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Correlating maternal and cord-blood inflammatory markers and BDNF with human fetal brain activity recorded by magnetoencephalography: An exploratory study

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ABSTRACT

Background: During gestation, the brain development of the fetus is affected by many biological markers, where inflammatory processes and neurotrophic factors have been of particular interest in the past decade.
Aim: This exploratory study is the first attempt to explore the relationships between biomarker levels in maternal and cord-blood samples and human fetal brain activity measured with non-invasive fetal magnetoencephalography (fMEG).
Method: Twenty-three women were enrolled in this study for collection of maternal serum and fMEG tracings immediately prior to their scheduled cesarean delivery. Twelve of these women had a preexisting diabetic condition. At the time of delivery, umbilical cord blood was also collected. Biomarker levels from both maternal and cord blood were measured and subsequently analyzed for correlations with fetal brain activity in four frequency bands extracted from fMEG power spectral densities.
Results: Relative power in the delta, alpha, and beta frequency bands exhibited moderate-sized correlations with maternal BDNF and cord-blood CRP levels before and after adjusting for confounding diabetic status. These correlations were negative for the delta band, and positive for the alpha and beta bands. Maternal CRP and cord-blood BDNF and IL-6 exhibited negligible correlations with relative power in all four bands. Diabetes did not appear to be a strong confounding factor affecting the studied biomarkers.
Conclusions: Maternal BDNF levels and cord-blood CRP levels appear to have a direct correlation to fetal brain activity. Our findings indicate the potential use of these biomarkers in conjunction with fetal brain electrophysiology to track fetal neurodevelopment.

1. Introduction

Pregnancy exhibits characteristics of an inflammatory response by elevations of cytokine levels as an immune response (Austgulen et al., 1994; Christian and Porter, 2014; Genc and Ford, 2010; Gillespie et al., 2016; Sacks et al., 1998; Sargent et al., 2006). Although many cytokines and other molecules participate in the inflammatory process (Del Giudice and Gangestad, 2018; Thayer, 2009), fetal imaging studies that have focused on brain development, brain architecture, and functional neural circuits have concentrated on two biomarkers: the acute-phase C-reactive protein (CRP) and the cytokine interleukin-6 (IL-6) (Del Giudice and Gangestad, 2018; Spann et al., 2018). The ease of identifying these molecules in serum or plasma is what makes them commonly used to assess the presence of inflammation (Dandona et al., 2004; Del Giudice and Gangestad, 2018), although moderately elevated levels of these molecules do not necessarily define an inflammatory state (Del

Abbreviations: BDNF, brain-derived neurotrophic factor; IL-6, interleukin 6; CRP, C-reactive protein; GA, gestational age; MEG, magnetoencephalography; fMCG, fetal magnetocardiography; PSD, power spectral density; RP, relative power.

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Giudice and Gangestad, 2018). IL-6 and CRP have a correlation or a shared variance because the expression of IL-6 in the liver triggers the synthesis of CRP (Del Giudice and Gangestad, 2018; Gabay and Kushner, 1999; Spann et al., 2018; Thayer, 2009). However, throughout the literature, there is no consensus on whether the plasma concentrations of IL-6 and CRP show an increasing, decreasing, or unaffected trend with gestational age (Belo et al., 2005; Christian and Porter, 2014; Dockree et al., 2021; Friis et al., 2013; Lekva et al., 2016; Watts et al., 1991). IL-6 during pregnancy has been recognized as a risk factor for developing fetal brain white-matter lesions and cerebral palsy (Boyle et al., 2017; Spann et al., 2018; Yockey and Iwasaki, 2018). Furthermore, IL-6 is recognized as a contributor in the pathophysiology of schizophrenia, autism (Wei et al., 2013; Yockey and Iwasaki, 2018), and neonatal brain connectivity and working memory performance at 2 years of age (Rudolph et al., 2018; Schmatz et al., 2010; Yockey and Iwasaki, 2018). Similarly, CRP may contribute to fetal brain development by playing its role in normal synaptic pruning and refinement (Canetta et al., 2014). However, elevated levels of maternal CRP may promote an increase of CRP levels in the developing offspring's brain, which could alter synaptic connectivity leading to the development of psychopathologies like schizophrenia (Canetta et al., 2014). Elevated maternal CRP concentrations can produce suboptimal placenta development, which interferes with fetal growth (Ernst et al., 2011; Spann et al., 2018). Likewise, elevated CRP levels during the perinatal period are associated with motor and cognitive limitations (Leviton et al., 2016). Some studies consider that an elevated combination of IL-6 and CRP in the perinatal period are associated with neurodevelopmental delay, risk of white-matter injury, and microcephaly (Bodnar et al., 2018; Inomata et al., 2014; Jiang et al., 2018; Leviton et al., 2016). However, the presence of inflammatory markers like IL-6 and CRP during pregnancy are less often studied in the context of whether they act directly on fetal brain development, and thus their effect on the developing fetal brain remains an area of active investigation.

