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Rapid and reliable tract-based spatial statistics pipeline for diffusion tensor imaging in the neonatal brain: Applications to the white matter development and lesions

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ABSTRACT

Purpose: The relatively poor image contrast and variation in the neonatal brain size are technical challenges associated with the typical tract-based spatial statistics (TBSS) for the target identification and normalization. This study aimed to develop a rapid and reliable pipeline for the neonatal TBSS.
Materials and methods: A rapid TBSS strategy was proposed based on the group-wise target choice for fractional anisotropy (FA) derived from diffusion tensor imaging (DTI). The most representative subject of the entire group was identified via (a) initial group-averaged template creation (b) followed by identification of the target with the minimum warp displacement score between the individual and the group-averaged template. The computation time, registration quality, measurement of regional values, and statistical analyses were evaluated in two applications: brain white matter development in normal term neonates, and alterations in preterm neonates with white matter lesions compared to the matched controls. These performances in the proposed pipeline were compared with those in the typical and previous neonatal TBSS workflows.
Results: Target choice using the proposed strategy is faster, compared with the previous TBSS pipelines, especially with the increase of the sample size. Registration errors between individuals and the target are assessed through warp displacement scores. Smaller warp displacement scores are observed for the proposed method than the typical pipeline. Due to the relatively accurate registration, the proposed method results in lower standard deviations and higher averaged values of FA across subjects. Additionally, more areas with significant changes related to the development and white matter lesions are detected using the proposed method than previous TBSS pipelines. The proposed pipeline provides stronger correlation between FA and gestational age, and larger difference between preterm neonates with white matter lesions and controls.
Conclusion: The proposed TBSS pipeline improves the efficiency and reliability of the DTI analysis in the neonatal brain.

1. Introduction

Diffusion tensor imaging (DTI) provides quantitative metrics for characterizing the microstructure of the human brain in vivo [1,2]. Tract-based spatial statistics (TBSS) is a powerful tool for the voxelwise analysis of the DTI data [3]. It has been widely used to assess the microstructural variations associated with brain development, training, disorders, and treatments [4–8]. The TBSS framework reduces local misalignments through projecting voxels onto the nearest location on white matter tract centers [3,4] and overcomes numerous problems in conventional voxel-based and regions of interest analyses [9]. The projection algorithm could moderate about 10% misalignment due to inaccurate image registrations [10]. Therefore, accurate registration prior to the projection is a key process for TBSS. Both the target and registration techniques could affect the accuracy and even the measurement of DTI metrics [3,4]. Unfortunately, the target choice procedure is time consuming in the typical TBSS pipeline [3,4]. Moreover, the relatively poor image contrast and variation in the neonatal brain size pose technical challenges to the target choice and the image registration [4]. To develop a rapid and reliable TBSS pipeline for the neonatal DTI data is critical for studies investigating the early brain development and pediatric disorders.

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Several studies have updated the TBSS pipeline using novel strategies [4,9,11,12]. On one hand, many advanced techniques have been adopted to improve the accuracy of the registration across subjects [4,9,12]. Considering the characteristics of neonatal brain images, an optimized TBSS protocol has been proposed with an additional linear registration of six degrees of freedom (DOF) [4]. Although the additional steps reduce registration errors obviously [4], the computation time for the neonatal TBSS becomes longer. On the other hand, effects of registration targets established using different strategies have been evaluated [3,4,9,11]. In the typical TBSS pipeline [3], a single-subject fractional anisotropy (FA) image with the minimum mean displacement score is selected as the target for the registration. To obtain this minimum score, the individual FA map should be registered to the map of every other subject. The computation time for this procedure increases sharply with sample size. Besides this single-subject strategy, the group-averaged FA has also been considered as the registration target in the revised TBSS pipeline [11]. The above strategies have advantages and drawbacks [13]. Single-subject target is biased in anatomical features [11,13] although it is sharper than an averaged image [3]. The group-averaged target is always generated based on the spatial intensity averaging after inter-individual registrations [11,13,14]. The utilization of a group-averaged image for highly nonlinear transformation remains an unresolved problem [13,15]. These issues could be partially resolved by choosing an individual target satisfying certain criteria of the group global features [13,15].

