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Exploring early human brain development with structural and physiological neuroimaging

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Abstract

Early brain development, from the embryonic period to infancy, is characterized by rapid structural and functional changes. These changes can be studied using structural and physiological neuroimaging methods. In order to optimally acquire and accurately interpret this data, concepts from adult neuroimaging cannot be directly transferred. Instead, one must have a basic understanding of fetal and neonatal structural and physiological brain development, and the important modulators of this process. Here, we first review the major developmental milestones of transient cerebral structures and structural connectivity (axonal connectivity) followed by a summary of the contributions from *ex vivo* and *in vivo* MRI. Next, we discuss the basic biology of neuronal circuitry development (synaptic connectivity, i.e. ensemble of direct chemical and electrical connections between neurons), physiology of neurovascular coupling, baseline metabolic needs of the fetus and the infant, and functional connectivity (defined as statistical dependence of low-frequency spontaneous fluctuations seen with functional magnetic resonance imaging (fMRI)). The complementary roles of magnetic resonance imaging (MRI), electroencephalography (EEG), magnetoencephalography (MEG), and near-infrared spectroscopy (NIRS) are discussed. We include a section on modulators of brain development where we focus on the placenta and emerging placental MRI approaches. In each section we discuss key technical limitations of the imaging modalities and some of the limitations arising due to the biology of the system. Although neuroimaging approaches have contributed significantly to our understanding of early brain development, there is much yet to be done and a dire need for technical innovations and scientific discoveries to realize the future potential of early fetal and infant interventions to avert long term disease.

Keywords

Fetal and neonatal brain development; MRI; Structural connectivity; Functional connectivity; EEG; MEG; NIRS

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1. Introduction

The human brain undergoes critical stages of development from embryonic period to kindergarten (Silbereis et al., 2016). During these periods neurons are born, migrate to their final locations, networks are formed, and then fine-tuned with pruning and myelination (for review see (Bystron et al., 2008)). During regional maturation and areal specification, sensory, language, and then higher-order cognitive functions, like social cognition, emerge (Bauman and Amaral, 2008). Thus, human brain development is a highly complex and orchestrated process that sets the framework for cognition, behavior, and emotions for the rest of one's life.

The general architecture of the human brain is achieved during the first six months of fetal life, driven by strong genetic influences (Bakken et al., 2016; Kang et al., 2011; Pletikos et al., 2014). These genetic influences are silenced during the third trimester, leaving environmental factors to influence the last phases of prenatal and early postnatal brain development (Pletikos et al., 2014). Given that humans, compared to other primates, have particularly prolonged gestational time, the importance of early brain development is being increasingly recognized. In fact, recent advances in neuroimaging and functional genomic techniques provide growing evidence that many genetic, neurological, and mental disorders (affecting almost every fourth person worldwide (Brundtland, 2001)) have their roots in altered prenatal brain development (Jamuar et al., 2014; Schlotz and Phillips, 2009; Silbereis et al., 2016; Walsh, 1999). In addition, adverse *in utero* environments or early adverse experiences such as prematurity or social deprivation have lifelong effects on brain health (Ment et al., 2009; Nelson et al., 2007; Raznahan et al., 2012). Fortunately, however, the plasticity and capacity for adaptation of the mammalian brain has been well documented over the past decades (Stiles and Jernigan, 2010), and offers considerable potential for optimizing brain outcomes through the development of early diagnostic tools and early interventions (Pineda et al., 2012, 2013, 2014). Thus, the study of prenatal and early postnatal human brain development, and the use of noninvasive insignificant risk tools for monitoring normal or altered human brain development are of utmost importance.

The challenges of characterizing early human brain development, that arise from the transient nature of brain structure and physiology, have led researchers towards animal models. Yet, simple translation of biological electroencephalography (EEG), near-infrared spectroscopy (NIRS), and magnetic resonance imaging (MRI) findings from animals to humans is almost impossible in many cases (e.g. maturation of the arcuate fascicle in relation to language development) due to species-specific differences, which exist on every hierarchical level (Kaas, 2016). Therefore, although animal research provides invaluable platforms to validate some concepts of early brain development and test certain interventions, it is critical to continue the study of human brain development beginning in fetal life.

The study of early human brain development remains a challenge, because imaging methods and analysis tools for this age range are in their infancy and are still emerging. There is a temptation to apply approaches used in the mature brain but the size, composition, and function of the developing human brain offers unique challenges to both the application and

interpretation of these methods. Here, we review current concepts of early brain development and the emerging imaging tools and analysis techniques for studying this critical phase of life. We focus **on three concepts:** i) structural development *(does the brain look as it should for age?),* ii) functional development *(does the brain function as it should for age?)* and iii) modulators of brain development (is *the brain in a healthy environment?).* For each of these concepts we discuss what is known from histology and developmental biology *(biological principles).* We then discuss what has been discovered with structural MRI (both *in vitro* and *in vivo*) and with functional neuroimaging modalities (functional MRI (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), and near infrared spectroscopy (NIRS)) with comments on both technological and biological limitations. The main objective of our article is to provide a comprehensive summary of human brain development revealed by neuroimaging techniques.

2. Structural development

Histology studies have revealed that the human fetal brain is composed of transient compartments. These compartments are sites of major neurogenic processes, and undergo structural reorganization during prenatal and postnatal development. Thus, the structure of the fetal and neonatal brain changes initially from day to day and then from week to week.

While histology remains a gold standard for characterization of these transient compartments, *ex vivo* and *in vivo* structural MRI and DTI have been successfully employed to characterize their spatio-temporal changes. In parallel with the structural reorganization of the transient fetal compartments, sequential development of axonal connectivity occurs. Development of structural connectivity can also be examined using DTI and tractography, both *ex vivo* and *in vivo*.

Both *ex vivo* and *in vivo* MRI studies have demonstrated that maturation of the cerebral cortex occurs from the primary to the association cortices and that development of the limbic and the projection axonal pathways precedes development of association ones. In this section we describe in detail the structural development of the fetal human brain with an emphasis on MRI techniques.

2.1. Transient fetal structures

2.1.1. Biological principles—Histological analysis of the developing human brain still remains irreplaceable for characterization of the brain structure and for identification of neurogenic processes that occur during prenatal and early postnatal development (Bayer and Altman, 2005; Bystron et al., 2008; Duque et al., 2016; Kostovic et al., 2014; Kostovic and Judas, 2007; Kostovic and Rakic, 1990; Mrzljak et al., 1992; O'Rahilly and Müller, 2006; Paredes et al., 2016; Petanjek et al., 2011; Smart et al., 2002). From 15 gestational-weeks (GW) onwards, the fetal telencephalon is composed of six transient compartments and the ganglion eminence. The six compartments are: 1. ventricular zone (VZ), 2. subventricular zone (SVZ), 3. intermediate zone, 4. subplate zone, 5. cortical plate, and 6. marginal zone. These compartments are sites of major neurogenic events (e.g. neuronal proliferation and migration, axonal outgrowth, areal differentiation), and display characteristic spatio-temporal histological differences.

Neuronal proliferation occurs predominantly in the germinal matrix, which consists of the ventricular zone, subventricular zone, and ganglionic eminence. From these zones neuronal precursors migrate towards their final destination in the cortical plate via radial (Rakic, 1971) or tangential migration (cortical gamma-Aminobutyric acid (GABA)ergic neurons primarily from ganglionic eminence (Ang et al., 2003; DeDiego et al., 1994; Marín and Rubenstein, 2003)). Proliferative zones decrease in their volume and thickness after 27 GW indicating cessation of neurogenesis and switch to gliogenesis. Of particular importance for human brain development is also an outer subventricular zone, which appears during mid-gestation (Kostovic et al., 2002; Smart et al., 2002) and is important for generation of upper cortical layers (Zecevic et al., 2005). After birth the proliferative zones are reduced to the thin subependymal zone that produces neurons in frontal lobe (Paredes et al., 2016) and mostly glial cells in other regions. The intermediate zone, situated between proliferative zones and future cortex, represents fetal “white matter” as this is a zone comprised primarily of axons (although neurons migrate through this zone). The subplate zone contains a mixture of post-migratory cells and temporarily arrested axonal fibers and therefore is considered a “waiting compartment” for axons (Kostovic and Rakic, 1990). The cortical plate (future cortex) is composed of densely packed post migratory neurons that form embryonic radial columns (Rakic, 1988). During the preterm period (approximately 26–36GW), the cortical plate resembles an adult cerebral cortex in that the basic six-layer lamination of cerebral cortex can be recognized (Brodmann, 1909). However, adult-like specific cytoarchitectonic features of neocortical areas (e.g. the difference in thickness between cortical laminae) are generally not achieved until 3 years of postnatal life (Judaš and Cepanec, 2007).

2.1.2. MRI

2.1.2.1. Ex Vivo MRI.: Although histology is the gold standard, human fetal postmortem tissue is often limited in both quantity and quality, restricting detailed 3D spatio-temporal analysis of transient fetal compartments and neurogenic processes. For this reason, researchers have used larger specimens and performed *ex vivo* MRI to characterize larger scale regional fetal brain development, often in correlation with histological images (Chong et al., 1996; Dovjak et al., 2017; Huang and Vasung, 2014; Huang et al., 2009; Trivedi et al., 2009; Huen et al., 2013; Kolasinski et al., 2013; Kostovic et al., 2014; Kostovic and Vasung, 2009; Rados et al., 2006; Takahashi et al., 2012, 2013, 2014; Vasung et al., 2016, 2017; Wang et al., 2015; Xu et al., 2014). However, there are challenges in comparing *ex vivo* MRI with histology due to differences in resolution of approximately 4 orders of magnitude.

Based on the MR signal intensities, from 15 to 37 GW, only five of the six transient fetal compartments can be recognized (Kostovic et al., 2002; Rados et al., 2006): 1. ventricular zone (characterized by T1w high signal intensity and T2w low signal intensity due to the tight packing of cells), 2. subventricular zone (split into inner SVZ of high T1w signal intensity that cannot be distinguished from VZ due to the dense packing of proliferating cells, and outer periventricular fiber rich zone of low T1w and high T2w signal intensity), 3. intermediate zone (moderate T1w and T2w signal intensity due to the mixed content of migratory cells and axons), 4. subplate zone (low T1w and high T2w MRI signal intensity due to its rich extracellular matrix), and 5. cortical plate (high T1w and low T2w signal intensities due to the tight packing of cells). Current methods cannot resolve the marginal

zone. As these regions are sites of major neurogenic events, the MR signal intensity of these compartments, as well as their quantitative measures (e.g. growth of cortical surface, volume, or thickness) (Fig. 1), show spatio-temporal differences (Kostovic et al., 2014; Kostovic and Vasung, 2009; Vasung et al., 2016). These differences likely reflect spatio-temporal variations in cytoarchitecture and should be studied in correlation with histological images.

Finally, certain neurogenic processes cannot readily be identified by neuroimaging techniques (e.g. individual migration of neurons or cellular apoptosis). However, the magnitude of these processes can be deduced from the MRI findings (e.g. massive neuronal migration is reflected by predominant radial coherence of the telencephalic wall seen on diffusion tensor imaging (DTI) (Takahashi et al., 2012; Xu et al., 2014), while accelerated myelination of pathways towards the end of the gestation (Yakovlev and Lecours, 1967) can be seen as intensity change in T1-weighted (T1w) and T2-weighted (T2w) MRI.

Structural reorganization of fetal telencephalon is accompanied by changes in cortical landscape.

As the surface area of the cortical plate increases exponentially (Vasung et al., 2016) the first cortical convolutions (gyri and sulci) start to appear. Although deep cortical fissures and some primary sulci (e.g. central, cingulate, parieto-occipital, and olfactory) start to appear during the fetal period (approximately between 11 and 25 GW), they become more elaborated (Chi et al., 1977) during the late second and third trimester (i.e. approximately between 26 and 34 GW). The elaboration of primary sulci coincides with the relocation of thalamo-cortical axons from subplate zone to cortical plate (Kostovic and Jovanov-Milosevic, 2006). During the third trimester, secondary gyri and sulci emerge, which parallels the abundant growth of associative cortico-cortical connections (Takahashi et al., 2012; Vasung et al., 2017). The pattern of convolutions is specific for each individual (Im et al., 2011; Lohmann et al., 1999) and has been called the fingerprint of each individual brain (Zilles and Palomero-Gallagher, 2015) that is already formed *in utero.*

Experimental work on fetal monkeys suggest that gyrification is related to axonal connectivity (Goldman and Galkin, 1978), while mathematical and physical models (e.g. (Foubet et al., 2018)), and research conducted using brain organoids argue that size, shape, placement, and orientation of the folds arise through spatio-temporal differences in mechanical stability of the cortex (Karzbrun et al., 2018; Tallinen et al., 2016). Taken altogether, the pattern of gyri and sulci, which is specific for each individual, might also reflect one's unique process of cortical reorganization *in utero,* and consequently, one's unique pattern of axonal connectivity.

In conclusion, *ex vivo* MRI in correlation with histological images remains a necessary first step towards the proper neurobiological interpretation of fetal MR images, bridging the gap between *in vivo* MRI and histology.

2.1.2.2. In Vivo MRI.: In the last two decades researchers have been able to successfully capture *in vivo* fetal and preterm brain development using structural MRI during different

developmental periods (e.g. (Childs et al., 1998; Chung et al., 2009; Felderhoff-Mueser et al., 1999; Garel et al., 2001; Gholipour et al., 2017; Girard et al., 1995; Glenn and Barkovich, 2006a, 2006b; Habas et al., 2010; Lan et al., 2000; Prayer et al., 2006; Rutherford, 2009; Mewes et al., 2006)). Recent technological advances in MRI acquisition and analysis (for detailed review on techniques please see (Gholipour et al., 2014; Manganaro et al., 2017)) broadened the information that we can collect during fetal brain development.

Despite the aforementioned challenges of fetal structural MRI, early *in vivo* studies have captured patterns of fetal lamination and transient fetal structures during different developmental periods (Girard et al., 1995; Girard and Raybaud, 1992; Glenn and Barkovich, 2006a, 2006b; Prayer et al., 2006). Moreover, some of them were able to produce 3D volume reconstruction of the fetal brain needed to quantify the transient fetal compartments during *in utero* development (e.g. (Clouchoux et al., 2012; Habas et al., 2010)). The majority of these studies provided evidence that during the second and third trimester the human brain undergoes substantial reorganization: the volume of cortical plate and surface are exponentially increases (Clouchoux et al., 2012; Andescavage et al., 2017), while its fractional anisotropy (reflecting microscopic tissue coherence) decreases (Ball et al., 2013; McKinstry et al., 2002). This loss in cortical coherence corresponds to neuronal differentiation, dendritic arborisation, and cortical axonal ingrowth described using histology (Mrzljak et al., 1992). During the same period, from 15 GW, the volume of the subplate zone increases. The subplate zone peaks in size between 26 and 32 GW and then gradually disappears a few months after birth (Corbett-Detig et al., 2011; Kostovic et al., 2014; Widjaja et al., 2010). The bell shaped curve of subplate volume most likely reflects ingrowth and outgrowth of axons, and their relocation from subplate (“axonal waiting compartment”) to cortical plate (Kostovic et al., 2014; Kostovic and Rakic, 1990). Using large datasets and the advances in MRI reconstruction techniques normative spatiotemporal MRI atlases of the fetal brain *in vivo* were produced recently ((Gholipour et al., 2017), for review see (Gui et al., 2015)). These probabilistic atlases of fetal brain open new vistas to studying age dependent changes that occur during reorganization of fetal telencephalon, in particular ones reflecting to the cortical plate surface. For example, recent work from Im et al. provided evidence that the foundations of the gyrification process are under strong genetic influences. Therefore, early mapping of cortical convolutions could, in future, serve as a diagnostic tool for identification of fetuses with various brain malformations (Im et al., 2017; Tarui et al., 2017).

In conclusion, the structure of the fetal brain is stage specific and changes from week to week during development. Although histology remains irreplaceable for identification of neurogenic events that occur during development, *in vivo* and *ex vivo* MRI can be used to characterize global, regional and temporal magnitudes of these processes. Such large- scale changes are difficult to capture with histology and may be beneficial in future for targeting such microscopic analysis.

2.2. Structural (axonal) connectivity

2.2.1. Biological principles—As early as 13 GW, there is a significant increase in the thickness of the internal capsule at the level of the junction between telencephalon and diencephalon. This increase in thickness indicates the appearance and increase in the number of projection fibers from thalamus (Hevner, 2000; Kostovic and Goldman-Rakic, 1983; Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2007). During the early fetal period (11–17 GW), several limbic bundles can be already recognized (e.g. fornix, stria terminalis, and cingulum) (Vasung et al., 2010). The appearance of limbic bundles is followed by the accumulation of afferent thalamocortical fibers in the intermediate and subplate zone (17–25 GW), and the appearance (26–34 GW) and completion of associational fiber bundles (35–40 GW). Association fiber bundles appear and accumulate within the "waiting compartment" i.e. subplate zone (Kostovic and Jovanov-Milosevic, 2006; Kostovic and Rakic, 1990). As fetal brain structure undergoes substantial reorganization during its development, it is recognized that the patterns of fetal structural connectivity are also transient during development. For example, during early development the motor cortex initially develops bilateral projections to the spine (Eyre et al., 2001) and callosal axons are produced in abundance (LaMantia and Rakic, 1990). However, during the course of development the ipsilateral corticospinal projections are eventually withdrawn (Eyre et al., 2001), while in primates approximately 70% of callosal axons retract after birth (LaMantia and Rakic, 1990). Nevertheless, the research on the establishment and reorganization of axonal connectivity during prenatal human development still remains scarce (Huang and Vasung, 2014; Huang et al., 2009; Kostovic and Jovanov-Milosevic, 2006; Kostovic et al., 2014; Kostovic and Judas, 2007; Vasung et al., 2017).

2.2.2. MRI

2.2.2.1. Ex Vivo MRI.: Diffusion imaging is an imaging method that relies on movement of water molecules in tissue. In the mature brain, axonal coherence and myelination have a dominant impact on water molecule movement (Mori and Zhang, 2006). Diffusion tensor imaging (DTI) has become the leading tool for studying the development of structural (axonal) connectivity and cytoarchitectonic reorganization in the human brain.

