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Construction of a neonatal cortical surface atlas using Multimodal Surface Matching in the Developing Human Connectome Project

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ABSTRACT

We propose a method for constructing a spatio-temporal cortical surface atlas of neonatal brains aged between 36 and 44 weeks of post-menstrual age (PMA) at the time of scan. The data were acquired as part of the Developing Human Connectome Project (dHCP), and the constructed surface atlases are publicly available. The method is based on a spherical registration approach: Multimodal Surface Matching (MSM), using cortical folding for driving the alignment. Templates have been generated for the anatomical cortical surface and for the cortical feature maps: sulcal depth, curvature, thickness, T1w/T2w myelin maps and cortical regions. To achieve this, cortical surfaces from 270 infants were first projected onto the sphere. Templates were then generated in two stages: first, a reference space was initialised via affine alignment to a group average adult template. Following this, templates were iteratively refined through repeated alignment of individuals to the template space until the variability of the average feature sets converged. Finally, bias towards the adult reference was removed by applying the inverse of the average affine transformations on the template and de-drifting the template. We used temporal adaptive kernel regression to produce age-dependant atlases for 9 weeks (36–44 weeks PMA). The generated templates capture expected patterns of cortical development including an increase in gyrification as well as an increase in thickness and T1w/T2w myelination with increasing age.

Introduction

During the third trimester, the developing brain undergoes significant increases in size and gyrification. At birth, all primary and secondary folding features of the human cerebral cortex have been well established (Hill et al., 2010), and spatially consistent distributions of major sulci can be observed across individuals (Meng et al., 2014). Understanding the mechanisms of these processes, and the characteristics of normal growth, is important for detecting possible abnormalities that could lead to neurodevelopmental disorders.

Improvements in brain imaging techniques have resulted in the increase of neonatal brain MR studies and the availability of high quality neonatal brain MR images. One such study is the Developing Human Connectome Project[1] (dHCP) led by King's College London, Imperial College London, and Oxford University. The goal of the project is to acquire and analyse structural, functional and diffusion Magnetic

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[1] http://www.developingconnectome.org.

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Resonance (MR) images of the brain from fetuses and neonates, in order to generate the first spatio-temporal connectome of early life. So far, the acquired dataset consists mainly of neonatal MR images, and thus we will focus on the neonatal cortical surface atlas construction in this paper.

Analysing and visualising the functional and structural changes in the cortex requires a framework for comparing cortical anatomy and brain functional activations across subjects. This can be achieved through the development of common template spaces (or atlases). However, it is challenging to construct fetal and neonatal volumetric, as well as cortical surface, atlases due to the rapid development of cortical anatomies over time. Several volumetric neonatal atlases have been constructed (e.g. Kuklisova-Murgasova et al. (2011); Serag et al. (2012); Makropoulos et al. (2016)). Of these, Kuklisova-Murgasova et al. (2011) constructed a 4D probabilistic volumetric atlas using rigid and affine registrations, and kernel regression; and Serag et al. (2012) built a spatio-temporal volumetric atlas using pairwise registrations, performed using volumetric Free-Form Deformations (FFDs) (Rueckert et al., 1999), where the resulting transformations were averaged using adaptive kernel regression. Using registrations among all subject pairs they eliminated bias towards any of the subjects. Makropoulos et al. (2016) built a spatio-temporal structural atlas of the brain for 82 cortical and subcortical structures based on an automatic segmentation algorithm for parcellating the neonatal brain.

However, volumetric atlases are limited in that they allow only volume-based analysis and are designed mostly for the analysis of subcortical structures, while cortical surface atlases allow the analysis of highly-convoluted and highly-variable cerebral cortex (Van Essen and Dierker, 2007). Furthermore, cortical surface atlases provide a reference space for surface morphometry and subsequent surface-based connectivity analysis in the developing brain (Wright et al., 2015). Another limitation of volumetric atlases is that volumetric registration is not well suited to aligning the cerebral cortical sheet, because in 3D it is necessary to align both the sheet itself and areas within the sheet, whereas in 2D it is necessary only to align areas within the sheet, a much simpler and better conditioned problem in the context of variable folding patterns (Fischl et al., 2008; Glasser et al., 2013, 2016b).

