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Abstract	In this paper we investigate the relationship between functional connectivity (FC) and early brain maturation. On one hand, the objective was to provide a model able to predict age in premature babies, on the other hand to shed light on the maturation mechanism of brain interdependencies in first stages of life. The study was a follow-up considering the data in (Koolen2016). FC was assessed through the means of mean squared coherence (MSC), phase locking value (PLV) and activity synchrony index (ASI). A feature selection indicated that coherence in beta bands and ASI were the best predictors of the postmenstrual age (PMA), so they were combined in a single multivariate linear regression model. The prediction performance showed the root mean square error equal to 2.05 weeks. Further, the results indicated a decrease/increase in coherence/ASI with age. This can be due to the shift from the thalamo-cortical connections to cortico-cortical connections,

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Linear and nonlinear functional connectivity methods to predict brain maturation in preterm babies

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Abstract

In this paper we investigate the relationship between functional connectivity (FC) and early brain maturation. On one hand, the objective was to provide a model able to predict age in premature babies, on the other hand to shed light on the maturation mechanism of brain interdependencies in first stages of life. The study was a follow-up considering the data in [1]. FC was assessed through the means of mean squared coherence *(MSC),* phase locking value *(PLV) and* activity synchrony index *(ASI). A feature selection indicated that coherence in β bands and ASI were the best predictors of the postmenstrual age (PMA), so they were combined in a single multivariate linear regression model. The prediction performance showed* the root mean square error *($\sqrt{MSE}$) equal to 2.05 $weeks$. Further, the results indicated a decrease/increase in coherence/ASI with age. This can be due to the shift from the thalamo-cortical connections to cortico-cortical connections, leading to more localized and task dedicated networks. Finally, a larger correlation of ASI and coherence was found in the left hemisphere compared to the right hemisphere.*

Keywords *Preterm infants, Early brain maturation, Coherence, ASI, Functional connectivity*

1 Introduction

The need for maturation charts of pediatric brain development in order to detect neural disorders has been widely discussed in literature [2]. Franke [2] has assessed the brain maturation through the study of functional connectivity (FC) using fMRI. In particular, the author focused on the prediction of the chronological age until adolescence using a support vector regression (SVR) in two cohorts of children, one born full-term and the other born prematurely. In the early newborns, as their brain matures, the EEG waveforms change their characteristics [3]. Therefore, the EEG can be a valuable, non-invasive and much easier recording procedure, than fMRI [4], to describe the wiring evolution of the neuron pools in the cerebral cortex. Gonzalez [4] argued the necessity to use new approaches to describe brain maturation beyond linear tools, such as the EEG spectrum. In particular, Gonzalez [4] applied linear and nonlinear methods to describe the functional EEG interdependencies. Among the linear methods, the *mean squared coherence* (MSC) has already been used in literature to evaluate maturation in children as function of age [5], and in preterm infants as function of gestational age or postmenstrual age (PMA) [6]. In addition, phase synchronization methods like *phase locking value* (PLV) have also been applied in brain maturation studies [4]. The goal of this study is twofold: on one hand, it aims to provide a simple model for the estimation of maturational age in these infants (as discussed by [7]), on the other hand it evaluates the brain connectivity in preterm neonates as function of the PMA, using linear and nonlinear methods to estimate FC, such as the *activity synchrony index* (ASI).

2 Methods

2.1 Dataset

This study was carried out using EEG recordings from 48 preterm neonates. 20 of these recordings have been used in a previous study [1]. The additional 28 subjects were recruited at the same neonatal intensive care unit (NICU), in the University Hospitals Leuven. The patients included in this study had a PMA ranging from 27 to 42 weeks. EEG measurements for each patient were recorded at least once during their stay at the unit and lasted at least 2 hours. The total number of recordings was 104. Labels for quiet sleep (QS) and active sleep/awake (AS) were provided. The EEG was recorded using a sampling frequency of 256 or 500 Hz. The measuring electrodes were located according to the 10-20 system. The monopolar electrodes (F_1,F_2,C_3,C_4,T_3,T_4,O_1,O_2) were chosen as first step to study FC among brain regions. Each channel was bandpass filtered between 1-20 Hz and downsampled to 100 Hz. Only the quiet sleep epochs were considered for this study, since the co-occurrence of activity bursts during quiet sleep has been considered as a key component in assessing background activity [8].