Massive neuronal migration, from proliferative zones to cortical plate, can be identified by the predominant radial coherence of the entire telencephalic wall (Xu et al., 2014) that ceases towards the third trimester (Fig. 2). In the cortical plate specifically, microscopic water movement is thought to be dominated by the dense packing of postmigratory neurons within the embryonic cortical columns (Huang et al., 2009, 2013). Thus, DTI derived values of fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD) have been employed to demonstrate transient fetal zones and their structural reorganization (e.g. (Widjaja et al., 2010; Huang et al., 2013)). Specifically, combining DTI and histology (Huang et al., 2013) elegantly showed that from 13 to 21 GW the high FA values across cortical plate reflect organized radial architecture of cortical plate. The gradual decrease of FA from 13 to 21 GW correlates with gene expression relevant for numerous neurological and psychiatric disorders (Huang et al., 2013). After 21 GW, FA of cortical plate continues to decline until 35 GW (Yu et al., 2016). The decline in FA shows spatio-temporal

differences across cortical plate until 35GW. After 35 GW the temporal FA decline is heterogeneous mostly in higher-order association cortex (Yu et al., 2016).

Aside from characterizing microstructural development, DTI and tractography can be used to identify the sequential appearance of fiber bundles. In order to better characterize structural maturation and connectivity during the past decade numerous diffusion models (Assaf and Basser, 2005; Basser et al., 1994; Özarslan et al., 2006; Tournier et al., 2004) and algorithms used for tract reconstruction, i.e. tractography (Chao et al., 2007; Mori et al., 1999; Tuch, 2002; Weinstein et al., 1999) have been developed. However, given the rapid changes in the fetal brain from week to week and altered cortical microstructural development in prematurely born infants, model-based reconstructions that require the assumption of a fixed diffusivity have limitations and care must be taken in the interpretation of the biological meaning of the parameters obtained at each stage of development. Given our emerging knowledge in the developing human brain, high angular resolution diffusion imaging (HARDI) (Hess et al., 2006) or Gaussian Mixture Models, may provide more useful and unbiased information of developing tissue microstructure (Ning et al., 2015; Rathi et al., 2014).

Despite these challenges there are several studies published using *ex vivo* human fetal DTI. All these studies confirmed findings already described in classical neuroanatomical textbooks: limbic, callosal, and projection fibers develop first, which is followed by a massive development of association pathways (Huang et al., 2006, 2009; Takahashi et al., 2012; Vasung et al., 2010, 2017).

2.2.2.2. In Vivo MRI.: Until now, there have been only a few groups that have successfully obtained and reconstructed *in vivo* fetal DTI data without the aid of sedation (Kasprian et al., 2008; Mitter et al., 2015a, 2015b). Kasprian et al. reported the development of sensorimotor and callosal fiber bundles at 24, 26, 31 and 35 GW (Kasprian et al., 2008) whereas Mitter et al. reported that the uncinate fasciculus and inferior fronto-occipital fasciculus can be seen as early as 20 GW (Mitter et al., 2015b). The results of both studies are in agreement with the DTI findings from *ex vivo* studies.

Compared to the acquisition and analysis of *in utero* fetal DTI, analysis of axonal connectivity in the newborn and infant human brain is a significantly easier task (e.g. see (Dubois et al., 2009; Dubois et al., 2014; Huang et al., 2006; Hughes et al., 2017; Rasmussen et al., 2017)).

Recently (Yu et al., 2016) showed that from 20 to 35 GW FA decrease is heterogenous across cortical plate, while from 35 to 40 GW the FA decrease remains nonuniform mostly in higher-order association cortex. These findings suggest differentiated cortical development patterns, with higher-order association cortex maturing the last (Yu et al., 2016). After the birth and until 2 years of life, association cortical areas are the fastest growing regions of cortex and show the biggest local gyrification index change (Li et al., 2014). Therefore, it is logical to assume that these rapidly changing regions will be also the most vulnerable ones.

The heterogenous maturation pattern of cortical plate is perturbed by premature birth. Premature exposure to the environment is related, in dose-dependent fashion, to the delay in cortical microstructural maturation (i.e. slower decrease in FA) (Ball et al., 2015). In addition, in prematurely born infants the decline in cortical FA (marker of micro-structural development) is directly related to the rate of cortical growth and predicted neurodevelopmental scores at 2 years of life. Thus, the utility of MRI studies of fetal and neonatal brain probably lie in their ability to predict potential neurologic, cognitive and behavioral outcomes of these children.

In conclusion, during the second and third trimester the pattern of cerebral cortex maturation shifts from being regionaly specific to more being more uniform. The development of axonal connectivity, on the other hand, happens in sequential order, with limbic and projection fibers developing first and association last. While it is known, from animal models, that axonal connectivity undergoes substantial refinement during fetal development, characterizing this reorganization in humans remains a challenging task. Finally, the establishment of structural connectivity and the maturation of cerebral mantle are biological sub-strates for development of sensorimotor functions (e.g. maturation of primary cortices and projection fibers), emotional development (e.g. maturation of limbic system) and establishment higher-order cognitive skills (e.g. maturation of prefrontal cortex and association fiber bundles).

2.3. Limitations

2.3.1. Technical limitations—Compared to *ex vivo* MRI, *in vivo* fetal MRI suffers from low resolution and motion artifacts. Due to the limitation in the resolution of MRI *(ex vivo* T1w-T2w MRI and DTI 0.2–0.4 mm, *in vivo* MRI and DTI 1–2 mm), visualization of smaller or thinner fetal structures (such as marginal zone) is not currently possible. Similarly, the changes in the cytoarchitectonic and myeloarchitectonic organization of the human fetal brain (such as appearance of cortical layers or neocortical myelination) are also not yet possible to explore. The transient fetal zones can be easily identified with *ex vivo* and *in vivo* MRI during the periods of their peak growth. However, the transient nature of these structures poses serious challenges in the proper interpretation of MRI signals once these zones start to dissolve (i.e. defining if certain transient structure disappeared or simply cannot be seen with the currently used techniques).

In addition, MR features such as coherent diffusivity lack specificity and therefore, can represent different tissue components at different times. For example, coherence of the cerebral mantle in the late first and early second trimester fetal brain is dominated by radial glial fibers (Xu et al., 2014), whereas in the late third trimester it is probably dominated by the complex spatial relationship and geometrical properties of axonal pathways (Wedeen et al., 2012). For this reason, we emphasize that interpretation of *ex vivo* and *in vivo* MRI findings should always be guided by developmental biological principles discovered with histological studies.

2.3.2. Biological limitations—The MR signal of *ex vivo* brain tissue is influenced by fixation and postmortem interval (Tovi and Ericsson, 1992). Therefore, the accuracy of *ex*

vivo imaging is limited by these factors. In addition, there are inherent challenges of scale when trying to interpret tissue microstructure based on an image with voxel sizes that is orders of magnitude larger than the cellular elements. Lastly, reliable axonal tracing techniques, focused specifically on axonal tracing in fetal brain (e.g. immunohis-toMRI), have not been developed yet.

3. Functional development

Functional reorganization of the fetal brain occurs in parallel with structural reorganization. Transient circuits in the fetal brain, which show endogenous and spontaneous activity, are gradually replaced by adult like, sensory-driven ones. This occurs concomitantly with the increase in cerebral metabolic demand.

The transition from endogenous to adult like circuitry, and the functional brain responses to environmental stimuli can be monitored with electrophysiological techniques (MEG or EEG), near infrared spectroscopy (NIRS), and functional MRI (fMRI). Regardless of the neuroimaging modality used, the majority of studies have demonstrated the existence of spontaneous brain activity before 26 GW, and the functional responses to environmental somatosensory stimuli after 26 GW. However, each of these techniques suffers from biological and technical limitations. For example, better understanding of the spatio-temporal maturation of synapses would improve interpretation of EEG/MEG findings, and more knowledge of angiogenesis and the emergence of neurovascular coupling would inform fMRI and fNIRS analyses.

Here, we summarize the basic principles of MRI, NIRS, and EEG/ MEG, and the studies that have used these techniques to probe the development of functional connectivity as well as the changing baseline metabolic demands that occur during early development.

3.1. Developing functional neuronal circuitry

3.1.1. Biological principles—Studying the structure of the fetal and neonatal brain is of high relevance for the assessment of proper brain development. However, studying its function has recently gained substantial attention. The first synapses in fetal central nervous system (CNS) appear in cervical spine during 8GW (Okado et al., 1979), followed by their appearance in marginal zone of telencephalon approximately during 9 GW (Larroche, 1981; Larroche and Houcine, 1982). The appearance of first synapses in the telencephalon coincides with the formation of the cortical plate (Molliver et al., 1973). From this moment onwards synaptogenesis occurs in a bilaminar pattern (Molliver et al., 1973), i.e. below and above cortical plate. However, the subplate zone becomes the major site of synaptogenesis from 12 GW (when subplate zone can be easily identified in histological sections (Kostovic and Rakic, 1990)) until 26 GW (26–32 GW, when subplate volume reaches its volume peak (Vasung et al., 2016)). The first synapses in the cortical plate appear during 20 GW (Kwan et al., 2012). From this moment onwards synaptogenesis continues progressively in the cortical plate following a deep-to-superficial pattern. This parallels relocation of axons from subplate to cortical plate, as proposed by (Kostovic and Judas, 2007). However, the majority of these prenatal synapses are thought to be transient (Huttenlocher, 1979) with two potential scenarios describing their prenatal and early postnatal structural reorganization: i) uniform

loss of synapses across entire cortex (Rakic et al., 1986) and ii) heterogeneous loss of synapses with association areas losing synapses last (Huttenlocher and Dabholkar, 1997).

Based on histological descriptions in humans (appearance of synapses, dendritic arborisation, and axonal tracings) and animal models (Allendoerfer and Shatz, 1994), three stages of fetal functional maturation have been proposed (Kostovic and Judas, 2007; Milh et al., 2006; Vanhatalo et al., 2005): i) an initial formation of fetal transient circuits with endogenous, spontaneous activity that are centered around subplate zone, ii) co-existence of fetal neuronal circuits with endogenous activity and neuronal circuits that display sensory-driven activity, and iii) establishment of adult like sensory-driven fetal circuits, which are centered around the cortical plate (i.e. layers I-VI of developing cerebral cortex) (Fig. 3).

The developing neuronal circuitry also exhibits regional differences. As noted above, the thalamic input plays a central role in the development of cortical circuitry. One primary function of the thalamus is to serve as a relay station for all cortical sensory systems in their interaction with the environment (proprioception, vestibular, tactile, auditory, visual, olfactory, and gustatory). Establishment of structural thalamocortical connectivity (around 26 GW when thalamo-cortical axons relocate from subplate to cortical plate (Kostovic et al., 2014; Kostovic and Judas, 2010; Krsnik et al., 2017)) is a first step towards establishment of sensory driven activity of neuronal circuits. The olfactory system develops first, in early fetal life. Olfactory fibers enter the brain around 39 days postconception at the site of the olfactory bulb. Around 41 post conceptual days olfactory tubercle and bud can be identified (Muller and O'Rahilly, 1989). However, the first synapses in the olfactory bulb are seen between 9 and 14 GW (Sarnat and Yu, 2016). Despite these facts, the first contacts between chemical stimuli from amniotic fluids and nasal chemoreceptors (first odor exposures) occur only after 16 GW, i.e. when nasal plugs dissolve (Som and Naidich, 2013), and fetal swallowing and breathing movements displace the amniotic fluid (Schaal et al., 2004). However, the fetal olfactory system remains immature during prenatal development (e.g. at term-age only 25% of olfactory bulb neurons are stained with NeuN (marker of neuronal maturity) while only 10% of olfactory axons are myelinated (Sarnat and Yu, 2016)). Following the development of olfactory and gustatory systems, other sensory systems develop (visual, auditory, and proprioceptive). Thus, behavioral responses of fetuses *in utero* to external stimuli such as light (Kiuchi et al., 2000) or nociception (Bellieni and Buonocore, 2012) can be observed around 26 GW. As previously mentioned, this is the stage of fetal brain development characterized by relocation of thalamocortical axons from cortical plate to subplate (Kostovic and Goldman-Rakic, 1983; Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2009; Krsnik et al., 2017) and the beginning of massive cortical synaptogenesis.

Multimodal histology studies provided indirect evidence for early presence of endogenous circuitry before 20 GW, and appearance of sensory-driven circuitry after 26 GW. Histological analysis of ex vivo fetal tissue can indicate some of the fundamental spatio-temporal processes in the maturation of cortical synaptic circuitry. However, to further understand the function of transient and permanent neuronal circuits and their role in later cognitive development and behavior we must study the developing brain *in vivo.* In addition,

studying brain development using *in vivo* techniques allows assessment of major networks on a larger scale.

3.1.2. Electrophysiology of the developing human brain

3.1.2.1. EEG.: EEG is a non-invasive method of electrophysiological imaging that measures the electric fields produced by neuronal activity in the brain. In the mature brain, the magnetic fields are primarily generated by extracellular postsynaptic currents in the apical dendrites of the cortical pyramidal cells (Olejniczak, 2006). The first study of human fetal electrical activity was performed with EEG and published in 1955 (Bernstine et al., 1955). Fetal EEG recordings of typically developing fetuses showed discontinuous (i.e. Tracé discontinu: sharp bursts followed by low frequency waves) and tracé alternant patterns (i.e. Tracé alternant: sharp bursts followed by shorter and higher amplitude intervals) (Sokol et al., 1974). On the other hand, certain fetal EEG waveforms such as sharp waves followed by prolonged low voltage EEG waves were shown to be related to intrapartum fetal distress, postpartum brain damage, and postnatal neurological abnormalities (Borgstedt et al., 1975; Sokol et al., 1974) (For a review on Fetal EEG studies, see (Anderson and Thomason, 2013)). Reported changes in fetal EEG recordings parallel the transition of neuronal circuits from the ones that are spontaneously active (i.e endogenously driven activity) to ones whose activity is sensory-driven (Kostovic and Judas, 2002, 2007; Vanhatalo and Kaila, 2010). Thus, EEG is an ideal tool to study general principles of cortical circuitry development. However, as fetal bioelectric signals show a strong attenuation as they pass through and reach the maternal abdomen surface, fetal EEG is not an optimal method to detect subtle changes in brain activity of the fetus. For this reason, researchers have primarily used EEG to characterize brain activity of prematurely born infants.

Neonatal EEG studies of prematurely born infants show that during mid-fetal to early preterm periods desynchronized patterns and patterns of discrete large spontaneous activity transient (SATs) waves dominate, transitioning to synchronized patterns of activity during the early to late preterm periods (Vanhatalo and Kaila, 2010) (Fig. 3). Studies show that SATs are observed at 23–24 GW, mostly over the sensory and associative cortices and are more widespread later throughout development (Kostovic and Judas, 2002, 2007; Vanhatalo and Kaila, 2010). In time, as the number of discrete SAT events decreases, continuous high frequency activity, that is required for most cognitive functions, slowly starts to increase (Hellstrom-Westas et al., 2006; Meyerson, 1968) with the establishment of large thalamocortical, callosal, and corticocortical connections (Vanhatalo and Kaila, 2010). Sensory-triggered evoked responses are mediated by the development of thalamocortical pathways, changing from subplate-induced slow cortical responses, until about 26 GW, to the conventional evoked responses (Vanhatalo and Kaila, 2010), most likely resulting from inputs from thalamus to the layer IV of the cortex (Krsnik et al., 2017). Within the first couple years of life, the development of cortical evoked responses continues (Innocenti and Price, 2005), which parallels the growth of short-range corticocortical connections (Kostovic and Judas, 2002).

The use of EEG to assess developmental brain activity dates to early 1974, when postnatal EEG recordings provided evidence that neonatal brain activity could predict later

developmental outcomes (Borgstedt et al., 1975; Sokol et al., 1974). In addition, EEG was also employed to characterize typical brain development during the first years of life. Mismatch negativity (MMN) responses and responses to oddball stimuli paradigms, where a series of standard stimuli is infrequently interrupted by deviant stimuli (Wanrooij et al., 2014), were successfully observed in infants as young as 2–3 postnatal months suggesting low-level auditory processing at this phase of life. In addition to the auditory processing, EEG has been proven useful in characterization of face processing (N290 and P400, precursors of the N170 event related potential (ERP), have been observed in early infancy in response to face stimuli (de Haan et al., 2002; Pascalis et al., 2002, 2005)), memory and attention in early infancy (negative central (Nc), positive slow wave (PSW), and negative slow wave (NSW) components of the ERP, were found to be present at birth (Courchesne et al., 1981; Hunter and Karrer, 1993; Karrer et al., 1998; Nelson and Collins, 1991, 1992; Nelson and deRegier, 1992)).

In addition to EEG's utility to characterize spontaneous and sensorydriven circuitry in normally developing infants, EEG has also been proven useful in the study of atypical brain development and infants in risk groups. For example, children who experience maltreatment show higher levels of low-frequency power in the theta band (related to drowsiness, sleep, and working memory in adults) and lower levels of higher-frequency power in the alpha and beta range (alpha activity related to modulation of attention states and beta to active concentration in adults) (Bick and Nelson, 2017; Zeanah et al., 2003).). Also, in infants at risk for autism, decreased frontal high-alpha power at age 3 months was associated with increased risk of reduced expressive language skills at 12 months of age (Levin et al., 2017; McDonald et al., 2017; Seery et al., 2014). Despite numerous technical challenges in performing EEG recordings, EEG is routinely performed in clinical setting for global overview of brain cerebral activity in high-risk newborns and for pre-surgical evaluation of epilepsy patients (Noachtar and Rémi, 2009). With the help of ambulatory EEG systems, continuous recordings can be performed for days or weeks, while the patients can continue their day to day activities, increasing the chance of predicting the outcome after perinatal asphyxia (De Vries and Hellström-Westas, 2005), or recording an ictal activity (Smith, 2005).

