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REVIEW ARTICLE

Electrophysiological monitoring of neurological functions at the acute phase of brain injury

An overview of current knowledge and future perspectives in the adult population

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The continuous monitoring of physiological parameters is now considered as a standard of care in intensive care units (ICU). While multiple techniques are available to guide hemodynamic or respiratory management, the monitoring of neurological function in unconscious patients is usually limited to discontinuous bedside neurological examination or morphological brain imaging. However, cortical activity is accessible at the bedside with electroencephalography (EEG), electrocorticography (ECoG) or evoked potentials. The analysis of the unprocessed signal requires a trained neurophysiologist and could be time consuming. During the past decades, advances in neurophysiological signal acquisition make it possible to calculate quantified EEG parameters in real-time. New monitors also provide ICU friendly display for a dynamic and live assessment of neurological function changes.

In this review, we will describe the technical aspects of EEG, ECoG and evoked potentials required for a good signal quality before interpretation. We will discuss how to use those electrophysiological techniques in the ICU to assess neurological function in comatose patients at the acute phase of brain injuries such as traumatic brain injuries, haemorrhagic or ischemic stroke. We will discuss, which quantitative EEG or evoked potentials monitoring parameters can be used at the bedside to guide sedation, evaluate neurological function during awaking and look for new neurological (encephalic or brainstem) injuries. We will present the state of the art and discuss some analyses, which may develop shortly.

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Introduction

The continuous monitoring of physiological parameters is now considered as a standard of care in intensive care units (ICU). The continuous display of vital signs on monitors allows the detection of unexpected events such as arrhythmia, as well as facilitating haemodynamic and ventilatory support optimisations.[1] Thus, the haemodynamic monitoring is part of anaesthesiologist and intensivist training with advanced techniques combining morphological and functional parameters (e.g. continuous cardiac output, ultrasonography or ST segment monitoring).[2–4] Conversely, the monitoring of neurological function in unconscious patients (sedated or following acute brain injury) is usually limited to discontinuous bedside neurological examination or morphological brain imaging. In the same way that cardiac activity can be recorded with electrocardiography (ECG), neuronal background or abnormal activities can also be recorded on scalp electroencephalography (EEG) and using evoked potentials. Nevertheless, the brain activity is more complex and of lower amplitude compared with ECG. The raw signal is thus more sensitive to artifacts and requires a dedicated training, usually restricted to

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neurologists and neurophysiologists. Over the past decades, quantitative indices have been developed from a simplified electroencephalogram (EEG) montage to tailor sedative administration by anaesthesiologists and are now widely used in the operating room.[5,6] However, while EEG and evoked potential changes can be observed during the course of brain injuries, their implementation at the bedside in the ICU remains limited. In collaboration with neurophysiologists, some centres have built programmes to train nonexperts in the interpretation of continuous EEG (cEEG) for seizure detection and basic pattern recognition with promising results.[7–11]

In this review, we will focus on acute brain injury neurophysiological monitoring, such as traumatic brain injury (TBI), subarachnoid haemorrhage, intracranial haematoma or stroke. We will describe the principle of electroencephalography and evoked potential acquisition and some basic features of the raw signal. We will also discuss which quantitative EEG or evoked potential monitoring parameters can be used at the bedside to guide sedation, evaluate neurological function during awakening, or look for new neurological injuries.[12] We will present the state of the art and discuss some analyses which may be developed in the near future.

Technical principles of electroencephalography and evoked potential acquisition

Since the amplitude of the EEG signal is small (in the order of 1 μV for evoked potential to 100 μV for EEG in comparison with 1 mV for ECG and 10 mV for EMG), the impedance of the interface between the electrode and the skin is critical. For long-term monitoring, silver (Ag-AgCl) cup electrodes with conductive pastes are usually preferred.[13,14] Gold electrodes are also available to avoid artifacts during magnetic resonance imaging (MRI), and more recently silver-epoxy-coated conductive plastic electrodes for computed tomography (CT).[15] The 10-20 system describes the location of scalp electrodes so that the distance between two electrodes is homogeneous. The amplitude of the signal between two contacts can thus be compared across the EEG montage. Nineteen electrodes cover the cortical areas over the convexity of the brain, with additional ECG, reference and ground; but in case of spatial restrictions (e.g. surgical scars, external ventricular drainage or intracranial monitoring) at least nine electrodes including one on the vertex (Cz) is usually sufficient,[16] leading to a partial loss of sensitivity to abnormal focal activities, which may be acceptable, when the focus is on the global modulation of brain function or on broad regional changes. Contrary to EEG, which analyses the spontaneous and continuous cortical electrical activity, the evoked potential technique uses an averaging method of fixed periods of the EEG signal triggered by repeated identical sensory stimulation. The response specifically evoked by the sensory input is thus extracted from spontaneous EEG activity. Because the noise (e.g. background EEG activity) is not correlated with the stimulation, its amplitude approaches zero when the number of stimuli increases. To improve the signal-to-noise ratio, subdermal needle electrodes are commonly used in the ICU.[16] The ICU setting implies multiple electrical devices, which may be responsible for noise and artifacts, in addition to movement and muscle activity. Therefore, assessing the signal quality is the first step before analysing electrophysiological data. Physicians should use muscle relaxant drugs when the activity has a low amplitude – such as for evoked potential measurement – to avoid muscle contraction artifacts.[14,16] In case of conscious patients, for example, undiagnosed locked-in patient, the usage of neuromuscular blockers might be a traumatic experience. It should, therefore, be kept only for situations where a careful behavioural examination fails to demonstrate any subtle signs of subjective experience or functional communication. The possibility of cognitive/motor dissociation should always be considered when using neuromuscular blockers, but it may be assumed that only a few patients might be conscious despite the absence of any behavioural sign of awareness. Importantly, the possibility of diagnosing such a dissociated state and revealing a neural signature of consciousness, lies in the technical feasibility and methodological reliability of the functional tests. Therefore, the risk–benefit ratio is favourable, when compared with the risk of untimely withdrawal of life-sustaining therapy.

