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# Toward the Automatic Quantification of In Utero Brain Development in 3D Structural MRI: A Review

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**Abstract:** Investigating the human brain in utero is important for researchers and clinicians seeking to understand early neurodevelopmental processes. With the advent of fast magnetic resonance imaging (MRI) techniques and the development of motion correction algorithms to obtain high-quality 3D images of the fetal brain, it is now possible to gain more insight into the ongoing maturational processes in the brain. In this article, we present a review of the major building blocks of the pipeline toward performing quantitative analysis of in vivo MRI of the developing brain and its potential applications in clinical settings. The review focuses on T1- and T2-weighted modalities, and covers state of the art methodologies involved in each step of the pipeline, in particular, 3D volume reconstruction, spatiotemporal modeling of the developing brain, segmentation, quantification techniques, and clinical applications. *Hum Brain Mapp 38:2772–2787, 2017.* © 2017 Wiley Periodicals, Inc.

**Key words:** quantitative MRI; fetal brain; spatiotemporal atlas; segmentation; growth pattern; volumetry; gyrification; ventriculomegaly

## INTRODUCTION

Quantitative image analysis of the in vivo fetal brain plays a crucial role in clinical decision-making and neuroscience research. During the last several years, a growing trend in using magnetic resonance imaging (MRI) for such studies is observed. MRI is the most common medical imaging modality for the diagnosis and follow-up of patients with brain abnormalities, and the understanding of normal neurodevelopment in adult brains. For fetuses, although ultrasound (US) is widely accepted as the primary technology for in utero imaging of the brain [Garel, 2008], US examination is often hampered by some limitations, including reduced amniotic fluid volume, maternal obesity, inappropriate fetal head position, multiple

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pregnancy, and bony reverberation artifacts from the skull [Glastonbury and Kennedy, 2002; Twickler et al., 2003]. Conversely, MRI offers superior contrast in soft tissues and an increased field of view compared to US. Prenatal diagnosis can therefore benefit from fetal MRI by complementing the findings in US. Indeed, in recent years, in utero MRI has shown to be of important added value in the study of disorders [Clouchoux et al., 2013; Kyriakopoulou et al., 2014; Scott et al., 2013] and early brain development [Clouchoux et al., 2012; Wright et al., 2014].

Quantification of fetal brains from MRI is more challenging than that of the adult brain as it requires additional processing techniques and makes some of the widespread techniques for adult brain MRI not applicable. In the pipeline to perform fetal brain MRI quantitative studies (see Fig. 1), the first challenges come from motion artifacts during image acquisition. While advances in fast MRI sequences help decrease acquisition times, the development of motion correction techniques allows obtaining high-resolution 3D images of the fetal brain from the several motion-corrupted acquired stacks. These studies also require the delineation of tissues and structures of interest in the 3D reconstructed volumes. For this purpose, automatic segmentation techniques are desirable over manual labeling as the latter is very time-consuming and subject to inter- and intra-rater variability. Therefore, quantitative approaches often rely on automated segmentation algorithms to achieve accurate and reproducible measurements. However, in this third stage of the pipeline (i.e., segmentation), researchers have to face new difficulties concerning the nature of the fetal brain. The rapid and complex cerebral changes in shape and appearance (e.g., transient laminar pattern and myelination) that occur during intrauterine growth make existing techniques for adult brains unfeasible and advocate for the development of novel approaches. This has increased the need to build spatio-temporal atlases of the fetal brain to capture these dynamic changes. Spatio-temporal atlases have shown to be useful for automatic segmentation, which is notably challenged by the low resolution of fetal brain images, the excessive amount of partial volume effects (PVEs), and the substantial dissimilarities in shape and MRI contrast between brains at different gestational ages (GAs).

There is a growing body of literature on fetal brain MRI. This work aims to provide an overview of the automated pipeline for performing quantitative analysis of fetal brain from structural MRI. Acquisition and reconstruction stages of the pipeline are not the main purpose of this review and are briefly discussed in Challenges of Fetal Brain MRI section. The reader is referred to the work by Studholme, [2011, and references therein] for a comprehensive review of these techniques. For each pipeline stage, the motivation and the difficulties that arise when working with fetal brain MRI are outlined from both clinical and methodological perspectives, and a literature review of the methodological advances is presented. Although this work mainly focuses on methods targeting the fetal brain in structural MRI, methods proposed for neonates are also discussed given the shared similarities once fetal-exclusive limitations are overcome. The rest of the article is organized as follows. Challenges of Fetal Brain MRI section overviews some of the challenges that arise in fetal brain MRI. Atlases of the Developing Brain section introduces the construction and use of spatio-temporal atlases. Segmentation of Brain Images section is devoted to segmentation techniques of tissues and other anatomical structures in fetal and neonatal brains. In Quantification of Early Normal Brain Development section, a broad view of quantitative studies of normal brain development is provided. Examples of Clinical Applications section describes potential clinical applications of fetal MRI in the study of early brain abnormalities. A discussion about the state of the art is presented in Discussion section. Finally, Conclusions section concludes the article.

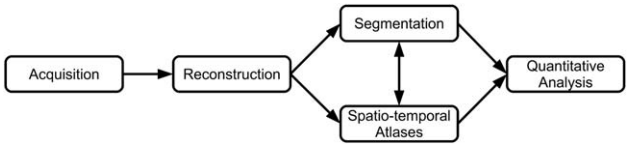


**Figure 1.**

Pipeline to perform quantitative analysis of fetal brain MRI. Fast MRI sequences are used in the first stage to acquire several motion-corrupted stacks of the fetal brain, which are then used to obtain the final motion-corrected 3D reconstruction (second stage). The third stage is for approaches to build spatio-temporal atlases to capture the dynamic changes of the fetal brain, which can serve as spatial priors in the segmentation of brain tissues and other structures of interest. The fourth stage is dedicated to quantitative studies (e.g., volumetry, gyrification).

## CHALLENGES OF FETAL BRAIN MRI

Difficulties with fetal brain MRI start to appear as early as in the imaging process. Acquisition of full 3D MRI of the fetal brain is still impractical due mainly to the thick slice acquisition necessary to achieve good signal-to-noise ratio and the presence of motion artifacts caused by spontaneous movement of the fetus and maternal breathing. Shortening the acquisition time would help decrease the likelihood of motion artifacts [Malamateniou et al., 2013]. Advances in fast MRI sequences, such as single shot fast spin-echo, in conjunction with post-processing techniques (i.e., motion correction and super resolution) have granted the means to gain broad insight into the in utero fetal brain by providing high-resolution 3D volumes. Typically, several motion-corrupted stacks of thick 2D slices are acquired in orthogonal orientations and then used to reconstruct a high-resolution motion-free 3D volume of the brain. Existing methods for motion correction and reconstruction [Kim et al., 2010; Murgasova et al., 2012]

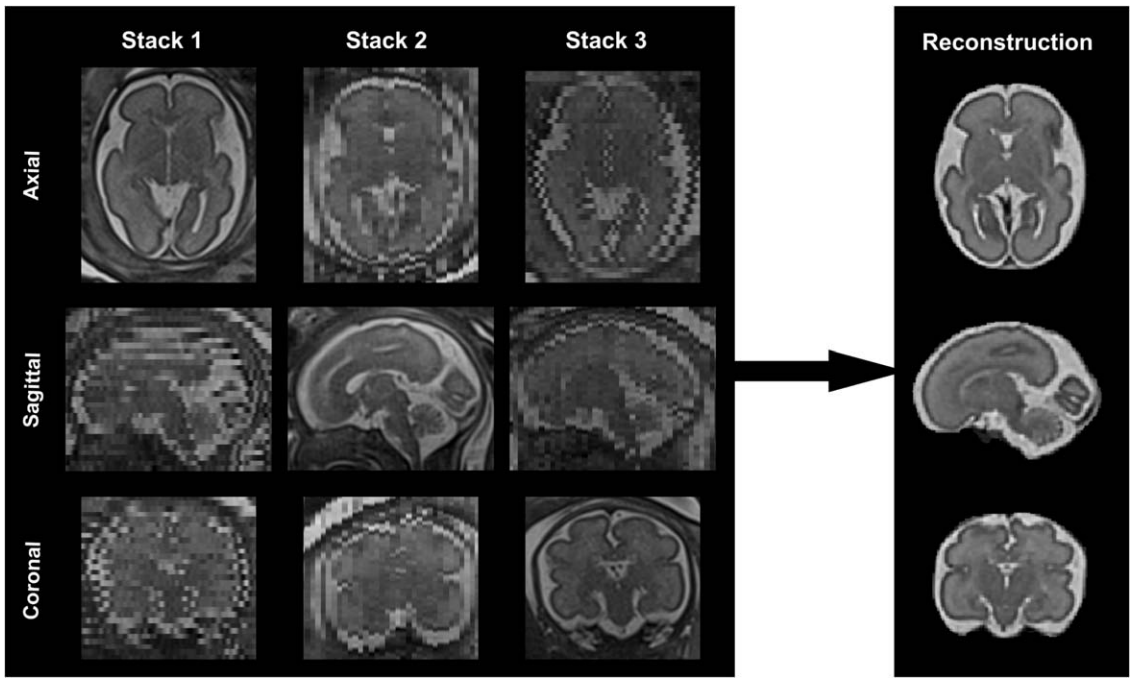


**Figure 2.**
Example of reconstruction from motion-corrupted stacks of 2D MRI slices. First three columns (i.e., stacks 1, 2, and 3) correspond to axial, sagittal, and coronal acquisitions, respectively. Fourth column is the final reconstruction. Rows, from top to bottom, show axial, sagittal, and coronal views, respectively, for each image.

require the delineation of the fetal brain (at least in one slice) from maternal tissue. However, Keraudren et al., [2014] proposed a fetal brain extraction method from 2D stacks, that combined with the reconstruction approach in Murgasova et al., [2012] provides a fully automated pipeline to obtain the final 3D volumes. A volume reconstruction example using this pipeline is shown in Figure 2. Recently, a GPU-accelerated slice-to-volume reconstruction method similar to Murgasova et al., [2012] was proposed in Kainz et al., [2015].

