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EEG as an indicator of cerebral functioning in post-anoxic coma

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ABSTRACT

Post-anoxic coma is one of the most serious conditions in the ICU. A reliable assessment of clinical evolution and outcome prognosis is challenging but capital in this context. In addition to the classical neurological examination, EEG is a precious tool to assess cerebral functions non-invasively. While therapeutic hypothermia and related sedation may delay clinical prognosis assessment, EEG can still provide accurate information. Here we summarize the most frequently encountered EEG patterns in post-anoxic coma and discuss their relations with outcome prediction. We also address the influence of temperature management on brain signals and the implication of the evolution of EEG patterns over time. Finally, we end with a view of the future prospects for EEG in post-anoxic management and prognostication.

INTRODUCTION

Early prognostication after cardio-respiratory arrest (CRA) represents one of the most important challenges in the ICU (Fugate *et al.*, 2012). The generalized anoxia, ischemia and the subsequent reperfusion after CRA lead to post-anoxic coma in the vast majority of survivors (Horn *et al.*, 2014), where the complete loss of awareness of the environment and the impairment of arousal (Laureys *et al.*, 2004) affect the clinical exploration of cerebral integrity. In order to assess the chances of survival in this population, multimodal evaluations combining brainstem reflexes (particularly pupillary, corneal, oculo-cephalic), motor response to painful stimuli, early myoclonus, somatosensory evoked potentials (SSEP), EEG, and serum biomarkers (especially neuron-specific enolase (NSE) and S100-B) are part of the current recommendations (Friberg and Cronberg, 2013; Fugate *et al.*, 2010; Sandroni, Cavallaro, Callaway, D'Arrigo, *et al.*, 2013; Sandroni, Cavallaro, Callaway, Sanna, *et al.*, 2013).

Over the last 10 years, the implementation of therapeutic hypothermia as a standard of care after CRA has significantly improved survival, particularly in patients with “shockable” rhythms (Bernard *et al.*, 2002; Oddo *et al.*, 2006; The hypothermia after cardiac arrest study group, 2002), even though the exact parameters of temperature management have been recently discussed (Nielsen *et al.*, 2013). However, it has been shown that TH and related pharmacological sedation may interfere with the assessment of some clinical variables (Al Thenayan, Savard, Sharpe, Norton, & Young, 2008; Rossetti, Oddo, Logroscino, & Kaplan, 2010), resulting in a delay of multimodal prognostic assessments (Cronberg *et al.*, 2013; Greer *et al.*, 2014).

In this context, the fact that EEG can non-invasively provide a direct reflection of brain activity in unresponsive patients, even in hypothermic conditions and when clinical testing is not contributory, makes it a valuable tool in the assessment of cerebral integrity in post-anoxic, comatose patients. The aim of this paper is to review the literature of the last 10 years reporting the value of EEG assessment in post-anoxic comatose patients treated with therapeutic hypothermia.

SPECIFIC EEG FEATURES

In the context of post-anoxic coma, the most frequently used features to describe EEG signals can be categorized into three main areas: (1) background activity, (2) reactivity to stimuli and (3) epileptiform patterns (Rossetti *et al.*, 2012). In the following section, we will describe these categories and relate their characteristics and incidence to the outcome and clinical evolution of post-anoxic comatose patients. **Table 1** summarizes these EEG features and their implication for outcome prognosis.

