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NARRATIVE REVIEW

Electroencephalogram in the intensive care unit: a focused look at acute brain injury

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Abstract

Over the past decades, electroencephalography (EEG) has become a widely applied and highly sophisticated brain monitoring tool in a variety of intensive care unit (ICU) settings. The most common indication for EEG monitoring currently is the management of refractory status epilepticus. In addition, a number of studies have associated frequent seizures, including nonconvulsive status epilepticus (NCSE), with worsening secondary brain injury and with worse outcomes. With the widespread utilization of EEG (spot and continuous EEG), rhythmic and periodic patterns that do not fulfill strict seizure criteria have been identified, epidemiologically quantified, and linked to pathophysiological events across a wide spectrum of critical and acute illnesses, including acute brain injury. Increasingly, EEG is not just qualitatively described, but also quantitatively analyzed together with other modalities to generate innovative measurements with possible clinical relevance. In this review, we discuss the current knowledge and emerging applications of EEG in the ICU, including seizure detection, ischemia monitoring, detection of cortical spreading depolarizations, assessment of consciousness and prognostication. We also review some technical aspects and challenges of using EEG in the ICU including the logistics of setting up ICU EEG monitoring in resource-limited settings.

Keywords: Electroencephalogram, Intensive care unit, Nonconvulsive seizures, Ischemia, Disorders of consciousness, Cortical spreading depolarization, Status epilepticus

Introduction

Electroencephalography (EEG) displays brain activity by detecting electrical potential differences between electrodes over time to help diagnose, manage and prognosticate cerebral pathology. Differences in electrical potentials recorded between two or more electrodes result in upward and downward waveforms (polarity) with different frequencies and scale (amplitude). By reflecting the summation of excitatory and inhibitory postsynaptic potentials generated by neurons in the immediately underlying cortex, electrical signals display neural oscillations and other dynamic features of cortical and subcortical activity (for electrode placement see Supplemental Fig. 1) [1]. In clinical practice, non-invasive, surface electrodes are primarily used but other technologies are emerging, such as subdural-strip electrodes to detect cortical spreading depolarization (SD) and intraparenchymal electrodes as part of multimodal brain monitoring for comatose patients [2, 3].

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EEG analysis traditionally relies on visual inspection by trained electroencephalographers, a time and labor-intensive process. At most centres, EEGs are only reviewed remotely a few times daily. Frontline bedside personnel with variable proficiencies in EEG interpretation play an important role in EEG monitoring, stretching from acquisition quality control to advanced EEG interpretation. Computational analysis also known as quantitative EEG (qEEG) allows rapid screening and display of large amounts of digitally recorded EEG. QEEG analyzes the frequency, amplitude, and time domains of the raw EEG signal using mathematical algorithms. Several qEEG packages are commercially available and generate a number of different graphs (also known as trends) that allow bedside physicians to rapidly screen long periods of EEG and detect gradual changes over time. QEEG is able to detect and quantify seizures, monitor for ischemia, bleeding, hydrocephalus, and brain swelling or herniation (Fig. 1). The time base of qEEG displayed on a screen can be adjusted allowing detection of subtle changes over longer epochs (hours to days) or to "zoom-into" clinically relevant events [2]. Commonly used trends include compressed spectral array, density spectral array, asymmetry relative spectrogram, fast Fourier transform spectrogram, rhythmicity spectrogram, amplitude EEG, alpha/delta ratio, suppression ratio, and seizure detection panel. Bispectral index (BIS) is a tool for quantitative EEG processing developed to monitor sedation in the operating room and while controversial has found some use in the intensive care unit (ICU) [4, 5]. The BIS monitor utilizes gel electrodes placed on the forehead to generate the signal [6] and has major limitations particularly in patients that do not receive neuromuscular blockade [7, 8].

Take-home message

Electroencephalography allows continuous monitoring of brain function in critically ill patients. In addition to assisting seizure detection and management, great potential lies in supporting the detection of secondary injury and aiding critical care management (e.g. ischemia, cortical spreading depolarizations), consciousness assessments, and neuroprognostication.

Definitions of EEG terminology are summarized in Table 1 [9, 10]. Normal EEG is infrequently seen in ICU patients. These patients frequently have dramatic sleep–wake disruption and various EEG abnormalities that have been inconsistently given a number of different labels and definitions [9]. Since 2012, the American Clinical Neurophysiology Society (ACNS) has published guidelines on critical care EEG terminology, most recently revised in 2021, in an effort to standardize descriptions of these complex patterns facilitating clinical communication and allowing meaningful scientific research [9, 11]. Based on this widely accepted terminology, training modules and self-assessment tools have been developed.

While the most frequent indication of EEG monitoring remains the detection of nonconvulsive seizures, EEG also carries potentially important information about underlying pathophysiologic processes, making it attractive for additional ICU indications such as behavioral assessments, prognostication, and ischemia detection [12–16].

We performed a PubMed literature search using the search terms “ICU” or “critical care” or “intensive care unit” and “EEG” for the most relevant articles related to ICU EEG monitoring in patients with acute brain injury (ABI). We limited the search to articles describing human subjects in English. We subsequently reviewed abstracts

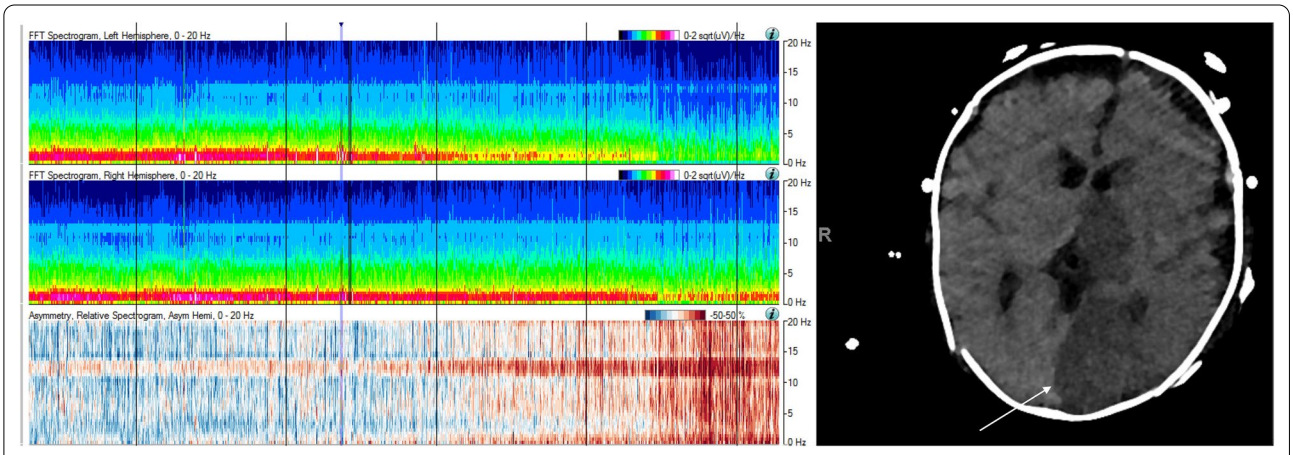

Fig. 1 In a term infant undergoing extracorporeal membrane oxygenation, there is a gradual loss of power of frequencies in the 1–12 Hz range over the left hemisphere observed on the color dense spectral array (top panel), with an increase in power over the right hemisphere (red) as evidenced by the relative asymmetry spectrogram. Subsequent neuroimaging demonstrates a left posterior circulation infarction with cerebral edema

and included articles based on their relevance to ICU EEG monitoring for ABI.

Commonly encountered EEG findings in the intensive care unit

Seizures, status epilepticus, and the ictal-interictal continuum

Seizures are commonly encountered in adult, pediatric, and neonatal ICUs [17]. Seizures in critical care are mostly electrographic without clinical correlate and would go unnoticed without EEG. Management of seizures and status epilepticus relies on EEG as recurrent seizures during ICU management are mostly electrographic. Definitions of electrographic seizures (ESz), electroclinical seizures (ECSz), electrographic status epilepticus (ESE), and ictal-interictal continuum (IIC) are summarized in Table 1 [9, 18, 19]. A number of qEEG panels have been explored to quantify seizure frequency, with spectrograms and amplitude-integrated EEG being the most widely available. Spectrograms utilize a computational algorithm called fast Fourier transform to process raw EEG signal to display the full range of recorded frequencies (often on the Y-axis) and power of the EEG signal (in different colors, the Z-axis) over time (often on the X-axis), with power representing the area under the curve of frequency and amplitude of the EEG signal [20]. The "solid flame" qEEG pattern represents a paroxysmal, abrupt onset of higher EEG power with a smooth edge similar to candlelight, and has been demonstrated to carry high accuracy for seizure detection (Fig. 2, Supplemental Fig. 2); however, corresponding raw EEG should always be reviewed for confirmation [21]. Amplitude-integrated EEG (aEEG) represents a qEEG method for seizure detection (widely used in neonates) based on the typical sudden increase in voltage that occurs with most seizures (Fig. 3) [22]. QEEG trends can be reviewed at the bedside by ICU clinicians (intensivists and trained nurses) for seizure identification with fairly high sensitivity but fairly low specificity.[23–25]. This low specificity necessitates a review of raw EEG to assure those false positive events detected by qEEG do not result in overtreatment.

