Biological Psychiatry

Review

Development of Brain Networks In Utero: Relevance for Common Neural Disorders

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ABSTRACT

Magnetic resonance imaging, histological, and gene analysis approaches in living and nonliving human fetuses and in prematurely born neonates have provided insight into the staged processes of prenatal brain development. Increased understanding of micro- and macroscale brain network development before birth has spurred interest in understanding the relevance of prenatal brain development to common neurological diseases. Questions abound as to the sensitivity of the intrauterine brain to environmental programming, to windows of plasticity, and to the prenatal origin of disorders of childhood that involve disruptions in large-scale network connectivity. Much of the available literature on human prenatal neural development comes from cross-sectional or case studies that are not able to resolve the longitudinal consequences of individual variation in brain development before birth. This review will 1) detail specific methodologies for studying the human prenatal brain, 2) summarize large-scale human prenatal neural network development, integrating findings from across a variety of experimental approaches, 3) explore the plasticity of the early developing brain as well as potential sex differences in prenatal susceptibility, and 4) evaluate opportunities to link specific prenatal brain developmental processes to the forms of aberrant neural connectivity that underlie common neurological disorders of childhood.

Keywords: Child, Connectivity, Fetal, MRI, Prenatal, Psychopathology

https://doi.org/10.1016/j.biopsych.2020.02.007

Disturbances in the complex connective architecture of the human brain is a ubiquitous property of mental and developmental disorders (1). Given that the large-scale systems of the brain take form before birth (2–4) and that many brain disorders likely have prenatal origin (5), understanding development and modeling of brain connections across fetal life in both health and disease is essential. Identification of both causes and consequences of disrupted prenatal connectivity may lead to more effective diagnosis and treatment of common neurological and developmental disorders.

The variety of methods for examining the brain as a collection of connected and dynamically active networks is expansive, and yet a number of methodological challenges and uncertainties color the field (6–9). These are described in greater detail in the Supplement. Despite these challenges, knowledge gained about structural connectivity, from diffusion-weighted imaging approaches, and about functional connectivity, from functional time series approaches, has revolutionized our understanding of the human systems-level brain organization. We better understand fundamental properties of normative development (10), aging (11), atypical development and disease (12–15), brain plasticity and learning (16), perturbations of large-scale systems by state and mood (17), and even evolutionary principles (18). In clinical research settings, connectomics approaches are being applied to assessment of treatment outcomes (19), prediction of recovery (20,21), diagnostic medicine (22,23), pharmacological manipulations (24,25), and preoperative brain mapping (26,27). Overall, evaluation of the human brain through a connectomics lens has enabled significant basic and translational discoveries about macroscale organization of the human brain.

This review is focused on the order and timing with which neural connections form across fetal development. Consideration is given to available methodologies for studying human fetal brain development, the relevance of prenatal brain network development to future neurobehavioral outcomes, and near-term opportunities for addressing unanswered questions. In addition, in the Supplement, we highlight evidence of prenatal environmental influences over brain development and consider prenatal origins of sex-specific disease risk.

METHODOLOGIES FOR STUDYING HUMAN PRENATAL BRAIN MACROCIRCUITRY

The predominant approaches for studying prenatal brain network development are 1) to examine ex vivo fetal brain specimens, 2) to study the preterm neonate prior to term equivalent age, and 3) to study the living fetus in utero. Each presents a unique set of conditions.

The ex vivo brain can be assessed in greatest detail and with the largest collection of available techniques. This approach has generated foundational knowledge about genetic processes and physical development of the fetal brain (28–31). Furthermore, multiple approaches—for example,

 ISSN: 0006-3223

diffusion magnetic resonance imaging (MRI), gene expression, and histology—can be applied to a single brain specimen to delineate fetal brain structures at macro- and microscopic levels and/or to examine concurrent gene expression and structural development (31,32). These studies draw on the strengths of each approach and provide beneficial reference for situations in which only one measurement is possible, such as in vivo diagnostic radiology. The challenge, however, is that ex vivo brain specimens cannot provide information about function, cannot be studied within a longitudinal framework, and when obtained during the second half of pregnancy are frequently the result of genetic or environmental abnormalities or insults. Furthermore, brain death results in diffuse physical and functional changes, including metabolic cellular injury and altered vascular regulation (e.g., permeability of the blood brain barrier), which influence extracted tissue measures and responses to surrounding conditions.