In quantitative MRI studies, one of the requirements is the labeling of the different regions of the brain. Nevertheless, segmentation is not forthrightly applicable as MRI suffers from noise, intensity inhomogeneity and PVE that may negatively impact the performance of image processing techniques. PVE is present when multiple tissues contribute to a single voxel producing a blurring effect, for instance, in the boundary between gray matter (GM) and cerebrospinal fluid (CSF). PVEs can lead to volume measurement errors in the range of 20%−60% [González Ballester et al., 2002] and are more recurrent in fetal brain MRI, as illustrated in Figure 3, due to its lower resolution when compared to adult brain images. In fetuses, these problems are accentuated because early brain development involves a rapid and complex sequence of morphological, functional, and appearance changes. Hence, in addition to the aforementioned obstacles, large tissue intensity variations are present in fetal (and neonatal) brains due to myelination and cell migration [Rutherford, 2001]. Myelination is the last stage of white matter (WM) development and takes place from the second half of gestation to the end of adolescence [Dubois et al., 2014], making the intensities of WM similar to those of both cortical and subcortical GM in T1-weighted (T1w) and T2-weighted (T2w) MR images. Neuronal migration occurs from the germinal matrix (GMAT), which is comprised of ventricular and subventricular zones, toward the cerebral wall to form the prospective neocortex. During this process of corticogenesis, the fetal brain goes through an intensive laminar organization, where the cortical plate (CP), the subplate (SP) and the intermediate zone (IZ) are formed, as shown in Figure 4. By the 27th gestational week (GW), however, intensity contrast between the IZ and SP begins to overlap and eventually transforms into neonatal WM [Prayer et al., 2006]. Also late in the 2nd trimester, the GMAT commences to gradually regress until it completely disappears by term [Girard and Chaumoitre, 2012]. These developmental processes make the segmentation of the developing brain in MRI more challenging as compared to adult brains.

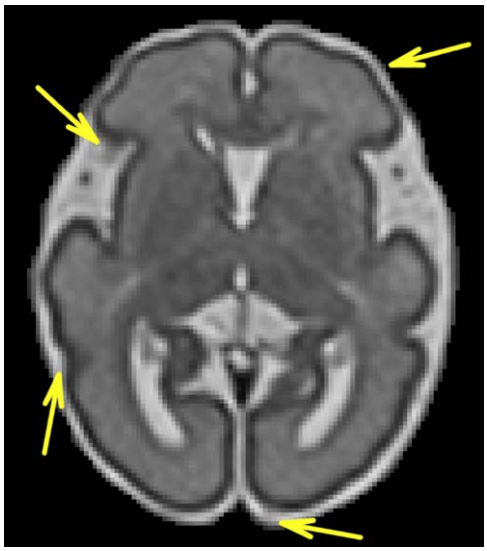

**Figure 3.**
Examples of partial volume effect (arrows) in the boundaries between GM and CSF, and background and CSF in an axial MRI slice of a 29 GWs fetus. [Color figure can be viewed at wileyonlinelibrary.com]

## ATLASES OF THE DEVELOPING BRAIN

The core *raison d'être* of brain atlases is to (1) serve as a common reference coordinate system for spatial normalization of a group of individuals to study intra- and inter-group variability, and (2) act as an atlas for segmentation of brain regions [Fonov et al., 2011, and references therein]. The study of the developing brain ought to be age-specific given transient laminar pattern and the evident vast differences in shape and appearance across age (see Fig. 5) that occur during the maturational process. This age-specific character of segmentation and processing techniques of the developing brain has driven research [e.g., Habas et al., 2010; Serag et al., 2012b] toward the use of spatio-temporal atlases instead of a single atlas at a particular time-point. Compared to conventional atlases, spatio-temporal atlases encode spatial as well as temporal variability. This allows to better retain the anatomical variability across age. Several atlases can be found in the literature for adult [Evans et al., 1993], pediatric [Wilke et al., 2003], infant [Joshi et al., 2004], neonatal [Murgasova et al., 2011; Serag et al., 2012a], and fetal [Habas et al., 2010] brains.

### Population-Specific Atlases

An ideal atlas of the human brain should have the desirable features of being (1) representative of the population, (2) unbiased, and (3) sharp (i.e., with high contrast). Using a single anatomy as an atlas precludes fair representation as the arbitrary choice of the reference template does not encompass the neuroanatomical variability of the entire population. To better accommodate this variability, population average atlases, such as the Montreal Neurological Institute (MNI) template [Mazziotta et al., 1995] for adult brains, were constructed. These atlases are built by averaging the anatomical images from a particular population, based on distinctive criteria such as age, gender, or ethnicity. The representative bias introduced when using a single-subject atlas can then, to some extent, be avoided using the MNI template. Still, when targeting pediatric brains, Wilke et al., [2003] found considerable differences in tissue distribution between pediatric and adult data, substantially appreciated in GM. Thus, spatial normalization of pediatric brain images to the MNI or other adult templates is less accurate [Shi et al., 2011] and might introduce a strong bias in anatomical quantification. This problem is especially important in younger brains due to their continuous development throughout childhood and adolescence [Paus et al., 1999]. Several researchers have therefore developed population-specific brain atlases for children and infants. Joshi et al., [2004] constructed a probabilistic atlas of anatomical structures from 8 T1w MR scans of 2-year-old children. Wilke et al., [2008] created reference pediatric templates from 404 healthy subjects aged 5–18 years. Recently, Fonov et al., [2011] built age-specific MRI atlases for 6 age groups in the range of 4.5–18.5 years. Along the same lines, Altaye et al., [2008] proposed a method to create an infant (9 to 15 months) probabilistic atlas, and demonstrated that the use of their atlas performed better than a default adult or pediatric template in segmenting the infant brain. Kazemi et al., [2007] built a neonatal brain template based on T1w MR images of 7 individuals with GA between 39 and 42 weeks.

The major requirements for the construction of these adult and pediatric atlases are twofold: (1) the definition

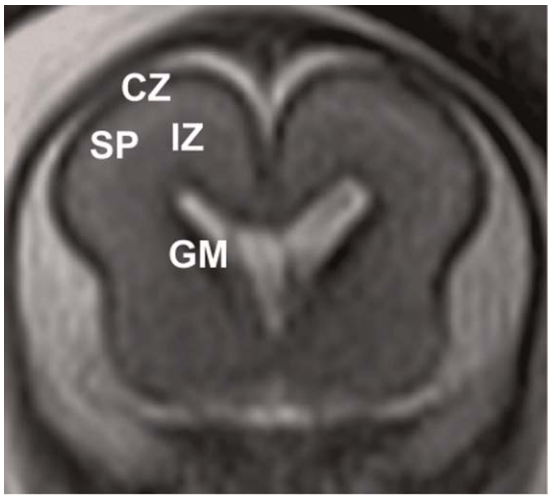


**Figure 4.**
Coronal T2W slice of a fetus at 23 GWs illustrating the laminar organization of the brain: the hypointense CP is the outermost layer. The SP is hyperintense relative to the CP and IZ. Immediatly beneath the SP, the hypointense IZ appears. The GMAT represents the innermost layer and is isointense to the CP.

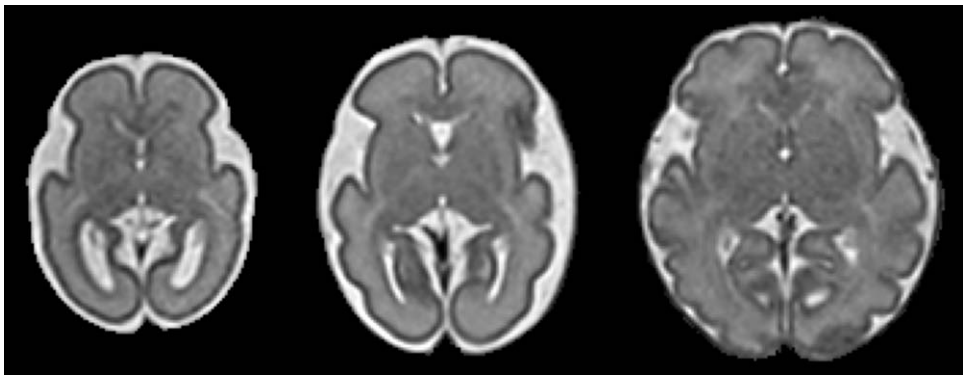

**Figure 5.**
Rapid brain maturation. From left to right: 26, 29, and 34 GWs fetal brains.

of a reference space, and (2) the transformation model that maps each brain to this common space. A potential source of bias comes forth in the selection or creation of the initial reference template during atlas construction. For example, Park et al., [2005] selected the initial template to be the closest brain to the geometrical mean in a low dimensional space. However, to reduce the dependence on any particular anatomy during normalization, the conventional approach is based on iterative strategies where the initial template is derived from the multiple anatomies in the database and successively updated in each iteration [Avants et al., 2010; Fonov et al., 2011]. Sharpness of atlases, conversely, is closely related to the transformation model. A single-subject based atlas has well defined anatomical boundaries. For the average atlases to exhibit sharp anatomical details, non-rigid registration seems to be more appropriate for building such atlases [e.g., Fillmore et al., 2015; Fonov et al., 2011]. To further enhance the anatomical details, Shi et al., [2014] proposed a patch-based sparse representation approach to fuse the information from the individual images after registration.

## Spatio-Temporal Atlases

Methods for building atlases of the human brain have evolved in parallel to the emergence of new imaging techniques, being closely linked to the age of the individuals under study because of the substantial structural changes existing between age groups. Atlases described above either were produced for infant and older populations, or have a sparse age coverage (i.e., temporal variability is covered by only a few discrete temporal points). The study of neonates and fetuses at a precise developmental period becomes difficult because changes in the developing brain occur in the order of weeks or even days. One way to circumvent this limitation is to provide atlases with a fine-grained temporal resolution. Beyond static population-specific atlases, the solution relies on the building of spatio-temporal atlases, whose purpose is to encode both longitudinal and inter-subject variability. For the temporal domain, brains along a certain age range need to be taken into account in the atlas creation, whilst, for the spatial domain, a sufficient number of subjects at a particular time-point is needed. Due to ethical and practical issues, building spatio-temporal atlases directly from repeated longitudinal imaging of the same subject is difficult, and they are therefore constructed from many individuals, scanned at different ages. Several methods exist in the literature to build this kind of atlases for neonates [Murgasova et al., 2011; Serag et al., 2012a, 2012b; Zhang et al., 2016] and fetuses [Dittrich et al., 2014; Gholipour et al., 2014; Habas et al., 2010; Serag et al., 2012b]. Table I summarizes the main features and datasets used for each of these methods. The time-varying dimension of these atlases is an advantageous characteristic in that it allows dynamic generation of average intensity images and corresponding prior tissue probability maps at any arbitrary time-point confined within the age range of the brain scans used to build the atlas.

