Clinical Neurophysiology in Disorders of Consciousness

Brain Function Monitoring in the ICU and Beyond

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Preface

> The seeker after truth is not one who studies the writings of the ancients and, following his natural disposition, puts his trust in them, but rather the one who suspects his faith in them and questions what he gathers from them, the one who submits to argument and demonstration […]Thus, the duty of the man who investigates the writings of scientists, if learning the truth is his goal, is […] applying his mind to the core and margins of its content, attack it from every side. He should also suspect himself as he performs his critical examination of it, so that he may avoid falling into either prejudice or leniency.
>
> Ibn al Haytam ("Alhazen") (965–1039)

Since the beginning of written accounts almost three millennia ago, disorders of consciousness have constantly intrigued and fascinated scholars and physicians. With the beginning of modern-era intensive care in the middle of the twentieth century, and particularly the continuous developments of technical and computer technologies, allowing easier recordings, more compact data storage, and smoother analyses, the last few decades have experienced a dramatic increase in the interest devoted to the study and therapy refinements of these patients. Given their non-invasiveness, the relatively broad availability, and the opportunity to study brain function in real time, neurophysiological investigations are routinely applied to complete clinical and radiological examinations in this setting, and represent a paramount tool for both clinical and scientific purposes.

This book is intended to cover in a single work clinical and research information related to the whole spectrum of neurophysiology applications in patients with disorders of consciousness. Its content spans from clinical aspects related to the management of patients in the intensive care unit, including EEG, evoked potentials, and related implications in terms of prognosis and clinical management (the first section, focusing on the acute setting and more clinical), to explorative research applications in subjects with ongoing consciousness impairment (the second section, devoted to the chronic patients, and more research-bound). While the first chapters give up-to-date information for the interested clinician, the following ones highlight the latter scientific developments, which open new exciting avenues in this field including an outlook on neuroimaging at the end. Given its interdisciplinary character, the book is directed to neurologists, neurophysiologists, neuro-intensive-care specialists, nursing personnel, clinical neurophysiology technologists, and researchers.

As compared to the several, already existing excellent publications in this field, this book reflects the lively interplay between clinical and research applications; we are very proud of the work by all the authors of the chapters, top experts in their respective fields, who provided the current state of the art. Each chapter has been thoroughly reviewed by us in order to minimize redundancy and incongruence; furthermore, a cross-referencing between chapters allows the reader a rapid overview of related topics across the book. However, as with each work written by several authors, some double coverage of distinct items is unavoidable; we believe that this may provide the reader with a spectrum of the existing knowledge, which cannot be summarized as a monolithic feature. The citation of the great medieval Arab scholar reminds us that knowledge is constantly evolving, and that only a critical and honest debate will allow identifying the best direction towards it.

Lausanne, Switzerland — Andrea O. Rossetti
Liège, Belgium — Steven Laureys

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Acute Coma in the Intensive Care Unit

1

Mauro Oddo

Contents

Abstract

In the last couple of decades, the intensive care unit (ICU) environment is experiencing a revolutionary metamorphosis in terms of integration of electrophysiological tools for diagnosis and therapeutic management. Patients with brain dysfunction in the ICU are frequently admitted and managed, either following primary (e.g., hypoxic-ischemic encephalopathy following cardiac arrest, hemorrhage, traumatic injury, status epilepticus) or secondary (e.g., sepsis, prolonged sedation, multiorgan failure) insults to the central nervous system. This implies not only enhanced awareness regarding the specificities of these challenging conditions, including highly trained technicians, specialized nurses, and medical staff, but also implementation of user-friendly, convenient, and reliable technical setups.

1.1 Epidemiology

Coma is a frequently encountered pathology in the intensive care unit (ICU) and is amongst the leading causes of admission in the ICU, together with cardiac and pulmonary diseases (Huff et al. 2012). Coma is a condition of profound consciousness impairment typically presenting as an unarousable state in patients with closed eyes, resulting from an acute failure of neuronal systems governing arousal and awareness, and

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represents a neurological emergency. Etiologies of acute coma are classically categorized as *primary*, i.e., due to intracerebral diseases (e.g., traumatic brain injury [TBI], subarachnoid hemorrhage [SAH], intracerebral hemorrhage [ICH], acute ischemic stroke [AIS], hypoxic-ischemic encephalopathy [HIE] after cardiac arrest [CA], immune-mediated or infectious encephalitis, status epilepticus [SE]), or *secondary* to systemic disorders affecting brain function (e.g., septic, metabolic, toxic encephalopathies) (Stevens and Bhardwaj 2006).

1.2 Acute Brain Dysfunction in the ICU

Primary acute cerebral diseases are a frequent cause of admission in the ICU (Fig. 1.1a). With the advancement of post-resuscitation care and the widespread implementation of therapeutic hypothermia, HIE after CA is probably the most frequent ICU admission for primary brain pathology in many centers. Intracranial hemorrhages are also frequent, with an increasing number of patients admitted because of secondary ICH due to antiplatelet or anticoagulant agents. Despite changes in the mechanisms of traumatic insult (increased TBI associated with fall in industrialized countries, increased number of traffic accident-related TBI in less industrialized countries), TBI remains an important cause of coma admission in the ICU. Status epilepticus, central nervous system infections, and the emergent occurrence of immune-mediated (e.g., anti-NMDA-receptor) encephalitis are less frequent, but on the other extent may often induce long ICU stay and ICU-related complications (such as ventilator-associated pneumonia, acquired ICU infections, thrombosis, gastrointestinal disturbances, only to cite some).

Secondary, functional brain disorders are commonly encountered in the ICU (Fig. 1.1b). Critical illness-related acute brain dysfunction (also called critical illness-related encephalopathy or delirium) has recently emerged as a frequent complication in mechanically ventilated patients even without primary acute brain injury, who are admitted to the ICU for a variety of medical and surgical conditions, particularly following severe sepsis, multiorgan dysfunction, circulatory shock, and major cardiovascular surgery (Ely et al. 2004). In fact, septic encephalopathy is a major cause of secondary acute brain dysfunction (Sonneville et al. 2013); sedation is also associated with an increased risk of encephalopathy, particularly with prolonged use of benzodiazepines (Pandharipande et al. 2006). More importantly, and somewhat alarming, critical illness-related acute brain dysfunction is not only an independent factor of worse outcome (Girard et al. 2010), but has also recently been associated with long-term neurological sequelae and impaired cognitive function among ICU survivors (Pandharipande et al. 2013).

1.3 The Role of EEG in the ICU (See Also Chap. 2)

Electroencephalography monitoring (EEG) provides essential information about brain function, particularly in comatose patients, and is increasingly being used in the ICU (Claassen et al. 2013). Long-term EEG recording has become a fundamental part of the so-called brain multimodal monitoring, i.e., the constellation of invasive (intracranial pressure and brain oxygen monitors, cerebral microdialysis technique) and noninvasive (EEG, transcranial doppler, near-infrared spectroscopy) technologies that allow a comprehensive scrutiny of the injured brain and help optimize the management of comatose ICU patients (Oddo et al. 2012). In this setting, the role, potential utility, and present use of EEG in the ICU have greatly evolved over the last decade (Fig. 1.2). The predominant place of EEG in the ICU consists in diagnosing and helping manage convulsive and nonconvulsive seizures and SE in neurological and neurosurgical ICU patients (Friedman et al. 2009; Rossetti and Lowenstein 2011; Rossetti and Oddo 2010), as well as in medical (Oddo et al. 2009) and surgical (Kurtz et al. 2014) ICU patients with septic or other forms of acquired encephalopathy. Another

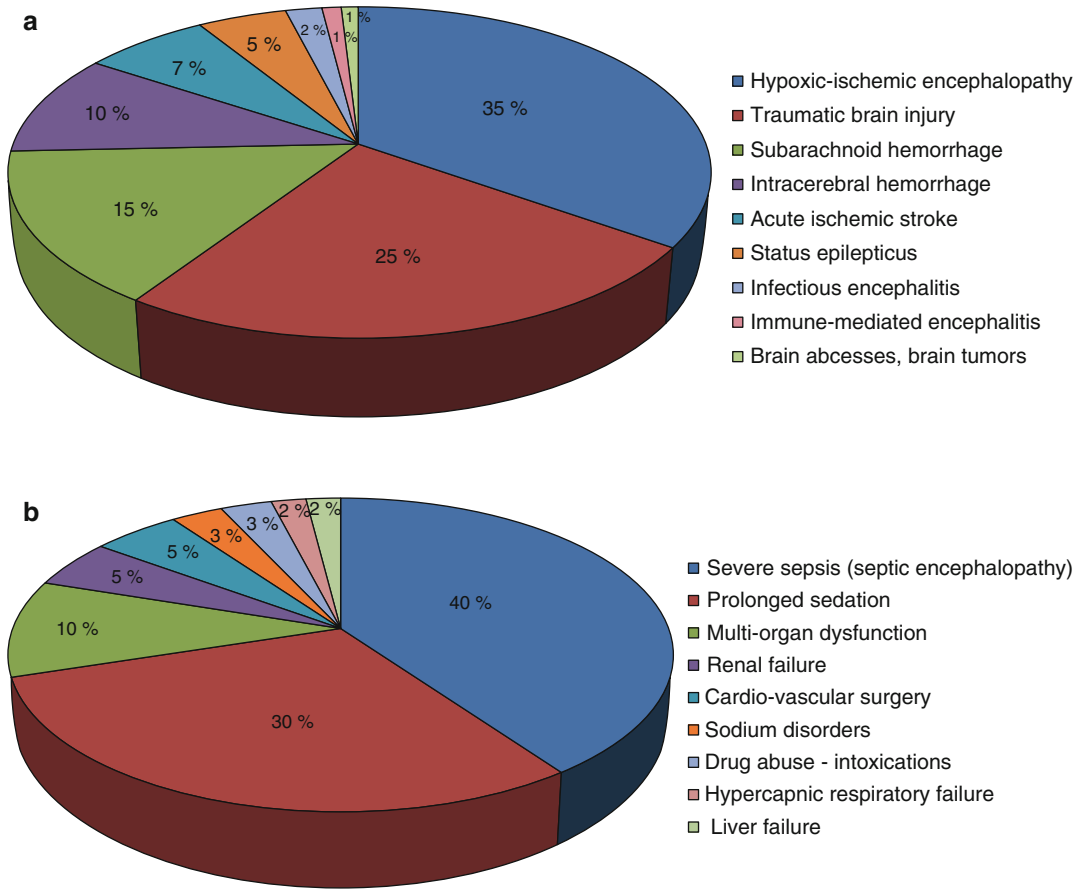

Fig. 1.1 Epidemiology of acute coma in the intensive care unit (ICU). Panel **a** illustrates the estimated distribution of ICU admissions for acute coma after primary brain injury in industrialized countries. Panel **b** illustrates the estimated distribution of ICU admissions for acute coma after secondary brain injury. Critical illness-related encephalopathy (delirium) and prolonged sedation are important causes of coma in the ICU

well-recognized role of EEG is to guide the titration of several sedative agents (midazolam, propofol, barbiturates) that are commonly used for pharmacological coma (see Chap. 4) in patients with refractory SE or refractory intracranial hypertension. There are other emerging, promising roles for EEG monitoring in ICU patients. A prominent one, exploiting quantitative EEG analysis, is to use EEG to continuously monitor the brain function at the bedside in patients with primary acute brain injury, aiming to detect in a timely fashion secondary cerebral insults (e.g., ischemia, elevated intracranial pressure, nonconvulsive seizures) that are known to further aggravate patient outcome (see Chap. 5). In particular, quantitative EEG has shown great potential for the detection of delayed cerebral ischemia after SAH (Foreman and Claassen 2012). It may be conceivable that using EEG in this context may prevent secondary injury and improve outcome; however, further studies are needed to confirm this issue. Finally, EEG, together with other electrophysiological tools such as somatosensory and auditory evoked potentials (see Chap. 6), is increasingly used in combination with clinical examination, in order to better understand the mechanisms of acute coma and to further improve outcome prognostication after acute brain injury, particularly in patients with HIE after CA (Oddo and Rossetti 2011; Taccone et al. 2014).

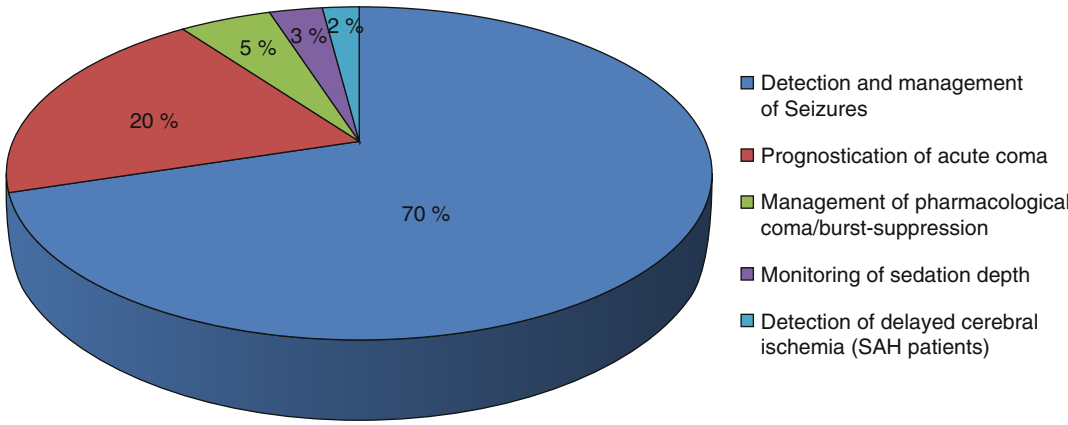

Fig. 1.2 Current indications and potential clinical utility of electrophysiological examinations in the ICU. EEG is primarily used to diagnose and manage seizures/status epilepticus. It has an emerging role and great potential in other conditions, mainly for the management of pharmacological coma, the monitoring of the depth of sedation in the mechanically ventilated patient, and as an additional noninvasive tool to detect secondary cerebral insults in acute brain injury patients, e.g., delayed ischemia after aneurysmal subarachnoid hemorrhage. Finally, EEG and evoked potentials have an important role in addition to clinical examination to improve coma prognostication, particularly after cardiac arrest

1.4 Conclusions and Perspectives

Implementation of EEG in the ICU is increasingly recognized as an important step for the care of critically ill patients. Integrating EEG into the ICU environment requires a specific expertise, including refined technical setup, highly trained EEG technicians, and specialized nurse and medical staff. EEG implementation in the particular setting of ICU may be a challenging task, and one that is still not available worldwide. A great challenge will be to render EEG monitoring in the ICU more accessible. Among others, future perspectives in this respect include increased collaboration between clinical neurophysiologists, epileptologists, and intensivists, and the development of modern technologies to improve interface and the accuracy in EEG interpretation in the particular ICU environment.

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2 Electroencephalography and Evoked Potentials: Technical Background

Vincent Alvarez and Andrea O. Rossetti

Contents

Abstract

Information provided by neurophysiological investigations is of outstanding importance for clinical practice and research dealing with patients with disorders of consciousness. However, because most of these patients are treated in the intensive care unit (ICU), some related problems must be known. The ICU is an environment full of electrical devices prone to produce artifacts, and patients with disorders of consciousness are exposed to many different treatments that may interfere with electrical signals and their interpretation. It is therefore highly important that the electroencephalogram (EEG) and the different sorts of evoked potentials (EP) are acquired under good conditions and according to current recommendations. This chapter reviews the technical background necessary to illustrate how to acquire good EEG/EP signals in the ICU, and will also focus on some practical pitfalls.

2.1 Electroencephalography (EEG)

Electroencephalography is the recording of the brain electrical activity and represents a unique way to look at the brain function in real time. This technique is very convenient for patients with disorders of consciousness in the intensive care unit: it is a noninvasive procedure that can be performed with a portable machine at bedside.

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Until the last decades of the last century, EEGs were recorded on paper. This limited the acquisition of large amounts of data and also the review of prolonged recordings. The development of digital EEG machines has completely changed the way we think about the EEG in the ICU. It is now possible to record and stock large amounts of data and also to apply complex signal analyses, such as spectral analyses and automatic seizure detection, rendering the review of prolonged records more effective. The importance of EEG evaluation has therefore increased and has become a standard in the evaluation of patients in the ICU with consciousness disorders (Kurtz et al. 2009) (see also Chap. 1). To understand how to record an EEG trace, each step between the brain EEG generators to the wave on the screen should be considered.

2.1.1 Basic Neurophysiology

The scalp EEG represents a graph of voltage differences between two different locations over time (Fisch 1999); the signal is recorded at the scalp but actually arises from pyramidal neurons located in the cortical layers, arranged in columns perpendicular to the brain's surface. The sum of thousands of synchronized postsynaptic potentials will generate electric currents recorded at the surface. The scalp EEG can only detect electrical potentials generated near the brain surface. Moreover, at least 6 cm^2 (or, roughly, one square inch) of the cortex with synchronous neuronal activity is needed to create a scalp potential (Fisch 1999). This surface activity is synchronized and modulated by complex neuronal networks involving interactions between the cortex and deep structures of the brain, mainly the thalamus, as well as other cortical areas. This will produce the rhythmicity and the waves of the brain activity seen on the EEG.

2.1.2 Impedance and Electrodes

The potentials recorded on scalp EEG are measured in microvolt (μV), typically 10–100, while, as a comparison, the electrocardiogram measures are in millivolt (mV). These voltage signals have to cross several layers and potential "electrical barriers" to reach the surface, such as the cerebrospinal fluid, the dura, the skull, and finally the scalp. Then, the current will go through electrodes and wires, which may also be considered as electrical obstacles. All these structures produce an opposition to the electric signal. In an alternating current (AC) circuit, this is called "impedance" and it is measured in Ω (Ohms). According to the International Federation of Clinical Neurophysiology (IFCN) guidelines and the American Clinical Neurophysiology Society (ACNS) recommendations, electrodes impedances should be checked before every recording and should not exceed 5,000 Ω (=5 kΩ) (Ebner et al. 1999; American Clinical Neurophysiology 2008). In practice, one can accept values up to 10 k Ω. Obtaining low and uniform impedances throughout all the electrodes is crucial in order to obtain a reliable EEG signal and avoid artifacts. On the other hand, impedances less than 1 kΩ may indicate a possible shortcut between electrodes and should be specifically addressed.

One of the major components of the impedance is the skin, particularly the outermost layer of dead cells (Eggins 1993). It is thus important to minimize this barrier by abrading the skin by applying an abrasive and conductive gel to a cotton swab and rubbing the skin before fixing the electrode. Then a conductive gel/paste should be used to assure a good contact between the scalp and the electrode. The second impedance component is the electrode itself, depending on its shape and its material.

There are many different types of electrodes available. Most contain a metal contact surface, an insulated wire, and a connecting pin. They are usually made of silver, gold, tin, or platinum and coated with chloride-treated silver. There is an important issue regarding metal electrodes and brain imaging, which is often required in critically ill patients: metal electrodes have to be removed because they can cause important artifacts. Moreover, while there is no safety issue with CT scan, classical electrodes may warm and cause scalp burns during MRI studies. Some newer electrodes are MRI and CT compatible and are made of con-

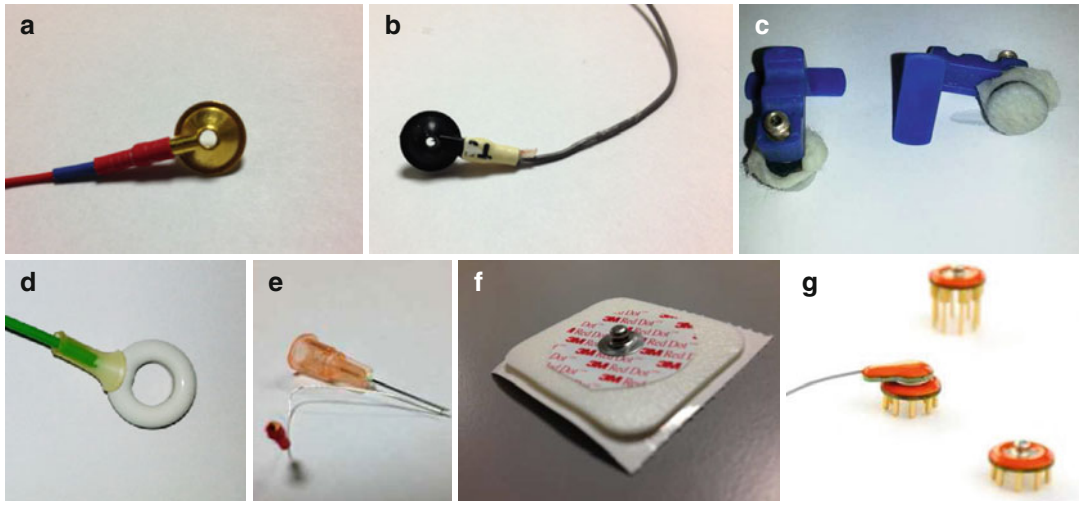

Fig. 2.1 Different types of electrodes. (**a**) Gold cup electrode. (**b**) Plastic cup electrode CT/MRI compatible. (**c**) Pad electrode. (**d**) Ring electrode. (**e**) Subdermal electrode (also available as MRI/CT compatible). (**f**) Auto-adhesive, pre-gelled, disposable electrode. (**g**) Dry electrode (g.SAHARA®, G-tec medical engineer, reprinted with kind permission)

ductive plastic with a thin silver coat, coupled with very short leads (Das et al. 2009). These conductive plastic electrodes, increasingly in view of their practical advantages, enable good quality EEG recording with no CT artifacts and only minor MRI changes, without any safety issues. Of note, this kind of system may need to be removed if a conventional arteriography is needed, as the projection of the electrodes and wires will impact on the interpretation of this investigation.

There are several different types/shapes of electrodes that can be used in the ICU (Fig. 2.1):

- *Cup electrodes* have typically a diameter of 4–10 mm and a hole on its top to allow the application of saline gel (for conduction), as on a typical EEG. For monitoring, these have to be fixed on the scalp with an adhesive plaster (Fig. 2.1a). Of note, after 10–14 days of recording, 2–3 days without electrodes ("electrode holiday") are advisable to prevent skin damages. These electrodes are recommended by the IFCN for EEG monitoring (Chatrian et al. 1996). CT-/MRI-compatible plastic cup electrodes are also available (Fig. 2.1b).
- *Pad electrodes* held in place with a rubber headset are convenient because they allow a precise placement even in patients with small skull defects or skin scars and avoid the fastidious work of standard cup electrodes fixation/removal. However, they are neither suitable for EEG monitoring, nor for patients with significant skull defects (Fig. 2.1c).
- *Ring electrodes* fixed with electrode holder on a textile cap allow a rapid placement (Fig. 2.1d). Moreover, commercially available caps are built according to the international 10–20 system (see below). However, these are not suitable for patients with skull defects or recent skin scars and do not assure a satisfying long-term contact for EEG monitoring. This type is also prone to shortcuts between different electrodes, because of the important amount of conductive gel needed.
- *Subdermal electrodes* made of stainless or platinum needles (Fig. 2.1e). Because these are placed under the epidermis, skin abrasion is not necessary. They can be applied very quickly; however, because of their small diameters, they may have a relatively high impedance (Freye E & Levy J. 2005) even though they penetrate the skin. Because of their subdermal position, they are only suitable for comatose patients and may induce local skin infection.
- *Disposable and pre-gelled pad electrodes* (Fig. 2.1f). These could possibly decrease the risk of cross-contamination inherent to stan-

dard electrodes and spare time to the technician team by eliminating the time required for disinfection. These electrodes are however difficult to use over the hair.

- *Dry electrodes* (Fig. 2.1g). This new type of electrodes is now commercially available but not routinely used in clinical practice. Their name is due to the fact that neither gel nor skin preparation is needed. In view of their quick application and good impedance, this type of electrodes may be more frequently used in the future.

Every electrode type has thus its advantages and disadvantages summarized in Table 2.1, but cup electrodes fixed on patient's scalp with an adhesive conductive paste, represent probably the most suitable type for EEG monitoring.

2.1.3 Electrode Position and Montages

2.1.3.1 Electrode Position: The 10–20 System

The IFCN proposes a unified electrode nomenclature and electrode placement, called the 10–20 system (Klem et al. 1999), which includes 21 electrodes providing a good scalp coverage. This international and widely adopted system should be used on every scalp EEG in the ICU. The electrodes are named with a letter, representing the anatomical region (Fp = frontopolar, F = frontal, C = central, P = parietal, T = temporal, and O = occipital), and a number (even numbers on the right and odd numbers on the left; midline electrode is called z (zero)) (Fig. 2.2). The

Table 2.1 Pros and cons for every type of EEG electrode

Electrode type	Pros	Cons
Cup electrodes	Good impedance	Time consuming
	Can be used for long-term monitoring	Technician needed
	Possible electrode placement modification if required (skull defects, skin scar, clip, etc.)	
	Recommended by the IFCN	
	CT-/MRI-compatible electrodes available	
Pad electrodes	Good impedance	Only some hours of good recording
	Relatively fast setup	Not suitable for patient with significant skull defect
	May be used on patients with minor skull defect	Technician most often needed
	Possible electrode placement modification if required (skin scar, clip, etc.)	
Ring electrodes	Good impedance	Only some hours of good recording
	Fast setup	Prone to bridge because of the important quantity of conductive paste needed
		Not suitable for patients with skull defects
		Electrode placement modification is impossible
		Technician most often needed
Needle electrodes	Fast setup	Only suitable for comatose patients. May have a relatively high impedance because of small diameter
	CT-/MRI-compatible electrodes available	Technician/nurse most often needed
		May be prone to skin infection
Disposable and pre-gelled electrodes	Fast setup	Difficult to use over hair, so full scalp coverage is impossible
	No risk of cross-contamination	Fair impedance
	Can be placed by any healthcare provider with minimal teaching	
Dry electrodes	Good impedance	Cost
	Fast setup because no skin preparation is needed	Mostly used for current research
		Not widely used in clinical practice

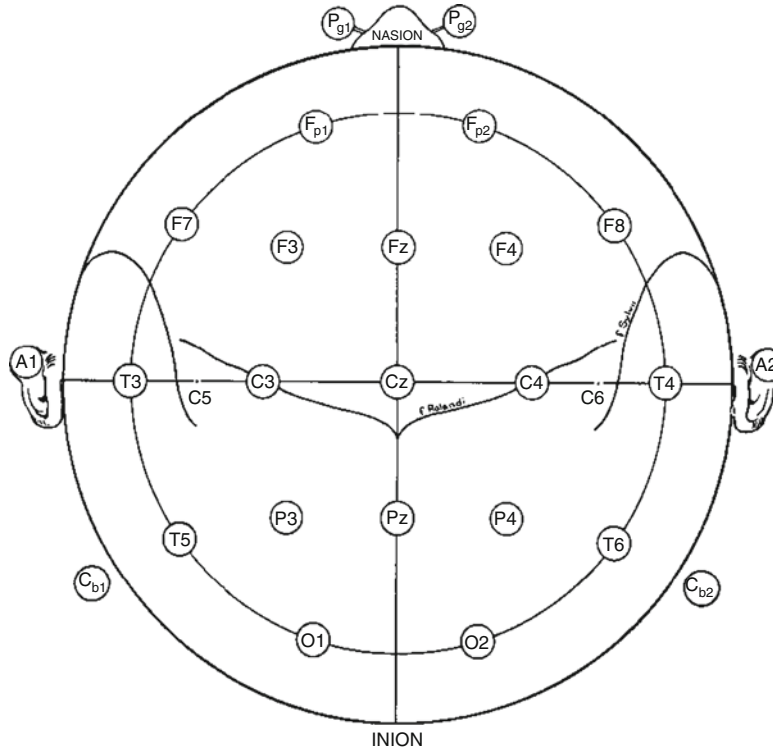

Fig. 2.2 A single plane projection of the head, showing all standard positions according to the 10–20 system (Adapted from Klem et al. (1999). © International Federation of Clinical Neurophysiology. Reprinted with kind permission from the International Federation of Clinical Neurophysiology)

system is called 10–20 because each electrode is separated with 10 or 20 % of an anatomical distance.

The guidelines edited by the IFCN provide detailed methods of the electrode placement based on anatomical landmarks (Klem et al. 1999). The first step is to place the midline chain of electrodes, Fpz, Fz, Cz, Pz, and Oz (Fig. 2.3), by measuring the distance between the nasion and the inion through the vertex. Of note, Fpz and Oz positions will not be covered by an electrode. The next step is to measure the coronal distance from the left preauricular point to the right one through Cz. This will provide the position of T3 (also named T7), C3, C4, and T4 (also named T8) (Fig. 2.4). Then, in order to obtain the position of Fp1, F7, T5 (also named P7), and O1 on the left and Fp2, F8, T6 (also called P8), and O2 on the right, a circumferential measurement of the head through Fz, T3, Oz, and T4 should be obtained (Fig. 2.5). Finally, F3 should be placed at the intersection of Fp1–C3 and F7–Fz, F4 at the intersection between Fp2–C4 and Fz–F8, P3 at the intersection of C3–O1 and Pz–T5, and P4 at the intersection between C4–O2 and Pz–T6. A cerebral or extracerebral reference electrode, a ground, and an electrocardiogram should be placed eventually.

2.1.3.2 Montages

The types of montages are highly variable in every center. The same montages used for routine EEG should be used. Some bipolar and referential arrangements are proposed by the ACNS (American Clinical Neurophysiology 2006a) and can be easily applied. Of note, the most popular is the traditional longitudinal bipolar montage (also known as "the double banana") (Fig. 2.6). The use of the 21 electrodes provided by the 10–20 system offers good scalp coverage, but, in selected cases, montages with fewer electrodes can be used. To determine brain death, for example (this only applies in certain countries), the distance between electrodes should be at least 10 cm. The ACNS recommends a bipolar montage using 10 electrodes, for example, F7-T5, F8-T6, F3-P3, F4-P4, and Fz-Pz (American Clinical Neurophysiology 2006b).

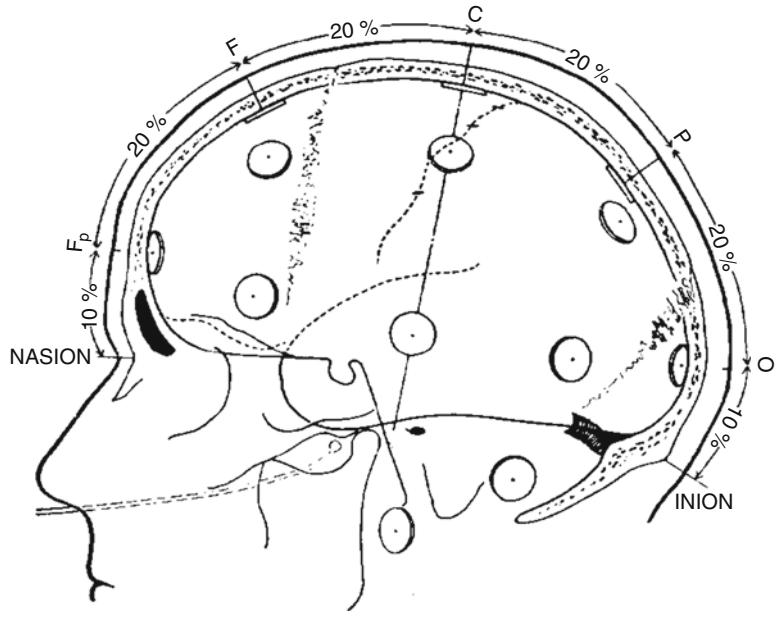

Fig. 2.3 Lateral view of the skull to show methods of measurement from nasion to inion at the midline. Percentages indicated represent proportions of the measured distance from the nasion to the inion (Adapted from Klem et al. (1999). © International Federation of Clinical Neurophysiology. Reprinted with kind permission from the International Federation of Clinical Neurophysiology)

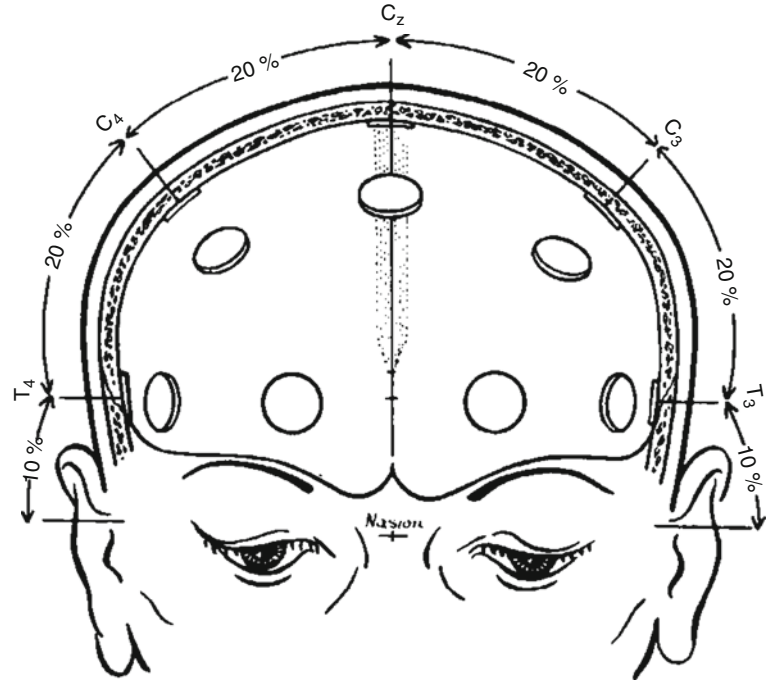

Fig. 2.4 Frontal view of the skull showing the method of measurement for the central line of electrodes as described in the text (Adapted from Klem et al. (1999). © International Federation of Clinical Neurophysiology. Reprinted with kind permission from the International Federation of Clinical Neurophysiology)

2.1.3.3 Other Montages/Electrode Positions

Anterior Temporal Electrodes

If the temporal regions are an important issue, two additional electrodes can be added to maximize the anterior temporal lobe coverage. These are called T1 (left) and T2 (right). They are placed one cm above the line cut at the third next to the ear, between the external angle of the eye and the preauricular point.

Extracerebral Electrodes ("Polygraphic Recording")

Additional electrodes placed near the eyes (to record eye movements), on selected muscles (to record particular body region of interest, such as

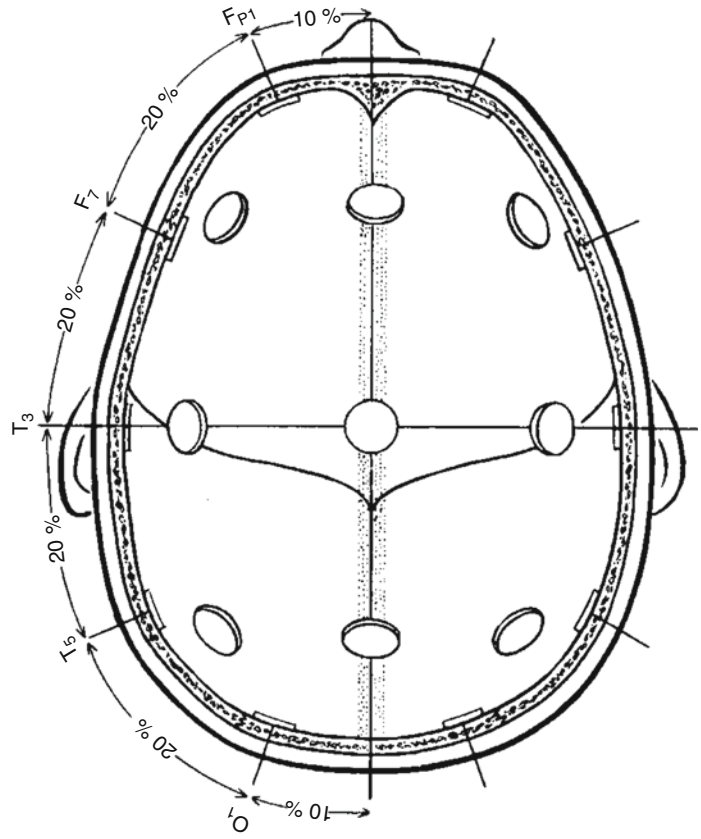

Fig. 2.5 Superior view with cross section of the skull through the temporal line of electrodes (Adapted from Klem et al. (1999). © International Federation of Clinical Neurophysiology. Reprinted with kind permission from the International Federation of Clinical Neurophysiology)

the tibial and the submental regions) and respiratory electrodes (measuring the movements of chest and abdomen) can also be added. These additional electrodes can be helpful to discriminate between cerebral or extracerebral activities and artifacts. A routine extracerebral electrode (pair) is the EKG.

"Subhairline" Montages

Because most of the centers cannot provide 24/7 EEG technician coverage, some simple montages that can be placed with auto-adhesive electrodes have been developed. To avoid scalp and hair issue, disposable and pre-gelled pad electrodes are placed just below the hairline. Of note, EKG electrodes can be used for this purpose. A study demonstrated a sensitivity of only 68 % but a 98 % specificity for seizure detection using a 4-channel commercial ICU bedside monitoring system (Young et al. 2009) (Fig. 2.7). Another study retrospectively recreated a digital "subhairline" EEG from standard 10–20 EEG by

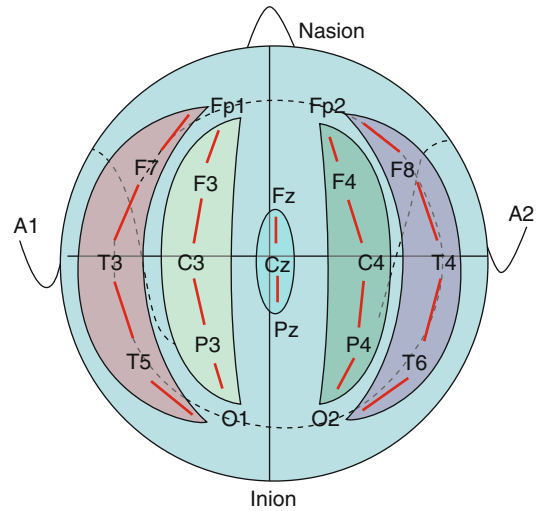

Fig. 2.6 The longitudinal bipolar or the "double banana" montage

using only 8 electrodes: Fp1, F7, T3, and T5 on the left and Fp2, F8, T4, and T6 on the right. The sensitivity for seizure detection was only 72 % (Kolls and Husain 2007). The addition of

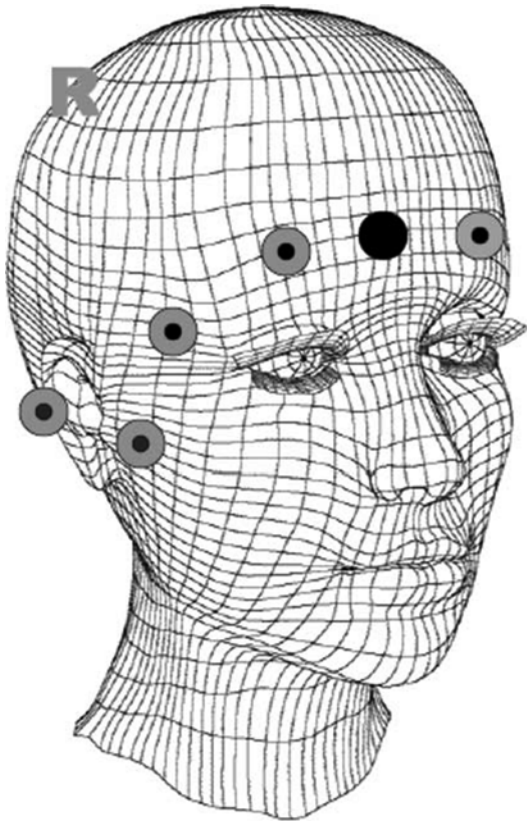

Fig. 2.7 Example of a "subhairline montage" (Adapted from Young et al. (2009), Figure 1, ©Humana Press Inc. Reprinted with kind permission from Springer Science + Business Media B.V.)

Fig. 2.8 Example of a disposable auto-adhesive EEG device (StatNet™, HydroDot Inc., reprinted with kind permission)

Cz seems to increase the sensitivity up to 92 % (Karakis et al. 2010).

Disposable Devices

Some disposable and quickly applicable "electrode systems" have been developed. For example, pre-gelled EEG headpieces, embedded with integrated wiring, are commercially available (Fig. 2.8). However, these only provide about 4 h of reliable recording with usually less than 21 scalp electrodes; they cannot be used on patients with skull defect, and, because of the disposable nature, related costs should be considered. It seems reasonable to consider this system when a standard electrode placement is not available and the EEG information is needed immediately.

2.1.4 Jackbox, Amplifiers, and Filters

2.1.4.1 Jackbox

Each electrode's wire will be plugged in a jackbox (Fig. 2.9). Many devices often surround the ICU beds; therefore, a small jackbox that can be placed near the patient's head is recommended. The jackbox should also be fixed and possibly sealed into a waterproof packing to avoid damage (Herman 2013). The jackbox contains the amplifiers; according to the IFCN (Ebner et al. 1999), at least 23 connectors (amplifiers) are required for clinical practice. However, larger capacity input systems are available (for higher special resolution and extracerebral electrodes).

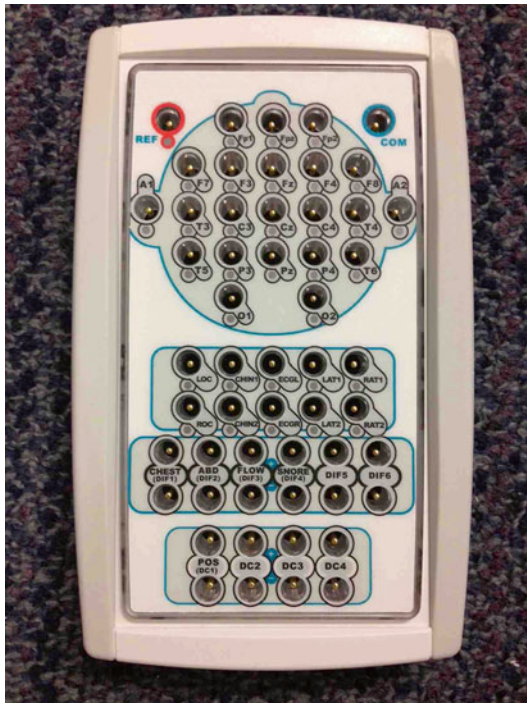

Fig. 2.9 An example of an EEG jackbox

2.1.4.2 Amplifiers

EEG amplifiers have two functions: discrimination and amplification (Fisch 1999). Discrimination is the ability to amplify the difference between two electrical potentials: the amplifier will subtract the signal of two different input EEG electrodes, between two adjacent scalp electrodes on a bipolar montage or between one electrode and a common reference for a referential montage, for example. Of note, the subtraction implies that signals common to both subtracted electrodes will be suppressed (this may also give rise to the "electrical bridge," when an analogous signal between two electrodes is seen as a flat line in a bipolar montage). Artifacts that are common to both electrodes will also be suppressed. In this way, an amplifier can sort out true EEG brain signals and artifacts. This discrimination power can be measured with the "common mode rejection ratio": the higher this ratio, the higher the discrimination power. With current EEG machines, the specified common mode rejection ratio should be at least >80 dB, typically 100 dB (Ebner et al. 1999). Then, the amplifier will increase the potential difference; this effect is called "gain" or sensitivity. A typical setting for EEG is 7–10 uV/mm.

2.1.4.3 Filters

Filters are used to exclude frequencies that are not generated by the brain. In clinical practice, frequencies of interest are between 1 and 30 Hz. Therefore, the low-frequency filter (synonymous with high-pass filter) should be set at 0.5–1 Hz and the high-frequency filter (or low-pass filter) at 70 Hz. A notch filter of 50 or 60 Hz (depending on the country) for power line artifacts should be used when needed. Of note, it is advisable to start the recording without the notch filter, as electrodes with loose contact to the scalp will tend to show a prominent notch artifact.

2.1.5 Digital EEG and Video

Nowadays, nearly all EEG recordings are digital. While the advantages are obvious, this implies some precautions.

2.1.5.1 Digitalization: Sampling Rate and Resolution

To be recorded on a computer, a wave has to be sampled. According to the Nyquist theorem, the sampling rate of a sinusoidal wave should be at least two times higher than the recorded frequency. However, this represents the strict minimum requirement, and to avoid aliasing effects (Fig. 2.10), the sampling rate should be at least 3 times the high-filter setting (American Clinical Neurophysiology 2006c). Since the high-frequency filter is typically set at 70 Hz, a 250 Hz sampling rate is reasonable for clinical purposes. Higher sampling rates may be used, but will produce much larger file sizes. Since recordings should be able to resolve EEG down to 0.5 uV, digitization should use a resolution of 12 or more bits (American Clinical Neurophysiology 2006c).

2.1.5.2 Screen

EEG traces should be read on working stations equipped with screens larger than 17", allowing a comfortable analysis. Multiple screens could even

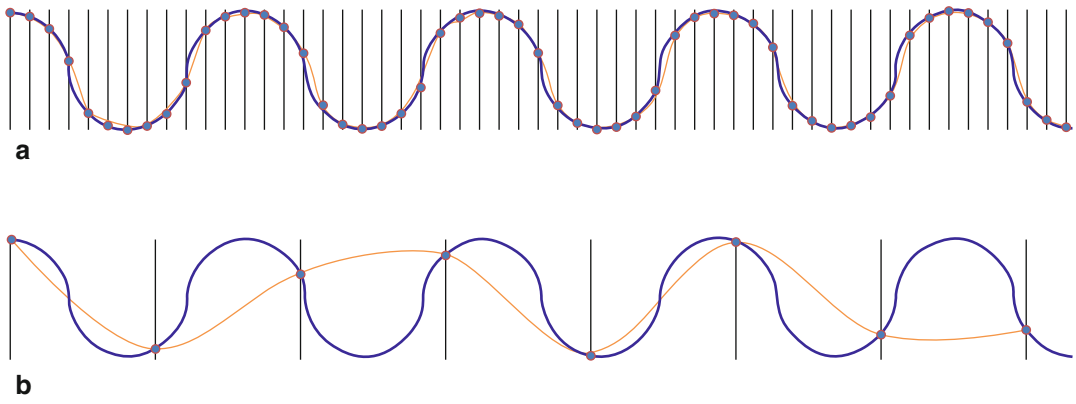

Fig. 2.10 Sampling rate and aliasing effect. In *blue*, original sinusoidal wave; in *orange*, digitalized sinusoidal wave; in *black*, sampling rate. (**a**) Due to appropriate sampling rate, the digital sinusoidal wave matches the original one. (**b**) Due to insufficient sampling rate, the digital wave looks too slow = aliasing effect

be better, especially if additional signals have to be evaluated (such as quantitative EEG analysis).

2.1.5.3 EEG Software and Network

Every EEG system has its own EEG software, featuring the basic requirements needed for a standard analysis. A complementary software providing spectral analysis, automatic seizure detection, symmetry index, and other features is advised for ICU monitoring. Indeed, these tools render the analysis of prolonged EEGs more efficient and may save considerable time (Moura LMVR et al. 2014). The software used on the recording machine should be user-friendly enough for inexperienced EEG healthcare providers, in order to easily add annotations on EEG trace. In the same setting, a "push-button" possibility (to mark an event of clinical significance) should be offered. Because ICU EEG should be interpreted at any time, an acquisition machine should be ideally plugged on a network and be accessible anytime from the working/reading station.

2.1.5.4 Data Storage

Data storage also represents an important issue. Prolonged continuous EEG recordings generate large amounts of information to be saved. The storage of the entire EEG traces and only the pertinent video part represents a good compromise. There is no consensus for the best data backup (CD, DVD, hard drive, secured network, etc.). While the latter seems to offer the best security, specifically advantages and disadvantages have to be weighed with each hospital informatics team and availabilities.

2.1.5.5 Video

Video recording is strongly recommended on every ICU monitoring. Many artifacts cannot be identified without a correlated video. Moreover, electro-clinical correlation can be carefully analyzed in case of seizures, for example. A wide-angle high-resolution camera is recommended. The zoom should set in a way that at least the face and the arms of the patients are seen. Because EEG machines are frequently moved, the framing should be checked and corrected regularly.

2.1.6 The EEG at the Bedside: Practical Aspects in the ICU

There are some highly relevant practical issues specific to the ICU to be considered before every EEG recording. Patients in the ICU are exposed to many external factors that can influence the EEG trace and thus its interpretation.

2.1.6.1 Body Temperature

It is known that even without brain pathology, hypothermia leads to progressive EEG slowing and finally EEG suppression (Mezrow et al. 1994), but without important clinical issue until a temperature under 30 °C. Indeed, in a series of 47 patients undergoing profound hypothermia for aortic surgery, the EEG first showed periodic complexes over a continuous background at a mean temperature of 29.4 °C (±3 °C), a burst-suppression pattern appeared at 24.4 °C (±4 °C), followed by a complete EEG silence at a 17.8 °C

(±4 °C) (Stecker et al. 2001). EEG can be recorded during mild therapeutic hypothermia to 32°–33 °C, after brain anoxia, for example (Rossetti et al. 2012), but this should be considered during interpretation, as the temperature and the related pharmacological sedation (this aspect seems to have more weight) may mildly slow and reduce the amplitude of the signals.

2.1.6.2 Medication

Sedative drugs, antipsychotic drugs, antiepileptic agents, and all compounds with an effect on the central nervous system could potentially alter the EEG trace. Patients in the ICU are particularly exposed to these drugs. All medication should be listed and known.

2.1.6.3 Skull Defect

A skull defect, as small as a burr hole or as big as a large craniotomy, can cause a "breach rhythm" (focal accentuation of fast activity) and can be misleading if unknown. There is no clear correlation between the size of the skull defect and the importance of the breach rhythm.

2.1.6.4 Muscular Activity

Unresponsive patients may present a variety of involuntary movements, like myoclonus or shivering, which can produce significant artifacts. If the EEG monitoring is non-interpretable because of movement artifacts, a transitory muscular blockade can be considered (Chatrian et al. 1996). Short-acting agents are preferred, such as vecuronium or succinylcholine. Only trained healthcare providers should administer these drugs; it is common practice to add some mild sedation at the same time; this should not impact the global architecture of the recordings.

2.1.6.5 Electrical Devices

Electrical interference can result from numerous sources in the ICU, in view of the high technical support needed to treat these patients. In case of any non-concordant findings on the curves, these devices have to be considered as an artifact generator, for example, mechanical ventilator, external cardiac support, dialysis devices, electric bed, anti-scar mattress, or perfusion pumps.

