Mismatch negativity to predict subsequent awakening in deeply sedated critically ill patients

Eric Azabou [1,2]*, MD, PhD; Benjamin Rohaut [3]*, MD, PhD; Raphael Porcher [4], PhD; Nicholas Heming[2], MD, PhD; Stanislas Kandelman [5], MD, ME; Jeremy Allary [5], MD; Guy Moneger [2], MD; Frédéric Faugeras [6], MD, PhD; Jacobo D. Sitt [6], MD, PhD; Djillali Annane [2], MD, PhD; Frédéric Lofaso[1], MD, PhD; Fabrice Chrétien [7], MD, PhD; Jean Mantz [7,8], MD, PhD; Lionel Naccache [6], MD, PhD; Tarek Sharshar [7,9], MD, PhD. on behalf of the GENeR (Groupe d'Explorations Neurologiques en Réanimation)

[1] Department of Physiology – Assistance Publique -Hôpitaux de Paris, Raymond-Poincaré Hospital, INSERM U 1179, University of Versailles Saint-Quentin en Yvelines - Garches, Paris, France

[2] General Intensive Care Unit – Assistance Publique Hôpitaux de Paris, Raymond-Poincaré Hospital, INSERM U 1173, University of Versailles Saint-Quentin en Yvelines - Garches, Paris, France

[3] Department of Neurology, Neuro-ICU, Columbia University, New York, NY, USA.

[4] Center for Clinical Epidemiology - Assistance Publique Hôpitaux de Paris, Hotel Dieu Hospital, University Paris Descartes, INSERM U1153, Paris, France

[5] Department of Anesthesiology and Intensive Care Medicine – Beaujon Hospital,

University of Denis Diderot, Clichy, France

[6] Institut du Cerveau et de la Moelle épinière, ICM, PICNIC Lab, F-75013, Paris, France

[7] Laboratory of Experimental neuropathology– Institut Pasteur - Paris, France

[8] Department of Anesthesiology and Intensive Care Medicine – European Hospital Georges Pompidou, Paris Descartes University, Paris, France

[9] Department of Neuro-Intensive Care Medicine, Sainte-Anne Hospital, Paris-Descartes University, Paris, France

* These authors contributed equally to this work.

Corresponding author: Pr Tarek Sharshar, MD, PhD
Department of Neuro-Intensive Care Medicine, Sainte-Anne Hospital, Paris-Descartes University, 1, Rue Cabanis 75014 Paris, France
Laboratory of Experimental neuropathology, Institut Pasteur 28, rue du Dr Roux, 75015 Paris France,
Email: tarek.sharshar@pasteur.fr; Email: tsharshar@gmail.com

DOI : https://doi.org/10.1016/j.bja.2018.06.029

Abstract

Background: Mismatch negativity (MMN) is the neurophysiological correlate of cognitive integration of novel stimuli. Although MMN is a well-established predictor of awakening in non-sedated comatose patients, its prognostic value in deeply sedated critically ill patients remains unknown. This prospective, observational pilot study was aimed at investigating the prognostic value of MMN for further awakening in deeply sedated critically ill patients.

Methods: MMN was recorded in 43 deeply sedated critically ill patients on day-3 of ICU admission using a classical "Odd-ball" paradigm that delivers rare deviant sounds in a train of frequent standard sounds. Individual visual analyses of recordings were performed as well as a group level analysis. MMN amplitudes were then analysed according to the neurological status (awake vs. not awake) at day-28.

Results: Median RASS [IQR] at the time of recording was -5 [-5 to -4.5]. Visual detection of MMN revealed a poor inter-rater agreement (Kappa = 0.17 95%CI [0.07 to 0.26]). On day 28, thirty (70%) patients had awoken while 13 (30%) had not. Quantitative group level analysis revealed a significantly greater MMN amplitude for patients who awoke compared to those who had not (mean [SD] = -0.65 [1.4] vs 0.08 [0.17] μV respectively; p = 0.003).

Conclusions: MMN can be observed in deeply sedated critically ill patients and could help predict further awakening. However, visual analysis alone is unreliable and should be systematically completed with individual-level statistics.

Keywords: Neuroprognosis, Deep sedation, Event related potentials, ERPs, ICU, MMN

Introduction

Despite the involved risks, deep sedation is still required in the management of about 20% of critically ill patients [1-4]. Deeply sedated critically ill patients are at risk to develop new brain dysfunction, such as delayed awakening and delirium, [5-7] which have a considerable impact on short and long-term outcome [3, 8-15]. Moreover, deep sedation can hamper the detection of either the occurrence or worsening of brain dysfunction in brain injured patients [16-17].

Therefore, detecting and monitoring the occurrence of brain dysfunction and predicting an outcome in deeply sedated brain injured patients are major and challenging concerns [18-22]. We recently demonstrated that the assessments of brainstem reflexes [23-24] EEG [25] or somatosensory and brainstem auditory evoked potentials [26] at the early stage of the ICU stay can predict 28-day mortality in deeply sedated critically ill patients. In addition to mortality, the prediction of awakening is also a relevant endpoint in these patients, especially those who required a prolonged deep sedation. The mismatch negativity (MMN) is an event-related potential (ERP) component that has been extensively demonstrated to be useful in predicting awakening in comas of various origins [27-29]. MMN is a neurophysiologic response which reveals the specific detection of rare and deviant sounds occurring in a train of frequent and standard sounds. The MMN reveals an automatic and unconscious detection of novelty which requires good perceptual discriminative capacity as well as iconic memory [28, 30]. The presence of an MMN is associated with a higher chance of awakening from a coma in non-sedated patients [27, 29, 31-40]. Moreover, it has been shown that MMN can be recorded in sedated patients, [41-45]. However, the prognostic value of MMN in a cohort of deeply sedated critically ill patients remains to be assessed. In this prospective observational pilot study, we aimed to investigate if MMN could be observed in patients receiving deep sedation and whether it could be useful for predicting awakening in these patients.

