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Early changes in brain structure correlate with language outcomes in children with neonatal encephalopathy

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ABSTRACT

Global patterns of brain injury correlate with motor, cognitive, and language outcomes in survivors of neonatal encephalopathy (NE). However, it is still unclear whether local changes in brain structure predict specific deficits. We therefore examined whether differences in brain structure at 6 months of age are associated with neurodevelopmental outcomes in this population. We enrolled 32 children with NE, performed structural brain MR imaging at 6 months, and assessed neurodevelopmental outcomes at 30 months. All subjects underwent T1-weighted imaging at 3 T using a 3D IR-SPGR sequence. Images were normalized in intensity and nonlinearly registered to a template constructed specifically for this population, creating a deformation field map. We then used deformation based morphometry (DBM) to correlate variation in the local volume of gray and white matter with composite scores on the Bayley Scales of Infant and Toddler Development (Bayley-III) at 30 months. Our general linear model included gestational age, sex, birth weight, and treatment with hypothermia as covariates. Regional brain volume was significantly associated with language scores, particularly in perisylvian cortical regions including the left supramarginal gyrus, posterior superior and middle temporal gyri, and right insula, as well as inferior frontoparietal subcortical white matter. We did not find significant correlations between regional brain volume and motor or cognitive scale scores. We conclude that, in children with a history of NE, local changes in the volume of perisylvian gray and white matter at 6 months are correlated with language outcome at 30 months. Quantitative measures of brain volume on early MRI may help identify infants at risk for poor language outcomes.

1. Introduction

The most common form of brain injury in newborns is associated with neonatal encephalopathy (NE) attributed to hypoxia-ischemia, which affects approximately 1.5–3 in 1000 live births (Kurinczuk et al., 2010). Of the long-term morbidities associated with NE, cognitive impairment is among the most significant. Cognitive deficits in survivors of NE can occur independently of motor disability (Pappas et al., 2015; Robertson and Finer, 1993; Robertson et al., 1989) and frequently result in an increased requirement for school services and other therapies in childhood (Pappas et al., 2015; Robertson and Finer, 1988; Robertson et al., 1989).

Language development, in particular, is vulnerable to disruption even in the setting of injuries that do not result in global cognitive deficits or cerebral palsy. Studies prior to the advent of therapeutic hypothermia showed that between one fifth and one third of survivors of NE who did not have severe cognitive or physical disabilities nevertheless presented with delays in receptive and expressive language in early childhood (D'Souza et al., 1981; Janowsky and Nass, 1987). Non-impaired survivors of moderate encephalopathy are also at

Abbreviations: Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; DBM, deformation based morphometry; NE, neonatal encephalopathy; NMS, neuromotor score

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increased risk for reading and spelling disorders at school age (Robertson et al., 1989).

Despite the potentially large number of children with language deficits after NE, there have been few attempts to identify biomarkers that might facilitate early identification and remediation of those at risk for delayed language development. We previously examined the relationship of injury patterns on neonatal MRI to later measures of language and cognitive performance (in this case, verbal and performance IQ scores on the Wechsler Preschool and Primary Scale of Intelligence-Revised [WPPSI-R] at 4 years of age) (Steinman et al., 2009). We found that increasing severity of injury in a watershed distribution (Barkovich et al., 1998) was associated with more impaired language-related abilities.

Regional changes in brain structure related to brain growth and early injury can be assessed on MRI quantitatively using advanced image processing and morphometry. Deformation-based morphometry (DBM), in particular, is designed to quantify brain regional volumes at the voxel level (Ashburner et al., 1998). An advantage of DBM over other morphometric techniques is that it does not require *a priori* differentiation of different tissue compartments. This technique is thus appropriate for morphometric analysis at various stages of brain development (Aljabar et al., 2008; Boardman et al., 2006), including in infancy, when the combined effects of neural proliferation, migration, and organization, as well as extensive myelination, often result in low tissue contrasts on MRI, which complicates tissue classification. DBM has been used to examine cortical and subcortical development at term-equivalent age in preterm infants (Ball et al., 2012; Boardman et al., 2006), as well as correlations between neonatal brain MRI and subsequent neurodevelopmental measures in children born preterm (Boardman et al., 2010; Ullman et al., 2015).

Here, we employed DBM to determine whether brain structural changes on MRI at 6 months of age can predict language, cognitive and motor outcomes at 30 months in a cohort of infants with a history of NE.

2. Materials and methods

2.1. Use of human subjects

This experiment was conducted as part of an ongoing prospective cohort study of infants at risk of hypoxic ischemic brain injury (the Birth Asphyxia MRI or BAMRI study), approved by the Institutional Review Board at the University of California, San Francisco. Informed consent was provided by the parents of the infants enrolled in the study.

2.2. Participants

Subjects in the present analysis were enrolled in BAMRI between August 2008 and June 2012, during which time the protocol included optional 3T MR brain imaging at 6 months of age, as well as assessment of neurodevelopmental outcomes at 30 months using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Of 112 infants enrolled in that period, 38 had MRIs under anesthesia at 6 months; 32 of these underwent testing with Bayley-III at 30 months. Of the six who had MRIs but not outcomes data, four had been lost to follow up, and the remaining two continued in the study but missed the follow up visit for testing at 30 months.

