Environment	Dimly lit room
Patient	Sitting position, head slightly reclined Fixing the centre of the lamp
Photic stimulator	Circular lamp (13 cm diameter) Intensity of flash: at least 0.7 Joule Viewing distance: 30 cm; angle: 13 degrees
Standard IPS procedure	*Flash frequencies*: 1-2-8-10-15-18-20-25-40-50-60 Hz *Eye conditions*: Eye closure, eyes closed, eyes open (5 s IPS and 5 s rest times, for each eye condition)
Appearance of PR	Lower threshold: appearance of PPR at a certain frequency In this case: skip the remaining of the series, start again with 60 Hz and go down (60-50-40-25...) until PPR again occurs (upper threshold)

During IPS, the technicians should apply the electrodes for monitoring eye movements and myoclonia of the limbs and face and a simultaneous video recording could be helpful or mandatory for a precise clinical correlation. For more sophisticated studies on individual photosensitivity, the following more extensive flash frequencies can be used: 1-2-6-8-9-10-13-15-18-20-23-25-30-40-50-60 Hz; the retest of photosensitive patients with these frequencies can allow to determine with higher accuracy the photosensitivity range.

The EEG technician, for the risk assessment, must have all the clinical information about the patient and must be alert to stop the IPS immediately upon the appearance of a photoparoxysmal response, since prolonged stimulation can trigger an epileptic seizure. Furthermore, it is helpful to previously describe the stimulation procedure to the patient, especially if naive, also explaining possible risks. It would also be important, for the patient or the family members, to sign the informed consent, especially in cases where the risk of triggering a seizure is higher. Table 14.2 summarises the methodology for IPS.

14.2.2 IPS-Induced EEG Changes

14.2.2.1 Photic Driving Response

The Photic Driving Response (PDR) consists of a physiological response to IPS, characterised by the appearance of a rhythmic posterior activity, with a frequency identical - or harmonically related - to that of the photic stimulus [24]. This response is time-locked to the light stimulus; it can be symmetrical or asymmetric (even up to 50%) and of variable morphology according to the stimulation frequency (Fig. 14.8). PDR is usually more evident in older children and in young adults, and its amplitude is higher in children and in elderly people in respect to adults. An abnormal PDR to low frequencies (less than 5 Hz) is observed in patients with severe diffuse encephalopathy, such as progressive myoclonic epilepsy, mitochondrial encephalopathy, ceroid lipofuscinoses and Creutzfeldt-Jakob disease. Changes in PDR, of poor clinical value, are also observed in various neuropsychiatric disorders: in patients with Alzheimer's disease and schizophrenia a decrease in PDR has been reported, whereas an increase has been observed in migraine and major depression [11].

14.2.2.2 Photomyogenic Response

The Photo Myogenic Response (PMR) (also called incorrectly 'photomyoclonic response') is a non-cerebral response characterised by the appearance of brief repetitive muscle spikes in the anterior regions of the head, induced by IPS (>at 8–20 Hz) and it should be considered as a physiological electromyographic artifact. The incidence of PMR is low (0.1–0.8%) and the muscular activity often increases gradually in amplitude as stimulation continues, ceasing promptly when the stimuli are stopped. Frequently, PMR is associated with flutter of the eyelids and vertical oscillations of the eyeballs, sometimes also with myoclonic jerks involving the face and the head [24]. PMR occurs less commonly in children than in adults and it seems to be correlated with muscular tension (Fig. 14.9).

14.2.2.3 Photoparoxysmal Response

The Photo Paroxysmal Response (PPR), also called incorrectly 'photoconvulsive response', is an abnormal response to IPS characterised by the appearance of epileptiform abnormalities.

The PPR has been classified into four phenotypically different types (Waltz criteria) [31]:

- Type 1, focal occipital spikes time-locked to the flashes.
- Type 2, parieto-occipital spikes with a biphasic slow wave.
- Type 3, parieto-occipital spikes with a biphasic slow wave and spread to the frontal region.
- Type 4, generalised spike-and-slow-wave or polyspike-and-slow-wave complexes.

Figures 14.10 and 14.11 show the different types of PPRs.

Only the more generalised spike-and-wave responses (type 3 and 4 PPRs) show a strong association with epilepsy, and they may continue after the end of visual stimuli for a few seconds. There are two types of PPRs: self-limited, which ceases before or when the IPS stops, and prolonged (or self-sustaining), which continues even after the flashes stop. The generalised prolonged and self-sustaining responses show a strong association with epilepsy and patients with a prolonged PPR more often have spontaneous epileptiform abnormalities on EEG than the patients with self-limited response [7].

