Mapping the developing human brain in utero using quantitative MR imaging techniques

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Abstract

Magnetic resonance imaging of the human fetal brain has been a clinical tool for many years and provides valuable additional information to compliment more common ultrasound studies. Advances in both MRI acquisition and post processing over the last 10 years have enabled full 3D imaging and the accurate combination of data acquired in different head positions to create improved geometric integrity, tissue contrast and resolution. This research is now motivating the development of new quantitative MRI based techniques for clinical imaging that can more accurately characterize brain development and detect abnormalities. In this paper we will review some of the key areas that are driving changes in our understanding of fetal brain growth using quantitative measures derived from inutero MRI, and possible directions for its increased use in improving the evaluation of pregnancies and the accurate characterization of abnormal brain growth.

1. Introduction

Our knowledge of the dynamic changes within the human brain in utero has been derived mainly from studies of animal fetal brain development [1, 2], postmortem human histology [3, 4] and more recently postmortem MRI [5, 6]. In humans, the use of magnetic resonance imaging (MRI) to examine living human fetal brain development in utero was, until around 10 years ago, focused on using multislice imaging techniques for visual radiological evaluation of morphology. The approach in day to day clinical use relied heavily on fast multi-slice imaging to freeze fetal head movements and provide the radiologist with basic 2D views of the developing brain. This type of imaging presents a significant advance over ultrasound studies that cannot provide the contrast between different brain tissues available to MRI. However, compared to adult brain MRI techniques, these types of studies are still crude. As a result it can be difficult to form reproducible interpretations for diagnoses or quantitative measurements for basic science studies, because of inconsistencies in slice positioning, image contrast and limited resolution. In general, the protocols rely on careful

planning of fast 2D slice acquisitions whereby motion is frozen within most slices to an extent that data is amenable to visual inspection by a radiologist. The inherent motion of the fetal head still precludes the routine use of longer 3D imaging techniques, or imaging that requires the collection of multiple images of the same anatomy to form a derived or parametric contrast. As such, evaluation of the brain morphology has been limited to a careful visual evaluation of slices acquired in poorly determined orientations.

Over the last decade, the use of faster snapshot slice acquisition techniques married with post-hoc computer vision approaches to 3D image estimation [7] has opened up a new window into the developing fetal brain. Full 3D imaging has always been possible on some fraction of cases where motion is by chance small during the imaging session. The key contribution has been to enable 3D imaging in the majority of cases to allow realistic studies to begin to be planned and executed. To compliment advances in clinical MRI there have been advances in our understanding of both normal and abnormal brain development that have begun to emerge from animal and postmortem studies. The underlying trend is to use techniques that can ensure accurate 3D imaging [8], and move toward the extraction of quantitative measures of brain development. In this article we will review how this methodology has been evolving to enable increased accuracy and reproducibility for in-utero MRI and highlight how this may impact both neuroimaging research and also the clinical evaluation of pregnancy.

2. Accurate Spatial Quantitation from 3D Structural Imaging

The development of techniques to robustly and accurately estimate full 3D head movements occurring between the accelerated acquisition of individual slices [9] in a multi-slice imaging study has been the basis for a range of new fetal imaging methodologies and studies. These include reconstruction based [9, 10, 11] and intersection based [12] between slice motion estimation techniques. In addition, techniques to remove the effects of changes in MRI signal strength between slices [13, 14] have enabled improved delineation of subtle developing tissue zones such as the sub-plate visible in T2W MRI. Most recently by ensuring high accuracy correction of motion, it has been possible to employ so-called super-resolution techniques when forming a 3D image from multiple 2D slices scattered by motion [15, 11]. These approaches extend a common technique in photographic image processing (super resolution) to the general problem of 3D imaging from 2D slices. This allows the deconvolution of the coarse through plane slice resolution by combining thick slices with fine in-plane resolution, that have been acquired in different anatomical planes. An example of the capabilities of such an approach are illustrated in figure 1 which compares an interpolation based estimation [9, 10] with an iterative deconvolution based method [16] for 3D image formation. This in particular results in much improved delineation of the complex cortical folding pattern emerging in the third trimester. In addition to resolution, the fusion of signal provides improved contrast that would normally be unavailable because of the imaging time required. Improved contrast to noise is important in the study of the subtle transient tissue zones that are apparent at earlier stages of gestation as illustrated in figure 2. Full 3D imaging in-utero has allowed these zones to be characterized in terms of shape and thickness during the key developmental period between 20 and 27GW [17].

2.1. Clinical Applications of Spatial Quantitation

More generally, quantitative MRI measurement techniques also encompass the accurate spatial quantitation of structures within the images, so that image geometric distortions and resolution become important factors in the image formation process. In the fetus early work made use of very careful human based measurements [18]. However, spatial quantitation is also dependent on methods beyond the domain of MRI physics and include higher level image analysis techniques including tissue segmentation [19]. These then allow a range of techniques including volume [20], surface [21], and layer thickness [17] based morphometric analyses.

