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Challenges in Pediatric Neuroimaging

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Abstract

Pediatric neuroimaging is challenging due the rapid structural, metabolic, and functional changes that occur in the developing brain. A specially trained team is needed to produce high quality diagnostic images in children, due to their small physical size and immaturity. Patient motion, cooperation and medical condition dictate the methods and equipment used. A customized approach tailored to each child's age and functional status with the appropriate combination of dedicated staff, imaging hardware, and software is key; these range from low-tech techniques, such as feed and swaddle, to specialized small bore MRI scanners, MRI compatible incubators and neonatal head coils. New pre-and post-processing techniques can also compensate for the motion artifacts and low signal that often degrade neonatal scans.

Keywords

Pediatric neuroimaging; MRI; fetal imaging; neonatal imaging

Background

Changes in the developing brain can be observed and measured though both structural and functional imaging. Pediatric neuroimaging presents a number of challenges, which vary based on the age of the patient. First and foremost, the pediatric brain is structurally and chemically different than the adult brain, as it changes rapidly during early growth and development (Barkovich and Raybaud, 2012). In addition to these intrinsic challenges posed by the changing brain, there are challenges posed by the children, especially those younger than 6 years of age, who are frequently unable to follow instructions and remain stationary during an MRI exam (Barkovich et al., 2017).

The small brain sizes in premature neonates and fetuses make obtaining adequate signal to noise difficult, especially if using a standard adult head coil. The developing brain

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morphology develops rapidly, with sulcation progressing significantly from 14 weeks post-conceptional age, when the lateral sulcus initially develops, to term corrected age, where all of the major sulci and gyri have formed (Barkovich and Raybaud, 2012). Sulcation patterns in a 28-week-old fetus are markedly different (much simpler) than in a term neonate and in older infants. As the brain continues to mature, the sulci deepen and grow in number, a process that continues through infancy (Fig. 1, 2, 3, 4). The neonatal brain has a very high water content, predominantly in the unmyelinated white matter. Brain water content decreases as axons become coated by myelin during the first two years of life and the more densely packed, hydrophobic, tissue displaces free water. In the myelinating brain, the MR signal characteristics of partially myelinated white matter are very similar to those of grey matter, resulting in poor grey matter-white matter contrast in the incompletely myelinated regions, most appreciable at 4 months of age (Barkovich and Raybaud, 2012). This poor grey-white contrast makes it difficult to automatically segment infant brains, particularly at 3 to 6 months of age (Wang et al., 2015).

In addition to structural changes, the chemical and functional composition of the pediatric brain changes dramatically during early development. The relative concentrations of brain metabolites differ in neonates compared to adults; neonatal brains have relatively higher choline concentration compared to N-acetylaspartate (NAA), the result of membrane and cell turnover during neural development (Barkovich and Raybaud, 2012). The large choline to NAA ratio in neonates, in contradistinction in the normal, smaller, ratio in adults, is similar to that seen in adult inflammatory lesions and brain tumors, which also have rapid cell and membrane turnover (Fig. 5) (Kugel et al., 1992; Vigneron et al., 2001). Metabolite concentrations vary throughout the brain at all gestational ages, as different regions mature at different rates and at different times (Barkovich and Raybaud, 2012).

Diffusion characteristics of the brain change during development, although the diffusivity of water varies throughout the brain at all ages due to microstructural differences (Partridge et al., 2005). As the brain myelinates and free water is displaced, diffusivity within the deep white matter decreases (Fig. 6). Fractional anisotropy (FA) increases with age as axons myelinate and mature; FA also varies with the compactness of the white matter tracts (Barkovich and Raybaud, 2012). The most recent advances in structural connectivity show that developmental changes in the connectome also reflect the maturation of white matter tracts and brain development (Fig. 7A–B). Node strength and edge number both increase as the normal brain matures and develops, and as brain networks mature (Fig. 7C–D) (Tymofiyeva et al., 2014).

Outside of physiological differences between pediatric and adult brains, gross motion of the neonate’s head is the major limiting factor to obtaining high quality scans. Neonates and young infants are can be successfully imaged without sedation as they can be fairly well controlled by using the feed and swaddle technique (discussed below), wrapped in a vacuum bean bag with ear muffs and eye covering. In contrast, older infants, toddlers, and young children can be very difficult to image without sedation (Barkovich et al., 2017). These children are old enough to be aware of the surrounding environment and react to noises, but they are not yet old enough to fully understand the purpose of the exam and follow instructions. Due to the high tissue water content, the key diagnostic sequences are spin echo

based T2 or EPI based diffusion. These acquisition methodologies are, unfortunately, either relatively slow or susceptible to motion artifacts (Fig. 8).

Motion is less challenging in fetal imaging, as while the fetus can be quite mobile within the uterus, multiple individually targeted single shot images can be obtained to cover the whole brain in standard anatomic planes. Largely because of signal to noise limitations due to the small size of a fetal brain and fetal motion (especially during the second trimester), conventional volumetric acquisitions are currently not routinely performed in fetal imaging (Brossard-Racine et al., 2017). Even imaging in a single anatomic plane can be challenging without careful technologist monitoring since fetal motion can cause the anatomy of interest to move out of plane between individual slice acquisitions. Fast single shot techniques such as single shot fast spin echo (ssFSE) or echo planar (EPI) based methods are generally employed to acquire diagnostic images of the fetal brain (Barkovich and Raybaud, 2012).

