Published in final edited form as:

Clin Neurophysiol. 2014 July ; 125(7): 1353–1359. doi:10.1016/j.clinph.2013.11.018.

Quantification of fetal magnetoencephalographic activity in low-risk fetuses using burst duration and interburst interval

Srinivasan Vairavan, PhD^a, Rathinaswamy B. Govindan, PhD^b, Naim Haddad, MD^c, Hubert Preissl, PhD^{d,e}, Curtis L. Lowery, MD^d, Eric Siegel, MS^f, and Hari Eswaran, PhD^d

^aGraduate Institute of Technology, University of Arkansas at Little Rock, Arkansas, USA
(Currently with Philips Research North America, Briarcliff Manor, NY, USA)

^bDivision of Fetal and Transitional Medicine, Children's National Medical Center, Washington, DC, USA

^cWeill Cornell Medical College in Qatar, Education City, Doha, Qatar

^dSARA Fetal MEG Center, Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

^eFetal MEG Center, University of Tuebingen, Tuebingen, Germany

^fDepartment of Biostatistics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Abstract

Objective—To identify quantitative MEG indices of spontaneous brain activity for fetal neurological maturation in normal pregnancies and examine the effect of fetal state on these indices.

Methods—Spontaneous MEG brain activity was examined in 22 low-risk fetal recordings with gestational age (GA) ranging from 30–37 weeks. As major quantitative characteristics of spontaneous activity, burst duration (BD) and interburst interval (IBI) were studied in correlation with GA and fetal state.

Results—IBI showed a decrease with gestational age (-0.21 sec/week, $P = 0.0031$). This trend was only maintained in the quiet-sleep state. With respect to BD, no significant trends were detected with GA and state.

Conclusion—IBI can be quantified as a fetal brain maturational parameter. The decrease in IBI over gestation was similar to the trend reported in the preterm neonatal EEG studies. Quiet sleep could be the optimal state to study such MEG maturational indices.

© 2013 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

Corresponding Author: Hari Eswaran Ph.D., University of Arkansas for Medical Sciences, 4301 W. Markham Slot 518, Little Rock, Arkansas 72205, USA, Tel: +1 501 686-5847, Fax: +1 501 603-1544, eswaranhari@uams.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Significance—With further investigation, indices extracted from spontaneous fetal brain activity may serve as an early warning for fetal neurological distress.

Keywords

Magnetoencephalography; fetus; EEG; quantification; burst duration; interburst interval; brain activity

1. Introduction

Although it has been common practice to evaluate the structure of the fetal brain using ultrasound (Awoust and Levi, 1983), the measurement of fetal electrocortical signals would open new horizons complementing the anatomical parameters of neurological maturation with new parameters for evaluating physiology and function.

Electroencephalography (EEG) has long been used to study neurological maturation and cerebral dysfunction in neonates (Parmelee et al., 1969) but its usefulness could not be extended to the fetal stage. Besides EEG, magnetoencephalography (MEG) (Hari and Salmelin, 2012) has been established during recent decades for the recording of human brain activity. This technique is non-invasive and records the magnetic fields corresponding to the electric currents generated by neurons in the brain. Unlike EEG, the MEG technique is not dependent on intervening tissue impedances, which makes it uniquely suited to study the magnetic fields generated in the fetal brain.

Since the ontogeny of spontaneous brain activity of the premature infant has been well-studied using EEG (Clancy et al., 2003; Scher, 2004; Mizrahi et al., 2004; Lamblin et al., 1999; André et al., 2010), we postulated that these trends occur even in the fetal stage of life and can be documented using fetal MEG (fMEG). Since its feasibility was reported by Rose and Eswaran in 2004, significant progress has been made towards evaluating spontaneous fMEG as a potentially viable technique to study fetal neurological maturation. fMEG patterns have been shown to share many similarities with established EEG features in premature infants at comparable ages. Some fMEG findings include (Rose and Eswaran, 2004; Eswaran et al., 2007; Haddad et al., 2011) (1) Signals equivalent to delta brushes and sharp transients of the neonatal EEG, (2) a decrease in the percentage of discontinuous epochs with advancing gestational age (GA), especially in quiet sleep, and (3) abundance of discontinuous epochs in quiet compared to active sleep, mainly before 35 weeks' GA.