All participants enrolled in BAMRI had NE (abnormal tone, feeding, alertness, respiratory status, or reflexes) and at least one of the following markers of hypoxia-ischemia in the immediate postnatal period: (*a*) 5 min Apgar score ≤ 5; (*b*) umbilical artery cord blood pH < 7.1; or (*c*) umbilical artery base deficit −10 or less. Infants were excluded from the study if they had evidence of *in utero* or perinatal infection, major anomalies of the brain or other organ systems, or evidence of congenital metabolic disease. Demographic characteristics for the subjects included in this study are listed in Table 1.[3] Findings on neonatal MRI are described in Table 2.

Table 1
Demographic characteristics of subjects in the present study (n = 32).

Sex	17 female/15 male
Primary home language	25 English/7 Spanish
Gestational age at birth (median, range)	39 w 2 d (36 w 1 d – 41 w 6 d)
Birth weight (mean, range)	3.25 kg (2.20–5.52 kg)
Apgar, 5 min (median, range)	3 (0–9)
Neonatal seizures	15/32 (47%)
Clinical seizures (with electrographic correlate or abnormal EEG)	10/15
Electrographic seizures (without clinical correlate)	5/15
Therapeutic hypothermia	29/32 (91%)

2.3. Outcome measures

In addition to the 6 month MRI and 30 month neurodevelopmental follow-up described above, each participant had a brain MRI during the first two weeks of life and neurological examinations at around 6, 12, and 30 months of age, the latter corresponding to the time point at which the neurodevelopmental scores in the present analysis were obtained. The MRI was reviewed clinically and scored for research by a pediatric neuroradiologist. The neurologic examination was performed by a pediatric neurologist and included an assessment of motor outcomes using a validated neuromotor score (NMS) from 0 (normal) to 5 (cranial nerve involvement and spastic quadriparesis) (Hajnal et al., 1999). The Bayley-III was administered by a clinical psychologist blinded to the child's neonatal course, in the child's native language.

2.4. Imaging data acquisition

The imaging protocol at 6 months included a standard set of sequences including T1-weighted, T2-weighted, and diffusion-weighted images acquired on a 3-Tesla General Electric Discovery MR750 system. For the present analysis, we utilized T1-weighted images that were acquired using sagittal 3-dimensional inversion recovery spoiled gradient echo (3D IR-SPGR) (repetition time [TR] = minimum; echo time [TE] = minimum; inversion time = 450.00 ms; field of view [FOV] = 256 × 192 mm^2; number of excitations [NEX] = 1.00; flip angle [FA] = 15°), yielding images with isotropic 1 × 1 × 1 mm^3 spatial resolution.

2.5. Template construction

To optimize registration across subjects, a template was constructed in an unbiased fashion from a larger set of MRI scans, representing all children in the larger cohort study with MRIs at 6 months of age (n = 60; 2 scans were excluded due to poor quality). This included scans from 22 infants enrolled in the study who had not yet reached 30 months of age by the time of the present analysis, as well as 6 infants 30 months or older with missing Bayley-III data; therefore, neurodevelopmental outcomes data were not available for these participants.

Each image underwent automated correction for intensity non-uniformity (Sled et al., 1998) and was then linearly registered to the MNI-ICBM 152 template using DARTEL, a diffeomorphic anatomical registration algorithm (Ashburner, 2007). We then used a robust

[3] There were no differences in sex distribution, median gestational age at birth, or average birth weight between the 32 subjects included in the study and the 6 who did not have outcomes data Of the latter, 3 were female; 5 underwent hypothermia; median GA at birth was 39w 4d; and mean birth weight was 3.45 kg. This group did have slightly higher 5 min Apgar scores (median 5, range 3–8);

Table 2
Neonatal MRI findings in the study population. Injury on neonatal MRI was classified according to previously defined criteria (Barkovich et al., 1998). The subject with both basal ganglia and watershed injury had extensive involvement of both cortical and subcortical structures.

Basal ganglia pattern injury	5/32 (16%)
Abnormal signal in thalamus	3/5
Abnormal signal in thalamus and lentiform nucleus	1/5
Abnormal signal in thalamus, lentiform nucleus and perirolandic cortex	1/5
Watershed pattern injury	7/32 (22%)
Single focal infarction	2/7
Abnormal signal in anterior or posterior watershed white matter	3/7
Abnormal signal in anterior or posterior watershed cortex and white matter	2/7
Basal ganglia and watershed pattern injury	1/32 (3%)

unbiased averaging method for age-appropriate brain atlases (Fonov et al., 2011). This method applied iteration of coarse-to-fine nonlinear warping between each image and an intermediate template that was created by estimating the average shape during the previous warping cycle. Warping was performed only within the brain mask in order to minimize any possible distortion due to various signals from nonbrain tissues.

At each iteration, we built a temporary template by averaging the individual images that were registered to the template constructed in the previous iteration. Registration accuracy at the current iteration was assessed using a voxel-wise map of standard deviation (SD) of the intensity distributions across the individual images resulting from registration to the template. A lower SD corresponds with better registration at a given voxel. At each iteration, our algorithm resulted in a map with lower SDs compared to the previous calculation, and we stopped the iteration of the registration and averaging process when no further decreases in SD were seen (*i.e.*, the registration did not become more accurate). Our SD map at the final iteration was less than ± 9. The intensity range of the averaged data was normalized to 0–100, corresponding to the results of Fonov and colleagues (Fonov et al., 2011). We performed additional processing to correct for intensity inhomogeneity due to positioning of subjects' heads within the coil.

