ABSTRACT
Preterm birth is associated with abnormal brain development and long-term neurodevelopmental impairment. Quantitative magnetic resonance (MR) studies of preterm brain injury have focused on morphological features such as shape and volume and on measures of tissue microstructure obtained from diffusion tensor imaging. In this work, we focus on longitudinal changes in signal intensity, which can offer a useful marker for mapping developmental changes. The proposed analysis framework utilises spatial normalization, intensity normalization and kernel regression. Changes over time in T1- and T2-weighted signal intensity were measured in subcortical grey matter and white matter. The study shows that quantitative signal change analysis on a large cohort is feasible, and that it can serve as a marker for developmental brain changes, both normal and abnormal, which might ultimately lead to a better understanding of the trajectory of early brain maturation.

Index Terms—Brain development, MRI, neonatal, spatio-temporal, longitudinal analysis

1. INTRODUCTION
The incidence of preterm birth is increasing and has emerged as a leading cause of neurodevelopmental impairment in childhood [1]. In early development, defined here as 24-44 weeks postmenstrual age, the brain undergoes more changes in size, shape and structure than at any other time in life but quantitative markers of this period of development are limited. Improved understanding of cerebral changes during this critical period is important for mapping normal growth, and for investigating mechanisms of injury associated with risk factors for maldevelopment such as premature birth. Quantitative measures of development will also assist research of interventions designed to reduce the burden of preterm brain injury.

Magnetic resonance imaging (MRI) is a powerful technique for assessing the developing brain as it is non-invasive and non-ionizing and provides high resolution images [2]. Qualitative and quantitative assessment of a number of developmental processes can be carried out including defining growth patterns, characterizing the sequence of myelination, and assessing microstructural tissue properties (using diffusion tensor imaging) [3].

Previous MR studies have tended to focus on morphometric or microstructural characteristics [4, 5, 6, 7] at one point in time such as term equivalent age - however time-varying intensity patterns resulting from changes in the underlying tissue properties may provide novel markers of development. In a study of tissue property changes, Prastawa et al. [8] proposed a framework for analyzing early maturation in white matter that generated a normative spatiotemporal model, providing 3D maps of absolute and relative indices of maturaton. This approach proposed a continuous model of intensity changes using modified Legendre polynomials applied to a multimodal dataset (T1W, T2W, PD, DTI) with 8 subjects that had been scanned at approximately 2 weeks, 1 year, and 2 years.

The aim of our work is to quantify signal intensity change on a longitudinal data set of 116 T1- and T2-weighted images acquired from premature infants between 29-44 weeks gestational age. To our knowledge, this is the first analysis of signal intensity changes in the developing brain for this age group derived from a cohort of this size.
2. METHODS

2.1. Subjects

This study was carried out using 116 MR scans of premature neonates. On visual inspection, infants with major focal lesions were excluded from the study. The range of gestational ages (GA) at scan was 29-44 weeks. Images were acquired on 3T Philips Intera system with the following parameters: T2 fast spin echo (FSE) TR = 8700ms, TE = 160ms, flip angle = 90 degrees and voxel sizes 0.86 × 0.86 × 1 mm; 3D MPRAGE (T1) TR 17ms, TE 4.6 ms, flip angle 13 degrees, voxel size 0.82 × 0.82 × 0.8 mm.

2.2. Preprocessing

A first step in the proposed framework is the masking of non-brain tissues which was carried out for each image in the database using the Brain Extraction Tool (BET) [9]. The resulting masks were visually inspected and where necessary, brain extraction was repeated for some of images with modified parameters until adequate masks were obtained.

Images were corrected for MRI field inhomogeneity using the N4 algorithm [10], which is a modified version of the originally proposed N3 algorithm [11] that includes a modified iterative update within a multi-resolution framework.

2.3. Spatial Normalization

Figure 2 illustrates the registration framework applied to the multi-modal longitudinal data used in our study. The T1- and T2-weighted MR scans were registered to a reference template for each gestational age. For that purpose, a spatio-temporal probabilistic brain atlas created by Murgasova et al. was used [12]. This atlas is publicly available1 and was created from the segmentations of 153 neonatal subjects aged 29-44 weeks using a kernel-based smoothing method. An average intensity template as well as the corresponding tissue probability maps indicating the sizes and shapes of a number of structures are provided for each time-point. The corresponding T2W average intensity template provided by the atlas is used as a reference template at each time point. In this step, the pairs of T1W and T2W scans acquired in each session are rigidly (R in Figure 2) co-registered. Each T2W scan is then affinely (A) registered to the reference template of the 4D atlas at the same time point. The resulting affine transformation is then used to transform both the T1W and T2W scans to the reference template.

