NeuroImage: Clinical 7 (2015) 622–630

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Stochastic process for white matter injury detection in preterm neonates ☆

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ARTICLE INFO

Article history:
Received 19 December 2014
Received in revised form 9 February 2015
Accepted 23 February 2015
Available online 26 February 2015

Keywords:
White matter injury
Preterm neonates
Stochastic process

ABSTRACT

Preterm births are rising in Canada and worldwide. As clinicians strive to identify preterm neonates at greatest risk of significant developmental or motor problems, accurate predictive tools are required. Infants at highest risk will be able to receive early developmental interventions, and will also enable clinicians to implement and evaluate new methods to improve outcomes. While severe white matter injury (WMI) is associated with adverse developmental outcome, more subtle injuries are difficult to identify and the association with later impairments remains unknown. Thus, our goal was to develop an automated method for detection and visualization of brain abnormalities in MR images acquired in very preterm born neonates. We have developed a technique to detect WMI in T1-weighted images acquired in 177 very preterm born infants (24–32 weeks gestation). Our approach uses a stochastic process that estimates the likelihood of intensity variations in nearby pixels; with small variations being more likely than large variations. We first detect the boundaries between normal and injured regions of the white matter. Following this we use a measure of pixel similarity to identify WMI regions. Our algorithm is able to detect WMI in all of the images in the ground truth dataset with some false positives in situations where the white matter region is not segmented accurately.

1. Introduction

In recent decades, improved neonatal intensive care unit (NICU) therapies have reduced the mortality and increased the survival rate of preterm neonates. However, developmental outcomes remain poor and we urgently need to improve the health and developmental trajectories of these children. Yet, despite advances in neonatal care, preterm birth (<37 weeks of gestation) remains a leading cause of childhood and lifelong disability (Hack et al., 2002; Nand et al., 2011). Very preterm infants, born at 32 weeks of gestation or younger, have the highest risk of poor outcome. More than half of these very preterm infants have serious developmental problems including cognitive, language, behavioral, sensory, or motor deficits (e.g., cerebral palsy) (Grunau et al., 1990; Grunau et al., 2002). Poor developmental outcomes place enormous burdens on the child, the family and the community (Bodeau-Livinec et al., 2008; Grunau et al., 2004; Lindstrom et al., 2007; Marlow et al., 2005; Miller et al., 2005; Oskoui et al., 2013; Roberts et al., 2009; Roberts et al., 2010; Saigal et al., 2003; Walsh et al., 2010). Consequently, the major remaining challenge in the care of the preterm is to optimize neurodevelopmental outcomes and reduce childhood and lifelong disabilities.

As clinicians strive to identify preterm neonates at greatest risk of significant cognitive or motor problems, accurate predictive tools are required. This will enable infants at highest risk to receive early developmental interventions, and will also enable clinicians to implement and evaluate novel treatments to improve these outcomes. The expertise to identify and quantify brain injury in preterms is limited by the nuances of interpreting neonatal brain MRI scans. Severe white matter injury (WMI) and abnormal white matter maturation is associated with poor neurodevelopmental outcome; however more subtle injuries are difficult to identify and their impact on cognitive and motor development remains less understood. Our software toolkit incorporating automatic WMI detection will facilitate rapid brain imaging of preterm neonates, including longitudinal evaluations, so that those at high risk of neurodevelopmental impairment receive timely and appropriate

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http://dx.doi.org/10.1016/j.nicl.2015.02.015

intervention and support, ultimately improving long-term outcomes. Thus, our goal was to develop a new system for automated detection and visualization of brain abnormalities in the preterm neonate. In this study, 177 very preterm born neonates (24–32 weeks gestation) were assessed with MRI at two time points, early in life around the time of birth, and at term-equivalent age.

Previous work has established multi-focal WMI as the characteristic pattern of brain injury in preterm neonates (Chau et al., 2009; Miller et al., 2005), and is most readily evident on T1 weighted images in the first weeks after birth. Unlike periventricular leukomalacia (PVL), or periventricular hemorrhage, an increasingly uncommon brain injury (Hamrick et al., 2004), multi-focal WMI is identified by MRI in one-third of preterm neonates, and predicts a higher risk of neurodevelopmental disabilities in this and other neonates cohorts followed through childhood (Chau et al., 2013; Miller et al., 2002; Miller et al., 2005; Woodward et al., 2012). More specifically, the burden of white matter lesions was more predictive of neurodevelopmental outcome than the lesion locations. WMI is also associated with more diffuse abnormalities of brain development (Back and Miller, 2014; Chau et al., 2009; Chau et al., 2012). While focal WMIs seen on MRI are associated with significant visual, motor and cognitive dysfunction, they are often indicative of concurrent abnormal maturation (Counsell et al., 2008; Krishnan et al., 2007; Miller et al., 2005; Woodward et al., 2006). WMI is followed by diffusely abnormal microstructural (e.g., Fractional Anisotropy) and metabolic brain development as preterm neonates grow to term age (Adams et al., 2010; Chau et al., 2009; Miller et al., 2002). These abnormalities in brain development persist through childhood with associated adverse neurodevelopmental outcomes (Adams et al., 2010; Chau et al., 2013; Counsell et al., 2008; Kalpakidou et al., 2012; Kesler et al., 2008; Ment et al., 2009; Mullen et al., 2011; Srinivasan et al., 2007). While other brain lesions occur in the preterm neonate, including intraventricular hemorrhage, these are readily diagnosed on neuroradiological review, with WMI being a risk for abnormal maturation and thus the focus of the study. Yet the clinical application of MRI is limited by the lack of methods to automatically detect and display areas of injury to the clinician. Thus, we focus on developing methods to identify WMI.

