Prediction of Brain Network Age and Factors of Delayed Maturation in Very Preterm Infants

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Abstract. Babies born very preterm (< 32 weeks postmenstral age), are at a high risk of having delayed or altered neurodevelopment. Diffusion MRI (dMRI) is a non-invasive neuroimaging modality that allows for early analysis of an infant's brain connectivity network (i.e., structural connectome) during the critical period of development shortly after birth. In this paper we present a method to accurately assess delayed brain maturation and then use our method to study how certain anatomical and diagnostic brain injury factors are related to this delay. We first train a model to predict the age of an infant from its structural brain network. We then define the relative brain network maturation index (RBNMI) as the predicted age minus the true age of that infant. To ensure the predicted age is as accurate as possible, we examine a variety of models to predict age and use one that performs best when trained on a normative subset (77 scans) of our preterm infant cohort dataset of 168 dMRI scans. We found that a random forest regressor could predict preterm infants' ages to within an average of ~ 1.6 weeks. We validate our approach by analysing the correlation between RBNMI and a set of demographic, diagnostic and brain connectivity related variables.

1 Introduction

Often when we look at a baby, we say things like "I can't believe he/she's only 6 weeks!". Such observations of the outer appearance of a baby may relate to our priors on how a baby should act at certain ages. In this work, we set out to estimate a baby's maturational age based on the appearance of the baby's white matter brain network instead of on the baby's outer appearance. Individuals' brains develop at different rates, which implies that a child's chronological age may not match its apparent neurodevelopmental age [12]. In particular, preterm birth can be associated with a higher risk of delayed neurodevelopment [5,11]. However, accurate determination of an infant's developmental age (e.g., via measurement of hormone levels or assessment of developmental milestones) can be challenging [6]. Also, the factors contributing to delayed brain network maturation are not fully known, nor is it known how this delay affects infant outcomes.

In this work, we begin to explore these questions by training a machine learning model to predict the post menstrual age (PMA) of each infant. Previous work has shown that a variety of high and low level features from the structural connectomes of normative preterm infants were well correlated with age [4]. Here, we use diffusion MRI (dMRI) based white-matter structural connectome data as input to predict the ages of each infant at the time of scan. The predicted ages are then used to compute the proposed relative brain network maturation index (RBNMI), which we analyse together with different clinical variables, some of which we expect to be associated with maturation delay.

A variety of previous works have explored age prediction using brain network data [3,6,8,10]. For instance, Robinson et al. examined the dMRI based structural networks of two normative adult groups with different age distributions (20-30 and 60-90 years old) [10]. They showed that subjects could be well classified ($\sim 84\%$ accuracy) into one of the two age groups using a maximum uncertainty linear discriminant analysis model. Dosenbach et al. examined the functional brain networks in a cohort of healthy children and adults between the ages of 7 to 30 years old [6]. They found that a support-vector machine, was able to classify the functional connectomes of children (7-11 years old) from the connectomes of adults (24-30 years old) with high accuracy (91%). Furthermore, Dosenbach et al. examined ages predicted directly via a support-vector regressor (SVR) and found that they best fit a non-linear asymptotic growth model. This suggests that early brain development is non-linear in time and that a non-linear model may better predict age from structural features of the brain. Liem et al. combined functional connectome data and cortical thickness information to predict the age of adults between 18 and 82 years old, also using an SVR model [8]. They reported that adults with cognitive impairment were predicted by the model as being older than their true ages and significantly more so than controls.

Smyser et al. used resting-state functional connectome data to train an SVR model to predict the age of infants born preterm [11]. They found that the predicted gestational ages of preterm infants were lower than those of the term infants, despite similar ground truth age distributions in the two groups, suggesting that the preterm infants were less developed at the same chronological age. Kawahara et al. used their proposed BrainNetCNN model to also predict the ages of preterm infants but from structural brain networks [7]. However, they noted that their focus was not on prediction of age but instead it was to validate the predictive capability of their novel CNN model and then apply it, primarily, to the task of predicting clinical outcomes.