Most of the aforementioned spatio-temporal atlases were created from T2w images using non-rigid [Dittrich et al., 2014; Gholipour et al., 2014; Habas et al., 2010; Serag et al., 2012a, 2012b; Zhang et al., 2016] rather than rigid registration [Dittrich et al., 2014; Murgasova et al., 2011]. Rigid registration is better suited for the spatio-temporal atlases to capture the variability across subjects, and this was used in Dittrich et al., [2014] for age estimation. For segmentation purposes, non-rigid registration provides more accurate results. Although, as pointed out in Murgasova et al., [2011], building the atlas with affine transformations may turn out to be advantageous for segmentation applications when the to-be-segmented image is non-rigidly registered to the newly created template. Furthermore, the spatio-temporal latent atlas in Dittrich et al., [2014] was built in a semi-supervised manner, where segmentations of ventricles and cortex were only available for a reduced set of images. During the construction stage, these segmentations are transferred to the remaining images to create prior

**TABLE I. Spatio-temporal atlases of the developing brain**

| | Modality | Fetal/ Neonatal | Subjects | GA | Structures | Type of segmentation | Registration | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Spatial | Temporal |
| (Habas et al. 2010) | T2w | Fetal | 20 | 21-25 | GM<br>WM<br>GMAT<br>VENT | Manual | Groupwise<br>Non-rigid<br>Segmentations | LS |
| (Murgasova et al. 2011) | T2w | Neonatal | 142 | 29-44 | WM<br>CoGM<br>CeGM<br>BS<br>CB<br>CSF | Automatic | Pairwise<br>Affine | KR |
| (Serag et al. 2012a) | T1w and T2w | Neonatal | 204 | 29-44 | WM<br>CoGM<br>CeGM<br>BS<br>CB<br>CSF | Automatic | Pairwise<br>Non-rigid<br>For each GA<br>(only T2w) | AKR |
| (Serag et al. 2012b) | T1w and T2w | Both | 204<br><br>80 | 29-44<br>(neonatal)<br>22-39<br>(fetal) | WM<br>CoGM<br>CeGM<br>BS<br>CB<br>CSF | Automatic<br>(neonatal)<br>Manual<br>(fetal) | Pairwise<br>Non-rigid<br>For each GA<br>(only T2w) | AKR |
| (Dittrich et al. 2014) | T2w | Fetal | 12 | 21-25 | VENT<br>CoGM | Manual<br>(only few) | Groupwise<br>Rigid or<br>Non-rigid | KR |
| (Gholipour et al. 2014) | T2w | Fetal | 40 | 26-36 | WM<br>CoGM<br>CeGM<br>GMAT<br>BS<br>CB<br>CSF | – | Groupwise<br>Non-rigid | AKR |
| (Zhang et al. 2016) | T1w and T2w | Neonatal | 35<br>(150 scans) | 0-12<br>(months) | WM<br>GM<br>CSF | Automatic | Groupwise<br>Non-rigid | AKR |

Abbreviations in the table: VENT, ventricles; CeGM, central GM; CoGM, cortical GM; BS, brainstem; CB, cerebellum; LS, least squares fitting; KR, kernel regression; AKR, adaptive kernel regression. Unavailable information is marked as –.

probability maps for the generated atlas. With regard to image modality, the neonatal spatio-temporal atlas in Serag et al., [2012b] was created from both T1w and T2w modalities. Although this multi-channel atlas uses T1w and T2w images, registrations were only performed on T2w images and resulting transformations were used to deform the T1w modality. A neonatal spatio-temporal atlas for both T1w and T2w modalities was also created in Zhang et al., [2016].

A distinguished feature that needs to be considered in the construction of spatio-temporal atlases is the modeling of the temporal dimension. The first work on building a spatio-temporal atlas of the fetal brain [Habas et al., 2010] used non-linear modeling of the temporal variations in a reduced age range of 21-25 GWs. However, in larger age ranges, there may be no subjects at the exact age of interest. Therefore, the works in Dittrich et al., [2014] and Murgasova et al., [2011] adopted a temporal kernel regression method to compute the weighted contribution of the temporal neighbors in the creation of the average brain templates. In Gholipour et al., [2014] and Serag et al., [2012a, 2012b], adaptive kernel regression was used to create their spatio-temporal atlases. Here, the adaptive kernel accounts for a sufficient number of subjects in the contribution to the atlas creation. This ensures a consistent level of detail for a synthesized atlas at any time-point when the brains are not uniformly distributed over the age range. Zhang et al., [2016] used a patch-based approach similar to Shi et al., [2014] for creating the atlas. However, the key improvement of this work over previous approaches is the temporal consistency of their atlas, as it

was built based on subject-specific longitudinal information (i.e., using 4.3 scans per subject in average).

## SEGMENTATION OF BRAIN IMAGES

Automatic tissue segmentation of the human brain in MRI has been incentivized by its many clinical applications. Cortex delineation, for instance, is a prerequisite for the study of cortical thickness and gyrification (see Quantification of Early Normal Brain Development section). The success of quantitative analysis is heavily sustained by the accuracy of image segmentation algorithms. While there is a plethora of MRI segmentation techniques for the adult brain [e.g., Greenspan et al., 2006; Ortiz et al., 2013; Pham and Prince, 1999], a limited number of works to segment brain MRI of neonates and fetuses exists in the literature. The poor spatial resolution of images, and the varying intensity distribution between tissues, dynamic shape changes and reduced contrast in the brain at such early ages render more challenging the automatic brain segmentation of this age group compared to adults.

### Segmentation of Neonatal Brain MRI

In the neonatal brain, WM exhibits substantial intensity variation due to the ongoing process of myelination that gradually reverses the WM-GM contrast, reaching a point around the ninth month when both tissues appear isointense [Barkovich, 2005]. This may mislead intensity-based segmentation algorithms to identify PVEs at the boundary between CSF and GM as the yet unmyelinated WM [Xue et al., 2007]. To cope with these systematic segmentation errors in neonates, several authors have proposed brain tissue segmentation methods combining intensity information with spatial priors and contextual information.

Among these works, an atlas-free approach [Xue et al., 2007] adopted the Expectation-Maximization (EM) algorithm with Markov Random Field (MRF) regularization for tissue classification combined with a knowledge-based strategy to correctly classify mislabeled PVEs at the CSF-GM boundary. Recently, another approach that does not require atlas priors was presented in Gui et al., [2012], where a watershed technique was used to segment the brain MRI of neonates based on information about tissue connectivity, structure and relative positions. Most of published works, however, used atlas-based approaches to guide the segmentation. Prastawa et al., [2005] developed an atlas-based automatic algorithm based on graph clustering and outlier removal. It used the EM scheme followed by a non-parametric kernel density estimation to obtain the final segmentation. Shi et al., [2010] proposed a joint registration-segmentation framework that used subject-specific tissue probabilistic atlases generated with adaptive fuzzy C-means [Pham and Prince, 1999] from follow-up data of the same subject. With the same purpose, an atlas-based approach interleaving registration and segmentation was used in Shi et al., [2011], which combined subject-specific cortical GM distribution with a data driven neonatal atlas. Weisenfeld and Warfield, [2009] presented an algorithm that iteratively performs sample refinement, segmentation, and fusion using STAPLE [Warfield et al., 2004]. Wang et al., [2011] proposed a level set segmentation framework with a thickness constraint in the cortical area, and combined local intensity information and atlas priors. This work was further improved in Wang et al., [2014] using a subject-specific atlas and incorporating non-local (i.e., patch) information. In Ledig et al., [2012], the spatio-temporal atlas in Murgasova et al., [2011] was used with an extended version of the EM algorithm incorporating a second-order MRF to penalize inconsistent labeling caused by PVEs. In a recent work, Anbeek et al., [2013] segmented eight different tissue classes in a supervised manner using intensity and voxel coordinates with K-nearest neighbors. Wang et al., [2015] also proposed an iterative supervised approach to segment the main tissues using random forest [Breiman, 2001] and features from several modalities (i.e., T1w, T2w, and fractional anisotropy images), including the estimated probability maps. On premature neonates, brain tissue segmentation was carried out in Beare et al., [2016] and Sanroma et al., [2016] on the dataset provided by the NeoBrainS12 challenge [Isgum et al., 2015]. Sanroma et al., [2016] proposed an ensemble approach that optimally combines the outputs of two complementary segmentation approaches (i.e., intensity-based and multiatlas label fusion). In Beare et al., [2016], a supervised approach was presented using a combination of unified segmentation, template adaptation and topological filtering.

Beyond the segmentation of the main tissues, methods for the parcellation of anatomical structures in the neonatal brain have been proposed in Gousias et al., [2013] and Makropoulos et al., [2014]. There is a notable overlap between tissue segmentation and parcellation in that both approaches make use of image intensities. Although in the latter case, intensity-based features are not sufficient as in the case of tissue segmentation, and spatial priors derived from atlases become also necessary. Therefore, Gousias et al., [2013] presented a multiatlas approach to segment the brain MRI in 50 regions using ALBERTs [Gousias et al., 2012], a dataset of manually annotated neonatal atlases. These atlases were also used in a hierarchical approach to label multiple brain structures using EM-MRF and knowledge-based rules for misclassified voxels [Makropoulos et al., 2014].

