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Prediction of cognitive and motor development in preterm children using exhaustive feature selection and cross-validation of near-term white matter microstructure

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ABSTRACT

Background: Advanced neuroimaging and computational methods offer opportunities for more accurate prognosis. We hypothesized that near-term regional white matter (WM) microstructure, assessed on diffusion tensor imaging (DTI), using exhaustive feature selection with cross-validation would predict neurodevelopment in preterm children.

Methods: Near-term MRI and DTI obtained at 36.6 ± 1.8 weeks postmenstrual age in 66 very-low-birth-weight preterm neonates were assessed. 60/66 had follow-up neurodevelopmental evaluation with Bayley Scales of Infant-Toddler Development, 3rd-edition (BSID-III) at 18–22 months. Linear models with exhaustive feature selection and leave-one-out cross-validation computed based on DTI identified sets of three brain regions most predictive of cognitive and motor function; logistic regression models were computed to classify high-risk infants scoring one standard deviation below mean.

Results: Cognitive impairment was predicted (100% sensitivity, 100% specificity; AUC = 1) by near-term right middle-temporal gyrus MD, right cingulate-cingulum MD, left caudate MD. Motor impairment was predicted (90% sensitivity, 86% specificity; AUC = 0.912) by left precuneus FA, right superior occipital gyrus MD, right hippocampus FA. Cognitive score variance was explained (29.6%, cross-validated R^2 = 0.296) by left posterior-limb-of-internal-capsule MD, Genu RD, right fusiform gyrus AD. Motor score variance was explained (31.7%, cross-validated R^2 = 0.317) by left posterior-limb-of-internal-capsule MD, right parahippocampal gyrus AD, right middle-temporal gyrus AD.

Conclusion: Search in large DTI feature space more accurately identified neonatal neuroimaging correlates of neurodevelopment.

1. Introduction

At near-term age the infant brain undergoes rapid growth and microstructural development (Brody et al., 1987; Dubois et al., 2006; Huang et al., 2006; Kinney et al., 1988; Nossin-Manor et al., 2013; Oishi et al., 2011; Rose et al., 2014). Brain microstructure abnormalities assessed at this age are plausible prognostic factors of neurodevelopment in preterm children (Aeby et al., 2013; Alvarez et al., 2011; Arzoumanian et al., 2003; Mukherjee et al., 2002; Rose et al., 2015, 2009, 2007; Van Kooij et al., 2011; Woodward et al., 2012). Although advances in neonatal medicine have increased the survival rate and positive outcome among children born preterm, 40–50% of very preterm infants still experience neurodevelopmental impairments such as cerebral palsy (CP), developmental coordination disorder, as well as cognitive and language delay (Spittle et al., 2011; Williams et al., 2010). CP affects 10–15% of very-low-birth-weight (VLBW) preterm children compared to 0.3% of children born full-term; among extremely preterm infants, cognitive and motor delay occurs in 33% and 18%, respectively, compared to 13% and 1% in children born full-term (Woodward et al., 2012).

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At term-equivalent age, reduction in cerebral volume and white matter (WM) immaturity has been reported in preterm infants compared to full-term neonates (Hüppi et al., 1998; Inder et al., 2005; Lee et al., 2013; Rose et al., 2008; Thompson et al., 2013, 2006). Neonatal neuroimaging holds potential for identifying early biomarkers of neurodevelopmental impairment to guide early intervention at a time of optimal neuroplasticity and rapid cognitive and motor development.

Diffusion tensor imaging (DTI) measures water diffusion in multiple directions. The movement of water molecules is restricted by cellular barriers (e.g. cellular membranes or axonal myelination where present), thus DTI can be used to obtain information about underlying tissue organization (Basser and Pierpaoli, 2011; Counsell et al., 2002; Hüppi et al., 1998; Pierpaoli et al., 1996). DTI quantifies fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). FA is a scalar between 0 and 1 that expresses the degree of restriction that limits diffusion to a distinct direction (Pierpaoli et al., 1996), in WM it is altered by fiber coherence, diameter, density, and myelination. MD is the average displacement of water molecules, AD is the displacement along the primary axis, and RD is the displacement perpendicular to the primary axis.

Brain development involves certain processes that change the dynamics of diffusion, e.g. decreased water content, contraction of extracellular space, myelination, and increased coherence of axonal structures (Dubois et al., 2008; Kinney et al., 1994; Nossin-Manor et al., 2013). FA, MD, AD, and RD values are affected by these changes and can assess brain development and maturation.

VLBW preterm infants typically undergo standard-of-care neuroimaging prior to discharge from the neonatal intensive care unit. Determining prognostic biomarkers on conventional structural brain MRI scans have been reported (Hintz et al., 2015; Miller and Ferriero, 2009). Employing DTI is a promising extension of neuroimaging techniques to assess early WM microstructure and may improve the overall prognostic accuracy for developmental outcomes (Arzoumanian et al., 2003; Rose et al., 2015, 2009, 2007).