2.2 Functional connectivity measures

In order to quantify the FC among the different EEG channels, three methods were applied. Since each method is applied on channels in a pairwise fashion and there are 8 monopolar electrodes, each FC index provides a matrix 8×8, where each row and each column represents a specific channel. The obtained matrix is symmetric because the coupling direction was not investigated. The first method was the cross-coherence, a linear method defined between signal x and y at frequency f as

$$k^2_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)} \quad (1)$$

where $P_{xy}(f)$ is the cross-spectrum between the two times-series and $P_{yy}(f)$, $P_{xx}(f)$ are the autospectra of the signals. k^2_{xy} was computed for each channel pair in 30s epochs without overlapping and the spectra were computed using the Welch method with 5 s windows and 50% overlapping, as suggested by [5]. For each pair, the MSC was computed in the frequency bands: δ (1-4 Hz), θ (4-8Hz), α (8-13 Hz), β (13-21 Hz) [4]. The second method used is PLV, which is defined as

$$PLV_{xy} = \frac{1}{N}\left|\sum_{t=0}^{N} e^{j\varphi_{xy}(t)}\right| \quad (2)$$

where $\varphi_{xy}(t) = \varphi_x(t) - \varphi_y(t)$. $\varphi_x(t)$ and $\varphi_y(t)$ represent the phases of the time series x and y and are derived from the analytical signal $\tilde{x}(t) = x(t) + jx_H(t)$ (or $\tilde{y}(t)$), where $x_H(t)$ is the Hilbert transform of $x(t)$. The complete signal, with a frequency band between 1-20 Hz, is used in this method. The last one is the nonlinear method ASI, which is computed by Räsänen [8] using the *energy weighted temporal dependency function* (ETDF):

$$ETDF_{xy}(\tau) = \sum_{ij} A(a_i)A(b_j)\frac{p^2(a_i, b_j)}{p(a_i)p(b_j)} \quad (3)$$

where a_i and b_j are downsampled and requantized versions of the channels $x(t)$ and $y(t)$, with $y(t)$ delayed by a lag τ. $A(a_i)$, $A(b_j)$ are the amplitudes respectively for the sample a_i and b_j. $p(*,*)$ and $p(*)$ are the joint and marginal probability distributions respectively. The ASI is defined as follows

$$ASI_{xy} = \frac{ETDF_{norm}(\tau = 0)}{(\frac{1}{101}\sum_{\tau=-50}^{\tau=50} ETDF_{norm}(\tau))} \quad (4)$$

where $ETDF_{norm}(\tau) = ETDF_{xy}(\tau) - \min\{ETDF_{xy}(k), k \in [-50, 50]\}$. $ETDF$ is derived from the definition of mutual information for different time lags between the signals [8]. Both PLV_{xy} and ASI_{xy} were computed on 5 min epochs without overlapping. These three indices provide 6 matrices 8×8 for each considered epoch (2 matrices for the the nonlinear methods, 4 matrices for the coherence). The matrices belonging to QS periods are subsequently averaged for each EEG measurement. In order to have a more general overview of neonatal brain connectivity, the average matrix can be used to derive indices of general synchrony, intra and interhemispheric connectivity, as well as anterior and posterior connectivity as shown in [1]. In particular, the last two are obtained as average values of matrix entries associated respectively to anterior electrodes and posterior electrodes. In a similar way, the intrahemispheric connectivity is measured as the average of the entries associated to the left or to the right electrodes. The interhemispheric connectivity is just the average of the symmetric channel combinations between hemispheres. In addition to the connectivity measures, the evolution and the loss of a discontinuity pattern in the brain electrical activity with maturation can be easily monitored by means of the *suppression curve* (SC), as thoroughly reported in [3]. This index was computed in 5 min epochs of EEG channels and was then averaged over all QS epochs.