Methods

Ethical statement

This prospective monocentric observational cohort study was approved by the local ethics committee "Groupement Hospitalier Universitaire (GHU) Paris Nord, Comité d'Ethique de Recherche Biomédicale" (approval number: CERB 11-071). Written informed consent was obtained from the patients' legal representatives; and the healthy control subjects for their participation in this study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [46] were followed thoroughly.

Patients

Consecutive mechanically ventilated and sedated patients were enrolled into the study from January 2013 to December 2015. ERPs were recorded on day-3 at the bedside in deeply sedated patients, defined as a Richmond Assessment Sedation Scale (RASS) < -3 [47]. Post-cardiac arrest and moribund patients, as well as patients in whom cerebral death was suspected as well as patients suffering from pre-existing of acquired neuropathies were not included. Since hypothermia may influence evoked potentials no recording whilst body temperature was below 35 °C was done [48-51]. We also recorded ERPs from a control group of 9 non-sedated, healthy subjects, age range 24 to 61 years, mean age 39 years ±14 [SD], 5 women; using the very same passive auditory odd ball paradigm procedure and equipment as that used for patients.

Baseline clinical data collection

Demographic characteristics (i.e. age, sex) as well as body weight, date and time of ICU admission, category of admission (medical or surgical), co-morbidities, pre-existing risk factors for delirium, main cause of critical illness and brain injury, the date and cause of initiation of mechanical ventilation (MV) and the date and cause of initiation and maintenance of sedation were collected. The Simplified Acute Physiological Score II (SAPS-II)[52] , the Sequential Organ Failure Assessment (SOFA)[53], as well as key interventions and standard biological tests needed to calculate these scores were recorded. Baseline data collection was performed following a previously described method [24].

Sedation and analgesia

The decision to initiate sedation and its subsequent management was overseen by the physicians in charge of the patient and followed recent guidelines [9, 14]. Sedation was administered through a continuous infusion of midazolam and/or propofol, alone or in combination with sufentanil. Total cumulative doses of administered drugs at the time of neuro-physiological examination were collected. The depth of sedation was monitored using the RASS [47], performed every 4 hours until awakening. Sedation was administrated as a titration aiming at obtaining the desired RASS [47]. The time of onset, the reason for administration and duration of sedation were collected as well as the time of awakening (defined by eye opening and visual contact >10 sec or RASS ≥ -1).

Neurological examination

At the time of recording, neurological examination, including assessment of brainstem reflexes was performed by senior ICU physicians, either neurologists or specifically trained intensivists [24]. The Glasgow Coma Scale (GCS), the Full Outline of Unresponsiveness (FOUR) score [54] and the RASS were assessed. Physicians in charge of the patient were not informed of the results of the neurophysiologic examination.

Methodology for Event Related Potentials recording and analysis

ERPs recordings

A Dantec™ / Natus –France Keypoint® portable machine was used for evoked potentials acquisition. ERPs were elicited by a passive auditory oddball paradigm using duration and frequency deviant sound according to the classical technique [27-28, 32, 55]. The stimuli were pure tones with a level of 80 dB delivered binaurally through inserted earphones. Eighty-five percent of the stimulations were frequent (standard) stimuli and fifteen percent were rare (deviant). Characteristics of the two types of auditory stimuli are as follows: the first stimulus consisted of a high frequency and long duration tone (2000Hz and 100 ms) and the second stimulus of a lower frequency and shorter tone (1000 Hz and 50 ms). The stimulation protocol included an automatic crossed design using the higher frequency and longer tone stimulus as the rare (deviant) during the first half of the recordings, and as the frequent one (standard) during the second half of the recordings [28-30, 55].

ERPs were recorded with active electrodes positioned at Fz (frontal) and Cz (central) according to 10-20 EEG system. The reference electrode was set at the right mastoid and the ground electrode on the forehead. Sterile hypodermic needle electrodes were used and inter-electrode impedance was kept below 3 kOhms. The amplification factor was 75 000. The signal was bandpass filtered with an analog 1–160 Hz filter and sampled every second from each stimulus onset. Elementary responses with amplitude greater than ± 10 µV were automatically rejected, thus eliminating eye movements and other artefacts. Standard and deviant responses were averaged online separately and stored when the average of 200 suitable deviant responses was reached [29]. After averaging, data were bandpass filtered with a 3-30 Hz and Butterworth filter of order 6, to exclude baseline shifts and high-frequency noise. Blocks of averaged standard responses and of deviant ones were stored for off-line analysis. Note that since this clinical acquisition setting does not allow captures of individual trials, but

performs an online averaging process, it does not allow performing individual inter-trials analysis.