Studies of the preterm neonatal brain provide foundational insight into late-gestation brain development and bypass some of the technical challenges of intrauterine brain imaging. Indeed, MRI studies of the preterm brain have generated fundamental knowledge about the order and timing of cortical folding, germinal matrix evolution, white matter development, and myelination. In the preterm neonatal brain, reliable electroencephalography and task-evoked stimulus response measures are also readily attained. However, an important consideration in studies of preterm brain development, as with postmortem brain studies, is that it is more likely that genetic and/or environmental hazards have influenced the brain. In addition, extrauterine experiences of the preterm neonate influence brain development, altering and potentially accelerating the course of development (33). In line with this, MRI studies comparing neuroanatomy of age-matched fetuses and preterm neonates have reported differences between groups that likely reflect differences in etiology, experience/exposure, and mechanics of imaging the fetus versus the newborn (34,35). Those results are demonstrated in Figure 1. Furthermore, functional MRI studies report widespread differences in neural functional systems in fetuses and neonates born preterm (4,36,37), calling into question representativeness of preterm neonatal studies for understanding typical human fetal development.

Neurosonography (ultrasound), MRI, and magnetoencephalography (MEG) are the primary techniques for examining the fetal brain in utero. Ultrasound is the mainstay for clinical screening of fetal intracranial anatomy. Transcranial Doppler ultrasound can also be used to evaluate blood flow in major arteries of the fetal brain. MRI also has widespread prenatal clinical utility and has arisen as the preferred methodology for fetal brain research studies. MRI offers multiple modalities by which to assess the fetal brain (e.g., metabolism, microstructure, connectivity) [see Table 1 (38–74) and Figure 2] and has the versatility to enable concurrent examination of the fetal body, placenta, and maternal compartment. Drawbacks of MRI are that scans are costly, MRI systems tend to be less available outside of major health systems and university settings, and contraindications for MRI are numerous and in pregnancy include large body mass, as some systems are limited by 60-cm bore size.

A small number of MEG systems have been specially built to measure fetal brain activity before birth. Fetal imaging with

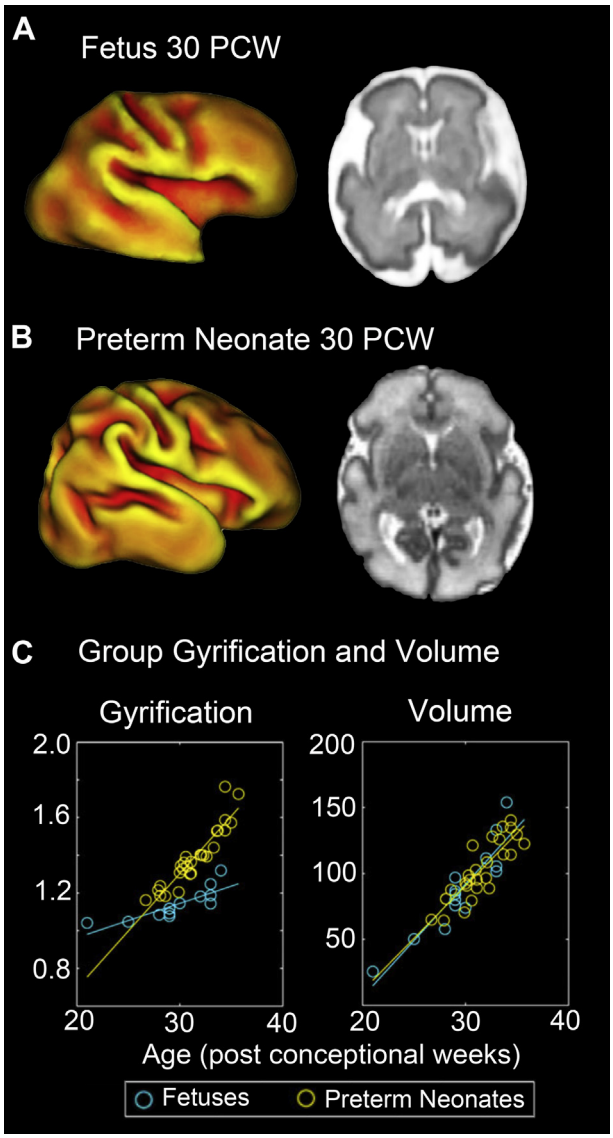

Figure 1. Anatomical evaluation of fetuses and preterm neonates scanned at the same postconceptional week (PCW). Representative surface renderings and T2-weighted anatomical images are provided for **(A)** a fetus at 30.0 weeks PCW and **(B)** for a preterm neonate, born at 28.7, scanned at 30.4 weeks PCW. **(C)** Group-level gyrification indices and volume measured inside a brain mesh (mL) are plotted. Whereas volume was consistent between groups, gyrification was significantly different between groups. These data likely reflect a combination of differential brain development out of the womb, differential brain development of the preterm brain, and differences in image attributes. Data courtesy of Julien Lefevre and colleagues. These data, along with detailed comparison of cortical folding patterns in utero and ex utero, are available in Lefevre *et al.* (34). For comparison of prenatal in utero and ex utero diffusion tensor imaging, see Lockwood *et al.* (35).

