Development of an Interhemispheric Symmetry Measurement in the Neonatal Brain

Ninah Koolen[1,2], Anneleen Dereymaeker[3], Katrien Jansen[3], Jan Vervisch[3], Vladimir Matic[1,2], Maarten De Vos[1,2,4], Gunnar Naulaers[5] and Sabine Van Huffel[1,2]

[1]*Department of Electrical Engineering (ESAT), division SCD, University of Leuven, Leuven, Belgium*
[2]*iMinds-KU Leuven Future Health Department, Leuven, Belgium*
[3]*Department of Pediatrics, University Hospital Gasthuisberg, Leuven, Belgium*
[4]*Department of Psychology, University of Oldenburg, Oldenburg, Germany*
[5]*Neonatal Intensive Care Unit, University Hospital Gasthuisberg, Leuven, Belgium*
{ninah.koolen, vladimir.matic, maarten.devos, sabine.vanhuffel}@esat.kuleuven.be,
{anneleen.dereymaeker, katrien.jansen, jan.vervisch, gunnar.naulaers}@uzleuven.be

Keywords: Preterm Brain, Symmetry, Channel Symmetry Index, Spectral Power, EEG, One-class SVM, Classification.

Abstract: The automated analysis of the EEG pattern of the preterm newborn would be a valuable tool in the neonatal intensive care units for the prognosis of neurological development. The analysis of the (a)symmetry between the two hemispheres can provide useful information about neuronal dysfunction in early stages. Consecutive and subgroup analyses of different brain regions will allow detecting physiologic asymmetry versus pathologic asymmetry. This can improve the assessment of the long-term neurodevelopmental outcome. We show that pathological asymmetry can be measured and detected using the channel symmetry index, which comprises the difference in power spectral density of contralateral EEG signals. To distinguish pathological from physiological normal EEG patterns, we make use of one-class SVM classifiers.

1 INTRODUCTION

Electroencephalogram (EEG) is a non-invasive and sensitive tool for assessing cerebral function in premature infants. The chronological changes in EEG background with increasing postconceptional age reflect the central nervous system maturation. Standard values of maturational features in premature EEG are already well described (Hellström-Westas, 2005; Vecchierini, 2007; Hayashi-Kurahashi, 2012; Le Bihannic, 2012). Chronic EEG background abnormalities are strongly associated with adverse neurological outcome in both preterm and full-term infants (Hellström-Westas, 2001; Okumura, 2002). These abnormal patterns must be scored and interpreted visually and, thus, subjectively. However, analyses and interpretation of multichannel neonatal EEG is difficult, requires expertise and is time consuming.

Therefore, objective criteria for the assessment of EEG abnormalities have to be established and automated background EEG analysis may contribute to reliable interpretation (Palmu, 2010). In previous research, we have defined features that can be calculated for each time signal, in other words, for each EEG channel independently (Koolen, 2013). However, EEG is a multichannel measurement, and all too often this spatial dimension is ignored. Spatial 'integration' is usually limited to concatenate the characteristics of different channels (Hunyadi, 2011). Here, we intend to exploit the available spatial information to quantify the interaction between the various areas of the brain using connectivity analysis. Such connectivity values can be highly relevant to make an accurate prognosis of the neurological outcome of the premature babies, since they are the mathematical quantification of the degree of connectivity between different brain regions. After all, it is commonly assumed that brain areas in very young babies are barely connected, and that during brain development through spontaneous interaction a sophisticated network is formed (Vanhatalo, 2006; Smyser, 2010). In this paper, the interhemispheric symmetry is examined: can we detect pathological asymmetry in electrophysiological activity between two hemispheres.

Interhemispheric asymmetry in premature infants is defined as a persistent amplitude difference of 50% over homologous areas in one hemisphere and must be persistent to all behavioural states to be significant (Holmes, 1993). In addition, abnormalities can be extracted from a difference in the power of the frequency domain. This abnormality in background pattern is frequently associated with lateralized pathology such as an underlying anatomical or acquired brain lesion (e.g. intraparenchymal haemorrhage, stroke, ischemic insults and congenital brain malformations) (Holmes, 1993; Van Putten, 2004).

