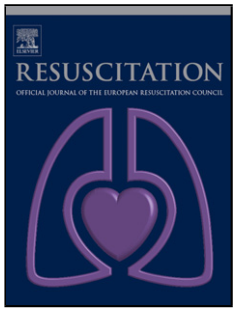
Title: Auditory discrimination improvement predicts awakening of postanoxic comatose patients treated with targeted temperature management at 36°C.
Authors: Pfeiffer C, Nguissi NAN, Chytiris M, Bidlingmeyer P, Haenggi M, Kurmann R, Zubler F, Oddo M, Rossetti AO, De Lucia M
Journal: Resuscitation
Year: 2017 Sep
Volume: 118
Pages: 89-95
DOI: 10.1016/j.resuscitation.2017.07.012



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PII: S0300-9572(17)30293-9
DOI: http://dx.doi.org/doi:10.1016/j.resuscitation.2017.07.012
Reference: RESUS 7245

To appear in: *Resuscitation*

Received date: 5-5-2017
Revised date: 29-6-2017
Accepted date: 10-7-2017

Please cite this article as: Pfeiffer Christian, Nguissi Nathalie Ata Nguepno, Chytiris Magali, Bidlingmeyer Phanie, Haenggi Matthias, Kurmann Rebekka, Zubler Frédéric, Oddo Mauro, Rossetti Andrea O, De Lucia Marzia.Auditory discrimination improvement predicts awakening of postanoxic comatose patients treated with targeted temperature management at 36°C.*Resuscitation* http://dx.doi.org/10.1016/j.resuscitation.2017.07.012

Auditory discrimination improvement predicts awakening of postanoxic comatose patients treated with targeted temperature management at 36°C

Running header: COMA-OUTCOME NORMOTHERMIA

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Manuscript to be submitted to: **Resuscitation**

Words in the Abstract: *244 words*
Words in the main text: *2982 words*
Figures: *2*
Tables: *3*

Abstract

BACKGROUND: Outcome prognostication in postanoxic comatose patients is more accurate in predicting poor than good recovery. Using electroencephalography recordings in patients treated with targeted temperature management at 33°C (TTM 33), we have previously shown that improvement in auditory discrimination over the first days of coma predicted awakening. Given the increased application of a 36°C temperature target (TTM 36), here we aimed at validating the predictive value of auditory discrimination in the TTM 36 setting.

METHODS: In this prospective multicenter study, we analyzed the EEG responses to auditory stimuli from 60 consecutive patients from the first and second coma day. A semiautomatic decoding analysis was applied to single patient data to quantify discrimination performance between frequently repeated and deviant sounds. The decoding change from the first to second day was used for predicting patient outcome.

RESULTS: We observed an increase in auditory discrimination in 25 out of 60 patients. Among them, 17 awoke from coma (68% positive predictive value; 95% confidence interval: 0.46-0.85). By excluding patients with electroencephalographic epileptiform features, 15 of 18 exhibited improvement in auditory discrimination (83% positive predictive value; 95% confidence interval: 0.59-0.96). Specificity of good outcome prediction increased after adding auditory discrimination to EEG reactivity.

CONCLUSION: These results suggest that tracking of auditory discrimination over time is informative of good recovery independent of the temperature target. This quantitative test provides complementary information to existing clinical tools by identifying patients with high chances of recovery and encouraging the maintenance of life support.

Keywords: Cardiac arrest, coma, targeted temperature management, EEG, mismatch negativity, multivariate decoding

1. Introduction

Cardiac arrest (CA) has an annual incidence of 50-110 /100’000 [1], with an approximately 10% successful resuscitation rate [2]. The considerable amelioration in recovery rate of hospitalized patients can be attributed to recent advances in therapeutic interventions, including the introduction of Targeted Temperature Management (TTM) targeting 33°C (TTM 33) [3] and, more recently 36°C (TTM 36) [4]. In this context, clinicians aim at providing early and accurate predictions of patients’ outcome in order to guide decision-making upon continuation of intensive treatment.

