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A left cerebellar pathway mediates language in prematurely-born young adults

R. Todd Constable[1], **Betty R. Vohr**[2], **Dustin Scheinost**[1], **Jennifer R. Benjamin**[3], **Robert K. Fulbright**[1], **Cheryl Lacadie**[1], **Karen C. Schneider**[3], **Karol H. Katz**[4], **Heping Zhang**[4], **Xenophon Papademetris**[1], and **Laura R. Ment**[3,5]

[1]Diagnostic Radiology, Yale University School of Medicine, New Haven, CT

[2]Pediatrics, Warren Alpert Medical School of Brown University, Providence, RI

[3]Pediatrics, Yale University School of Medicine, New Haven, CT

[4]Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT

[5]Neurology, Yale University School of Medicine, New Haven, CT

Abstract

Preterm (PT) subjects are at risk for developmental delay, and task-based studies suggest that developmental disorders may be due to alterations in neural connectivity. Since emerging data imply the importance of right cerebellar function for language acquisition in typical development, we hypothesized that PT subjects would have alternate areas of cerebellar connectivity, and that these areas would be responsible for differences in cognitive outcomes between PT subjects and term controls at age 20 years.

Nineteen PT and 19 term control young adults were prospectively studied using resting-state functional MRI (fMRI) to create voxel-based contrast maps reflecting the functional connectivity of each tissue element in the grey matter through analysis of the intrinsic connectivity contrast degree (ICC-d). Left cerebellar ICC-d differences between subjects identified a region of interest that was used for subsequent seed-based connectivity analyses. Subjects underwent standardized language testing, and correlations with cognitive outcomes were assessed.

There were no differences in gender, hand preference, maternal education, age at study, or Peabody Picture Vocabulary Test (PPVT) scores. Functional connectivity (FcMRI) demonstrated increased tissue connectivity in the biventer, simple and quadrangular lobules of the L cerebellum ($p<0.05$) in PTs compared to term controls; seed-based analyses from these regions demonstrated alterations in connectivity from L cerebellum to both R and L inferior frontal gyri (IFG) in PTs compared to term controls. For PTs but not term controls, there were significant positive correlations between these connections and PPVT scores (R IFG: $r=0.555$, $p=0.01$; L IFG: $r=0.454$, $p=0.05$), as well as Verbal Comprehension Index (VCI) scores (R IFG: $r=0.472$, $p=0.04$).

These data suggest the presence of a left cerebellar language circuit in PT subjects at young adulthood. These findings may represent either a delay in maturation or the engagement of alternative neural pathways for language in the developing PT brain.

Address for correspondence: R. Todd Constable, Ph.D. The Anlyan Center, MRRC 300 Cedar Street New Haven, CT 06511 todd.constable@yale.edu.

Keywords

Preterm; cerebellum; language systems; functional MRI; resting state intrinsic connectivity contrast degree

Introduction

Preterm birth is a major public health problem in the world today; 1.45% of all live born infants weigh less than 1500 g at birth,(Beck et al., 2010; Kochanek et al., 2012; Mathews et al., 2011) as many as one-third of prematurely-born infants experience significant cognitive handicaps during early childhood,(Neubauer et al., 2008; Robertson et al., 2009; Saigal and Doyle, 2008) and the impact of preterm birth on corticogenesis in the developing brain has been well described.(Kuklisova-Murgasova et al., 2011; Smyser et al., 2010; Woodward et al., 2006) In contrast, the majority of preterm subjects are reported to function normally at young adulthood,(Hack, 2009; Saigal et al., 2006) although the neurobiologic mechanisms supporting the adaptations of developing brain that permit such outcomes remain largely unknown.

Sophisticated neuroimaging strategies permit the interrogation of language systems in at risk populations and matched control subjects. The brains of preterm children are 5 – 6% smaller than those of matched term control subjects at school age,(Nosarti et al., 2002; Peterson et al., 2000) and numerous volumetric magnetic resonance imaging (MRI) studies demonstrate regions of vulnerability in those areas subserving language, including the temporal and parietal cortices and cerebellar hemispheres.(Boardman et al., 2010; Haldipur et al., 2011; Kesler et al., 2008; Lind et al., 2011; Nosarti et al., 2008; Parker et al., 2008; Tam et al., 2009) During the transition from childhood to early adolescence, the brains of preterm subjects do not exhibit the robust expansion of white matter systems characteristic of term controls, and longitudinal studies are significant for a paucity of gray matter pruning in both the temporal and frontal lobes notable in term controls.(Ment et al., 2009) Studies at young adulthood continue to document gray and white matter alterations in language systems in preterm subjects compared to typically developing subjects,(Nosarti et al., 2008) and recent data suggest both increased and decreased structural covariance between cortical and subcortical systems for the preterm group. (Nosarti et al., 2011) Of note, preterm subjects show alterations in structural covariance between left frontal language regions and both the left and right cerebellar hemispheres, implicating changes in functional connectivity during brain development in the prematurely born.(Nosarti et al., 2011)