In this work, we exclusively examine preterm infants and focus on robust measurement of delayed structural brain network maturation. Similar to Kawahara et al. and Robinson et al., we use structural connectome data from dMRI scans but unlike all previous age prediction studies on this modality, our work does not focus on classification of defined subject cohorts. Instead, we define a regression problem allowing us calculate our proposed RBNMI and then demonstrate the efficacy of our approach by examining the correlation of RBNMI with clinical variables and connectivity in the infant's connectomes (Section 2). We

find that ventriculomegaly (VM) and neuromotor outcome scores, as well as the connection between the left and right posterior cingulate gyri (among other connections) were significantly correlated with RBNMI (Section 3). Finally, we discuss these findings in Section 4.

2 Method and Materials

Preterm Infant Cohort Clinical and Connectome Data: The data examined here comes from a cohort of 115 very preterm neonates (born between 24 and 32 weeks gestational age) from the BC Children's hospital. Certain infants were scanned twice for a total of 168 diffusion MRIs used in this study (acquired between 27 and 45 weeks PMA). Structural connectomes were generated from dMRI scans of each infant based on a 90 region atlas segmentation. For details on the imaging protocol and connectome construction, see our previous work [4]. Associated with each dMRI scan was a T1 MRI scan from which

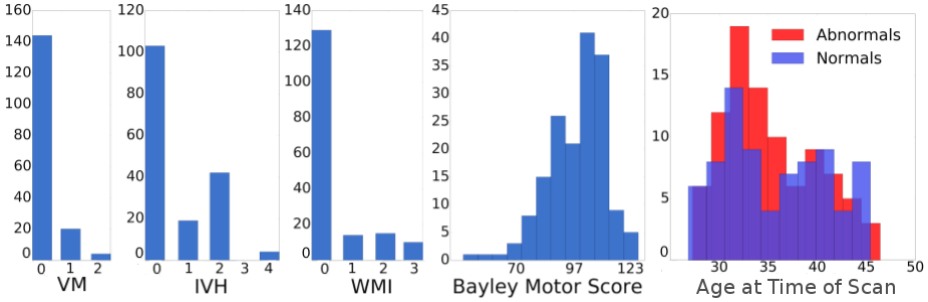

Fig. 1: Histograms of WMI, IVH, VM grades, Bayley motor outcome scores and scan ages (PMA) across all 168 scans in our preterm infant dataset.

grades of white matter injury (WMI, between 0 and 3), intraventricular hemorrhaging (IVH, between 0 and 4) and VM (between 0 and 2) were assessed. At 18 months after birth (corrected for prematurity), neuromotor outcomes of each infant were assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [1]. Motor outcome scores are normalized to have a mean of 100 and standard deviation of 15. In order to study the effects of maturation delay due to abnormal neurodevelopment, scans were split into normative and abnormal groups based on these assessments. Scans were considered abnormal if any WMI, IHV or VM was found to be present (i.e., > 0) or if neuromotor outcome scores were lower than one standard deviation below the mean (91 scans). All other scans were considered normal (77 scans). Figure 1 shows the distributions of ages, motor scores and brain injury variables across all scans.

Relative Brain Network Maturation Index: In order to compute the RBNMI, we require a model that can accurately predict the PMA at scan, $\mathbf{y}_i$, of a normative infant, i, from the adjacency matrix of its structural brain network,

$\mathbf{X}_i$. To this end, we trained 5 different machine learning types and compared their predictive performance on our normative group: 1) linear regression (LinReg), 2) multi-layer perceptron (MLP), 3) SVR, 4) bagging regression (BagR) and 5) random forests (RF). Of the proposed models, $\phi_k(\cdot)$, with respective hyperparameter settings, θ_k, we find $k^* = \arg\min_k \mathcal{E}_k(\theta_k; \mathbf{X}, \mathbf{y})$, the index of model which performed best on the normative data, where $\mathcal{E}_k$ is the predicted / ground-truth loss on a subset of the normative data *not* used to train the model.