2.1.6.6 Reactivity Assessment (See Also Chap. 5)

Reactivity should be assessed for every EEG performed on patients with impaired consciousness, unless there is a concern of raised intracranial pressure due to stimuli (Young 2000). EEG background reactivity is associated with a potential of recovery (Young et al. 1999), particularly in the context of brain anoxia (Rossetti et al. 2010). Timing of each stimulus has to be clearly noted on the EEG trace. Auditory stimuli (loud calling, hand clapping far from the electrodes) should be started first. Eye opening (under a light source) may be applied next. Then, noxious stimuli will be tested. Painful stimuli over the trunk are preferred. Indeed, temperature, focal compressive neuropathies, spinal cord lesions, and stroke can all make noxious stimuli applied on the limbs less reliable, while axial regions are mostly bilaterally represented in the brain. Sternal rubbing, pressure on the supraorbital nerve above the eyebrow, and mandibular advancement will produce EEG artifacts. We recommend nipple pinching, as it provides a strong noxious stimulus without inducing artifacts. We also recommend not performing stimulations less than 20" apart, in order to allow the patient (and the EEG) to recover to baseline.

2.1.6.7 Length of EEG: LTM or Spot EEGs? (See Also Chap. 5)

This major question is still unsolved, and the IFCN recommendations do not address it (Guérit et al. 1999). EEG monitoring is highly "resource consuming"; on the other hand, a continuous EEG undoubtedly appears attractive and allows the follow-up of the evolution of the patient's brain activity. It has recently been shown that two standard intermittent EEGs (20–30 min) show a comparable performance than continuous EEG for outcome prognostication and identification of epileptiform transients in a relatively small sample of comatose survivors of cardiac arrest (Alvarez et al. 2013). On the other hand, EEG monitoring detects more seizures (which are frequently non-convulsive) (Claassen et al. 2004) and has repetitively proven to be important for the management of comatose patients with subarachnoid hemorrhage (Lindgren et al. 2012),

intracerebral hemorrhage (Claassen et al. 2007), or traumatic brain injury. A recent retrospective study focusing on mechanically ventilated patients shows an association between the use of continuous EEG monitoring and a lower mortality rate (Ney et al. 2013). Overall, the recording length should be discussed for each case, based on the clinical setting and EEG availability on a daily basis.

2.2 Evoked Potentials

Evoked potentials (EPs) correspond to EEG alterations in response to a stimulus (Guérit 2005). The stimulus can be somatosensory (somatosensory evoked potential) (SSEP), auditory (auditory evoked potential (AED), or visual (visual evoked potential (VEP). There are different types of EPs, depending on the timing of recording: "short-latency" evoked potentials correspond to the recordings of signals generated by the ascending pathways and the primary cortex; "middle" or "long" latency potentials represent more complex waves reflecting brain network activities, such as "cognitive" potentials. In routine clinical practice, short-latency EPs are the most widely used. The main advantage of the EP technique is that it reflects the function of certain neuronal pathways, thus complementing structural information given by imaging studies; EPs are also relatively resistant to even consequent doses of pharmacological sedation, as opposed to the EEG. Moreover, EPs give numeric data that may prove useful for follow-up. In the ICU practice, SSEPs are widely used and AEPs far less frequently. Because VEPs require patient's attention for good signals, they are rarely, if at all, used in this setting and thus will not be discussed further.

2.2.1 General Considerations

EPs are, like EEG, recorded at bedside: the same practical considerations regarding artifacts as described above have to be kept in mind. Of note, EPs are generally highly "resistant" to sedation or hypothermia. Cortical somatosensory evoked potentials remain present even at a sedation level sufficient to induce an isoelectric EEG (Cruccu et al. 2008), albeit with some prolonged latency and reduced amplitude. Whereas EEG signals may disappear with body temperature under 24 °C, cortical somatosensory evoked potentials remain present until 21 °C and AEPs disappear only under 20 °C (Cruccu et al. 2008). These temperature cutoffs are usually not reached in clinical practice, even with therapeutic hypothermia. However, EP signal amplitude is much smaller than EEG, thus requiring multiple trial averaging. The number of trials depends on the type of EP.

The naming of the EP signal is quite intuitive. All are made up of one letter and a number: the letter *P* or *N* represents the wave polarity (*P* for positive and *N* for negative) and the number the delay (in ms) between the stimulation and the wave. For example, the main cortical wave obtained after median nerve stimulation is negative and appears at around 20 ms after the electrical stimulation; it is thus called N20.

2.2.2 Somatosensory Evoked Potential (SSEP) (See Also Chap. 6)

These represent the electrophysiological response to the stimulation of the sensory pathways (dorsal column–lemniscal system). SSEPs can be elicited from every nerve, although the median and the tibial nerves are the most widely used and recommended by the IFCN (Maugnière et al. 1999). In patients with consciousness disorders, SSEP assessment is frequently limited to the median nerve (Chatrian et al. 1996). Therefore, only the median nerve EP stimulation will be described.

2.2.2.1 Stimulation

SSEPs are usually obtained with bipolar electrical transcutaneous nerve stimulation. The IFCN recommendations are to use monophasic square electrical pulses of 100–500 μs with two electrodes (Maugnière et al. 1999). The anode (the positive electrode) should be placed on the wrist crease and the cathode (the negative

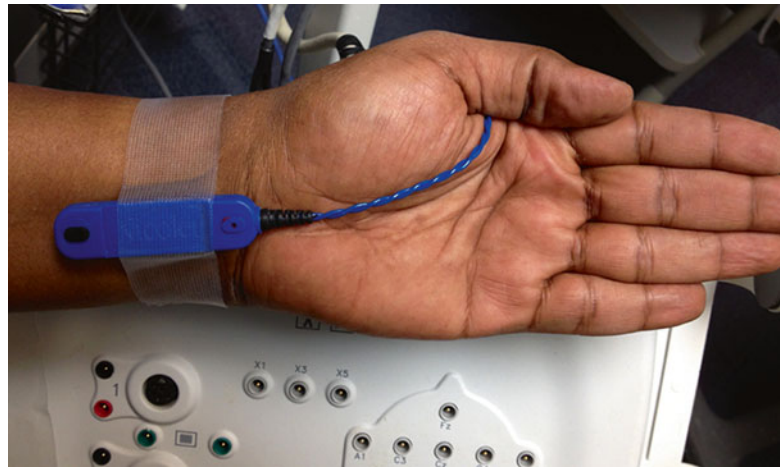

Fig. 2.11 An example of median nerve stimulation for SSEP: The anode (the positive electrode) is placed on the wrist crease and the cathode should be 2 cm proximally

electrode) should be 2 cm proximally (Fig. 2.11). The contraction of the thenar muscles can be used as an indicator of the correct location of stimulation. Both sides should be sequentially tested. The intensity of the signal should be just above the motor threshold. A stimulus rate of 3–5 Hz is recommended for routine practice (Cruccu et al. 2008); at least 500 trials should be averaged.

2.2.2.2 Recording

EEG disk electrodes should be used for recording with impedance lower than 5 kΩ. The filters should be set at 3 Hz for the low-frequency filters and 2,000 Hz for the high-frequency filters (Maugnière et al. 1999). In general, SSEPs are recorded at three levels: the peripheral, spinal cord, and cortex (Misulis and Fakhoury 2001a).

- A peripheral electrode is placed over the Erb's point ipsilateral to the stimulation (within the angle formed by the posterior border of the clavicular head of the sternocleidomastoid muscle and the clavicle, 2–3 cm above the clavicle). It is called *EPi* (for Erb's point ipsilateral).
- A spinal electrode is placed over C5 (or C6) spinous process. It is called *C5s*.
- Two cerebral electrodes are used: one ipsilateral (called *CPi*) to the stimulus and one contralateral (called *CPc*). These are placed halfway between C3 and P3 on the left (and labeled P3') and between C4 and P4 on the right (P4').
- A reference electrode (*Ref*) should be placed over the distal arm or the ipsilateral ear or over the Fz position, for example. A non-cephalic reference may provide more informative recordings but is technically more difficult (Cruccu et al. 2008).

The SSEP montage includes four channels:

- Channel 1: CPc–CPi (optional)
- Channel 2: CPc–Ref
- Channel 3: C5s–Ref
- Channel 4: EPi–Ref

Of note, some authors recommend a channel CPi–Ref (Misulis and Fakhoury 2001a) (see also Chap. 6). This channel is useful to record some deeper potentials called "far-field potentials." It does not provide any further information for outcome prediction in comatose patient in the acute setting. Thus, it is not recommended to perform it routinely in this setting.

2.2.2.3 Wave Names

Four waves are of particular interest in median nerve SSEPs in critically ill patients (Fig. 2.12):

- *N9*: It is recorded at Erb's point. N9 is particularly important because its presence assures that stimulation is effective and that the peripheral sensory system is functioning. An SSEP cannot be interpreted if N9 is not present.
- *N13*: It is recorded over the spinal electrodes and thus represents the potential generated by the dorsal horn neuron in the cervical medulla. As for N9, if N13 is not present, cortical SSEP should not be interpreted.

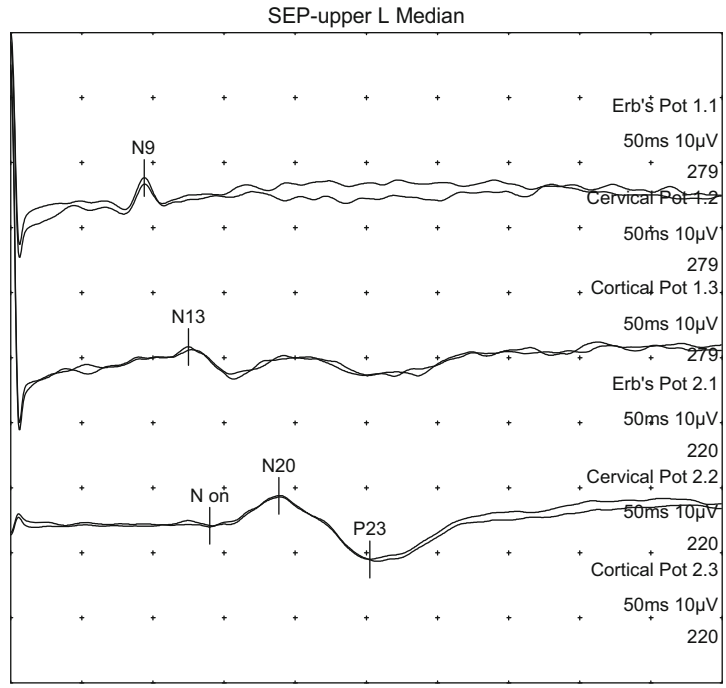

Fig. 2.12 Example of a normal SSEP obtained from median nerve stimulation. The *first line* represents the reference-Erb's point channel and displays N9. The *second line* represents the reference-cervical channel and displays N13, and the *bottom line* represents the reference-cerebral contralateral and displays N20 and P23

- *N20*: It is recorded over the parietal region and is generated by thalamocortical projections. Of note, although the negative (upward) N20 is the wave used for clinical interpretation, a small amplitude response can be identified thanks to the following positive (downward) wave; the latter should always be recognizable (see below).
- *P23*: N20 is usually followed by a positive deflection occurring 23 milliseconds after the stimulus.

Following parameters are important and should be described: the wave presence or not, the amplitude, and the latency.

2.2.3 Auditory Evoked Potential (AEP)

These represent the auditory pathway response to an auditory signal. The short-latency AEPs provide information about generators located between the acoustic nerve and the mesencephalon and thus allow a functional evaluation of the brainstem. For that reason, short-latency AEPs are frequently called the brainstem evoked potentials (BAEPs). These may be useful in cerebral death evaluation (in some countries), to assess brainstem dysfunction or to identify coma etiology when used in conjunction with other EPs (Chatrian et al. 1996). Middle- and long-latency auditory evoked potential are less frequently used in patients with consciousness disorders; these are "cognitive" potentials, and especially the "mismatch negativity" or the P300 may be of help for assessing prognosis in selected comatose patients (Tzovara et al. 2013). This topic is covered in Chap. 7.

2.2.3.1 Stimulation

Headphones or earplugs should be used to deliver a sound to the ear. Sounds consist usually of square wave "clicks," which should have these specificities (Misulis and Fakhoury 2001b):

- Stimulus duration, 100 µs.
- Stimulus rate, 8–10 Hz.
- Stimulus intensity: typically 70 dB in ICU (Freye 2005). The contralateral ear is "masked" with a white noise of 40 dB below the click level.
- While averaging 500 trials is enough for SSEP, BAEP should be based on 2,000 stimulations.

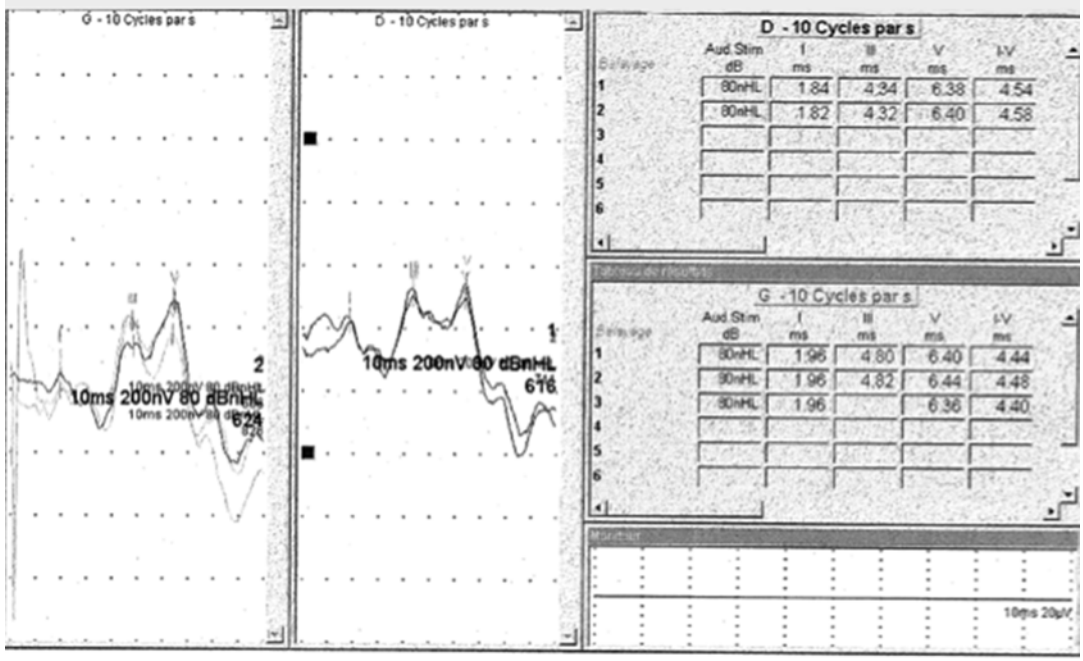

Fig. 2.13 An example of normal contralateral and ipsilateral brainstem auditory evoked potentials. Stimulation: 10 Hz at 80 dB. Wave latencies and I–V intervals are displayed on the right

2.2.3.2 Recording

- The filters should be set at 10–30 Hz for the low-frequency filters and at 2,500–3,000 Hz for the high-frequency filters:
- Four electrodes should be placed (Misulis and Fakhoury 2001b):
- One near each ear (e.g., ear lobe or over the mastoid), called *A1* and *A2*
- One over vertex on the scalp, called *Cz*
- And finally a ground at Fz or elsewhere over the head or the body

The BAEP montage includes 2 channels:

- Cz–A1
- Cz–A2

2.2.3.3 Wave Names

Five waves are described in BAEPs (Israel et al. 1999) (Fig. 2.13):

- *Wave I*: It is the first wave seen with ipsilateral ear stimulation and represents the acoustic nerve signal near the cochlea.
- *Wave II*: It is usually less consistent than Waves I and III (see below) and may be absent in normal subjects. It is thought to be generated by the proximal acoustic nerve near the cochlear nucleus.
- *Wave III*: It is usually one of the most prominent waves and probably generated by auditory pathways in the lower pons (including the upper olives).
- *Waves IV and V*: These waves are usually part of the same complex and are probably generated by the lateral lemniscus in the higher pons and the inferior colliculus in the caudal mesencephalon.

Several inter-wave distances are assessed. These are age dependent (especially in children). Normal values should be known for every BAEP laboratory according to the age of the subject:

- *I–V interpeak interval:* It represents the global response from the distal acoustic nerve to the midbrain. Its typical length is 4.5 ms.
- *I–III interpeak interval*: This interval reflects the conduction between the acoustic nerve and the pons. Its typical length is 2–2.5 ms.
- *III–V interpeak interval*: It correlates with the brainstem conduction time from the pons to the midbrain. Its typical time is 2–2.5 ms.

The presence of each wave is also of particular importance. If all waves are absent, a technical problem should be actively ruled out. A complete absence of response can however happen in severe hearing loss, acoustic nerve dysfunction, or brain death.

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Which EEG Patterns Deserve Treatment in the ICU?

3

Jong Woo Lee

Contents

Abstract

Paroxysmal and periodic patterns on continuously recorded EEG are commonly seen in the neurocritical care setting. As these patterns span the nonepileptic, interictal, postictal, and ictal continuum, accurate identification and appropriate management may present major challenges. This chapter will survey the most commonly seen EEG features, including sharp waveforms, rhythmic waves, lateralized and generalized periodic discharges, and subclinical seizures. To date, evidence-based guidelines for the management of these patterns are lacking; reasonable approaches to their management will be presented. Where continuous EEG monitoring is available, a stepwise approach with close follow-up of these uncertain EEG features may be reasonable in a large number of these cases.

3.1 Introduction

The proliferation of the use of continuous EEG monitoring in the intensive care unit (ICU) has led to the discovery that paroxysmal, rhythmic, and periodic patterns are very common (Chap. 1). These EEG features encompass a wide spectrum between nonepileptic, interictal, and ictal (Chong and Hirsch 2005). Management of such patterns is particularly challenging; delayed treatment of an ictal pattern may result in difficulty

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in ultimately controlling a seizure or may result in further brain damage. Overly aggressive treatment with antiepileptic drugs (AEDs) may conversely result in iatrogenic complications, such as side effects, pharmacokinetic interactions, or increased sedation, resulting in further morbidity in an already compromised patient.

This chapter will examine the most common patterns encountered in the neurocritical care setting. Two important caveats should be noted. Treatment decisions should be tailored to take account of the patient's comorbidities and severity of illness; with a similar brain injury and EEG pattern, one subject may be a candidate for aggressive intravenously infused anesthetic treatment whereas another patient should not be treated with this strategy. In addition, similar paroxysmal discharges in one particular underlying condition may not confer the same risk for seizures as compared to another condition; periodic lateralized epileptiform discharges (PLEDs) seen in metabolic dysfunction likely confer smaller risk for impending incontrovertible seizures as compared to PLEDs seen in brain tumors or other conditions with structural brain injury (Orta et al. 2009). These caveats inherently limit the ability to give all-encompassing guidelines for management for EEG patterns. Nonetheless, reasonable generalizable approaches to their treatment can be made.

3.2 Sharp Waveforms

In patients undergoing evaluation for epilepsy, isolated focal spikes or sharp waves have high specificity for impending clinical seizures. The existence of such discharges in a population with a reasonably high pretest probability for seizures translates into very high positive predictive value for seizures and is an indication for starting an AED. Although it may seem reasonable to presume that focal spikes or sharp waves have similar specificity in the ICU population as well, few formal studies have examined this systematically. The mere existence of a sharp waveform morphologically qualifying as a spike or sharp wave may not necessarily indicate similarly high risk for seizures. For example, in patients with acute ischemic strokes, focal spikes or sharp waves occur in 14 %, whereas seizures only in 2 % (Carrera et al. 2006).

The determination of a truly epileptiform focal spike/sharp wave is also challenging. Patients who have undergone a neurosurgical procedure may exhibit a "breach" rhythm. These waves consist of a wide variety of EEG changes, including predominantly a high-voltage 6–11 Hz mu-like (arciform) rhythm in the centrotemporal areas, as well as other sharp waveforms, at times with superimposed focal, low-voltage fast activity (Cobb et al. 1979). Discharges that markedly disrupt the background and associated with a field spanning more than two electrodes are particularly concerning for cortical irritability; at times, surface positive sharp waves should also be considered potentially epileptiform (Lee et al. 2010), especially in the presence of a brain parenchymal defect. However, breach patterns mimic features of, and may indeed be virtually impossible to distinguish from, epileptic sharp waves. Overly aggressive treatment of sharp waveforms is therefore not indicated.

In rare instances, one may encounter incontrovertible sharp waves from the hemisphere contralateral to a given lesion. The etiology of such patterns is unclear but may be due to subtle mass effect or possibly a result of previous, possibly silent, compromise of the contralateral hemisphere, for example, due to a scarring nidus from a previous silent ischemic process. In the absence of other clinical or electrographic indications, such patterns do not warrant treatment with an AED.

3.3 Periodic Patterns (See Also Chap. 5)

Periodic patterns, first described by Cobb and Hill (1950), are very commonly observed in the neurocritically ill population and present perhaps the most difficult challenge for clinicians and electroencephalographers as regards management. The gamut of periodic activity runs from manifestations of encephalopathy without any

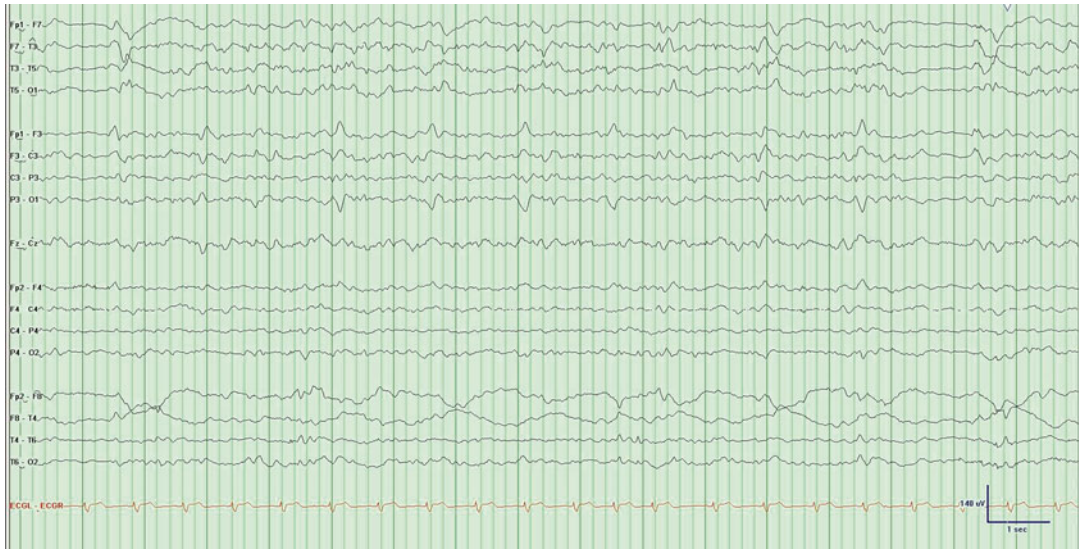

Fig. 3.1 An 84-year-old man with herpes simplex virus encephalitis. The EEG demonstrates lateralized periodic discharges (PLEDs or LPDs) on the left

proclivity toward epileptic activity to instances where distinguishing from frank status epilepticus is impossible. In an attempt to standardize the description of these patterns, the American Clinical Neurophysiology Society position paper on nomenclature subdivides these into lateralized periodic discharges (LPDs), bilateral independent periodic discharges (BIPDs), multifocal periodic discharges, and generalized periodic discharges (GPDs), replacing the frequently utilized terms periodic lateralized epileptiform discharges (PLEDs), biPLEDs, and generalized periodic epileptiform discharges (GPEDs). However, these terms are still widely employed in both the clinical and research arenas.

3.3.1 PLEDs/LPDs

PLEDs/LPDs (Fig. 3.1) have been long recognized as abnormal findings on EEGs, although their exact clinical significance is still unclear (Chong and Hirsch 2005). They are associated with nearly any type of structural abnormalities, including infectious, neoplastic, ischemic, hemorrhagic, and anoxic etiologies; therefore, they are not specific to any particular pathology. They are generally associated with poor prognosis, particularly in patients with neoplasms (Fitzpatrick and Lowry 2007; Orta et al. 2009). PLEDs have consistently been shown to be associated with seizures in 60–70 % of patients (Orta et al. 2009; Gaspard et al. 2013), but with some older studies reporting associations as high as 90 % (Snodgrass et al. 1989). Nonetheless, it is unclear whether PLEDs present an ictal phenomenon, an interictal pattern, a postictal pattern, or an epiphenomenon of brain injury. These features are associated with increase in glucose metabolism (Handforth et al. 1994) and blood flow (Assal et al. 2001; Ergun et al. 2006) and have also been reported as definite electrographic correlates to clinically apparent seizures (Singh et al. 2005), suggesting that at least some of them are definitely ictal phenomena requiring targeted treatment with AEDs (Garzon et al. 2001; Hughes 2010). On the other hand, patients with chronic PLEDs have been reported; in patients who experienced seizures, ictal discharges in the EEGs were distinct from the PLEDs, and during this time the PLEDs disappeared (Westmoreland et al. 1986), suggesting therefore that PLEDs are (also) interictal phenomena. As such, other authors have advised against routinely treating patients with these patterns, unless it can be established that they

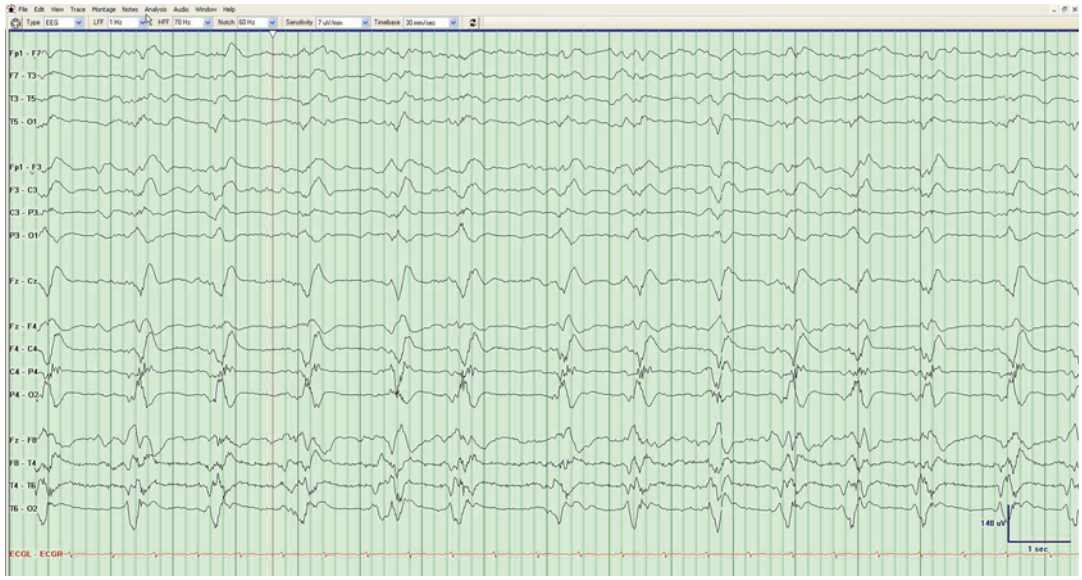

Fig. 3.2 A 78-year-old man with history of poststroke seizures. The EEG demonstrates *right* PLEDs and superimposed focal fast rhythmic discharges, consistent with PLEDs plus

represent a true ictal phenomenon rather than merely an interictal pattern (Rossetti and Oddo 2010). As depressed mental status is extremely prevalent in patients with PLEDs, determining whether PLEDs are ictal or not remains challenging.

We recommend starting or maintaining a conventional, nonsedating AED in all patients with PLEDs without escalating treatment unless clear ictal electrographic or clinical semiology is observed. To distinguish electrographic characterization of PLEDs more likely associated with seizures, a distinction between PLEDs proper versus PLEDs plus has been made (Reiher et al. 1991) (Fig. 3.2). The latter are associated with brief focal rhythmic discharges and are more frequently related to seizures. Another concerning findings are PLEDs whose frequency changes periodically over time, accelerating and decelerating, creating a sort of "accordion" appearance. More aggressive treatment may be warranted in such patients.

Although subtle movements are the most common manifestation of clinical seizures in the ICU population, in rare instances seizures may result in "negative" phenomenology. One example is ictal aphasia (Herskovitz and Schiller 2012), which may present with PLEDs without definite electrographic seizures. These aphasias resolve with the administration of AEDs and, as such, are to be regarded as ictal rather than a postictal phenomenon, and the associated PLEDs should be considered ictal as well. Similar presentations of PLEDs causing ictal monoparesis have been reported as well (Murahara et al. 2013). In general, though, there is insufficient evidence to determine whether electrographic PLED suppression is of any significant value, as these generally tend to be resistant to medication; complete suppression is rarely attempted due to the risk of overmedication.

In patients with severe unilateral brain pathology and encephalopathy, pseudo-PLEDs may result because severe pathology in the injured hemisphere suppresses what would otherwise have been generalized periodic discharges, resulting in PLED-like patterns over an intact hemisphere. Aggressive treatment with AEDs therefore may generally not be warranted in such patients.

3.3.2 BiPLEDs/BiPDs

BiPLEDs/BiPDs are defined as periodic discharges which are independently and simultaneously

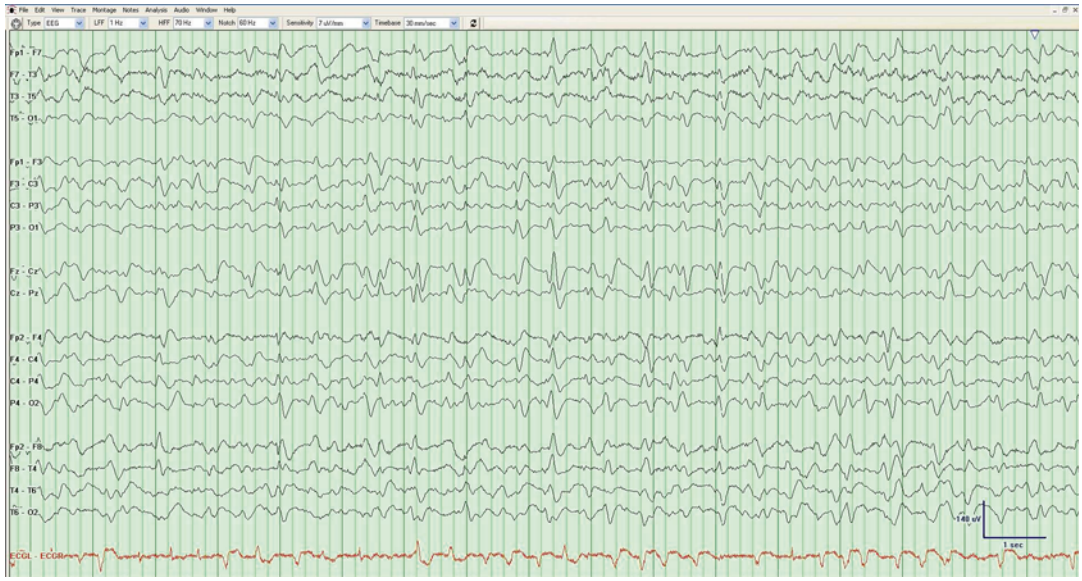

Fig. 3.3 A 61-year-old man with hepatic encephalopathy. The generalized periodic discharges have a triphasic morphology; this pattern should not be considered ictal

present in both hemispheres (Brenner and Schaul 1990). They are most typically seen in strokes, anoxic brain injury, or CNS infections (de la Paz and Brenner 1981) and are far less common than PLEDs, generally portending a more severe clinical state, as they are associated with higher risk for seizures, depressed consciousness, and mortality (de la Paz and Brenner 1981). As such, greater awareness regarding epileptic activity is required than in PLEDs, though the general approach to AED management is the same.

3.3.3 GPEDs/GPDs

GPEDs/GPDs are repetitive synchronous bilateral discharges occurring at regular or near-regular intervals. Among the periodic discharges, these remain the most difficult patterns to analyze, as they commonly span the gamut from the nonepileptic to status epilepticus, at times within a short period of time. GPEDs are nonspecific and may be seen in nearly any cause of depressed mental status. Although anoxic/metabolic or infectious etiologies were formerly believed to be the most common underlying cause (Husain et al. 1999; Yemisci et al. 2003), a recent large survey found that acute brain injury (44 %), acute systemic illness (38 %), and cardiac arrest (15 %) are often associated with these features (Foreman et al. 2012). The same group reported that GPEDs are more frequently associated with nonconvulsive seizures or nonconvulsive status epilepticus as compared to a control group undergoing EEG monitoring.

There is however a lower risk for seizures in patients whose GPEDs exhibit a triphasic wave morphology (Markand 2003) (Fig. 3.3), defined as complexes with a prominent surface negative deflection discharging every 1–2 Hz, often with an anteroposterior or posteroanterior phase lag (Brenner and Schaul 1990). The American Clinical Neurophysiology Society has defined "triphasic morphology" more formally as complexes with either two (positive–negative) or three (negative–positive–negative) phases, each longer than the preceding one (Hirsch et al. 2013). Generally, it is difficult or impossible to determine solely on waveform morphology whether GPEDs are seizure related or result from metabolic dysfunction (Husain et al. 1999). GPEDs discharging at rates higher than 3 or 4 Hz are generally considered to be of ictal nature (Young et al. 1996; Kaplan 2007) (Fig. 3.4). It has been

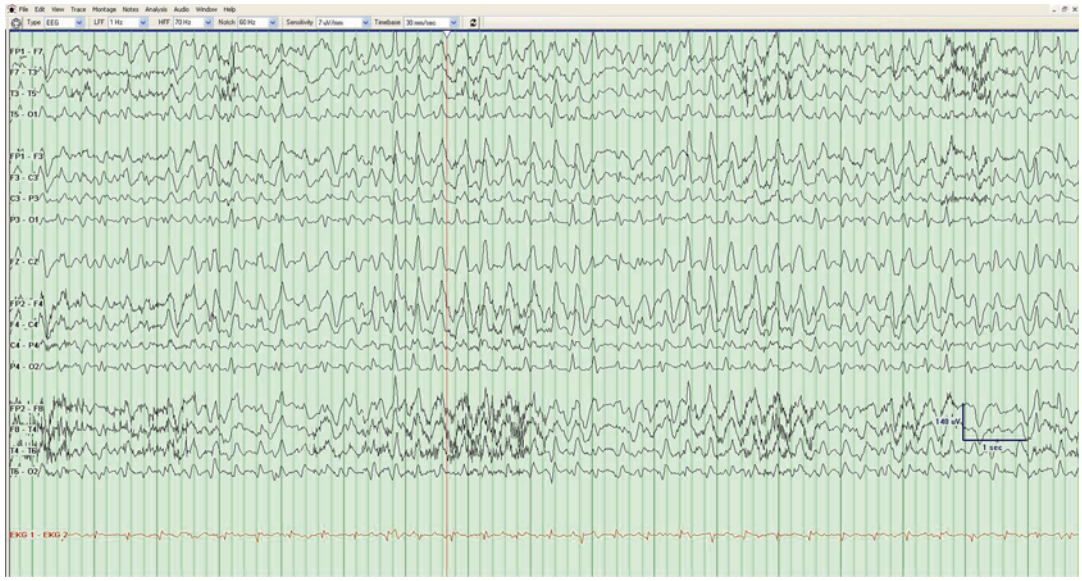

Fig. 3.4 A 64-year-old female after cardiac arrest. Generalized periodic discharges are synchronous with subtle concomitant eye movements, consistent with an ictal phenomenon

suggested that a challenge dose of intravenous benzodiazepine might be given in order to sort out the nature of the periodic pattern: a clinical or incontrovertible electrographic improvement (Jirsch and Hirsch 2007) would suggest an ictal phenomenon. In reality, this procedure is difficult to perform, as benzodiazepines will electrographically resolve both ictal and nonictal GPEDs. Furthermore, observing clinical improvement is extremely challenging as benzodiazepines will depress mental status in both scenarios.

In summary, AED management of these patterns must be done in conjunction with careful clinical and pathophysiological assessments. For example, GPEDs with triphasic morphology due to purely metabolic etiologies, without any clinical correlation, should not be treated with AEDs, whereas other GPEDs with clear manifestations of status epilepticus (Husain et al. 1999) deserve an aggressive management.

3.4 **Rhythmic Activity** (See Also Chap. 5)

Intermittent rhythmic activity, frequently in the delta range, was originally described by Cobb (1945). The most common pattern seen in acutely encephalopathic adults is frontal intermittent rhythmic delta activity (FIRDA) (Zurek et al. 1985). Although initially believed to be due to deep midline lesions causing increased intracranial pressure, it is a nonspecific feature that can be seen in a variety of structural and metabolic conditions, not independently associated with a greater risk of seizures (Accolla et al. 2011; Brigo 2011). As such, specific treatment for FIRDA with antiepileptic drugs is discouraged. Occipital intermittent rhythmic delta activity (OIRDA) is associated with genetic (idiopathic generalized) epilepsies in children (Gullapalli and Fountain 2003). Temporal intermittent rhythmic delta activity (TIRDA) is conversely related to a specific condition – mesial temporal lobe epilepsy (Reiher et al. 1989) – and correlated to seizures (Reiher et al. 1989; Normand et al. 1995). Neither OIRDA nor TIRDA is typically seen in patients in the ICU.

A recent study has explored the significance of lateralized rhythmic delta activity (LRDA), which is defined as unilateral, or bilateral asymmetric, repetitive delta waves having a uniform morphology (Hirsch et al. 2013). This pattern is encountered in approximately 5 % of patients who undergo continuous EEG monitoring (Gaspard et al. 2013), often appearing in short bursts, usually of 1 min or less, and most commonly

in the frontotemporal regions. These features were shown to be independently predictive of nonconvulsive seizures during acute illness. Patients with LRDA had seizures at a rate of 63 %, which is similar to lateralized periodic discharges. Nonrhythmic polymorphic delta waves, on the other hand, were not predictive of seizures. There is insufficient evidence at this time to determine whether LRDA should be routinely treated with an AED. Unlike PLEDs, there is no suggestion that LRDA is ictal in nature; it may merely be a marker of severe focal brain injury.

3.5 SIRPIDs (See Also Chap. 5)

Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs) are found in approximately 20 % of ICU patients undergoing continuous EEG monitoring and are considered to fall somewhere along the ictal–interictal continuum. Clinical or subclinical/electrographic seizures are found in about half of these patients; status epilepticus is more frequent in focal or ictal-appearing SIRPIDs (Hirsch et al. 2004). Other studies have shown no increase in regional cerebral blood flow and as a result have advocated against aggressive treatment (Zeiler et al. 2011). Experience in our own center indicates that SIRPIDs are a transitional, unstable pattern that either will evolve into more definitively ictal pattern or more commonly dissipate in time, in either case losing the stimulus-induced character. Our recommendation is to start a conventional nonsedating AED; if this is already prescribed, further escalation of treatment is not recommended. Although a solid evidence for this approach is lacking, we then minimize stimulating the patient any more than medically necessary. After cardiac arrest, SIRPIDs are associated with poor outcome (Alvarez et al. 2013), but in other instances, outcome is yet to be defined.

3.6 Nonconvulsive Seizures

Nonconvulsive seizures (NCS) are commonly found in the ICU setting, in between 18 and 35 % of patients (Privitera et al. 1994; Claassen et al. 2004). Of these, up to 75 % of patients are in nonconvulsive status epilepticus (NCSE) (Jordan 1992) (see Chap. 4). The determination of NCS can be challenging due to the fact that many of the observed waveforms lie in the ictal–interictal continuum. The Young criteria (Young et al. 1996) (Table 3.1) provide a reasonable guideline in determining whether a pattern is consistent with NCS. This has been modified by other groups to emphasize the importance of frequency/locational evolution and de-emphasize amplitude changes (Chong and Hirsch 2005) (Fig. 3.5).

Table 3.1 Young criteria for an electrographic seizure or a nonconvulsive seizure; in order to qualify, at least 1 of the primary criteria and ≥1 of the secondary criteria are needed, with discharges lasting >10 s

Primary criteria	
A.	Repetitive generalized or focal spikes, sharp waves, spike-and-wave, or sharp-and-slow wave complexes at >3/s
B.	Repetitive generalized or focal spikes, sharp waves, spike-and-wave, or sharp-and-slow wave complexes at <3/s and secondary criterion d
C.	Sequential rhythmic waves and secondary criteria a–c, with or without d
Secondary criteria	
(a)	Incrementing onset: increase in voltage and/or increase or slowing of frequency
(b)	Decrementing offset: decrease in voltage or frequency
(c)	Post-discharge slowing or voltage attenuation
(d)	Significant improvement in clinical state or baseline EEG after antiepileptic drug

After Young and Jordan (1996)

It has yet to be definitely determined whether NCS and NCSE independently cause neuronal injury or are mere epiphenomena of the underlying insult. NCSE occurring in the ICU is linked to a high mortality, and most of the morbidity from NCS is likely due to the underlying conditions, rather than the seizures themselves (Drislane 2006; Rossetti et al. 2006). In fact, there is no evidence of a clear neurocognitive deterioration after status epilepticus after eliminating progressive illness (Adachi et al. 2005), and aggressive treatment is likely to incur iatrogenic morbidities. However, other studies have shown deleterious effects associated with NCS. For instance, in patients with intracerebral hemorrhage, lesion expansion has been

demonstrated in patients with NCS (Claassen et al. 2007). In subjects with traumatic brain injury, an increase in intracranial pressure and lactate–pyruvate ratio (Vespa et al. 2007) as well as hippocampal atrophy (Vespa et al. 2010) has been observed in those patients with NCS. However, the nature of the causality still remains unclear.

It is reasonable to treat all patients with NCS with at least a conventional AED. Escalation of treatment must be decided on a case-by-case basis. In general, there are few, if any, scenarios where de novo intubation and administration of an intravenous anesthetic is indicated solely for the purpose of the treatment of an EEG pattern.

3.7 Anoxic Brain Injury

Prior to the introduction of therapeutic hypothermia, status epilepticus was a predictor of poor outcome in anoxic brain injury (Rossetti et al.

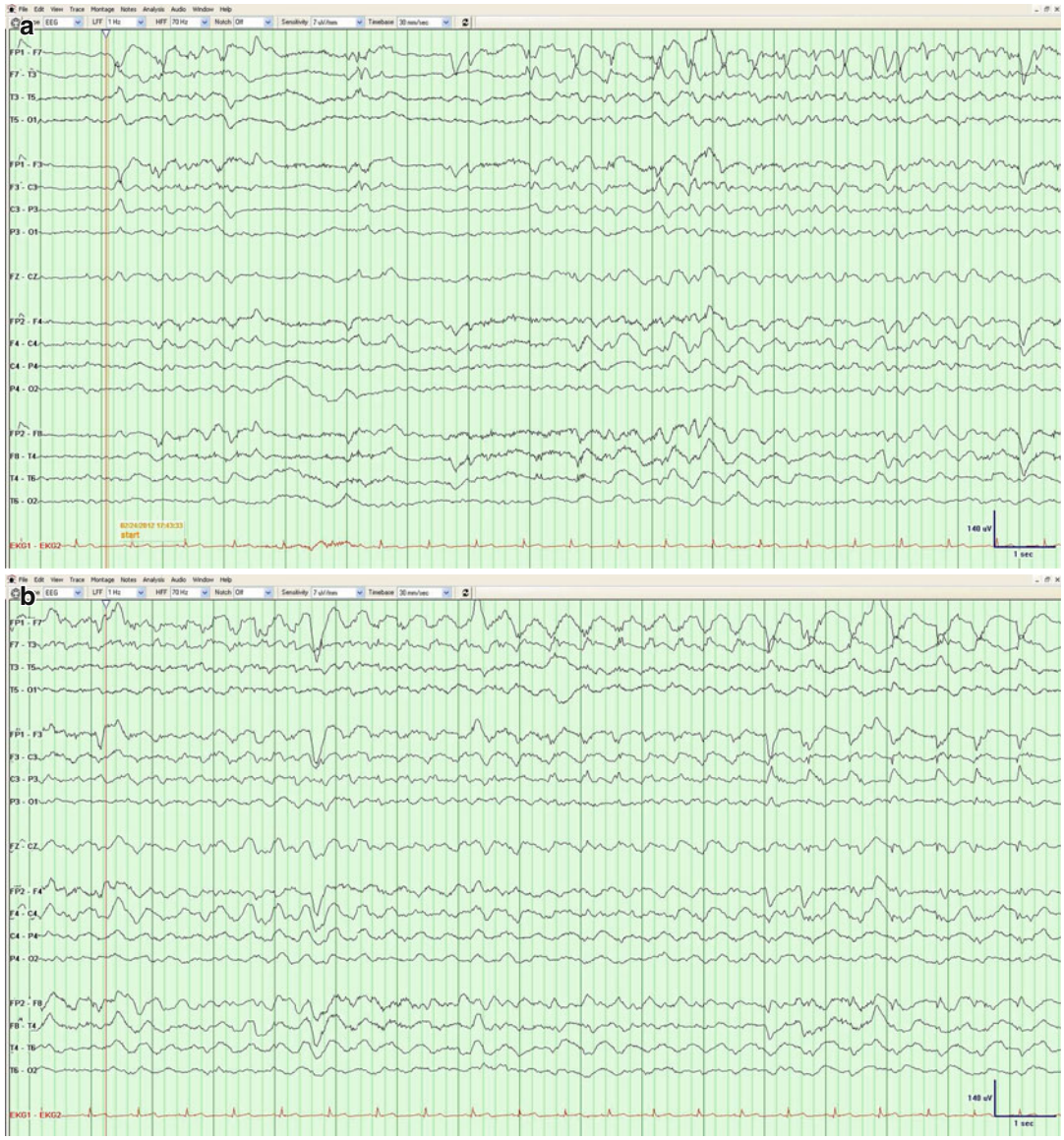

Fig. 3.5 (**a**–**e**) A 63-year-old man after meningioma resection. The evolution of morphology and frequency over the left anterior region is consistent with a nonconvulsive seizure

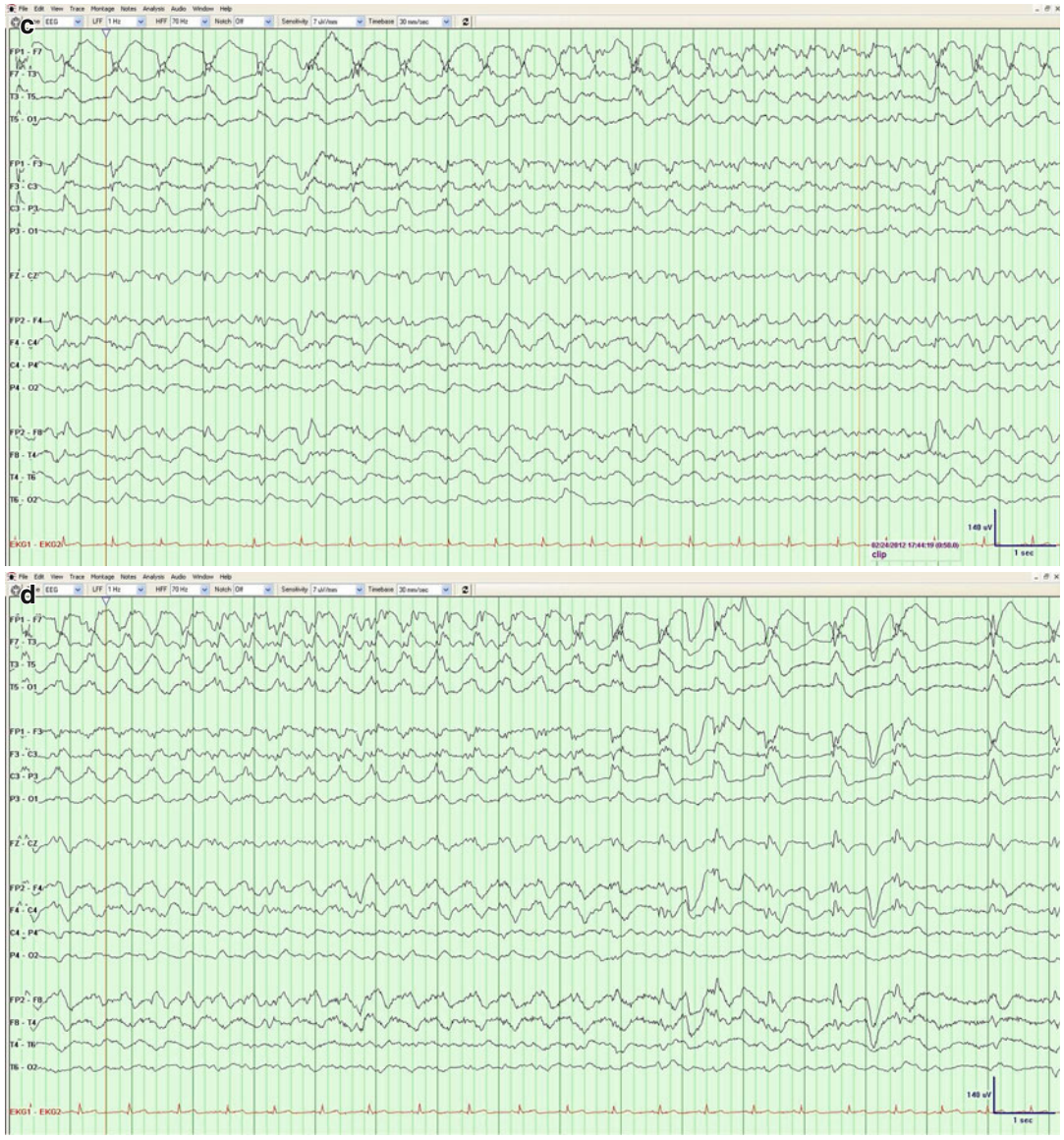

Fig. 3.5 (continued)

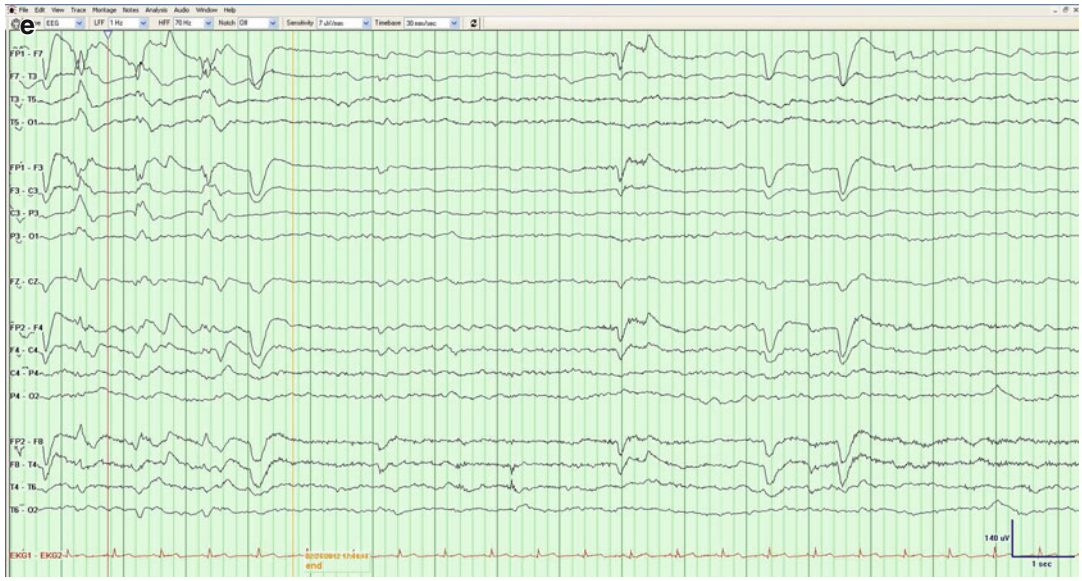

Fig. 3.5 (continued)

2007). In particular, myoclonic status epilepticus was considered an agonal phenomenon (Wijdicks et al. 1994). In these patients, treatment of the epileptiform patterns on EEG was considered futile. The introduction of therapeutic hypothermia has resulted in an increased attention to the related EEG patterns. Seizures are common, occurring in 9–33 % of patients (Rundgren et al. 2010; Mani et al. 2012; Rittenberger et al. 2012; Crepeau et al. 2013); these frequently occur early on, often during the cooling or rewarming (Rittenberger et al. 2012; Crepeau et al. 2013). Postanoxic status epilepticus is still a strong independent predictor of poor outcome (Rittenberger et al. 2012; Crepeau et al. 2013; Legriel et al. 2013), despite treatment with AEDs. Nonetheless, a small number of patients with postanoxic status epilepticus, including myoclonic status, have been reported to survive beyond the vegetative state (Rossetti et al. 2009; Lucas et al. 2012).

