NeuroImage 130 (2016) 24–34

Contents lists available at ScienceDirect

NeuroImage

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

Limited microstructural and connectivity deficits despite subcortical volume reductions in school-aged children born preterm with very low birth weight

Anne Elisabeth Sølsnes [a,1], Kam Sripada [a,*,1], Anastasia Yendiki [b], Knut Jørgen Bjuland [a], Heidi Furre Østgård [a], Synne Aanes [a], Kristine Hermansen Grunewaldt [a,c], Gro C. Løhaugen [a,d], Live Eikenes [e], Asta K. Håberg [e,f,g], Lars M. Rimol [a], Jon Skranes [a,d]

[a] Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway
[b] Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA
[c] Department of Pediatrics, St. Olav's Hospital, Trondheim, Norway
[d] Department of Pediatrics, Sørlandet Hospital, Arendal, Norway
[e] Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway
[f] Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway
[g] Department of Medical Imaging, St. Olav's Hospital, Trondheim, Norway

ARTICLE INFO

Article history:
Received 31 August 2015
Accepted 16 December 2015
Available online 20 December 2015

Keywords:
DTI
Cohort study
Connectivity
Tractography
Premature
Development

ABSTRACT

Preterm birth and very low birth weight (VLBW, ≤1500 g) are worldwide problems that burden survivors with lifelong cognitive, psychological, and physical challenges. In this multimodal structural magnetic resonance imaging (MRI) and diffusion MRI (dMRI) study, we investigated differences in subcortical brain volumes and white matter tract properties in children born preterm with VLBW compared to term-born controls (mean age = 8 years). Subcortical brain structure volumes and cortical thickness estimates were obtained, and fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were generated for 18 white matter tracts. We also assessed structural relationships between white matter tracts and cortical thickness of the tract endpoints. Compared to controls, the VLBW group had reduced volumes of thalamus, globus pallidus, corpus callosum, cerebral white matter, ventral diencephalon, and brain stem, while the ventricular system was larger in VLBW subjects, after controlling for age, sex, IQ, and estimated total intracranial volume. For the dMRI parameters, group differences were not significant at the whole-tract level, though pointwise analysis found shorter segments affected in forceps minor and left superior longitudinal fasciculus – temporal bundle. IQ did not correlate with subcortical volumes or dMRI measures in the VLBW group. While the deviations in subcortical volumes were substantial, there were few differences in dMRI measures between the two groups, which may reflect the influence of advances in perinatal care on white matter development.

Introduction

Preterm birth (gestational age < 37 weeks) is a worldwide problem, affecting 15 million newborns each year and burdening many survivors with lifelong cognitive, psychological, and physical challenges (Chang et al., 2013; Lawn et al., 2014; Saigal and Doyle, 2008). Advances in perinatal care, including the introduction of surfactant therapy for preterm infants, led to improved survival rates starting in the 1990s (Wilson-Costello et al., 2005). While survival rates have improved and prevalence of severe focal brain injuries, including intraventricular hemorrhages grades III and IV and cystic periventricular leukomalacia, has decreased, adverse long-term neurological outcomes are common in preterm-born individuals (Ferriero, 2004; Back et al., 2007). Low IQ and poorer attention/executive functions and academic outcomes have frequently been associated with very low birth weight (VLBW, birth weight ≤ 1500 g) and preterm birth (Løhaugen et al., 2010; Aarnoudse-Moens et al., 2009; Lund et al., 2012). Diffuse white matter injury including axonal abnormalities and gliosis is considered the dominant neuropathology in preterm-born infants and is believed to underlie many of these cognitive and sensorimotor deficits (Volpe et al., 2011; Haynes et al., 2011).

White matter near the lateral ventricles and in centrum semiovale has long been known to be especially vulnerable to perinatal injury

* Corresponding author at: Department of Laboratory Medicine, Children's and Women's Health, Medical Faculty, Norwegian University of Science and Technology, 7489 Trondheim, Norway.
E-mail address: kam.sripada@ntnu.no (K. Sripada).
[1] Shared first authorship.

http://dx.doi.org/10.1016/j.neuroimage.2015.12.029

among preterm-born individuals (Banker and Larroche, 1962), and hypoxia-ischemia and inflammation are considered the underlying causes behind periventricular white matter injury in preterms (Ortinau and Neil, 2015). Diffusion magnetic resonance imaging (dMRI), which measures Brownian motion of water diffusion of white matter bundles in the brain (Le Bihan and Johansen-Berg, 2012; Johansen-Berg and Behrens, 2014), has been used to identify white matter tracts that appear particularly sensitive to the effects of preterm birth and VLBW, such as corpus callosum and long-range association tracts (Counsell et al., 2008; Constable et al., 2008; Skranes et al., 2007; Eikenes et al., 2011; Ment et al., 2009; Mento and Bisiacchi, 2012; Hintz and O'Shea, 2008).

In line with the widely reported "encephalopathy of prematurity" of diffuse white matter injury and tissue loss typical among preterms, deviations in volumes of subcortical structures have also been reported in the VLBW population (Volpe, 2009; Boardman et al., 2010). Cerebral white matter, thalamus, globus pallidus, nucleus accumbens, and corpus callosum volumes may be vulnerable to neonatal risk factors such as VLBW (Bjuland et al., 2014). Deep gray matter abnormalities have been found in tandem with diffuse white matter injury among infants (Boardman et al., 2006), toddlers (Lowe et al., 2011), and school-aged children (Murray et al., 2014).