Fetal brain development is promoted by the expression of neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF) (Cai et al., 2017; Deuschle et al., 2018; Malamitsi-Puchner et al., 2006; Sahay et al., 2020; Su et al., 2021). BDNF and other neurotrophins are essential during prenatal and postnatal neurodevelopment because of their implication in neuroprotection, modulation of neurogenesis, and developing the nervous system, among other crucial roles (Malamitsi-Puchner et al., 2006; Sahay et al., 2020; Su et al., 2021). However, altered levels of perinatal BDNF have been suggested to affect fetal brain development, neural maturity and plasticity, and have been associated with fetal brain injuries that could lead to a variety of psychiatric and neurodegenerative disorders (Bayman et al., 2022; Briana and Malamitsi-Puchner, 2018; Briana et al., 2018; Dhobale, 2014; Spulber et al., 2010). Maternal BDNF plasma levels have been reported to decrease during pregnancy (Lommatzsch et al., 2006; Mayeur et al., 2011). This could be because neurotrophins are transported from the mother into various compartments of the fetal environment such as the amniotic fluid and the placenta (Cai et al., 2017; Flöck et al., 2016; Mayeur et al., 2011). In a recent study, Flöck et al., (2022) reported that amniotic-fluid BDNF levels have a maternal or placental source (Flöck et al., 2022). Furthermore, they reported that cord-blood BDNF reflects mainly its synthesis by the fetus (Flöck et al., 2022). Cord-blood BDNF has been reported to increase with gestational age (Cai et al., 2017; Chouthai et al., 2003; Flöck et al., 2016; Mayeur et al., 2011; Spulber et al., 2010). Cord-blood BDNF levels are said to act as a biomarker to reflect the degree of neural maturity (Cai et al., 2017), probably because these levels also may reflect the concentration of BDNF in the central nervous system (Briana and Malamitsi-Puchner, 2018; Cai et al., 2017; Chouthai et al., 2003). Additionally, cord-blood BDNF levels could be an indicator of possible insults in utero that alter the neurodevelopmental process (Spulber et al., 2010). Thus, it would be interesting to study the relationship of maternal and cord-blood BDNF levels with fetal neurological status.

With advances in technology, fetal brain activity can now be recorded non-invasively using magnetoencephalography (MEG) (Escalona-Vargas et al., 2018; Eswaran et al., 2007, 2012; Lowery et al., 2008). MEG is considered as a magnetic homologue of electroencephalography (EEG) and this technique is well suited for fetal recordings due to its non-invasive nature. Studies have shown that neurological maturation of the fetus can be tracked by extracting and assessing fetal spontaneous brain activity through spectral analysis (Escalona-Vargas et al., 2018; Eswaran et al., 2007, 2012; Lowery et al., 2008). This spectral analysis usually focuses on the maturational changes in the delta, theta, alpha, and beta waveforms, which has also been reported for term and preterm neonates (Avci et al., 2020; Okumura et al., 2006). Similarly, ratio coefficients between frequency bands have been used to quantify developmental changes in children (Doesburg et al., 2013). These ratios are usually used in cognitive and clinical neuroscience (Donoghue et al., 2020), and there seems to be no study on the association between power-spectral-density (PSD) measures of fetal brain activity and neurotrophic factors, inflammatory markers, and other maturation molecules. In this exploratory study, we hypothesized that there will be a correlation between inflammatory and fetal development biomarkers, specifically IL-6, CRP, and BDNF, in both maternal and cord-blood samples with measures of human fetal brain activity obtained by using fetal MEG (fMEG).

