Fetal Heart Rate Pattern in Prenatal Diagnosis – Fetal Autonomic Brain Age Score

Dirk Hoyer[1], Uwe Schneider[2]

[1]Jena University Hospital, Biomagnetic Center, Hans Berger Clinic for Neurology, Friedrich Schiller University of Jena, Germany
[2]Jena University Hospital, Department of Obstetrics, Friedrich Schiller University of Jena, Germany

Abstract

Fetal heart rate patterns provide valuable information about normal fetal maturation. For heart rate variability (HRV) analysis to be successful in prenatal diagnosis the selection of appropriate HRV indices is required. Those indices were organized according to universal principles of developmental biology. Key characteristics of evolution and self-organization are increasing fluctuation amplitude, increasing complexity and pattern formation. Related HRV indices were used to propose a fetal autonomic brain age score (fABAS). We estimated fABAS from magnetocardiographic recordings (21.4-40.3 weeks of gestation) preclassified in quiet (n=113, 63 females) *and active sleep (n=286, 145 females) by cross-validated multivariate linear regression models in a cross-sectional study. fABAS explained 66/63% (training / validation set) of the variance by age in quiet and 51/50% in active sleep. We conclude that functional autonomic brain age can be assessed based on universal developmental indices obtained from fetal heart rate patterns.*

1. Introduction

Universal principles of complex system behaviour provide a link between self-organization and adaptation, phylogeny, ontogeny, and individual development [1-5]. HRV can be considered as order parameter [6] of system controlled by the autonomic nervous system (ANS). Predominant universal principles of development are (i) increasing fluctuation amplitude, (ii) increasing complexity, and (iii) pattern formation.

Accordingly, increasing fluctuation amplitudes, increasing as well as decreasing complexity, and the differentiation of behavioral pattern were reported to be dependent on gestational age [7-9]. The increasing functional integration may furthermore be reflected by dependencies over longer time scales [10, 11].

The present report is a part of a more comprehensive outline recently published [12].

2. Methods

2.1. Subjects and data acquisition

In a cross-sectional prospective observational study 399 normal singleton fetuses, healthy according to standard obstetric observation methods in nonstress situation, obtained in the Biomagnetic Center (Jena University Hospital), were allocated.

The study was approved by the Local Ethics Committee of the Friedrich Schiller University. All subjects gave their written consent to be included in the study.

All magnetocardiographic recordings were performed during day time over a period of 30 min.

In the recordings the heart beats were detected and normal-to-normal (NN) beat intervals series calculated. The NN series were screened for artifacts, arrhythmias and non-stationarities and 10 min intervals of active and quiet sleep selected after a consensus decision by three independent obstetricians blinded to heart rate analysis according to an advanced version of standard criteria [12, 13]

2.2. HRV indices and statistical models

The HRV indices were organized according to their interpretation in the context of general developmental indices as shown in Table 1. Fluctuation amplitude was estimated based on quantiles in a robust way. Complexity was recently found strongly age dependent at coarse graining scale 3 [11]. Patterns of particular interest are decelerations and accelerations reflected in skewness and baseline stability is reflected in VLF/LF band power.

The fetal age was predicted by multivariate linear regression models (stepwise inclusion/exclusion of factors) for each sleep state independently. The resulting models are considered as fetal autonomic brain age score (fABAS). The models were 70/30 split sample cross-validated. P<0.05 was considered significant. For details see [12].

Table 1. Universal developmental characteristics and HRV indices, adapted from [12]

Parameter	Calculation	Interpretation
Fluctuation amplitude		
amplitude	20-95 inter-quantile distance of detrended NN interval series	Fluctuation range of heart beat intervals above an approximated baseline
Complexity		
gMSE(3)	Generalized Mutual Information at coarse graining level 3 of NN interval series	Complexity of heart rate patterns essentially modulated by complex sympatho-vagal rhythms
Pattern formation		
skewness	Skewness of NN interval series	Asymmetry, decline of deceleration and formation of acceleration patterns
pNN5	Percentage of differences between adjacent NN intervals > 5 ms	Formation of vagal rhythms
VLF/LF	Ratio between VLF (0.02-0.08 Hz) and LF (0.08-0.2 Hz) power	Baseline fluctuation in relation to sympatho-vagal modulations

3. Results

The resulting multivariate models included HRV indices of increasing amplitude, increasing complexity and pattern formation in active sleep. The missing amplitude increase in quiet sleep reflects the state definition in connection with the increasing frequency of active states (see Table 2).

Table 2. Multivariate regression models. Coefficient of determination R^2 (training / validation set), standardized regression coefficient beta, significance, from [12].

Parameter	R^2	beta	p-value
active			
amplitude		0.37	<0.001
gMSE3	0.51 / 0.50	0.22	<0.001
skewness		0.33	<0.001
pNN5		0.11	0.090
VLF/LF		0.12	0.012
quiet			
gMSE3		0.46	<0.001
skewness	0.66 / 0.63	0.24	<0.001
VLF/LF		-0.26	<0.001
pNN5		0.14	0.054

The resulting individual fABAS values are shown in Figures 1 and 2.

