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Neurological prognostication of outcome in patients in coma after cardiac arrest.

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Contents:

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Abstract:

Management of coma after cardiac arrest has evolved over the last decade, allowing an increasing proportion of patients to survive. Prognostication is an integrant part of post-resuscitation care; current recommendations suggest the use of a multimodal approach combining clinical examination with additional modalities, including electro-physiology, blood biomarkers and brain imaging, to optimise prognostic accuracy. Neurologists are increasingly confronted with raising expectations and the necessity to provide early predictions of long-term prognosis. Given this new scenario, a critical appraisal of how to optimally use these modalities, accounting for individual situations and availability of resources, is needed. The purpose of this manuscript is to provide a review of prognostic tools from a neurological standpoint, to summarise their value and potential clinical utility with attention to poor and good prognosis, and to suggest a stepwise multimodal algorithm, with specific attention to appropriate timings and optimal combination of available prognosticators.

We searched PubMed from Jan 2009, to January 2016, with the search terms “cardiac arrest”, “hypoxic-ischemic encephalopathy”, “prognosis”, “outcome”, “prognostication”, “clinical examination”, “myoclonus”, “status myoclonus”, brainstem reflexes”, “pupillary”, “pupillometry”, “motor reaction”, “pain”, EEG”, “reactivity”, “background”, “epileptiform” “status epilepticus”, “seizure”, “SSEP”, “N20”, “N70” “MMN”, “NSE”, “S100-b”, “brain CT”, “Brain MRI”, “diffusion”. We further searched bibliographies of relevant articles. We reviewed only clinical studies, randomised trials, and reviews published in English. The final reference list was generated on the basis of relevance to the scope of this Review.

Glossary: CA=cardiac arrest, CI=confidence interval, CT=computer tomography, EEG=electroencephalography, FPR=false positive rate, MRI=magnetic resonance imaging, N20 =the first cortical somatosensory evoked potential, TTM =targeted temperature management.

Case 1

A 60 year-old comatose woman is admitted after a cardiac arrest of respiratory cause. The first rhythm was asystole and the estimated total time from cardiac arrest to return of spontaneous circulation was 22 minutes. She undergoes targeted temperature management at 36° for 24 hrs. At day 2 after cardiac arrest, off sedation, clinical examination displays absence of motor response and all brainstem reflexes. The EEG is characterised by a monotonous alpha activity predominant in the anterior regions, and a non-reactive background to painful stimulation (**Figure 1**). Somatosensory evoked potentials (N20) are bilaterally preserved. At day 3, the second EEG shows a diffuse, slow and non-reactive background. Clinical examination differs from the previous day only for recovery of spontaneous breathing and presence of a right corneal reflex.

(see Page XX, section: When and what to use, and how to put it all together - Intensive car withdrawal**)**

Case 2

A 70 year-old woman is admitted in coma following a cardiac arrest due to ventricular fibrillation. The estimated total time from cardiac arrest to return of spontaneous circulation is 18 minutes. A myocardial infarction is diagnosed, and a primary angioplasty of occluded proximal right coronary artery is successfully realised. The patient is admitted to the intensive care unit, where sedation-analgesia and targeted temperature management to 33°C is maintained for 24 hours. EEG during hypothermia is reactive and nearly continuous. Upon awakening, she shows a return of brainstem reflexes, no reaction to pain, and bilaterally preserved early cortical somatosensory evoked potentials. A second EEG shows diffuse, continuous slowing, preserved reactivity and no epileptiform components. Serum neuron-specific enolase peaks at 40 µg/L. Seven days after admission, the patient is still in coma. Brain diffusion MRI shows hyper-intensities predominant in posterior cortical regions and hippocampi (see **Figure 4**, white arrows). The EEG is unchanged.

(see Page XX, section: When and what to use, and how to put it all together – How to deal with uncertainty**)**

Introduction

Cardiac arrest (CA) represents a major health problem[1] with a yearly incidence of approximately 50 to 110 per 100'000 persons worldwide.[2] Progress in advanced life support, access to emergent coronary angiography, implementation of targeted temperature management (TTM, with induced mild hypothermia to 33°C or strict normothermia at 36°C for 24 hours [3]), of post-resuscitation care targeting optimal support of cerebral and organ perfusion, and prevention of extra-cerebral systemic insults (hyperglycemia and infections), resulted over the last decade in an overall increase of CA survival,[4,5] and of chances to be discharged with good neurological recovery [3,6] and quality of life .[7-9]

In line with this evolution, CA has become a leading aetiology of coma and a frequent cause of admission to the intensive care unit. Clinicians involved in the care of comatose CA adults are confronted with increasingly optimistic expectations, and in the early phase of ICU management neurologists are regularly requested to provide predictions of long-term outcome. Post-CA brain dysfunction, predominantly resulting from global ischemia-reperfusion injury, is the principal determinant of prognosis. Additional factors may further alter brain function, mainly sedatives used to maintain TTM and post-CA organ dysfunction; these aspects might substantially delay recovery of cerebral function for up to 5-6 days [10], leaving caregivers and families with an unacceptably long delay of uncertainty. In this setting, despite neurological examination being the first and most important step for the evaluation of patients,[11] a growing body of clinical evidence demonstrates that the integration of additional modalities, including electro-physiological investigations, blood biomarkers of cerebral injury, and brain imaging, improves the accuracy of early (24-72 hours) coma prognostication.

Neurologic consultation and multimodal prognostic assessment has nowadays become an integrant part of post-resuscitation care. In practice, a complete battery of tests is either not always necessary according to the clinical situation, or not available in every facility; while university centers may dispose on almost unlimited resources, peripheral hospitals have to rely on fewer tools. While several excellent reviews and guidelines on this topic have been recently edited, most are addressed to intensivists or resuscitation specialists and essentially focus on prognosticators of poor outcome. [12-15] We here critically review recent literature in this evolving field and provide the value of each prognostic tool, highlighting false-positive rates (FPR) and

positive predictive values (point estimates and 95% confidence intervals, retrieved from original publications, meta-analyses, or calculated using binomial distributions) not only for poor, but also for favourable prognosis. Outcome was defined by cerebral performance categories (CPC, categorized as good: CPC 1 [back to baseline], or 2 [moderate impairment]; versus poor: CPC 3 [severe impairment], 4 [vegetative or comatose], 5 [dead])[16]. Of note, however, CPC 3 represents a heterogeneous condition: depending on the time of assessment and the possible further evolution of the patient, it may be related with a more favourable outcome. We also acknowledge the limited evidence supporting the use of each prognosticator, and the inevitable limitation imposed by the possibility of the so-called "self-fulfilling prophecy" (*i.e.* if a variable is a priori believed to be indicative of poor prognosis, leading to withdrawal of life-sustaining therapies, it will ultimately determine the outcome). [17,18]

Our purpose is to provide a general neurology audience with an updated, critical review of available prognostic tools for coma prognostication after CA in adults, to summarise their respective value and potential clinical utility, and to suggest a stepwise multimodal algorithm, paying specific attention to appropriate timings and combination of prognosticators. Finally, an outlook on promising emerging modalities will be offered.

