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Prenatal neural origins of infant motor development: Associations between fetal brain and infant motor development

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Abstract

Functional circuits of the human brain emerge and change dramatically over the second half of gestation. It is possible that variation in neural functional system connectivity in utero predicts individual differences in infant behavioral development, but this possibility has yet to be examined. The current study examines the association between fetal sensorimotor brain system functional connectivity and infant postnatal motor ability. Resting-state functional connectivity data was obtained in 96 healthy human fetuses during the second and third trimesters of pregnancy. Infant motor ability was measured 7 months after birth using the Bayley Scales of Infant Development. Increased connectivity between the emerging motor network and regions of the prefrontal cortex, temporal lobes, posterior cingulate, and supplementary motor regions was observed in infants that showed more mature motor functions. In addition, females demonstrated stronger fetal-brain to infant-behavior associations. These observations extend prior longitudinal research back into prenatal brain development and raise exciting new ideas about the advent of risk and the ontogeny of early sex differences.

Core systems of the brain are established prior to birth and are foundational to infants' emerging developmental competencies. Among the earliest to mature are the motor and

sensory systems, which support the ability of the infant to interact with and receive input from the world (Fransson, Åden, Blennow, & Lagercrantz, 2011; Gao et al., 2015; Grayson & Fair, 2017). At their start, neural systems are highly malleable (Stiles & Jernigan, 2010), enabling a learned fit between the early environment and the brain that will operate, and survive, within it. The brain is primed at birth to receive inputs from sensory organs, and the signals received play an essential role in advancing neurodevelopmental processes. Experimental disruption to normal occurrence and propagation of activity through sensorimotor systems leads to permanent loss of function in those systems and lasting atypical cortical organization. Elegant examples of this come from controlled developmental studies of rat barrel cortex (Tolner, Sheikh, Yukin, Kaila, & Kanold, 2012), mouse ocular dominance columns (Xu et al., 2011), and cat retinogeniculate pathways (Shatz & Kliot, 1982). Thus, sensorimotor systems are present at birth, and receptive to signals from the environment, which instruct further developmental patterning of neural systems. Moreover, these systems are capable of producing behavior, enabling the developing organism, or infant, to build representations of stimulus-response properties through interaction with the environment.

We expect that ontogenetic events occurring before birth set the stage for later human development in a way that varies from person to person, but direct longitudinal evidence linking the two is scarce. Recent advances in fetal functional magnetic resonance imaging (MRI) have enabled demonstration that individual differences in brain network integrity emerge in utero (Jakab et al., 2014; Thomason et al., 2013). One implication of these observations is that infants enter the world with unique neural assemblies that are influenced by intrauterine experiences, and it is against the background of this natural interindividual variation that experientially driven patterning of neural systems takes place. A second implication is that variation in neural development in utero may predict future development. The focus of the present study is to address this latter possibility, by examining the association between fetal sensorimotor brain system functional connectivity and infant postnatal motor ability.

Although numerous studies have linked neurological measures in high-risk *newborns* with subsequent infant development, direct evidence linking variation in human *fetal* brain networks to infant outcomes is entirely lacking. MRI studies of preterm infants at, or before, term-equivalent age have reliably identified specific mild variations in brain activity, structure, and metabolite ratios that predict behavioral outcomes (Drobyshevsky et al., 2007; Kendall et al., 2014; Keunen et al., 2016; Rose et al., 2009; Schumacher et al., 2013; van Kooij et al., 2012; Woodward, Anderson, Austin, Howard, & Inder, 2006). Related investigations have evaluated a number of other perinatal risk groups, with and without overt forms of encephalopathy, and these studies show similar associations between neural features at birth and both near and long-term neurobehavioral outcomes (Arca-Diaz et al., 2017; Johnson et al., 2015; Massaro et al., 2015; Rollins et al., 2017). Fewer studies have attempted to bridge normal neural variation in healthy newborns with neurobehavioral outcomes. One study, by Emerson, Gao, and Lin (2016), showed that, in typically developing infants, rate of transition toward interhemispheric functional asymmetry predicts language outcomes at age 4. The question that remains is whether functional integrity of core neural systems *prior* to birth relates to behavioral outcomes in infancy.

Sex-related brain and behavioral differences are apparent across the life course, but the exact processes that guide their prenatal emergence remains a topic of vigorous scientific inquiry. There is some evidence for differences in behavior between male and female fetuses, specifically for increased leg movement in males (Almli, Ball, & Wheeler, 2001), but findings are inconsistent, with many fetal behavioral studies reporting no differences, especially after controlling for wakefulness, which tends to be higher in males (DiPietro & Voegtline, 2017; Hata et al., 2016; Robles de Medina, Visser, Huizink, Buitelaar, & Mulder, 2003). A primary driver of sex differences in utero is exposure to hormones, such as testosterone, which begins to show varied concentrations between the sexes beginning as early as week 8 of gestation (Hines, 2010). Testosterone influences a number of fundamental neurodevelopmental processes, including cell survival and anatomical connectivity, and does so through widespread interactions with membrane receptors, transcription factors, growth factors, and other hormones (Papenfuss & Whitacre, 2009). In early infancy, social processes begin to act on sex-linked biology to further influence developmental outcomes. Adults typically perceive infant females as smaller, softer, and fine-featured, and tend to vocalize and look at them more than males; in contrast, they tend to be more physical with males (Ispa, Claire Cook, Harmeyer, & Rudy, 2015; Lewis, 1972).