These tools have been used to examine in 3D common clinical conditions seen in MRI of the human fetus. In particular, one of the most common conditions, ventriculomegaly which has been relatively crudely diagnosed by linear measurements of the ventricular space in 2D slices has recently been examined using motion corrected 3D T2W imaging. Scott *et al* have shown that in cases of mild ventriculomegaly [22], the shape of the ventricles have characteristic broad differences in shape that go beyond volume and linear dimensions. More interestingly, they were also able to detect significant delays in the cortical folding in mild ventriculomegaly, where there were no differences in overall brain tissue volumes when compared to normally developing fetuses. Such findings may be able to shed more light on the occurrence of delayed cognitive development in some cases of ventriculomegaly. In general ventriculomegaly, where ventricle size can be extreme, 3D image analysis has also shown measurable differences in brain growth [23].

There is an increasing body of literature showing congenital heart disease (CHD) leads to neurologic dysfunction shortly after birth prior to surgical interventions, in a significant proportion of this high-risk population. Early work in this population had identified abnormalities using spectroscopic imaging and measures of overall brain volume [24]. Using motion corrected 3D imaging of fetuses with with hypoplastic left heart syndrome (HLHS), Clouchoux et al have shown a progressive third trimester reduction in the volume of cortical gray and white matter and subcortical gray matter. These were apparently preceded by cortical folding delays in the frontal, parietal, calcarine, temporal, and collateral regions, indicating that subtle shape changes detectable by 3D imaging may be a more sensitive indicator of developmental problems.

Another key area where improved brain imaging in the fetus is expanding our knowledge of clinical populations is in the study of fetsus that are small for gestational-age. Here there is interest in looking more closely at brain growth. Recent work in this population using fast multi-slice fetal MRI has been able to detect characteristics differences in development in the insular cortex [25] when compared to the brain anatomy of normally developing fetuses.

3. Quantitative Contrast MRI

Within the MRI physics field, the term quantitative MRI generally refers to techniques focusing on the mapping of underlying material properties that induce basic MRI contrast [26]. These properties include Proton Density (PD), Longitudinal Relaxation (T_1), Transverse Relaxation (T_2), Magnetization Transfer (MT) and Spectroscopic estimation ^1H

of absolute metabolite concentrations. The term can also extend to include the quantitative measurement of motion of material within the tissues with techniques such as diffusion imaging (random motion of spins in a constrained homogeneous solution), perfusion (amount of blood traveling through capillaries in ml/s/gm of tissue) and flow (bulk motion of fluids such as blood) imaging. Unlike basic radiological imaging of 'weighted' image contrast (T_1W, T_2W) for visual inspection, these techniques are aimed at creating images whose contrast is calibrated and is therefore independent of machine and operator variations. Such methods can be more precisely termed quantitative contrast MRI. Quantitative contrast, although more expensive in requiring longer imaging times has been shown to be able to provide improved sensitivity over conventional weighed contrast [27]. As a result these approaches are becoming more widely used in the context of adult imaging, both for scientific studies and in clinical practice.

A key area of interest for in-utero brain studies is the possibility of better understanding and early detection of fetal brain abnormalities arising from environmental and maternal factors. Within this area, fetal alcohol exposure is the leading cause of environmentally induced birth defects and neuro-developmental mental retardation in the western world [28]. The resulting effects have been studied extensively in children and adults. Exposure inutero is known to be related to impairments in cognitive function and changes in behavior [29], that result in life long impairments [30] that have significant impact on health care and society as a whole. While current criteria for clinical diagnosis of Fetal Alcohol Spectrum Disorder (FASD) are reliable, they are only applicable in mid to late childhood [31]. MR based neuroimaging has been explored for pediatric imaging of brain growth after fetal alcohol exposure with the aim of identifying earlier biomarkers that may enable reliable diagnosis earlier in life [32] and could stimulate the development and use of more powerful treatment strategies as the brain is still developing functionally and structurally.

Neuroimaging studies in children who have been exposed to alcohol in utero have shown measurable differences in brain shape [33, 34]. Postnatally, this work has shown an overall reduction in brain size as well as characteristic shape differences. These include narrowing of the parietal region and reduced growth in the frontal lobe, cerebellar vermis, corpus callosum and caudate nucleus implying that alcohol exposure may be regionally specific.

The work of Zhou et al [35] and Fernandez et al [36] has shown differences in cortical thickness and its change with age in children exposed to alcohol in utero, and raise the question of whether in-utero measurements can be made to better characterize these conditions at an earlier stage. Measurements in fetal animal models of FASD have shown that early exposure results in cell number reductions in the cerebral cortex [37] and detected abnormal microscopic cellular organization [38] and also abnormalities in dendrite development [39].