Background activity

Continuity refers to the regularity of the cerebral activity along the duration of the recording. According to the 2012 ACNS guidelines (Hirsch *et al.*, 2013), the signal is “continuous” when the brain activity is not interrupted by any periods of attenuation (defined as periods of voltage $\geq 10 \mu\text{V}$ but $<50\%$ of the surrounding signal) or suppression (voltage $< 10 \mu\text{V}$); “discontinuous” when 10-49% of the recording is suppressed or attenuated, and “burst-suppression” when more than 50% of the signal consists of attenuation or suppression; a “suppressed” recording indicates a persistent voltage below $10 \mu\text{V}$ (Hirsch *et al.*, 2013). Several studies on EEG background activity in post-anoxic coma have reported the continuity dimension as one of the most indicative features of brain preservation. A continuous pattern in normothermia is associated with regaining consciousness with 100% specificity (Rundgren *et al.*, 2006), while burst-suppression has been shown to be related to mortality (100% specificity in Sadaka, Doerr, Hindia, Lee, & Logan, 2014) (Rundgren *et al.*, 2010; Sivaraju *et al.*, n.d.) and generalized suppression or burst-suppression with epileptiform activity to no recovery of awareness (Thenayan *et al.*, 2010). Burst-suppression with identical bursts has been recently identified as a distinct pathological EEG pattern, exclusively observed after cerebral ischemia and strongly associated with non survival (100% specificity) (Hofmeijer *et al.*, 2014).

However, despite the clear ACNS nomenclature, it may be difficult to reliably generalize some of these findings, because the cut-off between these categories may be hard to define in specific borderline situations: EEG features are a continuous variable rather than a categorical one.

Persistent low-voltage or isoelectric EEG patterns have been described to be highly reliable for predicting poor neurological outcome, similar to SSEP (100% specificity), and improvement to a

continuous, slow pattern has been associated with a good outcome (Cloostermans *et al.*, 2012), outlining the importance of the dynamic EEG assessment over time (see below).

Alpha or theta coma can be observed at times in post-anoxic patients. Alpha coma refers to the dominance of (low) alpha frequencies in unresponsive patients, with higher amplitudes in frontal compared to posterior areas (**Figure 1**) (Kaplan *et al.*, 1999). Theta coma refers to the same clinical context applied to theta frequencies; in fact these patterns may represent a continuum, and are classically characterized by their lack of reactivity (Sutter *et al.*, 2013). Alpha and theta coma, especially if showing progressive slowing over time, have been reliably linked to poor prognosis.

Reactivity to stimuli

Reactivity refers to any reproducible change in amplitude or frequency in the EEG signal, related to patient stimulation (**Figure 2**) (Horn *et al.*, 2014; Rossetti, Oddo, *et al.*, 2010). Various types of stimuli can be tested, the most frequently used in clinical practice being visual (eyes opening to light), auditory (claps, voice), and nociception (extremities, chest), with increasing likelihood of EEG reactivity. Reactivity is usually characterized dichotomously as being present or absent.

An unreactive EEG background had been demonstrated to be highly incompatible with good neurological recovery, and to be strongly associated with in-hospital mortality and no return to consciousness (93% specificity in Rossetti, Oddo, *et al.*, 2010; see also Thenayan *et al.*, 2010). Conversely, reactivity to stimuli has been reported to be strongly associated with recovery of awareness (94% specificity and 90% sensitivity in Thenayan *et al.*, 2010) and with survival (Crepeau *et al.*, 2013; Rossetti, Oddo, *et al.*, 2010; Tsetsou *et al.*, 2013). The high predictive value of reactivity to stimuli has led our group to include this evaluation to the variables recommended for the multimodal evaluation of prognosis (Oddo and Rossetti, 2014; Rossetti, Oddo, *et al.*, 2010).

Epileptiform patterns

The classical use of EEG in clinical practice aims at detecting epileptic seizures. In postanoxic coma, identification of epileptiform activity is important, as it has been associated with poor outcome (Horn *et al.*, 2014). In some patients, epileptic seizures can be detected during hypothermia (Crepeau *et al.*, 2013; Mani *et al.*, 2012; Rittenberger *et al.*, 2012), under sedation