The optimal AED management of patients with electrographic seizures undergoing therapeutic hypothermia remains unclear. On the one hand, the presence of seizures, particularly myoclonic status epilepticus, still portends extremely poor prognosis. On the other hand, it is unknown whether the presence of seizures may potentially cause additional morbidity in an already severely compromised brain. Particularly in a patient who presents seizure only upon rewarming and has other good prognostic signs (brainstem reflexes, reactivity on EEG, intact SSEP), suppression of seizures with an increase of an intravenous agent that may already be in place (e.g., midazolam) plus a moderate dose of a classical AED may be most reasonable, at least for some limited time (see also Chap. 5).

3.8 General Guidelines

Sharp, rhythmic, or periodic appearing discharges are all common in the ICU setting, and in many instances, the delineation between nonepileptic, interictal, postictal, and ictal patterns is difficult.

It cannot be overemphasized that, wherever possible, the underlying etiology for the potentially malignant pattern should be sought and, if possible, reversed, before purely symptomatic treatment with an AED is started. This is illustrated in Fig. 3.6, showing the EEG of a 64-year-old female with end-stage renal disease and a seizure at home. A right subdural hematoma was discovered. Initially, subtle electrographic seizures without clinical correlation were seen over the right frontal region (Fig. 3.6a–d) for which a conventional AED (phenytoin) was given. She refused dialysis and 5 days later was found to have increasing lethargy and myoclonic movements. EEG revealed high-amplitude GPEDs (Fig. 3.6e), leading initially to the initiation of a second (levetiracetam) and third (valproic acid) AED, without any benefit. Eventually, dialysis was reinstituted and two of the AEDs were discontinued, leading to a normalization of the EEG (Fig. 3.6f). This case demonstrates an initial appropriate symptomatic treatment of an epileptiform pattern (seizures as a result of a subdural hematoma), followed by the (eventual) treatment of an underlying etiology (renal failure) that was probably more effective than the AED escalation.

Although rapid treatment of status epilepticus is universally advocated (Chap. 4), in patients with uncertain patterns, it is advisable to temper treatment. Firstly, the potential drawbacks of anticonvulsants in critically ill patients have been demonstrated (Naidech et al. 2005). Secondly, it is uncertain whether aggressive treatment of NCS or even NCSE will result in improved outcome, as it has been postulated that nonconvulsive epileptic activity may be an epiphenomenon of an injured brain, at least in some cases (Bauer and Trinka 2010). Given the availability of medications that are easily administered with relatively low toxicity, a conventional nonsedating AED at a relatively low dose can be considered in patients with uncertain rhythms. Thereafter, careful monitoring without escalation of therapy until an uncertain pattern declares itself to be "malignant" or clearly epileptiform may be a better strategy than early escalation AEDs; in fact a large portion of the uncertain patterns will revert to clearly nonepileptic features. Further research is needed to determine the characteristics of patterns that will devolve into ictal patterns requiring treatment escalation.

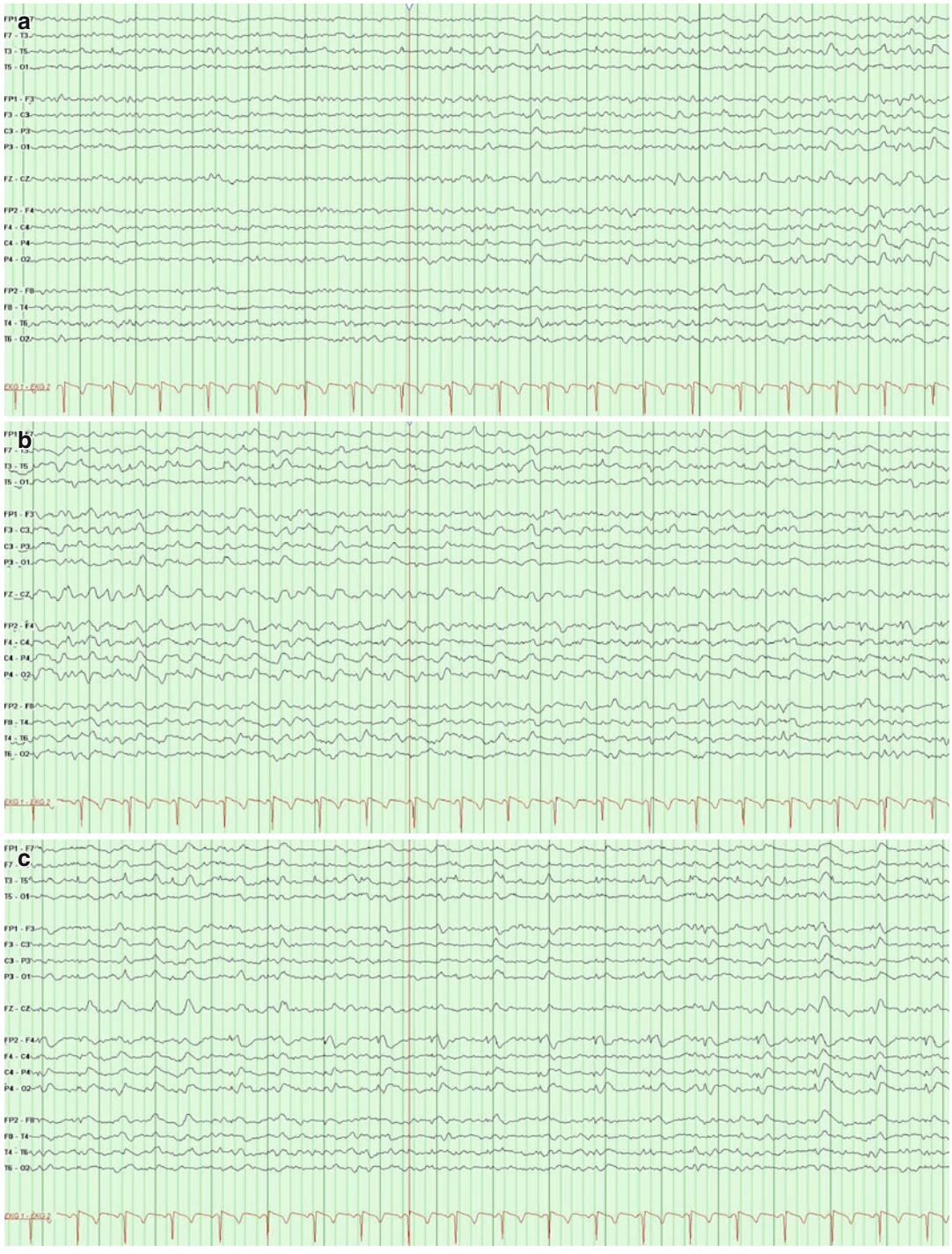

Fig. 3.6 (**a**–**d**) Initial EEG of a 64-year-old female with end-stage renal disease and right subdural hematoma, revealing subtle right frontal electrographic seizures. (**e**) EEG after 5 days of refusing dialysis, showing high-amplitude GPEDs (or GPDs). (**f**) EEG after dialysis, illustrating the resolution of the periodic pattern

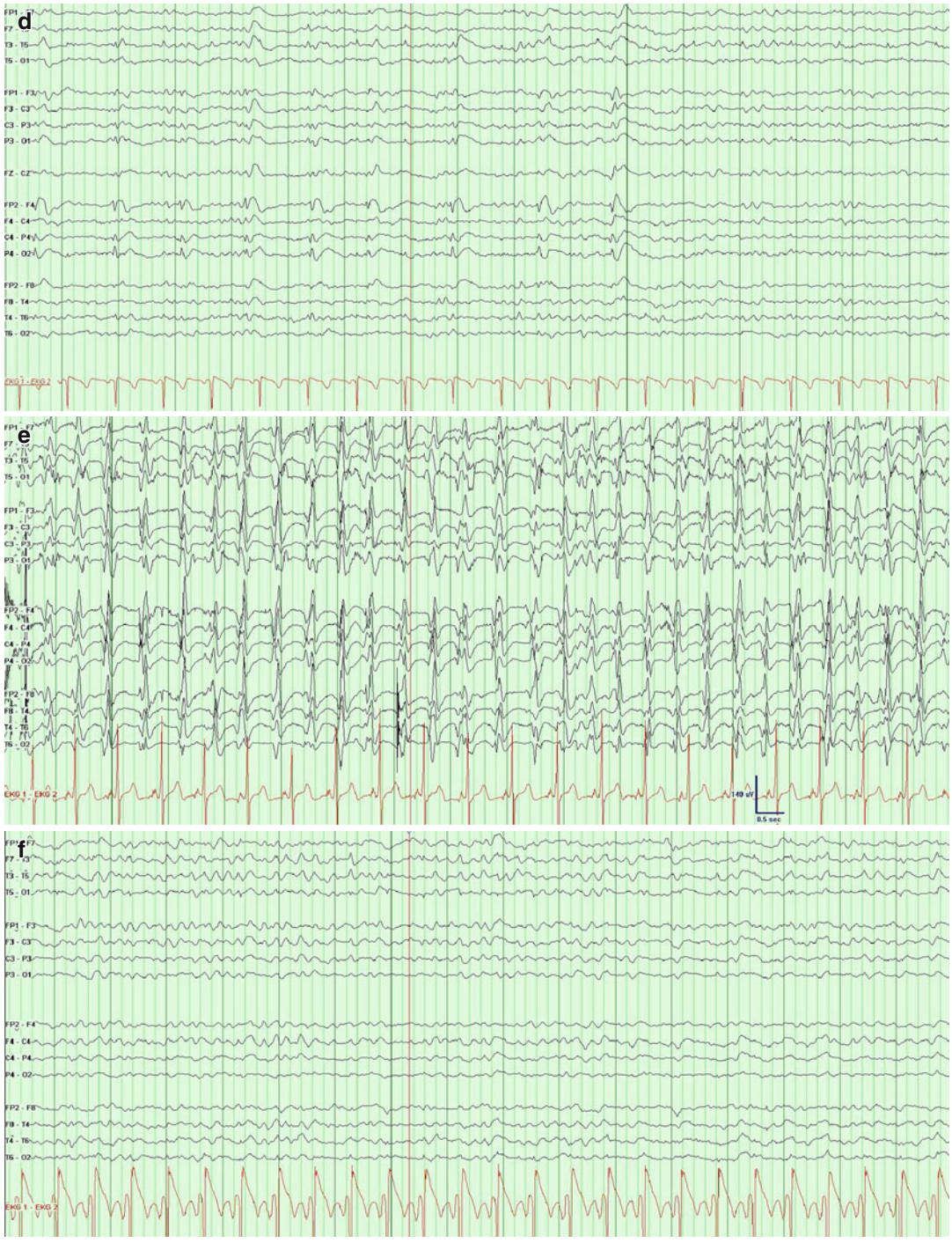

Fig. 3.6 (continued)

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EEG in Refractory Status Epilepticus

4

Martin Holtkamp

Contents

Abstract

EEG in refractory – and thus often long lasting and eventually subtle – status epilepticus is mostly characterized by generalized or lateralized periodic discharges. Based on EEG recordings alone, it is almost impossible to discern late forms of status epilepticus from various other severe nonepileptic encephalopathies. Periodic EEG patterns are not specific for circumscribed neurological conditions and are not pathognomonic for status epilepticus. Even disappearance of periodic discharges following administration of intravenous anticonvulsant does not prove the epileptic nature of specific EEG patterns. Generalized periodic discharges do not seem to be the cause and are not even a biological marker for poor prognosis. If the electro-clinical course allows making a definite diagnosis of refractory status epilepticus, EEG follow-up may help to tailor further therapeutic management.

4.1 Introduction

Status epilepticus (SE) represents the second most common neurological emergency following cerebrovascular accidents. Up to one third of patients do not respond to first- and second-line anticonvulsants, defining refractory SE. Especially if associated with severe disturbances of consciousness and/or breathing, this

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condition generally requires further management in an – at best neurological – intensive care unit. Changes of EEG patterns in the course of SE have been extensively studied. Refractory SE, which is often long lasting and thus subtle, is accompanied by a typical pattern mostly characterized by generalized and sometimes lateralized periodic discharges. The EEG in refractory SE is helpful in guiding further pharmacological management. One of the challenges in clinical practice is that EEGs from critically ill patients are often "cross-sectional," i.e., detailed information on the electro-clinical evolution of the condition are lacking. This makes critical care EEGs difficult to interpret, as periodic discharge patterns are not pathognomonic for SE, but are seen in severe nonepileptic encephalopathies as well. The main scope of this chapter is to describe the evolution of typical EEG patterns in various SE stages and to discuss the difficulties to discern these patterns from those encountered in nonepileptic conditions.

4.2 Refractory Status Epilepticus: Pathophysiological and Clinical Background

One of the most interesting features of epileptic seizures is the fact that in the vast majority of cases, fits are self-limiting. While pathophysiological processes underlying transition from the interictal to the ictal state, thus the onset of a seizure, are quite well understood, neurobiological mechanisms resulting in seizure cessation are still relatively elusive. One hypothesis is that termination of an epileptic seizure requires energy-dependent processes involving restoration of the Na^+–K^+ pump. Failure of these processes results in persistence of increased extracellular K^+ concentration facilitating continuous seizure activity and subsequently SE. Prolonged seizure activity induces internalization of postsynaptic $GABA_A$ receptors into the cell and thus GABAergic impairment (Chen and Wasterlain 2006; Kapur and Macdonald 1997). This concept is termed "receptor trafficking" and well explains both further maintenance of seizure activity – as endogenous GABA is less efficient – and progressive pharmacoresistance of the (exogenous) anticonvulsant drugs, most of which act on the $GABA_A$ receptor.

When defining SE clinically, first one has to consider how long self-limiting seizures commonly last. Video-EEG analyses of partial-onset seizures have demonstrated that the median duration of secondary generalized tonic–clonic seizures is 130 s and that of complex partial seizures 80 s (Jenssen et al. 2006). Retrospective data have shown that the likelihood of spontaneous termination of generalized tonic–clonic seizures is tightly related to seizure duration (42 % cessation after 10–29 min vs. 7 % after 30 min and more) (DeLorenzo et al. 1999). Keeping both findings in mind, an operational definition of SE of seizures lasting longer than 5 min has been suggested (Lowenstein et al. 1999); this has been adopted in the current European Federation of Neurological Societies treatment guidelines for all clinical forms of status epilepticus (Meierkord et al. 2010) (Fig. 4.1) and is widely used in clinical practice.

Once the SE diagnosis has been made, antiepileptic treatment (or maybe better, anticonvulsant treatment, as the agents used act symptomatically) needs to be initiated instantly. First-line treatment was assessed in some randomized controlled trials, favoring intravenous lorazepam or intramuscular midazolam (Treiman et al. 1998; Alldredge et al. 2001; Silbergleit et al. 2012) over other agents (particularly, phenytoin). In practice, it is reasonable to administer a benzodiazepine, a fast-acting drug class; of note, diazepam redistributes relatively quickly away from the brain and therefore may be less suitable than lorazepam, midazolam, or even clonazepam. Which of the second-line anticonvulsants is most effective is planned to be assessed in the near future in a multicenter randomized controlled trial (ESETT, established status epilepticus treatment trial) (Bleck et al. 2013). Though a unifying definition of refractory SE does not exist, most authors agree that failure of an intravenous benzodiazepine (in most cases lorazepam) and a second-line drug, such as (fos)

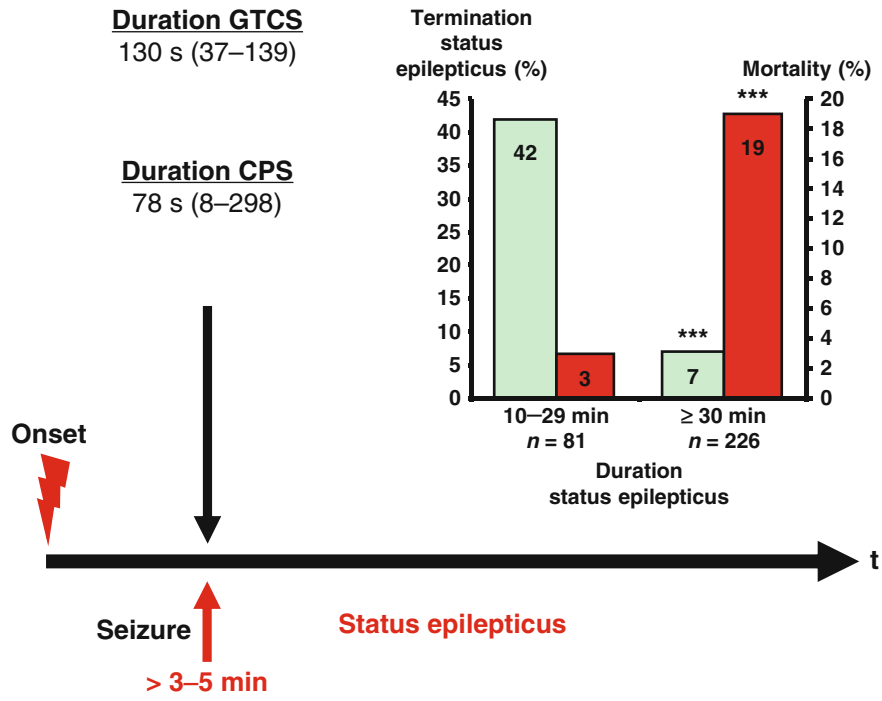

Fig. 4.1 When is a seizure status epilepticus? Definitions of status epilepticus are still heterogeneous. The typical, self-limited epileptic seizure clearly lasts less than 5 min (*GTCS* generalized tonic–clonic seizure, *CPS* complex partial seizure) (Jenssen et al. 2006). The longer an epileptic seizure lasts, the less likely it terminates spontaneously, but the higher is the mortality rate (DeLorenzo et al. 1999). These findings resulted in an operational definition of status epilepticus proposing that every epileptic seizure lasting more than 5 min is status epilepticus, requiring instant and appropriate anticonvulsant treatment

phenytoin, levetiracetam, or valproic acid, to terminate ongoing seizures defines refractoriness (Holtkamp et al. 2005b; Rossetti et al. 2005; Hocker et al. 2013). As opposed to first-line therapy, treatment of refractory SE is not based on high-evidence studies. Moreover, it seems reasonable to tune the further extent of treatment aggressiveness according to the clinical form. Complex partial SE (i.e., focal SE without severe consciousness impairment) itself does not seem to increase mortality rate or neurological/neuropsychological long-term sequelae. Therefore, pharmacological treatment regimens should try to avoid anesthetic anticonvulsants, at least initially. In contrast, generalized convulsive SE and its late clinical form – subtle SE (also called nonconvulsive SE in coma) – are accompanied by extensive neuronal excitotoxicity and induce potentially severe systemic challenges to the physiological homeostasis; thus long-term neurological and neuropsychological consequences represent a consistent risk (Meierkord and Holtkamp 2007). After failure of first- and second-line anticonvulsants, anesthetics such as barbiturates, midazolam, or propofol are highly recommended (Meierkord et al. 2010). Approximately, every fifth patient does not even respond to anesthetics, and seizure activity recurs after tapering. This condition has been termed malignant (Holtkamp et al. 2005a) or superrefractory (Shorvon 2011) SE.

The outcome of refractory SE is poorer than SE responding to the first-line treatment. In-hospital mortality has been reported to be as high as 30–40 %, either including (Sutter et al. 2013) or excluding (Hocker et al. 2013) hypoxic encephalopathy. Furthermore, duration of refractory SE is associated with poor prognosis (Sutter et al. 2013); survivors develop chronic epilepsy in 85 % of cases (Holtkamp et al. 2005b).

However, even after several days of refractory SE, neuropsychological outcome may be favorable at least in some patients (Cooper et al. 2009); therefore, one should not stop treatment, especially in younger individuals, in the absence of clear signs of irreversible and severe brain damage.

4.3 EEG in Critically Ill: Terminology and Criteria for Seizures (See Also Chaps. 3 and 5)

Clinicians reading EEGs are often asked to judge if an EEG recorded from a critically ill patient is SE or not. However, the SE diagnosis, as that of epilepsy in general, is majorly a clinical one, and the EEG is only one piece of the puzzle. Most periodic EEG patterns are unspecific and per se do not allow to make the diagnosis of SE. In this regard, the commonly used term "epileptiform" in descriptions of generalized or lateralized periodic discharges may be misleading and bears the risk of misdiagnosing nonepileptic conditions for SE. Therefore, one can appreciate the American Clinical Neurophysiology Society's undertaking to standardize EEG terminology in critical care – and the concept behind it (Hirsch et al. 2013). One of the main goals was to eliminate terms with clinical connotations, such indeed as the criticized term "epileptiform." Following the proposed nomenclature, the former well-known term "periodic lateralized epileptiform discharges (PLED)" is proposed to be replaced by the descriptive term "lateralized periodic discharges" (Fig. 4.2a). Analogously, "generalized periodic epileptiform discharges" (GPEDs) are now better labeled "generalized periodic discharges" (Fig. 4.2b). As stated, these patterns are unspecific; they do not necessarily indicate SE, but depending on the clinical context and course, they may do (Meierkord and Holtkamp 2007) (Fig. 4.3).

Electrographic seizures – either discrete or prolonged – are well defined either by repetitive epileptiform discharges at ≥3 Hz or by epileptiform discharges at 1–3 Hz with clear evolution of the seizure pattern by frequency, location, or waveform (Chong and Hirsch 2005). Figure 4.4 illustrates a discrete electrographic seizure against the background of generalized periodic discharges (Foreman et al. 2012).

4.4 Temporal Evolution of EEG in Status Epilepticus

The dynamic neurobiological processes underlying SE are well reflected by the evolution of EEG. Treiman was the first to demonstrate that EEG in generalized convulsive SE changes over time following five identifiable and stereotypical patterns (Treiman et al. 1990). At SE onset, (1) discrete seizures were identified that later (2) merge with waxing and waning amplitude and frequency of EEG rhythms. In the further course, the EEG shows (3) continuous ictal activity. With ongoing SE, (4) continuous ictal activity is punctuated by short low-voltage "flat periods," giving later way to the last pattern, which is characterized by (5) generalized periodic discharges on a "flat background" (Fig. 4.5). These five EEG stages correspond to the extent of generalized motor activity. At onset, (1) single generalized tonic–clonic seizures occur with short intervals that do not allow for full regain of baseline consciousness, defining SE. EEG patterns (2 and 3) correspond to overt generalized convulsive status epilepticus characterized by extensive motor signs. With emergence of EEG flat periods (4 and 5), the intensity of motor activity declines and either disappears completely or presents with only subtle, perioral, or extremity myoclonic twitches.

The five stages of EEG in human SE were reproduced in three different animal models, in which seizures were induced by intraperitoneal (IP) injection of kainic acid, by IP injection of homocysteine and prior epidural placement of cobalt, or by IP injection of pilocarpine. Independently of the model used, in all animals the same sequence of EEG stages was recorded (Treiman et al. 1990) (Fig. 4.5). Similarities between the human condition and these three different animal models underline the consistency

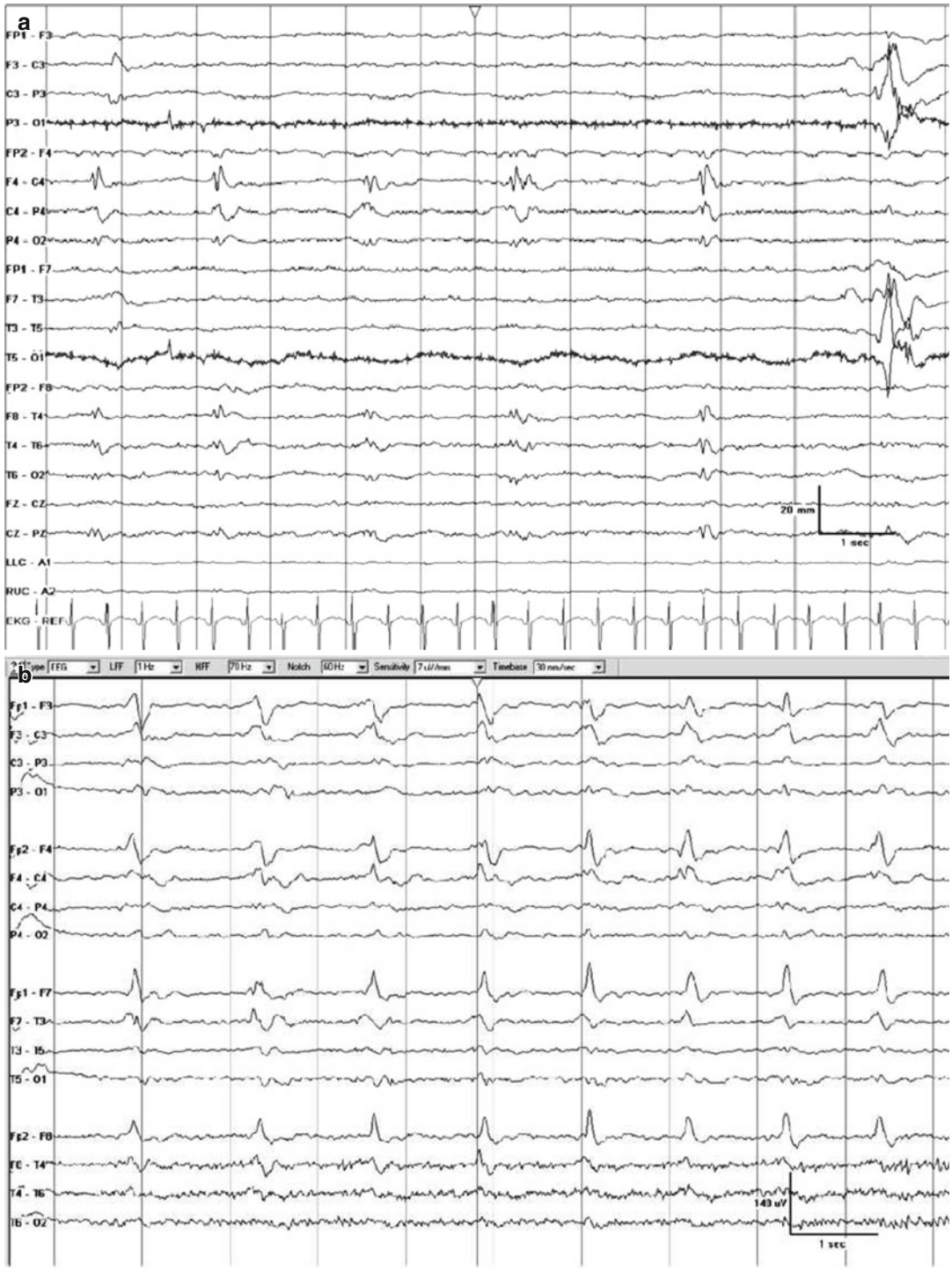

Fig. 4.2 Examples of periodic discharges. (**a**) Lateralized periodic discharges on the right at a frequency of approximately 0.5 Hz. (**b**) Generalized periodic discharges with sharp morphology at a frequency of approximately 1 Hz. Information on the clinical condition are not available (Hirsch et al. (2013). With permission from Wolters Kluwer Health)

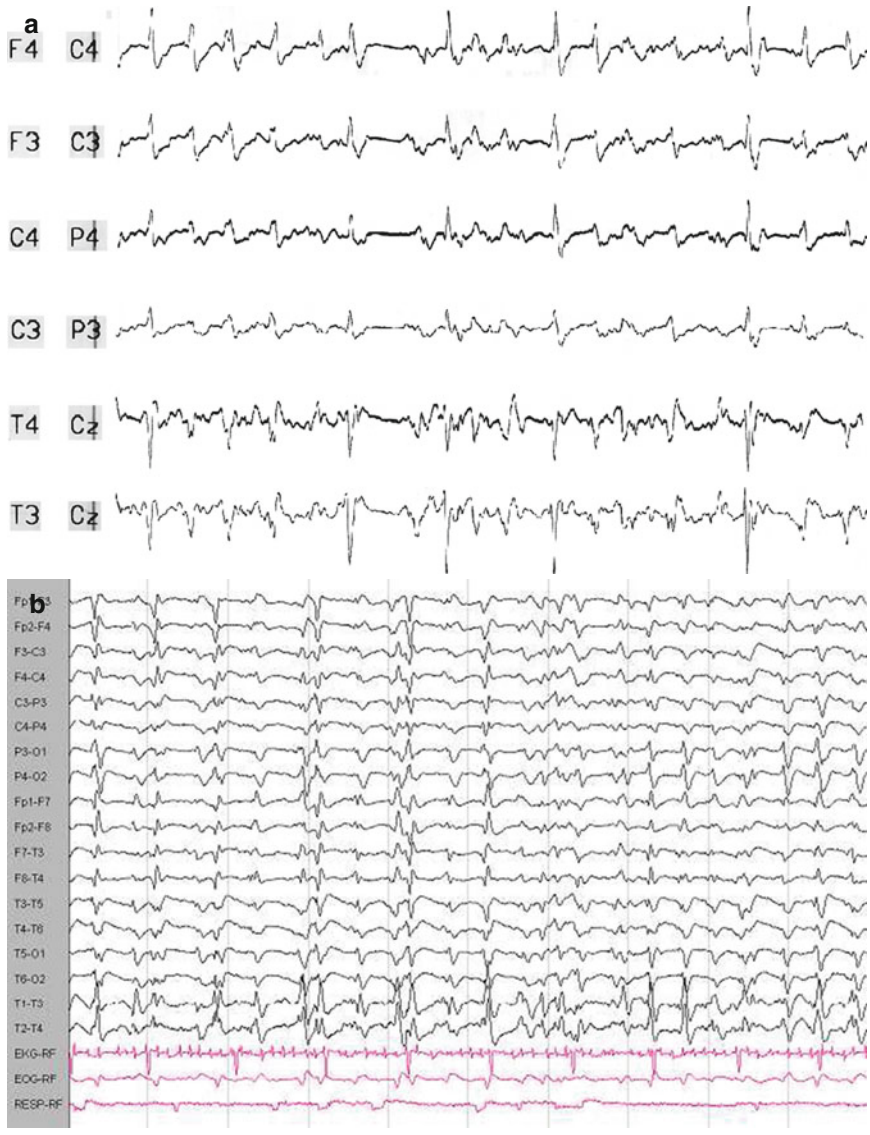

Fig. 4.3 Generalized periodic discharges. Both EEG traces demonstrate generalized periodic discharges punctuated by flat periods. The correct clinical diagnoses can only be made when the clinical course is considered. (**a**) This EEG is recorded from a 39-year-old woman who presented with new-onset discrete tonic–clonic generalized seizures that increased in frequency, without regain of consciousness. Etiology was assumed to be encephalitis without identification of a specific pathogen. In retrospect, she may had suffered from immune-mediated status epilepticus, but cerebrospinal fluid or serum specimen was not preserved. In the further course, she had continuous generalized motor seizures. She was treated unsuccessfully with benzodiazepines and phenytoin and subsequently with anesthetic anticonvulsants including propofol and thiopental. Even after tapering of the anesthetics, generalized periodic discharges indicated subtle status epilepticus, thus fulfilling the criteria for malignant (or superrefractory) status epilepticus. Clinically, discrete ("subtle") spontaneous perioral and extremity myoclonus was observed. Eventually, the patient died from electromechanical dissociation after 8 weeks of critical care treatment. (**b**) This EEG was recorded from a 58-year-old male patient 5 days after cardiopulmonary resuscitation due to ventricular fibrillation. The patient underwent standard treatment with hypothermia and simultaneous intravenous midazolam. Three days after the end of cooling and sedation, the patient was still comatose; he suffered from stimulus-sensitive myoclonus (occurrence during endotracheal suctioning or touching the patient). In this case, generalized periodic discharges indicate severe hypoxic encephalopathy. The patient was transferred to a rehabilitation clinic; the further course is unknown

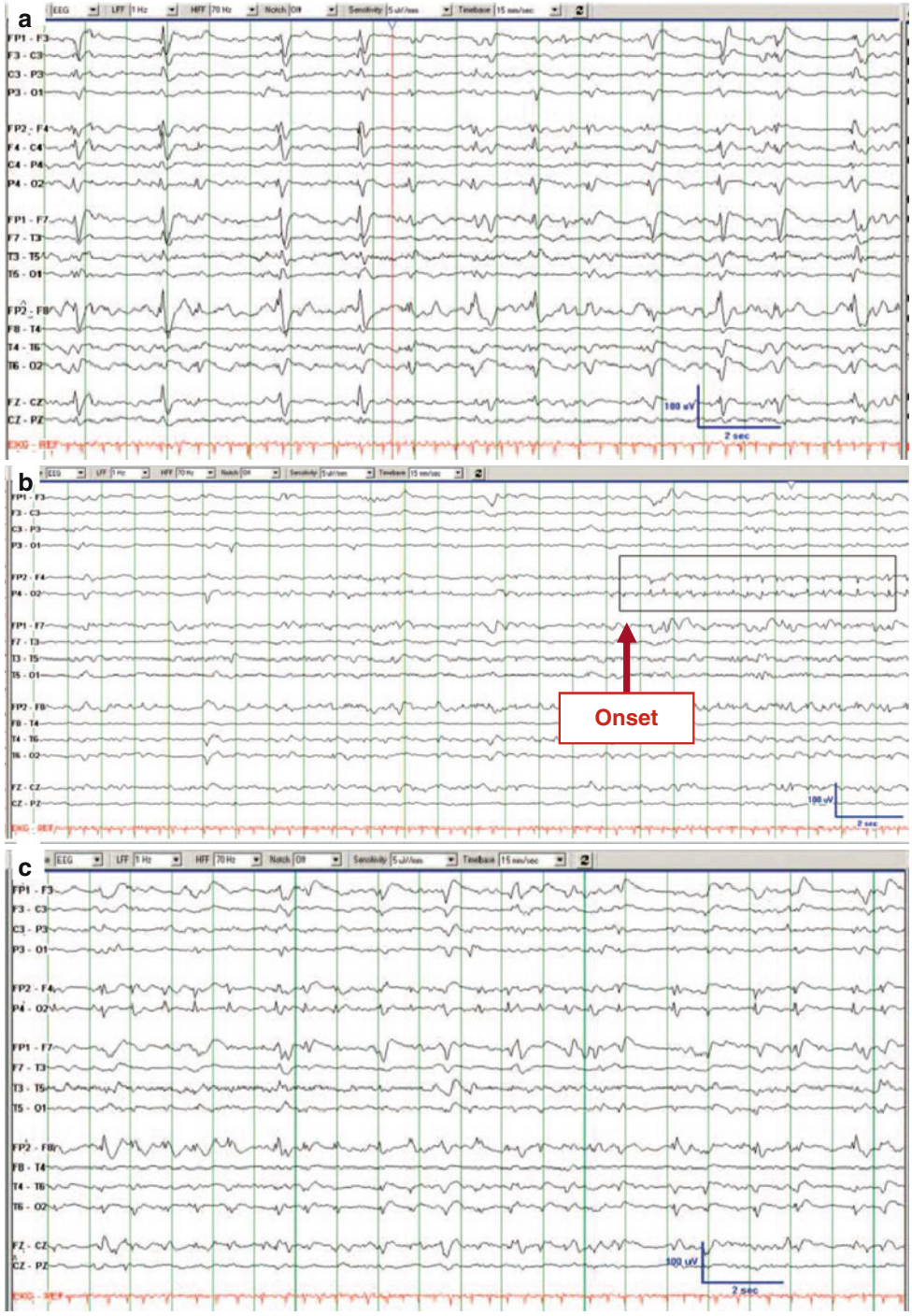

Fig. 4.4 Electrographic seizure. EEG trace recorded from a woman in her 40s, 3 days after liver transplantation complicated by sepsis and renal failure. She was comatose. (**a**) Her initial continuous EEG monitoring demonstrated frequent generalized periodic discharges, occasionally with triphasic morphology. (**b**–**d**) Three consecutive pages of EEG about 2 h later, when she developed focal status epilepticus with right hemisphere onset, maximal in the right frontal parasagittal region (**b**, *red arrow* "onset") that evolved before ending abruptly (**d**, *red arrow* "stop"). There was no clinical correlate on video (Foreman et al. (2012). With permission from Wolters Kluwer Health)

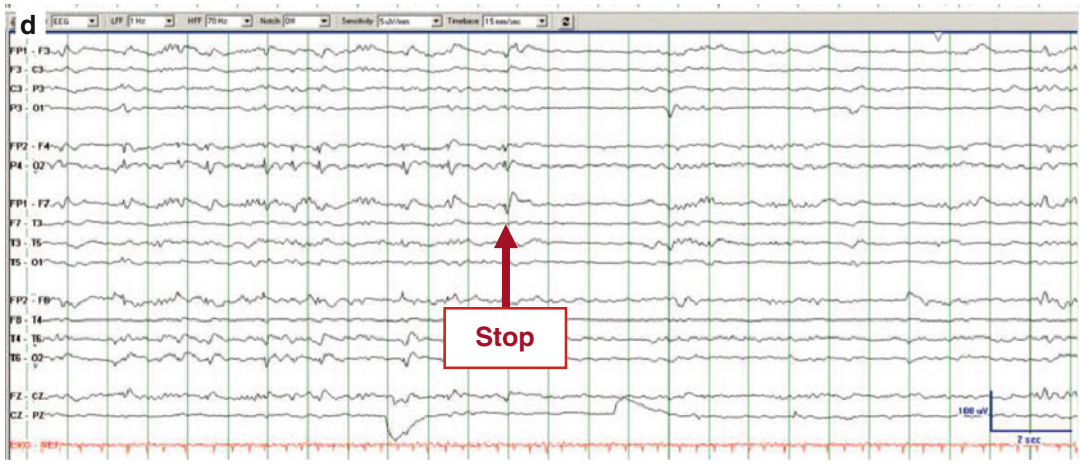

Fig. 4.4 (continued)

of EEG findings and thus of the underlying neurobiological processes.

4.5 Subtle Status Epilepticus

Subtle SE is the late manifestation of so far untreated or insufficiently treated overt generalized convulsive SE. The clinical hallmarks of subtle SE comprise a comatose state and the absence of prominent motor features. However, discrete ("subtle") muscle twitching may be present, and the EEG mostly shows generalized periodic discharges with flat periods (Fig. 4.3a), but lateralized and regional discharges may also occur.

The concept of subtle SE is very useful and has the potential to guide the clinician in cases where the correct diagnosis is immediately relevant for treatment decisions. This approach looses much of its diagnostic power if not used in the strict sense as representing the end point of "overt" SE (the latter denotes in fact generalized convulsive SE (Treiman et al. 1990, 1998)). In the initial descriptions, the concept of subtle SE was used in a wider sense, and also those patients were included in whom the condition was believed to be caused by severe encephalopathy and subtle SE may have been be a possible, unrecognized cause of coma (Treiman et al. 1984). In order to retain the cutting edge of the concept, the diagnosis of subtle SE should only be made in the presence of clearly suggestive EEG changes and if there is evidence of previous overt epileptic seizures or SE (Holtkamp and Meierkord 2011).

Subtle SE should be treated as aggressively as the overt variant. In a landmark randomized controlled trial, the intravenous (IV) administration of lorazepam, diazepam followed by phenytoin, phenobarbital, or phenytoin terminated subtle status epilepticus in 8–24 % of cases only; success rates were not significantly different among the four study groups (Treiman et al. 1998). As a comparison, the response rate in early overt generalized convulsive SE was 44–65 %, and the dramatic loss in efficacy of the predominantly GABAergic substances may be explained by modification of the $GABA_A$ receptor due to continuing seizure activity (Kapur and Macdonald 1997). Therefore, the European treatment guidelines recommend a prompt use of anesthetics such as barbiturates, midazolam, or propofol (Meierkord et al. 2010).

4.6 Mimics: Refractory Status Epilepticus Versus Nonepileptic Encephalopathies

As discussed above, periodic EEG patterns are not specific for SE, even if the morphology of discharges is sharp or spiky (Fig. 4.6a). For some cli-

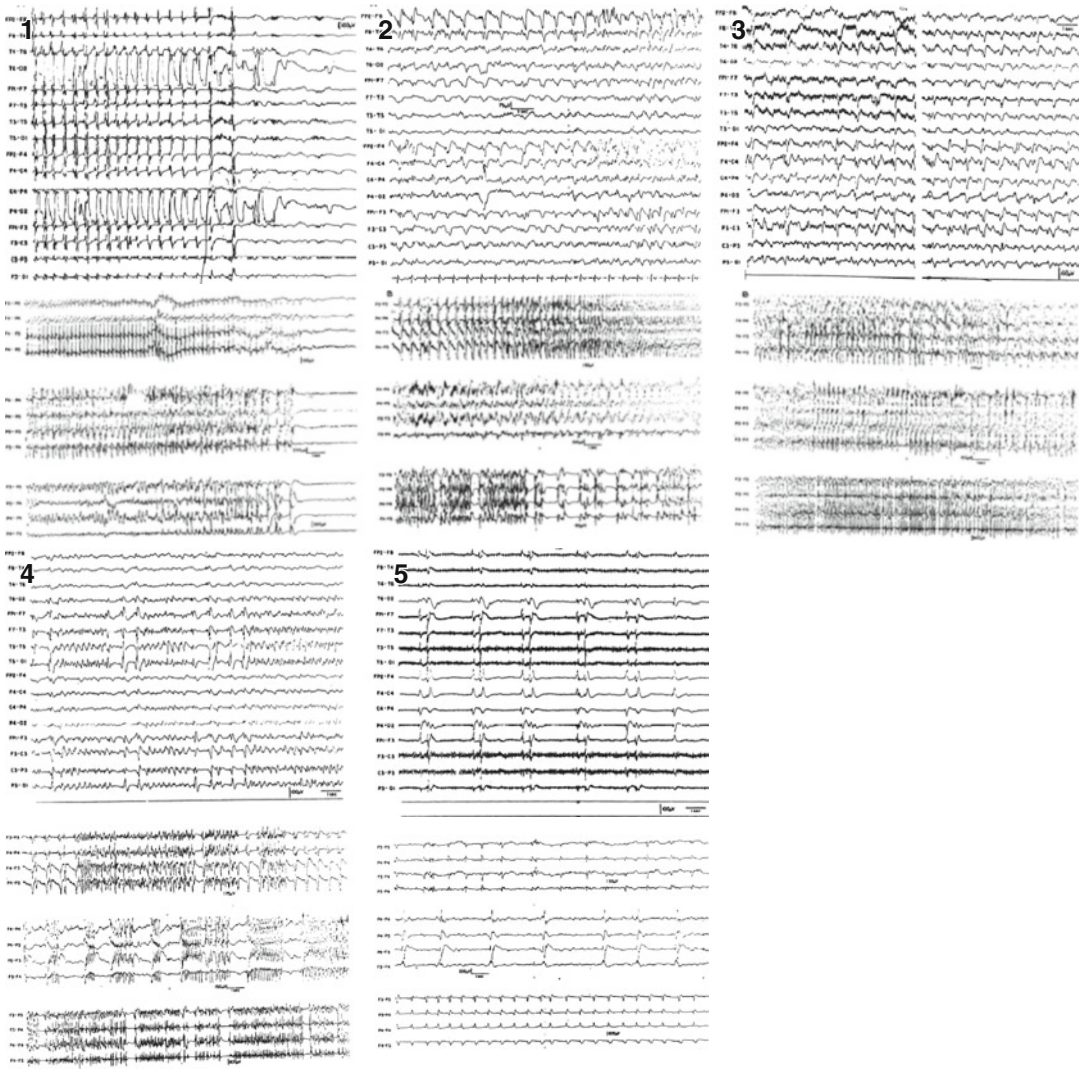

Fig. 4.5 Temporal evolution of EEG in generalized convulsive status epilepticus. EEG traces show temporal evolution in different stages of generalized convulsive status epilepticus in patients (*upper rows*) and rodents (*lower rows*). Stages: (*1*) discrete seizures, (*2*) merge with waxing and waning amplitude and frequency of discharges, (*3*) continuous ictal activity, (*4*) continuous ictal activity punctuated by short low-voltage "flat periods," (*5*) generalized periodic discharges on a "flat background" (Treiman et al. (1990). With permission from Elsevier)

nicians or clinical neurophysiologists, it may be tempting to "treat" these EEG patterns with IV anticonvulsants: all periodic EEG patterns will disappear with administration of anticonvulsant drugs, especially benzodiazepines (Fig. 4.6b). This mere electrographic "treatment success" again bears the risk to misdiagnose nonepileptic conditions as SE and to potentially harm the patient.

Several severe nonepileptic encephalopathies are relatively frequently accompanied by periodic EEG patterns with discharges of heterogeneous morphology. These include posthypoxic (Fig. 4.6a), septic, metabolic, and even neurodegenerative conditions (Fig. 4.7).