### Segmentation of Fetal Brain MRI

Automatic segmentation of fetal brain MRI is even more intricate, as in addition to the existing difficulties in neonates, fetal brains have a transient laminar pattern (see Challenges of Fetal Brain MRI section) and MRI quality is highly affected by fetal and maternal movements during acquisition. There is much less literature on fetal brain MRI segmentation. Table II lists the main characteristics of existing methods. One of the first works [Claude et al., 2004] proposed a semi-automated method to segment 3 regions (i.e., posterior fossa, brainstem and vermis) on a

**TABLE II. Fetal brain MRI segmentation methods**

| | Method | MRI | Spatial priors/constraints | Structures |
|---|---|---|---|---|
| [Claude et al., 2004] | Region growing<br>Semi-automatic | 2D<br>(one slice) | – | Posterior fossa<br>Brainstem<br>Vermis |
| [Bach Cuadra et al., 2009] | EM-MRF | 2D | Cortical distance map | Cortical GM<br>Central GM<br>WM<br>CSF |
| [Gholipour et al., 2011] | Level sets<br>Morphological op. | 3D | – | Brain<br>CSF |
| [Caldairou et al., 2011] | Topological K-means | 3D | Anatomical priors | Cortical GM |
| [Habas et al., 2008] | EM-MRF | 3D | Probabilistic atlas | GMAT |
| [Habas et al., 2010] | EM-MRF | 3D | Probabilistic atlas | Cortical GM<br>WM<br>GMAT<br>Ventricles |
| [Serag et al., 2012b] | – | 3D | Probabilistic atlas | Cortical GM<br>Lateral ventricles<br>Hemispheres |
| [Gholipour et al., 2012] | Multiatlas multishape | 3D | Multiple atlases | Lateral ventricles |
| [Koch et al., 2014] | Graph-based label propagation | 3D | Multiple atlases | Lateral ventricles |

Unavailable information or not used is marked as –.

single MRI slice of the fetal brain, using region growing based on intensity and gradient features. Also in 2D MRI, Bach Cuadra et al., [2009] developed an automatic labeling method for the main tissues that was performed independently in each slice using EM-MRF and anatomical priors in form of a cortical distance map. Bayesian segmentation was first performed to segment the fetal brain in seven different classes. GM and WM were modeled as a mixture of two Gaussians each, and two classes for mislabeled partial volume voxels, which were to be correctly classified during the MRF stage.

Among pioneering works in addressing the segmentation of fetal brains in 3D reconstructed MRI, Gholipour et al., [2011] used a semi-automated method with little user interaction based on intensity information, level sets, and morphological operations to deal with PVEs. Given that intensity information is insufficient to isolate cortical GM from WM, Caldairou et al., [2011] included anatomical priors through a topological K-means clustering algorithm to segment the cortex in an atlas-free approach. In Habas et al., [2008], the GMAT was segmented in fetuses at a reduced age range (20.5–22.5 GWs) using the EM framework with a single probabilistic atlas. However, with the advent of spatio-temporal atlases of the fetal brain, age-specific atlases can be generated at any GA to serve as priors in the segmentation process [Habas et al., 2010; Serag et al., 2012b]. Multiatlas segmentation approaches were also used in Gholipour et al., [2012] and Koch et al., [2014]. Gholipour et al., [2012] developed a method built over multiatlas segmentations that incorporates a shape model of structures and regional intensity values within a probabilistic framework to achieve automatic segmentation of multiple shapes with similar intensities. The main purpose was to accurately segment the lateral ventricles in subjects with normal, dilated, or fused ventricles. In Koch et al., [2014], a semi-supervised graph-based method was proposed to overcome the unavailability of subjects within certain GA ranges. After a first labeling stage where only atlases are able to propagate information, label probabilities of test images in subsequent iterations are also used to improve the labeling of images whose GA is not available in the training set. It is worth mentioning that several of the aforementioned segmentation methods for neonates and fetuses can be used interchangeably as long as the priors and the spatial constraints are consistent with the dataset under study. In fact, the method proposed in Ledig et al., [2012] for neonates was used by Wright et al., [2014] to segment fetal brain MRI.

## QUANTIFICATION OF EARLY NORMAL BRAIN DEVELOPMENT

Quantifying the patterns of normal gyrification and the underlying growth processes in the developing fetal brain from in utero MRI may offer insights into the changes that occur during normal fetal brain development, and provide a baseline for comparison to abnormal development. During early stages of fetal cerebral development the brain is lissencephalic in appearance [Rutherford, 2001]. However, as growth proceeds the brain undergoes drastic changes in its morphology. In the latter half of gestation, the normal process of human brain maturation is manifested by substantial increases in volume without equivalent changes in

thickness, and an increasing complexity of the CP following a highly orchestrated sequence of gyral-sulcal formation [Clouchoux et al., 2012; Rajagopalan et al., 2011a; Wright et al., 2014]. In particular, this sequence occurs in a hierarchical manner in which primary and secondary sulci form in a consistent spatio-temporal pattern during normal gestation, followed by tertiary sulci that show increasing variability across individuals [Bendersky et al., 2006; Studholme, 2011]. The timing of this has been considered an accurate marker of brain development [Garel et al., 2003], with any divergence from this pattern being conceived as a potential stable biomarker for abnormal functional development.

Several works inspect the global and regional patterns of tissue maturation in the developing brain to provide a comprehensive understanding of the maturational process the human brain embarks on from early weeks of gestation [Gholipour et al., 2011; Scott et al., 2013] up to approximately the second postnatal year [Aljabar et al., 2008], period where the majority of brain growth occurs [Rutherford, 2001]. Other studies reported the patterns of cortical convolutions [Clouchoux et al., 2012; Wright et al., 2014] that take place in the human brain during this period. This section offers an overview of the role MRI plays in the quantitative study and assessment of in utero brain development.

## Cortical Folding

The study of cortical folding is important because will aid clinicians in the understanding of normal gyrification and the detection of cortical maldevelopment. Evidence from MRI studies of preterm neonates [Dubois et al., 2008] may not be consistent with fetal brain development as prematurity per se may be considered a limitation in the representation of normal in utero neurodevelopment [Rutherford et al., 2008]. Indeed, preterm-born infants compared with term-born controls at term equivalent age showed alterations in cortical volume [Padilla et al., 2014] and folding [Melbourne et al., 2014]. When compared to fetal brains, prematurity also showed an impact on cortical folding [Lefèvre et al., 2015]. In fetuses, conclusions drawn from ex vivo studies [e.g., Bendersky et al., 2006] about sulcal emergence might be influenced by deformations inherent to brain fixation and the substantial fluid loss during histological processing [Dubois et al., 2008; Habas et al., 2012], which may slightly affect the measurements. With the possibility to perform in vivo fetal MRI, mapping of cortical folding has been initially restricted to analysis of 2D slices [Garel et al., 2003; Prayer et al., 2006]. This approach exhibits significant limitations in that 2D measurements are very dependent on the use of consistent 2D planes, which is susceptible to motion during acquisition. Furthermore, exact tissue boundaries may be difficult to find on thick 2D MRI slices due to PVEs. Volumetric reconstructions of the fetal brain, conversely, ensure selection of the appropriate planes and enable measurements that take advantage of the 3D anatomy of the brain.

To provide a reliable timeline of the normal in utero brain development, researchers have taken benefit of motion-corrected 3D reconstruction techniques, which can be easily integrated into an automated pipeline for the assessment and quantification of the timing of cortical folding. Using only cohorts of healthy fetuses, Clouchoux et al., [2012] delineated sulcal fundi in 12 fetuses between 25 and 35 GWs, Habas et al., [2012] presented a temporal mapping of the emergence of individual sulci in 40 MRI scans from 38 fetuses with age ranging 20–28 GWs, and Wright et al., [2014] studied global and regional gyrification measures in 80 fetuses over a wider age range of 22–39 GWs. All of these works used a surface-based approach, where curvature information was estimated on the inner CP surfaces extracted from WM segmentation. Following the pipeline illustrated in Figure 1, segmentations in Clouchoux et al., [2012] were obtained after 3D volume reconstruction [Gholipour et al., 2010] using an atlas-based approach with manual correction. In Habas et al., [2012], images were first reconstructed with the method in Kim et al., [2010] and automatically segmented using priors from a spatio-temporal atlas [Habas et al., 2010]. Also in Wright et al., [2014], images went through 3D volume reconstruction [Jiang et al., 2007] and automatic segmentation [Ledig et al., 2012].

Among their findings, Habas et al., [2012] showed that the increase in surface area related to gyrification is linear from 20 to 28 GWs. After the 28th GW, gyrification accelerates and becomes more complex [Clouchoux et al., 2012], following a non-linear growth model. In particular, a Gompertz model showed to best fit the folding measures studied in Wright et al., [2014]. Furthermore, they found a positive correlation of these folding measures with GA, which was stronger than that of GA and volume. Clouchoux et al., [2012] also created four average cortical templates evenly distributed along the age range of the subjects that showed the major changes in gyrification occurring during normal fetal brain development. A more precise timetable of early sulcation was reported in Habas et al., [2012], demonstrating that 3D MRI provided more sensitivity than 2D MRI in the detection of sulcal emergence. Establishing normative timing for gyrification in the fetal brain will allow identification of deviations in development and early treatment.

## Patterns of Tissue Maturation

Similarly as in the case of cortical folding, there exists a vast literature from postmortem [Huang et al., 2009], ex utero [Aljabar et al., 2008; Murgasova et al., 2011; Xue et al., 2007] and, in vivo fetal MRI [Kazan-Tannus et al., 2007; Limperopoulos et al., 2010; Prayer et al., 2006] and US [Endres and Cohen, 2001; Roelfsema et al., 2004] on tissue growth and laminar organization of the developing brain. However, as discussed in 5.1, generalizing the evidence from these studies to normal in utero brain maturation might render inadequate.

