Prognostic and diagnostic value of EEG signal coupling measures in coma

Frederic Zubler [a,*], Christa Koenig [a], Andreas Steimer [a], Stephan M. Jakob [b], Kaspar A. Schindler [a], Heidemarie Gast [a]

[a] Department of Neurology, Bern University Hospital, University of Bern, Bern, Switzerland
[b] Department of Intensive Care Medicine, Bern University Hospital, University of Bern, Bern, Switzerland

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HIGHLIGHTS

- Linear and non-linear quantitative EEG analyses help assessing outcome in coma.
- High level of synchrony between hemispheres was associated with mortality.
- High level synchrony within hemispheres was associated with survival.

ABSTRACT

Objective: Our aim was to assess the diagnostic and predictive value of several quantitative EEG (qEEG) analysis methods in comatose patients.
Methods: In 79 patients, coupling between EEG signals on the left–right (inter-hemispheric) axis and on the anterior–posterior (intra-hemispheric) axis was measured with four synchronization measures: relative delta power asymmetry, cross-correlation, symbolic mutual information and transfer entropy directionality. Results were compared with etiology of coma and clinical outcome. Using cross-validation, the predictive value of measure combinations was assessed with a Bayes classifier with mixture of Gaussians.
Results: Five of eight measures showed a statistically significant difference between patients grouped according to outcome; one measure revealed differences in patients grouped according to the etiology. Interestingly, a high level of synchrony between the left and right hemisphere was associated with mortality on intensive care unit, whereas higher synchrony between anterior and posterior brain regions was associated with survival. The combination with the best predictive value reached an area-under the curve of 0.875 (for patients with post anoxic encephalopathy: 0.946).
Conclusions: EEG synchronization measures can contribute to clinical assessment, and provide new approaches for understanding the pathophysiology of coma.
Significance: Prognostication in coma remains a challenging task. qEEG could improve current multi-modal approaches.

1. Introduction

Assessment of comatose patients is a notoriously difficult, but essential task. After initial stabilisation of vital functions, identifying the etiology of coma is necessary so that an appropriate therapy can be initiated (Edlow et al., 2014). In absence of rapid recovery of consciousness, it is of highest importance to evaluate the prognosis of comatose patients. Identifying those patients with no hope of recovery would allow considering withdrawal of support, both for ethical and economical reasons (Young, 2009; Howard et al., 2011).

Currently, no single method is capable of adequate etiological diagnosis and prognostication. Therefore, multimodal algorithms combining clinical examination, electroencephalography (EEG), evoked potential, and biomarkers have been proposed, aiming at improving prognostic indicators in coma (Bassetti et al., 1996; Oddo and Rossetti, 2014; Rossetti et al., 2010; Wijdicks et al., 2006). The majority of these studies have focused on patients with hypoxic–ischemic brain injury after cardiac arrest; the reasons being high incidence and still a very high proportion of non-survivors (Go et al., 2013). While therapeutic hypothermia (TH) has concurred to improve the prognosis for these patients, it has also further complicated the prognostication (Crepeau et al.,

* Corresponding author at: Department of Neurology, Bern University Hospital – Inselspital, Freiburgstrasse 4, 3010 Bern, Switzerland. Tel.: +41 31 632 21 11.
E-mail address: frederic.zubler@gmail.com (F. Zubler).

2013; Kamps et al., 2013; Rossetti et al., 2010). Multimodal prediction tools keep improving, even during TH (Oddo and Rossetti, 2014; Tjepkema-Cloostermans et al., 2014). However, the quest for an optimal algorithm continues, and novel complementary approaches are called upon. Quantitative EEG (qEEG) methods are emerging as possible candidates.

In essence, qEEG methods consist of computer-based analysis of EEG signals. Many of these methods are based on spectral decomposition of EEG signals, some of which have been applied successfully to automatic seizure detection (Gotman et al., 1997; van Putten et al., 2005), to detection of arterial spasm after subarachnoid hemorrhage (Foreman and Claassen, 2012), or as a prognostication tool after stroke (van Putten, 2007; van Putten and Tavy, 2004). Other qEEG methods have also been proposed as "surrogate encephalographer", allowing non-specialists to recognize conventional EEG patterns as a neurologist would (Cloostermans et al., 2011). Several qEEG methods have helped to refine the recognition of classical patterns, identifying for instance subtypes of status epilepticus (Rundgren et al., 2010) or burst suppression patterns (Hofmeijer et al., 2014). Finally, several methods such as amplitude-integrated EEG (Rundgren et al., 2010) or the recently proposed cerebral recovery index (Tjepkema-Cloostermans et al., 2013) have been applied to predict outcome of patients after cardiac arrest by identifying global (for the former) or more local (for the latter) features of the EEG signal similar to the ones that a trained electroencephalographer would focus on.