Prevalence of seizures and their association with outcomes

ESz are common in critically ill pediatric and adult patients, with prevalence rates ranging from 3 to 47% across a variety of conditions including traumatic brain injury (TBI), cardiac arrest, aneurysmal subarachnoid hemorrhage (aSAH), extracorporeal membrane oxygen support, and neonatal cardiopulmonary bypass (Supplemental Table 1). Many studies have linked seizures and IIC patterns to worsened outcomes in ABI patients. Additionally, the presence of ESz and ESE is associated with death or severe disability at hospital discharge in primarily non-brain-injured critically ill surgical ICU patients [26]. In the adult medical intensive care unit, the presence of seizures or IIC was independently associated with death or severe disability at hospital discharge [27]. Multiple pediatric cohort studies across a variety of conditions have linked seizure burden with mortality and impaired functional outcomes [18, 28].

Physiologic changes associated with seizures and periodic discharges

It remains unclear if electrographic seizures and IIC are a reflection or cause of ongoing brain injury, likely often both are true [17, 29]. Characteristic peri-ictal diffusion restriction can be detected in the grey matter on magnetic resonance imaging, reflecting excitatory neuronal injury; these are most commonly seen in the cortex, hippocampus and pulvinar [30]. Single-photon emission computed tomography studies evaluating IIC patterns have demonstrated increased cerebral blood flow (CBF) in areas in which periodic discharges (PDs) occurred, similar to regional increases in BF in patients with seizures [31, 32]. A small prospective study using positron emission tomography demonstrated hypermetabolism in patients with IIC (some would qualify as seizures with current definitions) that is associated with later development of status epilepticus [33]. However, generalizations from this study should be made with caution as many of these patients had an underlying neuroinflammatory disease and similar positron emission tomography findings are seen in patients with a neuroinflammatory disease without IIC.

Investigations utilizing multimodality neurologic monitoring further support the notion that both seizures and IIC may be associated with physiologic disturbances that can cause or exacerbate brain injury. In adult patients with aSAH, ESz were associated with tachycardia, tachypnea, and hypertension but only a very delayed increase in regional CBF, in addition to trends in elevated cerebral perfusion pressure and intracranial pressure [34]. Brain oxygenation tended to drop transiently and a brief decrease in jugular brain oxygenation suggested a brief global increase in oxygen extraction fraction. In adult patients with severe TBI undergoing cerebral microdialysis, PDs were associated with elevated lactate-pyruvate ratios, indicative of metabolic crisis [35]. In adults with aSAH, higher frequency PDs were associated with increases in regional CBF and cerebral perfusion pressure while brain tissue oxygenation remained stable, but at frequencies of 2.0 Hz or above, brain tissue oxygenation dropped [36]. These findings suggest

Table 1 Basic EEG terminology relevant for the intensive care unit

General EEG terms	
EEG	Differences in electrical potentials recorded between two or more electrodes representing the summation of excitatory and inhibitory postsynaptic potentials generated by cortical and subcortical structures
Montage	The arrangement of electrodes on the skull. Recordings can be visualized as one electrode compared to another (e.g., longitudinal bipolar, transverse bipolar montage) or one compared to many combined (e.g., referential montage). This visualization provides lateralizing and localizing information of the recorded EEG signal
Polarity	Upward and downward pointing waveforms (also known as positive and negative polarities). Negative voltages are plotted upward by convention
Location	Refers to the presumed origin of the EEG signal (i.e., frontal, temporal, parietal, central, and occipital cortex)
Amplitude	This relates to how large the waveform is (in microvolt [μV]). Usually range between 10 and 100 μV
Frequency	Cycles per second, measured in Hertz [Hz]. Activities of primary interest of EEG recorded from the scalp range between 0.5 Hz and 30–70 Hz frequencies. These frequencies are stratified into: delta frequencies for 0.5–4 Hz, theta for 4–8 Hz, alpha for 8–13 Hz, and beta for 13–30 Hz. Gamma frequencies (above 30 Hz) can be recorded but in practice it may be difficult to differentiate these signals from muscle artifact
Morphology	Shape of the waveform (i.e., sharp waves, spike-waves)
Prevalence	Intermittent or continuous activity
Synchrony	Whether waves are recorded simultaneously in different locations
Symmetry	Waveform symmetry between both hemispheres
Continuity	Presence or absence of intervening attenuation or suppression (low amplitude)
Background	Underlying EEG signal. Abnormal EEG backgrounds can vary from those that are comprised of continuous but slower (theta and delta frequencies) and/or suppressed waveforms, to burst suppression. A range of superimposed EEG findings including sporadic epileptiform discharges and rhythmic or periodic patterns (RPPs) are seen with cortical irritability and are associated with a higher risk for developing seizures
Periodicity	When patterns are occurring periodically (repeating at a set frequency with an interdischarge interval), they are called periodic, which can be focal (specific area), generalized (symmetrically involving both hemispheres simultaneously), bilaterally independent (asynchronously involving both hemispheres simultaneously), unilaterally independent (asynchronously involving two regions of the same hemisphere simultaneously) or multifocal (asynchronously involving three independent region simultaneously)
Normal EEG patterns	
Normal awake EEG	Continuous (no periods of EEG background suppression) and reactive to stimulation with an amplitude in the 10–50 μV range and frequencies predominant in the alpha and beta range (Fig. 2). In normal, relaxed adults, teens, and older children, eye closure elicits an alpha-frequency rhythm over the posterior brain regions known as the posterior dominant rhythm [PDR] (Fig. 9)
Normal sleep	Predominance of slow frequencies (mostly delta) except for REM sleep, when patterns more closely resemble the awake state. Characteristic EEG patterns called K-complexes and spindles are normal features that define stage 2 or non-REM sleep (Fig. 5, Supplement 4)
Normal neonatal patterns	Neonates demonstrate specific features (e.g., frontal sharp transients, delta-beta complexes [also known as delta brushes]) and patterns of discontinuity (e.g., tracé alternant, tracé discontinue) that can be normal depending upon conceptional age
Reactivity to stimuli	Change in frequency and/or amplitude when a patient is stimulated
Posterior dominant rhythm (PDR)	Electroencephalographic rhythm in the bi-occipital region, often that is sustained and well regulated to eye opening in healthy patients. Typically in the alpha range for normal healthy school-age, adolescent and adult patients
Abnormal EEG patterns	
Ictal	Repetitive EEG abnormalities that electrographically represent ongoing seizure activity
Electrographic seizures (ESz)	Defined as (a) epileptiform discharges averaging > 2.5 Hz and lasting ≥ 10 s, or (b) any pattern with definite evolution and lasting ≥ 10 s (Fig. 10)
Electroclinical seizure (ECSz)	Any EEG pattern with either (a) a definite clinical correlate time locked to the pattern (of any duration, and even if subtle), or both electroencephalographic and clinical improvement after administration of parenteral antiseizure medication
Electrographic status epilepticus (ESE)	Electrographic seizures (ESz) that lasts ≥ 10 continuous minutes or for a total duration of ≥ 20% of any 60-min period of recording
Ictal-interictal continuum (IIC)	Electroencephalographic patterns that do not qualify as either ESz or ESE but are considered *potentially ictal* and possibly contributing toward clinical impairment and/or brain injury. These typically involve periodic discharges (Fig. 11, Supplement 7) or lateralized rhythmic patterns between 1 and 2.5 Hz (Fig. 12)
Postanoxic myoclonus (PAM)	Involuntary generalized, segmental or focal of the body after hypoxic-ischemic brain injury. Can vary in rhythmicity. Maybe cortical or subcortical in generation

Table 1 (continued)

Myoclonic Status Epilepticus (MSE)	Not uniformly defined. Maybe practically defined as (1) myoclonic activity occurring once every 10 s longer than 10 min or (2) at least once for a minute and lasting longer than > 30 s
Postanoxic status epilepticus	Electroclinical or electrographic status epilepticus occuring after hypoxic-ischemic brain injury. May also include myoclonic status epilepticus

