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Running Head: Predicting awakening from post-anoxic coma

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Abstract

Objective: Most of the available clinical tests for prognosis of post-anoxic coma are informative of poor outcome. Previous work has shown that an improvement in auditory discrimination over the first days of coma is predictive of awakening. Here, we aimed at evaluating this test on a large cohort of patients undergoing therapeutic hypothermia and at investigating its added value on existing clinical measures.

Methods: We recorded electroencephalography responses to auditory stimuli in 94 comatose patients, under hypothermia and after re-warming to normal temperature. Auditory discrimination was semi-automatically quantified by decoding electroencephalography responses to frequently repeated vs. rare sounds. Outcome prediction was based on the change of decoding performance from hypothermia to normothermia.

Results: An increase in auditory discrimination from hypothermia to normothermia was observed for 33 out of 94 patients. Among them, 27 awoke from coma, resulting in a positive predictive value of awakening of 82% (95% confidence interval: 0.65-0.93). Most non-survivors showing an improvement in auditory discrimination had incident status epilepticus. By excluding them, 27 out of 29 patients with improvement in auditory discrimination survived, resulting in a considerable improvement of the predictive value for awakening (93%, with 95% confidence interval: 0.77-0.99). Importantly, this test predicted the awakening of 13 out of 51 patients for which the outcome was uncertain based on current tests.

Interpretation: The progression of auditory discrimination from hypothermia to normothermia has a high predictive value for awakening. This quantitative measure provides an added value to existing clinical tests and encourages the maintenance of life support.

1. Introduction

Coma after cardiac arrest is a leading cause of admission in the intensive care units. Since the early 2000s, therapeutic hypothermia (TH; [1]) has been increasingly applied as a standard care for cardiac arrest survivors [2], as it improves patients' neurological outcome and chances of recovery [3, 4]; more recently, targeted temperature management to 36°C has been advocated [5].

In this setting, patients' prognostication is typically based on a multimodal approach, where absence of brainstem reflexes, of electroencephalography (EEG) background activity and reactivity, and cortical somatosensory-evoked potentials (SSEP) are informative of a lack of improvement [6-10], and are currently used in multimodal prognostic algorithms [11, 12]. By contrast, the presence of these responses does not predict that the patient will recover from coma, with the exception of EEG background reactivity, which heralds survival in more than 80% [13]. However, this test is based on a qualitative measure, lacks standardization [14-17], and does not reach the high levels of accuracy typically observed in prediction of poor outcome. In other words, no quantitative tests can nowadays accurately predict a good outcome in routine clinical practice.

One promising prognostic tool in this context is the so-called Mismatch Negativity (MMN) [18-22]. The MMN paradigm (MMNp) consists of a series of regularly repeated (standard) sounds, which are randomly replaced by rare (deviant) ones [23, 24] and has been extensively used for studying basic neural mechanisms of auditory discrimination.

In a preliminary work using an MMNp and automated EEG analyses to quantify auditory discrimination at the single-patient level, we have shown that an improvement between

the first two days of coma is only observed in survivors [21]. Here, we aimed at confirming the prognostic value of this paradigm in a larger cohort of patients from two hospitals.

2. Materials & Methods

2.1 Post-anoxic comatose patients

Inclusion criteria

We prospectively recorded EEG from 99 post-anoxic comatose patients admitted to the Lausanne University Hospital from September 2009 to February 2015. Thirty of these patients have been already described [21]. We additionally considered 11 patients admitted at the Valais Hospital in Sion between June 2014 and February 2015. The total number of patients was 110. The study was approved by the Ethics Committees of the two institutions. All these patients had two clinical EEG recordings as will be described below (2.3 'EEG acquisition and pre-processing').

Critical care and clinical assessments

Therapeutic hypothermia (TH) treatment was administered according to a standard protocol [2], consisting of lowering the body temperature of the patients to 33°C for 24 hours, using ice-packs, intravenous ice-cold fluids and a surface cooling device (Arctic Sun System, Medivance) in the hospital of Lausanne; an intravenous catheter placed in the femoral vein (The Thermoguard XP Temperature Management System, Zoll) was used in the hospital of Sion, if hemodynamically tolerated, otherwise, a surface cooling device was also used. During this time, patients from the hospital of Lausanne received midazolam (0.1

mg/kg/h) and fentanyl (1.5 mg/kg/h) for sedation and vecuronium (0.1 mg/kg boluses) to control shivering, patients from Sion received propofol (2-3mg/kg/h); sedation was discontinued upon rewarming above 35°C. Mean amount of sedation during TH for each subject was retrieved on the computerized chart for the CHUV patients and from archives for the Sion patients. Patients with myoclonus and/or status epilepticus were treated with intravenous anti-epileptic drugs, which were discontinued if no clinical improvement was noted after at least 72 h [9]. The level of consciousness was assessed with the Glasgow Coma Scale [25] at regular intervals.

