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A new neonatal cortical and subcortical brain atlas: the Melbourne Children's Regional Infant Brain (M-CRIB) atlas

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ABSTRACT

Investigating neonatal brain structure and function can offer valuable insights into behaviour and cognition in healthy and clinical populations; both at term age, and longitudinally in comparison with later time points. Parcellated brain atlases for adult populations are readily available, however warping infant data to adult template space is not ideal due to morphological and tissue differences between these groups. Several parcellated neonatal atlases have been developed, although there remains strong demand for manually parcellated ground truth data with detailed cortical definition. Additionally, compatibility with existing adult atlases is favourable for use in longitudinal investigations. We aimed to address these needs by replicating the widely-used Desikan-Killiany (2006) adult cortical atlas in neonates. We also aimed to extend brain coverage by complementing this cortical scheme with basal ganglia, thalamus, cerebellum and other subcortical segmentations. Thus, we have manually parcellated these areas volumetrically using high-resolution neonatal T_2-weighted MRI scans, and initial automated and manually edited tissue classification, providing 100 regions in all. Linear and nonlinear T_2-weighted structural templates were also generated. In this paper we provide manual parcellation protocols, and present the parcellated probability maps and structural templates together as the Melbourne Children's Regional Infant Brain (M-CRIB) atlas.

Introduction

Investigating infant brain development in healthy and clinical populations is important for understanding the factors contributing to long-term neurodevelopmental (e.g., cognitive and motor) outcomes, and may help assess interventions designed to improve these outcomes (Anderson et al., 2015). An increasingly sophisticated set of analytical approaches allows investigation of volumetric characteristics, structural and functional connectivity, and network-based features of the brain. Key to such techniques are atlases that facilitate standardised identification of brain regions within- or between-which to make morphological and functional comparisons, and map correlations and connections (Gaillard et al., 2001; Klein and Tourville, 2012). Such atlases are readily available in adults, however warping infant brains to an adult template space is problematic (Richards et al., 2015; Richards and Xie, 2015).

Abbreviations: ANTS, Advanced Normalization Tools; BET, Brain Extraction Tool; FLIRT, FMRIB's Linear Image Registration Tool; FSL, Functional MR Imaging of the Brain Software Library; MANTiS, Morphologically Adaptive Neonatal Tissue Segmentation; M-CRIB, Melbourne Children's Regional Infant Brain atlas

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In neonates, although the major sulci and gyri seen in adults are already present (Chi et al., 1977; Cowan, 2002; Griffiths, 2010; Hill et al., 2010) morphological and tissue characteristics at this time do not map precisely to those in adults. Neonatal whole-brain volume is roughly one-third that of adults (Gaillard et al., 2001; Hill et al., 2010). This can result in larger voxels relative to brain size, leading to partial voluming compromising ability to resolve small structures (Beare et al., 2016; Heemskerk et al., 2013). Smaller voxel sizes can be used, however higher resolution images suffer from lower signal to noise ratio (Lodygensky et al., 2010). There are also tissue type differences due to lack of myelin (Gilmore et al., 2007; Shi et al., 2011), as well as greater variability in MRI intensity within tissue classes (Beare et al., 2016; Lodygensky et al., 2010) in neonates compared with adults. At term, myelination is in the initial stages of a spatially-progressing sequence of development (Kinney et al., 1988; Sampaio and Truwit, 2001; Yakovlev and Lecours, 1967), with myelinated white matter observed only in the brainstem and the posterior limbs of the internal capsule (Barkovich et al., 1988; Prastawa et al., 2005). Further considerations for the infant brain include differences in proportional brain region size originating from different regional trajectories of myelination (Gaillard et al., 2001), and greater structural variability found at the neonatal time point (Hoeksma et al., 2005).

In construction of atlases specific to neonates, two of the key factors that facilitate accurate parcellation are the MRI sequence and the parcellation technique used. Firstly, the MRI sequence determines tissue contrast, thus informing classification. On T_1-weighted images, which are strongly sensitive to lipid concentration, the absence of myelin in most of the brain results in low contrast between white and grey matter. T_2-weighted sequences, more sensitive to water content, provide greater tissue contrast due to higher cell density in grey matter (Counsell et al., 2003; Nowell et al., 1987). For this reason, many neonatal imaging tools and studies employ T_2-weighted images alone or in combination with other sequences. Secondly, in terms of parcellation, manual delineation is frequently acknowledged as the gold standard, and manually traced ground truth data is utilised as prior information in automated segmentation algorithms (de Macedo Rodrigues et al., 2015; Desikan et al., 2006; Gousias et al., 2013; Heckemann et al., 2006; Oishi et al., 2011; Warfield et al., 2004). Although painstaking and time consuming, the involvement of human operators allows the delineation of structures with complex or abstract areal boundaries. This can include boundaries that are contingent on highly variable individual local anatomy, are without an obvious morphological landmark, or have definitions derived using alternative modalities. Such ground truth in the neonatal brain is both desirable and in high demand.

