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Fetal Cerebral Magnetic Resonance Imaging Beyond Morphology

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The recent technological advancement of fast magnetic resonance imaging (MRI) sequences allowed the inclusion of diffusion tensor imaging, functional MRI, and proton MR spectroscopy in prenatal imaging protocols. These methods provide information beyond morphology and hold the key to improving several fields of human neuroscience and clinical diagnostics. Our review introduces the fundamental works that enabled these imaging techniques, and also highlights the most recent contributions to this emerging field of prenatal diagnostics, such as the structural and functional connectomic approach. We introduce the advanced image processing approaches that are extensively used to tackle fetal or maternal movement–related image artifacts, and which are necessary for the optimal interpretation of such imaging data.
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Introduction

The protracted cerebral maturation and the evolutionary expansion of the neocortex are prerequisites for our intellectual capacity,[1] and many of our highly developed cognitive abilities are associated with features of the central nervous system (CNS) that are known to be unique to humans.[2,3] This prolonged development means increased vulnerability of the human brain during gestation. Therefore, pathologic processes that interfere with prenatal neurodevelopment can result in disabling neurologic and psychiatric diseases postnatally. The impaired development of cerebral morphology and axonal pathways often accompanies severe developmental diseases and, therefore, the timely recognition, using noninvasive techniques, of any deviation from the normal developmental trajectories is mandatory for better prenatal clinical counseling. The improvements in prenatal sonography and magnetic resonance imaging (MRI) techniques have enabled the identification and visualization of fetal CNS anomalies before the age of human viability (24 gestational weeks [GWs]), and thus, this better characterization of prenatal developmental trajectories now has an important role in clinical decision-making. The technical advancements in MRI acquisition techniques have allowed fetal imaging to routinely involve a growing number of sequences. Fine-grained morphologic imaging relying on fast T2-weighted scans,[4,5] diffusion MRI (dMRI),[6] and dynamic MRI are now possible (for reviews of the most common fetal MRI acquisition techniques, see Brugger et al[7] and Saleem[8]).

The inclusion of prenatal MRI sequences that provide information beyond morphology holds the key to improving several fields of human neuroscience and clinical diagnostics. First, some of the human-specific aspects of normal brain

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development can be understood only with techniques that can depict the functioning, living brain. Translating results from postmortem studies, animal experiments, or studies on the prematurely born human neonate is not directly possible, and the functional characteristics of a preterm brain may not be equivalent to those of a normally developing *in utero* brain, and may also show differences at term-equivalent age.[9] The interrogation of the functional activity and the wiring of the maturing nervous system can refine our current assumptions about the age of fetal viability and the development of pain and somatosensory perception, and they can allow us to understand neuroplasticity.[10,11] Such investigations can extend our efforts in human brain mapping to the earliest possible period of life.[12] Second, more information beyond the morphologic information may allow the identification of new disease phenotypes and pathologic entities on the group level, or serve as a single-subject-level prognostic marker of neurodevelopment. In the latter case, quantitative comparisons could be made to the normally developing fetal population using computational imaging analysis. For example, diffusion tensor imaging (DTI) may characterize alternatively established pathways in the fetal brain in axon-guidance disorders and quantify the microstructural properties of these fibers.[13,14] By the same token, functional neuroimaging by means of blood oxygen level–dependent (BOLD) contrast MRI has the potential to detect the individual lag behind normal neural development not only in preterm neonates but also in utero.

This review focuses on MRI methods that characterize the diffusion phenomena, functional activity, and metabolism of the brain in normal and pathologic conditions. The impetus for this was that a growing number of research groups and clinical centers now use *in utero* approaches beyond structural (eg, T2-weighted) imaging,[15,16] and, simultaneously, an expanding number of studies deal with the technological challenges that arise with these acquisition techniques.[6,17-21] We analyzed *in vivo* studies that used dMRI, H^1 MR spectroscopy, and BOLD-based functional MRI as acquisition methodologies and studies that presented a feasible methodology with which to tackle the problems of image processing and analysis. The literature regarding these MRI modalities has grown significantly during the last 5 years, and, in addition to introducing the fundamental works in the field of each pre- and postnatal MRI approach, we aimed at reviewing the literature in this particular time window (2010-2015). Each acquisition technique is discussed in a separate chapter in this review. A dedicated chapter is included for the connectome approach, in which data from structural or functional connectivity measurements are interrogated by means of system-level network analysis, and the initial reports on the *developing fetal connectome* are introduced. Each chapter of our review follows the same structure:

- *The technique*: We introduce the most important publications from adult and prenatal studies that paved the way for the performance of the most recent *in utero* investigations.
- *Methodological challenges and solutions*: The challenges of and possible solutions to image acquisition, processing of fetal neuroimages, and interpretation of results.
- *The normally developing fetus*: The contributions of the presented image acquisition techniques to our understanding of normal human brain development are summarized.
- *The pathologically developing fetus*: Except for BOLD fMRI, we present how these approaches can characterize cerebral pathologies in utero.

Imaging the Developing Cerebral White Matter and Fiber Pathways

dMRI and Fiber Tractography: The Technique

After initial reports of diffusion-weighted imaging, DTI, and tractography in the early 1990s,[22-24] these techniques have revolutionized our possibilities to noninvasively visualize the connectivity of the human brain in vivo. When the motion of water molecules is restricted, this results in anisotropic diffusion.[25] There are various tissue components that may limit the Brownian motion of water molecules. As initially described by Beaulieu and Allen[23] in the giant axon of the squid, the axonal membrane is a major determinant in creating an anisotropic environment, which can be measured by diffusion-weighted imaging. This observation has been further refined, and other contributing factors, such as cytoskeletal structures or the axon potential, have been identified.[26,27] Currently, it has been proven that the presence of unmyelinated axons alone suffices to restrict water diffusion, as measured by dMRI.[27-30] DTI provides increased sophistication by resolving the directional dependence of the microscopic-scale diffusion, and thus it provides noninvasive depiction of diffusion through sampling of the magnitude and orientation of diffusion anisotropy.[31] Tractography is an image processing technique with which to visualize macroscopic-scale bundles of the white matter, reconstructed using in vivo dMRI data.[32] During the past decade, these technologies have evolved so that it is now possible to visualize fiber pathways probabilistically,[33,34] and imaging sequences have been optimized to more feasibly resolve crossing-fiber populations and diffusion phenomena at different weighting schemes. All of these have enabled population-wide efforts to image the human brain connectome.[35] Owing to the quantitative nature of these imaging techniques, they serve as elegant noninvasive tools with which to assess brain development at early fetal stages *in vivo*, as well as in and ex utero. DTI is an indirect measure of white matter maturation, as it reflects the maturation of oligodendrocyte precursors and the axon potential in functionally important developing white matter tracts.[26,36] This valuable data, based on animal experiments, can now be translated into the field of prenatal and preterm human brain imaging. Developmental asynchronies and asymmetries of developing white matter pathways[37,38] as well as longitudinal region-specific diffusion properties have been identified.[39,40] Postmortem DTI observations[41-43] serve as a valuable background in the interpretation of in vivo human data, but cannot be uncritically adapted to the in vivo imaging setting.[44] Currently, fetal in vivo DTI and tractography can be used in