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Authors: Tsetsou S, Novy J, Oddo M, Rossetti AO

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EEG reactivity to pain in comatose patients: importance of the stimulus type

Spyridoula Tsetsou (1), Jan Novy (1), Mauro Oddo (2), Andrea O. Rossetti (1)

Departments of Clinical Neurosciences (1), and Intensive Care Medicine (2),
University Hospital and Faculty of Biology and Medicine, Lausanne, Switzerland

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Address correspondence to:

Dr Andrea O. Rossetti

Service de Neurologie

CHUV-BH07

CH-1011 Lausanne, Switzerland

Phone: +41 21 314 1220

Fax: +41 21 314 1290

andrea.rossetti@chuv.ch

Abstract

Introduction: Electroencephalogram (EEG) background reactivity is a potentially interesting outcome predictor in comatose patients, especially after cardiac arrest, but recent studies report only fair interrater reliability. Furthermore, there are no definite guidelines for its testing. We therefore investigated the EEG effect of standardized noxious stimuli in comatose patients not reactive to auditory stimuli.

Methods: In this prospective study we applied a protocol using three different painful stimuli (bilateral nipple pinching, pinprick at the nose base, finger-nail compression on each side), grouped in three distinct clusters with an alternated sequence, during EEG recordings in comatose patients. We only analysed recordings showing any reactivity to pain. Fisher and χ^2 tests were used as needed to assess contingency tables.

Results: Of 42 studies, we analyzed 26 EEGs recorded in 17 patients (4 women, 24%); 12 did not show any background reactivity, 2 presented SIRPIDs, and 2 had massive artifacts. Nipple pinching more frequently induced a change in EEG background activity ($p < 0.001$), with a sensitivity of 97.4% for reactivity. Neither the order of the stimuli in the cluster ($p=0.723$), nor the cluster order ($p = 0.901$) influenced the results.

Conclusion: In this pilot study, bilateral, synchronous nipple pinching seems to be the most efficient method to test nociceptive EEG reactivity in comatose patients. This approach may enhance interrater reliability, but deserves confirmation in larger cohorts.

Introduction

Electroencephalogram (EEG) is broadly used in intensive care units (ICU) both as a diagnostic and as a prognostic tool in comatose patients[1-3]. EEG background reactivity represents an interesting outcome predictor, especially in survivors after cardiac arrest (CA), but also in other diseases in which the clinical examination is limited by anaesthetics drugs or therapeutic hypothermia [4-10]. Reactivity is mostly defined as a reproducible change in cerebral EEG activity (amplitude or frequency), including attenuation [5, 6], but to the best of our knowledge there are no formal guidelines for its testing [11]. Furthermore, therapeutic hypothermia and general anaesthesia can cause EEG slowing and amplitude attenuation[12, 13], rendering the visual analysis of EEG background reactivity more difficult.

EEG stimulations in comatose patients consist of visual (eye opening under light), auditory (clapping, loud name's calling) and nociception; while it is assumed that the first stimulus will be more informative, pain is generally viewed as the most robust. Furthermore, pain stimuli are routinely included in the physical examination of patients in coma[14, 15]; even if these do not show a visual behavioural response to external stimuli, a cortical reaction to noxious stimuli can be reflected by a change in EEG background activity.

This study was designed in order to explore the most efficient method to test EEG reactivity, taking into consideration the intensity of noxious stimuli as well as the timing of application.

Methods

Patients

We prospectively collected comatose patients treated in Intensive Care Unit (ICU) of our center (Centre Hospitalier Universitaire Vaudois CHUV) between 01.01.2015 to 30.04.2015, who needed an EEG recording to rule out seizures or as part of the routine assessment after CA. Most patients suffered from CA; this study was approved by the Ethics commission of our hospital. During EEG recording, all patients were in coma, defined as impairment of arousal and unresponsiveness with eyes closed, without spontaneous eye opening, response to voice, localization to painful stimuli, or verbal output[16].