Despite all these difficulties, by approaching pediatric neuroimaging differently than adult imaging, it is frequently possible to acquire a complete diagnostic or research imaging examination. We will discuss a number of strategies to cope with these challenges, from simple changes of staff protocols to those that involve specialized image acquisition methods, staff training, and imaging hardware.

Discussion

The unique challenges involved in successfully imaging the neonatal and pediatric brain necessitate a diverse compliment of approaches, which vary with patient age and condition. We will address some critical issues individually and then discuss a number of technical approaches for overcoming these challenges.

Patient Motion

The approaches for dealing with patient motion vary depending on the age of the child. For purposes of imaging, there are four major age groups to consider: fetuses, neonates and infants (0–1 year), young children (1–6 years) and older children (6 years and older). While sedation given to the mother is acceptable in some parts of the world for fetal imaging, it is not used in the United States and not considered for research studies.

Fetal motion is generally dealt with using both acquisition and post-processing techniques and will be discussed in more detail in the subsequent section.

Neonates and young infants move less extensively, given their relatively early developmental stage, and can sometimes be imaged without the need for any sedation. Our routine is to use a feed and swaddle technique and to coordinate the imaging with the infants' biorhythms. This inexpensive and low-tech approach is the first line method for improving image quality for children at this age (Barkovich et al., 2017). Successful feed and swaddle requires a well-trained and coordinated multidisciplinary team including neonatal nurses, MRI technologists, radiologists, and pediatric intensivists. The procedure involves careful coordination and communication starting long before the patient is scanned, to minimize disturbance to the infant as well as time spent outside of the NICU. After the study is

requested, technologists and the patient's bedside nurse discuss when the scanner will be available. When possible, the scan is performed during the infant's normal naptime. Roughly 30 minutes prior to the expected scan time, the patient is fed, and then swaddled. All lines, tubing, and monitoring equipment are exchanged with MR compatible devices and the MRI safety checklist is completed, all while still in the neonatal intensive care unit (NICU). Hearing protection is fitted, with both earplugs and overlying earmuffs. At our institution, we use an MR compatible bean bag body pillow, which is fastened loosely around the patient and can be tightened further by removing the air immediately prior to transport to the scanner (Fig. 9). At the pre-appointed time, the child is transported to the MR scanner, which is on hold for the patient. Ideally, the imaging protocol is kept to the minimum number of sequences required to answer the clinical question; noisiest sequences are held to the end of the scan. If the child becomes restless during the scan, an oral sucrose solution can be administered, this often calms the patient. We find this approach is frequently successful in limiting motion of neonates and younger infants.

Imaging young (2 – 6-year-old) children can be quite difficult, as these children nap less frequently than infants, are more mobile, are still often unable to understand the reason for the scan, and can have difficulty following verbal instructions. A dedicated child life team, mock scanners, and MR compatible video goggles can all help younger children acclimate to the scanner environment and stay still and cooperate with the scan (McGuirt, 2016). Still, this age is the most difficult and sedation, administered by an anesthesiologist, is still sometimes necessary. When an MRI examination is performed with sedation, it is critical prior to the end of the exam to ensure that all the necessary sequences are obtained and are of diagnostic quality in order to avoid repeated sedation.

Older children are frequently easier to image without sedation, especially when the reason for the scan and the process for scanning are explained to the child in advance. A dedicated child life team and practice session using a mock scanner can also help make the process less anxiety-provoking for these children (de Bie et al., 2010). In addition, for long examinations in children who have difficultly laying still, the scan can be broken into manageable 20 to 30 minute segments, allowing for brief breaks when necessary.

Fetal imaging

Fetal motion can be significant and is more problematic at earlier gestational ages (when the fetus can move freely in a relatively large volume of amniotic fluid)[1]; rapid single slice images or very rapid 2D sequences are most commonly acquired. Later in gestation, fetal movement is more restricted and motion is often less problematic. Because of frequent fetal motion and low signal from the small fetal brain, conventional 3D MR imaging is not used; however, 3D volumes of fetal brains can be obtained by combining numerous single slice acquisitions using Snapshot MRI with Volume Reconstruction (SVR) (Jiang et al., 2007). This technique requires the target anatomy to not change shape or size during the acquisition, and for the target to move sufficiently so that a complete evaluation of the entire sample can be obtained with repeated single slice acquisitions. Both conditions can be met

[1]Fetal Motion https://youtu.be/djJnsC_CddI Accessed September 2017

easily, since the brain is relatively non-deformable and the imaging plane can be moved if the fetus does not. With this method, overall signal to noise is increased, and an isotropic 3D volume of a manually defined sub-region is obtained from oversampling with numerous 2D acquisitions.

