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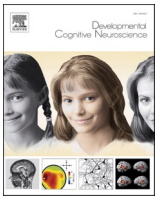

Is fetal MRI ready for neuroimaging prime time? An examination of progress and remaining areas for development

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ABSTRACT

A major challenge in designing large-scale, multi-site studies is developing a core, scalable protocol that retains the innovation of scientific advances while also lending itself to the variability in experience and resources across sites. In the development of a common Healthy Brain and Child Development (HBCD) protocol, one of the chief questions is "is fetal MRI ready for prime-time?" While there is agreement about the value of prenatal data obtained non-invasively through MRI, questions about practicality abound. There has been rapid progress over the past years in fetal and placental MRI methodology but there is uncertainty about whether the gains afforded outweigh the challenges in supporting fetal MRI protocols at scale. Here, we will define challenges inherent in building a common protocol across sites with variable expertise and will propose a tentative framework for evaluation of design decisions. We will compare and contrast various design considerations for both normative and high-risk populations, in the setting of the post-COVID era. We will conclude with articulation of the benefits of overcoming these challenges and would lend to the primary questions articulated in the HBCD initiative.

1. Introduction

Over the last decade, human neuroscience research has seen the burgeoning use of MRI to study the development of the brain, in utero. A combination of advances in imaging and analysis technology, coupled with the wide-spread availability of MRI has driven this growth. The earliest use of fetal MRI was as an adjunct to gestational ultrasound to better evaluate fetal anomalies (Hubbard et al., 1999). MRI provided improved anatomic detail, resulting from better image resolution and tissue contrast, allowing improved planning for fetal or neonatal interventional therapies (Quinn et al., 1998). As single shot T2 imaging became available across MRI vendors, fetal MRI became a standard clinical adjunct, used to perform more detailed studies and to rectify inconclusive ultrasound findings. Standard of care improved as providers could better plan for and prepare patients for treatments necessary for congenital anomalies, such as congenital diaphragmatic hernia, congenital heart disease, and pulmonary sequestration (Coakley et al., 2004). Increased use of fetal MRI has also borne considerable new insight into care for developmental neurologic indications, such as agenesis of the corpus callosum, cortical malformations, and brain tumors. More precise classification of neural atypicalities, again, better prepared patient families and providers as they develop long-term care plans. Within the realm of clinical care, the adoption of fetal MRI has been variable across fetal diagnostic centers and diagnoses (Perrone et al., 2021). Some of this variation is driven by access to an MR scanner and availability of fetal imaging expertise. Additional variability in use relates to cost and insurance coverage that can be barriers in standardization of care.

Outside of its wide-spread clinical use, fetal MRI has begun to accelerate pediatric health research. However, growth of this field has been slow due to natural complexity of the approach, including challenges in the mechanics of fetal MRI and in perceptions of these challenges. (for prior reviews see (Anderson and Thomason, 2013; van den Heuvel and Thomason, 2016)).

Technical challenges of fetal MRI arise both from the conditions of imaging the living fetus and from properties of fetal development. To the first, fetal size and encasement of the fetus within an independently moving maternal compartment dramatically alter imaging conditions.

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Table 1
Current progress in Fetal MRI and its role in advancing science.

	Developmental Process	MRI Technique	Studies and Findings
Brain	Structure	T2w	i Normative volumetric changes (Rajagopalan et al., 2011; Andescavage et al., 2016; Scott et al., 2011b; Habas et al., 2011) ii Recession of transient tissues (Scott et al., 2011b) iii Emergence of cortical folding (Habas et al., 2012; Gholipour et al., 2017) iv Neurodevelopmental changes in congenital heart disease and twin-to-twin transfusion syndrome (Rajagopalan et al., 2018; Andescavage et al., 2015; Donofrio et al., 2011; Clouchoux et al., 2013; Rajagopalan et al., 2020) v Differences between preterm and inutero brain development (Hüppi et al., 1998; Batalle et al., 2018; Lockwood Estrin et al., 2019)
	Functional Networks and Connectivity	rsFMRI	i Emergence of functional connectivity and networks (van den Heuvel and Thomason, 2016; Thomason et al., 2013) ii Disruptions of intrinsic brain circuitry in preterm infants (Thomason et al., 2017)
	Metabolism and other biochemical changes	MRS	i Normative biochemical profile of the brain across gestation (Limperopoulos, 2013) ii Variations in brain biochemistry in congenital heart disease and twin-to-twin transfusion syndrome (Rajagopalan et al., 2020; Limperopoulos et al., 2010)
Body	Lung Volume		i Risk prognostication in Congenital Diaphragmatic Hernia (Perrone et al., 2021; Tracy et al., 2010)
Placenta and Amniotic Fluid	Structure & Function	T2w and FMRI	i Normative changes in placenta across gestation (Turk et al., 2017), Zhu et al., 2015, (Melbourne et al., 2019) ii Pathologic placental changes associated with placental insufficiency, congenital heart disease (Sun et al., 2015; Zun et al., 2017)
	Biochemistry	MRS	i Changes in age related volume and composition of Amniotic Fluid (Bluml and Rajagopalan, 2018)