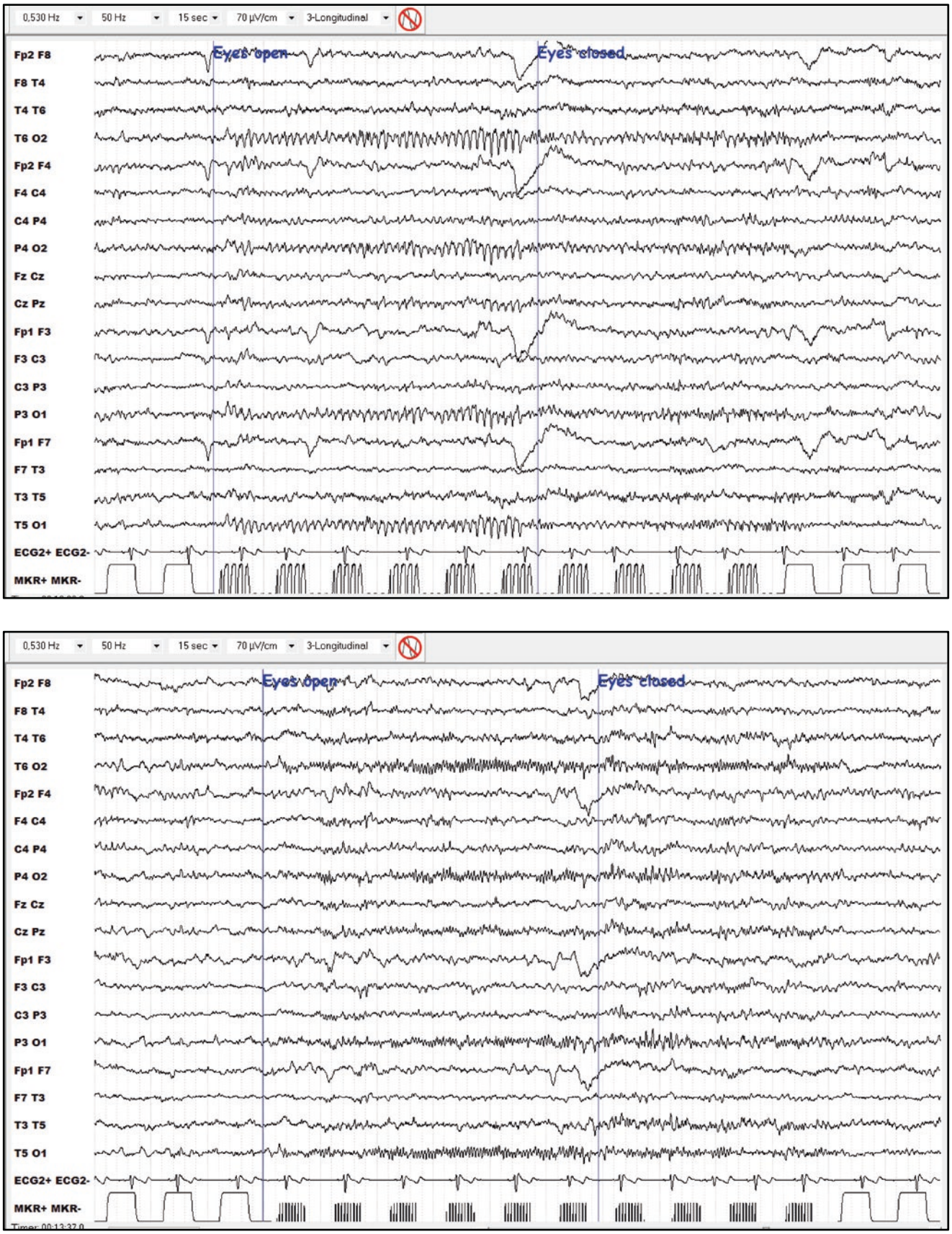

Fig. 14.8 Occipital Photic Driving Response (PDR) in a 19-year-old subject, at 8 Hz (upper) and 18 Hz (bottom)