Hardware

Imaging prematurely born neonates and other medically unstable infants can be extremely challenging for reasons other than motion. Many patients in the neonatal intensive care unit are too ill to be removed from their incubators for any length of time. In addition, transferring and transporting the life support equipment in the MRI suite can be time consuming and challenging. An MRI compatible incubator (commercially available for approximately $300,000), in conjunction with an incubator compatible high channel count phased array, brings the scanner environment to the NICU. The child can be moved to the MRI compatible incubator in the controlled NICU environment, then transported to the scanner in an MR compatible setting with all the MRI compatible life support equipment already in place and connected (Fig. 9). This reduces the time where an ill infant is out of the NICU, and minimizes stimuli immediately preceding the scan, decreasing unwanted patient motion. The high channel count phased array head coil is designed to fit inside the MR compatible incubator, with several coil sizes desired for different gestational ages (Fig. 10) (Keil et al., 2011). MR signal is already low when imaging neonates, so the customized fit of these specialized arrays helps maximize signal to noise (Fig. 11) while keeping the face unobstructed to allow for airway access, crucial in critically ill infants.

MRI scanners designed specifically for pediatric applications can improve image quality. Although scanner bore size is most commonly discussed in the context of adult patients who are larger than the scanner bore, small bore scanners are presently being developed for pediatric and neuroimaging applications (Weavers et al., 2016). A prototype small bore 3T scanner (37-cm head bore size) with increased gradient slew rates (85 mT/m and 700 T/m/s head gradient performance), has decreased distortion at air tissue interfaces, particularly when performing echo-planar imaging (EPI). In addition, the smaller scanner (weighing approximately 2000 pounds) is small enough to be installed near the neonatal intensive care unit, decreasing the time and difficulty of transport, and keeping the patient close to the NICU staff during the scan. The small-bore scanner’s most significant advantage is allowing for faster scans using higher gradient strength and slew rate.

Acquisition

Given the concurrent challenges of patient motion and low signal in pediatric neuroimaging, there are two competing goals in sequence design: to increase signal to noise while maintaining or shortening scan time. Pre- or post-processing to correct for patient motion can salvage what might have otherwise been a non-diagnostic study. Limited fast MRI with single shot fast spin echo imaging (SSFSE/HASTE) can be obtained rapidly, but suffers from poor lesion contrast and low spatial resolution (Patel et al., 1997). Radial acquisition of k-space can reduce motion artifact and decrease scan time, but results in image blurring and other artifacts (Forbes et al., 2003; Liu et al., 2014). Prospective motion correction (PROMO) is a technique which uses spiral navigators to perform real time rigid-body

motion tracking and correction during the dead time of a standard image acquisition (Brown et al., 2010) (Fig. 12). Butterfly navigators are another method of prospective motion correction using a modified spin-warp sequence (Cheng et al., 2012). Since image translation due to motion causes a linear phase in k-space, a spin-warp sequence in which the prewinder gradients are slightly modified to traverse the same trajectory at the beginning of each data acquisition can correct for that motion. Although most commonly used in fetal imaging, post processing using single volume reconstruction or patch volume reconstruction where either a single (SVR) or multiple (PVR) 3D volumes are reconstructed from oversampling with numerous 2D slices (Alansary et al., 2017; Jiang et al., 2007) can compensate for some motion and low signal.

Post-processing

Quantitative image analysis is increasingly important for both clinical imaging and research, and quantitative metrics of brain development will likely become an increasingly important tool in the future. Assessing normal brain development involves evaluating myelination and sulcation patterns and comparing those to age-matched norms. Currently, this is done qualitatively in clinical practice; however, cortical folding has recently been quantitatively measured as an objective marker of sulcation on neonatal MRI (Kim et al., 2016). As previously discussed, quantitative morphometry has been difficult to perform in infants due to incomplete myelination, which limits conventional automatic segmentation of grey and white matter. New deep neural-network based methods for brain segmentation have been much more successful in automatically segmenting infant brains, even at 4 months of age, when grey-white boundaries are most indistinct on T1 weighted sequences (Fig. 13) (Wang et al., 2015).

In addition to quantitative assessments of structural imaging, microstructural imaging using diffusion and resting-state fMRI (rs-fMRI) has become increasingly important in evaluating tissue function. Scalar metrics of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) have been widely used in clinical diagnoses, including the evaluation of neonatal hypoxic-ischemic encephalopathy and pediatric metabolic disease (Lemmon et al., 2017; Poretti et al., 2016; Tekes et al., 2015; Xu et al., 2013). More recent brain network investigations have begun to quantify changes during normal and abnormal brain development, which has potential to improve our ability to predict outcome (Cui et al., 2017; Emerson et al., 2016; Tymofiyeva et al., 2013; Tymofiyeva et al., 2014; Ziv et al., 2013; Zuo et al., 2017). The evolution of rs-fMRI default mode network patterns during development in both normal children and those who have suffered a prenatal or neonatal insult is another burgeoning avenue of investigation. Functional connectivity MRI, which includes both resting state and task based MRI, is another developing area of research in the neonatal and infant period (Gao et al., 2016). Since the plasticity is much greater in the developing brain than in the adult brain, detection of functional abnormalities in infancy may allow subsequent therapy to be more effective. In particular, early diagnosis of autism spectrum disorders (ASD), before clinical signs manifest, has spurred investigation into functional connectivity in infants. Premature birth is associated with motor and cognitive delay; for premature infants without structural injury, anatomic imaging often does not provide adequate risk stratification, but developing microstructural techniques may. The complexity

of the rs-fMRI covariance structure is decreased in premature neonates without structural injury compared to term neonates, which could partially explain their increased rates of motor and cognitive disability (Smyser and Neil, 2015; Smyser et al., 2016). Although microstructural evaluation of infant brains is currently an investigational tool, as more clinical associations are found, these methods may lead to earlier diagnosis and treatment.