Upon rewarming and off sedation, patients were examined by the neurology consultant. We considered the best clinical assessment within the first 72 hrs after cardiac arrest. Motor response to pain was categorized as flexion or better, versus extension or none (motor-Glasgow Coma Scale ≤2); brainstem reflexes as completely recovered versus not, and early myoclonus as present or not, in accordance with our previous studies [9, 26, 27]. EEG was recorded during and after TH, within the first 48-72 hrs, with nociceptive and auditory reactivity testing performed at bedside. Both EEG recordings were interpreted by certified electroencephalographers with categorization of three features: continuity of the background, presence of reactivity, and occurrence of epileptiform transients [26, 27]. Bilateral somatosensory evoked potentials were recorded during early normothermia; cortical N20 responses were categorized as present or bilaterally absent (no negative deflection at 18-25 ms followed by a positive wave).

Decisions for withdrawal of critical care were based on a multimodal approach with interdisciplinary discussions, and included at least two of the following criteria previously

validated by our group: incomplete recovery of brainstem reflexes, early myoclonus, unreactive EEG in normothermia, and bilaterally absent cortical somatosensory evoked potentials [9], assessed after return to normothermic conditions and off sedation. Importantly, decisions were not influenced by the results of the present study.

Patients' outcome was assessed at 3 months with a semi-structured phone interview, based on the Cerebral Performance Scale (CPC) score [28]. This scale ranges from 1 to 3 for survivors (CPC 1-2 corresponding to "good cerebral performance" without important cognitive deficits and CPC 3 corresponding to "severe cerebral disability" with cognitive deficits precluding independence). Non-survivors correspond to a CPC score of 5 ("death"). Within the survivors we consider two subgroups, those who had regained consciousness before the second EEG recording and those who woke up later in time. There were no patients with a CPC score of 4 (coma or vegetative state) at 3 months.

Here the term 'awake' refers to recovery of consciousness with or without the ability to communicate with the environment, and corresponds to a CPC score of 1-4 [29]. Non-survivors refer to patients who died from natural causes or due to withdrawal of life support, as described above.

2.2 Mismatch negativity paradigm

Patients were tested with an MMNp as described previously [21], using the same equipment as for the clinical EEG recordings. This consists of a series of 16-bit stereo sinusoidal tones, sampled at 44,1kHz with a 10ms linear amplitude envelop at their onset

and offset to avoid clicks. We presented the sounds in three identical blocks of 500 stimuli for each recording. In each block there were 350 'standard' sounds (70% of the total) consisting of 1000Hz tones with 100ms duration and 0ms inter-aural difference. The standard sounds were replaced pseudo-randomly by three types of 'deviant' sounds, which differed from the standard ones with respect to their pitch, duration or location. There were 50 deviant sound of each type in one block. Duration deviants were 1000Hz, 150ms duration and 0ms inter-aural difference. Pitch deviants were 1200Hz tones with 100ms duration and 0ms inter-aural difference. Deviants in location were 1000Hz tones, with 100ms duration and 700μs inter-aural difference, with the left ear leading.

All sounds were presented at a fixed interval. We employed two different inter-stimulus intervals using the same stimuli and experimental setup: for the first 35 patients (including the 30 patients of [21]), we used an inter-stimulus interval of 700ms, and for the all the remaining patients 750ms. We always recorded 3 blocks during TH and 3 during NT, resulting in 1500 presented stimuli per recoding.

2.3 EEG acquisition and pre-processing

Each patient had two EEG recordings at bedside, in the intensive care unit. The first took place within the first 24hours from coma onset under TH, and the second after re-warming to normal temperature, mostly within 36-48 hours after coma onset, off sedation. We used a clinical EEG recording system (Viasys Neurocare, Madison, WI, USA) with a sampling rate of 1000Hz, using 19 electrodes placed according to the international 10-20 system. Impedances were kept below 10kΩ. Data were referenced online to the Fpz electrode and

re-referenced offline to the common average reference. We preprocessed offline the EEG data using the same procedure as in [20].

We extracted EEG responses to deviant sounds from the three experimental blocks (maximum 500 trials per type of sound) and an equal number of responses to standard sounds. Patients with less than 80 artifact-free trials in any of the 2 EEG recordings were excluded.

2.4 Multivariate EEG decoding: Comparison between TH and NT

For analyzing single-patient EEG data we used a multivariate decoding algorithm based on EEG responses across the whole electrode montage [30-32], which can be used to quantify the differential responses to standard vs. deviant sounds at the level of each single patient/recording. It has been previously used for decoding responses in healthy subjects [33, 34] and comatose patients [21, 35].