with antiepileptic general anesthetics, such as midazolam or propofol. The range of epileptiform changes that can be detected in post-anoxic comatose patients is large, but the most frequently observed patterns are generalized periodic discharges (GPDs; Milani et al., 2014) (**Figure 3**), seizures (Knight et al., 2013; Sivaraju et al., in press) and status epilepticus (SE) (Legriel et al., 2013; Rittenberger et al., 2012; Rossetti et al., 2007). In our experience, we rarely see discrete seizures interspersed in the recording, as the great majority of patients with epileptiform discharges will show them in a nearly continuous manner, at least over the standard 20-30 minutes EEG. SE and seizures may manifest a large variety of EEG patterns, characterized by the common denominator of prolonged electrographic rhythmic, or periodic activity, which may show an evolution over time in terms of frequency, amplitude, and/or distribution (Sutter and Kaplan, 2013). This can at times be associated with myoclonus (i.e., nonconvulsive status epilepticus) (Rossetti et al., 2009). SE in post-anoxic comatose patients is in fact relatively common, occurring in 1/3 of resuscitated patients, (Knight et al., 2013; Legriel et al., 2013) and can be detected early after CA (12 hrs after resuscitation and during TH). While it is strongly and independently related to death (92% specificity in Rossetti et al., 2007) and to poor outcome (Legriel et al., 2013; Rittenberger et al., 2012; Sadaka et al., 2014) in this population, SE alone is not sufficient to lead to withdrawal of life support. Indeed, a minority of patients may survive with relatively good functional outcome if treated aggressively with anti-epileptic drugs (Rossetti et al., 2009; Westhall et al., 2013). Furthermore, it has been suggested that in this setting, SE has differential prognostic value if it develops from a burst-suppression versus a continuous background, with higher chances of survival in the latter case (respectively 0% and 20% of patients regaining consciousness) (Rundgren et al., 2010).

Each of these three EEG features conveys important information about outcome. In addition, gathering these three main EEG features can provide reliable prognostic value: it has been shown that the combination of burst-suppression, presence of status epilepticus, and lack of reactivity is always associated with non-survival (Fugate et al., 2010). In another study, the combination of reactivity, background frequencies (alpha, theta) and rhythmic delta activity (RDA) was associated with a lower mortality (0.43 adjusted hazard ratio, $p = 0.004$), versus periodic discharges (PD), burst-suppression or suppressed voltage that were associated with a higher mortality (1.62 adjusted hazard ratio; $p = 0.02$) (Søholm et al., 2014). As a consequence,

classifications that include the presence of any of the 4 EEG patterns (flat, continuous, burst-suppression and electrographic status epilepticus) (Friberg *et al.*, 2013), and recent grading scales of EEG severity (Crepeau *et al.*, 2013) have been proposed to help prognostication.

VALUE OF THESE FEATURES IN HYPOTHERMIA

Classical EEG characteristics of poor outcome are a suppressed (“flat”) background, burst-suppression patterns, or generalized epileptiform discharges on top of a suppressed recording (Crepeau *et al.*, 2015; Wijdicks *et al.*, 2006). Knowing that changes in temperature may influence the EEG signal, data obtained since the advent of hypothermia treatment were initially taken with caution (Crepeau *et al.*, 2015). However, earlier data from cardiac arrest patients show that the temperatures used during TH do not alter the EEG significantly (Stecker *et al.*, 2001).

Our group indeed observed that despite the effect of a lower body temperature and the sedation associated with TH, some EEG patterns during TH are already indicative of prognosis. In particular, absent EEG background reactivity and the presence of epileptiform transients seem to be robust predictors of poor outcome (Oddo and Rossetti, 2014; Rossetti *et al.*, 2012; Rossetti, Urbano, *et al.*, 2010). Moreover, reactivity to painful stimuli seems to be a stable marker, independent of temperature or sedation-analgesia (Rossetti, Urbano, *et al.*, 2010). Quantitative EEG variables such as burst-suppression ratio (BSR) and wavelet subband entropy (WSE) collected in the first 24 hrs in hypothermic conditions have been reported to be associated with neurological outcome (Wennervirta *et al.*, 2009). Using long-term amplitude-integrated EEG, a continuous signal at the start of recording, even while under TH, is strongly associated with recovery of consciousness (Rundgren *et al.*, 2010). Studies reporting continuous EEG recording initiated during TH and continued through rewarming confirm the prognostic value of EEG abnormalities in TH (Cloostermans *et al.*, 2012).