We obtained accurate brain masks using BEaST, a nonlocal mean-based label-fusion algorithm (Eskildsen et al., 2012) which was trained with 20 individual images (selected randomly from the set of 6 month images) with manually-labeled brain masks. The final template is shown in Fig. 1. The lower tissue differentiation observed in the anterior portion relative to the posterior is a typical pattern found at 6 months postnatally, due to ongoing myelination.

2.6. Deformation-based morphometry (DBM)

Each scan was first linearly and then nonlinearly registered to the template. While linear registration normalized intra-cranial volume across subjects, nonlinear registration yielded voxel-wise deformation fields between each individual 6 month MRI scan and the template. To examine local volume changes in each subject, the Jacobian determinant (henceforth, Jacobian) in the deformation field was computed at every voxel (Chung et al., 2001). This metric provides a simple and direct means of determining local volume changes, such as voxel-wise expansion (Jacobian > 1) or compression ($0 <$ Jacobian < 1), relative to the reference space (the 6 month MRI template). All Jacobian maps were smoothed using an 8-mm full-width at half-maximum isotropic Gaussian kernel. By inversely transforming the mask resulting from the BEaST algorithm to the native space in which MRIs were acquired, we also computed individual whole brain volumes, which were subsequently used to assess whether differences in global brain growth (in addition to regional brain volumes) are related to developmental outcomes.

2.7. Neurodevelopmental data analysis

We used a multivariate regression model to analyze correlations between demographic factors and neurodevelopmental outcome data, with Bayley-III language, cognitive, and motor composite scores as dependent (outcome) variables and birth weight, sex, gestational age at birth, and use of therapeutic hypothermia as independent predictors. The Bayley-III cognitive composite score was missing for one participant.

Birth weight and sex were selected as predictors because they have been shown to be associated with language and cognitive outcomes in clinical (Hintz et al., 2006; Linsell et al., 2015; Peacock et al., 2012) and non-clinical populations (Schjolberg et al., 2011; Takeuchi et al., 2016; To et al., 2004). There is also emerging evidence that the use of therapeutic hypothermia in patients with NE may result in improved neurocognitive outcomes (Azzopardi et al., 2014; Pappas et al., 2015; Zonnenberg et al., 2016). While all subjects in this study were born at 36 weeks or later, gestational age at birth was included to account for the interaction of gestational age with birth weight.

We also used univariate analysis of covariance (ANCOVA) to assess effects of injury observed on neonatal MRI (as described in Table 2) on Bayley-III language, cognitive, and motor composite scores. A separate ANCOVA model was constructed for each outcome score. The categorical predictor variables were basal ganglia injury (two levels: absent or present) and presence of watershed injury (three levels: absent, single focal infarction, bilateral injury) (Barkovich et al., 1998). Birth weight, sex, gestational age, and hypothermia were included as covariates.

2.8. Imaging data analysis

Statistical analysis was performed using SurfStat (http://www.math.mcgill.ca/keith/surfstat/) (Chung et al., 2010). The up-to-date version that was used in this study incorporated a module for voxel-based analyses, including DBM (Chung et al., 2010). The Jacobian determinant matrices were used as input data in a general linear model for DBM. To assess the association of voxel-wise and global brain volumes with functional outcomes, we included Bayley-III Motor, Cognitive and Language scores at 30 months of age as outcome variables. Birth weight, sex, gestational age at birth, and use of therapeutic hypothermia were included in the model as covariates, for reasons already described. Correction for multiple comparisons was based on Random Field Theory (Worsley et al., 2004) for regional analysis, and on Bonferroni adjustment for global analysis. To better localize findings with respect to the neocortex, we projected the voxel-wise *t* statistics to their nearest points on the cortical surface extracted from the template.

3. Results

3.1. Neuromotor outcomes

Of the 32 children in this cohort, 30 had neuromotor scores of 0–1 at 30 months, indicating normal motor examinations (NMS 0) or minor abnormalities in either tone or reflexes that were not functionally significant (NMS 1). Of these 30, 28 had normal MRIs and two had mild focal volume loss on conventional MRI at 6 months. The remaining two subjects had neuromotor scores of 3 (decreased power and tone or reflex abnormality) and both showed diffuse volume loss on conventional imaging.

3.2. Developmental outcomes

Mean Bayley-III composite scores by scale were: language, 98 (SD 14.6, range 56–121); motor, 96 (SD 15.2, range 52–118); cognitive, 107 (SD 20.5, range 55–130). Multivariate regression showed that the multivariate model as a whole (including the demographic variables of gestational age at birth, birth weight, sex, and use of therapeutic

