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Real-time multi-channel monitoring of burst-suppression using neural network technology during pediatric status epilepticus treatment

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HIGHLIGHTS

- Multichannel real time system that automatically identifies burst-suppression.
- Estimates burst-suppression index using neural network technology.
- Excellent agreement between automated and manual classification of burst-suppression.

ABSTRACT

Objective: To develop a real-time monitoring system that has the potential to guide the titration of anesthetic agents in the treatment of pediatric status epilepticus (SE).
Methods: We analyzed stored multichannel electroencephalographic (EEG) data collected from 12 pediatric patients with generalized SE. EEG recordings were initially segmented in 500 ms time-windows. Features characterizing the power, frequency, and entropy of the signal were extracted from each segment. The segments were annotated as bursts (B), suppressions (S), or artifacts (A) by two electroencephalographers. The EEG features together with the annotations were inputted in a three-layer feed forward neural network (NN). The sensitivity and specificity of NNs with different architectures and training algorithms to classify segments into B, S, or A were estimated.
Results: The maximum sensitivity (95.96% for B, 89.25% for S, and 75% for A) and specificity (89.36 for B, 96.26% for S, and 99.8% for A) was observed for the NN with 10 nodes in the hidden layer. By using this NN, we designed a real-time system that estimates the burst-suppression index (BSI).
Conclusions: Our system provides a reliable real-time estimate of multichannel BSI requiring minimal memory and computation time.
Significance: The system has the potential to assist intensive care unit attendants in the continuous EEG monitoring.

Abbreviations: A, artifact; B, burst; BCH, Boston Children's Hospital; BFGS, Broyden–Fletcher–Goldfarb–Shanno quasi-Newton backpropagation; BR, Bayesian regularization; BS, burst-suppression; BSD, burst-suppression dynamic; BSI, burst-suppression index; BSP, burst-suppression probability; CM, confusion matrix; EDF, European data format; EEG, electroencephalography; FN, false negative; FP, false positive; FPR, false positive rate; ICU, intensive care unit; LM, Levenberg–Marquardt; MSE, mean square error; NN, neural network; NPV, negative predicted value; PatternNet, pattern recognition NN; PPV, positive predicted value; ROC, receiver operating characteristic; RP, Resilient backpropagation; S, suppression; SCG, scaled conjugate gradient; SE, status epilepticus; TN, true negative; TP, true positive; TPR, true positive rate.

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1. Introduction

Status epilepticus (SE) is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (Trinka et al., 2015). Convulsive SE is the most common childhood neurological emergency in developed countries with 18–20 episodes per 100,000 cases per year in children younger than 16 years old (Chin et al., 2004; 2006). Because of its significant morbidity and mortality (Logroscino et al., 2001; Claassen et al., 2002; DeLorenzo et al., 1996), SE requires prompt diagnosis and treatment. After initial first- and second-line therapies, anesthetic agents are sometimes used if the episode fails to come under control.

In the setting of using anesthesia for seizure control, patients are invariably supported by mechanical ventilation and managed on an intensive care unit (ICU). The goal or target now is to induce and maintain a depth of anesthesia that will control and prevent seizures, yet avoid the possibility of overdosing the anesthetic agent, which leads to a cessation of all EEG activity as well as impairing cardiac function to the point that vasopressors are required to support life (Wilkes and Tasker, 2013, 2014; Tasker and Vitali, 2014). The dose of the anesthetic agent is frequently adjusted with the aim of achieving a characteristic EEG pattern, termed burst-suppression (BS), which consist of alternate periods of slow waves of high-amplitude (the bursts, B) and periods of low-amplitude EEG (the suppressions, S) that represent the interaction between neuronal excitatory dynamics and metabolism. The duration of the B and S periods varies with the concentration of the anesthetic agent. Higher concentrations lead to progressively longer duration S periods eventually causing continuous EEG suppression (Vijn and Sneyd, 1998; Young, 2000; Brenner, 2005; Ching et al., 2012a,b). These changes in the relative duration of B and S periods can be quantified by the burst-suppression index (BSI), which is a measure of the percentage of time within an interval spent in the suppressed state (DeGiorgio, 1993). When anesthesia is used in the treatment of SE, the standard approach is to control the suppression intensity of the EEG signal by continuously monitoring the BSI and manually adjust drug dosage. Current treatment protocols of SE typically target a BS pattern of 5–15 s suppressions alternating with 1–5 s bursts or equivalently BSI values of 50–95% (Cottenceau et al., 2008; Riker et al., 2003; Rossetti et al., 2011; Musialowicz et al., 2010; Wilkes and Tasker 2013).