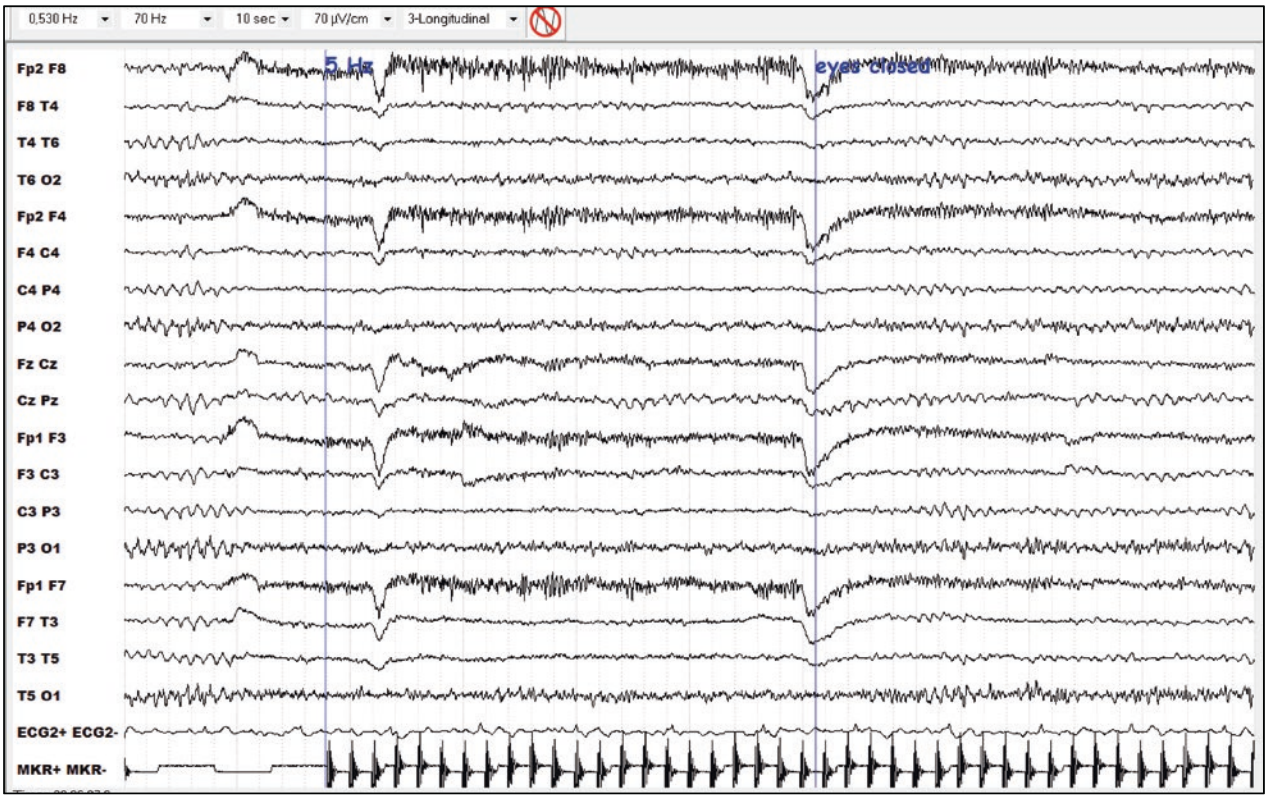

Fig. 14.9 Frontally Photo Myogenic Response (PMR) in a 35-year-old subject

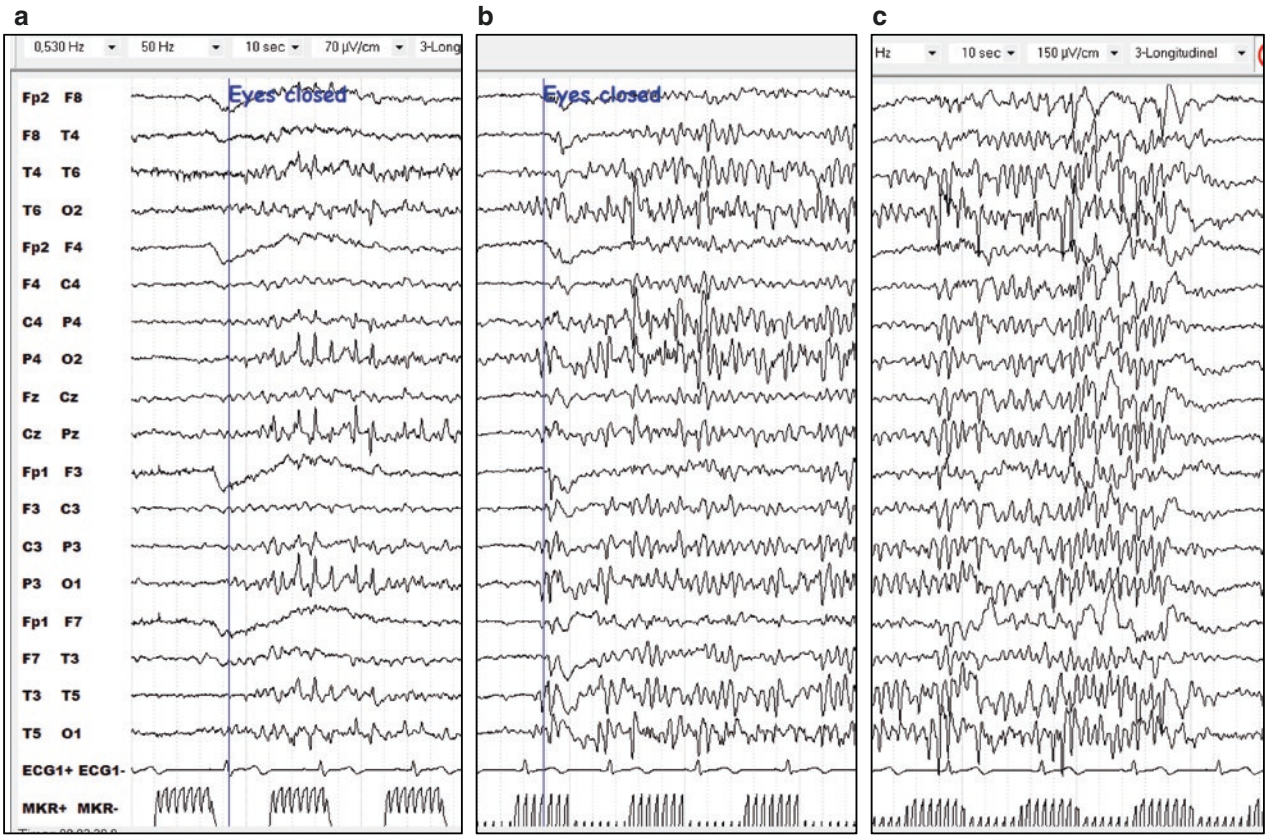

Fig. 14.10 Photo Paroxysmal Response (PPR) of type 1 (**a**), type 2 (**b**) and type 3 (**c**), according to Waltz criteria [31]

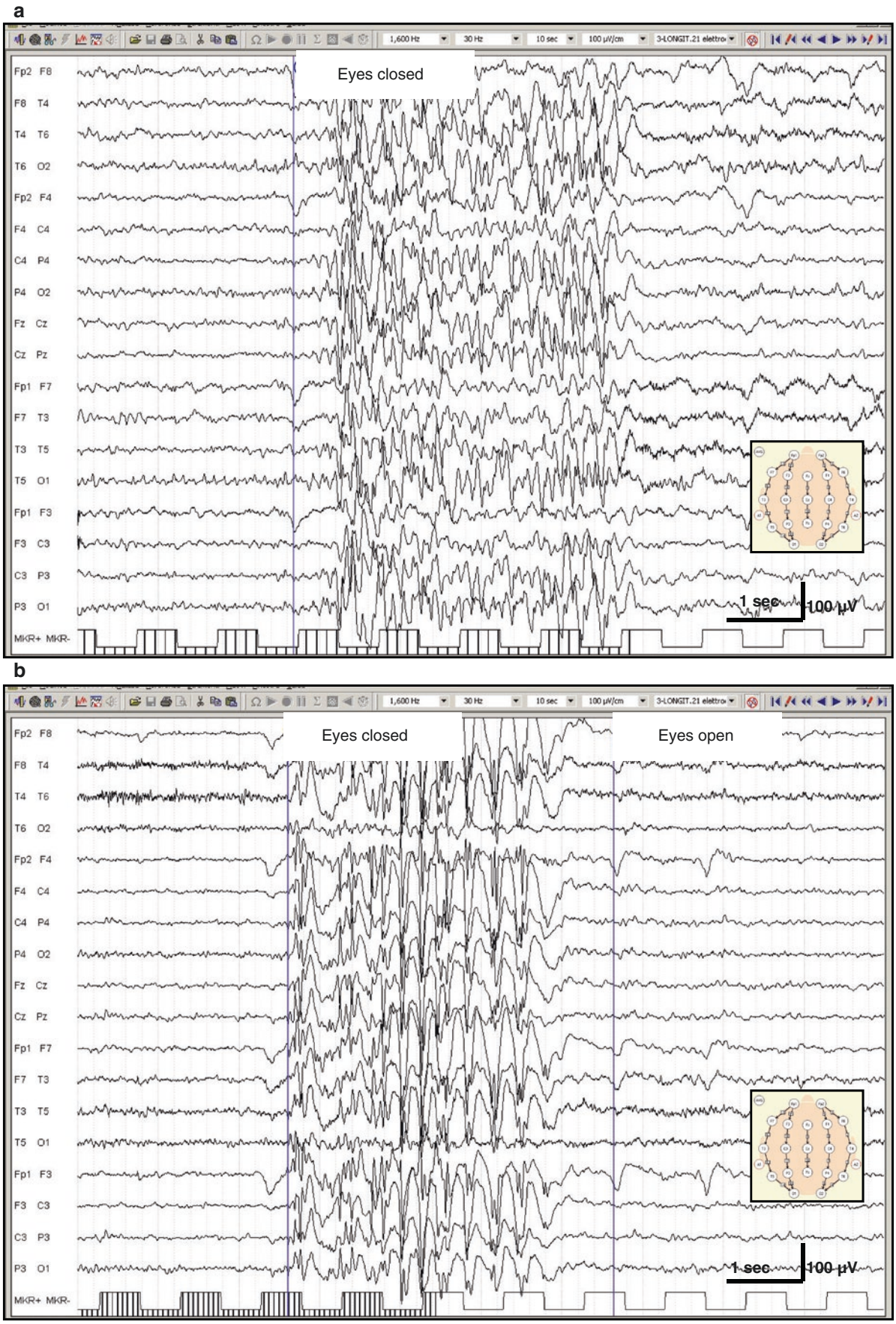

Fig. 14.11 Two examples of Photo Paroxysmal Response (PPR) type 4, in (**a**) self-limited and in (**b**) self-sustaining

Table 14.3 EEG patterns induced by IPS

Photic Driving Response (PDR)	– Time-locked to light stimulus – Same frequency or harmonically related to stimuli
PhotoMyogenic Response (PMR)	Repetitive muscle spikes over anterior regions (electromyographic response)
PhotoParoxysmal Response (PPR) Different types (Waltz criteria)	Epileptiform abnormalities induced by IPS 1. Focal occipital spikes time-locked to light stimuli 2. Parieto-occipital spikes and slow waves 3. Parieto-occipital spikes and slow waves, spreading to frontal regions 4. Generalised spike- or polyspike-and-slow-wave complexes – Self-limited – Prolonged/self-sustaining

Table 14.3 summarises the physiological and pathological EEG changes induced by Intermitten Photic Stimulation (IPS).

Occasionally, an epileptic seizure may occur in the laboratory during the IPS, particularly in a patient with evident photosensitivity, if IPS is not promptly stopped. The ictal manifestations that may be induced by IPS are absence seizures, tonic or tonic-clonic seizures and myoclonia, especially of the eyelids or limbs. Sometimes, during IPS, the patient with photosensitivity shows a negative myoclonus. As hyperventilation, IPS may also provoke psychogenic, non-epileptic seizures.

The PPRs in epileptic patients with photosensitivity are elicited by a broad range of flash frequencies, but those within the range of 10–20 Hz are the most provocative (in particular 18 Hz).

The prevalence of photosensitivity varies substantially among studies, also depending on age and gender, being highest in adolescents and in females [5, 11, 27].

In healthy children the prevalence of PPR has been reported in 1.3–8% of subjects, but higher percentages are reported in older studies that include EEG patterns non-characteristic of PPR [32]. In healthy adults examined with EEG—as aircrew candidates—PPR is identified in 0.4–0.7% up to 2.2% [28, 33, 34]. The variability of PPR prevalence in healthy subjects depends mostly on the methods of IPS and their definition.