2. Materials and methods

2.1. Sample collection

This study was approved by the University of Arkansas for Medical Science's Institutional Review Board and all the participants provided an informed consent to participate in the study. The study followed a convenience-sampling design in which subjects were eligible to participate only if they were scheduled for a caesarean delivery close to term according to their electronic health records. Subjects with both low-risk and high-risk pregnancies were eligible to participate; the only exclusions were for maternal ages less than 18 or over 40, or for fetal malformations, genetic anomalies, and non-singleton pregnancies. Table 1 provides the overall demographics of the participants with 23 English and Spanish-speaking mothers, aged 22–40 years, who received medical care at our institution's hospital where we have a good mix of low and high-risk population. As shown in the table there were several comorbid conditions in the high-risk patients while 12 of the 15 had diabetes as a common risk factor.

Approximately 8 ml of blood was collected from each mother 0–3 days before active labor, and approximately 8 ml of venous blood was collected from the umbilical cord of her neonate immediately after delivery. Blood was collected into sodium heparin tubes and placed immediately on ice. Plasma was collected after centrifuging the blood for 15 min at 2000×*g* at 4 °C. Plasma was frozen and stored at −80 °C.

Plasma biomarkers: CRP was measured in both maternal and cord plasma (diluted 1:10,000 in assay buffer) by ELISA (Cayman Chemical, Ann Arbor, MI, USA) following the manufacturer's protocol. BDNF and IL-6 were also measured in both maternal and cord plasma using the MILLIPLEX® MAP Human Myokine Magnetic Bead Panel (with only BDNF and IL-6 analytes) following the manufacturer's instructions. Data was acquired on a Luminex® 200 with xPONENT® software.

2.2. Data collection

The SARA (SQUID Array for Reproductive Assessment) system, with 151 non-invasive sensors, was used to record biomagnetic signals (Lowery et al., 2008). These signals encompass both the brain and heart signals of the fetus and signals from the maternal heart. Fetal MEG was extracted as a subset of the biomagnetic recordings. The analysis included one recording from each of the 23 pregnant mothers. At the time of recording, the fetuses ranged in gestational age (GA) from 36 to

Table 1
Maternal Demographics and health conditions.

ID#	Gestational Age (weeks/ days)	Maternal Age (years)	Maternal Race	Maternal Conditions
01	39w3d	23	White	N/A
02	39w2d	29	White	N/A
03	39w2d	35	Black	Type 2 Diabetes, CHTN, Obesity
04	38w3d	38	Asian	Type 2 Diabetes, CHTN, Hx of Renal Failure
05	37w2d	36	White	Type 1 Diabetes, Obesity, Seizures, Cocaine Abuse
06	39w1d	36	White	Type 2 Diabetes, Obesity, CHTN, +HPV
07	38w2d	27	White	Type 1 Diabetes, GHTN vs CHTN
08	37w2d	35	Black	Type 2 Diabetes, CHTN
09	36w6d	25	White	Type 1 Diabetes
10	38w1d	32	Black	hx PreEclampsia
11	39w0d	30	Black	N/A
12	39w2d	22	White	N/A
13	39w0d	25	Black	N/A
14	38w5d	40	Black	CHTN, Obesity, Sickle Cell Trait,
15	38w2d	32	White	Type 1 Diabetes, Hypothyroidism, Obesity, Asthma
16	39w1d	27	Black	Type 2 Diabetes, Obesity
17	38w5d	28	White	Type 1 Diabetes
18	39w1d	36	White	N/A
19	39w0d	31	White	N/A
20	37w0d	30	White	Type 1 Diabetes, GHTN
21	38w0d	32	Black	Type 2 Diabetes, Hypothyroid, Benign, essential hypertension, Obesity, SVT
22	39w0d	35	White	N/A
23	38w5d	31	Black	Obesity, Hypothyroidism

*CHTN: Chronic Hypertension *GHTN: Gestational Hypertension *SVT: Supraventricular tachycardia * HPV: Human papillomavirus.

39 weeks and had a mean GA (standard deviation [SD]) of 38.54 (0.78) weeks.

2.3. Measures

The biomagnetic signals were recorded in a continuous manner at a sampling rate of 312.5 Hz for a maximum of 20 min. From the raw biomagnetic recordings, the interfering maternal heart-signal components were attenuated with the frequency-dependent subtraction (SUBTR) method (Vrba et al., 2012). Afterwards, the fetal magnetocardiography (fMCG) tracings were also attenuated by applying a spatial-filter-based orthogonal projection algorithm (Vrba et al., 2004). Data devoid of maternal and fetal cardiac interferences was considered as the fMEG. Interference from background noise was removed by the implementation of a notch filter consistently to all recordings at 29.6 Hz.

