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Automatic detection of burst synchrony in preterm infants

Alex Zwanenburg[1], Eduard Meijer[2], Ward Jennekens[3], Carola van Pul[4], Boris Kramer[5] and Peter Andriessen[6]

Abstract— **Electroencephalographic characteristics are useful in assessment of the functional status of specific neuronal connections relative to postmenstrual age. Interhemispheric burst synchrony (IBS) is a measure of the functional connectivity between the hemispheres in the maturing preterm brain.**

An algorithm was developed to assess IBS and was used in a prospective, longitudinal EEG study on 18 very preterm infants (< 32 weeks gestational age) with normal follow-up at 2 years of age. The preterm infants underwent weekly 4-hour multi-channel EEG recordings, resulting in $n = 77$ EEGs.

After automated detection of bursts, the algorithm defines the start and end of interhemispheric synchronous burst activity, based on selection criteria found in literature. The algorithm was designed to emulate visual inspection, providing objective results in an automated manner.

This approach may be applied in clinical use and open novel avenues to automated analysis in EEG monitoring and, moreover, it may facilitate assessment of the functional status of interhemispheric connections. As such, assessment of low interhemispheric synchrony may be associated with brain injury.

I. INTRODUCTION

Electroencephalography (EEG) is a very useful tool for predicting neurological outcome in preterm and term infants [1], [2], [3]. Interpretation of EEG, in clinical settings, is commonly performed by trained observers. However, inter-observer differences in interpretation and the time-consuming nature of visual inspection are drawbacks of the use of human observers, and the ongoing development of the preterm brain, resulting in EEG changes, imposes further difficulties. Interpretation of the EEG would, therefore, benefit from objective, automated analysis algorithms.

Several EEG patterns, such as bursts and interbursts, which are prevalent in the preterm EEG [1], can display synchrony. Synchrony in the broad sense is the presence of similar EEG features of comparable duration measured almost simultaneously in different regions of the cortex. EEG synchrony is thought to reflect remote functional connectivity [4]. Interhemispheric burst synchrony (IBS) is synchrony between bursts in the left and right hemispheres. To measure IBS, both Lombroso and Anderson et al. visually inspected EEG recordings recorded during (quiet) sleep in otherwise healthy preterm neonates and compared the onset of bursts in both hemispheres [5], [6], [7]. Both groups studied changes in IBS with maturation. However they found conflicting results for the age group of 31 weeks conceptional age (CA) common to both studies. Whereas Lombroso found a large decrease in IBS compared to the previous week, Anderson found a non-significant difference. This is likely caused by the use of slightly different methods, as well as inter-observer differences. For instance, IBS is represented as a percentage, but the definition is not well-defined. Anderson et al. [5] defined the percentage as the number of 1-minute epochs where bursts were synchronous divided by the total number of epochs, whereas Lombroso [6] defined it as the number of synchronous bursts as a fraction of the total number of bursts. Moreover, what exactly qualifies as a synchronous burst differs between the authors, emphasizing the need for a clearer and more objective definition of IBS to facilitate comparison.

Furthermore, Tharp et al. demonstrated a close link between abnormal interhemispheric synchrony in preterm infants and death or major neurological sequelae [8]. However, because of the time-intensive nature of an IBS analysis, this measure is rarely used in clinical practice.

In this paper, we present a method for the automatic and objective detection of interhemispheric burst synchrony in otherwise healthy preterm neonates and we compare our results with those of Lombroso and Anderson et al.

II. METHODS

A. Subjects

For this study 18 subjects were recruited from the neonatal intensive care unit. All subjects were preterm infants < 32 weeks postmenstrual age (PMA, gestational age + postnatal age) at birth. The infants showed a normal follow-up at 2 years of age, with mental and motor scores > 85 according to the international Bayley Scores of Infant Development [9]. Approval was given by the hospital ethics committee and written informed consent was given by the parents. For further details on the study group see Niemarkt et al. [10]. The infants underwent weekly 4-hour EEG recordings, starting in the second week after birth. The recordings (n = 77) represented a large variability in PMA (28 - 36 weeks).