Clinical examination

Neurological examination is essential for prognostication, as it directly reflects brain function. Evaluation of brainstem reflexes, motor responses to pain, and myoclonus during the first 72 hours after arrest represented the standard evaluation before the advent of TTM [19] and retains its prognostic value in patients treated with TTM (at target temperatures of 32 to 36°C).[20] However, these features can be altered by TTM and residual sedation, therefore repeated assessments are often necessary. Clinical improvement can be heralded by appearance of eye tracking or movements to command. It is important to recognize that predictive performances of clinical examination may be limited by the fact that these responses were systematically used for clinical decisions in the studied cohorts, raising concerns regarding at least some degree of self-fulfilling prophecy.

Pupillary light and corneal reflexes

Bilateral absence of pupillary light reflexes at 72 hours is a robust indicator of poor prognosis, whether the patient is treated with TTM (FPR 0.5%, 95% CI: 0-2%)[12,13,17,20,21] or not (FPR 0.5%, 95% CI: 0-8%).[13,19,20] While absence of pupillary responses within 24 hours is not incompatible with good recovery, particularly in hypothermic patients (FPR 8%, 95% CI: 1-25%[13]), their presence at 72 hours poorly identifies patients who will awake (predictive value: 61%, 95% CI: 50-71%[20]). Lack of corneal reflexes at 72 hours also strongly correlates with poor prognosis, although with lower accuracy than pupillary reflexes, especially among patients who received sedatives or neuromuscular blockade (FPR 5%, 95% CI: 0-25%[13,17]); again, their presence is an unreliable predictor of good outcome (predictive value: 62%, 95% CI: 51-72%[20]).

Motor response

Absent or extensor response to pain at 72 hours was considered a reliable indicator of poor outcome before the broad utilization of TTM.[19] However, this is the physical sign most influenced by sedatives, opiates, and neuromuscular blockade; consequently, motor responses are less reliable in patients undergoing TTM (FPRs up to 10-24%, 95% CI: 6-48%).[17,18,22] Evaluation requires strong stimulation and the exclusion of residual effects of pharmacological sedation, which can be prolonged by TTM and/or reduced pharmacologic clearance (e.g., hypothermia, renal or liver dysfunction). [10] Timing and proficiency of the examination can greatly impact the elicited response and therefore its prognostic accuracy. Also, when assessing motor signs it is important to remember that while an extensor or absent response does not necessarily mean that the patient will not awaken, a flexor or even a localizing movement does not always signify that she will recover (positive predictive value 81%; 95% 66-91%).[18]

Myoclonus

Myoclonus has long been known to predict poor outcome after CA, [19,23] but recent reports of patients who achieved good prognosis despite early post-anoxic myoclonus [24-27] raised questions about its prognostic accuracy. Indeed, up to 9% of patients with myoclonus may survive.[25,28] Its precise characterization is crucial: not all “twitches” have the same prognostic implication, depending on semiology, duration and associated EEG findings. Generalized status myoclonus (multifocal spontaneous twitches lasting more than 30 minutes, occurring even under TTM and sedation) is commonly accompanied by malignant, unreactive EEG patterns (see next section)

and consistently associated with poor outcome (FPR 0%, 95% CI: 0-3%[20]). Conversely, brief myoclonic jerks restricted to the face or trunk, controllable with sedatives, along with a more benign (i.e.: continuous and reactive) EEG, do not portend an invariably poor outcome (FPR up to 5-11%, 95% CI: 3-26% [13 22]). These considerations may explain the markedly different FPR across studies and highlight the importance of careful clinical assessments and interpretation in the context of other prognosticators, especially EEG. Only this multimodal approach may prevent interrupting care too early in patients who still have chances of awakening.

Electroencephalography (EEG)

Its signal is generated by cortical post-synaptic potentials; this is a broadly available, non-invasive, relatively cheap real-time investigation of electrical brain activity, which has been routinely used for decades in this setting.[29] The recent regain in interest on EEG paralleled the important progresses in post-CA care and outcome. Prognostication has taken a renewed place, and in this context EEG is of great help, also considering that its features correlate with the degree of neuronal injury.[30] Availability of automated algorithms for its screening,[31] and of CT and MRI compatible electrodes,[32] have facilitated its use in critical care patients. Technical expertise is pre-requisite for correct interpretation.[33] The American Clinical Neurophysiology Society recently edited standardized guidelines for interpretation,[34] which have been validated in this setting,[35] and are strongly recommended to allow comparisons among different settings. While studies on quantitative analysis or reactivity did not use these features to decide withdrawing life-sustaining measures, background and epileptiform features may be affected by a self-fulfilling prophecy.

Mild hypothermia does not exert major effects on EEG interpretation, [36] whereas sedative agents used during TTM can have an impact depending on doses. Several recent studies suggest, however, that despite sedative infusions in the range of 0.1-0.2 mg/kg/hrs (midazolam) or 2-3 mg/kg/hrs (propofol), prognostic accuracy of EEG is better during the first 24 hrs (and TTM) than after 2-3 days;[37-39] of course, if sedation is much more important, EEG assessments (especially background and reactivity) may be influenced. EEG findings may be categorized into three main aspects:

Background activity

This represents the first parameter to be interpreted, and is readily informative of global cerebral functioning. Worsening of brain dysfunction goes alongside with increasing background slowing and decreasing amplitude. Several groups focused on the role of a low voltage (<20 µV) or isoelectric (suppressed) background at 24 hrs (FPR 0%, 95% CI: 0-17% [39,40]), of burst-suppression at any time (FPR 0%, 95% CI: 0-11%[39]), of burst-suppression with identical bursts (FPR 0%, 95% CI: 0-17%[41]), and of spontaneously discontinuous background during TTM (FPR 7%, 95% CI: 0-24% [30]) predicting unfavourable outcome. Conversely, a continuous background as soon as 12 hours after CA has been correlated with a high likelihood of awakening (positive predictive value 92%, 95% CI: 80-98% [37]); a normal voltage background at 24 hrs has a similar meaning (72%, 95% CI: 55-88% [39]). An exception is the so-called alpha-coma, an anterior prominent rhythm without reactivity that is associated with poor prognosis (9 out of 9 patients reported with poor outcome [42]) (**Figure 1**).

Background reactivity

Reactivity is elicited by auditory or noxious stimulations and is characterised by either transitory attenuation or increase of electrical activity (**Figure 2**). Lack of reactivity has been shown to correlate with poor outcome if assessed after TTM (FPR 7%, 95% CI: 1-15% [18,43]), even more robustly during TTM (FPR 2%, 95% CI: 0-9% [38,44]). Conversely, reproducible reactivity may indicate subsequent awakening, during TTM (positive predictive value 86%, 95% CI: 77-92%[45]), and thereafter (78%, 95% CI: 64-88%[18]). Finally, so-called "stimulus-induced rhythmic, periodic or ictal discharges" (SIRPIDs), not representing a physiological reactivity, occur in about 15% of patients and herald a poor prognosis (FPR 2%, 95% CI: 0-11%), particularly if observed during TTM and sedation.[46] An important limitation of EEG reactivity relies in the potential lack of generalization, mainly due to subjective assessment, variable inter-rater agreements;[35,47] a standardized stimulation protocol may improve this aspect.[48]

Epileptiform features

Sharp waves, (poly-) spikes, spike and waves are only exceptionally observed in isolation, as they very often present as repetitive (periodic or rhythmic) patterns. Occurrence of such features after TTM is related to poor outcome (FPR 9%, 95% CI: 2-21% [18]); this seems even more true if epileptiform discharges are observed during TTM, under sedation with antiepileptic properties

(FPR 0%, 95% CI: 0-30%[30,49]). Nevertheless, a subset of patients with electrographic status epilepticus appearing only after TTM and sedation weaning, especially those who have preserved brainstem reflexes, background reactivity and somatosensory evoked potentials, may have a chance of reaching reasonable functional outcomes.[50] Quantitative analysis suggests that subjects with epileptiform features reaching good outcome show higher background continuity, higher discharge frequency, but lower discharge periodicity.[51] We believe that these patients should be treated aggressively with anticonvulsants and, if needed, pharmacological coma. Treatment duration in this context is not known, but it does not seem reasonable to extend therapy beyond two weeks if the patient does not awaken.