In this study, we chose the representative FA image via (a) creating the initial group-averaged template to obtain the group global features (b) followed by identifying the target with the minimum warp displacement score between the individual and the group-average template. To improve the reliability of TBSS, linear and nonlinear registrations were combined during the image registration [4]. Based on these modified steps, a novel TBSS pipeline was proposed. The computation time, registration quality, measurement of regional values, and statistical analyses were evaluated in two applications: brain white matter development in the normal term neonates, and alterations in preterm neonates with white matter lesions compared to the matched controls. These performances in the proposed pipeline were compared with those in the typical and previous neonatal TBSS workflows.

2. Materials and methods

This study was approved by the local institutional review board. The parents of the neonates were informed regarding the goals and risks of the magnetic resonance imaging (MRI) scan, and requested for the written consent.

2.1. Theory

The proposed TBSS pipeline is outlined in Fig. 1. For comparisons, the target choice procedures in the typical and previous neonatal TBSS are also shown. In the typical and previous neonatal TBSS pipelines [3,4], the individual FA image with the minimum warp displacement score compared with others is selected as the final registration target. With $S_{i,j}$ denoting the warp displacement score between individuals i and j, the target choice procedure in a group containing N subjects is formulated as:

$$\min_{i=1,2,\cdots,N} \sum_{j=1}^{N} Si,j. \quad (1)$$

In total, the number of registrations is N^2. The T_{linear} and $T_{nonlinear}$ denote the computation time for linear and nonlinear registration respectively. The overall computation time of the target choice in the typical TBSS pipeline ($T_{typical}$) is calculated as:

$$T_{typical} = (T_{linear} + T_{nonlinear}) * N^2. \quad (2)$$

In the proposed TBSS pipeline, an initial group-averaged FA template is created using a common procedure for the template creation [14,16]. First, the anterior commissure-posterior commissure (AC-PC) line is aligned using a linear transformation [14]. The aligned FA images are averaged to create the first mean FA map. Then each aligned FA image is registered to the first mean FA map using the combination of six and twelve DOF linear registrations. The second mean FA map is created and considered as the initial group-averaged template for the next target choice step. Finally, warp displacement scores between individuals and the initial group-averaged template are calculated. An individual FA image with the minimum warp displacement score is selected as the target. This procedure can be formulated as:

$$\min_{i=1,2,\cdots,N} S_{i,temple}. \quad (3)$$

The total computation time for this proposed target choice procedure ($T_{proposed}$), including the initial group-averaged FA template creation and the minimum warp displacement score calculation, is determined by the following equation:

$$T_{proposed} = (2 * T_{linear} + T_{nonlinear}) * N. \quad (4)$$

In theory, the computation time $T_{proposed}$ (Eq. (4)) is smaller than $T_{typical}$ (Eq. (2)) when the sample size exceeds 2 ($N \geq 2$).

2.2. Subjects and data acquisition

Neonates were consecutively collected from the local neonatal intensive care unit.

Term neonates: This study identified 38 term neonates (24 males and 14 females; gestational age range: 37.00–41.43 weeks) without any MRI abnormalities or evidences of any clinical episodes that might cause cerebral damages.

Preterm neonates with white matter lesions and controls: The inclusion criteria of preterm neonates with white matter lesions was evidence of focal punctate lesions in the cerebral white matter present as hyperintensity on T1 weighted imaging (T1WI) and hypointensity on T2 weighted imaging (T2WI). Subjects with clinical diagnosis of congenital malformations of central nervous system, infections, metabolic disorders, hydrocephalus, gray matter lesions or major destructive white matter lesions such as cystic degeneration and infarction were excluded. Neonates matched for gender and gestational age who did not have any MRI abnormalities or evidence of clinical episodes that might cause cerebral damages were enrolled as controls. A total of 33 preterm neonates (17 males and 16 females; gestational age range: 30.71–35.86 weeks) with white matter lesions and 33 matched controls (17 males and 16 females; gestational age range: 30.14–36.29 weeks) were enrolled. The detailed demographics are listed in Table 1.

The MRI data used in this study were acquired for the clinical examination and diagnosis. To reduce the head movement and complete the MRI procedure, the patients were sedated with a relatively low dose of oral chloral hydrate (25–50 mg/kg) [17,18]. The potential risks of the chloral hydrate were fully considered [19]. The patient selection, monitoring, and management were performed strictly following the guidelines [20]. Neonates were laid in a supine position and snugly swaddled in blankets. A pediatrician was present during the MRI scan. Micro earplugs were inserted into the external