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Summary

The role of EEG in the context of prognostication in patients with acute disorders of consciousness in the intensive care unit has expanded over the last decades, in parallel with technical developments and refinements. This article will review the most common EEG patterns, and outline their prognostic implications. Then, several diagnostic categories will be analyzed regarding the prognostic role of the EEG. Finally, a brief overview will be offered on the most recent approaches, such as intracranial EEG or automated EEG interpretations. While the EEG is clearly and robustly established in the process of prognostication, its role is still that of a marker, rather than truly representing a tool generating therapeutic implications.

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Key words: reactivity, burst-suppression, triphasic waves, PLEDs, alpha coma, spindle coma, FIRDA, rhythmic delta activity, SIRPIDs, sleep, seizures, status epilepticus

Die Rolle des EEGs bei der Prognose von Patienten auf der Intensivpflegestation

Die Rolle des EEGs für die Prognose von Patienten mit Bewusstseinsstörungen auf der IPS hat in den letzten Jahrzehnten ein zunehmendes Interesse erfahren, das mit bedeutenden technischen Entwicklungen und Verbesserungen einhergegangen ist. Dieser Artikel wird die gängigen EEG-Charakteristika und ihre prognostischen Bedeutungen in diesem Zusammenhang erwähnen. In einem zweiten Schritt werden verschiedene klinische Diagnosen in Zusammenhang mit EEG-Aspekten diskutiert. Eine Übersicht über die neuesten Entwicklungen, inklusive intrakranielles EEG oder automatische Analysen, wird das Ganze abschliessen. Das EEG ist weit und breit für seine prognostische Bedeutung bei komatösen und stuporösen Patienten anerkannt, jedoch bleibt seine Rolle bisher eher diejenige eines prognostischen Markers als eines Werkzeugs, welches unmittelbare therapeutische Schlussfolgerungen generiert.

Schlüsselwörter: Reaktivität, burst-suppression, triphasische Wellen, PLEDs, alpha-Koma, Spindelkoma, FIRDA, Status epilepticus

Le rôle de l'EEG dans le pronostic des malades aux soins intensifs

Le rôle de l'EEG dans le pronostic auprès de patients ayant des troubles de la vigilance dans des soins intensifs a vécu une expansion remarquable au cours des dernières décennies, en même temps que les améliorations techniques. Cette contribution discutera des patrons EEG les plus importants dans ce contexte clinique, avant d'aborder des situations cliniques particulières à la lumière de la littérature EEG concernée. Finalement, un aperçu des développements les plus récents, tels que l'interprétation automatisée ou les enregistrements intracrâniens, sera donné. Le rôle de l'EEG est certainement solidement implanté dans les algorithmes de pronostication du patient avec atteinte de la vigilance; cependant, à ce stade, son rôle reste celui d'un marqueur de pronostic, plutôt que d'un outil générant des implications thérapeutiques.

Mots clés : Réactivité, burst-suppression, ondes triphasiques, PLEDs, alpha coma, spindle coma, FIRDA, état de mal

Background: some history

In parallel to the increasing use of the EEG for clinical purposes since the 1930s, electroencephalographers started unraveling changes occurring in physiological sleep and pathological consciousness impairment. After almost a century, this field still experiences a dynamic evolution. A brief overview of the most important classification systems will illustrate some approaches and the related terminology.

We owe Hockaday and her colleagues one of the first thorough descriptions of the alterations found in patients with acute cerebral anoxia [1]. The classification system relies on five grades, with background frequency and amplitude representing the dominant

variables (Table 1); while all patients with grade I and none with grade V survived, the other grades represented a progressive impairment of normal cerebral function. The relevance of background reactivity was added twenty years later. Based on his personal experience, in 1988 Synek refined the prognostic classification for comatose patients after trauma or cerebral anoxia; he also made the observation that the prognostic significance of EEG should be assessed not within a few hours after the beginning of coma [2]. The breakdown into several categories renders the classification very accurate on the one side, but also somewhat unpractical (Table 2); the Hockaday grades are scattered among different prognoses, as is background reactivity. Ten years later, Young proposed an updated system based on their observation of comatose patients (Table 3), and compared it to the Synek classification, finding a higher interobserver agreement [3]. Furthermore, they point-

ed out that *burst-suppression* implies flattening for at least 1 second/20seconds, while Synek did not specify the denominator.