After matching each T1W-T2W pair with their respective time-point reference, they were subsequently aligned to a single time-point reference, the atlas average intensity template at 37 weeks GA. This reference was selected as the target age to reduce the degree of deformation required from the other age groups as it lies in the middle of the age range for the group. Longitudinal registrations were carried out in two steps: A global transformation was first estimated using affine registration. Subsequently, using the result of the affine transformation as the starting point, a non-rigid (N) registration step was carried out. To achieve this, a non-rigid registration algorithm proposed by Rueckert et al. [13] is used.

Fig. 2: The registrations applied to the multi-modal longitudinal data in our framework. Transformations are rigid (R), affine (A) or non-rigid (N).

2.4. Intensity Normalization

In order to perform voxel-wise intensity comparisons across different scans, as well as needing to map all the scans to a common coordinate space, images with a common intensity range are required. T1W scans were normalized using high intensity of fatty tissue between the skull and the skin, which was manually segmented. T2W scans were normalized using high intensity values of CSF. The 90th percentile intensity values of the fatty tissue and CSF were then used for the normalization of T1- and T2-weighted scans, respectively. Thus we applied a multiplicative transformation in order to have a uniform value of the reference tissue (fat in T1W, CSF in T2W) across all scans of a single modality.

2.5. Kernel Regression

To measure signal intensity change, we first create a continuous spatio-temporal model dependent on a parameter t to represent time, which in our case is the gestational age of each subject at scan. To create such a spatio-temporal model, we use kernel regression [14], a non-parametric technique for estimating the conditional expectation of a random variable and for characterizing a non-linear relation between a pair of random variables.

Let $t_1, \ldots, t_n$ denote the gestational ages of the subjects at the time of scan and $y_1, \ldots, y_n$ denote the voxel intensity

1http://www.brain-development.org/
values taken at \( n \) time points. The average intensity at age \( t \) can be estimated as:

\[
y(t) = \frac{\sum_{i=1}^{n} w(t_i, t) y_i}{\sum_{i=1}^{n} w(t_i, t)}
\]

We use a Gaussian kernel as the weight function:

\[
w(t_i, t) = \frac{1}{\sigma \sqrt{2\pi}} e^{-\frac{(t_i - t)^2}{2\sigma^2}}
\]

The width of the kernel, \( \sigma \), is a parameter that is determined by the size of the input dataset and its distribution. Smaller values tend to introduce noise into the time-varying trajectory since it becomes influenced by individual examples, while values that are too large will tend to smooth out variation in which we are interested. For our data, good results are obtained for \( 2 < \sigma < 5 \).

### 3. RESULTS

In this study, we focused on changes in intensity within subcortical grey matter (GM) and white matter (WM). Figure 3 shows a map of patterns of intensity change over the full period, but there are more comprehensive analyses possible that can show for example the patterns of maturation and which areas change in what sequence. Our results indicate differing patterns of spatio-temporal signal change in T1W and T2W, respectively. Top-Right: Intensity change trajectories of posterior limb of internal capsule (PLIC) and the lateral aspect of the lentiform nucleus region which maturates with a slower rate. Error bars represent the standard deviation at each time-point.

As an example of different patterns of spatio-temporal signal change, Figure 4 (Top) shows the intensity change trajectories of the cross-section of the posterior limb of internal capsule (marked by square in Fig. 3) in both T1W and T2W MRI. It shows that signal intensity change trajectories of a single location can exhibit different rates of change and yet the general trend is similar. T1W intensities increase as a function of age in contrast to T2W intensities which decrease with age. Furthermore, Figure 4 shows (Bottom) the intensity change trajectories of the lateral aspect of the lentiform nucleus (marked by circle in Fig. 3) which maturates with a slower rate. The earlier maturation of the posterior limb of internal capsule is clearly visible, and hence the region of the internal capsule can be used as a reference to compare the maturation level of preterm babies comparing to this reference region.

### 4. CONCLUSION AND FUTURE WORK

We have quantified spatio-temporal signal intensity changes during early development using multi-modal MR imaging, atlasing and non-rigid registration. The results demonstrate maturational processes in tissue characteristics from 29 weeks onwards following preterm birth which are likely to repre-
sent pre-myelination [16] changes and alterations in water content [17]. The approach provides quantitative trajectories of signal intensity change that may be useful in providing age-specific normal values for mechanistic studies of preterm brain injury and for studying the effects of interventions designed to improve outcome following preterm birth. Furthermore, the method provides a time course of change for each location in the brain so that it can also act as the basis for exploring spatio-temporal patterns of change.

While our analysis framework is reliant on normalization accuracy, the results demonstrated are promising and more accurate normalization methods will be investigated. Future work will also make use of other modalities within our analysis framework as well as tracking signal intensity change in other brain structures.

5. REFERENCES


cycles of regional maturation of the brain.,” Regional De-
velopment of the Brain in Early Life, pp. 3–70, 1967.