Since its first description in 1929, the acquisition of EEG signals has undergone many technological improvements. The digitalisation of the raw signal with affordable computers now allows online quantitative measurements at the bedside. The visual analyses of 15 to 30 s pages of the EEG signal remain the gold standard but requires an experienced neurophysiologist and is time consuming. This may limit EEG use as a monitoring tool in the ICU where a faster interpretation is needed at the bedside to adjust treatment strategies.[17] The development of digital technology allows advanced signal processing algorithms to work in real-time at the bedside. The EEG signal is usually presented on a screen as multiple curves over time (i.e. time domain). The amplitude (μV) or power (μV^2) of the signal can be integrated over time to display trends over several hours or days. On the EEG curves, neurophysiologist differentiate different activities based on their frequency characterised visually from the raw signal (number of cycles per second, or Hz): delta (0 to 4 Hz), theta (4 to 8 Hz), alpha (8 to 13 Hz), beta (13 to 30 Hz), gamma (30 to 80 Hz). Mathematical functions such as the fast Fourier transformation can transform data from the time domain to the frequency domain. This allows analysing the changes of each frequencies' power over the recording period. The typical display called density spectral array (DSA) is a three-dimensional plot with time as the *x*-axis, the frequency band as the *y*-axis;

the power of each frequency band is color-coded (usually blue implies minimum power and red maximum power). More complex algorithms are also available to evaluate the degree of complexity of the EEG signal such as entropy metrics.[18]

The cortical and subcortical activities evoked by somatosensory, auditory or visual stimuli can be extracted from the EEG signal with evoked potentials. They can be recorded very early in the awakening process because the amplitude of most short-latency neurophysiological responses is not sensitive to sedation, contrary to central conduction times.[16,19] Brainstem Auditory Evoked Potentials (BAEPs) can be recorded along with somatosensory evoked potentials (SSEP) and Middle Latency Auditory Evoked Potentials (MLAEPs) at least 24 h after the onset of the coma. In the brainstem, the auditory stimulus (BAEPs) trigger five main waves recorded within 10 ms, which have proper generators: the distal (wave I) and proximal (wave II) portions of the auditory nerve VIII; then the caudal pontine tegmentum region (wave III); then the wave IV corresponds to the ascending volley through the lateral lemniscus from the superior olivary complex to the inferior colliculus located in the tectal (infero-posterior) part of the midbrain (wave V).[16] The following MLAEPs are composed by the Na (mesodiencephalic relay) and Pa (cortical) waves. The N20 cortical response of the SSEP after the median nerve electrical stimulation is the main neurophysiological response studied in the ICU. It is crucial to rule out confounding factors to avoid false-negative results: peripheral nerve lesions or spinal trauma; medullar or subcortical lesions; temperature less than 35 °C; metabolic encephalopathy and deep sedation. Therefore, peripheral and spinal evoked potentials should also be recorded concomitantly with the cortical one. Subdural haematoma, decompressive craniectomy and focal lesion's location should be considered in EP interpretation.[20] Early assessments allow an initial functional view of the primary insults. Conversely, the neuroprognostication process needs a minimal 24 to 48 h delay after withdrawal of sedation to rule out any remaining effect from sedation and to allow proper interpretation of the evoked potentials, combined with the patient behavioural assessment by the FOUR score, which is applicable in intubated patients (unlike the Glasgow coma score) and the Coma Recovery Scale – Revised (CRS-R) that can also be used at the bedside as the gold standard scale to assess the behavioural proofs of cortical function.

In the ICU environment with unstable patients who need multiple devices (for assistance or monitoring) and frequent transportation to brain imaging, the development of CT and MRI-compatible electrodes as well as the advances in queen analyses makes it possible to use cEEG at the bedside. The nurses' training to cEEG placement and surveillance is crucial to ensure a good signal quality. Conversely evoked potential remains more challenging because of multiple sources of artifacts and potent confounding factors and is currently only used in expert centres.

Sedation optimisation

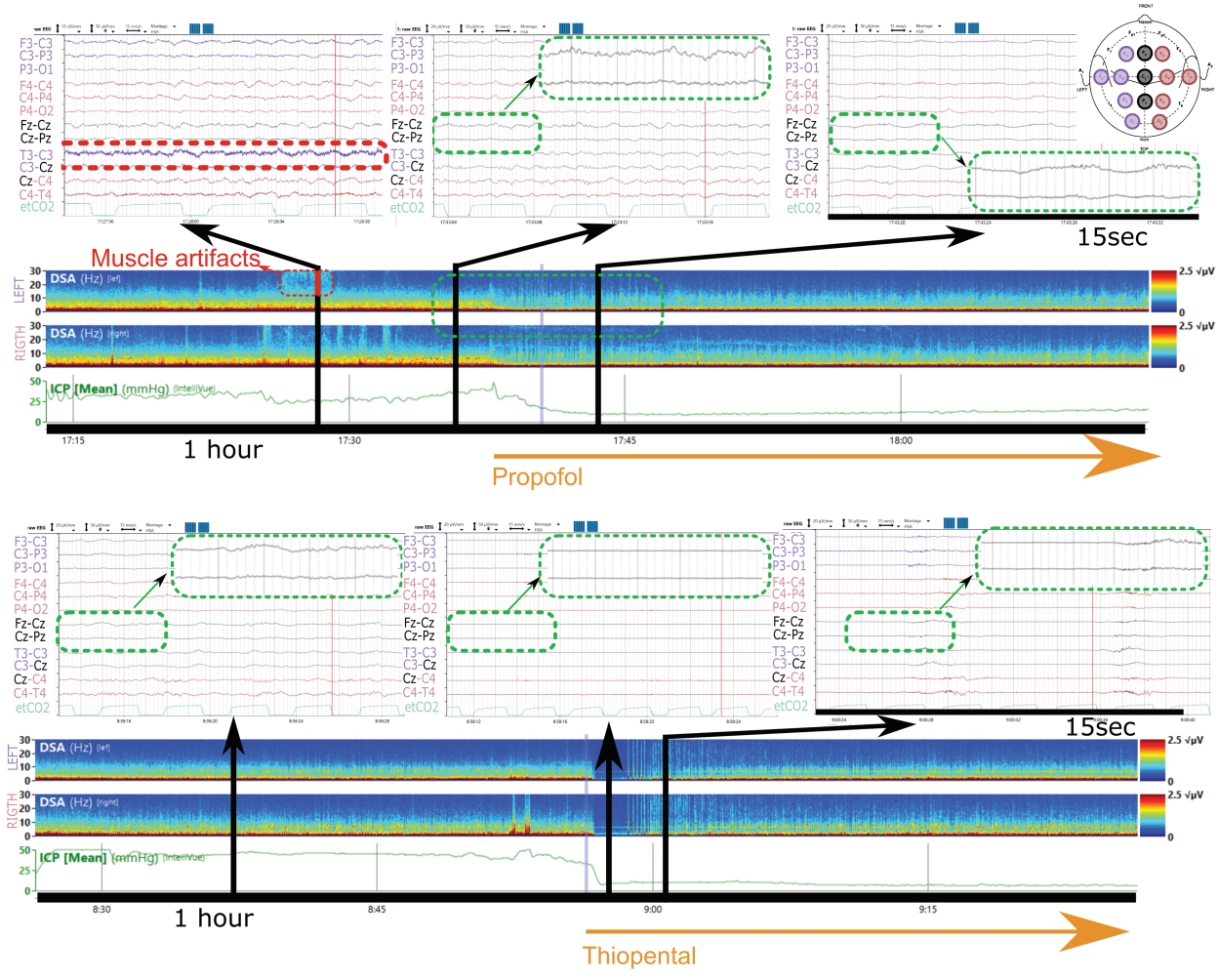
Most anaesthetic agents used at the acute phase of brain injury (e.g. midazolam, propofol or barbiturates) are positive allosteric modulators of the GABAa receptor. The gradual cerebral impregnation by these drugs produces a transient increase in beta activity followed by an EEG slowing with slow alpha then theta and delta oscillation followed by periods of EEG suppression up to an isoelectric trace.[18] Ketamine used alone at sedative doses induces fast oscillations (>25 to 30 Hz) superimposed to slow oscillations; however, at high doses it can also lead to EEG suppression.[18,21] Quantitative EEG parameters (qEEG), such as the bispectral index (BIS) or the entropy, have been used to guide sedation in the ICU but with a great variability between their value (from 0 = over sedated to 100 = fully conscious) and the clinical effect of sedation. BIS or entropy between 40 and 70 can be observed in patients with Ramsay sedation scale from 1 to 5.[22] Therefore, the interest of BIS parameters seems limited to predict an adequate sedation in patients treated with muscle relaxants. Moreover, the brain injuries expected in neuro-ICU patients also induce EEG changes making reduced frontal qEEG monitoring such as the BIS or entropy useless. Rather, cEEG monitoring may be used to prevent oversedation characterised by a discontinuous EEG signal (suppression, EEG amplitude <10 μV, for 10 to 49% of the time) or a burst suppression pattern (suppression for more than 50% of the time).[23]