This task is typically performed using a multimodal approach including the standardized predictors: bilateral absence of brainstem reflexes, absence of motor response to

pain and treatment-resistant myoclonus, unreactive or discontinuous electroencephalography (EEG) background activity, bilateral absence of N20 somatosensory evoked potentials (SSEP) and high serum neuron specific enolase (NSE). These markers are robustly related to poor neurological recovery (see [5] for an overview). By contrast, their presence does not predict whether the patient will recover from coma - with the exception of EEG background reactivity [6, 7], which however showed imperfect inter-rater agreement despite attempts for standardized interpretations (e.g. [8, 9]). Thus, the introduction of standardized quantitative tests for the prediction of coma outcome, specifically targeting identification of good prognosis, could complement and fill a prognostic gap in routine clinical practice.

In recent studies we have combined the use of a mismatch negativity (MMN) paradigm and automated EEG analyses to quantify auditory discrimination at the single-patient level [10-12]. We showed that improvement of auditory discrimination over the first two days of post-anoxic coma was informative about good outcome in a large cohort of consecutive post-anoxic comatose patients treated with TTM 33 (up to 93% positive predictive value, PPV, in [10]). In line with these results, an improvement in auditory discrimination correlated positively with functional and cognitive performance at awakening in survivors [13]. Despite these promising results in patients treated with TTM 33, it is currently unknown whether our method is valid in those undergoing TTM 36. Thus, the aim of our study was to update and to compare the PPV of this tool in patients treated with TTM 36 to the previously reported results in patients undergoing TTM 33.

2. Materials and Methods

2.1. Post-Anoxic Comatose Patients

We prospectively collected data from 84 consecutive patients older than 18 years successfully resuscitated after CA admitted to the medical-surgical intensive care units at the

University Hospitals of Lausanne (58 patients), Bern (23 patients), Fribourg (2 patients), Sion (1 patient) between July 2014 and February 2017. For this study we collected data from all patients receiving TTM 36 who were admitted to the participating hospital centers during the study period, given availability of the EEG recording equipment and experimenter, and a high probability of the patient being still alive for the first day EEG recording based on current clinical assessment. TTM 36 was applied for 24 hours using ice packs or intravenous ice-cold fluids together with a feedback controlled cooling device (Arctic Sun System, Medivance, Louisville or Thermogard XP, ZOLL Medical, Zug, Switzerland) followed by removal of TTM after 24 hours. Propofol (2-3 mg/kg/h), Midazolam (0.1 mg/kg/h) and Fentanyl (1.5 µg/kg/h) were given for analgesia-sedation, and Vecuronium, Rocuronium, or Altracurium for controlling shivering. Patients' outcome was defined as the best functional level reached within 3 month after CA. We considered both the results of clinical assessments during hospitalization using Full Outline of UnResponsiveness (FOUR; [14]), repeated at least twice within 72 hours following CA, and regular assessment of neurological state during hospitalization, as well as the result of a semi-structured phone interview at three months after CA using Cerebral Performance Categories (CPC; [15]): CPC 1 indicates full recovery; CPC 2 conscious with moderate disability; CPC 3 conscious with severe disability; CPC 4 coma or persistent vegetative state, and CPC 5 death. We consider as patients with good outcome (in the following 'Survivors', n = 34) those with CPC 1-3 at any time within three months after coma onset. All patients who died within three months from coma onset without ever awakening are considered within the poor outcome group (in the following 'Non-Survivors'; n = 26). All of them had a CPC 5. Of 84 patients, 15 were excluded from analysis because of missing second EEG recording (i.e. 8 awoke, 6 deceased, and 1 patient was transferred to a different hospital before 48 hours following CA). For our main analysis, we excluded 9 patients because a relevant comorbidity (e.g. second CA, multiorganic failure, or intracerebral

bleeding) unrelated to the initial CA was diagnosed only after our recordings, and caused death within 3 months. Because our approach is based on EEG recordings during the first two days following CA, our method cannot foresee such secondary events. Thus, the number of patients included for the analysis presented in the main text was 60. Informed written consent for participation in this study was obtained prior to EEG recordings from a family member, legal representative, or treating clinician not involved in this study. The study protocol was approved by the ethical commissions of each hospital.