EEG recordings

Video-EEGs were performed with 21 or 23 electrodes according to the international 10–20 system, for 20–30 min, or longer if necessary (Viasys Neurocare, Madison WI). In post-anoxic patients, as previously described[8, 10], the hypothermic EEG was performed at least 6 h after CA, at a temperature of 33–34°C (in all patients) and the normothermic EEG was performed after patients had a temperature of at least 35°C. When auditory stimulation was found not to be sufficient to elicit obvious reactivity for the technician, the study protocol was applied if a study physician was available. EEG background reactivity was tested on site by a certified technician together with a study physician using three noxious stimuli: bilateral, synchronous nipple pinching, pinprick at the nose base with a sharp wooden stick, and sequential finger-nail compression on each side. Stimulations were applied in fixed sequences grouped into three different clusters, which were at least sixty seconds apart from each other (i.e.: patients had 9 stimulations) (**Figure 1a**). No other stimuli or clinical examination were applied in the minutes preceding or during this protocol.

Definitions

Recordings were interpreted by 3 board-certified authors (ST, JN, AOR), and discrepancies resolved with discussion. We only considered EEGs showing at least one nociceptive reactivity, and excluded those with SIRPIDs (Stimulus-Induced Rhythmic, Periodic or Ictal Discharges) only, or artefacts rendering reactivity judgment difficult. EEG background reactivity was defined as any change (not necessary reproducible) in amplitude or frequency after a noxious stimulus, during visual inspection, recognizable A) without necessity to modify reading parameters (standard: 30 mm/sec, 10μV/mm, longitudinal bipolar montage) (**Figure 1b**), or B) only after reading parameters modifications (such as sensitivity and montage) (**Figure 1c**). Absence of any change in EEG background even after parameters modifications was considered as a non-reactive EEG (**Figure 1d**). For finger-nail compression, the best result (right or left side) was considered.

Statistics

Two-sided Fischer exact, or χ^2 tests were used as needed. Significance was set at $p < 0.05$. Calculations were performed with a Stata software, version 12 (College Station,

TX).

Results

During the study period, a total of 146 EEG were recorded in the ICU, and 42 EEGs were prospectively collected using this stimulation protocol; 16 had to be excluded: 12 did not show any background reactivity, 2 presented SIRPIDs, and 2 due to technical reasons (e.g., artefacts precluding their analysis as per protocol) (details in **Figure 2**). During one EEG recording noxious stimuli were applied in 2 (not in 3) sequences, but we did not exclude it.

The included 26 EEG recordings corresponded to 17 patients (4 women, 24%); the majority of them (n=10, 58%) suffered from CA, whereas 2 (12%) had subarachnoid or intraparenchymatous haemorrhage, 3 (18%) sepsis, 1 (6%) status epilepticus and 1 (6%) severe head trauma. Nine (35%) EEGs were recorded without the influence of any anaesthetic drug, and 5 (19%) were recorded under hypothermia (T°33-34°C).

The median duration between the first and second sequence of reactivity testing was 7.5 minutes (range: 1-29 minutes), whereas between the second and the third it was 1 minute (range: 1-20 minutes).

Table 1 illustrates EEG background reactivity results. Of the 3 different stimuli, bilateral nipple pinching most often led to a change in EEG background during visual inspection without changing reading parameters ($p < 0.001$). Adding the recordings in which reactivity was detected after reading parameter modification, 75/77 were reactive on nipple pinching (sensitivity of 97.4%); in other words, only 2.6% were only reactive with other stimulus types. Analysis according to the order of stimuli ($p = 0.723$, **Table 2a**) and of sequences ($p = 0.901$, **Table 2b**) did not show any significant differences. The use of hypothermia ($p=0.829$) and general anaesthetics ($p=0.284$), again, did not influence the interpretation of EEG reactivity. No obvious difference was observed between stimulations performed by the main investigator (ST, 20 recordings) and 3 other physicians (2 recordings each).

Discussion

This study, which to the best of our knowledge is the first to attempt providing an evidence for testing EEG background reactivity in comatose patients, suggests that nipple pinching seems the most accurate method, independently of the order of stimuli application.

