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Characterizing Large-Scale Human Circuit Development with In Vivo Neuroimaging

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Large-scale coordinated patterns of neural activity are crucial for the integration of information in the human brain and to enable complex and flexible human behavior across the life span. Through recent advances in noninvasive functional magnetic resonance imaging (fMRI) methods, it is now possible to study this activity and how it emerges in the living fetal brain across the second half of human gestation. This work has demonstrated that functional activity in the fetal brain has several features in keeping with highly organized networks of activity, which are undergoing a highly programmed and rapid sequence of development before birth, in which long-range connections emerge and core features of the mature functional connectome (such as hub regions and a gradient organization) are established. In this review, the findings of these studies are summarized, their relationship to the known changes in developmental neurobiology is considered, and considerations for future work in the context of limitations to the fMRI approach are presented.

Over the last century, pioneering postmortem studies have provided detailed information about the dramatic cellular and anatomical changes that occur in the human brain during the time leading to birth. While such studies have provided fundamental insights into how the structure of the fetal brain evolves on the micro- and mesoscale across this period, it is only recently that the critically important role that activity plays in early brain development has begun to be understood. Furthering this knowledge is vital, as it is increasingly recognized that altered patterns of activity before birth (either through genetic mechanisms or acquired lesions) frequently lead to permanent changes in brain structure, circuit organization, and function (Miguel et al. 2019). This has key implications for behavior and neurological function, with converging evidence now suggesting that early disruptions in brain connectivity (how distinct brain regions are structurally and functionally connected to one another) are a key pathological feature underlying neurodevelopmental conditions that are lifelong but manifest in child-

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hood such as autism (Testa-Silva et al. 2012; Deneault et al. 2018; Ciarrusta et al. 2020) and mental health disorders (e.g., schizophrenia) (Gilmore et al. 2010; Sigurdsson 2016).

In its earliest stages, neural activity occurs spontaneously in local circuits within clusters of developing neurons, and in doing so helps to enhance and/or modulate further neurogenesis, progenitor cell differentiation, and synaptogenesis (Luhmann et al. 2016). These processes have been studied in cutting edge in vitro and animal work, which are detailed in other articles in this special collection. Here, we instead focus on the large-scale patterns of coordinated neural activity that emerge in the second half of human gestation as the cortex and its macroscopic framework of axonal connections are established (Kostović and Jovanov-Milošević 2006). Importantly, much of the previous knowledge about these processes has been inferred from preterm-born infants studied in the equivalent period to the third trimester of gestation (28 to 40 postmenstrual weeks). However, information derived from infants that have been prematurely exposed to the ex utero environment is unlikely to be truly representative of "normal" fetal brain development. This can now be overcome through recent methodological advances in noninvasive neuroimaging, which for the first time enable in vivo study of the emergence of larger-scale neural "circuits" in human fetuses. Here the methods themselves are described, benefits and limitations are considered, findings are described in the context of known developmental neurobiology, and future directions for study are presented.

CHARACTERIZING BRAIN FUNCTION AND CONNECTIVITY IN THE BRAIN WITH NEUROIMAGING

Although the importance of integration and cooperative patterns of neuronal activity for brain function has long been established in neuroscience (Hebb 1949), understanding of the importance of large-scale neural circuitry and the concept of "functional connectivity" (long-range temporal correlations in activity between spatially distinct brain areas with neuroimaging) is relatively recent (Friston et al. 1993). The latter is generally considered to represent the ability of the brain to share information between different regions, each of which with their own specific processing role. The resulting correlated patterns of large-scale brain activity are thought to enable complex human behavior by providing the framework needed for integration and exchange of information during both extrinsically and intrinsically generated functions (van den Heuvel and Hulshoff Pol 2010). In addition to mapping the brain's functional connections, the "structural connectivity" of the white matter axonal pathways between brain regions can also be noninvasively mapped using diffusion magnetic resonance imaging (MRI) methods (Le Bihan et al. 2001). The resulting structural connectivity measures have been shown to significantly predict patterns of functional connectivity, suggesting that they represent the anatomical framework on which large-scale patterns of activity propagate (Honey et al. 2010).