2.2. Clinical Assessments

Neurological examination of pupillary, oculocephalic, corneal reflexes and motor reactivity to pain stimulation was assessed by a certified neurologist after withdrawal of TTM and weaning of pharmacological sedation (at least twice between 36 and 72 hours after CA, or more often if needed). Two clinical EEG recordings were performed, within 24 hours (at least 6 hours) after CA during TTM, and at 36-48 hours after CA after withdrawal of TTM at the time of clinical examination [16]. EEG background reactivity interpretation was performed by experienced electroencephalographers. Epileptiform EEG was defined as any repetitive periodic or rhythmic spikes, or sharp waves, or spike-waves [8]. Bilateral median nerve SSEP were recorded at least 24 hours after CA. NSE was measured at 24 and 48 hours after CA and analyzed with an automated immunofluorescent assay (Thermo Scientific Brahms NSE Kryptor Immunoassay, Hennigsdorf, Germany; and Roche Cobas Elecsys, Roche Diagnostics, Rotkreuz, Switzerland). Withdrawal of care was decided using a multidisciplinary approach, if two or more of the following criteria were present [17]: 1. Unreactive EEG background after TTM and off sedation, 2. Treatment-resistant myoclonus, 3. Bilateral absence of N20 in SSEP, and 4. Incomplete return of brainstem reflexes.

2.3. EEG Methods and Stimulation Protocol

Patients took part in a MMN protocol during concurrent EEG recordings described previously [10, 11]. A detailed description of the EEG acquisition, data processing, and multivariate decoding analysis methods can be found in the Supplemental Material.

3. Results

3.1. Comatose Patients' Outcome

Among the 60 patients analyzed (i.e. *'All Patients'* sample, 17 women, age mean = 67 years, SD = 12 years), 34 (57%) had a good outcome and 26 (43%) a poor outcome. Out of the 60 patients tested, 14 (23%) had an EEG with epileptiform features either on the first day (3 patients, 5%), on the second day (4 patients, 6%), or on both days following CA (7 patients, 12%). Because such epileptiform activity can affect evoked potential recordings [18, 19], and based on our previous results showing a high false positive rates for outcome prediction in these patients [10], we report a separate outcome prediction analysis for a reduced sample of 46 patients without epileptiform features (i.e. *'No Epileptiform Features'* sample, 12 women, age mean = 66 years, SD = 12 years) out of which 31 (67%) had a good outcome and 15 (33%) a poor outcome.

3.2. Outcome-Prediction for Patients Treated with TTM 36

3.2.1. All Patients Sample

Out of the 60 patients, the average decoding performance for 34 Survivors was AUC_{DAY1} = 0.611 ± 0.005 and AUC_{DAY2} = 0.615 ± 0.005, and for the 26 Non-Survivors decoding performance was AUC_{DAY1} = 0.627 ± 0.006 and AUC_{DAY2} = 0.616 ± 0.006 (**Figure 1-A**). We considered the change in decoding performance from Day 1 to Day 2 in accordance

with our previous studies [10, 11]. An improvement was observed in 17 of 34 Survivors (50%), whereas the majority of the Non-Survivors (18 of 26, 69%) showed a decrease in decoding performance (**Figure 2-A**). Overall, across all 60 patients, an improvement in AUC from Day 1 to Day 2 was observed in 25 patients, among whom 17 awoke from coma, resulting in 68% predictive value of good outcome (95% CI = 0.46 – 0.85; **Table 1**). The sensitivity (i.e., ratio of Survivors showing an increase) was 50% (95% CI = 0.32 – 0.68) and the specificity (i.e., ratio of Non-Survivors showing a decrease) was 69% (95% CI = 0.48 – 0.86). The predictive value of poor outcome (i.e. ratio patients showing decrease with a poor outcome) was 51% (95% CI = 0.34 – 0.69), and the overall accuracy was 58% (95% CI = 0.38 – 0.63; **Table 1**). For completeness and to ease comparison with previous studies, we report in **Table S1** the outcome prediction results including patients with comorbidities.

3.2.2. No Epileptiform Features Sample

Analysis of the data from 46 patients revealed an average decoding performance for 31 Survivors of AUC_{DAY1} = 0.601 ± 0.005 and AUC_{DAY2} = 0.612 ± 0.005 and for the 15 Non-Survivors decoding performance was AUC_{DAY1} = 0.625 ± 0.008 and AUC_{DAY2} = 0.610 ± 0.005 (**Figure 1-B**). An improvement was observed in 15 of 31 Survivors (48%), whereas the vast majority of the Non-Survivors (12 of 15 patients, 80%) showed a decrease in decoding performance (**Figure 2-B**). Thus, across these 46 patients, an improvement in AUC from Day 1 to Day 2 was observed in 18 patients, among whom 15 awoke from coma, resulting in 83% predictive value of good outcome (95% CI = 0.59 – 0.96, **Table 1**). The sensitivity was 48% (95% CI = 0.30 – 0.67) and the specificity was 80% (95% CI = 0.52 – 0.96). The predictive value of poor outcome was 43% (95% CI = 0.24 – 0.63), and the overall accuracy 59% (95% CI = 0.33 – 0.59; **Table 1**).