Spontaneous fetal MEG has also been explored in potentially pathological conditions (Eswaran et al., 2012; Kotini et al., 2002). Using spectral analysis and computing relative power between the frequency bands for both low-risk and intrauterine growth restricted (IUGR) fetuses, we have shown that the average relative power was highest in the lowest-frequency delta band, and decreased monotonically in higher frequency bands (Eswaran et al., 2012). Furthermore, when compared to fetuses exhibiting normal growth, the IUGR fetuses showed a significant difference in relative power only in the early part of the third trimester (28–31 weeks), suggesting that growth restriction may have a more pronounced effect on the fetal brain in early rather than the late stage of the third trimester (Eswaran et al., 2012).

To further enhance the utility of fMEG, in the current study we proposed to identify quantitative indices from the selectively identified discontinuous epochs in the recordings from fetuses in normal healthy pregnancies. A discontinuous pattern is characterized by the occurrence of bursts of MEG activity alternating with periods of quiescence. We investigated the interburst interval (IBI) and burst duration (BD) as quantitative indices for neurological maturation in low-risk pregnancies (Neimark et al., 2008). We studied the dependence of these parameters on GA and fetal state – mainly quiet and active sleep.

2. Materials and Methods

2.1 Instrument and Recording Procedures

The measurements in this study were performed using a non-invasive 151-channel SQUID (Superconducting Quantum Interference Device) fMEG system called SARA (SQUID Array for Reproductive Assessment). SARA, built by CTF Systems Inc., Port Coquitlam, BC, Canada, was specifically designed to study different aspects of maternal and fetal physiology (Preissl et al., 2004; Lowery et al., 2009). The sensors in the SARA system are arranged in a concave array. The mother simply sits and leans forward against the smooth surface of the array, allowing the SQUID sensors to receive signals from the anterior maternal abdomen. To reduce the effects of environmental noise, SARA is installed in a magnetically shielded room (Vakuumschmelze, Germany).

An ultrasound examination (GE Voluson 730) was performed prior to the fMEG recording to document general fetal position, head localization, and biometric measurements. The fMEG data were recorded in continuous mode at a sampling rate of 312 Hz with a bandwidth of 0-100 Hz. The recording times ranged from 10 to 30 minutes and were performed without any stimulation to the mother and the fetus.

2.2 Subjects

A total of 22 low-risk fetal recordings with GA ranging from 30 to 37 weeks were included in the study. The study protocol was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences (UAMS), and a signed consent for participation was obtained from each mother. Maternal demographics including age, weight, height, race and maternal medical conditions were recorded. Only pregnant women with no known maternal or fetal complications at the time of recruitment were included. The GA of the fetus was based on their last clinical visit as determined by their physician. The GA along with the position and distance of the fetal head from the maternal abdomen is shown in Table 1. The distance from the fetal head to the maternal abdomen ranged from 1.0 to 8.5 cm; thus, it is within adequate range of the SARA sensors for fMEG recordings.

2.3 Fetal MEG extraction

The overall approach consisted of extracting and quantifying fetal spontaneous MEG, and correlating it with fetal states. Figure 1 provides a flowchart outlining the steps involved in the processing of the data. Extraction of the spontaneous MEG data was accomplished by using a novel procedure (details in Vairavan et al, 2010) that combines Independent Components Analysis (ICA) (Hyvarinen and Oja, 2000) and Hilbert Phase (HP) (Govindan

et al., 2009) analysis. The quantification was done by computing BD and IBI of the discontinuous patterns. The state of the fetus was determined in parallel by computing its fetal heart-rate pattern and constructing its actocardiogram.

We applied the HP approach to the independent components (IC) to discriminate the spontaneous brain activity from rest. The unprocessed MEG data corresponding to the sensors in a small subset with a radius of 5 cm (encompassing 8 sensors) of 1-min duration were chosen and subjected to the steps shown in Figure 1 for the determination of spontaneous brain activity.