We adopt model (and hyperparameters), k^*, to create our prediction model, $\phi_k^*(\mathbf{X}, \theta)$, which we then use to compute the RBNMI of each scan. We trained this prediction model only on normative data because we do not want to train the model to ignore maturation delay. If abnormals were used for training then any discrepancy between the predicted and ground truth age of the infants in these scans would be treated as a prediction error to be minimzed by updating the model. This would negate the effect that we want to analyse. In contrast, we expect normative brain networks to have a lower chance of presenting apparent delay so we want the model to minimize the difference between predicted and ground truth age on these scans during training. RBNMI of a given scan is then defined as the ground truth age subtracted from the predicted age,

$$\text{RBNMI}_i = \phi_k^*(\mathbf{X}_i; \theta) - \mathbf{y}_i. \tag{1}$$

A negative RBNMI then implies that the infant associated with a scan is being predicted younger than its actual age and a positive RBNMI implies the opposite. Thus, we interpret negative RBNMI as delayed brain network maturation and positive RBNMI as accelerated maturation.

3 Results

Comparison of Age Prediction Models: We compared the predictive performance of each model (and across reasonable ranges of standard hyper-parameters) via cross-validation on the entire normal group. We found that an RF regressor with 200 trees outperformed the other models, with a mean absolute error (MAE) of 1.554 weeks and absolute error standard deviation (SDAE) of 1.197 weeks (Table 1).

Predicted Ages of Abnormal Versus Normal: To ensure an unbiased computation of RBNMI for both normal and abnormal scans, and to mitigate the influence of a particular training set, we computed the RBNMI of each scan multiple times during 50 rounds of Monte-Carlo cross-validation. In each round, 57 normative scans were randomly selected to be used for training a model. The RBNMI was then computed on those left-out 20 normative scans and 20 scans randomly selected from the abnormal group. Over 50 rounds, a neonate's age in each scan was predicted an average of ~ 5 times (i.e., ~ 5 trained models) and a minimum of twice. A t-test confirmed that, as hypothesized, the mean RBNMI of the abnormal group, averaged within each cross-validation round, was significantly lower than that of the normative group ($p = 0.0003$), implying that the connectomes of the abnormal group appeared less mature on average.

Method	MAE	SDAE
LinReg	6.284	4.230
MLP	7.223	5.080
SVR	1.712	1.366
BagR	1.559	1.255
RF	**1.554**	**1.197**

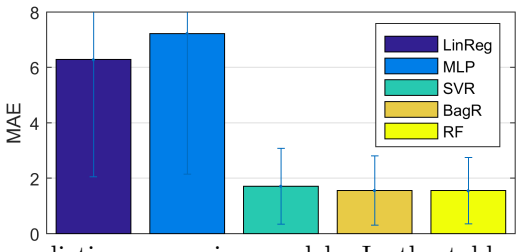

Table 1: Comparison of age prediction regression models. In the table (left), MAE and SDAE are reported for each model in weeks. The bar graph (right) reports the distributions of absolute prediction errors for each model.

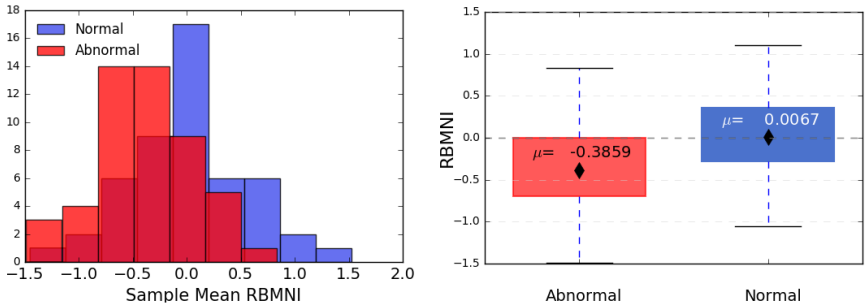

Fig. 2: Distribution of per group mean RBNMI values, averaged across the 20 scans within each of the 50 rounds of cross-validation, shown as histograms (left) and as box plots (right). Averaged RBNMI values in the abnormal group were significantly more negative than in the normal group.

Note that per-round averaged RBNMI values in normative and abnormal groups were both determined to be normally distributed via D'Agostino's K2 test for normality ($p = 0.642$ for normative group and $p = 0.953$ for abnormal group). To confirm our hypothesis that training on all data (not just the normal group) would train the model to ignore maturation delay, we also trained our model on scans in both groups, together (similarly to Liem et al. [8]). This resulted in mean RBMNI values of 0.214 for the normal group and -0.048 for the abnormal group (versus 0.006 and -0.386, respectively, when training only on the normal group). Thus, when trained on all data, the model predicts normative scans as presenting somewhat accelerated maturation and the abnormal scans as presenting only slightly delayed maturation, with an overall smaller difference between groups compared to when training on normals only, as expected.