As far as we know, only one term-age neonatal cortical surface atlas has been developed so far. This was constructed by Hill et al. (2010) using landmark-constrained surface registration of 12 term-born neonates (mean gestational age of 39 weeks). For this, six landmarks were delineated on each hemisphere for each subject. These were averaged across subjects and projected onto a standard sphere, used as a template. However, related atlases have been created by Li et al. (2015), who constructed a 4D cortical surface atlas of developing cortex in older infants, with seven time points starting at 1 month until 24 months of age; they used Spherical Demons (Yeo et al., 2010) within a diffeomorphic groupwise registration method. Also, Wright et al. (2015) used spectral surface matching (Lombaert et al., 2013) for constructing a spatio-temporal cortical surface atlas of the developing fetal cortex for each week of gestation from 23 to 37 weeks (total of 15 templates).

The aforementioned atlases are either constructed for one specific target age (Hill et al., 2010) or do not include neonatal data at the term age (Li et al., 2015; Wright et al., 2015). For this reason, we construct an unbiased, spatio-temporal, neonatal cortical surface atlas from age-matched groups of surfaces for each week of term gestation (9 templates in total, from 36 to 44 weeks). Group average maps for cortical folding (sulcal depth and curvature), thickness, myelination (Glasser and Van Essen, 2011), and regional labels (Makropoulos et al., 2014) (Fig. 2) have been generated, and per region evaluation of developmental trends have been explored.

The atlas is constructed using Multimodal Surface Matching (MSM) (Robinson et al., 2014, 2018), which is a spherical registration approach that allows flexible alignment of a wide variety of different types of features on the cortical surface, such as cortical folding and myelination. The versatility of MSM originates from using a modular discrete optimisation scheme that allows flexible choice of a similarity measure and is relatively insensitive to local minima. For the neonatal template construction we use a new and improved MSM that allows greater control over the smoothness of the deformations (Robinson et al., 2018). This was used in Glasser et al. (2016a) to align 449 adult, multi-modal data sets, to a group average template, during development of the Human Connectome Project's (HCP) multi-modal parcellation of the human cerebral cortex. It has the advantage of generating smooth distortions and improved alignment, especially in areas of significant feature variance attributable to population variability.

In this paper, neonatal templates are generated in a two stage-process. First, an unbiased volumetric reference space is initialised via affine alignment to a group average adult template Conte69 (FS_LR, Van Essen et al. (2012), used by the HCP), which resolves differences in the orientation of the subjects. This is left-right symmetric, and allows direct comparison between neonatal and adult feature sets as well as down-stream comparisons between the HCP healthy adult, baby connectome and life-span projects.[2] The bias towards the adult reference was removed by removing mean scaling from the final template. Following initialisation, the surface templates are iteratively refined, through alignment of fine-scale cortical folding patterns, to generate sharp, unbiased (and anatomically representative) templates for cortical surface analysis and visualisation.

Iterative refinement is commonly used in atlas construction. Evans et al. (1993) used iterative registration to build adult standard volumetric MNI (Montreal Neurological Institute) space. They used a two-stage procedure to construct a template brain that was approximately matched to the Talairach atlas. Guimond et al. (2000) built an average intensity, average shape template of their image set in an iterative manner, using the result of the previous iteration as the reference image. Their average brain models did not evolve significantly after the first iteration. Iterative refinement procedures are also commonly used in the building of adult cortical surface templates (Fischl et al., 1999b; Lyttelton et al., 2007).

The results presented here extend the work presented in Bozek et al. (2016), in which a preliminary proof of concept of the proposed method for building an unbiased neonatal cortical surface atlas for 38–42 weeks PMA (Post Menstrual Age) was described. In this paper we extend our previous work by including data from a wider range of ages, by using more datasets per week, and by using temporal kernel regression with the adaptive kernel width for averaging to overcome the variation in the distribution of subjects at different ages. Note, in this paper we move away from the computationally expensive, and not easily expandable, pairwise initialisation proposed in Bozek et al. (2016) in favour of affine alignment to an adult atlas. Further, we perform atlas refinement and add another cortical feature, namely cortical thickness. Finally, we perform the analysis of feature maps for left and right hemisphere within different cortical regions as well as computing gyrification index.

In the next section we provide an overview of the dataset (2.1), details on adaptive kernel regression 2.2, used features (2.3), and methods used to generate the atlas (2.4). In section 3 we present the generated cortical surface templates as well as the analysis of the obtained averaged cortical features for left and right hemispheres. Registration code used for generating atlas is available (https://github.com/ecr05/MSM_HOCR) and the atlases constructed from the dHCP cohort are publicly available for download from http://brain-development.org/brain-atlases/cortical-surface-atlas.

Methods

Dataset

MR images were acquired as a part of the Developing Human Connectome Project; this study was approved by the National Research

[2] https://www.humanconnectome.org.