Based on reconstructed 3D MRI of the fetal brain, Gholipour et al., 2011] carried out a volumetric study using automated segmentations of brain tissue in a cohort of 25 fetuses ranging from 19 to 39 GWs. In Corbett-Detig et al., [2011], global and local patterns of SP growth were studied through quantitative analyses of temporal changes in SP volume and thickness in 21 fetuses within the age of 20 to 26 GWs. From manual segmentations of the SP and supratentorial brain volume (as a sum of CP, WM, and GMAT), they also analyzed the relationship between volume and GA. From automatic segmentation of 48 scans of 39 fetuses with age between 21 and 31 GWs, Scott et al., [2011] presented volumetric growth trajectories of CP, SP and IZ, GMAT, deep gray nuclei, and ventricles. Morphometry was also used to study the complex series of local tissue volume changes the developing brain undergoes in its normal course toward acquiring its gyrencephalic adult aspect. Aljabar et al., [2008] had previously used tensor based morphometry (TBM) [Davatzikos et al., 1995] in a longitudinal study to provide global and local growth factor estimates of GM and WM for a cohort of 25 preterm subjects scanned at 1 and 2 years. TBM uses accurate spatial normalization of brain anatomy into a common reference space to capture the pattern of regional structural differences across a set of anatomies by computing the derivatives (i.e., Jacobian map) of the deformation fields required to bring each anatomy to the same stereotaxic space [Studholme, 2011]. For the in utero fetal brain, Rajagopalan et al., [2011a] provided a mapping of growth patterns by quantifying tissue locations that were expanding at a different growth rate than the overall cerebral tissue. TBM analysis combined with a linear model of age was used to create these maps from fetuses between 20 and 28 GWs. However, beside modeling magnitude of local tissue volume increase with scalar TBM [e.g., Dubois et al., 2008; Habas et al., 2012; Rajagopalan et al., 2011a], directional growth information is valuable to acquire more knowledge about fetal brain development. Rajagopalan et al., [2011b] extended the study beyond volume increase by incorporating its normal and tangential components on either side of the SP-CP interface, which permitted to model the variational growth patterns that underlie the mechanism of sulcation between both tissues. Furthermore, Rajagopalan et al., [2012] quantified brain development as a combination of volume and direction change patterns, and provided the principal growth direction at a particular location.

According to these studies, supratentorial brain volume increased quadratically with GA [Gholipour et al., 2011]. From 20 to 26 GWs, the increase in SP tissue was proportional with the increase in supratentorial volume, although at different rates among brain regions [Corbett-Detig et al., 2011]. Tissue-dependent growth rates were found in Scott et al., [2011], with CP growing faster than all other tissue zones, especially along the midline surface of the frontal and parietal lobes [Rajagopalan et al., 2011a]. Also, significant changes in direction of growth were found to occur primarily in the CP at locations corresponding to the formation of primary sulci. When the direction of cortical growth at any sulcus changes rapidly, it occurs in conjunction with change in direction of growth in the underlying cerebral mantle [Rajagopalan et al., 2012]. Finally, slower growth was found in the ventricular regions adjacent to the CP, and the GMAT, which begins to regress after 25 GWs [Corbett-Detig et al., 2011; Rajagopalan et al., 2011a].

### Interhemispheric Structural Asymmetries

Interhemispheric asymmetries have also been studied in fetal brain MRI to establish a precise timing for their in utero emergence. These asymmetries may be indicators of cortical functional specialization [Dubois et al., 2008], and alterations of this pattern may be useful as an early biomarker for abnormal neurodevelopment [Studholme and Rousseau, 2014]. Using fractal dimension analysis in outer cortical surfaces reconstructed from 2D slices, Shyu et al., [2010] found earlier development of cortical complexity in the right hemisphere than in the left in a cohort of 32 fetuses with GA between 27 and 37 weeks. This was also reported in preterm [Dubois et al., 2008] and term [Hill et al., 2010] neonates, particularly evident at the level of the superior temporal sulcus. Interhemispheric asymmetries were also analyzed in 3D reconstructed fetal brain MRI by Rajagopalan et al., [2011a], where the emergence of asymmetries was detected using TBM analysis based on symmetric groupwise registration of tissue maps of 40 fetal brains and their reflected versions along the sagittal midline. A similar approach was carried out in Rajagopalan et al., [2012] to detect directional asymmetries in the same cohort with GA between 20 and 28 weeks. They found significant local asymmetries in volume and growth direction in the periSylvian fissure, showing that asymmetries in this area start around 20 GWs. Among their findings, Habas et al., [2012] reported statistical significance of interhemispheric asymmetries in the periSylvian region by 23 GWs and in the parieto-occipital sulcus after 26 GWs.

In accordance with ex vivo studies and in conformity with asymmetries reported in adult and neonatal brains [Hill et al., 2010], these findings confirm that gyrogenesis occur earlier in the right hemisphere than in the left, and that cerebral interhemispheric asymmetries start during the intrauterine period.

## EXAMPLES OF CLINICAL APPLICATIONS

Brain malformations account for one third of fetal anomalies and 60% have no identifiable etiology [Rodríguez et al., 2010]. Although US is the standard imaging modality for fetal evaluation, it is well demonstrated that fetal MRI has a greater sensitivity to detect specific brain abnormalities that could be occult on prenatal US [Banović et al., 2014]. In this section, several contributions of fetal MRI to the diagnosis of brain abnormalities in utero are described. We will focus on quantification studies of

Intrauterine growth restriction (IUGR), congenital heart disease (CHD), and ventriculomegaly (VM).

### Intrauterine Growth Restriction

IUGR refers to a condition in which the weight of the fetus is below the 10th percentile for GA. This condition affects 10–15% of the population [Gardosi, 2011] and it is associated with a wide range of short- and long-term neurodevelopmental disorders. The effect of late-onset IUGR in the in utero development of the brain was studied by Egaña-Ugrinovic et al., [2013, 2014] from 2D MRI slices. In Egaña-Ugrinovic et al., [2013], differences in cortical development were assessed in 52 late-onset IUGR and 50 control fetuses. Late-onset IUGR fetuses, compared with controls, presented deeper fissures, more pronounced right asymmetry and smaller brain volumes. Corpus callosum development was analyzed in Egaña-Ugrinovic et al., [2014] using 117 late-onset IUGR and 73 control fetuses. The area of the corpus callosum was significantly smaller in IUGR fetuses compared to the control group. Furthermore, they found that these morphometric differences were in correlation with worse neurobehavioral performance. These findings reflect a perturbation in normal fetal brain development and can be used as potential biomarkers to predict abnormal neurodevelopment in pregnancies at risk.

### Congenital Heart Disease

CHD refers to a structural abnormality of the heart present at birth. A wide spectrum of brain abnormalities has been identified with CHD in preterm and term neonates before they undergo cardiac surgery, which may suggest the occurrence of abnormal brain development in utero [Donofrio and Massaro, 2010]. To better understand the impact of CHD in impaired neurodevelopment outcome, Limperopoulos et al., 2010] performed the first in vivo quantitative MRI study of 55 fetuses with CHD and 50 healthy fetuses between 25 and 37 GWs. Volumetric MRI analysis and spectroscopy showed a progressive deceleration in global brain growth (i.e., intracranial cavity and total brain volumes) and metabolism in the cohort with CHD over the third trimester of gestation. Using in utero MRI, Mlczoch et al., [2013] reported a 39% incidence of brain abnormalities in a cohort of 53 fetuses with age between 20 and 37 GWs with CHD. In Brossard-Racine et al., [2014], MRI scans of 144 fetuses with CHD and 194 controls of age ranging between 18 and 39 GWs were also studied for brain anomalies. Their findings showed a significantly higher frequency (23%) of structural brain abnormalities in the CHD group compared with less than 2% of recurrence in fetuses from the control group. This highlights the close relationship between heart and brain development. Based on segmentations of 3D high-resolution reconstructed volumes of 30 control fetuses and 18 fetuses diagnosed with hypoplastic left heart syndrome, Clouchoux et al., [2013] demonstrated a progressive third-trimester decline in volumetric growth of cortical GM, subcortical GM and WM, in addition to significant region-specific cortical development delays in the hypoplastic left heart syndrome group. These findings are consistent with postnatal data demonstrating that delayed fetal brain maturation and development in utero appears to begin in the third trimester [McQuillen et al., 2010].

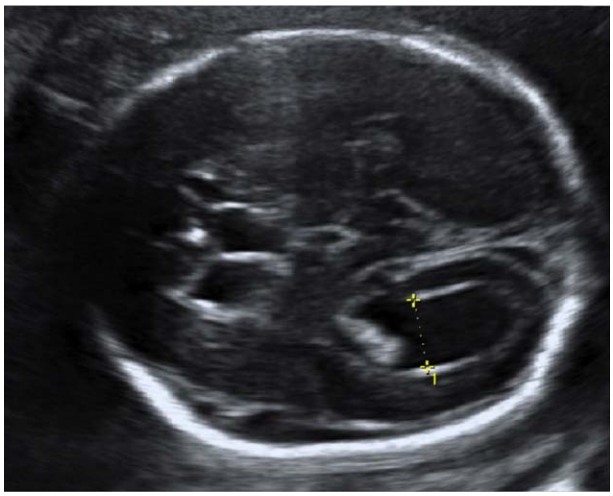

**Figure 6.**
Measurement of the atrial diameter in US. [Color figure can be viewed at wileyonlinelibrary.com]

### Ventriculomegaly

VM is one of the fetal brain anomalies that is frequently diagnosed during the gestational period. When no other anomalies are present, it is called isolated VM. VM is defined as a ventricular atrial diameter greater than 10 mm at any GA [Cardoza et al., 1988], while the width in normal subjects lies between 6 and 9 mm [Scott et al., 2013]. Atrial diameter measurements larger than 15 mm constitute severe VM, whilst measurements between 10 and 15 mm are classified into mild VM (10–12 mm) and moderate VM (12.1–15 mm) [Kyriakopoulou et al., 2014]. In case of isolated VM, this latter dichotomy is typically used as a prognostic biomarker of the neurodevelopmental outcome of the fetuses. That is, cases with isolated mild VM are generally associated with good outcomes, although some will have abnormal outcomes. A robust method to clearly distinguish between both cohorts is therefore critical in counseling pregnancies [Scott et al., 2013].

Whether in antenatal US or fetal MRI, routine assessment of VM relies on a simple 2D measurement of the atrial diameter (see Fig. 6) on a particular plane at the level of the atrium [Cardoza et al., 1988]. Nonetheless, reproducibility of these measurements is known to be variable, especially in US. The possibility of 3D fetal MRI simplifies volumetric measurements, and promotes computation of other features such as shape measurements. To the best of

our knowledge, VM has been studied in three works in the literature using motion-corrected 3D reconstructions of the fetal brain [Gholipour et al., 2012; Kyriakopoulou et al., 2014; Scott et al., 2013]. The volume of the ventricles has been shown to be more distinctive than the atrial diameter in diagnosing VM [Gholipour et al., 2012]. In Scott et al., [2013], volumetric and curvature analyses were performed to compare a group of isolated mild ventriculomegaly (IMVM) to a cohort of healthy fetuses between 22 and 25.5 GWs by identifying potential IMVM-specific deviations in tissue volume, and cortical and ventricular local surface curvature during fetal brain development. Except enlarged ventricular volume in IMVM, no significant difference was found in brain tissue or cortical volume between groups. However, evidence of cortical GM enlargement in IMVM fetuses was found in Kyriakopoulou et al., [2014] after analyzing the differences between 60 normal fetuses and 65 with IMVM across a wider age range of 22–38 GWs.