The data from the chosen subset of sensors were band-pass filtered between 0.5 and 25 Hz using a Butterworth filter with zero phase distortion. Further, this filtered data was then subjected to ICA decomposition. To delineate the components that correspond to the interfering sources from brain signals, the ICs were full-wave rectified (FWR) using first-difference operation followed by the computation of absolute values. The HP metric was computed for the FWR ICs. Potential interfering sources of fMEG are maternal and fetal cardiac signals and background noise. These sources were separated based on the previous finding (refer Vairavan et al., 2010) that the magnitude of the HP metric of FWR ICs decreases in the following order: Cardiac signals (maternal followed by fetal), fetal brain signals and background noise. Based on this property of the HP metric, we delineated the brain components from the rest of the components corresponding to interfering sources.

We further investigated the isolated brain- activity ICs for any cardiac residuals and fetal breathing activity. Even in a short window of 1 min, the duration that was chosen for analysis, stationarity of the data can be lost due to fetal movement. As a result, the independency constraint, a basic assumption of ICA, cannot be achieved, and this can leave partially attenuated cardiac signals (cardiac residuals) in the brain components. In order to investigate the cardiac-residual content of the detected ICs, a spectral estimation with a resolution of 1 Hz was performed. An occurrence of a distinct spectral peak at the frequency of cardiac pulsation (average heart rate in that one-minute window) was considered indicative of cardiac residuals, and windows that had this peak were discarded from the analysis.

In addition to the cardiac residuals, fetal breathing artifacts can also hamper the detection of spontaneous brain activity. In order to overcome this problem, we applied the following steps: 1) study the frequency signatures of fetal breathing as observed in the power spectrum of fetal heart rate and 2) look for a significant peak in the coherence spectrum between each IC and the heart rate in the fetal-breathing frequency range (Gustafson et al., 2011).

In the final step after the ICs have been separated from background noise, cardiac and breathing signals, we selected the top 5 IC channels based on the magnitude of HP metrics. These channels were used to determine discontinuous patterns in the data to quantify the burst parameters. Our HP metrics-based approach was used to detect the discontinuous patterns. The scoring methodology was verified by the neurologist as reported in our previous publication describing the algorithm (Vairavan et al., 2010). The discontinuous patterns were scored in windows of 30 seconds' duration in order to account for the longer

IBI. The HP metrics were computed for shorter windows of 4 sec with a 2-sec overlap. The discontinuous patterns were then investigated for BD and IBI. The details of the BD/IBI detection algorithm can be found elsewhere (Vairavan et al., 2009).

2.4 Behavioral State Quantification

In order to accurately quantify spontaneous fMEG data, we documented the behavioral state of the fetus (1F – quiet sleep, 2F – active sleep, 3F – quiet awake and 4F – active awake). As described above, in fMEG studies, the fetal heart signals i.e. fetal magnetocardiogram (fMCG) signals, are obtained as a byproduct. It has been shown that the fMCG is capable of accurately and reliably detecting cardiac rhythm (Leuthold et al., 1999; Lowery et al., 2003). In general, the peak of the QRS is detected to acquire the RR intervals and calculate the heart rate (Leuthold et al., 1999). Due to the high sensitivity of the fMCG to the orientation and position of the fetal heart, the magnitude of each QRS peak can be used to quantify gross body movements of the fetus (Zhao and Wakai, 2002; Govindan et al., 2011). As the distance of the fetal heart to the sensor array increases, the magnitude of the QRS decreases and vice versa. Rotational changes will also cause the magnitude of the fMCG to change. After extracting the information related to gross body movement and heart rate pattern from fMCG obtained during fMEG recordings, we then classified the fetal behavioral state using criteria defined by Nijhuis (1993). Further details on the classification methods are described in Haddad et al (2011). Based on this prior study on fetal states (Haddad et al., 2011) and the observation (Nijhuis, 1993) that the fetus spends the majority of time in either the quiet or active sleep states, we limited our data analysis to 1F (quiet sleep) and 2F (active sleep) states.

