



Review article

Critical care EEG standardized nomenclature in clinical practice: Strengths, limitations, and outlook on the example of prognostication after cardiac arrest

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ABSTRACT

We discuss the achievements of the ACNS critical care EEG nomenclature proposed in 2013 and, from a clinical angle, outline some limitations regarding translation into treatment implications. While the recently proposed updated 2021 version of the nomenclature will probably improve some uncertainty areas, a refined understanding of the mechanisms at the origin of the EEG patterns, and a multimodal integration of the nomenclature to the clinical context may help improving the rationale supporting therapeutic procedures. We illustrate these aspects on prognostication after cardiac arrest.

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Abbreviations: ACNS, American Clinical Neurophysiology Society; BIRD, Brief potentially ictal rhythmic discharge; BS, Burst suppression; CA, Cardiac arrest; DWI, diffusion-weighted MRI; fMRI, functional MRI; GPD, generalized periodic discharge; GRDA, generalized rhythmic delta activity; ESI, electric source imaging; ICU-EEG, intensive care unit-electroencephalography; IIC, Ictal-Interictal Continuum; ICU, Intensive care unit; LPD, Lateralized periodic discharge; MEG, Magneto-electroencephalography; NCSE, Non-Convulsive Status Epilepticus; NSE, Serum neuron-specific enolase; PET, Positron emission tomography; SE, Status epilepticus; SPECT, Single Photon Emission Computed Tomography; SSEP, Somatosensory evoked potentials; WLST, Withdraw of life sustaining treatment.

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1. Introduction

In 2013 a group of experts of the American Clinical Neurophysiology Society (ACNS) reviewed the ICU-EEG Terminology to establish a revised and standardized version (Hirsch et al., 2013). The aim was to simplify it and, at the same time, to establish it as a common language for the classification of EEG findings, improving their recognition, description, and generalization. An important purpose was to exclude all terms that may give an “a priori” determined clinical connotation to certain transients (e.g. “triphase waves”) or EEG patterns. For example, GPD and LPD were previously referred to as “generalized/lateralized periodic epileptiform discharges”, but since an epileptiform activity was not a consistent feature, the terminology was adapted suppressing this word (Hirsch et al., 2013).

Nevertheless, the “epileptiform” connotation of GPD and LPD has been repeatedly described subsequently (Westhall et al., 2018; Barbella et al., 2020a): the need of attributing a clinical significance to certain patterns still exist (Beniczky et al., 2013; Trinka and Leitinger, 2015; Westhall et al., 2016; Rodriguez Ruiz et al., 2017; Barbella et al., 2020a), and appears particularly important when clinicians want to orient themselves on the need to start or adapt pharmacologic treatments. This generated a new version of the Terminology (Hirsch et al., 2021), which adds clinical interpretations and definitions to certain EEG patterns, whereas the 2013 version was purely descriptive. In this sense, the new 2021 Terminology reintroduced some of those clinical connotations excluded by the 2013 version, with precise and punctual definitions.

This paper reflects the opinion of the authors and has the purpose to discuss the important achievements of the ACNS critical care EEG Nomenclature proposed in 2013, and to outline, from a practical-clinical standpoint, remaining limitations.

We recall that the optimal approach should focus initially on an accurate description of the EEG observed pattern, without the attempt to interpret findings, and, in a second step, integrate the EEG findings into the clinical context of the specific patient. We will put some emphasis on the second step, as it is at times put aside in practice. In the current literature on cardiac arrest prognostication, for example, EEG is still often considered as an isolated tool, without routinely integrating other clinical factors (Sandroni et al., 2020) and attributing to the EEG pattern an inherent clinical connotation that it does not always have.

The proposed new 2021 version of the ACNS terminology gives clinical connotations to specific EEG patterns by defining for instance the concepts of *seizure* and *status epilepticus*. In its light, new aspects of other EEG patterns could be identified, with the routine integration of few but specific parameters.