## DISCUSSION

The emergence of fast-sequence MRI combined with advanced techniques for motion correction [e.g., Jiang et al., 2007; Murgasova et al., 2012] has enabled the formation of 3D volumes of the in vivo fetal brain. This has supposed an immense step toward the understanding of the early cerebral maturational processes compared to conventional prenatal US, and the discovery of new 3D biomarkers associated with fetal brain anomalies that are more distinctive and reproducible. However, in contrast to the widespread techniques existing in the literature for adult brains, fetal brain MRI needs to be approached in a different manner due to the complex and rapid changes that occur in the brain. Methods working with MR images of the fetal brain must take into consideration the transient nature of several tissues (e.g., GMAT), the inverted contrast between tissues, and the substantial shape variation of the brain as growth proceeds. These challenges have stimulated the development of new methodological approaches that permit the study of the developing brain.

To better capture the dynamics of the laminar pattern and the changes in cortical folding, literature in fetal brain MRI encourages the creation of spatio-temporal atlases [e.g., Gholipour et al., 2014; Serag et al., 2012b], which shed light onto the fetal brain growth patterns by encoding temporal and inter-subject variability, and provide a common reference space for the study of the developmental process in the fetus. In addition, image processing techniques such as registration and segmentation may take advantage of these atlases to achieve better accuracy. Concerning segmentation methods of the fetal brain in MRI, the frequent PVE problem present in the boundary between CSF and GM, and the existing tissues at a particular GA have to be considered. Hence, atlas-based segmentation is highly useful in these scenarios to aid in segmentation, and spatio-temporal atlases have proved to be of great benefit.

State of the art segmentation methods allow to perform accurate volumetric analyses, providing a broader view than the standard 2D measurements used in clinical settings. Furthermore, studies concerning sulcation and gyrification of the cerebral cortex in the fetus are now easily viable through MRI, allowing for both qualitative and quantitative inspection. Segmentation of CP and SP is necessary for the study of cortical folding. Mapping and ordering the normal patterns of cortical folding [e.g., Clouchoux et al., 2012; Habas et al., 2012] can be used as a baseline to help detect regions of abnormal or delayed folding correlated with possible neurological disorders. Recently, spatio-temporal cortical surface atlases of the developing brain were created in Li et al., [2015] and Wright et al., [2015], providing patterns of cortical developmental trajectories at every point in the cortical surface and, therefore, establishing an accurate normative timing for gyrification.

In clinical settings, fetal brain MRI has become an important tool in confirming and complementing prior findings in US. Furthermore, now it is possible to develop automatic methods to facilitate the diagnosis of brain abnormalities in utero, and provide scalability to study large populations.

There are still many open directions to explore for researchers in fetal brain MRI. Reconstruction algorithms from motion-corrupted stacks rely on the segmentation of the brain from 2D slices. However, there exist no well-established segmentation approaches. In 3D reconstructed images of the fetal brain, the posterior medial part near the ventricles, for example, is a complicated region for the segmentation of the cortex. The availability of public databases with ground truth annotations and segmentation challenges, such as the NeoBrains12 [Isgum et al., 2015], for the fetal brain may boost research advances in this area. Regarding spatio-temporal modeling, existing atlases were created from healthy subjects and, therefore, only capture the morphological changes of the in utero brain in its normal course. A promising direction of future work could be the construction of disease-specific spatio-temporal atlases that show the dynamic disease-related changes in the brain and help understand disease progression. Another interesting direction of future work is to analyze the impact of congenital diseases in neurodevelopmental outcome. Longitudinal studies will allow neuroscientists to assess the effect of in utero brain anomalies in cognitive development and link the findings in structural MRI with brain connectivity and measurements from other modalities.

This work was restricted to T1w and T2w MRI. However, other imaging modalities, such as fMRI and DTI, can also be used to study the in vivo fetal brain. In Huang et al., [2009], DTI allowed both macro- and microscopic characterization of brain development, while fMRI was

also used to capture the emerging connectivity patterns in the fetal brain [Jakab et al., 2014]. Computational growth models conform another type of approach to understand the physical forces behind the formation of the cortical convolutions in the developing brain [Nie et al., 2010, 2011; Tallinen et al., 2016]. Combining the heterogeneous findings from all these modalities and approaches could synergistically improve the understanding of in utero brain development.

## CONCLUSIONS

In this article, we presented a thorough review of methodological advances to study early brain development from in utero structural MRI. The review outlined the challenging context for neuroscience research to achieve an improved understanding of in vivo fetal brain maturational mechanisms, motivated the need for the implementation of novel processing approaches, and reported the potential gains resulting from quantitative fetal MRI studies that can be realized in clinical practice.

## REFERENCES


Aljabar P, Bhatia KK, Murgasova MK, Hajnal JV, Boardman JP, Srinivasan L, Rutherford MA, Dyet LE, Edwards AD, Rueckert D (2008): Assessment of brain growth in early childhood using deformation-based morphometry. NeuroImage 39:348–358.

Altaye M, Holland SK, Wilke M, Gaser C (2008): Infant brain probability templates for MRI segmentation and normalization. NeuroImage 43:721–730.

Anbeek P, Išgum I, van Kooij BJM, Mol CP, Kersbergen KJ, Groenendaal F, Viergever MA, de Vries LS, Benders MJNL (2013): Automatic segmentation of eight tissue classes in neonatal brain MRI. PLoS One 8:e81895.

Avants BB, Yushkevich P, Pluta J, Minkoff D, Korczykowski M, Detre J, Gee JC (2010): The optimal template effect in hippocampus studies of diseased populations. NeuroImage 49: 2457–2466.

Bach Cuadra M, Schaer M, Andre A, Guibaud L, Eliez S, Thiran JP, 2009. Brain tissue segmentation of fetal MR images. In: MICCAI Workshop on Image Analysis for Developing Brain. Available at: https://infoscience.epfl.ch/record/141281/files.

Banović V, Škrablin S, Banović M, Radoš M, Gverić-Ahmetašević S, Babić I (2014): Fetal brain magnetic resonance imaging and long-term neurodevelopmental impairment. Int J Gynaecol Obstet 125:237–240.

Barkovich AJ (2005): Magnetic resonance techniques in the assessment of myelin and myelination. J Inherit Metab Dis 28: 311–343.

Beare RJ, Chen J, Kelly CE, Alexopoulos D, Smyser CD, Rogers CE, Loh WY, Matthews LG, Cheong JLY, Spittle AJ, Anderson PJ, Doyle LW, Inder TE, Seal ML, Thompson DK (2016): Neonatal brain tissue classification with morphological adaptation and unified segmentation. Front Neuroinform 10:12.

Bendersky M, Musolino PL, Rugilo C, Schuster G, Sica REP (2006): Normal anatomy of the developing fetal brain. Ex vivo anatomical-magnetic resonance imaging correlation. J Neurol Sci 250:20–26.

Breiman L (2001): Random forests. Mach Learn 45:5–32.

Brossard-Racine M, du Plessis AJ, Vezina G, Robertson R, Bulas D, Evangelou IE, Donofrio M, Freeman D, Limperopoulos C (2014): Prevalence and spectrum of in utero structural brain abnormalities in fetuses with complex congenital heart disease. Am J Neuroradiol 35:1593–1599.

Caldairou B, Passat N, Habas PA, Studholme C, Koob M, Dietemann JL, Rousseau F (2011): Data-driven cortex segmentation in reconstructed fetal MRI by using structural constraints. In: Computer Analysis of Images and Patterns. Berlin, Heidelberg: Springer Berlin Heidelberg pp. 503–511.

Cardoza JD, Goldstein RB, Filly RA (1988): Exclusion of fetal ventriculomegaly with a single measurement: The width of the lateral ventricular atrium. Radiology 169:711–714.

Claude I, Daire JL, Sebag G (2004): Fetal brain MRI: Segmentation and biometric analysis of the posterior fossa. IEEE Trans Biomed Eng 51:617–626.

Clouchoux C, Kudelski D, Gholipour A, Warfield SK, Viseur S, Bouyssi-Kobar M, Mari JL, Evans AC, du Plessis AJ, Limperopoulos C (2012): Quantitative in vivo MRI measurement of cortical development in the fetus. Brain Struct Funct 217:127–139.

Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, Tworetzky W, McElhinney DB, Brown DW, Gholipour A, Kudelski D, Warfield SK, McCarter RJ, Robertson RL, Evans AC, Newburger JW, Limperopoulos C (2013): Delayed cortical development in fetuses with complex congenital heart disease. Cereb Cortex 23:2932–2943.

Corbett-Detig J, Habas PA, Scott JA, Kim K, Rajagopalan V, McQuillen PS, Barkovich AJ, Glenn OA, Studholme C (2011): 3D global and regional patterns of human fetal subplate growth determined in utero. Brain Struct Funct 215:255–263.

Davatzikos C, Vaillant M, Resnick SM, Prince JL, Letovsky S, Bryan RN (1995): A computerized approach for morphological analysis of the corpus callosum. J Comput Assist Tomogr 20:88–97.

Dittrich E, Raviv TR, Kasprian G, Donner R, Brugger PC, Prayer D, Langs G (2014): A spatio-temporal latent atlas for semi-supervised learning of fetal brain segmentations and morphological age estimation. Med Image Anal 18:9–21.

Donofrio MT, Massaro AN (2010): Impact of congenital heart disease on brain development and neurodevelopmental outcome. Int J Pediatr 2010:12589–12596.

Dubois J, Benders M, Cachia A, Lazeyras F, Ha-Vinh Leuchter R, Sizonenko SV, Borradori-Tolsa C, Mangin JF, Hüppi PS (2008): Mapping the early cortical folding process in the preterm newborn brain. Cereb Cortex 18:1444–1454.