There has been a long debate on whether periodic EEG discharges are just the electrophysiological expression of severe brain disease or may reflect an "epileptogenic" potential: even if these discharges are nonepileptic, it was unclear if they have some excitotoxic properties harming the

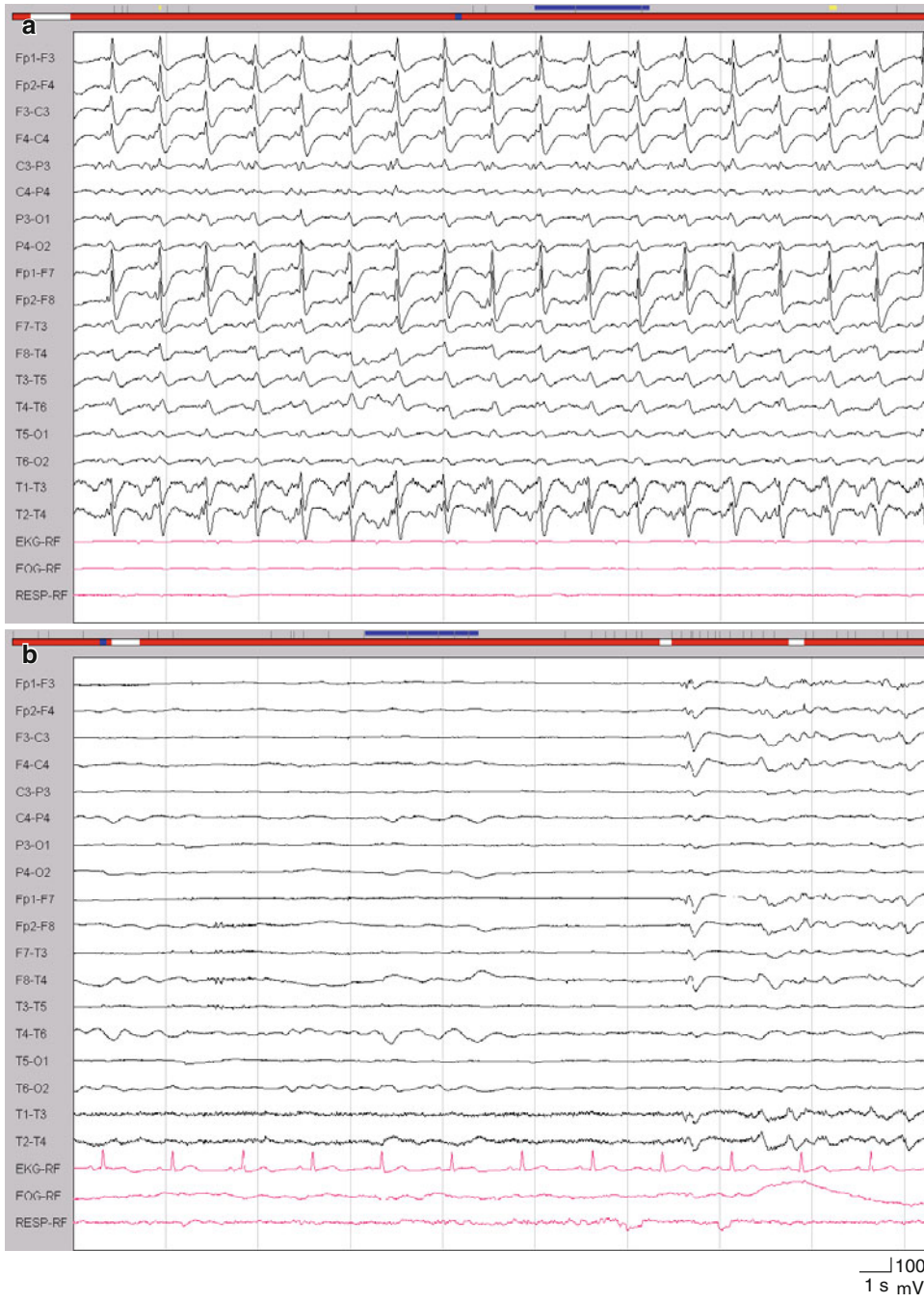

Fig. 4.6 EEG "treatment" with anticonvulsants. Both EEG traces are recorded in the same 65-year-old male patient with severe posthypoxic encephalopathy (**a**) prior to and (**b**) after intravenous administration of a benzodiazepine. (**a**) This EEG was recorded 7 days after cardiopulmonary resuscitation presumably due to ventricular fibrillation. The patient was free of sedative substances for more than 72 h and still comatose. The EEG demonstrates generalized periodic discharges with spiky morphology at a frequency of 2 Hz. (**b**) This EEG was recorded 10 min after an intravenous administration of 10 mg diazepam (indication unclear). Spiky generalized periodic discharges have disappeared; some "abortive" discharges occur at the right end of the trace. The alteration of the EEG pattern did not correlate with clinical improvement; the patient was still comatose

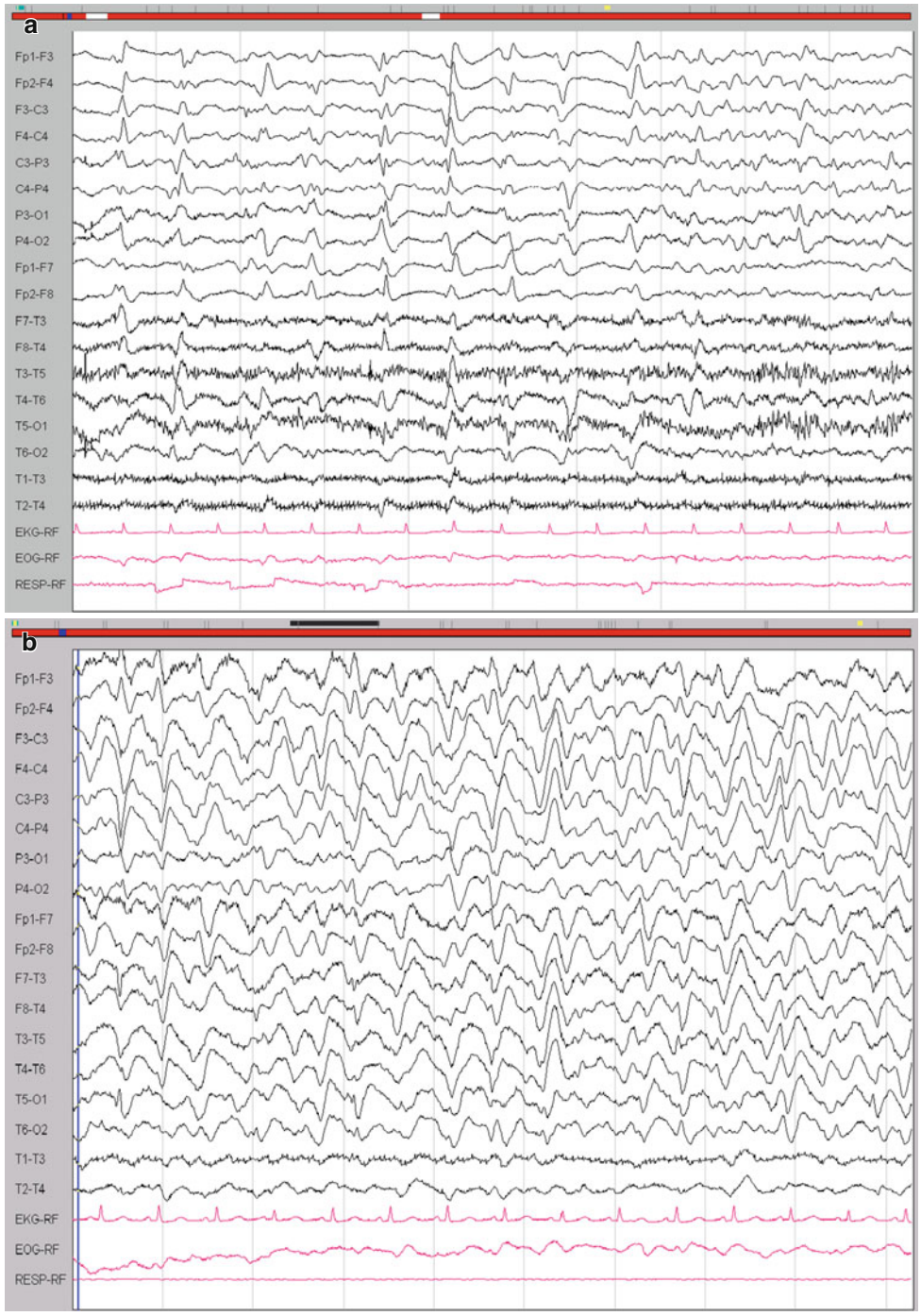

Fig. 4.7 Examples of periodic EEG patterns of nonepileptic origin. (**a**) EEG trace of a 72-year-old woman with septic encephalopathy demonstrating generalized periodic discharges at a frequency of slightly above 1 Hz. (**b**) EEG trace of a 38-year-old male patient with hepatic encephalopathy due to liver failure, generalized periodic discharges with triphasic morphology. This EEG pattern is typically seen in hepatic and other metabolic encephalopathies. (**c**) EEG trace of a 75-year-old woman referred to the neurological intensive care unit with the diagnosis of nonconvulsive status epilepticus. EEG demonstrated spiky generalized periodic discharges at a frequency of 2.5 Hz. Discharges disappeared following intravenous administration of 1 mg clonazepam (EEG trace not shown). Later, the diagnosis of sporadic Creutzfeldt–Jakob disease was made (Lapergue et al. (2010). With permission from Wolters Kluwer Health)

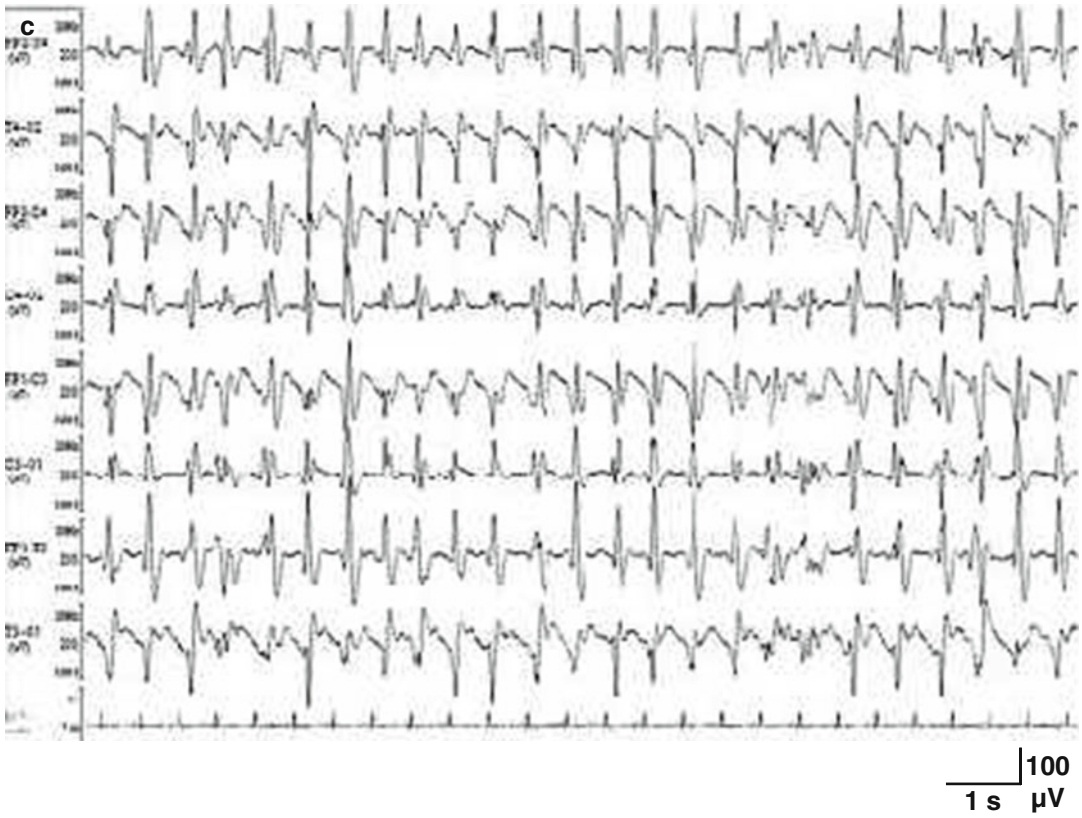

Fig. 4.7 (continued)

brain in addition to the underlying severe neurological disorder. This question is not just of academic interest, but implies direct treatment consequences. A recent well-designed case–control study has addressed this issue, comparing in-hospital outcome of 200 critically ill patients with generalized periodic discharges and 200 control patients with comparable severe brain injuries but without EEG discharges. It demonstrated that patients with generalized discharges had significantly more often nonconvulsive seizures and status epilepticus (Fig. 4.4). However, multivariate predictors of poor outcome were cardiac arrest, coma, nonconvulsive SE, and sepsis, but not generalized periodic discharges themselves (Foreman et al. 2012).

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Prognostic Utility of Electroencephalogram in Acute Consciousness Impairment

5

Andrea O. Rossetti

Contents

Abstract

The role of EEG in the context of prognostic assessment in patients with acute disorders of consciousness has expanded steadily over the last decades, paralleling technical developments and refinements; remarkably, recent collaborative efforts have led to a consensus proposal for the nomenclature of alterations commonly observed in this setting. This chapter will review the most common EEG patterns that are observed in this clinical context and outline their prognostic implications. Then, in a sort of "inverse solution approach," several diagnostic categories will be analyzed regarding the role of EEG on outcome prediction. Finally, an overview of the most recent tools, such as intracranial EEG or automated EEG interpretations, will be critically discussed. While EEG is well established in the process of prognostication, its role is still that of a marker of the clinical evolution rather than representing a tool generating therapeutic implications. Hopefully, future work will lead to a change of paradigm that may not only improve and expand current knowledge but also, more importantly, allow better care of patients.

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5.1 Historical Evolution of EEG Interpretation in Patients with Disorders of Consciousness

The EEG offers unique opportunities to investigate in real time the electrical brain activity, thanks to its noninvasiveness, high time resolution, broad availability, and cost-effectiveness. In parallel to the increasing EEG use for clinical purposes since the 1930s, pioneer electroencephalographers started unraveling changes occurring in physiological sleep and pathological consciousness impairment. After more than 70 years, this effort still experiences a lively and dynamic evolution, which, as a collateral effect, leads to some discrepancies in the taxonomy of particular EEG patterns. A brief overview of the most important classification systems will illustrate this aspect.

It was not until about five decades ago that a comprehensive study aiming at a systematic classification having prognostic purposes in the setting of coma has been conducted. We owe Hockaday and her colleagues a remarkable description of the alterations found in 39 patients with acute cerebral anoxia (Hockaday et al. 1965). The classification system relies on five grades, with background frequency and amplitude representing the dominant variables (Table 5.1); while all patients with grade I—and none with grade V—survived, the other grades represented a progressive impairment of normal cerebral function. Over the following years, this offered a basis for further developments, particularly after observing the relevance of background reactivity for prognosis (Markand 1984).

Based on his personal experience, in 1988 Synek refined the prognostic classification for comatose patients after traumatic injury or cerebral anoxia, adding complementary information to the five original grades and introducing some specific EEG patterns, in an attempt to allow a classification of as many traces as possible (Synek 1988). He also made the important observation that the prognostic significance of EEG should be assessed not too early (i.e., within a few hours) after the beginning of coma (Synek 1988). The breakdown into several categories renders the classification very accurate on the one side, but also somewhat unpractical (Table 5.2); the Hockaday grades are scattered among different prognoses, as is the background reactivity. Ten years later, Young and colleagues proposed an updated system based on their observation of 92 comatose patients, mostly postanoxic, some with traumatic injury (Table 5.3), and compared it to the Synek classification, finding a higher interobserver agreement (this was, however, tested among just two interpreters) and underscoring again the relevance of EEG reactivity (Young et al. 1997). Furthermore, they pointed out that *burst suppression* implies flattening for

Table 5.1 The Hockaday prognostic classification of EEG changes in postanoxic patients

Comment	Grade	Appearance
Normal	I	Predominant α with rare θ
Mildly abnormal	II	Predominant θ with rare δ
Moderately abnormal	III	Predominant δ
Severely abnormal	IV	Predominant δ with brief isoelectric intervals
Extremely abnormal	V	Nearly flat or flat record

Modified after Hockaday et al. (1965)

Table 5.2 The Synek prognostic classification of EEG changes in postanoxic and brain trauma patients

Comment	Grade	Appearance
Optimal	I	Predominant α with rare θ
Benign	II	Predominant θ, reactive
	III	Spindle pattern
	III	Frontal rhythmic δ
Uncertain	II	Predominant θ, not reactive
	III	Diffuse δ (regardless of reactivity)
	III	Diffuse δ with epileptiform discharges
	IV	α pattern coma, reactive
Malignant	III	Low amplitude δ
	IV	Burst suppression
	IV	Burst suppression with epileptiform discharges
	IV	α pattern coma, not reactive
	IV	θ pattern coma
Fatal	IV	Low-output EEG (<20 μV δ activity)
	V	Isoelectric EEG

Modified after Synek (1988)

Table 5.3 The Young prognostic classification of EEG changes in postanoxic and brain trauma patients

Category	Subcategory
I: θ/δ >50 % of the record	Reactive
	Not reactive
II: Triphasic waves	
III: Burst suppression	With epileptiform activity
	Without epileptiform activity
IV: α/θ/spindle coma (unreactive)	
V: Epileptiform activity (not in burst suppression)	Generalized
	Focal
VI: Suppression	Between 10 and 20 μV
	≤10 μV

Modified after Young et al. (1997)

at least 1 s/20 s, while Synek did not specify the denominator.

This illustrates the need for more uniformity in order to allow a generalizable understanding of what is described on EEG recordings. Very recently, a common effort of several North American experts has produced a detailed description of the EEG terminology in an intensive care setting (Hirsch et al. 2013). While unequivocal electrographic seizures should show generalized spike-wave discharges >3 Hz, or clearly evolving discharges of any type reaching a >4 Hz frequency, other recurrent patterns (periodic or rhythmic, but which would not be necessarily labeled as seizures) represent the subject of this classification, intended primarily to match a research need. The first main term is chosen according to the spatial distribution (i.e., *generalized*, *lateralized*, *bilateral independent*, or *multifocal*) and the second to describe the type of transients (i.e., *periodic discharges*, *rhythmic delta activity*, or *spike-waves*); to qualify, the discharges should recur at least six times. Then, modifiers come to play, such as prevalence over the recording, duration, frequency, sharpness, amplitude, and stimulus induction. The EEG background is described according to symmetry, predominant posterior frequency, reactivity, voltage, sleep transients, and continuity (i.e., *suppression* implies the whole recording being <10 μV, *burst suppression* that 50–99 % of the recording is attenuated, while a *discontinuous* trace is attenuated over 10–50 %). A comparison

Table 5.4 Older EEG terms and the newer terms after the standardized critical care EEG terminology proposed by the American Clinical Neurophysiology Society

Older terms	Newer terms
PLEDs (periodic lateralized epileptiform discharges)	LPDs (lateralized periodic discharges)
PLEDs+	LPDs plus (fast, rhythmic)
BIPLEDs (bilateral independent periodic lateralized epileptiform discharges)	BIPDs (bilateral independent periodic discharges)
GPEDs (generalized periodic epileptiform discharges)	GPDs (generalized periodic discharges)
Triphasic waves, most of the record	GPDs with triphasic morphology
FIRDA (frontal intermittent rhythmic delta activity)	GRDA (generalized rhythmic delta activity, frontal predominant)
SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges)	SI-GPDs or -RDA or -SW (spike-waves)
Lateralized seizure, δ frequency	Evolving RDA

Modified after Hirsch et al. (2013)

of this classification with historically common terms is given in Table 5.4; the aim to disentangle the descriptive terminology of recurrent discharges from an "epileptiform" connotation is clearly recognizable. While this very precise approach represents a seminal step in the optimal direction and appears very appropriate to serve as a basis for clinical EEG research in the intensive care environment, it may again be too detailed to allow its routine use in clinical practice, and it is just beginning to undergo validation in different geographical and clinical settings.

5.2 Particular EEG Patterns Found in Patients with Consciousness Impairment (See Also Chaps. 2 and 3)

5.2.1 Background Slowing and Reactivity

Several decades ago it has been observed, in cats, that lesions confined to the cerebral cortex lead to attenuation of the alpha background,

while subcortical lesions deafferenting the cortex induce polymorphic delta slowing (Gloor et al. 1977); unsurprisingly, this seems to apply also to humans (Kaplan and Rossetti 2011). The possible etiologies are extremely broad, including traumatic, infectious, ischemic, or hemorrhagic causes; importantly, a "lesion" should not only be understood as a structural defect but (especially for the cortex) may also encompass functional disturbances, such as alteration of the physiological blood flow (either locally or systemically, e.g., during a migraine attack or a syncope), metabolic disturbances, or the effects of sedative medications.

The previous section and Tables 5.1, 5.2, and 5.3 illustrate well the prognostic correlation of an increasing background slowing; it is however paramount to always perform activation procedures to test the background reactivity, including alerting sounds (or calling the patient's first name), eye opening, and painful stimulations. As a practical rule of thumb, to prevent biases owing to peripheral nerve impairment, it seems reasonable to apply the stimuli on the face or the trunk; furthermore, in order to allow the EEG to resume its non-stimulated background, stimulations should be performed at least 20–30 s apart. Even if a given recording appears very slow, a clear reactivity, understood as a reproducible change in terms of frequency and amplitude (regardless of the fact that either acceleration with amplitude attenuation or high-voltage slowing appears), heralds a relatively better prognosis (Markand 1984; Rossetti et al. 2010, 2012; Synek 1988; Young et al. 1997). Furthermore, in the era of portable video EEG, the correlation of stimuli application with the EEG signal is now very easy to assess.

5.2.2 Triphasic Waves

These EEG transients have been known for many decades and owe their appearance in the EEG literature to their seminal observation in patients with hepatic impairment (Foley et al. 1950). Triphasic waves are described as sharp deflections with two or three phases, where the second one has the highest amplitude and is generally surface positive; at times, a phase lag (i.e., a slight delay of a few tens of milliseconds of the positive wave in the anteroposterior or posteroanterior respect) may be observed (Fig. 5.1). These transients that often can be transitorily attenuated along with variation in consciousness are by no means specific to liver disturbance, as they have been observed with other metabolic disorders, as well as infections, neoplastic or ischemic lesions (Sutter et al. 2013b), intoxications, and prion diseases. They should be considered possibly epileptiform if occurring strictly unilaterally (Pohlmann-Eden et al. 1996); in this case they usually do not show any clear reactivity. While, again, reactivity has been described as favorable in terms of outcome (Sutter et al. 2013b), it is their evolution over time, rather than their mere presence, that should orient on prognosis: triphasics tend to disappear relatively quickly following correction of metabolic disorders, while they worsen in neurodegenerative conditions. Of relevance, triphasic waves may be attenuated or abolished by benzodiazepines; their disappearance in this context is thus by no means specific for an epileptiform nature (Fountain and Waldman 2001).

5.2.3 Periodic Discharges

These represent one of the most common findings in the ICU setting and are labeled as *generalized periodic* [*epileptiform*] *discharges* (GPEDs or GPDs) and, if lateralized, PLEDs or LPDs (Table 5.4); since their presence does not necessarily represent an ongoing seizure, as they lay somewhere on the so-called ictal-interictal continuum, the term "epileptiform" should indeed better be avoided (Chong and Hirsch 2005; Hirsch et al. 2013). Importantly, transients with a triphasic appearance occurring (pseudo-) periodically also qualify for this definition. It has been recently reminded that these features are observed in patients with hypoxic-ischemic encephalopathy, ischemic stroke, hemorrhage, encephalitis, and metabolic disturbances; they tend to occur more often in patients showing also electrographic seizures (occurring in about 45–70 % of those with periodic discharges),

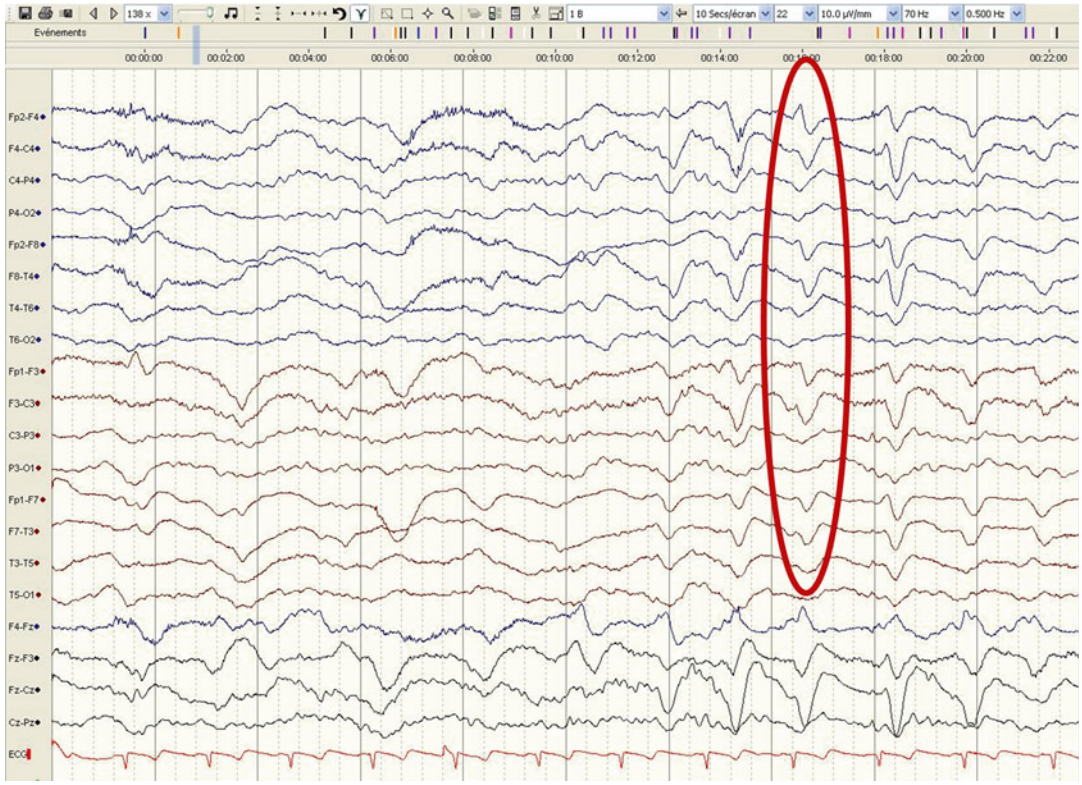

Fig. 5.1 Diffuse slowing and triphasic transients with a posteroanterior lag (*red ellipse*) in a 42-year-old man with a metabolic encephalopathy (longitudinal bipolar montage, 30 mm/s, 10 μV/mm)

but, somewhat counterintuitively, the impact on prognosis is not uniformly found: some authors recognize an independent association with poor outcome (Oddo et al. 2009), while others do not (Ong et al. 2012; Foreman et al. 2012), as opposed to the underlying EEG background reactivity (Ong et al. 2012).

5.2.4 Rhythmic Delta Activity

The summarizing eponym is RDA, but these features are also commonly labeled as frontal *intermittent*, *rhythmic delta activity* (FIRDA; see Table 5.4) because of the frequently observed anterior predominance. This EEG pattern is common and usually reactive to stimuli. Apart from the fact that symmetric rhythmic delta is not related to epilepsy, it represents a rather unspecific finding seen in patients with various structural brain lesions, toxic-metabolic disorders, brain infections, as well as other etiologies (Accolla et al. 2011; Sutter et al. 2013a). Symmetric delta slowing does not have any localizing value, but a marked asymmetric appearance may be associated with an underlying ipsilateral lesion (Accolla et al. 2011). As compared to triphasic waves and severe, diffuse EEG slowing, FIRDA seems to be related to a better outcome (Sutter et al. 2013a). Recently, the occurrence of lateralized rhythmic delta activity has been described in about 5 % of patients with impaired consciousness, with a prevalence of associated seizures similar to that observed with periodic discharges (Gaspard et al. 2013).

5.2.5 Stimulus-Induced Patterns

The first systematic description of stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs; see Table 5.4 for the last proposed terminology) is just 10 years old (Hirsch et al.

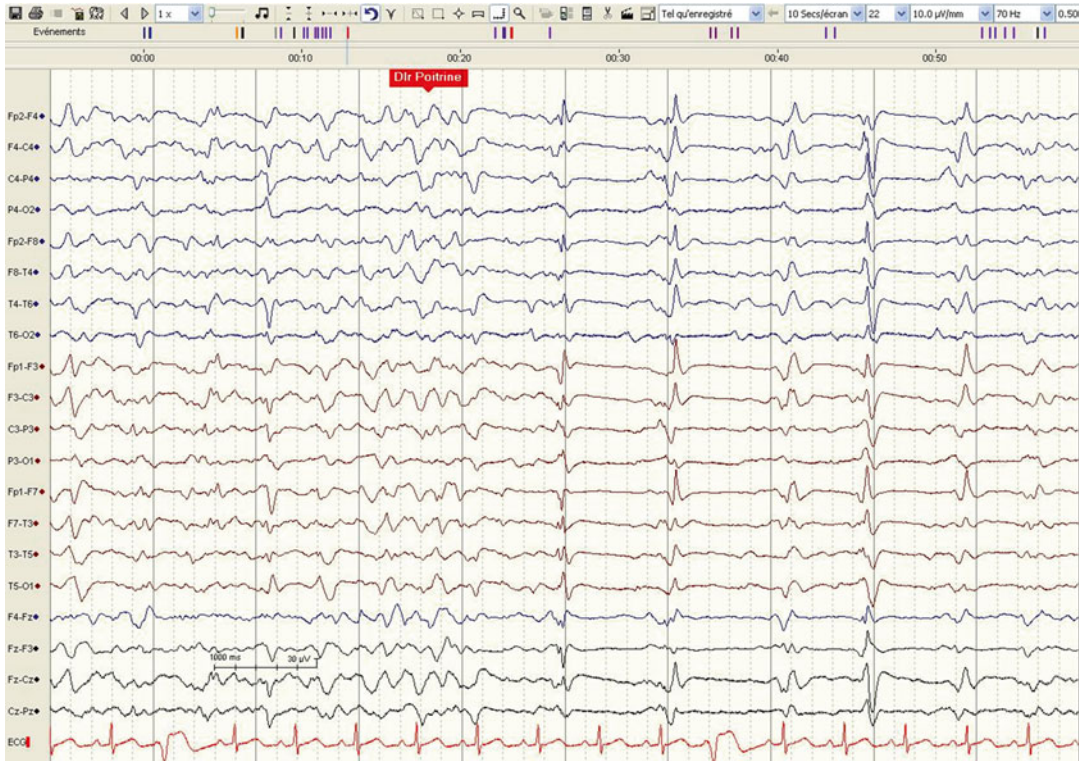

Fig. 5.2 Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs), in this case stimulus-induced generalized periodic discharges (SI-GPDs), in a 56-year-old man, during normothermia, 36 h after a cardiac arrest. The stimulation (pain applied to the chest) is marked in *red* (longitudinal bipolar montage, 30 mm/s, 10 µV/mm)

2004). These patterns, arising following any stimulation on the lying, comatose patient, are not exceptional, with a reported prevalence of 22 % in the original description of a neuro-ICU cohort, encompassing all the etiological spectrum seen in this setting (Fig. 5.2); as the authors pointed out, a video correlation to recognize the stimuli (at times very subtle, such as a monitoring noise or caregiver's steps beside the bed) is mandatory in order to differentiate these EEG features from spontaneous seizures. SIRPIDs may represent a heterogeneous EEG reaction that should not be regarded as a normal, physiological reactivity (the latter, as we have seen, is often related to a somewhat better prognosis): while some of these patterns clearly resemble electrographic seizures, others are not related to any ictal activity (Zeiler et al. 2011). Interestingly, SIRPIDs have received relatively little attention regarding their prognostic significance; recently, their occurrence in postanoxic patients undergoing hypothermia has however been related to poor outcome (Alvarez et al. 2013a).

5.2.6 Electrographic Seizures

Seizures and status epilepticus represent a common challenge for caregivers in the ICU setting, and are mostly nonconvulsive (Claassen et al. 2004) (Chap. 1); the therapeutic criteria and approaches are discussed in Chaps. 3 and 4. Their specific role in terms of clinical prognosis varies among the etiologies and population studies; that is, it is difficult to identify a common pattern summarizing their impact independently from the etiology and the extent of active comorbidities.

Earlier observations that myoclonic status following resuscitation after cardiac arrest, often correlating with periodic EEG discharges, is linked to a poor outcome (Wijdicks et al. 1994) have been corroborated in patients treated with

therapeutic hypothermia (Rossetti et al. 2007), particularly if electrographic seizures appear during cooling and despite pharmacological sedation (Rossetti et al. 2012). However, of note, prognosis does not prove invariably catastrophic for patients experiencing seizures after rewarming (Rossetti et al. 2009).

In patients with traumatic brain injury, seizures have also been independently associated with mortality (Hesdorffer et al. 2009), and it has been suggested that they aggravate cerebral damage (Vespa et al. 2007); similar findings also apply for subarachnoid hemorrhage (Claassen et al. 2006; Dennis et al. 2002), while in subjects with intracranial hemorrhage, although seizures have been associated with worse cerebral damage (Vespa et al. 2003), they do not seem to predict clinical prognosis independently (Passero et al. 2002; Claassen et al. 2007; Vespa et al. 2003). Acute seizures or status epilepticus in patients with ischemic stroke has been reported to be independently related to worse clinical outcome in hospital-based (very likely including a higher proportion of patients treated in the ICU) (Arboix et al. 2003; Knake et al. 2006) but not in population-based studies (Labovitz et al. 2001; Reith et al. 1997); globally, their occurrence is limited to about 2 % of the patients (Carrera et al. 2006). Patients with sepsis in the medical ICU are also subject to have (mostly nonconvulsive) seizures, which seem to correlate with worse prognosis (Oddo et al. 2009).

5.2.7 Alpha, Theta, and Spindle Coma

These EEG patterns are less frequent than the aforementioned; while they are mostly observed in comatose patients experiencing a cardiac arrest, they may also be found in subjects with toxic-metabolic disturbances, brain trauma, or infections (Kaplan et al. 1999, 2000). They are mainly defined by a dominant frequency and by a reversed spatial distribution, that is, the amplitude is usually higher in the frontal than in the posterior regions. The lack of reactivity to stimulations is regarded as characteristic by most (Young et al. 1997; Berkhoff et al. 2000) but not all authors (Kaplan et al. 1999).

Alpha and theta coma probably represent a common phenomenon: in fact, a transition among these frequencies has been described in several patients; alpha coma is usually seen at the low alpha band (7–8 Hz) (Synek and Synek 1984, 1988), and a progressive slowing leading to a diffuse EEG attenuation may be observed over some days (Fig. 5.3) in patients with poor prognosis. The mechanism is thought to be related to deafferentation of the cerebral cortex or cortical laminar necrosis or again drug intoxications (Kaplan et al. 1999). The presence of a reproducible variation of the background modulates the earlier assumption that alpha and theta coma invariably herald a poor outcome: the majority of patients showing a "reactive" alpha coma have been described to awaken, as opposed to those with no reactivity (Berkhoff et al. 2000; Kaplan et al. 1999). Spindle coma may reflect the preservation of thalamocortical loops following lesions located in the lower diencephalon, or in the brainstem, and therefore a lesser degree of brain dysfunction (Kaplan et al. 2000). This is illustrated by the fact that even if also in these cases background EEG reactivity plays a role for prognostic proposes, as opposed to alpha-theta coma, a considerable proportion of patients with nonreactive recordings may also awaken, thus conferring a better prognosis to this specific EEG pattern.

5.2.8 Sleep Spindles

While spindle coma is a pathologic condition with abundant spindles but lacking sleep-specific EEG features, the occurrence of physiological sleep patterns in patients with disorders of consciousness has recently been outlined as an important prognostic factor, likely reflecting the preservation of widespread brain regions and connections. This is nicely illustrated in patients with consciousness impairment following deep cerebral vein thrombosis involving the thalami and lacking spindles in the acute setting; the latter return upon resolution of the vasogenic thalamic

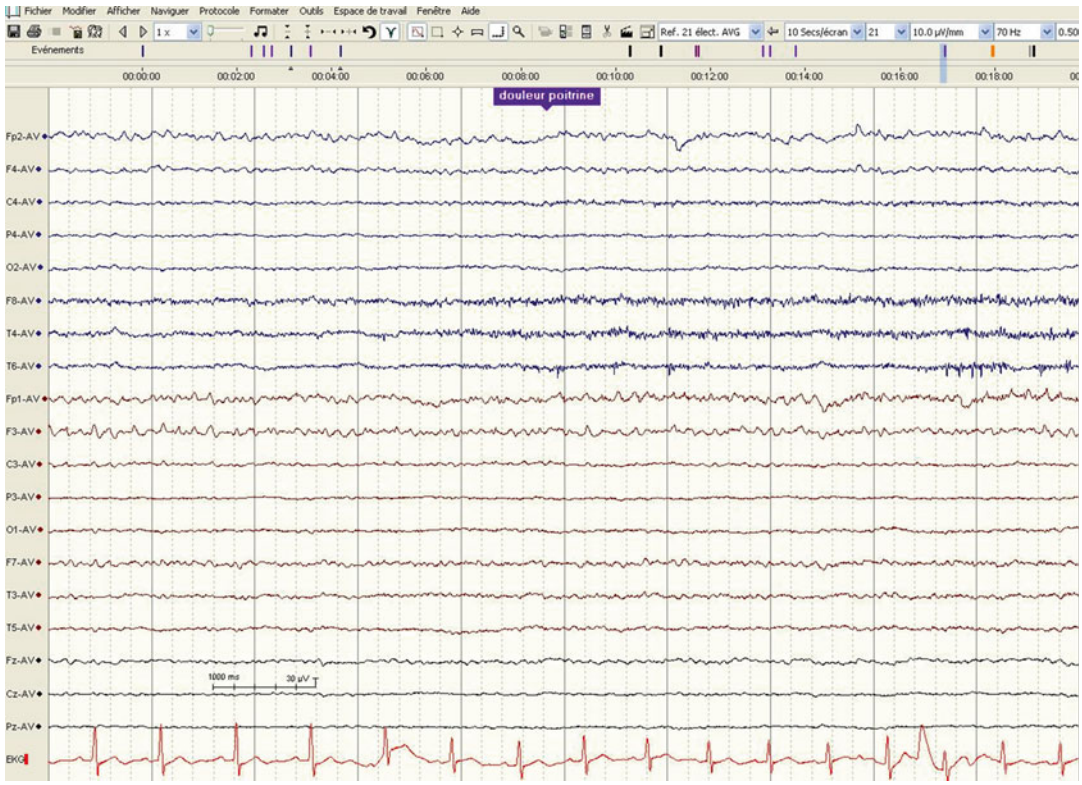

Fig. 5.3 Alpha-theta coma in a 43-year-old man, in normothermic conditions, 72 h after a cardiac arrest. The dominant frequency is 7 Hz, of higher amplitude in the frontal regions, without any reactivity to stimulations (pain applied to the chest, marked in *blue*; average referential montage, 30 mm/s, 10 µV/mm)

edema (Rossetti et al. 2005). In subjects with severe traumatic brain injury (Urakami 2012; Landsness et al. 2011) and anoxic-ischemic encephalopathy (Landsness et al. 2011), the occurrence of K complexes and sleep spindles clearly correlates with a lesser degree of consciousness impairment (i.e., vegetative—or nonresponsive wakefulness—versus minimally conscious states). Of note, these studies have been conducted in a rehabilitation setting, several weeks after the initial insult, and an improvement in the spindle occurrence was described relatively late, up to 150 days (Urakami 2012); therefore, one should not automatically infer that the lack of physiological sleep in the acute setting portends the same dismal prognosis. In fact, during the first few days, acute brain changes and pharmacological sedation usually prevent the appearance of the specific sleep transients.

5.3 Particular Clinical Situations

In recent years, therapeutic hypothermia has experienced an increasing popularity, mainly in the context of anoxic-ischemic brain injury in neonates and adults (Holzer 2010). Core temperature lowering might lead to concerns regarding the EEG interpretation in these conditions; however, EEG changes in relation with cooling in patients undergoing hypothermic circulatory arrest for surgical purposes have been systematically analyzed. It is not until below 30 °C that periodic complexes appear; the temperature has to sink below 24 °C in order to observe diffuse intermittent suppression and below 18 °C for electrocerebral silence (Stecker et al. 2001). Hence, the common application of therapeutic hypothermia to 33 °C does not lead to marked EEG changes, apart from some mild slowing or

amplitude attenuation that may also be induced by concomitant pharmacological sedation.

5.3.1 Hypoxic-Ischemic Encephalopathy: Adults

Outcome prognostication of comatose patients surviving a cardiac arrest has challenged clinicians for decades and has received increasing attention in these last years. The timing of assessment is critical, as electrophysiological evaluations within 12 (and maybe 24) h after the insult may lead to overestimation of the brain damage (Bassetti et al. 1996; Berkhoff et al. 2000), likely due to the acute, partially reversible neuronal electrical "shutdown." This not only applies for patients in normothermia but also for those undergoing controlled temperature lowering (Alvarez et al. 2013b).

In this clinical setting, the prognostic role of the EEG is well established. In normothermia, patterns of monotonous, very diffuse low voltage or repetitive electric seizures or status epilepticus or periodic discharges without any identifiable background are considered to herald a poor prognosis (Fugate et al. 2010; Rossetti et al. 2010; Thenayan et al. 2010; Rittenberger et al. 2012; Wijdicks et al. 2006); the lack of background reactivity is also a reliable prognosticator (Rossetti et al. 2010; Thenayan et al. 2010). The EEG during therapeutic hypothermia has been recently described to provide very valuable prognostic information, not only regarding the continuity of the tracing (an isoelectric recording during hypothermia, 24 h after the cardiac arrest, is tightly related to non-awakening (Cloostermans et al. 2012)) but also lack of background reactivity: this feature, despite the concomitant use of moderate doses of sedation, has been related to a reliable forecast of poor outcome (Fig. 5.4) (Rossetti et al. 2012). However, a reactive EEG (even during hypothermia) does not necessarily imply a favorable prognosis: in fact, the occurrence of a discontinuous background and elevated biological markers (serum neuron-specific enolase) may point to patients with a less favorable outcome despite early reactivity (Tsetsou et al. 2013). In parallel, explorations of automated, amplitude-integrated EEG softwares have been described, pointing to the favorable prognostic role of a continuous signal, without electrographic status epilepticus (Rundgren et al. 2006, 2010); these approaches are, however, still not widely applied.

Since the false prediction of death or non-awakening is still possible using EEG (numbers oscillate between 0 and 10 % according to different studies), a complete evaluation in normothermia and off sedation and a multimodal integration with other prognosticators (such as clinical examination, evoked potentials, and biological serum markers) are mandatory (Josephson 2010; Oddo and Rossetti 2011; Samaniego et al. 2011; Young 2009). This is underscored by the description of patients awakening despite postanoxic status epilepticus (Rossetti et al. 2009): these subjects had a particular clinical profile that helps identifying those deserving aggressive antiepileptic treatment, namely, preserved brainstem reflexes, reactivity of the EEG background, and early cortical somatosensory evoked potentials.

5.3.2 Hypoxic-Ischemic Encephalopathy: Neonates and Children

EEG alterations described in adults are also found in children undergoing therapeutic hypothermia after cardiac arrest (Abend et al. 2009) and, in general, bear the same prognostic value. Hypothermia up to 72 h is increasingly used also for neonatal asphyxia, where sedation is less frequently applied than in adults; in this clinical context, burst suppression or a diffuse, extremely low-voltage pattern heralds a poor prognosis, with a high specificity (Nash et al. 2011); background reactivity seems conversely to bear a favorable prognostic significance (Kessler et al. 2011). Given the popularity of cerebral brain function monitoring in this particular age group, considerable attention has been directed toward the prognostic significance of amplitude-integrated EEG: persisting burst suppression or very-low-voltage recordings with lack of development of a normal sleep-wake cycling or of

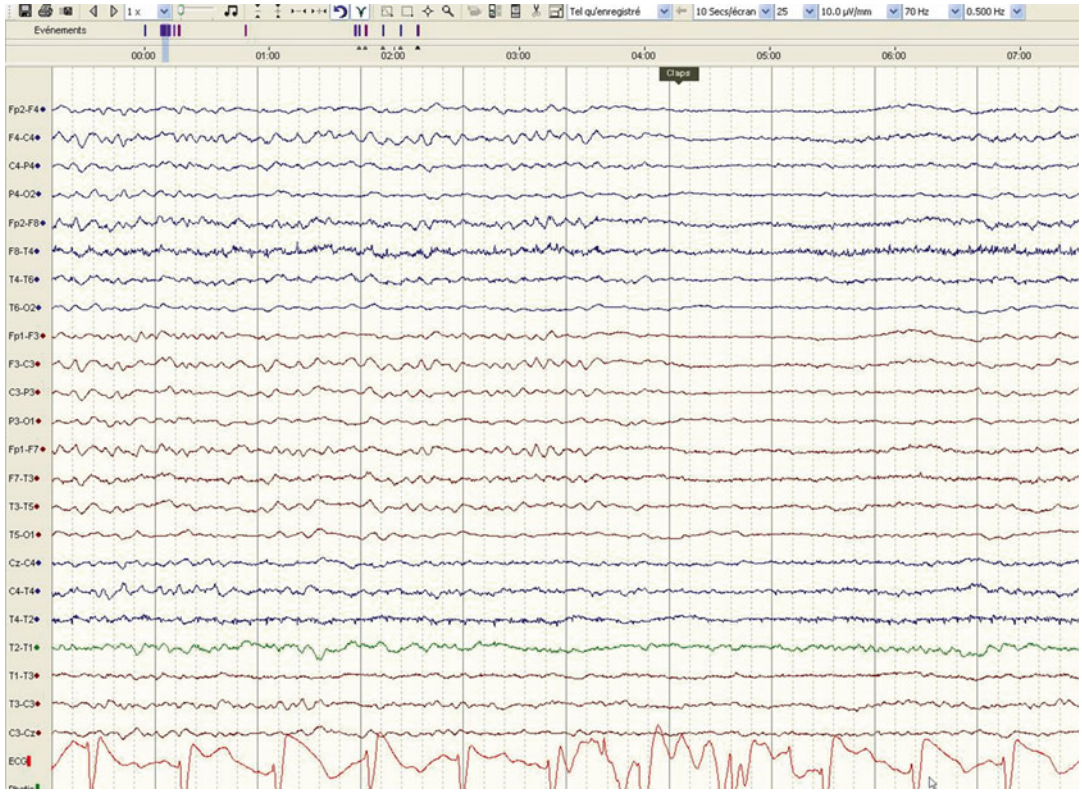

Fig. 5.4 Auditory stimuli (clapping of hands marked in *black*) induce a diffuse attenuation of the recording in a 63-year-old woman under mild therapeutic hypothermia 21 h after a cardiac arrest (bipolar longitudinal montage, 30 mm/s, 10 μV/mm)

recovery of a normal voltage background (even with discontinuous features) are related to poor outcome (Thoresen et al. 2010; Hallberg et al. 2010). It is important to underscore that, also for newborns, timing of the assessment is critical, especially for those undergoing hypothermia: evaluation during the first 24 h is in fact clearly less reliable than those performed after 36–48 h (Hallberg et al. 2010; Nash et al. 2011; Thoresen et al. 2010).

5.3.3 Traumatic and Hemorrhagic Etiologies

Subarachnoid hemorrhage represents a frequent acute trigger of consciousness disturbance in the ICU population. As mentioned above, patients experiencing seizures have a worse prognosis, and EEG may help identify them (Claassen et al. 2006; Dennis et al. 2002). However, EEG may also be helpful in terms of correlations with vasospasm, a complication usually developing a few days after the initial insult. This has been already observed two decades ago: early EEGs (on the first day) showing bilateral slow waves heralded a poor prognosis, mostly following ischemia and vasospasm (some days later), and recordings performed on day 5 tightly correlated with vasospasm if displaying focal slowing (Rivierez et al. 1991). These observations were confirmed some years later using continuous EEG with quantitative analyses: decreasing alpha variability might even precede by 2–3 days the insurgence of a vasospasm (Vespa et al. 1997). Nevertheless, to date, it has not been demonstrated that the use of EEG influences clinical prognosis.

An analogous approach has also proven useful to foresee prognosis in patients with moderate to severe traumatic brain injury (Vespa et al. 2002).

Furthermore, in this clinical situation, seizures are again related to worse clinical outcome (Hesdorffer et al. 2009; Vespa et al. 2007) and the development of hippocampal atrophy ipsilateral to the seizure focus (Vespa et al. 2010). However, as in other etiologies, it remains still unclear whether the prescription of antiepileptic treatment may have a prognostic impact (Stevens and Sutter 2013). Once again, electrographic reactivity bears an important prognostic information, as observed in a cohort of 50 patients that underwent auditory and nociceptive stimuli within 72 h after trauma: the vast majority (96 %) of subjects showing either an appearance of slow waves or a relative suppression had a favorable outcome, as opposed to those without any EEG changes following stimulations, 93 % of whom evolved to severe disability and vegetative state or died; the discriminative power of EEG reactivity resulted better than that of somatosensory evoked potentials (Gutling et al. 1995).

5.3.4 Other Conditions

The clinical situations listed above are by far not exhaustive. For example, toxic-metabolic conditions represent a frequent further etiology (Kaplan and Rossetti 2011). General anesthetics are often prescribed in the ICU setting, and a multitude of compounds, such as inhalation anesthetics (isoflurane), barbiturates (thiopental, pentobarbital), propofol (Akrawi et al. 1996), and also benzodiazepines, such as midazolam, may induce marked diffuse slowing, a discontinuous EEG, burst suppression, or even complete suppression, depending on their dosages. Interestingly, most drugs act principally by modulating the $GABA_A$ receptor and accordingly may diffusely enhance fast rhythms or spindle-like figures at low doses (Feshchenko et al. 1997). Of course, such changes will superimpose on the underlying focal or diffuse EEG alterations due to the respective clinical conditions.

Intoxications may considerably affect the EEG (Kaplan and Rossetti 2011). Opioids generally slow the background, while neuroleptic and antidepressant drugs (especially if displaying anticholinergic properties, such as olanzapine, clozapine, or high doses of tricyclics) may induce in addition generalized or focal epileptiform abnormalities, as well as triphasic waves (Amann et al. 2003; Silvestri et al. 1998); similar changes may be also observed with lithium (Caviness and Evidente 2003). Hypnotic compounds, which modulate $GABA_A$ receptors in a different way as compared to barbiturates and benzodiazepines, can also enhance beta activity (Bloetzer et al. 2007). Antibiotics with beta-lactam rings act as GABA antagonists, but under therapeutic dosages it is rare to observe clinically meaningful intoxications (with background slowing and triphasic transients) or seizure induction, apart from cefepime, especially with concomitant renal impairment (Jallon et al. 2000).

Metabolic disturbances are reflected on the EEG by progressive background slowing—up to complete EEG suppression in dramatic cases—and the appearance of rhythmic delta (FIRDA) or triphasic waves (Sutter et al. 2013a).

5.4 Outlook

Ongoing technological improvements, which not only have allowed to reach considerable performances in EEG video recordings at the patient's bed but also simplify data storage, are experiencing a new momentum in recent years, with the development of devices for automated EEG analysis (Wilson et al. 2004; Furbass et al. 2012; Sackellares et al. 2011). These softwares are already popular in several large North American centers widely using continuous EEG monitoring and are making their way also in Europe; they are based on several mathematical approaches using amplitude-integrated EEG signals of a standard 10–20 EEG montage, which allow not only seizure and spike detections but also artifact rejections (such as eye movements, muscle, or poor electrode contacts), and quantification of several indices (e.g., suppression ratio, alpha/delta ratio) that may prove important for a multimodal monitoring in brain-injured patients. Another important point is the possibility of a live display of the analyses during the recording, rendering potentially

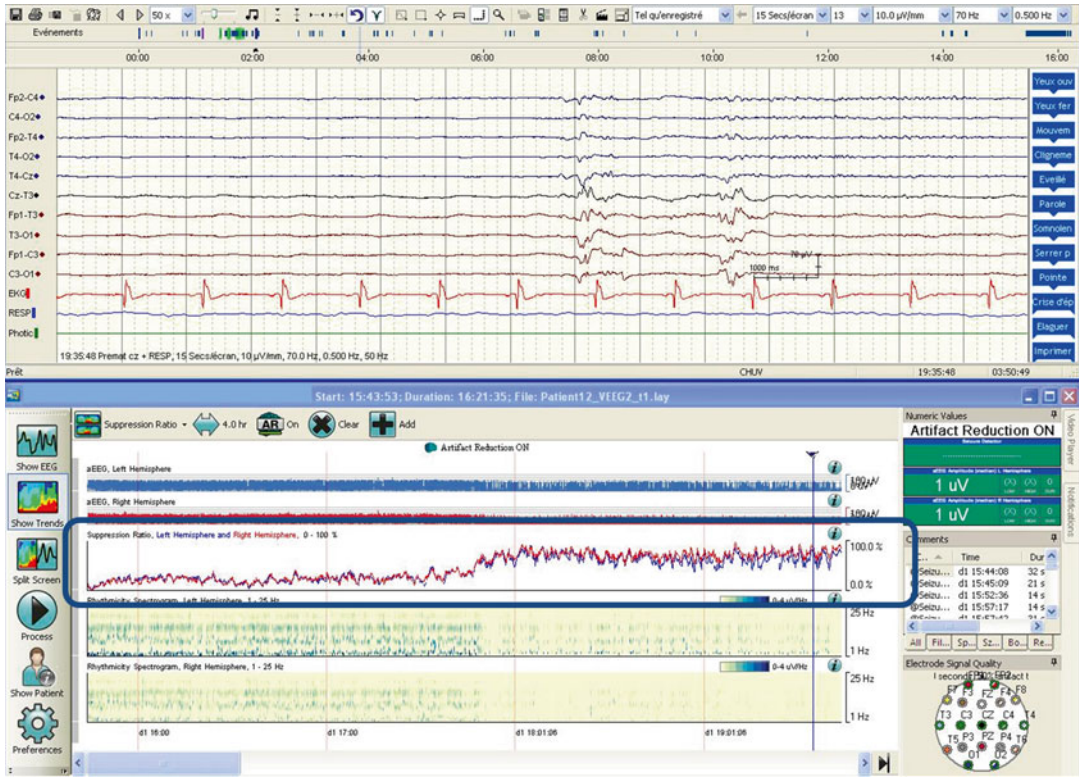

Fig. 5.5 *Upper panel*: raw EEG of a 73-year-old man under anesthetic treatment for refractory status epilepticus; the screen represents 15 s (bipolar longitudinal montage, 20 mm/s, 10 μV/mm). *Lower panel*: quantitative EEG over 4 h; the *blue box* highlights the suppression ratio, which may be easily followed in order to adapt the depth of sedation. The bar on the right shows the position of the raw EEG display

prognostic EEG information more accessible to non-trained caregivers (Fig. 5.5). While the performances are steadily improving, all methods still lack independent validations and therefore require, as a gold standard, inspection of the raw EEG trace (Fig. 5.6). It is probably a matter of time until most centers devoted to EEG recordings in the ICU will be provided with reliable softwares with automated EEG analysis; the expertise of the EEG reader will still be important for the interpretation of controversial patterns and the integration of the EEG data to the clinical situation.

