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Abstract

Objective: To quantify background EEG discontinuity in term neonates with hypoxic ischemic encephalopathy (HIE) using an automated algorithm (*NeoGuard_A*).
Methods: The EEG signal is segmented and these segments are classified into 3 classes, predominantly depending on the amplitude values into low, medium and high. Next, we create temporal profile signals for each amplitude class to determine the global distribution of these classes across all EEG channels. *Dynamic* interburst intervals (*dIBIs*) are detected when the low amplitude temporal profile signal exceeds a threshold value.
Results: Parameters of *NeoGuard_A* were optimized using 157h of continuous EEG (cEEG) recordings from 7 neonates with HIE. An experienced clinical neurophysiologist confirmed high visual agreement of 18802 detected *dIBIs* in terms of detection accuracy. Next, we analyzed a new dataset consisting of 1h cEEG segments selected from 38 neonates with HIE. Within this dataset, 4408 *dIBIs* were detected and 2273 were marked as *definite dIBIs* after visual verification. Statistical analysis of *definite dIBIs* revealed a significant relationship (interdependence) between duration and amplitude of *dIBIs*.
Conclusion: We show that *dIBI* is a robust parameter to classify a wide range (including mild and moderate) of background EEG discontinuities.
Significance: This study demonstrates significant interdependence between the duration and amplitude of EEG discontinuity, justifying the choice of *dIBI* as a classification parameter.

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Automated detection of *dynamic* interburst intervals in the EEG of neonates with hypoxic ischemic encephalopathy

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Key words: automated interburst interval detection; IBI; background EEG; perinatal asphyxia; HIE; EEG discontinuity.

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Highlights

- *Dynamic* interburst interval quantifies duration and amplitude of discontinuity in neonatal EEG.
- *dIBI* adequately characterizes milder background EEG abnormalities in neonates with HIE.
- We present an algorithm (*NeoGuard_A*) to automatically detect *dIBIs.*

Abstract

Objective: To quantify background EEG discontinuity in term neonates with hypoxic ischemic encephalopathy (HIE) using an automated algorithm (*NeoGuard_A*).
Methods: The EEG signal is segmented and these segments are classified into 3 classes, predominantly depending on the amplitude values into low, medium and high. Next, we create temporal profile signals for each amplitude class to determine the global distribution of these classes across all EEG channels. *Dynamic* interburst intervals (*dIBIs*) are detected when the low amplitude temporal profile signal exceeds a threshold value.
Results: Parameters of *NeoGuard_A* were optimized using 157h of continuous EEG (cEEG) recordings from 7 neonates with HIE. An experienced clinical neurophysiologist confirmed high visual agreement of 18802 detected *dIBIs* in terms of detection accuracy. Next, we analyzed a new dataset consisting of 1h cEEG segments selected from 38 neonates with HIE. Within this dataset, 4408 *dIBIs* were detected and 2273 were marked as *definite dIBIs* after visual verification. Statistical analysis of *definite dIBIs* revealed a significant relationship (interdependence) between duration and amplitude of *dIBIs*.
Conclusion: We show that *dIBI* is a robust parameter to classify a wide range (including mild and moderate) of background EEG discontinuities.
Significance: This study demonstrates significant interdependence between the duration and amplitude of EEG discontinuity, justifying the choice of *dIBI* as a classification parameter.

1. Introduction

Perinatal hypoxic ischemic encephalopathy (HIE) is a major cause of morbidity and mortality (Lawn et al., 2005) in newborns. Common neurodevelopmental sequelae in survivors include cerebral palsy, epilepsy, sensory and cognitive problems (Hagberg et al., 2001; Richardus et al., 2003). In clinical care of asphyxiated neonates, it is necessary to accurately assess the degree of HIE severity. For this purpose, both Thompson score and amplitude integrated electroencephalogram (aEEG) are frequently used. The former is assessed at 24-hour intervals and is therefore not suited for monitoring acute changes in brain function. The latter represents a compressed electroencephalogram (EEG) signal trend recorded with two electrodes. aEEG is sensitive for acute and dynamic changes in brain function, representing a very useful monitoring tool in the neonatal intensive care unit (NICU). However, aEEG is a simplified EEG signal that results in loss of clinically valuable information.

Electroencephalogram (EEG) is a widely available non-invasive bed-side test that is exquisitely sensitive for studying abnormalities of brain function and its recovery in neonatal HIE (Monod et al., 1972; Watanabe et al., 1980; Pezzani et al. 1986). It helps to guide treatment decisions and estimate neurodevelopmental outcome. However, use of EEG and continuous EEG (cEEG) monitoring in the NICUs has been limited due to lack of around the clock support to interpret this signal. Hence, there is an urgent need for the development of real-time devices to automatically quantify neonatal background EEG activity.

The assessment of *aEEG*/EEG signal and their dynamic changes enables accurate prognostication in two extreme categories of neonatal HIE. More specifically, the mildest forms of HIE, characterized by normal (to mildly disturbed) continuous EEG background with preserved or mildly disturbed sleep-wake cycles are associated with a good clinical outcome. In contrast, severe HIE, characterized by persistent EEG discontinuity with prolonged interburst intervals (IBIs) and absence of sleep-wake cycles is associated with a poor clinical outcome (Pezzani et al., 1986; Biagioni et al., 1999; Menache et al., 2002).

Compared to these two extreme groups, clinical and EEG assessment of mild and moderate neonatal hypoxic ischemic encephalopathy is challenging. These neonates express a broad range of EEG abnormalities (e.g. from mild to moderate EEG discontinuity). Also, their clinical outcome can be very different even for similar-appearing EEG patterns (Murray et al., 2009). On the other hand, it is necessary to accurately distinguish mild from moderate HIE neonates as this has treatment and prognostic implications. With the recent advent of therapeutic hypothermia (Perlman et al., 2010), it has become important to make this categorization promptly (<6 hours post partum), with moderate and severe HIE patients becoming candidates for this therapy. However, inter-observer studies in grading neonatal EEG background activity are lacking. Moreover, there is a lack of uniformity among researchers' visual EEG background grading systems (Walsh et al., 2011).

In clinical practice, to visually score the abnormality of neonatal EEG background, researchers examine amplitude, frequency content, discontinuity and recovery of sleep-wake cycles (Walsh et al., 2011). EEG discontinuity is the most robust parameter for the assessment of HIE severity (Biagioni et al., 1999; Walsh et al., 2011). More specifically, levels of suppression and duration of EEG discontinuity are correlated with the degree of the hypoxic encephalopathy and subsequent neurodevelopmental outcome (Pezzani et al., 1986; Biagioni et al., 1999; Menache et al., 2002). For quantified background EEG analysis, classical IBI is used for the assessment of mainly moderate to severe EEG discontinuity. To be accepted as a pathological 'burst-suppression' pattern in full-term HIE neonates, the amplitude of the suppressed interval is defined as lower than 5, 10 or 15μV (Lombroso et al., 1985; Biagioni et

al., 1999). However, mild and moderate EEG discontinuities cannot be characterized with such a strict definition of amplitude attenuation (Biagioni et al., 1999).

Recently, several studies have proposed automated methods to assess EEG background in neonates. In (Korotchikova et al., 2011), combination of quantified EEG (qEEG) features like EEG discontinuity, amplitude and frequency content were found to be useful to assess the severity of HIE in full-term neonates. Alternatively, other studies have presented algorithms for detection of burst/suppression patterns in full-term and premature neonates (Lofhede et al., 2010; Palmu et al., 2010; Jennekens et al., 2011; Mitchell et al., 2013). Indeed, these approaches are suitable for EEG analyses in severe term neonatal HIE and premature neonates but less suited for the assessment of mild and moderate EEG abnormalities.

In term neonates with mild and moderate HIE, two major problems confront the quantification of EEG signal. First, they express a complex EEG background pattern with varying degrees of EEG attenuation that are intermixed with periods of continuous EEG. Because of this, such patterns cannot be categorized into a simple dichotomy of either burst or suppression segments as done in neonates with severe HIE. Second, neonatal HIE is not static and EEG background activity evolves over time. It is challenging to reliably quantify the improvement/deterioration of the background EEG over longer periods of time. Recovery of EEG background is characterized by a progressive shortening of interburst intervals, an increase in amplitude of the suppressed periods and a return of sleep-wake cycles (Watanabe et al., 1980; Holmes et al., 1982). That is, in newborns recovering from HIE, EEG gradually becomes more continuous. In this situation, a method to detect severe EEG discontinuity (burst/suppression) will no longer function accurately. Because of all these characteristics, marked intra-patient and inter-patient variability in the EEG signal is more the rule than exception.

In this study, it was our goal to analyze evolving EEG discontinuities that cannot be included into the classical IBI definition and express higher amplitudes within the suppressed intervals. These patterns are difficult to accurately define and they lack a corresponding quantified parameter to characterize them. Therefore, we developed an automated method (*NeoGuard_A*, hereafter called algorithm A) to detect and analyze both milder and severe background EEG abnormalities and their evolution over time.

2. Methods

2.1. Dataset

Data for this study was recorded at the Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands. The database consists of 45 (=7+38) full-term neonates with perinatal asphyxia who underwent continuous EEG (cEEG) polygraphy monitoring between March 2003 and August 2007 as part of a prospective study that assessed the utility of cEEG in asphyxiated term neonates (Cherian et al., 2011). They were not treated with hypothermia. Clinical characteristics of these patients are given in the supplemental data file. The sampling frequency was 256 Hz. The recordings were started 2-48 (median 19) hours post partum, using a full set of 17 EEG electrodes (Fp1,2, F3,4, C3,4, Cz, P3,4, F7,8, T3,4, T5,6, O1,2) in 37 patients, whereas in eight patients a reduced set of 13 electrodes was used (P3,4 and F3,4 were not used). Polygraphy included ECG, respiration, electro-oculogram (EOG), chin EMG and limb movements. Subsequently, the EEGs were anonymized and converted to European Data Format. We analyzed EEG signals using bipolar montage resulting in 20 (or 12) channels.