Standard versus continuous EEG

Some groups advocate the use of continuous EEG for up to 48 hrs;[37,39] yet, two standard EEG recordings (20-30 minutes) including stimulations for reactivity performed within 48 hours of CA have been reported to offer comparable information to continuous EEG, [52] at lower costs.[53] Apart from the particular case of EEG monitoring of post-anoxic status epilepticus, intermittent EEG represents a valid alternative for centres with limited resources. Since electrical activity may evolve over time,[40,54-56] repeated assessments are advisable, in particular over the first 48 hrs following CA. Reduced montages with as few as two channels have been described, including amplitude-integrated analysis and bispectral index;[54-57] they may represent an alternative for assessing background and reactivity, however they are less sensitive for detection of epileptiform transients and epileptic seizures. Recordings performed too early may overestimate the degree of brain injury, and, on the other hand, very precocious epileptiform features seem rare (these most commonly appear after 12-24 hours[58]): for these reasons, depending on local availability, EEG assessments can be started at 12 hours after CA.[52] Earlier studies may detect some very early seizures, but should not be used for judging on background activity and reactivity.

Somatosensory evoked potentials

Early latency evoked potentials

These signals result from the averaging of cortical electrographic responses generated after repetitive electrical stimulations of the median nerve through afferent pathways to the contralateral postcentral gyrus, where a negative deflection appears about 20 ms after the stimulation (and is thus called N20) (**Figure 3**). While they are less widely available than EEG, particularly in peripheral hospitals, they have been extensively studied for prognostication after CA. Bilateral absence of the N20 response is robustly correlated with a poor outcome, mostly after TTM (FPR 0.5%, 95% CI: 0-2%[10,17,37,38,59]), but also during TTM (FPR 0%, 95% CI: 0-2% [13,59]). While the evoked potentials accuracy is extremely high for prediction of poor prognosis (notwithstanding a certain degree of self-fulfilling prophecy), their value to predict favourable outcome is disappointing, as positive predictive values of bilaterally present N20 oscillate from 40% (29-50%)[37] to 58% (95% CI: 49-68%)[38], clearly lower than a continuous, reactive EEG background (>80%).[45] Furthermore, evoked potentials have a lower sensitivity to detect patients who will die (43%; 95% CI: 31-57%) compared to absent EEG reactivity during TTM (74%; 95% CI: 62-84%);[38] of note that study did not include EEG reactivity for decision of supporting measures withdrawal. In line with this, evoked potentials do not provide additional information when EEG, clinical evaluation and biomarkers are also available, [37,38] reflecting the fact that while electroencephalographic waves are generated by cortico-cortical interplays, early-latency evoked potentials only represent averaged signals limited to an afferent pathway.[60] It has recently been suggested that quantitative assessment of the N20 amplitude offers additional prognostic information,[61] but this observation need to be replicated in different cohorts.

Middle latency evoked potentials

These are elicited by intra-cortical associative interactions, and may be recorded up to 100 ms following stimulation. While they should better reflect functional connectivity and thus allow prognostication of awakening, they are used far less commonly than early-latency potentials, due to technical recording issues. A study before the TTM era reported a PPV for awakening as high as 97% if middle-latency responses were present; [62] however, this was challenged by another study reporting that only 28% of those with middle-latency responses reached a good outcome. [63] A recent study suggests that the painful modality may be informative of consciousness recovery (PPV 100%, 95% CI 87-100%) even before EEG reactivity.[64]

Biochemical markers

Monitoring biomarkers of neuronal injury is a field of intense clinical investigation; an extensive summary is beyond the scope of this review, and the reader is referred to a recent document.[65] Although a wide variety of proteins have been identified, only neuron-specific enolase (a marker of neuronal damage) and S-100 beta (reflecting astrocyte damage) have been extensively studied by independent groups; this section thus concentrates on these two proteins, while other are presented in the "Promising newer prognostic tools" section. Studies on biomarkers can be affected at least in part by a self-fulfilling prophecy.

Neuron-specific enolase

This enzyme is released by dying neurons, and so far has been the most studied biomarker for CA prognosis. Elevated NSE levels correlate with the extent of neuronal injury and EEG alteration.[30] A prospective study before the advent of TTM found that a serum NSE > 33 µg/L between 24 and 72 hours after CA was uniformly associated with poor outcome (FPR 0%, 95% CI: 0-3%[66]). However, results were more variable in retrospective series without TTM (FPR 9%, 95% CI: 1-29% for the cut-off of 33 µg/L[20]; maximal levels in patients with good outcome ranging from 48 µg/L at 24 hrs to 80 µg/L at 72 hrs).[13,67]

The prognostic reliability of neuron-specific enolase has been further questioned by studies conducted in subjects treated with TTM at 33°C, where an unacceptably high FPR of up to 29% (95% CI: 11-33%) for a threshold of 33 µg/L was repeatedly shown.[10,17,20,30,68,69] It is nowadays not recommended to apply one particular threshold, [13,28] and the limit should be in any case higher than previously considered [70]. Whether there is a threshold beyond which good recovery is no longer possible is indeed matter of debate: while it is uncommon for to experience favourable recovery at NSE > 60-80 µg/L within the first 72 hours,[70,71] exceptional cases despite very high values (up to 151 µg/L) have been reported.[69,72] In a recent large multicenter study, cut-offs as high as 120 µg/L at 48 hrs and 50 µg/L at 72hrs were necessary to keep FPRs at 0-1%. [68] Trends on serial measurements over the first 72 hours could be more useful than a single value,[68] but the best way to interpret the results remains to be elucidated. Furthermore, levels <33 µg/L are inconsistently related to good outcome (positive predictive value 63%, 95% CI: 52-73% [38]).

An important caveat is sample handling and laboratory expertise. Variability in serum levels can be seen across laboratories or following different assessment methods;[73] spurious results can be observed when samples are haemolysed (e.g., during hypothermia).[74] Levels could also theoretically increase because of haemolysis in patients undergoing extra-corporeal membrane oxygenation; the extent of this phenomenon deserves further investigation, but in the meantime it is advisable to be cautious in this setting. Since neuron-specific enolase is also present in neuroectodermal cells, high levels can be encountered in patients with small cell lung carcinoma.