Dubois J, Dehaene-Lambertz G, Kulikova S, Poupon C, Hüppi PS, Hertz-Pannier L (2014): The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. Neuroscience 276:48–71.

Egaña-Ugrinovic G, Sanz-Cortes M, Figueras F, Bargalló N, Gratacós E (2013): Differences in cortical development assessed by fetal MRI in late-onset intrauterine growth restriction. Am J Obstet Gynecol 209:126.e1–126.e8.

Egaña-Ugrinovic G, Sanz-Cortés M, Couve-Pérez C, Figueras F, Gratacós E (2014): Corpus callosum differences assessed by fetal MRI in late-onset intrauterine growth restriction and its association with neurobehavior. Prenat Diagn 34:843–849.

Endres LK, Cohen L (2001): Reliability and validity of three-dimensional fetal brain volumes. J Ultrasound Med 20:1265–1269.

Evans A, Collins D, Mills S, Brown E, Kelly R, Peters T (1993): 3D statistical neuroanatomical models from 305 MRI volumes. IEEE Nucl Sci Symp Med Imaging Conf 3:1813–1817.

Fillmore PT, Richards JE, Phillips-Meek MC, Cryer A, Stevens M (2015): Stereotaxic MRI brain atlases for infants from 3 to 12 months. Dev Neurosci 37:515–532.

Fonov F, Evans AC, Botteron K, Almli CR, McKinstry RC, Collins DL (2011): Unbiased average age-appropriate atlases for pediatric studies. NeuroImage 54:313–327.

Gardosi J (2011): Clinical strategies for improving the detection of fetal growth restriction. Clin Perinatol 38:21–31.

Garel C (2008): Imaging the fetus: When does MRI really help? Pediatr Radiol 38:467–470.

Garel C, Chantrel E, Elmaleh M, Brisse H, Sebag G (2003): Fetal MRI: Normal gestational landmarks for cerebral biometry, gyration and myelination. Child's Nerv Syst 19:422–425.

Gholipour A, Estroff JA, Warfield SK (2010): Robust super-resolution volume reconstruction from slice acquisitions: Application to fetal brain MRI. IEEE Trans Med Imaging 29:1739–1758.

Gholipour A, Estroff JA, Barnewolt CE, Connolly SA, Warfield SK (2011): Fetal brain volumetry through MRI volumetric reconstruction and segmentation. Int J Comput Assist Radiol Surg 6: 329–339.

Gholipour A, Akhondi-Asl A, Estroff JA, Warfield SK (2012): Multi-atlas multi-shape segmentation of fetal brain MRI for volumetric and morphometric analysis of ventriculomegaly. NeuroImage 60:1819–1831.

Gholipour A, Limperopoulos C, Clancy S, Clouchoux C, Akhondi-Asl A, Estroff JA, Warfield SK (2014): Construction of a deformable spatiotemporal MRI atlas of the fetal brain: Evaluation of similarity metrics and deformation models. Med Image Comput Comput Assist Interv 17:292–299.

Girard NJ, Chaumoitre K (2012): The brain in the belly: What and how of fetal neuroimaging? J Magn Reson Imaging 36:788–804.

Glastonbury CM, Kennedy AM (2002): Ultrafast MRI of the fetus. Aust Radiol 46:22–32.

González Ballester MA, Zisserman AP, Brady M (2002): Estimation of the partial volume effect in MRI. Med Image Anal 6: 389–405.

Gousias IS, Edwards AD, Rutherford MA, Counsell SJ, Hajnal JV, Rueckert D, Hammers A (2012): Magnetic resonance imaging of the newborn brain: Manual segmentation of labelled atlases in term-born and preterm infants. NeuroImage 62:1499–1509.

Gousias IS, Hammers A, Counsell SJ, Srinivasan L, Rutherford MA, Heckemann RA, Edwards AD (2013): Magnetic resonance imaging of the newborn brain: Automatic segmentation of brain images into 50 anatomical regions. PLoS One 8:e59990.

Greenspan H, Ruf A, Goldberger J (2006): Constrained Gaussian mixture model framework for automatic segmentation of MR brain images. IEEE Trans Med Imaging 25:1233–1245.

Gui L, Lisowski R, Faundez T, Hüppi PS, Lazeyras F, Kocher M (2012): Morphology-driven automatic segmentation of MR images of the neonatal brain. Med Image Anal 16:1565–1579.

Habas PA, Kim K, Rousseau F, Glenn OA, Barkovich AJ, Studholme C (2008): Atlas-based segmentation of the germinal matrix from in utero clinical MRI of the fetal brain. Med Image Comput Comput Assist Interv 11:351–358.

Habas PA, Kim K, Corbett-Detig JM, Rousseau F, Glenn OA, Barkovich AJ, Studholme C (2010): A spatiotemporal atlas of MR intensity, tissue probability and shape of the fetal brain with application to segmentation. NeuroImage 53:460–470.

Habas PA, Scott J, Roosta A, Rajagopalan V, Kim K, Rousseau F, Barkovich J, Glenn OA, Studholme C (2012): Early folding patterns and asymmetries of the normal human brain detected from in utero MRI. Cereb Cortex 22:13–25.

Hill J, Dierker D, Neil J, Inder T, Knutsen A, Harwell J, Coalson T, Van Essen D (2010): A surface-based analysis of hemispheric asymmetries and folding of cerebral cortex in term-born human infants. J Neurosci 30:2268–2276.

Huang H, Xue R, Zhang J, Ren T, Richards LJ, Yarowsky P, Miller MI, Mori S (2009): Anatomical characterization of human fetal brain development with diffusion tensor magnetic resonance imaging. J Neurosci 29:4263–4273.

Isgum I, Benders MJ, Avants B, Cardoso MJ, Counsell SJ, Gomez EF, Gui L, Hppi PS, Kersbergen KJ, Makropoulos A, Melbourne A, Moeskops P, Mol CP, Kuklisova-Murgasova M, Rueckert D, Schnabel JA, Srhoj-Egekher V, Wu J, Wang S, de Vries LS, Viergever MA (2015): Evaluation of automatic neonatal brain segmentation algorithms: The NeoBrainS12 challenge. Med Image Anal 20:135–151.

Jakab A, Schwartz E, Kasprian G, Gruber GM, Prayer D, Schöpf V, Langs G (2014): Fetal functional imaging portrays heterogeneous development of emerging human brain networks. Front Hum Neurosci 8:852.

Jiang S, Xue H, Glover A, Rutherford M, Rueckert D, Hajnal JV (2007): MRI of moving subjects using multislice snapshot images with volume reconstruction (SVR): Application to fetal, neonatal, and adult brain studies. IEEE Trans Med Imaging 26:967–980.

Joshi S, Davis B, Jomier M, Gerig G (2004): Unbiased diffeomorphic atlas construction for computational anatomy. NeuroImage 23:151–160.

Kainz B, Steinberger M, Wein W, Kuklisova-Murgasova M, Malamateniou C, Keraudren K, Torsney-Weir T, Rutherford M, Aljabar P, Hajnal JV, Rueckert D (2015): Fast volume reconstruction from motion corrupted stacks of 2D slices. IEEE Trans Med Imaging 34:1901–1913.

Kazan-Tannus JF, Dialani V, Kataoka ML, Chiang G, Feldman HA, Brown JS, Levine D (2007): MR volumetry of brain and CSF in fetuses referred for ventriculomegaly. Am J Roentgenol 189:145–151.

Kazemi K, Moghaddam HA, Grebe R, Gondry-Jouet C, Wallois F (2007): A neonatal atlas template for spatial normalization of whole-brain magnetic resonance images of newborns: Preliminary results. NeuroImage 37:463–473.

Keraudren K, Kuklisova-Murgasova M, Kyriakopoulou V, Malamateniou C, Rutherford MA, Kainz B, Hajnal JV, Rueckert D (2014): Automated fetal brain segmentation from 2D MRI slices for motion correction. NeuroImage 101:633–643.

Kim K, Habas PA, Rousseau F, Glenn OA, Barkovich AJ, Studholme C (2010): Intersection based motion correction of multislice MRI for 3-D in utero fetal brain image formation. IEEE Trans Med Imaging 29:146–158.

Koch LM, Wright R, Vatansever D, Kyriakopoulou V, Malamateniou C, Patkee PA, Rutherford MA, Hajnal JV, Aljabar P, Rueckert D (2014): Graph-based label propagation in fetal brain MR images. In: MICCAI Workshop on Machine Learning in Medical Imaging. Springer International Publishing. pp. 9–16.

Kyriakopoulou V, Vatansever D, Elkommos S, Dawson S, McGuinness A, Allsop J, Molnár Z, Hajnal J, Rutherford M (2014): Cortical overgrowth in fetuses with isolated ventriculomegaly. Cereb Cortex 24:2141–2150.

Ledig C, Wright R, Serag A, Aljabar P, Rueckert D (2012): Neonatal brain segmentation using second order neighbourhood information. In: MICCAI Workshop on Perinatal and Paediatric Imaging. pp. 33–40. Available at: http://www.eng.ox.ac.uk/PaPI2012/Proceedings_files/PaPI2012_proceedings.pdf.

Lefèvre J, Germanaud D, Dubois J, Rousseau F, de Macedo Santos I, Angleys H, Mangin JF, Höppi PS, Girard N, De Guio F

(2015): Are developmental trajectories of cortical folding comparable between cross-sectional datasets of fetuses and preterm newborns? Cereb Cortex 26:3023.

Li G, Wang L, Shi F, Gilmore JH, Lin W, Shen D (2015): Construction of 4d high-definition cortical surface atlases of infants: Methods and applications. Med Image Anal 25:22– 36.

Limperopoulos C, Tworetzky W, McElhinney DB, Newburger JW, Brown DW, Robertson RL, Guizard N, McGrath E, Geva J, Annese D, Dunbar-Masterson C, Trainor B, Laussen PC, Du Plessis AJ (2010): Brain volume and metabolism in fetuses with congenital heart disease: Evaluation with quantitative magnetic resonance imaging and spectroscopy. Circulation 121:26–33.

Makropoulos A, Gousias IS, Ledig C, Aljabar P, Serag A, Hajnal JV, Edwards AD, Counsell SJ, Rueckert D (2014): Automatic whole brain MRI segmentation of the developing neonatal brain. IEEE Trans Med Imaging 33:1818–1831.