Our aim is to offer the reader some hints of reflection regarding an enhanced use of the ACNS nomenclature, in order to better account for clinical situations. At this purpose, we propose three ways that could help reaching a more efficient use of the ACNS nomenclature: (A) deep understanding of the pathophysiological mechanisms generating those EEG patterns; (B) integration of the ACNS terminology to the clinical context in order to define some “electroclinical profiles”, and to create a consensus on the significance of EEG patterns of ambiguous connotation; (C) standardization of the therapeutic procedures.

For practical purposes, we concentrate our reflexion on prognostication of comatose patients after cardiac arrest (CA), which represent a relatively uniform aetiology that has received considerable attention in the recent literature.

2. EEG Terminology

The ACNS Terminology (Hirsch et al., 2013) establishes a step-by-step description of the EEG with periodic or rhythmic patterns, by defining a **main term 1** related to the anatomical distribution (*Generalized, Lateralized, Bilateral independent, Multifocal*), and a **main term 2** pertaining on the graphical appearance of the pattern (*Periodic discharges, Rhythmic delta activity, Spike-wave or Sharp-wave*). Thereafter, **modifiers** may apply; the major ones are: *prevalence, duration, frequency, absolute amplitude, polarity, stimulus-induced, evolution, and plus (+)*. Finally, the EEG **background** can be *symmetric or asymmetric*, the *anterior-posterior gradient* can be present, absent or reversed, the *voltage* can be normal, low, or suppressed. The background can be *continuous, nearly continuous, discontinuous, Burst suppression, or suppressed*. EEG reactivity should be tested and described. The main changes in the newly version (Hirsch et al., 2021) regard definitions of *electrographic or electroclinical seizure/Status epilepticus*, the outline of the *brief, potentially ictal rhythmic discharges* (BIRDs), and the paramount concept of *Ictal-Interictal Continuum* (IIC).

3. Strengths

The 2013 terminology represents the great achievement of standardizing EEG features, and consequently enhancing the description and communication of EEG findings in critically ill patients (and beyond) within the scientific and clinical community. This is reflected by its increasing use in the literature. The Nomenclature’s wide approach makes it possible to refer it to the majority of patterns recorded in critical care setting (Gaspard, 2015), but it may be applied also in patients on the ward or even in outpatients. Moreover it can be quickly learned and used, with good interrater agreement among EEG readers with different level of expertise (Gaspard et al., 2014); indeed, validations across raters represented a paramount step towards generalization of this approach. The agreement is near perfect in defining the main terms (Gaspard et al., 2014), and for the description of the background, including “highly malignant” EEG patterns (suppression, suppression-burst, and periodic discharges on a suppressed background), which play a crucial role in the prognostication of post-CA patients (Westhall et al., 2015). Recent literature clearly recommends the widespread application of the Terminology, especially in this clinical setting (Cronberg et al., 2020; Sandroni et al., 2020).

4. Limitations

As already outlined, the Terminology was generated with the purpose to create a descriptive approach of EEG patterns, as a basis to ease research assessing the clinical pertinence of such patterns (Westhall et al., 2015; Gaspard, 2015).

The need to confer a clinical interpretation to those patterns raised from the first studies that applied the 2013 Terminology, in particular looking for an “epileptiform” connotation that was excluded (Beniczky et al., 2013; Trinka and Leitinger, 2015; Rodriguez Ruiz et al., 2017). A landmark study in this sense, applying the Terminology but specifically looking for a clinical correlate (Rodriguez Ruiz et al., 2017), demonstrated the association between frequency of rhythmic or periodic patterns and plus modifiers and the risk of seizure on long-term EEG, which increases with increasing frequency.

The need to outline a clinical implication of definite EEG patterns of the Terminology has emerged clearly also from the publication of the Salzburg criteria to define nonconvulsive Status epilepticus (NCSE) (Beniczky et al., 2013; Trinka and Leitinger, 2015), which specifically applied frequency and temporal evolution.