Next, the fetus is small in size, which pushes the limits of MRI resolution and signal to noise. Further, the fetus is rapidly developing and in non-uniform ways, which also impacts measurement strategies. For example, MRI spectroscopy studies of the growing fetal brain must grapple with using a constant voxel size versus averaging across variable tissue types. Further, angiogenesis likely influences vascular contribution to the Blood Oxygen Level Dependent (BOLD) signal but detailed information about this developmental coupling is as of yet unavailable (Avni et al., 2016; Levine, 2016). Similarly, changing tissue composition throughout gestation potentially introduces varying levels of partial volume effects in structural imaging. Thus, fetal growth, itself, interacts with MRI methodology.

Not surprisingly one of the greatest challenges to fetal MRI is motion originating both from spontaneous fetal motion and from maternal movement. Maternal movement takes many forms, including both whole body and internal movements, for example, cardiac pulsatility, digestion and respiration. An entire field of research is now dedicated to devising real-time or post-hoc motion compensation techniques for fetal MRI while still maintaining signal and biological data fidelity. While making steady progress over the last five years, this field and consequently fetal MRI itself is currently in its "toddlerhood" with the accompanying challenges and rewards. However, preceding these technical challenges, are public misconceptions regarding the safety and efficacy of fetal MRI, as it is often conflated with computerized tomography (CT) scans or X-Rays. Practice parameters set forth by the American College of Radiologists and Society for Pediatric Imaging prohibit the use of sedation and contrast agents in fetal MRI and recommend imaging after 18 weeks of gestational age. Working within these parameters, multiple long-term studies have established the safety of fetal MRI both at 1.5 T and 3 T (Ray et al., 2016; Chartier et al., 2019). A coordinated education and public relationship campaign from clinicians and researchers will improve general willingness to participate in fetal MRI studies.

2. Unique qualities of fetal MRI for advancing science

The combination of patient safety and higher image quality provided by MRI makes it a unique tool for longitudinal developmental studies. The high tissue contrast provided by single shot T2 imaging, commonly used for fetal structural MRI, has allowed scientists to capture fetal brain development in exquisite detail. The practice of using fetal MRI to rule out prenatal neurological pathology created an inventory of normally developing brains. Multiple cross-sectional studies (Table 1), leveraging this newly available data, established precise, quantitative landmarks (cortical folding, transient tissue development) for healthy fetal brain development (Garel et al., 2001; Perkins et al., 2007; Kyriakopoulou et al., 2013; Glenn, 2009; Prayer et al., 2006). Advances in retrospective motion correction algorithms (Rousseau et al., 2006; Camm et al., 2018; Kim et al., 2010a; Jiang et al., 2007; Gholipour et al., 2010; Pugash et al., 2009; Kuklisova-Murgasova et al., 2012) spurred further advancement in our understanding of various mechanisms of structural development of the fetal brain and developed spatiotemporal, baseline biomarkers (Scott et al., 2011a; Rajagopalan et al., 2011; Andescavage et al., 2017) to help identify aberrant brain development.