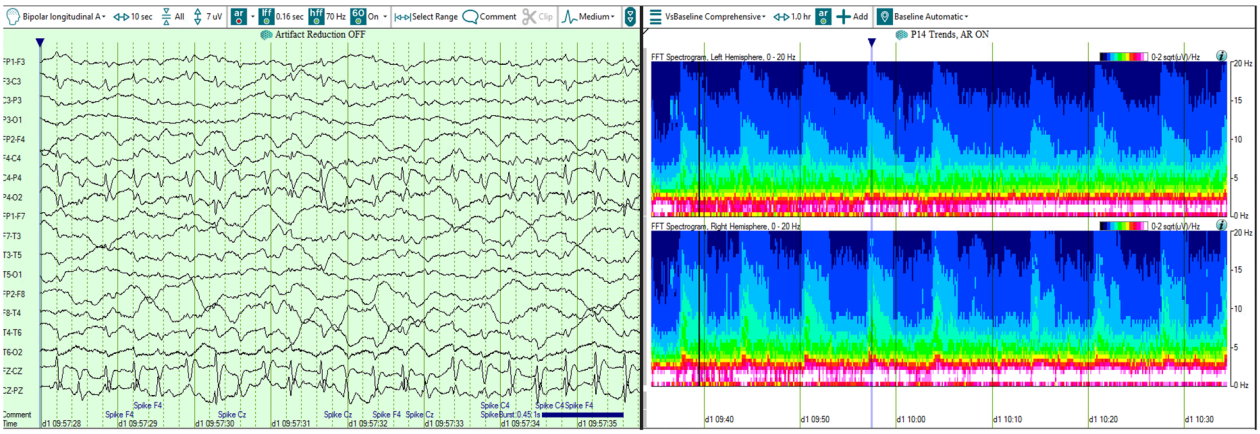

Fig. 2 Cyclical seizures over the right posterior region can be observed on raw electroencephalography (left) and are demonstrated with the flame sign on color-dense spectral array panels

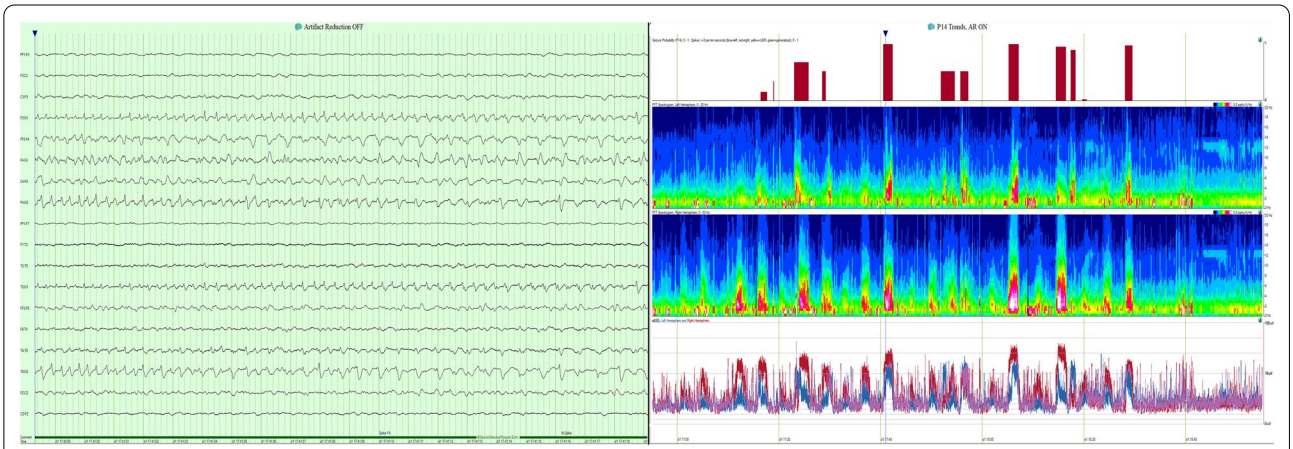

Fig. 3 Recurrent multifocal seizures are in a term neonate, which are appreciated on raw EEG (left) in addition to the identification of the 'flame sign' on color dense spectral array (right, middle panels) and increase in amplitude on the aEEG panel (right, bottom panel)

that increased metabolic demand from higher frequency discharges may be partially compensated, possibly due to limited vasoreactivity in ABI, and that compensatory mechanisms are insufficient with certain IIC patterns, especially those above 2.0 Hz.

Recovery of consciousness and prognostication

Bedside clinical examinations are crucial to predict recovery of consciousness; however, they are labor intensive and intermittent. Even careful standardized neurological assessments of consciousness may misclassify conscious patients as unresponsive [37, 38]. Impaired levels of consciousness may influence the decision to withdraw life-sustaining therapies in patients with ABI [39, 40]. Over the years, clinicians and researchers have explored the potential to augment the accuracy of prognostication models and several EEG-based techniques have emerged as promising. EEG was first linked to patient outcomes

over 50 years ago [41], classifying EEG of patients with hypoxic-ischemic brain injury (HIBI) based on frequency and amplitude [41]. Follow-up studies have further developed and automatized the generation of EEG features for neuroprognostication [42–45].

Advantages of using EEG for this purpose include its wide availability, low expense, non-invasive nature, and ability to continuously monitor physiologic signals of brain activity without interrupting clinical care. Challenges include expertise required in the interpretation of EEG patterns, obtaining high-quality recordings in an artifact-rich ICU environment, and confounders that may affect the EEG signal as well as the level of consciousness (e.g., sedative pharmacotherapy, temperature, and infection). Improved digital storage capacity and computational power have triggered a surge in the use of prolonged, continuous digital EEG recordings to predict and detect recovery of consciousness after ABI.

Resting-state EEG-raw EEG

Seizures and epileptic patterns may be associated with a depressed level of consciousness. Patients with mild encephalopathy often have a decrease in the frequency of the posterior dominant rhythm (PDR), excess slowing, and overall loss of faster frequencies [46]. Diffuse attenuation of the background is recorded with more severe encephalopathy [46]. Generalized periodic patterns with 'triphasic wave' morphology are commonly seen in different conditions including toxic/metablic encephalopathies (Fig. 4, Supplemental Fig. 3), but can sometimes be ictal themselves [47–49]. Loss of reactivity and a discontinuous or completely suppressed EEG are characteristic of severe encephalopathies [49]. Sleep architecture and the emergence of sleep spindles may reflect corticothalamic integrity, an important component of arousal mechanisms (Fig. 5, Supplemental Fig. 4) [51, 52].

Multiple EEG features have been included in prognostication algorithms for unconscious patients. Much of the published reports focus on patients with HIBI due to cardiac arrest. Poor outcome has been associated with suppressed background activity, burst suppression with identical or not identical bursts (the former indicating worse outcomes; Supplemental Fig. 5), and lack of continuous background activity. However, these patterns may be misleading when used in isolation, and good recovery may occasionally be seen. Therefore, the significance of EEG findings should always be assessed on a case-by-case basis using a multimodal approach [50, 53–55]. Continuous background activity with mixed frequencies is associated with a good prognosis [53, 54]. An exception to these general associations is the rare "alpha-coma" pattern. Unlike the normal alpha rhythm in healthy awake patients that close their eyes (PDR), in "alpha coma", unresponsive patients demonstrate an unreactive EEG in the alpha frequency range that predominates the frontal electrodes or is even seen throughout the brain (Fig. 6). In the postanoxic setting, this has been linked to poor outcomes and may be related to brainstem injury [56]. EEG reactivity to stimuli, defined as any change in the EEG signal to alerting stimuli, was proposed to improve the prognostic accuracy of EEG, [42, 57] although there remains a lack of standardization of reactivity testing and limited inter-rater agreement [58, 59]. Myoclonus may or may not be associated with epileptiform discharges on EEG. Myoclonic status (with or without EEG correlate) is associated with poor outcomes, but on a case-by-case basis may be treated with reasonable outcomes [60]. For example, postanoxic myoclonus with continuous background and narrow, vertex spike-wave discharges have been associated with favorable outcomes [61]. Reactivity is usually considered a predictor of a good outcome and should be included in the multimodal assessment of poor prognosis in a post-anoxia coma [62, 63]

Postanoxic status epilepticus (without myoclonus) may be associated with good outcomes and may justify an aggressive treatment approach in a subset of patients [64]. For example, in a prospective cohort study, 54% of patients with postanoxic status epilepticus lasting > 60 min and refractory to both intravenous benzodiazepine and an additional antiseizure medication (associated with no other predictors of bad outcomes) survived that were treated aggressively, and 44% of these patients had good neurological outcome (i.e., the ability to going back to work at 6 months); however, those with generalized PDs (most of whom had status myoclonus) did poorly [64]. Seizures are less common in HIBI patients with more severe injuries [61, 65]. It is also important to note that mild hypothermia and sedation do not significantly affect the prognostic accuracy of EEG in HIBI [45, 57, 66, 67]. The accuracy of EEG patterns for prognostication is likely time-dependent, as early detection of favorable patterns may be more accurate in predicting outcomes than unfavorable patterns. One study demonstrated that patients with early background recovery and late appearance of epileptiform activity were found to have good outcomes [68]. It is important to acknowledge that in the cardiac arrest literature, postanoxic myoclonus, myoclonus status and postanoxic status epilepticus have been used interchangeably, leading to misperceptions of the prognostic implication of postanoxic myoclonus [69].