And it was precisely these criteria together with the Status epilepticus (SE) ILAE definition (Beniczky et al., 2013; Trinka et al., 2015) that inspired the newer Terminology approach (Hirsch et al., 2021). Among the rhythmic and periodic patterns, the most critical for post-CA prognostication are those generalized (Westhall et al., 2016): GRDA is not associated with seizure at any frequency (Rodriguez Ruiz et al., 2017), and rather represents a different underlying mechanism related to dysfunction of deep generators in patients with encephalopathy or chronic lesions (Accolla et al., 2011; Sutter and Kaplan, 2013; Kim et al., 2021). On the contrary, generalized periodic discharges (GPDs) are related to a profound, potentially epileptic brain dysfunction, in particular when a Plus modifier is present (Rodriguez Ruiz et al., 2017).

GPDs represent indeed one of the best examples of the so-called “Ictal-interictal continuum”, an EEG signature of a dynamic pathophysiological state with a propensity to have seizures (Pohlmann-Eden et al., 1996).

Particularly interesting for the post-CA population are patterns such as not evolving, low frequency (0.5–2.5 Hz) GPDs in the absence of clinical manifestations, whose significance appears still controversial. No definitive consensus explains whether these represent an epiphenomenon of acute neuronal injury (severe encephalopathy), or an ictal phenomenon that needs to be treated specifically, as it was recently shown in a debate about the appropriate level of treatment aggressiveness for NCSE, even outside the CA setting (Rossetti et al., 2019).

An analysis of patients after CA showing refractory “status epilepticus” (defined as spike-waves > 2.5 Hz for at least 30 min) and receiving anticonvulsants and anesthetics (Beretta et al., 2018) suggests that GPD at < 2.5 Hz does not seem to represent ictal pattern, but rather an agonal EEG feature in severely injured subjects. Others seem to consider all frequencies of GPDs and LPDs as NCSE, for example in an ongoing study to establish if antiepileptic drugs are beneficial for patients presenting a NCSE after CA (Ruijter et al., 2014). The differentiation between treatable seizure-related GPDs from an irreversible GPDs in comatose subjects (Bauer and Trinka, 2010) is crucial for prognostication, since it implicitly implies the need to administer treatment in the first case, and its futility in the second.

Going beyond the mere description of GPDs in post-CA patients, recent evidence suggests that background continuity predicts potentially good outcome in particular if present within 12 h after cardiac arrest (Ruijter et al., 2015), highlighting the need of integrating multiple EEG information, sometimes in specific time-windows. This is in line with other studies in this clinical context, which show background continuity (for myoclonic status (Elmer et al., 2016)) and background reactivity (for myoclonic and NCSE (Rossetti et al., 2009)) being associated with potentially good outcome. To strengthen prediction of awakening beyond EEG features, other clinical parameters may be integrated, such as preserved brainstem reflexes (Rossetti et al., 2009; Bevers et al., 2018), of SSEP (Rossetti et al., 2009), or absence of anoxic lesion on brain MRI (Beuchat et al., 2020). The literature reports cases of good outcome in patients with 1–2 Hz GPD having responded to anticonvulsant drugs in the presence of brainstem reflexes, bilateral SSEP and low serum NSE levels (Rossetti et al., 2019).

A simulation model proposes the disruption between excitatory and inhibitory inputs (van Putten and Hofmeijer, 2015) at the origin of post-anoxic GPDs, suggesting that the mechanisms underlying their generation are similar to those involved in the generation of epileptic activity.

In order to better understand the nature of low-frequency GPDs, an EEG connectivity and source analysis study suggests a hyperactivity of the thalamo-cortical circuit taking the form of an oscillatory thalamic activity capable of inducing periodic cortical discharges, similarly to what happens in convulsive or NCSE. A limitation of this retrospective study is that 37/40 patients died early after withdrawal of life sustaining treatment (WLST) and no antiepileptic drug was tested, not allowing to confirm the epileptic nature of GPDs (De Stefano et al., 2020).