3.3. Outcome-Prediction: Comparison Between 36°C and 33°C Temperature Targets

Comparison of patients treated with TTM 36 (present study) to a different sample of patients treated with TTM 33 (previously published in [10]) suggests that outcome prediction perform similarly when excluding patients with epileptiform features: the positive predictive values and specificities were significantly above chance level, with overlapping confidence intervals (**Table 1**). However, the overall outcome prediction including all patients of the present study was not as robust as in the TTM 33 cohort.

3.4. Clinical Characteristics

We compared demographics and clinical characteristics between patients showing an increase and patients showing a decrease of decoding performance separately for Survivors (n = 35, **Table 2**) and Non-Survivors (N = 25, **Table 3**) and to assess if additional factors contributed to the outcome prediction results. There were no differences in gender distribution, age, CA etiology, return of spontaneous circulation (ROSC), presence/absence of brainstem reflexes, latency of clinical EEG assessment and in the majority of semi-quantitative markers of EEG (i.e. discontinuity, reactivity). However, for Non-Survivors we observed a difference regarding the presence of epileptiform EEG. Out of the 7 Non-Survivors showing an increase, 5 (71%) had an epileptiform first EEG, whereas out of the 18 Non-Survivors showing a decrease, this only occurred in 5 (28%). Thus, in line with our previous study, the increase of decoding performance in these patients (and therefore the occurrence as false positives) can be somewhat related to epileptiform activity [10].

4. Discussion

We found that an improvement in auditory discrimination over the first two days of coma predicts good outcome in patients treated with TTM 36, extending our previous findings in 94 patients treated with TTM 33 [10]. The higher predictive value of good outcome in TTM 36 when patients with epileptiform features were excluded confirm previous results obtained in TTM 33 ([10, 11]). Control analysis ruled out that these results were based on decoding performance from the first day alone (see Supplemental Material, **Table S2**). This suggests that our method is robust across different TTM target temperatures. These results are further in line with recent results of a large multicentric clinical trial showing that the chosen temperature target (i.e. 33°C, 36°C) did neither affect prognostic markers of poor outcome, nor the patient's outcome itself [4].

4.1. Comparison to Existing Prognostication Methods

Prognostication of coma outcome based on a multimodal approach typically considers incomplete brainstem reflexes, the presence of myoclonous, the absence of SSEP, an unreactive background EEG, and high NSE markers [5], which are highly predictive of negative outcome. Current propositions for predicting good outcome include reactive background EEG, with high PPV both for patients treated with TTM 33 [6] and TTM 36 [20] and as confirmed by similar results in our cohort when predicting outcome based on reactivity assessed on Day2 (see **Table S1**). However, the lack of standardization and inevitable subjectivity in its clinical assessment call for further developments of unbiased and quantitative predictors of good outcome after CA. A recent study used computer algorithm-based extraction of distinct EEG features upon which multivariate analysis achieved up to 83% accuracy for detecting positive and negative outcome [7]. However, in this approach the optimal choice for a classification threshold remains undetermined, which is a necessary step

for implementation in the clinical practice. In addition, it remains difficult to interpret physiologically due to the high dimensionality of the classified features. Our method overcomes some of the current limitations in available clinical predictors by providing a quantitative approach with a high PPV at a fixed classification threshold. In addition, it is applicable at bedside at the single-patient level and interpretable by linking functional improvement over time with survival rate. The lack of differences in the majority of clinical characteristics between patients improving or decreasing in decoding performance (with the only exception of epileptiform EEG on the first day) suggests that the predictive value of our method is not redundant with currently available clinical tests (see **Tables 2 and 3**). This is supported by the higher PPV and specificity for good outcome prediction when considering together reactive EEG on Day 2 and auditory discrimination improvement, as compared to these variables considered separately (**Table S1**, and [21] for comparisons to previous cohorts). Of note, comparisons between clinical data and the auditory test should be considered with some caution, as the former were known to clinicians and may have influenced patients' outcome.