By contrast, we wanted to investigate the utility of qEEG methods for extracting EEG features that are not easily accessible to a human observer. The motivation to do so was to provide the treating physician with additional information about a patient's condition, which could be for instance included into future multimodal prognostic algorithms. Therefore, beside an index based on spectral decomposition, we focused here on another class of qEEG methods, namely signal coupling measures. These measures detect synchronization between EEG signals, and have thus been used so far mainly to define so-called "functional brain networks" (Kramer, 2010; Stam and van Straaten, 2012; van Diessen et al., 2013). Since EEG signals do not always have a dominant frequency, synchronization is not meant in the classical sense of convergence of phase and frequency, but in the more general sense of symmetrical or asymmetrical interdependence between signals (Rulkov et al., 1995; Stam and van Dijk, 2002). Such methods are capable of distinguishing between conscious state, minimally conscious state and vegetative state (King et al., 2013; Sitt et al., 2014). In this retrospective study we show that qEEG coupling measures can contribute to the assessment of comatose patients, and that beside their diagnostic and prognostic value, these methods might contribute to a better understanding of the pathophysiology of coma.

2. Methods

2.1. Patients and study design

This retrospective study was conducted in the 30-bed intensive care unit and the 15-bed intermediate care unit (ICU) of the University Hospital of Bern, in Switzerland. Consecutive comatose patients (aged > 16 years) who had an EEG for medical reasons between January 2008 and January 2012 were included. Coma was defined based on the different elements of the Glasgow Coma Scale (GCS), namely: eye response value = 1, verbal response value $\leqslant$ 2, and motor response value $\leqslant$ 4. Only patients with good quality EEG recordings were included. We excluded patients suffering of brain hemorrhages or traumatic head injury, or with recent history of brain surgery. In case of multiple EEGs, only the first was analyzed. In patients who had been treated with therapeutic hypothermia, EEGs were performed after rewarming under normothermic condition. This study was approved by the cantonal ethics committee of Canton of Berne.

The etiology for coma was categorized into hypoxic/anoxic, and non-hypoxic. In the hypoxic/anoxic group were patients with cardiac arrest, hemorrhagic shock, large ischemic brain lesions or other anoxic conditions (e.g. suffocation). The non-hypoxic group was subdivided into the etiologies infectious, metabolic or drug-related, and epileptic. Concerning the clinical outcome, patients were grouped into alive or deceased at discharge from the ICU. Patients in the group "alive" were heterogeneous and included patients who had fully recovered as well as patients with impaired consciousness. The group of deceased patients consisted of patients for whom the decision to withdraw medical support and life sustaining therapies was made (those patients received palliative treatment) and patients who died instead of treatment. The latter group consisted only of two patients, thus the group of deceased patients was not split. The decision to withdraw life support was made by the treating physicians and the patients' surrogates if available. The most relevant determinants of this decision were a very low probability of survival, a high probability of severely impaired cognitive function. The quantitative EEG analysis was not available at the time of the decision to continue or withdraw treatment.

2.2. Data collection

Information about GCS score and medication (including sedation) at recording time was taken from the EEG report that was signed by the attending neurologist. Additional clinical and demographical data used for this work were collected in the electronic patient documentation system of the Bern University Hospital. For EEG recordings 21 electrodes were used (19 active electrodes placed on the scalp according to the international 10–20 system, one reference electrode, one ground electrode). Each recording was performed for a length of approximately 20 min, of which the first segments of 5 min without obvious artefacts were analyzed. We used a NicoletOne recording system with a C64 amplifier (VIASYS Healthcare, Inc., Madison, WI, U.S.A.). The sample rate was 500 Hz.

2.3. Quantitative EEG analysis

We considered four different bipolar derivations, corresponding to four different brain regions, namely F3–P3 for the left hemisphere, F4–P4 for the right hemisphere, F3–F4 for the anterior region, and P3–P4 for the posterior region (Fig. 1). Four different bivariate quantitative EEG (qEEG) methods were used to compute signal-coupling value between the left and right bipolar derivations, and between the anterior and posterior bipolar derivation. The four qEEG methods applied were (1) relative delta power asymmetry, (2) cross-correlation, (3) symbolic mutual information and (4) symbolic transfer entropy directionality. Each qEEG synchronization measure was repeatedly computed for epochs consisting of non-overlapping time windows of 10 s (=5000 sampling points); the average value over 30 epochs was used in statistical analysis. Signal analysis was done with MATLAB Version R2012a (MathWorks). Except for computation of relative delta power, the EEG signals were digitally band-passed filtered between 0.5 and 20 Hz before quantitative analysis, in order to remove DC shifts and high frequency artefacts.

2.3.1. Relative delta power asymmetry (RDP)

While power spectrum analysis is primarily a univariate measure, it can be used to define bivariate asymmetry indices. The first qEEG measure we used was the asymmetry in relative delta power