Automated interhemispheric symmetry analysis in preterm and term infants can be a valuable tool to detect neuronal dysfunction in early stages. Consecutive and subgroup analyses of different brain regions (as detected in frontal, central, temporal and occipital electrophysiological activity) will allow detecting physiologic asymmetry versus pathologic asymmetry. Correlation of this pattern with long–term neurodevelopmental outcome has to be defined.

In order to detect those abnormal patterns in a classification process, we will use the channel symmetry index (CSI) (Hunyadi, 2010). Both amplitude and frequency content are taken into account, since the CSI is based on the difference in the power spectral bands of the contralateral channels. Derived features from the CSI curves will serve as input for the classification. Due to an unbalanced dataset, we will make use of a one class Support Vector Machine (SVM) (Schölkopf, 2000, 2001).

2 DATA ACQUISITION

The proposed method is tested on EEG measurements, obtained with OSG equipment (OSG, Belgium). The purpose is to observe the symmetry between different brain areas. Therefore, we use multi-channel or 'full' EEG taken at 9 electrode locations (Fp1, Fp2, T3, T4, C3, C4, Cz, O1, O2). The sampling frequency is 250 Hz. The dataset contains EEG recordings of 47 newborns, born at a postmenstrual age (PMA) of 24-40 weeks, including patients with structural brain abnormalities (acquired or congenital) and clinical convulsions. To assess brain maturation, 20 preterm infants had several EEG measurements at consecutive moments with increasing PMA. This resulted in a total of 92 EEG measurements. In this way, we want to score physiologic brain symmetry in the developing premature brain. On the other hand, we can score brain symmetry in both preterm and term infants with pathologic conditions. Data containing artefacts (>30% of the whole measurement) were excluded from this study. In consideration of symmetry calculations between two EEG channels, signals of only these two channels are excluded in case that one electrode is disturbed. In other words, not the whole full-EEG is excluded. The data was labelled into two categories: pathologic asymmetry and physiologic normal symmetry. The protocol was approved by the ethics committee of the University Hospitals of Leuven, Belgium. A pre-processing step including a 50 and 100 Hz Notch filter and a 1-20 Hz band pass filter was applied on the data.

3 METHODOLOGY

3.1 Channel Symmetry Index

First, we investigate detecting asymmetry between different EEG channels based on a feature called *channel symmetry index* (CSI) (Hunyadi, 2010). This feature is defined as the power asymmetry in predefined frequency bands and is calculated between two contralateral channel pairs presented in formula 1 (O1 vs. O2, C3 vs. C4, T3 vs. T4, Fp1 vs. Fp2).

$$CSI(ch,F) = \sum_{f=F_{\min}}^{F_{\max}} \frac{PSD_{f,ch} - PSD_{f,opp}}{PSD_{f,ch} + PSD_{f,opp}} \quad (1)$$

where *ch* is a chosen EEG channel and *opp* its contralateral channel as can be found in Figure 1.

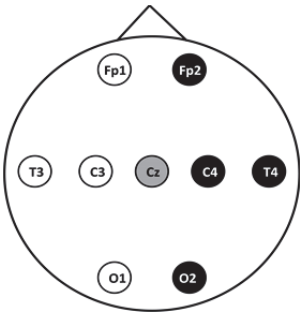

Figure 1: Electrode placements for 9 channel EEG measurement, contralateral channels are given in white-black (O1-O2, C3-C4, T3-T4, Fp1-Fp2).

The selected frequency bands correspond to the clinically relevant frequencies to monitor brain activity: delta band (1-4 Hz), theta band (4-8 Hz), alpha band (8-13 Hz) and beta band (13-21 Hz). A

CSI value is calculated for each 150 seconds of the EEG measurement, for each channel pair and each frequency band. A mean value is obtained by averaging the CSI values of the different frequency bands (Figure 2a). Subsequently, a patient specific box plot of these values over the whole EEG measurement is determined (Figure 2b).