MEG involves the mother sitting at a forward or reclined angle with a custom-fit MEG sensor array resting against her abdomen. MEG is sensitive to very small changes in magnetic properties of the brain that result from electrical current changes produced by active neural populations. Because MEG directly measures neural activity, it has very high

Table 1. Principal Imaging Modalities With Prenatal Applications

Imaging Approach	Information Obtained	Representative Perinatal In Vivo Human Studies
T1- and T2-Weighted Anatomical	Structural morphometry	Levine *et al.* (38); Prayer *et al.* (39); Gertsvolf *et al.* (40); Kyriakopoulou *et al.* (41)
Diffusion MRI	Fiber pathway organization, myelination, brain anatomy, and cellular morphology	Jakab *et al.* (42); Schneider *et al.* (43); Huang *et al.* (44); Kaspirian *et al.* (45); Mitter *et al.* (46); Righini *et al.* (47)
BOLD Functional MRI	Hemodynamic changes associated with neuronal activity; placental oxygenation	Schopf *et al.* (48); Thomason *et al.* (49); Jakab *et al.* (50); Fulford *et al.* (141); Sinding *et al.* (51); Blazejewska *et al.* (52)
Perfusion and Flow	Quantity of blood moving through capillaries in mL/s/g of tissue; bulk motion	De Vis *et al.* (53); Ouyang *et al.* (54); Jakab *et al.* (55)
Susceptibility-Weighted Imaging	Iron content, myelination, venography, oxygenation	Neelavalli *et al.* (56,57); Yadav *et al.* (58)
Magnetization Transfer	Myelination; vascular volume	Ong *et al.* (59); Nossin-Manor *et al.* (60)
NMR Spectroscopy	Metabolite spectral peaks	Wolfberg *et al.* (61); Girard *et al.* (62); Kok *et al.* (63); Bluml *et al.* (64); Limperopoulos *et al.* (65)
Magnetoencephalography	Cortical function	Fehlert *et al.* (66); Morin *et al.* (67)
Ultrasound	Intracranial anatomy, behavior (e.g., spontaneous limb and eye movement, response to stimuli); cerebrovascular dynamics (e.g., CBF velocity in the anterior, middle, and posterior cerebral arteries)	Inoue *et al.* (68); Chang *et al.* (69); Pugash *et al.* (70)

A number of modalities have been developed for studying the fetal and preterm human neonatal brain. In addition to modalities summarized here, perinatal quantitative MRI [valuative rather than relative estimates; minimize influence of machine and operator variation; cf. Grossman *et al.* (71); Studholme (72); Ferrie *et al.* (73); Clouchoux *et al.* (74)] is another notable area of active development.

BOLD, blood oxygen level–dependent; CBF, cerebral blood flow; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance.

temporal resolution. In contrast to functional MRI, which is reliant on detecting hemodynamic changes that lag 3 to 6 seconds behind neural activity, MEG detects electrical activity of neurons on the order of milliseconds. Disadvantages of fetal MEG are, again, expense, accessibility, and that MEG is not as good as functional MRI at precisely localizing brain activity. New frontiers in fetal brain imaging are discussed further in the Supplement.

PRENATAL BRAIN DEVELOPMENT

Overview of Emergent Brain Structure

The most rapid growth of the brain occurs in utero and in the first 20 postnatal weeks. At birth, the majority of systems that will compose the network architecture of the adult brain are already present (2–4). Proliferation of neural precursor cells, neuroblasts, occurs between the 4th and 20th weeks of gestation, whereas the production of glioblasts, precursors of nonneuronal cells, begins at about 19 weeks and continues after birth. The number of neuroblasts produced during human gestation exceeds the number of neurons in the adult brain and spinal cord. With time, these cells migrate, grow processes, and form synaptic connections. Synaptic density rapidly increases through combined processes of synaptogenesis, synaptic reorganization, and the formation of dendrites and dendritic spines. The genetically driven overproduction of dendrites, dendritic spines, and axons at this stage of life results in an excess of cells and synapses throughout the brain. Synaptic connections between select cells will be enforced through activity-dependent processes that alter cellular genetic and chemical signaling. In contrast, others of these cells will die and/or the connections between them will be remodeled (75–78). Processes driving the pruning and refinement of neural circuitry have been studied since the 1930s and 1940s (79), with notable contribution from Donald Hebb, who, based on seminal contributions regarding emergent neural circuitry and the basis of conscious learning, is credited for the adage, “cells that fire together, wire together” (80). During Torsten Wiesel’s Nobel Lecture in 1981, he emphasized that is not only activity or disuse that influences development of neural connections, but also competition, as experimentally it has been shown that even in a deprivation situation, cells can grow normally when competition is removed (81,82). These fundamental premises remain highly influential in fields of developmental physiology and neuroanatomy, as contemporary studies continually reaffirm the tight coupling between structure and function in development and maintenance of brain circuitry (83).