3.1.2.2. MEG.: MEG is a non-invasive method of electrophysiological imaging that measures the magnetic fields produced by neuronal activity in the brain. In the mature brain, the magnetic fields are primarily generated by intracellular postsynaptic currents in the apical dendrites of the cortical pyramidal cells (Baillet, 2017; Hamalainen et al., 1993). However, the source of the MEG signal in the fetus remains uncertain. The laminar identity of pyramidal neurons is determined by their birth order (Rakic, 1982), and their dendritic spines begin to appear around 26 GW (Mrzljak et al., 1988), which parallels ingrowth of thalamocortical axons (Kostovic and Rakic, 1990; Krsnik et al., 2017). The size of pyramidal neurons and the length of dendrites increases dramatically during the last trimester and early postnatally (Koenderink et al., 1994). In later developmental stages, there is a shift in the formation of the synapses and their activity from deep to superficial layers of the cortex, causing a change in the cortical electrical dipole. Cortical network formation and operation depends not only on these vertically (to pia matter) oriented pyramidal neurons

(majority of cortical neurons which are glutamatergic), but also on the GABAergic interneurons, some of which are oriented horizontally to pia. Studies suggest that GABAergic synapses are formed before glutamatergic synapses in the brain (Soriano et al., 1986), however, it takes longer for some of the early born GABAergic interneurons to reach the final destination. On the other hand, primate specific late born GABAergic neurons, produced in proliferative zones of dorsal telencephalon, show simpler and shorter migration trajectories (Fertuzinhos et al., 2009; Letinic et al., 2002; Radonjic et al., 2014; Rakic and Zecevic, 2003) for review see (Petanjek et al., 2009)). Furthermore, while GABA is an inhibitory neurotransmitter in the adult brain, at early stages of fetal development it acts as an excitatory neurotransmitter due to the high intracellular chloride ion (Cl^-) concentration of the immature post-synaptic neuron (Ben-Ari et al., 1989), leading to the generation of action-potentials (Tyzio et al., 2003). As a result, most of the initial activity recorded is generated by the interneurons that use excitatory GABA as a neurotransmitter, while most of the pyramidal cells are silent (Ben-Ari et al., 2004). In order to detect and amplify the small magnetic fields generated by neural activity of the brain, Superconducting Quantum Interference Device (SQUID) technology is used (Cohen, 1972; Hamalainen et al., 1993).

Since 1972, when MEG was first used to record human brain activity, there has been great advances to the technology, making MEG a popular tool to study typical and atypical brain development and function in clinical and research settings. MEG has excellent temporal resolution, down to less than a millisecond (Baillet, 2017), and spatial resolution, as high as a few millimeters (Schwartz et al., 2010). Furthermore, unlike the electrical currents measured by EEG, magnetic fields measured by MEG are not affected by the skull, fontanels, sutures, intervening tissue layers between the scalp and the brain (Lew et al., 2013; Okada et al., 2006, 2016), or the several layers of maternal abdominal muscle and tissue between the sensors and the fetal brain (Lowery et al., 2009). MEG signals, unlike EEG, are reference-free which makes them unaffected by the conductivity differences of the magnetic flux, providing an absolute measurement of brain activity (Braeutigam, 2013). For a comprehensive review of MEG as a technology and its comparison to EEG, see (Baillet, 2017; Braeutigam, 2013; Hamalainen et al., 1993).

The first fetal MEG studies used a system with only one magnetometer channel (Blum et al., 1985), which was followed by seven-(Eswaran et al., 2000; Wakai et al., 1996) and 31-channel SQUID systems (Schleussner et al., 2001). However, using a small sensor array that is not shaped to fit over the mother’s abdomen caused difficulties in optimally placing the sensors over the abdominal region to capture the majority of the signals. Therefore, an instrument that can cover the whole maternal abdomen, which will also provide a very small distance between the sensors and the fetal head to ensure good signal-to-noise ratio, was needed for the better success of fetal MEG recordings (Eswaran et al., 2000). With the construction of the first MEG device (Fig. 4) (SARA, SQUID Array for Reproductive Assessment, VSM Medical Technology Ltd., Canada) (Eswaran et al., 2002a, 2002b) specifically designed to record fetal brain activity, the success in measuring fetal neural activity has increased. A new fetalmaternal biomagnetic scanner that has a full-coverage whole body sensory array has been recently designed. This system will be able to detect in real time the biomagnetic signals of fetal heart and brain, as well as visualize uterine activity with significantly improved signal quality to existing systems (Lew et al., 2017).

Initially, neonatal and infant MEG recordings were performed with the use of adult or fetal MEG systems. However, these systems have a fixed helmet size (or sensor array) that is too large for a small infant head, leaving a large distance between MEG sensors and the developing brain, leading to low signal strength (Huotilainen, 2006). For this reason, in some of these studies, data from only one hemisphere could be recorded at a time by placing the infant on its side. Even then, adult MEG systems do not provide a high-density sensor array that is optimal for studying the infant brain, causing limitations in spatial resolution (Huotilainen, 2006; Okada et al., 2006). For this reason, the first MEG system optimized for neonatal studies, called babySQUID (Superconducting Quantum Interference Device (SQUID)), was developed (Okada et al., 2006) (Tristan Technologies, Inc., San Diego, CA, USA). This system had a shorter distance between the pickup coils and the scalp, taking advantage of the few millimeters of thickness of the infant scalp and skull, and therefore improving the sensitivity of the signal. Furthermore, the sensors were made small and the sensor density was kept high in the array, which only provided partial coverage, in order to provide increased spatial resolution. BabySQUID was followed with the development of full head pediatric MEG systems, such as the ChildMEG (Adachi et al., 2010; Johnson et al., 2010) (Yokogawa/KIT, Kanazawa, Japan), Artemis 123 (Roberts et al., 2014) (Tristan Technologies, Inc., San Diego, CA, USA), and the MagView Biomagnetometer (BabyMEG) (Tristan Technologies, Inc., San Diego, CA, USA) (Fig. 4) (Okada et al., 2016). With advancing MEG systems, detection of evoked (sensory triggered) cortical activity in a small number of averaged trials, and even in a single trial is now possible (Okada et al., 2016), a very important advance that enables more practical short duration recordings but also dynamic activity in typically developing children (He et al., 2011; Pizzella et al., 2014) as well as in children with neurological disorders such as epilepsy (Hunold et al., 2014; Papadelis et al., 2013). In order to increase the ability to detect these small signals from neural activity, which are about one billion times smaller than the Earth’s magnetic field, and to minimize environmental magnetic noise current MEG systems need be placed in magnetically shielded rooms (MSRs) (Hamalainen et al., 1993). However, there is active research to create MEG systems that can operate at room temperature and therefore large MSRs may not be required in the future (Boto et al., 2017).

In the first fetal MEG study exploring spontaneous brain activity, researchers were able to identify brain activity patterns similar to EEG recordings observed in premature infants at comparable ages (Sokol et al., 1974). While spontaneous MEG signals were observed to be more discontinuous at early GA, there was a decrease in the discontinuous pattern after 35 GW, and emerging continuous and tracé alternant patterns (Eswaran et al., 2000; Rose and Eswaran, 2004). For reviews on fetal MEG, see (Anderson and Thomason, 2013; Lowery et al., 2006; Preissl et al., 2004, 2005; Sheridan et al., 2010b). Spontaneous neonatal MEG recordings detected continuous slow, tracé alternant, and continuous polyfrequency patterns (Haddad et al., 2011; Vairavan et al., 2009) that were comparable to the results obtained by neonatal EEG recordings (Haddad et al., 2006). Developmental changes in sleep patterns in neonates between 36 and 48 weeks conceptional age have also been studied using MEG, where sleep patterns showed pronounced developmental changes and reached a mature form by 48 weeks. The mature sleep patterns are characterized by delta waves with higher

amplitude, absence of discontinuous patterns, and sleep spindles (Lutter et al., 2006). For a review of neonatal MEG studies, see (Huotilainen, 2006).

The first MEG study examining evoked (i.e. sensory driven) brain activity of the human fetus was conducted by Blum and colleagues in 1985. Researchers successfully recorded fetal auditory evoked neuro-magnetic fields, elicited by brief tone bursts, using a one-channel magnetometer that was placed over two mothers' abdomen above the auditory cortex of the fetuses at 34 and 35 GW (Blum et al., 1985). Subsequent studies recorded auditory-evoked fields from fetuses using seven- (Boas et al., 1995; Eswaran et al., 2000; Wakai et al., 1996) and 31-channel SQUID systems (Schleussner et al., 2001). Maturation of the auditory cortex has also been studied longitudinally in fetuses and the results showed a decrease in the latency of the auditory evoked magnetic field with increasing GW age (Draganova et al., 2007; Holst et al., 2005). Visual evoked responses have been detected in fetuses as early as 28 GW using fetal MEG (Eswaran et al., 2002b), with more reliable detection between 28 and 32 GW (Eswaran et al., 2004), showing a decrease in the response latencies with increased gestation in healthy fetuses (Eswaran et al., 2004). Decreased response latencies with increased GA is presumed to be due to myelination of the neural pathways (Holst et al., 2005), where increased myelination leads to faster signal transmission along the neural pathways, resulting in shorter response latencies (Tsuneishi and Casaer, 2000). Neonatal MEG evoked recordings studying evoked activity found auditory responses to repeated tones (Lengle et al., 2001) and tone pairs (Sheridan et al., 2010a). For a review of auditory MEG studies in infants, see (Huotilainen et al., 2008). Clear and replicable somatosensory evoked fields were elicited via tactile stimulation in premature and full term neonates and were observed in both primary and secondary somatosensory cortices (Lauronen et al., 2006; Nevalainen et al., 2008, 2012). Longitudinal studies that examined the maturation of the somatosensory cortex showed decreased response latencies with increasing age (Pihko et al., 2009). Somatosensory evoked field responses were found to be affected by the arousal state of the infant (Pihko and Lauronen, 2004). For a review of somatosensory MEG studies throughout development, see (Nevalainen et al., 2014). MEG studies also examined the visual evoked fields in full term neonates and showed that neonates exhibit neural mechanisms of visual habituation and (Matuz et al., 2012) response decrements in amplitude from the first to the last visual stimuli (Sheridan et al., 2008). Researchers used different strategies to increase the efficiency of neonatal MEG recordings such as using alternating auditory and tactile stimulation, and therefore shortening measurement time and/or increasing signal-to-noise ratio with the collection of more data (Pihko et al., 2011).

In addition to characterizing spontaneous and sensory-driven activations, MEG studies of fetuses (see (Dunn et al., 2015) for a review), as young as 28 GW, suggested the emergence and maturation of higher order cognitive functions by using an oddball paradigm and measuring mismatch field (MMF) responses (e.g auditory short-term memory (Huotilainen et al., 2005), sound discrimination (Draganova et al., 2005), and language learning (Draganova et al., 2007)). Evidence for lateralization of auditory processing was shown in fetuses 27–39 GW, with a right hemispheric dominance (Schleussner et al., 2004). In order to improve neurological testing and increase success rates, researchers developed comprehensive assessment protocols such as performing a series of recordings over a short

time window (Eswaran et al., 2002a), presenting both auditory and visual stimuli during short multiple recordings covering a one GW time period (Eswaran et al., 2005) and measuring fetal heart and brain activity simultaneously (Lowery et al., 2008), as well as assessing the behavioral states of the fetus; quiet or active sleep (Haddad et al., 2011). Neonatal and infant MEG studies also examined higher order cognitive functions such as studying the MMF responses to sound discrimination with the use of oddball paradigms of tones (Fig. 5) (Cheour et al., 2004; Draganova et al., 2005, 2007; Huotilainen et al., 2003) as well as speech sounds (Ferjan Ramírez et al., 2017; Kujala et al., 2004), semantic processing showing adult-like N400 responses that is modulated by semantic priming (Travis et al., 2011), and face processing showing a delayed, but otherwise similar, M170 response to faces compared to adults reflecting neurodevelopmental changes in the visual system (He et al., 2015).

MEG has been used to predict outcome following epilepsy surgery where it has been shown that postoperative seizure freedom was more likely to occur in children with restricted ictal onset zone compared to the children with bilateral MEG dipole clusters. The high concordance between EEG and MEG localization was also predictive of seizure freedom (RamachandranNair et al., 2007). MEG is also used for predicting language ability (Roberts et al., 2008) where right hemisphere M50 latency to auditory tones (Cardy et al., 2008), as well as impairments in rapid temporal processing of auditory tones (Cardy et al., 2005), have shown to be related to impaired language comprehension. Responses to auditory tone stimuli has shown delayed M100 latencies and reduced gamma band responses in autism compared to typically developing children indicating maturational abnormalities in the development of the auditory cortex in autism compared to typically developing children which could be used as a potential biomarker of autism (Edgar et al., 2015; Port et al., 2016) and can provide insight to the underlying mechanisms of language impairments observed in autism (Roberts et al., 2008). Finally, MEG systems are widely used in clinical practice more and more each day, particularly for refractory epilepsy patients. In the US, MEG is approved for clinical use by the Food and Drug Administration (FDA). Current billing codes allow for clinical use in the recording and analysis of spontaneous brain magnetic activity (for example localizing brain regions from which epileptic activity originates for optimization of epilepsy surgery) and evoked magnetic fields (for example identifying regions essential for normal brain function in pre-surgical patients to improve surgical planning) (Braeutigam, 2013; Papadelis et al., 2013).

3.1.3. Limitations

3.1.3.1. Technical.: Given the importance of direct non-invasive observation methods to extend our understanding of functional brain development inferred from histology and electron microscopy, it is important that the significant technical challenges to fetal, neonatal and infant EEG and MEG measurements are overcome. Fetal bioelectric signals show a strong attenuation as they pass through and reach the maternal abdomen surface where the surface EEG electrodes are placed. This attenuation is caused by the vernix caseosa, which is a greasy deposit that forms on the skin of the fetus about 25 GW and obscures the conduction of the electric signals to the maternal abdomen surface (Lengle et al., 2001). High-quality neuroelectric signals could be obtained with the direct attachment of the EEG

electrodes to the fetal scalp; however, this is invasive and could put the pregnancy at risk by exposing the fetus to possible bacterial infection (Eswaran et al., 2000). Therefore, fetal EEG is not an ideal method for assessing early neuronal activity. Postnatal EEG also has its challenges and shortcomings such as the application of source localization algorithms because of technical (e.g. difficulties with the digitization of EEG cap electrodes in neonates in Neonatal Intensive Care Unit (NICU) incubators) and anatomical (e.g. the inhomogeneity of the newborn skull and its limiting effects on source models) constraints (Roche-Labarbe et al., 2008). Furthermore, the electrical currents measured by EEG are affected by the skull, the intervening tissue layers between the scalp and the brain, the fontanels and sutures (Lew et al., 2013; Okada et al., 2006, 2016), or the several layers of maternal abdominal muscle and tissue between the sensors and the fetal brain (Lowery et al., 2009). As EEG measures the difference in electrical potential between two electrodes, one of the most common strategies is to place the second electrode (i.e. reference electrode) over an electrically quiet location on the scalp. However, finding a completely electrically quiet location and choosing the best reference has its challenges and can affect the measured signals (Lei and Liao, 2017).). Furthermore, the number of EEG sensors from which the data can be accurately analyzed is limited in infant studies since high-density EEG faces the problem of salt bridges between the electrodes when the head sizes are small (Papadelis et al., 2014).

Fetal and infant MEG systems are expensive, rare and not in commercial production. Fetal MEG is not a clinically billable study and only recently have infant sized MEG systems gained Food and Drug Administration (FDA) approval. In fetal MEG, not only the fetal neuronal signals but also magnetic signals generated by other sources such as maternal and fetal muscles and organs, and maternal and fetal movement, are recorded (Anderson and Thomason, 2013; Preissl et al., 2005). Accurate detection of the fetal neural signal among interfering signals is challenging (Lowery et al., 2006), and has led to the development of algorithms to mitigate this problem (Schneider et al., 2001; Vrba et al., 2004a, 2004b; Zappasodi et al., 2001). Cardiac activity can also cause artifacts in postnatal MEG due to the proximity of the infant heart to the sensors in the MEG helmet (Huotilainen, 2006). Proper localization of the fetal head position throughout the fetal MEG recording and the movement of the fetal head during measurements are other challenges (Anderson and Thomason, 2013; Eswaran et al., 2000). Among suggestions to overcome this problem is simultaneous 3D ultrasound during the fetal MEG recording (Micheli et al., 2010). Similarly, neonatal/infant MEG studies suffer from motion artifacts requiring the use of noise reduction algorithms (Cheour et al., 2004). Therefore, to ensure accurate source localization of activity, the infant’s head position needs to be continuously recorded (Cheour et al., 2004). Differences in the study designs and measurement strategies can lead to variable results (Dunn et al., 2015) as can differences in arousal states during the recordings (Huotilainen, 2006).

3.1.3.2. Biological.: Developmental confounders of fetal and postnatal MEG studies include the unknown source of brain MEG signals in the immature brain due to the shift in the formation of the synapses, their activity from deep superficial layers of the cortex, and the changing role of the GABA. Also, MEG detects signals primarily from the sulcal cortex, perpendicular to the scalp, and is relatively blind to the apical cortex, parallel to the scalp. As cortical folding occurs, morphological variations of cellular elements occur, which might

lead to differences in neuronal functioning between gyri and sulci, as proposed by (Hilgetag and Barbas, 2005). However, the impact of emerging gyrification on MEG signals is unknown.

As a conclusion, EEG and MEG are complementary techniques, which are both important for studying electrophysiological brain development and function in typical and atypical fetal and neonatal populations. While spontaneous brain activity can be measured as early as 24 GW, the first evoked brain responses do not occur until 26 GW. It is important to take into account the spatio-temporal maturation of synapses while interpreting EEG and MEG findings. With the advancements in software and hardware for these imaging modalities, their limitations are being overcome.

3.2. Vasculogenesis and the development of neurovascular coupling

3.2.1. Biological principles—In the human embryo, the rising of blood islands (seen mainly on yolk sac chorion and composed of splanchnopleuric mesodermal cells) marks the beginning of the process called vasculogenesis. The first primordial blood islands are seen in the mesoderm of yolk sac around 16 days after conception (Luckett, 1978). Some of these blood islands migrate to the head of the embryo in order to produce cranial vessels, initiating the process of vasculogenesis. The vasculogenesis of major cranial vessels (branches of internal carotid and vertebral arteries) occurs during the first 45 days after conception (Padget, 1948). Vasculogenesis is followed by angiogenesis, a process of proliferation of endothelial cells, migration, and sprouting of new vessels. This process begins with formation of pial anastomotic capillary plexus. Although invisible to the eye, it is recognized on images obtained by conventional optical microscopy in 6–7 GW old embryos (Marin-Padilla, 2012), when the cortical plate remains avascular and oxygen needs are met by diffusion. Around the 8th GW, intracerebral vascularization of human brain starts with the development of perforating cortical vessels. The growth and expansion of the cerebral cortex is accompanied by the expansion of the pial capillary anastomotic plexus and by a continued incorporation of capillaries from arachnoidal vessels or by local angiogenesis (Marin-Padilla, 2012). The precise spatio-temporal gene expression as well as the circulatory dynamics will determine which capillary vessels will become arterial, venous or regress (Kuban and Gilles, 1985; Udan et al., 2013). In addition, according to Marin-Padilla, the distance between perforating vessels remains essentially unchanged throughout the cortical surface (400–600 μm (μm)) regardless of age (Fig. 6 (Marín-Padilla and Knopman, 2011)), which has been confirmed in primate studies (Risser et al., 2009). In contrast, morphometric properties of the developing brain change tremendously over time. For example, from 15 to 42 GW the volume of the future cortex (cortical plate) increases 40 times (from 2000 to 80,000 mm^3) (Vasung et al., 2016). At the same time the surface area of the future cortex increases 50 times (from 1000 to 50,000 mm^2) (Vasung et al., 2016). Assuming that distance between perforating large-diameter blood vessels in cerebral cortex is a constant due to the limited draining system, an increase in cortical surface area from approximately 7000 mm^2 to approximately 16,350 mm^2 would relate to the increased number of perforating blood vessels from 63,000 to 147,000 as suggested by (Marin-Padilla, 2012) (Fig. 6).

