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(54) **METHOD FOR PREDICTING AWAKENING IN A COMATOSE PATIENT AND COMPUTER-IMPLEMENTED METHOD THEREOF**

VERFAHREN ZUR VORHERSAGE DES ERWACHENS BEI EINEM KOMATÖSEN PATIENTEN UND COMPUTERIMPLEMENTIERTES VERFAHREN DAFÜR

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a method for predicting awakening in a comatose patient based on his/her improvement in neural auditory discrimination in the early stage of coma. The invention further relates to a computer-implemented method thereof. These methods are for example used in a clinical routine for helping taking therapeutic decisions and optimizing clinical care for each specific patient. In embodiments, the method is implemented in a software embedded in a clinical EEG machine for fast and automatic prediction of patients' chance of surviving.

BACKGROUND ART

[0002] Impairment in auditory functions has been repeatedly reported in comatose patients (Fischer et al., 1999) and minimally conscious or vegetative state patients (Boly et al., 2011). Typically, these clinical populations show deficits in neural discrimination between repeated (standard) and rare (deviant) sounds as measured by electroencephalography (EEG) (Näätänen et al., 1978). The degree of discrimination between standard and deviant sounds is quantified by first computing the average of the EEG responses (Auditory Evoked Potentials, AEPs) to standard and deviant sounds. The difference of the average AEPs to the two types of sounds manifests typically at fronto-central electrodes and at ~100-150ms after the onset of deviation (Fischer et al., 1999; Todd et al., 2007; Wijnen et al., 2007; Garrido et al., 2009) and it is usually referred to as mismatch negativity (MMN) EEG component.

[0003] In previous studies on MMN in comatose patients, MMN evaluation requires the identification of a robust average Auditory Evoked Potential (AEP) in response to sounds (i.e. a significant modulation with respect to baseline of the average AEP at about 100ms post-stimulus onset). Therefore, data from a large percentage of patients are systematically disregarded (e.g. ~33% in one study by Fischer et al., 1999). Furthermore, this assessment requires an a priori hypothesis of the latency and the magnitude of AEP responses. In pathological conditions, making such hypotheses can be challenging, as AEPs can exhibit high inter-individual variability and differ from those of healthy subjects.

[0004] Interestingly, MMN appears to be absent in those comatose patients who do not awake from the coma. Therefore, the presence of the MMN is considered to be a predictor of awakening, with high predictive value for awakening (Fischer et al., 2004). However, because this experimental evidence is assessed at various delays after coma onset, it is still unclear whether this deficit is independent of the time of the recording. Moreover, post-anoxic comatose patients are nowadays often treated with mild induced Therapeutic Hypothermia (TH) which is known to have neuro-protective effects on the patients and to increase their chance of survival, but its effect on brain functions remains unknown.

[0005] At present, all the tests implemented in the clinical practice are informative of the chance of dying. Specifically, lack of return of brainstem reflexes at 72 hours, early myoclonus, and bilateral absence of early cortical somatosensory evoked potentials (SSEPc) have robust predictive value for death (Bouwes et al., 2009; Fugate et al., 2010; Rossetti et al., 2010).

[0006] Therefore, an object of the present invention is to propose a method performed during the very early phase of coma for predicting awakening in a comatose patient treated with TH protocol.

[0007] Another object of the present invention is to propose a robust method for predicting awakening in a comatose patient.

[0008] Another object of the present invention is to propose a computer-implemented method thereof.

SUMMARY OF THE INVENTION

[0009] This invention provides a method for predicting awakening in a comatose patient based on auditory discrimination measured by an electroencephalography machine. This invention has been validated in the context of comatose patients treated with Hypothermia during the first 24 hours of coma. This method comprises the following steps:

a) exposing the comatose patient treated with hypothermia to auditory stimuli within the first 24 hours from the onset of coma, said auditory stimuli comprising repeated standard and deviant sounds;

b) recording the patient's electrical activity in the form of electro-encephalographic data to measure the auditory evoked potential for each standard and deviant sounds of the auditory stimuli while said patient is in hypothermia state and allocating a first value which is informative of the degree of said auditory discrimination ;

c) exposing said patient to the same auditory stimuli as in step a) for the second time while in a normal temperature state typically within 72 hours and preferably within 48 hours from the onset of coma;

d) recording the patient's electrical activity in the form of electro-encephalographic data to measure the auditory evoked potential for each standard and deviant sounds of the auditory stimuli while said patient is in a normal temperature state and allocating a second value which is informative of the degree of said auditory discrimination; and

e) comparing the first and second values to determine whether there is an improvement of auditory

discrimination over time which is informative of whether the comatose patient will awake.

[0010] The present invention further provides a computer-implemented method for predicting awakening in a comatose patient based on auditory discrimination. The comatose patient was exposed to auditory stimuli comprising repeated standard and deviant sounds during two distinct periods. The first period occurred when the comatose patient was in a hypothermia state and the second period occurred when the comatose patient was brought back in his/her normal temperature and typically within 72 hours and preferably within 48 hours from the onset of the coma. The comatose patient was equipped with electrodes connected to an electroencephalography machine to record auditory evoked potential (brain responses to each auditory stimulus, hereafter "AEP"), for each standard and deviant sound of the auditory stimuli during the first and second periods. According to the invention the method comprises the following steps:

a. dividing all the recorded AEPs into two datasets, namely a training dataset and a testing dataset;
b. dividing the AEPs from the training dataset into a first and a second category, the first category grouping recorded AEPs in response to standard sounds and the second category grouping recorded AEPs in response to deviant sounds for each of the first and second periods;
c. computing two statistical models of AEPs from the training dataset for standard and deviant sounds respectively and for each of the first and second periods(i.e. eight statistical models of AEPs in total);
d. computing which of the two statistical models of step c) resembles best each of AEPs from the testing dataset for each of the first and second periods;
e. assigning each AEP from the testing dataset to a type of sound, standard or deviant, based on the computation of step d) for each of the first and second periods;
f. determining whether the type of sound assigned to each AEP from the testing dataset is the same as the type of sound that evoked this AEP, in order to conclude if, over all, across all recorded AEPs from the testing dataset for each of the first and second periods, there is a discrimination between standard and deviant sounds above chance level;
g. quantifying the degree of discrimination between standard and deviant sounds for each of the first and second periods in the testing dataset, and
h. comparing the degree of discrimination between standard and deviant sounds between the first and the second period to determine whether there is an improvement of auditory discrimination over time which is informative of whether the comatose patient will awake.

[0011] In embodiments of the invention, multivariate Gaussian distribution is applied to compute statistical models of the method.

[0012] In embodiments, the degree of auditory discrimination between standard and deviant sounds is quantified by measuring the area under a Receiver Operating Characteristic (ROC) curve.

[0013] In embodiments, auditory stimuli comprise one standard and three types of deviant sounds that differ from the standard sound respectively in pitch, in duration and in location, wherein for example steps a) to e) of the above computer-implemented method are preferably performed three times successively for auditory stimuli comprising standard sounds and deviant sounds with respect to pitch, standard sounds and deviant sounds with respect to duration, and standard sounds and deviant sounds with respect to location, respectively, in order to determine a value which is informative of the degree of auditory discrimination of the comatose patient for each type of deviant sounds, and wherein the three values corresponding to each type of deviant sounds are used separately or combined, for example averaged, to obtain one value representing the overall sound discrimination of said patient. In embodiments, auditory stimuli are presented in three successive runs, each run having for example a total of 500 sounds including standard and deviant sounds with respect to pitch, duration and location respectively. Standard sounds represent for example about 70% of the total of sounds, while each of the deviant sounds with respect to pitch, duration and location respectively represents around 10% of the total sounds.