3.1. Quantitation of Fetal Brain Cortical Microstructure

Most recently these basic cellular level findings have been translated to practical MRI measures by Leigland et al [40]. Specifically it has been shown that quantitative fractional anisotropy measures by MRI in the cerebral cortex remain higher in EtOH exposed fetuses when compared to unexposed fetuses. FA would normally decrease with age reflecting

differentiation of neurons [41]. The findings in EtOH exposure indicate that the morphological complexity of axonal and dendritic processes may not be increasing as would be expected during development, when EtOH exposure has occurred [40].

A disadvantage of diffusion MRI for basic science studies is its low resolution, however this can also be used to advantage in that the quantitative measurements made reflect the morphological properties of ensembles of cells. As such the technique can be used to provide a window into a useful scale of tissue property less accessible to single cell and microscopic imaging, that can be related more directly to macroscopic structures such as cortical folds.

3.2. Quantitation of Connectivity from Macroscopic Diffusion Patterns

Diffusion MRI can not only provide macro-structural information on a voxel level, but can be used to explore large scale consistency of microstructure in the form of diffusion based white matter connectivity measures, reflecting the underlying axonal connections [42]. Prior to the use of motion correction in fetal imaging, tractography of the fetal brain has been used in cases of limited motion to explore the formation of white matter connections [43] in-utero. The first work on extending between slice motion correction to fetal imaging [44] illustrated the potential power of the approach for more general studies of the fetus where significant motion was present. These early methods have been developed significantly over recent years. Model free approaches based on a 5D interpolation of diffusion data (3 spatial and two angular) have been explored by [45]. More recently, the work on iterative or deconvolution based image estimation of conventional T2W contrast, has been extended to diffusion data. This uses model based diffusion estimation using a DTI model [46] to form isotropic voxel resolution from multiple lower resolution slice planes. This approach was further developed specifically for fetal brain imaging to allow the combined estimation of slice orientation and isotropic image resolution [47] from multiple slice planes in a so-called unified approach to diffusion weighted slice alignment.

These types of approach, providing both motion robustness and increased spatial resolution, have enabled more powerful computational techniques to begin to be deployed to study the developing connectivity in the human brain as illustrated in figures 3 and 4. These techniques include global tractography (Figure 5), probabilistic tractography [45] and graph analysis [48]. In particular, early work has shown the ability of graph based metrics to detect the emergence of small world properties in the fetal brain before birth [49]. These more powerful motion-corrected based imaging and analysis techniques have also begun to be applied to clinical cases to identify new features of abnormal connectivity development [50] in utero.

3.3. Relaxation Properties of Developing Tissues

Quantitative $T*2$ measurements of early brain development using MRI of babies born prematurely [51] has shown values are elevated when compared to those seen in adults. This raises the question of whether those measurements are normal or represent some indication of injury after premature birth. Measuring such values in-utero will provide an age equivalent reference against which these values can be compared. In addition there has been

considerable interest in the use of functional imaging to study early brain growth using Blood Oxygen Level Dependence (BOLD) contrast. BOLD contrast and its measurement are dependent on the underlying relaxation properties of the tissue being studied. Given the very different nature of, in particular, mid gestation neuroanatomy, the optimum imaging parameters are not known for any functional MRI study.

For contrast based quantitation, in fetal MRI studies, the techniques are still in their infancy. This is primarily due to the requirement for multiple measurements in most quantitative MRI contrast techniques. Even relatively efficient techniques [52] used in adult studies requiring minimal image sets for parameter estimation are in-practical for fetal studies. As a result, the first fetal studies have recently focused on faster echo planar techniques. The first $R*2$ measurements made in-utero were as part of motion robust functional imaging [53] which collected multi-slice time series data using only two-echoes. Later work by Vasylechko [54] has used multiple echo times to form a more stable estimate of $T*2$ in the context of basic parametric imaging, using slice based measurements only. The technique acquired multiple echoes at each slice location before proceeding to imaging the next slice location. Such an approach minimizes motion between the subsequent echoes, but makes it less feasible to recover between-slice motion in order to reconstruct a 3D volume, because of the time between spatially neighboring slices. The recent findings based on this approach have indicated that there may be differences between the premature-neonatal and in-utero relaxation properties of tissues. Figure 6 illustrates the changes in $T*$ maps with age as the fetal brain develops over time. These are overlaid onto conventional T_2W images. We show the un-interpolated voxel dimensions to highlight the difference in resolution. Although much lower resolution, the $T*$ contrast between different developing tissue regions appears much more significant than that seen in basic T_2W imaging (eg figure 2).

