Longitudinal Measurement of the Developing Thalamus in the Preterm Brain Using Multi-modal MRI

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Abstract. Preterm birth is a significant public health concern. For infants born very preterm ($\leq$ 32 weeks completed gestation), there is a high instance of developmental disability. Due to the heterogeneity of patient outcomes, it is important to investigate early markers of future ability to provide effective and targeted intervention.

As a neuronal relay centre, the thalamus is critical for effective cognitive function and, thus, development of white matter connections between the thalamus and cortex is vital. By non-invasively examining the state of the thalamus we can monitor development in the preterm period. To track the development we develop a novel registration technique to combine data from multiple modalities, in order to derive the transformation from a preterm scan, to a scan of the same infant at term-equivalent age. By measuring the changes in diffusion parameters over this period on a per-voxel basis, we hope to provide unique insight into neurodevelopment.

1 Introduction

Preterm birth is the leading cause of neonatal mortality and is often associated with lifelong health problems for survivors [1]. Very preterm infants (delivered at fewer than 32 weeks completed gestation) have dramatically higher incidence of cerebral palsy, reduced neuro-motor function and other cognitive deficits, with the incidence and severity of disability increasing with earlier delivery [1].

Neurological sequelae are responsible for much of the group's disability: there is a recognised 'global amalgam' of disease and abnormal neurological maturation [2]. This 'encephalopathy of prematurity' is evident in the thalamus [3], a deep grey matter structure acting as a major relay centre for communication with the cerebral cortex. In the preterm period, thalamo-cortical connectivity is being developed and the primary gyri and sulci are forming, among other developmental milestones. These structural events underpin basic cognitive processes

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including the development of sensory perception [4]. In terms of medical imaging, reduced thalamic volume has been shown to correlate with later disability [3]. The developmental importance of the thalamus, and thalamo-cortical connections in particular, suggests that non-invasively measuring its growth, both in volume and microstructure, will have predictive value for future outcome.

In order to study longitudinal development, we require a good mapping for the thalamus at different timepoints. Common registration methods experience difficulties including a lack of T_1 contrast for the internal structures of the thalamus and the morphological changes in the thalamus. In this work we exploit complementary information from multiple MR modalities to improve biological plausibility. We use the structural computational connectivity to the cortex, as defined by probabilistic tractography, to generate sub-thalamic labels which should correspond to each other over the preterm period. Using this technique, our multi-modal registration retains the spatial arrangements of the different thalamic labels between the two timepoints. We use this registration to infer changes in microstructural parameters derived by fitting the Neurite Orientation and Dispersion Index (NODDI) model [5] to the data.

In this work we present a multi-modal registration technique that allows us to map, for the first time *in-vivo*, the rates of change of microstructural characteristics in the preterm period. Because of the critical importance of the thalamus to cognitive and developmental health, these maps may aid in identifying healthy and abnormal development in this at-risk population.

2 Methods

2.1 Data

We acquired volumetric T_1-weighted and diffusion-weighted data for 5 infants on a Philips Achieva 3T MRI machine at two time-points. All infants met the inclusion criteria of normal cerebral ultrasound and all scans successfully performed. The infants had a mean gestational age at birth of 26.0 ± 0.9 weeks. The first imaging data were obtained at 33.0 ± 1.9 weeks estimated gestational age (EGA) with a further acquisition at 42.1 ± 2.5 weeks (approximately term-equivalent age). Data were acquired with the infants in an MR-compatible incubator, whilst spontaneously asleep after feeding. The resolution of the T_1-weighted data was $(0.82 \times 0.82 \times 0.5)mm^3$ at TR/TE $=17/4.6ms$, acquisition duration $462s$. The diffusion weighted data had a resolution of $(1.75 \times 1.75 \times 2)mm^3$. Six volumes were acquired at b$=0s.mm^{-2}$, 16 directions at b$=750s.mm^{-2}$ and 32 directions at b$=2000s.mm^{-2}$ with TR/TE $=9s/60ms$; total acquisition duration of $703s$.