Development of fetal brain macrostructure follows a predictable timetable. MRI studies show that by approximately week 9, growth of the corpus callosum is initiated at 2 distinct loci that fuse between weeks 13 and 14 (84). By the end of the 4th month of gestation the first sulci appear. By the 22nd week of pregnancy, the interhemispheric fissure, the callosal sulcus, the parieto-occipital fissure, and the hippocampal fissures are present. By week 25, the central sulcus emerges at the lateral surface and with time extends anteriorly toward the midline until it abuts the interhemispheric fissure at approximately week 30. By week 33, all primary sulci are present. Garel *et al.* (85) have studied these processes in exquisite detail and

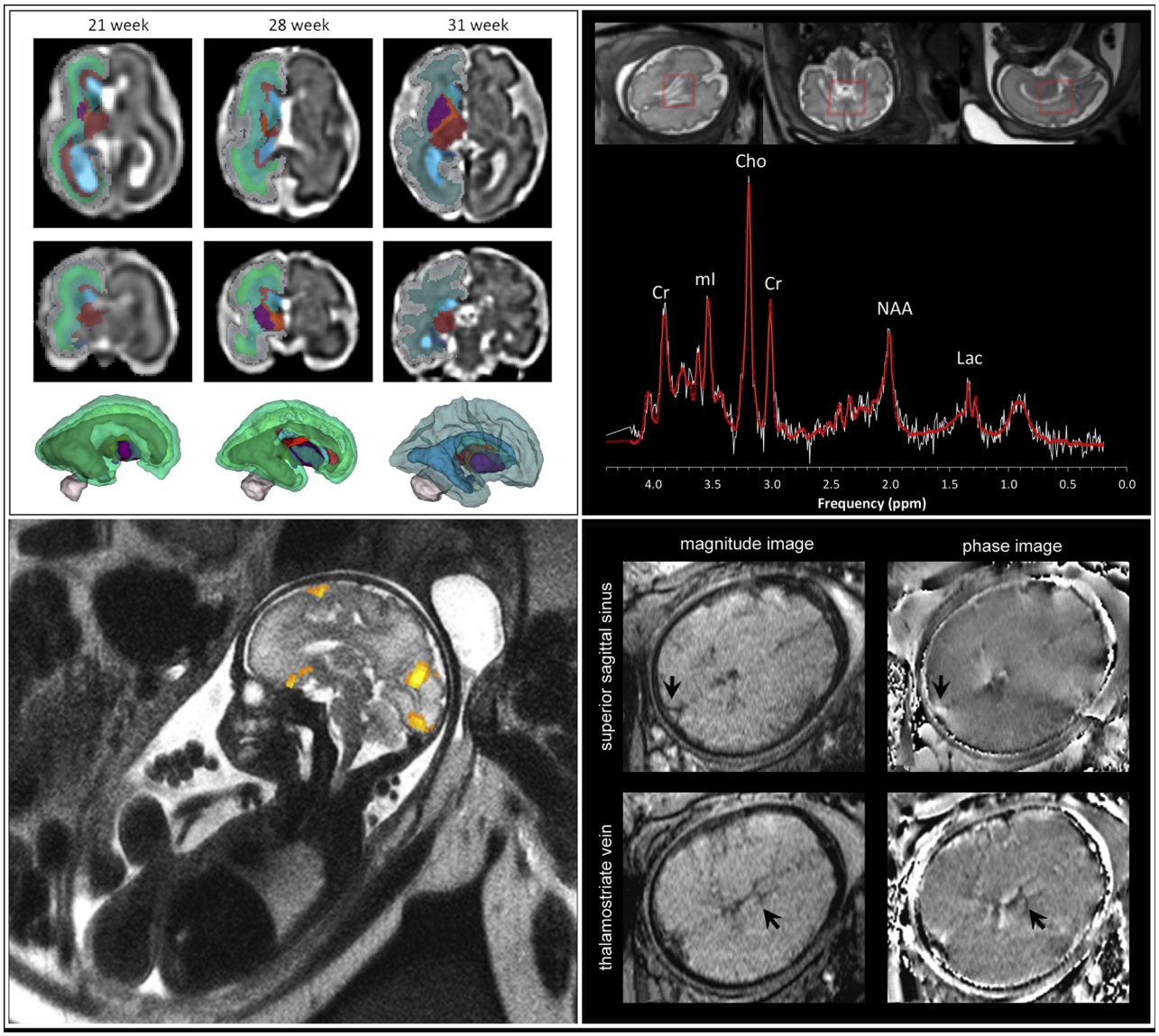

Figure 2. Multimodal in utero fetal magnetic resonance imaging. Images correspond to fetal anatomical reconstruction and segmentation (upper left); fetal magnetic resonance spectroscopy (upper right); fetal thalamocortical resting-state functional magnetic resonance imaging functional connectivity (lower left); magnitude and phase images from fetal susceptibility weighted imaging (lower right): arrowheads superior sagittal sinus (upper) and thalamostriate vein (lower). (Upper left) Anatomical images courtesy of Xiaojie Wang at Oregon Health Sciences University. (Upper right) Magnetic resonance spectroscopy images courtesy of Stefan Bluml and Vidya Rajagopalan at Children Hospital Los Angeles. (Lower panels) Functional magnetic resonance imaging and susceptibility weighted imaging data are from Moriah Thomason and Jaladhar Neelavalli and were acquired at Wayne State University. Cho, choline; Cr, creatine; Lac, lactate; ml, mobile lipids; NAA, *N*-acetylaspartate; ppm, parts per million.