Correlated patterns of neural activity can also be studied with a variety of neurophysiological (i.e., electroencephalography [EEG], magnetoencephalography [MEG]) and neuroimaging methods (i.e., positron emission tomography (PET), near-infrared spectroscopy (NIRS]). However, the majority of these methods are not easily applied to studying the in utero fetal brain as they measure signals either through the scalp or require injection of a radioactive tracer. In contrast, functional magnetic resonance imaging (fMRI) can provide an entirely noninvasive and safe measure of fetal brain activity, with relatively good whole-brain spatial sensitivity (usually a few millimeters cubed) and temporal resolution (usually a few seconds). The sampled blood oxygen level–dependent (BOLD) fMRI signal is an indirect measure of neural activity, as the contrast mechanism is generated by sampling temporal signal fluctuations arising from localized changes in the relative proportion of paramagnetic deoxygenated hemoglobin and diamagnetic oxygenated hemoglobin (Ogawa et al. 1990). These change due to the local alterations in cerebral blood flow that are associated with neural activity, through the carefully controlled neurovascular coupling cascade (Attwell and Iadecola 2002). In the seminal work of

Logothetis et al. (2001), fluctuations in the fMRI BOLD signal were found to most closely relate temporally to cortical local field potentials (LFPs) and thus represent the sum of synaptic inputs within a population of neurons, rather than their spiking output.

In the mature brain, fMRI has been widely applied to spatially map areas of activity in the brain associated with particular tasks, both within putative primary processing regions and more widely across the engaged network of associative regions (Bandettini et al. 1992; Kwong et al. 1992; Ogawa et al. 1992). However, a major advance in understanding the functional organization of the brain occurred when it was discovered that patterns of correlated low frequency (0.01 to 0.1 Hz) activity could also be reproducibly identified even at rest (i.e., in the absence of a particular task or stimulus), particularly between functional homolog regions in each hemisphere (Biswal et al. 1995). The energy cost of this resting activity is significant, with early PET studies demonstrating that transient periods of task induced neural activity are associated with only very small rises in oxygen metabolism from that which is already needed during the baseline resting condition (Fox et al. 1988). The spatial organization of resting patterns of activity across specific brain areas have been termed "resting state networks" (Snyder and Raichle 2012). In addition to recapitulating the spatial patterns of correlated activity induced by a particular stimulus or task (Cole et al. 2014), resting state networks in adults have been found to be highly reproducible both within a given subject and across large populations (Shen et al. 2018), suggesting that they are an intrinsic brain property that is preserved across behavioral states and people. While the repertoire of these networks continues to grow, the classical complement includes those covering the primary motor and sensory cortical regions in both hemispheres (the motor, somatosensory, primary visual, lateral visual, auditory networks), in addition to those often considered to be "higher order" networks incorporating the medial and lateral frontal regions, insular cortices, and anterior cingulate gyri (Beckmann et al. 2005; Damoiseaux et al. 2006). Of particular interest has been the so-called "default mode network," which encompasses the medial prefrontal cortex, precuneus, and the bilateral posteroinferior parietal lobes, and has been proposed to have a key role in facets of complex human brain processing such as self-referential thought (Raichle et al. 2001; Greicius et al. 2003).

The application of the above fMRI methods into the study of newborn infants demonstrated that even shortly after birth, resting state networks resembling those seen in the adult brain could also be reliably identified (Fransson et al. 2007). Of particular interest, extension of study populations into preterm-born infants imaged before the time of normal birth found a clear pattern of maturation, with the topology of resting state networks seen to progress from simple unilateral clusters of local connectivity in a single hemisphere in the youngest infants (<28 wk postmenstrual age) to distributed bilateral networks with long-range interhemispheric or anteroposterior patterns of connectivity by term equivalent age (Doria et al. 2010; Smyser et al. 2010). These results highlight a clear pattern of emerging functional connectivity, suggesting that the foundations of the brain's lifelong network architecture are established during the equivalent period to the third trimester of gestation. The key importance of this period is further emphasized by studies that have shown that altered functional connectivity in preterm-born infants is associated with later adverse neurodevelopmental outcome (Linke et al. 2018; Eyre et al. 2021; Cyr et al. 2022) and is sustained into later childhood and adulthood (Papini et al. 2016; Wehrle et al. 2018; Hadaya and Nosarti 2020).