Functional MRI (fMRI) provides important information about task-based activation and functional connectivity (fcMRI) patterns in preterm subjects compared to term controls. Preterm subjects activate alternative cortical regions for language tasks yet have the same cognitive scores as term controls at school age and adolescence, and task-based functional connectivity suggest the engagement of auxiliary neural systems for language in the prematurely-born. (Ment and Vohr, 2008; Nosarti et al., 2009) Seed-based fcMRI analyses in response to a language task show persistent engagement of both the left inferior parietal lobule (BA 40) and right hemisphere language regions including right BA 40 and inferior frontal gyrus, BA 44-45.(Gozzo et al., 2009) In a population of preterm subjects and term controls at age 16 years, connectivity from Wernicke's region, L BA 22, to R BA40 was negatively correlated with semantic testing scores, suggesting that this auxillary functional connection is present in those with the greatest cognitive need.(Myers et al., 2010)

Since emerging data imply the importance of right cerebellar function for language acquisition in typical development and preterm subjects have been previously shown to exhibit significance differences in cortical-cerebellar structural covariance, we hypothesized that PT subjects would have alternate areas of cerebellar connectivity, and that these areas would be responsible for differences in cognitive outcomes between PT subjects and term controls at age 20 years. Because numerous volumetric and microstructural studies have demonstrated profound changes in the preterm brain compared to term controls in studies ranging from the newborn period through young adulthood,(Miller and Ferriero, 2009) we employed a voxel based contrast mechanism that provides a summary connectivity measure, the network measure of *degree*, calculated from resting state fcMRI. The advantage of this approach is that it provides a whole-brain survey of connectivity that does not require *a priori* information to predefine ROIs, while allowing us to test the hypothesis that there are alterations in cerebellar connections for language in the prematurely born at young adulthood.

Methods

This study was performed at the Yale University School of Medicine, New Haven, CT and Brown Medical School, Providence, RI. The protocols were reviewed and approved by institutional review boards at each location. Subjects provided written consent for the study. All scans were obtained and analyzed at Yale University.

Subjects

The preterm cohort consisted of 19 subjects with no evidence for intraventricular hemorrhage (IVH), periventricular leukomalacia and/or low pressure ventriculomegaly on serial neonatal ultrasounds. Subjects had normal findings on conventional MRI studies and total ventricular CSF volume within 2 SD of the mean ventricular volume of term control subjects at 12 years of age; in addition, they had normal findings on conventional MRI studies at 18 – 20 years of age. They had no contraindications to MRI. All preterm subjects enrolled in the follow-up component of the “Multicenter Randomized Indomethacin IVH Prevention Trial” were sequentially invited for this MRI study when they reached 18 - 20 years of age. (Ment et al., 1994) The preterm subjects were recruited to the primary trial at 6 – 12 hours of age, and those who lived within 200 miles of New Haven, CT, were invited to participate in the imaging portion of the randomized clinical trial follow-up study at 8 to 12 years of age. The preterm young adults in this study are representative of the cohort of subjects with no evidence of neonatal brain injury with respect to gender, handedness, FSIQ scores, minority status, and maternal education.

Nineteen healthy, typically developing term control subjects, aged 18 to 20 years, were recruited from the local community at ages 8 to 12 years and group-matched with the PT subjects for zip code, gender and age. Similar to the preterm subjects, only subjects with normal findings on conventional MRI were included in this analysis.

The assessments of neonatal health status and neurologic outcome have been outlined in prior work.(Peterson et al., 2000) Blinded assessment of intelligence was performed using the Wechsler Intelligence Scale for Children-III (WISC).(Wechsler, 1991) Children also received the Peabody Picture Vocabulary Test –Revised (PPVT), (Dunn and Dunn, 1981) and the Rapid Digit Naming, Rapid Letter Naming, Blending Nonwords and Segmenting Nonwords subtests of the Comprehensive Test of Phonological Processing (CTOPP). (Wagner et al., 1999)

Functional Imaging

Imaging Parameters—Subjects were scanned in a Siemens 3T Tim Trio scanner. After a first localizing scan, a high resolution 3D volume was collected using a magnetization prepared rapid gradient echo (MPRAGE) sequence (176 contiguous sagittal slices, slice thickness 1mm, matrix size 192×192, FoV = 256mm, TR = 2530 ms, TE = 2.77 ms, flip angle = 7°). Next, a T1-weighted anatomical scan (TR = 300 ms, TE = 2.55 ms, FoV = 220 mm, matrix size 256×256, thickness = 6 mm thick, gap = 1mm) was collected with 25 AC-PC aligned axial-oblique slices. After these structural images, acquisition of functional data began in the same slice locations as the axial-oblique T1-weighted data. Functional images were acquired using a T2* sensitive gradient-recalled single shot echo-planar pulse sequence (TR = 1550ms, TE = 30ms, flip angle = 80, Bandwidth = 2056 Hz/pixel, 64*64 matrix, field of view: 220mm x 220mm, interleaved acquisition). Functional runs consisted of 190 volumes (5 minute scan length) with the first four volumes discarded to allow the magnetization to reach the steady-state.