Reactivity has been used relatively widely as a prognostic tool in comatose patients [4-10] and recent studies show divergent interrater agreements[17, 18]; it is crucial to test it in a reproducible manner to minimize false negative interpretations, which may have potentially devastating consequences. Nipples are rich in sensory receptors innervated by lateral and anterior cutaneous branches of the 3rd, 4th, and 5th intercostal nerves[19]; simultaneous bilateral stimulation is a highly intense stimulus activating both cerebral hemispheres, which can at least in part explain our results. Pinching of the nipples does not cause any permanent adverse event in our experience, as we have been performing this type of stimulation routinely on comatose subjects since more than 10 years (more than 2000 patients). The disadvantages of finger-nail compression (a stimulus widely applied in ICU during physical examination) are that it hardly can be performed simultaneously on both sides by the same examiner and, even if nail-fingers also are rich sensory areas[20], pain perception can be probably altered by peripheral vasoconstriction, hypothermia, neuropathy or cutaneous disorders. The nose base is also rich in sensory receptors, but the pinprick cannot be performed on both sides simultaneously, and in our experience may bleed following pinprick. Finally, pressing the examiner's knuckles into the patient sternum is an axial painful stimulus, but in our view not recommended due to possible bone distraction in case of pre-existing sternal or costal fractures or induction of hematomas, especially in resuscitated patients, as well as movement artefact induction.

Our study has limitations. First, the cohort is relatively small, as prospective recruitment was limited to over 4 months and analysis is based on 26 records (17 patients). Furthermore, as physicians performing the visual EEG interpretation also applied stimulations, analysis was not blinded; the study was not formally designed in this sense given the limited size of our EEG unit (2 senior an 2 junior physicians). The first author (ST) rescored all traces off-line several weeks to months after the recordings, and then compared the results with the EEG report written by 2 EEG fellows supervised by AOR or JN, without any discrepancy. This may be due, at least

in part, to the fact that she was trained 2 years before as an EEG fellow in our hospital, and may admittedly represent a limitation for generalizability. This study was restricted to painful stimuli, and was not designed to assess the relative sensitivity of visual or auditory stimulations; however, nociception is generally felt to be more sensitive that the other two modalities. While there were various aetiologies in our patients, most had postanoxic coma, and some were recorded more than once. We cannot exclude that the repetitive stimulations biased the results in some way. However, this was the only approach we could design in order to have the patients as their own controls for different stimulus type, and we addressed this issue by analysing the role of the stimulus order. Furthermore, we waited at least 20 sec. (up to several minutes) between stimuli: this approach seems to be corroborated by the lack of influence of stimulus order on the results. The analysis was only visual and not compared with quantitative approaches, which have recently shown promising results[17]. Finally, applying a stimulus in an intimate area (nipples) might raise ethical problems, at least in part depending on cultural differences. However, over the last 10 years we never experienced any issue in this context; we believe that if a specific stimulus can change for the best the interpretation of a medical prognostic tool, it should be performed.

Bilateral nipple pinching seems to be the most efficient method to test EEG reactivity background in comatose patients not reactive to auditory stimuli. While larger, ideally blinded studies are needed in order to validate these results, we believe that this approach may allow improving interrater reliability among EEG readers and thus have a positive impact on the management of comatose patients.

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Figure legends:

1A. Protocol of painful stimulations with 3 sequences of 3 stimuli each; the order of the stimuli changes within each sequence. **B.** Reactive EEG without reading parameters modifications (standard: 30 mm/sec, 10µV/mm, longitudinal bipolar montage). Douleur poitrine = chest pain (nipples pinching). **C.** Reactive EEG with reading parameters modifications (30mm/sec, 7µV/mm, longitudinal bipolar montage). Douleur doigts = pain on fingers. **D.** Non-reactive EEG. Douleur nez = Nose pain (pinprick).

