NeuroImage 157 (2017) 675–694

Contents lists available at ScienceDirect

NeuroImage

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

A tract-specific approach to assessing white matter in preterm infants

Diliana Pecheva[a,b], Paul Yushkevich[c], Dafnis Batalle[a], Emer Hughes[a], Paul Aljabar[a], Julia Wurie[a], Joseph V. Hajnal[a], A. David Edwards[a], Daniel C. Alexander[b], Serena J. Counsell[a,*], Hui Zhang[b]

[a] Centre for the Developing Brain, Division of Imaging Sciences & Biomedical Engineering, King's College London, UK
[b] Department of Computer Science and Centre for Medical Image Computing, University College London, UK
[c] Penn Image Computing and Science Laboratory (PISCL), Department of Radiology, University of Pennsylvania, Philadelphia, USA

ARTICLE INFO

Keywords:
Diffusion weighted MRI
Preterm
Infant
White matter
Tract-specific analysis

ABSTRACT

Diffusion-weighted imaging (DWI) is becoming an increasingly important tool for studying brain development. DWI analyses relying on manually-drawn regions of interest and tractography using manually-placed waypoints are considered to provide the most accurate characterisation of the underlying brain structure. However, these methods are labour-intensive and become impractical for studies with large cohorts and numerous white matter (WM) tracts. Tract-specific analysis (TSA) is an alternative WM analysis method applicable to large-scale studies that offers potential benefits. TSA produces a skeleton representation of WM tracts and projects the group's diffusion data onto the skeleton for statistical analysis. In this work we evaluate the performance of TSA in analysing preterm infant data against results obtained from native space tractography and tract-based spatial statistics. We evaluate TSA's registration accuracy of WM tracts and assess the agreement between native space data and template space data projected onto WM skeletons, in 12 tracts across 48 preterm neonates. We show that TSA registration provides better WM tract alignment than a previous protocol optimised for neonatal spatial normalisation, and that TSA projects FA values that match well with values derived from native space tractography. We apply TSA for the first time to a preterm neonatal population to study the effects of age at scan on WM tracts around term equivalent age. We demonstrate the effects of age at scan on DTI metrics in commissural, projection and association fibres. We demonstrate the potential of TSA for WM analysis and its suitability for infant studies involving multiple tracts.

Introduction

Diffusion-weighted magnetic resonance imaging (dMRI) is increasingly being used to study brain development and injury in infants. Using metrics derived from diffusion tensor imaging (DTI) (Basser et al., 1994) we have gained valuable insights into the effects of maturation and injury on white matter (WM) in healthy and patient infant populations. DTI analyses of WM have been used to assess quantitatively microstructural changes during normal development in infancy (Dubois et al., 2006; Gao et al., 2009) and through childhood to adulthood (Lebel et al., 2008); provide in vivo quantification of the spatio-temporal pattern of WM maturation (Dubois et al., 2008); assess differences in cerebral WM between term and preterm infants (Anjari et al., 2007; Huppi et al., 1998; Rose et al., 2008); and correlate DTI metrics with early developmental outcome in preterm infants (Counsell et al., 2008; van Kooij et al., 2012).

A number of approaches have been used to analyse DTI data during development. Manually-drawn regions of interest (ROI) (Gao et al., 2009; Huppi et al., 1998) or tractography using manually-placed waypoints (Bassi et al., 2008; Dubois et al., 2008; Dubois et al., 2006) are generally assumed to produce anatomically accurate results but these methods become prohibitively labour-intensive for large cohort studies. Subsequently a number of methods have been developed for automatic segmentation of WM tracts (Suarez et al., 2012; Zhang et al., 2010b). However, establishing correspondence between subjects' WM tracts can be problematic due to inter-subject variability in anatomy and DTI characteristics, which can result in differences in tractography or segmentation. It is possible to average the DTI metrics over the entire tract (Lebel et al., 2008) but localised differences may be missed. Correspondence can be achieved by sampling at equivalent levels along tracts (Groeschel et al., 2014; Verde et al., 2014) or parameterising WM tracts by arc length, essentially reducing entire

* Correspondence to: Department of Perinatal Imaging, Division of Imaging Sciences & Biomedical Engineering, Kings College London, 1st Floor South Wing, St Thomas' Hospital, London SE1 7EH, UK.
E-mail address: serena.counsell@kcl.ac.uk (S.J. Counsell).

http://dx.doi.org/10.1016/j.neuroimage.2017.04.057
Received 3 March 2017; Accepted 25 April 2017
Available online 27 April 2017

tracts to a single, core line (Corouge et al., 2006; Goodlett et al., 2009; O'Donnell et al., 2009; Verde et al., 2014; Yeatman et al., 2012). These methods have been used to study neurodevelopment in toddlers (Geng et al., 2012; Goodlett et al., 2009), WM heritability in twin neonates (Lee et al., 2015), infantile Krabbe disease (Gupta et al., 2015), and prenatal exposure to selective serotonin reuptake inhibitors (Jha et al., 2016). However these methods are more suitable for tubular rather than sheet-like tracts. Collapsing tracts such as the corticospinal tract into a single line, especially in the region of the fanning cortical projections, fails to appropriately represent the tract macrostructure and averaging over such a large area may obscure microstructural changes. Moreover, bundles such as the corpus callosum have to be separated into tubular regions and cannot be analysed as a whole.