Correlation of Clinical Variables with Maturation Delay: Next, we examined the relationship between brain network maturation delay and different clinical variables. In particular, we computed Pearson's correlation between RBNMI and 1) age (at time of scan), 2) gestational age (at time of birth), 3) sex, 4) WMI grade, 5) IVH grade, 6) VM grade and 7) Bayley neuromotor

outcome score. Table 2 shows that age was most significantly correlated and that VM and motor scores were also significantly correlated. Specifically, older scan ages, lower motor scores and higher grade (i.e., more severe) VM are all correlated with more delayed maturation. In contrast, gestational age at birth, sex, WMI grade, and IVH grade were all not found to be correlated with RBNMI.

Variable	r	p-val
age	-0.700	**5.14E-26**
birth age	0.007	0.925
sex	-0.036	0.641
WMI	-0.062	0.422
IVH	-0.028	0.723
VM	-0.158	**0.041**
Bayley motor	0.172	**0.026**

Table 2: Correlation between RBNMI and clinical variables. Age at the time of scan, VM and Bayley motor outcomes show significant correlations.

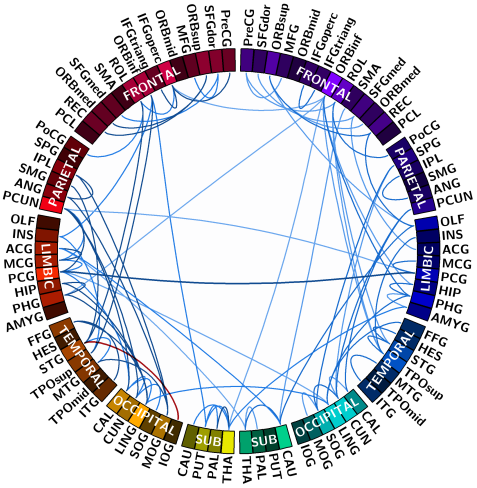

Fig. 3: Brain connections significantly positively (red) and negatively (blue) correlated with RBNMI.

Finally, we examined the correlation between RBNMI and the strengths (i.e., tract counts) of different edges (connections) in the infants' connectomes. False discovery rate was used to correct for multiple comparisons. Figure 3 visualizes edges with connectivities that were significantly correlated with maturation delay. All but one of the 85 significantly correlated edges were found to be negatively correlated with RBNMI (i.e., weaker edges correlated with more delay). Note that when training on both abnormal and normal data, only 14 of these same edges (i.e., a strict subset) were found to be significantly correlated to maturation delay. Also, these 14 edges were found to be *more* correlated when using our method of training on normative data only, (with a mean r-value of -0.386, compared to -0.345 when training on all data).

The strength of connectivity between left and right posterior cingulate gyrus (PCG) was found to have the strongest negative correlation with RBNMI. PCG regions were also associated with many other significantly correlated connections. Of all brain regions, the right inferior orbitofrontal cortex (ORBinf) had the most number of significant edges.

4 Discussion

Our results showed that age at the time of scan was significantly correlated with RBNMI (despite RBNMI being relative to true age). Those infants with apparent maturation delay may typically be developing more slowly, causing delay to be more pronounced at older ages. However it is also possible that the prediction model may be predicting ages biased towards the mean, making scans of older infants appear more delayed and scans of younger infants appear accelerated. Given that the MAE of the selected RF model (on normative scans) was only 8.6% of the infants' age range, the effect of predicting towards the mean, if present, is relatively small. While previous studies have found infants with earlier births to present greater delay of brain maturation, on average, we did not find gestational age at birth to be significantly correlated with RBNMI [11]. One possibility is that the lack of correlation between birth age and scan age caused the RF model to learn to be resilient to brain network variations due to birth age, as these cues would not help prediction of scan age. Another factor is that preterm birth alone has been shown not to affect neurodevelopment, so we may not necessarily expect to find greater maturation delay in those born earlier [2].