conclude that the best period to study gyration is between 28 and 34 weeks, as this is the period of the most rapid processes of sulcal development and, thus, the period when individual variation is most likely to be detected.

Sequence and Timing of Prenatal Fiber Tract Development

Histochemical and diffusion tensor imaging (DTI) studies of the fetal brain in vitro (32,44,86–88) and in utero (45,89–96) and in preterm neonatal brains (97–100) provide insight into the temporal order in which physical structures connecting different brain regions emerge across fetal development. Microscale myelination of the fetal brain is detectable as early as 20 weeks in the medial longitudinal fasciculus of the medulla and pons. Rapid myelination occurs over the first 2 years of human life, followed by a far more gradual and protracted increase in myelin and fiber bundles that continues well into the third decade of human life (101). This property of early rapid development, followed by prolonged maturation, is uniquely human and may reflect conservation of metabolic energy to support parallel demands of both body and brain growth (102).

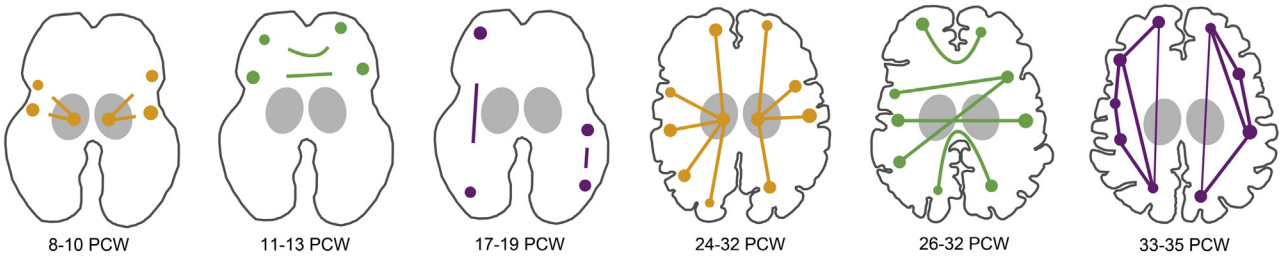

Figure 3. Schematic representation of prenatal fiber tract development across weeks of gestation. Initial stages include corticospinal development and nascent cross-hemispheric connections. Intrahemispheric local connectivity is then followed by development of thalamocortical afferents. In later stages, the commissural and thalamocortical fibers extend to the cortex and long-range association fibers extend within each hemisphere. PCW, postconceptional week. [Figure adapted with permission, from a comprehensive review by Keunen *et al.* (103).]

Major fiber pathways connecting distant brain regions begin to take form at the end of the first trimester and provide a scaffold for the development of long-range connections and large-scale neural systems. Projection fibers including the corticospinal tract extending from the internal capsule are the earliest to develop, followed by commissural fibers of the corpus callosum by week 13. Within-hemisphere association fibers, including the uncinate and inferior fronto-occipital fasciculi, also form early, followed by inferior longitudinal fasciculus, cingulum, and fornix. Significant development of long-range connectivity occurs in the third trimester. During that time, thalamocortical and callosal fibers will extend to innervate cortical regions, and intrahemispheric long-range association fibers will develop. Overview of these stages is provided in Figure 3 (103).

An active area of scientific inquiry is to develop MRI DTI methodology for examining the human fetal brain in utero. As mentioned herein, and articulated well by others (46), examination of the brain after death is complicated by alterations in tissue microstructure, cellular damage, brain edema, loss of supporting structures such as the skull and the meninges, and the fixation process itself. In utero tractography of the living human fetus is a major objective because it allows study of more normative conditions and enables examination of associations between 3-dimensional morphology of fiber tracts and concurrent conditions of the pregnancy, both of which are critical for understanding causes of neurological injury and disease. At present, successful in utero tractography has been achieved in several major tracts. However, slight differences in intrauterine and ex vivo results have been noted; tracts that have been successfully reconstructed in utero appear to develop on a slower timetable and have different characteristic shapes (90). Furthermore, data loss is a major consideration. In particular, it is difficult to achieve robust results uniformly across brain regions, and the proportion of scans lost to image artifacts and fetal movement can exceed 50%. However, this is an emergent field and recent developments in intrauterine DTI are promising. New studies have addressed replication (42,104) and cross-validation (35,91), which provide a basis for assessing reliability and accuracy of fetal DTI metrics. Furthermore, advances in fetal diffusion MR image acquisition and reconstruction, such as direction-sensitive slice-to-volume correction (35,105), are leading to higher success rates.

