USING ADVANCED MRI TO DETECT ALTERATIONS IN BRAIN GROWTH IN FETUSES WITH CONGENITAL HEART DISEASE

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Background

Why is this important? Congenital heart disease (CHD) is common, affecting almost 1% of live-births globally, and is associated with neurodevelopmental impairments persisting into adulthood. Understanding factors associated with these impairments and linking them to underlying biological mechanisms is vital if we are to develop interventions to prevent and treat them. There is some evidence that fetuses with CHD have impaired brain growth, but most studies are limited by small cohort sizes, or focus on specific diagnoses rather than the underlying physiology. Cerebral substrate delivery, referring to the delivery of oxygen, glucose and other nutrients to the brain, is thought to be an important factor in determining fetal brain growth during pregnancy.

Challenges: MRI is a safe, non-invasive method that can be used to image the fetal brain. However, acquiring fetal neuroimaging data is a technical challenge, given the sensitivity of MRI to motion and the fact that the fetal brain represents a relatively small, moving target, encased in fluid, with complex 3-dimensional structures. Reliable automatic labelling of different tissues and structures on fetal brain imaging is also difficult, due to the rapid changes in size, shape and tissue composition that occur in the fetal brain during pregnancy.

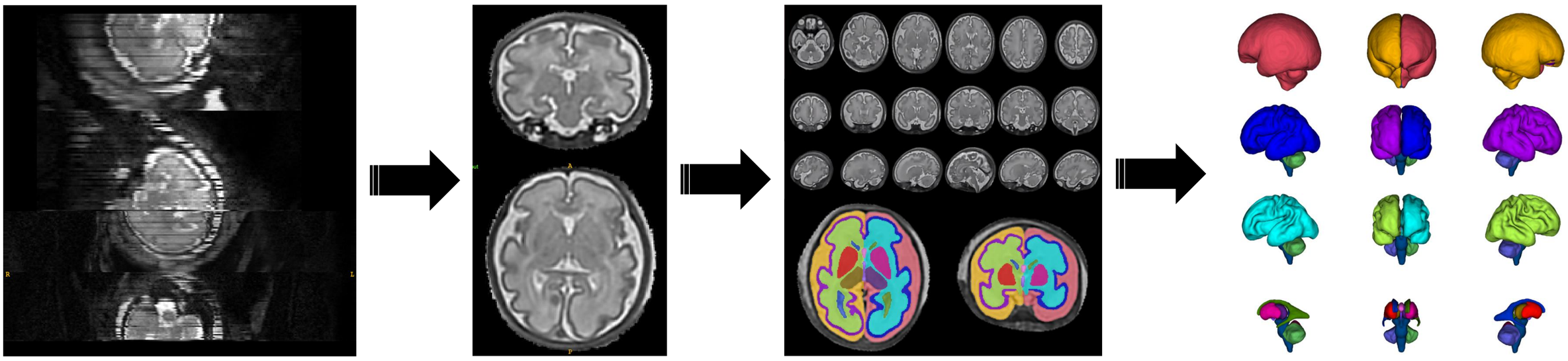
Aims: We aimed to explore how expected cerebral substrate delivery affects total and regional brain volumes in a large cohort of fetuses with CHD, using advanced motion-tolerant MRI.

Experimental methods

Study population: 380 fetuses (188 male), comprising 45 healthy controls and 335 with isolated CHD were scanned between 29 and 37 weeks gestation on a 1.5 Tesla MRI scanner at St. Thomas' Hospital in London. Fetuses were assigned into one of four groups by experts in fetal cardiology, based on their expected cerebral substrate delivery: Normal, or mildly, moderately or severely reduced.

Image acquisition and tissue segmentation: Multiple stacks of fetal brain images were acquired using a T2-weighted fast-spin-echo sequence. Slices in these stacks were aligned to account for fetal motion and combined to create high-resolution 3D 'volume' images of the fetal brain[1]. These 3D images were then automatically segmented using a neural network that had been created for this purpose[2], from which volumes were calculated for six brain tissue regions (cortical grey matter, white matter, deep grey matter (thalamus + putamen), cerebellum and brainstem (Figure 1). These were then summed to calculate whole brain tissue volumes.