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[1]A. Zwanenburg is with the Department of Medical Physics, Máxima Medical Center, De Run 4600 Veldhoven, The Netherlands a.zwanenburg at mmc.nl

[2]E. Meijer is with the Department of Medical Physics, Máxima Medical Center, De Run 4600 Veldhoven, The Netherlands e.meijer at mmc.nl

[3]W. Jennekens is with the Department of Medical Physics and Technology, Maasstad Hospital, Maasstadweg 21 Rotterdam, The Netherlands jennekensw at maasstadziekenhuis.nl

[4]C. van Pul is with the Department of Medical Physics, Máxima Medical Center, De Run 4600 Veldhoven, The Netherlands c.vanpul at mmc.nl

[5]B. Kramer is with the Department of Pediatrics, Maastricht University Medical Center and the Faculty of Health, Medicine and Life Sciences, Maastricht University, Postbus 616, 6200 MD Maastricht, The Netherlands b.kramer at maastrichtuniversity.nl

[6]P. Andriessen is with the Department of Pediatrics, Máxima Medical Center, De Run 4600 Veldhoven, The Netherlands p.andriessen at mmc.nl

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B. Data Aqcuisition

Electrodes were placed according to the international reduced 10-20 montage system [1]. The signal was recorded with a common reference electrode. The signal was band-pass filtered between 0.30 and 35 Hz using a 4^{th} order forward-backward Butterworth filter and sampled at sample frequency $f_s = 256$ Hz. The recorded signal was recombined to form 13 channels: Fp1-Fp2, C3-C4, O1-O2, Fp1-C3, Fp1-T3, C3-O1, C3-T3, O1-T3, Fp2-C4, Fp2-T4, C4-O2, C4-T4 and O2-T4.

C. Data Processing

Recordings were divided into non-overlapping 5 minutes segments. Artefacts were detected using a simple threshold technique and subsequently removed from analysis. The recording was subsequently analyzed using the algorithm described in this paper. Segments where artefacts were present for more than 5% of the duration and segments where continuous activity was present for more than 20% of the duration were excluded. This led to the complete exclusion of 3 EEG recordings.

D. Algorithm

EEG recordings were analysed based on an algorithm developed by our group [11]. Using an amplitude thresholding technique, the algorithm generated a list, partitioning the EEG recording into burst, interburst, artefact, continuous and undefined sections. The algorithm defined bursts as activity with an amplitude > 30 μV, simultaneously occurring in $\geqslant 4$ channels and lasting $\leqslant 20$ s. Likewise, continuous activity was defined as bursts lasting > 20 s. Defining IBS, we assumed that the difference between channels for both onset and end of the burst is within 1.5 s, the duration of the burst section differs no more than 2.0 s between the channels [6] and that $\geqslant 4$ channels are involved, including at least one pair of homologuous channels, e.g. C3-T3 and C4-T4.

An example to illustrate the working of the algorithm is presented in Figure 1.

For each channel b of the 13 channels we calculated the envelope function $E_{b,k} = \sqrt{2N_w^{-1}\sum_{i=k}^{k+N_w}(x_{b,i})^2}$,where $k = 1,\ldots,N-N_w$, with $N_w = 256$ the number of samples over which the signal $\vec{x_b}$ is averaged and N the number of samples in the recording. Then, for every burst we performed the following steps.

Step 1: The burst is, per channel, divided into sections where the envelope function exceeded the 30 μV threshold value. The start and end times of all sections in all channels are calculated.

Step 2: Based on the start times from step 1, we find L unique combinations of channels $\overrightarrow{f_{c,j}}$, with $j = 1,\ldots,L$, where the difference in start times between the channels is less than 1.5 seconds. From this we derive the corresponding L arrays $\overrightarrow{f_{t,j}}$ of start times.

Step 3: Step 2 is repeated for the end times of the sections found in step 1. This yields K unique combinations of channels $\overrightarrow{g_{c,k}}$, $k = 1,\ldots,K$ and end time arrays $\overrightarrow{g_{t,k}}$.