This illustrates the need for more uniformity, in order to allow a general understanding of what is described. Very recently, a common effort of several North American experts has produced a detailed description of the EEG terminology in an intensive care setting [4] (Table 4). 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 (which would not be necessarily labeled as seizures) represent the subject of this classification; the term “epileptiform” was avoided. The first main term is related to the spatial distribution, the second to describe the type of discharges; to qualify, the discharges should recur at least 6 times. Then, modifiers appear, such as prevalence

Table 1: The Hockaday prognostic classification of EEG changes in postanoxic patients (modified after [1]).

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

Table 2: The Synek prognostic classification of EEG changes in postanoxic and brain trauma patients (modified after [2]).

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 μ V δ activity)
	V	Isoelectric EEG

Table 3: The Young prognostic classification of EEG changes in postanoxic and brain trauma patients (modified after [3]).

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

Table 4: Older EEG terms and the newer terms after the standardized critical care EEG terminology proposed by the American Clinical Neurophysiology Society (modified after [4]).

Older Terms	Newer terms
PLEDs (periodic lateralized epileptiform discharges)	LPDs (lateralized periodic discharges)
PLEDs+	LPDs+
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 with frontal predominance)
SIRPIDs (stimulus-induced rhythmic, periodic, or ictal discharges)	SI- GPDs or RDA or SW (spike waves)
Lateralized seizure, δ frequency	Evolving RDA

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 $<10 \mu$ V, *burst-suppression* that 50 - 99% of the recording is attenuated, and a discontinuous trace is attenuated over 10 - 50%).

Particular patterns in patients with disturbed consciousness

Background slowing and reactivity

In cats, lesions confined to the cerebral cortex lead to attenuation of the alpha background, while subcortical lesions induce polymorphic delta [5]; unsurprisingly, this seems to apply also to humans in the emergency ward or in the intensive care unit (ICU) [6]. The etiologies are extremely broad. The previous paragraphs and **Tables 1 - 3** illustrate well the prognostic correlation of an increasing background slowing; it is however impor-

tant to always perform activation procedures to test the reactivity, including sounds, eye opening, and painful stimulations. It seems reasonable to apply the stimuli on the face or the trunk; furthermore, stimulations should be performed at least 20 - 30 sec. apart. Even on a very slow EEG, a clear reactivity (regardless of either acceleration with amplitude attenuation, or high-voltage slowing) heralds a better prognosis [2, 3, 7 - 9]. Furthermore, with video-EEG recordings, correlation of stimulations with the EEG signal is very easy to assess.

Triphasic waves

These EEG transients owe their appearance in the literature to their observation in patients with hepatic impairment [10]; they are described as sharp deflections with two or three phases, where the second one has the highest amplitude and is surface positive; a phase lag may be observed. These transients, which often can be attenuated along with variation in consciousness, are by no means specific to liver disturbance [11]. They should be considered possibly epileptiform if occurring strictly unilaterally [12]; in this case

they usually do not show any clear reactivity. Of relevance, triphasic waves may be attenuated or abolished by benzodiazepines, their disappearance in this context does therefore not imply any epileptiform nature [13].

Rhythmic delta activity

The eponym is RDA, but these features are also commonly labeled as *frontal intermittent, rhythmic delta activity* (FIRDA, see **Table 4**) because of the frequently observed anterior predominance. This EEG pattern is common, and usually reactive. Symmetric rhythmic delta is not related to epilepsy, and represents an unspecific finding seen in patients with various etiologies [18, 19]. A marked asymmetric appearance may be associated