Following acute brain injury, sedation may be used either to synchronise the patient with artificial ventilation, control seizures or treat intracranial hypertension. To achieve one or more of these goals, the doses of sedative agents vary as do the required plasma concentration.[24] This argues for cEEG monitoring to guide their administration, while carefully looking for overdosage or side effect. For instance, burst suppression patterns can be detected automatically or observed on the DSA display as periods of blue (suppressed activity) interspersed with periods of red-yellow (slow delta–theta and alpha oscillations, Fig. 1).[18,25]

Awakening from coma

After sedation withdrawal, the EEG should recover its normal background activity following the inverse course observed during the induction of anesthesia.[18] However, the recovery of consciousness can be delayed after acute brain injuries thus classifying patients as having prolonged 'disorders of consciousness' (DOC) related to strategic lesions on consciousness pathways (i.e. reticular formation, thalamus or basal ganglia) or diffuse injuries in large scale brain networks.[26] The CRS-R[27] can distinguish at the bedside, comatose patients *strico sensu* (i.e.

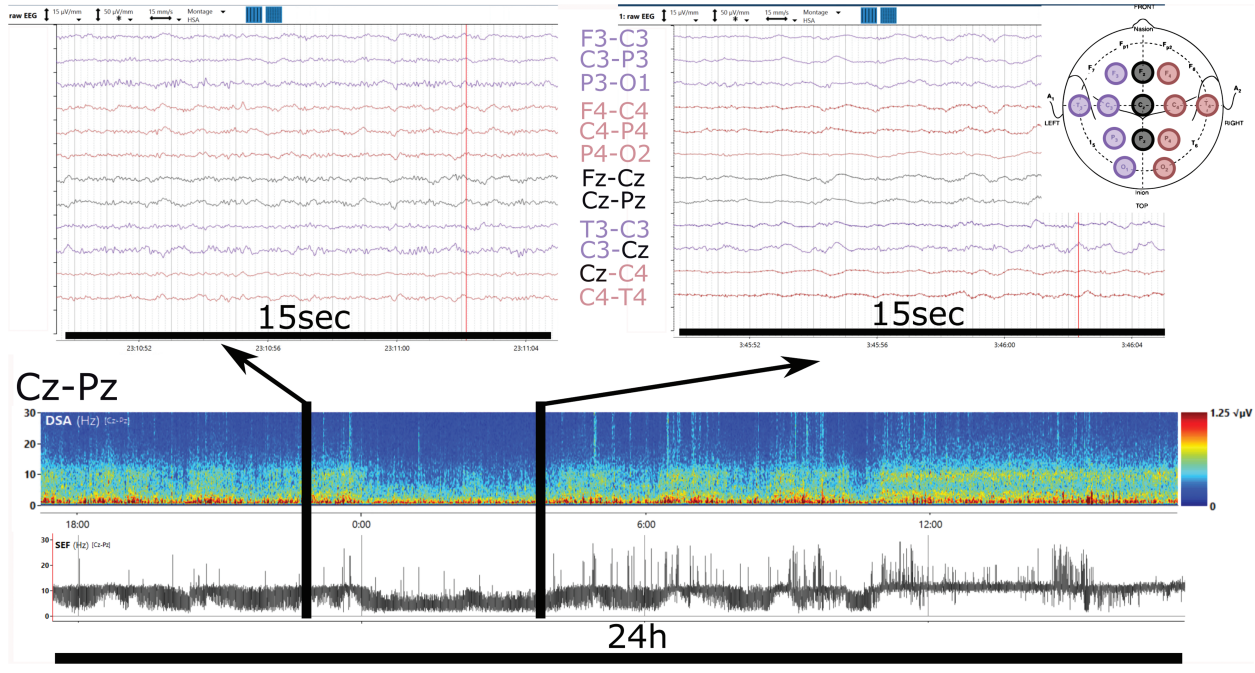
Fig. 1 Impact of sedation on unprocessed and quantitative electroencephalography.