2.2 Image Segmentation

To investigate thalamic connections to the cortex, we segmented the thalamus and produced labelled cortical regions. Neonatal image segmentation is difficult relative to the adult population because of poor image contrast, lower SNR and

the increased prevalence of motion artifacts. We use segmentation propagation [6] to fit a population-specific neonatal atlas [7] to the T_1-weighted data, generating a 50-label map for each subject. We then extracted the thalamus, and anatomical labels of the cortical regions. To segment the cortex itself, we used a probabilistic Gaussian mixture model approach initialised with a 6-class 4-D probabilistic atlas specific to the neonatal population [8], on intensity maps of the T_1 images. We corrected unsatisfactory segmentations manually. By combining the regional labels with the grey matter segmentation, we parcelated the cortex into frontal, temporal, occipital and parietal grey matter regions. These integer labels were propagated to diffusion space by affine registration of the T_1-weighted image to the diffusion space.

2.3 Multi-compartment Diffusion Data

To account for the high instance of motion and other imaging artifacts, it is necessary to remove some acquired diffusion volumes. To identify these, we took the spatial derivative of the sum of the signal across each slice in the direction perpendicular to the imaging plane. We removed volumes where the derivate value was an outlier and afterwards, checked manually and removed any further volumes that had significant artifacts. To bias-field correct the images, we registered each b$>$ 0 volume to the mean of the 6 b=0 images using affine registration.

To improve the alignment of the diffusion weighted images, we fit a diffusion tensor to these data and generated synthetic registration targets with the diffusion tensor model. Thus, each volume has a registration target depending on the b-vector of the acquisition and the b-value, reducing the influence of diffusion-induced contrast change on the registration. The data is registered using an affine transformation to these targets and the diffusion tensor model is fitted again. The b-vectors are rotated and the signal is scaled according to the Jacobian determinant of the transformation.

NODDI is a technique for modelling the signal from a twin-b-value diffusion acquisition to yield greater microstructural sensitivity than DTI measures, such as fractional anisotropy (FA) and mean diffusivity (MD) [5]. There are three model compartments: v_{iso} represents the isotropic diffusion volume fraction. v_{ic}, represents the fraction of intra-cellular volume; diffusion is modelled as sticks of zero radius, having a higher axial diffusivity than radial, in a Watson distribution (this has an orientation distribution (ODI) between 0 and 1). Finally, v_{ec}, the extra-cellular volume fraction relates to the space around the neurons where diffusion is hindered by the extra-cellular environment. Diffusion in this space uses a Gaussian anisotropic diffusion model. The signal equation for the model is: $S = (1 - v_{iso})(v_{ic}S_{ic} + (1 - v_{ic})S_{ec}) + v_{iso}S_{iso}$.

2.4 Longitudinal Infant Registration

In order to exploit the longitudinal data, registration must define a reliable, anatomically plausible longitudinal mapping of the preterm thalamus to the

term thalamus for each subject. To guide this registration we segment the thalamus into regions using probabilistic tractography from thalamic voxels to target cortical masks [9]. This results in a sub-thalamic labelling depending on projections to the cortex. We constrain registration to map regions with similar projections onto one another.

From the probabilistic tractography, we obtain a percentage in each voxel relating to each of the 8 cortical labels. We use this information to drive the registration, so that similar patterns of connection are maintained at preterm and term age. The method we use for non-linear registration is based on a cubic b-spline parametrisation of the transformation [10]. The spline parametrisation is, in our framework, used to define a continuous stationary velocity field over the space of the input images. Through a scaling-and-squaring approach, the field is exponentiated to yield a deformation field. Forward and backward transformations are optimised concurrently to ensure symmetry. The obtained forward and backward transformations are the inverse of each other because we use a stationary velocity field. Within the current experiment, the spacing between the cubic b-spline control points is set to 2.5 voxels width and the bending energy of the velocity field is used to regularise the transformation. The segmentation of the thalamic sub-areas is used to drive the registration within a multi-channel approach, where each channel corresponds to the fuzzy membership of projecting to a certain cortical endpoint. Because these are treated as probabilities, we use the symmetric Kullback-Leibler divergence (KLD) as a similarity measure and we weight the contribution from each of the 8 channels equally. The KLD is suitable for matching probability distributions. The registration thus aims to finding the single transformation that maps best each fuzzy membership from the scans acquired at 30 weeks, to its equivalent in the scans acquired at term equivalent age. The pipeline of the techniques used in this paper is summarised in Fig 1. The probability maps show the correspondence between the sub-thalamic regions at 30 and 40 weeks, which we aim to map onto each other in the registration.