The PPR has been also described as incidental finding in patients with other neurologic diseases (neurodegenerative disorders, migraine, etc.), but without a history of epilepsy. PPRs in non-epileptic persons rarely evolve into epilepsy [35].

Among Persons With Epilepsy (PWE), PPR is evident within a range of 0.6–5.5%, with a high prevalence in generalised genetic epilepsies of white people [5, 11, 36]. In patients with a generalised PPR, the likelihood of having epilepsy ranges approximately from 70 to 90% [37] and the likelihood of having seizures induced by IPS (photosensitivity epilepsy) is 60% [38]. The age of onset of the PPR is between 8 and 25 years, with a female predominance and a decline in IPS sensitivity after the age of 30. The PPR is a genetic trait and the epilepsies most strongly associated with photosensitivity are juvenile myoclonic epilepsy (up to 90%), generalised genetic epilepsy with tonic-clonic seizures (percentages variable from 8% to 20%) and eyelid myoclonia with absences (Jeavons syndrome) [39–41]. Waltz et al. in 1992 [31] highlighted that PPRs type 4 were present in a high proportion of the asymptomatic siblings of patients with epilepsy and recent studies have started identifying specific genes that convey risk for PPR [11]. Recent evidence points to CHD2 as a novel gene implicated in photosensitive epilepsy [42].

A high incidence of photosensitivity has also been reported in patients with progressive myoclonic epilepsies [43] and neuronal ceroid lipofuscinosis. Focal epilepsy is rarely associated with a PPR, but this pattern elicited by IPS has been described in some patients with temporal or occipital lobe epilepsy [44]. In this regard, recent studies have suggested that the Jeavons syndrome may be generated in the occipital areas [41, 45].

In patients with IPS-induced seizures, a clinical focal onset is actually often provable, due to the appearance of simple or complex visual symptoms (illusions or hallucinations). Visual symptoms are usually accompanied and/or followed by deviation of eyes and head on one side, or eyelids myoclonic jerks. Subsequently, spread of the epileptic discharge towards the limbic structures determines the appearance of automatisms typical of the temporal lobe epilepsy, with epigastric symptoms and loss of awareness.

The pathophysiological mechanisms underlying photosensitivity have been studied, but not yet fully clarified. Several studies have suggested that PPRs are triggered from the hypersyncronised visual cortex [46]. Patients with idiopathic occipital photosensitive epilepsy show increased Visual Evoked Potential (VEP) amplitude and abnormal latencies for high-contrast visual stimuli, suggesting a failure of cortical gain control (the gain control is the mechanism by which a biological system dynamically adjusts its sensitivity to the inputs) [47, 48]. In addition, patients with idiopathic generalised epilepsy have demonstrated less saturation of the VEP response amplitudes, thus reflecting an abnormality in neuronal gain control, possibly due to reduced GABAergic inhibition [49].

On the other hand, the hyperexcitability of the occipital cortex alone cannot fully explain the clinical and EEG corre-

lates of photosensitivity (motor symptoms associated with generalised epileptiform discharges). Current data indicate indeed that photosensitivity is the expression of an alteration of the visual system not limited to the occipital cortex, but extended also to the parietal and premotor cortex. Studies conducted using EEG in combination with functional Magnetic Resonance Imaging (fMRI) have described the metabolic and hemodynamic consequences of IPS in control subjects and in patients with PPR [50, 51]. IPS led to a significant activation of the visual cortex and, 3 s before the PPR onset, the cortical activation was also found in the parietal and in the premotor cortex [52]. In patients with eyelid myoclonus with absences (Jeavons syndrome), it have been demonstrated that visual system alterations involve a circuit encompassing the occipital cortex and the cortical/subcortical system physiologically involved in the motor control of eye closure and eye movements [41]. Furthermore, studies combining Transcranial Magnetic Stimulation (TMS) of motor cortex or visual stimulation of occipital cortex have demonstrated that the PPR is due to abnormal visuomotor interactions [53, 54]. Subsequently, the PPR is due to the hyperexcitability of occipital cortex that affects other regions via network interactions.

Finally, Vaudano et al. [55] studied the hemodynamic correlations of the alpha rhythm in photosensitivity epileptic patients, in comparison to patients without photosensitivity and healthy controls. The authors used EEG-fMRI to investigate if the fluctuations in the alpha rhythm were correlated with changes in the Blood Oxygenation Level-Dependent (BOLD) signal in cortical and subcortical regions. Whole brain functional connectivity was evaluated for two thalamic nuclei (posterior and medio-dorsal). In photosensitive patients the alpha-related BOLD changes decrease in the occipital, sensory-motor, anterior cingulate and supplementary motor cortices in comparison with other groups. Furthermore, the same brain regions showed abnormal connectivity with thalamus only in epileptic photosensitive patients. These results demonstrate that the cortical-subcortical network generating the alpha oscillation is different in persons with epilepsy and photosensitivity.

14.3 Other Methods of Visual Stimulation

14.3.1 Pattern Stimulation

A remarkable number of photosensitive patients are sensitive not only to IPS, but also to geometric patterns. The incidence of paroxysmal discharges induced by patterns varies widely across studies (from 5% to 72%) depending on the spatial and temporal characteristics of visual pattern and stimulation protocol [11, 56]. However, there have also been reported patients responding to these pattern, but not to IPS. The most activating geometric pattern consists of parallel lines or stripes with sharp edges, black-and-white and high-contrasted (Fig. 14.12) [29]. The stimulation can be performed with eyes open, in ambient light with a monitor

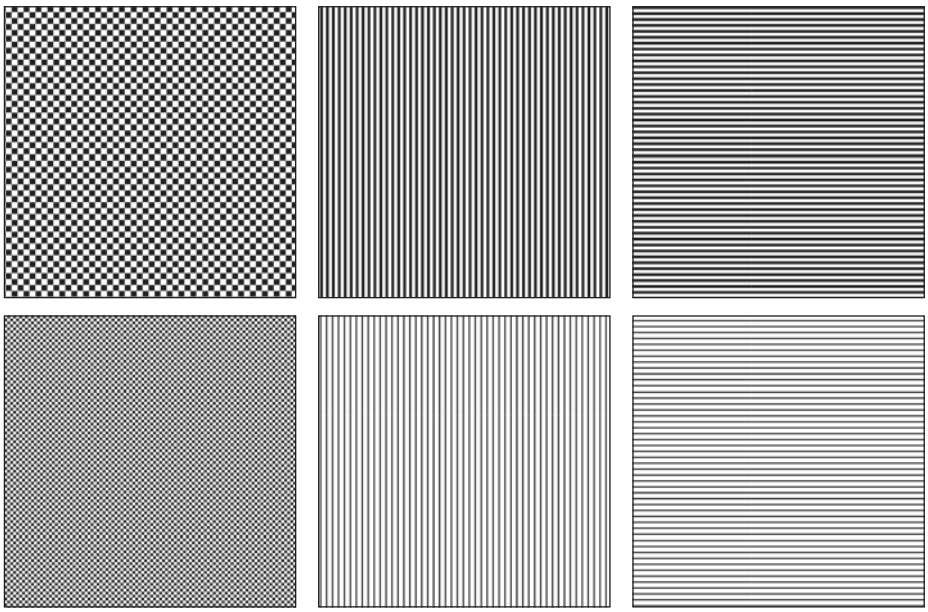

Fig. 14.12 Examples of geometric pattern used for the pattern stimulation

connected to an electronic grating generator, positioned 1 m from the patient's eyes. Each pattern is presented for 10 s, in oscillatory (optimal oscillation frequency, 15–20 Hz) or stationary modality, at spatial frequencies between 0.5 and 6 cycles/degree. Pattern sensitivity occurs in various epileptic syndromes, but according to Radhakrishnan et al. [57], it is a readily distinguishable subtype of the visually provoked reflex epilepsies.