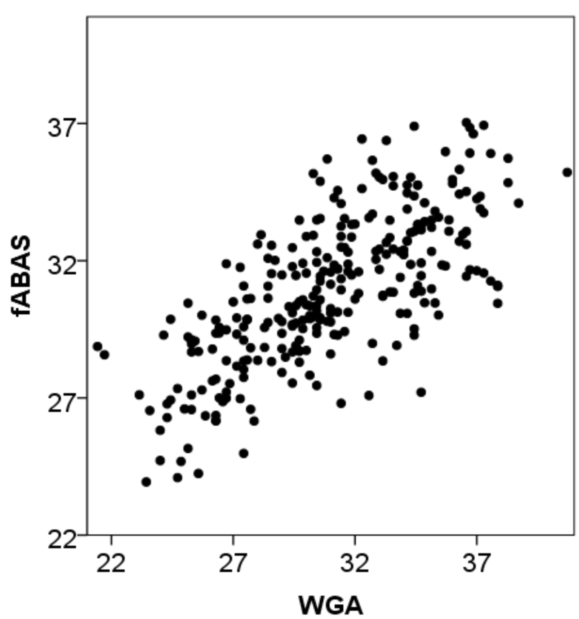

Figure 1. Fetal autonomic brain age score (fABAS) versus chronological age in active sleep (adapted from [12]).

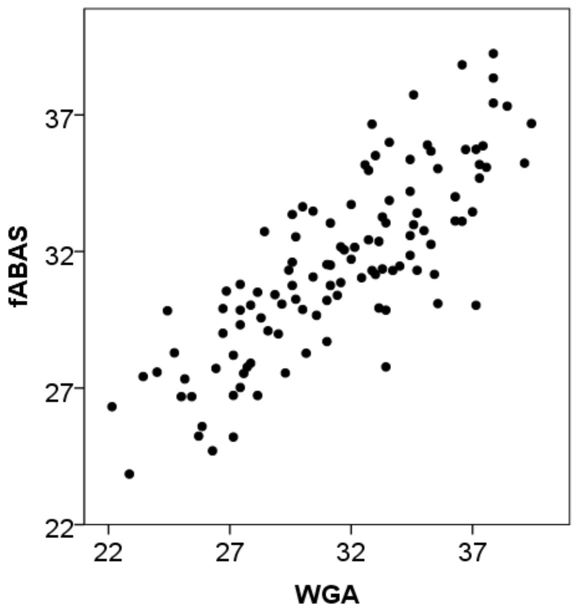

Figure 2. Fetal autonomic brain age score (fABAS) versus chronological age in quiet sleep (adapted from [12])

4. Conclusions

Universal principles of evolution and self-organization contribute to the individual fetal development. Based on corresponding heart rate patterns the "fetal Autonomic Brain Age Score" was proposed. The consideration of those principles in prenatal diagnosis may have implications for a more comprehensive understanding of fetal developmental disorders as well as for designing novel concepts in prophylaxis and therapy.

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References

[1] Bertalanffy Lv. General system theory : foundations, development, applications. New York, NY: Braziller, 1968.

[2] Kauffman SA. The Origins of Order: Self-Organization and Selection in Evolution. Oxford, New York: Oxford University Press, 1993.

[3] Nicolis G, Prigogine I. Self-organization in nonequilibrum systems : from dissipative structures to order through fluctuations. New York u.a.: Wiley, 1977.

[4] Haeckel E. General morphology I: General anatomy of organisms. II. General developmental history of organisms. [in german] Berlin, 1866.

[5] Darwin C. The orign of species. London, 1859.

[6] Haken H. Synergetics: An Introduction. Nonequilibrium Phase Transition and Self-Organization in Physics, Chemistry, and Biology. Berlin, New York: Springer Verlag, 1983.

[7] Van Leeuwen P, Cysarz D, Lange S, Gronemeyer D. Increase in regularity of fetal heart rate variability with age. Biomed Tech (Berlin) 2006; 51:244-7.

[8] Van Leeuwen P, Lange S, Bettermann H, Gronemeyer D, Hatzmann W. Fetal heart rate variability and complexity in the course of pregnancy. Early Hum Dev 1999; 54:259-69.

[9] Hoyer D, Heinicke E, Jaekel S, Tetschke F, Di Pietro Paolo D, Haueisen J, Schleusner E, Schneider U. Indices of fetal development derived from heart rate patterns. Early Hum Dev 2009; 85: 379-86.

[10] Gieraltowski J, Hoyer D, Tetschke F, Nowack S, Schneider U, Zebrowski J. Development of multiscale complexity and multifractality of fetal heart rate variability. Auton Neurosci 2013: Feb 25.

[11] Hoyer D, Nowack S, Bauer S, Tetschke F, Rudolph A, Wallwitz U, Jaenicke F, Heinicke E, Goetz T, Huonker R, Witte OW, Schleussner E, Schneider U. Fetal development of complex autonomic control evaluated from multiscale heart rate patterns. Am J Physiol Regul Integr Comp Physiol 2013; 304:R383-92.

[12] Hoyer D, Tetschke F, Jaekel S, Nowack S, Witte OW, Schleussner E, Schneider U. Fetal functional brain age assessed from universal developmental indices obtained from neuro-vegetative activity patterns. PLoS One 2013; 8:e74431.

[13] Nijhuis JG, Prechtl HF, Martin Jr CB, Bots RS. Are there behavioural states in the human fetus? Early Hum Dev 1982; 6: 177-95.

Address for correspondence:

Dirk Hoyer
University Hospital, Biomagnetic Center.
Hans Berger Department of Neurology
Erlanger Allee 101
D-07747 Jena
Germany

Dirk.Hoyer@med.uni-jena.de