Intracerebral electrodes are also receiving increasing attention, although, for the moment, for scientific purposes rather than straightforward clinical implications. For example, in patients with subarachnoid hemorrhages, seizures are seen more often intracortically (38 %) than on scalp derivations (8 %), and prognosis seems to be better for patients without any seizures (no risk of severe disability) than for those with scalp seizures (25 % risk) or with intracortical seizures only (50 % risk); the authors speculate that a certain brain function should be present in order for the seizure to spread to the cortex, but this remains to be verified (Claassen et al. 2013). In another study, spreading depolarizations were observed in half of the studied patients with severe traumatic brain injury and were associated with an increased risk of poor outcome (Hartings et al. 2011). Spreading depolarizations are also regarded as an electrical correlate to delayed ischemia in patients with subarachnoidal hemorrhage (Dreier et al. 2009) and correlate with EEG changes detected on the scalp (Drenckhahn et al. 2012). While these observations open exciting new avenues for the understanding of brain pathophysiology in these particular clinical conditions, there is still no answer regarding the

Fig. 5.6 *Lower panel*: the screen summarizes quantitative EEG data over 2 h in a 46-year-old woman emerging from anesthesia after a generalized convulsive status epilepticus. The *blue box* focuses on the automated seizure detection whose vertical red marks correspond to detected seizures. However (*upper panel*), the corresponding raw EEG recording (screen of 10 s; bipolar longitudinal montage, 30 mm/s, 10 μV/mm) shows an intermittent, sharply contoured delta slowing, but not an electric seizure

prognostic impact of seizure treatment, and an important limitation should be remembered: the sampled tissues are limited and often are not comparable among the studied patients in terms of concomitant pathological involvement (i.e., ipsilateral and close to the lesion versus contralateral). Future assessments in these and other clinical settings are clearly needed to unravel the prognostic role of intracerebral EEG.

Over the last decade, continuous EEG monitoring in the ICU has been markedly developed. It has been shown that this patient population should be monitored for at least 24 h in order to detect 88 % of seizures (and for 48 h in order to catch 93 % of events); the vast majority of seizures are nonconvulsive and thus easily overseen by clinical observation only (Claassen et al. 2004). More recently, however, in an analysis on 242 patients (not restricted to ICU, and as the former one including heterogeneous underlying diagnoses), the lack of epileptiform activity during the first 30 min of recording rendered a subsequent seizure on continuous EEG extremely unlikely (risk estimation: 3 % versus 22 % in those with epileptiform discharges (Shafi et al 2012). This important message suggests that a first routine EEG may help in identifying those subjects that would deserve EEG monitoring; this would greatly improve cost and time effectiveness, particularly in locations with relatively limited resources (this consideration, presently, still applies for the majority of large centers in the Western world, not to speak about developing countries). In the same order of ideas, in patients with postanoxic coma, it has been demonstrated very recently that repeated routine EEG recordings (which usually last 20–30 min) may prove as informative, particularly for prognostic purposes,

as continuous EEG monitorings, as in this specific setting tracings do not show significant changes over time during the first 24–48 h (Crepeau et al. 2013; Alvarez et al. 2013b).

In conclusion, EEG represents a very useful tool for prognostic assessment of patients with acute cerebral dysfunction; as every other prognosticator, however, it has to be integrated with other variables for it to become a multimodal approach that proves more robust for clinical forecast but also minimizes false-positive poor predictions (see also Chaps. 6 and 7). Somewhat disappointingly, EEG in the ICU still represents a prognostic marker, rather than a diagnostic tool with therapeutic implications. Since recent technical developments are rapidly changing the environment for clinicians and clinical neurophysiologists, it is hoped that the future will outline the best approaches in terms of effectiveness and define potential therapeutic consequences.

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Prognostic Use of Somatosensory Evoked Potentials in Acute Consciousness Impairment

6

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Abstract

Predicting the fate of ICU patients who are in coma is extremely challenging. In this context, somatosensory evoked potential (SSEP) can assist the multimodal neurological evaluation. In this chapter, we discuss the principles, applications and limitations of the SSEP in the ICU, with a focus on prognostication in comatose patients. Registration of the SSEP is a very reliable and reproducible method, if performed and interpreted correctly. During recordings, great care should be taken in improving the signal-to-noise ratio: if the noise level is too high, the peripheral responses are abnormal, or the response is not reproducible in a second set of stimuli; in these cases, interpretation of the SSEP cannot be done reliably. A bilaterally absent cortical response is a reliable predictor for poor neurological outcome in patients with a postanoxic coma, but not in patients with traumatic brain injury or stroke.

6.1 Introduction

Every patient remaining in coma in the intensive care unit (ICU) raises the question regarding outcome prediction (Chap. 1). Both the treating team and family members need information about the chances of recovery of consciousness and long-term functional outcome. Reliable information on this topic is necessary to decide on limitations

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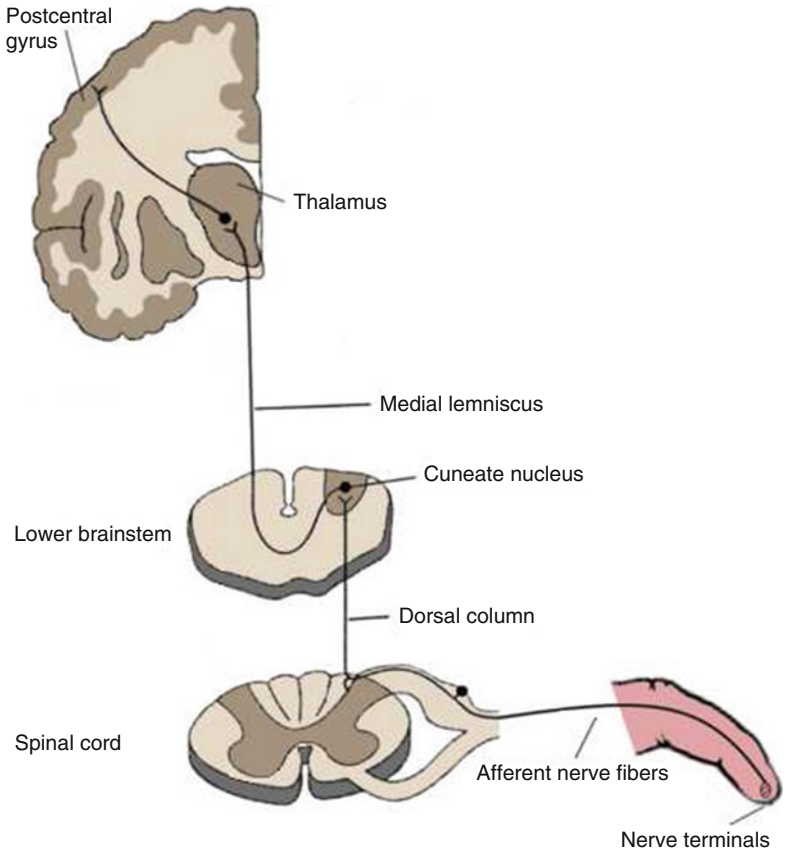

Fig. 6.1 The anatomical connections evaluated by the median nerve SSEP

or even withdrawal of supportive intensive care treatment. Somatosensory evoked potentials (SSEPs) are often used in this situation and can prove very useful depending on the condition underlying the coma.

6.2 SSEP Principles (see also Chap. 2)

The SSEP is a small (<10–50 μV) electrical signal, which can be recorded noninvasively from the skull, after giving a set of electrical stimuli to one of the peripheral nerves, evaluating the complete pathway from the peripheral sensory nervous system to the sensory cortex, running via the dorsal column and lemniscal pathway through the spinal cord, brainstem and thalamus (Cruccu et al. 2008). This pathway consists of four neuronal populations: the cell bodies of the first-order neurons are situated in the dorsal root ganglia, the trigeminal ganglion, the midbrain trigeminal nucleus and the vagal ganglion nodosum. The second-order neuron lies in the rostral part of the dorsal column (cuneate and gracile nuclei). Axons of these second neurons cross the midline and project to the ventroposterior nuclei of the thalamus (third-order neuron). From there, the pathway projects into the network of somatosensory cortex areas (fourth-order neurons), which include the primary and secondary somatosensory cortex, posterior parietal cortex, posterior and mid-insula and mid-cingulate cortex (Fig. 6.1).

SSEPs are usually evoked by bipolar transcutaneous electrical stimulation applied on the skin over the selected nerve and registered with disc electrodes along the tract. For example, in recordings of the median nerve, registration electrodes can be placed at the elbow, Erb's point (over the

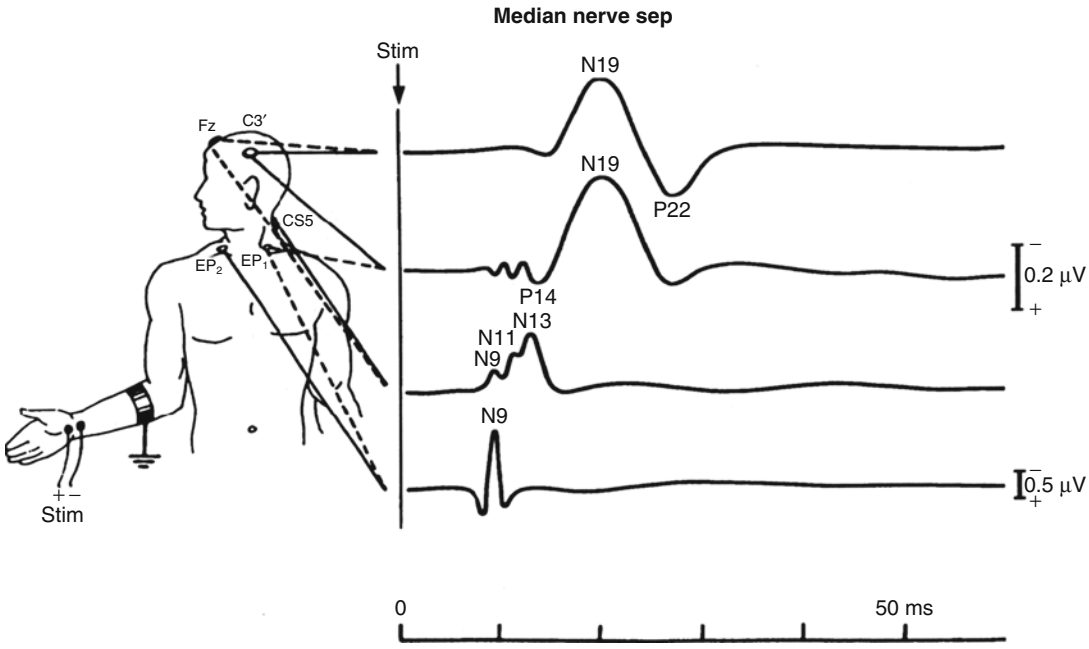

Fig. 6.2 Multiple recording sites of SSEP

plexus, above the clavicle) and cervical, parietal and frontal cortex (Fig. 6.2; see also Chap. 2). Cortical responses can only be interpreted reliably when the peripheral responses are present. In the nomenclature of SSEP waveforms, N or P followed by an integer is used to indicate the polarity (positive, respectively, negative) and the nominal poststimulus latency (in ms) of the recorded wave in a healthy reference population (e.g. P15, N20). The earliest cortical potential is the N20, which is generated in the primary somatosensory cortex, where thalamocortical cells undergo synaptic connections with the superficial and deep pyramidal cell layers (Allison et al. 1991). In comparison to cortical responses of greater latency, the N20 is the most robust, as this is the latest waveform to disappear following increasing levels of encephalopathy or pharmacological sedation; of note, however, the N20 is relatively independent to the level of sedation used in clinical settings (Cruccu et al. 2008). Since the cortical waveforms appearing later (such as P45, N60 and P/N100) are less reliable and more susceptible to changes by sedation, the N20 is widely used in almost all clinical prognostic questions.

6.3 Pitfalls and Limitations of SSEP Recordings in the ICU

One of the main problems of the SSEP interpretation is the interobserver agreement, which has been extensively described in several studies (Zandbergen et al. 2006a; Pfeifer et al. 2013). Zandbergen et al. investigated 56 consecutive patients with anoxic–ischaemic coma (Zandbergen et al. 2006a); these registrations were interpreted independently by five experienced clinical neurophysiologists. The interobserver agreement for SSEPs in anoxic–ischaemic coma was only moderate (kappa 0.52, 95 % CI 0.20–0.65): the main source of disagreement was related to the underlying electrical noise, implying difficulties in obtaining a reasonable signal-to-noise ratio. For recordings with a noise level of 0.25 μV or more, the mean kappa was as low as 0.34 (fair agreement), while for recordings with noise levels below 0.25 μV, the mean kappa improved to 0.74, which is a substantial agreement. Similar results have been reported by Pfeifer et al., again in subjects

admitted after cardiac arrest (Pfeifer et al. 2013). One way of integrating the SSEP information with other neurophysiological variables, in order to limit the aforementioned problems, may be a continuous SSEP registration combined with continuous EEG. This can be used to monitor deterioration in patients with severe brain injury (Amantini et al. 2009); however, such approaches are still rare in clinical practice. Of note, almost all literature regarding the use of SSEP for prognostication uses the absence or presence of short-latency cortical responses (N20). Whether the amplitude of cortical responses can be used is uncertain. During continuous SSEP and EEG registration, an N20 amplitude <1.2 μV has been used as a cut-off to describe an abnormal SSEP (Bosco et al. 2011), but it is important to underscore that this threshold does not reflect any evidence nor current practice for N20 analyses in the prognosis after cardiac arrest.

Efforts should be made to increase the signal-to-noise ratio as much as possible. As an orienting threshold, Zandbergen et al. recommend that the peak-to-peak amplitude of noise of the cortical and cervical leads should be lower than 0.25 μV after averaging, especially in the frequency of the SSEPs themselves (20–500 Hz) (Zandbergen et al. 2006a). Administration of muscle relaxants (together with modest doses of sedation, such as 5 mg of midazolam) often improves the quality of the SSEP registrations in patients with abundant muscle activity. Furthermore, disturbing electrical ICU equipment should be turned off as much as possible. Also, delivering more stimuli (up to 1,000 or more) and increasing the stimulus intensity could contribute to optimize the signal-to-noise ratio. In addition, it has been also suggested that the stimulus rate may influence the results of an SSEP recording (Robinson and Micklesen 2010) (see Chap. 2). Since the interpreting clinician is often not present during the actual SSEP registration itself, the role of the technician is crucial in obtaining reliable results.

6.4 Interpretation Criteria of SSEP

Additional criteria apart from the signal-to-noise ratio should be kept in mind when interpreting SSEP recordings. An N20 peak on one side can only be considered as present if it fulfils all of the following criteria (Zandbergen et al. 2006a):

- It should have an appropriate latency (i.e. appearing at least 4.5 ms later than the corresponding N13 peak recorded from the posterior cervical region in normal-stature adults).
- It should be present on the other side, and there should be a clear difference with the recording from the side ipsilateral to the stimulus. Therefore, it is recommended to record not only the contralateral sensory cortex after stimulation but also co-register the ipsilateral side. This prevents misinterpretation of the N18, which has its origin in the brainstem, as an N20 potential.
- Any potential should be clearly reproducible in a second set of stimuli.

Bilateral absence of N20 peaks requires the presence of normal potentials over Erb's point and the neck (N13), in order to ensure that the impulses have arrived in the central nervous system through an integer peripheral pathway. Figure 6.3 illustrates an example of an SSEP registration with present and absent N20 cortical responses.

6.5 Confounding Factors and Sedation

Cortical responses are generally not influenced by moderate pharmacological sedation or metabolic disturbances, factors that often hamper the clinical neurological examination in the ICU. However, massive intoxications, very severe biochemical or metabolic disturbances and anatomical (e.g. a high cervical) lesions should be actively ruled out. The cortical N20 responses may remain still visible even at sedation levels

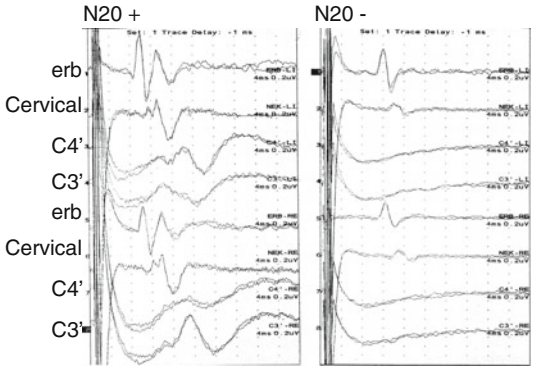

Fig. 6.3 Median nerve SSEP registration with and without cortical responses

sufficient to induce an isoelectric EEG (Cruccu et al. 2008; Rothstein 2004); nevertheless, care should be taken when high-dosed barbiturates are administered: high-dosed sodium thiopental induces an increase in latencies and decrease in amplitudes for median nerve SSEP and brainstem auditory evoked responses (Drummond et al. 1985). It is uncertain whether the amplitudes decrease to a level that the cortical response can no longer be identified. Patients with absent cortical responses during thiopental (or pentobarbital) coma prescribed to treat increased intracranial pressures who made a good recovery in the end have been reported in the literature (Robe et al. 2003). This suggests that very high-dosed barbiturates can depress SSEP cortical responses. Propofol produces minimal suppression of the SSEP amplitude, which at most may be quantified to a loss of less than 10 % (Langeron et al. 1999). Also, midazolam and opioids have only moderate effects on SSEP amplitudes and latencies (Langeron et al. 1999; Asouhidou et al. 2010; Laureau et al. 1999; Taniguchi et al. 1992). Remifentanil can lower the cortical components by 20–80 % when given at a high dose (0.8 mcg/kg/min) as used during neuromonitoring in the operating room (Asouhidou et al. 2010). On the other hand, as stated above, in some cases it may be even advisable to administer low-dose sedation to improve the quality of the SSEP recordings. This is especially the case in patients with generalized periodic discharges on the EEG (see Chaps. 3, 4 and 5), which in some situations can be suppressed after the administration of propofol. These periodic discharges often have larger amplitudes in comparison to the evoked potentials and can disturb the detection of cortical response.

6.6 Prognostication in Postanoxic Coma

Bilateral absence of short-latency (N20) SSEP responses has been identified as the most powerful prognosticator of poor outcome in patients who remain unconscious after a circulatory arrest (Rossetti et al. 2010; Bouwes et al. 2012). In patients not treated with hypothermia, bilateral absence of cortical N20 responses 24 h or more after the event represents a reliable predictor for a poor neurological outcome (which is understood as no recovery of awareness) (Zandbergen et al. 2006b). A recent systematic review of all SSEP registrations reported in patients admitted to the ICU after resuscitation from a cardiac arrest and treated with hypothermia showed a false-positive rate (FPR) as low as 0.007, with a 95 % confidence interval of 0.001–0.047 (Kamps et al. 2013). These registrations were performed after return of normothermia. Even registration during therapeutic hypothermia might already have a solid good prognostic value, but the confidence interval is wider (Tiainen et al. 2005; Bouwes et al. 2009).

Unfortunately, a bilateral preservation of the N20 does not imply a favourable outcome in patients after cardiac arrest. In fact, only a small proportion of patients with a poor outcome after resuscitation have negative SSEP responses resulting in a low sensitivity (Kamps et al. 2013; Cloostermans et al. 2012). This low sensitivity of the SSEP is also reflected in the large variability of EEG patterns that can be observed in patients with a preserved N20, including status epilepticus, or even extremely low-voltage EEG. As pyramidal cell synaptic function is mainly reflected by the EEG, while SSEP mainly evaluates the thalamocortical synaptic function,

a possible explanation for this peculiar constellation is selective hypoxic damage to the cortical pyramidal cells' synaptic function, with preserved thalamocortical synapses (van Putten 2012)

The prognostic value of late cortical SSEP responses reflects the function of associative cortical areas beyond the primary sensory cortex; although promising from a scientific point of view, it seems still not to be reliable enough to be used in daily clinical practice for treatment decisions in the clinical setting (Pfeifer et al. 2013; Zandbergen et al. 2006c).

6.7 Prognostication in Traumatic Brain Injury

In patients with severe traumatic brain injury (TBI), the results available on the reliability of SSEP to predict outcome have been contradictive. Sleigh et al. suggested, in a prospective and blinded cohort study including 105 patients, that median nerve SSEPs are reliable predictors for poor neurological outcome, with a 43 % sensitivity and no false positives (Taniguchi et al. 1992). In contrast, in several other studies, TBI patients have been described initially showing bilaterally absent N20 responses, who nevertheless later regained consciousness, with only minor disabilities (Cruccu et al. 2008). These results show that the absence of cortical SSEP responses does not represent a reliable predictor in this clinical context. The most likely explanation is that in head trauma, a transient N20 disappearance may be consecutive to focal midbrain dysfunction due to oedema (Cruccu et al. 2008) or focal cortical lesions. Therefore, SSEP should always be integrated with other neurophysiologic tools and clinical examination to improve the predictive value (Cruccu et al. 2008; Taniguchi et al. 1992). Moreover, in TBI patients, it is especially important to rule out traumatic lesions of the peripheral nerves, nerve roots or spinal cord, when using clinical neurophysiologic tests. To complicate issues, clinical examination of the peripheral nerves at times can prove difficult in patients with diminished consciousness.

6.8 Prognostication in Stroke

The use of median nerve SSEP registration in patients with severe ischaemic or haemorrhagic stroke was investigated by Su et al. (2010) and Zhang et al. (2011). The absence of cortical N20 response, at least on one side, or an abnormal bilateral N20–P25 amplitude ratio was reported to be statistically significantly correlated with a poor outcome (Su et al. 2010). Zhang reported that especially the absence of the N20 or the N60 (a late potential) contralateral to the lesion could help to predict a poor outcome in patients with severe stroke (Zhang et al. 2011). Besides the scientific interest of these studies, a sequential clinical assessment integrated with brain imaging studies appears more reliable and robust than the use of SSEP in this clinical setting.

In patients with subarachnoid haemorrhage, neither median nor tibial SSEP nor central conduction time of the median nerve SSEP can be reliably used as a valid outcome predictor. The patient's initial clinical grading still provides the only satisfying predictor (Wachter et al. 2011).

6.9 Prognostication in Sepsis

In patients with severe sepsis and septic shock, prolonged cortical SSEP peak latencies occur in 84 % of the patients. These latencies can be used to diagnose septic encephalopathy and its severity (Zauner et al. 2002). In these patients, however, SSEPs have not been reported to be helpful in determining the clinical prognosis.

6.10 Conclusions

SSEP can be used for prognostication in ICU patients with coma, as it represents a simple technique available at bedside, which can therefore be implemented relatively easily. Especially in patients with coma after cardiac arrest, this technique can give valuable additional information. However, physicians who base their treatment decisions on these techniques should be well aware of the inherent limitations and pitfalls.

Technicians who perform the recordings should be instructed on how to optimize the signal-to-noise ratio, in order to increase the reliability of this test.

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7 Prognostic Use of Cognitive Event-Related Potentials in Acute Consciousness Impairment

Marzia De Lucia and Athina Tzovara

Contents

Abstract

Electroencephalography (EEG) provides a powerful tool for evaluating the extent of intact cognitive functions in comatose patients at the bedside, mostly by recording responses to sensory stimuli, exemplified by the so-called event-related potentials (ERPs). Different ERP paradigms are informative of various levels of cognitive functions, ranging from basic auditory processing and auditory discrimination (i.e., mismatch negativity (MMN)) to novelty detection and detection of complex sound sequences. Among them, the MMN paradigm has proven especially useful, as the presence of an MMN response has been repeatedly associated with a favorable clinical prognosis. The high predictive power of MMN is basically driven by the absence of such a response in patients who fail to regain consciousness, mainly assessed several weeks or months after coma onset. However, the use of this paradigm in clinical routine has been limited so far, possibly due to the difficulty of assessing the presence of an MMN at the level of single patients. Multivariate EEG decoding methods provide a powerful tool for quantifying the degree of auditory discrimination, at the single-patient level with minimal a priori inclusion criteria, with very promising results in terms of prognostication of awakening. Moreover, recent evidence in patients in acute postanoxic coma treated with therapeutic hypothermia shows

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that auditory discrimination might still be intact during the first days of coma, irrespective of patients' outcome. Here, we propose a general framework for assessing the degree of auditory discrimination over time, as a process that degenerates in non-survivors and that improves in patients who eventually awake.

7.1 Introduction

Patients who survive severe brain damage often fall into a comatose state, during which they may be unresponsive to external stimuli and unable to communicate with their environment. In such conditions, it can be challenging for clinicians to evaluate the extent of preserved neural functions and whether comatose patients are able to consciously perceive their surroundings. Even though the majority of patients surviving a coma recover within a few days, some may remain in a state of reduced consciousness (vegetative or minimally conscious) for prolonged periods (Laureys et al. 2004). Clinical progress in the early resuscitation of these patients, including modern neuroprotective strategies such as therapeutic hypothermia (TH; Bernard et al. 2002), has resulted in an increasing number of patients awakening from coma, especially following cardiac arrest (Oddo et al. 2006). These advances encourage the neuroscientific and clinical community to reassess previous knowledge about preserved functions in the comatose patient and their link to prognosis (Bouwes et al. 2009; Rossetti et al. 2010). In addition, current efforts in translational research aimed at applying state-of-the-art neuroimaging methods to the clinical environment promise to ameliorate our understanding of the physiological basis of coma and ultimately to help improve overall quality of care for comatose patients (Amantini et al. 2011; King et al. 2013; Tzovara et al. 2013) (see also Chaps. 8 and 12). Among these methods, electroencephalography (EEG) provides a powerful and inexpensive tool for measuring neural response to sensory stimuli (event-related potentials, ERPs) in comatose patients at the bedside (Fischer et al. 1999, 2004; Bouwes et al. 2009).

Neuroimaging studies have considerably challenged standard clinical assessment, especially in the chronic phase. One exemplary case is provided by hemodynamic studies showing that patients with disorders of consciousness could be erroneously labeled as vegetative (also called unresponsive wakefulness), though actually able to communicate via "command-following" paradigms (Owen et al. 2006). These paradigms have provided quantitative evidence that patients without overt behavioral response to external stimuli were nevertheless able to modulate brain activity in association with voluntary answers (Owen et al. 2006; Cruse et al. 2011). The vast majority of these studies have, however, exclusively investigated patients with heterogeneous coma etiologies and in a vegetative state, or months after coma onset. The extent of intact cognitive functions during acute coma remains understudied, especially since the introduction of TH, which is increasingly used as a neuroprotective strategy during early postanoxic coma (Bernard et al. 2002; Choi et al. 2012). In the following section, we will review the most common applications of event-related potential in coma research, including recent results obtained in postanoxic comatose patients treated with therapeutic hypothermia.

7.2 Overview of Existing ERP Protocols

Measuring ERPs in response to sensory stimuli in patients with disorders of consciousness represents a powerful tool for assessing the extent of intact neural functions at the bedside (Fischer et al. 1999; Luaute et al. 2005; Daltrozzo et al. 2009). The interesting aspect of this research is twofold. On the one hand, a main focus is the understanding of the extent of brain processes that remain unaltered during coma and how this information relates to prognosis. On the other hand, assessing preserved functions during coma opens a window of investigation onto processes that can remain unaltered in the absence of consciousness or in a minimally conscious state (Bekinschtein et al. 2009; Faugeras et al. 2012).

This line of research is relevant for addressing unresolved questions in fundamental neuroscience about the relationship between cognitive processes and consciousness in humans (Boly et al. 2013). Access to this kind of investigation in comatose patients may complement similar research performed during sleep and under anesthesia (Chennu and Bekinschtein 2012).

One of the main efforts in the development of neuroimaging techniques applied in coma research is focused on establishing indirect communication channels with patients that may be conscious and potentially able to express willful responses (Owen et al. 2006; Cruse et al. 2011). During acute coma, neuroimaging techniques aim for a different goal, which is to assess the extent of intact neural functions in a condition where any form of conscious access to incoming sensory is extremely unlikely. In this context, the main interest relies in experimental protocols targeting basic sensory processing and cognitive functions which are largely based on implicit and automatic mechanisms (Lew et al. 2006).

Somatosensory evoked potentials (SSEPs; Zandbergen et al. 1998) and brain stem auditory evoked potentials (AEPs) have been widely used in clinical practice for predicting outcome in a variety of coma etiologies (Zandbergen et al. 1998; Gendo et al. 2001; Robinson et al. 2003; Bouwes et al. 2009) (see Chap. 6). The absence of early amplitude modulation in SSEPs provides an indirect measure of damage occurring at the level of the sensory pathways and/or at the level of primary sensory cortices. However, the early cortical response (N20) can be preserved both in patients with poor outcome and in those who later survive (Bouwes et al. 2009). While SSEPs mainly reflect processing at the level of sensory cortices and provide information about poor outcome, other ERPs, mostly reflecting cognitive processes, are informative as regards awakening or regaining of consciousness (Lew et al. 2006).

The auditory modality provides the most straightforward channel for recording cognitive ERPs, as it can be easily targeted in nonresponsive patients, either in coma (Kane et al. 1993; Fischer et al. 1999, 2004; Daltrozzo et al. 2009) or in vegetative/minimally conscious states (Neumann and Kotchoubey 2004; Kotchoubey et al. 2005; Boly et al. 2011). The most notable of these experimental protocols for measuring AEP is the so-called mismatch negativity (MMN) paradigm (Naatanen et al. 1978; Garrido et al. 2009); such a protocol can be based on a simple sequence of stimuli in which a frequent (standard) sound is repeated several times before being interrupted by a rare (deviant) sound with different acoustic properties. Classically, in healthy subjects, the negative difference (i.e., mismatch negativity) between the AEPs in response to deviant and standard sounds is mostly evident over the frontocentral regions at a latency of about 150 ms poststimulus (Garrido et al. 2009) (Fig. 7.1). MMN is considered a pre-attentive and preconscious marker of the brain's ability to discriminate sounds and can be measured even in conditions where any form of top-down contribution to sensory processing can be excluded, such as during sleep (Ruby et al. 2008; Sculthorpe et al. 2009) and deep anesthesia (Koelsch et al. 2006). The literature on MMN in comatose patients is extensive and has provided robust evidence of the relation between the MMN component and the patient's chances of awakening (Kane et al. 1993; Fischer et al. 2004; Luaute et al. 2005; Naccache et al. 2005; Wijnen et al. 2007; Tzovara et al. 2013). This has been demonstrated in a wide range of coma etiologies and measured from as early as a few days after coma onset (Kane et al. 1993) to weeks (Fischer et al. 2004; Naccache et al. 2005) or even months (Boly et al. 2011) (see also Chap. 9).

While MMN is mostly informative with regard to automatic processing of auditory regularities at the level of individual sounds, other more complex paradigms examine auditory processing at the level of groups of sounds (Bekinschtein et al. 2009). In this case, a regularity is established over few seconds, by repeating groups of five sounds and replacing them from time to time with deviant ones. The detection of a rare group of sounds at the neural level is much more demanding than the detection of a single sound, for example, in an MMN protocol, as the former requires subjects to be aware of the regularity, while the latter is thought to be more automatic (Bekinschtein et al.

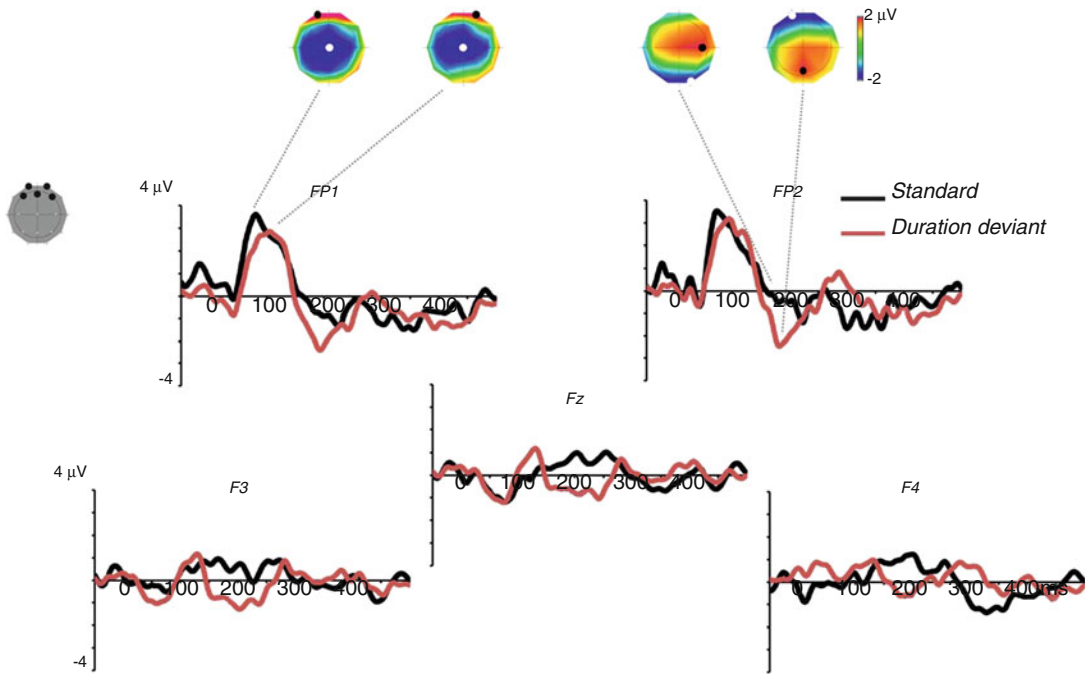

Fig. 7.1 Average AEPs for one exemplar control subject in response to standard and duration-deviant sounds (*black and red lines*, respectively) at five fronto-central electrodes. Voltage topographies at ~100 ms after stimulus onset exhibit prototypical N100 configurations with central negativity, for both standard and deviant sounds. The occurrence of the first negative difference between deviant and standard sounds and corresponding voltage topographies is observed at a typical MMN latency, between 150 and 200 ms. The white and black dots on the topographies represent the position of the minimum and maximum values across the whole electrode montage, respectively

2009). This more complex paradigm has therefore been linked to conscious processing, as previous studies have shown that the majority of patients who can detect this type of irregularity are either at a minimally conscious level (Bekinschtein et al. 2009) or eventually regain consciousness (Faugeras et al. 2012).

Other auditory paradigms that have been well studied in patients with impaired consciousness are based on oddball protocols (Sutton et al. 1965; Friedman et al. 2001). Oddball paradigms consist in repeating one standard event, typically a sound, and intermixing it with unexpected target or salient stimuli. In healthy subjects, the target stimulus elicits the so-called P300 response (see also Chaps. 9 and 11), a positivity on central electrodes occurring about 300 ms after the stimulus onset (Sutton et al. 1965). The difference between P300 and MMN is that the former typically requires the subject's attention or is associated with a highly salient event or a future action (Friedman et al. 2001). Moreover, the peak of the P300 response appears at later latencies as compared to the MMN (i.e., around 300 ms vs. ~150 ms poststimulus onset). Interestingly, a P300 response has also been reported during sleep (Pratt et al. 1999; Ruby et al. 2008) and even in coma, provided that the target stimuli are sufficiently salient (Signorino et al. 1995). Therefore, most studies have used neutral sounds as the standard stimulus, intermixed with the patient's own name as the target stimulus, due to its high saliency for the patient (Signorino et al. 1995; Fischer et al. 2008; Holeckova et al. 2008). In clinical conditions, a P300 is assessed at the level of the single electrode as an amplitude modulation over central regions and is typically found in about 40 % of comatose patients, tested on average at 20 days after coma onset (Fischer et al. 2008). The presence of a P300 response in these conditions correlates with the

patients' chances of awakening (around 85 % specificity for awakening (Fischer et al. 2008). However, when patients are in a vegetative or minimally conscious state several months after coma onset, the chances of detecting a P300 response become considerably lower (about 25 %; Fischer et al. 2010). This possibly reflects a long-term degeneration of attention-related processes in those patients who do not manage to recover and fully regain consciousness.

Other cognitive ERP paradigms that have been tested in unconscious patients are based on linguistic material and test neural responses to semantic or phonetic incongruencies (Kutas and Hillyard 1980). Such paradigms, in healthy controls, typically elicit an N400 component, appearing about 400 ms after the incongruency onset (Perrin and Garcia-Larrea 2003), and it can be elicited even in passive listening (Perrin and Garcia-Larrea 2003). Among patients with severe disorders of consciousness, the N400 has been mostly, but not exclusively, observed in patients with some minimal consciousness (Schoenle and Witzke 2004).

To summarize, the presence of ERP components related to novelty detection or semantic processing is likely to indicate a favorable outcome for comatose patients, but none of them seems robust enough to be used as a reliable predictor in a clinical environment. Before introducing them into routine clinical practice, it is imperative that they have practically no false-positive answers and that they have been validated in large cohorts of patients. One of the main potential candidates for implementing a test for prediction of awakening is the MMN.

7.3 Mismatch Negativity in Clinical Practice

Despite the extensive literature linking the presence of an MMN to the patient's chance of recovery (Kane et al. 1993; Fischer et al. 2004; Naccache et al. 2005; Wijnen et al. 2007) with a predictive value for awakening that far exceeds other paradigms, the use of MMN protocols in clinical practice has so far been rather limited. We believe that one main reason is the difficulty in assessing its presence at the individual level. Most previous studies assessing MMN in clinical studies rely on the estimation of the presence of an evoked activity at the level of AEP measured at a single-electrode level (Fischer et al. 1999, 2004). This assessment is based on the presence of the so-called N100 component (Hillyard et al. 1973), a negative deflection in the average AEP appearing over fronto-central electrodes, considered an "obligatory" marker of auditory processing at the level of the primary auditory cortices (Naatanen and Picton 1987). The estimation of this component relies on a somewhat subjective threshold regarding how this modulation should differ from an average baseline and has systematically implied the rejection of about 30 % of patients (e.g., in Fischer et al. 1999). Not only does this approach imply the rejection of patients who do not show any sign of intact auditory processing, but also, and more problematically, it implies the exclusion of patients exhibiting AEPs with poor signal-to-noise ratio, a situation occurring quite often in a clinical setting with many sources of electromagnetic noise (see also, e.g., Faugeras et al. 2012) (see also Chap. 2). As a consequence, MMN results based on including those patients who exhibit an N100 response are possibly biased by restricting the analysis to AEPs with a high signal quality and therefore more likely to also exhibit differential activity in response to different kinds of sensory stimuli. In addition, one should consider that AEPs in comatose patients are likely to be different from the stereotypical waveforms that can be measured in healthy subjects and also likely to vary among patients (see the ERPs in response to standard and deviant sounds in a control subject in Fig. 7.1 and a comatose patient in Fig. 7.2). Therefore, the validity of using the N100 component at the typical latency of average AEP measured in the healthy population can be limited, providing a second potential source of biased inclusion of patients exhibiting AEP similar to healthy subjects.

Improving the assessment of an evoked activity and of a differential response in auditory paradigms would be extremely worthwhile: in clinical practice, the potential utility of MMN as

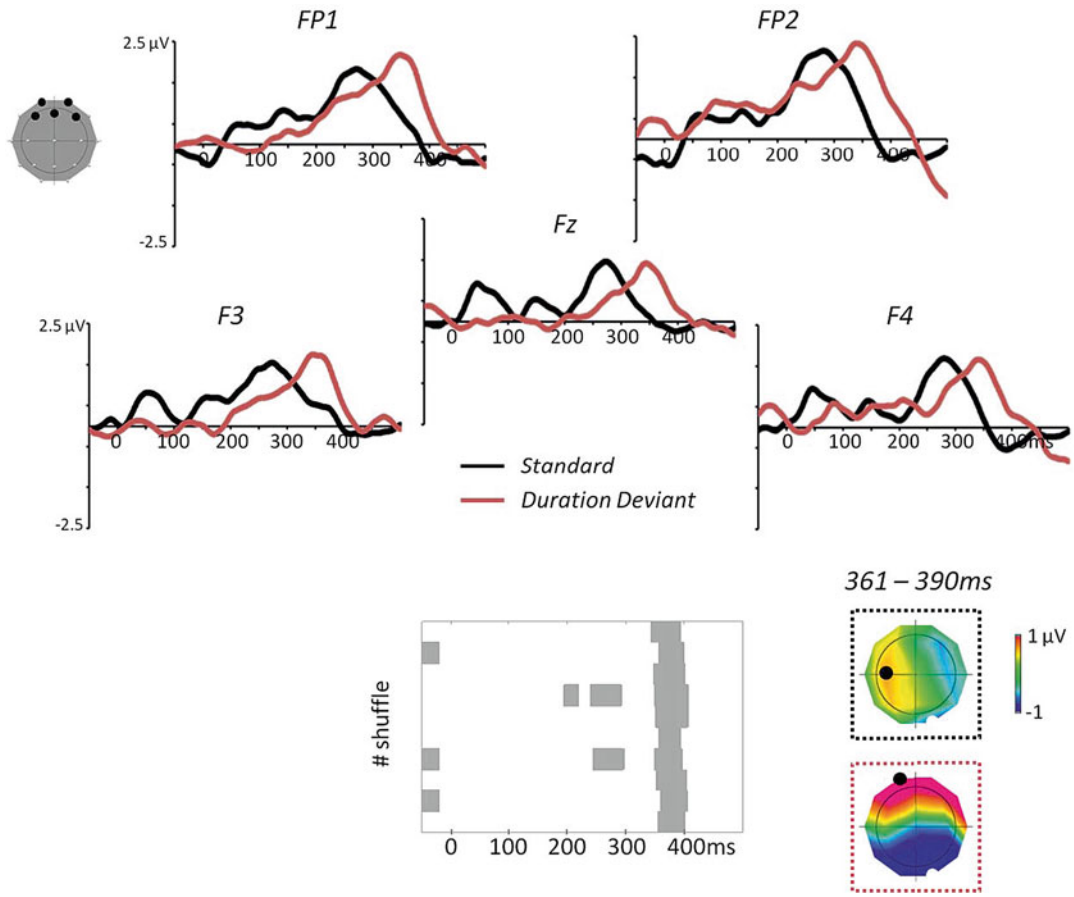

Fig. 7.2 Average AEPs in five fronto-central electrodes in response to standard vs. duration-deviant sounds and decoding results for an exemplar patient during the first 24 h of coma and under therapeutic hypothermia after cardiac arrest. The multivariate decoding algorithm provides a data-driven estimation of periods of differential activity across several data shuffles, as shown in the bottom panel. For this exemplar patient, the common periods of differences across all shuffles started around 360 ms and lasted up to ~390 ms poststimulus onset. The voltage topographies shown on the right are the ones observed in response to standard vs. deviant sounds during this period (the *white* and *black dots* on the topographies represent the position of the minimum and maximum values across the whole electrode montage, respectively)

a marker of good prognosis is enormous (Kane et al. 1993; Fischer et al. 2004; Luaute et al. 2005; Naccache et al. 2005; Wijnen et al. 2007; Tzovara et al. 2013). Its routine application during acute coma would potentially enhance the possibility of informing relatives and caregivers of the patient's prospects, as early and as accurately as possible; the second aspect to consider is economic since intensive care support is an expensive practice needing to be sustained and motivated by demonstrating its utility for the patients; finally, increasingly accurate information about the patient's early state could pave the way to optimizing rehabilitation care according to individual situations. Below, we will outline a method and a set of results providing an alternative to the classical estimation of the N100 and MMN response based on ERPs at the level of single electrodes.

7.4 Multivariate Decoding for Assessing Auditory Discrimination

An ideal approach for acute coma patients would be tailored to the individual and provide timely information. Patients can exhibit highly heterogeneous

patterns of activity and present various degrees of coma severity and different forms of brain damage. The assessment of a reliable response to auditory and sensory stimuli in general should therefore flexibly adapt to the pattern of response of each individual without specific inclusion criteria based on knowledge gathered in the healthy population. Moreover, there is an increasing need for quantitative evaluation of sensitive markers of intact neural functions in a context where the vast majority of the tests are based on prediction of poor outcome (Bouwes et al. 2009; Rossetti et al. 2010). The implementation of multivariate decoding at the level of single-trial EEG offers a possible solution for an unbiased evaluation of AEPs at the single-patient level (Tzovara et al. 2013).

Multivariate decoding methods are increasingly used in neuroimaging studies (Pereira et al. 2009; Weil and Rees 2010; Blankertz et al. 2011), presenting several benefits over univariate approaches. First, the framework of implementation of these techniques typically offers a clear separation between discovering a discriminative pattern in one set of data and then testing on a separate set of observations (Kriegeskorte et al. 2009). Second, multivariate decoding has turned out to be particularly sensitive in comparison to univariate analysis when the discriminative patterns between experimental conditions range across voxels in functional magnetic resonance imaging (Staeren et al. 2009) or several temporal windows and electrode positions in EEG measurements (Hausfeld et al. 2012). Third, it can typically be optimized by allowing a parameter selection that best adapts to the signal of specific patients without assuming specific a priori hypotheses about the type of response (De Lucia et al. 2011; King et al. 2013). Fourth, decoding algorithms naturally deal with single-trial information and therefore allow the exploration of events occurring at different latencies with respect to stimulus onset; this is in contrast to average ERP, which keeps only time-locked activity to stimulus onset (De Lucia et al. 2012). Many multivariate decoding algorithms rely on the extraction of optimal features in the signal that allow the best discrimination between experimental conditions (Lemm et al. 2011). Sometimes, this feature-extraction stage relies on well-known phenomena characterizing a specific process (De Vos et al. 2012). Many other attempts in the literature for developing optimal strategies of decoding rely on a blind search for features or combinations of the EEG signatures within a set of possible alternatives (Bourdaud et al. 2008; Murphy et al. 2011). The main drawback is obviously the difficulty of interpreting, from a neurophysiological perspective, what insight one gains by finding optimal class separation between experimental conditions. One proposition lies halfway between a blind search for combinations of optimal features and the adoption of some flexibility in the decoding strategy, while still allowing interpretation (Philiastides and Sajda 2006; Simanova et al. 2010). In this chapter, we illustrate a single-trial topographic analysis (Tzovara et al. 2012a, b) and its application in coma research (Tzovara et al. 2013).

This method is based on voltage topographies as measured time point by time point in continuous recordings. The main goal is to extract configurations in the voltage topographies occurring at latencies where the two experimental conditions of interest tend to differ. Discovering such voltage configurations provides information on the underlying distribution of active sources in the brain. Indeed, within each recording and at the level of each patient, occurrence of a different configuration at the topographic level can be interpreted as resulting from a difference at the level of brain regions and by extension of brain regions involved in stimulus processing (Murray et al. 2008). Discriminative voltage configurations can occur at several latencies, even when one could not assume a reliable presence of an evoked activity. In this type of method, we take advantage of possible distributed activity along one or several time windows of different length and appearing at variable latencies. The discovery of the latencies at which two experimental conditions tend to differ is also informative, as typical basic sensory processing occurs early in time (i.e., <150 ms), while processes characterized by increasing complexity and refinement happen at subsequent stages. The co-occurrence of more than one time period of differential activity can also be informative as regards the

existence of multiple levels in the process of a specific class of stimuli (De Lucia et al. 2012).

Single-trial topographic analysis foresees the existence of prototypical voltage configurations in relation to event-related activity at the level of the single EEG response. If these configurations exist and differ between experimental conditions, then the decoding algorithm should exhibit a significant decoding performance when classifying new independent trials as belonging to one of the two conditions. This method consists of three main steps; in the first, the algorithm learns a discriminative pattern across several possible combinations of the models' parameters; in the second, the optimized algorithm is tested about providing similar decoding performance on trials independent of those used for estimating and optimizing the models; the third step consists of assessing the significance of the obtained results. This can be carried out at the level of each single patient/recording; this level of analysis entails the estimation of a null distribution for the decoding value in a specific setting (i.e., after relevant parameter selection). The estimation of such a distribution is somewhat standard in classical applications of machine-learning techniques and decoding methods in neuroimaging studies and entails training several models across several label randomizations in the training dataset. The real decoding performance can then be compared by nonparametric tests to the distribution of the values obtained for the randomized version of the decoding algorithm (Pereira et al. 2009).

7.5 Auditory Event-Related Potentials in Early Coma

Clinical tests are usually repeated for several days in comatose patients in order to detect possible improvements over time (Kane et al. 1993). However, the vast majority of the literature on ERP reports the results related to a single measurement for each patient. In addition, these studies include subjects recorded at various delays after coma onset (Fischer et al. 2004; Naccache et al. 2005; Boly et al. 2011). These factors contribute to producing a body of evidence that may lead to an incorrect conclusion, especially regarding the absence of specific responses.

