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The Fetal Functional Connectome Offers Clues for Early Maturing Networks and Implications for Neurodevelopmental Disorders

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Review of Turk et al.

The cellular architecture of the developing brain under physiological conditions has been widely studied over the years using rodent models (Götz and Huttner, 2005), human fetal brains (Polioudakis et al., 2019), and, more recently, *in vitro* three-dimensional models of the primate and human developing brain (Rehbach et al., 2020). These studies provide extensive understanding of the cell biology of the mammalian brain as it develops. Unfortunately, studies on the functional connections underlying communication between regions in the developing human brain, the "functional connectome," have been few and underpowered (Jakab, 2019). Gaining a deeper understanding of normal circuit development within the human fetal brain is important for detecting early functional alterations caused by prenatal adverse environments and the fetal genetic architecture that can lead to pathology later in life.

In one of the largest fetal functional connectome studies to date, using resting-state functional magnetic resonance imaging (fMRI) data from 105 pregnant women [gestational weeks (GW) 20.6–39.6], Turk et al. (2019) applied graph theory analysis to describe functional brain dynamics during the late second to third trimester of pregnancy, aiming to understand the degree of maturity of the fetal functional connectome (Turk et al., 2019). The authors took two approaches to normalize fMRI data and thus allow statistical analyses across all samples spanning 19 gestational weeks. The first was to normalize to a single, median-aged infant brain template, and the second was to perform age-specific normalization to the nearest gestational week (Gholipour et al., 2017). A detailed network analysis showed that starting from GW 20, fetal brain regions are interconnected in a network that displays high modularity. With the group mean normalization, they identified the following four functional modules: occipital and parietal visuosomatosensory, midline prefrontal-temporal-insular, temporal, and an extensive lateral and midline frontal module. The age-specific approach revealed two additional modules, with the visual and somatosensory modules divided. It also highlighted the midline regions as the most strongly interconnected of the fetal brain.

These results are consistent with previous studies on the cellular and anatomic development of the nervous system. The biological underpinnings of functional connections between brain regions are established early during gestation. The human developing brain follows a temporal series of molecular events that are dependent on the fetal genome and its interaction with the environment. The human developing cortex is built in an inside-out manner, with deeper layers being generated before the upper layers, starting around GW 12. By GW 29, which is the median of the Turk et al. (2019) dataset, neuronal migration is largely complete, and the majority of neurons are in their final positions, where they start to form synapses (Monk et al., 2019). Most early development synaptic connections are transient and will be refined to permanent connectivity later, starting from GW 18–22 and peaking at GW 34, when 40,000 synapses are formed every second. By mid-gestation, the developing cortex receives glutamatergic, cholinergic, and monoaminergic inputs from the visual and somatosensory thalamus, the forebrain, and the brainstem. Thus, the cellular underpinnings of brain region specialization and inter-region communication are established starting as early as mid-second trimester and are refined to a more permanent state in mid-third trimester (Tau and Peterson, 2010). Turk et al. (2019) showed that the circuits that connect brain regions develop over this same time period. Thus, functional modules such as the visuosomatosensory network seem to develop in parallel with anatomic connections in the developing brain.

Moving a step forward, Turk et al. (2019) compared the fetal connectome with a previously published adult con-

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nectome from 42 subjects with a mean age of 29 years. There was a significant overlap at 66 anatomic regions between the fetal and the adult functional connectome, indicating that adult-like functional connectivity is established early in the womb. It is well established in the literature that with increasing gestational age, connection strength between brain regions increases (Thomason et al., 2014), resulting in a globally integrated organization of the fetal network that resembles the adult network (Wheelock et al., 2019). Turk et al. (2019) showed that the visual, motor, default mode, and temporal module each highly resemble the adult ones, whereas the frontomedial module resembles the adult level of development to a lesser degree. These differences in the developmental timing between brain regions is also apparent at the cellular level. The inputs from the somatosensory regions develop before those from the visual regions, and synaptogenesis of the primary motor regions begins earlier than that for anterior regions like the prefrontal cortex (PFC; Tau and Peterson, 2010). The advanced maturity of the visual, motor, default mode, and temporal modules indicates that to a degree the prenatal human brain already has the connectivity needed for higher-order information processing before birth. The medial frontal cortex, which is less developed according to the Turk et al. (2019) data, is associated with motor functions, cognitive control, social cognition (De La Vega et al., 2016), and decision-making (Bang and Fleming, 2018), with the most anterior parts of it associated specifically with reward, social processing, and episodic memory (De La Vega et al., 2016).

The results by Turk et al. (2019) add to existing knowledge of the early maturation of sensory information-processing modules and advance our understanding of the key brain regions of the fetal connectome. Smaller studies using resting-state fMRI and independent component analysis also showed that resting-state networks are detectable from mid-gestation, with a spatial distribution that implies maturation, primarily of sensory networks (Ferrazzi et al., 2014; Jakab, 2019). This is noteworthy in the context of neuropsychiatric disorders. It is becoming increasingly clear that intrauterine development is critical for psychiatric risk and that prenatal stress is associated with later changes in behavior, as well as cellular and molecular alterations, like reduced neurogenesis, reduced cortical thickness and folding, and altered glutamatergic signaling in the PFC (O'Donnell and Meaney, 2017). The advanced maturity of motor and default mode networks in the fetal functional connectome described by Turk et al. (2019) is particularly notable in this regard, because stronger connectivity in the adult default mode network has been associated with higher depression scores in patients with mild traumatic brain injury (Van Der Horn et al., 2017), whereas stronger recruitment of the somatomotor network was associated with sensitivity to external stimuli and mania (Shao et al., 2019). Until now, the effects of the prenatal environment on brain connectivity have only been studied *post hoc* with fMRI studies in the offspring of mothers experiencing stress during pregnancy (Eixarch et al., 2016). The ability to study fetal brain functional connectivity at the time when the exposure happens would be invaluable. Identifying dysfunctional connectivity as early as the fetal period in at-risk offspring would constitute a major step toward disease prediction, and possibly offer an early intervention window.

With the largest fetal brain fMRI cohort to date, Turk et al. (2019) make a significant contribution toward our understanding of normal physiological maturation stages of the human brain. This provides an important reference template for understanding the effects of neurodevelopmental disorders and prenatal adverse environment not only at the cellular level but also at the functional one. Future studies using a similar methodological approach in which fetal fMRI data are normalized to age-specific templates that better reflect the dynamic changes of the developing brain might detect deviations from normal physiological maturation of the connectome. Studying fetal functional connectivity in pregnant mothers suffering from mental illnesses will add fundamental information to the ongoing efforts of understanding the neuronal mechanisms of prenatal risk for neuropathology. The Allen Brain Institute is creating a combined dataset for the adult brain with anatomic information and *in situ* transcriptomic data of the same brains for which fMRI data exist in hopes of connecting all information levels of brain function (Hawrylycz et al., 2012). A similar approach could be imagined for the fetal brain, taking advantage of the age-specific analysis framework highlighted by Turk et al. (2019) and the transcriptomic data in the Allen Brain Atlas for the developing brain (Miller et al., 2014), which currently lacks imaging data. Such a dataset would be invaluable for the study of neuropsychiatric risk.

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