Serum S-100 beta protein

This protein is released by glial cells after brain insults, and also has extra-cerebral sources, such as adipose tissue and muscle. Levels are measured far less commonly than neuron-specific enolase, probably because of test availability (neuron-specific enolase serves also as a tumour marker), and thresholds for uniform identification of poor outcome have also been very variable across studies, regardless of whether TTM was used[13]. Given its shorter biological half-life, serum S-100 beta protein raises earlier, and high levels (>0.5 µg/L) could signal poor prognosis even within the first 24 hours.[75,76] Yet, since early prognostication using a single parameter should be discouraged, the practical value of this difference in kinetics is questionable.

Neuroimaging

Brain imaging can help revealing structural alterations and quantifying the extent of post-anoxic damage, and its application for coma prognostication is relatively new. Most studies are retrospective and many evaluated imaging as a single tool. Neuroimaging is currently used less frequently than clinical and neurophysiological examinations. Studies where clinicians were not blinded to imaging findings may have introduced some degree of self-fulfilling prophecy. However, when this was not the case a good correlation between extensive cortical injury on magnetic resonance imaging and poor outcome was found. [77,78]

Brain computed tomography (CT)

CT provides valuable information when the CA aetiology is uncertain and an intracranial haemorrhage should be ruled out. However, intracerebral causes of CA are very infrequent

(particularly following ventricular fibrillation) and the benefit of a routine brain CT on admission must be balanced with the potential delay in starting TTM and post-resuscitation care.[79] CT signs of brain hypoxia include loss or reduced gray-white matter discrimination and sulcal edema or effacement. Loss of gray-white matter discrimination within 2 hours after asphyxia seems a reliable predictor of poor prognosis (FPR 0%, 95% CI: 0-12%); the interobserver concordance was good, but identification of survivors was poor (positive predicted value 37%, 95% CI: 9-75%).[80] A multicenter study on patients undergoing hypothermia after CA found that although reduced gray-white matter ratios predicted poor outcome with FPR 0%, sensitivity (3.5-6%) was extremely low; furthermore, including CT findings into a multivariable model with other prognosticators did not improve prediction.[81] Another recent study came to similar conclusions (FPR 0%, 95% CI 0-4%; sensitivity 14-20%, moderate-to-good interrater agreement).[77]

Brain magnetic resonance imaging (MRI)

MRI has higher resolution than CT and can better identify structural abnormalities in the neocortex, deep grey nuclei, and hippocampi. Although the superiority of MRI on CT for outcome prediction has not been formally demonstrated, many recent investigations focused on MRI (particularly, diffusion-weighted MRI). In poor outcome patients, occipital and mid-temporal cortex and the putamen may exhibit restricted diffusion (bright signal on diffusion-weighted imaging, with corresponding dark signal on apparent diffusion coefficient maps) indicative of cytotoxic edema.[78] Quantitative assessments across different areas have been reported to have an FPR 0% (95% CI: 0-22%) for poor outcome in studies with excellent interrater agreement, [82,83]. A retrospective multicenter assessment using the same quantitative threshold also reported a slightly lower performance (FPR of 9% ; 95% CI: 2-25%)[84], similar to an FPR of 7% (95% CI: 2-18%) in a large retrospective multicenter study from Korea.[85] However, diffusion-weighted MRI did not perform as well in another recent study, where a very high FPR (54%; 95% CI: 26-80%) was reported [86] (**Figure 4**). Furthermore, lack of diffusion changes does not consistently predict a good outcome (positive predictive values: 73%, 95% CI: 45-92% [82]; or 75%, 95% CI: 63-85% [85]). It is recommended to perform MRI between 24-48 hours and 7 days after CA.[87]

Given the current relatively low level of evidence,[88] diffuse structural signs of post-anoxic injury on either brain CT or MRI seem less robust predictors than brainstem reflexes and

electrophysiological findings.[13] Difficulties inherent to transporting critically ill patients to the scanner and the still unclear prognostic value of imaging techniques (especially when evaluated only qualitatively) explain why they remain optional in most prognostication algorithms.[13,15,89,90]

In practice, we recommend brain CT for disclosing a cerebral etiology when an evident CA cause is lacking. Brain MRI may be considered in centres with high-volume and expertise to complement multimodal assessments in patients who, despite lacking unfavourable prognostic signs on clinical, electrophysiological, and blood tests, are in persistent coma after several days.

When and what to use, and how to put it all together

The optimal prognostic tool

Clinical examination is obviously mandatory in every patient, and electrophysiology is strongly recommended: even if pupillary light reflexes are lacking at 72 hours, we believe that one among EEG or evoked potentials is necessary to confirm prognostication of poor recovery. The EEG advantages are higher accuracy in early prediction of good recovery and sensitivity for poor prognosis, and seizures identification. Additional investigations may corroborate these evaluations, according to local practices and expertise. Available prognostic tools are summarized in **Tables 1 and 2**; the vast majority is oriented towards poor prognosis.

The optimal timing

While EEG performed at 12-24 hours after CA seems to be already very informative of prognosis, since TTM now represents the current standard of care, multimodal assessment including clinical examination and electro-physiologic studies (normothermic EEG and/or evoked potentials) has to be carried out after return to normothermia and discontinuation of sedation for a sufficient time. The earliest time window is after 48 hours; it is nevertheless mandatory to repeat clinical examination at 72 hours in those who do not show clear signs of awakening. [13,15] These early tests orient prognostication in the majority of patients: those already starting to awaken, or having convergent signs of irreversible brain injury (absent pupillary and corneal reflexes, EEG with burst-suppression background and no reactivity, absent cortical

evoked potentials) do not need additional tests. Biochemical markers or imaging are confirmatory tests for poor prognosis, but not mandatory in each case.

How to deal with uncertainty

Multimodal assessment is supported by a growing body of evidence and is strongly advocated whenever a doubt persists, since each single tool, when used alone, carries risks of false prediction. [13,15,37,38] Recent work has focused on the optimal combination of prognostic parameters: EEG background reactivity and/or continuity, clinical evaluation (particularly myoclonus and brainstem reflexes), and neuron-specific enolase seem to have the best predictive value to identify poor outcome patients. [37-39] Unfortunately, to date, no combination of tests heralding good prognosis can be supported by evidence.

We propose a stepwise approach, summarized in **Figure 5**. If, following the aforementioned investigations, the patient still remains comatose despite the lack of poor outcome predictors, intensive care should be continued while the two core prognostic tools (clinical examination and EEG) are periodically reassessed over the subsequent days. At that point, blood biomarkers should be available, but repeating them and evoked potentials beyond 72 hours does not appear to bring any additional useful information. Brain MRI may prove useful, as it can reveal alterations reflecting cerebral damage, whose significance needs to be interpreted according to the clinical context. **Case 2** is an illustrative example, where all prognostic tools were used: despite MRI alterations potentially portending poor prognosis, there was no other robust sign of poor outcome. In particular, the presence of repeated continuous, reactive EEG motivated to pursue intensive care, and the patient awoke shortly thereafter; at three months her CPC was 2.