Sex differences in brain development are apparent by infancy and persist across the life span (Caviness, Kennedy, Richelme, Rademacher, & Filipek, 1996; Choe et al., 2013; Gilmore et al., 2007; Koolschijn & Crone, 2013; Ruigrok et al., 2014; Tiemeier et al., 2010), and neurological differences between the sexes relate to cognitive ability (Satterthwaite et al., 2015). Evidence from the antenatal period demonstrates that fetal brain structure (de Lacoste, Horvath, & Woodward, 1991) and neonatal brain function (Thordstein, Lofgren, Flisberg, Lindecrantz, & Kjellmer, 2006) develop more rapidly in females, and this relates to hormonal signaling. Further, Knickmeyer et al. (2014) observed larger motor cortices in female newborns, and an inverse association between testosterone levels and both supplementary motor and paracentral lobule volumes in males. While these studies suggest marked motor differences may be present at birth, the number of studies that report sex differences in infant motor ability are surprisingly few. Many landmark publications that have produced infant motor performance age norms report nonsignificant sex differences (Bayley, 1965). Others either report nonsignificant female advantage (Góes, Méio, Mello, & Morsch, 2015; Neligan & Prudham, 1969), or collapse across or remove scales with apparent sex differences (Thalagala, 2015), making it possible that extant effects are underreported. The small number of studies reporting sex differences in infant motor performance highlight an important distinction, namely, that female infants excel in *fine* motor skill development, whereas males show *gross* motor advantages (Touwen, 1976). A study by Piek, Gasson, Barrett, and Case (2002) that examined coordination of infant movements across limbs reported a complementary sex dissociation in arm versus leg coordination. They found that in 6- to 18-week-old infants, female infants show more coordinated arm movements, whereas males show a trend toward more coordinated leg movements. Overall, differences in motor ability appear to be subtle in early development, becoming more marked with maturation (Thomas & French, 1985).

The primary goal of this investigation was to evaluate evidence of a prospective, longitudinal association between fetal sensorimotor brain system functional connectivity and infant

postnatal motor ability. We measured fetal brain resting-state functional connectivity (FC) during MRI scans that were performed in late pregnancy, and followed up infants and their mothers at 7 months postpartum ($N = 96$), at which time we assessed infant motor ability. We tested the hypothesis that increased FC within the fetal sensorimotor brain network would predict more mature individual motor ability at age 7 months. We also explored sex differences, examining whether this brain-behavior relationship differs between the sexes. Analyses accounted for other salient sociodemo-graphic factors that could influence our hypothesized relationships, including maternal education, income, fetal MRI motion, and maternal prenatal mood symptomology.

Method

Participants

One hundred forty-nine pregnant women were recruited into a longitudinal study of pediatric brain development during routine obstetrical appointments. Selective inclusionary criteria included no contraindications for MRI, maternal age < 18 years, and healthy singleton pregnancy. Individual cases were subsequently excluded due to high motion during fetal scan ($n = 22$) or missing outcome data at child age 7 months ($n = 31$), resulting in a final sample of 96 fetal cases (37 female; 59 male), maternal mean age of 25.9 years ($SD = 4.6$), for examination of longitudinal associations. The mean age of fetuses at the time of MRI was 33.1 weeks of gestation ($SD = 4.1$), and mean age at birth was 39 weeks of gestation ($SD = 1.4$). Sample descriptive statistics are provided in Table 1. All study procedures were approved by the Wayne State University Human Investigation Committee, and all women provided written informed consent prior to participation.

Prenatal fetal MRI

Fetal magnetic resonance exams were performed with a Siemens Verio 70-cm open-bore 3-Tesla scanner with a lightweight abdominal Siemens Flex Coil. The MRI examination lasted 45 min. Images were collected with the following parameters and system-derived estimates of specific absorption rate: echo planar imaging blood oxygen level dependent, response time/echo time 2000/30 ms, minimum 180 frames, axial 4-mm slice, specific absorption rate = 0.22 ($SD = 0.08$). For the final sample of 96 cases included in all analyses, frame count, after excluding high motion frames, was range = 90 to 330, $M = 155$, $SD = 48$. Fetal MRI motion was included as covariate in all subsequent analyses for included participants.

Study measures

Infant motor development.—At 7 months postpartum ($M = 7.4$ months, $SD = 0.5$) infants' developmental skills were assessed with the Bayley Scales of Infant Development (3rd ed.; Bayley-III; Bayley, 2006). In the current study, fine and gross motor subtests, as well as a scaled composite motor score, were evaluated. For these measures, scale scores on the fine and gross motor subtest range from 1 to 19; scores between 7 and 10 are considered to be typical development and scores below 4 indicate a developmental delay at $-2 SD$. The motor composite ranges from 45 to 145. Scores ranging from 85 to 115 are considered to be typical motor development, while scores at or below 70 are indicative of a developmental

delay at -2 *SD*. In the present sample, motor development scores ranged from 58 to 130 with a mean and *SD* of 97.01 and 13.7.

Maternal psychosocial adaptation.—During the prenatal period maternal anxiety symptoms were measured using the State Trait Anxiety Inventory (Spielberger, 1984). The State Trait Anxiety Inventory is an anxiety inventory with a trait subscale, used here, on which participants rate their anxiety on a Likert scale ranging from 1 (*almost never*) to 4 (*almost always*). Scores range from 20 to 80 with higher scores reflecting greater trait anxiety. Mothers also completed a demographic survey that included questions about education and income.