In a recent paper (Sølsnes et al., 2015), we reported significant differences in cortical architecture in our cohort of term-born controls recruited from the Norwegian Mother and Child Cohort Study and VLBW children born between 2001 and 2007, with increased cortical thickness frontally and occipitally, and reduced cortical surface area in widespread regions in the VLBW group, consistent with previous reports from year cohorts of VLBW teenagers born in 1986–88 (Skranes et al., 2007, 2013; Eikenes et al., 2011; Bjuland et al., 2013; Martinussen et al., 2005). It is not known whether these cortical deviations are secondary to the reported abnormalities in white matter tracts connected to these cortical regions or represent primary cortical injury.

This study therefore aimed to investigate subcortical volumes, white matter properties, and possible relationships between white matter tracts and the cortical changes previously reported in the same cohort of school-aged children. We explored group differences in fractional anisotropy and diffusivity using TRACULA, a novel tool for automated reconstruction of 18 major white matter tracts, as well as subcortical structure volumes using FreeSurfer. Moreover, we assessed structural relationships between white matter tracts of interest and cortical thickness of the tract endpoints. We also investigated possible relationships between neuroimaging findings and full-scale IQ scores and perinatal risk factors.

Methods

Participants

VLBW group

Preterm-born VLBW subjects (birth weight ≤ 1500 g), born between 2003 and 2007, were recruited based on admittance to the Neonatal Intensive Care Unit at St. Olav's University Hospital in Trondheim, Norway. Sixty-three children were invited and 57 agreed to participate in the study (Fig. 1). Age ranged from 5.0 to 10.5 years old (mean age =

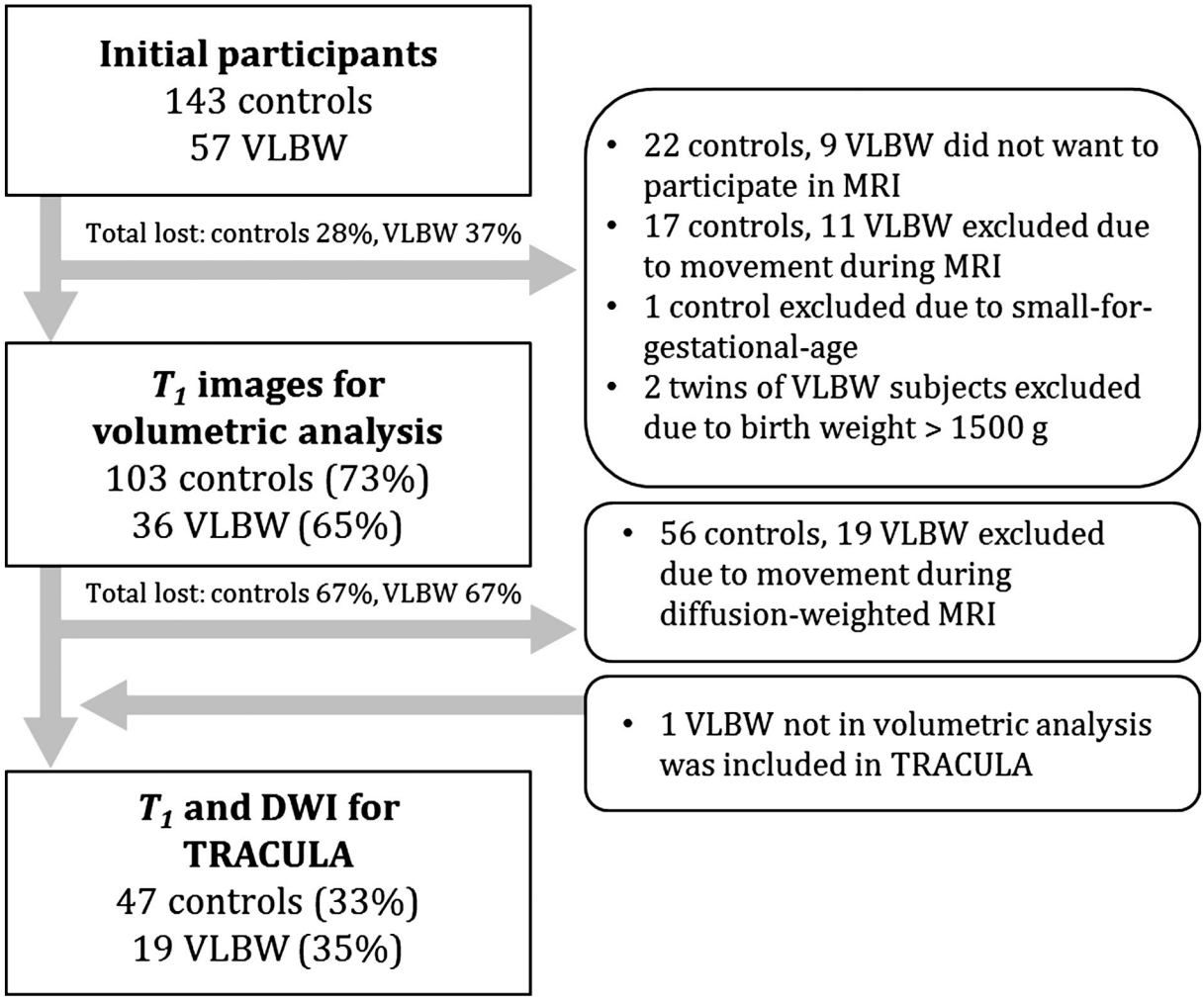

Fig. 1. Overview of participation and retention. Abbreviations: DWI: diffusion-weighted imaging; VLBW: very low birth weight.