

Brain Templates for Neonates with Congenital Heart Defects: Preliminary Results from an International Consortium

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Target audience

This work informs neurologists and provides valuable resources to neuroradiologists about brain development in neonates with congenital heart defects.

Purpose

Congenital heart defects (CHD) are among the most common birth defects with a prevalence of at least 9 out of 1000 births (36,000 neonates affected every year in the United States). There has been increasing awareness of short and long-term neurodevelopmental challenges in a large proportion of survivors¹. Hypoxic-ischemic brain injury to the white matter and delays in brain growth and maturation are common among these neonates with severe CHD. Clinical exam has limited predictive value and brain MR imaging has been an important tool to assess brain structure and acute injury in these newborn infants¹. However, there has been a lack of standardization in MR acquisition across institutions all over the world and it becomes increasingly hard to compare the results from different research groups due to the absence of reference frame, such as brain templates. The International Consortium on CHD Neonatal Brain MRI was established to coordinate efforts to tackle this problem of MR data normalization and provide an open common platform with tools for processing and analyzing brain imaging data in preoperative neonates with CHD. The aims of the Consortium include developing a set of high-resolution structural MRI templates of preoperative CHD brains. This paper presents preliminary results from the first attempts to normalize and process the data contributed by the Consortium members.

Methods

Multi-site brain MR acquisition: Imaging acquisition varied across sites and even within site. Siemens, Philips and GE MR scanners were used in this cohort, with magnetic field strength mostly at 1.5 tesla. In-plane voxel size was below 1 mm isotropically and slice thickness varied from 1 to 4 mm. In addition, image intensity profile, tissue contrast, MR intensity inhomogeneity, image artifacts were all dependent on the scanner and site.

Patient population: Via agreement with the Consortium, we have collected brain MR images of preoperative neonates from hospitals in Atlanta, Auckland, Houston, Melbourne, Philadelphia, San Francisco, Utrecht, Vancouver and Zurich with a total number of 467 subjects (male: 62%). Average gestational age at birth was 38.6 weeks (standard deviation 1.4 weeks, range 34-41) and MR scans were acquired at an average of 6.4 days (standard deviation 5.2 days) after birth and before cardiac surgical intervention. The cohort was comprised of more than 15 cardiac diagnoses in all, including two major diagnoses; hypoplastic left heart syndrome (HLHS, n=145) and transposition of the great arteries (TGA, n=141).

Template construction and volumetric analysis: The templates were constructed from an averaged image of aligned and deformed individual brains. We used open-source software Advanced Normalization Tools² (ANTs) to perform image registration between an initial/intermediate template and a subject image. The resultant template was not biased toward any individual subject in the cohort although an image with good quality was often chosen as the initial template. The construction process was iterative and stopped when convergence was achieved. We performed tissue segmentation of a proportion of subjects based on an external public neonatal brain template (<http://www.brain-development.org/>). Then these segmentations were transformed to the proposed template based on the same transformations in template construction and tissue probability at one voxel was determined by the ratio of appearances of a tissue label at that voxel of deformed individual subject to total number of subjects. The proposed templates were then used for tissue and lobar segmentation.

Results

Twelve templates specific to cardiac diagnosis, post-conception age (PCA, gestational age + postnatal age at time of scan) and site were constructed

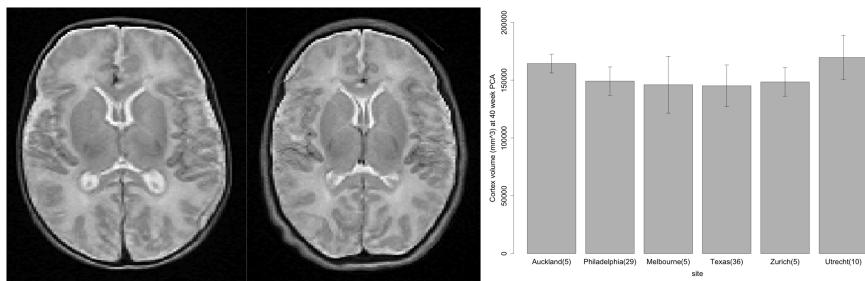


Figure 1. The left and middle panels are HLHS and TGA templates based on 10 subjects within 40-41 weeks PCA from Houston and Philadelphia. The right panel shows the mean cortex volumes of subjects from 6 sites (number of subjects in parentheses, error bar denotes standard deviation).

(Fig. 1). When we included subjects with different PCA, the resultant templates tended to be blurrier as shown in the site-specific templates. When the subjects were more homogenous in terms of age and/or diagnosis, the tissue contrast in template was enhanced even if individuals were from different sites. The volumes of cortex and white matter were mostly consistent across sites if age was controlled for (Fig. 1). Larger variance was seen in groups with smaller sample size. With regard to lobar and regional cortical volumes, similar results were observed. This indicated that the volumetric results were independent of scanner and geographic factors and the processing of inhomogeneous MR data generated consistent results. Considering brains with different PCA, we found a robust trend of growth over time. This trend remained when we separated the cohort into TGA and HLHS groups but we did not find a significant difference between the two groups.

Conclusion. We have demonstrated, in the experiment, the feasibility of normalizing these highly heterogeneous multi-center multi-scanner MR images by using high-deformation image registration to warp individual images to specific templates. The successful construction of specific templates based on site, age and cardiac diagnosis allows researchers to investigate brain development in a more homogenous subset and potentially increase the specificity and reliability of the findings. The Consortium is committed to open science principles and will release all templates and associated tools for the clinical and research community. Future work will include semi-automated white matter lesion and myelination detection and quantitation in these brain scans with the goal of automated processing of prospectively acquired scans.

References

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2. Avants, BB.; Schoenemann, PT. & Gee, JC. Lagrangian frame diffeomorphic image registration: Morphometric comparison of human and chimpanzee cortex. *Med Image Anal*, **2006**, *10*, 397-412