2.5 Statistical Analysis

Statistical analysis was conducted with SAS v9.3 (The SAS Institute, Cary, NC). Mixed-models regression techniques were used to model the correlation structure among different data points from the same recording. One-minute windows from each recording were classified into behavioral states as 1F, 2F, or failures to classify. Two mixed-models regressions were conducted. In the first regression, the behavioral-state information was withheld, all data points were used in the analysis, and the mixed model contained “GA” and “Recording” as the fixed effect and random effect, respectively. In the second regression, the behavioral-state information was provided, failures to classify were excluded from the analysis, and the mixed model contained “GA” and “State” as the fixed effects, and “Recording” and “State nested within Recording” as the random effects. Statistical tests were considered statistically significant if $P < 0.05$, and statistically at a trend level if $0.05 < P < 0.10$.

3. Results

There were 22 low-risk recording sessions with GA between 30 and 37 weeks with recording times up to 30 minutes. Figure 2 shows an example of discontinuous (2a) and continuous (2b) fMEG patterns from a 36-week-GA fetus. Figure 3 provides a representation of maternal MCG, fMCG, fMEG along with the fetal state as determined by

the changes in heart rate and actogram from a 36-week fetus. In the fMEG channel shown, there is an IC component output with arbitrary units.

A total of 974 BD and 479 IBI values were obtained, with maximums of 94 and 50 values, respectively, from a single recording. The variation of BD and IBI with GA are shown in the top and bottom, respectively, of Figure 4. IBI showed a significant decrease in average duration with GA (-0.2129 seconds per week, $P=0.0031$). With respect to BD, no significant trend (0.03440 seconds per week, $P=0.7804$) was observed.

In the next step, we incorporated the fetal-state measures to investigate the relationship of IBI and BD with GA. To accomplish this task, only the windows where the states could be determined were used. A total of 505 values were obtained for BD, with 387 in 1F and 118 in 2F. Similarly, a total of 415 values, 312 in 1F and 103 in 2F, were obtained for IBI. Figure 5 shows the variation of BD (top) and IBI (bottom) with respect to GA. The fetuses showed decreases in IBI with gestation that achieved statistical significance in the 1F state (-0.2615 seconds per week, $P = 0.0015$). Likewise, the 2F state showed a decrease over GA, although it was not significant (-0.1624 seconds per week, $P = 0.3017$). Furthermore, no significant correlations were observed in burst duration for either 1F or 2F states.

To evaluate the consistency of these findings between subjects, we estimated the variance components from the mixed-models analysis. Total variance (σ^2) is equal to sum of the variance between recordings ($\sigma^2_{\text{between}}$) and the variance within recordings (σ^2_{within}). The variance between recordings for BD and IBI were 0.14 and 0.05 squared seconds (sec^2), respectively, whereas the variance within recordings for BD and IBI were 52.6 and 8.5 sec^2 , respectively.

4. Discussion

This is the first attempt to establish maturational indices based on detecting the discontinuous patterns and computing the corresponding BD and IBI in fetal brain activity recorded by MEG. There are several EEG studies (Biagioni et al., 2007; Conde et al., 2005; Hahn et al., 2005) that underline the significance of quantification of discontinuous brain patterns which can shed light in the assessment of neurological maturation in preterm infants and neonates. Niemark et al. (2008) tracked the quantitative maturational changes in the EEG in very preterm infants that were recorded weekly for a month with a normal neurological follow-up at 6 months and one year of age. Their findings reveal that the mean IBI and the length of discontinuity decreased with conceptional age. In a previous study, we showed that there is a decrease in fMEG discontinuity with advancing GA (Haddad et al., 2011). In the current study, we additionally observed a similar IBI trend in the low-risk fetuses over GA. The mean $\pm$ standard error of IBI at 30 weeks was 7.04 ± 0.38 sec, and decreased to 5.55 ± 0.21 sec at the 37th week of gestation. This is a significant milestone in defining fMEG maturational indices in normal pregnancies. Establishing normative data is crucial when evaluating a diagnostic device before expanding into its potential applications to differentiate pathological conditions.