Dataset DA consists of cEEG segments from 7 neonates with mild and moderate background EEG abnormalities with no recorded epileptic seizures. In Table 1, we provide details of the EEG data studied. In total, we analyzed 157 hours of cEEG data. Dataset DA was used for the optimization of the algorithm A.

Table 1 here

Dataset DB consists of 1h cEEG segments selected from 38 neonates. cEEG segments were selected exactly one hour after the beginning of the recording. We did not exclude EEG segments due to presence of artifacts or epileptic seizures. Epileptic seizures were expressed in 18 neonates. The expressed EEG background patterns included mild, moderate and severe abnormality (Cherian et al., 2011) (see also supplemental data). Dataset DB was used for the validation phase of algorithm A. Neonates in Dataset DA and Dataset DB were non-overlapping.

2.2. Preprocessing

The EEG signals were filtered using high-pass and low-pass FIR filters at 0.7Hz and 20Hz. Next, we applied Blind Source Separation (BSS) techniques to remove physiological artifacts in the EEG. More specifically, pronounced muscle artifacts, continuously present on several EEG channels, were removed using Canonical Correlation Analysis (De Vos et al., 2010). Finally, ECG and respiratory artifacts were removed using Independent Component Analysis as described in (De Vos et al., 2011).

2.3. *NeoGuard_A:* definition and automated detection of *dynamic IBIs*

From literature study (Pezzani et al., 1986; Biagioni et al., 1999) and our personal EEG analysis experience, milder EEG discontinuities appeared to have higher amplitude levels than amplitudes defined with the classical interburst interval concept. Therefore, in our visual background EEG scoring system, we characterized both severe and mild EEG discontinuities. First, we defined severe EEG discontinuity as a pattern with amplitude less than 10μV observed in the majority of EEG channels (Cherian et al., 2011). Such severe amplitude suppressions correspond to the classical IBI defined similarly in the literature. Second, mild to moderate background EEG abnormalities tend to have higher amplitude within the suppressed periods that can range up to approximately 25μV in some of the EEG channels. Therefore, to encompass a wide range of EEG discontinuities into a unified definition, we define a *dynamic* interburst interval (*dIBI*) as a pattern with attenuated EEG activity (approximately <10μV) observed in more than half of the bipolar montage EEG channels that lasts more than 3 seconds. EEG activity in the remaining channels during the *dIBI* could range up to approximately 25μV. If EEG activity significantly higher than 25 μV is present within the *dIBI*, the interval would be considered as interrupted. In addition, the presence of distinguishable and alternating 'bursts' are always assumed within *dIBI* definition.

Consequently, the automated algorithm for *dIBI* detection is developed, consisting of two parts:

(a) *NeoGuard_A*, detects suppressed EEG intervals with high sensitivity according to the definition of *dIBI* and

(b) *NeoGuard_B*, selects a subset of accurately detected, *definite dIBIs* (described in Matic et al., 2013b, companion article).

The different steps of the algorithm are depicted in Fig. 1. Note that *NeoGuard_A* detects the majority of the suppressed EEG periods in a 'static way'. The goal of this part is that majority of suppressed EEG periods are accurately detected. On the other hand, within *NeoGuard_B*, we fully exploit the dynamic nature of *dIBI*, thereby resulting in an improved detection accuracy of *definite dIBIs*.

Fig. 1 here

A1. Adaptive segmentation of the EEG channels into quasi-stationary epochs

The main goal of the segmentation step is to distinguish and separate locally suppressed EEG periods from more active ones. First, the EEG signal is segmented using an adaptive segmentation algorithm that has been successfully applied for sleep analysis in newborns (Krajca et al., 1991; Paul et al., 2003). This algorithm segments EEG into quasi-stationary epochs using two fixed-length concatenated sliding windows. These windows are moved along the EEG signal and parameters related to amplitude (A_w) and to frequency content (F_w) are calculated within each window (Krajca et al., 1991):

$$A_w = \frac{1}{N_w}\sum_{i=1}^{N_w}|x_i|$$

$$F_w = \frac{1}{N_w}\sum_{i=2}^{N_w}|x_i - x_{i-1}|$$

Here, N_w represents the number of EEG samples in sliding windows. Accordingly, A_{w_diff} and F_{w_diff} are defined as the differences of A_w and F_w between the two concatenated windows. Then, a new signal, called *Total Difference* (*TD*), is calculated:

$$TD = A_{w_diff} + F_{w_diff}$$

As the next step, we smoothed the *TD* signal using a moving-average filter (of order 64) and thresholded it. In this way, *TD* local maxima that do not reflect valid change in EEG stationarity are removed from the *TD* signal. Next, local maxima are detected in the *TD* signal resulting in segment boundaries. Subsequently, in case of several local maxima occurring relatively close to each other, only the largest one is retained. This step ensures that the lengths of EEG segments are sufficiently long. Next, using combinatorial grid search, three algorithm parameters are optimized: the *TD* threshold level (2), length of the sliding windows (N_w=256) and the minimal duration of the EEG segments (0.75s). An experienced clinical neurophysiologist (PJC) visually checked the segmentation on dataset DA.

A2. Classification of segments into three amplitude classes: low, medium and high

After the segmentation, our goal is to detect EEG discontinuity observed in the majority of the EEG bipolar montage channels. Therefore, we assume that within the *dIBI* there will be many EEG segments with low and suppressed amplitudes. For this, we need to classify EEG segments according to amplitude content into 3 classes: low (L), medium (M) or high (H).

As the first step, the suppression level of EEG segments is assessed. We thresholded the segments with a value *T*, creating a new signal *amp*(*T*):

$$amp(T) = \begin{cases} EEG - T, & EEG \geq T \\ 0, & -T < EEG < T, \quad T > 0 \\ EEG + T, & EEG \leq -T \end{cases}$$

This signal reflects how much EEG amplitudes exceed the predefined thresholds. Here, we opted for threshold values of 10μV and 20μV. Thus, for every EEG segment two signals, *amp*(10) and *amp*(20), are obtained. Using these signals, we calculate parameters *area_amp*(10) and *area_amp*(20) for each EEG segment according to the formula:

$$area_amp(T) = \frac{\sum_{i=1}^{N} |amp(T)|}{(N/256)}, \qquad N - \text{number of samples in the segment}$$

This parameter represents the sum of absolute values of the *amp*(*T*) signal that is divided by the segment duration. We use *area_amp*(10) and *area_amp*(20) to quantify the amount of EEG activity above the predefined thresholds. Finally, the classification is performed using derived heuristic rules presented in Fig. 2.

In addition to the classification based on the amplitude content, we also classified slow EEG waves as suppressions. More specifically, slow waves can appear after abrupt bursts constituting suppressed periods. Hence, if the spectral edge frequency 90% (*SEF90*) is below 1Hz, a medium amplitude class segment is re-classified into a low amplitude class.

Fig. 2 here

We used combinatorial grid search to optimize the predefined parameters for this stage until it reached high agreement with the visual interpretation of the clinical neurophysiologist (PJC).

A3. Creating temporal profile signals and detecting *dIBIs*

Up to here, all EEG channels were analysed separately. In this last step, we merge the information present in different channels as follows. After classification, temporal profile signals are created for each of the 3 amplitude classes. Signal values represent the number of EEG channels in which this class was present at a particular time instant. The obtained values ranged from 0 up to a total number of bipolar EEG montage channels. For example, in Fig. 3, during the last 4 seconds, a low amplitude class is present in all 20 EEG channels. The temporal profiles of this EEG signal is illustrated in Fig. 4, where a Low amplitude Temporal Profile (LTP) signal reaches a maximum value of 20 in the last 4 seconds. In this way, these signals describe the spatial distribution of the amplitude classes.

Finally, to detect *dIBI*, we threshold the LTP signal at the value of one more than half the number of EEG channels. The time that the LTP signal exceeds this value results in the duration of *dIBI*. Thus, a low amplitude class and the LTP signal are the most important parameters for the detection of *dIBI* candidates.

The performance of algorithm A is illustrated in Fig. 3. First, the EEG signal is segmented and classification is depicted in colours: blue (low), magenta (medium) and red (high). In Fig. 4, the LTP signal is thresholded at the value 11. Consequently, in Fig. 3, two *dIBIs* are detected and marked with black rectangles. EEG activity from the 23rd till 25th second is not a *dIBI* as it is shorter than 3 seconds.

Fig. 3 here

Fig. 4 here

2.4. Assessment of *dIBI* amplitude

Compared to classical IBI definition, within *dIBI*, variable amplitude values are assumed. To get more insight into the morphology of *dIBI* patterns, it is necessary to estimate *dIBI* duration and *dIBI* amplitude values. First, automatically detected durations of *dIBIs* are visually confirmed. However, the second part, the accurate assessment of *dIBI* amplitude is not straightforward and many possibilities exist (Biagioni et al., 1999; Menache et al., 2002; Korotchikova et al., 2011). Nonstationarity of the EEG signal and complex multichannel structure make the amplitude estimation rather difficult. An additional requirement is that amplitude assessment is reliable both for full and restricted bipolar montage setting. That is, both for 20 and for 12 EEG channels. Therefore, we suggest two parameters to quantify the amplitude of *dIBI* suppressions.