14.3.2 Low-Luminance Visual Stimulation

The Low-Luminance Visual Stimulation (LLVS) is performed only with eyes open, with luminance ranging between 10 and 30 cd/m^2 [29]. The combination of low-luminance flickering at 18 Hz with red light and pattern modality has been reported as particularly useful for activating PPR [58]. For this stimulation, three different patterns can be used (dot pattern, vertical grating, or horizontal grating) with spatial frequency of 2 cycles/degree; a red strobo-filter can be used to produce a red flicker at >600 nm wavelength [29]. The importance of flickering colour/pattern was demonstrated in the famous Pokémon incident in Japan in December 1997. In this case, a TV cartoon containing a 4 s red/blue sequence flickering at 12 Hz elicited simultaneous seizures in 685 children; 76% of them had never presented a seizure before.

14.3.3 Fixation-Off Sensitivity

Fixation-Off Sensitivity (FOS) is a rare phenomenon induced by the elimination of central vision/fixation. FOS is characterised by continuous posterior or diffuse epileptiform discharges that appear 1–3 s after eye closure, persist throughout the EEG recording with eye closed and disappear immediately with eye opening (Fig. 14.13) [59, 60]. A definite diagnosis of FOS requires a demonstration that the epileptiform abnormalities also occur by impending central vision and fixation using Frenzel lenses or by placing a sheet of white paper 20 cm in front of the subject (with eyes open, but without fixation). The

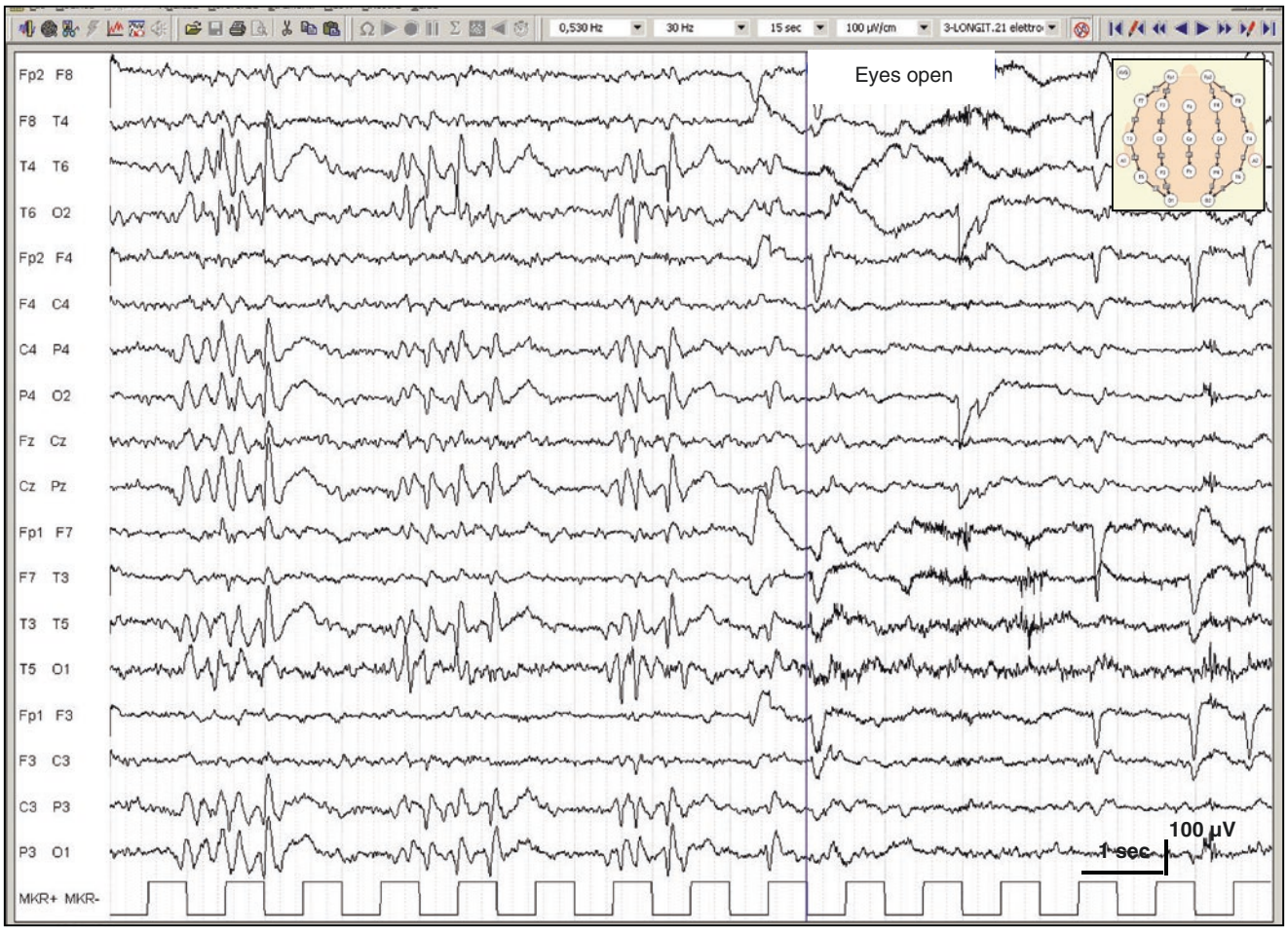

Fig. 14.13 Fixation-Off Sensitivity (FOS) phenomenon in a 26-year-old patient with focal epilepsy. With eyes closed, subcontinuous epileptiform abnormalities in the posterior regions of both hemispheres, without clinical correlates appear. Epileptiform activity immediately disappears with eyes opening

epileptiform abnormalities (spike, spike and wave, sharp wave) can be registered in patients without clinical epileptic seizures, but most commonly FOS is associated with occipital idiopathic childhood epilepsies or with focal or generalised symptomatic epilepsies. fMRI studies showed a correlation between posterior FOS and a focal activation of both extrastriate temporo-occipital and also of the frontal lobe regions [61]. Low-frequency repetitive TMS (rTMS) reduce FOS-related focal epileptiform activity [62]. In conclusion, based on the knowledge acquired so far, FOS seems to be the expression of the occipital hyperexcitability, but the exact mechanisms underlying this phenomenon remains somewhat obscure.