Analytic plan

Functional data preprocessing.—Time frames corresponding to periods of minimal fetal head motion were identified using FSL image viewer (<http://www.fmrib.ox.ac.uk/fsl/>). Brain-suite (Shattuck & Leahy, 2002) was used to manually generate three-dimensional masks for single reference images drawn from time periods, or segments, of fetal movement quiescence. Masks were binarized and applied only to frames corresponding to their select segment, and only those data were retained for further analyses, resulting in, on average, 31% of data censored, or eliminated, due to movement artifacts. It should be noted that this value underestimates total data motion censoring, given that excessive motion was an exclusionary criterion and resulted in exclusion of 22 cases. As a point of reference, prior fetal functional MRI (fMRI) studies have reported censoring 39%–41% of total number of acquired fMRI frames (Thomason et al., 2013, 2014, 2017). Each segment was manually reoriented, realigned, re-sliced, and normalized to a 32-week fetal brain template (Serag et al., 2012) using Statistical Parametric Mapping (SPM8) software implemented in Matlab (<http://icatb.sourceforge.net>). To correct for variation in normalization across segments within-participant, normalized images were then concatenated into one run, realigned, and smoothed with a 4-mm Gaussian kernel.

Independent component analyses (ICA).—Following preprocessing and quality assurance steps, fetal resting-state time series data were concatenated across all fetuses and submitted to group ICA implemented in Matlab using the Group ICA/IVA of fMRI Toolbox (GIFT; Calhoun, Adali, Pearlson, & Pekar, 2001). The Infomax (MST) ICA algorithm was used to estimate 30 components, after which visual inspection of spatial and temporal/spectral features was used to separate noise components ($n = 13$) from networks of interest ($n = 17$) following priors (Griffanti et al., 2017; Robinson et al., 2009). Resultant networks of interest met criteria of dynamic range >0.06 and power frequency ratio <2.0 (cf. Allen et al., 2011). GIFT was used to implement back reconstruction of single-subject spatial maps for the component corresponding to the sensorimotor system (Figure 1).

Group-level neuroimaging analyses.—Individual fetal sensori-motor maps were submitted to a full factorial model in SPM8. Bayley infant motor ability at 7 months (median-split) and sex were treated as separate factors, and gestational age at scan was included as a covariate. Conjunction analyses were used to isolate brain regions with both significant main effect of Bayley performance and sex interaction effects from constituent

maps thresholded at $p < .05$, resulting in four regions reaching $p < .05$ criteria for both main and interaction effects: anterior cingulate cortex (ACC; 8,29,6), prefrontal cortex (PFC; 8,40,0), cerebellum (2,-16,-26), and inferior parietal lobule (IPL; -24,-32,8). FC values from these regions were then exported from reconstructed single-subject spatial maps and exported into Mplus version 7.2 (Muthén & Muthén, 2014).

Structural equation modeling (SEM) was implemented in Mplus to test whether the brain-behavior associations were impacted by salient demographic variables: maternal education, income, fetal MRI motion, and maternal prenatal anxiety symptomology. SEM was implemented separately for the ACC, PFC, cerebellum, and IPL, where each model included the main effect of FC to motor ability, gender to motor ability, and the interaction of FC \times Gender predicting motor ability, with gross motor ability included as a continuous variable. In addition, we accounted for the associations between maternal education, income, fetal MRI motion, and maternal prenatal anxiety symptoms to motor ability in each model. Finally, to stringently rule out the impact of these variables on any significant brain-behavior associations, we also included pathways from maternal education, income, fetal MRI motion, and maternal prenatal anxiety symptoms to FC for each region and FC \times Gender interaction term. Models were tested in Mplus using maximum likelihood procedures with robust standard errors. Further, we corrected for multiple comparisons by applying a Bonferroni correction of $p < .0125$ to each model, determined by dividing .05 by 4, which reflects the total number of models tested. Significant interactions between motor ability and sex were probed by comparing the simple slopes for boys and girls separately. We established regions of significance for significant interactions using an online tool, www.quantpsy.org/interact/ (Preacher, Curran, & Bauer, 2006).

Results

Neonatal parameters, MRI data quality, demographic variables, and prenatal maternal self-report anxiety symptoms did not differ between male and female infants included in this study (see Table 1). In line with prior research, significant associations were observed among maternal age, income, and education, all $ps < .015$. In addition, as would be expected, infant gestational age at birth was related to birth weight, $r = .40$, $p < .001$.

Fetal sensorimotor network development

A robust fetal sensorimotor neural network emerged from the group-level ICA. The network included regions of the motor and sensory cortices, cerebellum, thalamus, posterior cingulate cortex, and striatum (see Figure 1). Greater FC, operationally defined as fMRI signal coherence between a given region and the mean signal for the fetal motor network, was positively related to infant 7-month Bayley-III composite motor scores ($M = 97.01$, $SD = 13.7$) in regions of the posterior cingulate cortex, supplementary motor cortex, medial temporal lobe, and superior frontal gyrus, and negatively related in regions of the ACC, insula, lateral cerebellum, and right inferior motor cortex, controlling for gestational age at scan. See Table 2 for a full list of regions in which fetal motor network connectivity was linked to age 7-month infant Bayley motor performance.