Several parcellated neonatal atlases have been developed (e.g., de Macedo Rodrigues et al., 2015; Gousias et al., 2012; Gousias et al., 2013; Oishi et al., 2011; Peterson et al., 2001; Peterson et al., 2000; Shi et al., 2011). Early parcellation schemes used in neonates consisted of divisions of the brain walled by vertical and horizontal planes at landmarks from the Talairach (Talairach and Tournoux, 1988) template space (e.g., Gilmore et al., 2007; Mewes et al., 2007; Peterson et al., 2000). Although providing a fast subdivision of the brain, such a scheme provides only a gross representation of anatomy. Subsequent work has incorporated anatomically-driven manual parcellation to varying extents. In a longitudinal cohort of 0-, 1- and 2-year-olds, Shi et al. (2011) warped the adult Automated Anatomical Labeling atlas (Tzourio-Mazoyer et al., 2002) to the space of each time point. Wu et al. (2014) warped the adult Desikan-Killiany-Tourville atlas (Klein and Tourville, 2012) from adult (Marcus et al., 2007) to neonatal space. Due to the many differences between infant and adult brains as outlined above, warping an adult atlas to neonatal brains is not ideal. Gousias et al. (2012) used T_2-weighted images to guide manual parcellation on higher-resolution T_1-weighted images, manually segmenting 50 areas on 5 term and 15 preterm neonates. Makropoulos et al. (2015, 2014) utilised and augmented Gousias et al.'s parcellation scheme as a training set in an automated 4-dimensional spatiotemporal segmentation protocol. This delineates 82 cortical and subcortical areas with reference to spatiotemporal structural templates (Serag et al., 2012) derived from scans acquired between 28–44 weeks' post-menstrual age. De Macedo Rogrigues et al. (2015) also created a manually segmented atlas using clinically acquired T_1 scans from healthy participants ranging between 0–2 years of age, including four neonates. These authors were able to consistently delineate 32 areas, however, partial volume effects restricted tracing to major sulci. Furthermore, the relative lack of grey-white matter contrast in the T_1-weighted scans for neonatal participants did not allow detailed parcellation. Oishi et al. (2011) developed a multicontrast atlas incorporating T_1-, T_2- and diffusion-weighted imaging data. This involved manual parcellation of 122 regions on a single-subject neonatal template image, projection of this onto a neonatal sample, and validation via manual segmentation on selected slices. The parcellation incorporated white matter tract regions, subcortical regions, and cortical regions that merge grey and underlying white matter. Despite the many merits of this neonatal atlas, there are no equivalent atlases available at later time points, making potential comparisons between infant, childhood and adult brains difficult.

The Desikan-Killiany (2006) atlas is one of the most commonly used parcellated cortical atlases in child and adult cohorts (Desikan et al., 2006). Therefore, we aim to replicate this atlas in neonates, enabling consistency in nomenclature between the adult and neonatal literature. To provide more extensive brain coverage, we aim to complement this scheme with subcortical and cerebellar segmentations. In this paper, we detail a volumetric manual parcellation scheme in 10 term-born infants, utilising high-resolution T_2-weighted images and initial automated tissue classification. We present these parcellations together with corresponding linear and nonlinear T_1- and T_2-weighted structural templates as the Melbourne Children's Regional Infant Brain (M-CRIB) atlas. The M-CRIB atlas provides substantial neonatal brain coverage and anatomical detail, and will facilitate a broad range of investigations at term age, and potentially longitudinally in combination with data from older cohorts.

Methods

Participants

10 healthy term-born (≥37 weeks' gestation) neonates (4 female, 6 male; gestational age at scanning 40.29–43.00 weeks, M=41.71, SD=1.31) were selected from a larger cohort of controls with MRI scans, recruited as part of preterm studies (Spittle et al., 2014; Walsh et al., 2014). Exclusion criteria for controls included any resuscitation at birth, admission to a neonatal intensive care or special care unit, birth weight less than 2.5 kg, and any congenital conditions known to affect growth and development. At 2 year follow up in these longitudinal studies, all 10 participants selected here had no major health problems, and no cerebral palsy or major cognitive delay. These studies were approved by human research ethics committees of participating hospitals, and informed parental consent was given for participation of each infant. The current subset was selected based on minimal motion or other artifact on T_2-weighted images.

MRI acquisition

Imaging was conducted at the Royal Children's Hospital, Melbourne, Australia, on a 3T Siemens Magnetom Trio Tim scanner with a 12-channel circular polarized volume extremity coil during infants' unsedated natural sleep. A transverse T_2 restore turbo spin echo sequence was used with: 1 mm axial slices, flip angle=120°, TR=8910 ms, TE=152 ms, FOV=192×192 mm, in-plane resolution 1 mm^2 (zero-filled interpolated to 0.5×0.5×1 mm), matrix=384×384. Three-dimensional T_1-weighted images were acquired using a magne-