2.3.1. Fetal brain activity

All fMEG recordings were inspected visually with the open-source Brainstorm software (Tadel et al., 2011) to discard any contaminated segments from subsequent analysis. Furthermore, all the participants did not complete the 20 min of recording therefore, for consistency we limited the analyses to the first 10 min. The Power Spectral Density (PSD) estimate was calculated using the Welch method for 2-s-wide windows with 50% overlap between successive windows for each channel. Averaging over all the channels was performed afterwards. The resulting PSD estimate was then divided into four standard frequency bands, namely, delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz) and beta (13–25 Hz). The relative power (RP) of each band was calculated as the proportion of its average power relative to the average power over the frequency range of 0.5–50 Hz (Eswaran et al., 2012). Additionally, we computed the ratios between the frequency bands.

Fetal brain activity, represented by fMEG, changes in relation to the fetal behavioral states (Haddad et al., 2011). With the fMCG tracings, a heart rate pattern and gross fetal movements were plotted as an actocardiogram. This actocardiogram was used to identify the four behavioral states defined by Nijhuis et al.: quiet sleep (1F), active sleep (2F), quiet awake (3F), and active awake (4F). These behavioral states, by definition, need to last a minimum of 3 min to be considered as such (Nijhuis et al., 1982).

2.4. Statistical analysis

Values of BDNF (in pg/mL), IL-6 (in mean-fluorescence-intensity units) and CRP (in ng/mL) were transformed to their natural logarithms to make them more normally distributed and less right-skewed. They then were subjected to correlation analysis using Pearson product-moment correlation coefficients to investigate their relationships with RP in the four frequency bands. First, we used coefficients of total correlation to quantify the strength of unadjusted associations between blood markers and RP values. Then we used coefficients of partial correlation to quantify the strength of associations between blood markers and RP values that remained after "partialling out" the confounding effect of diabetes status. We do not report p-values because this was an exploratory study with limited statistical power. Instead, we interpret the correlation coefficients heuristically, by considering them into effect-size categories using criteria suggested by (Cohen, 1992). With "|rho|" denoting the absolute value of the correlation coefficient, we considered any |rho| value higher than 0.25 as moderately correlated, and any higher than 0.45 as highly correlated.

3. Results

At the time of recording, the mothers ranged in age from 22 to 40 years, with a mean (SD) of 31.1 (4.9) years. Nine were Black, one was Asian, and 13 were White. The 3 Hispanic/Latino subjects included the Asian and 2 of the Whites. Obstetric characteristics had an average (SD) [range] of 2.8 (1.0) [1–4] for gravidity, 1.3 (0.8) [0–3] for parity, 7.1 (2.2) [1–9] for 1-min Apgar scores, 8.7 (0.6) [7–9] for 5-min Apgar scores, and 1.6 (1.6) [0–5] for the number of pregnancy risk factors. Individual-level details of the 23 participants' demographics and obstetric characteristics are shown in Table 1 and our previous publication (Mercado et al., 2024).

The four behavioral states were quantified for all the fetuses. Where state 1F occurred 55% and 2F occurred 28%, and 14% were indeterminate. Because of the low number of occurrences and short durations of the 3F and 4F states (awake states), the results are primarily considered in a fetal sleep state.

Pearson coefficients of total correlation between the RP of each band and the biomarkers of BDNF, IL-6, and CRP from both the maternal and cord blood are depicted in Table 2 and Fig. 1. When measured in maternal blood, BDNF has moderate total correlations with all the bands. Meanwhile, maternal IL-6 levels have moderate total correlations with delta (−0.252) and beta (0.302), while maternal CRP levels have negligible values. Among these values, the delta band presents negative correlations with both maternal BDNF (−0.396) and IL-6 (−0.252), and a barely positive correlation (+0.018) with the CRP maternal levels. We observe the opposite behavior with the other three bands, each of which show positive total correlations with maternal BDNF and IL-6, and negative total correlations with maternal CRP. In cord-blood, CRP has a moderately positive correlation with alpha (+0.390), a highly positive correlation with beta (+0.476), and a moderately negative correlation with delta (−0.350) bands. In contrast, IL-6 and BDNF levels in cord blood have negligible total-correlation values with the frequency bands.

Table 2 also shows the Pearson coefficients of total correlation between the frequency band ratios and the biomarkers. Maternal BDNF has

Table 2
Coefficients of total correlation between biomarkers and relative powers of frequency bands and their ratios. N = 23 for maternal samples and N = 19 for cord-blood samples.