In clinical practice, the identification of BS patterns and the differentiation between B periods is currently performed visually by the ICU nursing staff who estimate the approximate timing between one or more interburst intervals. The BSI is thus most often assessed as a 'guesstimate' rather than using a quantitative reproducible approach. Equally important is the practicality of such an approach. During this process, the ICU staff should continuously watch for subtle changes in the BS pattern interburst interval, and titrate anesthetic agents based on the calculated interval. Since these patients often require therapy for days (Wilkes and Tasker, 2014), it is unrealistic to expect the attendant staff to maintain minute-to-minute control of BS state by manually changing the rate of anesthetic administration in response to changes in the EEG signal. Thus, a closed loop feedback between the monitoring and the treating team members is required.

Many methods of varying complexity have been previously described for the detection of BS patterns (Kaiser, 1990; Thomsen et al., 1991; Arnold et al., 1996; Akrawi et al., 1996; Sherman et al., 1997; Griessbach et al., 1997; Leistritz et al., 1999; Muthuswamy et al., 1999; Bruhn et al., 2000a,b; Särkelä et al., 2002; Löfhede et al., 2007; Yoon et al., 2012; Chemali et al., 2013; Westover et al., 2013; Liang et al., 2014). All these methods have dealt with the EEG as a single channel (usually recorded from central areas) assuming that its activity represents the activity of the entire brain. This is because BS has classically been viewed as a 'global' state with synchronous activity throughout the cortex, a perspective that was derived from previous EEG studies in which periods of B and S have been shown to occur concurrently across the scalp (Clark and Rosner, 1973). However, recent evidence of intracranial electrocortigrams from patients who entered BS indicated that in contrast to previous characterizations, periods of B could be substantially asynchronous across the cortex (Lewis et al., 2013). Furthermore, it was shown that the state of BS itself could occur in a limited cortical region while other areas exhibit ongoing continuous activity.

Here, we describe the development of a multichannel EEG-based system that automatically identifies the BS patterns and estimates the BSI. The system was built using NN technology combining information from the amplitude, the frequency content, and the entropy of the EEG signal. The NN was trained using multichannel EEG data from pediatric patients hospitalized in the ICU and was validated against manual segmentation of the data by two board certified electroencephalographers. Different architectures and training algorithms were tested. The NN showing the best performance in terms of sensitivity and specificity for detecting the BS patterns was used for the design of the on-line system. The on-line system was incorporated into a commercial EEG device (eego™ mylab, ANT Neuro, Netherlands). Our system has the potential to assist ICU attendants with continuous monitoring of the EEG signal by providing reliable automatic estimates of the BSI in the treatment of pediatric SE.

2. Methods

2.1. Patients

We analyzed stored EEG data from 12 pediatric patients (7 males and 5 females) hospitalized in the ICU of Boston Children's Hospital (BCH) with generalized SE. These patients were a representative retrospective sample of BS pattern EEG recordings from all pediatric patients who underwent continuous EEG monitoring in the ICU. Demographic data, primary admission diagnosis, final diagnosis/discharge, the history of epilepsy and/or SE, and the anesthetic agents administered at the time of EEG recording are presented in Table 1. Review of clinical and EEG data was carried out with the approval of the local institutional review board.

2.2. EEG recordings and expert data segmentation

Given the retrospective nature of the study, we did not control the length of the EEG recordings. All EEGs were recorded using 19 silver/silver electrodes, affixed to the scalp according to the international 10–20 system. EEG data were recorded by using the XLTEK clinical EEG equipment (Natus Medical Inc., Canada) with a sampling rate of 200 Hz. The signals were referred to mastoids. Two board certified electroencephalographers independently reviewed the EEG recordings using in–house viewing and annotation software written in Matlab (MathWorks Inc., MA, USA). The software segments the continuous EEG recording into epochs of 500 ms duration, and allows the reviewer to classify each segment as B, S, or A. The review was based on the bipolar recordings of frontal-central electrodes (i.e., F3-C3 and F4-C4), but data from the complete array of recording channels was also available to the reviewer during the marking-up process. Only segments for which there was an agreement between the two electroencephalographers were used in further analysis. If a segment was annotated and classified by both reviewers as B, S, and A, then the segment was further used in the analysis. For the cases that there was not