3.2 Outcome Dependent Features

For classification, we need features to distinguish normal and abnormal EEG patterns. Based on the box plots, we have worked with four features:

- Median box plot
- Interquartile range (iqr) of the box plot: a statistical measurement to describe the spread of the data. iqr is calculated as the difference between the upper and the lower quartiles. This feature is similar to the range, although it is less sensitive to outliers, e.g. the movement of an electrode.
- Standard deviation (std) of the boxplot: variation from the average.
- Postmenstrual age (PMA): brain maturation may have an influence on the median of the box plot. The hemispheres connection is still developing.

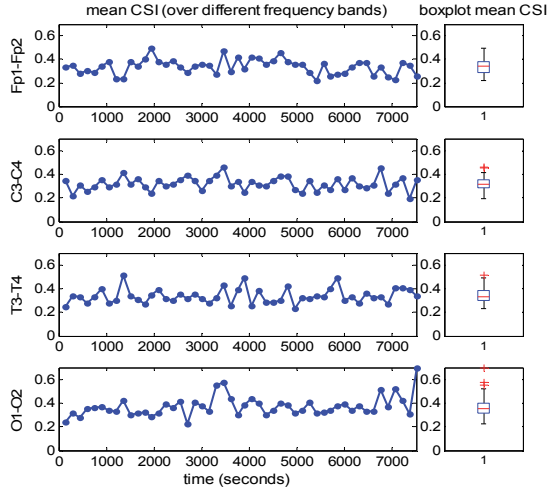

Figure 2: a. mean CSI values, averaged over frequency bands, shown for different channel pairs; b. box plot mean CSI.

3.3 One-class SVM Classification

A simple threshold on the median value of the patient box plots is not sensitive enough, leading to a lot of false positive detections. Therefore, we need to incorporate the different features into a more complex classification system. Here, a classifier is constructed and trained for every channel pair, resulting in four classifiers. Unfortunately, one classifier incorporating all features is not enough, since pathologies can result in lateralization of only one region of the brain. This means, the hemisphere's symmetry elsewhere in the brain can be normal compared to patients of similar age. In addition, there is a huge unbalance between the number of normal and abnormal classes (Figure 4).

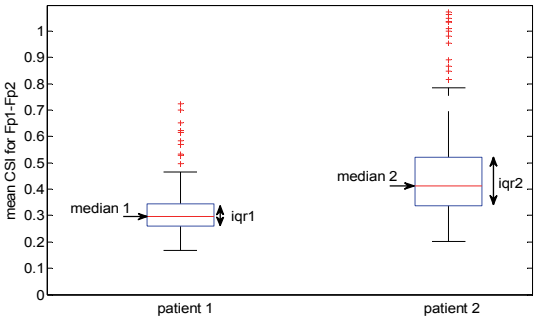

Figure 3: Different features for a normal patient (patient 1) and a patient with hemimegalencephaly-haemorrhage (patient 2), measurements taken at comparable PMA.

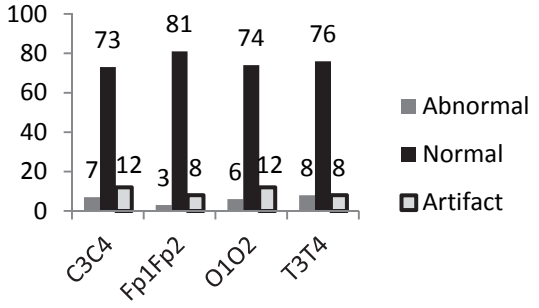

Figure 4: Number of normal/abnormal patients, number of data excluded for analysis since artefacts are present in the data.

For this purpose, one-class SVM classifiers are applied. It will give the value +1 in a small region capturing the pathological class and -1 for all other data points (normal class). The data is mapped in the feature space corresponding to the radial basis kernel function and to separate them from the origin with maximum margin (Schölkopf, 2000). On which side of the hyperplane a new point will fall in feature space, will decide to which class this point will belong.

The quadratic problem to separate the data from the origin is solved (Schölkopf, 2001):

$$\min_{w\in F,\varepsilon\in\mathbb{R}^l,\rho\in\mathbb{R}} \quad \frac{1}{2}\|w\|^2 + \frac{1}{\nu l}\sum_i \varepsilon_i - \rho \qquad (2)$$

$$\text{subject to } (w\cdot\phi(x_i)) \geq \rho - \varepsilon_i, \quad \varepsilon_i > 0$$

Here, w and ρ are a weight vector and an offset to parameterize the hyperplane in feature space associated with the kernel (Schölkopf, 2000). Outliers are those points defined as points on the wrong side of the hyperplane (within margin ρ of the origin). ε_i are the outlier distances from the hyperplane.