Recently, the importance of carrying out ERP recordings over several days in comatose patients after a cardiac arrest was emphasized by a study conducted in a group of postanoxic patients, assessed using a standard, clinical 10–20 montage with 21 electrodes (Tzovara et al. 2013). These results have shown that the degree of auditory discrimination can change over time, as it can already be detected with a time delay of one day between the two recordings (Figs. 7.3 and 7.4a). In Fig. 7.4, the average decoding performance is grouped with respect to the outcome and timing of the recording (during TH and normothermia –NT respectively), regardless of whether patients exhibited significant results individually. A visual check of these average decoding values provides initial insight into the overall level of auditory discrimination in the

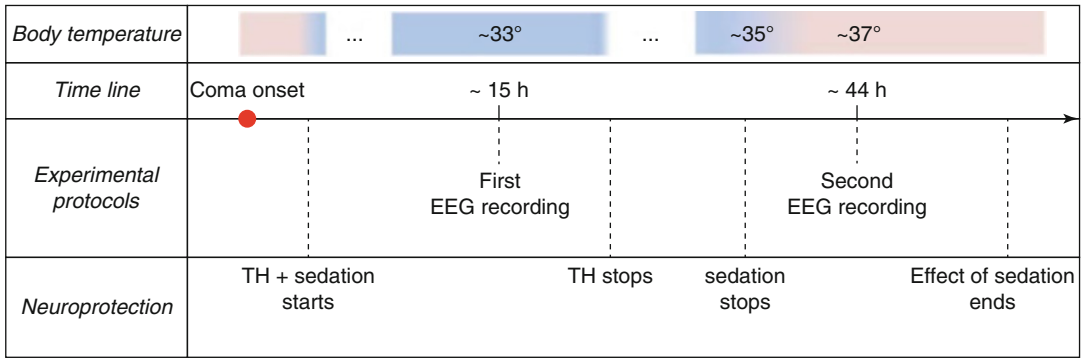

Fig. 7.3 Timeline of EEG recordings in correspondence to the various stages of sedation and TH, with corresponding patient body temperatures, as reported in Tzovara et al. 2013

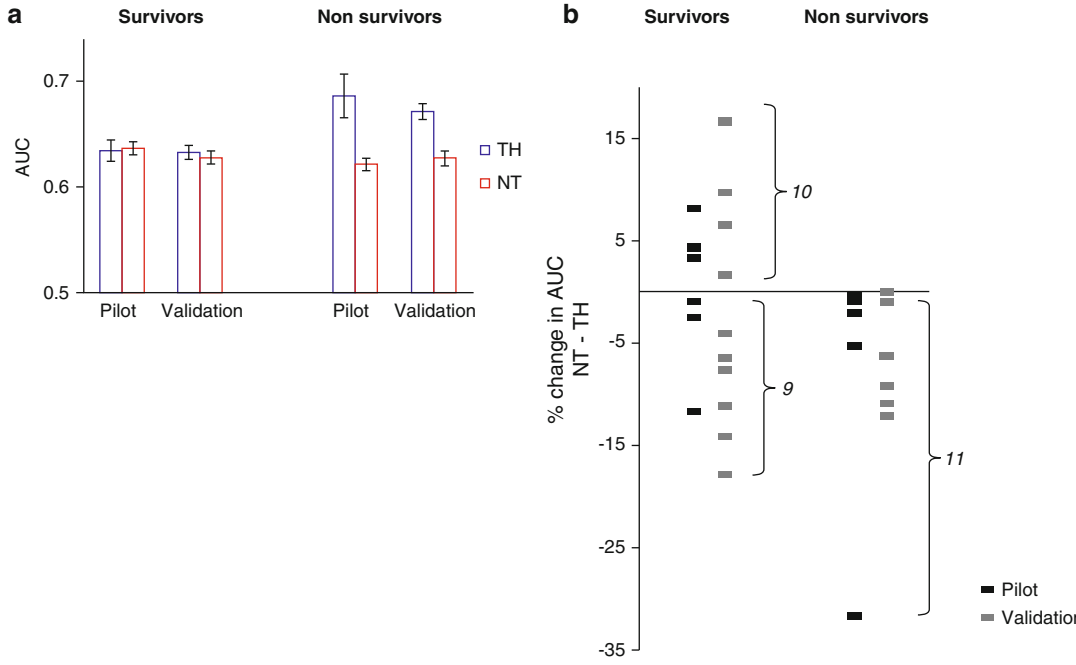

Fig. 7.4 (**a**) Decoding performance between standard and deviant sounds in two groups of postanoxic comatose patients (pilot and validation), grouped with respect to outcome and time of the recording (TH *and* NT); the highest decoding performance was obtained during TH for patients who later died and was followed by a decrease during NT, in both pilot and validation groups of patients. (**b**) Percentage of difference in the decoding performance between NT and TH, grouped with respect to outcome. An increase in decoding performance was only observed in a subgroup of survivors (100 % predictive power for survival and awakening at 3 months) (Data from Tzovara et al. 2013)

different groups and, most importantly, provides qualitative evidence of the relatively higher performance of patients with poor outcomes during TH (Fig. 7.4a). This pattern of results was first discovered in a pilot group of patients and then confirmed in an independent validation group, without any knowledge about patients' outcome. The higher decoding value at group level was also reflected in the degeneration of decoding performances from TH and NT in all the patients who later died (Fig. 7.4b). At the level of each single patient, the progression of the degree of auditory discrimination over time was highly informative regarding the patients' chances of survival, as only those who later survived improved their performance from TH to NT (Fig. 7.4b): across thirty patients this test provided a 100 % positive predictive power of survival and awakening within 3 months.

A major advantage of this approach is that the multivariate decoding algorithm did not require any preselection before analyzing individual patients' data. Provided that these results based on multivariate decoding are confirmed in a larger population, they encourage the implementation of this experimental protocol in clinical practice, where this test could complement existing ones, which so far mostly provide information about poor outcomes (Rossetti et al. 2010) (see Chaps. 5 and 6).

There is still a lot to be done to gain insight into the physiological mechanisms underlying the degeneration of auditory discrimination in patients who later die. Many explanations are possible and need to be tested. The first hypothesis is that auditory progression as measured by the described EEG protocol reflects some generic deterioration of auditory function in relation to neuronal death in poor-outcome subjects. However, this would not account for the relatively higher performance during TH displayed by these patients (Fig. 7.4a). In addition, if this

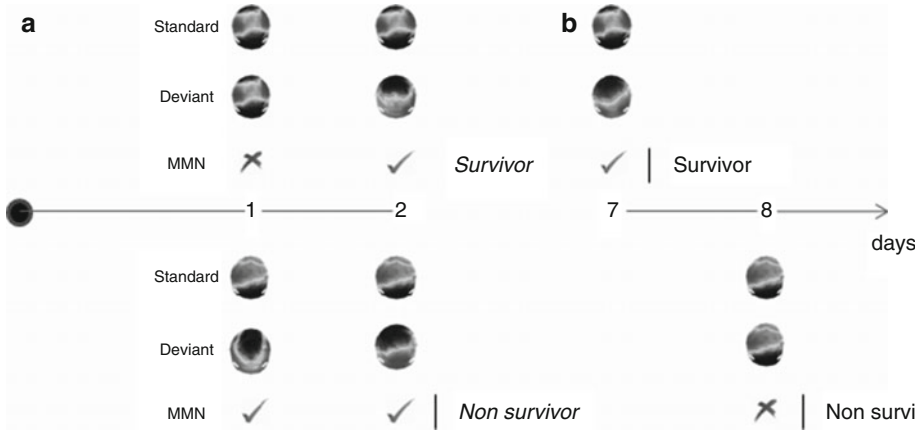

Fig. 7.5 (**a**) Early progression of auditory discrimination. (**b**) Auditory discrimination at variable latencies. Hypothetical evolution of EEG responses to standard and deviant sounds (here schematized as single voltage topographies) over the course of days in survivors and non-survivors (*upper* and *lower panels*, respectively). The progression of auditory discrimination, rather than the mere presence of it, allows the prediction of chance of survival in early coma (see also Fig. 7.4 for an overview on 30 patients). Previous literature has focused on variable latencies after coma onset, emphasizing the presence of a discriminative response to standard and deviant sounds in survivors (*upper panel* **b**) and the absence in non-survivors (*lower panel* **b**)

was the only explanation for the results, one would be able to observe the same response pattern with any kind of auditory protocol, which remains to be tested with other types of auditory experiments. A second hypothesis is about the sensitivity of EEG measurement in these different conditions. During TH and sedation (often including neuromuscular blockade), the presence of artifacts due to muscular activity, micro-movements, and eye movements can be considered negligible. This reduction of artifacts in comparison to normal temperature might lead to a higher EEG signal quality and possibly also in higher auditory discrimination performance in comparison to normothermia (Madhok et al. 2012). While this explanation needs further testing, it remains unclear why a higher sensitivity during TH would differentially affect patients who later survive and those who do not (Fig. 7.4a).

A possible clue for the interpretation of what precedes might come from investigating the properties of the EEG signal at rest (Heine et al. 2012; Lechinger et al. 2013). This line of investigation would provide both insight into the general quality of the measurement during TH, most importantly with regard to the degree of "physiological noise," and its relation to the evoked activity during the MMN protocol (see Wu et al. (2012) for the impact of hypothermia on SSEP). We expect that patients who later die may exhibit a slower and less rich physiological background activity during TH than the other group. These properties of the ongoing activity could explain a better detection of the discriminative signal between standard and deviant stimuli in the MMN paradigm. Moreover, they could provide insight into whether the obtained results are strongly dependent on the TH treatment or whether they would still be observed during early coma in other patients not treated with TH, as in the case of other coma etiologies (i.e., traumatic).

In previous studies, the sensitivity toward auditory sequence violation in patients who would later die has been mostly overlooked (Fischer et al. 1999, 2004; Daltrozzo et al. 2009). However the significant decoding performance in non-survivors (Tzovara et al. 2013) was obtained in an experimental context that had never been considered before: to the best of our knowledge, no other study focused on AEPs measured during an MMN protocol in patients treated with TH. Moreover, previous literature included patients at variable latencies after coma onset, suggesting that the results obtained so far on ERPs in comatose patients might reflect the tip of the iceberg with

regard to a phenomenon which starts very early after coma onset, that is, the degeneration of neural function in patients who will later die (Fischer et al. 1999, 2004; Daltrozzo et al. 2009). In Fig. 7.5, the panel b represents hypothetical EEG responses to standard and deviant sounds at several days after coma onset. This model could explain why at long latencies after coma onset a differential response to auditory stimuli is not observed in non-survivors. The evaluation of such responses over variable latencies of coma can possibly reveal a more complete image of the extent of preserved brain functions. Future ERP studies in early coma will possibly revise many common beliefs about the extent of preserved brain function in comatose patients and help to establish new markers of accurate prognosis.

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The Chronic Clinical Setting

8

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Contents

Abstract

The past 15 years have provided an unprecedented collection of discoveries that have increased our scientific understanding of recovery of human consciousness following severe brain damage. Differentiating between patients in "unresponsive/vegetative" and minimally conscious states still represents a major challenge with profound ethical concerns in terms of medical management. Valid diagnosis is of highest importance in chronic clinical settings, relying on standardized behavioral assessments and neuroimaging paradigms to detect subtle signs of consciousness. An improved assessment of brain function in coma and related states is not only changing nosology and medical care, but also offers a better-documented diagnosis and prognosis and helps to further identify the neural correlates of human consciousness. Recent treatment interventions aimed at accelerating the recovery of awareness show encouraging results, with improvements of behavioral signs of consciousness of severely brain-injured patients. These new insights in this field also raise new legal questions regarding treatment strategies, rehabilitation, and end-of-life decisions.

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8.1 Disorders of Consciousness

Patients with disorders of consciousness (DOC) represent an important proportion of the disabled population worldwide. Severe brain injury can lead to coma where patients remain unaware with their eyes closed and do not respond to external stimulation (Plum and Posner 1983). When patients open their eyes but remain unconscious, they are diagnosed with vegetative state (VS) (The Multi-Society Task Force on PVS 1994; Laureys and Schiff 2012). The European Task Force on Disorders of Consciousness, recognizing that part of the health care, media, and lay public feels uncomfortable using the unintended denigrating "vegetable-like" connotation (seemingly intrinsic to the term VS), proposed the alternative name "unresponsive wakefulness syndrome" (UWS) (Laureys et al. 2010). UWS is a more neutral and descriptive term, pertaining to patients showing a number of clinical signs (i.e., syndrome) of unresponsiveness (i.e., without response to commands or oriented voluntary movements) in the presence of wakefulness (i.e., eye opening).

Patients who evolve from the UWS/VS condition show nonreflexive, goal-directed behaviors (e.g., visual pursuit, reproducible responses to commands or localisation to pain) and hence are considered to be in a minimally conscious state (MCS) (Giacino et al. 2002). Patients with MCS demonstrate partially preserved fluctuating levels of awareness, but they remain unable to functionally communicate. Depending on the complexity of the demonstrated behaviors, it was recently proposed to subcategorize the MCS condition into MCS- (i.e., when only showing simple nonreflex movements, such as visual pursuit, orientation to pain, or non-contingent behaviors) and MCS+ (i.e., when patients recover the ability to respond to simple commands) (Bruno et al. 2011). Compared to the patients with MCS+, patients with MCS- may suffer from a significant general decrease in brain metabolism in the dominant hemisphere and particularly in regions that are functionally linked to speech comprehension and production, in motor and pre-motor areas and in sensory-motor areas (Bruno et al. 2012). Differential diagnosis for patients with MCS would therefore be mainly due to the functional recovery (or not) of speech-processing areas (Thibaut et al. 2012). Once these patients can communicate in a functional manner and/or show functional object use, they are diagnosed as having emerged from MCS (Giacino et al. 2002). These states lie between unconsciousness and awareness; the distinction between them has important therapeutic and ethical implications (Hirschberg and Giacino 2011). Patients in MCS are more likely to feel pain (Boly et al. 2008; Chatelle et al. 2014a, b) and might benefit from analgesic treatment or other interventions aimed to improve their interaction with the environment (Cruse et al. 2011; Lule et al. 2013; Thibaut et al. 2014). Patients in an MCS are also more likely to recover higher levels of consciousness than are patients with UWS/VS (Luaute et al. 2010; Hirschberg and Giacino 2011). Several countries have established the legal right of physicians to withdraw artificial life support from patients with UWS/VS (Gevers 2005; Perry et al. 2005; Ferreira 2007), but not from patients in a MCS (Manning 2012).

8.2 Behavioral Assessment

The detection of unambiguous signs of consciousness in severely brain-damaged patients is challenging and relies on disentangling automatic responses from nonreflex-oriented movements or command following. Motor responses may be ambiguous and inconsistent, potentially leading to diagnostic errors (Monti et al. 2009). A prospective study on coma survivors showed that the clinical consensus diagnosis of UWS/VS, attributed to 44 patients, was incorrect in 18 cases. Such a high rate of diagnostic error (i.e., 41 %) should prompt clinicians to use validated behavioral scales of consciousness before making the diagnosis of UWS/VS (Schnakers et al. 2009). While consensus-based diagnostic guidelines for DOC have been established (Giacino et al. 2002), there are no procedural guidelines regarding bedside assessment. Many different scales have been developed to assess patients in the chronic phase, and this last decade has

particularly been focusing on the differential diagnosis between UWS/VS and MCS. Table 8.1 gives a non-exhaustive overview of the behavioral scales used in the chronic setting.

The American Congress of Rehabilitation Medicine conducted a systematic, evidence-based review of these behavioral assessment scales and provided evidence-based recommendations for clinical use (Seel et al. 2010). It was suggested to use the Coma Recovery Scale-Revised (CRS-R; Giacino et al. 2004; Schnakers et al. 2008a – summarized in Table 8.2). CRS-R has excellent content validity, and it is the only scale to address all Aspen Workgroup criteria (i.e., items used to differentiate MCS from UWS/VS). The CRS-R also offers the advantage to systematically search for signs of nonreflex behavior (e.g., visual pursuit or oriented response to noxious stimulation) and command following, in a well-defined manner. Visual pursuit, for example, should be assessed by using a moving mirror, as it has been shown that a substantial number of patients will not show eye tracking of a moving object or person but will do so when using an auto-referential stimulus such as the own face (Vanhaudenhuyse et al. 2008). Conversely, signs such as visual blinking to threat (Vanhaudenhuyse and Giacino 2008) and visual fixation (Bruno et al. 2010) were shown not to necessarily reflect conscious awareness and could hence be compatible with the diagnosis of UWS/VS. It is important that the evaluations are repeated over time and performed by trained experienced assessors (Lovstad et al. 2010). Confounding factors such as drugs with sedative side effects (e.g., against spasticity or epilepsy) or the presence of infection or other medical complications should be accounted for. This situation is even more problematical when patients have underlying deficits with communication functions, such as aphasia, agnosia, or apraxia (Majerus et al. 2005, 2009). Hence, some behaviorally unresponsive patients could, despite the best clinical assessment, be underestimated in terms of residual cognition or conscious awareness (Giacino et al. 2014). Since the venue of functional neuroimaging, this challenging issue can be addressed by measuring brain activity at rest and during sensory stimulation in these patients (Di Perri et al. 2014; Gosseries et al. 2014a)

8.3 Neuroimaging Assessment

Behavioral scales make inferences about patients' awareness based on (the prensence/absence of) motor responsiveness. Functional neuroimaging (e.g., positron emission tomography (PET) and functional magnetic resonance imaging – fMRI) and cognitive evoked potential studies allow quantifying and noninvasively DOC patients brain activity at rest and during external activation (see Chaps. 9 and 12). fMRI activation studies in UWS/VS (Bekinschtein et al. 2005; Di et al. 2007; Fernandez-Espejo et al. 2008; Coleman et al. 2009) have confirmed previous PET studies showing preserved activation of "lower level" primary sensory cortices which are disconnected from "higher-order" associative cortical networks (i.e., frontoparietal associative cortices, cingulate gyrus, precuneus, and thalamus) (Laureys et al. 2004; Vanhaudenhuyse et al. 2010, 2011; Langsjo et al. 2012; Demertzi et al. 2013) employing auditory (Laureys et al. 2000; Boly et al. 2005), somatosensory (Boly et al. 2008), visual (Owen et al. 2002), or even emotional stimulations (Bekinschtein et al. 2004; Schiff et al. 2005).

These neuroimaging techniques have also been developed in order to detect "neural" (motor-independent) command following. Clinically unresponsive patients could perform mental imagery tasks, as shown by fMRI (Monti et al. 2010). Since this case report, similar "active" or "command following" paradigms have been tested in severe brain-damaged patients with different technologies such as event related potentials or electromyography (Bekinschtein et al. 2008; Schnakers et al. 2008b; Cruse et al. 2011; Habbal et al. 2014). Recently, it has been demonstrated that ^{18}F-fluorodeoxyglucose-PET showed the highest sensitivity in identifying MCS having a good overall congruence with repeated CRS-R diagnosis, when compared to mental imagery task in fMRI (Stender et al. 2014). Complementary to these approaches, methods are developed to detect recovery of consciousness in

Table 8.1 Behavioral scales used in chronic setting

Authors (year)	Scale's name (abbreviation)	Specificity (average execution time in minutes)	Behavioral content (Nb of subscale and nb of items)	Scoring for response	Total score and diagnosis
Giacino et al. (2004)	Coma Recovery Scale-Revised (CRS-R)	Differentiation between UWS/VS and MCS (25)	Auditory, visual, motor, oral, communication, arousal (6 and 23)	"Absent" or "present" (must be reproducible) Varies per item (e.g., at least 3 out of 4 times)	Total score 0–23 0 = coma; 23 = emergence from MCS. UWS/VS, MCS and emergence of MCS diagnosis based on the presence or absence of operationally defined behavioral responses to specific sensory stimulations (e.g., MCS if visual pursuit, responses to command)
Gill-Thwaites and Munday (2004)	Sensory Modality Assessment and Rehabilitation Technique (SMART)	Rehabilitation, differentiation between UWS/VS and MCS (60)	Auditory, visual, tactile, olfactory, gustatory, and motor functions, wakefulness, communication (8 and 8)	5 anchored responses	Each scale score 1–5. 1 = no response, 2 = reflex response, 3 = withdrawal response, 4 = localizing response, 5 = differentiating response MCS or higher if rated a score of 5 on at least one sensory modality on 5 consecutive administrations
Rappaport (2000)	Coma/Near-Coma Scale (CNC)	Post-comatose state, outcome (10)	Visual, auditory, command following, threat response, olfactory, tactile, pain, vocalization (8 and 11)	"Occurs 2–3 times," "occurs 1–2 times" or "does not occur"	Total score 0–44 Average item score: 0.00–0.89 = no coma, 0.90–2.00 = near coma, 2.01–2.89 = moderate coma, 2.90–3.49 = marked coma, 3.50–4.00 = extreme coma
Shiel et al. (2000)	Wessex Head Injury Matrix (WHIM)	Rehabilitation, subtle changes in MCS (30–120)	Basic behaviors, social/communication, attention/cognitive, orientation/memory (62 items)	"Absent" or "present"	Total score 0–62 1 = UWS/VS, 62 = emerging from post-traumatic amnesia

Ansell and Keenan (1989)	Western Neuro Sensory Stimulation Profile (WNSSP)	Rehabilitation, post-comatose state (45)	Auditory comprehension and visual comprehension, visual tracking, object manipulation, arousal/attention, tactile/olfactory (6 and 32)	Varies per items, 3–6 anchored responses	Total score 0–110 maximal Scores between 40 and 50 are generally required for eligibility for rehabilitation. The higher the score, the better
Hagen et al. (1987)	Levels of Cognitive Functioning – Rancho Los Amigos (RLA)	Post-comatose state, outcome (30)	Auditory, visual, motor and oral functions, communication, memory, reasoning, orientation, arousal (8 subscales)	"Absent" or "present"	Total score 1–8 I = no response, II = generalized response, III = localized response, IV = confused/agitated, V = confused/inappropriate, VI = confused/appropriate, VII = automatic/appropriate VIII = purposeful/appropriate

Abbreviations: UWS/VS unresponsive wakefulness syndrome/vegetative state, MCS minimally conscious state

Table 8.2 Summary of the American Congress of Rehabilitation Medicine evidence-based review of behavioral assessment scales for disorders of consciousness (Seel et al. 2010)

Scale	Free access	Guidelines of administration and scoring procedures	Content validity (i.e., enclosing diagnostic criteria)	Internal consistency	Inter-rater reliability	Test-retest reliability	Diagnostic validity	Outcome prediction
Coma Recovery Scale-Revised (CRS-R, Giacino et al. 2004)	Yes	Present	Excellent	Good	Good	Excellent within-subject agreement	Unproven	Not studied
Wessex Head Injury Matrix (WHIM, Shiel et al. 2000)	Yes	Present	Poor	Unproven	Unproven	Unproven	Unproven	Not studied
Western Neuro Sensory Stimulation Profile (WNSSP, Ansell and Keenan 1989)	Yes	Present	Poor	Excellent	Unproven	Unproven	Unproven	Unproven
Sensory Modality Assessment and Rehabilitation Technique (SMART, Gill-Thwaites 1997)	No	Present	Poor	Not studied	Excellent	Excellent within-subject agreement	Unproven	Unproven
Coma Near Coma (CNC, Rappaport 1992)	Yes	Present	Poor	Possibly unacceptable	Unproven	Unproven	Unproven	Not studied

ways that do not depend on the integrity of sensory pathways. Transcranial magnetic stimulation combined with electroencephalography can be performed at the bedside while bypassing subcortical afferent and efferent pathways and without requiring active participation of subjects or language comprehension (see Chap. 10). Hence, this complementary techinique could also permit an effective way to detect and track recovery of consciousness in patients with DOC who are unable to exchange information with the external environment (Rosanova et al. 2012, Casali AG et al. 2013 and Sarasso S et al. 2014). The validation of new promising neuroimaging-based differential diagnostic markers, such as quantified metabolic markers or resting state fMRI, is of primary importance to complement the differential diagnosis.

8.4 Treatment

Although our understanding of the neural correlates of consciousness has greatly evolved over the past years, daily care has not yielded specific, evidence-based medical treatments for patients with DOC. Pharmacological treatment to promote the emergence of consciousness can be administered in the subacute and the chronic (more than 1 month) phases. Frequently prescribed pharmacological treatments include dopaminergic (e.g., amantadine, apomorphine, methylphenidate, levodopa, bromocriptine) and GABAergic agents (e.g., zolpidem, baclofen) (Chew and Zafonte 2009; Gosseries and Charland-Verville, 2014; Thonnard et al. 2014). Next, there is a long history of brain stimulation in medical science, and research has long been focused on some cortical areas and deep brain structures like the prefrontal cortex and the thalamus. Only few techniques were studied scientifically in this population of patients. Deep brain stimulation showed behavioral improvement after the implantation of an electrical stimulator in the intralaminar nuclei (Schiff et al. 2009). However, and the number of patients who can benefit from this intervention is still limited. Recently, noninvasive transcranial direct current stimulation (tDCS) studies showed encouraging results, with improvements in the behavioral signs of consciousness of severely brain-injured patients (Thibaut et al. 2014). Short-duration anodal (i.e., excitatory) tDCS of left dorsolateral prefrontal cortex induced short-term improvement in patients with MCS of acute and chronic etiologies measured by behavioral CRS-R total scores. The long-term noninvasive neuromodulatory tDCS outcome clinical improvement remains to be shown. In the years to follow, interventions should multiply, and therapeutic measures need to be more accessible, controlled, and effective.

8.5 Ethical Challenges

Early since DOC appeared in the clinical setting, clinicians, scholars, theologians, and ethicists began to wonder how it is like to be in a state of altered consciousness (e.g., Thompson 1969). First, one of the most debatable issues about this population is pain perception. Painful experience is a first-person one and classic pain assessment requires the patients' verbal feedback (International Association of Pain Specialists (IASP 1994)). When it comes to severely brain-injured patients who are unable to communicate their feelings and possible suffering, the question of pain perception is far more complex (Chatelle et al. 2014a, b). According to survey attitudes among healthcare professionals to the question "Do you think that patients in a UWS/VS can feel pain?" 68 % of the interviewed paramedical caregivers ($n=538$) and 56 % of physicians ($n=1166$) answered "yes." Paramedical professionals, religious caregivers, and older caregivers reported more often that UWS/VS patients might experience pain. Following professional background, religion was the highest predictor of caregivers' opinion: 64 % of religious ($n=1{,}009$; 850 Christians) versus 52 % of nonreligious respondents ($n=830$) answered positively. To the question "Do you think that patients with MCS can feel pain?" nearly all interviewed caregivers answered "yes" (96 % of the medical doctors and 97 % of the paramedical caregivers). Women and religious caregivers reported more often that MCS patients might experience pain (Demertzi et al. 2009). Considering these results on varying

beliefs about pain perception in DOC, physicians and health-care workers' views on analgesia and symptom management may also be affected. The presence or absence of nociception is inferred via motor responses following noxious stimulation, such as stereotypical responses, flexion withdrawal, and localization responses (Schnakers and Zasler 2007). In patients with DOC, only a clear localization to noxious stimulation is considered to be an indicator of conscious perception (Giacino et al. 2002). In order to accurately nonverbally assess nociception in this challenging population, the Nociception Coma Scale-Revised (NCS-R) (Chatelle et al. 2012) has been proposed. It assesses motor, verbal, and facial behaviors behavioral responses at rest, during daily nursing care, and during nociceptive stimulation. A cut-off score of 4 and higher suggest the need of adequate pain management (Chatelle et al. 2014a, b).

Patients with chronic DOC may also pose ethical challenges requiring the mediation of legal authorities in order to regulate end-of-life decisions. When the clinical condition of a patient has been stabilized and denoted as irreversible, decisions about artificial nutrition and hydration limitation may come into play. In a European survey, the controversies around the clinical management at the end-of-life were reflected (Demertzi et al. 2011). Sixty-six percent of health-care professionals agreed to withdraw treatment in patients with UWS/VS for more than 1 year, whereas only 28 % agreed to do so for patients with MCS. In our study, we also found that end-of-life decisions are not always governed by clinical circumstances but rather, physicians' characteristics. Geographic differences as well as religious background were the variables that consistently predicted end-of-life statements. Residents from Northern and Central Europe, as compared to Southern Europeans, were more likely to agree with medically assisted nutrition and hydration withdrawal in chronic (> 1 year) UWS/VS, whereas religious respondents, older respondents, and women were less likely to find it acceptable. From a bioethical standpoint, withdrawing artificial nutrition and hydration is comparable to withdrawing mechanical ventilation, even if emotionally these two actions may be perceived differently (Laureys 2005). Despite the controversy as to whether artificial nutrition and hydration constitutes a medical treatment (Bernat and Beresford 2006), most of the medical community would agree with its being a medical therapy which can be refused by patients and surrogate decision makers (Steinbrook and Lo 1988). Patients with DOC represent a difficult group, ethically, for surrogate decision-making. The medical community needs policies to reach better internal agreement within the professional network and effective communication with patient communities and their families (Manning 2012; Bruno et al. 2013).

8.6 Conclusion

Disentangling between patients with MCS and UWS/VS represents a major challenge that can have heavy consequences, generating ethical and legal implications (Celesia 2000; Jennett 2002). The rapidly growing scientific findings on DOC must be taking into account for patients' future care needs and to promote adequate policies to keep up with the findings. Consciousness research leads to redefinition of recovery, clinical criterion for diagnosis, and as increasing impact on prognosis (Fins 2009). The constantly evolving neuroimaging research field is raising new questions and challenges for medical ethics. As a result, clinicians must increasingly answer requests from family members and surrogate decision makers about the new diagnostic and therapeutic procedures. Because most of these reported procedures remain investigational, clinicians must be aware of the level of evidence supporting them and of the unavoidable ethical and social issues involved in responding to such requests. Moreover, studies must be supported in order to address the sensitivity and specificity of the neuroimaging or electrophysiological tools. Multicentric studies and collaborative work seem also essential to gather comparable data for the clinical behavioral assessments and about the potential prognostic value of the neuroimaging technologies (Di et al. 2008; Coleman et al. 2009).

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Event-Related Potentials in Disorders of Consciousness

9

Boris Kotchoubey

Contents

Abstract

Event-related potential (ERP) is a useful method for assessment of covert cognitive functions in patients with severe disorders of consciousness (DoC). Having a poorer spatial resolution than fMRI, ERP possesses a high level of functional specificity and an excellent temporal resolution. ERP can be combined with different kinds of passive (pure stimulation) and active (instruction) tasks, which allow the investigator to check different cognitive abilities of the patients. ERP is a cheap, mobile, well-tested method; all recordings can be carried out immediately at a patient's bedside. A very broad number of cognitive processes can be tested; however, these processes are not necessarily related to consciousness. Although instruction tasks directly testing conscious awareness have also been used in combination with ERP, it remains unclear whether ERP has any advantages as compared to fMRI, the analysis of EEG oscillations, or even electromyography. Several middle-sized studies indicate that ERP can provide reliable predictors of the outcome of DoC; however, the results of these studies are inconsistent as concerns the exact role of ERP components as outcome predictors. This may be only addressed through large, multicenter longitudinal studies.

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9.1 Introduction

Evoked potential (EP) and event-related potential (ERP) are components of the EEG, time and phase locked to particular events, such as an external or an internal stimulus (e.g., the moment of muscle contraction). EP and ERP reflect, therefore, changes in the activity of neuronal populations strongly related to a specific event.

Despite conceptual similarity, the terms EP and ERP are not synonymous. The notion "evoked" presumes a strong causal relation between a stimulus and a response. This strong relation is assumed for early deflections of stimulus-related responses. These early deflections are also called "exogenous," meaning that their features are functions of the basic physical stimulus features: sensory modality, intensity, figure/background relation, etc. In contrast, later deflections of stimulus-related responses and other kinds of ERP are not "evoked" but "elicited," meaning that the corresponding events cannot be regarded as direct *causes* of these deflections. The components are also designated as "endogenous" because their features are supposed to depend not on stimulus features but rather on psychological characteristics of participants and their actual task. The borderline between "EP" and "ERP," as well as that between "exo-" and "endogenous" deflections, is not exactly defined. Most frequently, stimulus-related components with latencies up to 100 ms (after stimulus onset) are regarded as exogenous, components with latencies >200 ms as endogenous, and both terms may be applied to components between 100 and 200 ms (Picton and Hillyard 1988). From a functional point of view, it is important, however, that typical exogenous EP components reflect the propagation of stimulus-related excitation to the cortex, while later components manifest the processing of stimulus information in the cortex. Therefore, disturbances of the former indicate *sensory* disorders and the disturbances of the latter, *cognitive* disorders.

The basic methodology of EEG and ERP, the role of EP and ERP in the diagnosis and prognosis of acute disorders of consciousness (DoC), and the overview of other (non-stimulus locked) EEG oscillations are discussed in the other sections of this book (see in particular Chaps. 2, 5, 6, and 7). The present chapter is devoted to ERP in chronic DoC, in relation to their state of (disturbed) consciousness. I shall not discuss early (exogenous) EP, because these components, so important in acute coma (see Chap. 6), are not very informative in chronic conditions. It should be taken in mind, however, that exogenous EPs are prerequisites for using endogenous ERP in DoC. If the former are absent or severely disturbed, indicating disturbance of elementary sensory functions, the use of the latter for assessment of higher cognitive functions is impossible.

9.2 Functional Meaning of ERP Components

ERPs were largely investigated in reaction time (RT) experiments, in which participants receive instructions to respond (mostly manually) to particular stimuli according to particular task rules. In these experiments ERP can be regarded as a sequence of electrical deflections that happen between a stimulus and a response. This representation led to the idea that each component is a manifestation of a member in the processing chain leading from stimulus to response. This essentially behavioristic idea has subsequently been criticized on the basis of numerous findings demonstrating profound biophysical and neurophysiological similarities between ERP components having different positions in the putative processing chain, between ERP components to very different kinds of stimuli, and even between ERP components that precede particular events and those that follow these events (e.g., Kotchoubey 2006). Nevertheless, the very concept that different ERP components "manifest," i.e., make accessible, some aspects of otherwise covert cognitive operations remains valid. In the following, I shall summarize the present knowledge about the functional meaning of components, leaving aside the views still discussed.

N1 and P2 are still relatively exogenous and modality-specific components reflecting earlier and rather automatic stages of cortical processing.

Their latency and scalp location are modality dependent; e.g., the visual N1 can be up to 50 ms later than the auditory N1. The electrical sources of the N1 component are localized in the corresponding sensory areas.

The mismatch negativity (MMN) is recorded when the current stimulus deviates from the sensory model built by the brain on the basis of the preceding stimuli (Näätänen and Winkler 1999). Although some authors claim the existence of an MMN in different sensory modalities (e.g., Gayle et al. 2012), presently only *auditory* MMN has been tested in clinical practice. The standard paradigm to elicit an MMN is the so-called oddball paradigm, in which frequent and rare ("oddball") tones are randomly presented (see also Chap. 7). The former elicit N1 and P2 and the latter, in addition, the MMN. The frequency of rare tones is about 0.1 or even less. Since at least 150 rare tones are recommended (Duncan et al. 2009), the whole sequence includes at least 1,500 stimuli. The latency of the MMN is about 200–250 ms; therefore two or three stimuli per second can be presented, making together 8–10 min. The MMN has two main sources, in the temporal and frontal lobes. The largest negativity is usually recorded at Fz and the largest positive amplitudes in the same time window, at mastoid electrodes. This means that, in order to record an MMN, one should not use mastoid electrodes as reference.

In this typical paradigm, rare tones (also called deviants) deviate from the frequent tones (standards) by one feature, e.g., pitch or duration. The MMN also responds to very complex features such as a fine change in the spectrum of the tone or even repetition instead of the expected alternation (Tervaniemi et al. 1994). The presence of an MMN indicates the ability of the brain's sensory system to analyze the corresponding feature but tells nothing about other characteristics. Therefore, a multifeature paradigm has been proposed, in which up to five different capacities of auditory discrimination are tested at once (Näätänen et al. 2004). An example of such a paradigm is presented in Fig. 9.1. Each deviant differs from standards by only one feature and remains identical to the standards regarding all other features.

Like N1 and P2, the MMN is largely independent on attention (e.g., Näätänen and Alho 1995) and the functional condition of patients (Kotchoubey et al. 2003a). In particular, it is better expressed when subjects' attention is directed away from the auditory stimuli, and the subjects perform a different (e.g., visual) task. The MMN to attended stimuli is not suppressed, but it is overlaid with other ERP components such as N2b, which is strongly attention dependent (Näätänen et al. 2007).

The oddball paradigm is also used to elicit the component P3, or P300. This is a large positive deflection with a centro-parietal maximum and a latency between 300 and 400 ms (which may be delayed in brain-damaged patients). In contrast to the MMN, P3 is best pronounced in response to attended deviants; it is maximal when the eliciting stimuli are targets in a task (e.g., they should be counted) and smaller in a no-task condition ("just listen to stimuli") and can even disappear when the attention is deployed to other stimuli. The putative neural basis of P3 is a complex network including temporal and parietal cortical areas and subcortical centers such as the hippocampus. Therefore, while the MMN reflects a low-level, relatively passive sensory discrimination, P3 manifests higher-level, complex discrimination processes in which a stimulus is selected as a target.

The large amplitude of P3 permits to limit an oddball sequence to 200–300 stimuli. Bostanov and Kotchoubey (2006) obtained reliable P300 after only 9 deviants in a passive (just-listen) condition. Usually, however, 20–30 deviants should be averaged. On the other hand, the development of P3 requires more time than that of the MMN, and thus interstimulus intervals of at least 0.9–1 s are necessary (Duncan et al. 2009).

The difference between the MMN, N2b, and P3 is well illustrated in a dichotic listening paradigm, in which two stimulus trains are presented in parallel in two ears. The task is to count rare deviants in one ear, ignoring all stimuli in the other ear. The MMN is well pronounced in response to deviants in the ignored ear. N2b can be recorded to all stimuli in the attended ear, although its amplitude may be

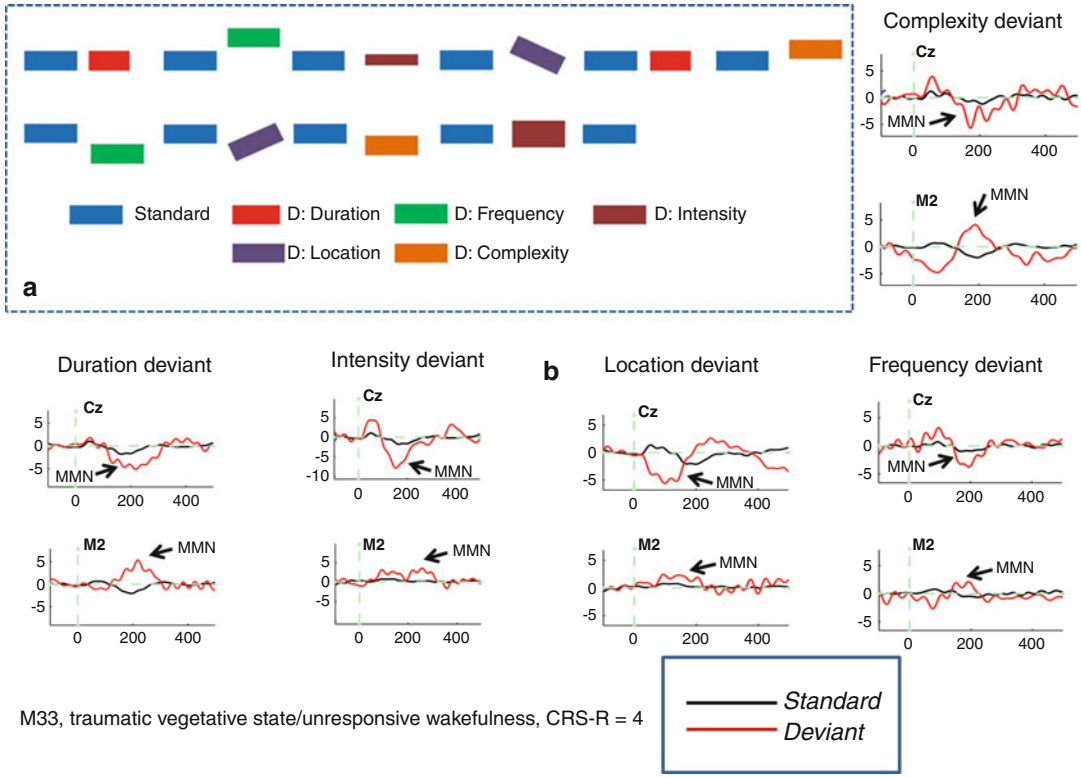

Fig. 9.1 (**a**) Schema of a multifeature MMN paradigm. The standard stimulus randomly alternates with one of the five deviants, each of which differs from the standard by one feature only being identical to the standard in respect to all other features (e.g., a complexity deviant has the same perceived pitch, loudness, duration, and location as the standards). (**b**) A vegetative-state/unresponsive wakefulnes patient who exhibited significant MMN responses to all five kinds of deviation. Negativity is plotted downwards. Note the large negative deflections around 200 ms post stimulus at Cz and simultaneous positive deflections at mastoids (M2). *CRS-R* Coma Remission Scale-Revised, full score

larger to deviants than to standards. A typical P3 is elicited only by target stimuli, i.e., by deviants in the attended ear.

The N400 is a specific ERP component elicited by violations of a meaningful context. A typical N400 paradigm includes sentences with a meaningless (semantically incongruent) final word, such as "The waiter served coffee with milk and shoes." Compared with a corresponding congruent ending (…"sugar"), the word "shoes" results in a large negative centro-parietal deflection with a peak latency of about 400 ms. The same effect can also be elicited by incongruent word pairs (*cat-moon*, compared with *cat-mouse*), semantic violations in a row of words (*tiger, wolf, bear, polecat, stomach*), or even by nonverbal stimuli such as a picture that violates the context of other pictures.

From the point of view of DoC, it is important to note that an N400 to semantic violations indicates a high-level processing of meaningful stimuli but does not prove *conscious* verbal comprehension. Congruent verbal expressions frequently contain strongly associated words. In the example above, the association between *coffee* and *sugar* is stronger than that between *coffee* and *shoes*. This different association strength can result in the node *sugar* being automatically (nonconsciously) activated by the node *coffee*. According to one of the suggested models, N400 amplitude is inversely related to the preceding activation of the corresponding node (Kiefer 2002; Silva-Pereyra et al. 1999). Therefore, when the end word *sugar* is presented, it elicits a smaller N400 than previously inactive *shoes*. If this model is correct, the differential N400

effect can emerge by means of a purely automatic activation process without participation of consciousness.

In addition to these stimulus-related ERP components, two response-related components should be mentioned: readiness potential (RP, also known as "Bereitschaftspotential") and contingent negative variation (CNV). The RP (Kornhuber and Deecke 1965) is a slowly rising negative deflection preceding voluntary movements: with a fronto-central maximum, it starts about 0.6–2 s before movement onset. Its main, symmetrical portion manifests the activity of the premotor cortex, particularly the supplementary motor area, which implies a nonspecific preparation to motor activity in general but not to a particular movement. Only the last portion of the RP (about 200 ms) includes strong participation of the primary motor cortex. When the voluntary movements are performed with hands (which is the case in most experiments), this involvement of the motor cortex is reflected in the RP having a larger amplitude on the contralateral side. This lateralized portion of the RP can also be recorded before signaled movements and not only before voluntary movements. An "inverted lateralization" (i.e., a larger negativity on the ipsilateral side) indicates covert preparations of the wrong response channel (Coles 1989).

The CNV is a predominantly frontal negative wave that appears between two strongly contingent events, most typically between two stimuli separated by a constant interval. In the standard paradigm (Walter et al. 1964), the second stimulus was a signal to a motor response, and the first stimulus had a warning function. Although this arrangement results in a large CNV, the same effect can be obtained when the first stimulus initiates a response, and the second one bears the information whether this response was correct or wrong. The CNV can also be recorded between the onset and offset of a stimulus having a sufficient and constant duration, even if no motor response is required (Bostanov et al. 2013). When the interval separating the two events is sufficiently long (3–4 s), one can see that the negative wave has two components. The early CNV manifests late stages of the processing of the first event, whereas the larger late CNV is related to the preparation to the second event.

9.3 The Problem of Individual Assessment

The ERP paradigms used in DoC patients were developed in experiments with healthy participants on the basis of a group analysis. In such experiments, the presence of an ERP component is determined after grand averaging of the waveforms of the whole group. The optimal time window for each component is defined by visual inspection of such a grand average waveform (e.g., 300–500 ms for the N400). The amplitude and latency of the component are then measured in this window, and the results are compared between groups or conditions.

This approach is not appropriate for the assessment of individual patients for the following reasons. Due to a severe brain damage, the relevant time window can be delayed and vary among patients. A component can be reliably present in a minority of patients but absent in most of them. As a consequence, the grand average across a DoC sample may not be representative for single patients. If, however, the time window is selected on the basis of patients' individual averages (rather than the grand average), a strong bias toward false-positive findings can follow. It is intuitively clear that, having unrestricted freedom of individual adjustment, we could find "significant" differences between almost any two waveforms. Finding the middle way between the Scylla of underadjustment (leading to information loss and false-negatives) and the Charybdis of overadjustment (leading to false-positives) remains a matter of art rather than science. The situation is even worse if ERP components are quantified by means of subjective assessment (Valdes-Sosa et al. 1987). Unfortunately, this method is still used by many research groups applying ERP in neurological patients. If the experts are aware of the clinical and demographic characteristics of the patient (which is often the case), their assessment can be biased by this knowledge.

Several methods have been suggested to solve this problem. From a statistical point of view, they vary in respect of power and statistical strength, and from the computational point of view, the difference is important between the permutation-based techniques and those not using permutation. A simple and useful non-permutational technique was proposed by Guthrie and Buchwald (1991). A running *t*-test is calculated at each consecutive time point across an interval that can be defined broadly enough to rule out subjectivity factors. Further, the covariation between adjusted points is estimated. This covariation determines the minimum length of the row of significant *t*-values necessary for identification of a significant ERP effect. Also correction by means of false discovery rate (FDR: Benjamini and Hochberg 1995) is only slightly more effortful than G&B. The method is broadly used in other domains of neurophysiology (e.g., fMRI studies) but has, to my knowledge, not been applied for ERP assessment of neurological patients. FDR, however, is prone to underestimation of the covariations between different time points and electrodes (Groppe et al. 2011a), and its results depend on the real presence or absence of an effect, i.e., on the number of false null hypotheses (Groppe et al. 2011b). Furthermore, some simulation experiments using FDR yielded a great variation in the number of false-positive findings (Korn et al. 2004), although more realistic simulations did not replicate these results (Groppe et al. 2011b).

Using permutation to correct for false-positives in ERP research and evaluation was suggested by Blair and Karninski (1993) and later on employed in the analysis of both ERP (e.g., Lage-Castellanos et al. 2008) and rhythmic EEG components (e.g., Laaksonen et al. 2008). The simple underlying idea is that if there is no difference between the conditions (e.g., "rare" versus "frequent"), then it does not matter which particular trial belongs to which condition. The result would be the same if we deliberately swap trials between conditions, except purely random variations. If we repeat this procedure, say, 10,000 times, we can see how often the resulted statistics (e.g., a *t*-test) will attain or even exceed the corresponding statistics obtained when the trials are correctly assigned to the conditions. The great advantage of permutation tests is that they are exact; this means that they do not result in statistical estimates of (or approximations to) some critical value but, rather, in this critical value itself. They are distribution-free and do not require any assumptions except that observations across subjects are mutually independent. The disadvantage is rather high computational demands. This is particularly true if permutation is carried out for each single data point as originally suggested. Then, having a rather moderate data set with 300 time points, 30 electrode channels, and 2,000 permutations (a minimum!), 18 million *t*-tests (or other similar statistics) have to be computed for one analysis.

To reduce this effort, one can group together the statistics obtained at adjacent time points and electrodes, resulting in a clustered data (Maris and Oostenveld 2007). Usually, statistics that do not reach a threshold level (e.g., at least two adjacent *t*-tests reaching an uncorrected *p*-value of 0.05) are filtered out before clustering. The resulting relatively small number of variables then undergoes a permutational analysis (Oostenveld et al. 2011; Groppe et al. 2011a). This method is implemented in MATLAB and used in several ERP studies. However, a problem of this procedure is the presence of several clustering parameters (the primary significance threshold, the definition of neighborhood, etc.) that are open for arbitrary decision and whose choice can strongly affect the results. When the most general question is asked, i.e., whether two responses of a patient differ or not, clustered permutation techniques appear to be superior to FDR and non-clustered permutation tests (Groppe et al. 2011b). However, the stronger the need to localize the difference and to ascribe it to a particular ERP effect, the more problematic is the use of the clustering method, because local events can be smeared by informal clusterization.

The technique of *t*-CWT (studentized continuous wavelet transformation: Bostanov 2003; Bostanov and Kotchoubey 2006) was introduced with the explicit aim of extraction of the maximum information contained in the difference

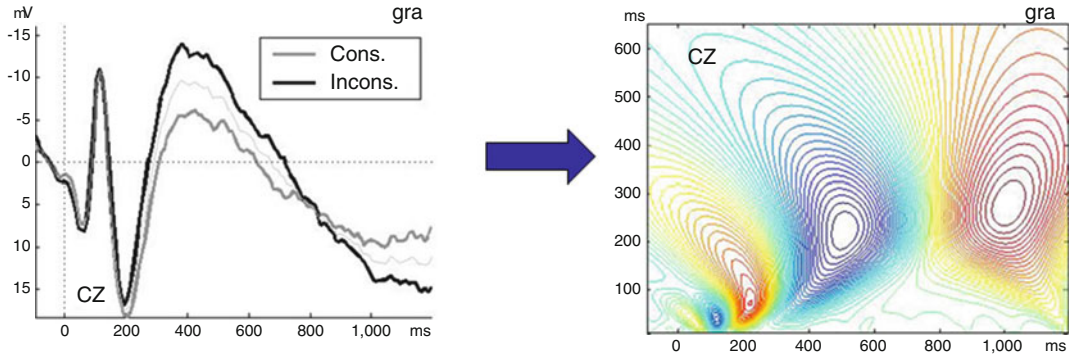

Fig. 9.2 *t*-CWT transformation allows us to transform a two-dimensional ERP (amplitude/time) into a three-dimensional pattern (amplitude/scale/time). *Left panel*: a typical ERP at Cz in a verbal paradigm with semantically consistent (*gray line*) and inconsistent (*black line*) words; the latter elicit an N400. Negativity is plotted upwards. *Right panel*: the same ERP after *t*-CWT transformation. The ordinate shows scale values (scale =1/frequency), while the amplitudes are shown in a color scale from *red* (positive) to *blue* (negative)

between two waveforms corresponding to the two conditions in a typical ERP experiment. In contrast to the univariate methods depicted above, *t*-CWT is a technique of a multivariate analysis that takes into account all covariations between spatial and temporal points. Studentization (i.e., the representation of the difference between two ERP waveforms or between one waveform and zero, in *t*-scores) allows the investigators to attain the optimal power possible with a given signal/noise ratio. The target ERP components can be identified and localized by means of a continuous wavelet transformation, which allows to represent the response as a three-dimensional figure with the axes time, scale (=1/frequency), and size (amplitude). Therefore, the windows for the components are defined in a fully objective manner (Fig. 9.2). It should be said that the main achievements of this method have their costs: the backside of the independence of covariations is the use of a parametric Hotelling test, whose assumptions (e.g., normal distribution) are not always fulfilled, and the optimization of information extraction has the disadvantage that the alpha inflation is not controlled but, in contrast, maximized. However, both problems are removed when the final set of data, again, undergoes a permutation test with at least a few thousand permutations. This test results in an unbiased, powerful, and distribution-free estimate of an ERP effect.

Although the *t*-CWT method is theoretically optimal, this does not mean that its additive value in the diagnostic use is practically significant as compared with simpler, less effortful procedures. Even if the method is much more powerful than the classical area analysis and several multivariate techniques such as the discrete wavelet transform (Bostanov and Kotchoubey 2006), it has not been directly compared with FDR and clustered permutation tests. Recent studies with both simulated (Real et al. 2014) and real DoC patients' data showed that *t-CWT* is significantly more sensitive than G&B procedure (as theoretically expected) but that the difference is not very large and partially compensated by speed and easiness of the running *t*-test. More data are necessary to give precise recommendations about using different quantitative methods of individual assessment of DoC subjects.

9.4 ERP Manifest Remaining Cognitive Processes in DoC Patients

About 20 years ago, several publications (Reuter et al. 1989; Marosi et al. 1993; Moriya et al. 1995) reported P3 findings in some patients diagnosed as vegetative/unresponsive wakefulness (VS/UWS). These early reports, however, were sporadic and clinically unreliable. Thus Marosi

et al. (1993) claimed to find "P3 in the vegetative state," although only two of the reported 23 patients apparently corresponded to the modern diagnostic criteria of VS, and no P3 was recorded in these patients. The first larger study was carried out by Schoenle and Witzke (2004) (preliminary data reported 8 years earlier: Witzke and Schönle 1996). They examined 43 VS/UWS patients and 23 patients "near vegetative state," who might roughly have fulfilled the criteria of the minimally conscious state (MCS). The N400 paradigm with semantically congruent and incongruent sentence endings was used. An N400 to semantic incongruence was found in 5 VS/UWS and 17 "near VS" patients. Among 54 severely brain-damaged but conscious patients, the N400 was obtained in 49 cases. This was probably the first indication that even "definitive VS" patients possess so-called higher cortical abilities, in this case the ability to semantic word categorization. Unfortunately, the method of N400 quantification was very subjective, and the raters might have known the diagnoses of patients.