In order to properly infer neuronal activity from vascular signals, it is important to understand not only vasculogenesis but also the emergence of neurovascular coupling. Neurovascular coupling is a regulatory signal chain, which provides for the metabolic needs of neuronal activity by focally increasing cerebral blood flow in response to local neuronal activation. Neurovascular coupling is just one facet of cerebrovascular reactivity, a series of overlapping regulatory pathways which enable the brain to assert control of its own blood flow for homeostasis and physiologic function (For review see (Willie et al., 2014)). Although the upstream signaling pathways of cerebrovascular reactivity are varied and complex, control of blood flow for all the pathways is affected similarly through myogenic-driven changes in the diameters of blood vessels. Since neurovascular coupling is the origin of the signals in functional MRI and NIRS neuroimaging (for review see (Buxton, 2010)), using these techniques to infer neuronal activity requires the coupling pathways to be sufficiently developed for neuronal signals to be transduced into changes in blood flow.

The cellular effectors of myogenic vascular reactivity must be motile cells, which are classically thought to be the vascular smooth muscle cell layers extending from pial arteries to precapillary parenchymal arterioles (see monograph by (Cipolla, 2010)). In the developing brain, these smooth muscle cell layers first form at 20–22 GW around the vessels, which will become the pial arteries (Kuban and Gilles, 1985; Nelson et al., 1991). Muscularization of the rest of the cerebral arterial tree is thought to proceed from these surface arteries into deeper parenchymal vessels, with some reporting completion of muscularization after term birth (Kuban and Gilles, 1985). Infants born preterm have limited control over the cerebral vasculature, which has long been recognized as contributing to the risk of cerebral hemorrhage (For reviews see (Brew et al., 2014; du Plessis, 2008)).*In vivo* evidence of postnatal development of cerebrovascular muscularization in preterm infants has recently been found from transcranial Doppler ultrasound (TCD) (Rhee et al., 2014). Although the effectors of cerebrovascular reactivity continue to develop after birth, functional NIRS (fNIRS) finds competent evoked hemodynamic responses to stimuli, albeit with immature forms, in even the youngest preterm infants (see fNIRS section). The difference between the early emergence of neurovascular responses and the observed rate of maturation of the cerebral muscularis leaves open the possibility that other effectors may contribute to functional vascular reactivity in the fetal and young infant brain.

In addition to vascular smooth muscle cells, pericytes are also contractile cells commonly associated with microvessels (For reviews see (Armulik et al., 2011; Attwell et al., 2016)). Pericytes are distinguished by their direct contact with endothelial cells, with which they share a common basement membrane. They are highly abundant in the central nervous system and are often found at pre- and post-capillary junctions. In animals, they are derived from the neural crest and are required to develop and maintain the blood-brain barrier during embryogenesis (Armulik et al., 2010; Daneman et al., 2010). Recently, pericytes have been implicated in capillary level control of cerebral blood flow (Hall et al., 2014; Mishra et al., 2016; Peppiatt et al., 2006), though this remains controversial (Hill et al., 2015). In humans, pericytes appear in cerebral tissue with the development of the vasculature, migrating along with endothelial sprouts (Allsopp and Gamble, 1979a; b; Hauw et al., 1975). Pericytes cover the vasculature of all cerebral regions but the density is significantly less in the germinal matrix compared to cortex or white matter (Braun et al., 2007). The role of pericytes in the

control of blood flow remains an open research question for the mature cerebral circulation and even more so for the developing one. Exploiting the developmental differences in effector populations may be a new potential avenue for investigating pericyte function.

The upstream neurovascular coupling signaling pathway, progressing through multiple cellular and molecular mediators, starting with neurons, involving astrocytes, and ending with vascular smooth muscle cells and possibly pericytes, is complex and not fully understood. Each step in this chain has potential for modification during development (See reviews by (Harris et al., 2011; Kozberg et al., 2016). For example, endothelial prostaglandins in neonates may serve similar roles in signaling cerebral vascular smooth muscle cells as nitric oxide does in more mature brains (Brian, 1998; Edwards et al., 1990). While the details of the neurovascular coupling pathways are still under investigation, significant differences between the developed and developing brain are already recognized. These differences should be considered when designing a fetal or neonatal neuroimaging study. Conversely, neuroimaging techniques will continue to serve an essential role for further discovery of the maturation process of neurovascular coupling.

3.2.2. MRI

3.2.2.1. Ex Vivo MRI.: To our knowledge, there are no human fetal brain studies of vascular development with *ex vivo* MRI. However, animal studies do exist. For example, (Berrios-Otero et al., 2009), performed an *ex vivo* study with mouse embryos to visualize cerebrovascular system development. In their study, a gadolinium-based contrast perfusion method was used and 3D micro-MRI data was acquired from multiple embryos between 10 and 17 days of gestation. However, due to the evolutionary differences between human and rodent brain development, it remains unknown which aspects of the intracerebral vascular development can be translated from rodents to humans.

3.2.2.2. In Vivo MRI.: Although structural *in vivo* MRI studies of structural vascular development in premature infants exist (Malamateniou et al., 2006), there is significantly more literature on evoked and resting-state fMRI (rs-fMRI) neuroimaging studies (an indirect indicator of neurovascular development). These studies are mostly focused on postnatal infant (i.e. preterm and term neonates as well as young infants) and less on fetal populations. This is partly due to the higher signal-to-noise ratio provided by the increased proximity of phased array coils to the brain, the ability to constrain motion, and more mature motion correction techniques available for postnatal neuroimaging.

3.2.2.2.1. Resting state functional connectivity MRI.: Resting-state functional connectivity MRI (rs-fcMRI) is a technique that relies on finding the statistical dependence (e.g. correlation) of low-frequency (>0.1 Hz) spontaneous fluctuations of fMRI signals between different brain regions, which in turn, define resting-state functional networks. The fMRI signal depends on relative changes in volume of oxyhemoglobin compared to deoxyhemoglobin, which is in turn dependent on cerebral blood volume, blood flow and oxygen consumption. Thus, when there is intact neurovascular coupling, fMRI reflects local neuronal function. In the adult brain, it has been shown that there is a significant correspondence between a wide variety of spatial patterns obtained from task-evoked and rs-

fcMRI maps (Smith et al., 2009). Because rs-fcMRI allows the simultaneous mapping of multiple networks in a single resting-state acquisition (<10min) without the use of any specific stimulation paradigm, it has been increasingly used to study subjects who cannot cooperate such as infants and young children (Doria et al., 2010; Fransson et al., 2007; Gao et al., 2015; Smyser et al., 2010). Since its adoption, rs-fcMRI techniques have been used to characterize not only the functional organization of cortical areas in the developing brain but also of subcortical structures such as the thalamus (Alcauter et al., 2014; Fair et al., 2010; Toulmin et al., 2015) which plays a critical role in early brain development (Koenderink et al., 1994; Kostovic and Jovanov-Milosevic, 2006; Kostovic and Judas, 2010; Krsnik et al., 2017).

Recently, technical advances in MRI hardware and motion correction techniques have led to the exploration of functional brain networks in the fetal period. In a pioneering work, Thomason and colleagues showed that it is feasible to map rs-fcMRI networks in healthy fetuses between 24 and 39 GW ((Thomason et al., 2013), Fig. 7). In line with previous reports in preterm infants, they showed regional variations in the functional connectivity patterns and noted that the functional connectivity strength increased with the gestational age of the fetuses. Subsequent studies provided more evidence of the heterogeneous development of functional connections in the fetal brain, following a primary to higher-order maturational sequence (Jakab et al., 2014; Thomason et al., 2013) with the earliest fetal brain regional activity detected at 22 GW (Jakab et al., 2014; Thomason et al., 2017).

Studies performed in the early postnatal period have shown significant differences between rs-fcMRI networks obtained in term-born and premature infants (Doria et al., 2010; Smyser et al., 2010). Specifically, symmetric patterns of spontaneous brain activity mostly associated to primary sensory networks (e.g. motor, visual and auditory networks) were consistently reported in term-born infants. In contrast, unilateral patterns or weaker versions of these networks were observed in prematurely born infants. In parallel, longitudinal studies in older infants and children have shown that as maturation progresses, higher-order association areas such as dorsal attention network and default mode network start to exhibit more mature topologies that resemble those typically found in adults and adolescents (Gao et al., 2015). These observations have motivated a wide range of rs-fcMRI investigations trying to track normal and abnormal developmental trajectories (Dosenbach et al., 2010) and to demonstrate the relationship between the integrity of rs-fcMRI networks and long-term neurodevelopmental outcomes in high-risk infants (Ball et al., 2015). In addition, recent work correlating rs-fcMRI and structural (axonal) connectivity with diffusion imaging shows promise for the combined approach to improve the understanding of early brain development (Ferradal et al., 2018).

3.2.2.2.2. Functional MRI.: Due to the challenges of providing consistent stimuli to the fetus, the majority of the research in fMRI with evoked responses comes from studying premature infants. However, prematurity affects brain development on every hierarchical level (Kwon et al., 2014; Ment et al., 2009), which has been linked to premature exposure to the environmental stimuli (e.g. (Benders et al., 2015)) as seen in experimental studies on primates (Bourgeois et al., 1989). Thus, it remains challenging to define the normal spatio-

temporal timeline of sensory system development. For this reason, we are still unaware of adverse (or beneficial) effects that these systems, if stimulated *in utero*, can have on fetus.

Research on early perceptual olfactory competence in human new-borns has so far focused on behavioral responses (i.e. changes in respiratory rate, sucking, facial expressions, body movements, directional orientation) upon exposure to different natural and artificial odors (Schaal et al., 2004). Recently (Adam-Darque et al., 2017), showed that newborns show adult-like fMRI patterns of cortical activation in response to olfactory and trigeminal odorants. Thus, potential effect (beneficial or adverse) of maternal nutrients on brain development during pregnancy could relate to certain long-term behavioral outcomes (e.g. maternal nutrition and amniotic scent leads to early development of preference for certain "healthy" food later in life (Mennella et al., 2001)). After the development of olfactory and gustatory systems, other sensory systems develop (visual, auditory, and proprioceptive). However, testing the functional specialization of cortical regions with fMRI in premature infants remains a challenging task. Several studies have reported lack of blood oxygenation level dependent (BOLD) signal in premature infants after visual stimuli (flashing strobe) around approximately 30 GW (Lee et al., 2012), predominantly left temporal and supramarginal area activation in a block-design language paradigm (listening to a fairytale) around 34 GW, followed by a bilateral temporal and fronto-opercular activation at term equivalent age (Baldoli et al., 2015), and positive BOLD activation in the contralateral primary somatosensory cortex after somatosensory stimulus carried out by a programmable hand interface at approximately 33 GW (Arichi et al., 2010). Although there is some evidence indicating maturation of these systems prenatally, to which extent sounds of different frequencies (e.g. music or maternal voice (Webb et al., 2015)) or simple exercise (somatosensory stimuli) during pregnancy influences fetal brain development remains unknown.

3.2.3. Near infrared spectroscopy—In order to probe functional responses at the bedside or in more natural environments, portable methods such as Near Infrared Spectroscopy (NIRS) have been developed. NIRS technologies use probes on the surface of the scalp that emit (source) and receive (detector) NIR light, which passes through the skull to probe the physiological properties of the brain. NIRS with the near-infrared spectral window spanning wavelengths from 650 nm (nm) to 950 nm, is a form of optical absorbance spectroscopy in tissues (Ferrari and Quaresima, 2012). Typically, sources and detectors are separated by 2–3 cm and 4 cm on infants and adults, leading to a sensitivity that extends about 1–1.5 cm and 2 cm respectively deep inside the tissue over a volume of several cm^3 (Fig. 8A).

NIRS allows quantitative measures of cortical hemoglobin oxygenation, namely oxyhemoglobin (HbO) and deoxyhemoglobin (HbR), and is well suited to the neonate given the thin skull and scalp but have yet to be used in the fetus given the long distances light needs to travel in the abdomen. Recent developments in diffuse optical spectroscopy, measuring infant brain physiology non-invasively at the patient's bedside (Fig. 8B) have made possible the use of these methods in routine clinical assessment without transporting unstable infants from the NICU to radiology departments. In addition, fNIRS techniques are also compatible with other electrical or magnetic monitoring systems and therapeutic

devices (i.e., pacemaker, hearing aids, cochlear implants, etc.). Moreover, fNIRS measurements can be easily integrated with fMRI, PET, MEG, amplitude integrated or conventional EEG to provide complementary information for cross validation (Huppert et al., 2006; Strangman et al., 2002) or to contribute to understanding neurovascular couplings. fNIRS is also portable and works well in the field, enabling neuroimaging studies of or to contribute to understanding neurovascular couplings. For example, the Brain Imaging for Global HealTh (BRIGHT) project based on Gambia and London, UK studies longitudinal brain development in infants in both settings to gain an insight into the effects of malnutrition, social or environmental difficulties and increased risk of disease, as well as other issues related to living in a low-resource context on infant development (Begus et al., 2016; Lloyd-Fox et al., 2017).

Functional NIRS (fNIRS) studies cortical brain function by indirect observation of neural activity through measurements of spontaneous or evoked changes in hemoglobin concentration in the region of activation. Unlike fMRI, which relies on changes in deoxyhemoglobin for BOLD contrast, fNIRS measures oxyhemoglobin increases with increased CBF and CBV (elicited by neuronal activation) to support the increased metabolic demand of the activated neurons (Fox et al., 1988; Licht et al., 1996). Given the similarities with the BOLD contrast, resting-state functional connectivity methods have been adapted to study spontaneous brain activity in the developing brain using fNIRS systems. Because of technical and logistical challenges involved with the design and implementation of large arrays, early reports were only limited to producing functional connectivity maps of single cortical region such as the visual cortex in term and prematurely born infants (White et al., 2012). Alternatively, other research groups have prioritized head coverage over imaging capability, using the time series of single NIRS channels (i.e., single source-detector measurements) rather than voxel data (Homae et al., 2010). More recently, technological advances have allowed simultaneous mapping of multiple functional resting-state networks in healthy neonates (Ferradal et al., 2016).

The fNIRS measurements show patterns of typical brain development (e.g., stronger connectivity in visual networks in comparison with higher-cognitive networks such as middle temporal visual area) and demonstrate strong spatial agreement with the patterns obtained from fMRI studies.

While resting state imaging methods have advantages in infants that can generally perform few tasks, task-evoked imaging studies are needed for validation and interpretation of resting-state analyses. fNIRS has significant advantages over other functional neuroimaging techniques (e.g., fMRI, positron-emission tomography (PET)) for studying brain function in neonates and infants. fNIRS allows the participant to receive stimuli, either auditory or visual in a more natural, non-restricted environment without any interference from the environmental noise (e.g. noise from the MRI scan), and with some degree of tolerance for movements. In fact, the majority of the fNIRS studies has been contributing to our understanding of language (Rossi et al., 2012), as well as perceptual and cognitive development (Bendall et al., 2016) from birth to childhood (Gervain et al., 2008). fNIRS is also suitable to study very young participants (premature infants) for whom fMRI cannot be easily adapted. For example, early development of certain linguistic skills can be identified

in prematurely born infants, approximately around 28 GW (Mahmoud- zadeh et al., 2013). In these infants, perception of change in human voice (male vs. female) or a change of phoneme (ba vs. ga) can be identified by distinguished hemodynamic responses (Mahmoudzadeh et al., 2013). The development of lateralization response for native language processing is also present at birth (Gervain et al., 2008; Peña et al., 2003). A few fNIRS studies have also investigated activation of sensory-motor areas in premature infants (Roche-Labarbe et al., 2014) and reported a more “premature” hemodynamic response function (HRF) with longer latency times and smaller amplitude in signal changes compared to the adult response, consistent with findings found in fMRI studies (Arichi etal., 2012).

3.2.4. Limitations

3.2.4.1. Technical.: Barium sulfate perfusion and X-rays (Plouraboué et al., 2004) were used to examine intra-cortical microvasculature in the *ex vivo* newborn and adult marmosets (Risser et al., 2009). However, almost 50% of specimens were discarded due to the unsatisfactory contrast agent injection. Thus, even if new advances in imaging might provide new vistas to explore intra-cerebral vasculature, due to the limited number of valuable *ex vivo* fetal specimens, novel and efficient approaches for *ex vivo* fetal tissue perfusion need to be developed. In addition, although animal models can provide basic understanding of certain principles of neurovascular development, there are evolutionary differences and species-specific patterns of intra-cerebral macrovascular and microvascular networks that must be taken into consideration (e.g. (Abbie, 1934)).

There are also many remaining challenges in the translation of fMRI and rs-fcMRI techniques to fetuses and infants. Due to unpredictable fetal motion and difficulty in achieving controlled environments for conventional fMRI paradigms, it remains nearly impossible to accurately test sensory functions of a fetus in-utero using fMRI. Physiological noise, arising from head motion, heart and respiration signals, is probably one of the biggest sources of contamination in fMRI signals. In resting state functional connectivity studies, it has been shown that head motion introduces spurious correlations (Power et al., 2012). Unfortunately, these motion-related patterns overlap with the patterns of higher-order association areas making the uncoupling of motion versus biological effects a challenging problem. Many denoising strategies have been proposed to cope, either retrospectively or prospectively, with motion-based noise that can be applied rather effectively in the postnatal period (see (Caballero-Gaudes and Reynolds, 2017)) for an extensive review on denoising techniques for the fMRI signal). However, motion-related artifacts in fetal images pose bigger challenges as maternal respiration can introduce large-scale fetal motion that cannot be compensated with the conventional motion correction techniques normally used in postnatal populations. In addition to the challenge in the motion correction, through-plane motion results in spin history artifacts (Friston et al., 1996), which cannot easily be removed by post-processing methods. Moreover, as a consequence of fetal motion, spatial changes in coil sensitivity will present as signal variation in different locations of a fetal brain. Although coil sensitivity related signal variations in a stationary subject will not affect the results of image analysis, for the case of fetal MRI, the BOLD signal changes have to be discriminated from the different signal intensity changes caused by unpredictable fetal and maternal motion in time series. As a result, in the recent years, there has been an increasing

effort in developing specific acquisition paradigms and analysis strategies suitable for fetal rs-fMRI (Ferrazzi et al., 2014; Seshamani et al., 2014). Furthermore, temporal and spatial resolutions are frequently reduced in fetal imaging in comparison with postnatal acquisitions.