3 Results

3.1 Thalamic and Cortical Segmentations

The cortical segmentations for a representative infant are shown for the preterm timepoint (Fig 2a) and at term equivalent age (Fig 2b). The broad patterns of the thalamus remain visually consistent and maintain the distinct homotopy previously seen in adults and primates. We verified the cortical and thalamic segmentations visually.

3.2 Cortical and Thalamic Volume Change

The average volumes of the cortical regions, and the thalamic subregions that principally project to them (Fig 3), show the growth of the cortical regions in every subject, with the thalamus also expanding in volume. The thalamic

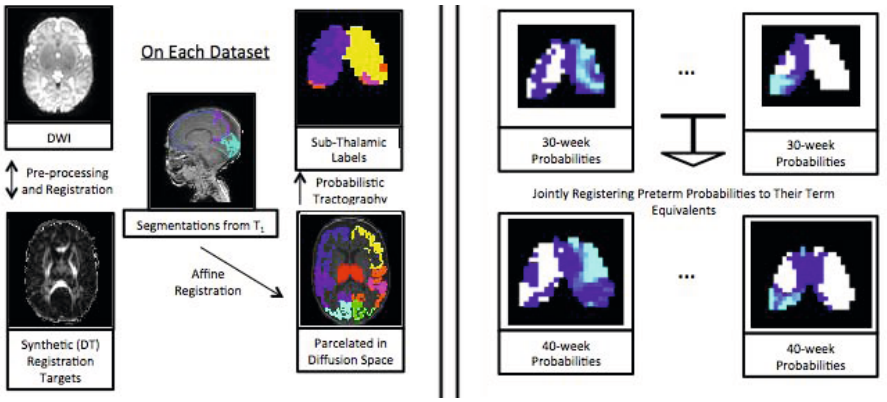


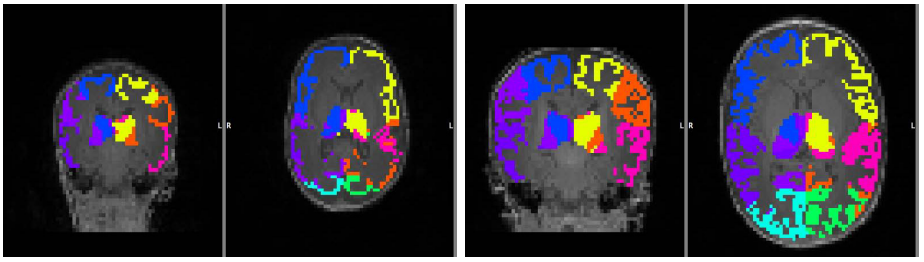
Fig. 1. The sequence of processing steps. For each timepoint, the steps on the left-hand side are performed independently. On the right there are some of probability maps (blue-light blue) overlaid on the mask of the thalamus (white). For each timepoint, there are 8 probability maps for connection to distinct cortical regions. A single transformation is calculated to jointly map the probabilities to each other.

regions display different growth rates, with the region projecting to the frontal cortex increasing in volume most; the frontal cortex has the greatest volume increase. The projections to the occipital cortex occupy a small proportion of the thalamus, because the volumes are taken after finding only the most likely projection in each region. Due to the small physical space occupied by the infant thalamus, we interpret this as a partial-volume effect.

3.3 Longitudinal Change in NODDI Parameter Maps

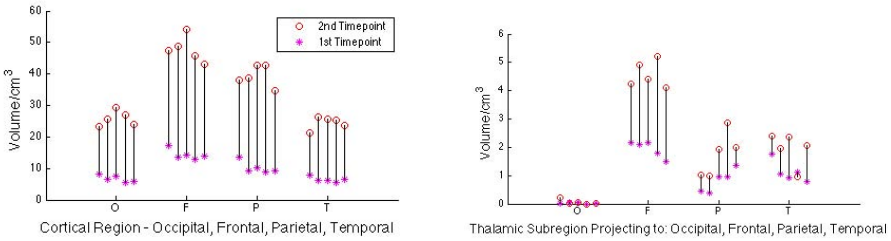
We have explained the necessity of a thalamic registration including information from the diffusion-weighted scans. Using these transformations, we can now show parameter change maps from the registered data (Fig 4).