1. *Suppression* is defined as a median value of the rectified EEG signal within the suppressed *dIBI* part across all EEG channels, resulting in a single value for each *dIBI*.
2. *Flatness* is calculated for single EEG channel independently within the suppressed *dIBI* part (Fig. 5). Two horizontal border lines are adjusted, so that they enclose 95% of all EEG samples within *dIBI*. The minimal possible distance between the two horizontal lines represents the parameter *flatness*. Next, *flatness* is calculated for each EEG channel and the obtained values are sorted into an ascending order. Finally, to estimate *dIBI* suppression level across all EEG channels, we define parameter *flatness3* as a median of the sorted *flatness* values within the 3rd quartile (50-75%) of the least attenuated EEG channels. Therefore, this parameter ensures a robust and accurate assessment of amplitude taking into account an overall multichannel structure. Note that *flatness3* also represents upper amplitude bound for more than half of EEG channels.

Fig. 5 here

3. Results

3.1. Dataset DA

Algorithm A, including adaptive segmentation, amplitude based classification and detection of *dIBIs*, was optimized using a training dataset DA. In total, 157h of cEEG from 7 neonates was processed and analyzed. The 18802 detected *dIBIs* were visually checked for accurately detected duration and precise burst/suppression transitioning. This meticulous evaluation of EEG discontinuity patterns enabled us to fix the parameters of the algorithm A. In addition, it revealed two important findings. First, longer *dIBIs* (>10s) had higher number of locally suppressed segments within the EEG channels. That is, values of the LTP signal ranged mostly from 80 to 100% of total number of EEG channels (16 to 20 channels in a registration using 20 bipolar montage channels). On the other hand, shorter *dIBIs* (<10s) had a tendency to express values of LTP signal from 60 to 80% of total EEG channels. Second, observing LTP and MTP signals, we got insight into the confidence level of *dIBI* detections. That is, *definite dIBI* detections were characterized with regular, 'pulse-like shapes' observed in the LTP signal. This is illustrated in Fig. 4, where the second detected *dIBI* is characterized with such a pattern in the LTP signal. On the other hand, in Fig. 4, the first detected *dIBI* has

an *ambiguous* morphology observed in the LTP signal. More specifically, it would be difficult to visually assess the exact *dIBI* duration of this EEG discontinuity. In addition, *dIBI* may be interrupted by an excessive amount of EEG activity within suppressed period. Such activity may be distributed within *dIBI* synchronously or randomly across EEG channels. Therefore, following these insights, we developed a method to refine the detections of *dIBIs* with the aim of increasing the classification certainty (as explained in Matic et al., 2013b, companion article).

3.2. Dataset DB

We processed a new test dataset DB to further analyze *definite*, correctly detected *dIBIs* that were visually validated. Here, it was our goal to get more insight into the relation of amplitude and duration of *dIBIs.* Also, we wanted to develop a more accurate definition of *dIBI* that could be used for further refinement of *dIBI* detections. Using algorithm A, 4408 *dIBI* candidates were detected within dataset DB that consisted of 38 neonates (clinical and EEG details of these patients are given in the supplemental data file). After visual checking of these detections, 2273 *dIBIs* were marked as *definite dIBIs*. We tended to select *dIBIs* without presence of artifacts or neonatal epileptic seizures that could potentially affect *dIBI* morphology. In addition, all *definite dIBIs* had accurately segmented burst/suppression transition borders. In contrast, 2135 *dIBIs* were excluded from further analysis as *missclassified*. These detections consisted of mixed groups that included falsely detected *dIBIs* due to *ambiguous* EEG morphology, presence of artifacts, epileptic seizures, interrupted *dIBIs*, or false detections due to limitations of the algorithm A. For instance, in Fig. 3, the first automatically detected *dIBI* would be labelled as a *misclassified* detection. This *dIBI* candidate does not have clear burst/suppression transitions and excessively variable amplitude is observed within the suppressed period in many EEG channels. In contrast, the second detected *dIBI* would be considered as *definite*, showing clear transitions between burst/suppression segments and suppressed period according to *dIBI* definition.

3.3. Interdependence of *dIBI* duration and amplitude

In this part, a relation between duration and amplitude of *dIBIs* is derived using the results from the analysis of dataset DB. All *definite dIBIs* (<40s) are depicted in Figs. 6 and 7 as single data points. Duration of *dIBIs* is plotted along the axes *x*, whereas assessed *dIBI* amplitude is plotted along the axes *y*. Both *suppression* and *flatness3*, though derived using different approaches, reflect similar interdependence between amplitude and duration of *dIBIs*. In Figs. 6 and 7, for *dIBIs* >20s, amplitude does not show statistical dependence on *dIBI* duration. These longer EEG discontinuities correspond to classical IBIs. In contrast, for *dIBIs*<20s, a strong interdependence of amplitude and duration can be observed. In Figs. 6 and 7, this correlation is coarsely approximated as linear for illustration purposes.

Fig. 6 here
Fig. 7 here

Furthermore, in order to detect and visually confirm a *dIBI* as *definite*, it is necessary to verify whether amplitude values of suppressed periods are within the expected range. While visually detecting classical IBIs, researchers assess whether the suppressed interval satisfies conditions imposed by an IBI definition (Menache et al., 2002). For example, they examine whether the amplitude of the suppressed period is less than 10μV. Our analysis highlights an additional challenge. It is not only necessary to define and assess amplitude

ranges for suppressed periods, but also to take into account the relationship with *dIBI* duration. Our proposed solution is to split *dIBIs* into four duration-related *dIBI* groups. Therefore, we opted for the following ranges of *dIBI* duration groups:

$$dIBI = \begin{cases} \text{group I}, & 3\text{s} \le dIBI < 5\text{s} \\ \text{group II}, & 5\text{s} \le dIBI < 10s \\ \text{group III}, & 10\text{s} \le dIBI < 20s \\ \text{group IV}, & 20\text{s} \le dIBI\,(< 60) \end{cases}$$

For these groups, we performed a 1-way analysis of variance (ANOVA) and found a significant difference in mean amplitude distribution (F-statistic=337.8, $p<0.001$). For *dIBI* amplitude assessment we used parameter *flatness3*. Furthermore, using results of ANOVA test, we performed multiple comparison test to compare all mean values among four *dIBI* duration groups. The results show that with a level of 0.001 there was a significant difference in the mean values for all between group comparisons. Accordingly, amplitudes of *dIBIs* groups, estimated with parameter *flatness3*, are depicted in Fig. 8. The conducted analyses support our hypothesis that EEG discontinuity is a *dynamic* pattern which cannot fit into classical IBI definition that is described with amplitude or duration thresholds alone.

Fig. 8 here

4. Discussion

The objective of this study was to develop an automated method to reliably assess a broad range of EEG background discontinuities in full-term asphyxiated neonates. Previously described automated methods for neonatal EEG analysis have been focused either on continuous (healthy neonates) or on severely discontinuous EEG patterns. For example, approaches for automated detections of sleep-wake cycles are proposed for healthy newborns (Scher 2004; Gerla et al., 2009). In contrast, for neonates with severe HIE, an automated 'burst-suppression' detection algorithm has been developed (Lofhede et al., 2010). To the best of our knowledge, this is the first study that used automated method to detect and examine milder EEG discontinuities. These patterns are predominantly expressed in neonates diagnosed with mild to moderate HIE. In addition, this group of neonates still represents a great challenge for clinicians to predict their neurodevelopmental outcome and to standardize a common visual grading system for their systematic study (Walsh et al., 2011). In this context, we defined a new, visually interpretable parameter, *dynamic* interburst interval (*dIBI*) as an extension of the classical IBI concept that quantifies duration of EEG discontinuity. In general, *dIBI* can be seen as a burst-suppression-burst pattern with a complex morphology observed in both suppression and burst periods. In addition, apart from temporal information, the novelty of *dIBI* is that it incorporates various amplitude levels of suppressed EEG periods. This is very important from the clinical point of view as we obtain additional information that describes the severity of amplitude suppression (Pezzani et al., 1986; Biagioni et al., 1999).

The algorithm *NeoGuard_A* is developed to detect both milder and severe EEG discontinuities and their evolution over time (e.g. 12-48h period post partum). It represents the translated visual interpretation of EEG discontinuity into a mathematical procedure for automated *dIBI* detection. To develop algorithm A, the main challenge was to quantify the correct amplitude levels within the suppressed EEG periods. First, the experienced clinical neurophysiologist visually interpreted suppressed periods and the expressed ranges of

amplitude values. To optimally match this interpretation, we processed an extensive dataset DA with respect to various algorithm parameters. For each set of parameters, individual detections of evolving suppressed periods were checked over 24h in seven asphyxiated neonates. Consequently, we fixed parameters of algorithm A after we reached a satisfying agreement of *dIBI* detections with visual interpretations of vast majority of EEG suppressions. In this way, we could ensure that algorithm A detects *dynamic* and evolving discontinuous EEG patterns using a 'static' approach. To detect shorter *dIBIs* (<10s) it was necessary to set the algorithm A to work with a very high sensitivity. Therefore, the LTP signal was thresholded with a low value. On the other hand, we also found that certain constantly suppressed and low voltage EEG patterns can have amplitude levels in the same interval range as shorter *dIBIs*. Therefore, further automated refinement steps are necessary to exclude such patterns and to keep only *definite dIBIs*.

