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Automatic segmentation of the hippocampus for preterm neonates from early-in-life to term-equivalent age

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ABSTRACT

Introduction: The hippocampus, a medial temporal lobe structure central to learning and memory, is particularly vulnerable in preterm-born neonates. To date, segmentation of the hippocampus for preterm-born neonates has not yet been performed early-in-life (shortly after birth when clinically stable). The present study focuses on the development and validation of an automatic segmentation protocol that is based on the MAGeT-Brain (Multiple Automatically Generated Templates) algorithm to delineate the hippocampi of preterm neonates on their brain MRIs acquired at not only term-equivalent age but also early-in-life.

Methods: First, we present a three-step manual segmentation protocol to delineate the hippocampus for preterm neonates and apply this protocol on 22 early-in-life and 22 term images. These manual segmentations are considered the gold standard in assessing the automatic segmentations. MAGeT-Brain, automatic hippocampal segmentation pipeline, requires only a small number of input atlases and reduces the registration and resampling errors by employing an intermediate template library. We assess the segmentation accuracy of MAGeT-Brain in three validation studies, evaluate the hippocampal growth from early-in-life to term-equivalent age, and study the effect of preterm birth on the hippocampal volume. The first experiment thoroughly validates MAGeT-Brain segmentation in three sets of 10-fold Monte Carlo cross-validation (MCCV) analyses with 187 different groups of input atlases and templates. The second experiment segments the neonatal hippocampi on 168 early-in-life and 154 term images and evaluates the hippocampal growth rate of 125 infants from early-in-life to term-equivalent age. The third experiment analyzes the effect of gestational age (GA) at birth on the average hippocampal volume at early-in-life and term-equivalent age using linear regression.

Results: The final segmentations demonstrate that MAGeT-Brain consistently provides accurate segmentations in comparison to manually derived gold standards (mean Dice's Kappa > 0.79 and Euclidean distance <1.3 mm between centroids). Using this method, we demonstrate that the average volume of the hippocampus is significantly different ($p < 0.0001$) in early-in-life (621.8 mm^3) and term-equivalent age (958.8 mm^3). Using these differences, we generalize the hippocampal growth rate to 38.3 ± 11.7 mm^3/week and 40.5 ± 12.9 mm^3/week for the left and right hippocampi respectively. Not surprisingly, younger gestational age at birth is associated with smaller volumes of the hippocampi ($p = 0.001$).

Conclusions: MAGeT-Brain is capable of segmenting hippocampi accurately in preterm neonates, even at early-in-life. Hippocampal asymmetry with a larger right side is demonstrated on early-in-life images, suggesting that this

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phenomenon has its onset in the 3rd trimester of gestation. Hippocampal volume assessed at the time of early-in-life and term-equivalent age is linearly associated with GA at birth, whereby smaller volumes are associated with earlier birth.

1. Introduction

Preterm birth is increasingly prevalent, with recent world-wide estimates at nearly 15 million babies born at less than 37 weeks gestation with an estimated 20% being born very preterm at less than 32 weeks (Chang et al., 2013). Very preterm-born children delivered at 24–32 weeks of gestation are at significantly high risk for developmental delays with 4–19% of them developing cerebral palsy (Moster et al., 2008; Saigal and Doyle, 2008), and 30%–60% exhibiting cognitive impairments, poor executive function and working memory, learning disabilities and motor dysfunction (Aarnoudse-Moens et al., 2009; Holsti et al., 2002; Mulder et al., 2010; Taylor et al., 2004; Vohr et al., 2003). This evolving constellation of motor and cognitive impairments recognized in preterm-born children is consistent with impaired cerebral growth impacting gray and white matter (Back and Miller, 2014; Chau et al., 2013). Given the increasing recognition of widespread brain dysmaturation in preterm neonates, there is an urgent need to quantify the growth of specific brain structures from early-in-life (Back and Miller, 2014).

Slower than expected brain growth, as detected by magnetic resonance imaging (MRI), is observed in very preterm-born children into the adolescent period (Mathur et al., 2009). In particular, the hippocampus, which is central to the developmental of learning and memory, has consistently been shown to be smaller in preterm-born children relative to term born controls (Gimenez et al., 2008; Nosarti et al., 2002; Thompson et al., 2008; Cheong et al., 2013; de Kieviet et al., 2012). This relative decrease in the rate of hippocampal development in children born very preterm has been associated with impaired cognition and working memory at 2 years of age (Thompson et al., 2008; Beauchamp et al., 2008) and school-age (Aarnoudse-Moens et al., 2009, 2012; Ford et al., 2011; Rogers et al., 2012). As the growth spurt of the hippocampus starts in the perinatal period (Insausti et al., 2010), it is of great importance to understand the hippocampal growth and development in very preterm neonates especially from early-in-life to term-equivalent age.