This algorithm consists of modeling the distribution of single-trial EEG responses across all electrodes using mixture of gaussians models in an *n*-dimensional space where *n* represents the number of electrodes (GMM; 32,33). The models are computed through an expectation-maximization algorithm [36] for each patient and recording (TH/NT) separately, using only one part of the available data (training dataset, consisting of 90% of the artifact-free single-trials). They are then fitted back to the single trials of the training dataset by computing posterior probabilities [37]. These represent the probability of every time-point and trial to be represented by the computed GMM models. Each trial in the

training dataset is decoded as being a response to a standard or a deviant sound according to which of the two models provide the highest posterior probability. The generalization of the decoding performance is then assessed by fitting them on the remaining 10% of the available single-trials (test dataset) and by assigning the test trials in one of the two experimental conditions (i.e. responses to standard vs. deviant sounds).

Decoding performance is measured as the Area Under the Receiver Operator Characteristic Curve (AUC; [38]), and it is computed for standard vs. each type of deviant sounds. The GMM model's parameters are optimized by repeating this whole procedure 10 times by splitting the data in training and test datasets in a way that the 10 test datasets never overlap. All AUC values reported here correspond to the mean value across all three contrasts (i.e. responses to standard sounds vs. deviants in duration, location or pitch). Full details about this algorithm have been reported elsewhere [32,33]. Here, we applied this algorithm with the same parameters as in our preliminary study based on the same paradigm and type of patients [21]. Outcome prediction was based on the change of decoding performance during NT (AUC_{NT}) vs. during TH (AUC_{TH}) and specifically on the percentage change in AUC values: $100^* (AUC_{NT}-AUC_{TH})/AUC_{TH}$.

2.5 Statistical analysis

The significance of outcome prediction results was assessed with 95% Confidence Intervals based on a binomial distribution. Unpaired t-tests for normally distributed continuous data were used for contrasting differences between patients' quantitative descriptors (see Tables1-2, e.g. age). Fisher exact or χ^2 tests were used as needed for categorical data.

3. Results

3.1 Patients' outcome

Among the 110 patients (99 at the CHUV and 11 in Sion), 9 (8%) were excluded from analyses: 2 because of technical reasons preventing data retrieval after recording, and 7 because of the limited artifact–free EEG data. Therefore, the number of analyzed patients was 101 (26 women, mean age: 61±1 years old, mean ± standard error, reported here and in the following). Among them, 38 (36%) did not survive at 3 months, of whom 5 progressed first to a vegetative state (CPC of 4) before dying. Fifty-six (55%) were conscious at the 3 months assessment (CPC score between 1 and 3). The vast majority of these 56 patients (45, 80%) did not report any major cognitive disability at 3 months and had a CPC of 1 or 2.

Seven patients were already awake, fully conscious and communicating with their environment during the second EEG recording (Glasgow Coma Scale ≥9) and were analyzed separately, because they may provide information about progression of neural processes in individuals with prompt recovery. Irrespective of their outcome, the other 94 were comatose during both recordings (Glasgow Coma Scale ≤ 8).

3.2 Outcome prediction based on the progression of auditory discrimination

The average decoding performance across the 38 non-survivors was AUC_{TH}=0.65±0.004 and AUC_{NT}=0.63±0.003, during TH and NT recordings, respectively (see Figures 1-2). In the

group of 56 survivors who were comatose during both recordings, the average decoding performance was AUC_{TH}=0.62±0.002 and AUC_{NT}=0.62±0.002 during TH and NT recordings (Figure 2, Survivors). Among the 7 survivors who had already regained consciousness before the 2nd EEG, decoding performance was AUC_{TH}=0.61±0.007 and AUC_{NT}=0.62±0.008 during TH and NT (Figure 2).

We considered the change in the decoding performance from TH to NT in accordance to our previous findings [21]. The vast majority (32/38, 84%) of non survivors showed a decrease in decoding performance (Figure 3, Non-survivors). Among the 6 patients who improved in their decoding performance, 1 first became vegetative before dying within 3 months (displayed as a separate sub-column 'Vegetative' within the non-Survivors in Figure 3), while the other 5 died without improving from coma ('non-Survivors, comatose' in Figure 3). We observed an improvement in decoding performance in 27 out of 56 survivors (48%) who were comatose during both recordings (Figure 3); among these, 21 reached a CPC of 1 or 2 at 3 months. Most patients showing a prompt recovery and who were not comatose during the second recording improved in their decoding performance (5 out of 7 (71%), 'Survivors, non comatose' Figure 3).