These considerations show how EEG criteria alone may sometimes be insufficient for the correct characterization of EEG patterns, especially in features belonging to the so-called “Ictal-interictal continuum”, as GPDs, and that other clinical or electrophysiological features may help orienting treatment. For example, Low Frequency GPDs on a reactive, continuous background, in a patient with preserved brainstem reflexes, flexor or better motor responses, low serum neuron-specific enolase (NSE), preservation of cortical SSEPs and no anoxic lesion at MRI, may be considered an “epileptic pattern”, potentially responding to anticonvulsant drugs. Or, to the contrary, an irreversible poor-outcome pattern when associated with non-reactive, suppressed background, lack of brainstem reflexes and cortical SSEPs, high NSE levels and diffuse anoxic lesions on MRI (Fig. 1). The EEG pattern appears to be the same, but clinical examination, complementary electrophysiological data, and imaging results are very different.

It is clear how the integration of a few but specific complementary parameters can add value to the EEG interpretation, overcoming the limits of a purely descriptive approach.

The concept of a “three-dimensional” biological continuum well shows this complexity in the interrelation between structural brain damage, epileptic activity and the degree of coma, and how an excessive epileptic activity may play a role in the worsening of the brain damage itself (Bauer and Trinka, 2010); however, if the structural damage is very important, the epileptic activity plays a negligible role.

As part of the prognostication assessment in post-CA comatose patients, based on the findings regarding rhythmic or periodic patterns, background and reactivity, the ACNS EEG criteria have been applied in order to define three EEG constellations, namely Highly malignant, Malignant and Benign (Westhall et al., 2016). If Highly malignant EEG predicts a poor outcome and a Benign EEG a good outcome, the Malignant patterns are yet of intermediate significance (Westhall et al., 2016; Rossetti et al., 2017; Beuchat et al., 2018). Within the Highly malignant patterns, we find Burst suppression (50–99% of recording consisting in suppression) that together with GPDs is one of the most studied EEG patterns in this clinical setting. Low voltage, suppressed or burst-suppressed background forecast unfavourable outcome (Rossetti et al., 2017), as generalized suppression and synchronous patterns with $\geq 50\%$ suppression (Ruijter et al., 2019). The background reactivity (which may be defined as a reproducible change in voltage or frequency to stimulation) is of help in this population of patients, as it is frequently described as predictor of good outcome (Rossetti et al., 2009; 2010; 2017; Admiraal et al., 2019; Barbella et al., 2020a). Unfortunately, the inter-observer agreement in the definition of reactivity in the ACNS terminology may be relatively inconsistent (Noirhomme et al., 2014; Gaspard, 2015; Duez et al., 2018; Admiraal et al., 2019) and this aspect remains a limitation, which can potentially be improved with protocolled testing (Tsetsou et al., 2015).

Burst-suppression is considered an independent predictor of bad outcome (Westhall et al., 2016; Barbella et al., 2020a), but not invariably (Cloostermans et al., 2012). For example, the presence of a burst theta spectral features that increase over time have been described to be associated with favourable outcome (Forgacs et al., 2020) and unexpectedly, these patients showed recoveries



Fig. 1. F, 68y, 48 h after asystole, no-flow 5 min, low flow 15 min, absence of anesthetic drugs; 19-channel EEG bipolar longitudinal montage. Distance between bold vertical bars: 1 s. ECG (electrocardiogram); SLI (intermittent luminous stimulation). Continuous, bilateral, periodic sharp waves at 1.5 Hz (GPDs), not reactive background. Clinical examination: FOUR score 6/16 (E1, M2, B2, R1). WLST on day 4.

following very prolonged coma (Greer, 2013; Weinstein et al., 2017; Forgacs et al., 2020). BS is in fact regarded by some authors as the expression of an innate protective mechanism to conserve neuronal energy with integrity of the cortico-thalamic network (Ching et al., 2012; Forgacs et al., 2020), that justifies continuation of intensive-care treatment. Actually, other EEG parameters on a burst-suppression background help to refine prediction: poor outcome is strongly associated with identical bursts (Hofmeijer et al., 2014; Barbella et al., 2020b), and “epileptiform” BS (BS with high amplitude polyspikes) in patients showing myoclonic status (Elmer et al., 2016). These two profiles of BS found their place in the new proposed Terminology (Hirsch et al., 2021). Similarly to post-anoxic SE, the presence of bilateral SSEP or flexor motor response herald favourable outcome (Rossetti et al., 2017).