The changes of unprocessed EEG (0.5 to 70 Hz) are presented on the upper panel. Note the presence of muscle artifacts on the left trace that are also visible on the density spectrum analyses (DSA left, red dashed square). The infusion of propofol for intracranial pressure control led to the disappearance of rhythms in the theta band. Later on, the administration of thiopental led to a complete suppression of background activity and the appearance of a burst suppression pattern. DSA, vertical-coloured bars of activity on a blue suppressed background; EEG, electroencephalography.

patients with nonopening eyes) from unresponsive wakefulness patients (i.e. the former vegetative state with eyes being at least inconstantly open)[28] and the minimally conscious state[29] when the patients present any sign of cortical function.[30] Acute EEG recordings within the first week after an acute brain injury provide functional information of cerebral recovery, such as the acceleration variability and reactivity of the background activity, that are predicative of awaking in comatose patients. The patterns, which can be observed before patients recover consciousness, are the appearance of a background activity in the high theta or alpha band with state changes and a gradient across cortical areas (the background activity should be of higher amplitude in posterior areas).[31–33] State changes are defined as more than 60 s changes of the background activity after stimulation, or the presence of sleep transients such as variability of the background activity, spindles or K-complex.[33] The endogenous oscillation (normally synchronised with exogenous information such as sun light 24 h cycles), is usually impaired during this acute phase of brain injury.[34] The ultradian changes observed in the ICU have shorter duration in the order of 2 to 8 h.[34,35] The recovery of a 24 h sleep–wake cycle activity is associated with awareness recovery,[36,37] but at the chronic phase, DOC patients can also have sleep–wake cycle, although their architecture is more heterogeneous.[38] The trends of EEG changes can be visualised with DSA plots with a compressed time scale (12 to 24 h, Fig. 2) as well as other qEEG metrics changes such as the median or 95% power frequency (or spectral edge frequency, Fig. 2), which reflects the content of the background activity. Conversely, there is currently no

Fig. 2 Background electroencephalography changes observed before awaking from coma.



The patient was spontaneously comatose with Glasgow coma score of 7 (E2, V1, M4). Note the presence of upper theta waves in the background activities (upper panel) with ultradian changes as observed on the density spectral analyses (DSA) and spectral edge frequency (SEF) of the Cz-Pz derivation (lower panel). The patient was responsive to an oral command 4 days later.

standardisation of the detection of EEG reactivity to an auditory or sensory stimulus, even during a routine EEG (i.e. 30 min recording). Machine learning algorithms have been developed and may be available in the future to have a robust evaluation of brain activation.[39]

Brainstem and cortical responses to a somatosensory or auditory stimulus can be more precisely evaluated with evoked potentials that are part of the electrophysiological asset for coma prognostication in the ICU.[16] The interpretation of SSEPs is mainly based on the amplitude of the N20 cortical component considered as absent if less than 0.2 μV (with a biparietal or parieto-frontal recording).[16]

Following cardiac arrest, the latest guidelines confirm the prognostic value of EEG and SEPs performed at least 24 h after circulation is restored and sedation eliminated. The authors proposed a delay of 72 h from admission (in absence of any cofounding factors – no sedation and no hypothermia) before engaging in any neuroprognostication process, which could be based on a multimodal assessment.[41] It may include some neurophysiological markers recorded as early as 24 h after admission (EEG and SSEPs). The bilateral abolition of N20 must be confirmed by at least another marker such as the absence of pupillary of corneal reflex, malignant EEG pattern (status epilepticus or burst suppression over an unreactive background after rewarming), Neuron Specific Enolase greater than 60 mg l^{-1} at 48 and/or 72 h, diffuse and extensive anoxic injury on brain CT or MRI.[40]

Early SSEPs can also be altered after TBI[41] or even abolished in a coma after a stroke or an intracranial haematoma[42] without a 100% specificity for the nonawakening prediction. The N20 abolition could be explained by focal lesions on the somatosensory pathway such as axonal lesions[16,43]; and cases of late normalisation after several weeks have been reported.[41] Moreover, Amantini *et al*. found that 73% of TBI patients with a bilateral SSEP abolition wake up but with a bad functional outcome in every case.[44] BAEP can evaluate the consequence of lesions in the pedonculo-pontine tegmental area.[19] As the auditory pathway is anatomically close to the reticular formation,[45] the abolition of BAEP could be associated with an unfavourable awakening outcome. However, as the reticular function is necessary but not sufficient to support the human conscious process, normal BAEPs cannot predict a favourable outcome.[46] If BAEP are observed, the subsequent MLAEP can be analysed. As they are very sensitive to sedation[47] and artifacts, neuromuscular blockers without sedation are advocated to allow their interpretation.[16] They are less used by neurophysiologist, and less data are available: a study showed bilateral abolition of the Pa had the same significance as the N20 abolition in postanoxic coma.[48] However, for a nonanoxic coma, preliminary result in a small cohort

reports few false-negative cases; this suggests that only the multimodal and bilateral abolition of 'Pa + N20' auditory and somatosensory cortical responses had a 100% predictive value for nonawakening for every cause of coma.[48] The presence of MLAEPs is strongly associated with a favourable outcome of awakening, like normal BAEPs and several patterns of SSEPs.[49] However, it does not predict the functional recovery. Therefore, we would recommend combining MLAEPs recording with SSEPs because of the limited level of evidence and the risk of misinterpretation (e.g. technical issues).[16] In conjunction with trained neurophysiological teams, multimodal protocols have been proven useful in a small cohort of patients with strategic lesions at the initial assessment[48] or for a follow-up[43] with complementary information given by the analysis of EEG and its reactivity.[42] Late cognitive evoked potentials such as the P300 or the mismatch negativity are also used later after the acute injury to predict consciousness recovery but are not in the scope of the current review.