Conclusion

Pediatric imaging is challenging due to rapid brain development. In order to meet these challenges, imaging methods and approach must also change with the patient's age. Fetal and neonatal/infant imaging are especially challenging due to the small brain size, high water content, rapid developmental changes and patient motion. The ideal techniques for fetal imaging are fast 2D images, which can be reconstructed into a 3D volume using snapshot volume reconstruction. For neonates, volumetric acquisitions are possible, even without sedation, with a dedicated multidisciplinary neonatal imaging team using a feed and swaddle approach. Children older than 5 years can often be scanned without sedation with the help of child life specialists, although techniques that correct for motion (either prospectively or via post-processing) may be needed to improve image quality. Hardware is another useful tool, with specialized neonatal head coils and narrow bore, high performance gradient MRI scanners providing improved image quality at young ages. Neuroimaging in pediatric patients requires the right hardware, software, and staff, to ensure the best imaging data for both clinical and research purposes, without sedation whenever possible.

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Highlights

- Rapid brain growth and development make pediatric neuroimaging challenging.
- Imaging infants using feed and swaddle can minimize motion without sedation.
- Custom hardware, software, and well-trained staff produce high quality images.
- Automated and quantitative techniques are revolutionizing pediatric neuroimaging.

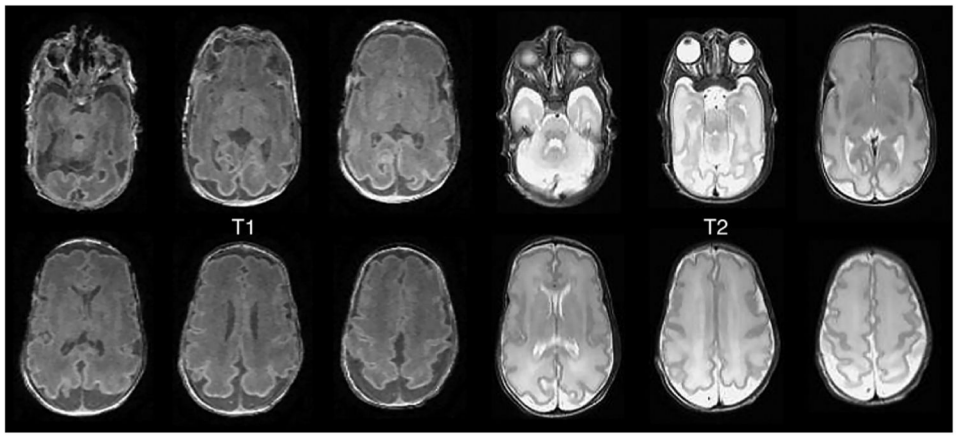

Figure 1. Normal 29-week premature neonate

T1 and T2 weighted brain MR images of 29-week gestational age premature infant. Note the simple sulcation pattern and high T2 and low T1 signal in the white matter due to minimal myelination.

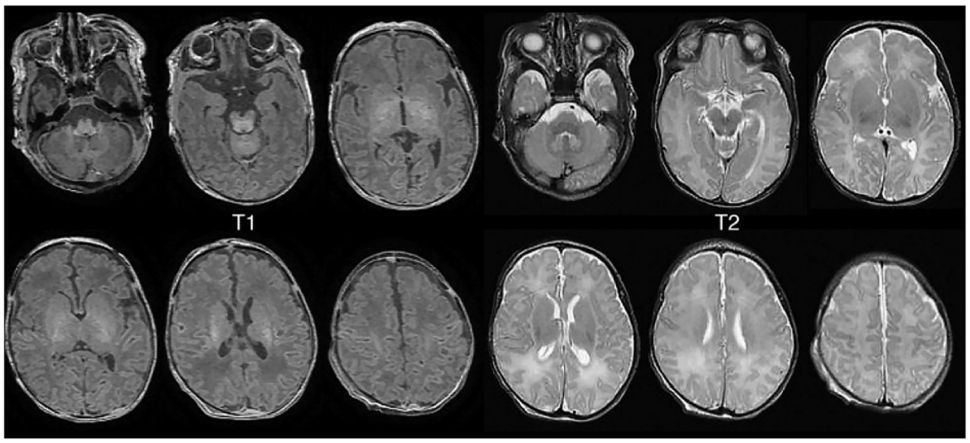

Figure 2. Normal term neonate

T1 and T2 weighted brain MR images of late term neonate. Note the increasing depth and complexity of the sulci with formation of most tertiary and quaternary sulci. Brain water content is decreased on T2 weighted imaging, and early myelination is seen, notably in the posterior limb of the internal capsule.