Voxel sizes in fetal fMRI and rs-fMRI studies have 2–4 mm thickness (Jakab et al., 2014; Thomason et al., 2017), with 8 mm smoothing kernel in some cases (Thomason et al., 2017) which results in resolutions at least two to four times greater than the cortical plate thickness during prenatal development (Vasung et al., 2016). Therefore, trying to localize functional networks and identify timing when spontaneous activity of fetal circuitry is replaced by activity that is sensory driven, using *in-utero* MRI, still remains elusive. The fMRI in premature infants, due to its superior spatial resolution, might provide better insight into spatio-temporal relationships of these reorganization processes, and differentiation of transient from permanent neuronal activity previously demonstrated by EEG (Dreyfus-Brisac, 1979; Milh et al., 2006; Vanhatalo et al., 2005) (Fig. 3). fMRI is also limited by low temporal resolution (down to 0.5–2 s) and therefore temporal characteristics of the brain function are more easily assessed with electrophysiological imaging methods, such as MEG (Anderson and Thomason, 2013). The combination of all these methodological factors make straightforward comparisons between fetal and postnatal data difficult and requires careful interpretation of the fetal fMRI results.

In addition to the general limitations of NIRS technologies (described later in 3.3.4.1), there are also some limitations for using NIRS in functional studies. fNIRS measures around 1.5–2 cm deep into the head, which is sufficient for measuring activation inside the cortex. Studies with cognitive stimuli that involve transient subplate zone or deep brain regions, such as basal ganglia and amygdala, cannot be fully investigated. Since most commercial fNIRS systems are CW based, they typically do not measure the differential path length factor (DPF) and therefore measure only relative change and not absolute concentrations of hemoglobin. Finally, good coupling between the NIRS sensors and the scalp is essential for high-quality fNIRS data. Although motion is a challenge, there are methods which reduce motion artifacts and are suitable for long-term measurements (Yücel et al., 2014).

3.2.4.2. Biological.: An important biological aspect not fully understood is the hemodynamic response to neuronal activity in the developing brain. In the adult brain, the overshoot of the oxyhemoglobin response is considered a surrogate of neuronal activity. This is based on the observation that increases in local neuronal activity during stimulation are followed by increases in local cerebral blood flow which in turn increase the NIRS HbO and BOLD fMRI signal. However, studies performed in young infants with fNIRS and fMRI present contradicting reports of positive (Arichi et al., 2012; Karen et al., 2008; Liao et al., 2012) and negative (Kusaka et al., 2004; Meek et al., 1998) hemodynamic responses during stimulation. Among the proposed mechanisms for these variations is that neurovascular coupling is still immature due to the developing neural and vascular networks at early postnatal ages. In effect, a recent study performed in mice using optical imaging shows that the hemodynamic response to somatosensory stimulation transitions from negative to positive as a function of developmental age (Kozberg et al., 2013). An inverted hemodynamic response was observed in P12-P13 rats (equivalent to human neonates) with

early signs of oxygen consumption followed by delayed, active constriction of pial arteries. The hemodynamic response transitions into a small adult-like positive response at an intermediate age group of P15-P18 rats. Finally, a classic adult hemodynamic response with an initial hyperemic (positive BOLD) phase that masks oxygen consumption and balances vasoconstriction is observed in P80 rats (equivalent to adult rats).

In a follow up study from the same group, they show that neural responses progress from focal unilateral to bilateral responses as interhemispheric functional connectivity becomes established (Kozberg et al., 2016). Although the translation from animal models to humans is not straightforward, these results have important implications in the interpretation of functional imaging studies in the fetal and postnatal stages as it reinforces that NIRS and fMRI responses are dependent on neurovascular development. This is particularly important when applying fMRI to the fetus, where differences in cortical surface growth reflect spatio-temporal differences in neurogenesis and neuronal differentiation (Vasung et al., 2016). These regional differences in cortical surface growth are accompanied by increased local angiogenesis needed to preserve the relatively constant distance between perforating blood vessels. The nature of the vascular response in this rapidly developing fetal stage is unclear and it is unclear if subplate or transient neural activity result in a vascular response.

In addition, even though the structural milestones (axonal connectivity) for functional sensory circuitry have been established around 26 GW (establishment of thalamo-cortical structural connectivity (Krsnik et al., 2017)), during the last two months of gestation the frontal cortex still displays small pyramidal neurons of layer III, layer IV that is still densely granular (especially in premotor and motor areas), persistence of the subplate zone (Kostovic et al., 2014), and immature cortico-cortical structural connectivity (Vasung et al., 2017). Thus, how these sensory stimuli are processed in immature fetal brain, and to which extent they are/will be important for higher-order cognitive function and consciousness later in life remains to be determined.

Finally, the conscious state of the fetus or neonate is likely to affect the functional activity (Mitra et al., 2017). Accurate determination of fetal conscious state remains elusive. Neonatal monitoring of sleep state requires EEG monitoring. However, studying awake neonates remains a challenge with current technology.

3.3. Metabolic demands

Certain angiogenic and vessel-derived factors, “angioneurins” (Segura et al., 2009; Zacchigna et al., 2008), direct both vascular and neuronal development. Prenatal synaptogenesis, formation of new synapses, occurs at a rate of approximately 42.3 million synapses per minute (Silbereis et al., 2016). Given that the rate of synapse production in the fetal primate brain is most likely genetically determined (Bourgeois et al., 1989), and given that approximately two thirds of the brain’s energy budget is spent on action potential of neurons (Du et al., 2008), the metabolic expenditure of the brain during development is most likely dominated by the maintenance of active synapses. Other cellular processes previously discussed including, neuronal migration, cellular differentiation, and myelination also demand energy at certain periods of development, but the proportions are unclear. In addition, it is also unclear how the energy budget of the developing brain redistributes in

response to disruptions in energy supply and alterations in demand. Therefore, in this section we focus on the metabolic demand of the brain at different stages and technology developed to monitor cerebral perfusion and metabolism. In the adult brain, the majority of energy is devoted to the synaptic processes that maintain the balance of excitatory and inhibitory activity (Raichle and Gusnard, 2002), and in terms of the energy budget of neuronal signaling, 50% is used on postsynaptic glutamate receptors and 21% on action potentials, with the remainder being devoted to neurotransmitter recycling, presynaptic neurotransmitter release and other related cellular activities (Howarth et al., 2012).

3.3.1. Biological principles—The adult human brain is approximately 2% of the entire body mass. Despite its small fraction of total body mass, brain metabolism accounts for almost 25% of the resting metabolic rate (Passmore and Durnin, 1955). The resting state energy expenditure is greater 50% in the mid first decade of life (Kennedy and Sokoloff, 1957; Kuzawa et al., 2014). In comparison, the neonatal brain is approximately 14% of total body mass and accounts for a staggering 55–87% of resting metabolic rate (Holliday, 1986; Kuzawa et al., 2014). Unfortunately, the data on brain energy expenditure in the human fetus remains limited. Little is known about fetal brain arteriogenesis (increase in the diameter of existing blood vessels), formation of arterioles (vessels that contribute the most to total peripheral resistance), and capillarogenesis (formation of vessels that have the highest total cross-sectional area and the lowest flow velocity). In addition, even less is known about immature auto regulatory properties of these newly formed cerebral vessels (Tweed et al., 1983). Given not only the extraordinary complexity of neurogenesis, but also its spatio-temporal gradient patterns (Bakken et al., 2016; Pletikos et al., 2014), it is unclear how the metabolic demands of the growing human fetal brain are met during its prenatal and early postnatal periods. In fact, it is unclear if cortical angiogenesis parallel the spatio-temporal neurogenic gradients and if neurogenesis leads vasculogenesis or vice versa (Walchli et al., 2015).

3.3.2. MRI

3.3.2.1. Ex Vivo MRI.: Crucial to using MRI for *in vivo* examinations of cerebral oxygen metabolism, *ex vivo* imaging is used to characterize the magnetic properties of fetal and adult blood specimens. MRI methods to measure blood oxygen saturation *in vivo* depend on the relationships between the different magnetic properties of deoxygenated and oxygenated blood. The magnetic susceptibility of blood changes between oxygenated and deoxygenated states reflecting the underlying magnetic properties of hemoglobin. *Ex vivo* imaging has established relationships between blood oxygen saturation and magnetic susceptibility (Jain et al., 2012; Weisskoff and Kiihne, 1992) or of the transverse relaxation rate (T_2) of blood (Lu et al., 2012; Portnoy et al., 2018; Zhao et al., 2007). These relationships are subtly different for fetal and adult blood and investigations into the root causes of these differences continue, whether due to the magnetic properties of fetal versus adult hemoglobin or fetal versus adult erythrocyte geometry.

3.3.2.2. In Vivo MRI.: MRI-based techniques for measuring cerebral perfusion during development include arterial spin labeling (ASL) and phase contrast MRI (PC-MRI). ASL gives information about regional perfusion in absolute units. ASL studies have found that

whole brain CBF increases rapidly in the first months after birth (e.g. from 7 ml/100 g/ min at 31 GW, to 29 ml/100 g/min at 52 GW (De Vis et al., 2013)) and that the distribution of regional perfusion changes during this time (Miranda et al., 2006; Ouyang et al., 2017). Studies of neonates with hypoxic ischemic encephalopathy showed that adverse outcomes were predicted by increased perfusion in the basal-ganglia and thalami (De Vis et al., 2014b; Massaro et al., 2013). Various groups have explored optimizations for ASL methods to accurately quantify CBF in neonates by measuring blood hematocrit and T_1, and by exploring the optimal labeling approach (Boudes et al., 2014; De Vis et al., 2014a). However, ASL is extremely sensitive to motion since the relatively small perfusion signal is isolated by subtracting a control image and one where blood has been magnetically labeled. Any motion occurring between the two acquisitions corrupts perfusion quantification.

PC-MRI is a robust alternative for measuring whole brain CBF, as it quantifies flow through large blood vessels supplying the brain. Studies using PC-MRI have also shown a dramatic increase in CBF in the first weeks of life (Liu et al., 2014a; Varela et al., 2012), as well as abnormal CBF related to congenital heart disease (Jain et al., 2014; Lim et al., 2015). PC-MRI has also been used to assess fetal hemodynamics (Prsa et al., 2014), identifying brain sparing physiology resulting from IUGR (Zhu et al., 2016) and normal cerebral blood flow in fetuses with congenital heart disease (Sun et al., 2015).

Whole brain cerebral metabolic rate of oxygen consumption ($CMRO_2$) can be estimated via Fick's principle by a combination of CBF and venous and arterial oxygen saturation. Several studies have successfully measured neonatal $CMRO_2$ in health and disease. When arterial oxygen saturation is measured using pulse oximetry, the crucial estimation of venous blood oxygen saturation has been performed using T_2 quantification (De Vis et al., 2014a; Liu et al., 2014b) and MR Susceptometry (Jain et al., 2014). Two of these studies found evidence for rapidly increasing $CMRO_2$ in the first weeks of postnatal life and the other showed strong correlation between MRI and NIRS based measurement of $CMRO_2$ in neonates with congenital heart disease (Jain et al., 2014).

Fetal $CMRO_2$ is more difficult to measure because of small cerebral vessel caliber, arterial blood that is not fully saturated and the difficulty of accessing physiological signals for gating MRI acquisitions. However, using a combination of PC-MRI and T_2 quantification one group has demonstrated that lower $CMRO_2$ in fetuses with congenital heart disease correlates with smaller brain volumes (Sun et al., 2015). These measurements of $CMRO_2$ are based on blood flows in the superior vena cava assuming that it mainly drains blood from the fetal brain. In order to track brain oxygen metabolism throughout development, fetal and neonatal measurements must be made with similar approaches and similar underlying assumptions, however, significant technical development must occur to make this possible.

3.3.3. Near infrared spectroscopy—Unlike other methods, NIRS can be performed at bedside and has sufficient temporal resolution to resolve dynamic physiological processes. Although NIRS provides non-invasive and continuous measures of oxygen concentrations in the tissue (SO_2) and estimates cerebral blood volume (CBV), neither SO_2 nor CBV are good surrogates of cerebral blood flow (CBF). The use of CBV, as a surrogate of CBF is based on the Grubb relationship (Grubb et al., 1974), which fails during fast dynamic changes (Jones

et al., 2002), with disease (Dehaes et al., 2014, 2015) or altered physiology (Roche-Labarbe et al., 2010). Also, SO_2 depends on both perfusion and consumption, therefore measurements of SO_2 alone are insufficient to make clear changes caused by changes in oxygen supply versus changes in cerebral metabolic demand (Boas and France-schini, 2011). Diffuse Correlation Spectroscopy (DCS) is an optical technology to measure cerebral blood flow non-invasively. DCS measurements are performed similarl to NIRS, but are based on entirely different physical principles and measure different physical quantities, making them complementary modalities. DCS measures diffuse dynamic light scattering from moving red blood cells in the tissue. In DCS, fluctuations in light speckle pattern are modeled with solutions to the correlation diffusion equation to determine an index of blood flow (BFi) in units of cm^2/s (Boas and Yodh, 1997; Durduran and Yodh, 2014). Although the units of BFi are not the conventional units of ml/min/100 g tissue for perfusion, BFi is reliably proportional to absolute flow, as demonstrated in simulations and validation studies against “gold standard” measurements (Buckley et al., 2012; Carp et al., 2010; Diop et al., 2011; Zhou et al., 2009).

Similar to MRI measures, DCS is combined with quantitative NIRS to estimate $CMRO_2$ through Fick’s principle. $CMRO_2$ has better sensitivity than SO_2 alone in detecting normal brain development in infants (Lin et al., 2013a; Franceschini et al., 2007; Roche-Labarbe et al., 2012; Roche-Labarbe et al., 2010) (Fig. 8C–F). In premature infants, tempora-l–parietal differences in hemodynamic parameters with stable $CMRO_2$ may reflect differences in microvasculature (Fig. 6), whereas increases in average brain $CMRO_2$ appear to be more tightly coupled to gestational age than chronological age, which may reflect the genetic program for synaptogenesis (Roche-Labarbe et al., 2012).

In addition to studying the hemodynamic changes with normal development, this technique has also been employed in term infants with hypoxic ischemic encephalopathy (HIE). CBF and CMRO2 are reported to be sensitive in response to neuroprotective hypothermia therapy whereas SO_2 is insensitive to metabolic suppression (Buckley et al., 2013; Dehaes et al., 2014, 2015). In addition, there is emerging interest for new biomarkers across different neurologic diseases in children (Buckley et al., 2013; Dehaes et al., 2015) and a wide range of conditions specifically for pediatric neurocritical care including cardiopulmonary arrest, septic shock, extracorporeal membrane oxygenation and cardiac surgery (Ferradal et al., 2017).

3.3.4. Limitations

3.3.4.1. Technical.: Robust methods for MRI-based measurements of regional oxygen metabolism from mid-gestation through adulthood are still needed. Techniques for more accurate quantitative measures of regional cerebral oxygenation are being developed (Alderliesten et al., 2013; Bolar et al., 2011) and the effects of motion on oxygenation measures is being explored (Stout et al., 2017), but unpredictable fetal motion remains a significant challenge. Future work also needs to address the inaccuracies in CBF measurements that arise from making measurements without synchronizing to the neonatal or fetal heart rate.

Transcranial NIRS and DCS methods have their own set of drawbacks. Though DCS measures absolute flow, its units are unconventional and lack physiological intuition. Determination of absolute flow requires independent measurements of the optical properties of the tissue, though these can be conveniently provided by time resolved NIRS. Comparison of NIRS and DCS values across subjects is valid for infants (Dehaes et al., 2014), but skull thickness variations in older children limits comparisons without independent radiological measurements of the skull geometry. NIRS and DCS are both subject to unwanted signals from blood flow in the scalp, though DCS generally has twice the sensitivity of NIRS to cortical signals (Selb et al., 2014). NIRS and DCS are also influenced by extracerebral pathological tissue, such as edema and subdural hematoma, when they occur in the region of measurement. On balance, DCS has the potential to equal or exceed the performance of other non-invasive methods like TCD while expanding them to perform continuous monitoring that is currently not possible.

3.3.4.2. Biological.: It is important to recognize the role of anatomy. Although PC-MRI CBF measurements based on different combinations of vessels supplying (basilar artery, internal carotid arteries, and vertebral arteries) and draining (superior sagittal sinus, straight sinus, jugular veins) the brain show strong correlations (Rodgers et al., 2013), the underlying assumptions about flow distributions in large vessels and between large vessels, infrequent variations and anomalies in cerebral vessels (e.g. persistent primitive vessels that regress during early gestation or vessels that persist to adult life but regress prematurely), and microvasculature must be considered when comparing absolute CBF measurements between studies. More detailed information about neonatal perfusion and $CMRO_2$ measurements can be found in (Proisy et al., 2016) and (Liu et al., 2014b).

In conclusion, it still remains unclear how biological processes such as brain metabolic demands, angiogenesis, synaptogenesis and synaptic pruning interact to influence results of functional studies performed with sophisticated neuroimaging tools. In addition, it is not clear how these biological processes, that are the underpinnings of functional connectivity, modulate structural connectivity in the developing human brain. The possibility of using functional tasks or stimulation to optimize connectivity in the developing brain is becoming an area of active research. To this end, we believe that multimodal brain imaging and further development of technology will be pivotal for proper assessment of fetal and neonatal brain functional and structural connectivity as well as their interactions.

4. Modulators of brain development

The brain does not develop in isolation. Its development is modulated by the environment. The placenta serves as the critical interface between the environment and the fetus, enabling the supply of gas and nutrients through vessels to the fetal brain. The peak of angiogenesis in the placenta occurs during the last two trimesters, which parallels the structural and functional reorganization of the fetal brain, and an increase in its metabolic demands.