Malamateniou C, Malik SJ, Counsell SJ, Allsop JM, McGuinness AK, Hayat T, Broadhouse K, Nunes RG, Ederies AM, Hajnal JV, Rutherford MA (2013): Motion-compensation techniques in neonatal and fetal MR imaging. Am J Neuroradiol 34:1124–1136.

Mazziotta JC, Toga AW, Evans A, Fox P, Lancaster J (1995): A probabilistic atlas of the human brain: Theory and rationale for its development: The International Consortium for Brain Mapping (ICBM). NeuroImage 2:89–101.

McQuillen PS, Goff DA, Licht DJ (2010): Effects of congenital heart disease on brain development. Prog Pediatr Cardiol 29:79–85.

Melbourne A, Kendall GS, Cardoso MJ, Gunny R, Robertson NJ, Marlow N, Ourselin S (2014): Preterm birth affects the developmental synergy between cortical folding and cortical connectivity observed on multimodal MRI. NeuroImage 89:23–34.

Mlczoch E, Brugger P, Ulm B, Novak A, Frantal S, Prayer D, Salzer-Muhar U (2013): Structural congenital brain disease in congenital heart disease: Results from a fetal MRI program. Eur J Paediatr Neurol 17:153–160.

Murgasova MK, Aljabar P, Srinivasan L, Counsell SJ, Doria V, Serag A, Gousias IS, Boardman JP, Rutherford MA, Edwards AD, Hajnal JV, Rueckert D (2011): A dynamic 4D probabilistic atlas of the developing brain. NeuroImage 54:2750–2763.

Murgasova MK, Quaghebeur G, Rutherford MA, Hajnal JV, Schnabel JA (2012): Reconstruction of fetal brain MRI with intensity matching and complete outlier removal. Med Image Anal 16:1550–1564.

Nie J, Guo L, Li G, Faraco C, Miller LS, Liu T (2010): A computational model of cerebral cortex folding. J Theor Biol 264:467–478.

Nie J, Li G, Wang L, Gilmore JH, Lin W, Shen D (2011): A computational growth model for measuring dynamic cortical development in the first year of life. Cereb Cortex 22:2272–2284.

Ortiz A, Górriz JM, Ramírez J, Salas-González D (2013): Improving MRI segmentation with probabilistic GHSOM and multiobjective optimization. Neurocomputing 114:118–131.

Padilla N, Alexandrou G, Blennow M, Lagercrantz H, édén U (2014): Brain growth gains and losses in extremely preterm infants at term. Cereb Cortex 25:1897–1905.

Park H, Bland PH, Hero AO III, Meyer CR (2005): Least biased target selection in probabilistic atlas construction. Med Image Comput Comput Assist Interv 8:419–426.

Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC (1999): Structural maturation of neural pathways in children and adolescents: In vivo study. Science 283:1908–1911.

Pham DL, Prince JL (1999): Adaptive fuzzy segmentation of magnetic resonance images. IEEE Trans Med Imaging 18:737–752.

Prastawa M, Gilmore JH, Lin W, Gerig G (2005): Automatic segmentation of MR images of the developing newborn brain. Med Image Anal 9:457–466.

Prayer D, Kasprian G, Krampl E, Ulm B, Witzani L, Prayer L, Brugger PC (2006): MRI of normal fetal brain development. Eur J Radiol 57:199–216.

Rajagopalan V, Scott J, Habas PA, Kim K, Corbett-Detig J, Rousseau F, Barkovich AJ, Glenn OA, Studholme C (2011a): Local tissue growth patterns underlying normal fetal human brain gyrification quantified in utero. Neuroscience 31:2878–2887.

Rajagopalan V, Scott J, Habas PA, Kim K, Rousseau F, Glenn OA, Barkovich AJ, Studholme C (2011b): Spatiotemporal morphometry of adjacent tissue layers with application to the study of sulcal formation. Med Image Comput Comput Assist Interv 14:476–483.

Rajagopalan V, Scott J, Habas PA, Kim K, Rousseau F, Glenn OA, Barkovich AJ, Studholme C (2012): Mapping directionality specific volume changes using tensor based morphometry: An application to the study of gyrogenesis and lateralization of the human fetal brain. NeuroImage 63:947–958.

Rodríguez MR, Martínez FDV, Ten PM, Pedregosa JP, Fernández-Mayoralas DM, Jiménez M, de la Peña M (2010): Fetal MRI in CNS abnormalities. Relevant issues for obstetricians. Rev Argent Radiol 74:385–396.

Roelfsema NM, Hop WCJ, Boito SME, Wladimiroff JW (2004): Three-dimensional sonographic measurement of normal fetal brain volume during the second half of pregnancy. Am J Obstet Gynecol 190:275–280.

Rutherford M, Jiang S, Allsop J, Perkins L, Srinivasan L, Hayat T, Kumar S, Hajnal J (2008): MR imaging methods for assessing fetal brain development. Dev Neurobiol 68:700–711.

Rutherford MA (2001): MRI of the neonatal brain. Available at: www.mrineonatalbrain.com.

Sanroma G, Benkarim OM, Piella G, Ballester MÁG (2016): Building an ensemble of complementary segmentation methods by exploiting probabilistic estimates. In: MICCAI Workshop on Machine Learning in Medical Imaging. Springer International Publishing. pp. 27–35.

Scott JA, Habas PA, Kim K, Rajagopalan V, Hamzelou KS, Corbett-Detig JM, Barkovich AJ, Glenn OA, Studholme C (2011): Growth trajectories of the human fetal brain tissues estimated from 3D reconstructed in utero MRI. Int J Dev Neurosci 29:529–536.

Scott JA, Habas PA, Rajagopalan V, Kim K, Barkovich AJ, Glenn OA, Studholme C (2013): Volumetric and surface-based 3D MRI analyses of fetal isolated mild ventriculomegaly. Brain Struct Funct 218:645–655.

Serag A, Aljabar P, Ball G, Counsell SJ, Boardman JP, Rutherford MA, Edwards AD, Hajnal JV, Rueckert D (2012a): Construction of a consistent high-definition spatio-temporal atlas of the developing brain using adaptive kernel regression. NeuroImage 59:2255–2265.

Serag A, Kyriakopoulou V, Rutherford MA, Edwards AD, Hajnal JV, Aljabar P, Counsell SJ, Boardman JP, Rueckert D (2012b): A multi-channel 4D probabilistic atlas of the developing brain: Application to fetuses and neonates. Ann BMVA 53:1–14.

Shi F, Fan Y, Tang S, Gilmore JH, Lin W, Shen D (2010): Neonatal brain image segmentation in longitudinal MRI studies. NeuroImage 49:391–400.

Shi F, Shen D, Yap P, Fan Y, Cheng J, An H, Wald LL, Gerig G, Gilmore JH, Lin W (2011): CENTS: Cortical enhanced neonatal tissue segmentation. Hum Brain Mapp 32:382–396.

Shi F, Wang L, Wu G, Li G, Gilmore JH, Lin W, Shen D (2014): Neonatal atlas construction using sparse representation. Hum Brain Mapp 35:4663–4677.

Shyu K, Wu Y, Chen T, Chen H, Hu H, Guo W (2010): Analysis of fetal cortical complexity from MR images using 3D entropy based information fractal dimension. Nonlinear Dyn 61:363–372.

Studholme C (2011): Mapping fetal brain development in utero using MRI: The big bang of brain mapping. Annu Rev Biomed Eng 13:345–368.

Studholme C, Rousseau F (2014): Quantifying and modelling tissue maturation in the living human fetal brain. Int J Dev Neurosci 32:3–10.

Tallinen T, Chung JY, Rousseau F, Girard N, Lefevre J, Mahadevan L (2016): On the growth and form of cortical convolutions. Nat Phys 588–593.

Twickler DM, Magee KP, Caire J, Zaretsky M, Fleckenstein JL, Ramus RM (2003): Second-opinion magnetic resonance imaging for suspected fetal central nervous system abnormalities. Am J Obstet Gynecol 188:492–496.

Wang L, Shi F, Lin W, Gilmore JH, Shen D (2011): Automatic segmentation of neonatal images using convex optimization and coupled level sets. NeuroImage 58:805–817.

Wang L, Shi F, Li G, Gao Y, Lin W, Gilmore JH, Shen D (2014): Segmentation of neonatal brain MR images using patch-driven level sets. NeuroImage 84:141–158.

Wang L, Gao Y, Shi F, Li G, Gilmore JH, Lin W, Shen D (2015): Links: Learning-based multi-source integration framework for segmentation of infant brain images. NeuroImage 108: 160–172.

Warfield SK, Zou KH, Wells WM (2004): Simultaneous Truth and Performance Level Estimation (STAPLE): An algorithm for the validation of image segmentation. IEEE Trans Med Imaging 23:903–921.

Weisenfeld NI, Warfield SK (2009): Automatic segmentation of newborn brain MRI. NeuroImage 47:564–572.

Wilke M, Schmithorst VJ, Holland SK (2003): Normative pediatric brain data for spatial normalization and segmentation differs from standard adult data. Magn Reson Med 50: 749–757.

Wilke M, Holland SK, Altaye M, Gaser C (2008): Template-O-Matic: A toolbox for creating customized pediatric templates. NeuroImage 41:903–913.

Wright R, Kyriakopoulou V, Ledig C, Rutherford MA, Hajnal JV, Rueckert D, Aljabar P (2014): Automatic quantification of normal cortical folding patterns from fetal brain MRI. NeuroImage 91:21–32.

Wright R, Makropoulos A, Kyriakopoulou V, Patkee PA, Koch LM, Rutherford MA, Hajnal JV, Rueckert D, Aljabar P (2015): Construction of a fetal spatio-temporal cortical surface atlas from in utero MRI: Application of spectral surface matching. NeuroImage 120:467–480.

Xue H, Srinivasan L, Jiang S, Rutherford MA, Edwards AD, Rueckert D, Hajnal JV (2007): Automatic segmentation and reconstruction of the cortex from neonatal MRI. NeuroImage 38:461–477.

Zhang Y, Shi F, Wu G, Wang L, Yap PT, Shen D (2016): Consistent spatial-temporal longitudinal atlas construction for developing infant brains. IEEE Trans Med Imaging 35:2568–2577.