Overall, in the cohort of all 94 patients recorded while still comatose, an improvement in AUC values from TH to NT was observed for 33 patients, among which 27 awoke from coma beyond a vegetative state, resulting in 82% predictive value of awakening (0.95 CI: 0.65-0.93). The sensitivity (i.e. the ratio of survivors showing an increase) was 48% (0.95 CI: 0.35-0.62); the specificity (i.e. the ratio of non survivors with a decrease in decoding) was 84% (0.95 CI: 0.68-0.94); finally, the predictive value of non-survival (i.e. the ratio of

patients with poor outcome among the ones with a decrease) was 52% (0.95 CI: 0.39-0.65). The overall accuracy of outcome prediction was 63% (0.95 CI: 0.52-0.73).

3.3 Factors influencing outcome prediction

Clinical and electrophysiological variables potentially influencing the results are summarized in Table 1 for survivors and 2 for patients with poor outcome. None of these differed significantly for patients with an increase in decoding performance vs. a decrease (Tables1 and 2, last columns).

Interestingly, we observed that some mis-classified patients (i.e. non-survivors with an improvement in decoding performance, Table 2) had an epileptiform EEG, either during TH (2/6 misclassified patients), or during NT (4/6 patients). These pathological EEG patterns were present in 21 patients in total: 8 patients during both TH and NT recordings (all later died), 4 during TH only (all later died), and 9 during NT only (7 later died). Epileptiform activity can prevent the detection of evoked responses to the auditory stimuli. Indeed, trials affected by epileptiform activity are typically discarded in evoked potential studies [39, 40]. For this reason, we examined whether the outcome prediction of the algorithm could improve by excluding patients with epileptiform EEG during at least one of the recordings. Indeed, we observed this pattern in 4 patients with an improvement in decoding performance; all later died. Exclusion of these 4 patients would result in 27/29 comatose subjects with improvement in decoding and later awakening, leading to a predictive value for awakening of 93% (0.95 CI: 0.77-0.99). Importantly, these results were confirmed when considering only patients not been included in our previous study (denoted with gray

rhombi in Figure 3) [21]. In this sub-cohort of 64 patients (38 survivors and 26 non survivors), we observed an improvement in auditory discrimination for 23 patients (17 later awoke), leading to a predictive value for awakening of 74% (95% CI: [0.52-0.90]), or 90% (95% CI: [0.67-0.99]) when excluding patients with epileptiform activity.

3.4 Added value of the progression of auditory discrimination over the clinical assessment

We focused on the correctly predicted patients (i.e. survivors with an increase in AUC values), and examined whether some of them had an uncertain clinical evaluation at the time of the second EEG and MMNp recording. There were a total of 51 patients (51% of the 101 studied patients) who had either one unfavorable predictor (N=6 patients, reported in Table 3) [27], or no unfavorable predictors, but nevertheless remained comatose even after stopping the hypothermic treatment and sedation more than 3 days after cardiac arrest (N=45 patients). Among them, 13 (25%) had an improvement in MMNp. If the MMNp results had been taken into consideration during this early clinical evaluation, the number of patients with an uncertain outcome at 48-72hours after coma onset would have dropped to 38 patients out of 101 (38% of the patients). In other words, the use of the MMNp could benefit the clinical routine by improving outcome prediction for 13 patients out of 51, resulting in relatively narrowing down the percentage of patients with uncertain outcome by 15% (relative change in the ratios of patients with uncertain outcome before (51%) and after (38%) inclusion of the MMNp, normalized by the difference of the two).

4. Discussion

This study shows that an improvement in auditory discrimination over the first two days of coma is predictive of post-anoxic patients' chances of awakening, extending our previous findings based on 30 patients [21] to 94 comatose patients (see also [42, 43]). The above-chance level predictive value of the proposed test for awakening (i.e. 82% when including all EEG recordings or 93% when excluding patients with epileptiform EEG activity) should encourage its implementation in clinical practice, in order to complement other available tests, which are mainly predictive of poor outcome [7-10]. This tool provides an added value, as it correctly predicts that some patients would have survived even though they had at least one unfavourable clinical predictor or a long persisting coma., in accordance with a previously published study [44]. Conversely, the low performances in predicting non-survivors prevent the use of this MMNp to identify patients with poor outcome.

The present results may represent a conservative estimation of the true predictive power of our test. Indeed, some non-survivors had their critical care suspended because of current recommendations based on the available clinical tests [9, 27]. However we cannot exclude that some non-survivors showing improvement in decoding performance would have actually survived if the critical care was not suspended. Indeed the only misclassified patients without epileptiform EEG (i.e. a non-survivor with an improvement in AUC values) died after withdrawal of life-support due to a pre-existing dismal clinical situation.