[0014] According to the method of the invention, prediction of the awakening in a comatose patient is performed by comparing the responses of said patient to the same or similar auditory stimuli at two distinct moments after the beginning of the coma and in different thermal conditions (hypothermia vs. normothermia). Experiments demonstrated that an improvement of the patient's response over time, from hypothermia to normothermia, was a reliable indication that he or she would eventually awake.

[0015] Furthermore, predicting awakening of a patient through a relative data comparison as in the present method, i.e. by comparing data to each other that have been collected from the same patient and in response to the same or similar stimuli, allows for a more robust prediction than methods based for example on the comparison of data collected from a patient to absolute threshold values and/or models that require a higher minimum level of signal for the comparison, and thus for the prediction, to be valid.

DESCRIPTION OF THE FIGURES

[0016] The invention will be better understood thanks to the following detailed description with reference to the attached drawings, in which:

Figure 1 shows examples of ROC curves plotted

according to an embodiment of the invention for an exemplary patient who later awoke (a) and a patient who did not survive the coma (b). ROC curves are the plots of True Positives vs. False Positives when discriminating between two conditions, for example between standard and any type of deviant sounds (here duration deviants). The median ROC curve obtained during the first EEG recording and under TH is displayed in solid lines and the one obtained during the second recording and in NT in dashed lines. For the survivor (panel a), the median Area Under Curve (AUC) in TH was 0.61 and in NT 0.67, leading to an improvement in AUC values of +0.06, which reflects an improvement in auditory discrimination performance. For the non survivor (b), the median AUC in TH was 0.78 and in NT 0.61, leading to a drop of -0.17, reflecting in turn deterioration of auditory discrimination.

Figure 2a) represents decoding results obtained by an embodiment of the method of the invention: the graph represents the average decoding performance, with an indication of the standard error mean (s.e.m.), for a pilot group of 12 patients. The decoding performance was measured as the AUC (Area Under Curve) obtained when discriminating responses to standard versus one type of deviant sound (in terms of duration, location or pitch). The decoding performance was averaged across three types of deviant sounds and across patients, under hypothermic (TH) and under normothermic (NT) conditions, respectively. The decoding is especially high for non-survivors and during TH. This decoding performance typically decreases from TH to NT in non-survivors.

Figure 2b) represents the outcome prediction corresponding to the results of Figure 1a). The difference in decoding performance from TH to NT - evaluated independently for each patient - is used for predicting the patients' outcome. In the pilot group (grey rhombi and rectangles), an improvement on the average decoding performance from TH to NT conditions is only observed in survivors (rhombi), resulting in a positive predictive value of 100%. All non-awakening patients show a drop in their performance. These results have been replicated on a validation group of 18 patients (panel b, black rhombi and rectangles), whose data analysis was done blindly to their outcome.

Figure 3 is a schematic representation of the procedure and exemplary voltage topographies for a patient who did not awake. The first EEG recording was typically performed at about 15 hours after the cardiac arrest, during TH (hypothermia) and the second at approximately 44 hours, after re-warming and under normothermic conditions. A worsening in decoding performance was observed in all the patients who did not awake from coma. Typically, based on the first EEG recording during TH, an accurate decoding performance was obtained which resulted from topographic differences in responses to standard and deviant sounds (voltage topographies estimated by the single-trial model along 100-300ms post-stimulus onset; left panel). However, during NT, the estimated voltage topographies over the same time window did not differ for the two types of sounds (right panel) and decoding was not above chance. Such a drop in decoding performance was observed in all patients who did not awake from coma.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The method for predicting awakening in a comatose patient according to embodiments of the invention is based on the evolution of auditory discrimination over time which is informative of the chances that the comatose patient will awake. More specifically, according to this method, the patient, after being resuscitated following current recommendations (2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Circulation 2005:112:IV1-203), is first treated with hypothermia during the first 24 hours of the onset of coma (his/her temperature is lowered for example to about 33 degrees Celsius), a treatment known to produce general neuroprotective effects at early stages of coma (Holzer, 2010).

[0018] During a first period, the patient is exposed while in hypothermia state to auditory stimuli comprising a repetitive sequence of sounds. For example, a relatively rare deviant (d) sound can be interspersed among a series of frequent standard (s) sounds (e.g., *sssssssssdsssssssdsssdssss*..., where s represents a standard sound and d a deviant sound). The deviant sound can differ from the standard ones in one or more perceptual features such as for example pitch, duration and/or location.

[0019] The electrical activity of the patient while exposed to the auditory stimuli is recorded in the form of electro-encephalographic data through an electroencephalography machine to measure the Auditory Evoked Potential (AEP) in response to each standard and deviant sound. A first value quantifying the degree of the auditory discrimination during the first period is then allocated, for example calculated, on the basis of the AEPs recorded during the first period.

[0020] The comatose patient is then exposed to the same auditory stimuli during a second period while in a normal temperature state and typically within 72 hours from the onset of coma and preferably within 48 hours. The electrical activity of the patient while exposed to the auditory stimuli is again recorded in the form of electro-encephalographic data through the electroencephalography machine to measure the auditory discrimination. A second value quantifying the degree of the auditory discrimination during the second period is allocated, for

example calculated, on the basis of the AEPs recorded during the second period. The first and second values are then compared to each other to determine whether there is an improvement of auditory discrimination over time, which is informative of whether the comatose patient will awake.

[0021] The computer-implemented method for predicting awakening in a comatose patient according to embodiments of the invention allows quantifying auditory discrimination on the basis of Auditory Evoked Potentials (AEPs) that are obtained for example as explained above.

[0022] The AEPs recorded during each of the first and second periods are randomly divided into two datasets, namely a training dataset including for example 90% of the recorded AEPs and a testing dataset including for example the remaining 10% of the recorded AEPs. Other proportions between the training dataset and the testing dataset are however possible within the frame of the invention.

[0023] This data partition allows estimating the statistical models that will be used for evaluating the auditory discrimination on one part of the data (training), and then testing how well this discrimination generalizes to the test dataset (testing).

[0024] The AEPs from the training dataset are for example divided into a first and a second category, the first category grouping AEPs recorded in response to the standard sounds of the auditory stimuli and the second category grouping AEPs recorded in response to the deviant sounds of the auditory stimuli, for each of the first and second periods.

[0025] If the auditory stimuli comprised more than one type of deviant sounds, the AEPs recorded in response to each type of deviant sound are preferably grouped in a different category. Accordingly, in embodiments, the recorded AEPs are for example separated, for each of the first and second periods, into a first category grouping the AEPs recorded in response to standard sounds of the auditory stimuli, a second category grouping AEPs recorded in response to a first type of deviant sounds of the auditory stimuli, a third category grouping AEPs recorded in response to a second type of deviant sounds of the auditory stimuli, etc.

[0026] In embodiments, a statistical model is then computed for the AEPs of each category for each of the first and second periods, respectively. From the training dataset, one statistical model of AEPs is thus for example computed for the response to the standard sounds and one statistical model of AEPs is computed for the response to each type of deviant sounds, and for each of the first and second periods respectively. In embodiments, this for example results in a total of eight different models of AEPs when the auditory stimuli comprised three types of deviant sounds. The statistical models are for example computed using a multivariate Gaussian distribution on the AEPs of each category. This estimation is based on clustering the measured AEPs in response to standard and deviant sounds in few representative configurations of electrical activity. Other methods are however possible within the frame of the invention for computing a model representative of the AEPs of each category.