4.2. Impact of Epileptiform EEG on Good Outcome Prediction

We found that inclusion of patients with epileptiform EEG resulted in a lower PPV for good outcome for the TTM 36 sample of this study. This was related to the fact that the majority of Non-Survivors with an increase in decoding performance (i.e. 5 out of 8 patients, 63%) had epileptiform EEG on the first and/or second day after coma onset. Among the 14 patients with these features 7 (50%) showed an increase of decoding performance, suggesting chance-level performance in this subset (formal statistical evaluation was not performed due to the low number of patients). Notably, the vast majority of subjects with an epileptiform EEG in our study (i.e. 12 out of 14 patients, 86%) had a poor outcome, in line with previous

studies [17, 22]. Indeed, the high-amplitude epileptiform activity can strongly affect evoked potential recording [18, 19] in particular in the context of single-trial analysis as used in the present study [10]. Thus, it remains a challenge for future studies to assess whether our method could be improved by implementing an automated detection of epileptiform activity (see [23] for a review).

4.3. Brain Mechanisms of Auditory Discrimination Progression

Anoxia-induced brain swelling in the acute phase after CA is associated with diffuse brain damage in thalamus, basal ganglia, cerebellum, hippocampus, frontal, and parietal cortices [24-26]. Neural degeneration over time in these regions has been described in non-survivors of CA [27, 28]. Because neural processing in hippocampal [29-31] and fronto-parietal regions [32, 33] plays a crucial role for sensory-memory trace formation and violation detection, the progression of auditory discrimination measured in our study might directly reflect the progression of anoxia-induced functional impairment in these brain regions. This interpretation receives support from diffusion-weighted magnetic resonance imaging studies that showed distinct signal abnormalities in the acute, subacute, and chronic stages following hypoxic-ischemic encephalopathy (see [34] for a review). Thus, our EEG results obtained within 48 hours after CA index the progression of acute effects of anoxia on the brain, whereas they might not provide information of subacute and chronic processes that contribute to the final outcome. In addition, the neural structures involved in generating the MMN are not exclusively limited to processing auditory signals. Instead, the MMN is thought to be a consequence of predictive brain function to be found in any sensory modality (e.g. somatosensory: [35-38]; visual: [39-41]; across modalities: [42-44]) as suggested by both modality-specific and -unspecific neural correlates identified in healthy subjects [45]. In patients, it remains currently unknown whether progression of, e.g. somatosensory

discrimination would show comparable predictive power as for the current results obtained for auditory stimulation - in particular, when considering that absence of cortical somatosensory responses (i.e. SSEPs) are indicative of poor outcome [5]. Future studies including MMN paradigms across sensory modalities will elucidate the potential mechanism underlying the generation of a violation detection response in these patients.

4.4. Limitations and outlook

Although our results were obtained in a blinded fashion to the clinicians responsible for end-of-life decisions, thus ruling out a contribution of self-fulfilling prophecy, we cannot exclude that end-of-life decisions affected the overall results – in particular, regarding three patients showing an increase with poor outcome later on (i.e. false positives). Our current results represent therefore a conservative estimation of the 'true' PPV of the proposed method. EEG reactivity seems already very robust in the present cohort in terms of sensitivity towards prediction of good outcome and the improvement of auditory discrimination seems basically to raise its specificity (at cost of sensitivity). One future possibility for improving the overall predictive power of our approach is considering progression of auditory discrimination alongside other qualitative prognostic marker of negative outcome prediction [5].

Contributions

Concept and study design: C.P., M.H., R.K., F.Z., M.O., A.O.R., and M.D.L.; data acquisition and analysis: C.P., N.A.N.N., M.C., P.B., M.H., and R.K.; drafting the manuscript and figures: C.P., A.O.R., and M.D.L.

Conficts of interest: none.

Acknowledgments

We thank all EEG technicians from the involved hospitals for invaluable help with EEG recordings. We thank Christine Staehli, R.N., and Daria Solari, M.D., from the CHUV, Dragana Viceic, M.D., and Marco Rusca, M.D., from the Hopital de Sion, Ettore Accolla, M.D., and Sebastien Doll, M.D., from the Hôpital de Fribourg for providing clinical information for some of the patients. We are indebted to Rupert Ortner and Christoph Guger for technical support. This research was funded by EUREKA-Eurostars, Grant Number E! 9361 Com-Alert to Marzia De Lucia.