Comparison with other clinical tests

Current prognostication typically concentrates on incomplete brainstem reflexes, the presence of myoclonus, the absence of SSEP, and the absence of background EEG reactivity,

along with serum markers or brain imaging [8, 9, 45, 46] due to their high predictive value for poor outcome. However they are mostly based on qualitative and practitioners' subjective judgment. Both these aspects are improved by the test proposed here.

Another advantage of the current test is its quantitative and automatic implementation of AEP analyses [30] at the single-patient level. The overall implementation of the test remains relatively cost-efficient, as it is based on the same EEG recording and setup as used for clinical monitoring, and can be carried out at bedside. The prediction results can already be available from the second day after coma onset and may encourage the sustenance of life support in patients for which the clinical examination provides uncertain evidence or in patients who remain comatose for several days.

Limitations and future directions

Whether this test is also predictive of awakening in patients who do not receive a TH treatment is still unknown and will be the subject of future investigations, particularly in light of recent evidence questioning the optimal target temperature [5]. One possible future improvement is the overall time it takes to compute the results for each patient, including approximately 20 minutes of EEG recording and few hours for the analysis. Moreover, the test requires some minimal levels of expertise for its implementation. Finally, this approach has only been validated so far in two hospital centres, including a subset of patients already reported [21] . Conversely, the fact that this paradigm was not used for clinical prognostication and its results were unknown to the clinical team (avoiding the so called "self fulfilling prophecy") strengthen our results.

Conclusions

Progression of auditory discrimination over the first two days of coma is informative of the patient's chances of awakening. Pending validation in other cohorts, our results encourage the use of this test in the clinical practice, especially in cases of uncertain outcome under the current clinical prognostic approach.

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Author contributions

Concept and study design: AT, AOR, DV, MR, MO, MDL; Data acquisition and analysis: AT, AOR, EJ, TS, DV, MDL; Drafting the manuscript and figures; AT, AOR, EJ, MDL.

Potential conflicts of interest:

Authors AT and MDL are mentioned as inventors in a US patent entitled: “Method for predicting awakening in a comatose patient and computer-implemented method thereof” (application number: 14/383165). The patent is owned by Lausanne University Hospital and is currently not licensed. Authors AOR, EJ, TS, DV, MR and MO report no disclosures.

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Figure/Table Captions

Figure 1. AEPs in response to standard and duration deviant sounds for one exemplar comatose patient and results of single-trial decoding for TH and NT recordings. (a,b) We display responses to standard (black lines) and duration deviant sounds (gray lines), recorded at fronto-central electrodes. (c,d) Results of single-trial decoding, including discriminative time-periods and voltage topographies over these periods. This information was used for decoding the stimulus category (i.e. standard or deviant sounds) across 10 data splits. This exemplar patient was a survivor for which our decoding algorithm showed an improvement in AUC values from TH to NT (AUCTH=0.61 and AUCNT=0.63), leading to an accurate prediction.

Figure2. Average decoding performance across all patients, split according to their outcome (survivors/non survivors) and to whether they were comatose in the 2nd EEG recording (comatose/non-comatose). The black bars refer to AUC values obtained for the first recording and under TH and the gray ones to the second recording, after re-warming to normal temperature. Decoding performance corresponds to average AUC values for decoding EEG responses to standard vs. the three types of deviant sounds, evaluated for each patient/recording separately.

Figure3.

Outcome prediction results for 94 comatose and 7 control patients. Rhombi refer to the % change in decoding performance for individual patients, from TH to NT recordings. Decoding performance for the vast majority of non-survivors decreased (32/38 patients). Decoding performance improved from TH to NT for 33 patients; out of them, 27 awoke

beyond a vegetative state within three months and 6 had a poor outcome (1 fell in a vegetative state and 5 died). Survivors non-comatose are patients who were fully awake and had already regained consciousness before the 2nd EEG recoding; the majority of them had an increase in decoding performance (5 out of 7 patients).

Table 1. Clinical description of survivors, split according to whether their decoding performance from TH to NT increased or decreased. Spontaneous EEG in TH/NT refers to the clinical part of EEG, which had been carried out with the same EEG setup, right before the MMNp EEG recording in TH/NT. The last column refers to results of the statistical comparison in patients with increase vs. decrease. Categorical variables (for example Etiology) were contrasted with Fisher's exact test (p-values are reported in the last column). For continuous variables we carried out unpaired t-tests and we additionally report the |T|-values in parentheses.