14.4 Sleep and Sleep Deprivation

According to American Clinical Neurophysiology Society [1], sleep EEG recording should be performed whenever possible, even if not alternatively with the awake recording. As a matter of fact, there are evidences that sleep EEG helps make a better classification of an epileptic syndrome that helps for the diagnosis in patients with suspected epilepsy [5]. The sleep recording should include wakefulness, drowsiness and at least 40 min of sleep [2].

It is well known that some types of epileptic seizures can be closely related to the sleep-wake rhythm and that it is common to observe, in sleep EEG, the appearance of epileptic abnormalities that are not present in the awake recording. Moreover, in patients with epileptiform abnormalities in the awake EEG, the increase or spatial change of the abnormal features (focal vs multifocal or diffuse pattern) can be observed during the sleep EEG. Sleep, therefore—like hyperventilation and photostimulation—can be considered a method of EEG activation, easy to perform and completely harmless.

In patients who previously had a normal standard awake EEG, the recording during sleep has a variable diagnostic yield percentage, from 11% to 92%; this wide variability is due to the differences in study design, the specific characteristics of patient population, etc. In summary, from the evidences in the literature review, it can be argued that sleep may activate Interictal Epileptiform Discharges (IEDs) in about 30% of persons with epilepsy, mostly in those with epilepsies sleep-related or with seizures at awakening.

Prolonged night-time recordings in patients with epilepsy have shown that not all the sleep stages are equally in activating EEG abnormalities, but that the most important information is obtained from the early stages (N1–N2) and from awakening, while the stages N3 and R are the less activating. For this reason, it is generally sufficient to record in the EEG laboratory only a brief (40–60 min) period of daytime sleep, allowing to record N1 and N2 sleep stages and awakening (afternoon nap).

The evaluation of the effect of the various stages of sleep on IEDs, focal or generalised is particularly interesting. The focal IEDs most commonly increase at sleep onset; they reach the maximum of their activity in N2 stage (with tendency to multifocal or diffuse spread) and then fall in R sleep to levels lower than seen in wakefulness, remaining well localised (Fig. 14.14). This influence of sleep on focal IEDs is evident in the epilepsy with centro-temporal spikes; in this type of epilepsy, rolandic spikes have the maximal activity in N1 and N2 sleep and appear to be related to sleep spindle synchronisation. In addition, the diffuse IEDs, characteristic of the genetic generalised epilepsies, usually increase in N sleep (>in stages N1 and N2). Typically, spike rates increase with sleep onset, continue to increase during sleep progression, diminish sharply in R sleep and increase in the morning after awakening. During the N sleep, the generalised IEDs often become more disorganised, with shorter bursts of polyspikes, at quasi-periodic recurrence ('fragmented' epileptiform activity) (Fig. 14.15) [63, 64]. In the R stage, the discharges are instead rare and quite similar to those of the awake state. Closely related to the sleep-wake rhythm are the generalised IEDs of the juvenile myoclonic epilepsy; in this type of epilepsy, the IEDs are often only observed at sleep onset and at awakening, disappearing completely during the course of sleep. Moreover, the provoked and early awakening seems to be more activating on IEDs than spontaneous awakening.

In summary, both focal and generalised IEDs appear to be activated by N sleep and inhibited by R sleep. During N sleep, the EEG synchronisation processes are particularly active (involving the thalamocortical circuits) and the same hypersynchronous oscillations of cortical neurons that determine the appearance of sleep spindles, K complexes and slow hypersynchronous EEG activity can therefore facilitate the IEDs appearance. Conversely, increased brainstem excitatory inputs in R sleep depolarize the thalamocortical cells and induce EEG desynchronisation, being responsible also for the inhibition of IEDs [64].

Studies on the microstructure of sleep have shown that there is an association between IEDs recurrence during N sleep and different phases of Cyclic Alternating Pattern (CAP). CAP is considered a marker of sleep instability and IEDs are activated mostly during the phase A, while phase B exerts a powerful and prolonged inhibitory action. The NCAP period represents instead an intermediate stationary level. Both in generalised and focal epilepsies, the IEDs and seizures have an onset in correlation with the phase A of CAP. The only exception is the epilepsy with centro-temporal spikes of childhood, in which the frequency of discharges does not show any significant modification by comparing the two phases of the CAP and the CAP and NCAP period [65–67].