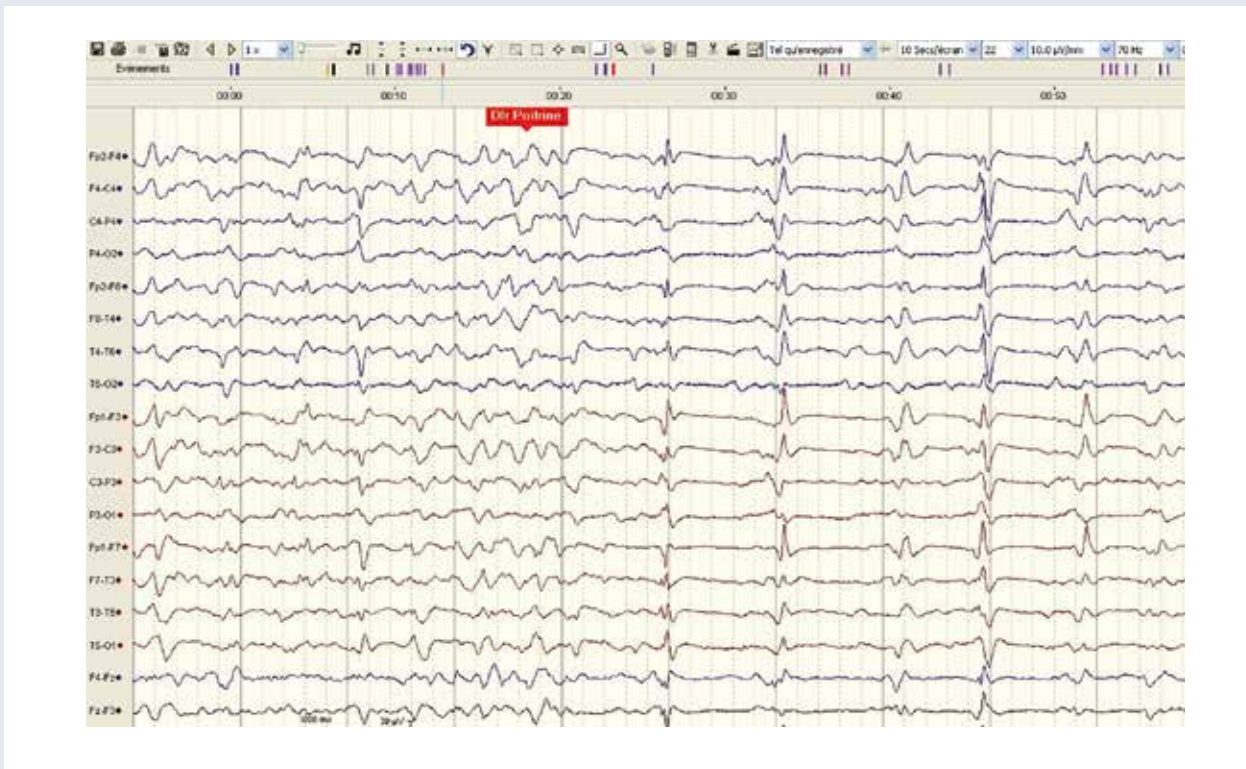


Figure 1: Stimulus-induced rhythmic, periodic, or ictal discharges (SIRPIDs), in this case stimulus-induced generalized periodic discharges (SI-GPD), in a man, during normothermia 36 hours after a cardiac arrest. The painful stimulation is marked in red (longitudinal bipolar montage, 30 mm/sec, 10 μ V/mm).

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 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 [4, 14]. Many etiologies may be responsible, and the impact on prognosis is not uniform: some authors recognize an independent association with poor outcome [15], while others don’t [16, 17].

with an underlying ipsilateral lesion [18]. As compared to triphasic waves and severe, diffuse EEG slowing, FIRDA seems to be related to a better outcome [19]. Recently, occurrence of lateralized rhythmic delta activity has been described, with a prevalence of associated seizures similar to that observed with periodic discharges [20].

Stimulus-induced patterns

The first systematic description of stimulus-induced rhythmic, periodic or ictal discharges (SIRPIDs, see **Table 4** for the last proposed terminology) is recent [21]. These patterns had a prevalence of 22% in the original description of a neuro-ICU cohort, encompassing a broad etiological spectrum (**Figure 1**); as the authors