Associations between brain and motor outcomes in boys and girls

Conjunction analyses identified four brain regions in which FC values predicted motor outcomes differently in males and females. These were areas of the PFC, somatomotor cerebellum, IPL, and ACC. FC associations for each of these regions are plotted in Figure 2. SEM performed for each region confirmed that brain–behavior associations remained significant even after controlling for prenatal maternal anxiety and psychosocial variables and accounting for multiple comparisons (Bonferroni $p < .0125$). Interactions between sex and FC values in those models were significant for the cerebellum and PFC, but not for the ACC and IPL (see Table 3). The region of significance analysis conducted for the cerebellum and PFC established that brain–behavior relationships were significant for high FC values only (see Figure 3). That is, there were no significant differences between males and females in how fetal cerebellum and PFC motor network connectivity related to infant motor ability at approximately the bottom half of the FC values. Estimates of simple slopes between fetal FC and Bayley motor performance, separated by sex, demonstrated significant slopes were present in females, $ps < .01$, but not in males, $ps > .3$ (see Table 4).

With regard to sex differences in postnatal motor ability, we observed a trend for better motor performance in female compared to male infants, $t = 1.85$, $p = .069$. Examination of sex differences separately for fine and gross motor performance revealed fine, $t = 2.14$, $p = .037$, but not gross, $p = .258$, motor functioning was significantly more mature in females than in males at 7 months postnatal age.

In post hoc analyses, we examined potential distinctions between neural FC and outcomes when stratified by fine and gross motor performance. We observed that the relationship between fetal IPL FC was uniquely related to gross but not fine motor skills when these were considered as correlated dependent variables. In contrast, for the other three areas exhibiting both gender and composite motor effects (ACC, PFC, and cerebellum), the association between FC and fine and gross motor outcomes were not distinct. In other words, with the exception of the IPL, fetal FC is correlated with both fine and gross motor ability in a similar way to the composite score; for the IPL, FC strongly predicts gross but not fine motor outcomes in infancy.

Discussion

Neural processing in the newborn brain depends on global connective systems present at birth. The ordered steps by which the brain becomes organized into a collection of interactive highways for information transfer across gestational development are presently not well understood. To our knowledge, this study is the first report on fetal brain–function and infant–behavior associations. Specifically, we address the extent to which strength of FC within the fetal sensorimotor neural system predicts variation in infant motor ability at age 7 months, and examine infant sex as potentially influencing this effect.

We observed that several regions in the fetal brain have connective patterns that relate to subsequent infant motor ability (Table 2). Observed effects support a model of more rapid infant motor development relating to earlier specialization of neural systems that support sensorimotor function. Specifically, we observed that regions that support motor function,

particularly prefrontal regions, the posterior cingulate, and supplementary motor regions, show increased connectivity with the motor network in fetuses that will develop motor abilities more rapidly in infancy. The idea that more rapid specialization of fetal neural systems predicts more advanced motor ability in infancy, over and above variation introduced by age of the fetus at the time of MRI, fits with previous developmental literature showing that infants that “start out ahead” tend to go on to be individuals that “stay ahead.” For example, earlier attainment of motor milestones in early childhood is related to better cognitive performance and completion of higher educational levels later in life (Murray, Jones, Kuh, & Richards, 2007; van Batenburg-Eddes et al., 2013).

In addition to observing brain regions in which fetal FC and child motor ability were positively related, we identified a separable set of regions that showed the reverse effect. These were regions of the anterior cingulate, insula, and lateral cerebellar regions, where diminished FC was associated with more advanced infant motor ability. Thus, it is not just enhanced signal coherence within neural systems that relates to individual motor outcomes, but also reduced connectivity to potentially superfluous regions. In this context, significant negative correlations could result from more active reorganization or pruning in individuals that will develop infant motor abilities more quickly. Another possibility is that these are extraneous connections that are more often present in individuals that reach motor milestones more gradually. An example is in the cerebellum where advanced motor outcomes were associated with decreased lateral cerebellar FC and increased midline anterior cerebellar FC. Prior studies in large samples of adults demonstrate that the cerebellum possesses multiple representations of the cerebral cortex (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Guell, Schmahmann, Gabrieli, & Ghosh, 2018). Of note, regions of the cerebellum that Buckner, Guell, and others showed to be mapped to sensorimotor cortical regions encompass the region in which we observed a positive association with future motor ability. On the contrary, the region of the cerebellum in which we observed reduced connectivity predicting future motor ability fell within regions of the cerebellum they identified as linked to cognitive and association cortices. One can imagine that in assembling neural systems, increased functional integrity within the system is balanced with reductions in unnecessary connections. Our observations in the cerebellum dissociation noted here may be an example of this.

We observed that female infants demonstrated higher motor development scores than males, especially in the fine motor domain. While investigators commonly report language performance differences between male and female infants (Neligan & Prudham, 1969), few studies report sex differences in motor skills during infancy, and in the limited studies we found, sex differences occur in fine motor skills or upper limb coordination, rather than in gross motor performance (Piek, Gasson, Barrett, & Case, 2002; Touwen, 1976). Thus, the current observations replicate prior developmental sex differences, and add greater context, establishing that fetal neural system development may set the stage for later variation in motor ability.