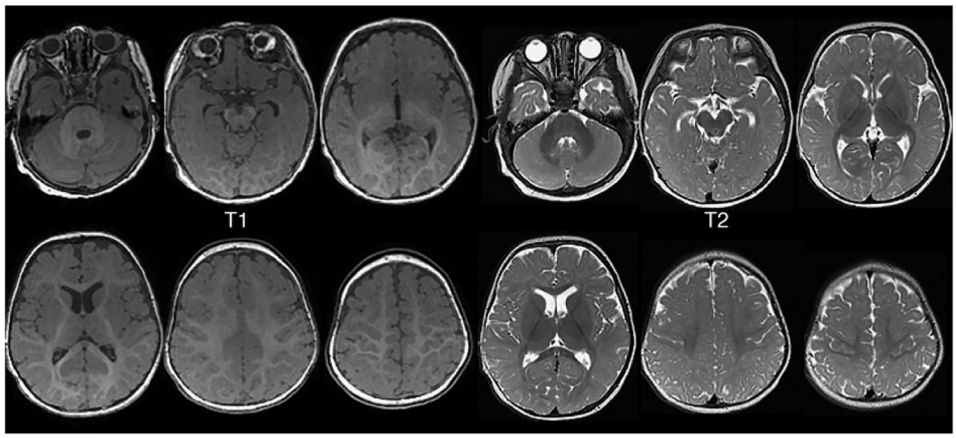

Figure 3. Normal 6-month-old infant

T1 and T2 weighted brain MR images of 6-month-old infant. The sulcal pattern has matured further and myelination has progressed to the pre-and post-central gyri.

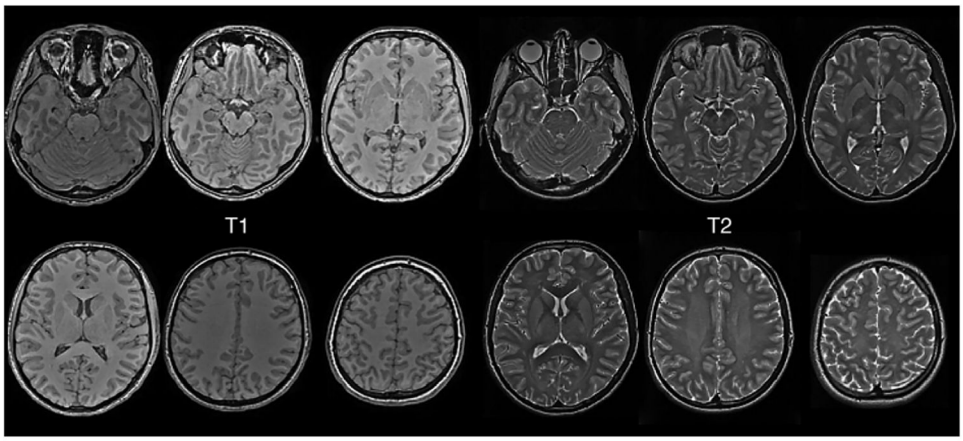

Figure 4. Normal 14-year-old child

T1 and T2 weighted brain MR images of 14-year-old child. An adult sulcation pattern is present, with all tertiary and quaternary sulci formed and fully developed. Myelination is complete with normal adult pattern of high T1 and low T2 white matter signal.

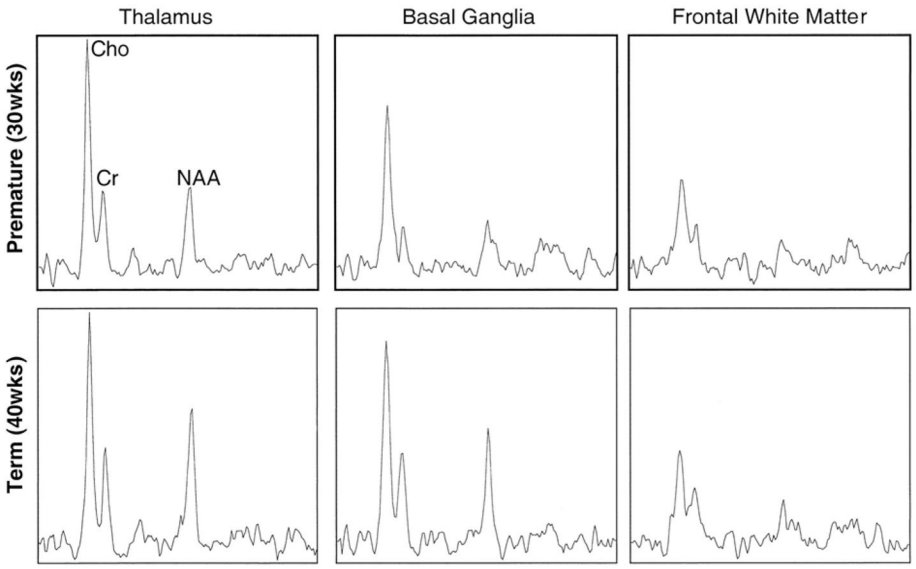

Figure 5. Proton MR spectroscopy of premature and term neonates

Note the low NAA to choline ratio which increases with increasing gestational age. Reprinted with permission from (Vigneron et al., 2001)