The prognostication literature is less robust for patients with non-anoxic injuries [70–72]. Seizures have been

associated with increased mortality across a spectrum of neurological, medical and surgical ICU patients [72]. Reactivity suggests favorable outcomes in patients with TBI and metabolic or toxic encephalopathies [73, 74].

Resting-state EEG-quantitative analysis

Analysis of digitally recorded EEG signals exploring power, amplitude, complexity and inter-signal relationships (i.e., functional connectivity, network analysis) can be related to the level of consciousness and may improve the ability to accurately prognosticate recovery after ABI [71, 75–79]. The distribution of EEG power can be displayed as spectral plots (x-axis frequency in Hz, and y-axis power in dB) recorded over a set timeframe to investigate features linked to anterior forebrain corticothalamic integrity [76]. EEG recordings can be used as the source and characteristic spectral power plots have been associated with the degree of thalamocortical disconnection that may track recovery. Recovery in patients treated with neuro stimulants may be tracked with these measures of thalamocortical integrity [75]. Clinically unconscious patients with resting EEG patterns that resemble those of conscious patients are more likely to recover in subsequent weeks [80]. Although qEEG is a promising tool, it is not currently used routinely in clinical practice to prognosticate recovery of consciousness.

EEG recorded with passive perturbation

Perturbation tasks evaluate averaged EEG signals in response to a stimulus (i.e., somatosensory, auditory) – also called evoked/event-related potentials (ERPs) [81]. In clinical practice, somatosensory evoked potentials (SSEP) are most commonly used in the context of diffuse brain injuries such as HIBI and TBI [44]. These visualize the averaged electrical response of the central nervous system following repeated electrical stimulation of a peripheral nerve, such as the median nerve at the wrist. Absent cortical responses (i.e., N20, the negative wave 20 ms after stimulation) indicate severe injury and are predictive of poor recovery with high specificity in patients with HIBI and TBI [44, 82]. Another example is the use of auditory ERPs, although less commonly used in clinical practice. Distinct responses to standard and deviant tones may reflect higher cognitive processing and subsequently predict recovery [44]. ERPs can be classified into low- and high-order. Low-order ERPs (within 300 ms of the stimuli) are usually seen in primary sensory pathways and as a result of direct detection of the stimulus. High-order ERPs (usually more than 300 ms after the stimuli) result from the recruitment of multiple brain regions and may require more complex methods for detection [44]. Responses seen in high-order ERPs may reflect higher cortical processing and subsequently higher chances of recovery.

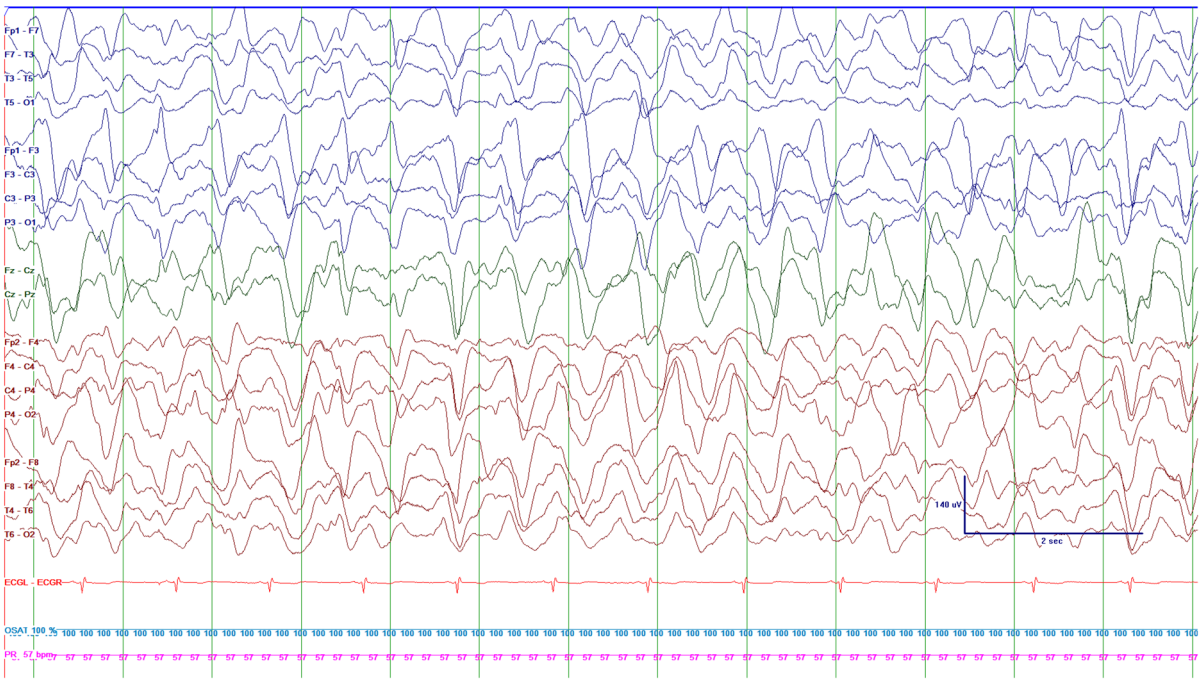

Fig. 4 Generalized periodic sharp waves are observed with triphasic morphology in a patient with hepatic encephalopathy

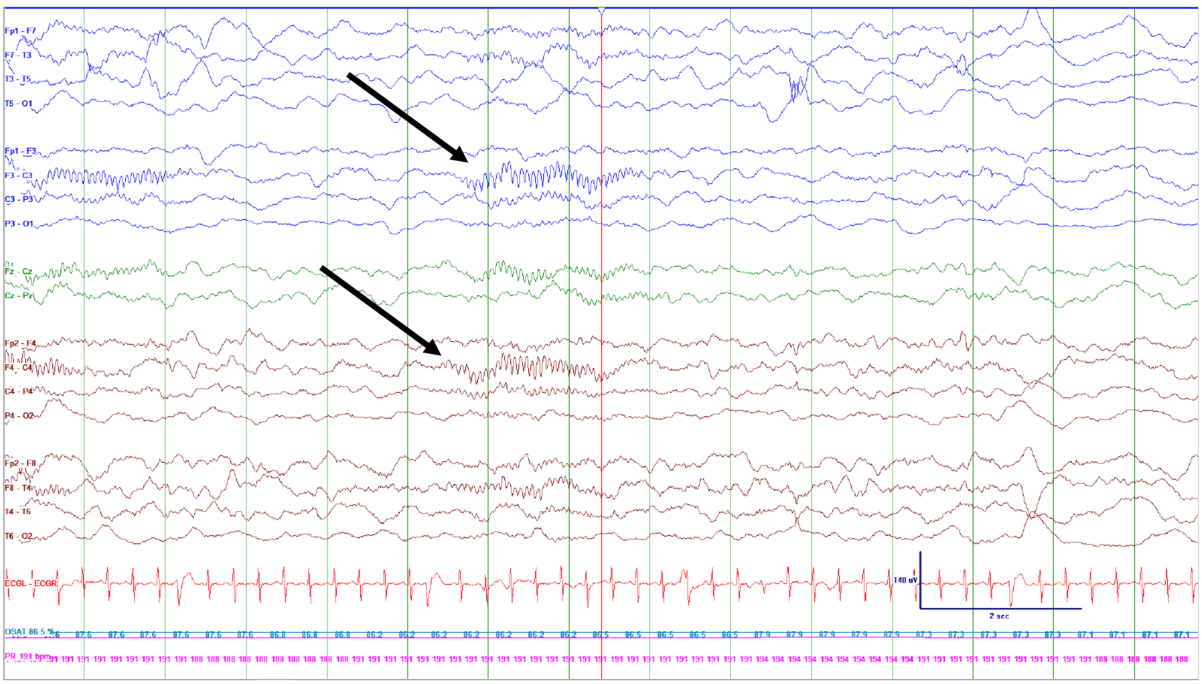

Fig. 5 Example of sleep spindles observed over the bilateral hemispheres (arrow), indicative of corticothalamic function