These maps are generated from subtracting the registered preterm parameters from the term parameters. In terms of DTI parameters, the mean diffusivity shows little regional pattern. The FA decreases in the posterior portions of the thalamus, which project mainly to the temporal cortex. In terms of the NODDI parameters, the ODI seems to be closely related to the FA - there is high dispersion where there is low FA. More interestingly, all infants show significant increases in v_{ic}, which suggests an increase in cellular density. Thus, as the volume of the region increases, the cellular density increases significantly. Infant (d) has a higher magnitude of change for v_{ic}, which is likely to be because the infant had the longest time between scans (4 weeks greater than the next). For this infant, the thalamic and cortical volumes have increased a similar amount to the other infants, suggesting that the bulk growth and microstructural growth may not be entirely synchronous. On average, the changes happen mainly in



(a) (b)

Fig. 2. For (a) and (b), the Thalamus (centre), labelled by colour according to which cortical region it is most likely to project to. (a) is at 31.4 weeks, (b) is at 42.0 EGA. Note the similarities in the thalamic labels between the two timepoints.



(a) (b)

Fig. 3. For each infant we plot the cortical volumes for each region (a) and the thalamic subvolumes that project to the cortical regions (b).

the middle of the image, which projects to the frontal cortex. Thus the different diffusion parameters seem to highlight growth rates in different sections of the thalamus, which has the potential to identify specific future neurological deficits.

4 Discussion

The registration we have defined assumes that the probability of a thalamic region being linked to a particular cortical region as given by the tractography is meaningfully related to how the physical connections in the voxel are arranged. Thus, similarity between timepoints is defined by a similar distribution of probabilities to a given cortical mask region. However, there is no guarantee that the probabilities reflect the mix of connections in the actual brain, although comparable adult studies indicate that they do. If the probabilities are meaningful, an interesting extension would be to treat these probabilities as memberships to different tissue classes. Thus we could investigate the distributions of NODDI parameters in different thalamic regions.

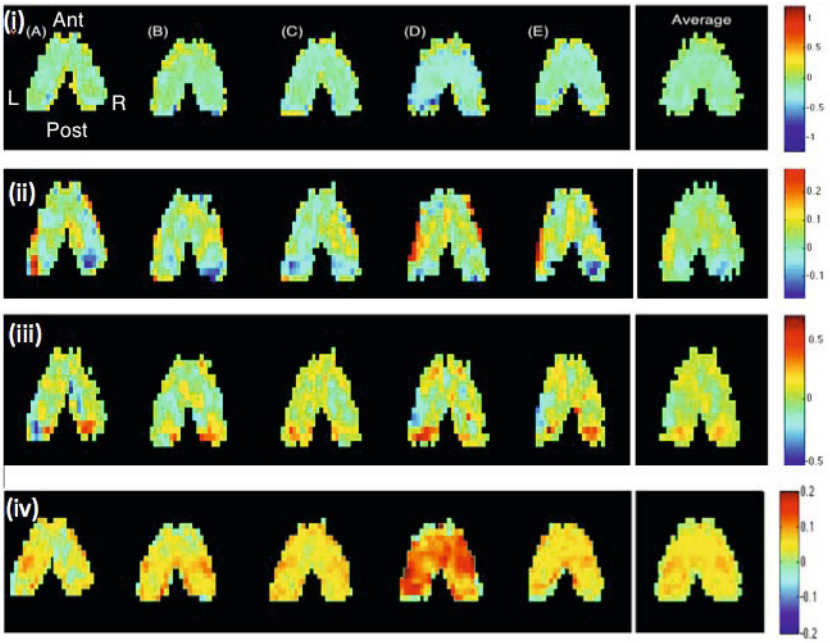


Fig. 4. The maps of parameter change in the thalamus for each infant. (i) is MD in $10^{-3}mm^2s^{-1}$, (ii) is FA, (iii) is ODI, (iv) is v_{ic}