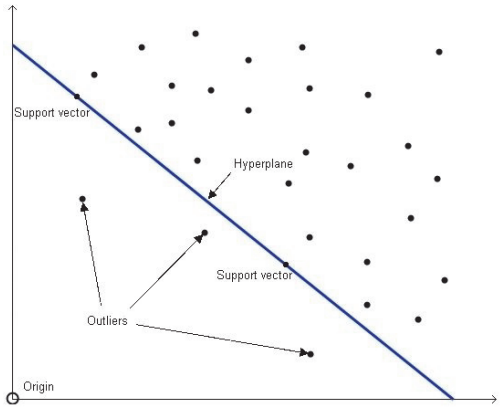

Figure 5: Principle of the quadratic problem of the one-class SVM (Fourie, 2011).

In order to choose the best subset of model parameters, we have trained the hyper parameters of this classifier, namely ν and γ. ν is an upper bound on the fraction of training errors and a lower bound of the fraction of support vectors. When ν decreases, a misclassification will have a large impact on the objective. This can also result in overfitting of the data. First, ν is adapted from 0.05 to 0.2 in steps of 0.05, since it resembles how many outliers can be without the class. For the data (Figure 4), this is a percentage of around 10% for each group. γ is constrained to a default value by 1/number_features=0.25 (Chih-Chung, 2011).

As we applied the RBF kernel, γ represents the width of the Gaussian kernel, representing the boundary to catch all the training data within the class. Therefore, in a next step ν and γ are adjusted simultaneously to find the optimal set of hyper parameters. ν (range 0.05 to 0.2) is adapted in steps of 0.05 and γ (range 0.1 to 0.7) in steps of 0.15.

We made use of leave-one-out 10-fold cross-validation (loo-cv) to optimize the model parameters. Thereby, a comparison of the accuracies of the models built on each subset is carried out. Due to the small sample at disposal, a result in term of best loo-cv error is presented here, as a (necessarily small) test set would not be very informative. Moreover, within a small test set there is necessarily huge variability. The loo-cv error is called the specificity of the model (true negative rate). After the model is trained, we can define the sensitivity as the true positive rate. In other words, how many abnormal EEG patterns have been found by the SVM model.

4 RESULTS AND DISCUSSION

Results of the optimization of the four one-class SVM classifiers are shown in Table 1. For the C3C4 classifier, $\nu = 0.15$ is chosen to be the optimal value. For the other 3 classifiers, $\nu = 0.1$ gives the highest sensitivity and specificity. Grid search for optimal combination of γ and ν by adapting them simultaneously resulted in the same optimal value for the model parameter γ (=0.25). Due to the relatively small sample size, both high sensitivity and specificity are difficult to obtain. Therefore, we set the minimum specificity on 70%, considering that not too many false alarms can be given in case there is no pathological pattern.

We want to emphasize that we want to detect patients with lateralized lesions; cases confirmed by clinical doctors through lesion(s) on MRI images. For example, lateralized lesions can be hemimegalencephaly or cases with convulsions. These cases were found by all four optimized one-class SVM classifiers. However, there are still some false negatives in the C3C4 classifier and T3T4 classifier. That is, there exists always three false negatives for the T3T4 classifier; abnormal patterns which are not detected (Table 1). Two of these false negatives are not detected by most T3T4 classifiers. An explanation could be that one patient has corpus collosum agenese, what affects more the asynchrony instead of the asymmetry. The other false negative has mainly asymmetry in only one frequency band (theta), which is presumably not picked up by the classifier as we work with the average over the different frequency bands (CSI). In fact, clinical doctors visually detected the lesion on the other hemisphere on the MRI than they did on the EEG measurement, indicating it is hard to specify the lateralization. In addition, one patient with pathologic asymmetry is never detected by the C3C4 classifier. The pathologic EEG pattern, comparing the C3 and the C4 channel, is very short compared to the length of the whole measurement. Moreover, the lesion is located in the thalamus (=sub cortical), which is less pronounced in the cortical EEG signals. Overall, the Fp1Fp2 and the O1O2 classifiers are performing well, all pathologies are detected.