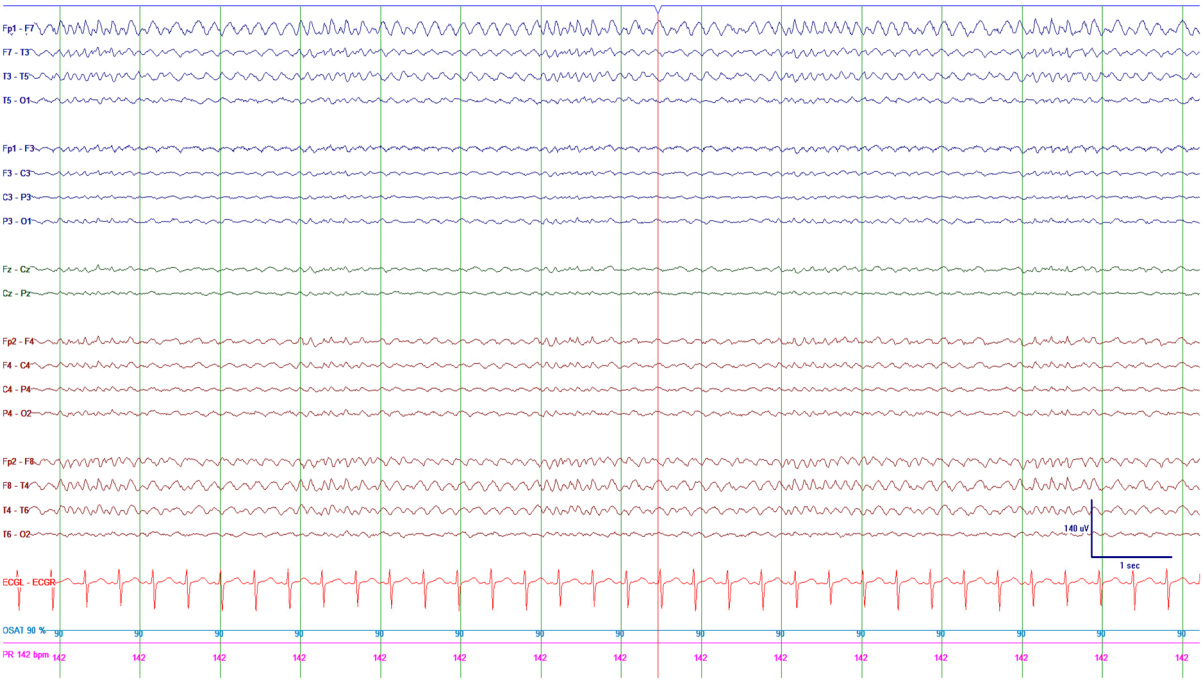

Fig. 6 An alpha coma pattern is observed in a 2-year-old female after a submersion injury and hypoxic-ischemic brain injury

EEG recorded with active perturbation

Evaluating brain responses to stimuli that assess the patient's ability to interact (e.g., a motor command) are labeled as active perturbation tasks. This technique allows investigators and clinicians to determine if the patient is actively engaging with specific tasks. Cognitive motor dissociation (CMD) is a state in which the patient willfully modulates brain activity (detected either by functional MRI or EEG) to verbal commands (e.g., to move their hand), but does not demonstrate a behavioral sign such as a motor response [12, 13, 83–86]. CMD can be detected in 15% of acute brain injured adult patients who appear clinically unresponsive on the exam using EEG, contrasting the EEG response to motor commands "keep opening and closing your right (left) hand" as compared to "stop opening and closing your right (left) hand" [12]. This diagnosis is made after power spectral density analysis of the EEG signal, and using machine learning algorithms to determine if the recorded EEG signal was significantly different between the two commands (Fig. 7). Patients with CMD diagnosed in the ICU have a higher chance of functioning independently 1 year after the injury [12].

Recommendations

The 2020 AHA guidelines recommend intermittent or continuous EEG monitoring for patients in a coma to evaluate for seizures [87]. In the 2021 European Resuscitation Council and European Society of Intensive Care Medicine guidelines, highly malignant EEG patterns at > 24 h after cardiac arrest are integrated into the prognostication algorithm. Highly malignant patterns include suppressed background with or without PDs or burst suppression [61, 63, 88, 89]. Other patterns described as predictors of poor outcomes in the European guidelines include the presence of seizures on EEG during the first 72 h, absence of background reactivity, and bilaterally absent SSEP N20 responses [63]. For both anoxic and non-anoxic injuries, the 2018 American Academy of Neurology and the 2020 European Academy of Neurology guidelines endorse EEG following perturbation tasks if these are available, but are primarily guided by data from patients with chronic disorders of consciousness as evidence in the critical care setting is only now emerging [90, 91]. Passive and active perturbation tasks (e.g., motor command) have the potential to improve the management of ICU patients. However, this research may bring to the surface ethical and societal dilemmas when caring for vulnerable populations and equity questions will need to be addressed [81]. Lastly, brain–computer interfaces that utilize EEG may offer an opportunity for alert ICU patients with a limited ability to communicate to connect to the outside world, but many challenges will have to be overcome to make this a commonly used reality [92–94].

Ischemia detection

Cortical layers III and V neurons play a prominent role in the generation of EEG signals and are exquisitely sensitive to ischemia, making EEG a potentially useful tool for perfusion monitoring [95]. EEG changes associated with ischemia follow a somewhat predictable order: (1) Loss of faster frequencies (> 6–8 Hz) is usually seen when CBF is below 35 ml/100 g/min, which corresponds to anaerobic metabolism and neurotransmitter release (i.e. glutamate); (2) with further reduction in CBF (18–25 ml/100 g/min), an increase of slower frequencies (4–7 Hz) is seen, which corresponds to lactic acidosis and declining adenosine triphosphate; (3) increase of even slower frequencies (1–4 Hz) occurs with further worsening of CBF (12–18 ml/100 g/min), which corresponds to sodium–potassium pump failure, and increased intracellular water content; (4) finally, EEG signal suppression occurs with CBF levels below 10–12 ml/100 g/min, corresponding to calcium accumulation, anoxic depolarization, and cell death [95].

In patients undergoing carotid endarterectomy, half had decreases in alpha, beta, and theta power and an increase in delta power at a median of 4 min after carotid cross-clamping [96]. Similarly, in patients with acute ischemic strokes, there is an increase in slower frequencies and a decrease in faster frequencies that correlate with CBF [97]. These changes are reflected on the EEG within seconds, and EEG improvement may precede clinical recovery after the restoration of blood flow by up to 100 min.[98–100] Delta-Alpha Ratio (DAR) or Delta-Theta/Alpha–Beta Ratio (DTABR) were highly correlated with stroke outcomes up to 1 year later [99].

Clinically, ischemia monitoring in the ICU is most established for the detection of delayed cerebral ischemia (DCI) in SAH patients. Common parameters used to evaluate ischemia in patients with SAH include Alpha/Delta Ratio (ADR), Relative Alpha Variability (RAV), and total power [14, 101–105]. These EEG measures usually precede a diagnosis of DCI by other methods (by hours to days) and may increase DCI detection sensitivity [101, 103, 104]. Increased slowing, new epileptiform activity, and seizures have been reported in patients with DCI [13]. Combining these EEG findings with qEEG features can provide daily pretest-probability assessments for DCI [14]. Combining EEG for detection of epileptiform findings and transcranial Doppler ultrasound (other qEEG measures were not utilized in this study) may improve the accuracy of diagnosing DCI when compared to either modality alone [106].

Using EEG for ischemia monitoring has multiple limitations, including expertise required for interpreting data, effects of different confounders (e.g., medications, temperature, toxic/metabolic disturbances) on EEG signals, and availability of qEEG software to generate quantitative data. In clinical practice, using EEG monitoring in patients with SAH is most helpful for comatose patients with high-grade SAH who are at higher risk for developing DCI. The 2014 international multidisciplinary consensus conference on multimodality monitoring in neurocritical care "suggests" EEG as a tool to detect DCI in comatose SAH patients, in whom the neurological

examination is unreliable. [107] EEG acquisition systems with improved signal-to-noise ratios will be important for improving the use of EEG as a reliable tool for DCI detection across the spectrum of high-risk patients.

Cortical spreading depolarization (SD)

Although many intensivists are aware of this phenomenon, the detection, reporting, and analysis of SD remain mostly in the research domain and are limited to a few centers. SD is a wave of electrophysiological hyperactivity (followed by inhibition) that slowly propagates across the cortex. SD leads to an abrupt breakdown of transmembrane ion gradients, altered vascular response, synaptic architecture changes, and cytotoxic edema subsequently leading to depression in electrical activity in an injured brain [108–111]. The influx of large cations and loss of membrane potentials results in depression in a cortical activity that spreads slowly at rates of 2–6 mm per minute [110]. Injured brain tissue is susceptible to SDs which are seen in conditions such as HIBI, hypoglycemia, ischemic stroke, aSAH, TBI, and seizures (Fig. 8, Supplemental Fig. 6). [15, 110, 112–116] In brain-injured patients, a vasoconstrictive response with an insufficient restorative vascular response is hypothesized to cause further ischemia that worsens the initial injury (secondary injury) [117, 118]. The acutely injured brain often cannot recover, leading to prolonged or terminal depolarization – the electrophysiologic correlate of neuronal cell death.