Intensive care withdrawal

To minimise the risks of false pessimistic predictions, interruption of life-sustaining measures should be considered only in the presence of at least two tools with very low FPR for poor outcome (i.e., clinical examination plus electrophysiology), without any discordant information between tests (e.g., clinical signs of recovery of awareness, such as eye tracking or following orders, or a continuous, reactive EEG). While FPR point estimates of the aforementioned tools are all below 2%, confidence intervals for EEG are relatively wide; this reinforces the need of a

multimodal approach. **Case 1** illustrates how clinical examination and EEG after 48 hours from CA orient towards a poor prognosis with high accuracy, even with preserved evoked potentials. Indeed, intensive care was withdrawn and the patient died shortly thereafter.

Decision about withdrawal of life-sustaining measures is an essential, although potentially challenging, part of care. This should be reached through interdisciplinary consensus (at a minimum including the intensivist and the neurologist/neurophysiologist) and with close involvement of the patient's family, considering the patient's known or written directives, if available, as well as her biological and psychosocial backgrounds. The use of an algorithm must always be tailored to each individual situation. It is to underscore that when supportive care is continued in patients without overt interaction for several weeks or months, only a subset might show improvement of awareness beyond one year, but virtually all of them will remain in a severe, dependent state and have poor quality of life [91]. In the relatively few instances where prognosis cannot be determined, we conduct detailed family discussions during the first two-three weeks, so to clarify what would be the maximal acceptable and tolerated degree of functional impairment, and provide commensurate care based on individual preferences and values, in order to avoid futile treatment resulting in a severe handicapped survival.

Promising novel prognostic tools

The need of identifying additional prognosticators derives from two considerations: potential usefulness of quantitative assessments, and need for robust tools not only for poor, but also for good outcome. Given their exploratory nature, studies on these parameters are less hampered by the self-fulfilling prophecy, as they are still not used for prognostication in practice. The most important barriers to wider applicability of these techniques are the uncertain generalisability (i.e.: most tools were investigated by just one or a few groups), and limited availability (this seems especially true for biomarkers and long-latency evoked potentials).

Automated pupillometry

Automated devices to quantify pupillary responses to light stimuli are available on the market; preliminary studies suggest that quantitative infrared automated pupillometry may be superior to

standard qualitative examination.[92] Until validation, correlation with direct visual examination remains necessary.[93]

Long-latency evoked potentials

These represent higher-order cortical reaction occurring more than 100ms after stimulation of the primary sensory areas. The response to deviant auditory stimuli in a sequence of standard stimuli, called mismatch negativity, was described after several days or weeks following CA in the pre-TTM era, and its presence is highly predictive of awakening.[94] Recently, this approach has been refined by means of automated voltage topography analysis of records performed during acute coma: the vast majority of patients showing a progression of auditory discrimination between the first and the second assessment within the first 48 hrs had a good recovery.[95] This novel paradigm may identify very early patients with favorable prognosis.[96]

Other biomarkers

Several proteins have been proposed, such as plasma neurofilament heavy chain,[97] serum glial fibrillary acidic protein,[98] brain derived neurotrophic factor, and tau protein,[99] but sample sizes are limited: further data are needed before these biomarkers can be routinely used. Elevated levels of systemic proteins, such as serum procalcitonin, are found in the first 48 hours following global ischemia-reperfusion injury, and have been associated with increased mortality.[100]

Cerebral oxygenation

Low cerebral oxygenation levels, a marker of poor prognosis,[101] can be assessed invasively, but this is not practical in CA patients. It can also be estimated non-invasively by means of near-infrared spectroscopy and the measurement of regional cerebral oxygen saturation.[102] This approach was tested in an extra-hospital setting to predict likelihood of resuscitation after CA.[103] A recent meta-analysis including 9 studies and 315 patients found that higher initial and average cerebral oxygenation are associated with greater chances of return of spontaneous circulation,[104] but to date no robust data are available to predict in-hospital or long-term prognosis.

Conclusion

Prognostication after CA has become an integral part of post-resuscitation care. Neurological consultation is increasingly requested, and neurologists are confronted by caregivers and families with expectations for high accuracy in outcome prediction. Over the last decade, post-CA prognostication has evolved towards a multimodal approach relying on clinical examination and

judicious integration of the information provided by multiple tests. Prognostication should never be based on a single indicator: while some variables have a very low FPR for poor outcome, they do not occur in isolation (e.g. bilateral absence of cortical responses on somatosensory evoked potentials would not be expected in patients with localizing responses on physical examination or a reactive EEG background). Multimodality assessment provides reassurance about the reliability of a prognostic estimation by offering concordant evidence from different sources, which should all make sense together. This approach is supported by an abundant body of clinical evidence and is strongly recommended. [13-15,89,90]

Confounders, however, exist: sedative drugs undergoing delayed clearance with hypothermia and renal or liver injury must always be formally excluded. Self-fulfilling prophecy is an important issue, intrinsic to virtually all studies on prognostication after CA.[17,18] We acknowledge that no major prognosticator has been tested in a strictly blinded manner, and that evidence level is globally low to very low. Notwithstanding these limitations, relying on an algorithm incorporating information from multiple modalities is at present the best way to maximize prognostic reliability. When this remains uncertain, additional time and utilization of the full set of modalities is clearly recommended. The stakes are too high to rush or take chances.

While most available literature focuses primarily on indicators of poor prognosis, in this review we also highlight early predictors of good recovery, especially EEG background and reactivity. Estimating prognosis after CA is not only about delivering bad news; it is also, and hopefully more frequently so in the future, about identifying reliable signs of good prognosis that can be confidently shared with families; this can prove very rewarding and represents an important task of neurologists involved in the care of CA patients. An additional, stimulating challenge for the upcoming years will be to further refine our understanding of which factors can predict excellent cognitive recovery.

Authors contributions:

All authors contributed equally to this work searching the literature, analysing the data, drafting the manuscript, and reviewing it for important intellectual content. The figures were prepared by AOR (Figure 5 with the help of Mrs J. Scheurer, CEMCAV, CHUV, Lausanne).

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Table 1: Overview of prognosticators including their estimated false positive rates (1-specificity) in adult patients treated with targeted temperature.

		Feature related to good outcome	Positive predictive value (95%CI)	Feature related to poor outcome	False positive rate (95%CI)
Clinical examination	Pupillary light reflex	Bilaterally present >72hrs	61% (50-71%)	Bilaterally absent >72h	0.5% (0-2%)
	Corneal reflex	Bilaterally present >72hrs	62% (51-72%)	Bilaterally absent >72h	5% (0-25%)
	Early myoclonus	NA		Present <48 hrs with epileptiform EEG (status myoclonus)	0% (0-3%)
				Present <48 hrs with continuous, reactive EEG	5-11% (3-26%)
	Motor reaction to pain	Flexion or better >72 hrs	81% (66-91%)	Absent or extension posturing >72h	10-24% (6-48%)
EEG	Background	Continuous at 12-24 hrs	92% (80-98%)	Diffuse suppression or low voltage at 24 hrs	0% (0-17%)
		Normal voltage at 24 hrs	72% (53-86%)	Burst-suppression at 24 hrs	0% (0-11%)
	Reactivity to stimuli	Present during hypothermia	86% (76-92%)	Absent during hypothermia	2% (0-9%)
		Present after return of normothermia	78% (64-88%)	Absent after return of normothermia	7% (1-15%)
	SIRPIDs	NA		Present at any time	2% (0-11%)
	Repetitive epileptiform transients	NA		Present during hypothermia	0% (0-30%)
				Present after return of normothermia	9% (2-21%)
SSEP		Bilaterally present	58% (49-68%)	Bilaterally absent after return of normothermia	0.5% (0-2%)
Serum NSE		<33 µg/L at 48 hrs	63% (52-83%)	> 120 µg/L at 48 hrs >68 µg/L at 48 hrs	0% (0-1%) 1% (1-3%)
Brain CT		Normal gray-white matter at 2-48 hrs	37% (9-75%)	Reduced gray-white matter ratio at 2-48 hrs	0% (0-12%)%
Brain MRI		Absence of reduced diffusion at 24hrs - 7days	73% (45-92%)	Reduced diffusion at 24hrs - 7days	0% (0-22%), 54% (26-80%)