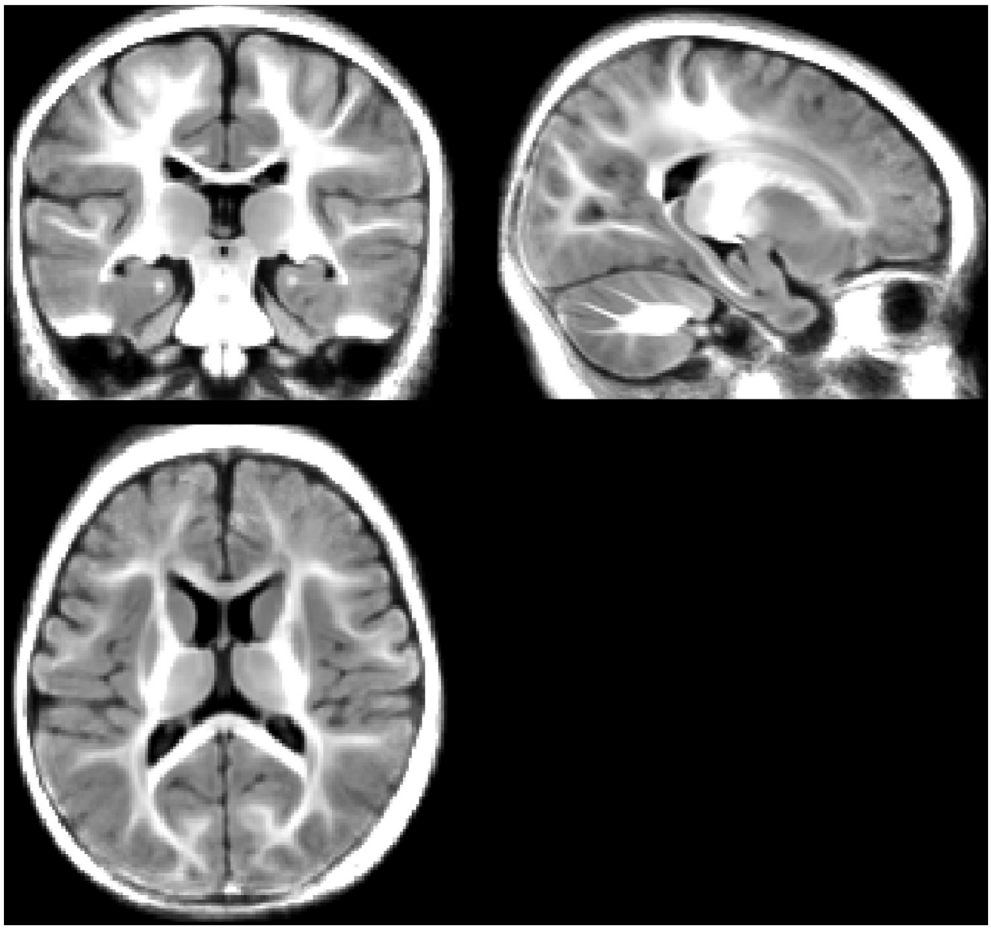

Fig. 1. Template for 6 month old infants with NE.

Table 3
Mean Bayley-III Language composite scores by demographic covariate. Gestational age and birth weight were included in the model as continuous variables, but means are presented here in stratified groups for ease of clinical interpretation.

	n	Bayley-III Language (mean ± SE)	*p*	$p_{adjusted}$
Sex			0.167	0.016
Female	17	101 ± 3.18		
Male	15	94 ± 4.04		
Hypothermia			0.881	0.885
Treated	29	98 ± 20.3		
Untreated	3	96 ± 2.25		
Gestational age			0.645	0.777
36–38 weeks	8	98 ± 6.49		
38–40 weeks	12	95 ± 3.62		
40 + weeks	12	100 ± 4.19		
Birth weight			0.052	0.006
2.20–3.00 kg	15	93 ± 3.63		
3.01–5.52 kg	17	102 ± 3.42		

hypothermia) was predictive of language scores ($F(31,5) = 2.91$, $p < 0.05$) but not of motor or cognitive scores. Of the individual predictors for language scores, only sex ($t = -2.57$, $p < 0.02$) and birth weight ($t = 2.97$, $p < 0.01$) emerged as significant (Table 3). In this cohort, mean language scores for males (94 ± 4.04) were lower than for females (101 ± 3.18). Lower birth weight was also associated with poorer language scores.

Analyses of covariance showed that type of injury on neonatal MRI was not predictive of language scores ($F(32,7) = 2.05$, n.s.) or of cognitive scores ($F(31,7) = 1.84$, n.s.), accounting for demographic covariates. The model for motor scores was significant ($F(32,6) = 2.43$, $p < 0.05$), due to a significant effect of basal ganglia injury ($t = 11.12$, $p < 0.005$).

3.3. Correlation of global brain volume with outcomes

Lower whole brain volume was associated with lower language ($r = 0.61$; $p < 0.0001$) and cognitive scores ($r = 0.48$; $p = 0.005$; significant after Bonferroni correction) at 30 months. The association with motor scores was marginal ($r = 0.41$; $p = 0.02$; not significant after correction).

3.4. Correlation of regional brain volume with outcomes

DBM analysis showed that decreased regional brain volume at 6 months was associated with lower Language scores at 30 months ($p < 0.05$ after random field theory-based correction; $p < 0.001$ was used to define initial supra-threshold clusters). Significant clusters were identified in several cortical and subcortical regions, including the left supramarginal gyrus, left posterior and superior temporal gyrus, and right insula, as well as inferior frontoparietal subcortical white matter (Fig. 2). We did not find significant correlations between regional brain volume and motor or cognitive composite scores.