Depolarizations are accompanied by very slow (< 0.1 Hz) but high voltage shifts in brain electrical activity, best detected via direct current (DC) recordings from the cortical surface, but these can potentially be detected from alternating current (AC) recordings with proper filtering or qEEG (both via hardware and software filters) [119]. The secondary depression of standard EEG frequencies (the "depression" component) is usually focal and may occur over prolonged epochs [120]. As a result, this activity (both the DC shift and the focal depression) may be missed on scalp EEG [110]. Spatial resolution of

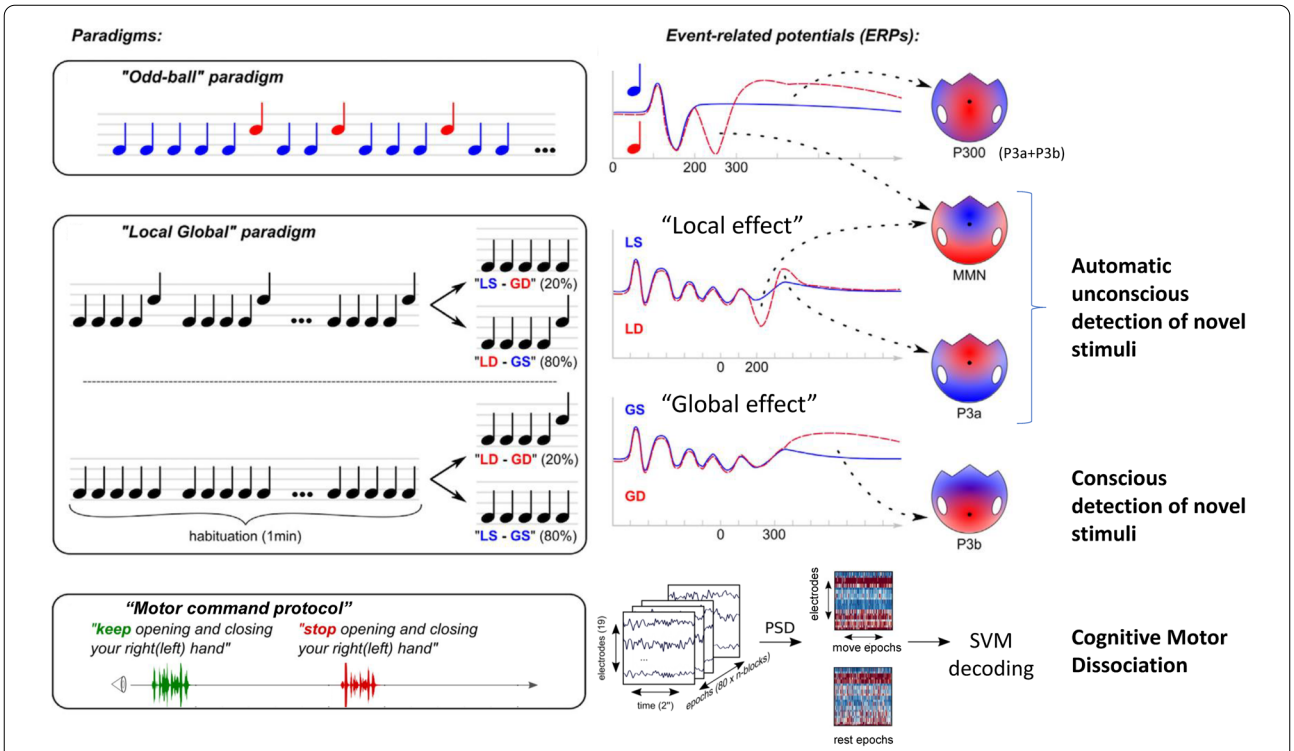

Fig. 7 Diagram describing different paradigms for evaluating event-related potentials with local and global effects to evaluate unconscious or conscious detection of novel auditory stimuli, in addition to the "motor command protocol" utilized for assessing motor command following using electroencephalographic power spectral density [7]

scalp EEG is on the order of centimeters squared, while SD happens over millimeters squared area. However, approximately 40–70% of depolarizations seen on cortical electrodes (subdural strips with multiple contacts placed directly over the injured brain or by a mini-depth electrode placed via an intracranial access bolt) correlate with decreases in amplitude on scalp EEG [121, 122] (Figs. 9, 10, 11, 12).

SDs have been associated with worse outcomes in TBI patients. The addition of this data to a six-month outcome prediction model (International Mission for Prognosis and Analysis of Clinical Trials in TBI [IMPACT] model, commonly used for TBI) increased the amount of variance that could be explained by the IMPACT model alone [15, 123]. In a subsequent study, the development of clusters of SDs (defined as ≥ 3 SD within a 2 h period) or isoelectric SDs was independently associated with lack of motor recovery in the hospital and worse functional outcomes at 6 months [16]. SDs have also been associated with increased infarct volume in ischemic stroke patients [124–127]. In patients with SAH, the appearance of clusters of SDs coincided with DCI, independent of angiographic vasospasm [128]. A phase III study of 170 patients undergoing strip electrode recordings after SAH, a total of 60 min per 24-h period of SD-related depression of high-frequency activity was associated with the development of reversible delayed neurological deficits and the duration of delayed depressions were significantly associated with the development of DCI, serving as a biomarker for this phenomenon [129].

In clinical practice and before SD monitoring becomes more available and feasible, the priority for intensivists should be focused on optimizing and managing secondary insults (such as hypotension, hypoxia, hypoglycemia, fever, and other metabolic disturbances) to prevent the cascade of secondary injury that may initiate or result from SDs [130]. Hopefully, detection and either treatment or prevention of SDs will become practical in the near future [131, 132].

Logistics of using EEG in the ICU

Technologists

Neurodiagnostic technologists may vary with respect to their experience and responsibilities should be tailored accordingly to the performance of EEGs, reactivity assessments, and maintaining technical quality of continuous ICU EEG recordings [3].

Recording technology

Disk and cup scalp electrodes are typically used in ICU continuous EEG monitoring; these are made of gold, silver or silver chloride material. Subdermal needles and wire electrodes are also available [133]. While safe in the computed tomography (CT) scanner, they can cause substantial artifact. Specialized electrodes made with conductive plastic and non-ferrous metals are compatible with both CT and MR imaging, and can cause minimal artifact [134, 135]. Daily inspection for skin breakdown and infection is important, and the use of intermittent periods of scalp rest is often helpful during prolonged monitoring. Using subcutaneous electrodes is another option [3, 136] Electrodes are usually arranged using the international 10–20 system with a 21-electrode montage (Supplemental Fig. 1). Electrodes are placed in standardized locations (e.g., the international 10–20 system) most commonly using 21-electrodes. For visualization of the recorded EEG signal bipolar (i.e., the potential difference of one electrode is recorded compared to another one, typically a neighboring electrode) and referential montages (i.e., one electrode is compared to a distant one or to the combination of many others, then also referred to as average) are commonly used. Intracranial EEG can be performed with intraparenchymal depth or subdural strip electrodes for the detection of epileptiform abnormalities and SDs not readily detectable on surface EEG [137–140].

ACNS provides standards for critical care EEG amplifiers, converters, and the necessary hardware and software used to collect ICU EEG data [3]. Monitoring of SDs ideally utilizes direct-current amplifiers [139]. Synchronized video and audio recordings are recommended to assess associations of changes in clinical behavior with specific EEG findings and help identify artifacts and patient stimulation. Bedside EEG annotation of relevant information by bedside ICU personnel is helpful and frequent review of EEG is needed. Bedside and central monitoring stations can allow for sufficiently trained personnel to screen for changes that require urgent assessment.

Interpretation

ACNS provides consensus recommendations regarding personnel and technical specifications for continuous EEG monitoring for critically ill adults and children [3]. Training may occur through various pathways; including fellowship in clinical neurophysiology, epilepsy, or neurocritical care training that offers sufficient teaching and exposure to EEG. For neonates, ACNS guidelines recommend EEG interpretation by a clinical electroencephalographer at least twice per 24-h epochs and more often as indicated [141]. At a minimum, a daily written report within the medical record is recommended that synthesizes key EEG findings.