CI=confidence intervals, CT=computed tomography, EEG= electroencephalography, MRI=magnetic resonance imaging, NSE= (serum) neuron-specific enolase, NT=normothermia, SIRPIDs= stimulus induced rhythmic, periodic, or ictal discharges, SSEP=somatosensory evoked potentials, TTM= targeted temperature management.

Table 2: Overview of strenghts and weaknesses of main prognostic tools.

Prognostic tool	**Strengths**	**Weaknesses**
Clinical examination	- Very low FPR for poor prognosis (especially pupillary light reflex) - Identify early signs of awareness	- Motor response may have high FPR (up to 25%) for poor prognosis - Reliability may be reduce by lingering sedation, organ failure, and hypothermia - Myoclonus not invariably correlating with death (needs to be integrated to EEG).
Electroencephalography	- Low FPR for poor prognosis (especially absence of continuous background and reactivity) - Good accuracy in predicting favorable prognosis (especially presence of background and reactivity) - Allows detection and management of seizures	- Lack of standardization for stimulus application (reactivity) - Requires expert interpretation.
Early somatosensory evoked potentials	- Very low FPR for poor prognosis	- Low accuracy in predicting favorable prognosis - Lower sensitivity than EEG for predicting poor prognosis - Requires expert interpretation - Not available everywhere
Biomarkers	- Additional tool to confirm poor prognosis	- Not reliable to identify favorable prognosis - Requires experienced laboratory and expert interpretation
Brain imaging	- Additional tool to confirm poor prognosis	- Not reliable to identify favorable prognosis - Requires high-volume centers and expert interpretation

FPR: false positive rate

Figure legends

1: Alpha coma, a frontally predominant alpha rhythm in a comatose patient, nonreactive to painful stimulation (marker in the middle on the top) in a 70 year-old woman, 3 days after cardiac arrest. The patient did not show any brainstem reflexes but had bilateral N20; she subsequently died. Bipolar longitudinal montage, 30mm/sec, 10 µV/mm, HFF 70 Hz, LFF 1.0 Hz.

2: Background reactivity to auditory stimuli ("clap") in a 57 year-old man during therapeutic hypothermia, 20 hours after cardiac arrest. Upon return to normothermia, he had preserved brainstem reflexes and somatosensory evoked potentials, and subsequently awoke. Reduced bipolar longitudinal montage, 20mm/sec, 10 µV/mm, HFF 70 Hz, LFF 0.5 Hz.

3: A. Example of normal, early-latency somatosensory evoked potentials, showing, from bottom to top, a plexus (Erb), cervical (N13), and a cortical response (N20, arrow) in a 33 year-old man who later awoke. **B.** Example of absence of the N20 (arrow) despite presence of a plexus and cervical response in a 16 year-old girl (who did not survive).

4: DWI weighted brain MRI of a 60 year-old patient 7 days after a cardiac arrest of respiratory origin. Hyper-intensities reflecting reduced water diffusion are mostly seen in posterior cortical regions and hippocampi (white arrows).

5: Stepwise multimodal algorithm for outcome prognostication in comatose adults after cardiac arrest. Step 1 includes mandatory investigations, while Step 2 and 3 include confirmatory, optional tests. *EEG may be intermittent or continuous. For details, please see text.