We also discovered that associations between fetal neural sensorimotor system connectivity and infant motor behavior were particularly strong in females. This is illustrated in slope values provided in Table 4, and in plots of FC separated by participant sex in Figure 3. Prior

studies report sex differences in developmental trajectories, and report that female mental abilities stabilize at an earlier age (Bayley, 1966), and that early speech ability predicts subsequent verbal ability in females only (Bayley, 1968). Here, we also find that females show a behavioral advantage and that longitudinal associations between brain and behavior are stronger in females. Nancy Bayley remarked, “The girls appeared to be more resilient in returning to their own characteristic inherent response tendencies. Boys, on the other hand, were more permanently affected by the emotional climate in infancy” (1968, pp. 14–15). This sentiment inclines that female infants may have a less malleable disposition than their male counterparts, and it appears that our neuroimaging findings may fall in line with this position. We may be observing that the female fetal brain may be more “hard-wired” and less susceptible to early environmental programming.

The idea that females may be less sensitive to environmental programming dovetails nicely with prior observations that insults and injuries sustained during the perinatal period have larger negative consequences in males than in females. Evidence for enhanced male susceptibility has been observed across numerous conditions, including stress exposure (Bale & Epperson, 2015), prematurity (Ingemarsson, 2003; Skiöld et al., 2014; Whitfield, Grunau, & Holsti, 1997), and negative caregiving (Barnett & Scaramella, 2013; Góes et al., 2015; Mileva-Seitz et al., 2015). Recognition that maladaptive outcomes are more frequent in males across exposure types suggests that a general mechanism, or common pathway, may contribute to overall greater male vulnerability in early life. Findings from this study provide a candidate pathway in neural system functional integrity.

If males are more sensitive to environmental programming than females, the implications of this warrant consideration. It is notable that increased sensitivity to environmental programming may be disadvantageous under conditions of adversity, but may be advantageous when conditions are more favorable. In a review on prenatal origins of behavioral differences, Coe and Lubach (2005) address the adaptive nature of flexibility, stating “fetal vulnerability to adverse events experienced by the mother may be a price paid for the adaptive benefits and flexibility gained by allowing developmental processes to be responsive to the environment. As long as the extrinsic conditions remain within a tolerable norm, then the reactions of the fetus and young infant serve a useful function and benevolently guide development” (p. 48). Within this framework, flexibility is adaptive under more favorable conditions.

In conclusion, the present study demonstrates for the first time that variation in the human fetal neural connectome correlates with infant motor ability. This relationship was significant even after controlling for salient sociodemographic factors that could influence our hypothesized relationships, including socioeconomic disadvantage and maternal prenatal anxiety. In addition, brain–behavior relationships were influenced by the sex of the child such that slope of effects was strongest in female participants. These observations extend prior longitudinal research back into prenatal brain development, and raise exciting new ideas about the advent of risk, and the ontogeny of early sex differences.

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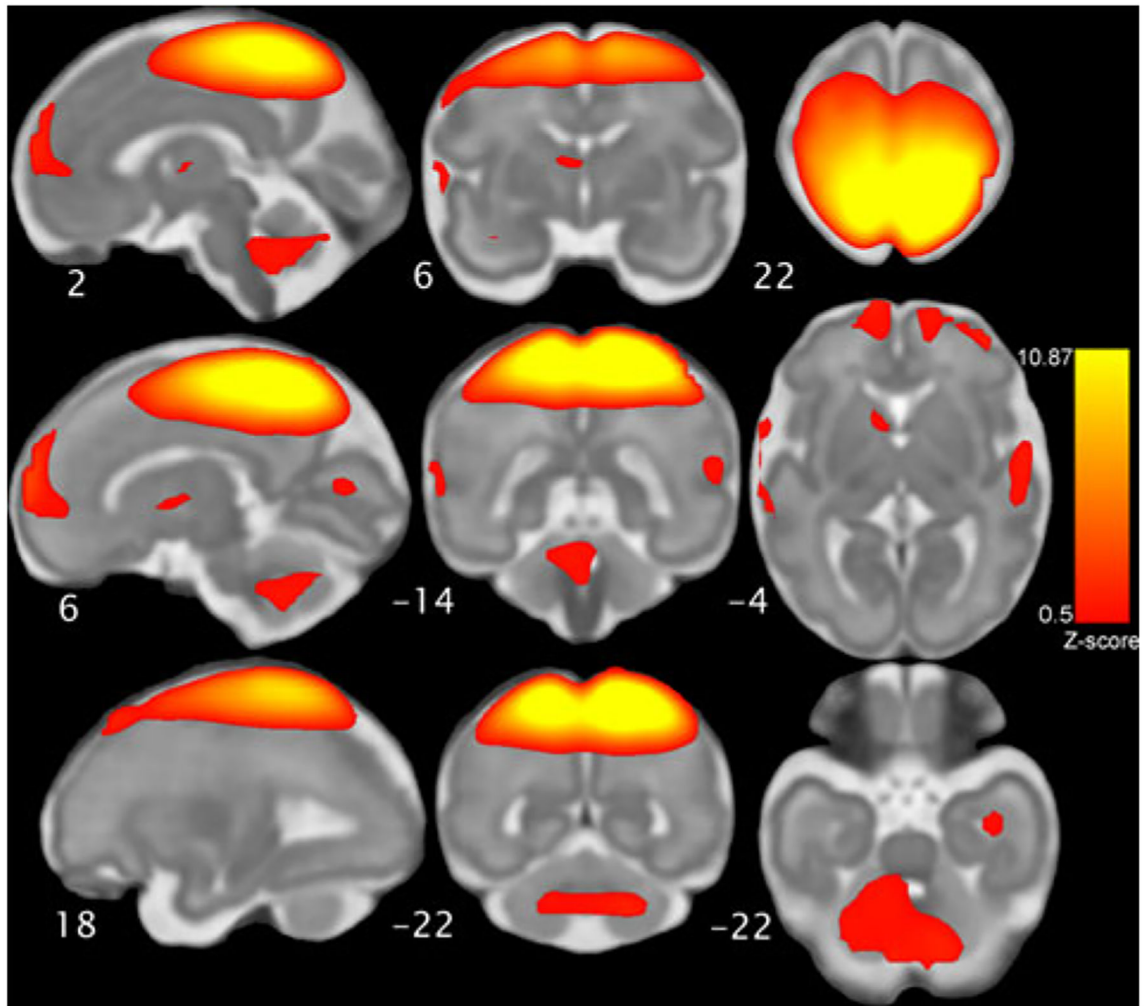


Figure 1.