NEUROBIOLOGICAL DEVELOPMENT UNDERLYING THE ESTABLISHMENT OF LARGE-SCALE CIRCUITRY IN THE FETAL BRAIN

Across the 40 wk of gestation, the human cortex undergoes an extremely rapid but highly programmed sequence of microstructural and macrostructural maturation that is presumed to lay the anatomical framework needed for the aforementioned patterns of long-range connectivity (for review, see Pöpplau and Hanganu-Opatz

2023; as well as Kostović et al. 2019; Molnár et al. 2019). The formation of the cortex in this time is a protracted process that is characterized by proliferation and tangential/radial migration of neural progenitor cells from the ventricular and outer subventricular zones (Marin and Rubenstein 2003). These cells first reach their final location on the outer cortical surface from 12 wk of gestation, with this process largely complete by approximately 30 wk, although it continues even up to 2 yr of age in specific cortical regions (Cadwell et al. 2019). Migration occurs earlier in the dorsal brain (peaking in the occipital lobe at 20 wk of gestation) compared with parietal (peaking at 23 wk) and frontal regions (peaking at 26 wk) (Trivedi et al. 2009; Paredes et al. 2016). During this time, genetic mechanisms and signaling pathways direct neuronal differentiation, leading to the characteristic anatomical features seen in the mature cortex such as lamination (Cadwell et al. 2019), which is seen first in the primary sensory and motor cortices at 25 wk of gestation, with the full adult complement of distinct lamina seen by 32 wk (Bystron et al. 2008; Kostović et al. 2019). Cortical folding rapidly proceeds across the third trimester of gestation such that the majority of the mature brain's sulcal landmarks can be identified by full term (van der Knaap et al. 1996; Yun et al. 2020). During this time, endogenously generated synchronous neural activity occurs in early circuits and is critical during the aforementioned processes by guiding fundamental processes including synaptogenesis, neuronal maturation, and dendritic arborization (Khazipov and Luhmann 2006). Ex vivo studies suggest this evolves from spontaneous events that spread locally in the form of oscillatory calcium waves and giant depolarizing potentials, before further neurochemical maturation (specifically that of the GABA and glutamate neurotransmitter systems) enables large amplitude bursting events in the latter half of gestation (Khazipov and Luhmann 2006).

The thalami are of particular interest as the emerging thalamocortical axonal pathways are known to provide key inputs into the developing cortex, additionally helping to guide cortical areal differentiation and establish the circuitry underlying sensory integration across the life span (Sur and Rubenstein 2005; Price et al. 2006; Kostović and Judaš 2010; Krsnik et al. 2017). The sequence of thalamocortical maturation begins with fiber outgrowth at 8–9.5 gestational weeks, pathfinding at 9–14 wk, "waiting" in the cortical subplate region between 14 and 22 wk, and finally ingrowth into the cortical plate at 23–24 wk (Krsnik et al. 2017). Thalamic afferents and early-generated transient subplate neurons synapse during the waiting period (Wess et al. 2017). These synapses play a key role in forming a functional template for the development of thalamocortical networks and overall cortical architecture (Ohtaka-Maruyama et al. 2018; Molnár et al. 2020). A fundamental feature of these developing neural circuits is spontaneous activity, which begins in the subplate neurons even before the establishment of cortical layers (Luhmann et al. 2022). The critical importance of this activity has been demonstrated by selective surgical ablation of the subplate in rodents, which abolishes spontaneous cortical activity and disrupts permanent cortical organization (Tolner et al. 2012).

The above developmental changes in tissue microstructure and structural connectivity can be characterized in the postmortem and living fetal brain with diffusion MRI (Takahashi et al. 2012; Huang and Vasung 2014; Vasung et al. 2019; Wilson et al. 2023; Zheng et al. 2023). This includes visualizing the dissolution of the developing cortical plate's radial organization in the second trimester (which persists longer within the gyral crests in comparison to the sulcal depths) (Takahashi et al. 2012). In preterm infants, systematic changes in diffusion MRI-derived microstructural metrics are suggestive of a predominant increase in dendritic arborization and neurite growth in cortical gray matter between 25 and 38 wk of gestation (Batalle et al. 2019). Related methods have also been used with in utero MRI data to characterize maturational changes in microstructure seen within transient tissue layers (intermediate zone, subplate, and cortical plate) as they grow and dissolve in fetuses, with specific developmental trajectories associated with distinct thalamocortical white matter pathways (Wilson et al. 2023). These pathways are presumed to represent bun-

