An optimized, 3D, high-resolution MR imaging protocol to study in-utero gyrification and myelination of the brain of non-human primate.

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Introduction: Because non-human primates (NHPs) and humans share a highly orchestrated pattern of cerebral development, imaging of fetal brain maturation in NHPs provides an excellent opportunity to validate theories regarding gyrification of the cortex. Formation of the cerebral landscape, or primary gyrification, begins in the early stages of telencephalic development. Its onset coincides with completion of neuronal proliferation and migration, and its progression is accompanied by an explosive increase in cerebral growth. Compared to human studies, structural imaging in NHPs is challenging because of the small brain size (2-200 fold smaller volume, depending on the species), and fetal brain volumes that are only 10-50% of their adult size. The sizes of cortical gyri and sulci scale allometrically with brain size, so spatial sampling comparable to that of high-quality human studies (~1.0 mm^3) requires a brain-size-adjusted sampling volume on the order of ~150 $microns^3$. Our objective was to enable a longitudinal study of the gyrification of the *in utero* NHP brain by developing an isotropic 3D protocol with a superior signal-to-noise ratio, low SAR, and good contrast among gray matter (GM), white matter (WM), CSF, and amniotic fluid.

Methods: The lack of WM/GM T_1 contrast in the fetal brain usually limits *in utero* imaging to T_2-weighted pulse sequences. This contrast is normally achieved by setting the echo time to a value longer than the T_2 of WM, and using fast spin echo (FSE) sequences to permit segmented, respiratory-gated acquisitions with reasonable imaging times. Unfortunately, the usefulness of FSE for fetal imaging in NHPs is severely limited by its radiofrequency specific absorption rate (SAR). This energy deposition may cause an unsafe elevation of the core body temperature of small primates (~20-30 kg). To overcome the SAR limitations of the FSE sequences, we chose a 3D balanced gradient echo (TrueFISP) sequence. Such sequences are notable for providing the highest level of signal per TR-interval among all MR sequences. This makes the TrueFISP sequence highly desirable for SNR-limited high-resolution 3D imaging. Image contrast in a TrueFISP pulse sequence depends on the T_2/T_1 ratio as opposed to T_2. Tissues with long T_2 relaxation times show very high signal. Our protocol uses very short (400 ns), high bandwidth time product (~6) excitation pulses to increase regional tissue contrast through magnetization transfer (MT) saturation. The sequence is sufficiently flexible to be adapted for segmented, respiration-triggered acquisition of imaging data. The typical respiration frequency of 8-10 breaths/min and 1 second trigger delay time allows data acquisition cycles of 3-4 seconds. Segmentation for respiratory gating was achieved by acquiring all of the in-plane phase-encoding steps within a single acquisition cycle. A short TR allows one to acquire the 300-500 phase-encoding lines associated with a single value of the partition gradient within a single respiration cycle (~3 seconds). Typical parameters were TE/TR/α = 1.86ms/3.8ms/40°. The approach to the steady state was accelerated with five half-α, half-TR prepulses. Animal subjects. Six pregnant dam (*Papio hamadryas Anubis)* were imaged the total of 10 times between weeks 17 and 25 of pregnancy. The animals were imaged using a Siemens Tim Trio scanner equipped with multi-channel body array coils. All experimentations were performed under IACUC-approved protocols.

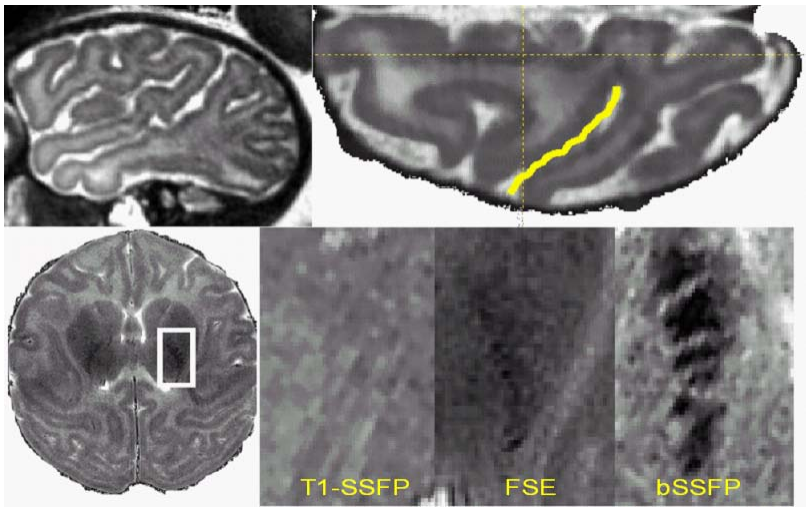

Figure 1. Top row, sagittal and axial slices of a fetus at week 24 of *in utero* development. Bottom row, sequence comparisons in early myelinating areas of internal capsule (white box, left).

Results: Images produced by this protocol showed excellent regional brain tissue contrast, presumably due to MT saturation of the GM signal. Preliminary measurements indicated that tissue contrast was much (~50%) higher than predicted based on the T1/T2 relaxometry measurements (Figure 1 top). Additionally, this protocol showed much higher contrast in the earlier myelinating areas, located in the internal capsule, than either T_1-w SSFP or T_2-weighted FSE sequences (Figure 1 bottom).

Conclusion: The reduced complexity of the primate brain and compressed rate of cerebral development make the NHP an invaluable research model to study *in utero* brain maturation. Our preliminary longitudinal imaging experiments showed that brain development in NHP could be studied in exquisite detail.

Acknowledgements: All experiments were performed under IACUC-approved protocols. This work was supported, by the following grants :(K01 #EB006395), (NIH #P51-RR013986), (#1R01AG029412-01) and (#P01 HD047675 and R24 RR013632).