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Early prediction of cognitive deficits in very preterm infants using functional connectome data in an artificial neural network framework

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ABSTRACT

Investigation of the brain's functional connectome can improve our understanding of how an individual brain's organizational changes influence cognitive function and could result in improved individual risk stratification. Brain connectome studies in adults and older children have shown that abnormal network properties may be useful as discriminative features and have exploited machine learning models for early diagnosis in a variety of neurological conditions. However, analogous studies in neonates are rare and with limited significant findings. In this paper, we propose an artificial neural network (ANN) framework for early prediction of cognitive deficits in very preterm infants based on functional connectome data from resting state fMRI. Specifically, we conducted feature selection via stacked sparse autoencoder and outcome prediction via support vector machine (SVM). The proposed ANN model was unsupervised learned using brain connectome data from 884 subjects in autism brain imaging data exchange database and SVM was cross-validated on 28 very preterm infants (born at 23–31 weeks of gestation and without brain injury; scanned at term-equivalent postmenstrual age). Using 90 regions of interests, we found that the ANN model applied to functional connectome data from very premature infants can predict cognitive outcome at 2 years of corrected age with an accuracy of 70.6% and area under receiver operating characteristic curve of 0.76. We also noted that several frontal lobe and somatosensory regions, significantly contributed to prediction of cognitive deficits 2 years later. Our work can be considered as a proof of concept for utilizing ANN models on functional connectome data to capture the individual variability inherent in the developing brains of preterm infants. The full potential of ANN will be realized and more robust conclusions drawn when applied to much larger neuroimaging datasets, as we plan to do.

1. Introduction

The high risk of neurodevelopmental impairments is a major concern for parents and clinicians caring for premature babies, especially for those born very preterm (Jarjour, 2015). Up to 40% of very preterm infants (i.e. ≤32 weeks gestational age) in the United States are diagnosed with cognitive deficits at 2 years of age (Hamilton et al., 2016). Unfortunately, cognitive impairments cannot be accurately diagnosed until 3 to 5 years of age (Hack et al., 2005; Ment et al., 2003; Spencer-Smith et al., 2015). While recent studies demonstrate the importance of genetic factors in premature birth (Zhang et al., 2017) and outcome, there remains a gap in our knowledge about early identification of infants at high-risk for cognitive deficits. This gap limits our ability to target early interventions (Nordhov et al., 2010; Spittle et al., 2012) to the highest risk infants during periods of optimal neuroplasticity in the first 3 years after birth to enhance their ability to reach their full intellectual potential.

The human brain is a highly interactive and organized system that exhibits functional units. Each brain unit is connected to multiple other units. Resting-state functional connectivity MRI (fcMRI) has made possible quantitative mapping of the connections within and between these units. The architecture conveys intrinsic information about the connectivity of the brain, referred to as the brain connectome (Glasser et al., 2016; Sporns, 2013), which has opened a window for observing the human mind (Sporns, 2013; Sporns et al., 2005). Mathematically, a connectome is a graph, representing the brain connectivity (described as a set of edges) between pairs of brain regions of interest (ROI) (described as a set of nodes). The connectome can also be encoded as an

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adjacency matrix, in which each entry represents the brain connectivity between each pair of ROIs.

Research supports the notion that cognitive deficits may result from a perturbation of neural connection and communication (Fei et al., 2014). The brain connectome also shows a high degree of individual or inter-subject variability (Finn et al., 2015). Investigation of the brain connectome will improve our understanding of how individual brain organizational changes influence cognitive function, resulting in an improved individual risk stratification. Brain connectome studies in adults and older children have shown that abnormal network properties may be useful as discriminative features for early diagnosis in a variety of neurological conditions. Many of these studies have exploited machine learning models using brain connectome data for such early prediction (Arbabshirani et al., 2013; Barkhof et al., 2014; Fei et al., 2014; Finn et al., 2015; Jie et al., 2014a; Jie et al., 2014b; Khazaee et al., 2015; Khazaee et al., 2016; Prasad et al., 2015; Sacchet et al., 2015; Vanderweyen et al., 2015; Wee et al., 2012; Wee et al., 2016; Zhan et al., 2015; Zhu et al., 2014). The progress has now begun to be extended to neonatal population (Kawahara et al., 2017; Smyser et al., 2016; Ziv et al., 2013).

Brain connectome data are inherently complicated and have high dimensionality, which makes it very challenge to effectively extract intrinsic information embedded in the data. The most popular method is through principal component analysis (PCA), however, it is a linear method. The complexed patterns embedded in the brain connectome data may not be explained linearly. In addition, it is unclear how many components are needed to reconstruct the data to a reasonable approximation, as many of the components are trivial. On the other hand, significant progress has been made on learning high-level representation of the raw data using artificial neural network (ANN) model (Hinton and Salakhutdinov, 2006).