Once baseline comparisons for early brain development were established, it allowed researchers to understand how nonoptimal developmental conditions altered early brain development (Table 1). Notably, altered brain development due to ex-utero development of prematurely born infants could now be quantitatively compared to the baseline of in utero development. Multiple large studies have pin pointed global and regional structural differences in brain development in preterm infants compared to fetuses at specific gestational ages (Hüppi et al., 1996; Rajagopalan et al., 2017a; Hüppi et al., 1998). The availability of baseline, in utero brain developmental maps have allowed researchers to identify how specific alterations to brain growth trajectories in preterm infants (Inder et al., 2005) correlate to long-term developmental deficits even if the global brain developmental measures are comparable to term born infants (van et al., 2015; Hedderich et al., 2020; Bouyssi-Kobar et al., 2016). Groundbreaking studies, using functional MRI (fMRI), have measured spontaneous activity in the fetal brain (Turk et al., 2019; Hykin et al., 1999; Thomason et al., 2017) and have mapped the emergence of intrinsic functionals networks and connectivity architecture in the fetal brain across gestation. These studies have enabled our understanding of disruptions to intrinsic brain macro-circuitry in preterm infants (Benders et al., 2015; Damaraju et al., 2010) and its relationship to the risk of cognitive and/or emotional

deficits in older preterm born children (Hüppi et al., 1996; Lawrence et al., 2010).

Fetal MRI based research has also been transformative in allowing the clinical research community to disentangle the contributory effects of a congenital anomaly on the sequelae of postnatal brain developmental deficits from the detrimental side effects of intensive, postnatal surgical interventions. For example, the spectrum of neurocognitive deficits observed in survivors of CHD have long been attributed to multiple, intensive surgical corrections immediately following the infant's birth. Studies using fetal MRI have now strongly established that, in addition to global brain delay, fetuses with CHD also have a delayed cortical development (Clouchoux et al., 2013; Donofrio et al., 2011; Leonetti et al., 2019; Rajagopalan et al., 2018) The use of fetal MRI has presented a new diagnostic tool to associate postnatal risk of neurologic impairment in this population to status of prenatal brain development (Peyvandi et al., 2016). Similarly, prenatal MRI has improved prognosis of impaired lung function in congenital diaphragmatic hernia and improved early identification of survivors at the highest risk of co-morbid neuromotor anomalies (Gorincour et al., 2005; Tracy et al., 2010; Radhakrishnan et al., 2019). Management of multiple pregnancies, particularly monochorionic-monoamniotic pregnancies has improved since fetal MRI research established the efficacy of laser coagulation surgery and also provided insight into the origins of varied risk profiles for individual twin pairs (Tarui et al., 2012; Weisz et al., 2014). Research efforts, leveraging magnetic resonance spectroscopy (MRS), to measure developmental changes to brain biochemistry in the fetus are also underway (Limperopoulos, 2013; Evangelou et al., 2016).

Outside of the fetal brain, MRI offers a broad range of measures to study multiple aspects of the intrauterine environment. More recently, MRI has proved to be a panoply in understanding the human placenta and its role in determining lifetime outcomes. Together with extensive innovation in adapting MRI techniques, many recent studies have provided invaluable information on the structure, function and biochemistry of the placenta across gestation (Siauve et al., 2015; Porras et al., 2017; Rajagopalan et al., 2017b; Harteveld et al., 2020). Further, this research is being extended to understand how pathophysiological conditions in the placenta or the fetus interact with the other (Andescavage et al., 2015; Zun and Limperopoulos, 2018; Luo et al., 2017; León et al., 2018). Research into using fetal MRI to estimate the volume and composition of the amniotic fluid for diagnostic purposes is also underway (Didier et al., 2019; Bluml and Rajagopalan, 2018). Fetal and placental MRI imaging together with DNA methylation studies have a potential role to help decipher epigenetic mechanisms related to adverse environmental events including maternal substance abuse and impact on the immature brain.

3. Fetal MRI and HBCD study design

The collection of articles assembled in this special issue focus on topics relevant to the upcoming national NIH Healthy Brain and Child Development (HBCD) initiative. The overarching goal of HBCD will be to rigorously evaluate human brain development from the beginning of life and to build knowledge about the impact of environmental factors on the developing child (Jordan et al., 2020). Preparations and coordination that have supported the Phase 1 period of this project are appropriate for a large investment of resources and human capital. The HBCD study will require establishment of a core common protocol across more than two dozen sites.

Much of Phase 1 activities have involved taking stock of what is possible across a diverse collection of representative institutions. Formal assessment of the logistics of a complex longitudinal study necessitates classifying methodological and design choices along axes of plausibility and scientific importance. Plausibility encompasses such things as scientific expertise, local infrastructure, and cost. Scientific importance is fit to stated research objectives (did we achieve what we came here to do?) and is a general question about ways in which large-scale scientific investment can accelerate fields of study. An initiative on the scale of HBCD will train generation(s) of scientists, bring innovative tools rapidly to scale, and has the power to transform a cottage industry, such as fetal MRI, into a field.