Within algorithm A, the main use of the LTP signal is to detect *dIBIs* in stage (A3). In addition to that, careful examination of LTP and MTP signals provided insight into the morphology of corresponding *dIBIs*. General shape and fluctuations of these signals showed correlation with certainty of *dIBI* detections. Moreover, causes of false detections were analyzed by observing morphology of the LTP and MTP signals. Thus, we were able to determine whether a misclassification was produced due to the segmentation process, the presence of artifacts or due to other paroxysmal EEG activity that interrupts *dIBI*.

Within this study, we also processed an extensive test dataset from 38 neonates. The adequate number of neonates and large number of detected *dIBIs* enabled us to analyze a variety of different *dIBI* morphological patterns. Next, we visually checked and selected *definite dIBI* detections, where duration can be interpreted with high certainty. The superiority of the *dIBI* parameter compared to the classical IBI is observed for *dIBI* durations less than 20s. We showed that a significant number of shorter EEG discontinuities expressed higher amplitude levels that cannot fit into the classical IBI definition. Inclusion of these patterns enabled us to better characterize neonates with mild and moderate HIE (background EEG grades 1, 2 and 3; see supplemental data). In addition, we found a strong correlation between duration and amplitude of *dIBIs*. This interdependence revealed a new challenge. Upper amplitude bounds of suppressed periods need to be redefined and reset in respect to duration of *dIBIs*. This relationship also represents a justification to introduce a *dIBI* as a new parameter for automated background EEG classification. Subsequently, to provide a refined definition of *dIBI*, we modelled the interdependence of amplitude and duration of *dIBI* as a piecewise constant. Thus, we obtained four different duration groups characterized by different *dIBI* morphology. Finally, our *dIBI* analysis and the new adopted definition represent a 'data-driven' approach. We derived it by quantifying a plethora of EEG discontinuities observed in a large number of neonates at different post partum time of the recordings.

We would also like to address an important issue regarding the effect of filter settings on the analysis of EEG background activity. EEG discontinuities mainly represent periods of brain quiescence and these are expected to be predominantly composed of low frequencies. To match visual interpretation of EEG discontinuity adequately, during the optimization phase (A1-A2), we were careful to set the high-pass filter value (we selected 0.7Hz using FIR filter; Matic et al., 2012). This filter value expressed a high sensitivity for amplitude of the suppressed periods. More specifically, too low high-pass filter values can result in the expression of high amplitude 'activity' in suppressed EEG segments (slow waves and/or artifacts). For instance, in the study of (Biagioni et al., 1999) 0.2Hz value was used during visual EEG analysis. In our experience, this filter value can produce falsely high amplitudes within suppressed periods in neonates with HIE (due to increased vulnerability to slow artifacts, sweat potentials etc.). On the other hand, a value of 1.6Hz for the high-pass filter

was reported in (Lofhede et al., 2010). Such high values however can excessively filter out EEG activity and falsely enhance duration and level of suppression observed in mild and moderate EEG abnormalities. Therefore, in order to compare both visual and automated background EEG analysis systems it is necessary to standardize applied high-pass filters and applied cut-off frequency values.

The strength of algorithm A is that it accurately detects suppressed EEG periods. On the other hand, within test dataset DB, an expert EEG reader marked only a subset of detected suppressions as *definite dIBIs*. Therefore, algorithm A would represent the first part of a decision-support system for an automated EEG-based assessment of neonatal HIE severity. The main requirement of such a system is high certainty and reliability. However, due to many hindering factors observed both in complex multichannel EEG structure and omnipresent artifacts, using only algorithm A, we are not in a position to offer a reliable fully automated EEG analysis system. It is necessary to perform an additional study of *dIBI* detections and to exploit revealed *dynamics* of EEG discontinuity in order to improve the detection accuracy of *definite dIBIs*. This will help us to gain more insight into the confidence level of detected *dIBIs* and whether or not to include them in further EEG background analysis. The refinement step of *dIBI* detections is described in (Matic et al., 2013b, companion article).

Acknowledgments

We thank the neurotechnologists who made the high quality EEG recordings and patients and parents for their co-operation.

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Legends to figures

Figure 1. Flow chart of the algorithm for automated detection of *dynamic* interburst intervals. *NeoGuard_A* consists of three stages and it detects *dIBIs* with high sensitivity. In *NeoGuard_B,* subset of correctly detected – *definite dIBIs,* are selected using machine learning classifiers, whereas *misclassified dIBIs* are excluded from further analysis (described in Matic et al., 2013b, companion article).

Figure 2. The heuristic rules developed for the classification of EEG segments are presented on the left. An illustration of the segmentation process and the classification into 3 amplitude classes: low (blue), medium (magenta) and high (red), are depicted on the right.

Figure 3. Performance of algorithm A. The EEG signal is segmented into quasi-stationary epochs. Next, segments are classified into amplitude classes: low (blue), medium (magenta) and high (red). Black rectangles are automatically detected *dIBIs* with algorithm A. The first detected *dIBI* cannot be regarded as a *definite dIBI* because of its *ambiguous* morphology. On the other hand, the second detected *dIBI* would be visually marked as *definite* by the majority of EEG readers within an absolute error of 1 second.

Figure 4. Temporal profile class signals created for the EEG signal in Fig. 3. Respectively they correspond to low (blue), medium (magenta) and high (red) amplitude classes. In this example, Low amplitude Temporal Profile (LTP) signal is thresholded at the value 11 (=20 channels/2 +1). The time interval when this signal exceeds the threshold determines the duration of *dIBI*. The activity from the 23rd till the 25th second is not a *dIBI* as it is shorter than 3 seconds.

Figure 5. Illustration of how the parameter *flatness* is calculated within the suppressed *dIBI* part (4s long) for a single channel. Two horizontal red lines are adaptively adjusted until they meet two criteria. First, they need to enclose 95% of the signal samples. Second, the calculated distance between them has to be minimal. In this example the calculated distance is 14 μV. Next, parameter *flatness3* is calculated as a median of a 3rd quartile (50-75%) of the least attenuated EEG channels.

Figure 6. Interdependence of *dIBI* duration and amplitude expressed with parameter *suppression*. The data points represent 2079 definite *dIBIs* (<40s). There is a strong correlation between the two parameters for the duration of *dIBI* (<20s): 1807 data points, Spearman ρ=-0.61, p<0.001. In contrast, there was no significant correlation between the two parameters for *dIBI* duration in the range from 20s till 40s: 272 data points, Spearman ρ=-0.1, p=0.1.

Figure 7. Interdependence of *dIBI* duration and amplitude, expressed with parameter *flatness3*. Data points represent 2079 definite *dIBIs* (<40s). There was a strong correlation between the two parameters for *dIBIs* (<20s): 1807 data points, Spearman ρ=-0.51, p<0.001. In contrast, correlation between the two parameters for *dIBI* duration from 20s to 40s was less significant: 272 data points, Spearman ρ=-0.14, p=0.02.

Figure 8. Amplitude distribution of EEG discontinuities, as assessed with parameter *flatness3,* is depicted for each *dIBI* group. Groups are defined according to duration of *dIBI* in the following intervals: Group I: 3s≤*dIBI*<5s; Group II: 5s≤*dIBI*<10s; Group III:

10s≤*dIBI*<20s; Group IV: 20≤*dIBI* (<40s). There is a statistically significant difference in mean amplitude values between groups as shown with ANOVA test (*F*-statistic=337.8, $p<0.001$) and further confirmed with multiple comparison procedure at a level of 0.001.

Figure 1
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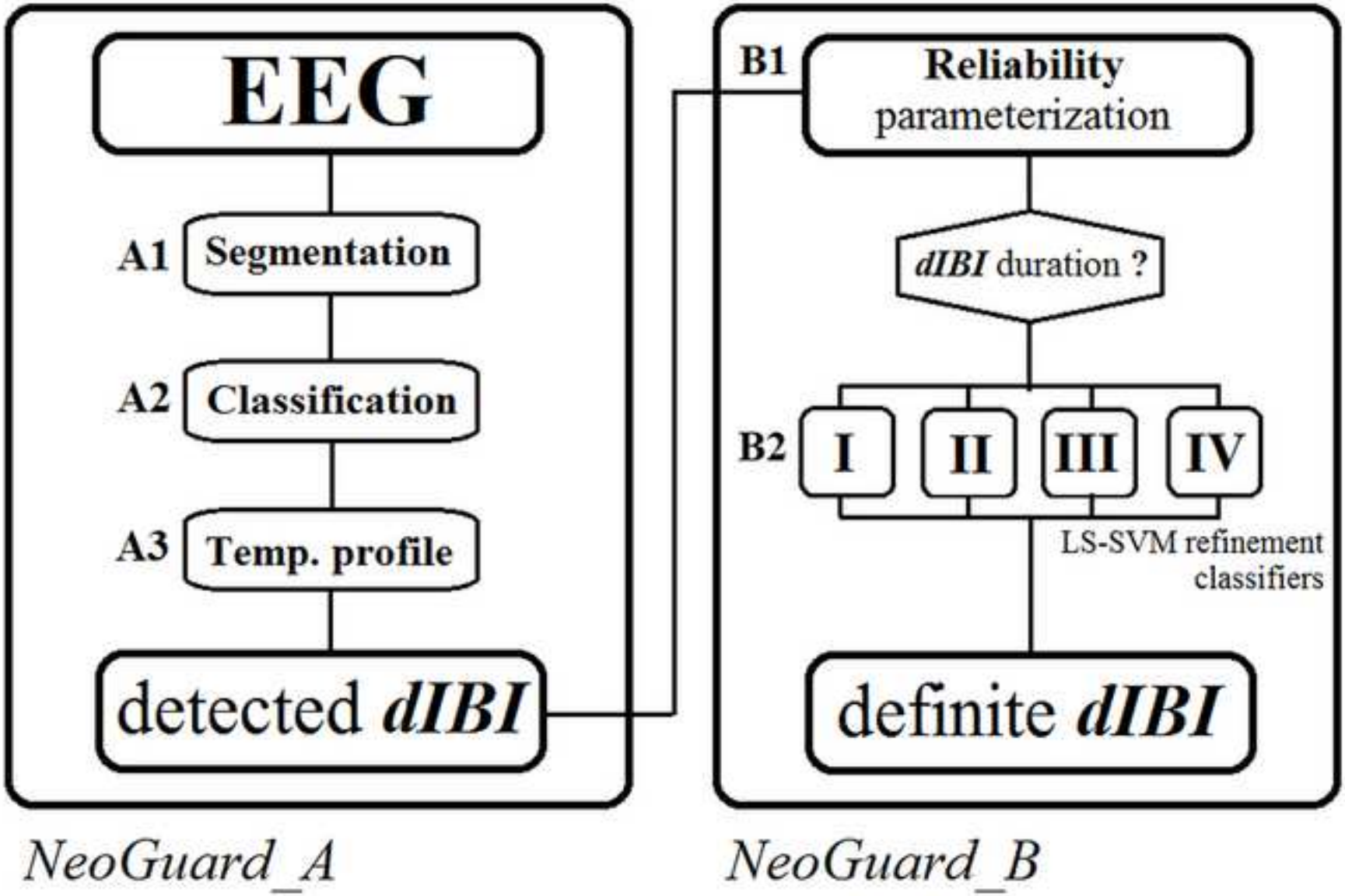