2. Flow diagram of the study.

Tables

Table 1:
Effect of the three stimuli on EEG background reactivity (any reactivity in any stimulus type)

	Nipples	Nose	Fingers	Fisher
EEG: Reactive without modification of reading parameters	60	33	35	
EEG: Reactive with modification of reading parameters	15	22	24	
EEG: Non reactive	2	22	19	
p-value				<0.001

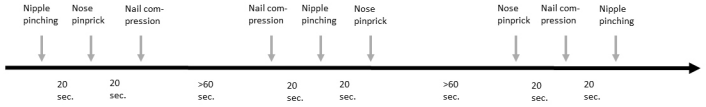
Table 2a:
Effect of the order of stimuli in the sequences on EEG background reactivity (any reactivity in the corresponding order of stimulus)

	1st stimulus of each sequence	2nd stimulus of each sequence	3rd stimulus of each sequence	χ^2
EEG: Reactive without modification of reading parameters	44	40	44	
EEG: Reactive with modification of reading parameters	17	22	22	
EEG: Non reactive	16	15	11	
p-value				0.723

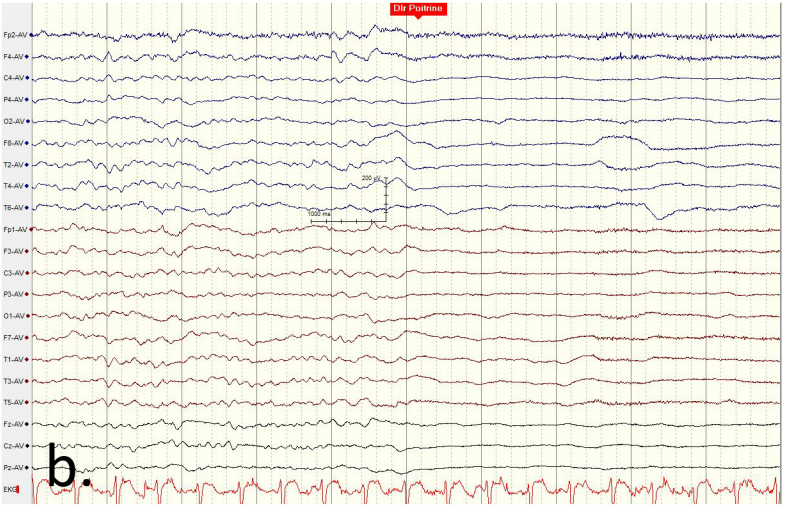
Table 2b:
Effect of the order of sequence on EEG background reactivity (any reactivity in the corresponding sequence)

	1st sequence	2nd sequence	3rd sequence	Chi squared
EEG: Reactive without modification of reading parameters	41	44	43	
EEG: Reactive with modification of reading parameters	20	21	21	
EEG: Non reactive	17	13	12	
p-value				0.901