Kotchoubey et al. (2005) applied a quantitative assessment of ERP components, in which the only subjective factor remained the definition of individual component time window. The integral amplitude was automatically measured in this window in each single trial and then statistically compared between conditions (e.g., standards versus deviants in the oddball paradigm; semantically congruent versus incongruent words in semantic paradigms). These authors reported even higher than (Schoenle and Witzke 2004) rates of N400 in both VS/UWS and MCS patients. This finding has recently been confirmed by Balconi et al. (2013) and Steppacher et al. (2013) using objective ERP evaluation techniques; the latter study included a sample of as many as 175 DoC patients.

As regard P3, it could be obtained in 20–25 % of DoC patients (Witzke and Schönle 1996; Kotchoubey et al. 2001, 2005; Cavinato et al. 2009 [only traumatic VS/UWS patients], Schnakers et al. 2008 [P3 found only in MCS but not in VS/UWS], Fischer et al. 2010; Müller-Putz et al. 2012; Guger et al. 2013; Steppacher et al. 2013). This may indicate activation of complex cortico-subcortical networks in response to target stimuli in many patients. Unfortunately, large brain damage of some patients makes it sometimes difficult to distinguish between the "real" P3 (also called P3b) from the so-called novelty P3 (or P3a), reflecting more superficial orienting response to novel stimuli (Kotchoubey 2005; Fischer et al. 2010).

More conservative approaches may result, however, in substantially lower rates of P3. Faugeras et al. (2012) used a design in which P3, if recorded, could necessarily be the P3b; they obtained this component only in 7 of 13 conscious patients, 4 of 28 MCS, and 2 of 24 VS/UWS, while these two also changed to MCS in a few days after examination. Chennu et al. (2013) used a system of 91 electrodes to separate P3a from P3b and found a P3a in 1 of 9 VS/UWS and 3 of 12 MCS patients. These poor results are particularly surprising because this study was one of a very few in which both ERP and fMRI measures of cognition in DoC patients, and the fMRI experiment (Owen et al. 2006) revealed the ability to follow instruction in 4 VS/UWS and 5 MCS patients. Therefore, the high-level ability to understand and consistently follow verbal commands was found with a rate more than twice as high as the low-level involuntary orienting reaction manifested in the P3a.

The MMN is already used in acute coma as a standard EEG measure (e.g., Fischer et al. 1999, 2010) (see also Chap. 7). The component was also found in some one-third of VS/UWS and MCS patients (Kotchoubey et al. 2005; Wijnen et al. 2007; Fischer et al. 2010; Luauté et al. 2010; Faugeras et al. 2011, 2012; Risetti et al. 2013), indicating these patients' ability to sensory discrimination. Recent experiments using the multifeature MMN paradigm (Guger et al. 2013) indicate that this ability can be retained in an even larger number of patients than that identified with a unifeature paradigm (see Fig. 9.1 above). Significant differences between VS/UWS and MCS were reported only by Boly et al. (2011) in a study with 13 MCS and 8 VS/UWS patients, in which the ERP data underwent a source analysis with a following dynamic causal modeling (DCM) analysis. The data were

interpreted as suggesting that top-down connections from the frontal cortex to primary auditory areas, presented in both healthy individuals and MCS patients, were lacking in VS/UWS, while bottom-up connections from the auditory to the frontal cortex remained preserved in all patients. However, the lack of any sign of an MMN in the primary data of VS/UWS patients and the dramatic differences between these data and those of all other MMN studies strongly question the use of complex mathematical techniques such as DCM (King et al. 2011). Most probably, both feedforward and feedback connections were broken in this small sample of VS/UWS patients (King et al. 2011). Only one study (Faugeras et al. 2011) investigated the CNV preceding the last stimulus in the sequence and probably reflecting anticipation of this stimulus; this wave was obtained in 12 of 28 MCS patients, 9 of 24 VS/UWS patients, and 8 of 13 conscious patients.

What about a presumable hierarchy of these components? As stated above, the lack of early subcortical EP components precludes the emergence of later, cortical ERP components. On the other hand, almost all patients having at least partially preserved brain stem auditory EP also exhibit cortical exogenous components P1, N1, and P2 or at least some of these three. Within the cortical components, however, no strict rule like "if X is absent, Y must be absent too" can be established. Recent studies (Guger et al. 2013) demonstrated that there is no earlier ERP effect whose loss completely rules out a later effect; thus there can be an MMN without N1, P3 without N1 and MMN, etc. (see also Kotchoubey et al. 2005). This means that an ERP test battery applied for DoC patients should always check *all* important cognitive components and that the examiners should not stop when initial findings are negative.

As regards *emotional* stimuli, Bostanov and Kotchoubey (2004) recorded a component N300 in response to affective exclamations. The wave is, most probably, an early variety of the N400 related to violations of emotional – instead of semantic – context. Later on, the N300 was also found in VS/UWS and MCS patients with mostly left hemispheric lesions (Kotchoubey et al. 2009). In the same study, a magnetoencephalographic analysis of the N300 showed, however, that it cannot be attributed to emotional processing directly but, rather, to a later cognitive process of detection of affective mismatch.

Another kind of *affective*, highly meaningful stimuli is a subject's own name (SON) that in healthy individuals elicits P3 of larger amplitude as compared with other similar stimuli (Berlad and Pratt 1995). Kotchoubey et al. (2004) applied this stimulus in a group of VS/UWS patients and did not find a significant amplitude differences between SON and another stimulus of the same frequency in any of them. A single MCS patient developed a paradoxical response in form of a slow frontal negativity instead of a parietal P3. No SON response in VS/UWS was also found in a later study (Schnakers et al. 2008); however, these authors found a clear P3 increase to SON in MCS. Qin et al. (2008) investigated a mixed group of acute and chronic DoC patients: 7 of 12 patients exhibited a significant increase of the MMN (rather than P3) to SON. Two studies led to more positive results. One of them yielded both MMN and P3 effects to SON (in the passive condition) in almost every patient: 7/8 VS/UWS and 3/3 MCS (Risetti et al. 2013). In the other study, a P3 increase to SON was found in 3/5 VS/UWS and 6/6 MCS patients, although the response was considerably delayed in VS/UWS as compared with MCS; in addition, the authors examined four patients with locked-in syndrome (LIS) and also obtained the effect in each of them (Perrin et al. 2006). The design of the last study was different from a typical oddball, as a patient's own name was presented among other, unrelated names.

SON data illustrate one more important point in using ERP in DoC: stimuli that are most efficient in eliciting a response must possess sufficient complexity. The own name is a much more complex stimulus than simple tones, and it elicits more reliable responses. Likewise, Jones et al. (2000) obtained significant MMN in VS/UWS patients to such complex auditory pattern deviation as a transition from oboe to clarinet. Both P3 and MMN in DoC are significantly more frequent and have significantly larger amplitudes when

elicited by changes in harmonic tones than by acoustically equivalent changes in sine tones (Kotchoubey et al. 2001, 2003a).

ERPs have also been used to study learning in DoC. The simplest learning process of cortical habituation appears to be preserved in VS/UWS: the component N1 decreased after ten repetitions of the same tone and recovered to a tone of different pitch in a group of 33 patients (Kotchoubey et al. 2006). In contrast, Faugeras et al (2012) studied a higher-level process of ERP changes in the course of pattern stimulation. Learning effects similar to those in healthy controls were observed in one VS/UWS patient of 24 and 2 MCS patients out of 28.

9.5 ERP and Consciousness

The preceding section summarizes ERP evidence that the brain of many DoC patients is able to various kinds of stimulus processing, involving distributed cortico-subcortical networks and even the processing of word meaning. The number of VS/UWS and MCS patients who exhibit such abilities is too large to be explained by occasional diagnostic errors. However, the main diagnostic criteria of DoC include the severe disorder (MCS) or the lack (VS/UWS) of *consciousness*, not of *information processing*. This is not the same: even very complex processing operations in the brain can be done without participation of conscious awareness (van Gaal and Lamme 2012). This is equally true for the passive brain responses to the own name, which persists in coma (Fischer et al. 2008) and stage II sleep (Perrin et al. 1999). A warning should be expressed against the confusion between consciousness and attention: the fact that P3 is highly sensitive to attentional manipulations does not prove that the presence of a P3 indicates conscious perception of stimuli (Daltrozzo et al. 2012). A demonstration of preserved information processing abilities is not a proof of conscious awareness (Celesia 2013).

After a breakthrough study of Owen et al. (2006), it became clear that neurophysiological techniques can not only help to clarify the functional condition of patients' brain but also directly demonstrate *consciousness* in presumably unconscious patients. To use the ERP technique for this purpose, active paradigms should be applied, in which patients are instructed to perform a task, and the ERP data should permit the examiner to judge (in the absence of behavioral responses) whether the patient could understand the instruction. A most direct proof of consciousness can be obtained if an instruction (e.g., to move the right or left hand) is given and if ERPs demonstrate that the patient undertakes attempts to follow this instruction. To date, such a proof has been provided in patients with total locked-in syndrome (Kotchoubey et al. 2003b; Schnakers et al. 2009) but not in DoC. Another active paradigm exploits the response to a patient's own name described above. Schnakers et al. (2008) asked 8 VS/UWS and 14 MCS patients to count their own name presented as a target deviant in an oddball paradigm. The P3 amplitude to SON in the MCS group was not only significantly larger than to other stimuli but also significantly larger in the counting condition than during passive presentation of the same stimuli. No ERP response in any condition was recorded in the VS/UWS group. At the individual level, P3 amplitude increment in the counting condition was found in four MCS patients but in none of the VS/UWS subjects. A similar result was obtained when the target stimulus was a name unfamiliar to the patient. Also Risetti et al. (2013) found an effect of counting instruction to the SON response only in MCS but not in VS/UWS patients. These results indicate, first, that at least some MCS patients are able to intentionally follow instructions and, second, that the instruction is efficient in these patients, independently of the nature of stimulus; the patient's own name can be replaced with another stimulus of comparable complexity (Fig. 9.3).

Other stimuli only rarely resulted in a significant ERP response according to instruction. Chennu et al. (2013) found this response to the to-be-counted word in 1 VS/UWS patient but in none of 12 MCS patients. Another group examined 22 VS/UWS patients using a slightly modified version of oddball in which complex pattern deviations should be counted. A significant P3b to the counted stimulus was obtained in two

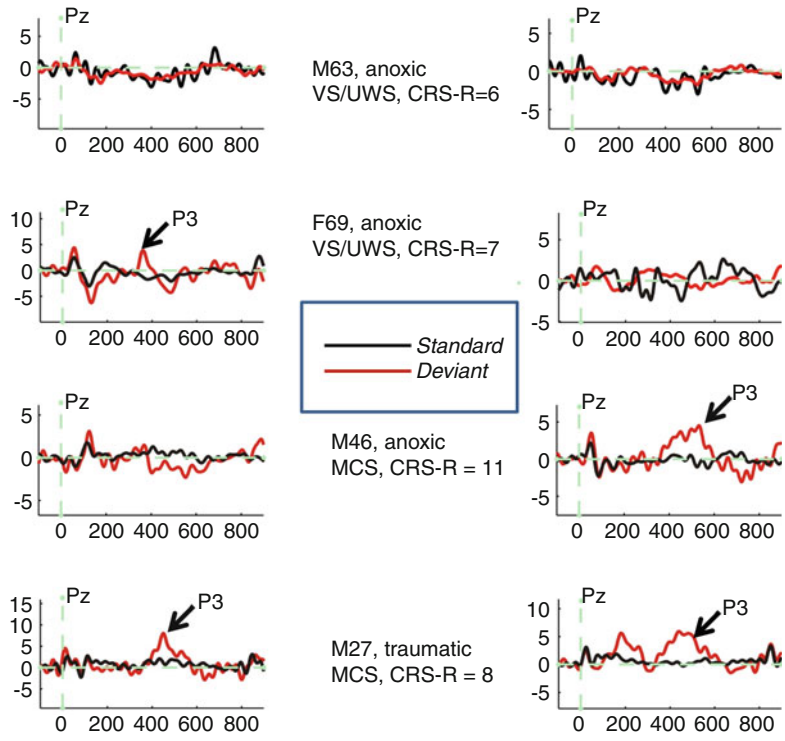

Fig. 9.3 Different outcomes of an oddball paradigm with two harmonic tones in four DoC patients. *Left column*: instruction "just to listen." *Right column*: instruction to count deviants. Negativity is plotted downwards. Pat. M63: no P3 in any condition. Pat. F69: P3 only in the passive condition. Pat. M46: P3 only in the active condition. Pat. M47: P3 in both passive and active conditions. *VS/UWS* vegetative/unresponsive wakefulness state, *MCS* minimally conscious state, *CRS-R* Coma Remission Scale-Revised, full score

patients whose diagnosis was changed to MCS within a few days after examination (Faugeras et al. 2011). In healthy individuals, this P3 response disappeared when they did not attend to the deviants (Bekinschtein et al. 2008), replicating the well-known attention effect on P3 (see above). Therefore, the positive findings in the two patients should be attributed to their following the instruction (i.e., the presence of active conscious intention) rather than to the nature of pattern deviation as such.

9.6 Diagnosis and Prognosis

As a common result of most studies, ERPs do *not* differentiate between VS/UWS and MCS (Balconi et al. 2013; Faugeras et al. 2011, 2012; Fischer et al. 2010; Kotchoubey et al. 2009; Perrin et al. 2006; Ragazzoni et al. 2013). Conclusions that "ERP were related to state of consciousness" should be taken with great caution. They are typically drawn either when taking into account conscious patients, in addition to VS/UWS and MCS, or when ERP effects coincide with some behavioral consciousness scale but *not* with the clinical borderline between VS/UWS and MCS (e.g., Wijnen et al. 2007). Two notable exceptions are Schoenle and Witzke (2004) and Schnakers et al. (2008), demonstrating large VS/MCS differences. In the former, however, the presence of ERP components was subjectively evaluated by a non-blinded rater. The latter included probably a particularly severe VS/UWS group, because even N1 was totally absent, although this component is typically recorded in most VS/UWS patients. Kotchoubey et al. (2005) data shed light on this issue. Most MCS patients have moderate (theta, 4–7 Hz) slowing of the background EEG oscillations (e.g., Leon-Carrion et al. 2008). If they are compared to VS/UWS patients with a similar EEG pattern, no difference in any ERP component can be found; however, VS/UWS patients with a severe slowing of the EEG rhythmic activity (delta, $\leq$3 Hz) do not demonstrate significant ERP components beyond (in a few cases) N1. Therefore, the results of other studies comparing

VS/UWS and MCS may critically depend on the exact "mixture" of VS/UWS patients with moderate versus severe background EEG disturbance in a particular sample (see also Chap. 5).

In contrast to the diagnosis, *etiology* seems to be a factor affecting ERP responsiveness in DoC. Particularly, late ERP components are more frequently found among traumatic patients than patients with anoxic brain injury (e.g., Cruse et al. 2012; Fischer et al. 2010; Kotchoubey 2005; Steppacher et al. 2013). The problem of diagnosis in DoC is closely related with that of *prognosis* (Bruno et al. 2011a; Gawryluk et al. 2010). Even taking into account important clinical variables such as etiology and time since the accident leaves a high degree of uncertainty. Therefore, a search for neurophysiological predictors remains an actual task.

Kotchoubey et al. (2005) retrospectively collected 6-month follow-up data in 23 VS/UWS and 20 MCS patients. Clinical improvement was observed in nine VS/UWS patients (four became MCS, five communicative) and ten MCS patients (all communicative). Patients who showed an MMN later improved significantly more frequently than patients without an MMN, and the same tendency approached significance for the N400. The importance of the MMN was confirmed by Dutch authors (Wijnen et al. 2007). Although they examined only ten VS/UWS patients, all of whom recovered, the study had several important advantages: it was prospective (rather than retrospective in Kotchoubey et al. 2005), the sample was homogenous, and each patient was examined every 2 weeks for a period of 3.5 months. The increase of MMN amplitude preceded clinical recovery, but the strongest change happened after the transition from VS/UWS to MCS, when the patients were able to inconsistent command following (in terms of Bruno et al. 2011b, the strongest MMN change coincided with the transition from MCS− to MCS+).

The MMN finding is noteworthy for two reasons. First, it reliably predicts the outcome of acute coma (Fischer et al. 1999; Daltrozzo et al. 2007) (see also Chap. 7). The acute pathological process in the brain and the chronic conditions such as VS/UWS and MCS differ substantially in their morphology and pathophysiology, and thus factors determining their temporal course are generally different. Nevertheless, the same ERP component may be an important index of brain function in both coma and chronic DoC. Second, the fact that the MMN predicts recovery of consciousness may appear strange, given that the component is largely independent of the actual state of consciousness. The presence of an MMN does not indicate that the patient is able to consciously perceive stimuli at the moment of examination but that this ability is not detected by clinical methods. Rather, the MMN may manifest the yet silent reserves of the brain that will later be realized in form of conscious awareness.

Several smaller studies can be mentioned here. In one of them, a young man with a traumatic VS/UWS was examined using ERP every 3–4 months. From month 6 post ictum, he regularly exhibited normal responses in both oddball (P3) and word pair paradigm (N400). The clinical condition did not change until month 22, when the patient suddenly regained full-blown awareness (Faran et al. 2006). Another study, already cited above (Faugeras et al. 2011), found two very recent (15 and 25 days post ictum) patients with a significant P3 to complex pattern deviation in a counting condition. Both patients developed an MCS within the next 7 days. No P3 in the same condition was obtained in 20 VS/UWS patients, only two of which changed to MCS in the next 7 days. Qin et al (2008) observed 3-month follow-up improvement in 4/9 patients with N1 and 0/3 patients without N1, as well as in 4/7 patients with an MMN to SON and 0/5 patients without the MMN. However, their sample also included patients in acute coma state. These data should be assessed as preliminary.

The predictive trend for the N400 observed by Kotchoubey et al (2005) was replicated in a recent study, the largest and most careful study to date (Steppacher et al. 2013). From the sample of 175 examined DoC patients, 53 VS and 39 MCS patients were followed up from 2 to 15 years (mean 8.3) after the accident. The target ERP components were determined using two methods: the most common visual expert assessment

and the theoretically most informative *t-CWT*. Both methods yielded the same result: the presence of the N400 was strongly associated with clinical improvement during the following years (*p*-values between .0001 and .035). The predictive value of the N400 did not depend on diagnosis (VS/UWS, MCS) or etiology (traumatic, hypoxic, others). In contrast, the presence of oddball P3 was unrelated to the outcome in any diagnostic or etiological group (*p*-values between .35 and 1.0).

Contrary to the other reports, a significant predictive effect for P3 was found in a study with 34 traumatic VS/UWS patients (Cavinato et al. 2009), and for middle-latency auditory EP components in a study with 39 MCS patients (Luauté et al. 2010). In the latter study ERPs were recorded in the acute period, and the patients were followed up to 5 years. All of them were in MCS after 1 year (additionally, 12 VS/UWS patients were investigated, but none of them changed the diagnosis after 1 year). In the MCS group, N1 also contributed to the long-term outcome, but the MMN did not. Finally, Wijnen et al. (2014) were the only group who used visual (flash) stimulation in 11 VS/UWS patients und found a significant correlation between the expression of exogenous EP components and the clinical improvement 1 year later.

The lack of consistency in these data should not be surprising, as it has at least two reasons. First, the very large differences in patient samples: this concerns diagnosis (VS/UWS, MCS, coma), etiology (purely traumatic versus strongly mixed groups), and time post ictum (from few days in Faugeras et al. 2011 to several years in Luauté et al. 2010). This limitation also applies, however, in a least extend, to studies on correlates of cognition presented in Sect. 4, which might explain differences in the frequencies of ERP components. Second, and more specifically for prediction studies, the results critically depend on the initial set of independent variables which the search for predictors starts with. This set was rather small in all studies mentioned above. Including additional variables might radically change the final results. Reliable information on the predictive role of ERP and other neurophysiological variables (e.g., sleep EEG and fMRI) can only be obtained in a *large multicenter longitudinal study* involving a broad set of potential clinical, neurophysiological, and demographic predictors.

9.7 Conclusion

Event-related potential (ERP) represents a useful method for assessment of covert cognitive functions in patients with severe DoC. Having a poor spatial resolution as compared with fMRI and PET, ERPs possess a high level of functional specificity and an excellent temporal resolution, permitting to follow on-line information processing operations in the brain. ERP can be combined with different kinds of passive (pure stimulation) and active (instruction) tasks, which allows the investigator to check different cognitive abilities of the patients. Being a branch of the EEG, ERPs share all the advantages of the latter. The method is cheap, mobile, and well tested; all recordings can be done immediately at a patient's bedside. A very broad number of cognitive processes can be tested using ERP, most of which, however, are not necessarily related to consciousness. Although instruction tasks directly probing conscious awareness have also been used in combination with ERP, it should be further investigated whether ERPs have any advantages in instruction tasks as compared to fMRI (Monti et al. 2010), other EEG techniques (Goldfine et al. 2011), or even the simple electromyography (Bekinschtein et al. 2008).

A major limitation of the ERP methodology is a weak reflection of affective processes, an issue important from both theoretical and practical points of view. Many caregivers are primarily interested in such questions as whether their patients can feel pain and whether an emotional contact with them can be established. ERP can hardly shed light on the former question and rather limited in relation to the latter. Both pain and emotional perception are strongly mediated by the activity of deep brain structures that is not expressed in ERP components. On simple biophysical reasons, it appears highly improbable

that ERP can manifest the activity of the insula, amygdala, or cerebellum. The activity of the anterior cingulate cortex, which also plays an important part in emotional processing, can be manifested in ERP (Nieuwenhuis et al. 2003; Cannon et al. 2009) but only in specific, very complex tasks that cannot be applied in DoC.

The following issues appear presently of major importance in ERP studies of DoC:

1. General assessment: How long should an ERP examination be, and how many stimuli have to be presented? The answer in basic studies is simply "the more, the better," but in DoC patients using too long paradigms can easily result in habituation and fatigue and thus in false-negatives. But how to determine the optimal length?
2. Assessment of consciousness: Can it be done in a passive paradigm? Active instruction tasks necessarily lead to false-negatives (Kotchoubey and Lang 2011), because many patients have conscious feelings but cannot follow instruction.
3. Assessment of prognosis: A large, well-controlled study with a representative DoC sample and a sufficient number of independent variables is necessary. Studies with a 10–50 patients and 5–10 independent variables appear of limited value.

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Transcranial Magnetic Stimulation and Electroencephalography

10

Olivia Gosseries, Olivier Bodart, and Marcello Massimini

Contents

Abstract

Diagnostic assessment in severely brain-injured patients with disorders of consciousness is largely based on behavioral examinations. This approach can lead to misdiagnosis, giving rise to inaccurate prognosis and inappropriate treatment care. Concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) may provide a biological measure of the level of consciousness at the individual level by assessing functional integration and differentiation in the brain. Here we review a series of recent TMS-EEG studies that assess brain complexity in normal wakefulness, during physiological (sleep), pharmacological (anesthesia), and pathological (brain injury) conditions. TMS-EEG may contribute to unveiling the pathophysiology of disorders of consciousness due to severe acquired brain injury. This technique could also help clinicians in their decision making and provide support for treatment intervention.

10.1 Introduction

Behavioral examination is the current gold standard for the diagnosis of patients suffering from severe brain injury with disorders of consciousness (Bodart et al. 2013). However, this approach may be misleading as it relies on the

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clinician to determine whether observed behaviors are reflex or volitional. The clinician may, for instance, not be aware of underlying motor, sensory, or cognitive impairments that can mask awareness. Behavioral and neuroimaging studies suggest that some patients considered to be unconscious at the bedside actually retain some conscious awareness (Monti et al. 2010; Schnakers et al. 2009). Establishing an accurate diagnosis of the level of consciousness is critical for ensuring accurate prognosis and for establishing the most appropriate plan of care. Yet, to date, there is no scientifically well-grounded measure of the level of consciousness that is independent of processing sensory inputs and producing appropriate motor outputs. Concurrent transcranial magnetic stimulation (TMS) and electroencephalography (EEG) may however provide a biological measure of the level of consciousness at the individual level, in pathological states but also in normal physiological and pharmacological conditions (Gosseries et al. 2014). In this chapter, we describe the basic principles of TMS-EEG technique and how this technique can aid in assessing cortical excitability, effective connectivity, and brain complexity in different conditions of (un)consciousness.

10.2 Transcranial Magnetic Stimulation

TMS is a noninvasive method of modulating the cortex using the principles of electromagnetic induction (Hallett 2000). Briefly, when a charge is passed through the wires of a TMS coil, a perpendicular magnetic field is produced. This field easily penetrates the skull and creates an electric current in the underlying cortex. TMS can be delivered through single, paired, or repetitive pulses that cause brief neuronal depolarization and discharge of action potentials (Lapitskaya et al. 2009b). Delivered over the motor or the visual cortex, single-pulse TMS induces motor evoked potentials (Lapitskaya et al. 2009a) or phosphenes (Kastner et al. 1998), respectively. Paired-pulse TMS and repetitive TMS can be used to assess cortical inhibition, facilitation, and plasticity. Repetitive TMS has been used to induce a sustained inhibition (<1 Hz) or activation (>1 Hz) of the neuronal population, which permits stimulation of brain areas and subsequent observation of behavioral and cognitive changes (Miniussi and Rossini 2011).

In the last several years, TMS has been combined with high-density EEG and a neuronavigation system (Fig. 10.1) to directly measure the activity of the brain itself, instead of measuring muscular activity or behavioral responses derived from the TMS stimulation. In this way, single-pulse TMS induces focal neuronal discharge at the cortex surface, and an EEG measures cortical electrical responses both locally and at distant sites (Fig. 10.2). This enables the study of cortical excitability (i.e., amplitude of the initial response to TMS) under the site of stimulation and long-range cortical effective connectivity (i.e., the overall effects of the perturbation) with good spatiotemporal resolution (Massimini et al. 2009). The neuronavigation system allows precise stimulation of a selected brain area and ensures stability of the position of the stimulation as well as reproducibility among different sessions (Casarotto et al. 2010). Studies demonstrated that reliable responses to cortical stimulation could be derived without being substantially affected by TMS-induced artifact thanks to new hardware solutions, improved EEG amplifier technology, and advanced data processing techniques (Rogasch and Fitzgerald 2013; Gosseries et al 2014). Using recent source modeling and statistical analyses, it is thus possible to detect the spatio-temporal dynamics triggered by a direct cortical stimulation in different conditions, such as normal wakefulness, sleep, anesthesia, and brain lesion (Casali et al. 2010, 2013).

10.3 Normal Wakefulness

During wakefulness, as shown in Fig. 10.2, TMS triggers sustained long-range and complex patterns of activation (Massimini et al. 2005). These TMS-EEG responses vary depending on

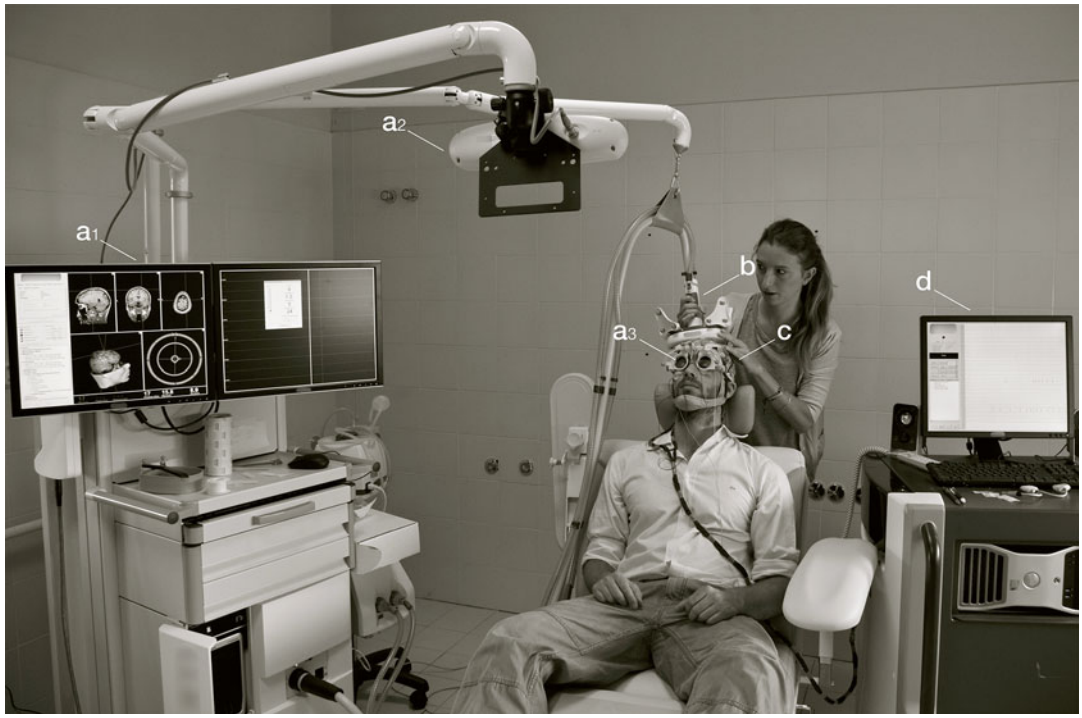

Fig. 10.1 Neuronavigated TMS-EEG system. The neuronavigation system is composed of a 3D head model and targeting system (*a1*), an infrared camera (*a2*), and glasses (*a3*) that are covered with reflective balls for infrared tracking. The stimulation coil (*b*) is also covered by these reflective balls for accurate localization of the stimulation point. The EEG system has a 60-electrode EEG net (*c*) connected to a compatible EEG amplifier and recording system (*d*). TMS-EEG: transcranial magnetic stimulation coupled with high-density electroencephalography (Taken from Napolitani et al. (2014))

the site of stimulation, because each brain area tends to preserve its own natural frequency (Rosanova et al. 2009). For instance, TMS consistently evoked alpha-band oscillations (8–12 Hz) in the occipital cortex, beta-band oscillations (13–20 Hz) in the parietal cortex, and fast beta/gamma-band oscillations (21–50 Hz) in the frontal cortex (Rosanova et al. 2009). Brain regions tend to oscillate at their natural frequencies also when indirectly stimulated by TMS, via cortical connections. More recently, cortical excitability has been shown to increase with time awake (Huber et al. 2013). Short-term memory tasks have also been found to increase the strength and the spatial spread of the electrical currents induced by TMS (Johnson et al. 2012). Finally, training on a working memory task increases effective connectivity across frontoparietal and parietooccipital networks (Kundu et al. 2013).

10.4 Sleep

Navigated TMS-EEG has also been used to study the transition from wakefulness to sleep. When TMS is applied during non-REM (NREM) sleep, a state where awareness is typically massively reduced, it triggers a large positive-negative wave that usually stays localized under the stimulation coil and dissipates quickly (Massimini et al. 2005). In this condition, increasing the stimulation intensity results in a global positive-negative wave much like spontaneous NREM sleep slow waves (Massimini et al. 2007). This stereotypical response still

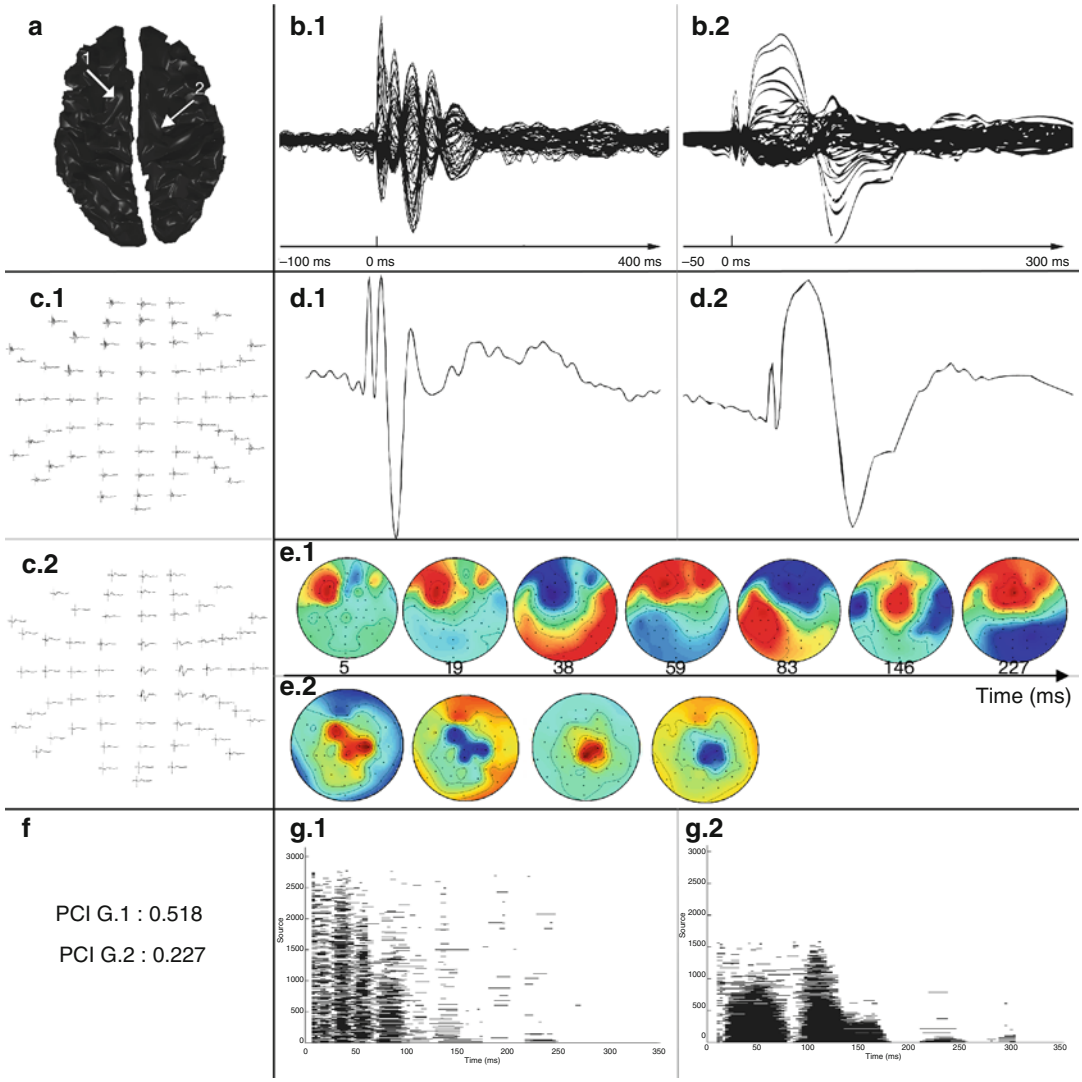

Fig. 10.2 Typical TMS-EEG findings in conscious and unconscious states. (**a**) Stimulation target (*arrow*) on the subject's brain (1 = healthy subject, 2 = patient in a vegetative state/unresponsive wakefulness syndrome). (**b**) Average TMS-EEG response over the 60 electrodes in a healthy awake subject (**b1**) and in a patient in a vegetative state/unresponsive wakefulness syndrome (**b2**). (**c**) TMS-EEG response across space (i.e., channels) for the healthy subject (**c1**) and the unconscious patient (**c2**). (**d**) Typical TMS-EEG response under the stimulation coil in conscious (**d1**) and unconscious states (**d2**). (**e**) Change in the localization of maximum activity across time on EEG topography plots (**e1** for conscious and **e2** for unconscious state). (**g**) Binary matrices of significant source activation across time for both consciousness (**g1**) and unconsciousness (**g2**). The compression of these matrices helps computing the perturbational complexity index (PCI) (**f**)

lacks the complexity of the response observed in wakefulness, suggesting that while the thalamocortical system remains reactive during NREM, it loses its capacity to generate differentiated patterns of neural activity. In REM sleep, even though the brain is isolated from the external world, awareness can be present under the form of vivid dreams that can be reported verbally immediately after awakening. The TMS-EEG response in REM is a complex and widely distributed, high-frequency response that is quite similar to the one observed during wakefulness

(Massimini et al. 2010). This suggest that the complexity of cortico-cortical casual interactions may signal consciousness independently of sensory access and motor outputs.

10.5 General Anesthesia

In addition to physiological shifts, transition from wakefulness to unconsciousness can be driven by means of pharmacological agents. When performed on subjects under midazolam-induced general anesthesia, TMS triggers a large positive-negative wave that stays localized under the stimulation coil and vanishes rapidly (Ferrarelli et al. 2010). This response is very similar to the one observed in the NREM sleep. Likewise, when subjects are awakened from midazolam general anesthesia, they cannot report any conscious content (Bulach et al. 2005). Midazolam acts exclusively on GABA-A receptor and thus is likely to inhibit the thalamocortical system, preventing it to engage in a widespread differentiated communication with distant cortical areas, which leads to unconsciousness. When subjects awake from this unconscious state, with tapering doses of midazolam, TMS-EEG responses become more and more complex and widespread, recovering the characteristics observed in healthy awake subjects.

10.6 Severe Brain Injury

Another population subject to unconsciousness is represented by patients with severe brain injuries. Different disorders of consciousness compose this population, and solely based on clinical evaluation, it can be challenging to disentangle patients with an unresponsive wakefulness syndrome (formerly known as vegetative state) from those who are in a minimally conscious state (Schnakers et al. 2008). While both are awake and show some sort of sleep–wake cycle, the former only show reflexive responses to stimulations (Laureys et al. 2010), while the latter show minimal signs of consciousness such as visual pursuit or response to command (Giacino et al. 2002). Neither can, by definition, communicate nor report their (un)consciousness. Performed on patients with a vegetative state/unresponsive wakefulness syndrome, who show no signs of consciousness, TMS triggers the stereotypical local, slow, and short-lasting wave that has been observed in NREM sleep and general anesthesia (Fig. 10.2). Sometimes, no responses at all can be elicited, especially in patients with post-anoxic brain injuries. On the other hand, patients in a minimally conscious state, who show limited but reproducible signs of consciousness, invariably respond to TMS with a more complex, widespread, high-frequency wave very similar to the one observed in wakefulness (Rosanova et al. 2012). In patients with a locked-in syndrome, who are fully conscious but completely paralyzed except for eye movement, TMS triggers the same complex response we have previously observed in healthy awake subjects (Rosanova et al. 2012). These results indicate a clear-cut difference of TMS response between unresponsive and minimally conscious patients, which has also been confirmed recently (Ragazzoni et al. 2013).

A subset of severe acquired brain-injured patients was also evaluated several times in the acute setting. The first assessment took place 48 h after the end of sedation, as they emerged from coma, whereas the second TMS recording was performed either when they improved from vegetative state/unresponsive wakefulness syndrome to minimally conscious state (three patients) or after at least 30 days if there was no recovery of consciousness (two patients). The last recording was set up as soon as the three patients who improved recovered functional communication (i.e., emergence of the minimally conscious state). In the first TMS assessment, all patients were awake but unconscious and four of them demonstrated a stereotypical slow and local positive-negative wave, similar to the response observed in chronic unresponsive patients. The fifth patient did not demonstrate any TMS-EEG response. When the patients recovered signs of consciousness and communication, the TMS-EEG response regained characteristics seen in healthy awake subjects, being more complex and widespread than previously observed in the same subject. Interestingly, one of the patients who improved to minimally conscious

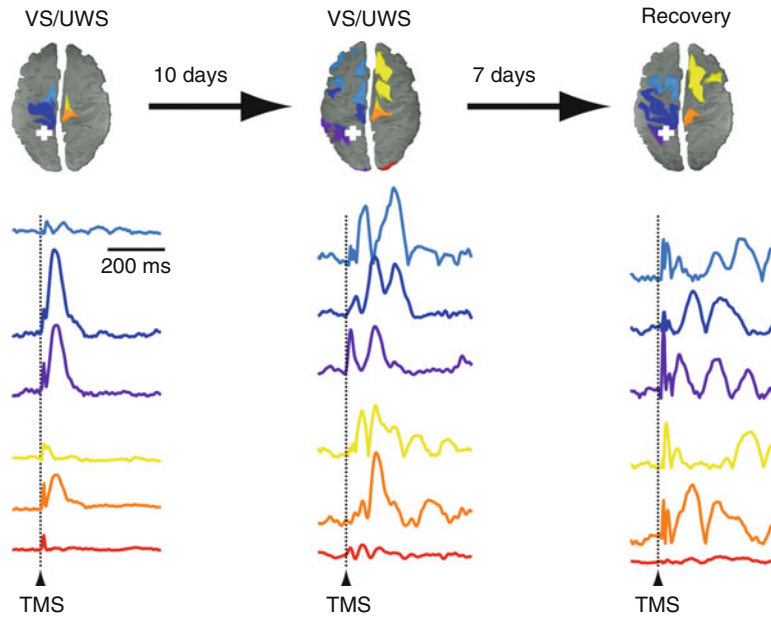

Fig. 10.3 Recovery of coma and TMS-EEG responses. Recovery of consciousness in a patient with severe brain injuries is accompanied by the recovery of complex, widespread, and differentiated EEG activations in response to TMS, depicted here at the cortical source level (*colored traces*) (Taken from Sarasso et al. (2014)). *VS/UWS* vegetative state/unresponsive wakefulness syndrome

state was behaviorally back in an unresponsive state on the day of the examination, but widespread and complex brain responses could still be detected, even if at the bedside, no sign of consciousness could be observed (Fig. 10.3). The two patients who did not recover signs of consciousness and remained in an unresponsive state did not show any modification of their TMS-EEG responses. Although based upon a limited number of patients, these observations are important as they show that TMS-EEG is sensitive to changes in the consciousness level, and that it has the advantage to be applied at the bedside of patients with acquired severe brain injuries.

10.7 Measuring the Level of Consciousness

Clinical application of this technique could be made even more accessible with the recent development of newer analysis techniques. Indeed, so far the distinction between conscious and unconscious subjects was mainly based upon a careful inspection of the TMS response. More objective quantitative approaches can be designed to allow researchers to easily compare different subjects and conditions. General indices reflecting cortical excitability and effective connectivity were first developed (Casali et al. 2010). However, these indices do not allow a direct comparison between subjects. For this reason, the perturbational complexity index (PCI) was recently developed (Fig. 10.2). PCI is computed starting from TMS-evoked potentials by (1) extracting the source model of cortical activation from the preprocessed scalp EEG signal, then (2) running a permutation statistical test to detect significantly activated source and plotting them against time in a binary matrix (3) compressing this matrix using a Lempel–Ziv algorithm and normalizing the data. This approach has been tested on more than a hundred TMS-EEG sessions on healthy subjects in various conscious and unconscious states, as well as in patients with chronic disorders of consciousness. It appears that PCI can distinguish, at the single-subject level, between conscious (healthy awake subjects, locked-in patients and minimally conscious patients), and unconscious conditions (vegetative state/unresponsive wakefulness patients, healthy subjects under general anesthesia using midazolam, xenon, and propofol and during NREM sleep) (Casali et al. 2013). This may open the doors to an easy-to-use system to objectively assess brain's capacity for consciousness, hopefully helping clinicians make accurate treatment decisions and discuss the patient's state with their relatives.

10.8 Conclusion

Differentiating between conscious and unconscious patients still represents a major clinical, ethical, and medicolegal challenge. While behavioral assessment remains the current clinical standard for detecting awareness, it cannot stand alone any longer as recent studies have reported that patients considered unconscious at the bedside can have preserved awareness (Cruse et al. 2011; Stender et al. 2014). The TMS-EEG technique may provide a neurophysiological measure of the level of consciousness at the single-subject level in physiological, pharmacological, and pathological conditions. The basic evidence is that, during conscious states, such as normal wakefulness, REM sleep, minimally conscious state, and locked-in syndrome, the brain is able to sustain long-range and complex activity patterns marked by a differentiated, diffuse, and long-lasting evoked response, which gives a high value of PCI. During unconscious states, such as NREM sleep, anesthesia, and vegetative state/unresponsive wakefulness syndrome, TMS triggers a stereotypical, local, and short-lasting response, which gives a low value of PCI (Fig. 10.2). Importantly, this technique can be used at the bedside and does not require the participation of the subject, neither requires language processing nor functioning afferent/efferent pathways, which is of particular interest when assessing patients with severe brain injuries. Further studies should confirm these inaugural results on a larger sample. Only then, this technique may be incorporated into the clinical routine in order to help the diagnosis, prognosis, and treatment monitoring of patients with disorders of consciousness.

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Brain-Computer Interface for Assessing Consciousness in Severely Brain-Injured Patients

11

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Abstract

Brain-computer interfaces (BCIs) are tools that allow overcoming motor disability in patients with brain injury, allowing them to communicate with the environment. This chapter reviews studies on BCI applications in patients with disorders of consciousness, including EEG and fMRI applications, with a critical appraisal regarding false-positive and false-negative results. The role of steady-state visually evoked potentials and of the cognitive evoked potential P3 (or P300) will be highlighted. Future research has to overcome several challenges limiting current BCI application in routine practice and provide more reliable tools for diagnosis. Alternative protocols might be of interest in the development of easy-to-use systems for caregivers.

11.1 Introduction

Motor disability poses a significant challenge for clinicians working with patients with severe brain injury and especially disorders of consciousness (DOC), in terms of diagnosis, care, and rehabilitation (Schnakers et al. 2009; Cruse et al. 2011; Owen et al. 2006; Monti et al. 2010). Indeed, behavioral assessment, which remains the traditional way to evaluate consciousness (i.e., command-following and/or communication) in these patients, is highly dependent on motor

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abilities. In this context, paraclinical tools to detect signs of consciousness that bypass the motor pathway are needed. Brain-computer interface (BCI) constitutes an interesting approach as it allows direct recording of the brain activity without requiring behavioral responses (Wolpaw et al. 2002). Recent studies show that there are command-specific changes in signals recorded with electroencephalography (EEG) or functional magnetic resonance imaging (fMRI) in patients with severe motor disabilities and that about 18 % of the patients being diagnosed as unconscious at the bedside might actually be able to follow a command by modulating their brain activity with respect to the relevant task (Schnakers et al. 2008a, 2009; Cruse et al. 2011; Monti et al. 2010; Chatelle et al. 2012; Goldfine et al. 2011; Lulé et al. 2013). These techniques could help improve the diagnosis of patients with DOC. However, poor performance (Lulé et al. 2013; Kubler et al. 2009), motor dependence (Kubler and Birbaumer 2008; Combaz et al. 2013; Piccione et al. 2006), and the need for time-consuming user training (Kubler and Birbaumer 2008; Birbaumer 2006; Neuper et al. 2003) are well-known limitations of BCI for detecting command-following and communication in conscious brain-injured patients. Furthermore, the high rate of false negatives (patients showing command-following at the bedside but not detected with BCI; 22–94 % (Monti et al. 2010; Schnakers et al. 2008b; see also Chatelle et al. 2014)) and the issue of false positives (patients detected as showing command-following with BCI who are actually unconscious (Cruse et al. 2013; Goldfine et al. 2013)) highlights the current need to develop more reliable tools for the diagnosis of patients with DOC. Indeed, having reliable systems would have a real impact on providing care such as treatment (in particular, pain and anxiety) and rehabilitation, as well as on quality of life (Kubler et al. 2006).

Here we review the studies on BCI applications for detecting response to command in patients with DOC. We then highlight the main challenges that will need to be overcome in future research and suggestions from studies conducted in healthy controls and motor-disabled patients that may be applied to the severely brain-injured population.

11.2 Brain-Computer Interfaces and Diagnosis in Disorders of Consciousness

A BCI is a system allowing for communication between the brain and the external environment. It is therefore independent from any peripheral neural or muscular activity (Wolpaw et al. 2002). This system is based on cerebral activity that can be measured using techniques such as EEG, fMRI, implanted electrodes (electrocorticography – EcoG (Hochberg et al. 2006)), or functional near-infrared spectroscopy (fNIRS; (Sorger et al. 2009)). The primary function of a BCI is to provide the subject a virtual keyboard where each covert "key press" constitutes a choice of an item from a set of items. This choice is made through the control of neuroelectrical activity (Sellers and Donchin 2006; Sellers et al. 2006). A specific algorithm translates the extracted features into commands that represent the users' intent (see Fig. 11.1). These commands can control effectors to select items such as words, images, or devices. Recent development has shown the usefulness of BCIs for controlling motor prosthesis and cursors, providing a means of communication, and accessing the Internet (Hochberg et al. 2006; Citi et al. 2008; Yoo et al. 2004; Mugler et al. 2010; Sellers et al. 2010; Lee et al. 2009).

In the context of DOC, the first goal of a BCI is to detect command-specific changes in brain signals as evidence of conscious thoughts. Then, if the patient is able to reproducibly follow a command using the system, the software and hardware can be extended to test communication. The acquisition of voluntary responses such as command-following and functional communication is keystones in diagnosis as defined by behavioral criteria (Giacino et al. 2002; Plum and Posner 1966; Laureys et al. 2010). The presence of command-following indicates emergence from the vegetative/unresponsive wakefulness

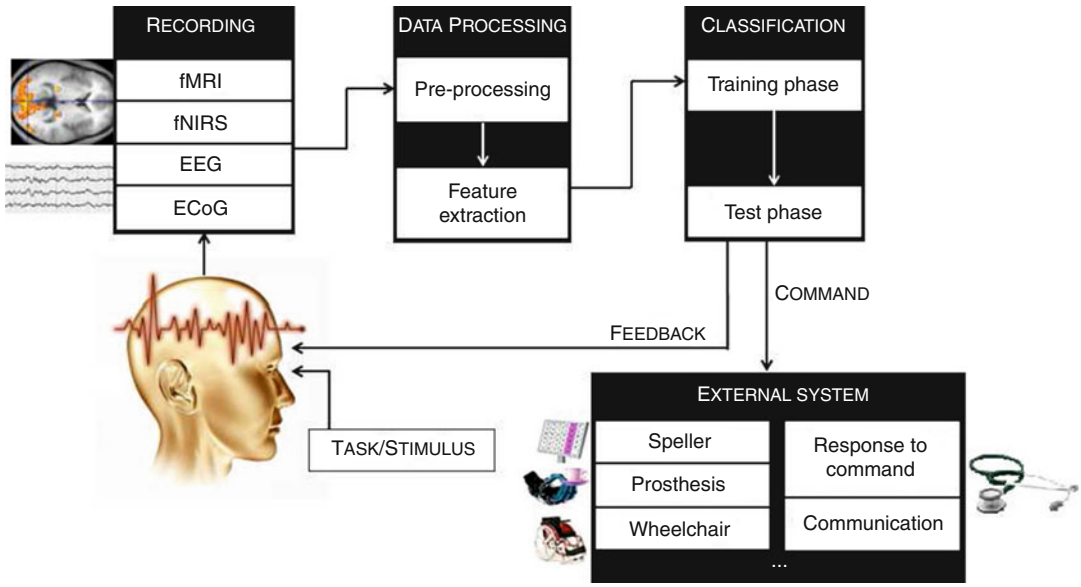

Fig. 11.1 A typical brain-computer interface schema. Modifications of brain activity due to a task/stimulus are recorded with fMRI, fNIRS, EEG, or ECoG. These neural data are pre-processed before discriminative features are extracted. Machine learning techniques are then used to train classifiers to detect statistical patterns in the features that are reliably associated with prespecified (supervised) volitional states of the user. The trained classifier is then used to classify new features corresponding to states now selected by the user to communicate choices. Finally, the result of the classification is fed back to the user to help him/her train themselves in the use of the BCI and to control external devices (e.g., word spelling, control of a wheelchair, a robotic prosthesis) or to help clinicians detect a response to command or functional communication

state (VS/UWS; (Laureys et al. 2010)) or recovery of a minimally conscious state (MCS; (Giacino et al. 2002; Bruno et al. 2012)). The recovery of functional communication indicates the emergence from MCS (EMCS; (Giacino et al. 2002)). Command-following and functional communication also distinguish locked-in syndrome (LIS) (Plum and Posner 1966) from VS/UWS patients. Because a better outcome for MCS versus VS/UWS patients has been reported (Luauté et al. 2010), patient access to rehabilitation is likely to be influenced by the clinical diagnosis. In addition, a recent study of 108 patients with traumatic brain injury reported that 56–85 % of patients showing command-following before discharge from the acute inpatient rehabilitation were functioning independently by 5 years post-injury, as compared to 19–36 % of patients who did not show command-following at discharge (Whyte et al. 2013). It remains unclear whether it was the presence of command-following, the quality of rehabilitation treatment (e.g., duration, hours of therapy, etc.), or both that contributed to better outcomes for command-followers. For LIS patients, the difficulty to recognize unambiguous signs of consciousness in the acute stage often results in the diagnosis being delayed or even missed (Laureys et al. 2005), with potentially catastrophical implications. Conversely, an early diagnosis allows clinicians to start developing a communication tool tailored to the patients' residual abilities.

