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Age-related increases in long-range connectivity in fetal functional neural connectivity networks *in utero*

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ABSTRACT

Formation of operational neural networks is one of the most significant accomplishments of human fetal brain growth. Recent advances in functional magnetic resonance imaging (fMRI) have made it possible to obtain information about brain function during fetal development. Specifically, resting-state fMRI and novel signal covariation approaches have opened up a new avenue for non-invasive assessment of neural functional connectivity (FC) before birth. Early studies in this area have unearthed new insights about principles of prenatal brain function. However, very little is known about the emergence and maturation of neural networks during fetal life. Here, we obtained cross-sectional rs-fMRI data from 39 fetuses between 24 and 38 weeks postconceptual age to examine patterns of connectivity across ten neural FC networks. We identified primitive forms of motor, visual, default mode, thalamic, and temporal networks in the human fetal brain. We discovered the first evidence of increased long-range, cerebral-cerebellar, cortical-subcortical, and intra-hemispheric FC with advancing fetal age. Continued aggregation of data about fundamental neural connectivity systems *in utero* is essential to establishing principles of connectomics at the beginning of human life. Normative data provides a vital context against which to compare instances of abnormal neurobiological development.

1. Introduction

One of the major achievements of human fetal brain development is the establishment of functional neural networks. Detailed understanding of normal processes of brain circuit formation is essential for discovering consequences of injury/insult, periods of vulnerability, and for early detection of clinically significant neural anomalies.

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The bulk of what is known about human brain connectional ontogeny comes from histological and magnetic resonance imaging (MRI) studies performed on post-mortem fetal brain specimens. These histological and MRI studies have shown that transient physical structures serve as scaffolding for axonal proliferation and cell migration (Kostovic and Jovanov-Milosevic, 2008) and that, in harmony with brain gyrification, long-range association pathways begin to be established during the second half of gestation (Kostović and Jovanov-Milosevic, 2006; Takahashi et al., 2012).

Until recently, quantification of neuroconnectivity during the fetal period has proven elusive for human *in vivo* brain research. However, recent advances in diffusion and resting state MRI have provided new means for non-invasive study of neural circuit formation in the perinatal period (Mailath-Pokorny et al., 2012). Tractography analyses of fetal brain diffusion tensor imaging data has demonstrated emergence of white matter pathways in the transient intermediate zone, splenium, and genu, consistent with *in vitro* findings (Kasprian et al., 2008). Resting-state functional MRI (rs-fMRI) applied to prematurely born human infants has shown that, as the preterm neonate grows, neural circuit functional activity becomes increasingly synchronized (Smyser et al., 2010) and that intrinsic connectivity networks (ICNs) are largely formed by 42 weeks postmenstrual age (Doria et al., 2010). However, preterm neonates are not ideal substitutes for learning about typical fetal brain development, because the underlying reason for preterm delivery and environmental factors cannot be disentangled from neurological observations in these cases. Important questions remain about large-scale neural organization, and establishment of ICNs prior to birth.

Recent investigations have established the utility of rs-fMRI for quantifying neural network development *in utero*. The first fetal rs-fMRI study was performed in pregnant women referred to MRI for suspected neurological anomalies discovered during fetal sonography. The investigators qualitatively compared functional connectivity (FC) networks in 16 fetuses that had healthy MRI results and minimal movement. They concluded that in the majority of cases temporal lobe networks were lateralized, whereas frontal and occipital networks were bilateral (Schöpf et al., 2012). Subsequently, two human fetal FC studies have been performed, assessing fetuses recruited as part of research studies, rather than as part of clinical follow-up. Statistical group-level comparisons of FC in 25 healthy fetuses demonstrated that cross-hemispheric connectivity increases with advancing postconceptual age, and that midline cross-hemispheric connectivity precedes lateral connectivity (Thomason et al., 2013). Graph theoretical analyses in 33 fetuses revealed that synchrony of activity across neural networks is increased in older, compared to younger, fetuses. In addition, connectivity between the posterior cingulate cortex (PCC) and other brain areas becomes more negative with increasing postconceptual age (Thomason et al., 2014). These studies provided the first indication that human fetuses possess basic forms of neural connectivity networks and that rs-fMRI may become instrumental for determining principals of human FC *in utero*.

Age-related changes in resting-state networks *in utero* remain unclear. We obtained cross-sectional rs-fMRI data from 39 fetuses between 24 and 38 weeks postconceptual age to examine patterns of connectivity across ten functionally integrated ICNs. Following prior work in neonates (Smyser et al., 2010), we measured fMRI covariation in sensorimotor, cingulate, occipital, prefrontal, temporal, and thalamic regions. Employing seed-based connectivity analysis (SCA), we interrogated qualitative and quantitative changes in ICNs associated with advancing fetal age. We predicted that homotopic and long-range connectivity would be strongest in older fetuses, across neural networks, and that within network covariance would be higher and between network covariance would be lower in older fetuses. The latter would be fitting with emergence of independently functioning ICNs.

2. Methods

2.1. Participants

Rs-fMRI data were collected from healthy pregnant women and their fetuses recruited from obstetrical clinics located within the Detroit Medical Center. Initial contact was made by physicians to potential participants in their care and followed up by one-on-one discussion with a member of the research team who explained study procedures and answered questions. Participants were informed that their participation in research was voluntary and not part of their prenatal care. They were assured that they were not selected on the basis of any medical findings, and it was explained that their choice to participate would not influence their future medical care. Exclusionary criteria included: presence of MRI contraindication, fetal central nervous system abnormality, and maternal size larger than would comfortably be accommodated in a 70-cm open-bore MRI system. Inclusionary criteria included: singleton pregnancy between 24 and 38 weeks postconceptual age, and maternal age $\geq$18 years. Written, informed consent was obtained prior to participation. All experimental procedures were approved by the Human Investigation Committee of Wayne State University.

Data were collected from a total of 39 pregnant women (median maternal age = 23 years, range = 18–37 years). The median gestational age (GA) of their fetuses was 32 weeks (range = 24 + 4 to 37 + 6, weeks + days) at the time of MRI. Seven fetal participants were excluded prior to group level analyses due to (a) having fewer than 100 fMRI volumes after removing high movement frames (n = 4), or (b) because they went on to be born preterm (n = 3), leaving a total of 32 participants. fMRI data from 22 of these participants has been reported previously (Thomason et al., 2014, 2013).

2.2. Measures

Information about maternal health practices were obtained using a 45-item health questionnaire which assessed frequency of engaging in specific health behaviors related to diet, exercise, medical adherence, alcohol and tobacco use and exposure, and sleep (adapted from Jackson,