[0027] The AEPs from the testing dataset are then compared to the computed statistical models. For each AEP of the testing dataset for each of the first and second periods, a statistical model which best simulates it is selected. This selection is done for example according to the best fit of the estimated multivariate Gaussian distribution for each of the two conditions. Each AEP from the testing dataset is then assigned to a type of sound for each of the first and second periods and according to the selected model as described above.

[0028] The type of sound assigned to each AEP from the testing dataset is then compared with the corresponding type of sound of the auditory stimuli that evoked this AEP, in order to conclude whether there is a discrimination between standard and deviant sounds for each of the first and second periods.

[0029] The results of the comparison for each of the first and second periods are then for example represented in the form of a Receiver Operating Characteristic (ROC) curve. The degree of discrimination between standard and deviant sounds for each of the first and second periods is then quantified by measuring the area under the corresponding Receiver Operating Characteristic (ROC) curve. The ROC curve represents a standard measures of performance of discrimination between two conditions and its Area Under Curve (AUC) can range between 0.5 in case of poor discrimination up to 1 for an ideal case. Illustrative but in no ways limiting examples of ROC curves as used within the frame of the invention are shown in Fig. 1.

[0030] Finally, according to the method of the invention, the degree of discrimination between standard and deviant sounds between the first and the second period are compared to each other to determine whether there is an improvement of auditory discrimination over time which is informative of whether the comatose patient will awake.

[0031] Applying the method of the invention, successful sound discrimination during early stages of post-anoxic coma and under TH in a large cohort of patients was shown independently of their outcome. Even patients who did not awake from coma exhibited differential patterns of EEG activity in response to standard/deviant sounds (Figure 2a). Improvement of sound discrimination during the early phase of coma is predictive of awakening and survival at three months, with 100% positive predictive value (Figure 2b; Figure 3 for an overview).

[0032] The results obtained by the method of the invention show intact auditory discrimination in early phases of coma and even in comatose patients who eventually die and suggest that impairment in neural mechanisms for sound discrimination is a process that occurs over time (Figures 1-3). Indeed, the auditory functions can be

still intact during the first day after coma onset, largely independent of the patients' final outcome.

[0033] The Glasgow coma scale indicated that, during the corresponding analyses, all patients were deeply unconscious during both TH and NT recordings. The high decoding performance during HT and NT provides new evidence about intact auditory functions in a deep unconscious state and during early stages of coma. A possible source of discrepancy with recent literature on intact brain function in comatose patients is the difference in the treatment of these patients (including hypothermia).

[0034] At present, in a clinical routine, prognostication of coma after cardiac arrest and TH profits from a multimodal approach. Specifically, lack of return of brainstem reflexes at 72 hours, early myoclonus, and bilateral absence of early cortical somatosensory evoked potentials have robust predictive value for death (Bouwes et al., 2009 ; Fugate et al., 2010; Rossetti et al., 2010). However, all these tests are not informative of the chance of surviving. The present method thus offers a possibility to bridge the prognostic gap, as it identifies those patients who will awaken in an automatic and quantitative fashion. Moreover, this method provides early and automatic outcome prediction (within ~2-3 days after the coma onset), without disregarding any patient from analysis. Importantly, all analyses were done blindly to patients' outcome and were not used at any point for influencing the clinicians' decision for treatment. Clinicians caring for patients were unaware of the results, so that therapeutic attitudes and decisions were not influenced.

[0035] The results obtained by the method of the invention show that early assessment of auditory functions based on EEG multivariate analyses promises to provide a highly informative test of the chance of surviving of comatose patients treated with TH and to largely revise our understanding of intact cerebral functions in deep unconscious state.

EXAMPLE

EEG data acquisition

[0036] 30 post-anoxic comatose patients have been included in the study (10 women; mean age 63 $\pm$ 2 years old). They had been admitted from December 2009 to July 2011 to the Department of Critical Care Medicine, Centre Hospitalier Universitaire Vaudois (CHUV-Lausanne University Hospital), Lausanne, Switzerland. All patients were treated with mild TH after resuscitation from cardiac arrest, to 33°C for 24 hours. The study was approved by the Ethics Committee of the institution.

[0037] Level of consciousness was assessed based on the Glasgow Coma Scale (GCS) at regular intervals (every two to three hours) during the first 2-3 days after coma onset. All patients scored 3 or 4 during these first 2-3 days, indicating a deep unconscious state.

[0038] All patients were managed according to a standard protocol (Oddo et al., 2006); they were resuscitated following current recommendations (2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2005;112:IV1-203) and treated with mild TH to 33°C for 24 hours, using ice-packs, intravenous ice-cold fluids and a surface cooling device (Arctic Sun System, Medivance, Louisville, CO, USA) for the maintenance of TH, during which midazolam (0.1 mg/kg/h) and fentanyl (1.5 μg/kg/h) were administered for sedation, and vecuronium (0.1 mg/kg boluses) to control shivering.

[0039] Patients with myoclonus and/or status epilepticus were treated with intravenous antiepileptic drugs, which were discontinued if no clinical improvement was noted after at least 72 hours. An interdisciplinary decision on withdrawal of intensive care support (Rossetti et al., 2010) was based on a multimodal approach including at least two of the following (assessed in normothermia at least 48-72 hours after cardiac arrest): incomplete recovery of brainstem reflexes, early myoclonus and bilaterally absent cortical somatosensory evoked potentials (SSEP). In particular, results of the present study were not used for this decision. The patients' clinical outcome at three months was categorized as awakening (i.e. beyond a vegetative state) vs. death.

[0040] Within the 30 patients, the first 12 (the first 12 admitted to the hospital) formed a pilot group and the rest a validation group. As it will be clear in the following, data from the pilot group were analyzed in a more exploratory manner and results were validated in the validation group (18 patients). All analysis in the validation group was done blindly to the patients' outcome.

[0041] Electrodes were set up on the head of each comatose patient and were connected to an EEG machine. Earplugs were inserted in the patient's ears. A script was launched on a computer which was connected to the EEG machine. While the script ran, auditory stimuli comprising standard and deviant sounds were sent to the earplugs and "triggers" were sent to the EEG machine Triggers are markers that are recorded together with the EEG that can be used to determine when each sound is presented.

[0042] The patient was then brought back to his/her normal temperature after about 24 hours from the beginning of the hypothermic treatment. The second EEG recording took place after rewarming and typically within 48 hours from the beginning of the hypothermia. The procedure was identical to the one for the first recording and the same protocol and auditory stimuli were used.

