Somatosensory and auditory deviance detection for outcome prediction during post-anoxic coma

SUPPLEMENTAL MATERIAL

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1. Supplemental Methods

1.1. Auditory and Tactile Stimulation Protocols

Each patient was presented with an auditory and a tactile MMN protocol. The auditory protocol (described previously in [1, 2]) consisted of a series of 16-bit stereo sinusoidal tones, sampled at 44.1 kHz, with a 10-ms linear amplitude envelope at onset and offset to avoid clicks was presented at 75 db loudness on in-ear stereo headphones (model ER-4P, Etymotic Research). Sounds were presented in three identical blocks of 500 stimuli for each recording. In each block there were 350 "standard" sounds (70% of the total) consisting of 1000 Hz tones with 100 ms duration and 0 ms interaural difference. The standard sounds were replaced pseudorandomly by three types of "deviant" sounds, which differed from the standard ones with respect to their pitch, duration, or location. There were 50 deviant sounds of each type in one block. Duration deviants were 1000 Hz, with 150 ms duration and 0 ms interaural difference. Pitch deviants were 1200 Hz tones with 100 ms duration and 0 ms interaural difference. Deviants in location were 1000 Hz tones, with 100 ms duration and 700 μs interaural difference, with the left ear leading. Sounds were presented at a fixed 750 ms inter-stimulus interval. We always recorded three blocks during the first day recording and three blocks during the second day recording, resulting thus in 1500 presented stimuli per recoding.

After having completed the auditory protocol, each patient was presented with the tactile MMN protocol. A vibrotactile stimulator (g.VIBROstim, Guger Technologies, Graz, Austria, 13500 rpm maximum speed, 22.5 ms until maximum rotation) was attached to the left index finger of the patient and vibro-tactile stimuli of 100-ms ('standard' stimulus) or 150-ms duration ('deviant' stimulus) were presented in a pseudorandom order in two blocks consisting each of 400 standard (80% of the total) and 100 deviant (20% of the total) stimuli. Only one type of deviant (duration) was presented for the tactile stimulation protocol, because in healthy subjects the duration deviant is highly detectable, easy to administer, and duration

deviants for the auditory protocol showed highly informative about patient's outcome in our previous studies [1, 2].

1.2. EEG Acquisition and Preprocessing

Each patient had two EEG recordings at bedside in the intensive care unit. The first recording took place within 24 hours after coma onset during TTM and the second recording at approximately 36-48 hours after coma onset after withdrawal of TTM, off sedation. A g.tec EEG system (i.e. g.HIamp, Guger Technologies, Graz, Austria) with a sampling rate of 1200 Hz and 62 active electrodes placed according to the 10-20 system was used. In order to allow comparison between the present results and previous studies using the same auditory stimulation protocol, we restricted the analysis to 19 EEG channels corresponding to the clinical EEG montage used in [1, 2]. Across all patients the impedances were kept <10 kΩ and the data was referenced online to the Fpz electrode and in the course of preprocessing the average reference was computed. We preprocessed the EEG data offline using the same procedure as in [1-3]. We extracted EEG responses to deviant stimuli and an equal number of responses to standard stimuli for the auditory and tactile protocols across all experimental blocks.

2. Supplemental Results

2.1. Outcome Prediction for Patients Without Epileptiform Features

Out of the 66 patients included for the main analysis, 11 (17%) had an EEG with epileptiform features either on the first day (2 patients, 3%), on the second day (3 patients, 5%), or on both days following CA (7 patients, 9%). Because such epileptiform activity has been shown to increase the false positive rate for outcome prediction base on our method [1, 3],

we report in **Table S1** the outcome prediction results based on the auditory and tactile protocol for a reduced sample of 55 patients without epileptiform features (11 women, age mean = 65 years, SD = 13 years) out of which 39 (71%) had a good outcome and 16 (29%) a poor outcome.

Table S1: Prognostic values for good outcome for comatose patients excluding those with epileptiform features (n = 55) based on the progression of auditory and tactile discrimination. Values above chance level are highlighted in bold.