To benefit from a BCI, the patient would need to first understand the task and repeat it several times, then to be able to attend to stimuli/questions while retaining task information in working memory. However, current BCIs require that the patient have much more capacity than required by behavioral testing, leading to undetectable command-following in many patients. When looking at the results obtained in studies of patients with DOC, we therefore need to take into account the number of patients showing command-following with the system, and how

many of them were able to follow a command at bedside that could not be detected by the system (i.e., false negatives; see Table 11.1). False-positive rate should also be considered, but will not be discussed here as it is difficult to determine the level of consciousness of patients diagnosed unconscious but showing response to command with a BCI.

11.3 Absence of Motor Responses and Brain-Computer Interfaces

The first study showing the possibility of detecting response to command with BCI was conducted by Owen et al. in 2006 and reported that one patient diagnosed as being in VS/UWS was able to follow the instruction to "imagine playing tennis" and "walking through her house" during an fMRI session (Owen et al. 2006). The paradigm consisted of several sessions of mental imagery followed by a resting period, both lasting 30 s. This patient displayed similar brain activation as compared to healthy volunteers for both tasks. In addition, the patient behaviorally evolved into MCS a few months after the study. In a follow-up study (Monti et al. 2010) including 54 patients (23 VS/UWS and 31 MCS), five (four VS/UWS) showed ability to willfully modulate their brain activity according to the task. One of them was also able to answer simple questions, e.g., "Is your father's name Alexander?" using one task for "yes" and the other for "no." However, out of 18 patients showing command-following at the bedside, only one could be identified with the system (false-negative rate: 94 %). Bardin et al. (Bardin et al. 2011) investigated the use of a different imagery task instructing patients to imagine themselves swimming or playing tennis with their right hand, using a similar protocol to the one used by Owen et al. (2006) and Monti et al. (2010). Out of six patients (three MCS, two MCS/emerging MCS, one LIS), three were able to follow commands with the system (one MCS, one MCS/emerging MCS, one LIS). However, of the five patients who were able to follow commands at the bedside, two of them could not be identified with the system (false-negative rate: 40 %). Similarly, using an active task in fMRI task (counting a target-neutral monosyllabic word in an auditory sequence of nontargets words), Monti et al. reported preserved working memory abilities in a MCS patient exceeding that which could be observed with standard behavioral assessment (Monti et al. 2009). This patient was able to follow a command and communicate non-functionally at the bedside. Finally, three patients (one VS/UWS, two MCS) were instructed to either count the occurrences of a target word ("yes" or "no") or to simply relax and passively listening to a sequence of "yes" and "no" presented in a random series of numbers (Naci and Owen 2013). Command-following could be detected in all of the patients, and two patients (one VS/UWS and one MCS) were able to focus their attention to communicate correct answers to two different binary ("yes" or "no") questions such as "are you in a supermarket?" or "is your name Steven?" Because the latter two studies included few patients, and the results have not been replicated yet, interpretation of false-negative rates has not been conducted.

These first BCI studies showing response to command in DOC patients were conducted using fMRI, a technique that has many limitations preventing it from being applied universally to the DOC population. First, ferrous metallic implants are a contraindication to MRI, preventing many patients from undergoing this procedure. Even if implants are nonferrous, metal in the head can cause significant image artifact, making the analysis of the results difficult or impossible. Second, fMRI is sensitive to motion, which can result from reflexive movement in the scanner, general restlessness, or decreased patient cooperation. Images that are affected by significant motion artifact cannot be interpreted. Specifically, over three years of the European FP7 project DECODER during which the fMRI active sport/navigation paradigm described above was used in clinical settings at the Centre Hospitalier Universitaire de Liège, 169 patients were elected for the fMRI procedure. From this cohort, only

Table 11.1 Studies using brain-computer interfaces (BCIs) and alternative systems in patients with disorders of consciousness for assessing response to command and communication with false-negative ratios (patients showing command-following at the bedside, but not detected by the BCI)

References	Technique used – brain response	Task	Total number of patients included	False-negative ratio (%)
BCI applications				
Owen et al. (2006) and Monti et al. (2010)	fMRI – motor imagery	Playing tennis vs. walking through your house (command-following and communication)	55 (24 VS/UWS; 31 MCS)	17/18 (94 %)
Bardin et al. (2011)	fMRI – motor imagery	Swimming (command-following and communication)	6 (3 MCS; 2 exit MCS; 1 LIS)	2/5 (40 %)
Monti et al. (2009)	fMRI – P3	Count a target word – neutral (command-following)	1 (MCS)	0/1 (0 %)[a]
Naci and Owen (2013)	fMRI – P3	Count a target word – neutral (command-following and communication)	3 (1 VS/UWS; 2 MCS)	0/1 (0 %)[a]
Schnakers et al. (2008a, 2009)	EEG – P3	Count a target word – subject's own name (command-following)	23 (8 VS/UWS; 14 MCS; 1 LIS)	2/8 (25 %)
Lulé et al. (2013)	EEG – P3	Count a target word (communication)	18 (3 VS/UWS; 13 MCS; 2 LIS)	5/6 (83 %)
Goldfine et al. (2011b)	EEG – motor imagery	Swimming vs. walking through your house (command-following)	3 (1 MCS, 1MCS/exit MCS, 1 LIS)	1/3 (33 %)
Cruse et al. (2011, 2012a)	EEG – motor imagery	Squeeze your right hand vs. move your toes (command-following)	39 (16 VS/UWS; 23 MCS)	13/15 (87 %)
Cruse et al. (2012b)	EEG – motor imagery	Squeeze your right vs. left hand (command-following)	1 (VS/UWS)	Not applicable
Pokorny et al. (2013)	EEG – P3	Count the number of deviant tones (command-following and communication)	12 (1 VS/UWS, 10 MCS, 1 exit MCS[b])	1/3 (33 %)[b]
Chennu et al. (2013)	EEG – P3 (20 patients also seen with fMRI active task used in (Owen et al. 2006; Monti et al. 2010))	Count the number of target word (command-following)	21 (9 VS/UWS; 12 MCS)	EEG: 7/7 P3b (100 %), 5/7 P3a (71 %); fMRI: 3/7 (43 %)
Alternative systems				
Bekinschtein et al. (2008)	EMG – muscle activity	Move your right hand (command-following)	10 (8 VS/UWS, 2 MCS)	0/1 (0 %)[a]
Stoll et al. (2013)	Infrared camera – pupil dilation	Perform arithmetic problem (communication but command-following with the MCS patient)	13 (12 LIS; 1 MCS)	0/1 (0 %)[a] when used for command-following, but 9/12 (69 %) when used for communication

The ratio percentage is calculated by dividing the number of patients who responded to command at the bedside, but did not show response to command with the system by the total number of patients' response to command at bedside

[a]Not interpretable as only one patient showing command-following has been tested with this system

[b]Based on CRS-R data obtained from Pokorny et al. Note that for four patients, subscales scores were not available, preventing the current analysis in terms of false negatives

60 studies yielded active paradigm data that were interpretable, outlining the difficulties in generalizing this approach. The main reason for data rejection was artifact caused by head motion in the scanner. Finally, many clinical settings do not have access to MRI because it is an expensive technique to implement. Furthermore, fMRI requires executing complicated data processing methods, which necessitates involvement of personnel with expertise in this area. Given these limitations, EEG may be better suited for assessing DOC patients as it is not contraindicated by metallic implants and is less sensitive to motion. EEG is relatively inexpensive, and compact systems can be readily deployed at the bedside. In recent years researchers have been developing EEG-based BCI to assess response to command in DOC.

As suggested by fMRI studies, BCI using imagination of movement may be a reasonable supplement to observation of actual movement during standard behavioral assessment. EEG studies have shown that motor imagery is associated with a power decrease (event-related desynchronization) in the sensorimotor or mu rhythm (8–15 Hz; (Pfurtscheller et al. 1997; Neuper et al. 2005)), focused in the motor region that is implicated in the movement being imagined (Pfurtscheller and Lopes da Silva 1999). Goldfine and colleagues (2011) recorded EEG from three patients showing command-following at the bedside (MCS, MCS/emerging MCS, and LIS), while they were involved in motor imagery and spatial navigation tasks. The session alternated eight 15-second periods of mental imagery with 15-second periods of rest. All of the patients demonstrated the capacity to generate mental imagery on the same tasks on independent fMRI studies. With univariate comparisons (individual frequencies), these investigators showed evidence of significant differences between the frequency spectra accompanying the two imagery tasks in one MCS patient (however, results were not stable between the two runs) and one LIS patient (false-negative rate: 33 %).

In another study from Cruse and colleagues, motor imagery tasks were investigated in 16 VS/UWS (Cruse et al. 2011) and in 23 MCS patients (Cruse et al. 2012a). Eight (three VS/UWS, five MCS) were able to voluntarily control their brain activity in response to a command ("imagine squeezing your right hand" versus "imagine moving all your toes"). Out of 15 patients showing command-following, 13 could not be identified by the system (false-negative rate: 87 %). In order to decrease the cognitive load required to complete the task (e.g., minimize task switching and the duration of the session), the latter study used a block design with instructions to perform motor imagery following each of 15 subsequently presented tones. However, in this population block design may be problematic because changes in the EEG signal across and within blocks may be influenced by vigilance and motor artifacts leading to lack of independence between trials. For this reason, these results should be interpreted cautiously because dependence between trials was not accounted for in the statistical analyses. This issue is specifically relevant for the severely brain-injured population, and BCI studies in the future will need to take it into account (Cruse et al. 2013; Goldfine et al. 2013).

In an attempt to circumvent the statistical pitfalls of block design, an alternate paradigm has been investigated. In this paradigm, each trial is started with one of three instructions (i.e., "try to move your right hand," "try to move your left hand," and "and now, relax") that are presented through sounds in a randomized order. Because the instructions are presented before each trial as oppose to at the beginning of a block, significantly less working memory capacity is required to carry out the task. In addition, this method is technically less challenging and more efficient as it requires the use of only four electrodes. The utility of this paradigm as a diagnostic tool has been reported in a single patient diagnosed as being in a VS/UWS at bedside (Cruse et al. 2012b). However, this type of protocol still requires higher-level cognitive abilities, such as sustained attention and task switching, as compared to behavioral assessment.

Several studies have suggested that motor imagery cannot be reliably used in motor-disabled patients (Kasahara et al., 2012; Fiori et al., 2013). Instead of motor imagery, Nijboer et al. has

recommended the preferential use of the P3-based BCI in patients with severe motor impairment (Nijboer et al. 2010) (see also Chap. 8). The P3 response (also called P300) is a positive deflection in the EEG appearing around 200–500 ms following a target stimulus (see also Chaps. 7 and 9). The advantage of the P3 is that it can be elicited by meaningful stimuli and requires a limited working memory load from the patient. Some of the earliest EEG-based BCI systems were based on the P3 component (Farwell and Donchin 1988; Donchin et al. 2000). The successful use of P3-based BCIs by a larger population of healthy users versus the sensorimotor rhythm has also been reported by Guger et al. (Guger et al. 2009; Guger et al. 2003). Moreover, many studies have shown that this system is feasible and practical for patient groups (see, e.g., Sellers et al. 2006; for a review, Hoffmann et al. 2008; Manyakov et al. 2011) and offers a stability of the performance over time in this population (Sellers et al. 2010; Nijboer et al. 2008; Silvoni et al. 2009). Consequently, auditory P3 responses are more likely to be usable by a greater number of patients (Chatelle et al. 2012). However, some of the most successful P3-based BCI systems are based on visual P3 responses which may be difficult to elicit in brain-injured patients as they frequently present with gaze fixation impairments (Lew et al. 2009; Alvarez et al. 2012) preventing them from attending to visual stimuli. Schnakers et al. proposed using an auditory P3 for detecting command-following using EEG (Schnakers et al. 2008a). They used a paradigm instructing patients to count the number of times a name (subject's own name or unfamiliar name) was presented within an auditory sequence of random names in 22 patients (eight VS/UWS, 14 MCS) (Schnakers et al. 2008a). Results showed that five out of 14 MCS patients showed significantly larger P3 responses when actively counting the occurrence of their own name as compared to when only passively listening to it. In addition, four other MCS patients showed a response only when they were asked to count an unfamiliar name as compared to passive listening. These results suggest that fluctuation of vigilance may play a role in task performance in this population. The eight VS/UWS patients did not show any response to the active task. The same paradigm has been used in a patient behaviorally diagnosed as being comatose, who showed a significant difference between the passive and the active task (Schnakers et al. 2009). Following this finding, this patient was reassessed and diagnosed with complete LIS. This extreme case illustrates the clinical utility of BCI as a supplement to behavioral assessment. Using this paradigm, two out of eight patients showing command-following at bedside could not be detected with the system (false-negative rate: 25 %). Similar results have been replicated in a recent study including patients with DOC (Risetti et al. 2013).

When the data were analyzed offline, one LIS patient reached 79 % accuracy. Out of six patients showing command-following at bedside (four MCS, two LIS), five could not be detected with the system (false-negative rate: 83 %). However, these results should be interpreted cautiously because the offline analysis used data from both the command-following and communication sessions to determine the presence of command-following.

A study by Lulé et al. used a four-choice auditory-based paradigm for communication with three VS/UWS, 13 MCS, and two LIS patients (Lulé et al. 2013). After a command-following training phase (four runs of counting "yes" or "no's"), each patient was asked to communicate by answering 10 questions (counting "yes" or "no's" depending on the answer). When using the system online, no patient could achieve performances allowing communication (>70 % accuracy (Kubler and Birbaumer 2008)). When the data were analyzed offline, one LIS patient reached 79 % accuracy. Out of six patients showing command-following at bedside (four MCS, two LIS), five could not be detected with the system (false-negative rate: 83 %). However, these results should be interpreted cautiously because the offline analysis used data from both the command-following *and* communication sessions to determine the presence of command-following.

Pokorny et al. tested a different auditory P3-based paradigm based on tone stream

segregation allowing for binary decisions in 12 patients (10 MCS, one VS/UWS, one emerging MCS[1]). Two tone streams with infrequently and randomly appearing deviant tones were presented to the patient. This paradigm is suggested to be simpler than the previous ones as only two classes of stimulation are used. The patients were asked to count the number of deviants in one stream and thus modulate the P3 response in the attended stream. Only five patients could achieve results above chance level, and none of them achieved performances allowing communication with the system. In addition, response to command could be detected in nine patients after averaging all the responses obtained, although in two of them the response duration was very short (between 30 and 60 ms). Finally, out of three patients showing response to command at bedside (two MCS, one emerging MCS[1]), two could be detected with this paradigm. Note that command-following in the emerging MCS patient could not be detected with BCI. It is important to highlight that this paradigm was first used in healthy controls and had to be adapted to be usable with patients with DOC, reflecting the difficulty of applying a BCI paradigm efficient in non-neurologically impaired samples to brain-injured patients. Modifications to the paradigm included using fewer electrodes, adding a simple paradigm to habituate the patient to the task and to test the presence of a P3 response, using blocks of five consecutive trials with the same target stream instead of a randomized order to decrease the cognitive load, and adding additional auditorily presented instructions at the beginning of each run (Pokorny et al. 2013).

Finally, extensive research on attention involving healthy subjects has suggested that the P3 response should be deconstructed into separable subcomponents represented by the P3a and P3b. The relatively early frontally centered novelty P3a is thought to reflect exogenous attention, triggered by "bottom-up" stimulus novelty that may be task irrelevant. The later, parietally focused target P3b, on the other hand, is seen as a marker of "top-down" or volitional engagement of endogenous attention to task-relevant targets to be consolidated into working memory and made available for conscious access (Polich 2007). Based on this idea, Chennu et al. (2013) used a task designed to engender exogenous or endogenous attention, indexed by the P3a and P3b components, respectively, in response to a pair of word stimuli presented auditorily among distracters. They included 21 patients (nine VS/UWS; 12 MCS). Among these patients, three of them (MCS) generated only early non-discriminative responses to targets, suggesting that involuntary bottom-up attentional orienting might be preserved in a greater proportion of patients. In addition, one patient in VS/UWS generated a P3a as well as a P3b response, suggesting a preserved "top-down" or volitional engagement of endogenous attention. Out of the seven patients showing command-following at bedside, none of them generated a P3b (false-negative rate: 100 %), and only two of them showed a P3a (false-negative rate: 71 %). Interestingly, 20 of these patients were also administered the fMRI paradigm developed by Owen et al. (Owen et al. 2006; Monti et al. 2010). In six patients in whom a discernible P3a/P3b response could be elicited, a response to command using fMRI tennis imagery task could be detected. This discrepancy may be explained by vigilance fluctuation, as the paradigms were completed at different times. These results also suggest that the level of difficulty required by this attention task is too high to enable a good rate of detection of conscious patients. However, the VS/UWS patient who showed P3a/P3b responses did also show a response to command with the fMRI, supporting that the presence of a P3a and P3b may highlight a preserved volitional attention process.

11.4 Systems to Detect Response to Command at Bedside

BCI research has classically focused on systems using sophisticated EEG or fMRI techniques, which may be practical for clinical diagnosis, but

[1] Based on CRS-R data obtained from Pokorny et al. Note that for four patients, subscales scores were not available, preventing the current analysis in terms of false negatives.

become challenging in daily use. For this reason, other tools have also been developed and tested in patients with DOC to detect motor-independent response to command at bedside.

Bekinschtein et al. studied 10 patients with DOC (eight VS/UWS, two MCS) using electromyography (EMG; recording of muscle activity) (Bekinschtein et al. 2008). They auditorily presented four different 30 s blocks of commands to the patient: "Please try to move your right hand" and "Please try to move your left hand." At the end of the block, the instruction was "Please do not move, stay still." Two control auditory phrases were used: "Today is a sunny day" and "It is raining outside today." They reported that one VS/UWS patient and both MCS patients demonstrated an increased EMG signal specifically linked to the command, suggesting that electromyography could be used to objectively detect residual motor responses in this population. One MCS patient could follow command at bedside and showed increased EMG activity with the system.

Stoll et al. (2013) investigated the applicability of an alternative physiological signal, the pupil dilation, that can be readily and noninvasively measured with robust, inexpensive, easy-to-use equipment, to communicate with motor-disabled patients and patients with DOC. Pupil dilation has been related to a variety of cognitive functions and is a response that could be used to circumvent the challenges associated with the practical use of traditional BCI approaches. Twelve LIS patients (seven typical LIS and four severely brain-injured LIS with supratentorial lesions) and one MCS patient were included in the study. They reported that three out of seven LIS patients showed significantly higher performances than chance when answering yes-no questions using pupil dilation. However, none of the severely brain-injured LIS patients reached significance. Interestingly, they also used pupil response to detect command-following in one MCS patient following command at bedside. In this study, nine out of 12 patients could communicate at bedside, but could not use the system (false-negative rate: 69 %).

Although preliminary results suggest that these tools may provide simpler bedside methods of detecting command-following and communication with the potential to assist the clinician and improve the accuracy of diagnosis, some limitations prevent their use in patients with DOC. First, EMG still necessitates the preservation of some residual voluntary muscle activity which would prevent its use in patients with severe paralysis or chronic spasticity. Second, pupil response can be altered by the use of centrally acting drugs. Finally, as in fMRI and EEG, restlessness can lead to non-interpretable results. However, future studies should start using these alternative systems in conjunction with EEG and/or fMRI to investigate the integrity of cognitive function in this population.

11.5 Guidelines for Future Research

The high false-negative rate achieved with current BCIs highlights the need to develop more accurate paraclinical diagnostic tools for the DOC population (see Table 11.1). Indeed, a system that is not sensitive to detecting patients diagnosed as conscious at the bedside could not be reliably used in patients with unclear diagnoses. Similarly, a system which is very sensitive and detects signs of consciousness in all patients behaviorally diagnosed as conscious but also a majority of unconscious patients would not be specific enough to be reliable for clinicians. Currently, research on BCI in patients with DOC will have to overcome a number of challenges:

1. Brain-injured patients are likely to present arousal fluctuation, fatigue, and limited attention span, especially in MCS (Giacino et al. 2002). For this reason, paradigm complexity (stimulus, instructions) and duration are important factors to consider when evaluating BCI applications. Moreover, multiple repetitions of the BCI session must be considered to ensure a reliable diagnosis and account for fluctuation. In terms of communication, evaluation should be assessed with simple questions as severely brain-damaged patients may have difficulty giving accurate answers to

trivial yes/no questions (Nakase-Richardson et al. 2009).

2. Brain injury can be associated with sensory deficits (such as cortical deafness, blindness, or oculomotor impairments (Lew et al. 2009; Alvarez et al. 2012; Pogoda et al. 2012; Rowe et al. 2013)). While BCI research in healthy participants seems to highlight better performance with a visual as compared to auditory or tactile BCIs (Kubler et al. 2009; Halder et al. 2010; Pham et al. 2005), the key challenge here will be to develop reliable systems offering stimuli, instruction, and/or question presentation through multiple domains. A recent study reporting the applicability of a vibrotactile P3-based BCI in LIS patients might enable us to provide systems using a wider range of modalities taking into account various sensory deficits (Lugo et al. 2014).
3. A certain amount of cerebral reorganization and neuroplasticity might occur in several cases resulting in the recruitment of other brain areas during the performance of a given cognitive task, limiting a direct comparison with results observed in healthy controls (Chennu et al. 2013; Nam et al. 2012). In addition, future studies should take into account the topographic and latency variability observed in healthy subjects to interpret patients' data (Kaufmann et al. 2011; Bianchi et al. 2010).
4. Suboptimal data quality due to movement, ocular, and respiration artifacts in these challenging populations may also be confounding factors that need to be overcome with the assistance of appropriate statistical analyses. It also needs to be pointed out is that, in EEG, the classification accuracy achieved with a BCI naturally depends on the quality and inter-trial consistency of the data used to train the classifier (Goldfine et al. 2011, 2013; Cruse et al. 2013). This is problematic for most patients with DOC, particularly those in MCS, who are prone to frequent and prolonged bouts of fatigue and fluctuation of vigilance preventing them from paying attention for sufficiently long periods. For many patients, this limitation will adversely affect the classification results (e.g., dependency). It is therefore important to design protocols accordingly (i.e., avoid using blocks of the same stimulation and long-lasting sessions; assess the patient at different time periods (Cruse et al. 2013; Goldfine et al. 2013)), in order to decrease the number of false negatives. In addition, this will help us to take care of the false positives (patients detected as "responders" with the system who are actually unconscious (Goldfine et al. 2013)).
5. The success of active paradigms relies on the patient's willingness to do the task, which might be decreased in case of loss of motivation (Nijboer et al. 2010; Kleih et al. 2010) or akinetic mutism (Giacino 1997; Royal College of Physicians, 1996). These factors must be considered with care as we cannot distinguish a patient lacking motivation to do the task from one who is unconscious.
6. Finally, negative findings should be interpreted cautiously, as significant variability in brain responses are observed in control subjects. For example, some healthy participants lack expected ERP and fMRI responses (Lulé et al. 2013; Guger et al. 2003, 2009; Logie et al. 2011; Cui et al. 2007).

Among the different designs developed in healthy controls and tested in DOC, motor imagery BCIs are relatively less hindered by problems of stimulation modality. There is relatively little stimulation that needs to be presented, and this can be effectively delivered with sounds. Studies on their use in some patients with DOC have produced promising results (Monti et al. 2010; Goldfine et al. 2011). This knowledge, along with the fact that motor imagery (e.g., playing tennis vs. spatial navigation imagery) in fMRI has already allowed a patient to communicate when he was unable to do so at bedside (Monti et al. 2010), bodes well for similar BCI paradigms. However, motor imagery usually requires training of the participant before reliable performance can be achieved, which poses a significant challenge in a population of DOC, as illustrated by the high rate of false negatives achieved in previous studies on imagery tasks (Monti et al. 2010; Goldfine et al. 2011; Cruse et al. 2012a). A recent study suggested that imagery of complex

and familiar actions may result in EEG responses that are more reliably classified as compared with simpler or unfamiliar actions in healthy volunteers (Gibson et al. 2014). Tailoring those paradigms to the patient's previous habits may help increase the sensitivity of these systems.

In this context, P3-based BCI designs could also be of interest since they rely on "automatic" responses of the brain to salient stimuli and hence require relatively little explicit user training. As highlighted earlier, previous findings by Schnakers et al. (2008a), Chennu et al.(2013), Monti et al. (Monti et al. 2009), and Naci and Owen (2013) have shown that some patients with DOC can generate consistent changes in EEG and fMRI when asked to selectively attend to task-relevant stimuli. Moreover, the P3 paradigm seems to be the most sensitive in terms of false-negative rates as compared to the other designs studied recently (see Table 11.1). Eventually, if successful with a patient, a P3-based BCI for spelling words and sentences using a predictive language support program could provide a true, multiclass system with relatively high efficiency. Moreover, a study using a visual P3 in healthy subjects has reported that 89 % of the participants were able to use the system with an accuracy between 80 and 100 % (Guger et al. 2009), as compared to another study showing only 20 % of the users achieving those performances with motor imagery-based BCI (Guger et al. 2003). Since we know that the most successful P3-based BCI is visually based, it may also be possible to adapt a visually based BCI for patients with eye control disabilities using individually presented rather than presenting multiple stimuli on the same screen. This approach has been successfully tested in LIS by Hoffman et al. (2008), but has not yet been applied in DOC.

Other kind of BCIs were only studied in healthy controls and LIS but can be of interest for patients with DOC. Steady-state visually evoked potentials (SSVEPs; (Vialatte et al. 2010; Regan 1989)) are the oscillatory electrical responses of neurons in the visual cortex to stimuli that are repeatedly presented (or flashed) at frequencies above 6 Hz. SSVEPs are easy to detect, as their frequency content is completely determined by the visual stimuli used to elicit them. The advantage of this response is that it has a high signal-to-noise ratio and EMG artifacts (Regan 1966; Gray et al. 2003). However, systems developed and successfully tested in healthy subjects and motor-disabled patients (Combaz et al. 2013; Parini et al. 2009) are highly dependent on eye motor control movement, which may prevent its use in patients with DOC. An alternative approach based on covert attention will therefore need to be tested in DOC (Lesenfants et al. 2011).

Finally, Birbaumer and colleagues (Birbaumer et al. 1999, 2000; Elbert et al. 1980) have worked on the development of slow cortical potentials-based BCIs (SCPs). SCPs are slow voltage changes generated in the cortex that occur over periods of 0.5–10.0 s. Usually, negative SCPs are associated with motor movement and other functions involving increased cortical activation, while positive SCPs are associated with reduced cortical activation (Birbaumer 1997). This system has been tested in patients with late-stage amyotrophic lateral sclerosis and has been shown to be capable of providing basic communication capacities (Kubler et al. 1999). However, the main problem is again that the most successful system uses visually based feedback (Pham et al. 2005; Birbaumer et al. 2000), and a relatively long period of training is needed (Birbaumer 2006). On the other hand, SCPs have the advantage of being the most stable over long periods (Chatelle et al. 2012).

Altogether, BCI applications may offer many possibilities for patients with DOC, but further work must be done before BCI can be used as a supplemental tool to the current behavioral "gold standard" for assessment of consciousness. We think that an extensive collaborative project between researchers, including data sharing to enable comparison between paradigms, analyses, and patient's demographic and clinical data is needed to efficiently answer the issues highlighted here. In addition, studies will need to focus not only on the decrease of false negatives, but also on the decrease of false positives in order to develop reliable tools for clinicians.

In the future, BCI could help us detect cognitive impairment at an early stage, using a binary

communication code (Schnakers et al. 2008b) with such systems (Müller-Putz et al. 2013), and guide rehabilitation programs accordingly. In addition, BCI could also be used for motor rehabilitation in patients with DOC, as previous literature has suggested that motor imagery training could induce a modification of cortical activity in healthy volunteers and stroke patients ((Pichiorri et al. 2011; Page et al. 2009; Santos-Couto-Paz et al. 2013; Dickstein et al. 2014) for a review, see (Teo and Chew 2014)). In addition, studies have shown its interest to help in the recovery of motor function of the paralyzed limb in stroke patients (Jackson et al. 2001; Prasad et al. 2010; Page et al. 2007) as well as in patients with traumatic etiology (Sacco et al. 2011; Oostra et al. 2012). Given evidence that injured brain regions retain the ability to generate motor imagery of actions they cannot perform (Cruse et al. 2011; Owen et al. 2006; Monti et al. 2010; Goldfine et al. 2011; Cruse et al. 2012a), motor imagery-based BCIs could be an ideal candidate for early motor rehabilitation (Bruno et al. 2011) in patients with severe motor disabilities. However, we will need to investigate whether this is still possible for patients with chronic severe motor disabilities (Birbaumer et al. 2012).

Finally, it is important to note that, in order to use any of the paradigms presented above, the patient needs to be able to understand the task requirements, and therefore we need to be cautious as these systems will not be sensitive to detect patients suffering from language impairments (which is very likely to be the case for many patients, as shown in (Majerus et al. 2009)). In that case, language-independent paradigms will be needed (e.g., (Casali et al. 2013; Phillips et al. 2011; Malinowska et al. 2013; Faugeras et al. 2011; King et al. 2013) for a review, see (Boly and Seth 2012)).

11.6 Conclusion

In this chapter, we reviewed the current stage of the development of BCI and other alternative tools for the diagnosis of patients with DOC. We highlighted the great impact that these systems could have on rehabilitation strategies, quality of life, and prognosis. Currently, results obtained in patients with DOC will need to be interpreted with caution. Indeed, results from these studies show that the likelihood that a covertly aware patient might go undetected (i.e., the false-negative rate) is likely to vary significantly across different paradigms. In addition, the suitability of different BCI designs for single patients is variable and will need to be assessed on a case-by-case basis. While some patients have been shown to be able to generate reliable P3 responses to task-relevant stimuli, others have demonstrated the ability to consistently perform mental imagery in response to command. Hence, none of these tests applied individually to look for command-following can currently be used to interpret negative results, without combining findings from multiple testing methods to mitigate against the level of uncertainty. Similarly, we think that positive findings should not be taken as clear evidence of consciousness but should rather be used as an opportunity to discuss clinical findings.

Future research will need to overcome several challenges limiting current BCI application in DOC in order to provide more reliable tools for diagnosis. Studies on BCIs in healthy participants could be used as a basis for the development of new paradigms, but there is a need to conduct extensive testing with patients likely to benefit from various BCI systems in their daily lives (Kubler et al. 2006), since we know that often results from controls do not generalize well to patient groups (Pokorny et al. 2013; Hill et al. 2006). Alternative systems such as EMG or pupil dilation might also be of interest especially in the development of easy-to-use systems for caregivers.

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Imaging Correlations in Non-communicating Patients

12

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Contents

Abstract

The diagnosis and medical management of patients with acute or chronic disorders of consciousness (DOC) are challenging. Motor-independent functional neuroimaging technologies are increasingly employed to study covert cognitive processes in the absence of behavioural reports. Studies with functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) performed in this patient population have utilized active, passive and resting-state paradigms. Active paradigms refer to mental imagery tasks that measure wilful modulation of brain signal in specific brain areas, aiming to detect command-following. Passive paradigms are used to measure brain responses to external sensory stimulation (e.g. auditory, somatosensory and visual). Alternatively, in resting-state paradigms, spontaneous brain function is assessed while subjects receive no external stimulation and are instructed to let their mind wander. Independently from each other, these methods have shown differences between healthy controls and patients, as well as among patients with DOC. However, these techniques cannot yet be used in clinical settings before robust information at the single-subject level will be provided: it is expected that multimodal research will improve the single-patient diagnosis, shed light on the

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prognostic biomarkers, and eventually promote the medical management of patients with consciousness alterations.

12.1 Introduction

In the 1950s the intensive care unit welcomed the mechanical ventilator, which allowed patients to sustain heart function and systemic circulation after traumatic and non-traumatic brain injuries. Ever since, some of the surviving patients were found to suffer from altered states of consciousness that were never encountered before. Patients could now lie in a coma for hours to weeks with eyes closed and were hence considered unaware of the surroundings and of themselves. In cases where they opened their eyes but remained unresponsive to any external stimulation, they were considered to be in a vegetative state (VS; Jennett and Plum 1972) or, as most recently coined, unresponsive wakefulness syndrome (UWS; Laureys et al. 2010). It was only in 2002 that the medical community recognized another entity which characterized patients showing signs of fluctuating yet reproducible remnants of nonreflexive behaviour; these patients were said to be in a minimal conscious state (MCS; Giacino et al. 2002).

The diagnosis and medical management of patients with acute or chronic disorders of consciousness (DOC) are challenging, mainly because these patients are unable to communicate. For example, pain[1] in patients with DOC can only be inferred through behavioural observation (Schnakers et al. 2012). Interestingly, such observations are not unanimous among clinicians. As evident by a recent survey, more than half of medical doctors (56 %) thought that patients in a VS/UWS feel pain (Demertzi et al. 2009), despite official criteria denouncing such experience from these patients (The Multi-Society Task Force on PVS 1994). Similarly, clinicians' opinions differed when more ethically challenging issues were concerned, such as the limitation of life-sustaining therapies. Indeed, clinicians appeared more reluctant to withdraw treatment from patients in MCS (28 % agreed) than from those in UWS (66 % agreed) (Demertzi et al. 2011). The agreement with withdrawal of life-sustaining treatment in patients in a UWS is also supported by others (Kuehlmeyer et al. 2012). Taken together, these studies show that the medical management of pain as well as discussions regarding end-of-life decisions is highly influenced by the diagnostic category. As such, the need for valid and sensitive tools to improve accurate diagnosis of patients with DOC is increasing. To date, diagnostic assessment is mainly based on observing motor and oro-motor behaviours at the bedside. As these assessments are prone to false-negative diagnosis (Schnakers et al. 2009), motor-independent neuroimaging technologies may aid the search for residual cognitive function of non-communicating patients.

12.2 Neuroimaging Can Aid Diagnosis

Functional neuroimaging methods have offered the possibility to objectively study cognitive processing in the absence of behavioural reports. Functional magnetic resonance imaging (fMRI) quantifies brain function derived from blood-oxygen-level-dependent (BOLD) changes. Position emission tomography (PET) measures different aspects of metabolic function according to the type of the administered radioactive tracer. The structural properties of the brain can also be revealed by means of anatomical MRI, while diffusion tensor imaging (DTI) measures white matter integrity. Below we will refer to experimental paradigms that have been most frequently adopted to infer covert cognitive abilities in non-communicating patients suffering from DOC (Fig. 12.1).

12.2.1 Active Paradigms

Active paradigms refer to mental imagery tasks which measure wilful modulation of brain signal in specific brain areas, aiming to detect command-

[1] The unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (Loeser and Treede 2008).

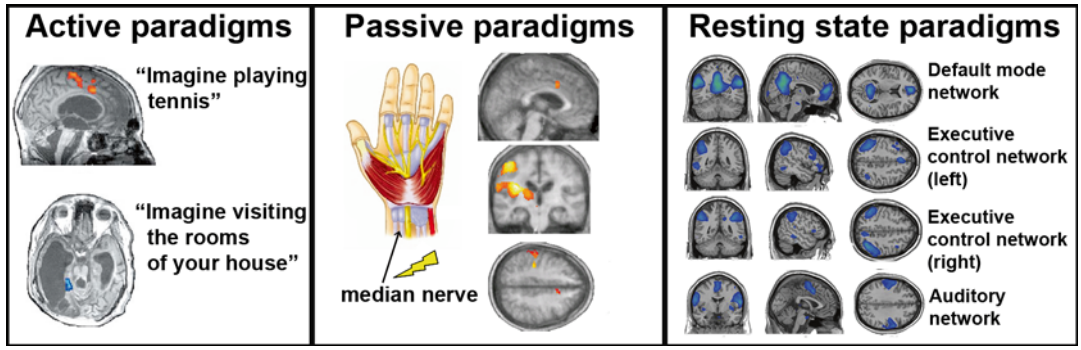

Fig. 12.1 Neuroimaging paradigms in assessment of residual cognitive processes in DOC

following. Command-following in patients with DOC is of major clinical importance because, according to standardized behavioural assessment, this behaviour differentiates patients in MCS from patients in UWS (Bruno et al. 2011b; Giacino et al. 2004). At the bedside, command-following is tested by asking patients to follow simple object-related and the non-object-related commands. Those patients that can follow the commands "consistently"[2] or "reproducibly"[3] are said to be in MCS. In the fMRI environment, two mental imagery tasks have been shown to encompass reproducible cortical activations across healthy controls, namely, thinking about playing tennis (encompassing primarily supplementary motor area) and imagining visiting the rooms of one's house (encompassing primarily parahippocampal cortex; Fig. 12.1, left panel) (Boly et al. 2007). When this paradigm was employed in a behaviourally unresponsive patient, her brain activity was indistinguishable from healthy controls. Since this patient was able to comprehend and execute the mental imagery commands in a sustainable manner, the behavioural diagnosis was challenged, and the patient was no longer considered as in UWS (Owen et al. 2006). In a larger cohort ($n=54$) of patients with DOC, the same paradigm confirmed that not all behaviourally assessed VS/UWS patients were unresponsive (Monti et al. 2010). Indeed, command-following was observed in five patients, two of whom showed no signs of awareness when evaluated behaviourally. Interestingly, one patient was able to further use this technique to provide yes/no responses to autobiographical questions which could not be elicited at the bedside. Based on the command-following rationale, other mental tasks for evidencing response to command in patients with DOC have been employed. For example, with a silent picture-naming task, complete and partial preservation of the object-naming brain network was observed for all patients in MCS and two in VS/UWS (Rodriguez Moreno et al. 2010). By instructing patients in VS/UWS to move their hand, voluntary behaviour was also evidenced for two patients who activated premotor cortex (consistent with movement preparation) in the absence of overt muscle activity (Bekinschtein et al. 2011). Similarly, using selective auditory attention, all 3 assessed patients (2 MCS and 1 VS/UWS) were able to convey their ability to follow commands, and 2 of them (1 MCS and VS/UWS) were even able to use attention to correctly communicate answers to several binary questions (Naci and Owen 2013). Residual cognitive capacities in patients DOC has also been assessed using a hierarchical fMRI approach, starting from command-following tasks similar to those described above, to question tasks using binary choice responses and eventually multiple choice responses (Bardin et al. 2011).

[2] When the patient follows both object-related and non-object-related commands in all eight administered trials (i.e. four trials per command).

[3] When the patient shows three clearly discernible responses over the four trials on any one of the object-related or non-object-related commands.

A criticism of using mental imagery tasks to unfold cognition and/or to communicate relies on patients' limited short-term memory resources and restricted attention span. As a result, relatively long scanning intervals might be necessary to increase the signal-to-noise ratio, which in turn contributes in patients' fatigue and ultimately in lack of their vigilance (Naci et al. 2013). Additionally, patients may suffer from other cognitive (i.e. aphasia, apraxia) and sensory impairments (i.e. blindness, deafness), from small or easily exhausted motor activity, pain, sedative medication, sleep disturbances and/or medical complications (such as infections), which can interfere with the direct assessment of command-following. In these cases, however, absence of responsiveness does not necessarily correspond to absence of awareness (Sanders et al. 2012). Alternatively, residual cognitive function in patients with DOC has been further assessed by means of passive and resting-state paradigms which overcome the above-mentioned limitations.

12.2.2 Passive Paradigms

Passive paradigms measure brain responses to external sensory stimulation (e.g. auditory, somatosensory and visual), while the subject is not performing any mental task. Using PET, the administration of simple auditory clicks in patients in VS/UWS was shown to activate primary auditory cortices (Laureys et al. 2000c), whereas patients in MCS demonstrated more widespread activation in the secondary auditory cortex, as well as temporal and frontal areas (Boly and Faymonville 2004). More recently a difference between patients in VS/UWS and MCS was observed in the impairment of backward connectivity from frontal to temporal cortices, as evidenced by an EEG mismatch negativity paradigm using auditory clicks (Boly et al. 2011) (see also Chap. 9). When more complex auditory stimuli were administered, differential brain responses between patients and controls, as well as between patient groups, were also observed. For example, sentences which were manipulated at different levels of auditory intelligibility[4] and semantic ambiguity[5] were presented to a patient in VS/UWS. The patient presented consistent and similar-to-controls responses in the auditory cortex as a response to intelligible speech stimuli as well as partially intact responses to semantically ambiguous stimuli (Owen and Coleman 2005). Also, in an fMRI task of passive listening to narratives played forward and backward, one patient in VS/UWS (out of three) and one patient in MCS (out of four) showed cerebral responses very similar to healthy controls (Fernández-Espejo et al. 2008). Another salient auditory stimulus which has been preferred because of its attention-grabbing properties is the patient's own name. With the own-name paradigm, it was shown that one patient in VS/UWS exhibited activation in medial prefrontal cortex, left temporoparietal and superior frontal cortex, which is again similar to activation observed in controls (Staffen et al. 2006). With a similar own-name paradigm, two out of seven patients in VS/UWS and all four patients in MCS showed activation not only in the primary auditory cortex but also in higher-order associative temporal areas, which are thought to be implicated in the conscious processing of the incoming stimuli. Interestingly, these two patients in VS/UWS subsequently recovered to MCS as observed 3 months after their fMRI scan, highlighting the prognostic value of this paradigm (Di et al. 2007). This prognostic utility was further supported by data of seven out of eight patients in VS/UWS who progressed to MCS and showed speech-specific or semantic responses to sentence stimuli 6 months earlier in their fMRI assessment (Coleman et al. 2009).

In the somatosensory modality, painful electrical stimulation of the median nerve of the wrist encompassed the entire "pain matrix" (including the anterior cingulate cortex and insular areas; Fig. 12.1, middle panel) in patients in MCS. On the other hand, patients in VS/UWS

[4] Speech in noise was used as a form for distortion by adding a continuous pink-noise background to sentences.

[5] Sentences containing at least two ambiguous words, either homonyms or homophones.

showed restricted activation to lower-level subcortical and primary cortical areas (Boly et al. 2008; Laureys et al. 2002), indicating that MCS patients are more likely to experience the administered stimuli as painful.

In the visual modality, when pictures of different emotional valences were presented to patients in MCS by means of fMRI, visual activation similar to healthy controls was found for patients (Zhu et al. 2009). A more recent case study on visual cognition used a battery of tests in a MCS patient. Specifically, the battery first assessed passive visual processing whereas, at the final level, it assessed the ability to voluntarily switch visual attention though the focus on competing stimuli. This approach revealed appropriate brain activations, undistinguishable from those seen in healthy and aware volunteers suggesting that the patient retained the ability to access his own visual representations (Monti et al. 2013).

Taken together, the rationale behind passive experimental paradigms is that an indistinguishable response between patients and controls is indicative of covertly preserved cognitive processing in these patients (Owen 2013). Generally, these paradigms have shown that auditory, visual and somatosensory activation is restricted to lower-level sensory regions in patients in VS/UWS, while brain activation is widespread in MCS reaching higher-level associative areas. The limitations of using this approach stem from patients' pathologies and technical requirements. Indeed, patients can present variant clinical picture, ranging from visual problems, motor spasticity, somatosensory hypersensitivity and cortical auditory deafness, which can prevent the administration of external stimuli. Also, the technical setup of these examinations are not always straightforward, and therefore cannot be widely used across medical and research institutions.

12.2.3 Resting-State Paradigms

Alternatively, increasing attention is being paid to resting-state paradigms (Soddu et al. 2011). In these paradigms, spontaneous brain function is assessed while subjects receive no external stimulation and are instructed to let their mind wander. As such, this approach surpasses the limitations which are raised by the other two types of experimental tasks.

Using PET at rest, it was shown that patients in VS/UWS exhibit decreased brain metabolism up to 40 % of normal value (Laureys et al. 2000b; Tommasino et al. 1995). Nevertheless, recovery from the VS/UWS does not coincide with the resumption of global metabolic levels. It rather seems that some areas are more critical to consciousness than others. Indeed, patients suffering from DOC show decreased metabolism in a widespread network encompassing frontoparietal areas, such as lateral prefrontal and posterior parietal regions as well as midline anterior cingulate/mesiofrontal and posterior cingulate/precuneal associative cortices (Nakayama et al. 2006; Silva et al. 2010). Importantly, recovery from the VS/UWS parallels the restoration of connectivity in these areas (cortico-cortical) but also between these regions and the thalamus (thalamo-cortical) (Laureys et al. 2000a, 1999). More recently, it was shown that patients in MCS retain metabolism in the lateral frontoparietal areas, whereas midline regions are highly dysfunctional (Thibaut et al. 2012). Broadly speaking, the midline cortices are assumed to mediate self-related cognition, whereas frontoparietal cortices are thought to mediate awareness of the environment (for a short review, see Demertzi et al. 2013a). As such, these data suggest that patients in MCS are characterized by altered self-awareness besides their abilities to, at least to a certain extent, interact (but not communicate) with their surroundings.

In fMRI, the resting-state network approach has been used lately to quantify various higher-order and sensory-related systems (Damoiseaux et al. 2006; Laird et al. 2011; Smith et al. 2009). These networks show differential connectivity alterations under different states of unconsciousness (Heine et al. 2012), highlighting their importance when assessing consciousness levels. In a recent investigation of fMRI resting-state connectivity in patients with DOC, it was found that, among the long-range systems, the default mode network (DMN, which encompasses precuneus,

medial prefrontal cortex and bilateral temporoparietal junctions) and bilateral executive control or frontoparietal networks were severely disturbed in patients with DOC (Fig. 12.1, right panel) (Demertzi et al. in press). This implies that these systems might be important to sustain consciousness-related processes. Interestingly, it has been found that the resting brain is characterized by a switch between the dominance of the DMN (linked to "internal" or self-awareness) and the bilateral frontoparietal network (linked to "external" or environmental awareness; Fox et al. 2005; Fransson 2005). More recently, it was found that such alternating pattern not only happens spontaneously in the brain but also has a behavioural counterpart. In other words, behavioural reports of "internal awareness" were linked to the activity of the DMN, whereas subjective ratings for "external awareness" seem to correlate with the activity of lateral fronto-parieto-temporal regions (Vanhaudenhuyse et al. 2010), which are part of the so-called executive control network, exhibiting increase of activity during attention-demanding cognitive tasks. These findings imply that the anti-correlated pattern between the internal (DMN) and external (executive control network) awareness systems is of functional relevance to the phenomenological complexity of subjectivity (Demertzi et al. 2013b). This assumption is further supported by evidence from patients who show severely disrupted connectivity in one or both systems. For instance, in a brain dead patient, functional connectivity of the DMN was absent (Boly et al. 2009), whereas in patients with DOC, albeit preserved, functional connectivity of the DMN showed consciousness level-dependent decreases (Soddu et al. 2012; Vanhaudenhuyse et al. 2010).

Next to the investigation of reduced connectivity, the presence of pattern of hyper-connectivity might also be informative of patients' brain function. Indeed, it was recently showed that the subcortical limbic system (including the orbitofrontal cortex, insula, hypothalamus, and the ventral tegmental area) exhibits paradoxically increased fMRI connectivity with the DMN in patients with DOC (Di Perri et al. 2013). These results were considered as suggestive of a persistent engagement of residual neural activity in self-reinforcing neural loops, which, in turn, could disrupt normal patterns of connectivity in patients.

12.3 Conclusions

Functional neuroimaging has been employed to test imaging correlations in patients not able to communicate as a result of severe brain damage. Nevertheless, parallel to function, information about the brain's anatomy also sheds light on the differential neuropathology of patients with DOC. For example, recent studies suggest that the structural connectivity assessment by means of DTI is severely disrupted in patients in coma. Specifically, the connections from the brainstem to the thalamus, also known as the ascending arousal system, have been shown to be seriously impaired in patients (Edlow et al. 2012). Although one could expect that patients with such severe structural damage show poor recovery rates, this is not necessarily the case, especially when the assessment of axonal injury is shortly after the accident. For example, structural imaging of a patient suffering from altered states of consciousness 8 weeks after a traumatic accident showed severe damage in the corpus callosum, brainstem and bilateral white matter; nevertheless, 1 year after injury, this patient had regained consciousness and reintegrated in the community (Edlow et al. 2013). In more chronic patients, it has been shown that structural connectivity assessment could correctly classify patients in UWS versus MCS with a 95 % accuracy in a group of 25 patients (Fernández-Espejo et al. 2011). These studies imply that the assessment of structural connectivity is of salient clinical importance especially when it is known that structure is linked to function (Sui et al. 2014). Ideally, maximal information about patients' clinical picture can be obtained by combining different technologies (Bruno et al. 2011a; Gantner et al. 2013); the use of functional imaging together with electroencephalography is very promising, as recently done with transcranial magnetic stimulation and EEG (TMS/

EEG; Casali et al. 2013; Rosanova et al. 2012) (see also Chap. 10). Multimodal assessment of patients using the aforementioned neuroimaging methods is expected to bring us closer to patient-specific underlying neuropathology, which in turn could aid diagnosis and prognosis (Bruno et al. 2011a).

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