Functional Network Development Beginning In Utero

Patterning of neural circuitry begins early in development, before many of the sensory organs are functional. Activity is initially incoherent and unorganized; however, as neuroblasts mature, migrate, and form connections, a rich repertoire of spontaneous activity patterns emerge (106,107). Spontaneous neural activity reverberates through circuits in the form of propagating waves that reinforce appropriate connections and trigger essential activity-dependent signaling processes. Neural activity recorded using electroencephalography in preterm neonates has revealed regular occurrence of intermittent high amplitude bursts known as spontaneous activity transients. Spontaneous activity transients emerge during midgestation, appear to originate in temporal and insular regions (108,109), and, importantly, predict more favorable brain and behavioral outcomes (110). With maturation of thalamocortical afferentation, beginning at approximately week 24, and dissolution of the temporary subplate, more complex electrical signals emerge and the first evoked potentials may be recorded (111). In parallel, the fetus begins to respond to nociceptive signals, light, speech, and sound (112–115).

New knowledge about the order and timing with which the human fetal functional connectome takes form has arisen from recent fetal functional MRI resting-state functional connectivity (RSFC) studies. The first of these studies confirmed what has been observed ex vivo and in animal studies, that large-scale networks take form in the prenatal period and that inter- and intrahemispheric connectivity increase with advancing gestational age (48,49). A study by Jakab *et al.* (50) also showed peak increases in connectivity between gestational weeks 24 and 31, with peak inflection at 27 weeks, and these investigators highlight that this corresponds with the period of maximum growth of the human fetal subplate and increasing synaptogenesis in the cortical plate that occur in this developmental window. These were important initial studies because they provided proof of concept that despite the technical and interpretive challenges of fetal MRI (116,117), it is possible to measure global properties of prenatal brain functional development in healthy human fetuses. Fetal RSFC studies that have followed have provided evidence that strength of long-range connectivity linearly increases with advancing fetal age, interhemispheric connections show sigmoidal growth, and cross-hemispheric homotopy follows

overlaid posterior-to-anterior and medial-to-lateral gradients (49,50,118). A study of fetuses that subsequently went on to be born preterm compared with age-matched term-born fetuses demonstrated that differences in neural connectivity observed in the preterm brain begin before delivery (37).

Fetal RSFC studies using graph models and network-based inference approaches confirm that the fetal brain is organized with adultlike network properties. Van den Heuvel *et al.* (119) isolated fetal RSFC hubs, or highly connected nodes within the brain network, in several areas of the temporal lobe, the precentral gyrus, and the cerebellum (119). These investigators note that these hubs share partial spatial overlap with observed hubs in the neonatal brain and that these are among the first areas of the brain to myelinate. A recent study by Turk *et al*. (120) compared the overall brain connectome structure in adults and in fetuses during the second and third trimesters and observed a robust degree of organizational overlap of 61.66%. The fetal connectional "blueprint" included 4 functional modules, compared with 5 in the adult group. This study also confirmed that the fetal connectome shows significant rich club organization, such that central nodes communicate preferentially with one another, enhancing total network efficiency (120). Additional fetal RSFC studies using network approaches have shown that modularity decreases and efficiency increases in the fetal brain network with age (120,121). Decreased modularity is likely to reflect initial outgrowth of projections and formation of connections. Later in development, neural systems will be pruned and connections refined such that networks will become more specialized and segregated, which is reflected in prior accounts of increased modularity and efficiency across child development (122,123). Together these investigations demonstrate the presence of a functional connectomics blueprint before birth that may be foundational to future brain health.

PRENATAL ORIGINS OF COMMON NEURODEVELOPMENTAL PROBLEMS

Human brain development is protracted by comparison to other species. As a result, we are a species with a long early window of plasticity, during which we remain both open to programming by the environment and primed for experiential learning. When the developmental program is thrown off course, due to either genetic disposition or environmental insult, or these in combination, the brain is well equipped to attempt to compensate. There are many examples in the literature of animals administered experimental brain lesions in windows of high developmental plasticity, and in these studies, the rewiring of neural systems to work around the injury is striking (124). In humans, these resilient responses to miswiring events or early brain injury are also evident (33). The challenge, however, is that compensation is not the same as correction, and what may arise from an early injury or deviation in developmental wiring may have long-ranging implications that are not immediately evident (125).