ERPs analysis

Individual visual analyses of ERPs were separately performed by five trained neurophysiologists (EA, BR, FF, JS and LN), blinded to the clinical data. P1/N1, MMN and P300 of each patient were scored as present or absent on a visual wave detection basis, according to a standardized criterion including waves' polarity, expected latency range and a minimal amplitude threshold value using the superposed curves and the difference curve (deviant minus standard). The inter-observer agreement rates between five raters were assessed using Fleiss' Kappa scores. ERPs grand-averages across subjects were computed and both conditions were compared using a sample-by-sample paired t-test. Differences were considered significant only if we could observe at least 10 consecutives p-value $< .05$ (corresponding to effects lasting ≥ 10 ms). In addition to the visual analysis and in order to circumvent the impossibility to compute individual inter-trial statistics with our clinical setting, we quantified individual amplitude values of MMN for each patient during the time-window defined on the group lever (on the grand average). Because of poor inter-rater agreement, we chose to estimate individual MMN amplitudes by subtracting deviant minus standard curves over the time window previously defined at the group level analysis (i.e. 250 to 269 ms). For controls, we measured individual P1, MMN and P300 amplitudes form baseline to the peak. For patients, MMN amplitudes were measured on the subtracted curve (deviant minus standard) during the time window defined at the group-level. Individual MMN amplitude values of patients who awake and those who did not after discontinuation of sedation were then compared using a Wilcoxon rank-sum tests (bilateral). Finally, we computed correlations between these individual MMN's values and variables of interest using Spearman correlation coefficients. All analyses were performed using the R statistical software version 3.4.0.

Follow-up

During sedation, GCS, FOUR, and RASS were assessed daily. After discontinuation of sedation, GCS and CAM-ICU [11] were assessed daily for detecting awakening, consciousness recovery and delirium. Coma was defined by GCS below 8, awakening by eye opening and visual contact >10 sec (=RASS $\geq$ -1), delirium by a positive CAM-ICU and consciousness recovery by GCS of 15 associated with a negative CAM-ICU. Duration of mechanical

ventilation, sedation, and length of ICU stay; date of awakening, and when applicable, of death as well as the cause of death were collected. Delayed awakening was defined by the absence of awakening within the first three days following discontinuation of sedation.

Results

Patients' baseline characteristics and outcome data

From January 2013 to December 2015, 43 consecutive mechanically ventilated and deeply sedated patients were included. Baseline characteristics of the patients are presented in Table 1. Fourteen (33 %) patients were admitted to the ICU for brain injury and 29 (67%) for a non-neurological critical illness (Table 1). Coma and acute respiratory failure were the main indications for mechanical ventilation. Deep sedation was mainly required for synchronization of the ventilator or for severe intracranial hypertension. At the time of recording, 38 (88 %) patients were sedated by midazolam, 7 (16 %) by propofol, with respective median [IQR] cumulative doses of 5 [4.25 to 10] and 10 [3 to 40] mg/kg/min. Sufentanil was given to 35 (81 %) patients with a median [IQR] cumulative dose of 20 [8.7 to 30] µg/kg/h. The median [IQR] RASS and FOUR score were -5 [-5 to -4.5] and 4 [2 to 6] respectively. Overall median [IQR] duration of sedation was 9.5 [4 to 14] days (Table 1)**.** By day 28 of admission, 30 (70%) patients had awoken. All patients who had not awoken died by day 28. Causes of death were brain death in 2 patients and multiple organ failure in 11 patients. A decision to limit active treatments occurred in 3 patients, without being based on the results of the ERPs. Patients who will wake up exhibited less severe critical illness, according to SAPS-II and SOFA scores but GCS, RASS and cumulative doses of midazolam, propofol and sufentanil did not significantly differ between the two groups.

ERPs data

Visual interpretation:

Visual interpretation of ERPs: Fleiss' Kappa inter-rater agreement scores obtained among five trained neurophysiologists who performed blinded visual interpretations of patients' ERPs probing P1/N1, MMN and P300 were all < 0.2 (respectively: k [95%CI] = 0.05 [-0.04 to 0.14], 0.17 [0.07 to 0.26] and 0.18 [0.08 to 0.27]). These results indicate a poor agreement and emphasize the difficulty in visual detection of ERPs recorded in critically ill patients while no individual inter-trials statistics are available. Visual interpretation of the 9 healthy volunteers' recordings revealed latencies and amplitudes of the N100, MMN and P300 components recorded at Cz position were as following: mean

Table 1 – Patients' main characteristics at time of inclusion (ERP) and at follow up.

Variables	
n (women %)	43 (44 %)
Age (years) - mean ± SD	59 ± 20
SAPS II – median [IQR]	48 [31 to 59]
Etiologies	
Sepsis – n (%)	13 (30%)
ARDS – n (%)	16 (37 %)
Traumatic brain injury – n (%)	7 (16%)
Stroke – n (%)	7 (16%)
At time of inclusion (ERP recording time)	
RASS – median [IQR]	-5 [-5 to - 4.5]
GCS – median [IQR]	3 [3 to 3]
FOUR score – median [IQR]	4 [2 to 6]
Body temperature - mean (SD) °C	36.2 (1.1)
Drugs used for sedation:	
Midazolam – n (%)	38 (88 %)
Sufentanil – n (%)	35 (81 %)
Propofol – n (%)	7 (16 %)
Atracurium – n (%)	4 (9.3 %)
SOFA – median [IQR]	11[8 to 14]
At Follow up	
Duration of sedation (days) – median [IQR]	9.5 [4 to 14]
Duration of mechanical ventilation (days) – median [IQR]	15 [8 to 29]
Delirium or Delayed awakening post sedation – n (%)	28 (65 %)
Awake at Day-28 – n (%)	30 (70 %)
Length of stay in the ICU (days) – median [IQR]	19.5 [11.25 to 36]