Table 2. Clinical description of patients with poor outcome, split according to whether their decoding performance from TH to NT increased or decreased. Spontaneous EEG in TH/NT refers to the clinical part of EEG, which had been carried out with the same EEG setup, right before the MMNp EEG recording in TH/NT. The last column refers to results of the statistical comparison in patients with increase vs. decrease. Categorical variables (for example Etiology) were contrasted with Fisher's exact test (p-values are reported in the last column). For continuous variables we carried out unpaired t-tests and we additionally report the |T|-values in parentheses. We report statistical tests for patients with poor outcome for reasons of completeness (see also Table 1), even though there were only 6

patients with an increase in decoding performance and the statistical power of these tests may be limited.

Table 3. Correctly classified survivors by the progression of auditory discrimination, but with one or two unfavorable outcome predictors based on currently used clinical tests. Here we show a summary of the clinical description for patients who had at least one unfavorable predictor among the following: absence of brainstem reflexes, or SSEP, as evaluated during the NT recording (noted with "x"). Additionally, we display the number of days from the cardiac arrest until the patients' extubation.

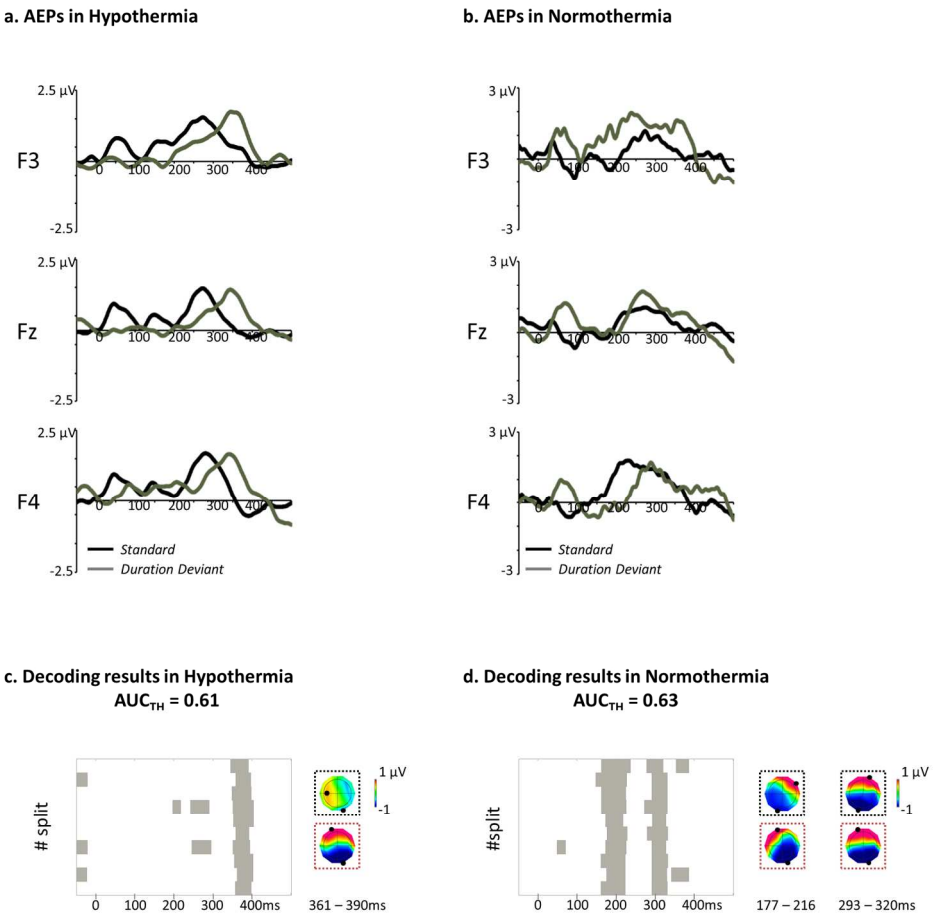

Figure 1: AEPs in response to standard and duration deviant sounds for one exemplar comatose patient and results of single-trial decoding for TH and NT recordings. (a,b) We display responses to standard (black lines) and duration deviant sounds (gray lines), recorded at fronto-central electrodes. (c,d) Results of single-trial decoding, including discriminative time-periods and voltage topographies over these periods. This information was used for decoding the stimulus category (i.e. standard or deviant sounds) across 10 data splits. This exemplar patient was a survivor for which our decoding algorithm showed an improvement in AUC values from TH to NT (AUCTH=0.61 and AUCNT=0.63), leading to an accurate prediction.
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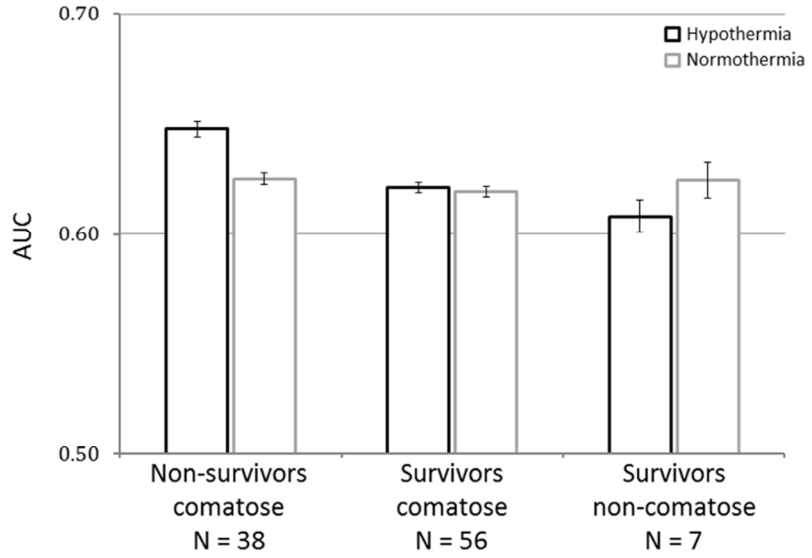