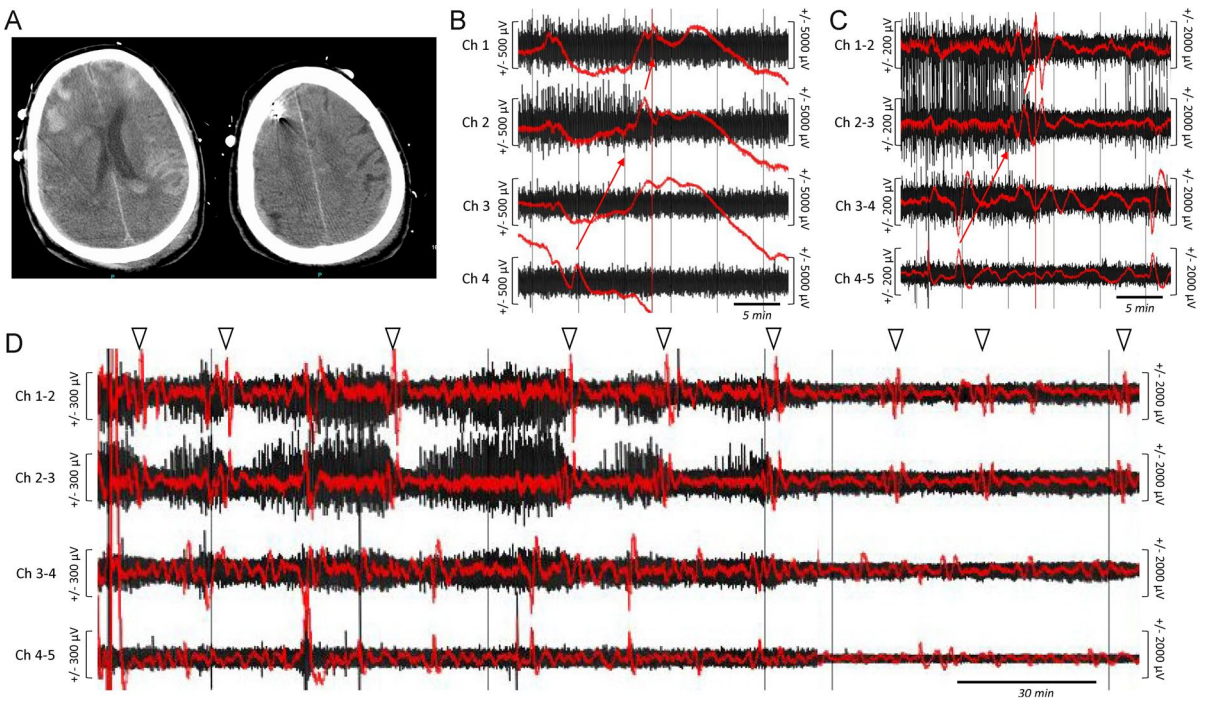

Fig. 8 Clusters of spreading depolarizations on depth electrode monitoring after severe traumatic brain injury. A 76 year old man was admitted after a fall. His initial Glasgow Coma Scale score was 7 and he had bilaterally reactive pupils. A right frontal multimodality monitoring bolt was placed at the bedside in the intensive care unit which included a depth electrode. Hours later, he developed a worsening of his neurological exam. **A** Post-bolt non-contrast head CT demonstrates widespread contusions, traumatic subarachnoid hemorrhage, and intraventricular hemorrhage. The location of the bolt within the right frontal cortex is shown. **B** An example of spreading depolarization (SD) using referential electrocorticography (ECoG). The black band represents high-frequency EEG and the red band represents DC-centered signal. A negative DC potential is observed in channel 4 initially, followed by spread (red arrows) to channels 2 and 1. The depolarization in channel 4 occurred despite low voltage activity in the high-frequency band, defining an isoelectric spreading depolarization. The region of cortex recorded in channels 2 and 1 in contrast exhibits higher amplitude high-frequency activity that subsequently becomes depressed for approximately 10 min. **C** Using bipolar recording and near-DC low pass filtering (0.005 Hz), the same spreading depolarization can be visualized which displays the negative potential with an artificial 'triphasic' appearing morphology. Note the enhanced clarity of the focal regions of high-frequency depression. **D** Over a 6-h window, a cluster of spreading depolarizations occurs (denoted by white arrowheads), defined as 3 or more SD within a 2 h window. The restoration of high-frequency activity after each SD becomes progressively lower in amplitude until finally, the SDs become isoelectric

Intermittent versus continuous EEG

Controversy remains regarding the optimal duration of EEG monitoring particularly in resource-limited settings. A recent multicenter randomized controlled trial (Continuous EEG Randomized Trial in Adults [CERTA]) [142] compared continuous to intermittent, routine EEG in patients who had not had prior seizures and found no difference in mortality in ICU patients. However, seizures and anti-seizure modifications were more frequent in those undergoing continuous monitoring. This trial had many limitations, although it did suggest that repeated, routine EEG studies are reasonable in resource-limited settings [143]. Of note, these serial EEGs are not necessarily easier for the EEG technologist than continuous monitoring. A scoring system (2HELPs2B score) with the use of clinical and EEG features maybe beneficial to identify higher-risk patients who need longer EEG recording [144, 145]. More prolonged EEG monitoring may support a goal-directed management support of patients with refractory status epilepticus, both in upper-middle and high-income countries [146].

Navigating resource-limited settings

The logistics of ICU EEG acquisition and interpretation require substantial resources. Several technologies have been developed including abbreviated montages, peel and stick electrodes, electrode caps/bands and simplified user-friendly EEG machines that help facilitate timely performance of EEGs by bedside ICU personnel. These technologies may assist smaller centers in identifying patients who require transfer to centers that can facilitate continuous EEG monitoring [147, 148]. Many centers may not have sufficient resources to facilitate frequent reviews of continuous EEG. Several studies have

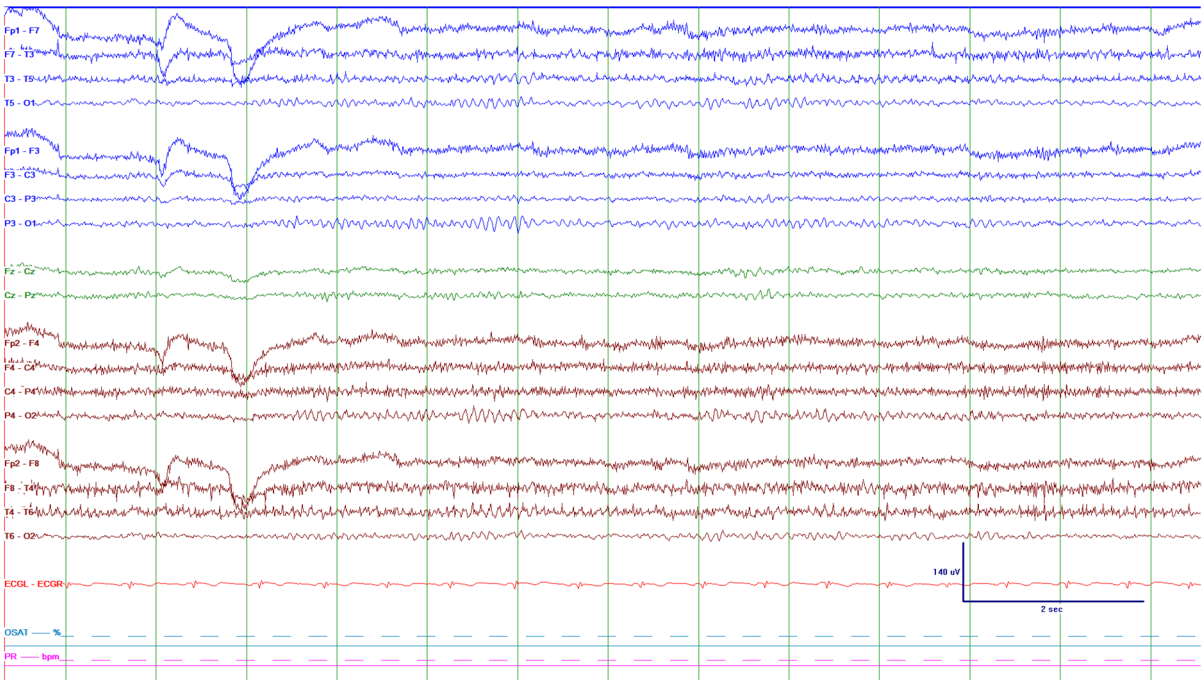

Fig. 9 Example of normal awake background in an adult patient with a posterior dominant rhythm in the alpha (8–13 Hz) range