In this paper, we propose a Stacked Sparse Autoencoder (SSAE) based ANN framework for early prediction of cognitive deficits in very preterm infants based on functional connectome data. Specifically, we build an unsupervised SSAE model using functional connectome data from 884 subjects in autism brain imaging data exchange database (ABIDE) to discover low-dimensional latent representations/features from the original high-dimensional data. 28 very preterm infants are used to cross-validate a support vector machine (SVM) classifier to predict cognitive deficit. We hypothesize that our proposed ANN framework analyzing functional brain connectome data at birth can accurately predict cognitive deficits at 2 years corrected age at an individual level in very preterm infants.

2. Methods

2.1. Overview

The proposed ANN framework for early prediction of cognitive deficits consists of three components: 1) construct whole brain functional connectome; 2) implement SSAE to take functional connectome as input and extract its high-level connectome features (these features capture the embedded salient information that is useful for differentiating a single subject); and 3) implement SVM (Arbabshirani et al., 2017; Chang and Lin, 2001; Levman and Takahashi, 2015) classifier to conduct 2-class classification (i.e. high risk of cognitive deficits vs. low risk) using extracted functional brain connectome features. This research design is summarized in Fig. 1.

2.2. Subjects and cognitive assessments

The Nationwide Children's Hospital Institutional Review Board approved this study and written parental informed consent was obtained for every subject. The data for this study is from a cohort of 28 very preterm infants, ≤32 weeks gestational age, cared for in the neonatal intensive care unit at Nationwide Children's Hospital. Infants with known structural congenital central nervous system anomalies, congenital chromosomal anomalies, or congenital cyanotic cardiac defects were excluded. In addition, parents were not approached for consent if their infant remained on persistently high mechanical ventilator support (e.g., peak inspiratory pressure > 30 and/or fraction of inspired oxygen > 50%) within the first 28 days after birth. All 28 infants now reached 2 years corrected age and completed their standardized Bayley Scales of Infant and Toddler Development III test. The Bayley-III normative cognitive scores are on a scale of 50 to 150, with a mean of 100 and standard deviation (SD) of 15. We grouped our cohort using a cut-off of 85 into those at high vs. low risk for cognitive deficits (i.e. two classes). A child with a cognitive score of < 85 is considered to have moderate to severe deficit and is comparable to a child with a mental developmental index < 70 on the Bayley-II (Johnson et al., 2014). The demographic information for these infants are provided in Table 1. We conducted two-sided *t*-tests (assuming unequal variance) and found that between the high and low risk groups, there were no significant differences in birth weight ($p = 0.08$), gestational age at birth ($p = 0.28$) and postmenstrual age at scan ($p = 0.34$). There was significance difference of cognitive scores ($P < 0.0001$) between two groups.

2.3. MRI acquisition

Infants were scanned on a 3T GE HDx scanner equipped with an eight-channel infant head coil (Lammers Medical Technology, Germany). Functional images were collected using a single-shot echo planar image sequence sensitized to T2* weighted blood oxygenation level dependent (BOLD) signal changes. Acquisition parameters are: repetition time TR = 3000 ms, echo time TE = 35 ms, flip angle FA = 90°, resolution 2.8 × 2.8 × 3.0 mm^3. A total of 100 frames were collected in 5.2 min. This acquisition time was chosen because it was more clinically feasible without compromising data quality (Van Dijk et al., 2010). Anatomical scans were conducted with a Proton Density/T2-weighted sequence (TR/TE1/TE2 = 11,000/14/185 ms, FA = 90°, resolution 0.35 × 0.35 × 2 mm^3). All subjects were scanned during natural sleep without the use of any sedation after being fed and swaddled. A 3T MRI-compatible transport incubator (Nomag 3.0IC, Lammers Medical Technology, Germany) was used for the inpatient scans. MRI noise was minimized using Insta-Puffy Silicone Earplugs (E.A.R. Inc., Boulder, CO) and Natus Mini Muffs (Natus Medical Inc., San Carlos, CA).

2.4. Whole-brain functional connectome construction

A four-dimensional fcMRI dataset requires extensive preprocessing before resting-state network analyses can be conducted (Glasser et al., 2013; Smith et al., 2013). We developed a neonatal-optimized pipeline, (He and Parikh, 2015) that can be briefly summarized as follows: 1) Reorientation – acquired scans are aligned with anterior commissure (AC) - posterior commissure (PC) line into a standard image plane; 2) Skull stripping – remove non-brain parts of the image; 3) Realignment – align each time point's frame to the mean frame, reducing the effects of subject head motion during the acquisition; 4) Normalization – align fcMRI frames to the same subject's high-resolution structural image using rigid body registration and also align this structural image to a neonatal template (Shi et al., 2011) using affine transformation. This allows both fcMRI and structural images to be in the same “standard space” reference coordinate system; 5) Spatial smoothing – apply isotropic Gaussian filter with 6 mm kernel to improve signal-to-noise ratio and ameliorate the effects of functional misalignments across subjects; 6) Band-pass filtering (0.008 < f < 0.09 Hz) – remove the lowest and highest temporal drifts in the data; 7) Motion artifact reduction – detects corrupted time points using motion scrubbing (Power et al., 2012) and regresses this confounding factor out of the data (Behzadi et al., 2007). The above preprocessing methods are achieved using FMRIB Software Library (FSL, Oxford University, UK), Statistical Parametric