[0043] 19 electrodes were used for both recordings and were arranged following the international 10-20 system. A sampling rate of 1024Hz was used with an online reference to the Fpz electrode. All electrodes' impedances were kept bellow 10kΩ. All EEG recordings were performed in the clinical environment, while patients were lying on their beds, without interrupting the clinical routine. An auditory mismatch negativity paradigm was used for the auditory stimuli. The stimuli comprised one standard and three types of deviant sounds, with a constant

inter-stimulus interval of 700ms. Standard sounds consisted of 1000Hz sinusoidal tones of 100ms duration and 0μs Interaural Time Difference (ITD). The pitch deviant sounds were 1200Hz sinusoidal tones of 100ms duration and 0μs ITD. The duration deviant sounds were 1000Hz sinusoidal tone of 150ms duration and 0μs ITD. Finally, the location deviant sounds were 1000Hz sinusoidal tones of 100ms duration and 700μs ITD (left ear leading). A 10ms linear amplitude envelope at stimulus onset and offset was applied to all stimuli to avoid clicks. All stimuli were 16 bit stereo sounds sampled at 44.1 kHz. These proprieties were in accordance with other MMN studies (Todd et al., 2008), but other implementations of the auditory stimuli are also possible. A block of trials included 500 stimuli and lasted approximately 7 minutes. Stimuli were presented in a pseudo-randomized order, such that at least one standard stimulus intervened between deviants. 3 blocks were recorded resulting in 1500 trials per participant (1050 for the standard sound and 150 for each type of deviant sound).

EEG preprocessing

[0044] Signal from all electrodes was filtered with a bandwidth filter from 0.1 to 40Hz in order to reduce artifacts (noise in the signal). Specific parts of the EEG signal, hereafter referred as "single trials", were extracted around each sound starting from -50ms before the presentation of the sound up to 500ms after the sound's onset.

[0045] Single trials where the EEG signal seemed to be corrupted because of the artifacts were excluded. This was done by excluding single-trials when the voltage measured by any of the electrodes exceeded a threshold of +/- 100 μVolts. During the whole recording, signal from each electrode was visually checked on the EEG machine to determine whether any of the electrodes was systematically noisy. In such case, this particular electrode was excluded and its activity was interpolated according to the activity of the neighbour electrodes.

[0046] As a result, approximately 100 single trials were obtained in response to each type of sound.

EEG analysis

[0047] The EEG analysis was done on the recording during the hypothermic condition and the normothermic condition separately. Sounds that were presented frequently ('standard sounds', presented about 70% of the single trials), and the other sounds ('rare, or deviant sounds') were compared in order to determine whether there was a statistically significant difference between the EEG responses to one type of sounds and another.

[0048] For quantifying the difference in neural responses to standard vs. deviant sounds, a multivariate EEG analysis was used (Tzovara et al., 2013).

[0049] The advantage of using this multivariate technique is that it is not biased by a priori hypotheses about electrode location(s) at which stimulus-related activity is expected. Therefore, it is less affected by transient artifact-contaminated activity appearing at some specific electrodes than classical analyses of single-electrode average AEPs. In addition, it provides a way to quantify differences in neural responses at the level of the single patient, without preliminary assessment of minimal inclusion criteria.

[0050] This method is based on modelling the voltage topographies of the single-trial AEPs by a Multivariate Gaussian distribution (i.e. mixture of Gaussians, GMM). This analysis was performed separately for each patient and for each of the two recording datasets (i.e. that under TH and that under NT conditions). GMM estimation was based on part of the available trials (Training dataset) and was then used to decode the category of sounds (standard/deviant) on a separate part of the dataset (Test dataset). Decoding performance is indicative of the degree of difference in single-trial brain responses to standard vs. deviant sounds. Importantly, because the analysis is based on voltage topographies, an accurate performance is a direct result of the activation of different neural generators in response to the two sounds categories; a difference in scalp topographies forcibly reflects a difference in the configuration of the underlying generators (Murray et al., 2008). Decoding performance was measured as the area under the Receiving Operating Characteristic curve (AUC - Green and Swets, 1966), with an AUC value of one corresponding to perfect decoding.

Auditory discrimination in comatose patients

[0051] In the pilot group of 12 patients, the average decoding performance was high for all patients, irrespective of their outcome and for all three types of deviant sounds (Figure 2a). The best performance was observed during TH and for non-survivors (Figure2a, Non-survivors, TH). Moreover, sound discrimination, based on the decoding performance, was at similar levels between patients who awoke and those who did not, both under TH and NT. Importantly, auditory discrimination as measured by the decoding performance was not predictive of the final patients' outcome neither under TH or under NT (at least at this very early stage of coma).

Prediction of awakening

[0052] By contrast, the change in the AUC from TH to NT was predictive of the patients' outcome in this pilot group (Figure 2b, y-axis, grey points). An increase in the AUC from first (TH) to second (NT) recording was only observed in survivors (Figure 2b, grey rhombi), as all patients who did not awake from the coma had unchanged or decreased decoding performance (Figure 2b, grey rectangles). This result was obtained by averaging the AUC obtained using the three types of deviants as this provided the best prediction of awakening. These first results on the pilot group gave 100% positive predictive value, i.e. all patients with an improvement in the

decoding performance from TH to NT awoke from coma and survived at three months.

Validation group

[0053] Data from 18 additional consecutive patients (validation group) were further recorded. All data analysis in this validation group was performed blindly to their outcome, ensuring an objective measure of the predictive value of the method. Results based on this validation group confirmed the observations in the pilot group: an improvement in the decoding performance from TH to NT was only observed in patients awakening from coma and surviving at three months (Figure 2b, black rhombi and rectangles). Overall, in both groups of patients (pilot and validation) the change of auditory discrimination from TH to NT accurately predicted the clinical outcome for 21/30 of them (70% accuracy), with 100% specificity (and positive predictive value for awakening and survival at 3 months), and 53% sensitivity. The average decoding performance for survivors, across the three types of deviant sounds, was 0.63 $\pm$ 0.01 (mean $\pm$ s.e.m.) during TH and 0.63 $\pm$ 0.01 during NT, while for non-survivors it was 0.67 $\pm$ 0.02 during TH and 0.63 $\pm$ 0.01 during NT. Moreover, the results provide evidence of intact neural discrimination between standard and deviant sounds during the early phase of coma, largely independent of patients' outcome (Figure 3 for a summary on the method and our results).

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Claims

1. A Method for predicting awakening in a comatose patient based on auditory discrimination measured by an electroencephalography machine, the method comprising the following steps:

   a) exposing the comatose patient treated with hypothermia to auditory stimuli within the first 24 hours from the onset of coma, said auditory stimuli comprising repeated standard and deviant sounds;
   b) recording the patient's electrical activity in the form of electro-encephalographic data to measure the auditory evoked potential (AEP) for each standard sound and for each deviant sound of the auditory stimuli while said patient is in hypothermia state and allocating a first value which is informative of the degree of said auditory discrimination ;
   c) exposing said patient to the same auditory stimuli as in step a) for the second time while said patient is in a normal temperature state;
   d) recording the patient's electrical activity in the form of electro-encephalographic data to measure the auditory evoked potential for each standard sound and for each deviant sound of the auditory stimuli while said patient is in a normal temperature state and allocating a second value which is informative of the degree of said auditory discrimination; and
   e) comparing the first and second values to determine whether there is an improvement of auditory discrimination over time which is informative of whether the comatose patient will awake.

2. The method according to claim 1, wherein step c) is performed within 72 hours and preferably within 48 hours from the onset of coma.