A possible limitation of the study is that the earliest recording included was collected at 30 weeks GA. Although it may be valuable to record brain activity earlier than what we have

reported in this study, there are several issues that can limit the possibility of including fetuses below 28 weeks GA. The extraction of brain signals in earlier GA is limited by the decrease in signal to noise ratio. Further, the fMEG studies including auditory and visual evoked responses that have been reported start only at 28 weeks GA based on the fact that most of the sensory development reaches a certain maturation milestone around 24 weeks GA.

The gradual reduction in the IBI with advancing GA was only noted during quiet sleep. In our previous work (Haddad et al., 2011), we found a decrease in the amount of fMEG discontinuity with advancing GA mainly during quiet sleep, again without a significant trend in active sleep. Thus, it may be reasonable to suggest that quiet sleep may be the optimal state to study fMEG evolution through different GAs. The fact that quiet sleep produces more predictable and consistent trends could be related to the characteristic of cerebral activity recorded during a state of relatively low gross fetal body movements. In neonatal EEG recorded during quiet sleep, the dominant signals include short duration high-voltage discharges interspersed with long attenuated segments. In the case of active sleep, the EEG consists of a more semi-continual pattern of mid to high-voltage activity with relatively higher gross body movements. Considering the fact that, in general, fMEG records low magnetic field signals, the short duration high amplitude activity collected during quiet sleep has a better detection rate compared to the background with a clear separation between the bursts and the IBIs, leading to an accurate estimate of the IBI length and its evolution with advancing GA. In contrast, active sleep segments have a longer continuous pattern which may result in more contamination from movement artifacts. This greater susceptibility to artifacts can result in fewer segments detected thus making the active sleep state recordings less optimal for reliable quantitative analysis. Furthermore, the variance within a recording constitutes >99% of total variance for both BD and IBI. This observation is consistent with the fact that the burst phenomenon is a highly dynamic process that shows wide variation during the course of a single recording. However it also implies that the findings are consistent between subjects.

Although the neurophysiological basis of the findings are not fully understood, previous reports have suggested that the decreases in IBI and the amount of discontinuity associated with advancing gestational age are related to the maturation of the hyperpolarizing inhibitory action of GABA and the corresponding intracortical interneuronal circuits. Early in development, GABAergic transmission has a rather excitatory role, allowing the generation of the intermittent bursts of activity. During maturation, the expression patterns of chloride-regulating molecules change, rendering a more hyperpolarizing and inhibitory GABA effect. This is paralleled by a reduction in the intermittent spontaneous bursts and the IBIs separating them, with the emergence of continuous rhythms in different frequency bands (Rivera et al., 1999; Vanhatalo and Kaila, 2006). With regards to BD, although it did not prove to be a useful maturational variable in our study, this parameter needs to be explored further since even in the preterm EEG recordings there are conflicting results on its trend with conceptional age. Biagioni et al (2007) reported observing no significant variation with BD with age whereas Hayakawa et al (2001) showed an increasing trend.

In EEG studies on pre-term infants, the IBI is sensitive not only to brain maturity but also to the presence of neurological illness. It has been demonstrated that IBI is related to adverse outcome and abnormalities seen in cranial ultrasound (Biagioni et al., 2007). In a prospective study, Benda et al (1989) established that the prolonged IBI (>30 sec) is related to intraventricular hemorrhages and fatal outcomes. Furthermore, Conde et al (2005) observed significantly longer IBI in preterm infants with major ultrasound lesions. IBI was proven to be a reliable MEG maturational parameter in the current study. In the future, we plan to evaluate these indices in pregnancies at risk for compromised neurological development. We would like to study whether absolute measurements and trends of IBI throughout GAs can separate normal pregnancies from the ones at risk. For that purpose, we are in the process of performing studies in pregnancies with IUGR, fetal chromosomal abnormalities, malformations, and maternal chronic diseases related to increased risk for fetal hypoxia.