Table 1: Specificity (%) of the four trained one-class SVMs with 10-fold cross-validation. Sensitivity (%) on detecting the abnormal EEG patterns. For this small sample, we would go for ν =0.15 in case of the C3C4 classifier and ν = 0.1 for the three other classifiers.

	C3C4		Fp1Fp2		O1O2		T3T4	
ν	spec	sens	spec	sens	spec	sens	spec	sens
0.05	67.12	42.86 (3/7)	61. 72	66.67 (2/3)	74.32	100 (6/6)	64.47	62.5 (5/8)
0.1	71.23	57.14 (4/7)	71.60	100 (3/3)	75.67	100 (6/6)	73.68	62.5 (5/8)
0.15	76.71	71.43 (5/7)	67.9	66.67 (2/3)	75.67	100 (6/6)	68.42	62.5 (5/8)
0.2	68.49	85.71 (6/7)	66.67	66.67 (2/3)	68.92	83.33 (5/6)	61.84	62.5 (5/8)

In future, other classification models can be applied to this problem, which also take the unbalance between classes into account. For example, weighted least squares-support vector machines (LS-SVM) can be trained (Cawley, 2006). In general, weighted loss functions are appropriate to balance the contribution of classes that are not equally represented. Nevertheless, further improvement of the applied one-class SVM model is possible by adding more features into the training phase. Thereby, we think of asymmetry defined in clinical papers; a ratio of amplitude difference. Another possibility is to search more localized in time, in case of convulsions, instead of calculating features over the whole EEG measurement. However, this will probably lead to a higher rate of false positive detections introduced by short-time artifacts. In addition, more patients will be incorporated in future to refine and tune the model. In this way, normal values for the channel symmetry indexes can be established, dependent on the physiologic maturation.

5 CONCLUSIONS

The developed algorithm is a successful strategy to detect abnormal lateralized lesions in the neonatal brain. Based on non-invasive EEG measurements, we can extract useful features to distinguish physiological from pathological asymmetry. Therefore, we have used characteristics derived from the channel symmetry index as input features for a classifier. Moreover, automated assessment creates possibilities to look over a longer period of time in an objective way including the experience of clinical doctors. Future work will focus on fine-tuning the algorithm based on a larger dataset, adding clinical relevant features to the classifier, and trying out other weighted SVMs. Measuring and analyzing connectivity in the neonatal brain is of added value and high interest for the overall assessment in the Neonatal Intensive Care Units for EEG diagnosis.

ACKNOWLEDGEMENTS

I want to thank M. Signoretto, B. Hunyadi and M. Milosevic for their valuable discussions. Research supported by Research Council KUL: GOA MaNet, PFV/10/002 (OPTEC), several PhD/postdoc & fellow grants; Flemish Government: FWO: Postdoc grants, projects: G.0427.10N (Integrated EEG-fMRI), G.0108.11 (Compressed Sensing) G.0869.12N (Tumor imaging) G.0A5513N (Deep brain stimulation) IWT: PhD grants, projects: TBM 070713-Accelero, TBM 080658-MRI (EEG-fMRI), TBM 110697-NeoGuard iMinds: SBO dotatie 2013, ICONs: NXT_Sleep, FallRisk Flanders Care: Demonstratieproject Tele-Rehab III (2012-2014) Belgian Federal Science Policy Office: IUAP P719/ (DYSCO, `Dynamical systems, control and optimization', 2012-2017); ESA AO-PGPF-01, PRODEX (CardioControl) C4000103224 EU: RECAP 209G within INTERREG IVB NWE programme, EU HIP Trial FP7-HEALTH/ 2007-2013 (n° 260777), EU MC ITN TRANSACT 2012 (n° 16679), ERC Advanced Grant: BIOTENSORS (n° 39804), ERASMUS EQR: Community service engineer (n° 539642-LLP-1-2013).