Total Correlations	BDNF		IL-6		CRP	
(no adjustment)	Maternal	Cord blood	Maternal	Cord blood	Maternal	Cord blood
log(RP-delta)	**−0.396**	0.026	**−0.252**	−0.158	0.018	**−0.350**
log(RP-theta)	**0.353**	0.011	0.177	0.026	−0.114	0.245
log(RP-alpha)	**0.375**	−0.176	0.237	0.097	−0.127	**0.390**
log(RP-beta)	**0.359**	−0.049	**0.302**	0.160	−0.010	**0.476**
log(theta/delta)	**0.408**	−0.010	0.235	0.108	−0.070	**0.331**
log(alpha/delta)	**0.395**	−0.104	**0.251**	0.131	−0.077	**0.379**
log(beta/delta)	**0.381**	−0.040	**0.285**	0.162	−0.014	**0.427**
log(alpha/theta)	0.147	**−0.321**	0.171	0.133	−0.060	**0.336**
log(beta/theta)	0.140	−0.073	0.238	0.185	0.100	**0.410**
log(beta/alpha)	0.098	0.231	**0.254**	0.196	**0.254**	**0.385**

Bold numbers indicate >0.25 correlations (>0.25 moderate; >0.45 high); RP, relative power.

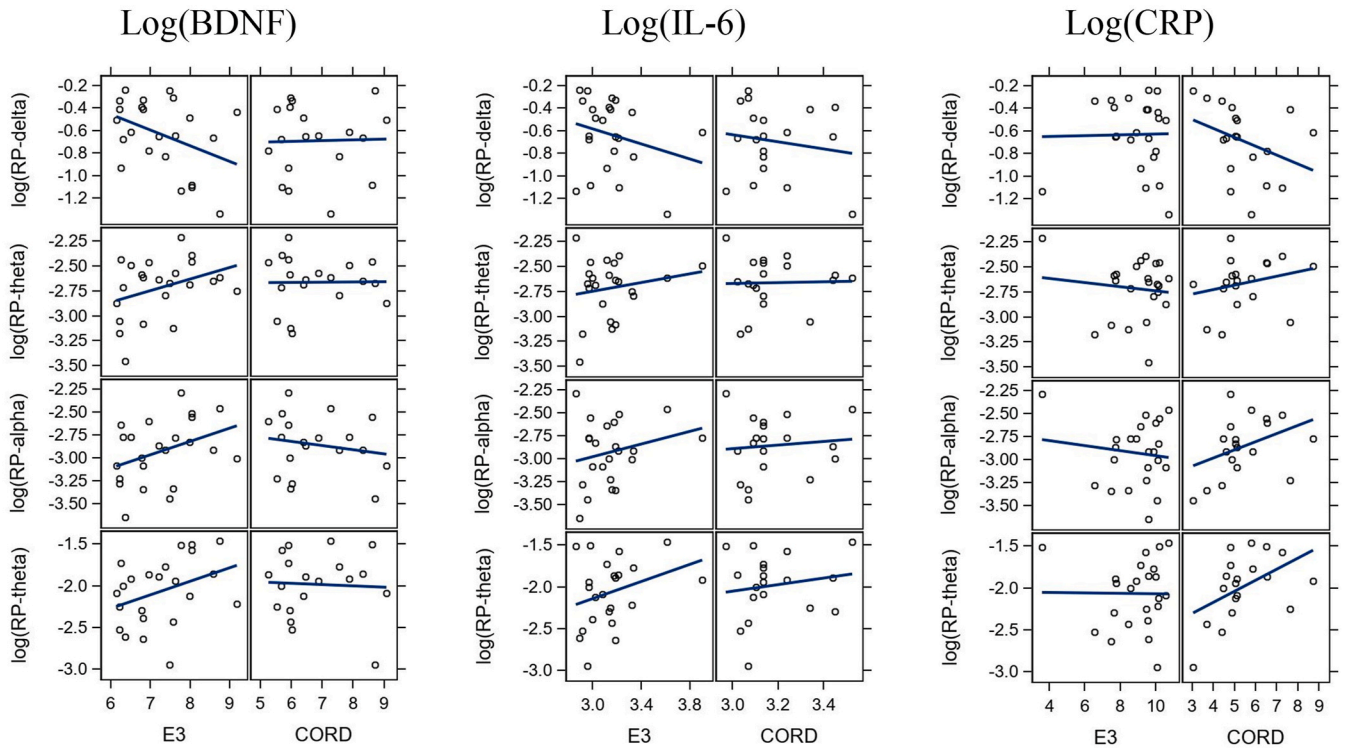

Fig. 1. Plots of the data before adjusting for diabetes status. The regression lines depict total correlation between the relative power of each band and the biomarkers of BDNF, IL-6, and CRP from both the maternal and cord blood.