In summary, fMEG is being investigated as a non-invasive tool to evaluate the fetal brain. Significant advances in this field have been achieved so far, but we still have a lot to learn. Expanding on our knowledge in this field may lead to the addition of a highly useful tool in managing complications such as prematurity, in-utero asphyxia, preeclampsia and IUGR. Deviations from the normal maturational indices, once established, may serve as an early warning for fetal neurological distress.

Acknowledgments

This study was supported by grants from the National Institutes of Health (NIH) R01EB007826 and 5R01NS036277-03, USA, and Hubert Preissl was supported by DFG (TR-SFB 654).

References

- André M, Lamblin MD, d'Allest AM, Curzi-Dascalova L, Moussalli-Salefranque F, S Nguyen The T, et al. Electroencephalography in premature and full-term infants. Developmental features and glossary *Neurophysiol Clin*. 2010; 40:59–124.
- Awoust J, Levi S. Neurological maturation of the human fetus. *Ultrasound Med Biol*. 1983; 2:583–87. [PubMed: 6400283]
- Benda GL, Engel RC, Zhang YP. Prolonged inactive phase during the discontinuous pattern of prematurity in the electroencephalogram of very-low birthweight infants. *Clin Neurophysiol*. 1989; 72:189–197.
- Biagioni E, Frisone MF, Laroche S, Kapetanakis BA, Ricci D, Adeyi-Obe M, et al. Maturation of cerebral electrical activity and development of cortical folding in young very preterm infants. *Clin Neurophysiol*. 2007; 118:53–9. [PubMed: 17095296]
- Clancy, RR.; Bergqvist, AGC.; Dlugos, DJ. Neonatal electroencephalography. In: Ebersole, JS.; Pedley, TA., editors. *Current practice of clinical electroencephalography*. Philadelphia, PA, USA: Lipincott/Williams and Wilkins; 2003. p. 160-234.
- Conde JR, de Hoyos AL, Martinez ED, Campo CG, Perez AM, Borges AA. Extrauterine life duration and ontogenic EEG parameters in preterm newborns with and without major ultrasound brain lesions. *Clin Neurophysiol*. 2005; 116:2796–809. [PubMed: 16253552]
- Eswaran H, Haddad N, Shihabuddin BS, Preissl H, Siegel ER, Murphy P, et al. Non invasive Detection and Identification of Brain Activity Patterns in the Developing Fetus. *Clin Neurophysiol*. 2007; 118:1940–46. [PubMed: 17638586]