Previously we reported neurodevelopmental outcome in relation to near-term regional WM assessed on DTI in 6 subcortical WM regions (4 bilateral regions, 2 regions of the corpus callosum) selected based on functional relevance, in the same cohort of VLBW preterm children, using standard statistical techniques (Rose et al., 2015). In contrast, the current study employs statistical learning approaches with exhaustive feature selection and leave-one-out cross-validation of 51 WM regions (48 bilateral regions, 3 regions of corpus callosum) to investigate utilizing DTI based multivariate linear models in the NICU for early prognosis. Search in large feature space may more accurately identify neonatal neural correlates of neurodevelopmental delay, and ultimately inform neuroprotective treatment to improve quality of life for preterm children. Here we use a statistical learning approach to examine near-term WM microstructure in VLBW preterm neonates in relation to cognitive and motor outcome at 18–22 months adjusted age. We hypothesized that WM microstructure in a subset of three near-term brain regions, identified using statistical learning approach of exhaustive feature selection and cross-validation, would demonstrate higher predictive value for cognitive and motor development at 18–22 month of adjusted age, compared to using standard techniques.

Our analysis utilized machine learning applied to linear models using a standard exhaustive feature search and cross-validation. Exhaustive feature search is an optimal feature selection method that is employed when the size of dataset and the number of required features allow the exhaustive feature selection to be computation feasible (Wang et al., 2016). Cross-validation is the most widely-used technique to estimate generalization capability and prediction error of a machine learning model (Hastie et al., 2009).

This approach was selected for its simplicity of design, generalization capability, and potential for use in other cohorts and clinical applications.

2. Methods

Participants were selected based on criteria of gestational age at birth ≤ 32 weeks, VLBW (birth weight ≤ 1500 g), and absence of evidence of genetic disorder or congenital brain abnormalities. 102 infants treated at Lucile Packard Children's Hospital (LPCH) from 1/1/10–12/31/11 participated, representing 76% of eligible infants who were admitted to the NICU over the two-year period. Parents were approached prior to scheduled routine MRI and consent was obtained for this IRB-approved study. 66 of the 102 neonates had successful DTI scans, collected at the end of routine MRI scan, prior to discharge.

Of the 66 neonates who had both near-term MRI and DTI, 60 returned for follow-up neurodevelopmental assessment at 18–22 months; 59 completed cognitive BSID-III, and 60 completed motor BSID-III. Cognitive and motor development was assessed using the BSID-III composite cognitive and motor scores, as well as fine motor and gross motor sub-scores of BSID-III, adjusted for age, as previously described (Rose et al., 2015).

2.1. MRI data acquisition

Brain MRI scans were performed on 3 T MRI (GE Discovery MR750, GE 8-Channel HD head coil, Little Chalfont, UK) at LPCH. A 3-plane localizer was used, and an asset calibration was prescribed to utilize parallel imaging. Sagittal T1 FLAIR image parameters were: TE = 9l.0, TR = 2200, FOV = 20 cm, matrix size = 320 × 224, slice thickness 3.0 × 0.5 mm spacing, NEX = 1. T2, DWI, and DTI axial scans were prescribed using a single acquisition, full-phase field of view (FOV). The axial fast spin echo T2 imaging parameters were: TE = 85 ms, TR = 2500, FOV 20 cm, matrix = 384 × 224; slice = 4.0 mm × 0.0 mm spacing. Axial T2 FLAIR parameters were: TE = 140, TR = 9500, FOV = 20 cm, slice = 4.0mmx0.0 mm, inversion time = 2300, fluid attenuated inversion recovery matrix = 384 × 224. Axial DWI parameters were: TE = 88.8, TR = 10,000, FOV = 20 cm, slice = 4.0mmx0.0 mm spacing, matrix = 128 × 128. Coronal T1 SPGR parameters were: TE = 8, TR = 3, slice = 1.0mmx0.0 spacing, FOV = 24 cm, matrix = 256 × 256.

2.2. Radiological assessment

Structural MRI was assessed for degree of WMA and significant cerebellar abnormality. Radiological evaluation was performed by an experienced pediatric neuroradiologist (X.S.) and confirmed by a second (K.Y.), both were masked to all other participant data. A form validated for near-term neuroradiological assessment (Hintz et al., 2015) was used to score WMA (1–3) according to a widely used classification system (Hintz et al., 2015; Horsch et al., 2010; Woodward et al., 2006): (i) extent of WM signal abnormality, (ii) periventricular WM volume loss, (iii) cystic abnormalities, (iv) ventricular dilation, and (v) thinning of the CC. High inter-rater agreement (96%–98%) for moderate-severe WMA using this classification was reported (Hintz et al., 2015; Woodward et al., 2006). Significant cerebellar abnormalities included significant cerebellar lesions defined by Hintz et al. and/or significant cerebellar asymmetry of ≥ 3 mm in the anterior-posterior or medial-lateral direction (Hintz et al., 2015).

DTI was calculated based on diffusion weighted images (DWI) obtained along 25 orientations with slice thickness of 3 mm, matrix size of 128 × 128, and 90-degree flip angle on a 3 T MRI (GE Discovery MR750, GE 8-Channel HD head coil) at LPCH at the end of routine MRI acquisition. A repetition of DTI sequence was successfully collected in 64 of 66 cases. Infants were swaddled and fed, and typically remained asleep during the scan. Sedation typically was not utilized for routine near-term MRI, and was not utilized as part of the research protocol.