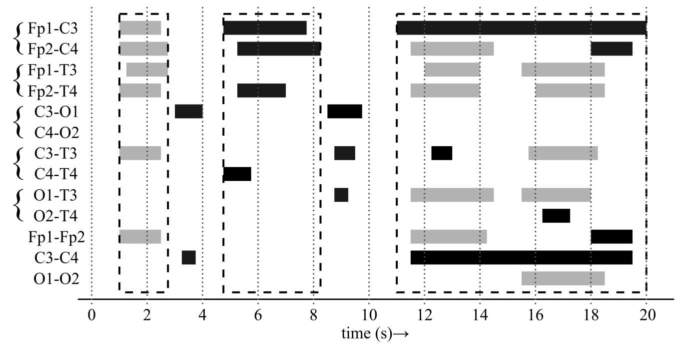

Fig. 1. Example to illustrate the algorithm. For every channel, the sections where the activity exceeds the > 30 μV threshold are shown as rectangles. The 3 bursts, as detected by the algorithm of Jennekens et al. [11], are marked by dashed lines for the duration of the burst. Light gray rectangles represent sections that are interhemispherically synchronous and black rectangles represent sections that are not. The curly brackets indicate pairs of homologous channels. The first burst is completely synchronous, since all sections within the burst fall within the bounds imposed on differences in times of onset and end and in duration. Furthermore, at least one pair of homologous channels is active, e.g. Fp1-C3 and Fp2-C4. The second burst is not interhemispherically synchronous, since the difference in end times and duration of the sections between channels is too large to form a set of at least 4 sections. The third burst represents a more complex situation. The duration of this burst is defined by the activity in Fp1-C3. Within this complex burst, several sections are not part of the synchronous burst activity because of length (the activity in channels Fp1-C3 and C3-C4 being too long and C3-T3 and O2-T4 being too short, respectively) and onset (Fp2-C4 and Fp1-Fp2).

Step 4: We generate all permutations of start and end times in the various channels. Having found L channel combinations $\overrightarrow{f_{c,j}}$ and K channel combinations $\overrightarrow{g_{c,k}}$, $K \cdot L$ channel combinations $\overrightarrow{h_{c,m}} = \overrightarrow{f_{c,j}} \circ \overrightarrow{g_{c,k}}$, where $\circ$ is the entrywise product operator and $m = 1,\ldots,K \cdot L$, with corresponding start $\overrightarrow{h_{t,s,m}}$ and end times $\overrightarrow{h_{t,e,m}}$, are formed.

Step 5: Most permutations contain invalid combinations of start and end times, e.g. when in a permutation there is a channel where the end of a burst section would precede the start thereof. The following checks are performed to remove invalid combinations: **a**: Remove all channels where the end time is before the start time. **b**: Remove all channels where the particular start time is not closest to the end time. **c**: Burst sections on different channels are demanded to be similar in duration, within 2 seconds. This creates one or more different combinations of channels, and we select the combination with the highest number of channels. If there is more than one of these, the combination of channels where the variance between durations is minimal is chosen.

Step 6: Subsequently, the interhemispheric synchrony of this selection is checked by demanding that at least one pair of mirror symmetrical channels in both hemispheres is involved.

Step 7: If the combination of channels involves 4 or more channels, and was marked as synchronous in the previous step, $\overrightarrow{h_{c,m}}$, $\overrightarrow{h_{t,s,m}}$ and, $\overrightarrow{h_{t,e,m}}$, corrected in step 5, are stored.

Step 8: After performing steps 5 to 7 $K \cdot L$ times, M_p combinations of channels $\overrightarrow{h_{c,k}}$, where $0 \leqslant M_p \leqslant K \cdot L$ and $k = 1,\ldots,M_p$, with corresponding start and end times, $\overrightarrow{h_{t,s,k}}$ and

$\overrightarrow{h_{t,e,k}}$, are found that present interhemispheric synchronous bursts. Where $M_p \neq 0$, some of the combinations represent separate burst sections, while others are variations of each other. A separate burst section shares no start and end times on the involved channels with any other separate burst. An example of separate burst sections are shown in Fig. 1. Within a burst section, it is possible that there are different combinations of channels that are essentially variations of each other, sharing at least one start or end time. We separate the various combinations into M_{sep} separate sections, each section consisting of $M_{v,j}$ variations, where $j = 1, \ldots, M_{sep}$.