The fetal sensorimotor resting state network, which was derived from group independent components analysis of resting state scans obtained in 96 fetuses. The network component map pictured here is threshold at $Z = 0.5$ and displayed on a 32-week gestational age template for anatomical reference. The network includes motor and sensory cortices, cerebellum, striatum, thalamus, and bilateral insula. Neurological convention is used.

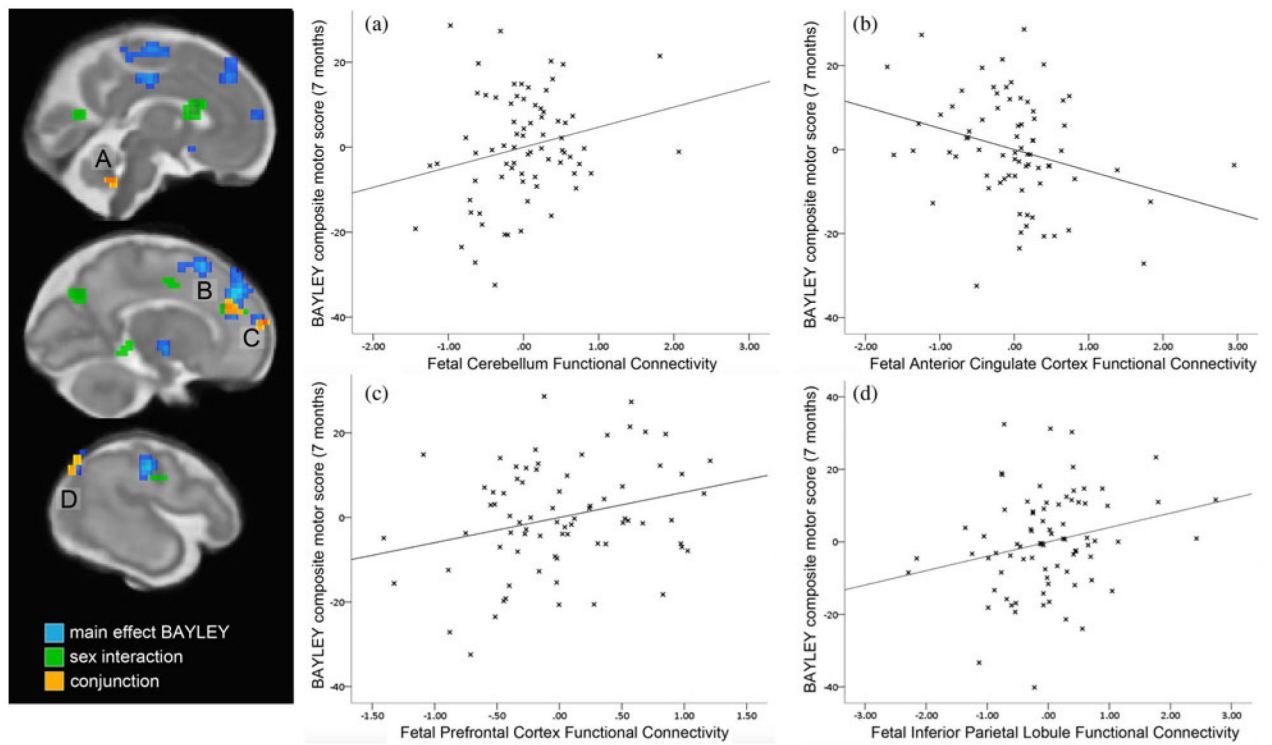


Figure 2. Scatterplots depicting significant associations between fetal functional connectivity and Bayley performance at infant age 7 months. Scatterplots depict mean signal extracted for each subject from 3-mm radius spheres positioned at the center of mass in regions associated with both motor outcomes and sex differences, shown in left panel in orange and projected onto 32-week fetal reference anatomical brain images. We observe that for the cerebellum, prefrontal cortex, and inferior parietal lobule, increases in functional connectivity to the motor system predicts better Bayley scores. The reverse is true for the anterior cingulate cortex (ACC), suggesting decreased signal coupling between the fetal motor system and ACC is indicative of better future motor outcomes.