REFERENCES

Cawley, G. C., 2006. Leave-One-Out Cross-Validation Based Model Selection Criteria for Weighted LS-SVMs. In *IJCNN,* IEEE: p. 1661-1668.

Chih-Chung Chang and Chih-Jen Lin, LIBSVM : a library for support vector machines. In *ACM Transactions on Intelligent Systems and Technology*, 2: 27:1--27:27, 2011. Software available at http:// www.csie.ntu.edu.tw/~cjlin/libsvm.

Fourie, C., van Niekerk, A., Mucina, L., 2011. Optimising

a one-class SVM for geographic object based novelty detection. In *Proceedings of the first AfricaGeo conference*. Cape Town, South Africa: p. 1-25.

Hayashi-Kurahashi, N., Kidokoro, H., Kubota, T. et al., 2012. EEG for predicting early neurodevelopment in preterm infants: an observational cohort study. In *Pediatrics*, 130: p.891-897.

Hellström-Westas, L., Klette, H., Thorngren-Jerneck, K., et al., 2001. Early prediction of outcome with aEEG in preterm infants with large intraventricular hemorrhages. In *Neuropediatrics*, 32: p. 319-324.

Hellström-Westas, L. and Rosén I., 2005. Electroencephalography and brain damage in preterm infants. In Early Human Development, 81: p. 255-261.

Holmes, G. and Lombroso, T., 1993. Prognostic value of background Patterns in the neonatal EEG. In *Journal of Clinical Neurophysiology*, p. 323-352.

Hunyadi, B., De Vos, M., Signoretto, M., et al., 2011. Automatic Seizure Detection Incorporating Structural Information. In *Artificial Neural Networks and Machine Learning–ICANN*, 6791: p. 233–240.

Hunyadi, B., De Vos, M., Van Paesschen, W., et al., 2010. A mimicking approach for human epileptic seizure detection. In *Proc. of the International Biosignal Processing Conference.* Berlin, Germany: p. 1-4.

Koolen, N., Jansen, K., Vervisch, J., et al., 2013. Automatic burst detection based on line length in the premature EEG. In *Proc. of the 6th International Conference on bio-inspired systems and signal processing (BIOSIGNALS).* Barcelona, Spain: p. 105-111.

Le Bihannic, A., Beauvais, K., Busnel, A., et al., 2012. Prognostic value of EEG in very premature newborns. In *Arch Dis Child Fetal Neonatal*, 97: p.106-109.

Okumura, A., Hayakawa, F., Kato, T., et al., 2002. Developmental outcome and types of chronic-stage EEG abnormalities in preterm infants. In *Developmental Medicine and Child Neurology*, 44: p. 729-734.

Palmu, K., Wikström, S., Hippeläinen, E., et al., 2010. Detection of 'EEG bursts' in the early preterm EEG: Visual vs. automated detection. In *Clinical Neurophysiology*, 121: p. 1015-1022.

Schölkopf, B., Smola, A. J., Williamson, R. C., et al., 2000. New Support Vector Algorithms. In *Neural Computation*, 12: p. 1207-1245.

Schölkopf, B., Platt, J.C., Shawe-Taylor, J., et al., 2001. Estimating the Support of a High-Dimensional Distribution. In *Neural Computation,* 13: p. 1443-1471.

Smyser, C. D., Inder, T. E., Shimony, J.S., et al., 2010. Longitudinal analysis of neural network development in preterm infants. In *Cerebral cortex*, 20: p. 2852-2862.

Vanhatalo, S. and Kaila, K., 2006. Development of neonatal EEG activity: from phenomenology to physiology. In *Seminars in fetal & neonatal medicine*, 11: p. 471-478.

Van Putten, M. and Tavy, D., 2004. Continuous Quantitative EEG Monitoring in Hemispheric Stroke Patients Using the Brain Symmetry index. In *Stroke*, 35: p. 2489-2492.

Vecchierini, M. F., André, M., d'Allest, A. M., et al., 2007. Normal EEG of premature infants born between 24 and 30 weeks gestational age: Terminology definitions and maturation aspects. In *Clinical Neurophysiology*, 37: p.311-323.