Seizure 30 (2015) 120–123

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Probability of detection of clinical seizures using heart rate changes

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ARTICLE INFO

Article history:
Received 12 May 2015
Received in revised form 18 June 2015
Accepted 21 June 2015

Keywords:
Clinical seizures
Heart rate based detection
Detection probability
Factors/variables
Regression models

ABSTRACT

Purpose: Heart rate-based seizure detection is a viable complement or alternative to ECoG/EEG. This study investigates the role of various biological factors on the probability of clinical seizure detection using heart rate.

Methods: Regression models were applied to 266 clinical seizures recorded from 72 subjects to investigate if factors such as age, gender, years with epilepsy, etiology, seizure site origin, seizure class, and data collection centers, among others, shape the probability of EKG-based seizure detection.

Results: Clinical seizure detection probability based on heart rate changes, is significantly ($p < 0.001$) shaped by patients' age and gender, seizure class, and years with epilepsy. The probability of detecting clinical seizures (>0.8 in the majority of subjects) using heart rate is highest for complex partial seizures, increases with a patient's years with epilepsy, is lower for females than for males and is unrelated to the side of hemisphere origin.

Conclusion: Clinical seizure detection probability using heart rate is multi-factorially dependent and sufficiently high (>0.8) in most cases to be clinically useful. Knowledge of the role that these factors play in shaping said probability will enhance its applicability and usefulness. Heart rate is a reliable and practical signal for extra-cerebral detection of clinical seizures originating from or spreading to central autonomic network structures.

1. Introduction

Automated detection of epileptic seizures originating from or spreading to central autonomic network (CAN) structures [1–6] using heart rate changes [7–15], is gaining acceptance as either a valuable complement or as an alternative to cortical electrical signals (e.g., ECoG) due to their: (a) Higher signal-to-noise ratio (mV for EKG vs. μV ECoG; (b) Greater ease and economy of recording (EKG requires 2 electrodes for indirect but all encompassing monitoring of ictal activity in CAN structures, while the same number of scalp or intracranial electrodes would yield inadequate coverage [16]; (c) Lower processing and computational analysis cost [13] due to EKG's lower signal complexity than ECoG.

Since seizure detection using heart rate is in an early developmental stage, more knowledge about its power and reliability is desirable to meaningfully assess its clinical applicability. The magnitude of relative changes in heart rate at seizure onset, is the single most important biological factor governing the probability of detection using this variable [13], which is subject not only to fluctuations in type and level of physical activity, but also to various other factors. The degree to which age, gender, seizure class (e.g., simple vs. complex partial), etiology (e.g., lesional vs. cryptogenic) or hemispheric location (left vs. right) of the epileptogenic zone may impact the probability of clinical seizure detection is unknown. Also, the plasticity (e.g., accommodation or potentiation) of the central and peripheral autonomic system [17] raises relevant questions such as: Does the intensity of the ictal cardiac response depend on the length of the course of epilepsy? If yes, is it enhanced or blunted?

The importance of identifying which factors and the degree to which they shape the cardiac response to seizures and through it, the probability of detection of clinical seizures, motivates this investigation. To this end, the probability of detection (which in this study corresponds to True Positive detections) of clinical seizures using heart rate changes was investigated as a function of: Subjects' age and gender, years with epilepsy, etiology, site of origin, seizure class, electrode type (subdural vs. depth) used for localization of the epileptogenic zone, and data collection epilepsy centers.

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http://dx.doi.org/10.1016/j.seizure.2015.06.007
1059-1311/

2. Methods and materials

2.1. Data sets

This investigation utilizes the data of an extensive validation of an EKG-based seizure detection algorithm published elsewhere [13,14]. Only details deemed necessary to properly frame this work will be provided herein. Seventy-nine ECoGs (72 subjects; 6935 h, 266 clinical seizures) with simultaneous EKG were analyzed with two different seizure detection algorithms: One was applied to ECoG [18,19] and the other to EKG [13,14]. These data, from which all identifiers had been removed, were collected with approval from the Human Subjects Committee of each of the contributing centers. One data set (33 subjects; 98 clinical seizures; 4–8 h recordings; total duration 352 h) was contributed by the Minnesota Epilepsy Group, Montreal Neurological Institute, Stanford Medical Center and the University of Kansas Medical Center (“Multi-Center”) and the other (39 subjects, 168 clinical seizures; full stay recordings, 6583 h) by the University of Kansas Medical Center (“Full Stay”). Each subject’s ECoG recorded with depth and/or subdural electrodes had a case report form containing clinical information and the times of onset and termination for each seizure, as scored by the epileptologists at the contributing centers. For analyses purposes, all seizures originating from the same epileptogenic zone were lumped into one “observation” regardless of the total number of seizures from that zone; subjects with more than one independent epileptogenic zone contributed more than one “observation” provided seizures from each zone occurred during the monitoring session (e.g., subject 21 had 2 seizures originating from the right temporal lobe, 1 seizure from the left temporal and 1 seizure from the left frontal lobe for a total of 4 seizures, but contributed only 3 observations to the data because 2/4 seizures originated from the same zone).