We also found that VM was significantly negatively correlated with RBNMI, as we would expect, but that grades of WMI and IVH were not significantly correlated with RBMNI. This suggests that VM may be a more important factor in delayed brain maturation. This finding agrees with the study by Ment et al. who found VM to be more important than IVH and a number of other factors in predicting neurodevelopmental outcome scores at 4.5 years of age [9]. Bayley neuromotor outcome scores, assessed at 18 months after birth (corrected for prematurity) were not found to be significantly correlated with VM but were significantly negatively correlated with RBMNI. This suggests that delayed brain network maturation shortly after birth may be at least partly responsible for lower neuromotor scores later in development. The relatively weak correlation ($r = 0.172$) is likely, in part, due to the long period of development between scan and Bayley assessment, in which many factors (e.g., environmental factors) can influence brain development.

Finally 84 edges, including edges from the PCG, which is known to be central to the default mode network, and from the ORBinf, which is important for language comprehension, were found, to be significantly correlated with RBNMI. Regions and connections strongly correlated with RBNMI are likely those that are developing most rapidly during the age range of the cohort, and thus are learned by the model to be most predictive of apparent age.

5 Conclusions

We proposed a method to examine brain network maturation delay in infants using a random forest classifier on structural connectome data. We demonstrated that the random forest model performed best on this task when compared to models used in previous studies for similar tasks. We found that maturation of

structural connectomes was *delayed* in those preterm neonates with abnormal development. While VM was found to be associated with delayed maturation (being significantly correlated), WMI and IVH were not. Neuromotor outcomes were also found to be significantly decreased in those with delayed maturation. Finally, an analysis of individual edges in the connectomes revealed the PCG and ORBinf regions in both hemispheres were most correlated with delay. In future work, we intend to explore the use of our RBNMI on broader range of demographic and diagnostic variables in order to formulate a more complete understanding of how delayed brain network maturation manifests in preterm infants. We also plan to apply the RBNMI to infants of different age cohorts to learn how delayed maturation presents at different stages of neurodevelopment.

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References

1. Bayley, N.: Bayley Scales of Infant Development - Third Edition. Harcourt, San Antonio (2006)
2. Bonifacio, S.L., et al.: Extreme premature birth is not associated with impaired development of brain microstructure. The Journal of pediatrics 157(5), 726–732 (2010)
3. Brown, C.J., Hamarneh, G.: Machine Learning on Human Connectome Data from MRI. arXiv (2016)
4. Brown, C.J., Miller, S.P., Booth, B.G., Poskitt, K.J., Chau, V., Synnes, A.R., Zwicker, J.G., Grunau, R.E., Hamarneh, G.: Prediction of Motor Function in Very Preterm Infants Using Connectome Features and Local Synthetic Instances. In: International Conference on Medical Image Computing and Computer-Assisted Intervention (MICCAI). pp. 69–76. Springer Berlin Heidelberg (2015), `http://link.springer.com/10.1007/978-3-319-24574-4http://link.springer.com/10.1007/978-3-319-24553-9{_}9`
5. Chau, V., et al.: Abnormal brain maturation in preterm neonates associated with adverse developmental outcomes. Neurology 81(24), 2082–2089 (2013)
6. Dosenbach, N.U.F., et al.: Prediction of Individua Brain Maturity Using fMRI. Science 329(5997), 1358–1361 (2011)
7. Kawahara, J., et al.: BrainNetCNN: Convolutional neural networks for brain networks; towards predicting neurodevelopment. NeuroImage pp. 1–9 (2016)
8. Liem, F., et al.: Predicting brain-age from multimodal imaging data captures cognitive impairment. NeuroImage (2016)
9. Ment, L.R., et al.: The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics 104(2), 243–248 (1999)
10. Robinson, E.C., et al.: Identifying population differences in whole-brain structural networks: A machine learning approach. NeuroImage 50(3), 910–919 (2010)
11. Smyser, C.D., et al.: Prediction of brain maturity in infants using machine-learning algorithms. NeuroImage 136, 1–9 (2016)
12. Wolff, P.H., et al.: Associated movements as a measure of developmental age. Developmental medicine and child neurology 25(4), 417–429 (1983)