4. Summary

The last ten years has seen a number of methodological advances that have improved our ability to image the growing human fetal brain. Initial work focused on 3D image formation in the presence of motion during fast multi-slice imaging. This in particular moved 3D MRI imaging as a tool for use in a small subset of fetuses where there is limited motion, to a tool that can be generally applied for practical clinical and basic science studies. These methods have since been further developed to provide both improved contrast and improved spatial resolution for conventional T_2W anatomical imaging. The same basic idea has been generalized to create model based quantitative multi-slice imaging methods that make use of between slice motion correction to combine MRI measures needed for quantitative contrast imaging. Current examples include 3D diffusion and relaxometry based imaging. These techniques promise to dramatically expand our understanding of normal and abnormal brain development in-utero and provide a range of new tools for the clinician when evaluating pregnancies.

Acknowledgments

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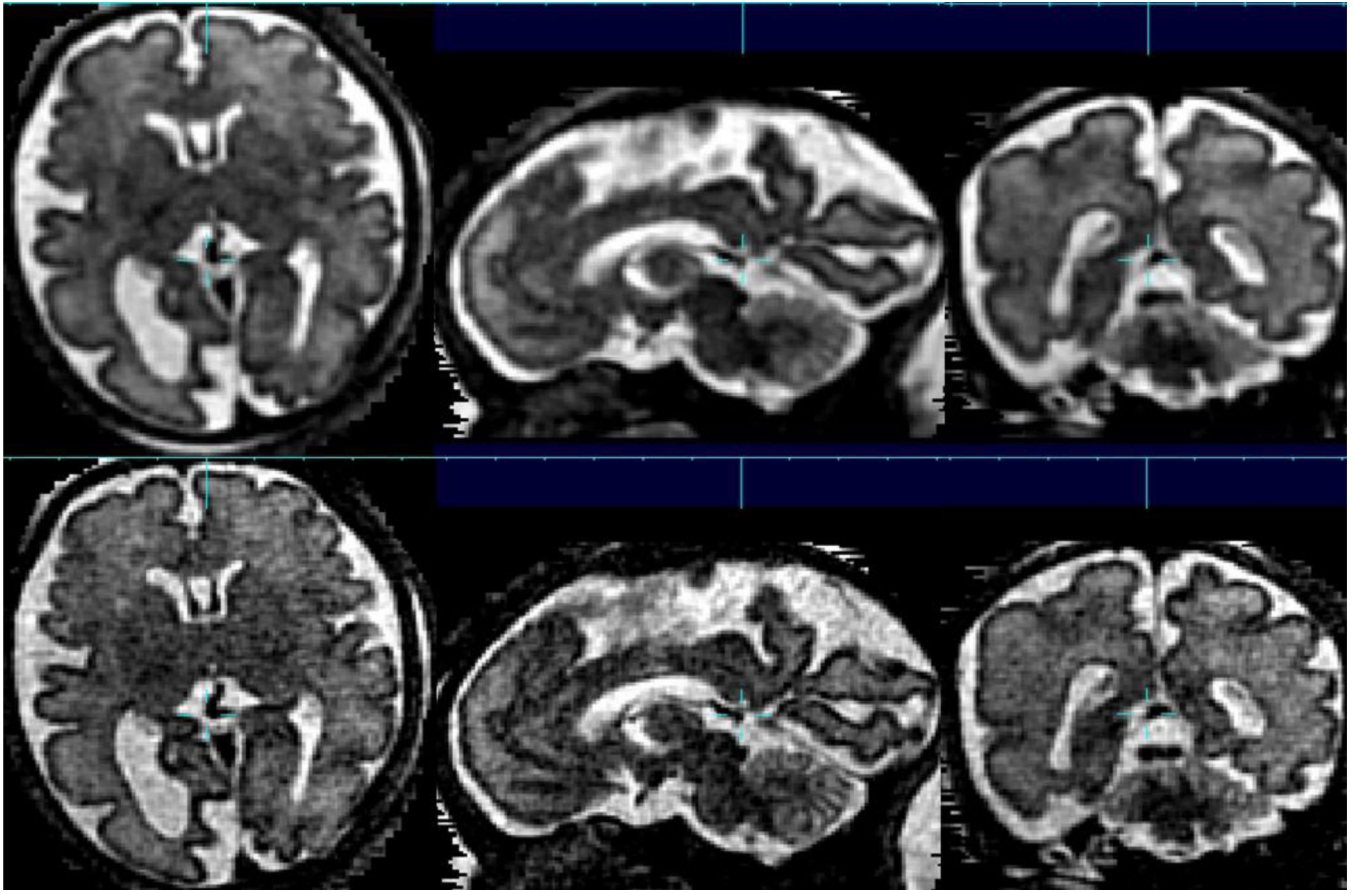
Figure 1.
An example of the advantages of between slice motion correction combined with deconvolution based 3D image reconstruction (lower row) from multi-slice data, allowing a voxel size of 0.75×0.75×0.75mm to be formed from multislice, multiplane acquisitions with original slice thickness of 3.3*mm*. For comparison, a direct interpolation based estimated is shown in upper row. Such