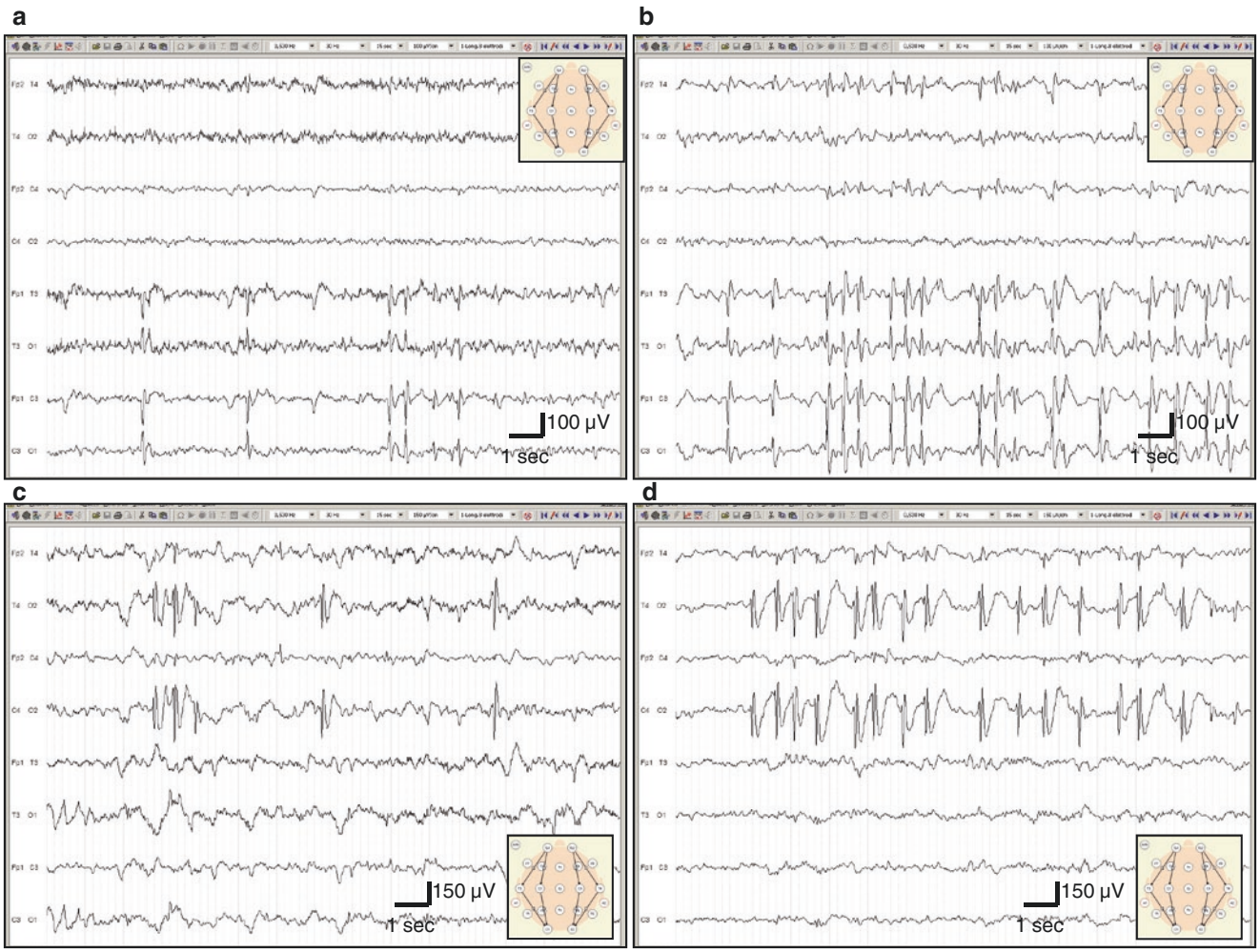

Fig. 14.14 Two examples of sleep-induced focal epileptic activity increase during N2 stage. Top: focal centro-temporal spikes during wake (**a**) in an 8-year-old child and their increase during sleep, with tendency to contralateral anterior regions diffusion (**b**). Bottom: right occipital epileptiform abnormalities in an awaken 6-year-old child (**c**) and their increase during light sleep (**d**)

Another EEG activating method, closely related to mechanisms of induction of sleep, is the so-called Sleep Deprivation (SD). Loss of nocturnal sleep is one of the major trigger for epileptic seizures, both in the healthy and epileptic people. In the 18–24% of epileptic adults, seizures are elicited by sleep deprivation and about 30–70% of persons with epilepsy having a nonsignificant standard EEG patterns show a pathological EEG activation after a long and forced awake period [68, 69]. Since it has been described that EEG recordings after SD do not show particular abnormalities in healthy subjects and in patients with neurological disorders other than epilepsy, this activating procedure is considered specific for persons with epilepsy, already diagnosed or only suspected.

However, the diagnostic yield of SD is still under discussion, also because the numerous studies carried out on this topic have been conducted with different methods, in patients with different types of epilepsy and, sometimes, also treated with antiepileptic drugs.

The SD method varies significantly from one centre to another, with length of sleep deprivation ranging from 3 to 36 h and the duration of EEG recording ranging from 30 min to 24 h.

In our laboratory, EEG recording in adults is usually performed early in the morning, after a total night-time sleep deprivation, while children are generally woken up early at night, with only partial deprivation (6–8 h). The EEG recording (as prolonged as possible) includes a quiet awake period, followed by falling asleep and recording at least N1–N3 stages; after waking up, both IPS and HV are performed (the SD accentuates the response both to photostimulation and to hyperventilation) (Fig. 14.16).

While most of the literature studies used 24 h of SD, some studies confirmed the activating effect of partial SD as

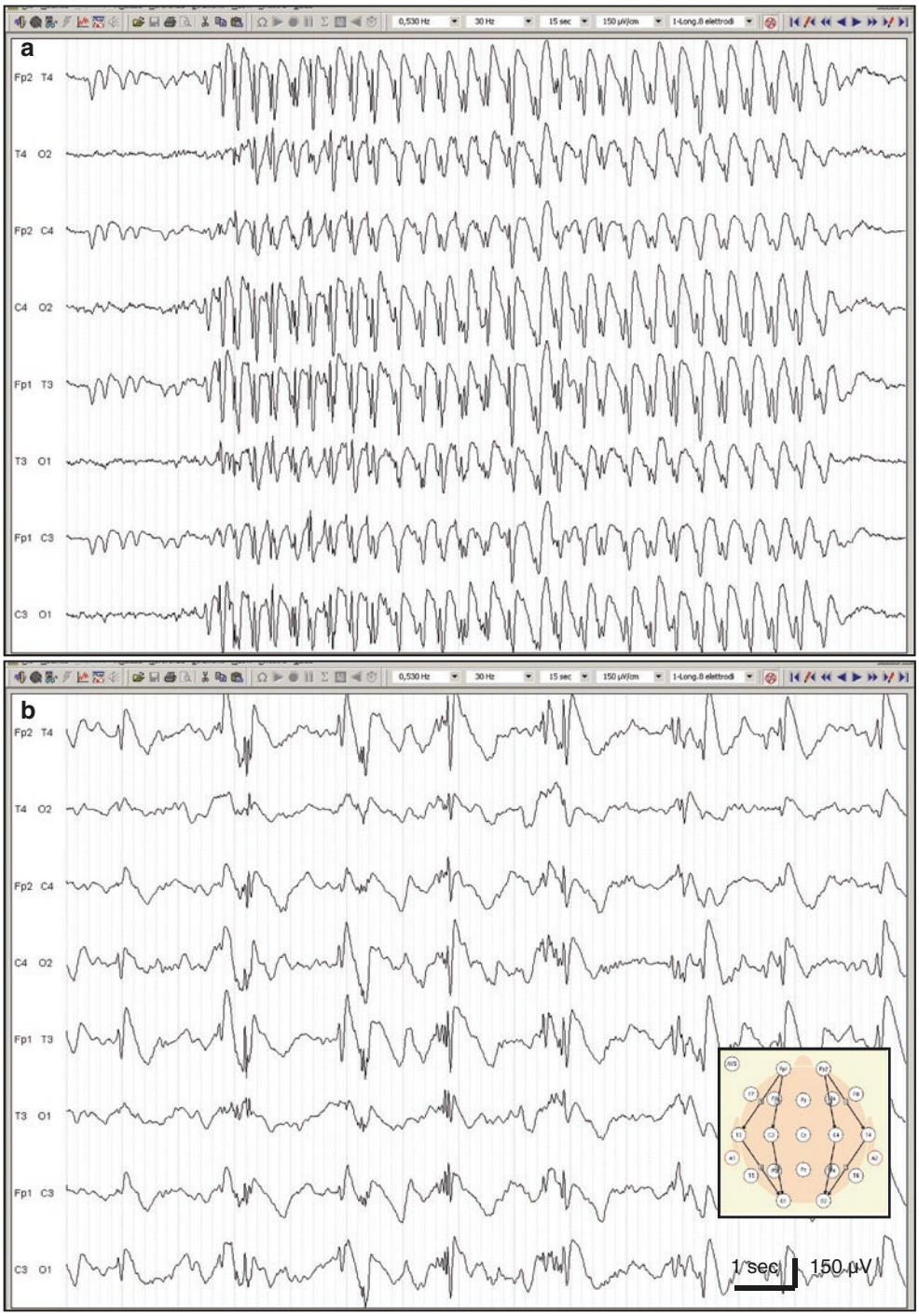

Fig. 14.15 Typical discharge of spike-and-wave complexes at 3 Hz in an awake adolescent with generalised epilepsy with absences (**a**). During N2 stage of sleep (**b**), the epileptic activity is organised in brief bursts of polyspikes-and-wave complexes, at quasi-periodic recurrence

well [5, 70, 71]. Giorgi et al. [72] evaluated the role of a simple SD-EEG protocol in a wide population of de novo patients with suspected epileptic seizures; the protocol consisted of waking up at 2:00 a.m. and EEG monitoring from 8:00 until 10:30 a.m. The authors report 91.1% specificity for epilepsy diagnosis and showed IEDs in 41.2% of all patients. According to authors, the IEDs yield in SD-EEG is higher than in second routine EEG for focal epilepsies. Nevertheless, these results are not confirmed by Renzel et al. [73] who studied patients with suspected epilepsy with an EEG after 24 h SD and comparing the results with those of a previous routine EEG. The overall sensitivity is of 25%, superior in patients with idiopathic generalised epilepsy, compared to patients with focal epilepsies (65% vs. 17%). Recently, Baldin et al. [11] found that in their population-based study, the yield on the first sleep EEG was 16.45%, consistent with a previous literature studies, and that it did not differ between generalised and focal seizure types.