	Audio	Tactile
Positive Predictive Value (95%CI)	**0.85 (0.62-0.97)**	0.72 (0.47-0.90)
Sensitivity (95%CI)	0.44 (0.28-0.60)	0.33 (0.19-0.50)
Specificity (95%CI)	**0.81 (0.54-0.96)**	0.69 (0.41-0.89)
Negative Predictive Value (95%CI)	0.37 (0.21-0.55)	0.30 (0.16-0.47)
Accuracy (95%CI)	0.55 (0.29-0.53)	0.44 (0.21-0.43)

2.2. Outcome Prediction Based on Different Auditory Deviants

The auditory discrimination analysis in the main text was based on the average decoding performance across three deviants (duration, location, and pitch), whereas tactile discrimination analysis was based on a single deviant (duration) tested. To allow a direct comparison of tactile discrimination results we report below and in **Table S2** outcome prediction results separately for the auditory duration, location, and pitch deviant.

Duration deviant. The average decoding performance for 41 Survivors was AUC_{DAY1} = 0.605 ± 0.007 and AUC_{DAY2} = 0.626 ± 0.007, and for the 25 Non-Survivors decoding performance was AUC_{DAY1} = 0.619 ± 0.010 and AUC_{DAY2} = 0.608 ± 0.009. The progression of decoding performance from Day 1 to Day 2 showed a 72% positive predictive value (95% CI = 0.55 – 0.86; **Table S2**).

Location deviant. The average decoding performance for 41 Survivors of AUC_{DAY1} = 0.610 ± 0.006 and AUC_{DAY2} = 0.616 ± 0.008, and for the 25 Non-Survivors decoding performance was AUC_{DAY1} = 0.631 ± 0.006 and AUC_{DAY2} = 0.607 ± 0.009. The progression of decoding performance from Day 1 to Day 2 showed a 76% positive predictive value (95% CI = 0.55 – 0.91).

Pitch deviant. The average decoding performance for 41 Survivors of AUC_{DAY1} = 0.629 ± 0.008 and AUC_{DAY2} = 0.607 ± 0.007, and for the 25 Non-Survivors decoding performance was AUC_{DAY1} = 0.629 ± 0.012 and AUC_{DAY2} = 0.627 ± 0.012. The progression of decoding performance from Day 1 to Day 2 showed a 63% positive predictive value (95% CI = 0.41 – 0.81).

Thus, the above-chance level predictive value for good outcome in the main analysis was driven by the high positive predictive values of the duration and location deviant. A similar result, in particular for duration deviants, was previously observed by Tzovara et al. (2013).

Table S2: Prognostic values for good outcome for comatose patients based on the progression of auditory discrimination shown separately for duration, location, and pitch deviant. Values above chance level are highlighted in bold.

	Duration	Location	Pitch
Positive Predictive Value (95%CI)	**0.72 (0.55-0.86)**	**0.76 (0.55-0.91)**	0.63 (0.41-0.81)
Sensitivity (95%CI)	0.63 (0.47-0.78)	0.46 (0.31-0.63)	0.37 (0.22-0.53)
Specificity (95%CI)	0.60 (0.39-0.79)	**0.76 (0.55-0.91)**	0.64 (0.43-0.82)
Negative Predictive Value (95%CI)	0.50 (0.31-0.69)	0.46 (0.31-0.63)	0.38 (0.24-0.54)
Accuracy (95%CI)	0.62 (0.45-0.69)	0.58 (0.35-0.58)	0.47 (0.27-0.49)

3. Clinical Characteristics

We compared demographics and clinical characteristics between patients showing an increase and patients showing a decrease of decoding performance separately for Survivors (n = 35, **Table 3**) and Non-Survivors (N = 25, **Table 4**) and to assess if additional factors contributed to the outcome prediction results. There were no differences in gender distribution, age, CA etiology, return of spontaneous circulation (ROSC), presence/absence of brainstem reflexes, latency of clinical EEG assessment and in the majority of semi-quantitative markers of EEG (i.e. discontinuity, reactivity). However, for Non-Survivors we observed a difference regarding the presence of epileptiform EEG. Out of the 7 Non-Survivors showing an increase, 5 (71%) had an epileptiform first EEG, whereas out of the 18 Non-Survivors showing a decrease, this only occurred in 5 (28%). Thus, in line with our previous study, the increase of decoding performance in these patients (and therefore the occurrence as false positives) can be somewhat related to epileptiform activity [1].

Table S3: Clinical description of Survivors (n = 41), split according to whether from Day 1 to Day 2 their decoding performance for the auditory protocol increased or decreased.