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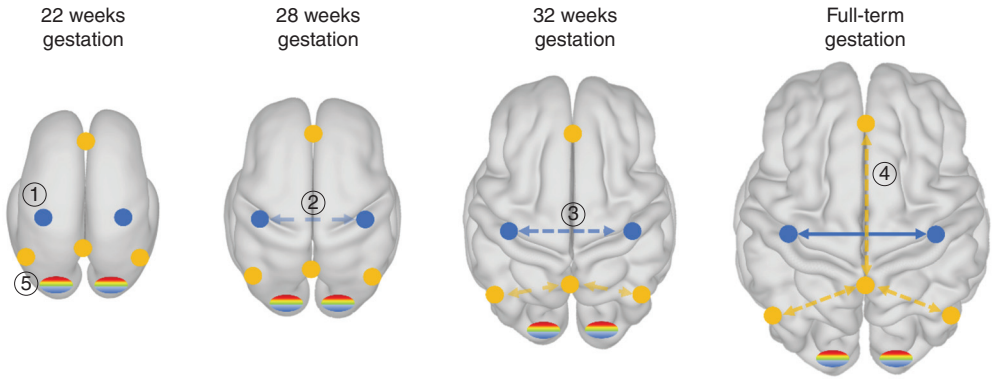
dles of emerging premyelinated axonal fibers that (in keeping with histological studies) mature in a tract-specific manner: with the commissural and projection fibers (corpus callosal and corticospinal tracts) visible by 22 wk gestation and the optic radiations becoming more evident later (Wilson et al. 2021). Although already visible, the microstructure of these tracts is still significantly changing and becoming more organized, consistent with the hypothesis that the anatomical framework underlying the brain's long-range connectivity is still being established in the fetal period (Jakab et al. 2017; Jaimes et al. 2020; Machado-Rivas et al. 2021; Wilson et al. 2021).

EXPLORING CHANGES IN LARGE-SCALE FUNCTIONAL CONNECTIVITY IN THE FETAL BRAIN

Despite its clear appeal as a noninvasive and safe means of studying in utero whole brain neural activity, the application of fMRI to study fetal brain activity is relatively recent and thus there are relatively few published studies. Such work is essential as the existing knowledge derived from preterm infants is unlikely to be truly representative of "normal" in utero brain development. The potential of studying in utero brain activity in fetuses using fMRI was first described in pioneering studies that showed simple and spatially indistinct areas of activity in response to auditory stimulation (Moore et al. 2001), visual stimulation (Fulford et al. 2003), and at rest (Schöpf et al. 2012). With advances in both MR image acquisition and processing strategies, the field has expanded significantly in the last 10 yr, particularly in studies characterizing the functional organization of the fetal brain in the resting state over the third trimester of human gestation.

Broadly speaking, the results of these studies (summarized in Fig. 1) have shown that:

1. Resting state networks can be readily identified in the fetal brain from at least 19–20 wk gestation.
2. As seen in preterm infants, resting-state networks progress from single areas of activity in



① Resting state networks can be seen at the start of the third trimester as areas of local connectivity only.
② Long-range patterns of connectivity including interhemispheric connections emerge across the third trimester.
③ Long-range patterns of connectivity are established first in primary sensory and motor networks.
④ Connectivity is established later in higher-order and associative networks.
⑤ Complex network features such as gradient organization are already established in fetal networks.

Figure 1. Summary of changes in large-scale connectivity seen in the fetal brain across the second half of gestation with functional magnetic resonance imaging (MRI). Functional MRI (fMRI) can be used to identify reproducible spatial patterns of correlated brain activity, which are distributed across specific brain regions (indicated by colored circles in the figure) into "resting state networks." These can be readily identified in the fetal brain from the start of the second half of gestation and show specific features suggesting that they are highly organized and undergo a systematic pattern of maturation through to full-term gestation.

a single hemisphere to more distinct adult-like topographies encompassing both hemispheres as the brain's long-range patterns of connectivity emerge.

3. Maturation of resting state network connectivity occurs earlier in the primary sensory and motor systems compared to those associated with higher-order associative and cognitive systems.

4. Specific features of mature complex network structure can already be identified in the fetal period, suggesting that their establishment is fundamental to the brain's functional organization across the life span.