Fetal MRI is now used around the world, but fetal imaging in research is certainly not ubiquitous. To feature fetal MRI in a core HBCD Phase II protocol would require an additional level of training and knowledge dissemination into a project already laden in ambition of scope and scale. The challenge, however, is to take that 30,000-level view and objectively assign value to each of the various options one has in study design. Subject area experts raise the following points in support of fetal MRI being a core common element of the HBCD design protocol:

i Research strategy: given that the primary focus of HBCD is in understanding the effect of major prenatal factors influencing the developing brain, data on the fetal brain before birth would prove central to disentangling postnatal influences from prenatal factors particularly for the question of substance exposure. The particular case of prenatal substance exposures, including fetal MRI in HBCD provides valuable insight into the origins of changes to neurodevelopmental trajectory and its association to varied outcomes in these children. Fetal MRI biomarkers also provide a foundation to early prognostication of children at high risk for adverse outcomes. This sets the stage for redefining or developing surveillance, interventions, family support and public policy programs for these children.

ii Participant Engagement: Evidence from existing literature on recruitment and retention for studies focused on pregnancy through childhood shows that familiarity to study procedures and positive experiences during prenatal correlate with increased retention (Lamvu et al., 2005; Price et al., 2016). Similarly, our own experiences have shown that participants that complete prenatal MRI are more familiar and more comfortable with infant MRI studies therefore improving study retention. Women from communities traditionally underrepresented in research have also indicated that increased access health information about pregnancy and early childhood (periods not traditionally covered for those without private insurance) as a major reason for staying in pregnancy longitudinal studies (Daniels et al., 2006).

iii Subject compliance: Processing and analysis of fetal MRI works on the fundamental assumption that issues of motion are corrected post-hoc. There is robust, ongoing research to address fetal and maternal motion MRI (Jiang et al., 2007; Gholipour et al., 2010; Kim et al., 2010b; Zanin et al., 2011). Data loss or failed acquisition due participant motion in the scanner is less of an issue in fetal MRI than in unsedated infants and toddlers (infant/toddler has trouble staying asleep for the length of the scan). Therefore, cost of a failed scan/visit both for the study team and for the participating family is lower in fetal MRI.

iv Costs: A related consideration is that cost per visit to obtain fetal MRI is lower than infant/toddler MRI since scanner is only used for active image acquisition (no time to allow infant/toddler to fall into natural sleep) and no failed acquisitions (see iii). Increased support personnel cost associated with infant/toddler scanning is not necessary in scanning pregnant mothers.

v Data Fidelity: Data from the fetal timepoint can alleviate attrition in the neonatal period which is fraught with multiple uncertainties especially in high-risk families. Even in high-resource settings, cultural and ethnic practices around the postpartum/neonatal period influence attrition rates during this period. Concerns of infection in a healthy or vulnerable infant (particularly in the post-COVID era) have risen as a consideration for missing visits among participating families.

vi Opportunity: HBCD could provide the right impetus to accelerate growth in fetal (body and brain), maternal and placental imaging.

The potential for technological and biological innovations is by far the largest in this field compared to others that have been indicated as central to HBCD. It would also serve to harmonize research methods, technology and protocols between the pre and postnatal periods giving rise to truly longitudinal study of early life development.

Given the timing of this article, it is hard to know if fetal MRI will factor into the core HBCD protocol. Like with all the design considerations the valuation will be made. Importantly, fetal MRI presents one of those difficult decision points that must be factored in when implementing such a large and interdisciplinary study at scale.