increased spatial resolution is particularly important in studying the cortex in later stages of gestation where the brain is becoming highly folded and complex, with many of the gyri and sulci already formed, while the brain remains relatively small in relation to its final adult size.
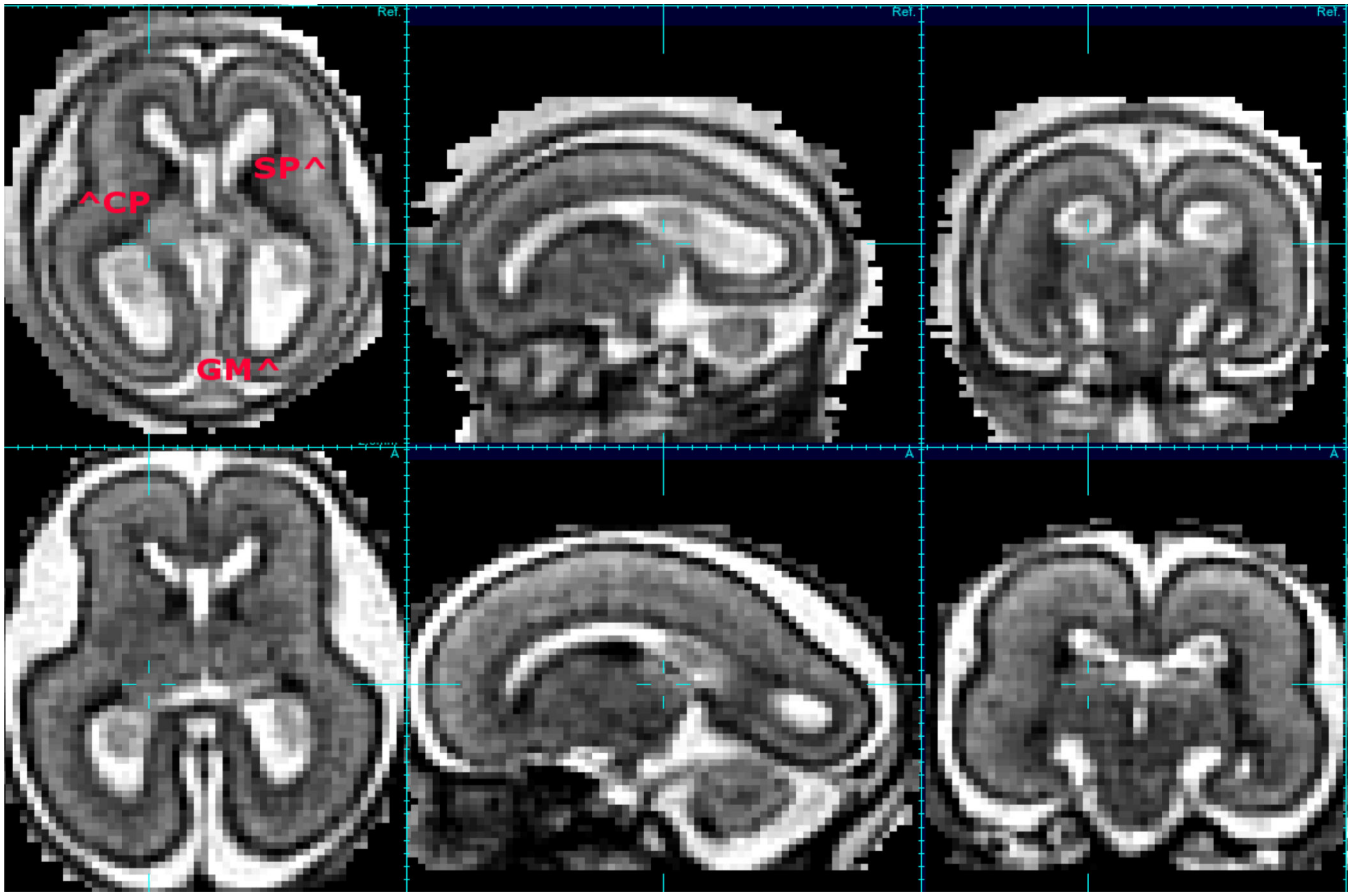
Figure 2.
An example of a motion correction 3D image of conventional T2W contrast (motion corrected $1.0 \times 1.0 \times 1.0$mm HASTE imaging) at 20GW and 23GW showing changes in contrast of developmental zones (CP=Cortical Plate, GM=Germinal Matrix, SP=Subplate) over a short time interval with sub-plate visible in the brain at 20GW loosing contrast over the next 3 or so weeks.
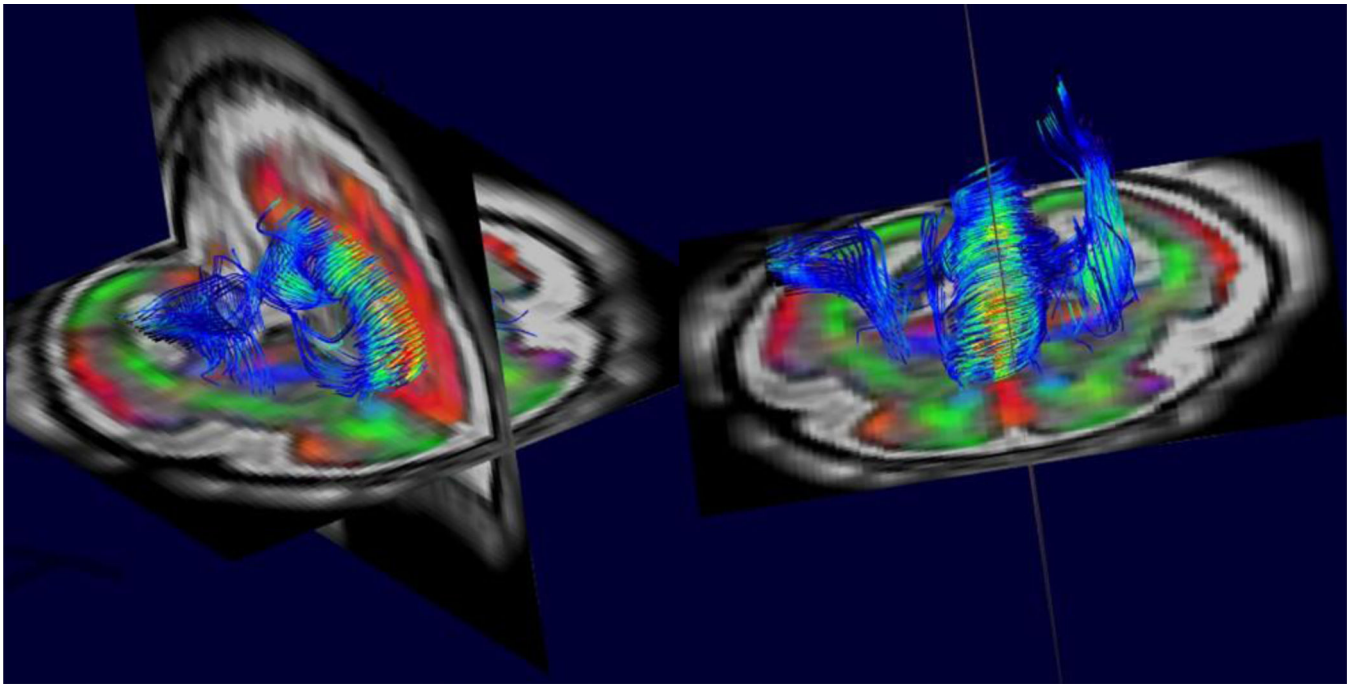
Figure 3.