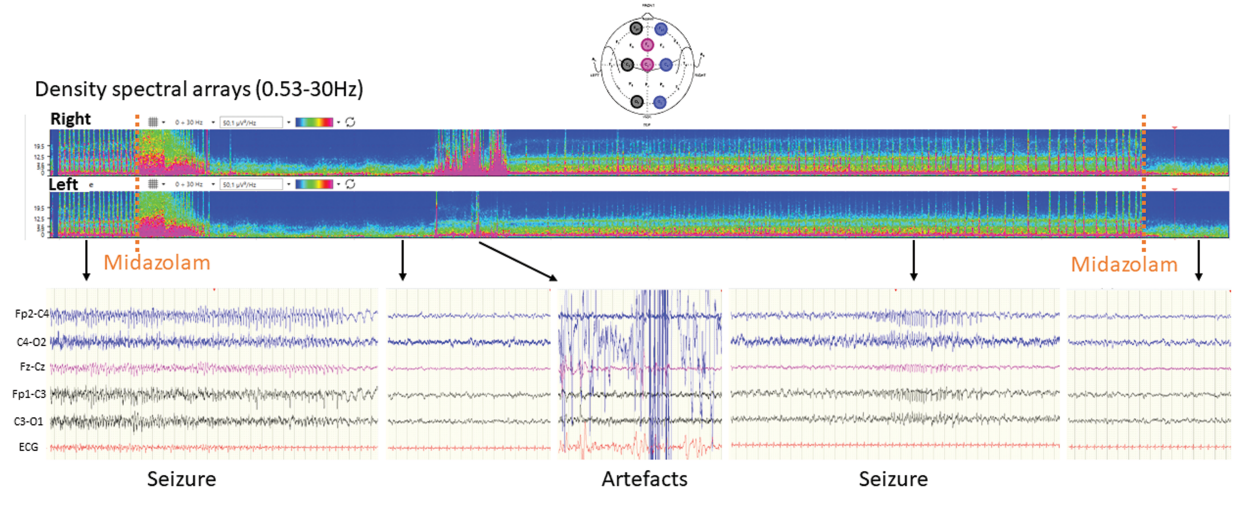
Altogether, for patients who remain comatose after sedation withdrawal, a long cEEG (>24 h) with compressed DSA analyses can rule out a functional and treatable cause of coma (nonconvulsive SE). Routine EEG is sufficient to assess background activity and its reactivity to stimuli. Analysing ultradian changes preceding clinical improvement or the disappearance of pathological EEG patterns remains a research topic. Early and repeated evoked potentials can also help to predict a poor outcome in case of persistent alterations. Given that no marker has a perfect diagnostic accuracy, we would argue to combine EEG, evoked potential, brain imaging and behavioural assessment for early prognostication.

Assessing the risk of seizure

The management of status epilepticus is beyond the scope of the current review. After acute brain injuries, seizures occur in 10 to 30% patients.[50–52] The stratification of the risk of seizures from inter-ictal activities (e.g. spikes, periodic discharges or rhythmic activities) requires the review of unprocessed EEG by a neurophysiologist. Several authors have created risk scores, such as the 2HELPS2B proposed by the American Clinical Neurophysiology Society, which would justify a prolonged cEEG monitoring that includes the presence of brief rhythmic discharges, rhythmic delta activities, lateralised periodic discharges, especially if they are frequent ($>2\ s^{-1}$).[52,53] qEEG parameters such as an increase in the total EEG power or amplitude (e.g. view on an amplitude-integrated EEG, or with the DSA display) can help physicians to detect nonconvulsive seizure, but their sensitivity is of approximately 80% with some false positives, especially in patients with muscular activity, and false negatives, especially if the seizure involves a small cortical area.[11] Algorithms trained with supervised machine learning are also now available to find rhythmic patterns and seizures.[54] However, for a precise seizure detection and the identification of interictal patterns, the analysis of the unprocessed EEG by an expert remains mandatory (Fig. 3).

Therefore, we advocate for a close collaboration between neurointensivists and neurophysiologists. Neurointensivists should be aware of cEEG indication ('is the suspicion high enough to increase the care burden with a continuous EEG?'), manage the nonmedical staff training to have a good EEG signal. The ICU staff should be able to detect and eventually correct artifacts to facilitate the

Fig. 3 Seizure detection on quantitative and unprocessed electroencephalography.



The presence of repeated seizures at the beginning of the recording can be identified in the raw EEG. Each seizure is visualised as a coloured vertical bar on the density spectral analyses. Note that the presence of artifacts also led to vertical-coloured bars. The DSA can, therefore, help review continuous EEG but the diagnosis of seizures requires the analyses on the unprocessed EEG. EEG, electroencephalography.

off-line EEG interpretation by neurophysiologist. Indeed, this cooperation is mandatory to avoid misinterpretations with the risk of false-negative (nontreated SE) and false-positive diagnosis (over-treatment by antiepileptic and general anaesthesia for unspecific grapho-elements).

Monitoring cortical injury

Following acute brain injury, a mismatch between the metabolic demand and supply (mainly oxygen and glucose) will lead to a reduction in neuronal activity. This has been reported in preclinical models of global cerebral ischaemia, hypoglycaemia or hypoxaemia,[55,56] or in the patient during the evolution to brain death.[57] If there is no metabolic supply available (e.g. ischaemic stroke or cardiac arrest), several minutes after the interruption of neuronal activity, all brain cells will lose their ionic gradient. Subsequently neurons and astrocytes will lose their membrane potential, leading to a reversible cellular depolarisation and swelling (cytotoxic oedema). The transient depolarisation that starts in the core of the injured area will then propagate to surrounding cortical tissue (2 to 6 mm min^{-1}) and can be recorded with platinum–iridium cortical electrodes. This propagating wave has been termed cortical spreading depolarisation.[58,59] Unfortunately, spreading depolarisation cannot be recorded with scalp EEG electrodes and requires electrocorticographic electrode (ECoG).[60] The ECoG electrodes can be placed at the cortical surface during a surgical intervention or through a fold inside the cortex. The electrodes should be connected to a DC amplifier recording the signal from 0 Hz while common EEG amplifiers have an analogue high-pass filter with 0.5 Hz cut-offs.[61] New advances on ECoG placement and recordings will make it easier for nonexpert centres to start such monitoring shortly.[62,63]