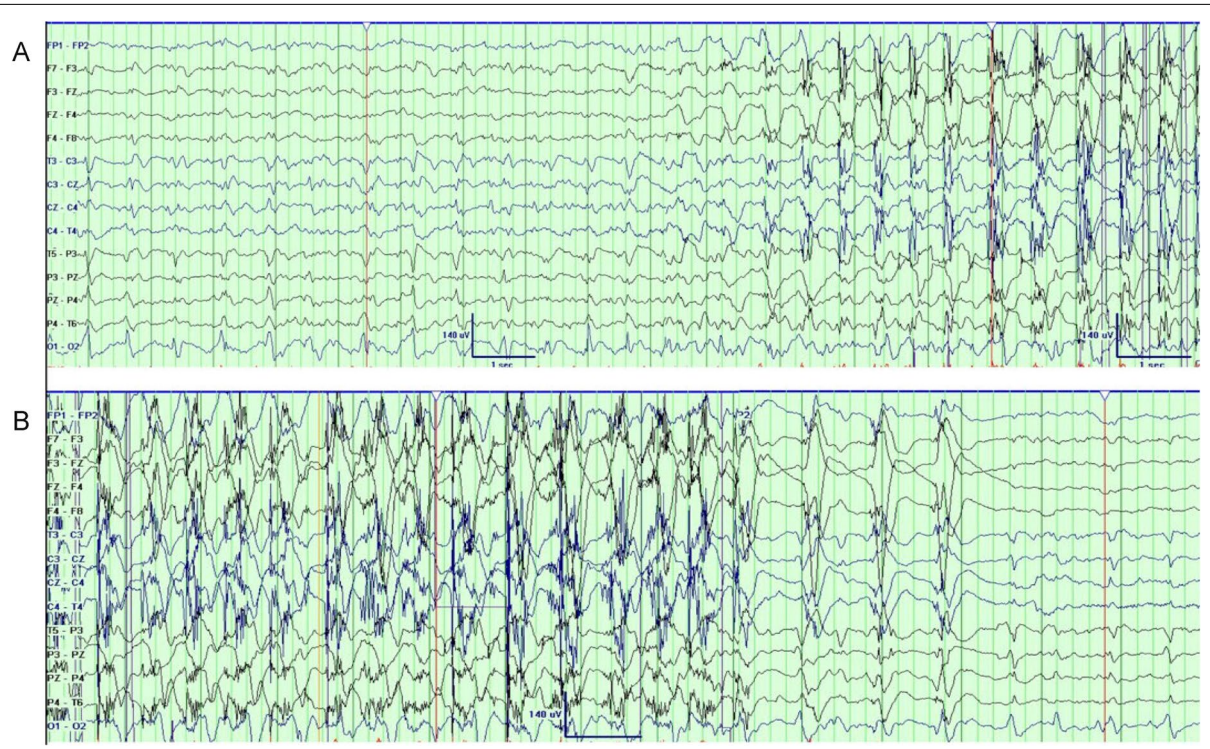

Fig. 10 Example of an electrographic seizure manifesting with definitive spatiotemporal evolution over 10 s in duration

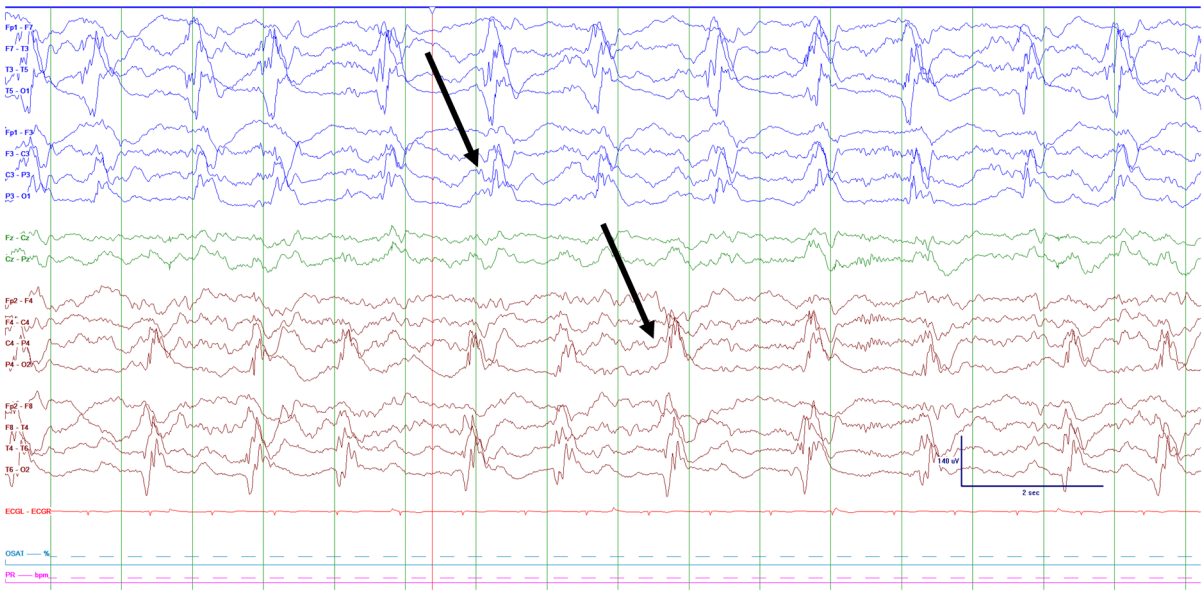

Fig. 11 Bilateral independent periodic discharges with embedded polyspikes (BiLPDs + , arrow) are observed in a patient with posterior reversible encephalopathy syndrome

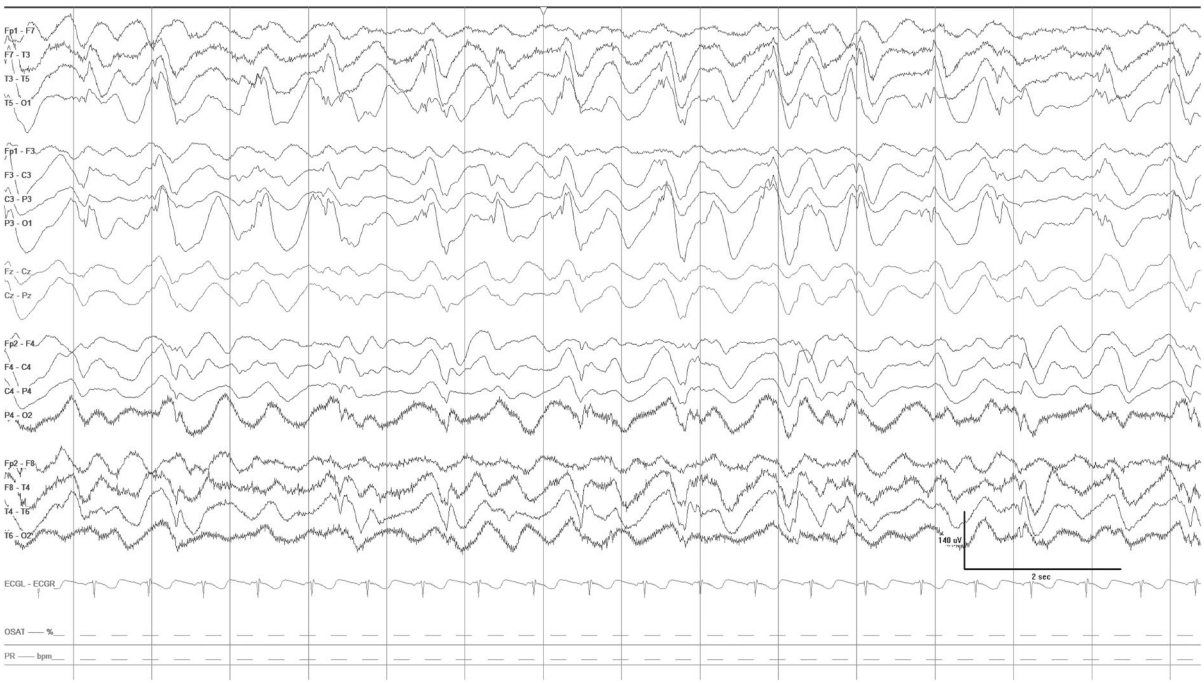

Fig. 12 Lateralized rhythmic delta activity with embedded spikes (LRDA + S) observed in a patient with meningoencephalitis with acute symptomatic seizures

suggested that non-EEG experts such as bedside ICU personnel can be trained in the acquisition and troubleshooting of EEGs, as well as screening continuous raw EEG and qEEG for seizures [25, 148].

Some challenges are unique to low and middle-income countries. EEG equipment from major manufacturers, when available through importation, arrives at prohibitive costs to medical institutions, which is a disincentive

to more widespread use in critically ill patients. Local EEG manufacturers may be scarce. There may be insufficient availability of advanced training for technologists and ancillary staff. Apart from rare specialized academic institutions with neurophysiology departments, many general public hospitals in low and middle-income regions lack the capacity to perform ICU EEG monitoring. Some private institutions and hospital networks have developed capacity through the implementation of outside tele-EEG services to cover multiple institutions with remote centralized EEG reading, cloud-based storage, and telemedicine-based real-time notification of findings to intensive care teams. Wider implementation of ICU EEG monitoring in these regions will likely require lower-cost equipment technology, additional training, and remote monitoring with tele-EEG services.

Future Developments

Institutional protocols designed around the best available evidence and expert consensus are recommended. Key factors that should be considered when developing institutional protocols include (1) what ICU EEG indications the centre can support (Supplemental Table 2), (2) what patient population is served (e.g., underlying diagnosis of the patients), (3) what monitoring length should be triggered based on specific EEG findings (e.g., continuous monitoring for super-refractory status epilepticus), (4) what the local context is (i.e., number of available technicians, available EEG readers, frequency of review.

Conclusion

EEG is a powerful tool to monitor the brain in critically ill patients. Beyond detection of seizures, continuous EEG is increasingly being used for behavioral assessments (especially to detect covert consciousness), prognostication, ischemia monitoring, and detection of cortical SDs. The improvement of storage capacity, computational power, and detection and prediction algorithms are the driving forces toward improving the utilization of EEG in the ICU—a step closer toward a personalized medicine approach to predicting, detecting and preventing secondary neuronal injury in critically ill patients.

Supplementary Information

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Author Contributions

Conceptualization and drafting of the manuscript: AA, BA, BR and JC. Critical Revision of the manuscript for important intellectual content: SE, BF, NG, EG, LJH, PK, VL, JK, PV and SZ.

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Declarations

Conflict of interest

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