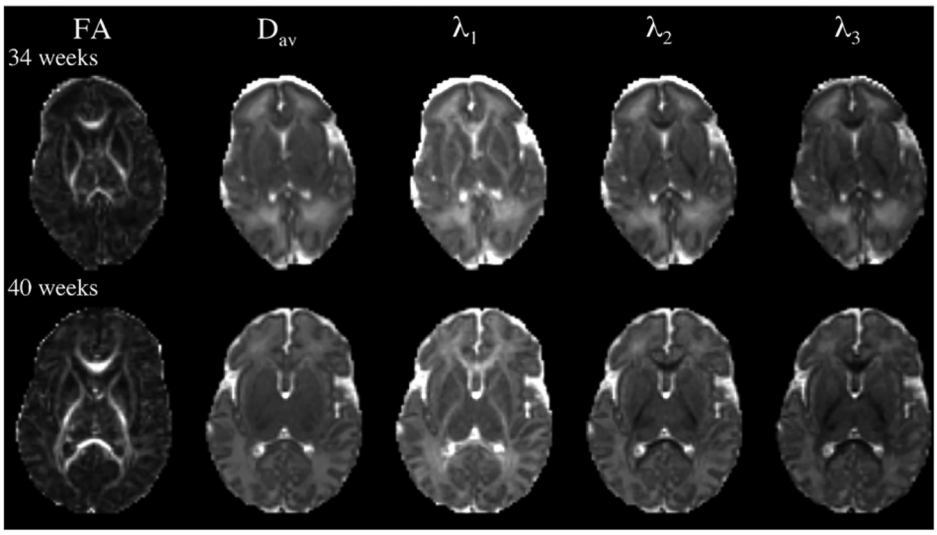

Figure 6. Neonatal diffusion tensor imaging

Neonates at 34 and 40 weeks gestational age. Note the reduced diffusivity and increased fractional anisotropy in the white matter. Reprinted with permission from (Partridge et al., 2005)

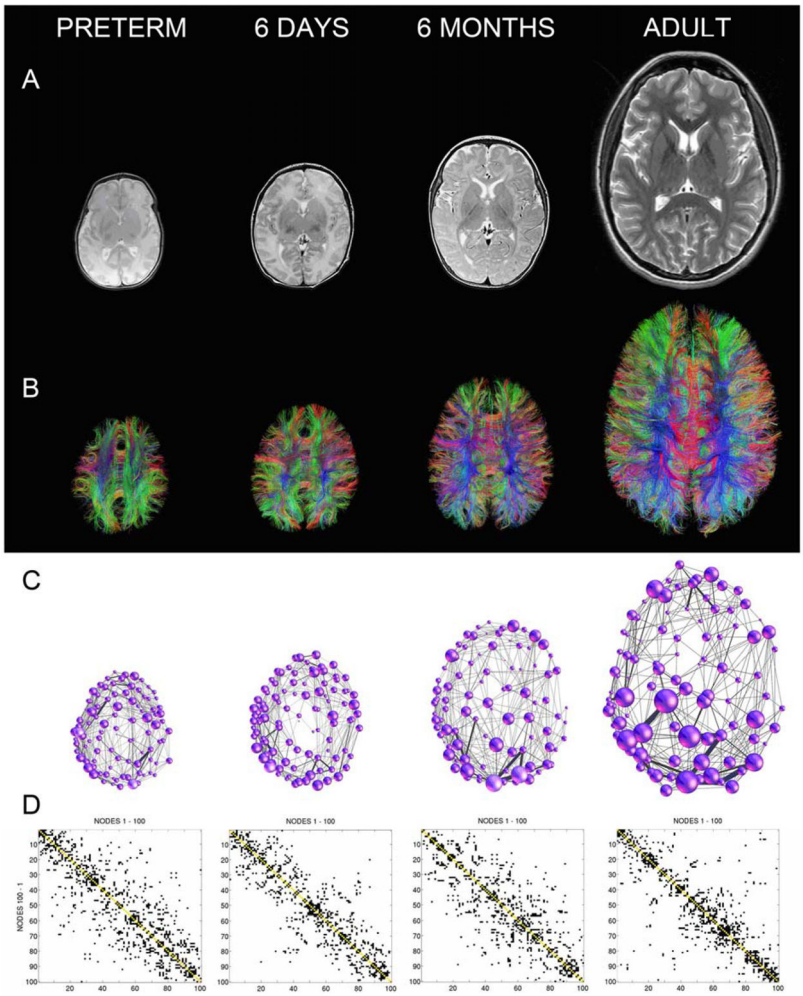

Figure 7. Maturation of the "baby connectome": examples of brain networks at four different ages

(A) Anatomic T2 weighted MRI images.

(B) Tractograms reconstructed based on DTI data.

(C) Brain networks represented as weighted graphs. The size of the nodes is proportional to the node degree.

(D) Binary connectivity matrices.