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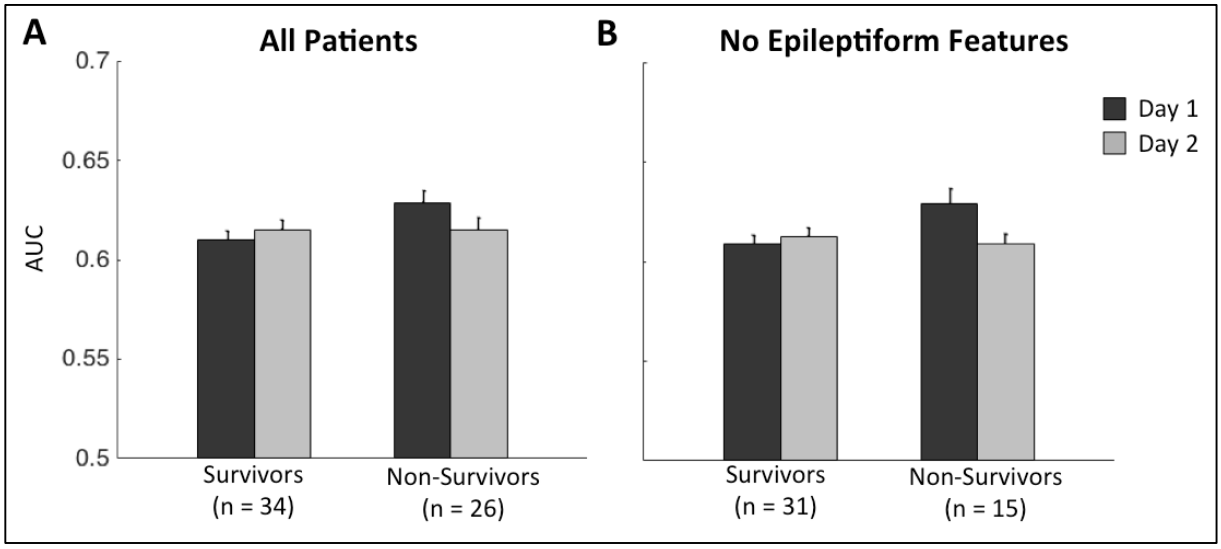

Figure 1: Average decoding performance across all patients (n=60, left panel) and for the reduced sample of patients without epileptiform features (n=46, right panel), split according to their outcome (Survivors, Non-Survivors). Black bars refer to the area under the curve (AUC) values obtained for the first day recording (Day 1) under TTM 36 and grey bars refer to AUC values of the second day recording (Day 2) after withdrawal of temperature control. Decoding performance corresponds to average AUC values for decoding EEG responses to standard versus three types of deviant sounds evaluated for each patient/recording separately.