To ensure that these findings were not driven by a small number of subjects with significant neurodevelopmental impairment and/or focal volume loss, we examined the correlation between the average Jacobian within each significant region and language scores for each subject (adjusted for other outcome variables and covariates included in the model) (Fig. 3). In four representative regions, we found strong linear relationships between these two measures across all subjects within the cohort ($t = 3.8$–7.6, $p < 0.001$).

The plot in Fig. 3 reveals one notable outlier with a low Language score (56) and low brain volume; notably, this outlier was one of the two subjects with diffuse volume loss visible on conventional MRI, and was also the only subject who had severe watershed and basal ganglia

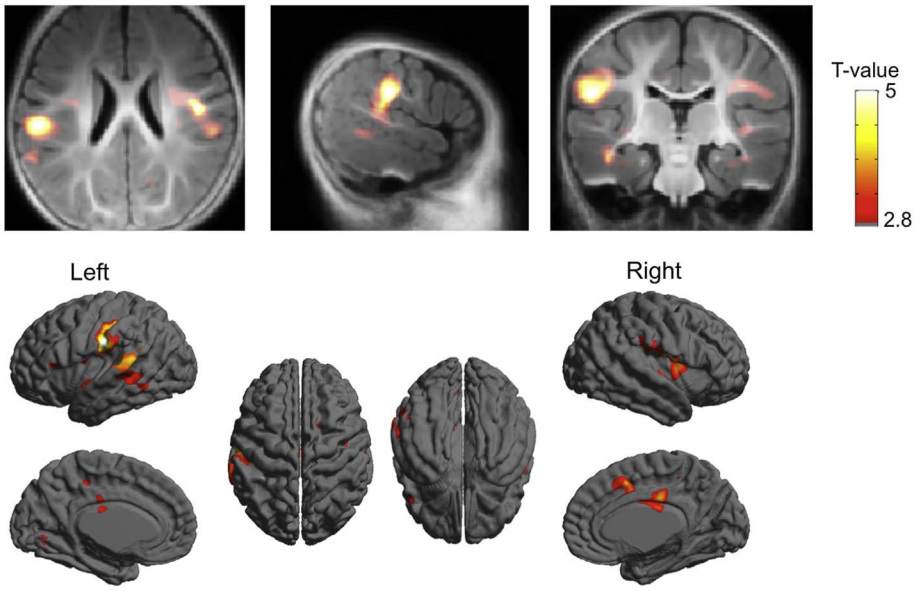

Fig. 2. Areas in which regional brain volume was correlated with Bayley-III Language composite score ($p < 0.05$, corrected using Random Field Theory (Worsley et al., 2004)). The cortical surface was extracted from the template and inflated to better visualize clusters buried within sulci.

injury on neonatal MRI. We thus repeated the analysis without this outlier. When this subject was removed from the analysis, the pattern of regional volume changes was very similar to the original pattern ($p < 0.05$, corrected; Fig. 4).

3.5. Effects of demographic variables on regional brain volume

We conducted *post hoc* DBM analyses to identify areas in which regional brain volumes correlated with the demographic variables shown to have a significant relationship with Bayley-III language scores—namely, sex and birth weight. Birth weight correlated with volumes in mostly posterior brain regions bilaterally, including the posterior portions of the left superior and middle temporal gyri and the right temporal-parietal junction, posterior inferior temporal gyrus, and posterior insula, and white matter tracts corresponding primarily to the posterior part of the superior longitudinal fasciculus (Fig. 5). We found no significant correlation between sex and regional brain volume ($p > 0.1$).

3.6. Relative contribution of demographic variables and regional brain volume to prediction of outcomes

The findings described above suggest that regional brain volumes at 6 months, birth weight, and sex have independent effects on language outcomes at 30 months. We performed an additional statistical analysis to assess the relative contribution of each of these variables to the Bayley-III language outcome measure. First, we constructed univariate linear regression models including an intercept for each of the three variables. We then computed the mean squared error (MSE) for each variable to evaluate its prediction accuracy. We compared this MSE with the MSE computed when all three variables were included in a single multivariate regression model (Fig. 6). This analysis showed that (uncorrected) regional brain volume was the most accurate predictor of language scores, with an increase of only 0.7% compared to the MSE of the multivariate model (4.2%). Prediction using birth weight and sex was less accurate, with about 2.5-fold increases in prediction error compared to the multivariate model (11.3%, 11.2% *vs.* 4.2%).

4. Discussion

A previous study from our group demonstrated that the degree of injury on MR imaging in the neonatal period in children with NE secondary to hypoxia-ischemia but without functional motor impairment was correlated with future verbal abilities (Steinman et al., 2009). Specifically, this study showed that greater injury affecting watershed cortex and white matter predicted lower verbal IQ scores measured at 4 years of age.