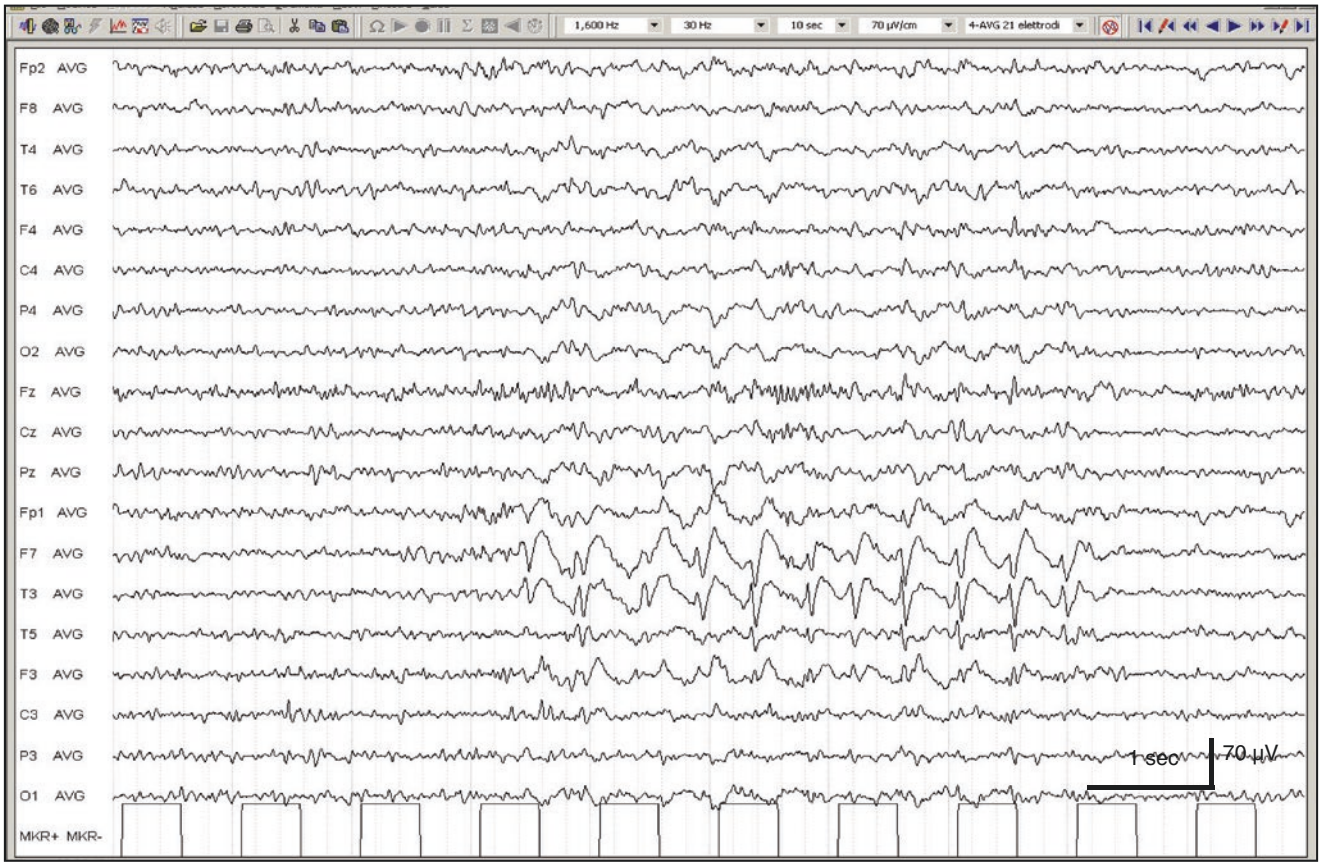

Fig. 14.16 A 25-year-old patient with temporal lobe epilepsy. Basal EEG without remarkable abnormalities. During hyperventilation, after 24-h sleep deprivation, clear focal epileptiform abnormalities in left temporal region appear

It is still debated whether the EEG activation induced by SD is merely due to the drowsiness and sleep (consequent of SD) or whether SD per se has an activating effect [64, 74]. Using transcranial magnetic stimulation, Badawy et al. [75] have demonstrated that cortical excitability increased at short and long interstimulus interval in patients with epilepsy after SD. In the generalised epilepsies, these changes were significant in both hemispheres while, in focal epilepsies, they were localised in the seizure focus hemisphere.

Finally, the results of studies on drug-induced sleep are conflicting [5] and it is preferable to obtain a natural sleep. In agitated and fearful children, it is however sometimes necessary to use a mild sedation, classically with chloral hydrate or with alternative sedatives such as dexmedetomidine, hydroxyzine or melatonin [71, 76].

14.5 Other Stimulation

Specific activation procedures can be applied to patients with reflex epilepsy, from auditory or somatosensory stimuli to more complex stimuli such as eating, reading, writing, etc. (see Chap. 28 on Reflex Epilepsy). Repetitive acoustic stimulation through click trains can trigger epileptic abnormalities both in patients with focal epilepsy (especially of the temporal lobe) and, more rarely, with generalised epilepsy [77]. Moreover, acoustic stimulation is extremely effective in all those cases in which the level of alertness is fluctuating. For these reasons, it would be useful that each EEG machine is equipped also with a sound stimulator. It is also known that, in some types of epilepsy, reflex seizures can be triggered by listening to particular musical pieces, songs and other structured sound sources; therefore, in the laboratory, an instrument for the reproduction of such stimuli should always be available. The application of somatosensory stimuli at the extremities of the limbs can induce the appearance on the EEG of the epileptiform graphoelements both in children with benign epilepsy with centro-temporal spikes as well as in non-epileptic persons.

Each stimulus (i.e. finger tapping) should be administered 5–10 times with an interstimulus interval of 2 s. In epileptic children with centro-temporal spikes, it should be observed on the scalp, after stimulation of tibial or median nerves, the giant somatosensory evoked potentials (giant SEPs), due to a hyperexcitability of primary somatosensory and motor cortices.

These features are recorded also in progressive myoclonic epilepsies and in cortical reflex myoclonus [11, 78–80].

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