4. Enhancing the impact of HBCD through innovation

A unique aspect of early human development, particularly the brain, is its lengthy developmental timeline, which is a double-edged sword - simultaneously enabling adaptivity and plasticity, but also placing developing neural systems at prolonged risk to insult and injury. The first 1000 days of a child's life, from conception to their 2nd birthday, is an important and sensitive period of development, during which lifelong patterns of physical, metabolic, cardiovascular, and cognitive health are established. As mentioned above, this developmental window encapsulates the formative prenatal period of development, and includes processes such as neurulation, neurogenesis and migration, gliogenesis, and the early stages of myelination predominantly within the brainstem and cerebellum. Past large-scale pediatric neuroimaging studies have relied upon *qualitative* T_1 and T_2-weighted (T_1w) imaging (Gilmore et al., 2012; Knickmeyer et al., 2008; Giedd et al., 1999; Noble et al., 2015) to examine brain anatomy and cortical morphology and morphometry (Ashburner and Friston, 2000); combined with DTI to examine white matter architecture (Lebel et al., 2008; Supekar et al., 2010; Lebel and Beaulieu, 2011; Wolff et al., 2012). While these measures provide an important overview of macroscopic organization, they inform only indirectly on developmental processes such as myelination and evolving cytoarchitecture that play fundamental roles in learning and cognitive development. While informative, these measures do not fully capture the richness of tissue maturation, specifically aspects, such as myelination, that are environmentally sensitive and relate to cognitive outcomes. With respect to study outcomes, an imaging protocol based entirely on qualitative metrics runs the risk of identifying important gross anatomical changes, without providing insight into the underlying features or mechanisms.

Following birth, myelination continues in a well-characterized spatiotemporal arc, which broadly speaking, proceeds from deep brain regions to association areas, and from the back to the front of the brain rapidly over the first 2 years of life, slowing through the remainder of childhood, and continuing on into the 2nd and 3rd decades of life. Evolving alongside the white matter, maturation of the cortical myeloarchitecture also advances rapidly over the first 2 years of life, and in association with evolving neurobehavioral functions. The ontogenic pattern of myelination is tightly regulated by neural activity (Ishibashi et al., 2006; Fields, 2005; Demerens et al., 1996) and coincides with the emergence of cognitive skills and abilities (van der Knaap et al., 1991; Nagy et al., 2004; Casey et al., 2005; Fornari et al., 2007; Fields, 2008), and contributes to developmental plasticity. Preceding myelination, the growth of new synaptic connections (synaptogenesis) begins by the 5th week of gestation and drives the enlargement of the fetal and infant brain, which reaches 80 % of its adult size by age 2yrs (Gilmore et al., 2012; Knickmeyer et al., 2008). The increasing pace of synaptogenesis throughout the latter half of pregnancy results in an excess of synapses at birth (Huttenlocher, 1990; Peter, 1979). Synaptic pruning throughout later childhood and adolescence eliminates many of these connections, with synapses that receive constant input preserved whilst disused connections are eliminated. While pruning continues throughout the lifespan (Shankle et al., 1998), peaking during the transitions from child-to-adolescence and adolescence-to-adulthood (Levitt, 2003), the pattern of axonal connections remains relatively constant after age 2 (Innocenti and Price, 2005; Luo and O'Leary, 2005). Thus, myelination and synaptic pruning work together in '*competitive collaboration*' to ultimately yield the efficient and integrated functional systems that underlie cognitive, behavioral, and intellectual skills and abilities. Diffusion tensor imaging, to assess both fiber architecture and coherence, and structural connectivity, can also provide continuous quantitative measures across the pre- and post-natal age spectrum. Driven by the Developing Human Connectome project, significant advancement has been made in fetal DTI acquisition methods, corollary field calibration techniques, and analysis pipelines (Bastiani et al., 2019; Hutter et al., 2018; Tournier et al., 2020) to the point that whilst not routine, fetal DTI is no longer an insurmountable task.

A challenge in HBCD is to effectively characterize these changes in a challenging study-population, i.e., infants and toddlers that are difficult to image for long periods of time. This challenge is amplified by the desire to harmonize acquisition protocols across the entirety of the study - a challenge that often results in a race to the lowest common denominator and choices that reflect "what can be measured" rather than "what should be measured", detracting from the study's outcomes and importance. A practical alternative to this 'one-size-fits-all' approach is a hybrid model that combines a central core set of measures alongside 'site specific' measures that are captured on sub-sets of children. Such an approach is currently the foundation of the NIH Environmental Influences on Child Health Outcomes (ECHO) study (echochildren.org) and allows integration and harmonization of data across the full cohort without restricting innovation or novel measure inclusion. An important goal of HBCD is to measure the impact of pre- and post-natal exposures, such as *in utero* substance exposure (Bertrand et al., 2018; Kozhimannil et al., 2019), poor maternal mental and physical health, maternal and child nutrition (Dobbing, 1964), and other environmental and psychosocial exposures can impair on child neurodevelopmental outcomes. These exposures could specific developmental processes (e.g., iron deficiency impacting myelination (Georgieff, 2007)) and, ultimately, impact cognitive or behavioral outcomes. NIH's landmark study on child neurodevelopment should serve as the incubator for newer MRI techniques that allow us to measure these developmental processes based on specific biological hypothesis.