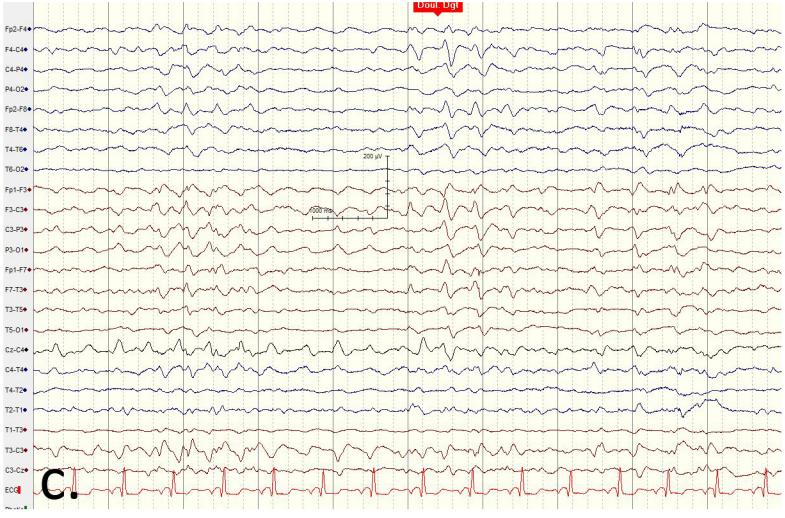
Figure 1



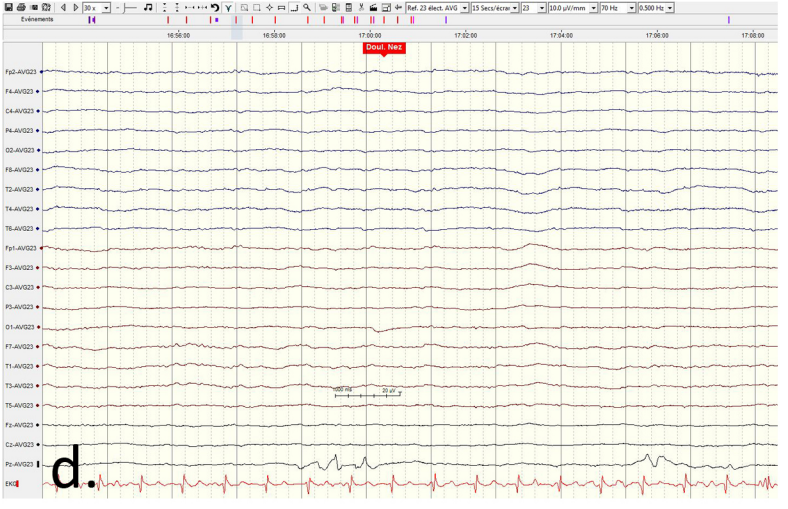
a.



b.

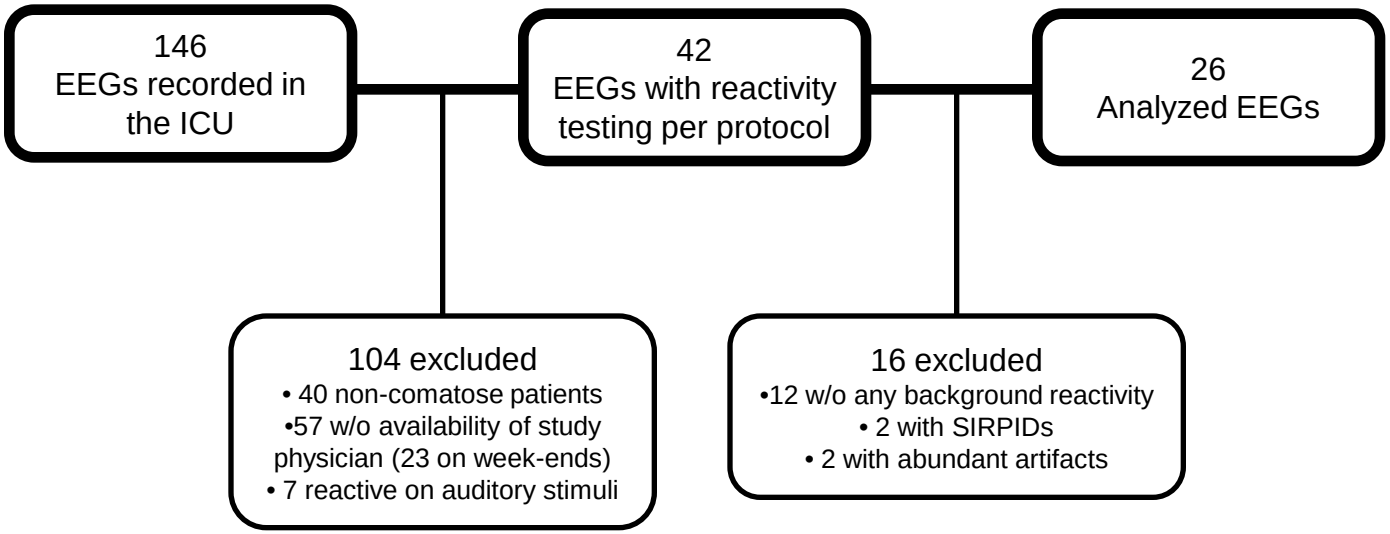


c.



d.

Figure 2


146
EEGs recorded in the ICU
42
EEGs with reactivity testing per protocol
26
Analyzed EEGs
104 excluded
• 40 non-comatose patients
•57 w/o availability of study physician (23 on week-ends)
• 7 reactive on auditory stimuli
16 excluded
•12 w/o any background reactivity
• 2 with SIRPIDs
• 2 with abundant artifacts