An example of between slice motion corrected high resolution 3D diffusion tensor imaging from combined multi-slice and multi-plane DWI. This allows tractography based analysis to quantify the development of white matter connections within the fetal brain based on the estimates of water diffusion over the brain. Note also the color coded direction map of the surrounding anatomy that highlights the highly radial structure of the cortex at this early stage of development. This contrasts with the cortical microstructure of the adult cortex which provides no directional constraints on the diffusion of water..
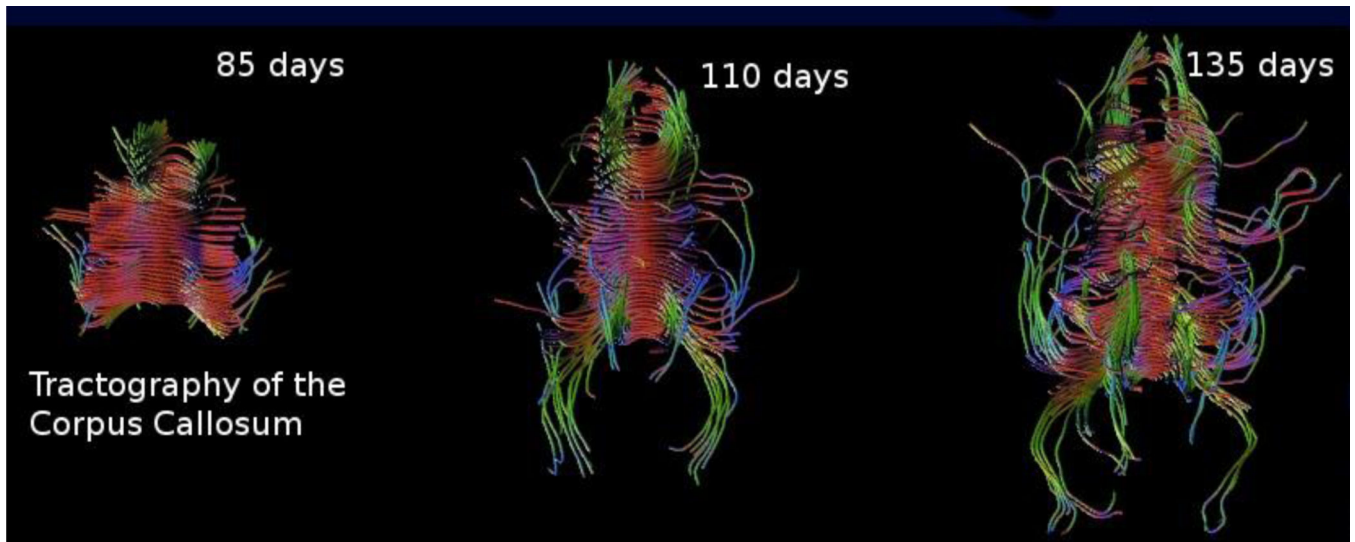
Figure 4.
For basic science studies of how the human brain develops, a key advantage of MRI is the ability to study normal brain anatomy over time. Here we see the development of the corpus callosum as imaged by motion corrected DTI [47] and mapped by tractography.