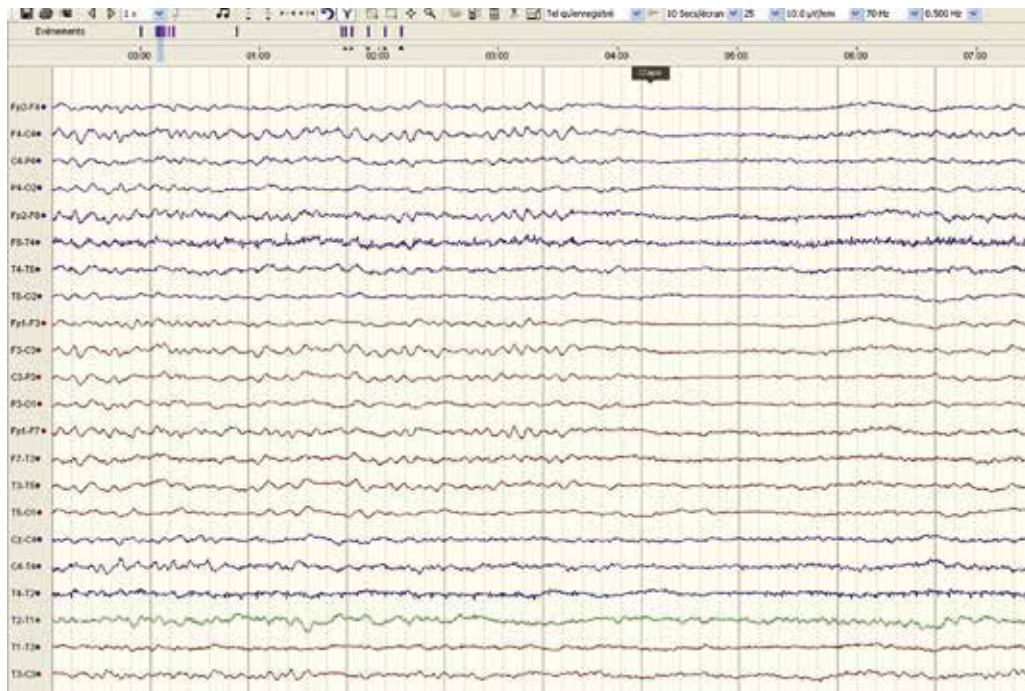


Figure 2: Auditory stimuli (clapping of hands marked in black) induce a diffuse attenuation of the recording in a woman under mild therapeutic hypothermia, 21 hours after a cardiac arrest (bipolar longitudinal montage, 30 mm/sec, 10 μ V/mm).

pointed out, a video-correlation to recognize the stimuli is mandatory. SIRPIDs may represent a heterogeneous EEG reaction that should not be regarded as a normal reactivity. Interestingly, SIRPIDs have received relatively little attention regarding their prognostic significance, but recently, their occurrence in postanoxic patients undergoing hypothermia has been related to poor outcome [22].

Electrographic seizures

Seizures and status epilepticus represent a common challenge for caregivers in the ICU. 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 cardiac arrest, often along with periodic EEG discharges, is linked to poor outcome [23] has been corroborated recently, particularly if seizures appear during cooling and despite pharmacological sedation [8], while prognosis is not invariably catastrophic for patients experiencing seizures after rewarming [24]. In patients with brain trauma, seizures have also been independently associated with mortality [25], and it has been suggested that they aggravate cerebral damage [26]; similar findings also apply for subarachnoid hemorrhage [27], while in subjects with intracranial

hemorrhage they do not seem to independently predict prognosis [28 - 30]. Acute seizures or status epilepticus in patients with ischemic stroke have been reported to be independently related to worse clinical outcome in hospital-based [31], but not in population-based studies [32]; globally their occurrence is limited to about 2% of the patients [33]. Patients with sepsis in the medical ICU are also subject to (mostly nonconvulsive) seizures, which correlate with bad prognosis [15].

Alpha, theta and spindle coma

These EEG patterns are relatively infrequent; mostly observed in comatose patients experiencing a cardiac arrest, they can also be found in subjects with other etiologies [34, 35]. They are mainly defined by the dominant frequency, and by higher amplitude in the frontal regions. Lack of reactivity to stimulations is regarded as characteristic [3, 36], but not by all authors. Alpha and theta coma probably represent a single phenomenon, and are usually seen at the low alpha band (7-8Hz) [37, 38], and a progressive slowing leading to a diffuse EEG attenuation may be observed over some days in patients with poor prognosis. 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 [34, 36]. Spindle coma may reflect the preservation of thalamo-cortical loops following lesions located in the lower diencephalon or brainstem, and therefore a lesser degree of brain dysfunction [35].

Sleep spindles

The occurrence of physiologic sleep patterns in patients with disorders of consciousness has recently been outlined as an important prognostic factor. This is illustrated in patients with consciousness impairment following deep cerebral vein thrombosis involving the thalami and acutely lacking spindles; these return upon resolution of the vasogenic edema [39]. In subjects with severe traumatic brain injury [40, 41] and anoxic-ischemic encephalopathy [41], occurrence of K complexes and sleep spindles correlates with a lesser degree of consciousness impairment. Of note, these studies have been conducted in a rehabilitation setting, up to 150 days after the initial insult [40]; therefore, one should not be automatically infer that the lack of physiologic sleep in the acute setting portends the same dismal prognosis.