BOLD MRI with maternal hyperoxia utilizes oxygen as a tracer to capture the dynamics of oxygen transport from the mother to the fetus. Glucose chemical exchange saturation transfer methods show potential to monitor glucose transport between the mother and the

fetus. Thus, proper placental vascular development, oxygen transport to the fetus, and glucose exchange can be monitored noninvasively with newly developed neuroimaging techniques.

The majority of studies of placental function have demonstrated altered brain development following placental injury. For the purposes of this review, we focus on the role of the placenta in brain development and discuss the emerging imaging methods that are rapidly evolving due to the Human Placenta Project (https://www.nichd.nih.gov/research/HPP/Pages/default.aspx).

4.1. Role of the placenta in brain development

4.1.1. Biological principles—It is important to acknowledge the role of the placenta in the process of fetal brain development. The placenta serves as a critical interface between the mother and the fetus, enabling the exchange of gas and nutrients (e.g. oxygen and glucose). The human placenta is composed of the chorionic plate on the fetal side and the basal plate on the maternal side. Fetal arteries and veins are connected to the chorionic plate through the umbilical cord and in the placenta, vessels branch into small structures called villi. Maternal spiral arteries enter the intervillous spaces with maternal blood perfusing these villi. Blood flow in fetal capillaries and the intervillous space enables exchange of nutrients and waste products between the mother and the fetus (Benirschke and Driscoll, 1967). In addition, the placenta synthesizes hormones (e.g. Human chorionic gonadotropin, estriol, progesterone) and neurotransmitters (serotonin (Bonnin et al., 2011)), transports hormones (e.g. androgens), immunoglobulines (maternal Immunoglobulin G (IgG)), other growth factors and nutrients from the mother to the fetus while removing waste from the fetus. Although it is tempting to conceptually separate mechanical and endocrine function of placenta, these two are actually tightly linked as human chorionic gonadotropin (hCG) has been shown to promote angiogenesis and vasculogenesis in the uterine vasculature (Berndt et al., 2009; Toth et al., 2001). Increase in angiogenesis and vasculogenesis ensures maximal blood supply to the placenta and the fetus (Berndt et al., 2009). Vasculogenesis of placenta starts around 21st day after conception, which is followed by branching angiogenesis (from 6^{th}-27 GW approximately) driven by high placental levels of vascular endothelial growth factor (VEGF). From 27th GW onwards the VEGF levels drop and angiogenesis switches from branching angiogenesis to nonbranching. This switch causes an increase in the fetoplacental impedance (for review see (Kaufmann et al., 2004)).

In addition to its role in vasculogenesis, hCG has been shown to promote an anti-macrophage inhibitory factor that modulates the immune response during pregnancy and prevents destruction of foreign fetal and placental tissue (Akoum et al., 2005). Thus, by providing essential immune and endocrine functions, normal functioning of placenta is crucial for maintenance of pregnancy and fetal well-being (Andescavage et al., 2015). In fact, through these interactions with the fetus, the placenta plays a central role in modulating gene expression and serves as a programming agent for adult diseases (Howerton et al., 2013; Thornburg et al., 2010).

Placental insufficiency causes fetal malnutrition, chronic fetal hypoxia, and an altered endocrine status which can affect fetal brain development and result in alterations of

neuronal connectivity and myelination leading to the long-term cognitive deficits (Malhotra et al., 2017; Rees et al., 2008; Tolsa et al., 2004). With significant placental insufficiency, fetal growth rate decreases due to chronic fetal hypoxia and malnutrition. In severe cases, fetal cardiac output is redistributed in order to protect the brain. However, this redistribution does not ensure normal brain growth (Malhotra et al., 2017). Several placental pathological findings such as high-grade chronic villitis and fetal thrombotic vasculopathy have been linked to brain injury in neonates (Ernst et al., 2016). As a result of these findings, Ernst (Ernst et al., 2016) proposed to use placental pathology to predict the risk for hypoxic-ischemic brain injury.

4.1.2. MRI

4.1.2.1. Ex Vivo MRI.: While the histopathological studies of placental vasculature help to understand angiogenesis of placental villi, quantitative description of the placental vasculature pattern and the placental perfusion across whole organ are also critical. There is a growing interest in *ex vivo* placental MRI studies. Earlier studies mainly focused on the visualization of the placental vasculature by using MR angiography (MRA) for manually perfused *ex vivo* placentas (Chen et al., 2017; Rasmussen et al., 2014). In (Rasmussen et al., 2014), the fetal placental blood flow was computed as the sum of voxels in the visible blood vessels, and a positive correlation between fetal placental blood vessel volume and fetal size at birth was reported. In a similar study (Chen et al., 2017), MRA was performed after an optimized contrast agent injection to the placenta and a method to visualize 3D vasculature models was presented. These early studies show the potential of visualization of the 3D placental vascular structure to direct placental sampling for histopathological studies. A more recent study by (Ha et al., 2017) provided an MRI compatible perfusion chamber design with an integrated seven channel coil array. His chamber setup provides an opportunity to perform high-resolution *ex vivo* imaging while maintaining realistic physiology of a placenta and enable the validation of *in vivo* findings related to vascular anatomy and placental function.

4.1.2.2. In Vivo MRI.: Due to the critical role of the placenta in brain development, better assessment of placental function during pregnancy is crucial. However, none of the current clinical detection methods for placental function (i.e. monitoring fetal growth and Doppler assessment of blood flow in the umbilical arteries) offers direct information about gas or nutrient transfer in the placenta, or about its microstructure. Given the shortfalls in clinical care, a number of techniques are in development in an attempt to improve diagnostic capabilities, and hence the fetal developmental outcomes.

Recent studies have validated the potential of MRI for the assessment of the placental morphology (Damodaram et al., 2010), alterations in its microstructure (Linduska et al., 2009) and functional change in the placenta in terms of blood oxygenation and the water perfusion during gestation (Aimot-Macron et al., 2013; Bonel et al., 2010; Brunelli et al., 2010; Derwig et al., 2013; Frias et al., 2015; Gowland et al., 1998; Huen et al., 2013, 2014; Javor et al., 2013; Luo et al., 2017a; Sivrioglu et al., 2013; Sorensen et al., 2009, 2013b; Taillieu et al., 2006).

The first perfusion study performed in healthy human placentas using non-selective/selective inversion recovery echo planar pulse sequence measured T1 relaxation time *in-vivo*. The authors reported the average value of the perfusion rate for a normal placenta (Gowland et al., 1998). One of the earlier MRI studies achieved promising results to demonstrate the disrupted placental perfusion compared to controls (Brunelli et al., 2010). However, the usage of gadolinium as a contrast agent in this study raised the concern related to the fetal exposure to gadolinium. It has been suggested that fetal exposure to gadolinium might be associated with a higher risk of adverse outcomes (Ray et al., 2016). For this reason, BOLD MRI with hyperoxia has been proposed as a promising alternative to gadolinium based approaches (Aimot-Macron et al., 2013; Huen et al., 2013; Huen et al., 2014; Luo et al., 2017a; Sorensen et al., 2013a; Sorensen et al., 2009; Wedegärtner et al., 2006). BOLD MRI with a maternal hyperoxia paradigm utilizes Oxygen (O_2) as a tracer, and aims to capture the dynamics of oxygen transport from the mother to the fetus in placenta. The principle of BOLD MRI depends on the magnetic state change of hemoglobin (Hb) when binding to O_2, which causes MRI signal increase. Since fetal Hb has a higher binding affinity to O_2 than maternal Hb, and fetal Hb in the arterial blood is much less saturated than maternal Hb (70% vs 98%), O_2 uptake is expected in the fetal blood during maternal hyperoxia, and as a result, image signal intensity changes. Before Luo et al. (2017a,b), placental BOLD MRI hyperoxia studies focused on reporting the average signal intensity change in the region of interest (e.g. whole placenta), and they neither discussed the spatiotemporal variations nor provided a quantitative biomarker, such as the association of perfusion with placental function. On the other hand, in this study (Luo et al., 2017a) a new measure, a time to plateau (TTP), has been provided as a result of spatiotemporal analysis of BOLD MRI time series in monochorionic diamniotic twin population. Fig. 9A and B demonstrate segmented volumes that belong to discordant twins (i.e. 20% discordance) corresponding to the red points in Fig. 9C–E. For twin A, the larger brain volume (168 cm^3 vs. 124 cm^3) and faster average TTP (1.4 min vs 3.0 min) were estimated compared to twin B. In the same study, it is reported that mean placental TTP positively correlated with placental pathology ($p < 0.01$) and negatively correlated with birth weights ($p = 0.0003$) when mixed model regression was applied. Additionally, a significant correlation between average TTP and brain volume ($r = -0.86$, $p = 0.02$) was observed, as the larger placental TTP value is associated with a smaller brain. Therefore, MRI with maternal oxygen exposure is a promising tool for the early assessment of proper placental vascular development and oxygen transport to the fetus, which have an impact on the growth trajectories of the brain.

In addition to the perfusion studies, other modalities of MRI have been useful in the assessment of placental function such as proton magnetic resonance spectroscopy (MRS). In the developing fetal brain it is known that increasing N-acetylaspartate (NAA) peak with gestational age reflects the increase in the number of neurons and in the case of fetal growth restriction reduction in NAA/choline ratio could be a critical biomarker of impaired neuronal metabolism. In (Denison et al., 2012), a potential of MRS in an abnormal placenta as an earlier biomarker of intrauterine hypoxia was tested, but found that these biomarkers are likely to develop only during advanced stages of the placental insufficiency. Lastly, newly developed glucose chemical exchange saturation transfer (glucoCEST) methods show

potential to monitor glucose transport after an oral glucose load (Luo et al., 2017a, 2017b). However, this methodology is still under development.

4.1.3. Limitations

4.1.3.1. Technical.: Although MRI opens new vistas for exploration of the placental role in fetal brain development and fetal programming, the full potential of MRI to noninvasively monitor placental function in real time demands further technical development. Signal non-uniformity in MR images driven by variations in magnetic field within the pregnant abdomen and the placenta's complex non-rigid motion driven by maternal respiratory rate, fetal heart rate and fetal motion still severely limit contrast, resolution and the method of image acquisition (Mala- mateniou et al., 2013; Studholme, 2011; Turk et al., 2017; You et al., 2016).

4.1.3.2. Biological.: Although MRI has potential to assess placental function in terms of blood oxygenation or glucose transport, several physiological factors such as spontaneous non-labor contractions (Sind- ing et al., 2016) and maternal position related aortocaval compression (Ponrartana et al., 2015) may change utero-placental circulation and the changes in the circulation affect the placental oxygenation, and consequently the MRI measures. However, monitoring and analyzing these confounding physiological factors may contribute to our understanding of placental development during pregnancy progression (Sinding et al., 2016).

5. From structure, function, and connectivity to complex systems

The human brain is a system. As such, highly sophisticated computational methods, dedicated to the analysis of multimodal neuroimaging data, have recently been developed. These methods offer a theoretical framework for conceptualizing biological processes through the structural integration and functional segregation of brain regions during development.

Studies that use these methods indicate that brain structure and function during the third trimester and newborn periods display small world configuration, rich-club properties, and modular organization. Although the maturation of functional and structural brain networks proceeds from primary to higher-order functional regions, their spatio-temporal maturation pattern is not identical, while the coupling of the functional and structural brain networks continues even to early adulthood. Altered development of structural and functional networks has already been detected in neurological and developmental disorders, though clinical utility remains to be determined.

The recently emerging scientific concept of brain connectomes (brain regions and their inter-connections (e.g. fiber pathways, temporal correlations, gene co-expression, structural covariance) (Sporns et al., 2005)) offers a more comprehensive way to study the emergence of complex networks in the developing human brain at a macro-scale. In addition, such computational methods offer a theoretical framework for conceptualizing biological processes (gene co-expression, areal maturation, development of structural connectivity) or cognition through the structural integration and functional segregation of brain regions

during development. In order to construct connectomes the connectivity matrix first needs to be established. Connectivity matrices are composed of network nodes (segmented brain regions) and connections between nodes (structural connections (e.g. diffusion tractography), morphological correlations (e.g. cortical thickness), functional correlations (e.g. fMRI, EEG or MEG signal), or gene co-expression correlates). Once the connectivity matrices are constructed graph theory methods (Rubinov and Sporns, 2010), such as ontogeny of topological organization, are used in order to characterize network properties.

5.1. Global network properties

Available data support the notion that during third trimester (Song et al., 2017), newborn period (Fransson et al., 2010) and in prematurely born babies (van den Heuvel et al., 2015) structural and functional baby-brain networks already display a small world configuration (the mean geodesic distance between pairs of nodes is small relative to the total number of nodes in the network). This small world configuration is optimal for efficient segregation and integration of information as energy expenditure is reduced to minimum (Watts and Strogatz, 1998), while the global efficiency (short path length) and local efficiency (local clustering) are high. In addition to the small-world properties baby-brain networks also display richclub properties (Ball et al., 2014; Cao et al., 2017a,b; Cao et al., 2016b). Rich-club description refers to organization of the network where ‘rich-club’ regions (hubs, i.e. node (region of the brain) that have dense connections or centralized position) have higher number of connections between themselves than it would be expected by chance. As children grow the number of connections between rich-club regions increases which indicates a progression towards more efficient networks. Increase in efficiency of networks in childhood most likely supports increase in global and local exchange of information.

Lastly, modular organization of functional networks has also been detected in fetal and newborn brains (Cao et al., 2017a,b; Thomason et al., 2014; van den Heuvel et al., 2015). Modular organization refers to a network that has dense connectivity within a cluster (module or assembly of neighboring brain regions) but sparse inter-cluster connectivity that is mostly achieved through previously mentioned hubs. The age related increase in modularity of functional networks in baby brain is believed to favor local specialization and global integration. After birth and during postnatal development the modularity of brain networks declines as these modules become more interconnected.

5.2. Regional maturation revealed by network analysis

Although both structural and functional network analysis reveals small-world, rich-club, and modular properties the maturation pattern between structural and functional networks differ. Around term equivalent age hubs revealed by structural DTI analysis emerge in dorsomedial frontal, parietal, and hippocampal cortices (Tymofiyeva et al., 2014; van den Heuvel et al., 2015). On the other hand, at term equivalent age hubs of functional networks arise in predominantly primary sensory regions (somatosensory, visual and auditory) (Cao et al., 2017a,b; Cao et al., 2016b). Nevertheless, the coupling of the functional and structural brain networks continues to increase until early adulthood (Hagmann et al., 2010; van den Heuvel et al., 2015). A recently published excellent review from (Cao et al., 2017a,b) argues that both functional and structural network maturation follows the histologically described

pattern (Kostovic and Judas, 2009) from primary to higher-order functional regions. In addition, the authors propose that functional co-activation between different brain regions most likely refines existing structural connections following the Hebbian rule (Cao et al., 2017a,b)).

5.3. Implications of network analysis in early detection of abnormal development

Baby brain network and connectomic analyses open new vistas for characterizing normal and abnormal brain development. Moreover, recent data indicate that altered structural and functional brain networks can be detected following preterm birth (Batalle et al., 2017; Kim et al., 2014), in neonates with genetic risk for schizophrenia (Shi et al., 2012), in infants with intrauterine growth restriction (Batalle et al., 2012), adolescents with prenatal exposure to stress (for review see (Scheinost et al., 2016)) or cocaine (Li et al., 2013). In addition, application of newly developed and sophisticated tools for automatic data analysis, such as artificial intelligence, to characterize and detect normal and abnormal human brain development, are at their very beginnings. For example (Stevenson et al., 2017), recently used artificial intelligence (support vector regression) in order to an independently interpret EEG signals from a premature infants. Their results support the notion that artificial intelligence, in the era of Big Data, can be successfully used for correct estimation of functional maturity of the baby brain. Thus, these novel and sophisticated analyses will be most likely able to help in early detection of babies whose brain development is altered.

As much as this is an exciting field, we would like to emphasize that the technological and biological limitations are important to take into consideration when interpreting imaging findings and image analysis results. It is critical to consider the features that are driving the classification of one subject as normal or abnormal and the role of these limitations to not overinterpret the biological significance of the findings.

6. Summary and future directions

The study of early brain development in health and in disease remains a frontier of science. Not only are there challenges in imaging the fetal and infant brain due to its small size and motion. There are also unique challenges arising from the dynamic and regionally specific nature of human brain development. Developmental changes in anatomical sub-strate, neurological activity and physiological responses must be taken into consideration when using neuroimaging to study brain development. In addition, the impact of other environmental factors such as those mediated by the placenta can have life-long effects on brain development but are difficult to capture with current technologies.

Although the combination of histology, and both *ex vivo* and *in vivo* fetal MRI can give us substantial information about different periods of fetal development, there remain tremendous inter-individual differences. These differences are most likely driven by a combination of genes and environment given that they arise during the third trimester (a period in development when areal differences in gene expression are silenced (Pletikos et al., 2014)). Thus, similar to the research focused on the aging brain (Iturria-Medina et al., 2016), incorporation of genome, epigenome and gene expression data, well-constructed machine learning approaches and data sharing (such as e.g. Developing Human Connectome Project

(Hughes et al., 2017)) will play an important role in characterizing normal and abnormal fetal development. In addition, projects involving web based systems to share, organize, generate reproducible analyses, and visualize medical data (e.g. ChRIS-A (Pienaar et al., 2015) will be helpful in this task.

We envision a future where we not only understand normal brain development, but are able to diagnose disease and optimize treatment *in utero*. In working towards this future much remains to be accomplished since the complexities of the biological processes involved and technical challenges makes this research area exceptionally difficult. Thus for future innovation, collaboration between at least three major expert groups is necessary: 1. biological experts (ex. neuroscientists, geneticists and developmental biologists), 2. technical experts (ex. physicists, engineers, computer scientists and mathematicians) and 3. clinical experts (ex. radiologists, neonatologists, neurologists, cardiologists and obstetricians). The noninvasive neuroimaging methods described here will almost certainly play a critical role as each modality provides unique insight into the anatomy and physiology of early brain development.