Considerable research has begun to address differences in neuroconnectivity that underlie common neurodevelopmental disorders. For example, a number of studies have shown that autism spectrum disorder (ASD) is associated with altered connectivity between and within regions associated with social cognition and also with cross-network integration (126). Dyslexia has been linked to weaker connectivity in the posterior reading network, altered connectivity of the visual word form area, and reduced functional segregation between the default mode network and frontoparietal control regions (19,127). Widespread neural circuitry appear to be affected in attention-deficit/hyperactivity disorder, leading to suggestion that the complexity of attention-deficit/hyperactivity disorder miswiring parallels the heterogeneity seen in attention-deficit/hyperactivity disorder behavioral phenotypes (19,128). Prior reviews address the development of neural networks across a number of childhood neurological disorders in greater detail (1,10,129).

The challenge in investigations of neural underpinnings of common neurological diseases of childhood is that results across studies are mixed and at times contradictory. Uddin *et al.* (130) address mixed results in ASD MRI studies and highlight that in contrast to increased connectivity in children with ASD, adults and adolescents tend to show diminished connectivity. Solomon *et al.* (131) report differential effects in older and younger ASD groups as well. These findings have led to the suggestion that some of the disparities across the extant literature may be resolved by placing findings in a developmental framework, explicitly evaluating age and pubertal status. Hernandez *et al.* (132) arrived at a related conclusion in their review of ASD neuroconnectivity; they suggested that vast genetic and phenotypic heterogeneity characteristic of the disorder likely contribute to contradictory results. Taken together, much has been gained from developmental imaging studies, including enhanced understanding of developmental plasticity and growth and also insight into neural correlates of disease. Yet, many would agree that currently, clinical imaging biomarkers for early human diseases are absent. It is difficult to resolve whether this is because disorders may lack specific and sensitive neural biosignatures and/or whether variation in approaches taken in human imaging studies are stalling clinical progress. To the latter, in the 1962 words of Teuber and Rudel (133), "it is unfortunately true that the effects one observes are largely a function of the questions that are being asked."

With advances in early life MRI it may soon be possible to go back farther and understand where the wiring events deviate from normal to give rise to intellectual problems and disorders of childhood. In a longitudinal framework it is possible to bridge early connectome development with later developmental outcomes. A recent study by Wolff *et al.* (134) demonstrated that measures of connectivity in the corpus callosum and cerebellar pathways at age 6 months predicted repetitive behaviors and sensory responsiveness, respectively, at age 2 years. A recent study by our group (135) demonstrated that even in utero it is possible to detect differences in connectivity that relate to subsequent infant motor outcomes at age 7 months. Using longitudinal approaches such as these, it will be possible to begin to tackle critical questions about how variation in prenatal brain development relates to long-term neurobehavioral outcomes. This is a critical research direction, because in the future, perinatal imaging biomarkers could inform diagnoses, inspire novel intervention strategies, and serve as a new basis for monitoring treatment progress.

Two principles that make linking aberrant neural developmental processes to either concurrent or future outcomes are interdependency and relative timing. Across development,