Particular clinical situations

In recent years, moderate therapeutic hypothermia has experienced an increasing popularity, mainly in the context of anoxic-ischemic brain injury in neonates and adults. Of interest, it's not until below 30°C that periodic complexes appear on the EEG, the temperature has to lower below 24°C in order to observe diffuse intermittent suppression, and below 18°C for electrocerebral silence [42].

Hypoxic-ischemic encephalopathy: adults

The timing of assessment is critical, as electrophysiological evaluations within 12 hours after the insult may lead to overestimation of the brain damage [36, 43, 44]. In normothermia, patterns of monotonous, diffuse low voltage, or repetitive electric seizures or status epilepticus, as well as periodic discharges without any identifiable background, are considered to herald a poor prognosis [9, 45 - 48]; lack of background reactivity is also a reliable prognosticator [9, 46]. The EEG during therapeutic hypothermia has been recently described to provide valuable prognostic information, not only regarding the continuity of the tracing (an isoelectric recording during hypothermia, 24 hours after the cardiac arrest, is tightly related to non-awakening [49]),

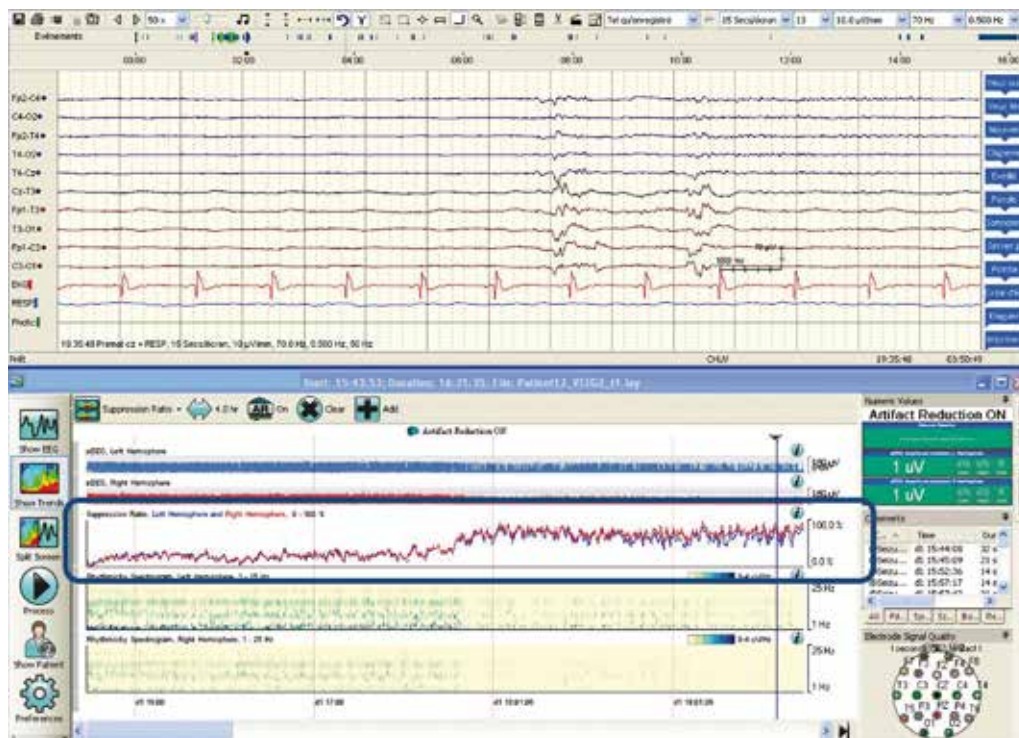


Figure 3: Upper panel: raw EEG of a man under general anesthetic for refractory status epilepticus; the screen represents 15 seconds (bipolar longitudinal montage, 20 mm/sec, 10 μ V/mm). Lower panel: quantitative EEG over 4 hours; the blue box highlights the suppression ratio, which may be easily followed in order to adapt the sedation.

but also lack of reactivity: this feature, despite the use of moderate doses of sedation, has been related to a reliable forecast of poor outcome (**Figure 2**) [8]. In automated, amplitude integrated EEG softwares to the favorable prognostic role of a continuous signal, without electrographic status epilepticus has been outlined [50]; this approach is however not widely applied.

Since the false prediction of death or non-awakening is still possible using EEG (numbers oscillate between 0% and 10%), a complete evaluation in normothermia and off-sedation, and the integration with other prognosticators is mandatory [51, 52]. This is underscored by the description of patients awakening despite postanoxic status epilepticus [24]: these subjects had a particular clinical profile, namely preserved brainstem reflexes, reactivity of the EEG background, and early cortical somatosensory evoked potentials.