Abbreviations: SAPS-II: New Simplified Acute Physiology Score; ERP: Event Related Potentials; ARDS: Acute Respiratory Distress Syndrome; RASS: Richmond Assessment Sedation Scale; SOFA: Sepsis-related Organ Failure Assessment; ICU: Intensive Care Unit.

latencies (SD) in ms: N100= 140 (71), MMN= 186 (21) and P300= 339 (28); and mean amplitudes (SD) in µV: N100= -2.15 (1.33), MMN= -1.23 (0.65) and P300= 1.77 (1.75).

Group analysis:

Figure 1 features grand average ERPs curves recorded at Cz and Fz scalp positions from the group of 9 non-sedated healthy volunteers in our laboratory (A), the 43 deeply sedated critically ill patients (B), the subgroup of 13 deeply sedated critically patients who did not awake (C) and the subgroup of 30 deeply sedated patients who awoke (D), using the same recording paradigm. The P1/N1 complex as well as the MMN were easily distinguishable in healthy volunteers. While the P1/N1 complex was challenging to be identified in deeply sedated critically ill patients, a significant MMN was observed at around 260 ms latency range (from 250 to 269 ms). Compared to non-sedated healthy controls, MMN was slightly delayed in deeply sedated critically ill patients. As featured in Figure 1, ERPs obtained at the Fz location did not appear to be of added value compared with those recorded at Cz which seemed relatively more robust and reproducible. We therefore limited quantitative analysis of ERP in this study to data obtained in the Cz position.

Individual analysis:

MMN amplitudes computed on the time-window defined at the group level in patients who awoke were significantly larger than in the group of non-awoken patients: mean [SD] = -0.65 [1.4] vs 0.08 [0.17] µV; Wilcoxon p-value = 0.003; Figure 2. MMN amplitudes' values did not correlate either with clinical severity score on the day of recording (day-3 SOFA scores; Spearman correlation coefficient r = 0.24, p-value = 0.11), nor with initial severity (admission SAPS-II scores, r = - 0.023, p-value: 0.89). Furthermore, MMN amplitudes did not correlate with the cumulative dose of midazolam (r = 0.009, p-value: 0.95), sufentanil (r = -0.2, p-value: 0.21) or propofol (r= -0.039, p-value: 0.8).