There are also EEG activity changes that are observed during brain ischaemia or energetic mismatch. Under physiological condition, CBF ranges between 46 and 62 ml 100 g^{-1} min^{-1}.[64] The ischaemic threshold below which irreversible damage occurs has been defined after TBI, stroke or carotid surgery around 15 ml 100 g^{-1} min^{-1}.[65–67] Below 30 ml 100 g^{-1} min^{-1}, there is a progressive loss of higher frequencies in favour of a slower background rhythm. These changes can be reversible, for example, after thrombolysis of an ischaemic stroke, supporting the assumption that EEG changes occur before reaching irreversible damage.[68] When CBF drops below the ischaemic threshold with irreversible cell death, all frequencies are suppressed with an isoelectric trace, which mirrors the terminal depression of neuronal activity.[69,70] In the normal brain, the fast background rhythm (in the alpha or high theta band) has fast fluctuations, which can be visualised on a graphical display (e.g. alpha power over time). The decrease of the alpha power with the absence of variability is observed during diffuse oedema or subcortical lesions after TBI and delayed cerebral ischaemia (DCI) after subarachnoid hemorrhage.[71–73]

The contribution of EEG has implications in comatose patients after a subarachnoid haemorrhage. As their neurological examination is unreliable without continuous sedation, EEG changes constitute a reliable surrogate of neurological function to detect DCI. The decrease of the background activity with an increase in slow delta activity has been summarised in a single metric such as the alpha–theta/delta ratio or the alpha/delta ratio (ADR). The threshold that should be used (duration and percentage of decrease) is not defined. Yet a prolonged decrease (several hours) and deep reduction (>40%) is predicative of DCI with a sensitivity around 80% and a specificity around 70%.[35,74–76] The appearance of lateralised periodic discharges, which reflect a focal cortical injury is also observed when DCI occurs.[76] All those alarms can be measured up to several days before physicians had diagnosed DCI, thus granting more time to start first therapeutic tiers.[77] So far, we are unable to identify when irreversible damage occurs based on electrophysiological continuous monitoring. The ideal moment when to start new therapeutics before the onset of irreversible damage is the matter of ongoing and further research.

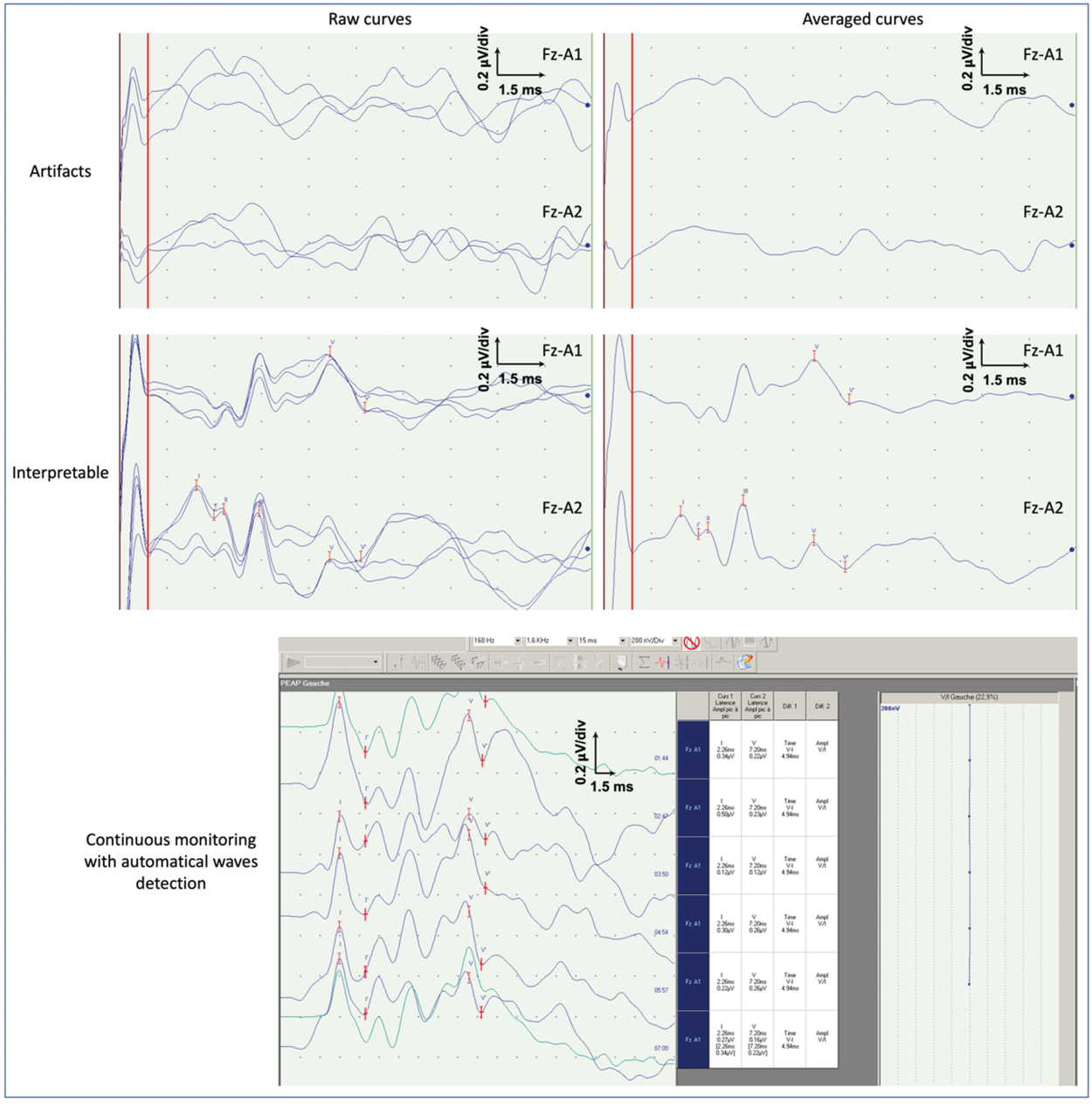
Spreading depolarisation

(1) Spreading depolarisation is the pathophysiological event under cellular oedema observed as an ADC signal reduction on MRI.[77]
(2) Spreading depolarisation can induce an increase or a decrease of CBF depending on the condition.
(3) Spreading depolarisation is now considered as a marker of ongoing cortical injury and a pathological process that participates to lesion progression.
(4) Experts agree that the initial management when spreading depolarisation is observed would be to optimise cerebral perfusion and metabolism (O_2 and glucose).
(5) There is currently no consensus on the best therapeutic strategy if SD persists.[59]