Figure 2

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```
if area_amp(10) < 50 then CLASS = LOW
 else
   if area_amp(20) < 100 then CLASS = MEDIUM
    else
      CLASS = HIGH
    end
end

if CLASS == MEDIUM & SEF90 < 1Hz then CLASS = LOW
```

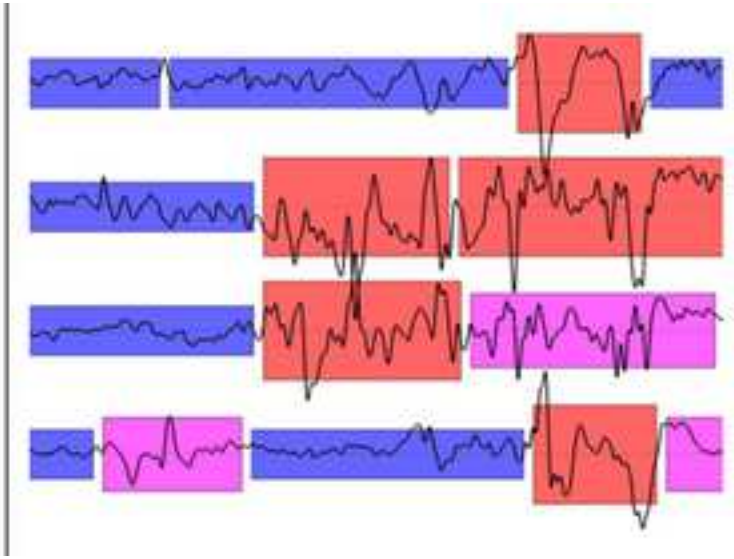


Figure 3

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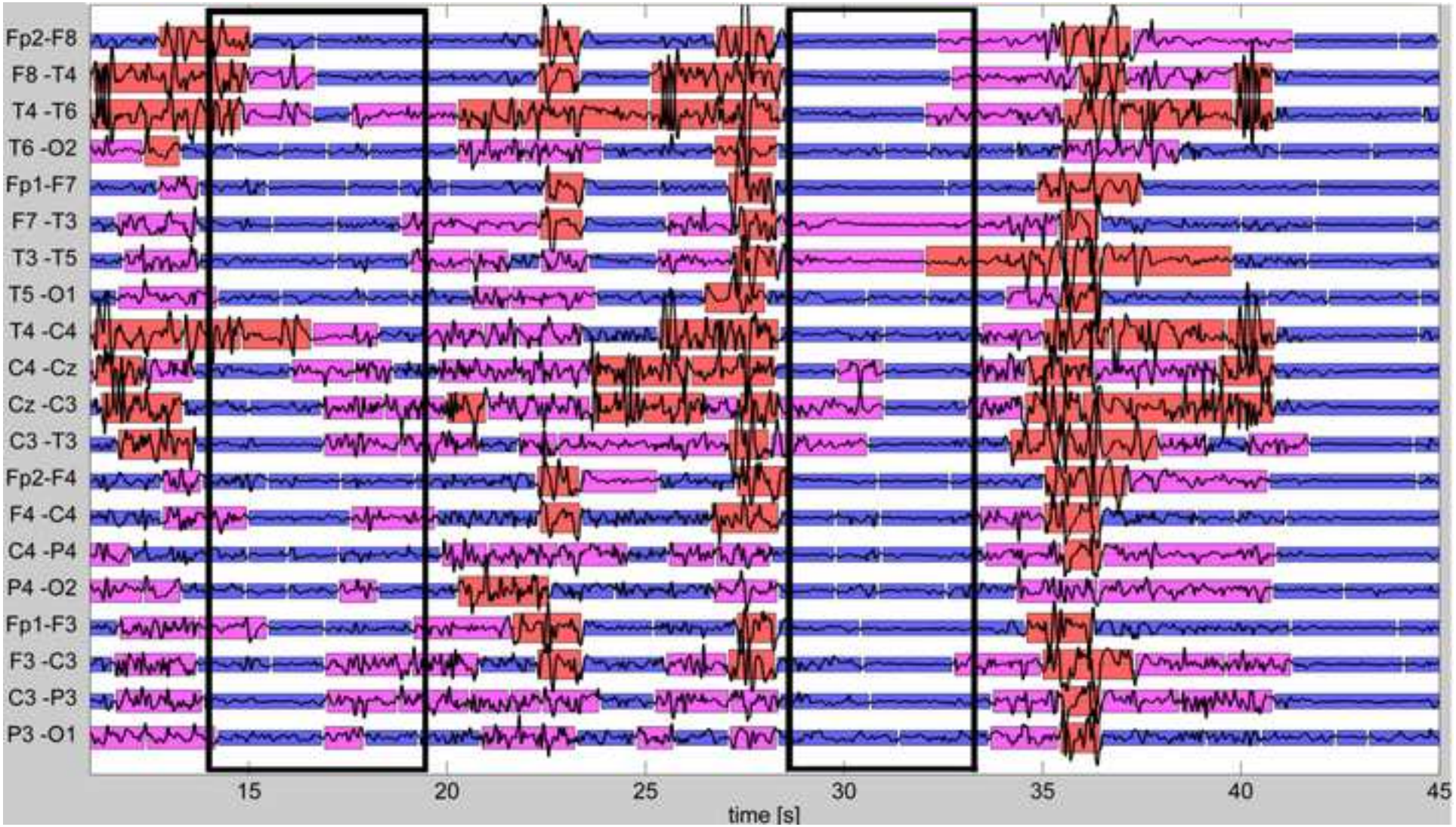


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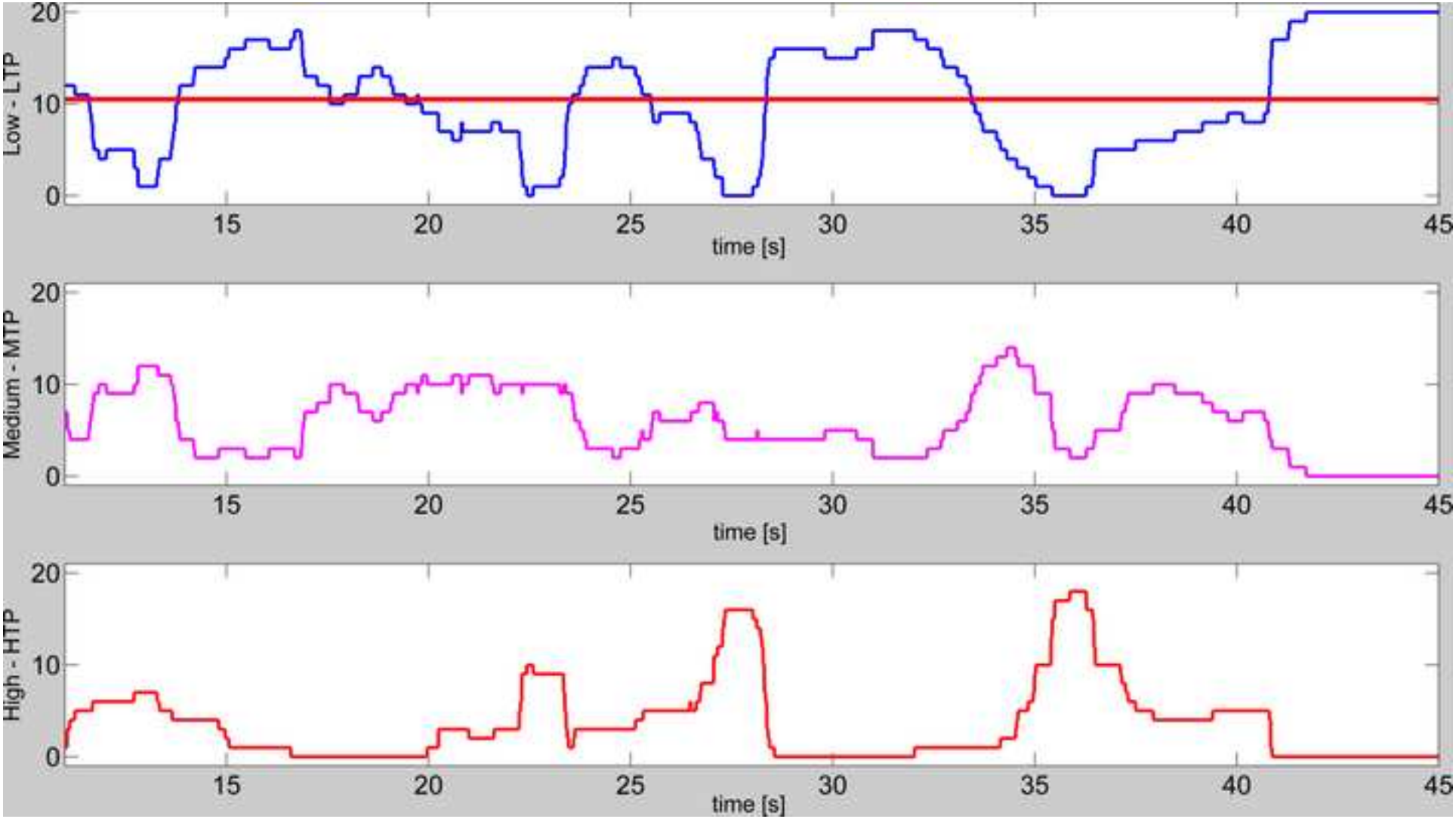


Figure 5

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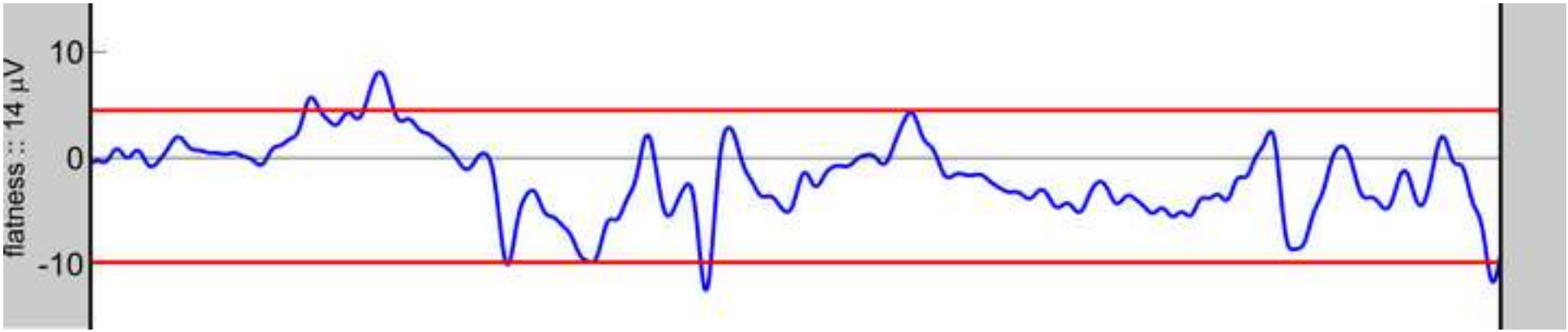


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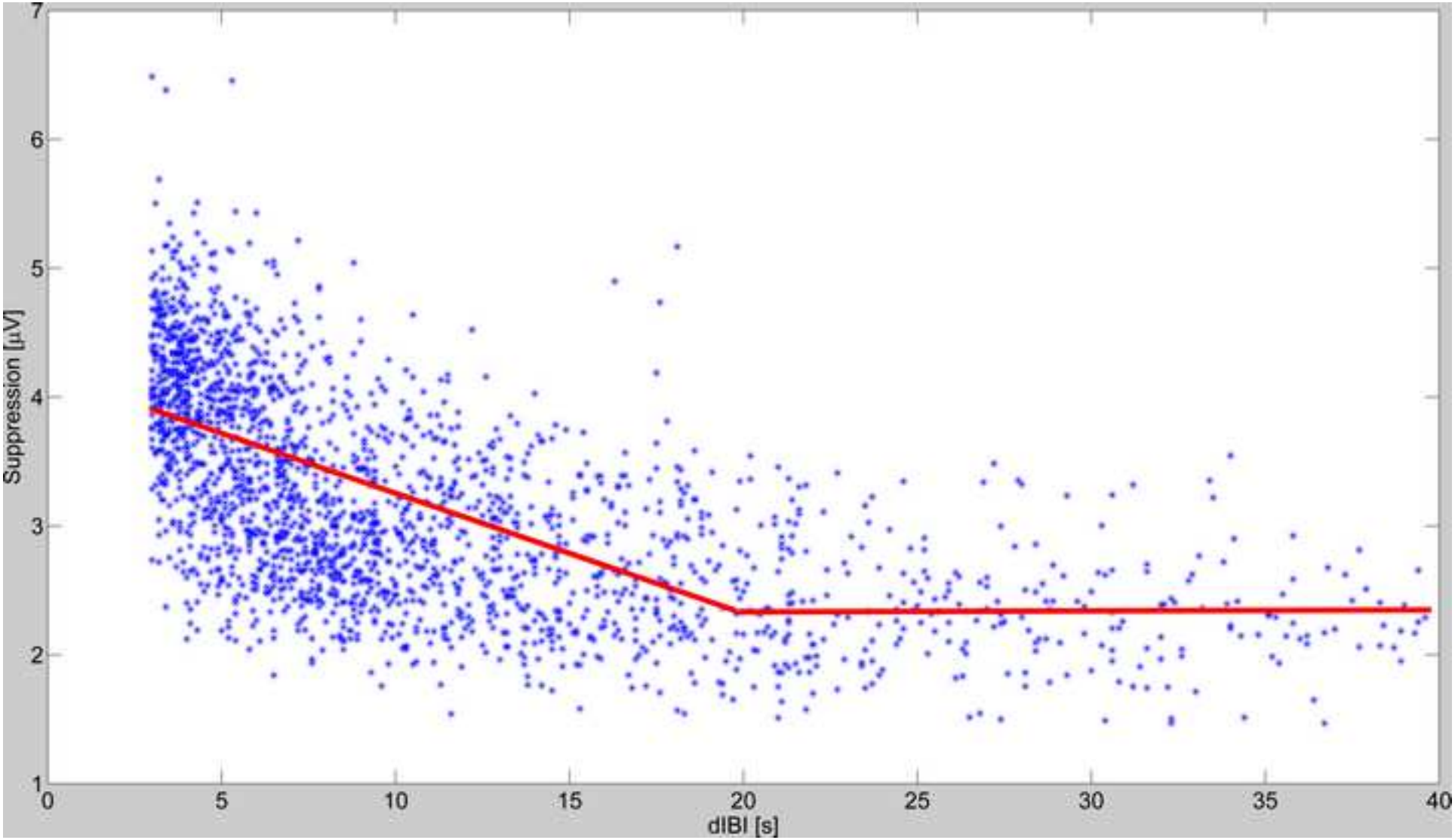


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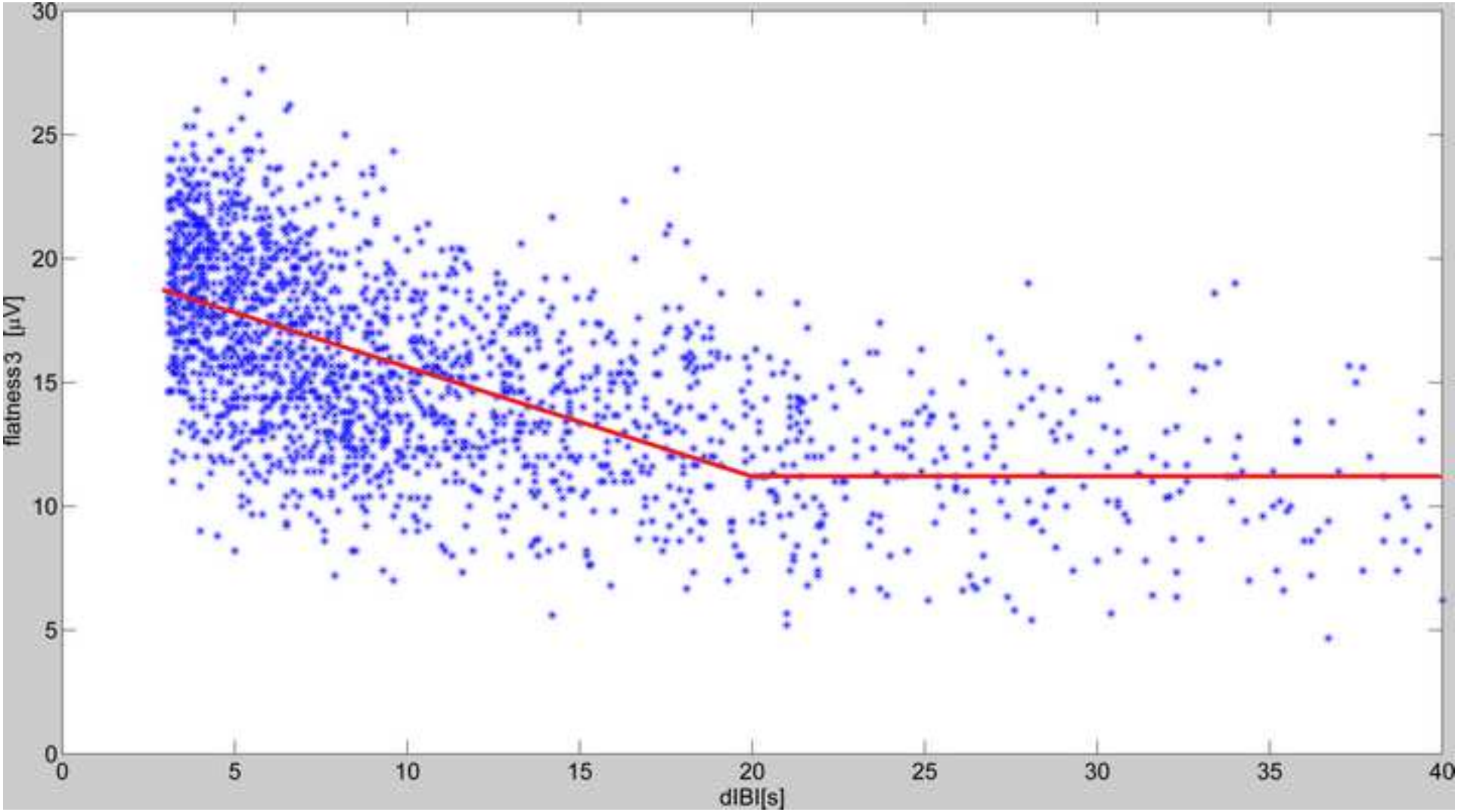


Figure 8

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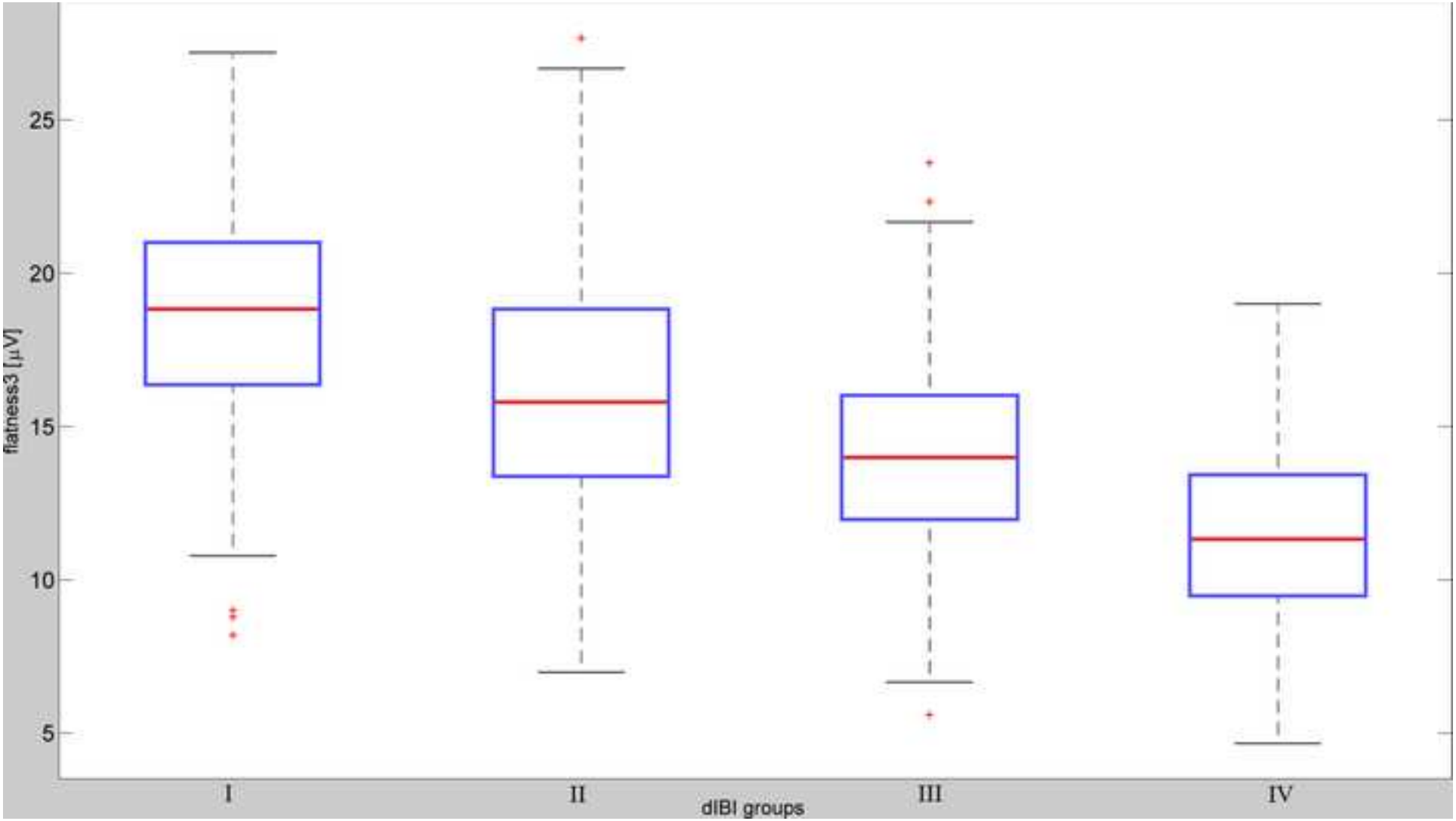


Table 1

Patient No.	*h EEG analyzed*	*No. of detected dIBIs*	*EEG background abnormality (grade)*	*MRI findings*	*Clinical outcome*
1.	34	3225	Mild (1)	Normal	Normal
2.	24	3290	Mild (1)	Mild watershed injury	Normal
3.	6	810	Mild (2)	Watershed injury bilateral O	No follow-up data
4.	25	383	Mild (2)	Mild hemorrhagic WM injury	Normal
5.	21	5480	Moderate (3)	Watershed injury bilateral FPO	Normal
6.	24	2657	Moderate (3)	TBG injury	Severe handicap
7.	23	2957	Moderate (4)	TBG injury	Severe CP
Total	157	18802			

Table 1. Details of dataset DA. Number of automatically detected *dIBIs* is shown per patient. They were visually checked during an optimization phase of the algorithm A. Background EEG abnormality was graded visually using the classification system presented in (Cherian et al, 2011), with 1 being mild and 8 being the most severe, abnormality. *h*: hours, *O*: occipital, *WM*: white matter, *FPO*: fronto-parieto-occipital, *TBG*: thalamus-basal ganglia, *CP*: cerebral palsy.

Details of patient selection, clinical and EEG characteristics of neonates included in this study

The 45 neonates (21 females) included in this study were part of a larger cohort of 119 newborns who underwent continuous EEG monitoring (cEEG) as part of a prospective study that evaluated the utility of cEEG monitoring in term neonates with perinatal asphyxia. The inclusion criteria for EEG monitoring were: clinical features of encephalopathy, and having at least one of the following features of birth asphyxia: a) arterial pH of umbilical cord blood ≤7.1, b) Apgar score ≤5 at 5 minutes, and c) high clinical suspicion (like fetal distress, umbilical cord prolapse, difficult labor, or a history of convulsions). Babies with congenital cardiac abnormalities and multiple congenital anomalies were excluded (Cherian et al., 2011). EEG background was visually scored according to an in-house developed grading system (Table 1).

Table 1. EEG background scoring based on evolution of discontinuity & SWC over 24 h

Grade	*DurIBI*	*AmpIBI*	*SWC*	*Improve*	*Reac*	*Variab*	*Other findings*
0	NA	≥25-50	++	NA	+	+	Normal for CA
1	≤5	10-25	+/-	↑SWC	+	+	↑ ShW, <6 sec runs of theta/delta
2	<10	<10	-	↓IBI	+	+	*
3	10-20	<10	-	to grade 2	+	+	-
4	>20	<10	-	to grade 2	+/-	+/-	-