In the current study, we showed that underdevelopment of cortical gray matter and subcortical white matter at 6 months of age, presumed to be due to an early hypoxic-ischemic insult, predicts poorer language skills in early childhood. While global decreases in volume were found to predict lower cognitive and language abilities, regional volume measurement was a more specific predictor for variability in language outcomes. The specific regions implicated include left posterior perisylvian cortex and subcortical white matter and right insula and prefrontal cortex, which are engaged in language processing in early infancy (Dehaene-Lambertz et al., 2002). For the most part, these changes were not associated with visible injury on MRI at 6 months or with

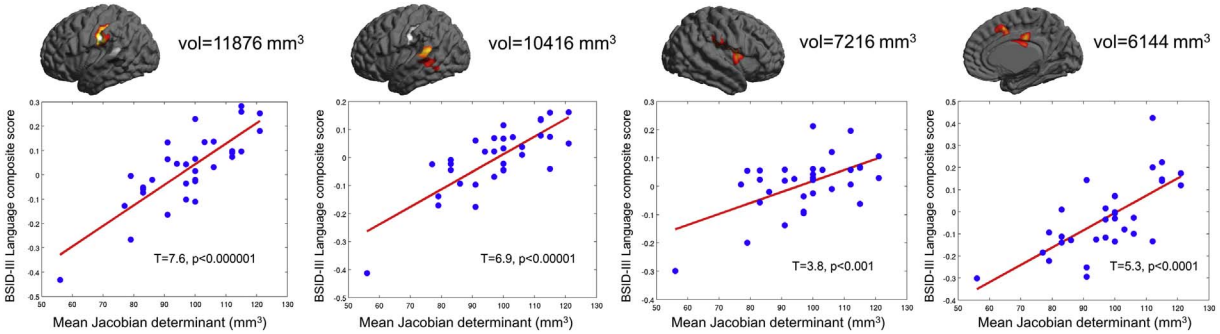

Fig. 3. Correlation between regional brain volume and Bayley-III Language composite score.

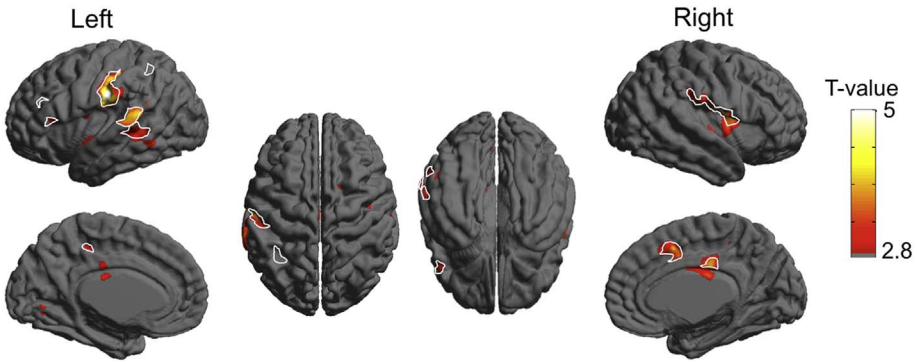

Fig. 4. Clusters in which there was a significant association between regional brain volume and Language ($p < 0.05$, corrected) after removal of the outlying subject. The colored areas display the original pattern of significant clusters while white outlines represent the new pattern after removing the outlier. Most large clusters overlap between the original and new analyses. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

abnormal neuromotor outcomes. We did not find any significant association between 6 month imaging and outcomes outside the domain of language.

We did examine the relationship between qualitative injury on neonatal MRI and 30 month outcomes in our cohort; this analysis showed that watershed or basal ganglia injury on neonatal MRI did not predict language outcome, with the important caveat that relatively few of the subjects had injury visible in the neonatal period, and even fewer had severe patterns of injury. The presence of injury in a basal ganglia distribution in the neonatal period was predictive of motor outcomes at 30 months, consistent with earlier findings that this pattern is a sensitive marker for motor impairment (Harteman et al., 2013; Krageloh-Mann et al., 2002; Martinez-Biarge et al., 2011; Miller et al., 2005). However, we focused mainly on quantitative voxel-wise changes in regional brain volume as a predictor of outcomes, rather than expert ratings of global injury. This allowed us to identify multiple brain regions that may constitute a network whose integrity appears to be important for early language development.

Our analysis focused on MRIs obtained at 6 months rather than in the neonatal period. In a clinical setting, MR imaging is generally obtained only in the neonatal period. However, we hypothesized that changes in brain growth are related to long-term outcomes, and these are not expected to be evident immediately after injury. Quantitative differences in brain volume measured at 6 months may thus be a more sensitive predictor of later outcomes than neonatal MRI, as acute signal change may not always result in permanent structural changes, especially for less severe injuries. On the other hand, given the greater clinical availability of neonatal MRI, it will be important to use quantitative morphometric techniques to investigate the relationship between acute changes and long-term outcomes in future work.

We note that the correlation between brain volume at 6 months and language scores at 30 months is observed not only for subjects with lower scores on the Bayley-III, but also for those who scored at or above the normative mean. Indeed, as noted above, the mean Bayley-III Language score for this cohort (98) was close to the normative mean, which is consistent with the observation that, for most subjects, language skills were within the average range. (This was also true in the cohort studied by Steinman et al. (2009), using a different outcome measure: mean verbal IQ on the WPPSI-R for their subjects was 96, SD 21; only the group with the greatest degree of injury had a mean score significantly lower than the population average.) This raises the question of whether our findings are indeed reflective of effects of injury, as we have assumed, or of variation in normal development.