Reprinted from (Tymofiyeva et al., 2013)

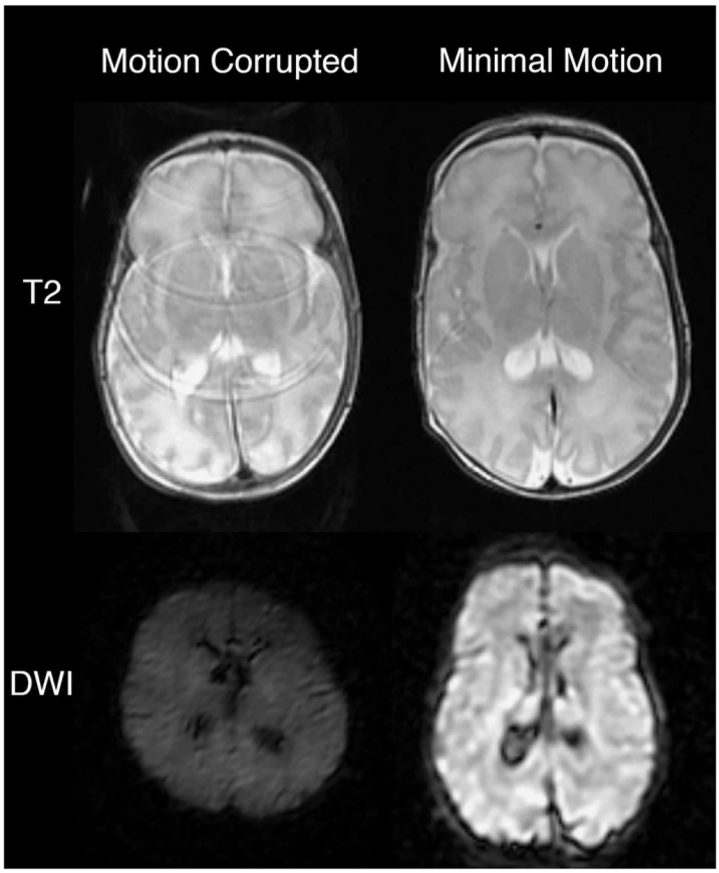

Figure 8. Motion Degradation

Motion corrupted T2 and diffusion weighted images (DWI) show signal dropout and wrap artifact when compared to images obtained with minimal motion.

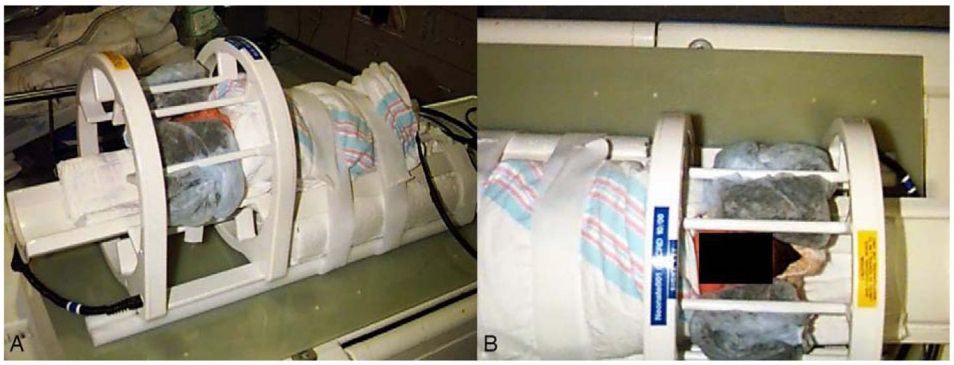

Figure 9. Feed and swaddle

Neonate secured in bean bag wrap on MRI scanner table with hearing protection and head coil in place.

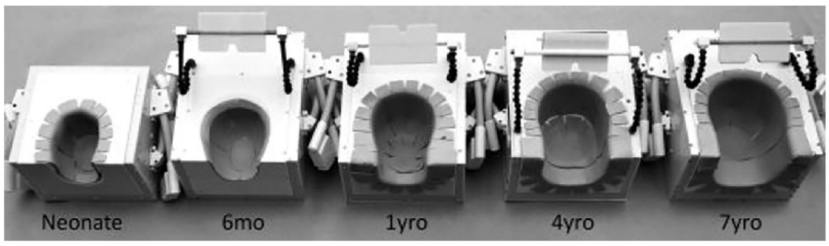

Figure 10. Neonatal Head Arrays

High channel count phased arrays designed to fit in an MR compatible incubator and sized to fit neonates of a range of gestational ages. Reprinted with permission from (Keil et al., 2011)