2.3 Linear Regression and statistical analysis

One of the main objectives of this study is to develop a model for the prediction of PMA. On one hand we evaluated the performance of a model containing information coming from the different features extracted from the EEG signals. On the other hand, in order to evaluate whether the use of different features improves the prediction capabilities of the model, we also study the performance of different regression models using features from ASI, PLV or coherence analysis solely. In both cases a linear multi-variable model was chosen. A total of 229 features were extracted from each recording. For the PLV and coherence matrices, only the off-diagonal upper triangular elements were considered as input for the model. For the ASI matrix also the diagonal elements were included. Due to the reduced amount of training points, 104, we performed a feature selection procedure prior the training of the multivariate models. First, the predictive power of each feature, individually, was assessed by means of the *root mean squared error* ($\sqrt{MSE}$), which was computed from results of a linear regression between each feature and the PMA. For this phase the data was split in training set and a test set (2/3-1/3) 100 times. After the estimation of the model on the training set, the performance as $\sqrt{MSE}$ and Pearson's correlation (ρ) between the prediction and the response variable in the *test set* were reported as median with *interquartile range*, i.e. q_{50}(IQR) for each variable. In the first case, the model considering all the extracted attributes, eleven features with lowest $\sqrt{MSE}$ were selected for the final model. Afterwards, we applied least absolute shrinkage and selection operator (LASSO) regression from the obtained features set to reduce even more the number of input regressors and the amount of redundant information. For the models using ASI, PLV and coherence as input only the LASSO procedure was used in order to reduce the dimensionality of the input space. Once the features were

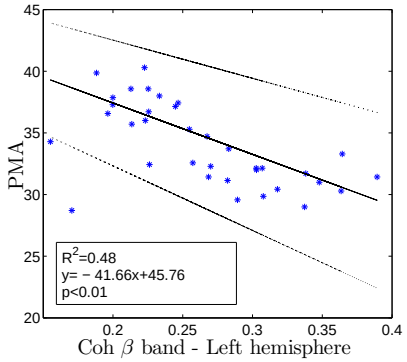

Figure 1: Regression plot of PMA as function of $k^2_{LEFT}(\beta)$ on the *test set*.

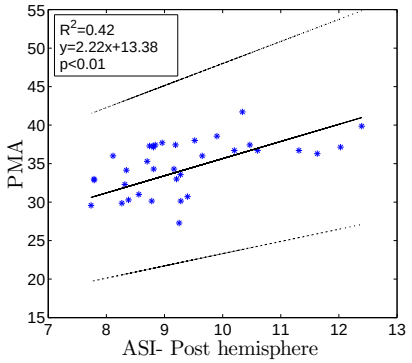

Figure 2: Regression plot of PMA as function of ASI_{POST} on the *test set*.

selected, the dataset was divided once again in training set and a test set (2/3-1/3) in order to train the different multivariate models. For both cases, the data splitting and the LASSO were performed 100 times. The performance of the different models were measured using fraction of explained variance R^2 and the $\sqrt{MSE}$ on the *test set*, presented as q_{50}(IQR).

3 Results

Table 1 shows the features with lowest MSE on the test set as individual predictors of PMA, the Pearson's correlation (ρ) and the number of times when the correlation is significant. For each iteration or re-estimation of the model, the correlation was always significant for most of the twelve features. Among the top eleven features, the SC was the best to describe brain maturation using neonatal EEG. SC shows a negative correlation with PMA, as shown in [3]. Looking at linear methods, the coherence in β band is the attribute that mostly reflects the cerebral evolution of the infants, with the lowest $\sqrt{MSE}$, compared to the coherence in other bands (Table 1). The remaining features belong to the different ASI indexes (Table 1). As shown in [6], $MSC(\beta)$ presents a negative correlation with age. An example of linear regression between MSC in the left brain hemisphere ($k^2_{LEFT}(\beta)$) and PMA is reported in Figure 1. Table 1 also shows that ASI is the nonlinear connectivity index that describes the

Features	$\sqrt{MSE}$ $(weeks)$	ρ (%)
SC	2.23(0.37)	-78.28(8.16) §
$k^2_{LEFT}(\beta)$	2.62(0.43)	-69.40(11.66) §
ASI_{C_4,C_4}	2.73(0.33)	66.14(7.31) §
ASI_{POST}	2.79(0.41)	59.91(10.36) §
ASI_{C_3,C_3}	2.80(0.30)	62.43(9.80) §
$k^2_{C_4,O_2}(\beta)$	2.81(0.38)	-62.54(11.79) #
ASI_{O_1,O_1}	2.82(0.40)	61.03(13.15) §
ASI_{LEFT}	2.83(0.34)	62.66(9.69) §
ASI_{C_3,C_4}	2.90(0.39)	57.54(11.06) §
ASI_{O_2,O_2}	2.91(0.45)	59.63(14.29) §
ASI_{ANT}	2.92(0.42)	58.27(12.64) §

Table 1: The best eleven predictors of PMA with the lowest MSE using a linear regression model. MSE and Pearson's ρ are reported as q_{50}(IQR). § means $p \leq 0.05$ for each iteration, # means $p \leq 0.05$ for more than 90 iterations.