As is the case for GPDs, it is evident also for BS, how other EEG or clinical parameters may help the correct prognostication assessment, but also how, even correctly described following the standardized nomenclature, BS can be the object of different managements, making difficult the interpretation of discrepant outcomes. Outcome prediction seems in fact more reliable integrating information in a multimodal approach: EEG patterns combined with timing, background continuity, reactivity, and amplitude features, integrating also clinical examination, serum NSE, and MRI seems more reliable in the prediction of outcome for prognostication in post-anoxic myoclonus (Bevers et al., 2018; Beuchat et al., 2020). A recent systematic review concludes indeed that a multimodal approach, including EEG, is strongly recommended (Sandroni et al., 2020).

5. Perspectives

Here we propose three alternative ways envisaging a more efficient use of the nomenclature, better suitable to serve the clinical situations.

(A) a better understanding of the pathophysiological mechanisms generating a definite EEG pattern and the brain structures involved, in order to understand if the electrical signal is the result of a pathological neuronal synchronization emerging from the disequilibrium between excitatory-inhibitory mechanisms with a

“ictal” meaning. If those transients “only” reflect diffuse, irreversible injury of thalamo-cortical circuitries, or rather a residual activity of affected regions with a latent capacity for functional recovery across the cortico-thalamic system. Different electrophysiological and imaging technologies could be used in order to investigate networks involved in the generation of these patterns (Herlopian et al., 2018). In particular, recent literature showed how electric source imaging (ESI) and connectivity analysis at EEG can investigate networks and mechanisms at the origin of specific EEG patterns in post-anoxic patients, such as slow frequency GPDs (De Stefano et al., 2020). Both low and high-density EEG can be used, since studies showed that in case of high signal-noise ratio, such as in the case of GPD or burst-suppression, the reliability of low density ESI is not inferior than high-density EEG (van Mierlo et al., 2017; Coito et al., 2019).

Resting-state fMRI has been recently shown to perform significantly better than diffusion-weighted MRI (DWI) in the prediction of good outcome in post-anoxic patients (Pugin et al., 2020), can as well investigate functional brain connectivity. Nevertheless, the poor temporal resolution of MRI would not allow a precise correlation between the transient at EEG and the brain region(s) generating such transient, and therefore this technique, even if useful for prediction purpose, could hardly be used, in our view, for investigating networks underlying specific EEG patterns.

One possible approach could be simultaneous EEG-fMRI recording to investigate the anatomy involved in specific EEG patterns. For example, during generalized spike-wave discharges in generalized epilepsy, EEG-fMRI studies have consistently shown a thalamic activation associated with widespread neocortical deactivation (Hamandi et al., 2006). In the assessment of the severity of hypoxic-ischemic brain injury, DWI is recognized as a strong predictor tool for poor outcome (Hirsch et al., 2015). In this case as well, if the question is to establish the “ictal” nature of a specific pattern, it is difficult to attribute DWI changes to its epileptic nature or to the underlying brain dysfunction. Finally, PET and SPECT represent promising tools, allowing studying respectively the changing in brain metabolism and in perfusion. PET results for GPD patterns are not uniform, showing both hypometabolism and hypermetabolism (Struck et al., 2016), whereas other studies

on post-CA patients showed how SPECT allowed to determine whether the patterns were ictal or not (Zeiler et al., 2011).

(B) integration of the ACNS Terminology to the clinical context: neurological examination, timing of presentation of the EEG pattern, co-medication including sedation, other electrophysiological variables (somatosensory evoked potentials), imaging (morphologic and possibly functional MRI), laboratory values and standardized outcome (ex. Cerebral Performance Categories and/or modified Rankin Scale scores within 3–6 months) should be combined in order to create some “electroclinical profiles” that can be used as help for clinical purposes (Fig. 2). This ideally would allow creating consensus on the significance of those EEG patterns that still have an ambiguous connotation. (Table 1)