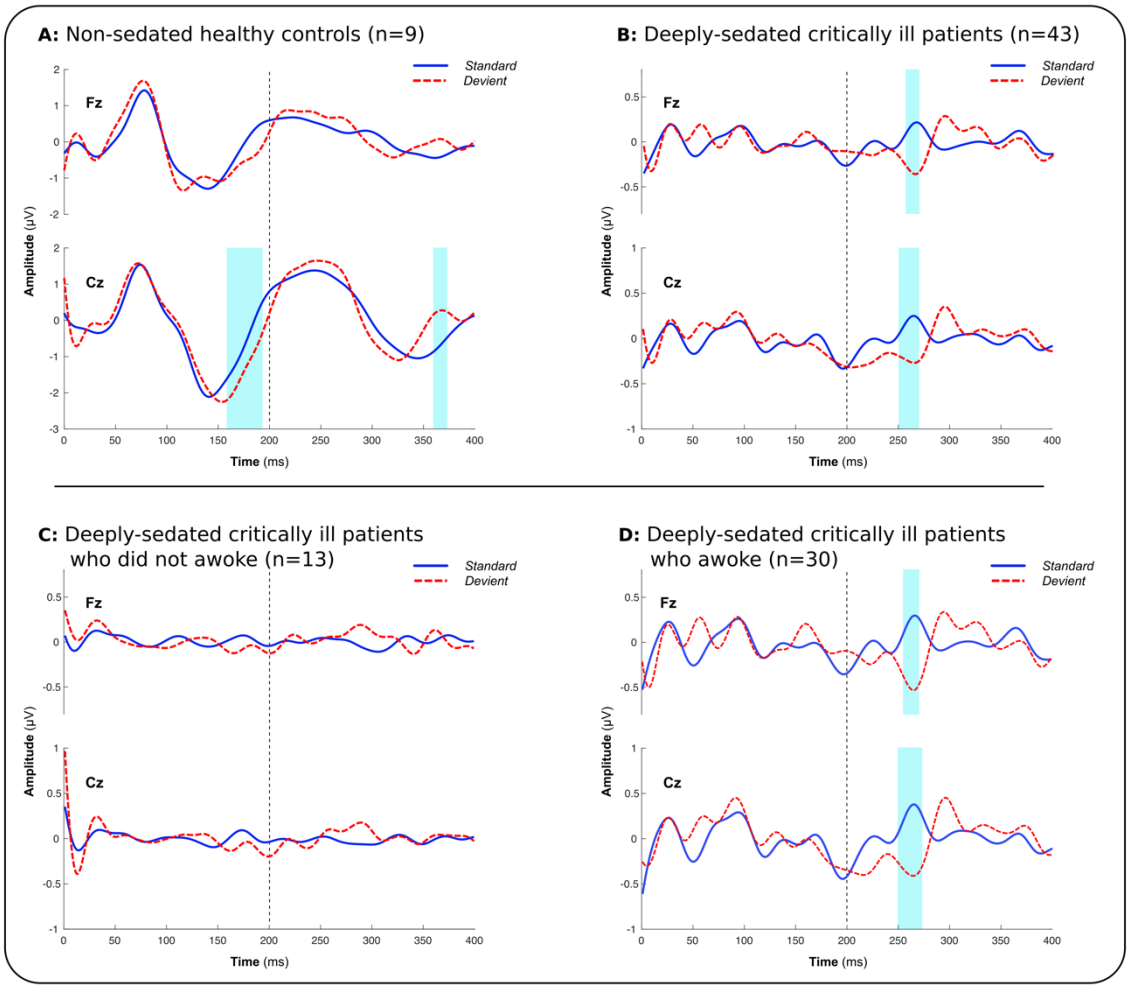

Figure 1: Grand average ERPs curves recorded at Cz and Fz scalp positions from the group of 9 non-sedated healthy volunteers in our laboratory (A), the 43 deeply sedated critically ill patients (B), the subgroup of 13 deeply sedated critically patients who did not awake (C) and the subgroup of 30 deeply sedated patients who awoke (D), using the same recording paradigm. Blue areas show significant differences (paired t-test p-values $<.05$ for a duration $\geq$ 10ms).

However, the MMN amplitudes were significantly lower in the subgroup of patents with RASS -5 compared to those with RASS -4 (Wilcoxon p-value = 0.0017). MMN median amplitudes did not different between patients with or without brain injury (Mann-Whitney test, p-value = 0.55).

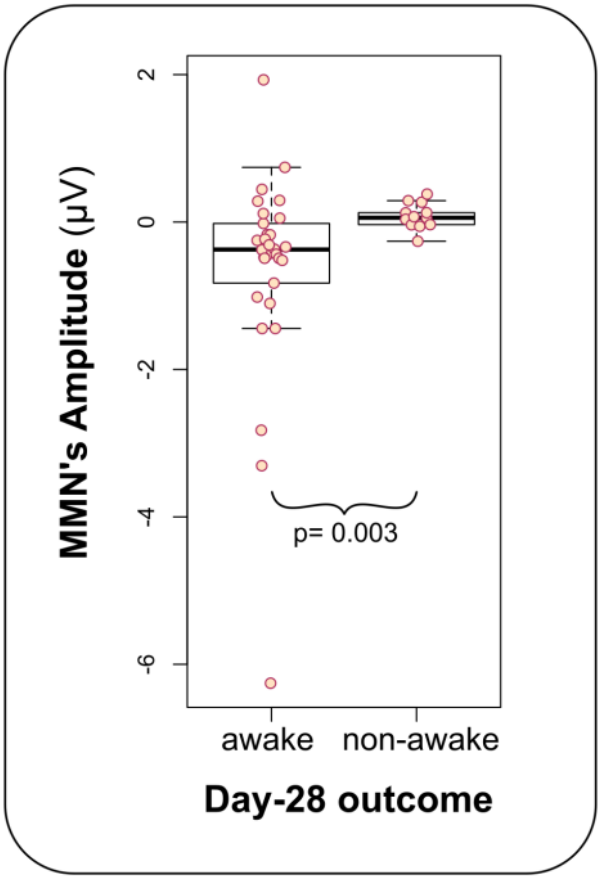

Figure 2. Individual patient mismatch negativity (MMN) amplitudes according to Day 28 awakening outcome (Wilcoxon test).

Discussion

Three main findings emerge from this study. First the auditory MMN can be observed in critically ill patients receiving deep sedation. Secondly, the preservation of MMN seemed associated with awakening after discontinuation of sedation. Third, classical visual interpretation of individual ERPs seemed not reliable in ICU.

Compared to healthy volunteers, MMN observed in deeply-sedated patients was of smaller amplitude and the P300 component was totally suppressed (Figure 1). These results are consistent with previously reported data describing effects of deep sedation on brain signals

[56-59]. Human and primate study of general anesthesia support that sedatives agents such as ketamine (a NMDA-antagonist) and propofol (a GABA-A agonist) reduce neural complexity and disrupt brain network connectivity, leading to dramatic decrease of the EEG signal power and ERPs components [60-63]. Using the local-global ERP paradigm [64-65], that dissociates two hierarchical levels of auditory predictive coding by examining the brain responses to a first order (local) and a second order (global) sequence violations, Uhrig and colleagues demonstrated that both, propofol, and ketamine preserve initial auditory processing, but disturbs short-term and long-term auditory predictive coding mechanisms, in primates [63].

As previously described for non-sedated comatose patients, the observed relationship between "preserved MMN" and "occurrence of awakening" after discontinuation of sedation could be explained by a better preservation of higher cortical function. The current results are complementary to our previous studies on prognostication in deeply sedated critically ill patients which probed the predictive value of brainstem and sub-cortical functions, yielding a systematic approach for ICU-physician [23-26]. Indeed, in these populations, abolition of cough reflex, heterogeneous abolition of brainstem reflexes, increased SSEP intracranial conduction time and absence of EEG reactivity are associated with increased mortality while the presence of MMN seems to be associated with awakening. However, we would like to emphasize that these clinical or neurophysiologic tests can be used for assessing the patients' severity but not to support decision for care limitations or withdrawal. We also acknowledge that a multimodal approach integrating these clinical and neurophysiological markers should be tested in a larger cohort. This is the purpose of a multicenter observational study that we are currently conducting (ClinicalTrials.gov number: NCT02395861).