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Abbreviations:

ASL	arterial spin labeling
Bf	Basal forebrain
BOLD	blood-oxygenation-level dependent
Bs	Brain stem
CNS	central nervous system
CBF	cerebral blood flow
CBV	cerebral blood volume
$CMRO_2$	cerebral metabolic rate of oxygen
Cl^-	chloride ion
CW	continuous wave

CW-NIRS	continuous wave NIRS
CP	Cortical plate
CC	cortico-cortical
HbR	deoxyhemoglobin
DCS	diffuse correlation spectroscopy
DTI	diffusion tensor imaging
EEG	electroencephalography
ERP	event-related potential
FDA	Food and Drug Administration
FA	fractional anisotropy
FD-NIRS	frequency-domain NIRS
fMRI	functional MRI
fNIRS	functional NIRS
GABA	gamma-Aminobutyric acid
GW	gestational week
glucoCEST	glucose chemical exchange saturation transfer
HRF	hemodynamic response function; Hb, hemoglobin
hCG	Human chorionic gonadotropin
HIE	hypoxic ischemic encephalopathy
IgG	immunoglobulin G
ICA	independent component analysis
BFi	index of blood flow
CBFi	index of cerebral blood flow
$CMRO_{2i}$	Index of cerebral metabolic rate of oxygen
IZ	intermediate zone
CC	cortico-cortical fibers
MRI	magnetic resonance imaging
MEG	magnetoencephalography
MZ	marginal zone

MD	mean diffusivity
MMF	mismatch field
MMN	mismatch negativity
NIRS	near-infrared spectroscopy
Nc	negative central
NSW	negative slow wave
NICU	Neonatal Intensive Care Unit
O_2	Oxygen
SO_2	oxygen concentrations in the tissue
HbO	oxyhemoglobin
DPF	path length factor
PC-MRI	phase contrast MRI
PSW	positive slow wave
PET	positron-emission tomography
RD	radial diffusivity
ΔCBF	regional changes in CBF
rs-fMRI	resting state fMRI
rs-fcMRI	resting-state functional connectivity MRI
SARA	SQUID Array for Reproductive Assessment
sCC	short cortico-cortical
SGA	small for gestational age
Sc	Spinal cord
SAT	spontaneous activity transient
Sp	subplate neurons
SP	subplate zone
SVZ	subventricular zone
SQUID	Superconducting Quantum Interference Device
Th	thalamus
BRIGHT	The Brain Imaging for Global HealTh

TD-NIRS	time-domain NIRS
TR-NIRS	time-resolved NIRS
TTP	time-to-plateau
TCD	transcranial Doppler ultrasound
T1w	T1-weighted
T2	transverse relaxation rate
T2w	T2-weighted
VZ	ventricular zone

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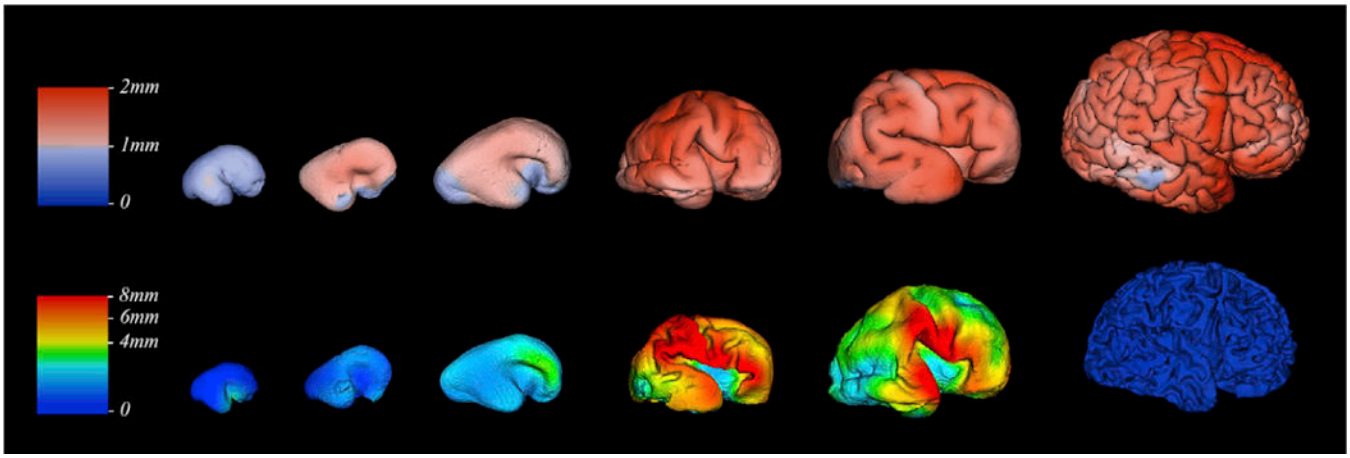

Fig. 1. Thickness of transient fetal zones during prenatal development.

Thickness of cortical plate (upper row) and subplate compartment (bottom row) measured in millimeters (color coded bars on the left) at 15, 18, 20, 26, 32, and 42 GW (left to right). (Reproduced with permission from (Vasung et al., 2016)).

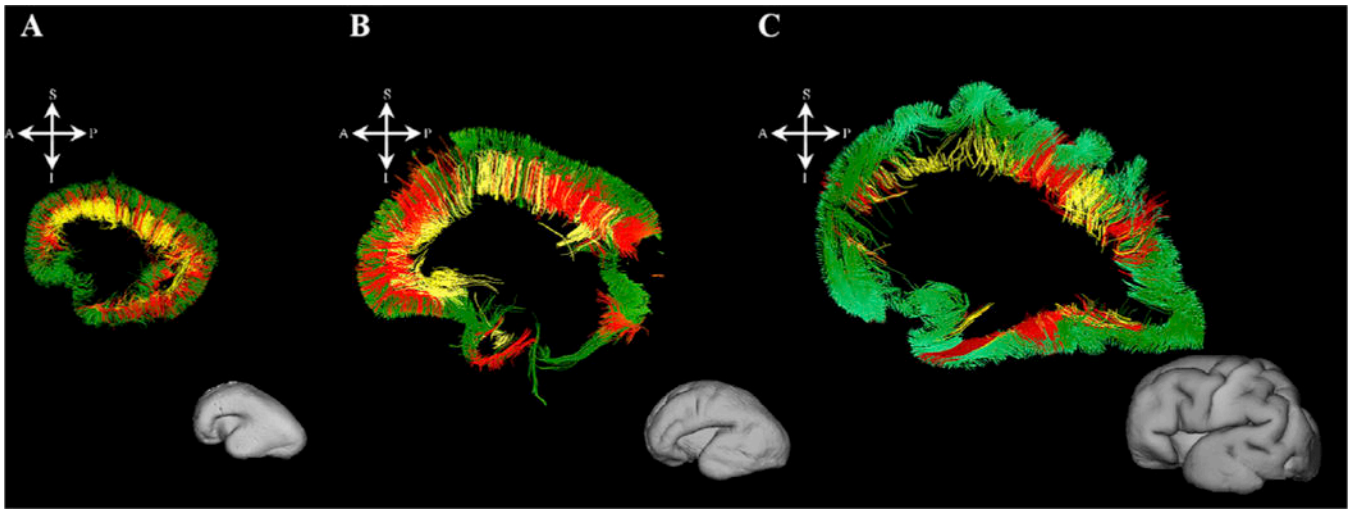

Fig. 2. Radial coherence of the telencephalic wall during mid-fetal and prenatal periods.

Reconstruction of radial streamlines stretching from cortical plate to the subplate/or intermediate zone (in green) in 20 GW (A), 26 GW (B), and 32 GW (C) old fetal brains. Adjacent to the each sagittal slice is an illustration of the reference brain surface reconstructions of the 20 GW (A), 26 GW (B), and 32 GW (C) brains of similar age from Zagreb Neuroembryological Collection. Reference orientations [anterior (A), posterior (P), superior (S), inferior (I), left (L), and right (R)] are placed in the left upper corner of each slice. Streamlines connecting proliferative zones with lower subplate zone (in yellow), streamlines connecting proliferative zones and cortical plate (in red). Arrow in C indicates fibers stretching from one gyrus to adjacent gyrus (cortico-cortical fibers) showing U-shape. (Reproduced with permission from (Vasung et al., 2017)).

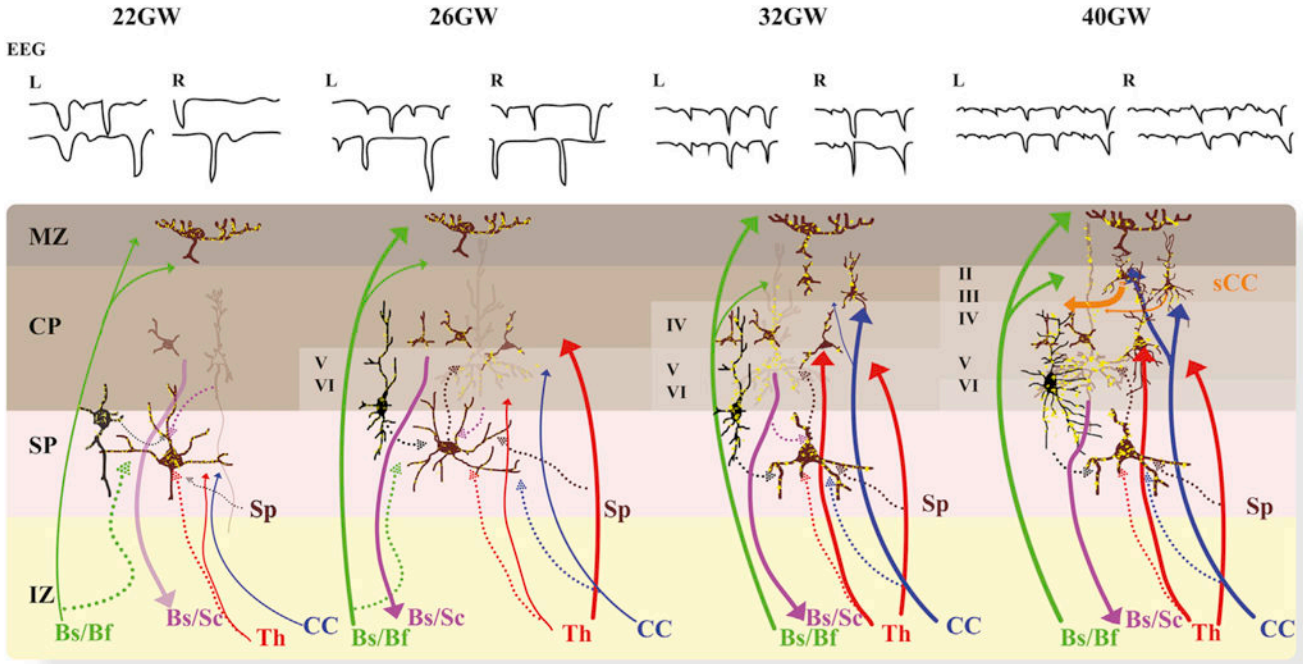

Fig. 3. Illustration of cortical circuitry development in human fetal brain aged 22, 26, 32, and 42 GW.

The illustration is based on histological descriptions: neurons according to (Mrzljak et al., 1992), axonal pathways according to (Hevner, 2000; Kostović, 1986; Kostovic and Goldman-Rakic, 1983), cortical lamination according to (Kostovic and Judas, 2007, 2009), and dendritic spines/synapses according to (Molliver et al., 1973; Mrzljak et al., 1992). At 22 GW thalamo-cortical axons wait in subplate zone. At 26 GW thalamo-cortical axons establish synapses with neurons in future layer IV while cortico-cortical and callosal axons (blue, CC) “wait” in the subplate zone and establish transient synapses with subplate neurons. At 32 GW cortico-cortical axons (belonging to the long associational pathways) and callosal axons (CC) move to the future cortex and establish the synapses with pyramidal neurons of the upper cortical layers. At 42 GW short cortico-cortical axons (sCC) establish synapses with pyramidal neurons of upper cortical layers (II, III) of neighboring areas. During this time circuitry with sensory-driven activity develops (solid lines). Dotted lines represent elements of transient circuitry with endogenous (spontaneous) activity. Bolded lines show elements of adult like circuitry (transient circuitry with spontaneous activity that has been refined or strengthened through sensory-driven activity). Synaptic spines are marked with yellow dots. Note the changes in EEG recordings (upper row) that parallel transition of neuronal circuitry from one with spontaneous “endogenous” activity to one with sensory-driven activity. During mid-fetal to early preterm periods desynchronized patterns and patterns of discrete large spontaneous activity transient (SATs) waves dominate (22–26 GW), transitioning to synchronized patterns of activity during the early to late preterm periods (32–40 GW)) (Illustrated according to the findings of (Vanhatalo and Kaila, 2010)). Abbreviations: Intermediate zone (IZ); Subplate zone (SP); Cortical plate (CP); Marginal zone (MZ); Thalamus (Th); Brain stem (Bs); Basal forebrain (Bf); Spinal cord

(Sc); Subplate neurons (Sp); Long cortico-cortical and callosal fibers (CC); Short cortico-cortical fibers (sCC); Cortical layers (II-VI); Left (L); Right (R); Gestational weeks (GW).

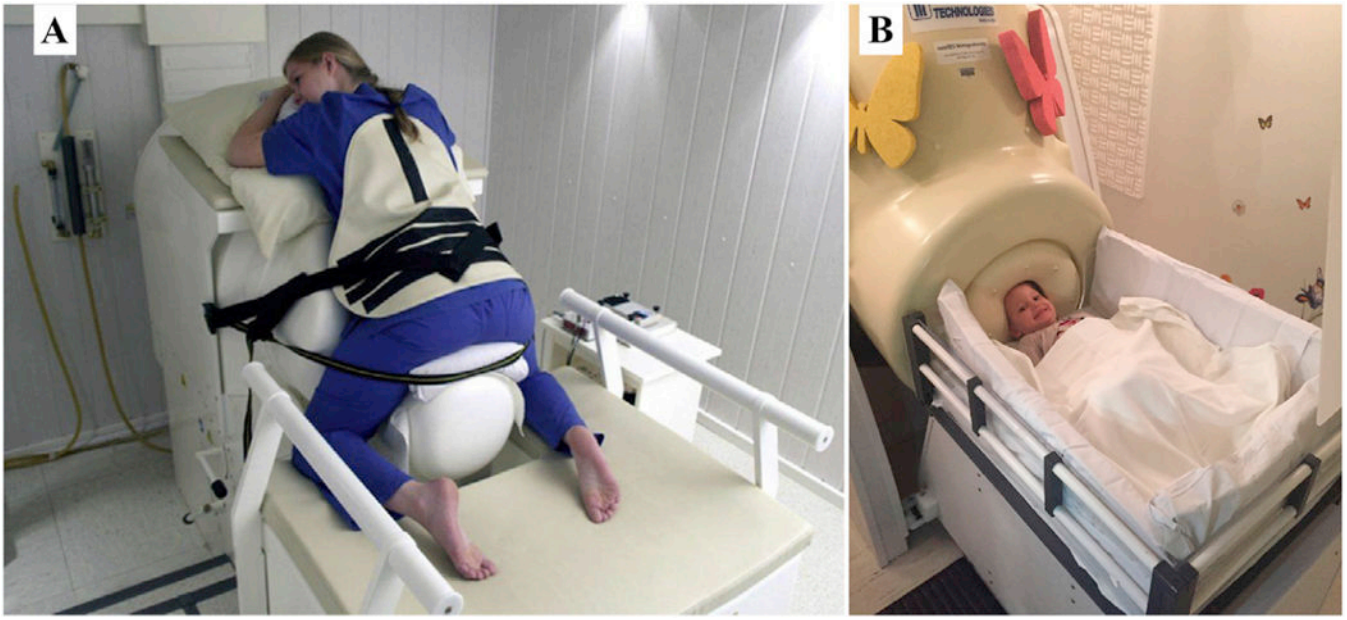

Fig. 4. SARA MEG Equipment and the MagView Biomagnetometer (BabyMEG) System.

(A) Pregnant subject positioned in SARA device prior to a fetal MEG scan (Reproduced with the permission from (Anderson and Thomason, 2013)). (B) View of a healthy 4 year old child lying on the bed of the BabyMEG system, with the head in the helmet (Reprinted with the permission of AIP Publishing from (Okada et al., 2016)).

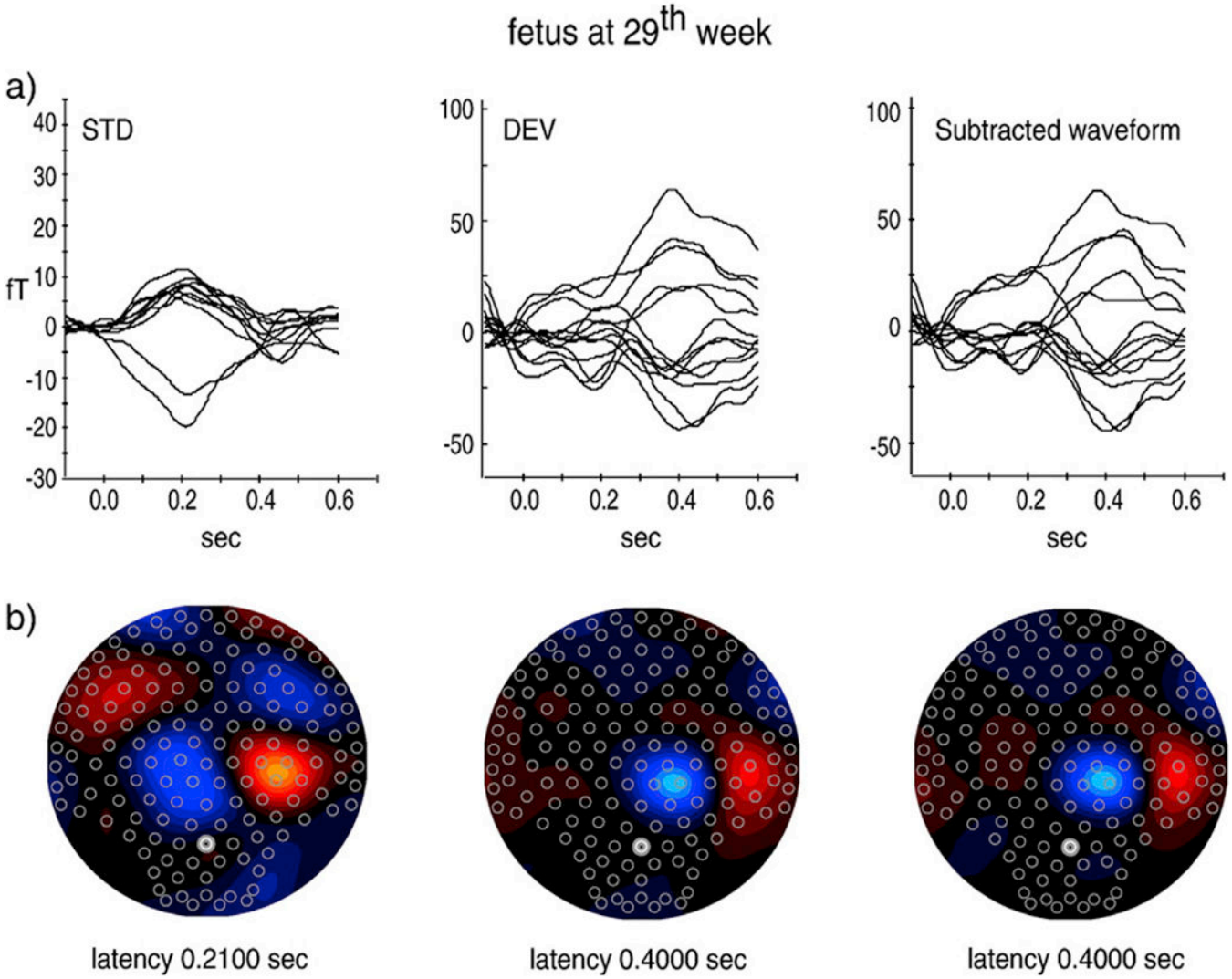

Fig. 5. Magnetic field maps of the pregnant abdomen with a fetus at 29 weeks gestation.