Figure2. Average decoding performance across all patients, split according to their outcome (survivors/non survivors) and to whether they were comatose in the 2nd EEG recording (comatose/non-comatose). The black bars refer to AUC values obtained for the first recording and under TH and the gray ones to the second recording, after re-warming to normal temperature. Decoding performance corresponds to average AUC values for decoding EEG responses to standard vs. the three types of deviant sounds, evaluated for each patient/recording separately.
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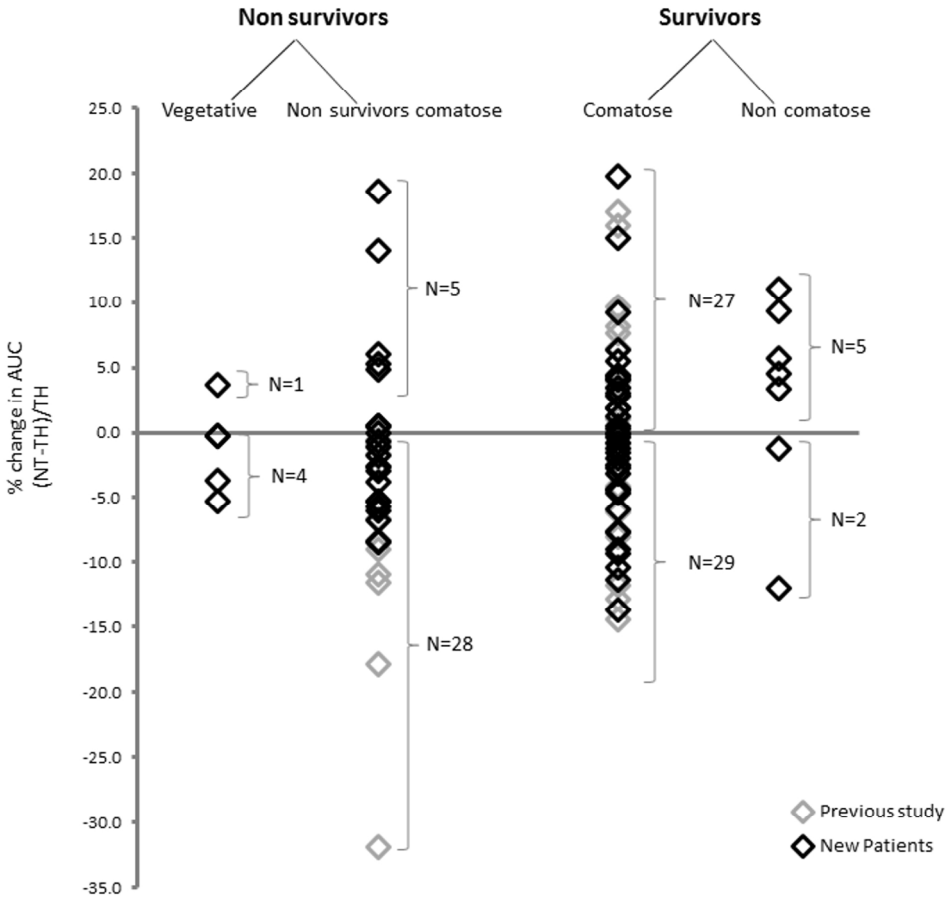

Figure 3: Outcome prediction results for 94 comatose and 7 control patients. Rhombi refer to the % change in decoding performance for individual patients, from TH to NT recordings. Decoding performance for the vast majority of non-survivors decreased (32/38 patients). Decoding performance improved from TH to NT for 33 patients; out of them, 27 awoke beyond a vegetative state within three months and 6 had a poor outcome (1 fell in a vegetative state and 5 died). Survivors non-comatose are patients who were fully awake and had already regained consciousness before the 2nd EEG recoding; the majority of them had an increase in decoding performance (5 out of 7 patients).
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Survivors (n = 56)