Though group analysis is valuable in a research setting, for a clinical use, clinicians need reliable individual results. In this study we used a typical evoked potential recorder very similar to common equipment available in any clinical neurophysiological department. Contrarily to research devices, these clinical devices perform an online averaging of trials which precludes any further inter – trials statistics. Our results clearly confirmed that this traditional visual interpretation, although reliable for other evoked potentials analysis (like somatosensory, brainstem auditory or visual evoked potentials), is totally unreliable for the interpretation of ERPs in the very unfavourable signal/noise ratio ICU environment. We think that any further study should enable inter-trail statistics. However, if the research community generally agrees on the need of statistics for ERPs interpretation, several concerns have been raised on the important variability of the methods across studies and there is still no gold-

standard [66-67]. Since we were able to demonstrate the existence of an MMN at the group – level, we could probe individual MMN amplitudes accordingly to the latency observed at the group level. This methodological approach was in some extend validated by the fact that the MMN amplitudes were correlated with the occurrence of awakening after discontinuation of sedation. However, we acknowledge that the overlap of MMN values between patients who will eventually awake compared to those who will not suggest that this method of amplitude estimation on a defined time window should be use with caution in a clinical setting. An alternative solution allowing some inter-trial reliability while using clinical devices that perform online average, could have been to separate the total number of stimulations in a few (e.g. 4 or 5) different averaged series (e.g. of 50 deviants and around 300 standards) to visually assess the reproducibility of ERPs across series during the recording. This suggestion has been included in recent guidelines[68].

Study limitations

Since our aim was to assess the predictive value for awakening of MMN in deeply sedated patients, we have opted to study both primarily brain-injured and non-brain-injured patients. MMN has previously been shown as predictive of awakening in comatose patients independently of the aetiology of the coma [32]. Trying to identify neurophysiologic differences between brain-injured and non-brain-injured patients might have been hampered by a lack of power. Since we did not adjust statistical tests for multiple comparisons, our results should be viewed as exploratory. This limitation is mitigated by the fact that we tested a small number of scientific hypotheses—those pertaining to the association of a preserved MMN and awakening.

One may argue that the prognostic value of MMN could simply reflect the negative effect of an over sedation, as it was correlated with RASS and cumulative dose of midazolam. In addition to sedation, the MMN amplitude might also depend on many other factors, notably the severity of organ failures. Indeed, it tended to be related to the SOFA score. As we previously discussed, it's difficult to disentangle these two possibly combined effects on brain responses [23, 26]. We hypothesized an interaction between these two factors: the same amount of sedative agent could have a stronger effect on brain functions accordingly to the intensity of critical illness, reflecting that way the brain dysfunction. However, only investigating a larger cohort would enable to address the respective influence of critical illness and sedation but also to identify other factors (i.e. type of sedative agents, duration of sedation etc.).

Conclusion

This pilot study suggests that the preservation of MMN is predictive of awakening in deeply sedated critically ill patients, primarily brain-injured or not. However, the detection of MMN cannot be based on visual analysis. We acknowledge that our result needs to be confirmed on a larger cohort and with robust individual inter-trial statistics. Investigating with a multimodal approach on a larger cohort is warranted for confirming these results, to identify new determinants of MMN and to confirm its prognosis value against other neurological and neurophysiologic responses.

Details of authors contributions

EA, BR, RP, NH, FL, FF, JDS, LN, JM and TS contributed to the conception and design of the study. EA, BR, SK, JA, GM, FF, JDS and NH performed data acquisition. EA, BR, RP, SK, JA, GM, NH, FC, DA, FL, JM, LN and TS contributed to interpretation and analysis of the data; drafted the manuscript; critically revised the manuscript; gave final approval; agreed to be accountable for all aspects of the work.

Declaration of interests

None of the authors have any conflict of interest to be disclosed.

Funding

This work was supported by the Assistance Public–Hôpitaux de Paris (AP–HP; BR) the Amicale des Anciens Internes des Hôpitaux de Paris and the Syndicats des Chefs de Cliniques et Assistants des Hôpitaux de Paris (AAIHP-SCCAHP; BR) & the Philippe Foundation (BR).

References

1 Lee CM, Mehta S. Early sedation use in critically ill mechanically ventilated patients: when less is really more. *Crit Care* 2014; **18**: 600

2 Ranzani OT, Simpson ES, Augusto TB, Cappi SB, Noritomi DT. Evaluation of a minimal sedation protocol using ICU sedative consumption as a monitoring tool: a quality improvement multicenter project. *Crit Care* 2014; **18**: 580

3 Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015; **350**: h2538

4 Tanaka LM, Azevedo LC, Park M, et al. Early sedation and clinical outcomes of mechanically ventilated patients: a prospective multicenter cohort study. *Crit Care* 2014; **18**: R156

5 Constantin JM, Momon A, Mantz J, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. *Anaesth Crit Care Pain Med* 2016; **35**: 7-15