moderate correlation values for all ratios with the delta band (0.408 with theta/delta, 0.395 with alpha/delta, and 0.381 with beta/delta). Maternal IL-6 is moderately correlated with the alpha/delta (0.251), beta/delta (0.285), and beta/alpha ratios (0.254). Meanwhile, maternal CRP is only moderately correlated with the beta/alpha ratio (0.254). With regards to cord-blood BDNF, other than a moderate negative total correlation with the alpha/theta ratio (−0.321), all ratios have negligible sizes when correlated to cord-blood BDNF. Similarly, cord-blood IL-6 has only negligible correlations with all the ratios, although all are positive. On the other hand, cord-blood CRP has moderate positive total correlations with all the ratios. This can be visualized in Fig. 2.

A partial-correlation analysis was used to partial out diabetic status to determine the relationship that remained between the biomarkers and the frequency bands, and their ratios, once the confounding effect of diabetes was removed (see Table 3). This analysis yielded moderate partial correlations for maternal BDNF levels with all bands and cord-blood CRP levels with the delta, theta, and alpha bands. Cord-blood CRP maintained its highly positive correlation with the beta band. However, the partial correlations (Table 3) generally are similar to the total correlations (Table 2) indicating that diabetes has relatively little confounding influence on the relationships between biomarker levels and RP in the four frequency bands and their ratios. The only considerable exception is maternal IL-6, with changes in the delta band (decreased to −0.216), the alpha/delta ratio (decrease to 0.203), and the beta/theta ratio (increase to 0.298).

4. Discussion

In this exploratory study, we found that fetal developmental biomarkers relate to MEG power-spectral-density parameters reflecting fetal brain development. We found that maternal BDNF levels negatively correlate with RP in the delta band, and positively correlate with RP in the rest of the bands, which is consistent with the notion that maternal BDNF supports fetal neurological development (Antonakopoulos et al., 2018; Kodomari et al., 2009) and is reflected by a shift away from the delta band toward higher frequencies (Eswaran et al., 2012; Scher et al.,