During this early period, patients at risk of intracranial hypertension are often sedated in order to control intracranial hypertension or optimise ventilation. Although queen changes can be biased by ongoing sedation, the SSEP cortical response is still observed and may be used for early detection of brain injury progression. For instance, the N20 alteration can anticipate the evolution towards brain death within 24 h after a coma in the postanoxic[78] and traumatic settings.[79] In these studies, Scarpino *et al.* found that a bilateral abolition or a unilateral abolition with a contralateral pathological response was an early uniform pattern, which predicted brain death in 77.5% of nonanoxic cases.[79] Among anoxic cases, the

sensitivity was high (100%) but the specificity was low (62.3%) and was not improved by CT scan analysis.[78] Amantini *et al.*[80] used SSEPs in addition to EEG in 68 patients (TBI or haemorrhagic stroke) managed with an intracranial pressure (ICP) monitor. All patients presenting a clinical deterioration during the monitoring had a significant alteration of the N20 amplitude (from abolition to half reduction). The SSEP changes occurred before the intracranial hypertension events in 30% of cases. Interestingly, the neurophysiology additive value was observed in patients with moderate ICP values (20 to 40 mmHg), while EEG was not informative because of its sensitivity to deep sedation. The correlation between SSEP monitoring and short-term clinical outcome was better than ICP in another study from the same group.[81] Indeed, neurophysiology might assess more accurately

Fig. 4 Auditory evoked potential monitoring in the intensive care unit.



The intensive care environment is challenging for evoked potentials recordings because of many electrical sources of artifacts. Therefore, the first step before starting continuous monitoring is to check the reproducibility of the curves (e.g. upper panel) to avoid misinterpretation. Once there is a correct setup, the automatic detection of the BEAP peaks allows detecting changes in amplitude and conduction time (lower panel).

Table 1 Current and future neurophysiological monitoring indication

Clinical situation	Current relevant monitoring	Future monitoring
Awaking from coma (without sedation or hypothermia)	cEEG with DSA for NCSE detection; repeated routine EEG and EP for prognosis	Automated reactivity analysis on cEEG; conscious processes detection and arousal fluctuations over 24 h.
DCI detection after SAH (no sedation)	cEEG with ADR, raw EEG review by neurophysiologist	ECoG for SD detection
Supratentorial injury	cEEG for sedation optimisation and NCSE detection	ECoG for SD detection; EP monitoring (SSEPs for rostro-caudal deterioration)
Posterior fossa injury		EP monitoring (BAEPs for brainstem compression)

ADR, alpha/delta ratio; BAEP, brainstem auditory-evoked potentials; cEEG, continuous electroencephalography; DC, decompressive craniectomy; DCI, delayed cerebral ischaemia; EP, evoked potential; SD, spreading depolarisation; SEP, somatosensory-evoked potential.

the actual metabolic mismatch during critical moments of lesion extension. SSEPs monitors with *ad hoc* protocols were adapted to the technical constraint of ICU, to overcomes a rare use in clinical practice.[82] They have been proven useful in a test phase to detect patterns of brain compression leading to SSEPs impairment.[83] Assessing early these ongoing processes before the final stage would help avoid unfavourable outcomes related to secondary lesions caused by a pressure necrosis phenomenon.[84]

Altogether, in spontaneously unconscious patients at risk of new neurological injuries such as DCI after SAH, cEEG with the ADR monitoring is useful combined to a multimodal approach. However, a precise maker of ADR changes to start new treatment remains to be clarified. In sedated patients, evoked potential monitoring allows the detection of cortical injuries but requires experienced teams and further validation studies to demonstrate an outcome improvement. When patients have a surgical procedure or require intracranial monitoring, the placement of ECoG electrodes for spreading depolarisation monitoring is now becoming more feasible and represents a future evolution in specialised neurological ICUs.

Monitoring brainstem dysfunction

Some authors have proposed that brain dysfunction could be assessed without formal brain injury, such as after sepsis.[19] This has led to the introduction of the concept of brainstem dysfunction as a novel marker of late mortality in general ICU.[85] However, the pattern of brainstem dysfunction was mainly clinical (e.g. the most weighted sign to predict higher mortality with the BRASS score was an absence of a grimacing response associated with preserved oculocephalic responses).

The analyses of changes in brainstem evoked potentials (mainly BAEPs) could be relevant in confirming the consequences of an ICP increase.[86] The increase of Peak V latency appeared for ICP = 30 mmHg and anticipated the pupillary signs of herniation in four out of five cases. The authors proposed it as a novel criterion to guide surgical therapy, but it was not confirmed in a later interventional trial.[87] Some authors have proposed that a prognostic value of BAEPs could be based on a dynamic interpretation of waveform changes rather than their punctual normality. This suggests that only continuous monitoring would be useful during the early phase at risk of brainstem injury progression.[88] In some cases, high ICP (>40 mmHg) could be well tolerated at the neurophysiological level: this pattern was associated with a favourable outcome (9/11 survival and one unrelated death from sepsis). On the contrary, a time-locked positive correlation between ICP rise and interpeak I–V latency was followed by brain death (10/11 cases). However, as the last response of BAEPs (peak V) is generated in the low mesencephalon (inferior colliculus), such recordings might not be the most appropriate to detect rostrocaudal deterioration: The consequences of supratentorial brain herniation [between the medulla oblongata (P14 relay) and the N20 cortical generator] could be detected by analysing N20 alteration (assuming its previous presence on earlier recordings or an intact lemniscus pathway on brain imaging, Fig. 5).