It may not be possible to answer this question definitively without comparative imaging and neurodevelopmental follow-up data from children without a history of neonatal encephalopathy or other risk factors for perinatal brain injury. However, there is reason to believe that average performance according to Bayley-III norms is not a specific indicator of typical language development. A number of studies have shown that the Bayley-III underestimates rates of developmental delay in term and preterm infants using standard cut-offs (Anderson et al., 2010; Johnson et al., 2014; Lowe et al., 2012; Spencer-Smith et al., 2015). For example, in children born at earlier than 30 weeks gestational age, the Bayley-III Expressive and Receptive Language subscales at 2–3 years underestimate the prevalence of language impairment at 4–5 years (Spencer-Smith et al., 2015; Woods et al., 2014). In some cases, mean scores of control groups are up to 10 points higher than the normative mean (Anderson et al., 2010; Lowe et al., 2012). The Bayley-III may also be an insensitive measure for later problems with literacy and language-related academic skills.

To the extent that variability in regional brain volumes in our study cohort is a result of early injury, the finding of lower volume on DBM within the areas identified here may be a biomarker of risk for poorer language performance in survivors of NE, regardless of the precise cut-offs used to define clinical impairment. We did observe that some subjects with visible brain injury have lower language performance and quantitatively lower volumes by DBM, but did not specifically assess the association between brain volume and injury in this subgroup as the number of subjects was very small. We cannot exclude the possibility that differences in brain volume independent of injury are associated with variation in language skills at 30 months.

4.1. Neuroanatomical considerations

The cortical regions in which decreased volume was most strongly associated with lower language scores included the left supramarginal and posterior superior temporal gyri. These brain areas are involved in language production and comprehension in adults. Interestingly, there is evidence that the same regions are implicated in language processing within the first 6 months of life, supporting the hypothesis that they are critical components of the developing language network.

Studies using optical topography have shown that healthy neonates have increased hemodynamic activity over left temporal-perisylvian regions when listening to speech in their maternal language (Arimitsu et al., 2011; Pena et al., 2003; Sato et al., 2012), and to nonwords that adhere to the phonotactic constraints of natural languages compared to

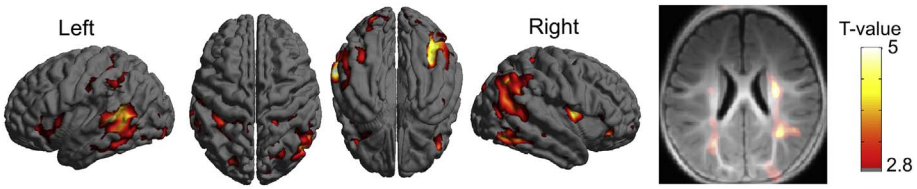

Fig. 5. Areas in which birth weight predicted regional brain volume ($p < 0.05$, corrected using Random Field Theory (Worsley et al., 2004)).

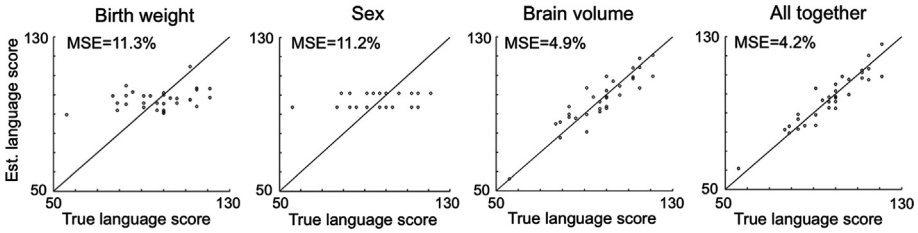

Fig. 6. Prediction accuracy for birth weight, sex, and regional brain volume on Bayley-III language outcomes at 30 months. Each plot represents prediction accuracy as mean squared error (MSE), based on the distance between estimated language scores and observed (true) language scores. In other words, the closer the points were positioned towards the diagonal line, the more accurate the prediction was. The brain volume was the best predictor as its MSE was lowest among the variables and similar to the prediction when all the variables were used.

those that do not (Gomez et al., 2014). Hemodynamic changes in the left supramarginal gyrus are seen in neonates specifically in response to phonological contrasts (Arimitsu et al., 2011). By 1–4 months of age, a left posterior perisylvian (superior temporal and inferior parietal) preference for language processing can be demonstrated using electrophysiology (Dehaene-Lambertz and Baillet, 1998) and functional magnetic resonance imaging (Baldoli et al., 2015; Dehaene-Lambertz et al., 2002; Shultz et al., 2014).

While these findings suggest that language is processed preferentially in left posterior temporal and inferior parietal brain areas in infancy, they do not establish that the integrity of these regions is essential for language development. It could be the case that even if these areas are damaged or otherwise functionally compromised, other regions are (or can be) engaged in the same developmental processes, so that language outcomes are not affected. For example, Dehaene-Lambertz et al. (2004) showed that a neonate with a left perisylvian infarct had intact ERP discrimination responses to phonetic features in speech, demonstrating that other brain regions—presumably including homologous right hemisphere areas—can also contribute to early language perception (Dehaene-Lambertz et al., 2004).

To date, there are scant data showing that the left temporal bias in infant language processing is functionally significant. Studies of children with perinatal stroke suggest that those with left temporal damage are more likely to have a strong disadvantage in proportion of comprehended words produced at 10–17 months and in mean utterance length at 19–44 months, compared to those with strokes in other locations (Bates et al., 1997), but precise anatomical data were lacking. One study has shown that in infants born preterm, decreases in MR diffusivity metrics in the left superior temporal gyrus at term equivalent age were associated with increased Bayley-III Language scores at 24 months (Aeby et al., 2013), which is concordant with our results.