These data support the assumption that characterization of benign or severe EEG patterns early after CRA, and even during hypothermia, already provide accurate information concerning outcome (Crepeau *et al.*, 2013; Rossetti *et al.*, 2012). It has recently been claimed that EEG patterns in TH have similar value to normothermia (Crepeau *et al.*, 2015), but one should be cautious with early recordings which may overestimate brain dysfunction (Alvarez *et al.*, 2013): it seems therefore reasonable to wait at least 9-12 hours after CA before starting the recordings.

Evolution

It has been shown that improvement of EEG findings over time is associated with a better outcome, and conversely a worse EEG grade heralds a poor prognosis (Crepeau *et al.*, 2013). It is important to assess the evolution of EEG in this clinical setting: transient fluctuations of the signal as well as more long-lasting transitions of EEG abnormalities are frequent and can serve as marker of brain injury evolution (Bauer *et al.*, 2013).

Two recent papers from our group using standard 20 minutes EEG recordings focused on the evolution of background reactivity from TH to normothermia. In the first, only patients showing a reactive EEG in TH were selected (Tsetsou *et al.*, 2013): reactivity during TH was strongly associated with survival, especially if the EEG remained reactive after rewarming. The second study reported the evolution of subjects with an initially non-reactive EEG (Juan *et al.*, 2015); as compared to the majority of patients with a persistently non-reactive EEG after return to normal temperature - those recovering reactivity in normothermia had a higher prevalence of preserved brain functions (brainstem reflexes, motor response) and an 8% chance of awakening (versus 0%) (Juan *et al.*, 2015). Taken together, these two studies suggest that assessment of the EEG background reactivity in hypothermia is a reliable tool for survival prediction. Specificity seems very high, as no patients survived after a non-reactive EEG background was recorded during hypothermia (Juan *et al.*, 2015), and sensitivity appears to be reasonable, as 86 % of patients with EEG reactivity during TH, survived (Tsetsou *et al.*, 2013).

PERSPECTIVES

A wide range of EEG patterns can be observed in comatose patients after CRA, and **Table 1** summarizes their significance in this setting. Continuous recordings over longer time periods maximize the chances of detecting abnormal patterns.

EEG has several advantages making it highly valuable in an ICU environment. As a portable device, it can be set up at bedside at any time without any invasive requirement, and removed easily if needed. Compared to other brain imaging methods EEG is cheap, broadly available, and except in the case of head wounds, there is almost no contra-indication to the placing of an EEG cap (Alvarez and Rossetti, n.d.).

Compared to multichannel cEEG, continuous recording with a reduced number of electrodes has the advantages of being simpler, and does not require robust neurophysiology expertise to initiate and interpret monitoring. However a reduced montage does not allow an adequate evaluation of reactivity (Friberg *et al.*, 2013) and may miss important information, such as more focal seizures (admittedly a relatively rare issue in this sort of patient), or when muscular or electrical artifacts are present. Recently, the usefulness of cEEG in postanoxic patients has been challenged, as it seems that routine recordings performed during mid-TH and after rewarming bear a comparable amount of information for clinicians, do not alter patients' prognosis, and are much less expensive (Alvarez *et al.*, 2013; Crepeau *et al.*, 2014).

As a further relative limitation, EEG interpretation requires specialized training and is subject to inter-individual variability, especially for patterns not belonging to the extremes of abnormality or normality (Westhall *et al.*, 2015). Moreover, despite the aforementioned guidelines and standardized terminology, each study still reports a different way of qualifying the EEG patterns, different criteria for withdrawal of intensive care, and for outcome characterization, which add difficulty to gathering results from different centers.