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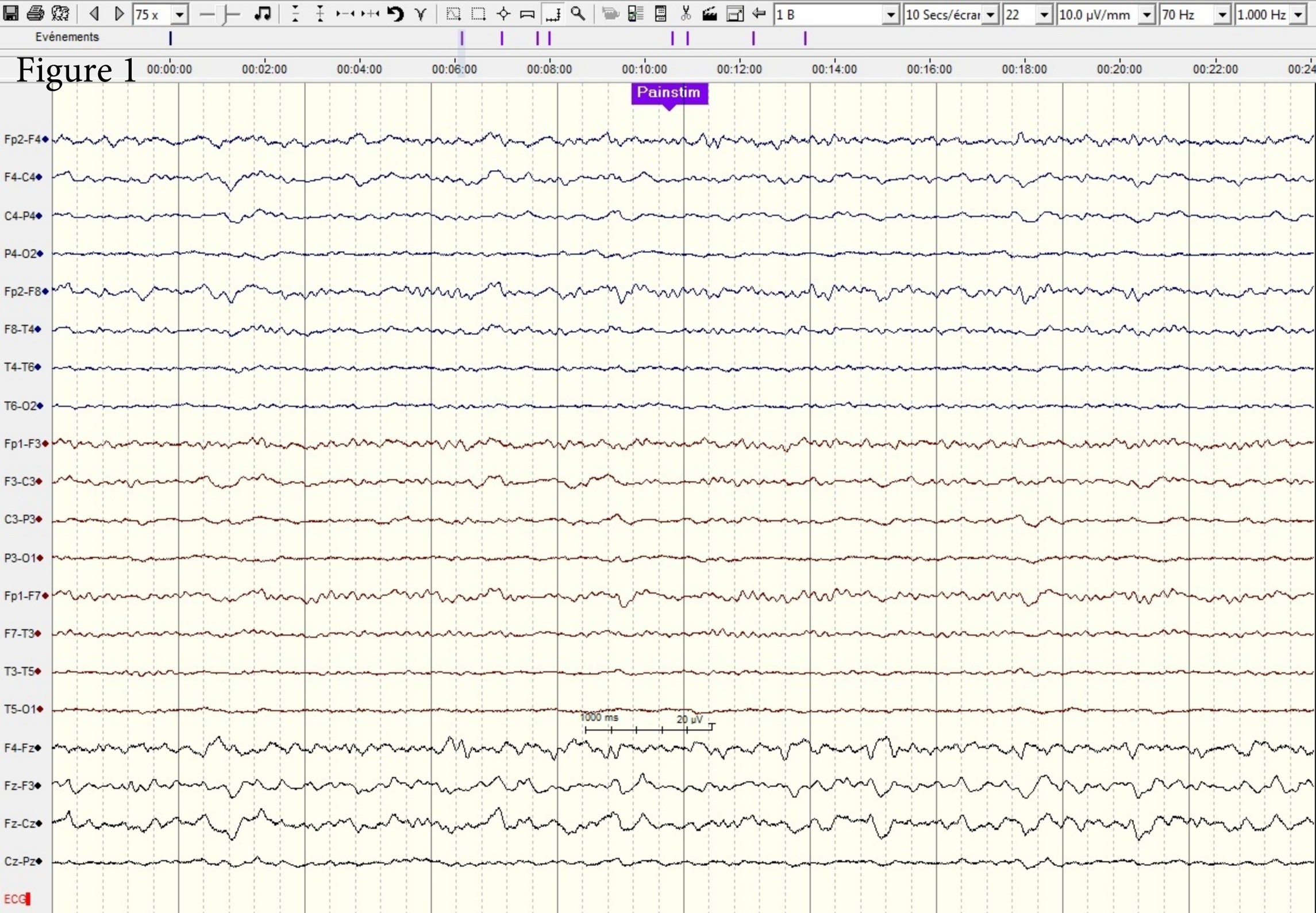
Figure 1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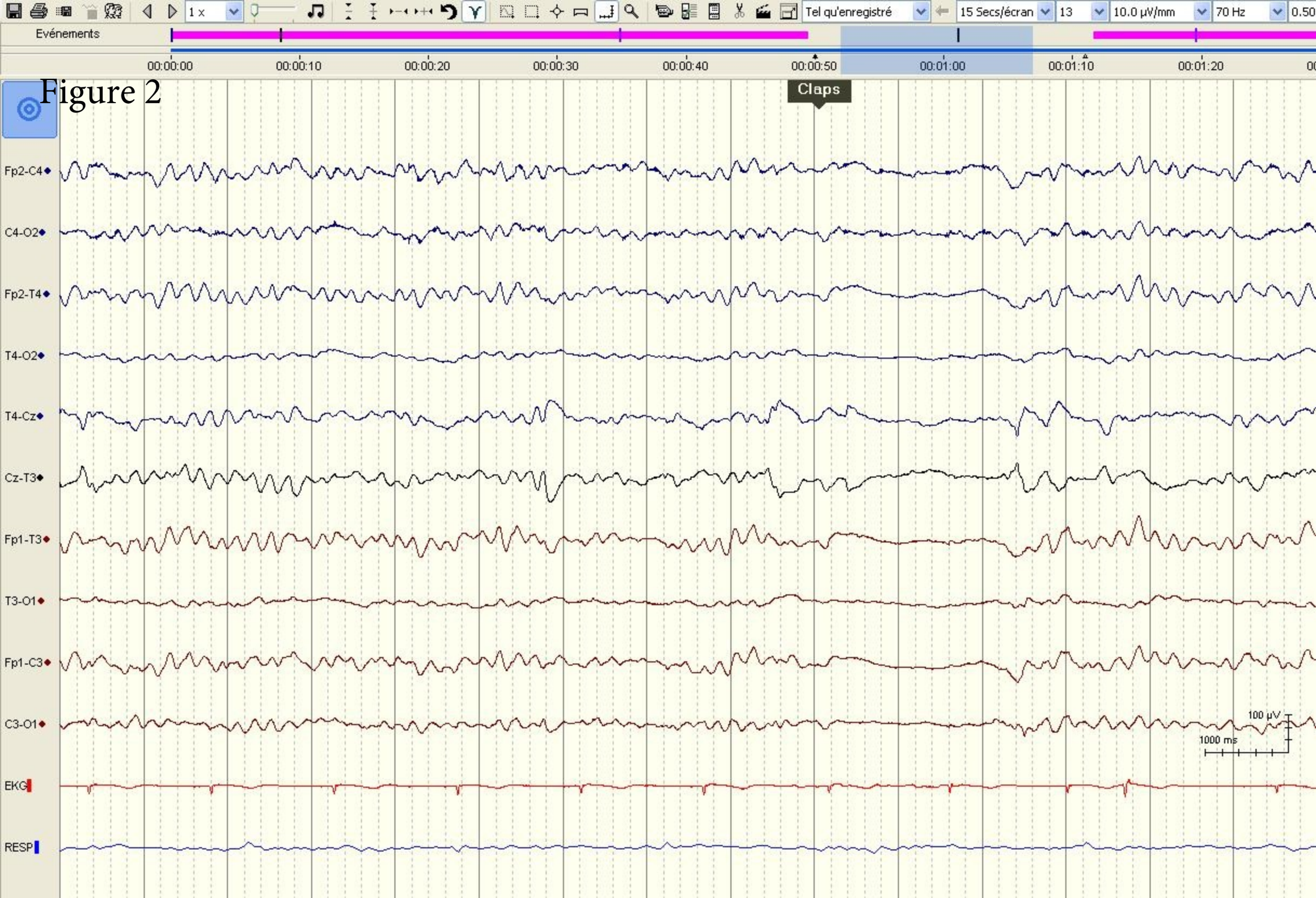
Painstim
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
F8-T4
T4-T6
T6-O2
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
F4-Fz
Fz-F3
Fz-Cz
Cz-Pz
ECG
1000 ms
20 µV

Figure 2


1 x
Tel qu'enregistré
15 Secs/écran
13
10.0 µV/mm
70 Hz
0.50
Evénements
00:00:00
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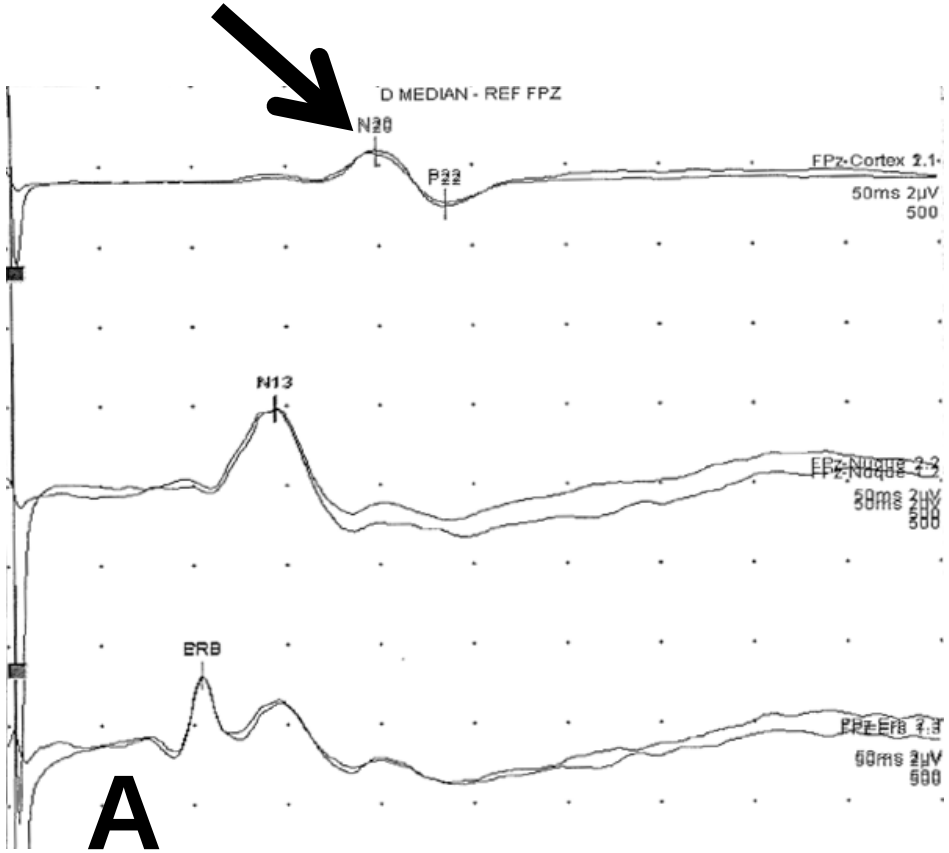
00:00:20
00:00:30
00:00:40
00:00:50
00:01:00
00:01:10
00:01:20
Claps
Fp2-C4
C4-O2
Fp2-T4
T4-O2
T4-Cz
Cz-T3
Fp1-T3
T3-O1
Fp1-C3
C3-O1
100 µV
1000 ms
EKG
RESP