Another area in which we observed a significant association between regional brain volume at 6 months and language outcomes was the right insula and inferior frontal operculum. Activation of right frontal cortex has been observed in awake infants processing speech (Dehaene-Lambertz et al., 2002) and may specifically be involved in recognizing phonological sequences (Benavides-Varela et al., 2012). The DBM results illustrated in Fig. 2 corroborate a crucial role for the right frontal region in language processing in infancy.

Finally, we noted volume changes related to language outcomes in subcortical white matter regions subjacent to inferior parietal cortical regions in both hemispheres. Some prior studies have shown associations between white matter integrity and language skills in children born preterm. Both qualitative ratings of severity of white matter injury (Iwata et al., 2012; Reidy et al., 2013; Woodward et al., 2012) and quantitative measures of white matter volume (Cheong et al., 2016; He and Parikh, 2013) predict later language and cognitive outcomes in this population. Regional associations between white matter MRI metrics in infancy and language outcomes have been examined in several populations, mostly implicating major white matter bundles such as the corpus callosum (Counsell et al., 2008; Massaro et al., 2015; Swanson et al., 2015) and corticospinal tracts (Deniz Can et al., 2013; Massaro et al., 2015). Specific intra-hemispheric tracts are not as well-studied in this context, but myelination of white matter underlying frontal and temporal cortex, including the areas implicated here, has been shown to correlate with receptive and expressive language abilities in healthy infants and toddlers (O'Muircheartaigh et al., 2014).

4.2. Demographic effects

Language outcomes at 30 months, corrected for other demographic variables, were worse for boys than for girls in our study sample. Several studies of children born extremely preterm have also found that male sex is associated with poorer language outcomes at this age (Hintz et al., 2006; Linsell et al., 2015; Peacock et al., 2012; Skiold et al., 2014; Wood et al., 2005; Young et al., 2016). The reason for this effect is not clear. It may be related to differences in cerebral white matter development or cortical volume (Kesler et al., 2008; Skiold et al., 2014); however, in this study, there was no effect of sex on regional brain volume at 6 months.

Likewise, we found that lower birth weight, controlling for sex and gestational age at birth, predicts lower language scores at 30 months. Although birth weight is clearly an important predictor of outcomes in the preterm population, there is also evidence that small for gestational age full term infants are at higher risk for developmental delays, and specifically language delays, in early childhood (Arcangeli et al., 2012; Savchev et al., 2013; Takeuchi et al., 2016; Vohr et al., 1988; Walther and Ramaekers, 1982). Our findings suggest that one reason for this association might be that at 6 months, birth weight is associated with brain volumes in posterior cortical and subcortical regions including those that are important for early language skills, as described above.

4.3. Limitations

A major limitation of this study was that we did not have data regarding maternal education or socioeconomic status for this cohort. These variables are known to mediate differences in receptive and expressive language skills and risk for language delays in early childhood (Dollaghan et al., 1999; Fernald et al., 2013; Howard et al., 2011; Ko et al., 2013; Patra et al., 2016; Wild et al., 2013), and may also be related to measures of brain growth (Betancourt et al., 2015; Hanson et al., 2013; Luby et al., 2013) and function (Tomalski et al., 2013), with one study showing effects on structural MRI as early as 5 weeks (Betancourt et al., 2015). It is conceivable that the specific findings affected here could be modulated by exposure to language in the first 6 months of life. If this were the case, it would not necessarily alter the conclusion that brain volumes on 6 month MRI are predictive of language skills, but might support the argument that the observed effects are not entirely attributable to injury.

As we have noted already, the subjects included in this study generally had good neuromotor and cognitive outcomes. In part, this may reflect an inherent selection bias (*i.e.*, children who were more mildly affected were more likely to undergo imaging at 6 months and to follow up at later time points). While this limits our ability to generalize our conclusions to the larger population of survivors of NE, it seems probable that children with mild injuries are those most likely to present with relatively isolated cognitive deficits, and thus constitute the population for which sensitive biomarkers of potential language impairment may be most clinically valuable.

A related limitation, also discussed above, is the lack of a comparison group of children without brain injury. Without such a comparison we cannot be confident that the effects described are related to NE *per*

se, as opposed to developmental variation attributable to other causes. On the other hand, this also does not have a direct bearing on the validity of the relationship between brain volumes and outcomes as described for this population. Further studies will be necessary to determine whether similar effects are present in infants without brain injury, as well as in other clinical populations at risk for brain injury (for example, infants born prematurely and those with congenital heart disease). If indeed the areas we have described are crucial for development of early language skills, we should find a similar pattern of correlations between brain volume and language outcomes in other populations, although the effect size of such correlations could vary depending on variability in both the predictor and outcome variables. On the other hand, if the same relationship is not seen in other populations, it might suggest that outcomes after NE are affected by interaction between changes in regional brain volume and other factors unique to this condition (such as, perhaps, global volume loss).

5. Conclusions

This study uses morphometric MRI analysis to demonstrate an association between regional brain volume changes and early developmental outcomes in a specific cognitive domain. Changes were identified in a relatively circumscribed set of cortical and subcortical regions, which corresponds well to the areas known to be engaged in early language processing from functional neurophysiological studies in infants; the convergence of these results and those of earlier studies thus provides critical evidence defining the brain network important for language acquisition. The findings may help identify survivors of perinatal brain injury who are at risk of language delay or impairment.

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