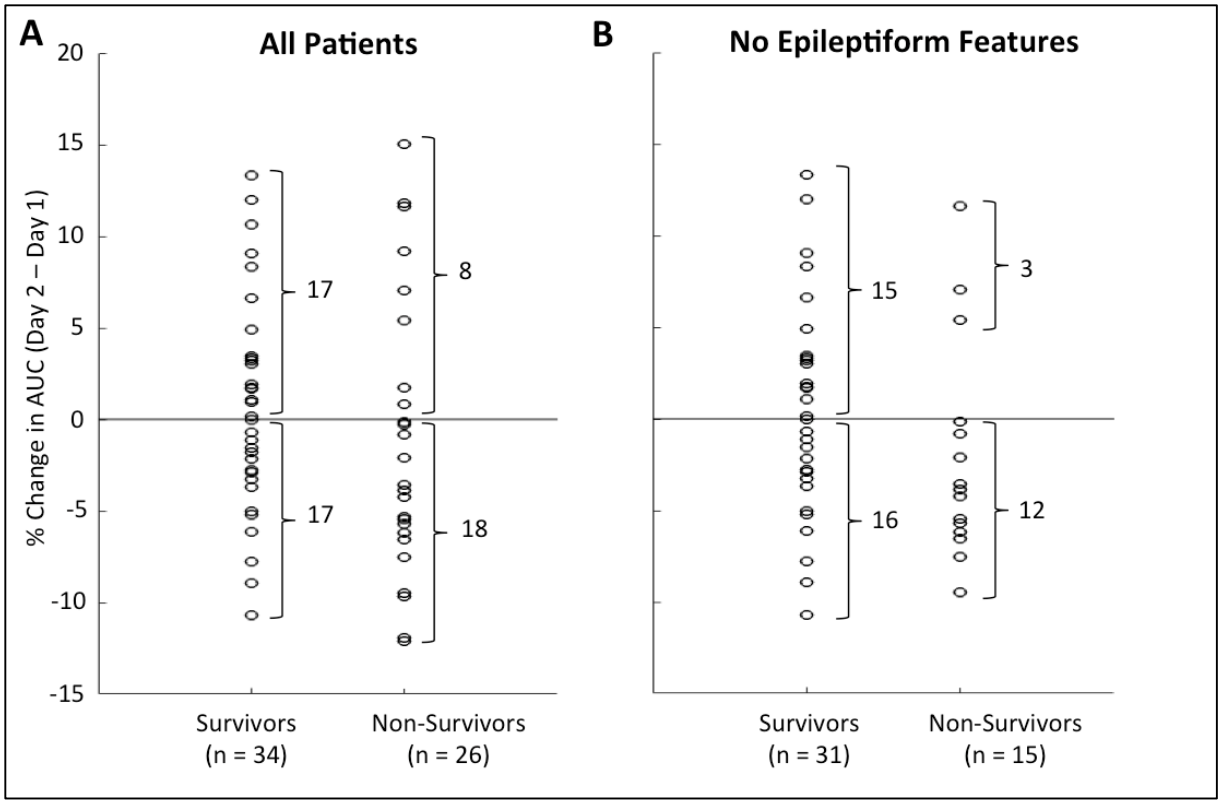

Figure 2: Outcome prediction results across all patients (n=60, left panel) and the reduced sample of patients without epileptiform features (n=46 right panel), split according to patients' outcome (Survivors, Non-Survivors). Circles refer to the percentage change in decoding performance for individual patients from Day 1 under TTM 36 to Day 2 without temperature control. AUC: area under the curve.

Table 1: Prognostic value for good outcome for patients of the present study treated with TTM 36 and for patients from a previous study treated with TTM 33 [10]. Results are shown separately for analyses across all patients and across subgroup of patients without epileptiform features. Values above chance level are highlighted in red.

	TTM 36 Sample		**TTM 33 Sample (Tzovara et al. 2016)**	
	All Patients n = 60	**No Epileptiform Features n = 46**	**All Patients n = 94**	**No Epileptiform Features n = 73**
Positive Predictive Value (95%CI)	**0.68** (0.46-0.85)	**0.83** (0.59-0.96)	**0.82** (0.65-0.93)	**0.93** (0.77-0.99)
Sensitivity (95%CI)	**0.50** (0.32-0.68)	**0.48** (0.30-0.67)	**0.48** (0.35-0.62)	**0.50** (0.36-0.64)
Specificity (95%CI)	**0.69** (0.48-0.86)	**0.80** (0.52-0.96)	**0.84** (0.69-0.94)	**0.89** (0.67-0.99)
Negative Predictive Value (95%CI)	**0.51** (0.34-0.69)	**0.43** (0.24-0.63)	**0.52** (0.39-0.65)	**0.39** (0.24-0.55)
Accuracy (95%CI)	**0.58** (0.38-0.63)	**0.59** (0.33-0.59)	**0.63** (0.41-0.60)	**0.60** (0.35-0.55)

Table 2: Clinical description of Survivors (n = 34), split according to whether from Day 1 to Day 2 their decoding performance increased or decreased.