- Eswaran H, Govindan RB, Haddad N, Siegel ER, Preissl HT, Murphy P, et al. Spectral power differences in the brain activity of growth-restricted fetuses. *Early Hum Dev.* 2012; 88:451–4. [PubMed: 21982162]
- Govindan RB, Vairavan S, Wilson JD, Preissl H, Vrba J, Lowery CL, et al. Understanding dynamics of the system using Hilbert phases: an application to study neonatal and fetal brain signals. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2009; 80:046213. [PubMed: 19905421]
- Govindan RB, Vairavan S, Umit UD, Wilson JD, McKelvey SS, Preissl HT, et al. A Novel Approach to Track Fetal Movement Using Multi-sensor Magnetocardiographic Recordings. *Ann Biomed Eng.* 2011; 39:964–72. [PubMed: 21140290]
- Gustafson KM, Allen JJ, Yeh HW, May LE. Characterization of fetal diaphragmatic magnetomyogram and the effect of breathing movements on cardiac metrics of rate and variability. *Early Hum Dev.* 2011; 87:467–75. [PubMed: 21497027]
- Haddad N, Govindan RB, Vairavan S, Siegel ER, Temple JR, Preissl HT, et al. Correlation between Fetal Brain Activity Patterns and Behavioral States: An exploratory fetal magnetoencephalography study. *Exp Neurol.* 2011; 228:200–5. [PubMed: 21237155]
- Hahn JS, Monyer H, Tharp BR. Interburst interval measurements in the EEGs of premature infants with normal neurological outcome. *Electroencephalogr Clin Neurophysiol.* 1989; 73:410–8. [PubMed: 2479519]
- Hari R, Salmelin R. Magnetoencephalography: From SQUIDS to neuroscience. *Neuroimage.* 2012; 61:386–96. [PubMed: 22166794]
- Hayakawa M, Okumura A, Hayakawa F, Watanabe K, Ohshiro M, Kato Y, et al. Background electroencephalographic (EEG) activities of very preterm infants born at less than 27 weeks gestation: a study on the degree of continuity. *Arch Dis Child Fetal Neonatal Ed.* 2001; 84:F163–7. [PubMed: 11320041]
- Hyvarinen A, Oja E. Independent component analysis: algorithms and applications. *Neural Networks.* 2000; 13:411–30. [PubMed: 10946390]
- Kotini A, Koutlaki N, Anninos P, Liberis V, Hatzimihail A, Anastasiadis P. Fetal magnetoencephalography in intrauterine growth retarded pregnancies. *Prenat Diagn.* 2002; 22:1093–7. [PubMed: 12454964]
- Lamblin MD, Andre M, Challamel MJ, Cursi-Dascalova L, d'Allest AM, De Giovanni E, et al. Electroencephalography of the premature and term newborn. Maturation aspects and glossary. *Neurophysiol Clin.* 1999; 29:123–219. [PubMed: 10367287]
- Leuthold A, Wakai RT, Martin CB. Noninvasive in utero assessment of PR and QRS intervals from the fetal magnetocardiogram. *Early Hum Dev.* 1999; 54:235–43. [PubMed: 10321790]
- Lowery CL, Campbell JQ, Wilson JD, Murphy P, Preissl H, Malak SF, et al. Noninvasive antepartum recording of fetal S-T segment with a newly developed 151-channel magnetic sensor system. *Am J Obstet Gynecol.* 2003; 188:1491–97. [PubMed: 12824983]
- Lowery CL, Govindan RB, Preissl H, Murphy P, Eswaran H. Fetal neurological assessment using noninvasive magnetoencephalography. *Clin Perinatol.* 2009; 36:701–9. [PubMed: 19732622]
- Mizrahi, EM.; Hrachovy, RA.; Kellaway, P. Atlas of neonatal electroencephalography. Philadelphia, PA, USA: Lipincott/Williams and Wilkins; 2004. Elements of normal neonatalencephalogram; p. 55-91.
- Neimark HJ, Andriessen P, Pasman J, Vles JS, Zimmermann LJ, Oetomo SB. Analyzing EEG maturation in preterm infants: The value of a quantitative approach. *J Neonatal Perinatal Med.* 2008; 1:131–144.
- Nijhuis, JG. Fetal behavioral states. In: Chervnak, FA.; Isaacson, GC.; Campbell, S., editors. *Ultrasound in obstetrics and gynecology.* Vol. 1. Boston (MA): Little, Brown and Co.; 1993. p. 447-55.
- Parmelee AH, Akiyama Y, Stern E, Harris MA. A periodic cerebral rhythm in newborn infants. *Exp Neurol.* 1969; 25:575–84. [PubMed: 4243503]
- Preissl H, Lowery CL, Eswaran H. Fetal Magnetoencephalography: Current Progress and Trends. *Exp Neurol.* 2004; 190:S37–43. [PubMed: 15498540]
- Rose DF, Eswaran H. Spontaneous neuronal activity in fetuses and newborns. *Exp Neurol.* 2004; 190:S37–43. [PubMed: 15498540]