In future, we will explore a joint registration that segments and registers the thalamus concurrently, based on information from both timepoints. The registration could be compared with known embryology/histology and the predictions of structural organisation tested. In this work the choice of cortical regions was influenced by the atlases available. It would be of interest to add the motor cortex as a target region due to the prevalence of motor-related disabilities in this cohort. From 30-40 weeks EGA, inter-hemispheric connections are being established [4] and future work will examine this. Also, we will use orientation information from the diffusion data to infer the local changes in principal orientation.

To test the growth parameters as early markers of cognitive function, the infants in this study will be followed up with psychological and neuromotor testing. The cortical regions have known functional properties and so a growth disturbance in a certain part of the thalamus is hypothesised to indicate a corresponding specific deficit.

In this work we have demonstrated the correspondence between the subthalamic labelling at two timepoints during development. The similarity in the probabilities linking various cortical regions motivates a registration technique that uses this information. We utilised information from tractography and intensity information from T_1-weighted scans in order to constrain the registration

by known anatomical priors - i.e. that the spatial pattern of connections remain relatively unchanged in the preterm period. We used this mapping to plot the changes in parameters derived from the diffusion imaging. The high developmental importance of the thalamus suggests that monitoring its development has the possibility of providing early markers of future cognitive health. By mapping local changes in the thalamus and using registration designed especially for this region, this work may lead to more specific functional predictions in this vulnerable population.

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References

1. Marlow, N., Wolke, D.: Neurologic and developmental disability at six years of age after extremely preterm birth. New England Journal of Medicine 352, 9–19 (2005)
2. Volpe, J.J.: Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurology 8(1), 110–124 (2009)
3. Ball, G., Boardman, J.P., Rueckert, D., Aljabar, P., Arichi, T., Merchant, N., Gousias, I.S., Edwards, A.D., Counsell, S.J.: The effect of preterm birth on thalamic and cortical development. Cerebral Cortex 22(5), 1016–1024 (2012)
4. Kostović, I., Judas, M.: The development of the subplate and thalamocortical connections in the human foetal brain. Acta Paediatrica 99(8), 1119–1127 (2010)
5. Zhang, H., Schneider, T., Wheeler-Kingshott, C.A., Alexander, D.C.: NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. NeuroImage 61(4), 1000–1016 (2012)
6. Cardoso, M.J., Wolz, R., Modat, M., Fox, N.C., Rueckert, D., Ourselin, S.: Geodesic information flows. In: Ayache, N., Delingette, H., Golland, P., Mori, K. (eds.) MICCAI 2012, Part II. LNCS, vol. 7511, pp. 262–270. Springer, Heidelberg (2012)
7. Gousias, I.S., Edwards, A.D., Rutherford, M.A., Counsell, S.J., Hajnal, J.V., Rueckert, D., Hammers, A.: Magnetic resonance imaging of the newborn brain: manual segmentation of labelled atlases in term-born and preterm infants. NeuroImage 62(3), 1499–1509 (2012)
8. Kuklisova-Murgasova, M., Aljabar, P., Srinivasan, L., Counsell, S.J., Doria, V., Serag, A., Gousias, I.S., Boardman, J.P., Rutherford, M.A., Edwards, A.D., Hajnal, J.V., Rueckert, D.: A dynamic 4D probabilistic atlas of the developing brain. NeuroImage 54(4), 2750–2763 (2011)
9. Behrens, T.E.J., Johansen-Berg, H., Woolrich, M.W., Smith, S.M., Wheeler-Kingshott, C.A.M., Boulby, P.A., Barker, G.J., Sillery, E.L., Sheehan, K., Ciccarelli, O., Thompson, A.J., Brady, J.M., Matthews, P.M.: Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nature Neuroscience 6(7), 750–757 (2003)
10. Rueckert, D., Sonoda, L.I., Hayes, C., Hill, D.L., Leach, M.O., Hawkes, D.J.: Non-rigid registration using free-form deformations: application to breast MR images. IEEE Transactions on Medical Imaging 18(8), 712–721 (1999)