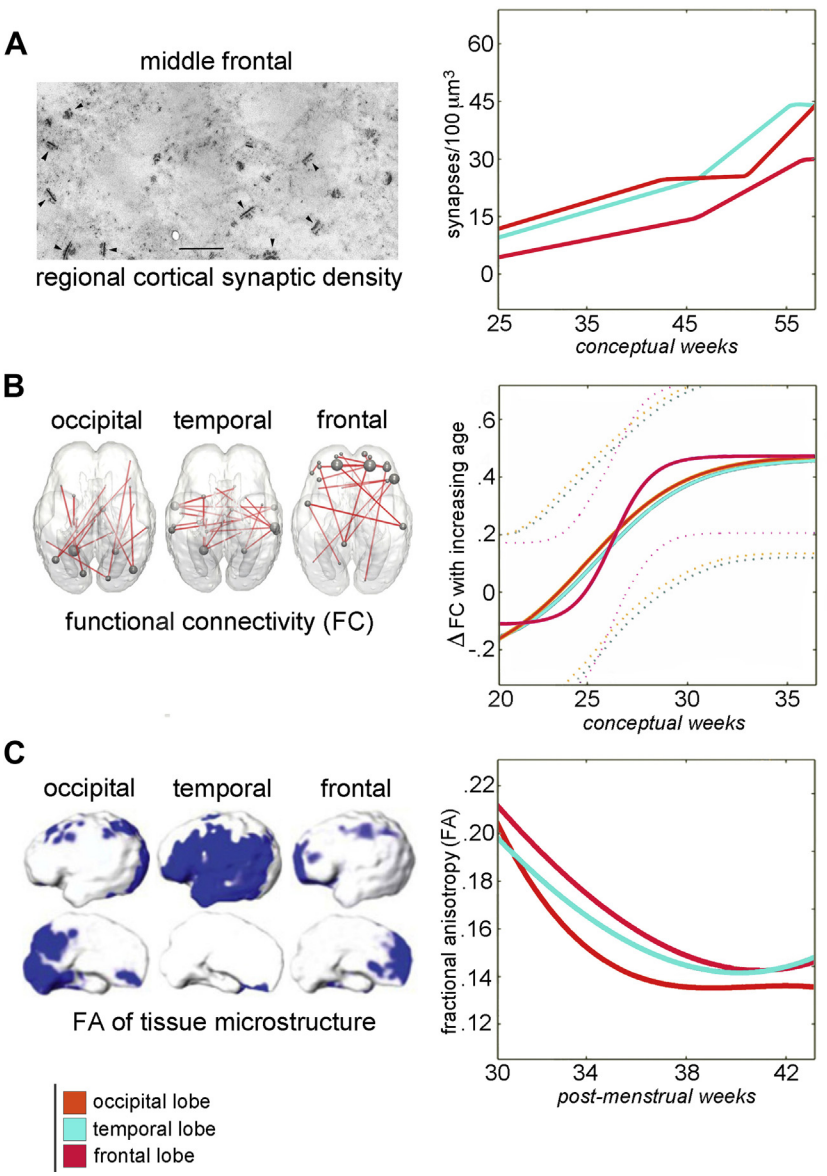

Figure 4. Region-specific rates of fetal brain maturation. These data presented by **(A)** Huttenlocher and Dabholkar (142), **(B)** Jakab *et al.* (50), and **(C)** Ouyang *et al.* (143) depict prenatal synaptic density, functional connectivity and fractional anisotropy, respectively, across different regions of the brain. Line colors are consistent across data sets and demonstrate varied prenatal maturational time courses across regions and across modalities. Interactions between regions are likely to be influenced by this innate property of heterogeneous regional development. Scale bar in panel **(A)** = 1 µm. FA, fractional anisotropy; FC, functional connectivity.

different brain regions mature at different rates (see Figure 4), and as a result, interactions between regions change over time. To alter development in a single region at a single time point is likely to spur both immediate and long-term changes that are not obviously causally related. It is as if the brain were a system of levers and pulleys; removal of a gear will shift the balance in all that remain. Furthermore, the association across gears is time dependent. When one removes a gear at different times and in different places, then the variety of possible outcomes is multiplied.

FUTURE DIRECTIONS

With increased ability to noninvasively measure and model maturation of the human fetal brain, new opportunities surface. Beyond the core necessity of establishing normative properties of human development, there is increasing interest in isolating deviations from typical brain development that precede behavioral problems of childhood. By identifying and monitoring fetuses at elevated risk of future developmental problems—for example, those at increased risk for preterm delivery or with congenital defects—we can isolate patterns of neural development that differentiate those that subsequently exhibit neurodevelopmental problems. Such biomarkers have the potential to inform treatment decisions and novel intervention strategies and could serve as the basis for monitoring progress following intervention. Overall, a major future direction for basic neuroscience and perinatal medicine is to perform longitudinal studies that will anchor the meaning of observed fetal brain effects in the context of individual human developmental trajectories.

Advances in noninvasive imaging can also serve to better bridge human and animal studies. Animal models inform much of what we understand about human development, yet building homology between animal and human studies can be challenging (136–138). By unveiling capacity to evaluate the human brain before birth, we are better equipped to perform parallel human and animal studies that capitalize on complementarity of these approaches. For example, MRI could be used to establish the order and timing with which thalamocortical connections emerge over human gestation, and this information could be referenced to genetic variation, intrauterine exposures, and/or later outcomes. By comparison, animal studies could be used to isolate chemical and/or molecular processes that are necessary for the formation of thalamocortical circuitry (cf. 139,140) and/or to study the effect of chemical, hormonal, or micronutrient manipulations on this circuitry. Combination of these approaches yields mechanistic and causal understanding of human growth that could not be achieved using either approach in isolation.

Another significant opportunity in the future of fetal imaging is to pair advanced imaging methods with progress in acquiring and analyzing biological and environmental "omics" data obtained during pregnancy. Materials obtained from the human body can report on past and present gene and chemical activity as well as profile microorganisms inhabiting body material. In this way, samples obtained during pregnancy can be used to assess numerous bodily processes, such as gene transcription, inflammation, and hormone activity, and also to profile micronutrients and chemical products absorbed from the environment. Some of the currently available methods can even report on fetal systemic responses; for example, fetal exosomes can be isolated in maternal blood, and as tooth buds (future baby teeth) form in the fetal mouth they record information in a temporal order (like rings of a tree) that can later be analyzed. Future studies will bridge this fundamental biomarker data with measures of fetal brain development to attain understanding about the regulatory influence of, or programming by, the maternal body over fetal brain growth and development.

ACKNOWLEDGMENTS AND DISCLOSURES

This project was supported by the National Institutes of Health Grant Nos. MH110793, DA050287, ES032294, and MH122447.

The author reports no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Jul 24, 2019; revised Jan 5, 2020; accepted Feb 5, 2020.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2020.02.007.

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