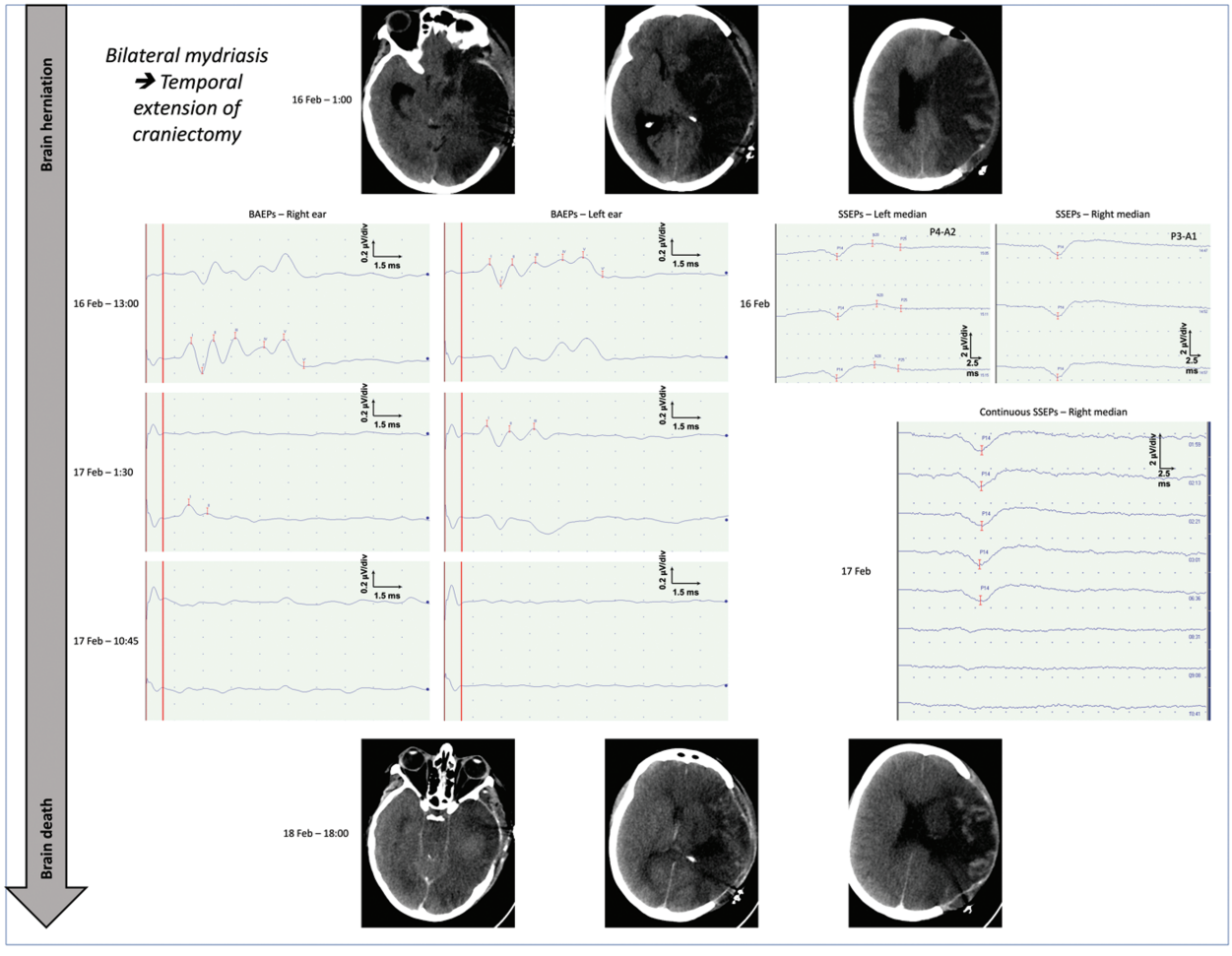
BAEP's timely assessments[89] was proposed to guide treatment in case of brainstem compression on the pons level by expansion lesions in the cerebral posterior fossa (e.g. cerebellar haematoma or stroke).[90] Although not yet demonstrated by appropriate studies, BEAP monitoring could be even more relevant to select the best candidates and the most appropriate timeframe to intensify the medicosurgical treatment in this specific context (Fig. 4).

The continuous monitoring of evoked potentials outside the operating room is currently restricted to expert centres. Even if it represents a promising technique for patient with posterior fossa lesions (BAEPs) and rostrocaudal brain herniation (SSEPs and BAEPs), recording and interpretation require an extensive training. In addition, implementing such a monitoring in routine neuro-ICU would request further studies to demonstrate a significant improvement of the outcome for selected cases.

Conclusion and perspectives

In patients with an unreliable neurological examination because of ongoing sedation or consequent to brain injuries, electrophysiological monitoring can be a reliable surrogate of neurological function. It can be continuous (EEG, ECoG) or discontinuous (EEG or evoked potential). The current indication and perspectives are summarised in Table 1. All electrophysiological data (e.g.

Fig. 5 Evoked potential changes during new neurological injury.



Case report of a 40-year-old woman admitted to ICU after a decompressive craniectomy (DC) at D1 after a complete left-middle cerebral artery stroke. Despite an early arousal, she presented a clinical mesencephalic compression (Kernohan–Wolman syndrome): right mydriasis and ipsilateral right decerebration. The increased intra-cranial pressure worsens progressively from D4 to D6, despite the DC, intubation, ventilation and deep sedation. On D6, a bilateral mydriasis led to enlarge the DC, which allowed the restoration of pupillary symmetry. To go further in brainstem function assessment, we added evoked potential multimonitoring with early brainstem auditory-evoked potentials (BAEPs) and somatosensory-evoked potential (SSEP). We observed initially a response of the right somatosensory cortex after stimulating the left median nerve and the persistence of a mesencephalic response (peak V). The progression of the left temporal herniation was associated with the progressive disappearance of the brainstem potential (at first: disappearance of peak III to V, up to a complete loss of all BEAPs); and with the progressive loss of the right cortical (N20) and subcortical (P14) responses of the SSEP. Brain death occurred on D8.

ECG or EEG) raw signal should be reviewed to ensure its quality and look for abnormal activities. Then, quantitative data can be computed and displayed over time to evaluate slower changes and tailor therapeutic strategies. qEEG is useful to guide sedation, look for seizures or new cortical injuries. For coma prognosis, a dynamic and multimodal approach (EEG, evoked potential, clinical examination, MRI) is advocated. To achieve this, anaesthesiologist and intensivist should be trained in electrophysiological analyses. As the interpretation of EEG and evoked potential signals can be challenging when they are not normal, intensivists should work in close collaboration with neurophysiologist, especially when outcome predictions are discussed as no withdrawal of life-sustaining therapy should be decided on an isolated result. Future improvements in electrophysiological signal acquisition and analyses will include ECoG recording for spreading deploarisation detection, evoked potential and cEEG monitoring for new cortical and brainstem injuries and an automatic detection of seizures.

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