Quantitative (q)T_1 and qT_2 relaxometry, myelin water imaging, magnetization transfer imaging, diffusion, and magnetic resonance spectroscopy can provide improved sensitivity to changing tissue microstructure, its physical and chemical composition, as well as specificity to fundamental developmental processes. In addition, if implemented as part of the fetal imaging protocol, quantitative approaches can provide continuous measures from fetal through post-natal development that are not otherwise possible. While quantitative relaxometry is not routinely performed as part of fetal imaging, methods developed for cardiac applications (e.g., T_1 measurement using Modified Look-Locker, MOLLI (Messroghli et al., 2004)) may be directly transferrable. Techniques for susceptibility weighted imaging could similarly be retooled and repurposed for T_2 and/or T_2* measurement (Neelavalli et al., 2014). Variations of these techniques have already been shown in fetal imaging (Sun et al., 2015; Seed et al., 2012; Xu et al., 2020), and show robust measurement even in the presence of fetal and other physiologic motion.

An important, albeit less promoted, aspect of quantitative imaging, including fetal and infant qT_1, qT_2, and DTI is their reduced sensitivity to differences in scanner manufacturer, software, and acquisition hardware (Bottomley et al., 1984; Deoni et al., 2008). This aspect makes them ideal for longitudinal studies of development, multi-site data harmonization and integration, and cross-center data sharing. Phantoms, such as the NIST "Phannie" or more broadly available Magphan and 'known' phantoms provide a ground truth that further ensures measures collected across time and imaging centers, and before and after hardware and software upgrades, are reliable and consistent. In addition,

Table 2
Areas for progress or innovations in Fetal MRI.

	Developmental Process	MRI Technique	Areas for Development/ Innovation
Brain	Synaptogenesis, Tissue microstructure	Quantitative MRI (qMRI)	i Continuity into post-natal period ii Harmonization across sites and MRI vendors iii Retooling existing methods for fetal MRI
	Structural Connectivity	DTI	i Best practices for acquisition and processing ii Data integration from fetal to postnatal studies

scanner and cloud-based software, including such entities as Caliber MRI (qmri.com), Synthetic MRI (syntheticmr.com), and Olea Medical (olea-medical.com), provide reliable quantitative MRI calculation, calibration, and synthetic image generation. HBCD provides a fertile ambiance for further development of these tools, and incorporation of diffusion imaging metrics, from current pediatric and adult applications, to fetal imaging. As, to date, few large-scale fetal imaging studies have been performed, best practices for harmonization and data integration are still be developed and detailed. However, the expertise brought together by HBCD offers the perfect opportunity to develop these best practices and push fetal MRI into the mainstream (Table 2).

Through innovation, the HBCD study has the potential to advance and derive new understanding of fetal, infant, and early child neurodevelopment - extending beyond the qualitative and morphometric standards of past investigations and establishing new reference metrics sensitive to the fundamental developmental processes. In doing so, data from HBCD will provide crucial insight into potential mechanisms of action, that more sensitively relate exposure to outcome, and point towards specific targets of intervention.

5. Conclusion

Over the last decade, fetal MRI has provided valuable insight into the various structural and functional facets of the developing human fetus. Initial progress focused on simultaneously characterizing normal fetal growth and advancing image processing and analysis techniques. Currently, multiple small-scale studies are leveraging these advances to investigate the relationship between various social/environmental factors and intrauterine development. By compelling innovations in design and technology, the HBCD study is likely to accelerate advances in the field of early neuroimaging and neurodevelopment with lasting influence. HBCD is also poised to transform knowledge about early human development through detailed longitudinal assessment of maturational trajectories. The NIH emphasizes centrality of a lifespan approach in their "Across the Lifespan Policy". Inclusion of fetal developmental timepoints has challenges and benefits, and also certainly speaks to this core value in understanding human life in its entirety

DataStatement

The article does not include any data as it is a commentary on methods and innovations.

Declaration of Competing Interest

The authors report no biomedical financial interests or potential conflicts of interest.

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