5	10-20	<10	-	No	+/-	+/-	-
6	>20	<10	-	to grade 5	-	-	-
7	10-20	<10	-	Worsen	-	-	↑ IBI >20 sec
8[†]	>20	<10	-	No/worsen	-	-	

SWC: sleep-wake cycles. ***h***: hours, ***CA***: conceptional age. ***NA***: not applicable. ***IBI***: inter-burst interval. ***DurIBI***: length of IBI in seconds. ***AmpIBI***: mean amplitude of IBI in µV. ***Improve***: improvement in 24 h. ***React***: reactivity. ***Variab***: variability. ***ShW***: sharp waves. * Excessive inter-hemispheric asynchrony and amplitude asymmetry were also classified as at least grade **2**. [†] includes also persistent low voltage (<10 µV) and isoelectric EEG background. ↑ increased. ↓ decreased.

EEG grades 1 and 2 were further grouped into 'mildly abnormal' EEG background, grades 3 and 4 into 'moderate' and grades 5 to 8 into 'severe' abnormalities of EEG background.

As the aim of the present study was to develop an automated method for correctly classifying mild and moderate EEG background abnormalities, majority of the selected neonates had EEG grades 1 to 4.

Neuroimaging

Magnetic resonance Imaging (MRI) scans of the brain were performed in the first week after birth (median day 4) in all patients according to an asphyxia protocol on a 1.5 Tesla scanner. All scan sessions included conventional T1& T2-weighted spin-echo, and proton density images, as well as diffusion weighted images with apparent diffusion coefficient mapping. Images were classified using information from all sequences, by an experienced pediatric neuroradiologist who was unaware of the results of the EEGs and outcomes (Swarte et al., 2009). The patients were further clustered into two classes, depending on whether there was injury to deep grey matter (thalamus and striatum) and posterior limb of internal capsule or not, which is known to be a very good predictor of neuromotor outcome (Barkovich et al., 1998).

Outcome assessment:

A pediatrician unaware of the EEG results performed follow-up examinations until at least two years of age, using Bayley Scales of Infant Development (BSID) (Bayley, 1993). Patients with a normal short-term development at one year, who were not further followed at our clinic, were assessed with a telephone questionnaire based on the Pediatric Stroke Outcome Measure (deVeber et al., 2000) administered to the parents. Those in whom cerebral palsy (CP) was detected were referred to the pediatric neurologist. In these patients, the Gross Motor Functional Classification System (GMFCS) (Palisano et al., 1997) was used to classify the severity of CP.

Outcome was classified into five categories:

1. normal
2. mild motor disability (no CP) or language/cognitive delay
3. moderate disability, CP (GMFCS 1 or 2)
4. severe disability (GMFCS 3-5 or Mental Developmental Index [BSID MDI] < 70)
5. dead.

RESULTS

All neonates were full-term (> 37 weeks), with a median (range) weight of 3420 (1850-4400) gm. EEG monitoring was started at a median (range) of 19 (2-48) hours post-partum. The median (range) duration of cEEG was 27 (8-96) hours.

EEG background activity over 24h was graded as mildly abnormal (grades 1, 2) in 26, moderately abnormal in 10 (grades 3, 4) and severely abnormal in 9 (grades 5-8).