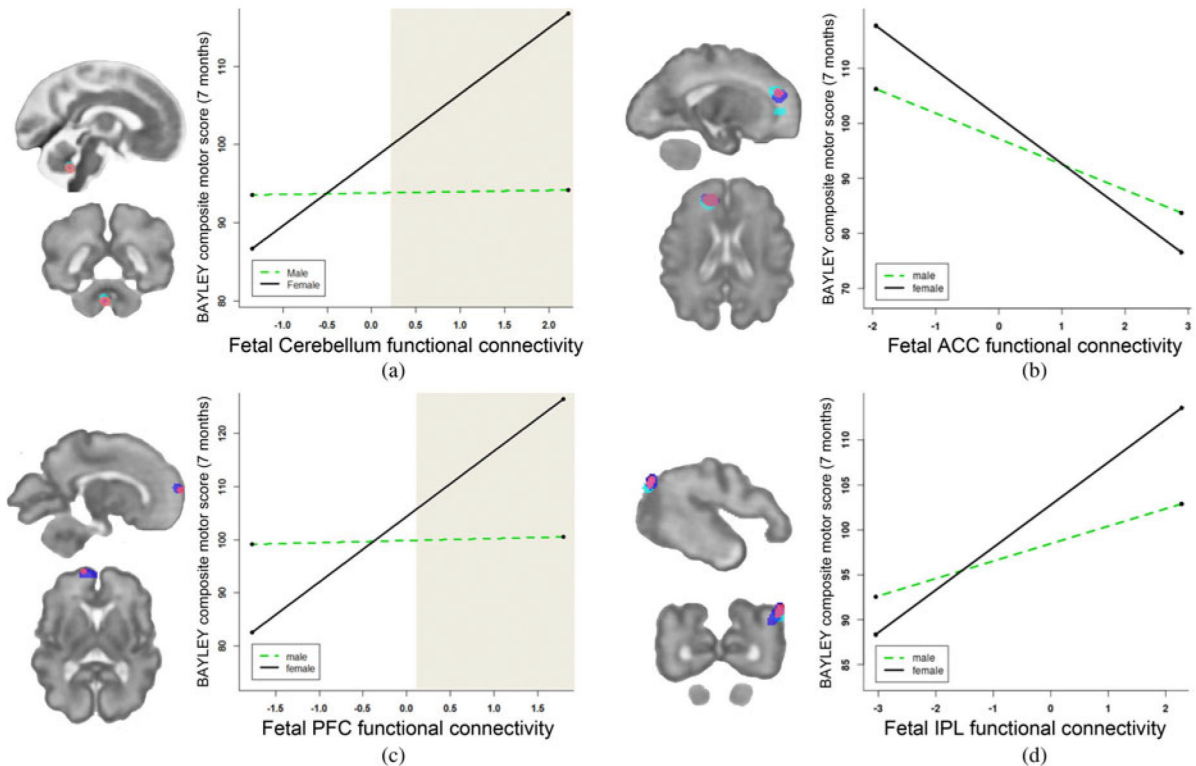


Figure 3.

Sex differences were observed in four brain regions exhibiting associations between fetal functional connectivity and Bayley motor performance at 7 months postnatal age. Mean functional connectivity values are plotted by median Bayley performance and by sex, and given for (a) the cerebellum, (b) the anterior cingulate (ACC), (c) the prefrontal cortex (PFC), and (d) the inferior parietal lobule (IPL). Structural equation models controlling for maternal education, income, anxiety, and motion during magnetic resonance imaging demonstrate significant sex interactions in the cerebellum, $p = .03$, and the PFC, $p = .002$. An examination of the region of significance in sex interactions showed these effects to be significant at higher fetal functional connectivity values (see shaded regions in [a] and [c]). When groups were tested individually, brain–behavior associations were significant among girls ($ps < .01$), but not boys ($ps = .3$), across all four areas (see Table 4). Brain images to the left of plots highlight areas from which functional connectivity is plotted, corresponding to main effects of Bayley motor outcome (dark blue), interaction of Motor \times Sex (cyan), and the conjunction of these (fuchsia) at $p < .05$.

Table 1.

Summary of data and participant characteristics

	Males (<i>n</i> = 59)	Females (<i>n</i> = 37)
Infant variables, <i>M</i> (<i>SD</i>)		
Fetal gestational weeks at delivery	39.1 (1.7)	38.9 (1.2)
Birth weight (g)	3280 (550)	3059 (531)
Infant age at lab visit (months)	7.4 (0.5)	7.5 (0.5)
Maternal ethnicity, <i>n</i> (%)		
African American	44 (75.6)	30 (81.1)
Caucasian	8 (13.6)	3 (8.1)
Asian American	0	1 (2.7)
Other	4 (6.8)	0
Maternal education, <i>n</i> (%)		
No GED/high school diploma	4 (6.8)	6 (16.2)
GED/high school diploma	22 (37.3)	10 (27.0)
Some college	25 (42.4)	16 (43.2)
2-year college degree	1 (1.7)	0
4-year college degree	3	1 (2.7)
Masters or doctorate	1 (1.7)	0
Annual household income, <i>n</i> (%)		
<\$10,000	15 (25.4)	12 (32.4)
\$10,000-\$20,000	19 (32.2)	6 (16.2)
\$20,000-\$30,000	10 (17.0)	5 (13.5)
\$30,000-\$40,000	0	3 (8.1)
>\$40,000	5 (8.5)	5 (13.5)
Marital status, <i>n</i> (%)		
Single	38 (64.4)	17 (45.9)
Married/partnered	16 (27.1)	16 (43.2)
Divorced	1 (1.7)	0
Employment status, <i>n</i> (%)		
Employed	39 (40.6)	28 (29.2)
Unemployed	12 (12.5)	5 (5.2)
Prenatal maternal variables, <i>M</i> (<i>SD</i>)		
Maternal age at scan (years)	25.9 (4.8)	26.0 (4.3)
Maternal prenatal anxiety symptoms	36.5 (8.5)	35.5 (7.8)
fMRI data characteristics, <i>M</i> (<i>SD</i>)		
Fetal gestational weeks at scan	33.3 (3.9)	32.6 (4.4)
Number of fMRI frames analyzed	158 (52)	148 (40)
Translational mean movement (mm)	0.2 (0.1)	0.2 (0.1)
Rotational mean movement (degrees)	0.4 (0.2)	0.4 (0.2)

Note: Chi-square tests compared race/ethnicity, education, and income between groups and two-sample *t* tests compared all other variables. All comparisons were nonsignificant, using two-tailed, $p < .05$.

