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Monitoring burst suppression in critically ill patients: Multi-centric evaluation of a novel method

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H I G H L I G H T S

- Fully automatic computational method to detect burst suppression patterns in critical care EEG.
- Insensitivity to EEG artifacts and periodic patterns makes the system suitable for clinical use in real-time patient monitoring.
- Multi-centric evaluation including the EEG of 88 patients showed high sensitivity and specificity.

A B S T R A C T

Objective: To develop a computational method to detect and quantify burst suppression patterns (BSP) in the EEGs of critical care patients. A multi-center validation study was performed to assess the detection performance of the method.
Methods: The fully automatic method scans the EEG for discontinuous patterns and shows detected BSP and quantitative information on a trending display in real-time. The method is designed to work without setting any patient specific parameters and to be insensitive to EEG artifacts and periodic patterns. For validation a total of 3982 h of EEG from 88 patients were analyzed from three centers. Each EEG was annotated by two reviewers to assess the detection performance and the inter-rater agreement.
Results: Average inter-rater agreement between pairs of reviewers was $\kappa = 0.69$. On average 22% of the review segments included BSP. An average sensitivity of 90% and a specificity of 84% were measured on the consensus annotations of two reviewers. More than 95% of the periodic patterns in the EEGs were correctly suppressed.
Conclusion: A fully automatic method to detect burst suppression patterns was assessed in a multi-center study. The method showed high sensitivity and specificity.
Significance: Clinically applicable burst suppression detection method validated in a large multi-center study.

1. Introduction

Burst suppression is an electroencephalogram (EEG) pattern consisting of intermittent periods of very low voltage brain electrical activity ("suppression"), alternating in a quasi-periodic fashion with periods of higher amplitude activity ("bursts"). Burst suppression patterns (BSP) are found in a wide range of pathological and clinically-induced conditions, including anesthetic-induced coma, hypothermia (Pagni and Courjon, 1964; Nakashima et al., 1995) deep (Ching et al., 2012; Westover et al., 2015), or arising spontaneously as a result of anoxic brain injury (Niedermeyer et al., 1999; Rossetti et al., 2012). The definition for burst durations and for suppression amplitudes varies depending on patient age and clinical context, ranging from 0.5 to 30 s for the duration of a burst and

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from 5 to 20 μV for suppression amplitudes (Shellhaas et al., 2011; Zschocke and Hansen, 2011; Hirsch et al., 2013). Although commonly described as a generalized phenomenon, BSP can be asynchronous across the cortex and can occur in limited cortical regions. Local cortical dynamics of BSP were analyzed in Lewis et al. (2013) and are reported in Sperling et al. (1986), Lazar et al. (1999) and Mader et al. (2014).

Manual evaluation of BSP in the EEG is a widely used but impractical approach. Manual evaluation lacks objectivity, and is not feasible for continuous monitoring over multiple hours. Several automatic or semi-automatic detection methods exist in the literature. The recent work of Murphy analyzed burst and suppression segments of pre-term infants using various mathematical features (Murphy et al., 2015). The method was validated using preselected EEG segments and resulted in high agreement compared to three reviewers. A detection method based on the line length feature using the EEG of 10 pre-term infants was presented in Koolen et al. (2014). An automatic classification method for burst and suppression events was validated in (Westover et al., 2013) on 20 critical care EEG recordings that were selected based on clinical EEG reports. The detection algorithm was trained on these 20 EEGs and showed high agreement compared to human annotations. Numerous other methods exist in literature that use various mathematical features to detect BSP (Thomsen et al., 1991; Lipping et al., 1995; Bruhn et al., 2000, 2006; Jaggi et al., 2003; Liang et al., 2014) but include a limited number of patients.

This work will present a fully automated detection method to find burst suppression patterns in multi-channel EEG. The method is insensitive to EEG artifacts and periodic patterns and can be calculated in real-time. We present detection performance results from an evaluation of continuous EEG recordings from 88 adult patients from three intensive care units.

2. Methods

2.1. Automatic detection method

A computational method is presented that automatically detects burst suppression patterns (BSP) in digital multi-channel electroencephalograms (EEGs). The method works fully automatically without the use of training data and without estimation of patient-specific parameters. Data is analyzed in real-time to allow continuous patient monitoring. The goal is to graphically visualize the detection results over large time scales of up to several days in a quantitative EEG interface similar to the approach shown in (Fürbass et al., 2015a). Fig. 1 shows examples of burst suppression and periodic pattern detections of a 20 h EEG recording.