In order to tackle these limits, recent work has focused on the development of new methods. In particular, automated algorithms have been developed to reduce the subjective part of EEG interpretation (Noirhomme *et al.*, 2014), but are still very far from routine clinical use. More advanced analyses, including single-trial topographic interpretation applied to mismatch negativity paradigms (Tzovara *et al.*, 2013) or comparison of small-world characteristics of EEG spontaneous activity (Beudel *et al.*, 2014) are showing promising results in outcome prediction, but, again, these are still the subject of scientific research and are not (yet) ready for clinical application. The increasing awareness of the ACNS nomenclature should lead to a uniform way of reporting EEG, and thus help with the cross-correlations of clinical reports (Sivaraju *et al.*, in press; Westhall *et al.*, 2015). Besides large multicenter studies, this seems the only way to improve current knowledge in this field, where in any case a diagnostic tool (such as the EEG) should not be used alone for prognostic purposes: multimodality appears the best approach to a potentially deleterious self-fulfilling prophecy.

Disclosures

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FIGURES CAPTIONS

Figure 1: EEG showing a pattern of alpha-theta coma in a 43-year-old man. The activity is frontally predominant and non-reactive, recorded 3 days after cardiac arrest, during normothermia (30mm/s, 10 μ V/mm, average referential montage).

Figure 2: Background reactivity with diffuse attenuation demonstrated on the EEG after calling out the patient's name in a 62-year-old woman during therapeutic hypothermia (30mm/s, 10 μ V/mm, bipolar longitudinal montage).

Figure 3: Generalized periodic discharges (GPDs) on a suppressed background in a 78-year-old man after return to normal body temperature (30mm/s, 10 μ V/mm, average referential montage)

Table 1: Summary of the relevant EEG features in comatose patients after cardiac arrest, and their prognosis significance.

EEG feature	Prognosis significance	Power
Continuous background	Regaining consciousness	100% specificity in NT (Rundgren <i>et al.</i> , 2006)
	Good outcome (CPC 1-2)	0.91 PPV in TH (Rundgren <i>et al.</i> , 2010)
Burst-suppression		100% specificity (Cloostermans <i>et al.</i> , 2012)
	Mortality	100% specificity in TH (Rundgren <i>et al.</i> , 2010; Sadaka <i>et al.</i> , 2014)
	Poor outcome (GOS 1-3)	100% specificity at any time (Sivaraju <i>et al.</i> , n.d.)
	Poor outcome (CPC 3-5)	100% specificity (Cloostermans <i>et al.</i> , 2012)
Burst-suppression with identical bursts	Death	100% specificity (Hofmeijer <i>et al.</i> , 2014)
Isoelectric or low voltage		
No reactivity	No awareness recovery	94% specificity (Thenayan <i>et al.</i> , 2010)
	Mortality	93 % specificity in NT (Rossetti, Oddo, <i>et al.</i> , 2010)
Status epilepticus		100% specificity in NT (Tsetsou <i>et al.</i> , 2013)
	Poor outcome (CPC 3-5)	94% specificity (Legriel <i>et al.</i> , 2013)
		100% specificity (Rittenberger <i>et al.</i> , 2012)
	Mortality	92% specificity (Rossetti <i>et al.</i> , 2007)
Epileptiform transients	Poor outcome (CPC 3-5)	100% specificity (Rossetti <i>et al.</i> , 2012)

Abbreviations: *CPC* Cerebral Performance Category; *GOS* Glasgow Outcome Score; *TH* therapeutic hypothermia; *NT* normothermia; *PPV* positive predictive value.