3. A computer-implemented method for predicting awakening in a comatose patient based on auditory discrimination, wherein a comatose patient was exposed to auditory stimuli comprising repeated standard and deviant sounds during two distinct periods, the first period occurring when the comatose patient was in a hypothermia state and the second period occurring after the first period when the comatose patient was brought back to his/her normal temperature, the comatose patient having been equipped with electrodes connected to an electroencephalography machine to record auditory evoked potential (hereafter "AEP") for each standard sound and for each deviant sound of the auditory stimuli during the first and second periods, the method comprising the following steps:

   a) dividing all the recorded AEPs into two datasets, namely a training dataset and a testing dataset;
   b) dividing the AEPs from the training dataset into a first and a second category, the first category grouping AEPs recorded in response to standard sounds of the auditory stimuli and the second category grouping AEPs recorded in response to deviant sounds of the auditory stimuli for each of the first and second periods;
   c) computing two statistical models of AEPs from the training dataset for each standard and deviant sounds respectively and for each of the first and second periods;
   d) computing which of the two statistical models of steps c) resembles best each of AEPs from the testing dataset for each of the first and second periods;
   e) assigning each AEP from the testing dataset to a type of sound based on the computation of step d) for each of the first and second periods;
   f) determining whether the type of sound assigned to each AEP from the testing dataset could be associated to the corresponding type of sound of the auditory stimuli that evoked this AEP, in order to conclude whether there is a discrimination between standard and deviant sounds for each of the first and second periods;
   g) quantifying the degree of discrimination between standard and deviant sounds for each of the first and second periods, and
   h) comparing the degree of discrimination between standard and deviant sounds between the first and the second period to determine whether there is an improvement of auditory discrimination overtime which is informative of whether the comatose patient will awake.

4. The computer-implemented method according to claim 3, wherein said second period occurs within 72 hours and preferably within 48 hours from the onset of coma.

5. The computer-implemented method according to claim 3 or 4, wherein a multivariate Gaussian distribution is applied to compute said statistical models.

6. The computer-implemented method according to claim 3, 4 or 5, wherein the degree of discrimination between standard and deviant sounds is quantified by measuring the area under a Receiver Operating Characteristic curve.

7. The computer-implemented method according to any one of claims 3 to 6, wherein the auditory stimuli comprise one standard and three types of deviant sounds.

8. The computer-implemented method according to claim 7, wherein the three types of deviant sounds differ respectively in pitch, in duration and in location from the standard sound.

9. The computer-implemented method according to claim 8, wherein steps a) to e) of claim 3 are performed three times successively for an auditory stimuli comprising respectively standard sounds and deviant sounds with respect to pitch, standard sounds and deviant sounds with respect to duration and standard sounds and deviant sounds with respect to location in order to allocate a value which is informative of the degree of auditory discrimination of the comatose patient for each type of deviant sounds, and wherein the three values corresponding to each type of deviant sounds are averaged to obtain one value representing the overall sound discrimination of said patient.

10. The computer-implemented method according to claim 9, wherein the auditory stimuli are presented in three successive runs, each run having 500 sounds in total including standard and deviant sounds with respect to pitch, duration and location respectively.

11. The computer-implemented method according to claim 10, wherein standard sounds represents about 70% of the total of sounds of each run, and wherein each of the deviant sounds with respect to pitch, duration and location respectively represents around 10% of the total sounds of each run.

12. The computer-implemented method according to any one of the preceding claims, wherein two AEP responses of the second category for the same type of signal are averaged in order to reduce signal's noise.

Patentansprüche

1. Verfahren zum Vorhersagen des Erwachens eines Komapatienten aufgrund einer auditiven Unterscheidung, die durch eine Elektroenzephalographiemaschine gemessen wird, wobei das Verfahren die folgenden Schritte umfasst:

   a) Beaufschlagen des Komapatienten, der mit Unterkühlung behandelt wird, mit Höranreizen innerhalb der ersten 24 Stunden ab dem Einsetzen des Komas, wobei die Höranreize wiederholte Standardgeräusche und abweichende Geräusche umfassen;
   b) Aufzeichnen der elektrischen Aktivität des Patienten in der Form von enzephalographischen Daten, um das hervorgerufene Hörpotenzial (AEP) für jedes Standardgeräusch und für jedes abweichende Geräusch der Höranreize zu messen, während der Patient in einem Unterkühlungszustand ist, und Zuweisen eines ersten Wertes, der für den Grad der auditiven Unterscheidung aussagefähig ist;
   c) Beaufschlagen des Patienten mit denselben Höranreizen wie in Schritt a) zum zweiten Mal, während der Patient in einem normalen Temperaturzustand ist;
   d) Aufzeichnen der elektrischen Aktivität des Patienten in der Form von enzephalographischen Daten, um das hervorgerufene Hörpotenzial für jedes Standardgeräusch und für jedes abweichende Geräusch der Höranreize zu messen, während der Patient in einem normalen Temperaturzustand ist, und Zuweisen eines zweiten Wertes, der für den Grad der auditiven Unterscheidung aussagefähig ist; und
   e) Vergleichen des ersten und des zweiten Wertes, um zu bestimmen, ob es eine Verbesserung der auditiven Unterscheidung mit der Zeit gibt, was darüber aussagefähig ist, ob der Komapatient erwachen wird.

2. Verfahren nach Anspruch 1, wobei der Schritt c) innerhalb von 72 Stunden und vorzugsweise innerhalb von 48 Stunden ab dem Einsetzen des Komas ausgeführt wird.

3. Computerimplementiertes Verfahren zum Vorhersagen des Erwachens eines Komapatienten aufgrund einer auditiven Unterscheidung, wobei ein Komapatient mit Höranreizen beaufschlagt wurde, die wiederholte Standardgeräusche und abweichende Geräusche während zweier individueller Zeitdauern umfassen, wobei die erste Zeitdauer stattfindet, während der Komapatient in einem Unterkühlungszustand war, und die zweite Zeitdauer nach der ersten Zeitdauer stattfindet, wenn der Komapatient zurück zu seiner/ihrer normalen Temperatur gebracht wurde, wobei der Komapatient mit Elektroden ausgestattet worden ist, die mit einer Elektroenzephalographiemaschine verbunden sind, um ein hervorgerufenes Hörpotenzial (nachstehend "AEP") für jedes Standardgeräusch und jedes abweichende Geräusch der Höranreize während der ersten und der zweiten Zeitdauer aufzuzeichnen, wobei das Verfahren die folgenden Schritte umfasst:

   a) Aufteilen aller aufgezeichneten AEPs in zwei Datengruppen, und zwar eine Schulungsdatengruppe und eine Testdatengruppe;
   b) Aufteilen der AEPs von der Schulungsdatengruppe in eine erste und eine zweite Kategorie für die erste und die zweite Zeitdauer, wobei die erste Kategorie AEPs gruppiert, die als Reaktion auf Standardgeräusche der Höranreize aufge-

zeichnet wurden, und die zweite Datengruppe AEPs gruppiert, die als Reaktion auf abweichende Geräusche der Höranreize aufgezeichnet wurden;

c) Berechnen von zwei statistischen Modellen von AEPs aus der Schulungsdatengruppe jeweils für jedes Standardgeräusch und jedes abweichende Geräusch und die erste und die zweite Zeitdauer;

d) Berechnen, welches der beiden statistischen Modelle von Schritt c) am besten jedem der AEPs von der Schulungsgruppe für die erste und die zweite Zeitdauer gleicht;

e) Zuweisen eines jeden AEPs von der Testdatengruppe zu einem Geräuschtyp aufgrund der Berechnung von Schritt d) für die erste und die zweite Zeitdauer;

f) Bestimmen, ob der jedem AEP von der Testdatengruppe zugewiesene Geräuschtyp dem entsprechenden Geräuschtyp der Höranreize, der dieses AEP hervorgerufen hat, zugeordnet werden konnte, um zu folgern, ob es eine Unterscheidung zwischen Standardgeräuschen und abweichenden Geräuschen für die erste und die zweite Zeitdauer gibt;

g) Quantifizieren des Grads der Unterscheidung zwischen den Standardgeräuschen und den abweichenden Geräuschen für die erste und die zweite Zeitdauer und

h) Vergleichen des Grads der Unterscheidung zwischen den Standardgeräuschen und den abweichenden Geräuschen zwischen der ersten und der zweiten Zeitdauer, um zu bestimmen, ob es eine Verbesserung der auditiven Unterscheidung mit der Zeit gibt, die darüber aussagefähig ist, ob der Komapatient erwachen wird.