Features	$\sqrt{MSE}$ $(weeks)$	R^2
Best eleven	2.05(0.44)	.64(.14) §
PLV matrix	2.72(0.66)	.37(.26) §
ASI matrix	2.80(0.57)	.37(.25) §
$k^2_{xy}(\delta)$ matrix	3.19(0.91)	.16(.51) §
$k^2_{xy}(\theta)$ matrix	2.63(0.43)	.40(.30) §
$k^2_{xy}(\alpha)$ matrix	2.85(0.58)	.35(.23) §
$k^2_{xy}(\beta)$ matrix	2.63(0.43)	.42(.20) §

Table 2: Comparison between the different multivariate regression models to predict PMA. MSE and R^2 are reported as q_{50}(IQR). § means $p \leq 0.01$ for each iteration.

evolution of the brain with lowest $\sqrt{MSE}$. The selected ASI indexes cover most of the brain region: posterior, anterior and left (ASI_{POST}, ASI_{LEFT}, ASI_{ANT}). It can also be noticed that auto-ASI (the ASI computed between a channel and itself) of channels C_4, C_3, O_1 and O_2 are listed in the top eleven. Figure 2 shows the linear regression between ASI_{POST} and PMA, where a positive correlation can be seen, as reported in Table 1 and in [1]. Table 2 shows the performance of the regression models using a multivariate approach. The combination of best features in a linear multivariate regression increases the prediction performance, i.e. the total $\sqrt{MSE}$ is reduced to 2.05 $weeks$, as shown by Table 2. The median fraction of explained variance is $R^2 = .64$ ($p \leq 0.01$). Table 2 compares the performance also with the other models where the features come from the 6 FC connectivity matrices, as described above. However, the model in which best features are selected outperforms the other ones. One can also observe that matrices of coherence in β and θ bands have better performances in terms of MSE and R^2 compared to the nonlinear index matrices, whose prediction power is comparable with the best individual features in Table 1. All the regression models were statistically significant in all 100 iterations.

4 Discussions

As discussed by [3], the brain maturation is reflected by the progressive disappearance of bursts in the EEG, leading to a more continuous waveform. Indeed, the maturation modifies the amplitude distribution in the signal, making the SC a good predictor of PMA [3]. By combining different FC measures a better model for the prediction of PMA was obtained. Further, these results are comparable with the ones obtained by [7], whose slightly lower MSE can be explained by the usage of a smaller cohort of babies and a more complex regression model. Besides the methodological aspects, interesting neurophysiological aspects emerge. The coherence decreases with the postnatal maturation, as shown by Table 1 and Figure 1. Meijer [6] highlighted that this reduction is on one hand a consequence of the EEG waves evolution (reduction of bursts, that are also called δ bursts or brushes), on the other hand of the development of more localized and decentral connections for specific tasks. In the early development, the infant brain is moving from thalamocortical connections to cortico-cortical connections, which tend to separate the brain region from a functional point of view. This is also reflected by the relative increase of EEG power in β band, as shown in [7] and [4]. An important aspect of this study is that the decrease of coherence was accompanied by an increase of ASI, i.e. an increase of synchrony of neonates' cerebral activity [1]. It is interesting to notice that some of the best individual features to predict age are the auto-ASI, as symptom of more localized connections. For sake of completeness, the increase in auto-ASI values can be due to the reduction of the discontinuity pattern in the infant EEG with maturation. Moreover, both ASI and coherence in β bands are showing left spatial indices more correlated with PMA, probably due tot the left asymmetry shown by [1].

5 Conclusion

The study showed that FC connectivity measures can improve the PMA prediction performance compared to EEG features, like SC, by means of multivariate linear regression. In addition, FC connectivity changes with the postnatal maturation. In particular, the EEG coherence in β band and ASI show specific trends with PMA: the first one decreases and the latter one increases with increasing age. This might be a consequence of the shift from thalamocortical to cortical-cortical connections in the neonates cerebral networks.

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