6 Mantz J, Josserand J, Hamada S. Dexmedetomidine: new insights. *Eur J Anaesthesiol* 2011; **28**: 3-6

7 Pandharipande PP, Sanders RD, Girard TD, et al. Effect of dexmedetomidine versus lorazepam on outcome in patients with sepsis: an a priori-designed analysis of the MENDS randomized controlled trial. *Crit Care* 2010; **14**: R38

8 Balzer F, Weiss B, Kumpf O, et al. Early deep sedation is associated with decreased in-hospital and two-year follow-up survival. *Crit Care* 2015; **19**: 197

9 Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med* 2013; **41**: 263-306

10 Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; **286**: 2703-10

11 Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; **29**: 1370-9

12 Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA* 2004; **291**: 1753-62

13 Jiang SY, Zhao YY, Zhao XG. Correlation of early over-sedation with clinical outcomes in mechanically ventilated patients: further studies are needed. *Crit Care* 2014; **18**: 597

14 Shehabi Y, Bellomo R, Mehta S, Riker R, Takala J. Intensive care sedation: the past, present and the future. *Crit Care* 2013; **17**: 322

15 Shehabi Y, Chan L, Kadiman S, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. *Intensive Care Med* 2013; **39**: 910-8

16 Ordas-Bandera CM, Sanchez-Marcos C, Janeiro-Lumbreras D, et al. [Neurological examination in patients undergoing sedation with propofol: a descriptive study]. *Rev Neurol* 2014; **58**: 536-40

17 Woien H, Balsliemke S, Stubhaug A. The incidence of delirium in Norwegian intensive care units; deep sedation makes assessment difficult. *Acta Anaesthesiol Scand* 2013; **57**: 294-302

18 Amantini A, Grippo A, Fossi S, et al. Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. *Clin Neurophysiol* 2005; **116**: 229-35

19 Fossi S, Amantini A, Grippo A, et al. Continuous EEG-SEP monitoring of severely brain injured patients in NICU: methods and feasibility. *Neurophysiol Clin* 2006; **36**: 195-205

20 Haupt WF, Hojer C, Pawlik G. Prognostic value of evoked potentials and clinical grading in primary subarachnoid haemorrhage. *Acta Neurochir (Wien)* 1995; **137**: 146-50, discussion 50

21 Logi F, Fischer C, Murri L, Mauguiere F. The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. *Clin Neurophysiol* 2003; **114**: 1615-27

22 Zhang Y, Su YY, Haupt WF, et al. Application of electrophysiologic techniques in poor outcome prediction among patients with severe focal and diffuse ischemic brain injury. *J Clin Neurophysiol* 2011; **28**: 497-503

23 Rohaut B, Porcher R, Hissem T, et al. Brainstem response patterns in deeply-sedated critically-ill patients predict 28-day mortality. *PLoS One* 2017; **12**: e0176012

24 Sharshar T, Porcher R, Siami S, et al. Brainstem responses can predict death and delirium in sedated patients in intensive care unit. *Crit Care Med* 2011; **39**: 1960-7

25 Azabou E, Magalhaes E, Braconnier A, et al. Early Standard Electroencephalogram Abnormalities Predict Mortality in Septic Intensive Care Unit Patients. *PLoS One* 2015; **10**: e0139969

26 Azabou E, Rohaut B, Heming N, et al. Early impairment of intracranial conduction time predicts mortality in deeply sedated critically ill patients: a prospective observational pilot study. *Ann Intensive Care* 2017; **7**: 63

27 Fischer C, Luaute J, Nemoz C, Morlet D, Kirkorian G, Mauguiere F. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. *Crit Care Med* 2006; **34**: 1520-4

28 Fischer C, Morlet D, Bouchet P, Luaute J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin Neurophysiol* 1999; **110**: 1601-10

29 Naccache L, Puybasset L, Gaillard R, Serve E, Willer JC. Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure. *Clin Neurophysiol* 2005; **116**: 988-9

30 Naatanen R. The mismatch negativity: a powerful tool for cognitive neuroscience. *Ear Hear* 1995; **16**: 6-18

31 De Giorgio CM, Rabinowicz AL, Gott PS. Predictive value of P300 event-related potentials compared with EEG and somatosensory evoked potentials in non-traumatic coma. *Acta Neurol Scand* 1993; **87**: 423-7

32 Fischer C, Luaute J, Adeleine P, Morlet D. Predictive value of sensory and cognitive evoked potentials for awakening from coma. *Neurology* 2004; **63**: 669-73

33 Grapperon J, Vidal F, Bruschera D, et al. [Auditive and somato-sensory event-related potentials in comas: prognostic value for awakening, social and professional reinstatement]. *Ann Fr Anesth Reanim* 2004; **23**: 102-8

34 Guerit JM. [Prognostic contribution for potentials evoked in unit of intensive care]. *Ann Fr Anesth Reanim* 2004; **23**: 99-101

35 Guerit JM, Amantini A, Amodio P, et al. Consensus on the use of neurophysiological tests in the intensive care unit (ICU): electroencephalogram (EEG), evoked potentials (EP), and electroneuromyography (ENMG). *Neurophysiol Clin* 2009; **39**: 71-83

36 Guerit JM, Verougstraete D, de Tourtchaninoff M, Debatisse D, Witdoeckt C. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships, prognostic value, and origin of components. *Clin Neurophysiol* 1999; **110**: 1260-9