(C) establishment of common, standardized therapeutic procedures adapted to critical care patients. These are often already under anaesthetics, and the conventional treatment protocols for SE may not be applicable straightforwardly; the concept of refrac-

tory and super-refractory SE may be consequently somewhat different. Also, clinical improvement required by the Salzburg criteria (Beniczky et al., 2013; Trinka and Leitinger, 2015) for defining NCSE can be difficult to establish in these patients. Pharmacologic trials could be proposed in order to establish validated standardized therapeutic approaches in terms of aggressiveness, duration and timing, as it is the case currently (Ruijter et al., 2014). This would be particularly interesting for EEG patterns in the IIC, since in case of an ictal significance without a predominant structural damage, anticonvulsants or anaesthetics may change prognosis and the absence of treatment would potentially worsen the arousal/awareness system by aggravating metabolic needs (Bauer and Trinka, 2010). This is particularly relevant in the population of post-CA patients, for whom withdrawal of life sustaining treatment is still one of the main causes of death (Geocadin et al., 2019).

6. Conclusion

Scientific and clinical communities have increasingly applied the validated 2013 ICU-EEG ACNS Terminology, which improved description of the EEG patterns in the ICU and the communication among centers. Nevertheless, a pure descriptive EEG-based approach without the routine integration of other clinical factors bears, in our opinion, some limitations in particular in the clinical characterization of those EEG patterns that still have a borderline connotation, as it has been illustrated for comatose patients after CA. We propose that a combination of understanding of the mechanisms at the origin of the EEG patterns, multimodal integration of the nomenclature to the clinical context, and a homogeneity in therapeutic procedures among centres may lead to a more efficient use of the ACNS nomenclature, improving the rationale supporting adequate therapeutic choices in these difficult to treat patients.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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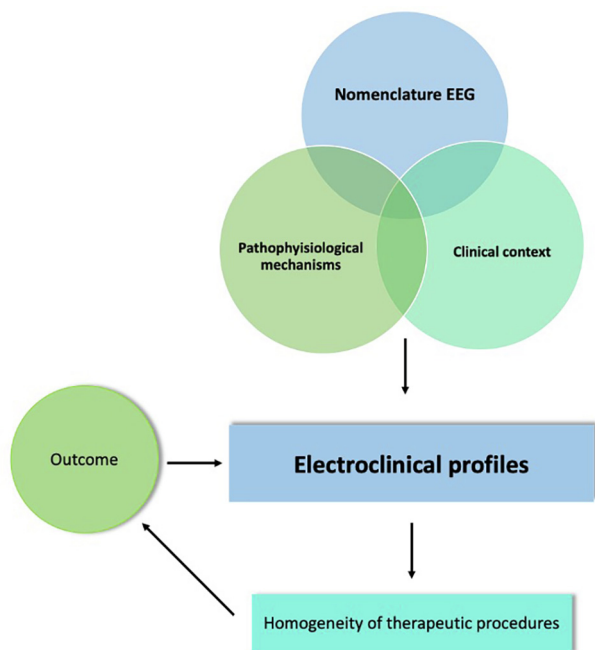


Fig. 2. EEG Terminology integrated to the clinical context and comprehension of pathophysiological mechanisms generating specific EEG patterns would allow to define the electroclinical profiles, which should be used to orient treatment and standardize therapeutic procedures. Homogeneity of therapeutic procedures would allow reliable outcomes measures that can improve the correct characterization of the electroclinical profiles and potentially suggest changing therapeutic procedures.

Table 1

Items proposed in order to establish the “electroclinical profiles” in post-cardiac arrest patients.

ELECTROCLINICAL PROFILES	
EEG	Main EEG pattern Background reactivity and continuity Timing of presentation
Co-medication	Sedation (which drug, dose/kg, timing of administration)
Clinical neurological examination	Brainstem reflexes (pupillary and corneal) Flexor motor response
Electrophysiological test	Somatosensory evoked potentials (SSEP)
Laboratory values	Serum neuron-specific enolase (NSE)
Imaging	Brain CT or MRI (morphologic and possibly functional)
Outcome	CPC and/or mRS after at least 3–6 months

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