Seizures were recorded in 18 patients and were treated according to protocol with anti-epileptic drugs. Brain MRI was done in 44.

Two-year follow-up data (in survivors) was available for 42 patients.

Severe EEG background abnormalities were significantly associated with the presence of deep grey matter injury on MRI (Table 2) as well as poor clinical outcome (defined as severe handicap or death, outcome categories 4 or 5) (Table 3).

Table 2. Number of patients expressing injury to deep grey matter (Thalami-Basal Ganglia, TBG) on MRI in neonates with varying grades of EEG background abnormality

Presence of TBG injury	**EEG grades**							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Yes	0	0	2	4	1	3	1	2
No	11	15	3	1	1	0	0	0

Table 3. Number of patients with different outcome categories in neonates with varying grades of EEG background abnormality

Outcome category	**EEG grades**							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	9	8	3	1	0	0	0	0
2	1	2	0	0	0	0	0	0
3	0	0	0	0	1	0	0	0
4	1	1	2	3	0	1	0	0
5	0	1	0	1	2	2	1	2

Case study example

To illustrate the motivation to introduce dynamic interburst interval (*dIBI*) as a new parameter, we analyze the EEG discontinuities of a neonate with HIE whose background EEG is showing a gradual recovery. EEG recording was started at 19h post partum. After expressing severe EEG discontinuity initially (*dIBIs* ranged from 10-25s) background EEG improved over the next 24h. MRI on day 5 post-partum showed mild bifrontal and occipital watershed zone injury. Subsequently, this neonate had a normal outcome at 6-month follow-up (2-year follow-up was not available). First, we detected suppressed EEG periods using algorithm A by processing the following 1h cEEG epochs: 21-22h, 27-28h, 33-34h and 39-40h post partum. Using *NeoGuard_B*, we refined the detections and selected *definite dIBIs* by exploiting dynamics of EEG discontinuities. That is, *dIBIs* whose duration can be accurately interpreted with a high inter-rater agreement were selected. In the figure below, we show the duration and the amplitude of automatically detected *dIBIs*. These *dIBI* detections were visually checked and confirmed by the clinical neurophysiologist. Together with a shortening of *dIBI* duration, there is a trend of an amplitude increase within the suppressed EEG periods. Thus, with a single *dIBI* parameter, we can effectively monitor the evolution of the EEG background recovery.

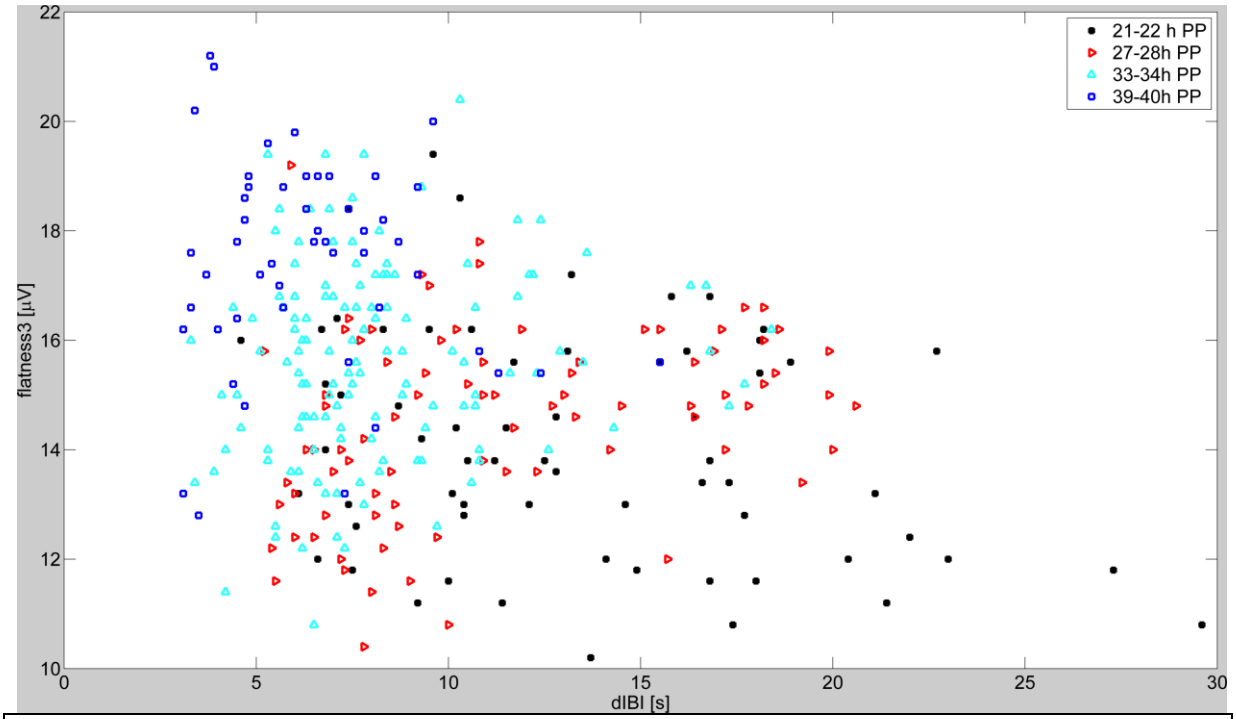


Figure. Using automated method (algorithms *NeoGuard_A* and *NeoGuard_B*), *dIBIs* are detected at different 1h time periods at 6h intervals post partum (PP). *dIBIs* detected within 1h cEEG form a "cloud" of data points. They are dispersed both in amplitude and duration of *dIBI*. Recovery of background EEG observed at every 6h intervals shows shortening of *dIBIs* and subsequent increase of amplitude of suppressed periods.

Video

The attached video file shows the *NeoGuard* (*A+B*) algorithm in action, automatically classifying *definite dIBIs* in a neonate with mild HIE.

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It has not been published previously except in abstract form.