Step 9: For each j of the M_{sep} burst sections we need to determine which of the $M_{v,j}$ variations is the most suitable, based on the temporal distribution of start and end times. To do this, we sum the variance in start times and the variance in end times for each i of the $M_{v,j}$ variations and choose the variation i for which the sum is minimal.

Thus, we have determined for each burst whether it is interhemispherically synchronous, and in case it is, the channels involved in the underlying burst sections, and their respective onset and end times, are stored.

E. Analysis

In general, IBS is a measure of the amount of interhemispheric synchronous bursts compared to the total amount of bursts. Unfortunately, IBS is calculated in several ways, based on subjective visual inspection of the EEG [5], [7]. Therefore, to compare with the available literature we chose to use the following two representations of IBS, one based on the duration of synchronous bursts and another based on whether a burst can be marked as synchronous: 1) IBS_1: The total duration of synchronous bursts - corrected for possible overlap between separate synchronous bursts on different channels - divided by the total duration of bursts. 2) IBS_2: The number of bursts marked as synchronous divided by the total number of bursts, with the restriction that if a burst is a combination of separate synchronous bursts, only one is counted.

For each recording and each infant, the medians of the values for IBS_1 and IBS_2 in the 5-minute segments analyzed are calculated. From the medians, the population means are calculated and ranges (minimum value - maximum value) are given for different weeks PMA. Significance of changes for subsequent weeks is calculated using Student's two-sided paired t-test. A result with $p < 0.05$ is considered significant.

Results found by Lombroso [7] and Anderson et al. [5] are given in ranges, which were not further specified by the authors.

III. RESULTS

We analysed the available EEG recordings for our study group with the algorithm described above. Results are presented in Table I and in Figure 2.

Both representations of IBS show no significant changes between subsequent weeks, similar to the trend found by Anderson et al. Lombroso found a sharp decrease in the group of 33 weeks PMA and an increase afterwards. Values for IBS_1 are lower than IBS_2. Values for IBS_1 are outside the ranges given by Lombroso except for 33 and 34 weeks PMA and are outside the range given by Anderson et al. altogether. Values for IBS_2 partly overlap the ranges given by Lombroso except for 33 and 34 weeks PMA. These partly overlap the ranges given by Anderson et al. as well, though the values for IBS_2 tend to be lower.

TABLE I

COMPARISON OF IBS PERCENTAGES BETWEEN STUDIES

PMA (wks)	No.	IBS_1 (%)	IBS_2 (%)	Lombroso (%)	Anderson (%)
28	3	56 (53-60)	87 (83-88)	90-100	
29	6	62 (58-69)	86 (79-95)	90-100	92 (80-100)
30	13	59 (52-63)	82 (74-91)	90-100	
31	12	58 (48-69)	83 (71-89)	80-100	94 (79-100)
32	16	56 (47-70)	83 (76-95)	80-100	
33	12	56 (44-65)	85 (76-92)	50-70	94 (86-100)
34	7	56 (48-72)	85 (79-94)	50-70	
35	5	51 (46-56)	83 (76-88)	60-80	

Legend: In the first column the postmenstrual age (PMA) is given. The second column contains the number of recordings during the specific week, after exclusion of 3 EEG recordings (see Methods, Data Processing). Third and fourth columns contain data for IBS_1 and IBS_2, given as mean and (min. - max.) range. The fifth column contains data from Lombroso [7]. The sixth column contains data from Anderson et al. [5]. Data in fifth and sixth columns were originally given as a function of conceptional age (CA) and converted to corresponding PMA for comparison.