Hypoxic-ischemic encephalopathy: neonates and children

EEG alterations described in adults are also found in children under therapeutic hypothermia after cardiac arrest [53], and in general, bear the same prognostic value. Burst-suppression or a diffuse, extremely low-voltage pattern herald a poor prognosis [54]; background reactivity seems conversely to forecast a good outcome [55]. Considerable attention has been directed towards the prognostic significance of amplitude-integrated EEG: persisting burst-suppression or very low-voltage recordings with lack of a normal sleep-wake cycling are related to poor outcome [56, 57]. Also for newborns, timing of the assessment is critical, especially for those undergoing hypothermia: evaluation during the first 24 hours are less reliable [54, 56, 57].

Traumatic and hemorrhagic etiologies

EEG may be helpful in terms of correlations with vasospasm in patients with subarachnoid hemorrhage, not only to unravel subclinical seizures: recordings displaying focal slowing correlate with vasospasm [58]. These observations were confirmed using continuous EEG with quantitative analyses: decreasing alpha variability might precede by 2 - 3 days the insurgence of a vasospasm [59]. Nevertheless, to date, it has not been demonstrated that EEG influences clinical prognosis in this context. An analogous approach has also proven useful in patients with moderate to severe traumatic brain injury [60]. However, as in other etiologies, it remains still unclear whether the prescription of antiepileptic treatment may have a prognostic impact [61].

Other conditions

The clinical situations listed above are by far not exhaustive. For example, toxic-metabolic conditions are frequently encountered in this context [6]. General anesthetics are often prescribed in the ICU, and a multitude of compounds, such as inhalation anesthetics, barbiturates, propofol, and midazolam, may induce diffuse slowing, a discontinuous EEG, burst-suppression, or even complete suppression. Since most drugs act principally by modulating the GABA_A receptor, these may enhance fast rhythms or spindle-like figures at low doses [62]. Intoxications may considerably affect the EEG [6]. Opioids generally slow the background, while neuroleptics and antidepressants may induce in addition generalized or focal epileptiform abnormalities, as well as triphasic waves [63, 64]; similar changes may be observed with lithium [65]. Hypnotic compounds, which modulate GABA_A receptors in a different way as compared to barbiturates and benzodiazepines, can also enhance beta activity [66]. Antibiotics with beta-lactam rings act as GABA antagonists, but under therapeutic dosages it is rare to observe intoxications or seizure-induction, apart from cefepime [67]. 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 [19].

Outlook

The ongoing technological improvements, which not only have allowed 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 [68 - 70]. These are already popular in several North American centers, 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, and quantification of several indices (e.g., suppression ratio, alpha/delta ratio) that are important for a multimodal monitoring in brain injured patients. Furthermore, the possibility of a live display of the analyses during the recording renders EEG information more accessible to non-trained caregivers (**Figure 3**). 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. Intracerebral electrodes are also receiving increasing attention, although, for the moment, rather for scientific purposes than clinical implications. For example, in patients with subarachnoid hemorrhages, seizures are seen more often intracortically (38%) than on scalp (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) [71]. In another study, spreading depolarizations were observed in half of the studied patients with severe traumatic injury, and were associated with poor outcome [72]. Spreading depolarization may correlate with delayed ischemia in patients with subarachnoid hemorrhage [73]. 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 prognostic impact of seizure treatment, and an important limitation should be remembered: sampled tissues are limited and often are not comparable among the studied patients in terms of concomitant pathological involvement.

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 48 hours in order to detect 93% of (mostly nonconvulsive) seizures [74]. 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 EEG minutes rendered extremely unlikely a subsequent seizure on continuous EEG (3%, versus 22% in those with epileptiform discharges). This suggests that a first routine EEG may help identifying those subjects that would deserve EEG monitoring [75]. Similarly, in patients with postanoxic coma, it has been demonstrated that repeated routine EEG recordings may prove as informative as continuous EEG monitorings [44, 76].

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 a multimodal approach that proves more robust for the clinical forecast, but also minimizes false positive poor predictions. Somewhat disappointingly, EEG in the ICU still represents rather a prognostic marker than a diagnostic tool with therapeutic implications. It is to hope that the future will outline the best approaches in terms of effectiveness and define potential therapeutic consequences.

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