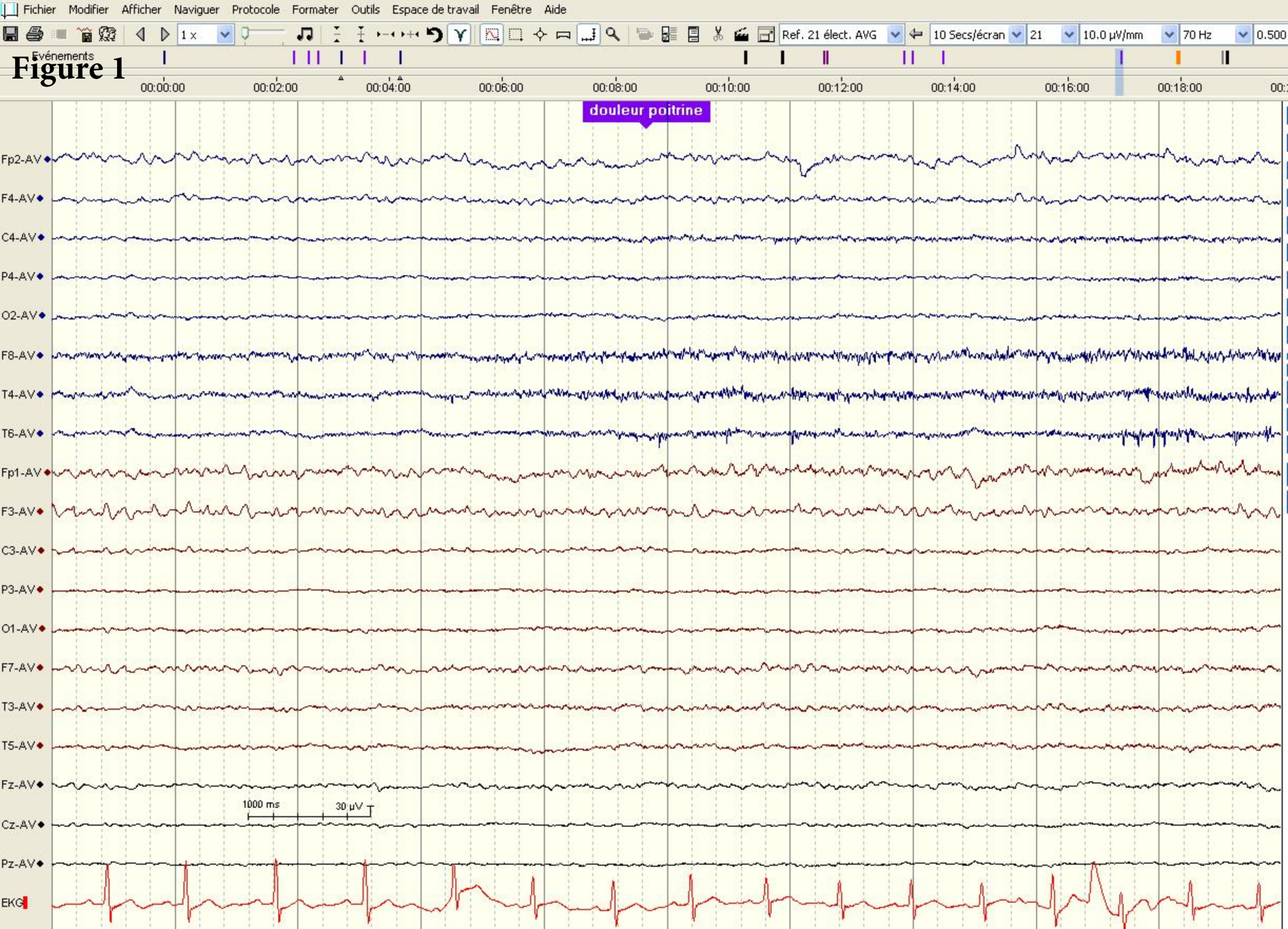


Figure 2