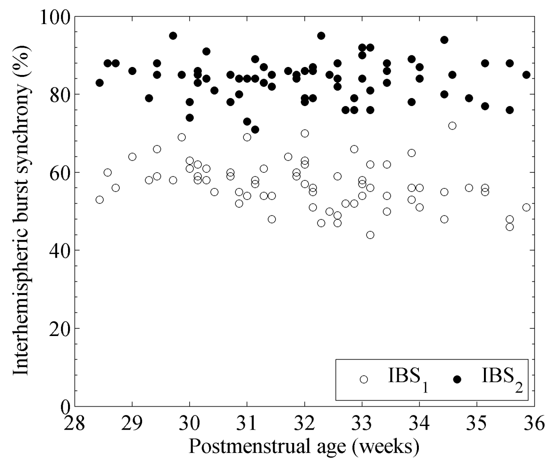

Fig. 2. Interhemispheric burst synchrony as function of postmenstrual age for IBS_1 and IBS_2. A data point represents the median value for the recording.

IV. DISCUSSION

A method to objectively characterize IBS in preterm infants was developed. Based on the partition of signals in burst and interburst patterns we were able to determine automatically, through several steps, the synchrony of a burst and the channels involved. The algorithm allows fast and automatic determination of IBS, making it feasible to use in hospital environments.

The algorithm was designed to closely follow the way one may visually inspect an EEG recording, as can be observed in Fig. 1. We obtained criteria from literature to assess: 1) the correct channel combinations, 2) start and 3) end times of burst sections in the channels. In this way we were able to establish the interhemispheric synchrony of a single burst.

We were unable to find a clear definition of what constitutes an interhemispheric synchronous burst in literature. We restrict ourselves to synchronous bursts occuring in mirror symmetrical locations in both hemispheres, but it is possible that earlier research used a broader definition of bursts roughly simultaneously anywhere in both hemispheres, which is less strict. Our algorithm easily would accommodate a different definition by changing step 6 to look for burst sections on different channels anywhere, as long as they are in different hemispheres.

In our study, we found a difference between the two representations of IBS we proposed, as the range of values for IBS_1 was lower than for IBS_2. We observed that this is caused by the definition of a burst as introduced by the burst detection algorithm used, which will extend a burst until the envelope function for all channels is below the threshold [11]. We observed that by removing this extension, values for IBS_1 and IBS_2 became comparable, although ranges for IBS_1 tended to remain lower.

Our data do not show the same trend as Lombroso: both IBS_1 and IBS_2 show no significant dependence on PMA. The data given by Lombroso are a composite of various studies, one of which is an earlier paper by Lombroso [6], which describes the development of IBS from 33 to 43 weeks PMA. In this study, infants were recruited who were born between 32 and 34 weeks gestational age. In our study, as well as in Anderson et al., infants of varying gestational ages were included. We suggest that the different findings are partly caused by the wider range in gestational age at inclusion in our study, and the potential influence of processes related to the preterm birth. In our case, such processes are desynchronised, as within a certain week there are infants with different gestational ages at birth, whereas in the study of Lombroso, these influences would be mostly synchronised. We do not know if there is an influence of gestational age on IBS. Literature suggests that, depending on the EEG characteristic studied, there is either a significant or not significant effect of gestational age in age-matched infants, see e.g. Conde et al. [12], Niemarkt et al. [13], Scher et al. [14] and Sisman et al. [15]. Another factor is that we did not look specifically at quiet sleep, due to lack of eye movement recordings, and resorted to excluding segments with continuous activity.

Though the data given by Anderson et al. are sparse, our results seem to follow the same trend. IBS_2, which compares best to the results by Anderson et al., tends to be lower. This is due to different criteria for onset and end time differences between channels. We restricted this to 1.5 s maximum difference, in accordance with Lombroso, where Anderson et al. used 2.0 s. Re-analysing the data with 2.0 s instead of 1.5 s resulted in higher values for IBS_2, closer to the range found by Anderson et al, but without a change in trend.

The available literature shows no clear definition of burst synchrony. This study proposes a clear definition of IBS and, moreover, an objective way of determining synchrony. Further research should establish a range of values for IBS in normal preterm infants. Based on these ranges abnormal development of interhemispheric connectivity may be determined at an early stage, potentially indicating developing brain injury [8].

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