Only ECoGs containing clinical seizures and with good quality EKGs (determined through expert visual analysis) were included in the final analyses. Clinical seizures were defined as those having electrographic and clinical/behavioral manifestations. This study focuses on clinical seizures, because unlike electrographic or sub-clinical seizures, they pose serious risks to patients which may be managed through automated interventions (warnings and/or therapy delivery) triggered by heart rate-based detections.

Seizures originated from mesial temporal structures in the majority of patients; epileptogenic tissue was localized to the frontal neocortices in a small number of subjects. All seizures were “focal” at onset and were not pre-selected based on the presence of heart rate changes. For safety and other reasons (e.g., video-ECoG signal quality), the subjects were sedentary for the duration of the recordings.

2.2. EKG-based seizure detection

The EKG-based seizure detection algorithm “localizes” R waves and determines R-R sequences thus yielding a relative heart rate that is transformed into detection intervals [13]. EKG-based seizure detections were first classified as either True Positive (TP) or False Positive (FP) based on whether or not they were temporally correlated with visually validated ECoG detections, as determined by an epileptologist at each of the contributing centers. Each ECoG validated clinical seizure was used to define a time interval during which EKG-based detections overlapping this interval would be classified as TPs [13]. Validated ECoG detections that were not detected by the EKG algorithm were classified as False Negatives (FN) detections. Only TPs clinical seizures were included in the regression analysis.

2.3. EKG-based seizure intensity, duration and severity

Measures of intensity, duration and severity for seizures detected using ECoG [20,21] were applied to seizures detected using heart rate changes, since they are statistically equivalent and thus clinically meaningful [14]. (a) Seizure intensity (*Szi*) was defined as the maximal ictal heart rate (*Max HR*; bpm) recorded during an event; (b) Seizure duration (*SzDur*) was defined as the time (in s) the HR spends above a “threshold”), and (c) Seizure severity (*SzSev*) as the product of *MaxHR* and *SzDur*.

2.4. Statistical analyses

The dependence of probability of detection (which in this study corresponds to True Positive detections) of clinical seizures using EKG on various factors such as age, seizure class, etc. was investigated by applying a logistic regression model to the seizure time series:

$$P = \frac{\exp(\beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p)}{\{1 + \exp(\beta_0 + \beta_1 X_1 + \ldots + \beta_p X_p)\}} \quad (1)$$

where the detection probability P, is estimated based on the linear combination $\beta_0 + \beta_1 X_1 + \cdots + \beta_p X_p$, corresponding to the following factors that typify the patient samples: (a) *Data set* (“Full Stay” = 1; “Multi-Center” = 2); (b) *Age group* [{10–19} = 1; {20–29} = 2; {30–39} = 3; {40–49} = 4; {50–59 years} = 5]; (c) *Gender* (Male = 1; Female = 2); (d) *Etiology* (Congenital = 1; Cryptogenic = 2; Infection = 3; RH factor incompatibility = 4; Trauma = 5; Tumor = 6; Vascular = 7); (e) *Seizure class* (Not Reported = 1; Complex partial = 2; Generalized Tonic-Clonic = 3; Simple Partial = 4); (f) *Seizure topography* (Right Temporal = 1; Left Temporal = 2; Right Extra-temporal = 3; Left Extra-temporal = 4; Other = 5); (g) *Years with epilepsy*, and (h) *Electrode type* (e.g., subdural).

The effect of each of these factors on the variation in the observed proportions of seizures detected was investigated individually using the logistic regression model specified above, starting with models containing only factors such as age and gender that are known to influence heart rate, and increasing their complexity as required to better assess which ones contributed to the observed variation in the proportion of detected seizures, expressed as a probability.

3. Results

3.1. Model 1

Age, Gender and Data set origin were the factors (β) selected for this model since the first two markedly influence heart rate and data heterogeneity (given the differences in sample size and the large number of contributing centers) deserves investigation as a potentially important source of variation.

3.1.1. Results

Age and gender, not data set, were both significant contributors to variation in the proportion of detected clinical seizures with age being the most significant. Further model fitting revealed that a better model for the probability of detecting a seizure was a quadratic function of Age (Age^2) and the factor Seizure Class. This model accounts for 33.5% of the variation in the data, which is very highly significant ($p < 0.001$), with the probability of detecting a seizure being much lower for simple than for complex partial seizures.

3.2. Model 2

In this model the observed proportions of clinical seizures detected was plotted against the factors Dataset, Age, Gender,