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Universal characteristics of evolution and development are inherent in fetal autonomic brain maturation

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ABSTRACT

Adverse prenatal environmental influences to the developing fetus are associated with mental and cardiovascular disease in later life. Universal developmental characteristics such as self-organization, pattern formation, and adaptation in the growing information processing system have not yet been sufficiently analyzed with respect to description of normal fetal development and identification of developmental disturbances. Fetal heart rate patterns are the only non-invasive order parameter of the developing autonomic brain available with respect to the developing complex organ system. The objective of the present study was to investigate whether universal indices, known from evolution and phylogeny, describe the ontogenetic fetal development from 20 weeks of gestation onwards. By means of a 10-fold cross-validated data-driven multivariate regression modeling procedure, relevant indices of heart rate variability (HRV) were explored using 552 fetal heart rate recordings, each lasting over 30 min. We found that models which included HRV indices of increasing fluctuation amplitude, complexity and fractal long-range dependencies largely estimated the maturation age (coefficients of determination 0.61–0.66). Consideration of these characteristics in prenatal care may not only have implications for early identification of developmental disturbances, but also for the development of system-theory-based therapeutic strategies.

1. Introduction

Individual ontogenetic development does not follow a hardwired program. It is initiated by the fusion of egg and sperm at conception. A process of growth, adaptation and self-organization takes place based on the genetic code and intrauterine environmental influences. A better understanding of the developmental mechanisms of these processes together with a corresponding diagnostic assessment could help to identify adverse fetal developmental trajectories, justify developmental-theory based therapeutic strategies and guide favorable behavior during pregnancy.

The system-theoretic approach is based on the behavior of open dissipative systems which is universal in evolutionary processes in physics and nature (Bertalanffy, 1968; Nicolis and Prigogine, 1977; Kauffman, 1993; Haken, 1983). The dynamics of these processes are typically characterized by increasing fluctuation amplitude, and increasing complexity and pattern formation.

As early as 1866, Haeckel had described similarities between the phenomena of phylogeny (evolution of species) and ontogeny (development of the individual fetus) (Haeckel, 1866). Although his statement “ontogeny repeats phylogeny” no longer matches the knowledge of modern developmental biology, it indicates similarities between the two phenomena that today can be explained by means of the universal mechanisms of self-organization and adaptation in association with the individual genetic code.

We recently applied these universal system-theory indices to fetal heart rate rhythms, (also known as heart rate variability, HRV). The indices provide a representative order parameter of the developing autonomic brain in relation to the developing complex organ systems. We found that > 50% of the heart rate dynamics between 24 und 38 weeks of gestation could be explained by indices related to the increasing fluctuation amplitude, and increasing complexity and pattern

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formation (Hoyer et al., 2013b; Hoyer et al., 2014). The resulting functional fetal autonomic brain age score (fABAS), initially developed using magnetocardiographic (MCG) recordings, has in the meantime been confirmed using independent MCG and cardiotocographic (CTG) recordings of normal fetuses by other study centers (Hoyer et al., 2015; Hoyer et al., 2017). Furthermore, we could show that fABAS values are decreased in intrauterine growth restricted (IUGR) fetuses, a result that indicates their developmental deviation (Hoyer et al., 2013b; Hoyer et al., 2015; Hoyer et al., 2017).

Long-range self-similar (fractal) correlations in morphological and temporal structures are essential in evolution and phylogeny (Green, 1991). They were not taken into consideration in the previously developed fABAS. However, the evolving fetal integrative autonomic control was reported as being associated with increasing functional associations across time scales of heart rate patterns (Wallwitz et al., 2012; Gieraltowski et al., 2015). Therefore, the list of HRV parameter candidates was extended to include fractal long-range correlations, estimated by detrended fluctuation analysis (DFA) (Peng et al., 1995). Furthermore, the list of complexity measures was extended to include symbolic dynamics (Cysarz et al., 2015) and Lempel Ziv complexity (LZC) (Lempel and Ziv, 1976).