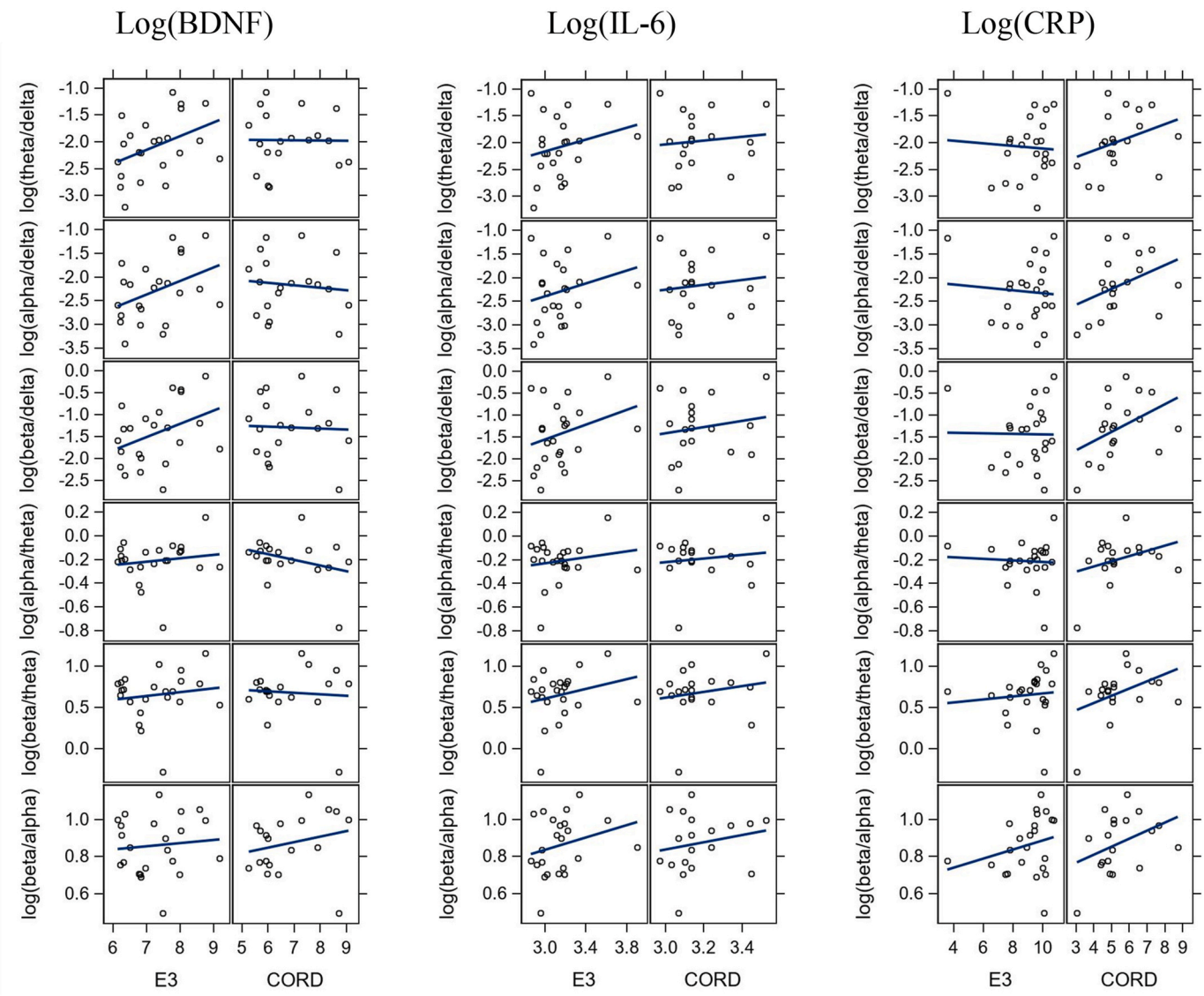

Fig. 2. Plots of the data before adjusting for diabetes status. The regression lines depict total correlation between the frequency band ratios and the biomarkers of BDNF, IL-6, and CRP from both the maternal and cord blood.

Table 3
Coefficients of partial correlation between relative powers of frequency bands and biomarkers after "partialling out", i.e., removing, the confounding influence of diabetes status. N = 23 for maternal samples and N = 19 for cord-blood samples.

Partial Correlations	BDNF		IL-6		CRP	
adjusting for Diabetes	Maternal	Cord blood	Maternal	Cord blood	Maternal	Cord blood
log(RP-delta)	**−0.355**	−0.014	−0.216	−0.139	−0.007	**−0.356**
log(RP-theta)	**0.259**	0.080	0.097	−0.009	−0.072	**0.256**
log(RP-alpha)	**0.308**	−0.132	0.181	0.073	−0.096	**0.402**
log(RP-beta)	**0.333**	−0.033	**0.279**	0.152	0.007	**0.477**
log(theta/delta)	**0.339**	0.047	0.175	0.082	−0.033	**0.343**
log(alpha/delta)	**0.339**	−0.060	0.203	0.109	−0.047	**0.388**
log(beta/delta)	**0.349**	−0.012	**0.256**	0.149	0.007	**0.431**
log(alpha/theta)	0.178	**−0.328**	0.191	0.134	−0.069	**0.337**
log(beta/theta)	0.221	−0.109	**0.298**	0.207	0.077	**0.416**
log(beta/alpha)	0.218	0.183	**0.351**	0.241	0.230	**0.406**

Bold numbers indicate >0.25 correlations (>0.25 moderate; >0.45 high); RP, relative power.

1994). Furthermore, all three band ratios involving the delta band have moderate positive correlations with maternal BDNF. Our findings also point to the fact that the fetal development may be assisted by the maternal BDNF that reaches the fetal brain through the utero-placental barrier (Antonakopoulos et al., 2018; Flöck et al., 2016, 2022; Kodomari et al., 2009), since cord-blood BDNF levels have mainly negligible correlations with RP in the four bands. BDNF plays a crucial role in the modulation of neurogenesis and maturation of neural pathways during