Patterns of significant functional connectivity have been studied in human fetuses from as young as 19–20 wk gestation (Turk et al. 2019; De Asis-Cruz et al. 2021a). In general, these early resting state networks are seen as localized clusters of activity that isolate to single brain regions rather than the long-range patterns of long-range connectivity characteristically seen in the mature brain, suggesting that the underlying spontaneous activity occurs initially across local processing units as the associated short-range connectivity emerges (Schöpf et al. 2012; Thomason et al. 2013, 2015; Ferrazzi et al. 2014). These may relate to evolving forms of spontaneous neuronal activity events that are endogenously generated and then propagate across the surrounding cortex, and are considered to be a hallmark of the developing mammalian brain in the perinatal period (Luhmann et al. 2016). An important alternative explanation is that the correlated fluctuations in the fMRI BOLD signal may be non-neural in origin, and may instead only represent isolated temporal variations in cerebral blood flow as the mechanisms underlying neurovascular coupling may be too immature to support neural activity in the same way as it does in the mature brain (Kozberg and Hillman 2016b; Kozberg et al. 2016). However, this hypothesis is not in keeping with the reproducible finding of several distinct resting state networks in fetuses each with their own unique low frequency time courses and topographies, which appear independent from the time course of cardiovascular pulsations and the anatomical location of early blood vessels alone (Thomason et al. 2013, 2015; Ferrazzi et al. 2014; Kim et al. 2023b) and spatially resemble those seen in preterm infants (Doria et al. 2010). Furthermore, large-scale patterns of resting electrical neural activity can also be readily seen in fetuses with MEG (Eswaran et al. 2007; Sheridan et al. 2010).

A further key observation across studies is the evolution and establishment of long-range patterns of connectivity across human gestation, with initially immature local patterns of activity maturing toward the adult-like resting-state network topology seen in full-term neonates (Eyre et al. 2021). This is most striking when looking at interhemispheric functional connectivity between homolog regions (e.g., the primary motor cortices), which increases linearly across the third trimester (Thomason et al. 2013, 2015). As with preterm infants and later childhood (Doria et al. 2010; Gilmore et al. 2018), this is seen to occur first in the primary motor and sensory cortices, before within the frontal and associative regions. These themes are also apparent when using an alternative approach in which the networks themselves are defined by age-related changes in their constituent functional connectivity, as opposed to the traditional method of characterizing "average" networks across the entire study population (Karolis et al. 2023). In keeping with emerging patterns of long-range connectivity across gestation, the identified fetal "matnets" have symmetrical spatial distributions encompassing functional homolog regions. Together, these changes result in a maturational decrease in global synchrony and increasing lateralization, which is significantly predictive of gestational age (Kim et al. 2023a; Taymourtash et al. 2023). Importantly, these developmental changes are also accompanied during the same period by increases in structural connectivity measures within key white matter pathways including the corpus collosum, inferior longitudinal fasculi, and thalamocortical tracts (Jaimes et al. 2020; Machado-Rivas et al. 2021; Wilson et al. 2021, 2023).

Functional connectivity in the mature brain has been found to have specific characteristics that optimize efficient information exchange

and can support the dynamic, flexible processing required for adaptive environmental interaction and complex sociocognitive functioning (Sporns 2022). This is supported by a "gradient" organization, whereby the underlying patterns of functional and structural connectivity topographically vary in a continuous manner across the entire cortical surface (Margulies et al. 2016; Bernhardt et al. 2022). Functional connectivity within resting state networks is similarly nonuniform between constituent regions and varies in a graduated manner (Haak et al. 2018). Surprisingly, this seemingly complex but fundamental property can also be robustly identified within fetal resting state networks from as early as 25 wk gestation (Willers Moore et al. 2023). A further key feature of the mature functional "connectome" is the presence of hub regions that have a critically important role in information integration and efficient processing (van den Heuvel and Sporns 2013). These densely connected hub regions are also present in the fetal brain within specific parts of the primary and associative cortices (van den Heuvel et al. 2018; Turk et al. 2019). As these largely recapitulate those seen in preterm infants and later across the life span, this suggests that their establishment is a fundamental developmental process that is intrinsically generated and directed across early life (van den Heuvel et al. 2015). Further detailed studies have found that this development is also reflected in age-related changes of specific graph theory metrics including small-world index, normalized clustering and path length, global and local efficiency, and modularity (De Asis-Cruz et al. 2021b) and changes in thalamocortical connectivity (Taymourtash et al. 2023). The developmental trajectories of these measures appear to undergo a transition at 30–31 wk gestation, perhaps reflecting the developmental switch from endogenously generated to sensory-driven activity (Luhmann et al. 2016).