- Rivera C, Voipio J, Payne JA, Ruusuvuori E, Lahtinen H, Lamsa K, et al. The K/Cl co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. *Nature*. 1999; 397:251–5. [PubMed: 9930699]
- Scher, M. Electroencephalography of the newborn: normal and abnormal features. In: Niedermeyer, E.; Lopez da Silva, F., editors. *Electroencephalography: basic principles, clinical applications, and related fields*. Boston, MA: Lippincott–Williams and Wilkins; 2004.
- Vairavan S, Eswaran H, Haddad N, Rose DF, Preissl HT, Wilson JD, et al. Detection of discontinuous patterns in spontaneous brain activity of neonates and fetuses. *IEEE Trans Biomed Eng*. 2009; 56:2725–9. [PubMed: 19695985]
- Vairavan S, Eswaran H, Preissl HT, Wilson JD, Haddad N, Lowery CL, et al. Localization of Spontaneous Magnetoencephalographic Activity of Neonates and Fetuses Using Independent Component and Hilbert Phase Analysis. *Proc IEEE Eng Med Biol Soc*. 2010; 1:1344–47.
- Vanhatalo S, Kaila K. Development of neonatal EEG activity: From phenomenology to physiology. *Semin Fetal Neonatal Med*. 2006; 11:471–8. [PubMed: 17018268]
- Zhao H, Wakai RT. Simultaneity of fetal heart rate acceleration and fetal trunk movement determined by fetal magnetocardiogram and actocardiography. *Phys Med Biol*. 2002; 47:839–46. [PubMed: 11931474]

Highlights

- Examined fetal neurological maturation indices in normal pregnancies using magnetoencephalographic recordings.
- Interburst interval (IBI) decreases with gestational age - a trend similar to EEG findings in premature neonates.
- Tracking IBI in quiet sleep state could provide valuable insight into fetal neurological maturation.

Fig 1.

The flowchart provides an overview of the data processing steps to extract and quantify fetal spontaneous activity. BD and IBI are extracted and correlated with fetal behavioral states which are obtained by processing the actocardiogram.

Fig 2.

An example of a (a) discontinuous and (b) continuous brain pattern observed in fMEG data recorded from a 36 week GA fetus. The amplitude is measured in magnetic field units of Tesla (1fT = 10^{-15} T). Discontinuity feature marked on tracing shows bursts of activity separated by flat or lower voltage IBI.

Fig 3.

A representative tracings from a 36 week GA fetus showing one channel each of maternal MCG, fetal MCG and fetal MEG respectively. The fMEG channel is an IC component output with arbitrary units. The bottom tracing shows the corresponding fetal heart rate pattern (labeled HRP- A) and the actogram (fetal movement). The heart rate unit (bpm) is marked on the left horizontal axis and the actogram unit is marked on the right horizontal axis (cm). The fetal state as determined by the changes in heart rate and actogram is labeled as “Quiet Sleep”.

Fig 4. Variation of BD (top) and IBI (bottom) with gestational age. The BD and IBI values along with standard error are shown in seconds with gestational age in weeks.

Fig 5.

Variation of BD (top) and IBI (bottom) with gestational age separated by fetal states 1F and 2F. The BD and IBI values along with standard error are shown in seconds with gestational age in weeks. The 1F and 2F state correspond to quiet and active sleep states respectively.

Table 1

Fetal head position and distance as recorded by ultrasound prior to MEG recordings.

Subject ID	GA wk	Distance to from the maternal abdomen head (cm)	Head position relative to maternal abdomen determined by US
ntlr29	36w5d	5.7	low midline
ntlr15	37w2d	2.8	low midline
spont-pat23	32w6d	6.4	low midline
spont-pat05	32w	5.1	low right
ntlr21	36w1d	5.5	low midline
spont-pat12	37w	4.1	low midline
ntlr27	36w1d	2.4	high right
ntlr05	33w5d	5.7	low midline
spont-pat11	36w3d	4.0	low midline
spont-26	33w5d	7.0	low midline
spont-27	30w2d	6.4	low midline
ntlr14	35w2d	9.1	low left
ntlr18	36w2d	5.2	low midline
spontpat01	35w	7.5	low midline
spont-21	34w	1.0	high right
spont03	32w	4.3	low left
spontpat02	37w	3.7	low left
spont-pat04	32w	3.3	low left
spont-pat24	36w4d	8.5	low midline
ntlr08	34w2d	5.2	low midline
ntlr01	37w3d	6.1	low right
ntlr17	35w6d	5.5	low midline