The present work aims at validating the previous finding that universal developmental characteristics reflected in HRV parameters essentially model fetal autonomic maturation. Validation will be undertaken in an objective way by using a data-driven statistical algorithm under consideration of the extended HRV parameter set.

2. Materials and methods

2.1. Subjects

Data was obtained from the study database at the Biomagnetic Center, Department of Neurology and from the Department of Obstetrics, both at the Jena University Hospital. A total of 552 recordings from 185 mothers with singleton normal maturating pregnancies during non-stress situations aged between 18.8 and 40 weeks of gestation (WGA) were included in the study. Approval was obtained from the local Ethics Committee of the Friedrich Schiller University. All subjects gave their written consent to participate in the study.

The following conditions served as exclusion criteria for the normal cohort:

Maternal:

- known heart disease
- diabetes mellitus
- medication affecting cardiac functions
- abuse of nicotine, alcohol or drugs
- previous administration of synthetic glucocorticoids

Fetal:

- known chromosomal abnormalities
- sonographically identified malformations
- uterine contractions during recording
- cardiac arrhythmias
- previous glucocorticoid exposition
- intrauterine growth restriction (IUGR)

2.2. Workflow

In a 10-fold cross-validation procedure, relevant HRV parameters were selected from the entire HRV parameter set using a sequential floating forward selection procedure. Fig. 1 illustrates the workflow from data collection to the regression models. In essence, this sequence follows 8 points, which can be summarized as follows:

1. Acquire data and calculate Normal-to-Normal (NN) beat intervals
2. Calculate 58 HRV features
3. Divide samples randomly into K-fold cross-validation with nearly equal sample sizes regarding the fetus ID
4. For each polynomial order $p = 1, 2, 3$
   a) for each fold k = 1, …, K
      i) Find a subset of good features that produce a low standard error, using a sequential floating forward selection algorithm in combination with the 1 SE, 2 SE and 3 SE rule on all samples except those in fold k
5. Accumulate the subsets found by means of selection with the different SE rules
6. For each fold k = 1, …, K
   a) Train a multivariate regression model using just the feature subsets from step 4 and using all of the samples except those in fold k
   b) Use the trained regression model to predict the gestational age of the fetuses for the samples in fold k
7. Accumulate the standard error estimates from step 6 b) over all K folds to produce the cross validation estimations of the prediction errors for the considered models
8. Test for significant differences between the models using Wilcoxon signed rank test

2.3. Data acquisition

All measurements were taken in a magnetically shielded room at the Biomagnetic Center using the vector-magnetograph ARGOS200 (ATB, Chieti, Italy) with 195 channels. The recordings were performed during daytime over a period of 30 min with a sampling rate of 1024 Hz.

Pregnant women were positioned supine or with a slight twist to either side to prevent compression of the inferior vena cava by the pregnant uterus. The Dewar was positioned as close as possible above the fetal heart as determined by sonographic localization but without contact.

In the recordings, the heart beats were detected using an independent component-based strategy (Schmidt et al., 2014) and NN beat intervals series were calculated. The NN series were screened for artifacts and non-stationarities. The frequency of corrected artificial beats was below 5%.

2.4. Developmental characteristics & HRV parameters

Based on the NN interval series, 58 HRV parameters were calculated. The considered parameters are organized in Table 1 according to the universal developmental characteristics. For calculation details, see individual references.

2.5. Statistical modeling

34 linear and 24 nonlinear HRV parameters were calculated using MatLab, version 2014a. Some of the features such as the Sample Entropy and the Maximum Lyapunov Exponent are either very similar due to the calculation procedure and differ only in their parametrization, or they differ in the used window size. For example, the feature LZC was calculated on the complete signal. But LZC_{512} was calculated on 50% overlapping HR segments with a length of 512 heartbeats accumulated and then averaged.

All further steps were processed using the statistical computing and graphical visualization software R, version 3.4.1. The HRV feature matrix was divided into nearly equal-sized folds. Care was taken to ensure that all measurements derived from one fetus remained together to avoid possible interdependencies between the trainings and the test data in the cross-validation scheme.

The next main step involved the feature subset selection (FSS). The aim is to select a suitable subset of features out of the calculated HRV