CONSIDERATIONS FOR STUDYING THE FETAL BRAIN WITH fMRI AND FUTURE DIRECTIONS

There are several significant challenges for the acquisition of in utero fMRI data, not only due to those associated with ensuring safety for the mother and fetus, but also due to the problems inherent to acquiring MR images from an uncooperative subject inside a unique uterine environment (Manganaro et al. 2023). Image-acquisition sequences must work within the constraints required to ensure appropriate levels of energy deposition and noise, to account for the effects of the maternal tissue and organs on magnetic field inhomogeneity, and are generally associated with reduced signal-to-noise ratio due to the physical distance between the fetus and the receive coil (Christiaens et al. 2019). Perhaps the most significant challenge is overcoming the considerable effects of motion artifact that arise due to unavoidable maternal (breathing and body movements) and spontaneous fetal movements during image acquisition (You et al. 2016; Sobotka et al. 2022). This is particularly important as it has long been known that head motion leads to nonneural changes in the fMRI signal, which can significantly affect the identification of activity and lead to spurious patterns of functional connectivity (Hajnal et al. 1994; Power et al. 2014; Satterthwaite et al. 2019).

One relatively common approach for addressing this potential problem has been to identify and completely exclude data time points corrupted by motion artifact (Thomason et al. 2013, 2015, 2017, 2018; van den Heuvel et al. 2018; Turk et al. 2019). While this approach has had some success in exploring the early emergence of functional connectivity in fetuses, such "motion scrubbing" of data is relatively inefficient (as sometimes a large amount of the collected data is discarded), does not address associated geometric image distortions, and importantly limits studies to specific behavioral states when the fetus is inactive. As a result, several recent studies have now described comprehensive frameworks that encompass tailored image acquisition, processing, and analysis strategies, which together have been designed specifically to address the aforementioned limitations (Seshamani et al. 2013; Ferrazzi et al. 2014; You et al. 2016; Scheinost et al. 2018; Sobotka et al. 2022; Taymourtash et al. 2022; Karolis et al. 2023). While a detailed review of these methodologies is beyond the scope of this article, they have been reviewed (e.g., van den Heuvel and Thomason 2016;

Rajagopalan et al. 2021) and some of the processing strategies empirically evaluated elsewhere (Ji et al. 2022).

A further key consideration is the indirect nature of the fMRI BOLD signal, as the relationship between neural activity and dynamic changes in cerebral blood flow and the oxygen-binding state of hemoglobin is unlikely to be stable across early human brain development (Harris et al. 2011; Kozberg and Hillman 2016a). This complicates interpretation, as one cannot assume that changes in BOLD signal amplitude or localization have the same meaning in fetuses as is accepted in adult fMRI studies. To overcome this, detailed studies are needed to combine data from other MR contrasts (anatomical, tissue composition and microstructure, vascular density, and blood flow) together with information derived from animal models. While there are spatial similarities and developmental trends between the patterns of activity seen in fetuses and preterm infants with fMRI, studies are also needed for systematic comparison. Such work is likely to be nontrivial due to inherent differences in data acquisition and artifacts in studies of the two populations, resulting in discrete processing and analysis strategies. Last, further work is needed to understand how changes in the fetal functional connectome are influenced by maternal and environmental factors such as toxins and stress (Thomason et al. 2019, 2021; van den Heuvel et al. 2021; Hendrix et al. 2022) relate to behavior (Thomason et al. 2018; Ji et al. 2023), disease, and potentially can predict later neurodevelopmental outcome.

CONCLUSIONS

In the second half of gestation, neural activity in the human brain undergoes a marked transition as its lifelong framework of long-range circuitry is established. This is reflected in the emergence of topographically organized and reproducible patterns of functional connectivity, which can be noninvasively studied in the womb, using recent advances in methods like fMRI. These studies hold great promise not only for characterizing the fundamental developmental processes that occur in this juncture, but also for providing much needed new insight into how these processes are altered by environmental factors and disease, and ultimately may lead to difficulties later in life.

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