2. Methods

Parametric modeling, e.g., Gaussian, requires a large number of samples and consistency of the underlying distribution for validity. Based on the Law of Large Numbers (Rao, 1989) asymptotically the average of an arbitrary distribution tends towards the Normal (Gaussian) distribution. However, given a small sample size this assumption may not be accurate. There are also several additional constraints in our dataset compared to usual adult brain MRI datasets. First, the infant brain undergoes rapid changes, thus it is difficult to register different infant brains to a specific model and compute an Atlas representing the average infant brain. Second, WMI in preterm neonates tend to be diffused over a region of an MRI, compared to tumors which show up as a clearly identifiable connected region. Third, the absolute intensities of pixels in an injured region may be similar to intensities in non-injured regions; thus, it is difficult to identify WMIs considering intensities alone. Thus, our earlier attempts at identifying WMI using thresholding techniques (Cheng et al., 2013) had limited success.

A characteristic of WMI is the abrupt intensity variation observed in an MRI relative to surrounding pixels. We detect such changes using a stochastic process which avoids the need for assumptions regarding any underlying distributions, such as Gaussian.

Before detecting WMIs we need to segment the white matter region of the brain and distinguish it from the gray matter. There are several algorithms in the literature, such as (Zhang et al., 2001), that have shown promising results in differentiating between the gray and white matter regions. However, these methods work on adult brains and large datasets where structures do not vary significantly among subjects. We extended our Fluid Vector Flow (Wang et al., 2009) algorithm using a fuzzy mask for white matter boundary detection. Our fully automatic 3D algorithm (Wang et al., 2010) can be combined with fuzzy clustering for brain white matter segmentation, following skull stripping (Fischmeister et al., 2013). Results on various sections on a premature brain are shown in Fig. 1. We followed the steps below that were applied to T1-weighted MRI scans (coronal volumetric T1-weighted images: TR, 36; TE, 9.2; FOV, 200 mm; slice thickness, 1 mm; no gap) acquired on a Siemens Avanto 1.5 T scanner (Erlangen, Germany).

1 Pre-processing to enhance contrast;
2 A new Normalized Gaussian Mixture Model computed using Expectation Maximization;
3 Computing a Gaussian Bayesian Brain Map;
4 Processing this brain map to highlight the white matter and initialize a Fluid Vector Flow algorithm;
5 Automatic initialization assisted by fuzzy clustering, supplemented with a 3×3 median filter; and;
6 Using Fluid Vector Flow to segment the target region.

Though our results look promising the accuracy in delineating the white matter region still needs improvement. It can be observed from Fig. 1 that some regions outside the actual white matter are also detected by the current algorithm. Thus, further work is needed to make the accuracy more reliable. Furthermore, accurate delineation of the white matter region is not the focus of this work. Thus, we relied on manual delineation of the white matter as the starting point to test our WMI detection method. Our approach to limiting analysis to the white matter region is consistent with recent work by others, e.g. Deoni et al. (2013).

Assuming that the white matter region can be reasonably segmented (Zhang et al., 2001) in the brain, we have developed a stochastic algorithm for detecting WMIs. The absolute intensities of pixels in an injured region may be similar to intensities in non-injured regions; thus, it is difficult to identify injuries considering intensities alone. However, a characteristic of injuries is the abrupt intensity variation observed relative to surrounding pixels. We detect such changes using a stochastic process which avoids the need for assumptions regarding any underlying distributions. To improve the robustness of our approach we stretch the histogram of a white matter region and group small range of intensities. The probability of intensities in nearby pixels being similar (very different) is assumed to be high (low). Based on this assumption, and the statistical properties of a small subset of the images we are working with, a transition probability matrix is estimated which gives the likelihood of changing from one intensity at a given pixel to another intensity at an adjacent pixel. A very small (statistically defined) transition probability indicates the possibility of an injury. Following the identification of significant transition boundaries, we grow regions by considering statistically close nearby values.

Detailed steps in our algorithm are described below.

- Divide pixel values into $(N + 1)$ intervals to improve robustness and add consistency when processing different images with varying range of pixel values. These intervals can be considered as the State Space $\{s_0, s_1, \ldots, s_N\}$ of a stochastic process (Hoel et al., 1972).
- Compute the Conditional Transition Probability Matrix for pairs of transformed pixel values, details described below. The transition probability $P(X(i, j) = s_n, \text{X\_neighbor}(i, j) = s_b)$ is the probability of transition from Sate s_n to State s_b at adjacent pixel locations; with adjacency being defined by 8-connectivity (Rosenfled, 1970). For simplicity, we consider the transition probabilities for adjacent pixels on a 2D image. However, the approach can be generalized to non-adjacent pixels by introducing another dimension in the matrix reflecting distance between pixels. The method can be extended to 3D volumetric images by considering adjacency of voxels defined by 26-connectivity (Bertrand, 1994).
- Mark potential boundaries of WMIs considering the transition