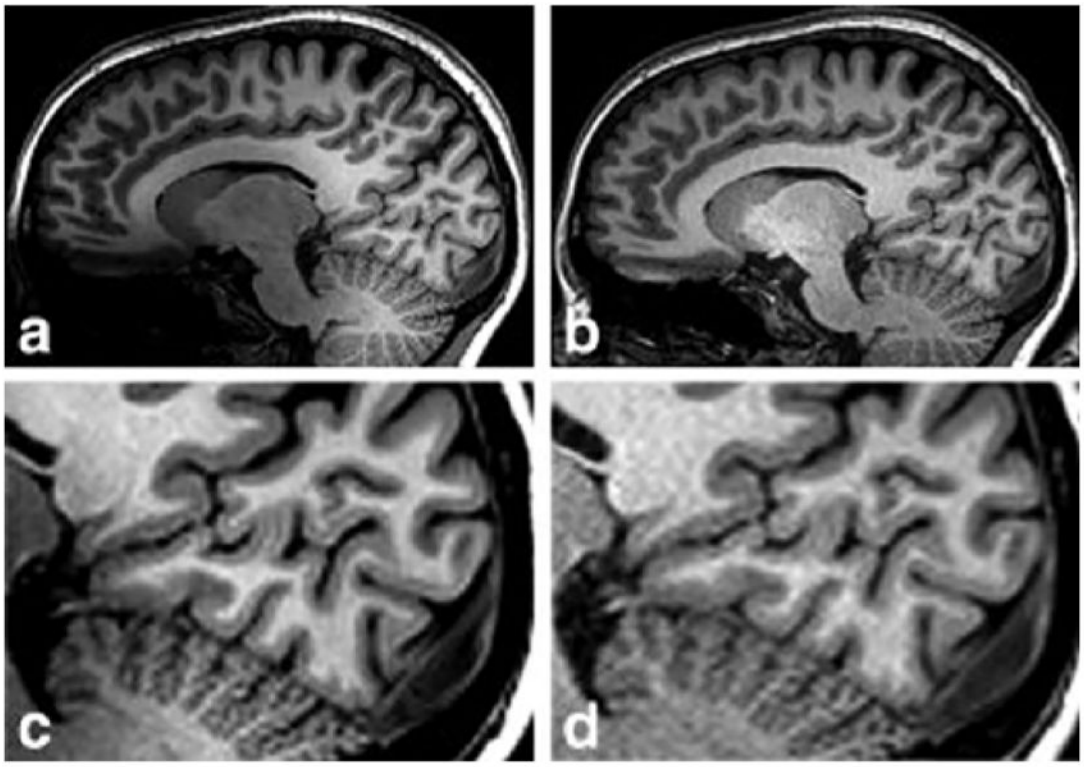

Figure 11. Phased array performance

Improved signal to noise seen on T1 weighted spoiled gradient echo images when 4-year-old (a and c) and adult (b and d) coils are used. Reprinted with permission from (Keil et al., 2011)

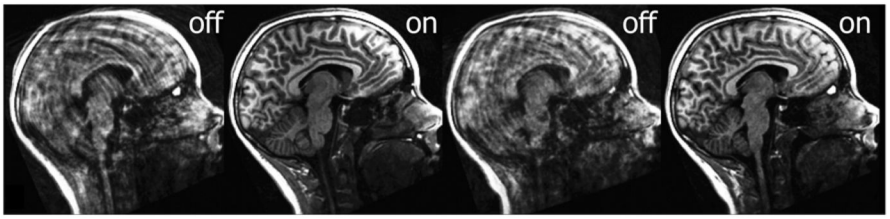

Figure 12. Prospective motion correction (PROMO)

The method uses spiral navigators to perform real-time rigid-body motion tracking and correction during the dead time of standard image acquisition. Reprinted with permission from (Brown et al., 2010)

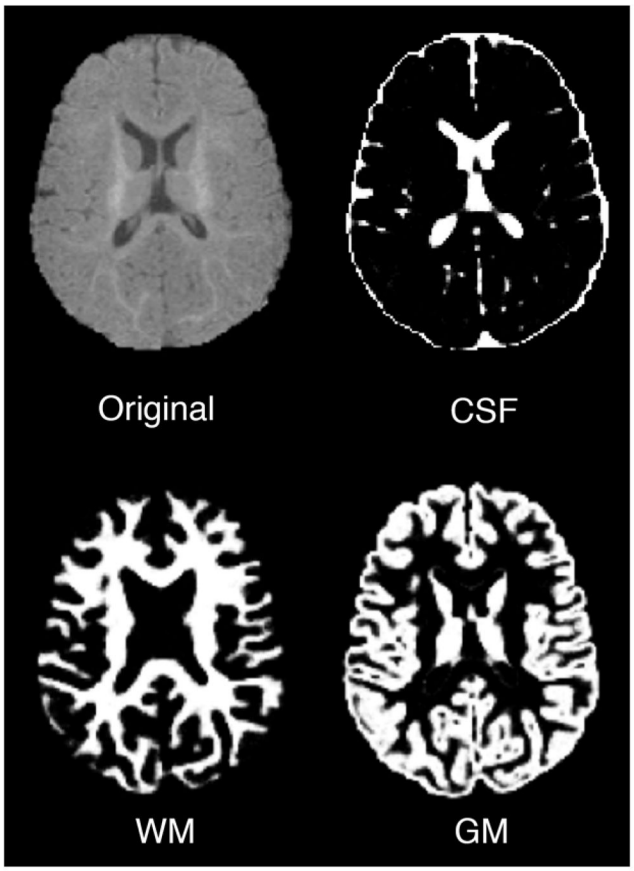

Figure 13. Infant Brain Segmentation

Automatically segmented grey and white matter volumes in a 6-month-old, performed using deep neural networks. Reprinted with permission from (Wang et al., 2015)