Accurate segmentation of brain structures is the key to successful volumetric analysis of hippocampal development, which may be of particular clinical significance in predicting development outcomes (Peterson et al., 2000; Choe et al., 2013). Automatic segmentation of neonatal brain images faces several challenges. Tissue contrast on T1- or T2-weighted images, an image property that many algorithms rely upon for automated segmentation, is the inverse of what is typically observed in infants and adults (Fig. 1). In addition, the brains of preterm neonates are at a much earlier stage in the gyrification process than are full-term neonates (Fig. 1). A surge in synapse formation and activity occurs at the third trimester, during which the volumes of cerebral cortical gray and myelinated white matter increase about 4- to 5-fold (Limperopoulos et al., 2010). Due to many of these factors, quantitative volumetric and/or morphometric assessment of the hippocampus for preterm infants have only been performed at term-equivalent age or later, primarily using manual segmentation (Beauchamp et al., 2008; Gousias et al., 2012; Lodygensky et al., 2005, 2008; Peterson et al., 2000; Rogers et al., 2012; Thompson et al., 2008, 2009, 2013, 2014).

To date, there are several automatic brain tissue classification techniques developed for neonates (Anbeek et al., 2013; Cardoso et al., 2013; Gui et al., 2012; Prastawa et al., 2005; Shi et al., 2011; Wang et al., 2014; Weisenfeld and Warfield, 2009; Xue et al., 2007; Yu et al., 2010). However only a limited number of algorithms have been developed to achieve detailed delineation of specific brain structures, such as the corpus callosum, basal ganglia, thalamus, hippocampus and amygdala. Nishida et al. developed a semi-automated segmentation method, which was capable of segmenting a brain into 30 brain regions (Nishida et al., 2006). They validated their results in 12 neonates aged 31.1–42.6 weeks using visual inspection rather than by comparison to gold-standard manual segmentations. Gousias and colleagues compared the use of multi-atlas and model-based segmentation (based on a maximum-probability representation) on the MR images of 5 term and 15 preterm infants scanned at term (Gousias et al., 2013) using label-based encephalic ROI templates (ALBERTs) of 50 manually segmented anatomical brain regions as inputs (Gousias et al., 2012). Makropoulos and colleagues extended this work and that by Xue et al. (2007) by implementing a multi-structure Expectation-maximization (EM) based segmentation technique for neonatal brain parcellation (Makropoulos et al., 2014) using both the subject-specific tissue classification information with the nonlinearly transformed labels of the ALBERTs.

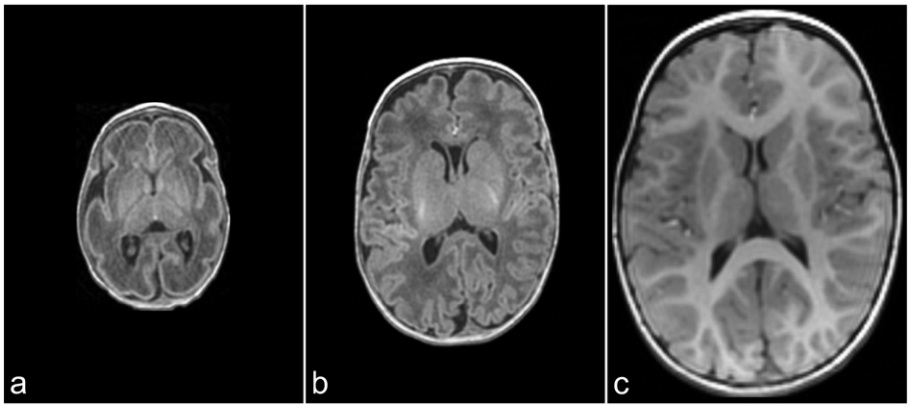

Fig. 1. Axial images from T1-weighted MR of the same preterm-born child at different ages demonstrating rapid brain growth and maturation which occurred from 29 weeks GA to 2 years of age. a. 29 weeks gestational age (GA); b. 40 weeks GA; c. 2 years. The white and gray matter contrast on images acquired at 29 and 40 weeks of GA is the inverse of that on the 2 year image.
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