	Survivors with Increase, n = 17	**Survivors with Decrease, n = 17**
Female gender, No (%)	3 / 17 (18%)	5 / 17 (29%)
Age, yr mean ± SD (range)	64 ± 13 (36-83)	69 ± 12 (51-86)
Time to ROSC, min mean ± SD (range)	21 ± 12 (8-50)	30 ± 43 (3-180)
Non cardiac etiology, No (%)	5 / 17 (29%)	5 / 17 (29%)
Absent Pupillary reflex, No (%)	1 / 17 (6%)	0 / 17 (0%)
Absent Corneal reflex, No (%)	3 / 17 (18%)	3 / 17 (18%)
Absent Motor response, No (%)	4 / 17 (24%)	3 / 17 (18%)
Early myoclonus, No (%)	0 / 17 (0%)	1 / 17 (6%)
First EEG: Unreactive background, No (%)	1 / 17 (6%)	4 / 16 (25%) *Missing: 1*
First EEG: Discontinuous EEG, No (%)	3 / 17 (18%)	8 / 16 (50%) *Missing: 1*
First EEG: Epileptiform EEG, No (%)	0 / 17 (0%)	0 / 16 (0%) *Missing: 1*
Second EEG: Unreactive background, No (%)	0 / 14 (0%) *Missing: 3*	0 / 16 (0%) *Missing: 1*
Second EEG: Discontinuous EEG, No (%)	1 / 14 (7%) *Missing: 3*	0 / 16 (0%) *Missing: 1*
Second EEG: Epileptiform EEG, No (%)	2 / 14 (14%) *Missing: 3*	1 / 16 (6%) *Missing: 1*
Bilaterally absent N20 on the SSEP, No (%)	0 / 9 (0%) *Missing: 8*	0 / 14 (0%) *Missing: 3*
NSE, median μ g/l, SD (range)	24 ± 10 (15-52)	22 ± 17 (13-59)

NSE > 75 µg/l, No (%)	0 / 11 (0%) *Missing: 6*	0 / 11 (0%) *Missing: 6*
Time to first EEG, h mean ± SD (range)	20 ± 7 (9-36)	21 ± 10 (8-46)
Time between recordings, h mean ± SD (range)	25 ± 7 (18-46)	23 ± 9 (6-48)

Table 3: Clinical description of Non-Survivors (n = 26), split according to whether from Day 1 to Day 2 their decoding performance increased or decreased.

	Non-Survivors with Increase, n = 8	**Non-Survivors with Decrease, n = 18**
Female gender, No (%)	3 / 8 (38%)	6 / 18 (33%)
Age, yr mean ± SD (range)	72 ± 13 (46-84)	65 ± 12 (45-86)
Time to ROSC, min mean ± SD (range)	25 ± 12 (5-40)	24 ± 9 (15-50)
Non cardiac etiology, No (%)	1 / 8 (12%)	4 / 16 (25%) *Missing: 2*
Absent Pupillary reflex, No (%)	3 / 7 (43%) *Missing: 1*	4 / 17 (24%) *Missing: 1*
Absent Corneal reflex, No (%)	6 / 7 (86%) *Missing: 1*	11 / 17 (65%) *Missing: 1*
Absent Motor response, No (%)	7 / 7 (100%) *Missing: 1*	15 / 17 (88%) *Missing: 1*
Early myoclonus, No (%)	2 / 7 (29%) *Missing: 1*	9 / 17 (53%) *Missing: 1*
First EEG: Unreactive background, No (%)	6 / 7 (86%) *Missing: 1*	16 / 18 (89%)
First EEG: Discontinuous EEG, No (%)	6 / 7 (86%) *Missing: 1*	15 / 18 (83%)
First EEG: Epileptiform EEG, No (%)	5 / 7 (71%) *Missing: 1*	5 / 18 (28%)
Second EEG: Unreactive background, No (%)	5 / 6 (83%) *Missing: 2*	10 / 16 (62%) *Missing: 2*
Second EEG: Discontinuous EEG, No (%)	3 / 6 (50%) *Missing: 2*	8 / 16 (50%) *Missing: 2*
Second EEG: Epileptiform EEG, No (%)	2 / 6 (33%) *Missing: 2*	6 / 16 (38%) *Missing: 2*
Bilaterally absent N20 on the SSEP, No (%)	3 / 5 (60%) *Missing: 3*	7 / 11 (64%) *Missing: 7*

NSE, median µg/l, SD (range)	87 ± 261 (20-583)	98 ± 144 (30-414)
NSE > 75 µg/l, No (%)	2 / 4 (50%) *Missing: 4*	5 / 8 (62%) *Missing: 10*
Time to first EEG, h mean ± SD (range)	20 ± 6 (10-24)	22 ±11 (6-48)
Time between recordings, h mean ± SD (range)	24 ± 4 (19-30)	26 ± 11 (18-64)