37 Kane NM, Butler SR, Simpson T. Coma outcome prediction using event-related potentials: P(3) and mismatch negativity. *Audiol Neurootol* 2000; **5**: 186-91

38 Kane NM, Curry SH, Butler SR, Cummins BH. Electrophysiological indicator of awakening from coma. *Lancet* 1993; **341**: 688

39 Kane NM, Curry SH, Rowlands CA, et al. Event-related potentials--neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Med* 1996; **22**: 39-46

40 Lew HL, Dikmen S, Slimp J, et al. Use of somatosensory-evoked potentials and cognitive event-related potentials in predicting outcomes of patients with severe traumatic brain injury. *Am J Phys Med Rehabil* 2003; **82**: 53-61; quiz 2-4, 80

41 Heinke W, Kenntner R, Gunter TC, Sammler D, Olthoff D, Koelsch S. Sequential effects of increasing propofol sedation on frontal and temporal cortices as indexed by auditory event-related potentials. *Anesthesiology* 2004; **100**: 617-25

42 Koelsch S, Heinke W, Sammler D, Olthoff D. Auditory processing during deep propofol sedation and recovery from unconsciousness. *Clin Neurophysiol* 2006; **117**: 1746-59

43 Mainardi LT, Kupila J, Nieminen K, et al. Single sweep analysis of event related auditory potentials for the monitoring of sedation in cardiac surgery patients. *Comput Methods Programs Biomed* 2000; **63**: 219-27

44 Pandin PC. Can electrophysiological assessments of brain function be useful to the intensive care physician in daily clinical practice? *Crit Care* 2004; **8**: 437-9

45 Ypparila H, Nunes S, Korhonen I, Partanen J, Ruokonen E. The effect of interruption to propofol sedation on auditory event-related potentials and electroencephalogram in intensive care patients. *Crit Care* 2004; **8**: R483-90

46 von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014; **12**: 1495-9

47 Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**: 1338-44

48 Bouwes A, Doesborg PG, Laman DM, et al. Hypothermia after CPR prolongs conduction times of somatosensory evoked potentials. *Neurocrit Care* 2013; **19**: 25-30

49 Guerit JM, Fischer C, Facco E, et al. Standards of clinical practice of EEG and EPs in comatose and other unresponsive states. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl* 1999; **52**: 117-31

50 Lang M, Welte M, Syben R, Hansen D. Effects of hypothermia on median nerve somatosensory evoked potentials during spontaneous circulation. *J Neurosurg Anesthesiol* 2002; **14**: 141-5

51 Zanatta P, Bosco E, Comin A, et al. Effect of mild hypothermic cardiopulmonary bypass on the amplitude of somatosensory-evoked potentials. *J Neurosurg Anesthesiol* 2014; **26**: 161-6

52 Le Gall JR, Neumann A, Hemery F, et al. Mortality prediction using SAPS II: an update for French intensive care units. *Crit Care* 2005; **9**: R645-52

53 Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; **22**: 707-10

54 Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: The FOUR score. *Ann Neurol* 2005; **58**: 585-93

55 Duncan CC, Barry RJ, Connolly JF, et al. Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clin Neurophysiol* 2009; **120**: 1883-908

56 Akeju O, Song AH, Hamilos AE, et al. Electroencephalogram signatures of ketamine anesthesia-induced unconsciousness. *Clin Neurophysiol* 2016; **127**: 2414-22

57 Hagihira S. Brain Mechanisms during Course of Anesthesia: What We Know from EEG Changes during Induction and Recovery. *Front Syst Neurosci* 2017; **11**: 39

58 Murphy M, Bruno MA, Riedner BA, et al. Propofol anesthesia and sleep: a high-density EEG study. *Sleep* 2011; **34**: 283-91A

59 Wang J, Noh GJ, Choi BM, et al. Suppressed neural complexity during ketamine- and propofol-induced unconsciousness. *Neurosci Lett* 2017; **653**: 320-5

60 Boly M, Moran R, Murphy M, et al. Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. *J Neurosci* 2012; **32**: 7082-90

61 Kim PJ, Kim HG, Noh GJ, Koo YS, Shin TJ. Disruption of frontal-parietal connectivity during conscious sedation by propofol administration. *Neuroreport* 2017

62 Lee H, Noh GJ, Joo P, et al. Diversity of functional connectivity patterns is reduced in propofol-induced unconsciousness. *Hum Brain Mapp* 2017

63 Uhrig L, Janssen D, Dehaene S, Jarraya B. Cerebral responses to local and global auditory novelty under general anesthesia. *Neuroimage* 2016; **141**: 326-40

64 Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L. Neural signature of the conscious processing of auditory regularities. *Proc Natl Acad Sci U S A* 2009; **106**: 1672-7

65 Raimondo F, Rohaut B, Demertzi A, et al. Brain-heart interactions reveal consciousness in non-communicating patients. *Ann Neurol* 2017

66 Naccache L, Sitt J, King JR, et al. Reply: Replicability and impact of statistics in the detection of neural responses of consciousness. *Brain* 2016; **139**: e31

67 Gabriel D, Muzard E, Henriques J, et al. Replicability and impact of statistics in the detection of neural responses of consciousness. *Brain* 2016; **139**: e30

68 Andre-Obadia N, Zyss J, Gavaret M, et al. Recommendations for the use of electroencephalography and evoked potentials in comatose patients. *Neurophysiol Clin* 2018