Brain areas in which fetal motor network functional connectivity positively or negatively predicts infant Bayley performance at 7 months

Table 2.

Region	BA	k	F	T	vol (mm ³)	x	y	z
<i>Positive</i>								
Posterior cingulate cortex	L30*/31/7	154	12.51	3.54	1232	-8	-16	-2
Supplementary motor cortex	R6	53	9.13	3.02	424	0	4	22
Superior frontal gyrus	R6	38	9.31	3.05	304	8	18	22
Prefrontal	R10	38	7.9	2.81	304	8	40	0
Medial temporal lobe	L20	37	10.3	3.21	296	-20	-4	-24
Inferior parietal lobe	L7	37	10.18	3.19	296	-28	-30	14
Temporal pole	R38*/20	24	9.13	3.02	192	32	6	-18
Parahippocampal gyrus		20	9.91	3.15	160	-22	-22	-10
<i>Negative</i>								
Anterior cingulate cortex	R32*/8/9	118	12.55	-3.54	944	6	30	12
Motor cortex	L2	89	10.61	-3.26	712	-28	0	14
Insula	L13	68	9.11	-3.02	544	-20	18	-8
Cerebellum		48	10.32	-3.21	384	-12	-24	-16
Subgenual area	L25	38	10.28	-3.21	304	-2	10	-10
Supramarginal gyrus	R40	27	9.71	-3.12	216	36	-8	12

Note: Significant clusters are reported for regions in which fetal functional connectivity positively or negatively predicted motor performance at 7 months post-natal age, given at $p < .05$, and k -min = 20.

Table 3.

Fetal intrauterine functional connectivity relates to higher infant motor function in structural equation models accounting for sex, movement during the scan, and salient maternal characteristics

Fetal cerebellar functional connectivity	<i>B</i>	<i>SE</i>	β	<i>p</i>
Gender	-4.32	2.99	-0.15	.161
Motion	19.64	11.52	0.14	.086
Maternal education	-0.60	1.04	-0.04	.570
Income	-0.35	0.48	-0.06	.464
Prenatal anxiety	-0.05	0.52	-0.01	.918
<i>Cerebellum functional connectivity</i>	8.47	3.22	0.37	.003
<i>Cerebellum Functional Connectivity</i> × Gender	-8.29	4.08	-0.24	.030
Fetal anterior cingulate cortex (ACC) functional connectivity				
Gender	-3.98	2.92	-0.14	.183
Motion	11.88	11.33	0.09	.302
Maternal education	-1.62	1.15	-0.12	.171
Income	-0.32	0.42	-0.05	.458
Prenatal anxiety	0.05	0.43	0.01	.905
<i>ACC functional connectivity</i>	-8.51	3.28	-0.44	<.001
<i>ACC Functional Connectivity</i> × Gender	3.86	4.04	0.13	.301
Fetal prefrontal cortex (PFC) functional connectivity				
Gender	-4.58	2.81	-0.14	.109
Motion	18.18	10.39	0.12	.074
Maternal education	-1.59	1.47	-0.11	.308
Income	-0.32	0.47	-0.05	.498
Prenatal anxiety	-0.37	0.51	-0.07	.446
<i>PFC functional connectivity</i>	12.32	3.13	0.48	<.001
<i>PFC Functional Connectivity</i> × Gender	-11.94	4.30	-0.35	.002
Fetal inferior parietal lobule (IPL) functional connectivity				
Gender	-4.31	3.02	-0.15	.16
Motion	15.25	11.46	0.11	.18
Maternal education	-0.19	1.10	-0.02	.86
Income	-0.20	0.43	-0.03	.64
Prenatal anxiety	-0.32	0.52	-0.06	.53
<i>IPL functional connectivity</i>	4.74	1.36	0.30	<.001
<i>IPL Functional Connectivity</i> × Gender	-2.79	2.41	-0.12	.240

Note: Connectivity of the ACC negatively predicts motor outcome; all other regions are positively related to infant motor ability at 7 months.

Table 4.

Estimated simple slopes for associations between fetal functional connectivity and Bayley performance in male and female infants

	<i>B</i>	<i>SE</i>	<i>t value</i>	<i>p value</i>
Female				
Cerebellum	8.47	3.22	2.63	.0105*
ACC	-8.51	3.28	-2.59	.0112*
PFC	12.32	3.13	3.93	.0002**
IPL	4.74	1.36	3.48	.0008**
Male				
Cerebellum	0.18	5.20	0.04	.9721
ACC	-4.65	5.22	-0.89	.3758
PFC	0.38	5.34	0.07	.9435
IPL	1.94	2.78	0.70	.4871

Note: Simple slopes estimated for male and female fetal functional connectivity predicting Bayley motor scores at 7 months. ACC, anterior cingulate cortex. PFC, prefrontal cortex. IPL, inferior parietal lobule.

* $p < .05$.

** $p < .001$.