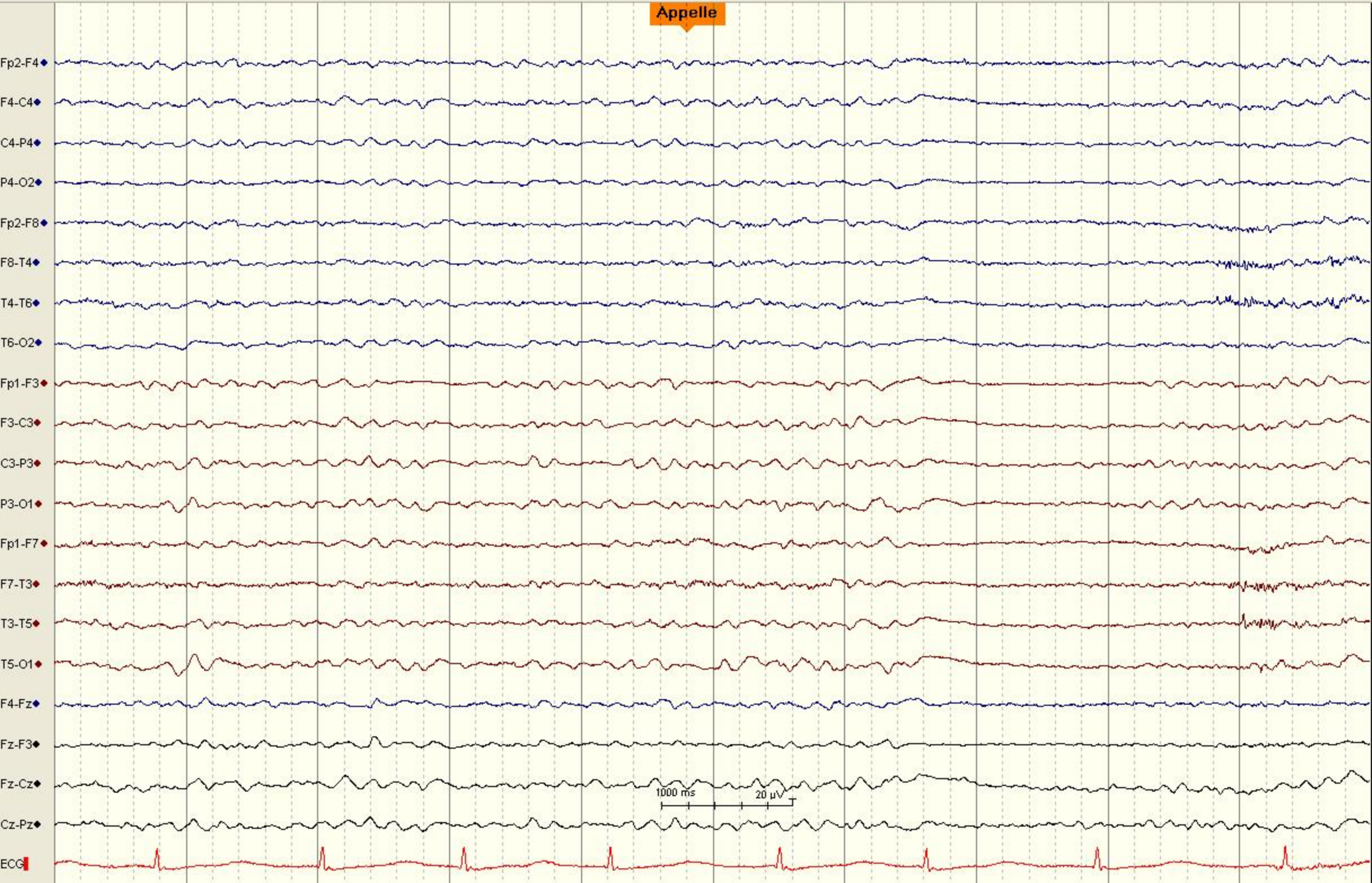


Figure 3