(A) Overlay of channels with maximal magnetic field amplitudes in response to the deviant, standard tone and subtracted waveform. (B) Magnetic field distribution of the responses at the maxima in the vicinity of the fetal head, the marker indicates the position of the fetal head coil (Reproduced from (Draganova et al., 2007), with permission).

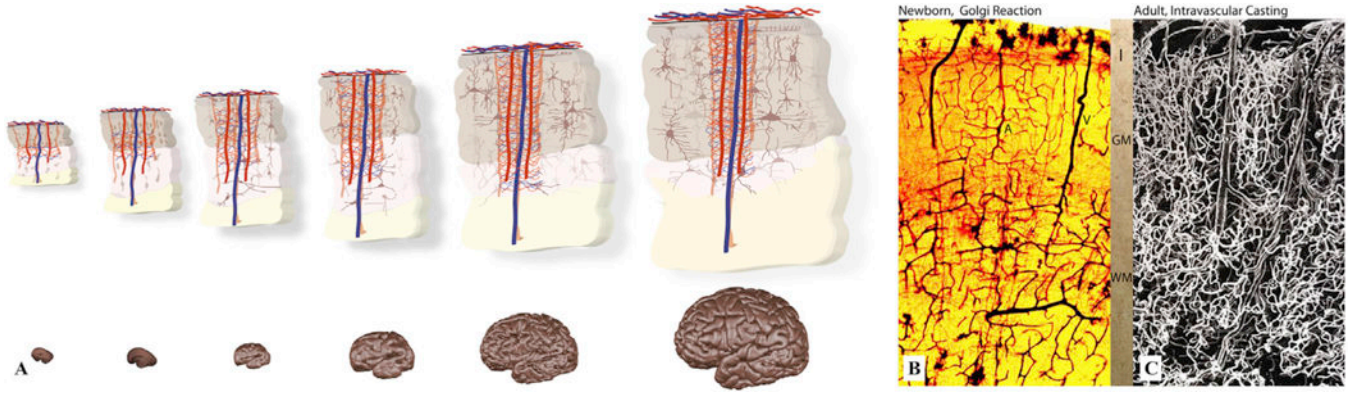

Fig. 6. Development of intracerebral vascular system.

(A) Illustration based on the histological findings from Croatian Institute for Brain Research and (Mar- in-Padilla, 2012) showing proposed longitudinal changes in the process of cortical angiogenesis in 15, 22, 26, 35, 37, and 42 GW old brains (Reproduced from (Vasung et al., 2017b)). Sections orthogonal to the pia are shown in upper row, 3D reconstruction of cortical surface is shown in bottom row. Transient fetal zones are shown in colors (brown cortical plate/cortex, pink-subplate, yellow-intermediate zone/white matter). Perforating arteries (red), perforating venules (blue). (B, C) **Photomicrographs comparing the intracerebral extrinsic and intrinsic microvascular compartments of a newborn (B) and adult (C) human brains.** The reproduction in (B) is from a rapid Golgi preparation of the motor cortex of a newborn infant and that in (C) is from an intravascular casting of an adult human brain, from the work of (Duvernoy et al., 1981). Despite the significant differences in brain size and weight (newborn ca. 410 g and adult ca. 1350 g) the overall dimension, vascular composition and structural organization of their intracerebral extrinsic and intrinsic microvascular compartments are remarkable similar. These structural and organizational similarities mirror the similar developmental and physiological constraints that endure through the prenatal and postnatal functional maturations of cortical neurons (Marin-Padilla and Knopman, 2011). In both brains (B, C), there are more intrinsic capillaries with smaller intercapillary spaces identified in the gray matter than in the white matter. The abundance of intrinsic capillaries through the cortex gray matter protect the functional activity of its neurons, in both normal and abnormal conditions. Key (B): I, first lamina; GM, gray matter; WM, white matter; A and V, arterial and venous vessels; and in (C) 6, pial vein; 5, venule; 1, arteriole; 3, deep arteriole; 2, recurrent arteriole. Figures B and C are reproduced from (Duvernoy et al., 1981; Marin-Padilla, 2012), with permission.

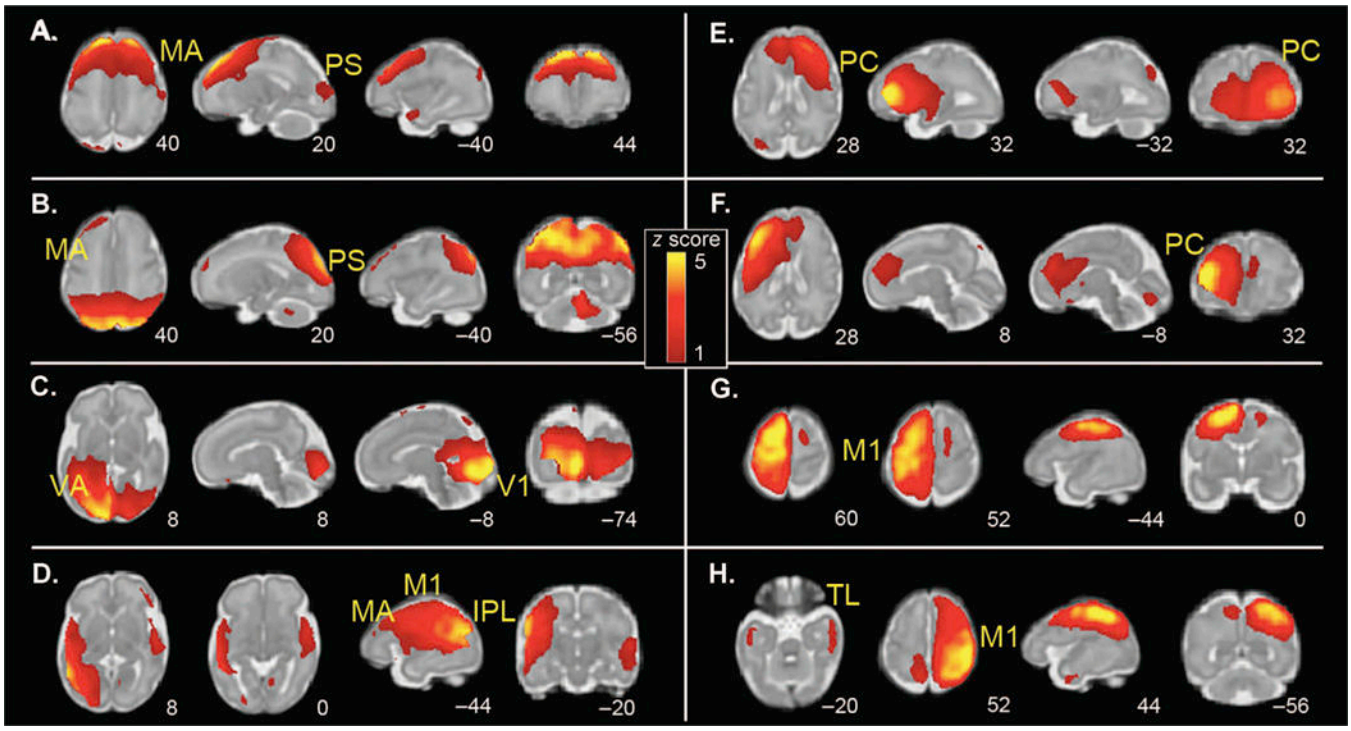

Fig. 7. Group ICA of spontaneous fMRI activity patterns in 25 fetuses (24 to 38 weeks of gestation).

Sample axial, sagittal, and coronal slices corresponding to bilaterally represented independent components from ICA are overlaid onto the template of a 32-week fetal brain. The left side of the figure corresponds to the left side of the brain. Coordinates identifying slice locations are provided below each slice using the MNI coordinate space. ICA was used to derive a total of 14 maximally statistically independent brain networks, 8 of which were bilaterally distributed. (A to H) The following networks were detected: (A) motor association (MA) cortex; (B) peristriate (PS) cortex; (C) primary visual (V1) and visual association (VA) cortex; (D) inferior parietal lobule (IPL), primary motor (M1), and motor association cortex; (E) right frontal cortex; (F) left frontal cortex; (G) left primary motor cortex; and (H) right primary motor cortex and bilateral temporal lobe (TL). Reproduced from (Thomason et al., 2013), with permission.

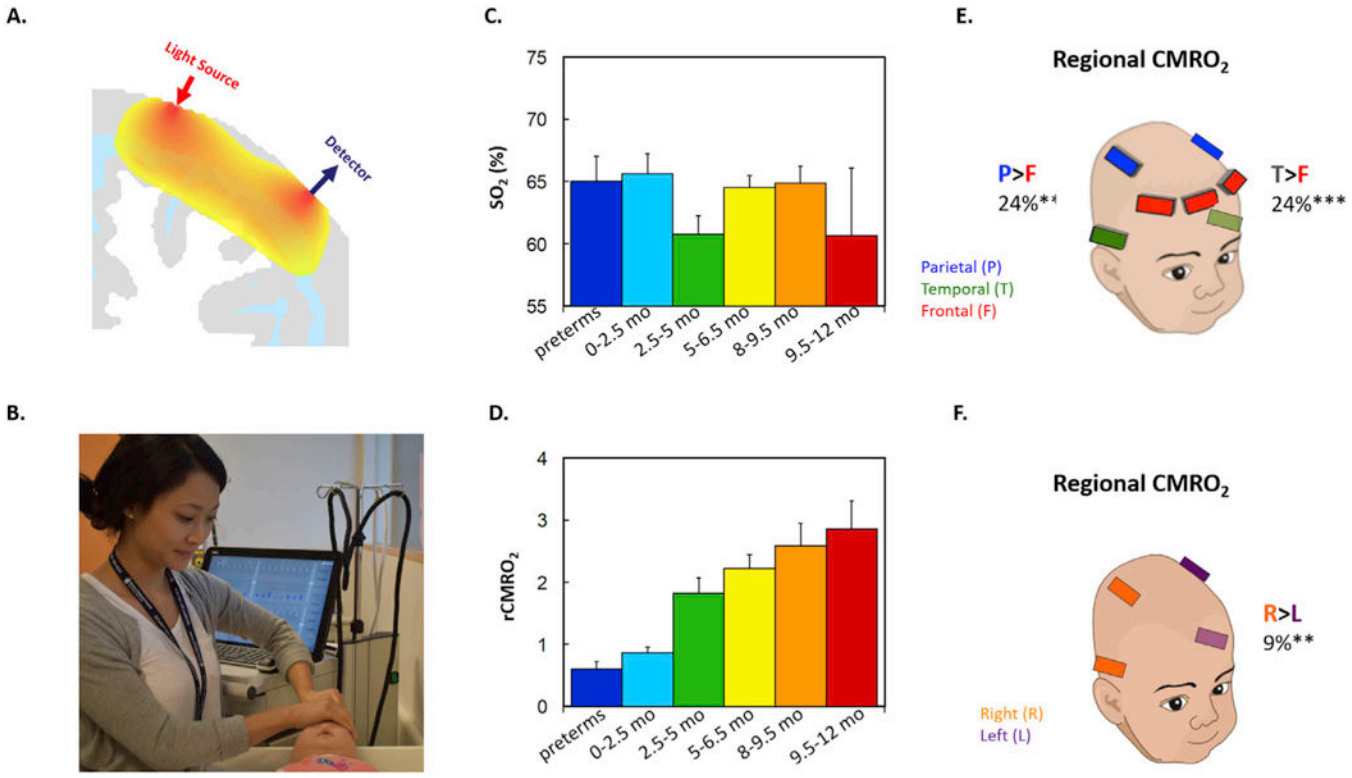

Fig. 8. Non-invasive, transcranial near-infrared spectroscopy (NIRS) measurement of the cerebral cortex.

(A) Across section of a 3D Monte Carlo simulation of the sensitivity map of a transcranial NIRS measurement on an adult head. The source detector separation is 4 cm. Red colors indicate regions of greater measurement sensitivity. Because light must travel through the scalp and skull to reach the brain, NIRS measures a mixture of cerebral and extracerebral signals. The simulation was performed using the MCX Monte Carlo simulation software described in Fang and Boas (2009) (B) Demonstration of combined frequency domain NIRS (FD-NIRS) and diffuse correlation spectroscopy (DCS) with an infant phantom. (C–D) In a cohort of 47 healthy infants measured by FD-NIRS/DCS during first year of life, $CMRO_2$ increased with age while SO_2 remained constant. Thus, $CMRO_2$ measured with advanced NIRS techniques is more sensitive to neural development than SO_2 measured by ordinary cerebral oximeters. (E–F) Regional and hemispheric differences in newborns. Higher $CMRO_2$ in the parietal and temporal regions than frontal and higher in right than in the left suggest different regional maturation rate in newborns. * indicates $P < 0.05$; ** indicates $P < 0.01$; *** indicates $P < 0.001$ for paired student t-test. Figures generated from data published in (Franceschini et al., 2007) and (Lin et al., 2013b).

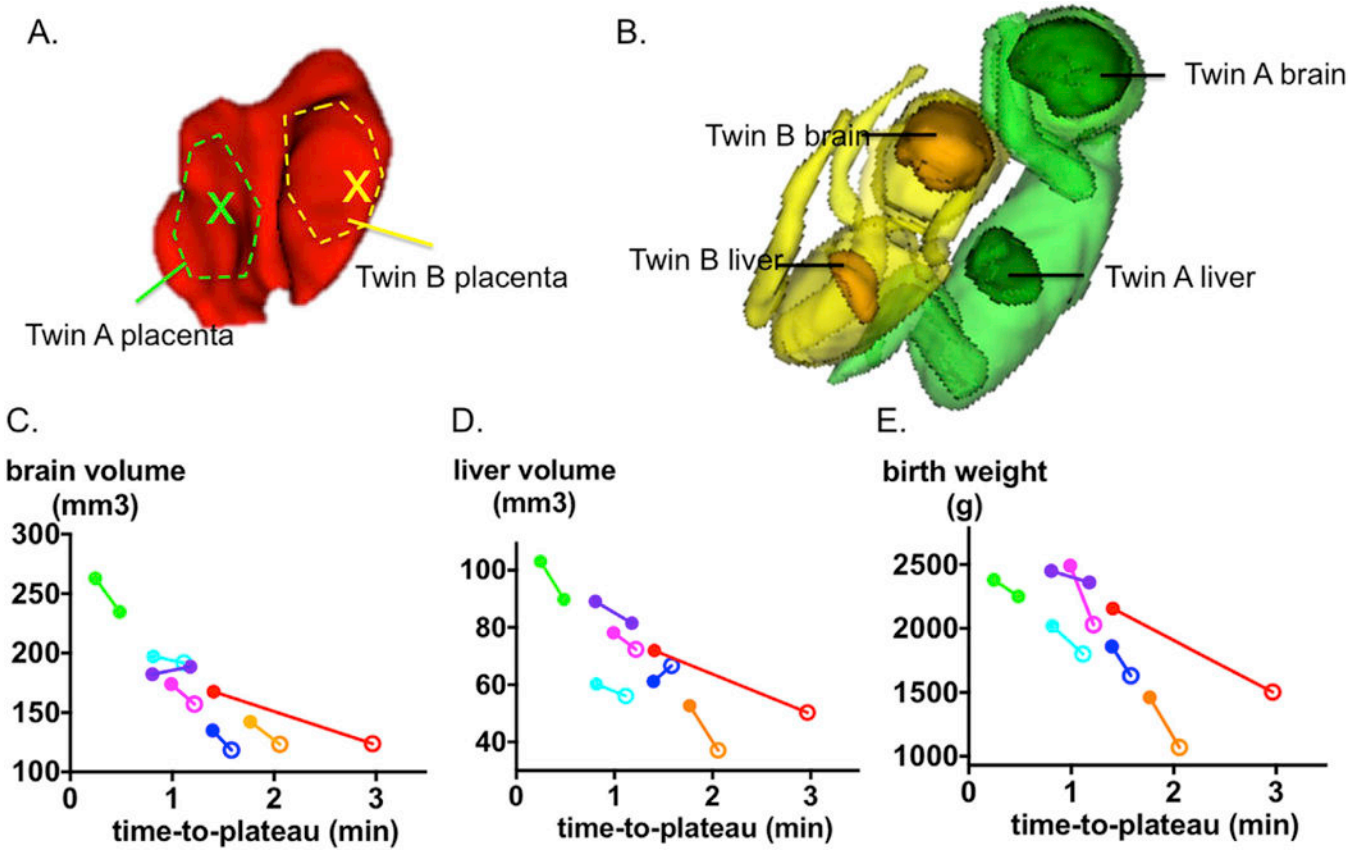

Fig. 9. Illustrations of segmentation volumes and of mean time-to-plateau (TTP).

(A) placenta for the discordant twin pair with indication of ROI segmentation used for the average TTP calculation. (B) 3D view of segmented fetal brains and livers in the corresponding discordant twin pair (red points in (C–E) below). (C–E) Brain volume, liver volume and birth weight respectively as a function of the average TTP. The brain and liver volume were measured at the time of the scan. Twin pairs are connected by solid line, and are assigned same color. Hollow circles denotes fetuses that proved to be small for gestational age at birth. (Reproduced with permission from (Lew et al., 2017)).