	Survivors with Increase, n = 19	Survivors with Decrease, n = 22
Female gender, No (%)	2 / 19 (11%)	4 / 22 (18%)
Age, yr mean ± SD (range)	62 ± 14 (18-83)	66 ± 14 (27-86)
Time to ROSC, min mean ± SD (range)	22 ± 15 (8-60)	18 ± 13 (3-45)
Non cardiac etiology, No (%)	6 / 19 (32%)	5 / 22 (23%)
Absent Pupillary reflex, No (%)	1 / 19 (5%)	0 / 22 (0%)
Absent Corneal reflex, No (%)	3 / 19 (16%)	3 / 22 (14%)

Absent Motor response, No (%)	6 / 19 (32%)	5 / 22 (23%)
Early myoclonus, No (%)	0 / 19 (0%)	1 / 22 (5%)
First EEG: Unreactive background, No (%)	1 / 18 (6%) *Missing: 1*	5 / 21 (24%) *Missing: 1*
First EEG: Discontinuous EEG, No (%)	3 / 18 (17%) *Missing: 1*	10 / 21 (48%) *Missing: 1*
First EEG: Epileptiform EEG, No (%)	0 / 18 (0%) *Missing: 1*	0 / 21 (0%) *Missing: 1*
Second EEG: Unreactive background, No (%)	0 / 16 (0%) *Missing: 3*	0 / 21 (0%) *Missing: 1*
Second EEG: Discontinuous EEG, No (%)	0 / 16 (0%) *Missing: 3*	1 / 21 (5%) *Missing: 1*
Second EEG: Epileptiform EEG, No (%)	2 / 16 (13%) *Missing: 3*	0 / 21 (0%) *Missing: 1*
Bilaterally absent N20 on the SSEP, No (%)	0 / 12 (0%) *Missing: 7*	0 / 18 (0%) *Missing: 4*
Time to first EEG, h mean ± SD (range)	18 ± 7 (6-36)	19 ± 8 (6-42)
Time between recordings, h mean ± SD (range)	28 ± 20 (9-97)	22 ± 7 (3-34)

Table S4: Clinical description of Non-Survivors (n = 25), split according to whether from Day 1 to Day 2 their decoding performance increased or decreased.

	Non-Survivors with Increase, n = 7	Non-Survivors with Decrease, n = 18
Female gender, No (%)	2 / 7 (29%)	6 / 18 (33%)
Age, yr mean ± SD (range)	67 ± 11 (46-80)	65 ± 11 (45-86)
Time to ROSC, min mean ± SD (range)	27 ± 10 (12-40)	24 ± 9 (15-50)

Non cardiac etiology, No (%)	2 / 7 (29%)	4 / 16 (25%) *Missing: 2*
Absent Pupillary reflex, No (%)	1 / 6 (17%) *Missing: 1*	3 / 16 (19%) *Missing: 2*
Absent Corneal reflex, No (%)	4 / 6 (67%) *Missing: 1*	9 / 16 (56%) *Missing: 2*
Absent Motor response, No (%)	6 / 6 (100%) *Missing: 1*	14 / 16 (88%) *Missing: 2*
Early myoclonus, No (%)	0 / 6 (0%) *Missing: 1*	9 / 16 (56%) *Missing: 2*
First EEG: Unreactive background, No (%)	5 / 6 (83%) *Missing: 1*	15 / 17 (88%) *Missing: 1*
First EEG: Discontinuous EEG, No (%)	5 / 6 (83%) *Missing: 1*	14 / 17 (82%) *Missing: 1*
First EEG: Epileptiform EEG, No (%)	3 / 6 (50%) *Missing: 1*	5 / 17 (29%) *Missing: 1*
Second EEG: Unreactive background, No (%)	4 / 5 (80%) *Missing: 2*	9 / 15 (60%) *Missing: 3*
Second EEG: Discontinuous EEG, No (%)	3 / 5 (60%) *Missing: 2*	6 / 15 (40%) *Missing: 3*
Second EEG: Epileptiform EEG, No (%)	2 / 5 (40%) *Missing: 2*	5 / 15 (33%) *Missing: 3*
Bilaterally absent N20 on the SSEP, No (%)	2 / 4 (50%) *Missing: 3*	7 / 11 (64%) *Missing: 7*
Time to first EEG, h mean ± SD (range)	20 ± 6 (11-24)	22 ±11 (6-48)
Time between recordings, h mean ± SD (range)	28 ± 9 (20-44)	26 ± 11 (18-65)

References

1. Tzovara A, Rossetti AO, Juan E, et al. Prediction of awakening from hypothermic post anoxic coma based on auditory discrimination. Annals of neurology. 2016 Feb 23;79(5):748–57.

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