4. Computerimplementiertes Verfahren nach Anspruch 3, wobei die zweite Zeitdauer innerhalb von 72 Stunden und vorzugsweise innerhalb von 48 Stunden ab dem Einsetzen des Komas stattfindet.

5. Computerimplementiertes Verfahren nach Anspruch 3 oder 4, wobei eine multivariante Gauß-Verteilung angewendet wird, um die statistischen Modelle zu berechnen.

6. Computerimplementiertes Verfahren nach Anspruch 3, 4 oder 5, wobei der Grad der Unterscheidung zwischen Standardgeräuschen und den abweichenden Geräuschen durch Messen der Fläche unter einer Empfängerbetriebseigenschaftskurve quantifiziert wird.

7. Computerimplementiertes Verfahren nach einem der Ansprüche 3 bis 6, wobei die Höranreize ein Standardgeräusch und drei Typen von abweichenden Geräuschen umfassen.

8. Computerimplementiertes Verfahren nach Anspruch 7, wobei sich die drei Typen von abweichenden Geräuschen jeweils in der Tonhöhe, der Dauer und dem Ort von dem Standardgeräusch unterscheiden.

9. Computerimplementiertes Verfahren nach Anspruch 8, wobei die Schritte a) bis e) nach Anspruch 3, drei Mal nacheinander für Höranreize, die jeweils Standardgeräusche und in Bezug auf die Tonhöhe abweichende Geräusche, Standardgeräusche und in Bezug auf die Dauer abweichende Geräusche und Standardgeräusche und in Bezug auf den Ort abweichende Geräusche umfassen, ausgeführt werden, um einen Wert zuzuweisen, der für den Grad der auditiven Unterscheidung des Komapatienten für jeden Typ von abweichenden Geräuschen aussagefähig ist und wobei die drei Werte, die jedem Typ von abweichenden Geräusch entsprechen, gemittelt werden, um einen Wert zu erhalten, der die gesamte Geräuschunterscheidung des Patienten repräsentiert.

10. Computerimplementiertes Verfahren nach Anspruch 9, wobei die Höranreize in drei aufeinanderfolgenden Durchgängen dargestellt werden, wobei jeder Durchgang insgesamt 500 Geräusche umfasst, die Standardgeräusche und jeweils in Bezug auf die Tonhöhe, die Dauer und den Ort abweichende Geräusche umfassen.

11. Computerimplementiertes Verfahren nach Anspruch 10, wobei die Standardgeräusche ungefähr 70 % der gesamten Geräusche eines jeden Durchgangs repräsentieren und wobei jedes der in Bezug auf die Tonhöhe, die Dauer und den Ort abweichenden Geräusche jeweils ungefähr 10 % der gesamten Geräusche eines jeden Durchgangs repräsentieren.

12. Computerimplementiertes Verfahren nach einem der vorhergehenden Ansprüche, wobei zwei AEP-Antworten der zweiten Kategorie für denselben Signaltyp gemittelt werden, um das Rauschen des Signals zu verringern.

Revendications

1. Procédé de prédiction de réveil chez un patient comateux basé sur une discrimination auditive mesurée par un appareil d'électroencéphalographie, le procédé comprenant les étapes suivantes :

a) exposer le patient comateux traité avec une hypothermie à des stimuli auditifs dans les 24 premières heures de l'apparition du coma, lesdits stimuli auditifs comprenant des sons standard et déviants répétés ;

b) enregistrer l'activité électrique du patient sous la forme de données électroencéphalographiques pour mesurer le potentiel évoqué auditif (AEP) pour chaque son standard et pour chaque son déviant des stimuli auditifs, tandis que ledit patient est dans un état d'hypothermie, et affecter une première valeur qui est informative du degré de ladite discrimination auditive ;
c) exposer ledit patient aux mêmes stimuli auditifs que dans l'étape a) pour la seconde fois tandis que ledit patient est dans un état de température normale ;
d) enregistrer l'activité électrique du patient sous la forme de données électroencéphalographiques pour mesurer le potentiel évoqué auditif pour chaque son standard et pour chaque son déviant des stimuli auditifs, tandis que ledit patient est dans un état de température normale, et affecter une seconde valeur qui est informative du degré de ladite discrimination auditive ; et
e) comparer les première et seconde valeurs afin de déterminer s'il y a une amélioration de la discrimination auditive dans le temps qui est informative du fait que le patient comateux va se réveiller.

2. Procédé selon la revendication 1, dans lequel l'étape c) est exécutée dans les 72 premières heures et de préférence dans les 48 premières heures de l'apparition du coma.

3. Procédé mis en oeuvre par ordinateur pour prédire le réveil chez un patient comateux basé sur une discrimination auditive, où un patient comateux a été exposé à des stimuli auditifs comprenant des sons standard et déviants répétés pendant deux périodes distinctes, la première période ayant eu lieu lorsque le patient comateux était dans un état d'hypothermie et la seconde période ayant eu lieu après la première période lorsque le patient comateux a été ramené à sa température normale, le patient comateux ayant été équipé d'électrodes reliées à une machine d'électroencéphalographie pour enregistrer le potentiel évoqué auditif (ci-après « AEP ») pour chaque son standard et pour chaque son déviant des stimuli auditifs au cours des première et seconde périodes, le procédé comprenant les étapes suivantes :

a) diviser tous les AEP enregistrés en deux ensembles de données, à savoir un ensemble de données de formation et un ensemble de données de test ;
b) diviser les AEP de l'ensemble de données de formation en une première catégorie et une seconde catégorie, la première catégorie regroupant les AEP enregistrés en réponse à des sons standard des stimuli auditifs et la seconde catégorie regroupant les AEP enregistrés en réponse à des sons déviants des stimuli auditifs pour chacune des première et seconde périodes ;
c) calculer deux modèles statistiques d'AEP à partir de l'ensemble de données de formation pour chaque son standard et chaque son déviant, respectivement, et pour chacune des première et seconde périodes ;
d) calculer lequel des deux modèles statistiques des étapes c) ressemble le plus à chacun des AEP de l'ensemble de données de test pour chacune des première et seconde périodes ;
e) affecter chaque AEP de l'ensemble de données de test à un type de son sur la base du calcul de l'étape d) pour chacune des première et seconde périodes ;
f) déterminer si le type de son affecté à chaque AEP de l'ensemble de données de test pouvait être associé au type de son correspondant des stimuli auditifs qui ont évoqué cet AEP, afin de conclure s'il y a une discrimination entre des sons standard et déviants pour chacune des première et seconde périodes ;
g) quantifier le degré de discrimination entre les sons standard et déviants pour chacune des première et seconde périodes, et
h) comparer le degré de discrimination entre les sons standard et déviants entre la première période et la seconde période pour déterminer s'il y a une amélioration de la discrimination auditive au cours du temps qui est informative du fait que le patient comateux va se réveiller.