Figure 3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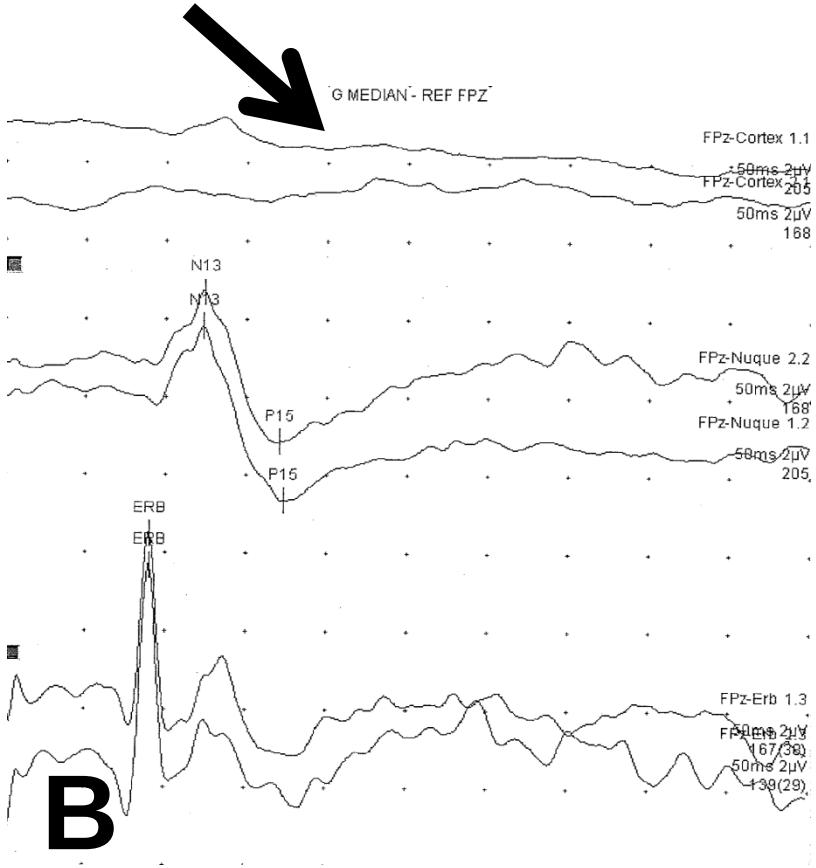
P22
FPz-Cortex 2.1
50ms 2µV
500
N13
ERB
A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50ms 2µV
168
N13
N13
P15
P15
FPz-Nuque 2.2
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ERB
ERB
FPz-Erb 1.3
50ms 2µV
50ms 2µV
B

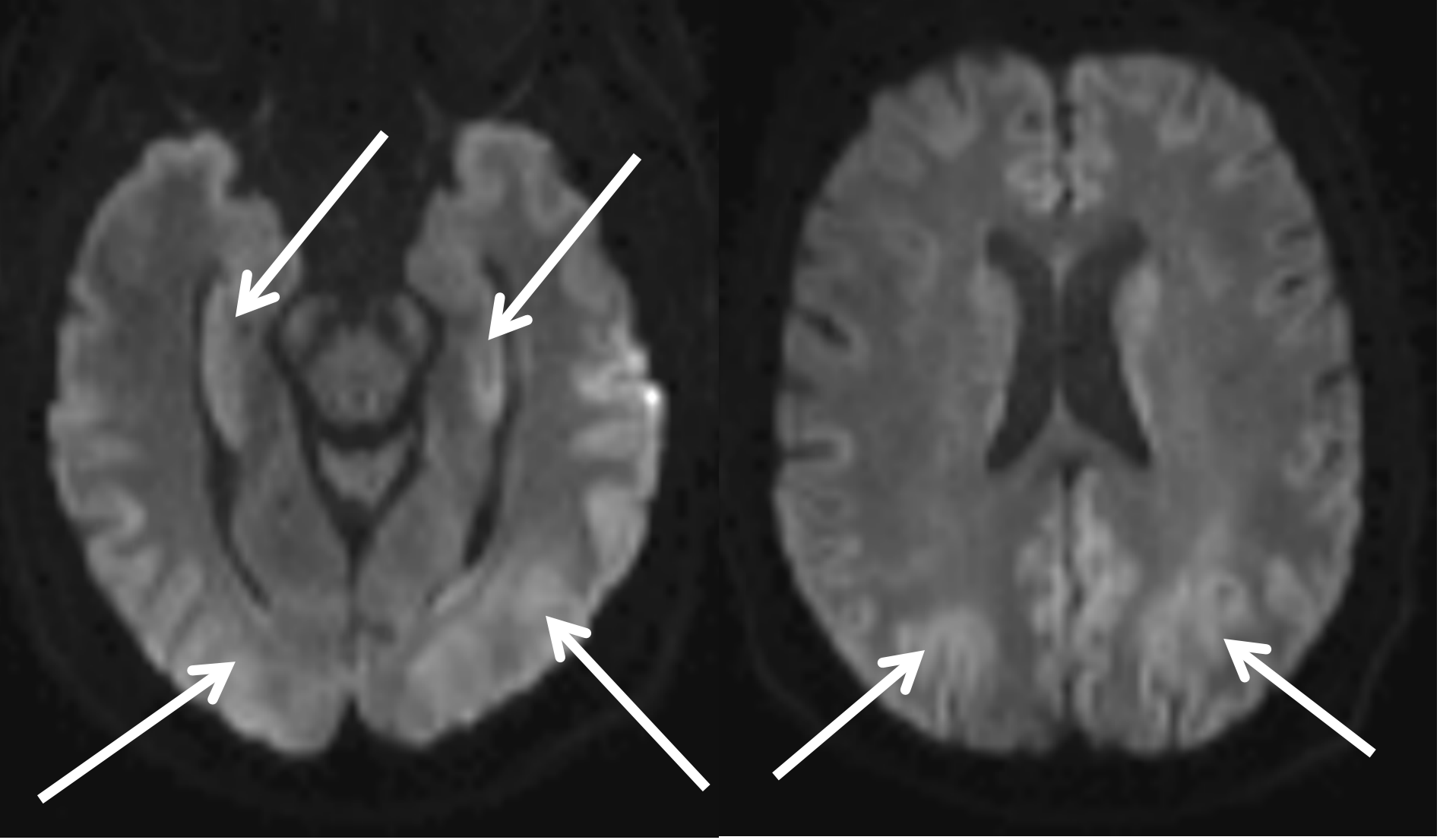

Figure 4

Figure 5