neurodevelopment (Su et al., 2021). Specifically in animal models it has been shown that maternal BDNF reaches the fetal brain via the utero-placental barrier, possibly supporting the development of the fetal central nervous system (Kodomari et al., 2009). Further studies have confirmed the presence of the neurotrophic factor BDNF in the amniotic fluid of early mid-trimester pregnancies, with significantly higher BDNF levels being observed in the amniotic fluid of severely growth-restricted fetuses compared to normal fetuses. On the other hand, fMEG has shown the ability to track fetal maturation including the case of adverse in-utero conditions (Escalona-Vargas et al., 2018; Eswaran et al., 2012). The PSD of fMEG tracings represent a simple yet quantitative tool for an objective assessment of fetal brain signals which consists of a mix of spontaneous background activity within 0.5–25 Hz encompassing the four frequency bands (delta, theta, alpha, and beta). In general, background electrophysiological brain activity in an early gestation fetus/-neonate represents slow waves which is predominantly in the delta band (Cainelli et al., 2021; Haddad et al., 2006). As the fetus continues to mature, beyond 35 weeks of gestation there is a shift towards a more continuous brain pattern which represents a shift towards the higher frequencies in the PSD. For example, PSD analysis of fMEG signals when applied to growth restricted fetuses showed differences in the spectral bands as compared to normative ones, thus pointing towards altered neurodevelopmental trajectory (Eswaran et al., 2012). We believe that since maternal BDNF possibly has a role to play in the fetal neurodevelopment, this effect can in turn be tracked by recording fetal brain activity using magnetoencephalography.

It has been reported that elevated CRP levels during the perinatal period are associated with cognitive or motor limitations years later (Leviton et al., 2016). However, these assertions are usually for maternal or newborn levels. In this study, we find that the strength and direction of the correlations between the fetal RP bands and cord-blood CRP levels are very similar to those between fetal RP bands and maternal BDNF levels. This finding may reflect the role of BDNF in the parallel activation of anti-inflammatory mechanisms (Antonakopoulos et al., 2018; Malaeb and Dammann, 2009).

We also found that maternal IL-6 has some moderate correlation with the fetal brain spectral activity, mainly its involvement with the delta and beta bands. However, these relations were not consistent, and this needs to be further investigated. Regarding the cord-blood IL-6 levels, they do not appear to have any appreciable correlation with fetal brain spectral activity. Furthermore, partial-correlation analysis indicated that diabetes had little confounding influence on the relationship between the studied biomarkers and fetal brain activity. The current exploratory study provides a preliminary insight into the potential metrics of fetal brain spectral activity that can be studied in relation to developmental biomarkers using MEG technology. The strength of the study includes the first attempt to explore the relationship between biomarkers and direct human fetal brain electrophysiology.

The limitation of this study includes a small cohort with short recording duration. The participants were a mix of both high and low risk pregnancies, so there could have been several confounding factors that could influence the results. Our sample size of 23 subjects was too small to allow us to control for more than one confounder without incurring a high risk of overfitting. We chose to control for diabetes because it was the most prevalent risk factor. Additionally, we limited our analysis to IL-6 although several cytokines could be involved in the inflammation process. Since the study was exploratory in nature we chose IL-6 specifically because in animal models it has been shown to influence the fetal brain. Further in humans, through MRI, it has been shown that there is a correlation between maternal inflammation during pregnancy with the newborn brain (Graham et al., 2018). Thus, this study though modest, is a natural extension of studying the effect in the fetal stage of life.

5. Conclusions

The present exploratory study demonstrates a relationship between fetal brain spectral activity and blood-plasma levels of the neurotrophic factor, BDNF, and the inflammatory markers IL-6 and CRP. For both maternal BDNF and cord-blood CRP, there is a negative correlation with activity in the delta band, and positive correlations with activity in the alpha, beta, and theta bands, reflecting fetal brain development by shifting power from the delta band towards higher frequencies. Maternal BDNF levels and cord-blood CRP levels appear to be directly related to fetal brain development. Although a small pilot study, we do not observe a major effect of pre-gestational diabetes on the correlations between the studied biomarkers and fetal brain activity. Overall, our findings indicate the potential use of maternal BDNF and cord-blood CRP levels in conjunction with fetal brain electrophysiology to track fetal neurodevelopment. In future, by assessing the appropriate biomarkers in conjunction tracking fetal brain maturation with MEG especially in high-risk pregnancies that are a result of adverse maternal-fetal conditions can lead to better clinical management of pregnancies.

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Availability of data and material

All de-identified data will be made available on request and will be subject to institutional policies.

CRediT authorship contribution statement

Luis Mercado: Formal analysis, Writing – original draft, Writing – review & editing. **Shannon Rose:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Diana Escalona-Vargas:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Nafisa Dajani:** Conceptualization, Investigation. **Eric R. Siegel:** Formal analysis, Writing – original draft, Writing – review & editing. **Hubert Preissl:** Conceptualization, Methodology, Supervision. **Hari Eswaran:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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