The major steps in the whole detection procedure are outlined in Fig. 2. First, the EEG is segmented into consecutive and non-overlapping detection segments of 15 s. All further processing is based on these detection segments. Scalp EEG artifacts are removed using the PureEEG method (Hartmann et al., 2014). The PureEEG method is based on a neurophysiological model and utilizes an iterative Bayesian estimation scheme to remove artifacts like movement, muscle, line noise, and loose electrode artifacts. Further analysis is based solely on the output of the PureEEG module. All subsequent detection and classification steps therefore assume that the activity measured in the EEG channels are of cerebral origin. The EEG channels are converted to bipolar longitudinal and transversal montages following ACNS recommendations (American Clinical Neurophysiology Society, 2006).

Next, a channel-wise detection of burst suppression events is performed. In each EEG channel x_t the peak-to-peak amplitude is measured by subtracting the minimum from the maximum digital value in non-overlapping chunks of 0.4 s. Only EEG samples of the current detection segment are used. The peak-to-peak time series of channel x_t is smoothed by a moving average filter resulting in $y_t^S = \frac{1}{n}\sum_{i=1}^{n}|x_{t+i}|$. The length of the averaging window n is chosen so that the minimum time for a suppression event is covered. Here, a minimum duration of 1.5 s for suppression events is assumed. The same procedure but with a window length of 0.5 s is repeated resulting in the time series y_t^B. The samples of the time series y_t^S and y_t^B are then used to detect suppression events in the channel. An event may include several chunks of 0.4 s. A chunk is defined as part of a suppression event if either a chunk with double amplitude follows in 1.5 s ($y_{t+1.5}^B/y_t^S > 2$) or if a chunk with double amplitude precedes with 1.5 s distance ($y_{t-1.5}^B/y_t^S > 2$). All remaining chunks in the detection segment are part of a suppression event if their amplitude is below the amplitude of the initially detected suppression chunk. All chunks that are not marked as part of a suppression event at this processing step are part of a burst event if the peak-to-peak amplitude is higher than double amplitude of the surrounding suppression chunks. Fig. 3 shows the processing steps of the channel-wise detection procedure.

The channel-wise detection information is then used as input to a hierarchical cluster algorithm to find spatial groups of the same activity type. The $k \times k$ distance matrix M_S includes the time distance between the middle points of k suppression chunks. The variable k is the total number of suppression chunks in the detection segment. Chunks that were neither marked as suppression nor burst do not contribute to the distance matrix and are also not considered further. The distance matrix is then used to create a hierarchical cluster tree. The Euclidean distance between two chunk positions $a = M_S^{i,j}$ and $b = M_S^{i,j}$ defined as $d(a,b) = \sqrt{\sum_i (a_i - b_j)^2}$ is used to measure the distance between two chunks. The unweighted average distance algorithm using the cluster linkage criteria $\frac{1}{|A||B|}\sum_{a\in A}\sum_{b\in B} d(a,b)$ defines the dissimilarity between two groups of suppression chunks A and B. The same procedure is repeated for chunks of burst activity. The normalized cluster tree is cut with a constant cutoff factor to create burst and suppression clusters. By solely utilizing the middle point as distance metric an influence of the spatial location of the suppression or burst activity is avoided. This also means that channels used to build up a cluster do not have to be spatially adjacent (e.g. cluster C_{SUPP}^4 in Fig. 2). In a next step the best fitting cluster for each time point is determined. Clusters are sorted descending according to their duration. Starting with the longest cluster and by elaborating each cluster in the sorted list, the first cluster that covers a time point is accepted. Subsequent overlapping clusters are reduced in time to be non-overlapping with accepted clusters. Clusters with durations less than the minimum requirement for burst or suppression will be discarded. This approach will discharge parts of the suppression or burst chunks that are not time aligned with the majority of the other chunks in the cluster. This also means that there is no need for a single channel to fully cover the time span of the cluster. All channels are treated equally, the method do not exploit the spatial location of the involved channels. The resulting clusters represent burst or suppression detections that span several EEG channels and extend over a certain time period. In this method clusters need to span at least 40% of the cortical area covered by electrodes to be further used in the detection procedure. The minimum coverage value of 40% was determined empirically and serves as a sensitivity parameter of the method (see Section 4).

An important task in automatic detection of BSP is to avoid false detections of other EEG patterns that consist of discontinuous waveforms. A defining feature of periodic patterns is that they contain regularly repeating waveforms of duration less than 0.5 s. The inter discharge interval of PDs range from a fraction of a second to several seconds and can therefore share some features of burst