Exploiting the sheet-like structure of many WM tracts, tract-based spatial statistics (TBSS) was introduced (Smith et al., 2006) and initiated the practice of projecting volumetric data onto a WM skeleton. Although it has proven to be a valuable analysis tool for studying development (Anjari et al., 2007; Ball et al., 2010; Counsell et al., 2008; Rose et al., 2008; van Kooij et al., 2012), recent studies have discussed the potential pitfalls of TBSS (Bach et al., 2014; de Groot et al., 2013; Edden and Jones, 2011; Schwarz et al., 2014; Van Hecke et al., 2010; Zalesky, 2011). A particular limitation of TBSS is a lack of anatomical specificity due to the construction of the skeleton for the entire WM, rather than separately for each individual WM tract. Although TBSS is useful when there is no a priori hypothesis regarding the anatomical location of an effect of interest, it makes it impossible to distinguish between adjacent WM tracts such as the inferior longitudinal and inferior-fronto-occipital fasciculi.

Tract-specific analysis (TSA) (Yushkevich et al., 2008) is an alternative WM analysis method that creates skeleton models of individual WM tracts onto which diffusion data can be projected for statistical analysis. In TSA, subjects are registered to a study-specific template using a tensor-based algorithm (Zhang et al., 2006). Following registration, tracts of interest are delineated from the template using deterministic tractography and manually-drawn regions of interest. From the tractography results, a medial surface is determined for each tract that simultaneously defines its skeleton and boundary (Yushkevich and Zhang, 2013). The skeleton also describes local tract thickness via the radius function defined as equal to the radius of the maximal inscribed sphere within the boundary centred at that point on the skeleton. Diffusion data from every subject is then projected onto the skeleton, similarly to TBSS. TSA samples data to be projected onto each point of the skeleton by searching along the unit normal from that point to the tract boundary. The tract boundary defines the stopping criteria. This aims to limit potential voxel misassignment from neighbouring tracts. The TSA framework allows for either a maximum-value or mean-value data projection strategy. In the maximum-value strategy, the tensor with the highest FA value is selected. In the mean-value strategy, the average tensor is computed and from this average tensor, scalars such as FA are computed. Statistical analysis of projected diffusion data is then carried out at each point on the skeleton. The key aspects of the TSA and TBSS pipelines and their differences are summarised in Table 1.

TSA offers potential advantages as an analysis tool. It is automated therefore reducing the time cost and inter-rater variability which affect manual-input methods. It characterises WM tracts as surfaces rather than aggregating tracts into a single core line thereby capturing the overall tract morphology. Theoretically TSA also offers improvements over TBSS by (i) employing a tensor-based rather than scalar-based registration; (ii) defining tracts individually and so making it possible to distinguish between adjacent tracts; and (iii) having a data projection search stopping criteria intended to limit crossing over into neighbouring tracts. TSA has been successfully applied to study pathologies such as paediatric chromosome 22q11.2 deletion syndrome (Yushkevich et al., 2008) and amyotrophic lateral sclerosis (Zhang et al., 2010a), and changes in DTI metrics over the lifespan (Chen et al., 2016), however has not been previously applied to study infant populations. Moreover, the performance of TSA has not been assessed extensively.

Table 1
A summary of the key aspects of the TSA and TBSS pipelines.

Aspect	TSA	TBSS
Registration	Tensor-based	Scalar-based (FA)
Search direction	Perpendicular to the skeleton surface	Direction of maximum change within a local 3x3×3 voxel neighbourhood.
Choice of voxel to project	Maximum FA tensor or mean tensor	Maximum FA tensor
Stopping criteria	Tract boundary	Skeleton distance map
Statistical resolution	Point on surface	Voxel
Multiple comparisons	Suprathreshold cluster analysis	Threshold-free cluster enhancement

Table 2
Perinatal characteristics of the study group.

Perinatal clinical characteristic	
Median (range) gestational age at birth	30.64 (24–32.86) weeks
Median (range) postmenstrual age at scan	41.93 (38.57 – 47.14) weeks
Median (range) day age at scan	84 (142 – 48) days
Median (range) birthweight	1218 (655–1960) grams
Median (range) days of ventilation	0 (0 – 40) days
Small for gestational age[a] (number of infants)	13

[a] Defined as < 10th birthweight percentile.

The aim of this study is to evaluate the performance of TSA within the context of preterm infant data. We compare TSA with native space tractography as a gold standard, and with TBSS, a similar and widely-used method. Despite some known limitations, TBSS remains a widely-used tool, having been cited over 3000 times (618 alone since 2016). Our evaluation of TSA involves (i) an assessment of TSA's ability to align WM tracts from different subjects and the accuracy of its data projection step in comparison to TBSS; and (ii) an application of TSA for the first time to a cohort of preterm infants at term equivalent age to determine whether TSA is able to detect developmental changes in diffusion properties of WM tracts.

Methods

Subjects

Permission for this study was granted by Queen Charlotte's and Hammersmith Hospitals Research Ethics Committee (07/H0704/99) and written parental consent was acquired prior to imaging. MR data were collected from 53 preterm subjects who were imaged between February and July 2013. All images were reviewed by an experienced perinatal neuroradiologist and cases with major focal lesions were excluded. Five data-sets were excluded; 2 unilateral haemorrhagic infarction, 1 cerebellar infarct, 1 cerebellar haemorrhage and 1 infant had temporal and cerebellar haemorrhages with cerebellar hypertrophy. 48 subjects (23 female) born at a median (range) gestational age (GA) of 30.6 (24.0–32.9) weeks and imaged at a median age of 41.9 (38.6–47.1 weeks) weeks post-menstrual age (PMA) were analysed in this study. The perinatal characteristics of the study group are summarised in Table 2.

Data acquisition

MR imaging was performed on a 3-T MR system sited on the neonatal intensive care unit. T1- and T2-weighted MR imaging and single shot echo planar dMRI data were acquired using an 8-channel