4. Procédé mis en oeuvre par ordinateur selon la revendication 3, dans lequel ladite seconde période se produit dans les 72 premières heures et de préférence dans les 48 premières heures de l'apparition du coma.

5. Procédé mis en oeuvre par ordinateur selon la revendication 3 ou la revendication 4, dans lequel une distribution gaussienne à plusieurs variables est appliquée pour calculer lesdits modèles statistiques.

6. Procédé mis en oeuvre par ordinateur selon les revendications 3, 4 ou 5, dans lequel le degré de discrimination entre les sons standard et déviants est quantifié en mesurant l'aire sous une courbe d'efficacité du récepteur.

7. Procédé implémenté par ordinateur selon l'une quelconque des revendications 3 à 6, dans lequel les stimuli auditifs comprennent un type standard et trois types de sons déviants.

8. Procédé mis en oeuvre par ordinateur selon la revendication 7, dans lequel les trois types de sons déviants diffèrent respectivement en hauteur tonale,

en durée et en localisation par rapport au son standard.

9. Procédé mis en oeuvre par ordinateur selon la revendication 8, dans lequel les étapes a) à e) de la revendication 3 sont exécutées trois fois successivement pour des stimuli auditifs comprenant respectivement des sons standard et déviants par rapport à la hauteur tonale, des sons standard et déviants par rapport à la durée et des sons standard et déviants par rapport à leur localisation afin d'attribuer une valeur qui est informative du degré de discrimination auditive du patient comateux pour chaque type de son déviant, et où les trois valeurs correspondant à chaque type de son déviant sont moyennées pour obtenir une valeur représentant la discrimination sonore globale dudit patient.

10. Procédé mis en oeuvre par ordinateur selon la revendication 9, dans lequel les stimuli auditifs sont présentés en trois sessions successives, chaque session comprenant 500 sons au total comprenant des sons standard et des sons déviants qui diffèrent respectivement en hauteur tonale, en durée et en localisation.

11. Procédé mis en oeuvre par ordinateur selon la revendication 10, dans lequel les sons standard représentent environ 70 % du total des sons de chaque session, et dans lequel chacun des sons déviants, qui diffèrent respectivement en hauteur tonale, en durée et en localisation, représente environ 10 % du total des sons de chaque session.

12. Procédé mis en oeuvre par ordinateur selon l'une quelconque des revendications précédentes, dans lequel deux réponses AEP de la seconde catégorie pour le même type de signal sont moyennées afin de réduire le bruit des signaux.

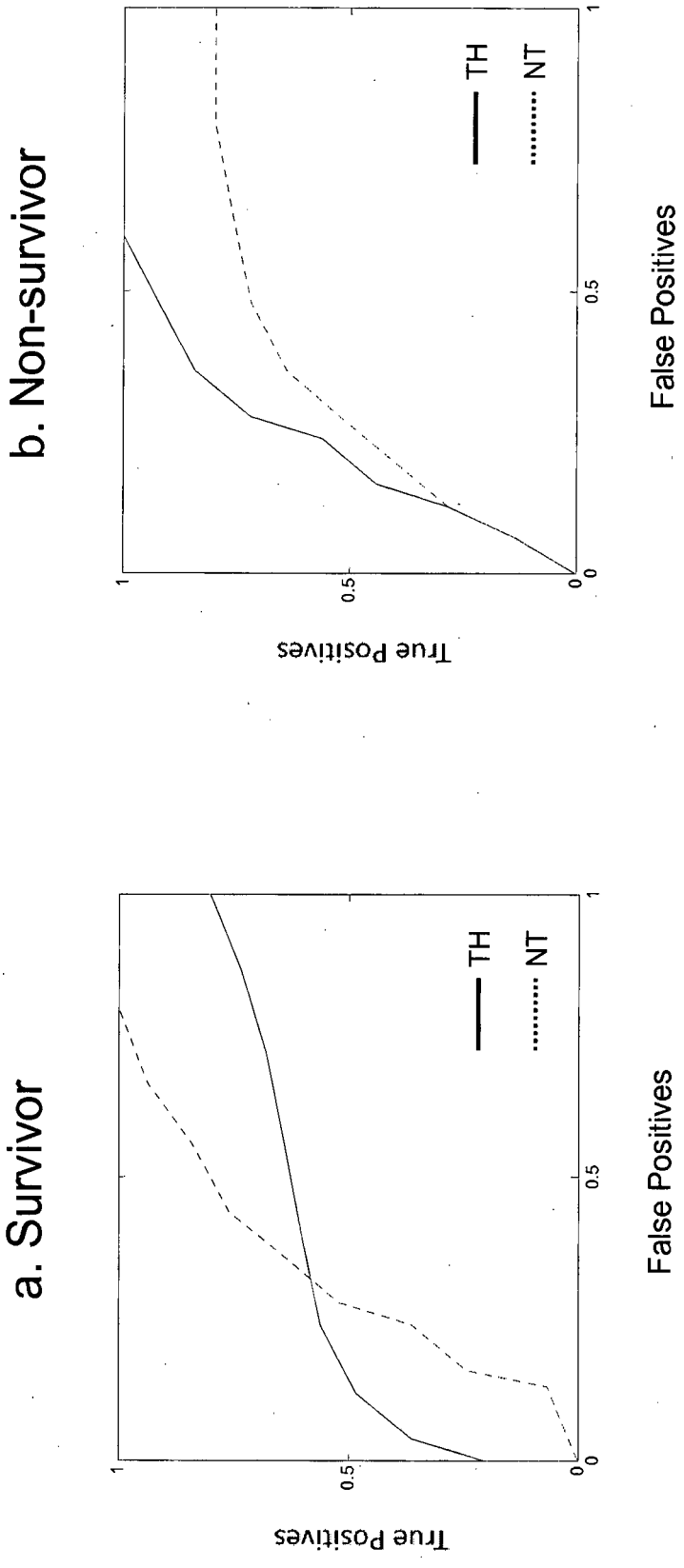
a. Survivor
b. Non-survivor
True Positives
False Positives
TH
NT
0
0.5
1