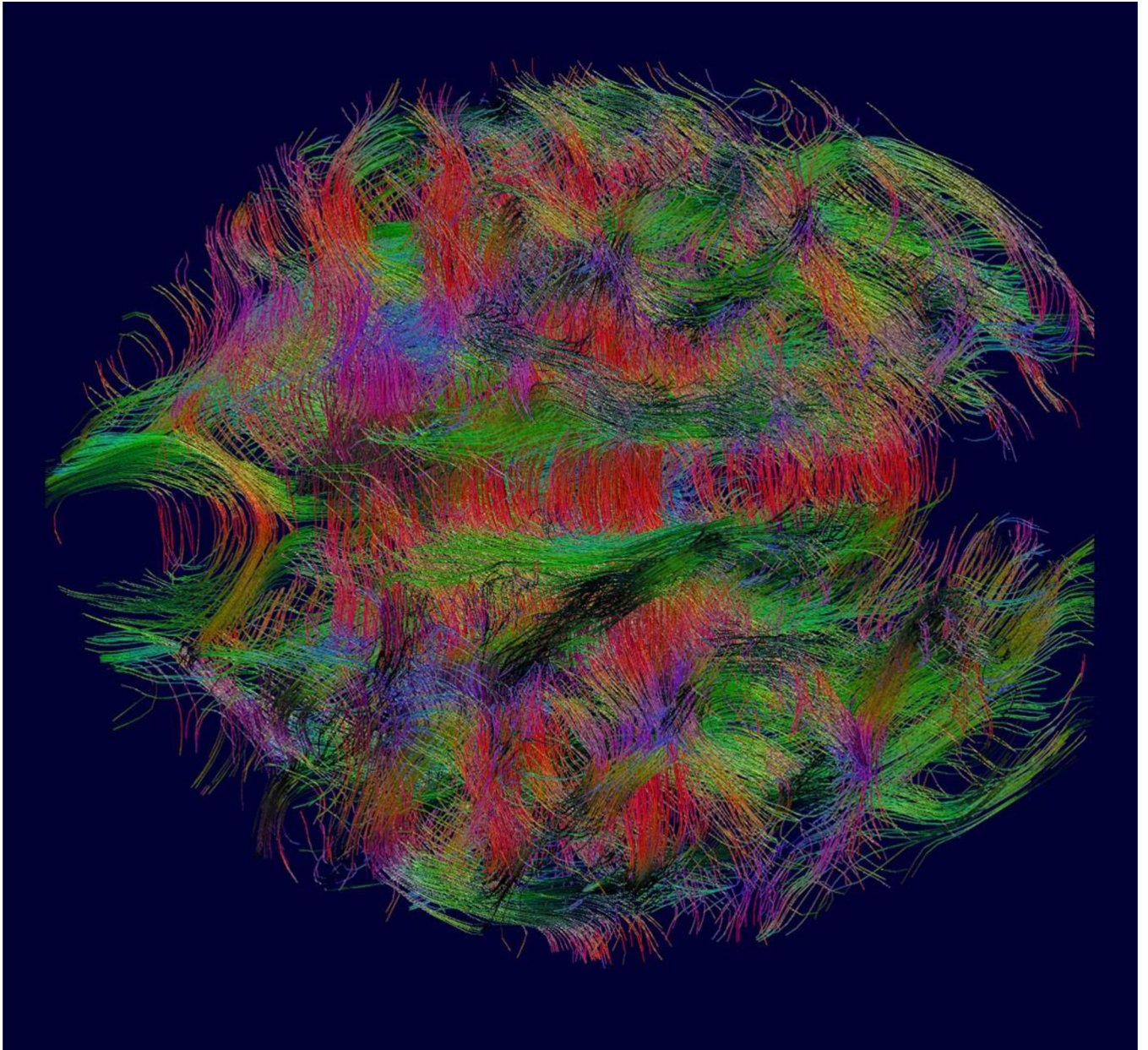
Figure 5.
Global tractography of fetal white matter can be used on motion corrected whole brain diffusion imaging studies to create a summary of interconnections between cortical and subcortical grey matter. Combined with graph analysis methods, this type of data allows us to study the development of small world connectivity [49] in the developing fetus
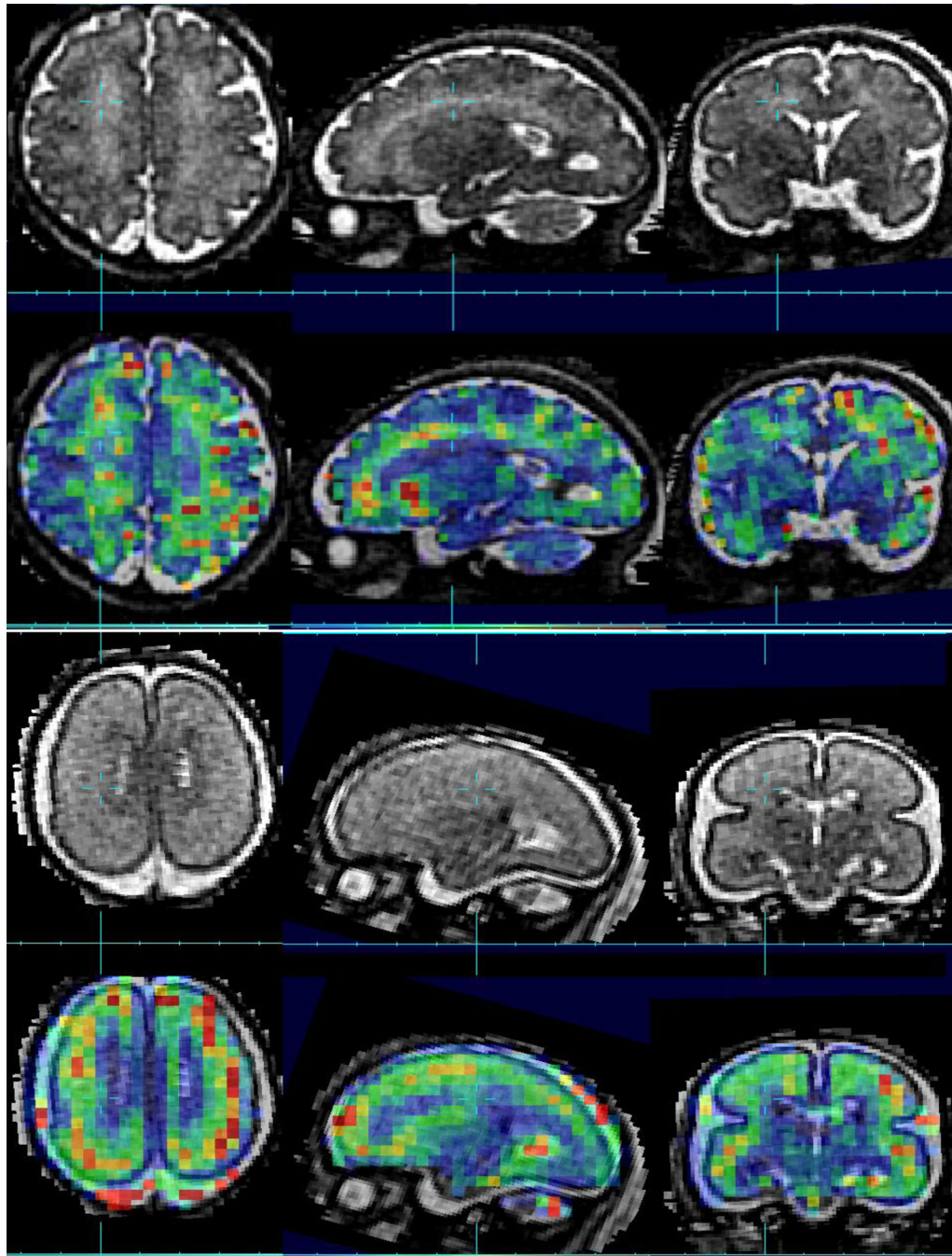
Figure 6.
Example Conventional T_2W contrast ($1.0 \times 1.0 \times 1.0$mm HASTE imaging) with a color overlay of quantitative $T*2$ imaging estimates ($3.0 \times 3.0 \times 3.0$ mm dual echo EPI) in the same fetus imaged at 20GW (lower row) and 35GW (upper row)..