The manuscript is not under consideration for publication, nor will it be submitted for publication, elsewhere until a final decision has been made by this journal.

The undersigned certify that each has participated sufficiently in the work to take responsibility for its truthfulness and validity and has read the complete manuscript.

Conflict of interest disclosure:

All funding sources supporting this work are acknowledged. The authors will disclose to the editor any pertinent financial interests associated with the manufacture of any drug or product described in this manuscript.

ALL AUTHORS MUST SIGN

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cover letter first of two companion papers

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To

Prof. dr. D. Burke,

Editor,

Clinical Neurophysiology

Dear Prof. Burke,

Herewith I send you a paper titled 'Automated detection of dynamic interburst intervals in the EEG of neonates with hypoxic ischemic encephalopathy' for favor of publication in the journal Clinical Neurophysiology.

This paper represents the first of two articles.

We describe an automated method (NeoGuard_A) for the detection of EEG discontinuities in term neonates with hypoxic ischemic encephalopathy (HIE). Interburst interval (IBI) is a well-recognized parameter to quantify background EEG abnormalities. Although useful for the quantification of severe HIE, classical IBI is not suited to characterize milder HIE and evolution of background EEG abnormalities. Moreover, lack of a uniform IBI definition in the literature as well as non-uniformity among visual background EEG scoring systems make it difficult for clinicians to adopt the results from published studies into their practice. Therefore, it was our goal to detect and study a broad range of EEG discontinuities, especially incorporating milder ones, and to monitor the evolution of these patterns within the first three days of newborn's life. With the assistance of a clinical neurophysiologist, we quantified dynamics within EEG discontinuities. More specifically, by statistical analysis, we found that

shorter EEG discontinuities tend to have higher amplitude values and more variability within the suppressed periods. We thus extended the concept of classical IBI and defined dynamic interburst interval to quantify burst-suppression-burst complexes with variable amplitude values.

Further refinement of dIBI detections is addressed in our companion paper, 'Improving the reliability of automatically detected dynamic interburst intervals in neonates with hypoxic ischemic encephalopathy', where we exploit the revealed dynamics and design a system which is robust to hindering factors present in automated EEG analysis. The overall system represents the first step towards fully automated quantification of background EEG abnormalities and grading of HIE severity, for continuous brain monitoring in neonatal ICUs, through a data-driven approach. We also hope by this to circumvent some of the problems like high inter-rater disagreement in the visual grading of EEG background activity.

Sincerely,

Vladimir Matic