Decoding performance		Patients with increase (n=27)	Patients with decrease (n=29)	Statistics p-value (|t|)
Age (years)		63 ± 2	60 ± 3	0.89 (0.38)
Time to ROSC (min)		16±2	17±1	0.78 (0.28)
Etiology	Cardiac	22	27	0.10
	Pulmonary	5	1	
	Other	0	1	
Spontaneous EEG in TH	Non reactive	0	1	1
	Discontinuous	12	12	1
	Epileptiform	0	0	1
Sedation during TH	MDZ (mg/kg/h)	0.12 ± 0.02	0.11 ± 0.01	0.50 (0.67)
	PRO (mg/kg/h)	0.64 ± 0.19	0.49 ± 0.18	0.58 (0.56)
Spontaneous EEG in NT	Non reactive	0	0	1
	Discontinuous	4	5	1
	Epileptiform	0	2	0.49
Early clinical evaluation (predictors of poor outcome)	Absence of Brainstem	7	3	0.17
	Absence of Motor	8	8	1
	Presence of myoclonous	0	0	1
	Absence of SSEP	1	0	0.48
EEG recordings	Time to 1st EEG (hours)	18±1	17±1	0.94 (0.07)
	Time between recordings (hours)	25±1	31±3	0.04 (2.08)

Table 1. Clinical description of survivors, split according to whether their decoding performance from TH to NT increased or decreased. Spontaneous EEG in TH/NT refers to the clinical part of EEG, which had

been carried out with the same EEG setup, right before the MMNp EEG recording in TH/NT. The last column refers to results of the statistical comparison in patients with increase vs. decrease. Categorical variables (for example Etiology) were contrasted with Fisher's exact test (p-values are reported in the last column). For continuous variables we carried out unpaired t-tests and we additionally report the |T|-values in parentheses.

Patients with poor outcome (n = 38)

Decoding performance		Patients with increase (n=6)	Patients with decrease (n=32)	Statistics p-value (|t|)
Age (years)		67±5	63±3	0.63 (0.49)
Time to ROSC (min)		30±5	31±3	0.87 (0.16)
Etiology	Cardiac	3	23	0.52
	Pulmonary	3	7	
	Other	0	2	
Spontaneous EEG in TH	Non reactive	4	22	1
	Discontinuous	5	27	1
	Epileptiform	2	10	1
Sedation during TH	MDZ (mg/kg/h)	0.14 ± 0.03	0.10 ± 0.01	0.20 (1.31)
	PRO (mg/kg/h)	0.56 ± 0.41	0.50 ± 0.18	0.91 (0.11)
Spontaneous EEG in NT	Non reactive	3	20	0.66
	Discontinuous	5	22	0.65
	Epileptiform	4	11	0.19
Early clinical evaluation (predictors of poor outcome)	Absence of Brainstem	3	20	0.66
	Absence of Motor	5	27	1
	Presence of myoclonous	3	7	0.31
	Absence of SSEP	1	12	0.64
EEG recordings	Time to 1st EEG (hours)	21±3	17±1	0.22 (1.23)
	Time between recordings (hours)	27±3	29±2	0.75 (0.33)

Table 2. Clinical description of patients with poor outcome, split according to whether their decoding performance from TH to NT increased or decreased. Spontaneous EEG in TH/NT refers to the clinical

part of EEG, which had been carried out with the same EEG setup, right before the MMNp EEG recording in TH/NT. The last column refers to results of the statistical comparison in patients with increase vs. decrease. Categorical variables (for example Etiology) were contrasted with Fisher's exact test (p-values are reported in the last column). For continuous variables we carried out unpaired t-tests and we additionally report the |T|-values in parentheses. We report statistical tests for patients with poor outcome for reasons of completeness (see also Table 1), even though there were only 6 patients with an increase in decoding performance and the statistical power of these tests may be limited.

	Early clinical evaluation Absence of:		Days to extubation
	Brainstem	SSEP	
P1	x		4
P2	x	x	5
P3	x		4
P4	x		3
P5	x		16
P6	x		N.A.

Table 3. Correctly classified survivors by the progression of auditory discrimination, but with unfavorable outcome predictors based on currently used clinical tests. Here we show a summary of the clinical description for patients who had at least one unfavorable predictor among the following: absence of brainstem reflexes, or SSEP, as evaluated during the NT recording (noted with "x"). Additionally, we display the number of days from the cardiac arrest until the patients' extubation. This measure does not apply for P6, as he had a tracheotomy before extubation. N.A.: Not Applicable.