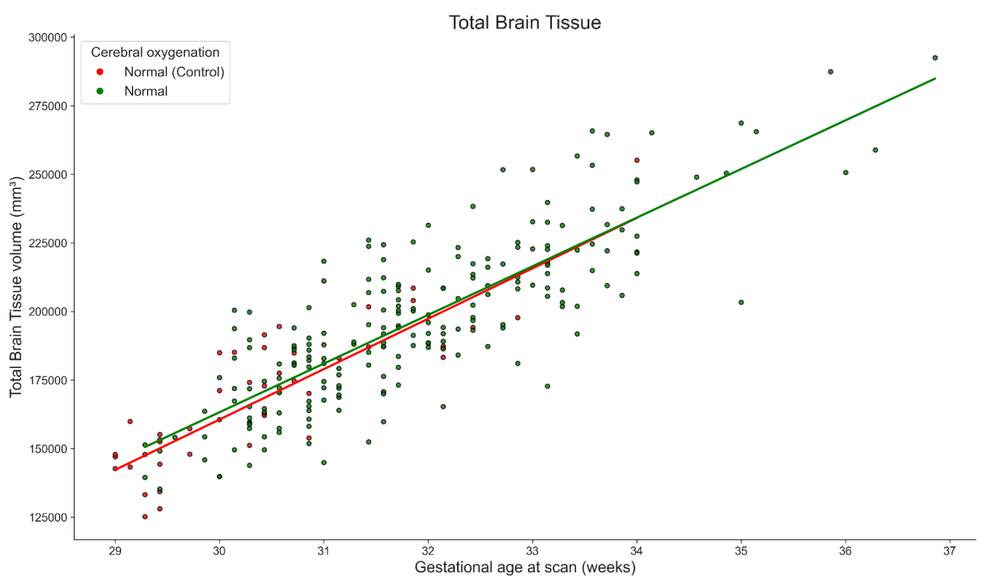
Statistics: ANOVA was used to test for differences in brain volumes between groups, after accounting for sex and gestational age at scan. P-values were corrected for multiple-testing and reported as P_{FDR}. P_{FDR}-values <0.05 were considered statistically significant.



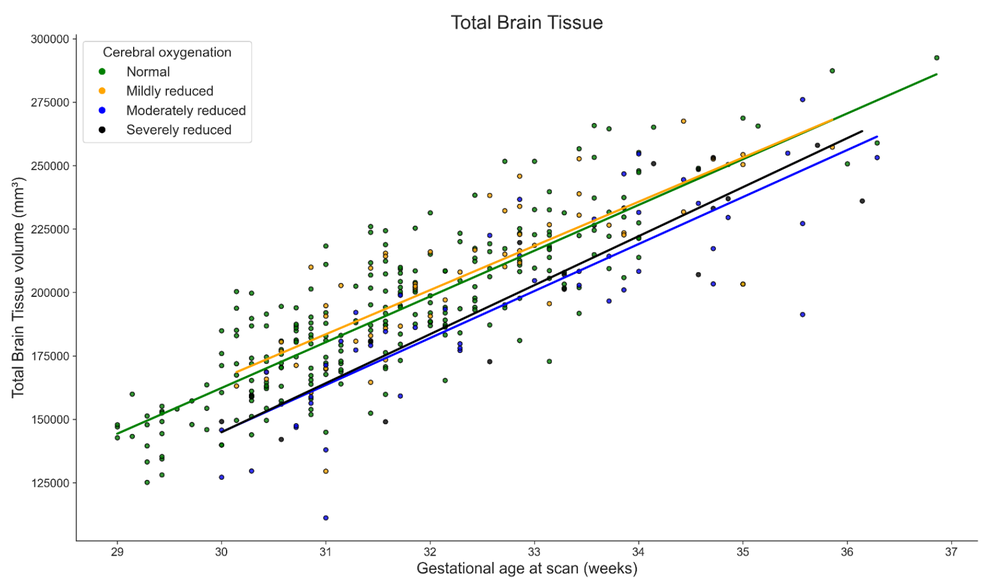
Acquired fetal MR imaging data | Reconstructed fetal brain images | Automatic segmentations of different tissue types | 3D visualisations of different fetal brain regions

Results

Data was analysed from 336 fetuses with CHD - 209 in group 1, 56 in group 2, 47 in group 3 and 19 in group 4 - along with comparable imaging data from 45 healthy control fetuses. All imaging was performed between 29 and 37 weeks gestation. Two important results were identified:



1) No significant differences were observed in total or regional brain volumes between control fetuses and fetuses with CHD but normal cerebral substrate delivery.



2) Total and regional brain volumes were smaller in fetuses where cerebral substrate delivery is reduced. These reductions in brain volumes are evident in-utero from 30 weeks gestation.

Conclusions

We used automated MRI reconstruction and segmentation techniques to generate sub-millimetre resolution, motion-tolerant fetal brain images and show that (1) fetal brain growth is not impaired in CHD subtypes associated with normal cerebral oxygen delivery, and (2) reduced cerebral oxygen delivery in-utero is associated with smaller total and regional brain volumes in fetuses with CHD. This has important implications for understanding the impaired brain development seen in individuals with CHD, supporting the hypothesis that cerebral substrate delivery is a key mediator of fetal brain growth in-utero. The image acquisition and analysis tools described here represent the result of extensive collaboration between academics and clinicians, putting cutting-edge research to use to address real-world clinical problems.

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