Figure 1

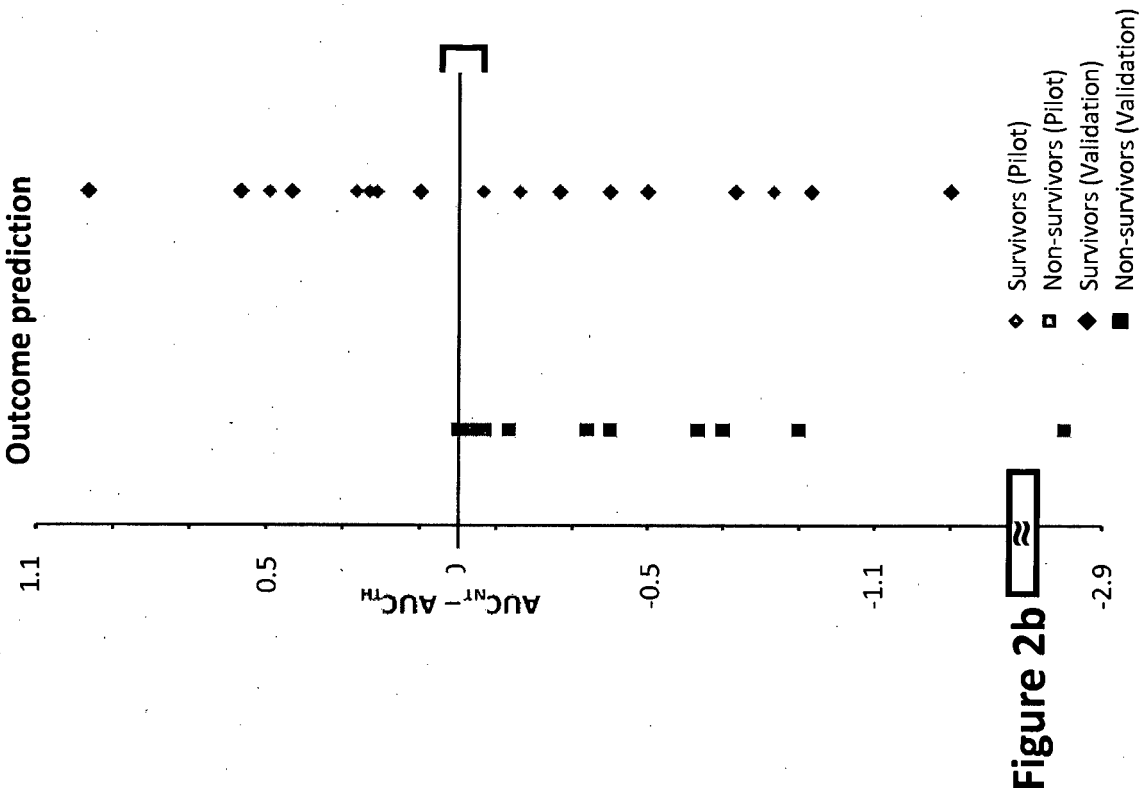

Figure 2b

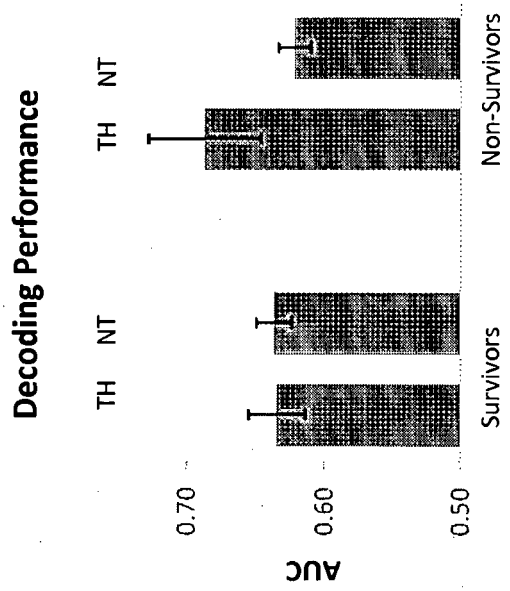

Figure 2a

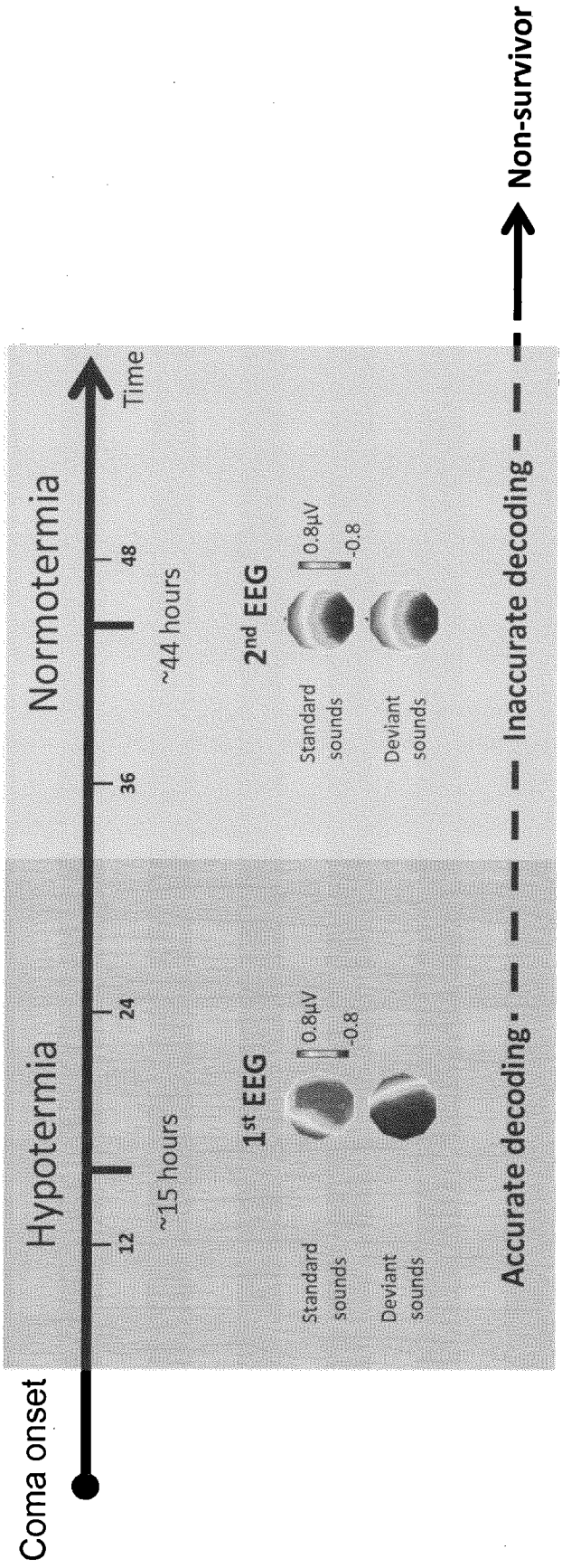
Coma onset
Hypotermia
Normotermia
Time
12
24
36
48
~15 hours
~44 hours
1st EEG
2nd EEG
0.8µV
-0.8
Standard sounds
Deviant sounds
Accurate decoding
Inaccurate decoding
Non-survivor

Figure 3

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	用于预测昏迷患者中的觉醒的方法及其计算机实现的方法		
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摘要(译)

本发明涉及一种用于基于彗差早期阶段的听觉辨别的进展来预测昏迷患者的觉醒的方法。当所述患者暴露于包括重复标准和异常声音的听觉刺激时，在两个不同时期期间从患者获取EEG测量值。第一个时期发生在昏迷患者处于低温状态时，第二个时期发生在昏迷患者处于正常温度状态时，优选在昏迷开始后2-3天内。本发明还涉及其计算机实现的方法。

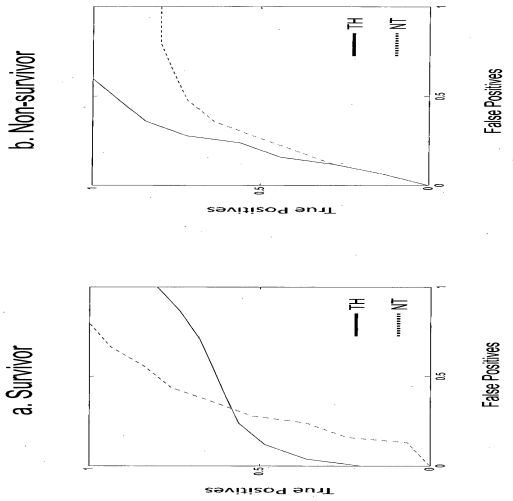

Figure 1