Preprocessing—Images were slice time corrected using sinc interpolation and motion corrected using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). All further analysis was performed using BioImage Suite (http://bioimagesuite.org). Several covariates of no interest were regressed from the data including linear and quadratic drift, six rigid-body motion parameters, mean cerebral-spinal fluid (CSF), and mean white matter. The overall volume mean was removed for each individual volume in the 4D sequence. Finally, the data were low passed filtered via temporally smoothing with a zero mean unit variance Gaussian filter (approximate cutoff frequency=0.12Hz).

Intrinsic Connectivity Contrast Degree (ICC-d) estimation—After preprocessing, the two resting state runs were concatenated and the distribution of connections for each voxel was then calculated in each subject’s individual space. First, a gray matter mask was applied to the data so only voxels in the gray matter were considered in the calculation of connectivity. The gray matter mask was defined on a template brain and warped to the individual subject’s space using a series of transformations described below.

Next the functional connectivity of each voxel based on the network measure of *degree*(Martuzzi et al., 2011; Rubinov and Sporns, 2010) was calculated for each individual subject for subsequent group analysis to localize tissue elements in the cerebellum that exhibited differential ICC-d. The degree measure was calculated for each voxel using a correlation threshold of r=0.25 to determine whether or not two voxels were connected. To allow group statistical comparisons, the values in the individual ICC-d maps were normalized to fit a Gaussian distribution with zero mean and unitary variance. For each subject, the degree mean and standard deviation over all gray matter voxels was calculated. Then each voxel was normalized by, first, subtracting this degree mean and, then, dividing by this degree standard deviation. This normalization ensures all subject maps are consistently scaled but does not alter the intrinsic connectivity pattern.(Buckner et al., 2009) To ensure that any ICC-d differences were not due to our choice of thresholds, this analysis was repeated with a range of thresholds (r=0.25 +/− 0.10) similar to Buckner(Buckner et al., 2009) and Tomasi.(Tomasi and Volkow, 2010)

All single subject results were first spatially smoothed with a 6mm Gaussian filter and warped to a common template space through the concatenation of a series of linear and non-linear registrations. First, a non-linear transformation was applied to warp the individual MPRAGE (3D anatomical) image to the template brain. Next, the individual 3D anatomical acquisition was linearly registered to the individual T1 axial-oblique (2D anatomical) images. Finally, the functional series were linearly registered to the 2D anatomical image. All transformations were estimated using the intensity-only component of the method implemented by BioImage Suite as previously reported in Papademetris et al.(Papademetris et al., 2009) Differences between preterm and term subjects for each measure were identified using a t-test with significance accessed at p=0.05. AFNI AlphaSim (http://

afni.nimh.nih.gov/afni) was used to correct for multiple statistical comparisons across the whole brain (cluster size=8640mm^3).

Seed-to-Whole Brain Connectivity Analysis—A reference region in the L cerebellar area of differential ICC-d was defined based on this ICC-d difference map (center of mass Talairach coordinates 27, 38, 6, threshold p<0.05 corrected) on the MNI reference brain as aspects of the inferior and superior semilunar, simple, biventer and quadrangular lobules, and transformed back (via the inverse transform obtained as described above) into individual subject space. The time-course of the reference region in a given subject was then computed as the average time-course across all pixels in the reference region. This time-course was correlated (using Pearson correlation) with the time-courses of all other voxels in the brain to create a map of r-values, reflecting ROI-to-whole brain connectivity (Myers et al., 2010). These r-values were transformed to z-values using Fisher's transform, and averaged across scans in each subject to yield one map for each subject representing the strength of correlation to the cerebellar ROI in terms of Gaussian variables, which was then spatially smoothed (6mm diameter Gaussian).

Statistical Methods—Demographic and cognitive data were analyzed using standard chi-squared statistics for categorical data. Continuous-valued data and ROI-based connectivity values were analyzed using t-tests to compare groups. Pearson's correlations were employed to examine the relationships between connectivity and cognitive outcome measures.

For the purposes of this report, p values < 0.05 were considered significant. All analyses were performed using SAS/STAT® 9.22 (SAS Institute Inc., Cary, NC).

Results

Subject population

Neonatal characteristics of the preterm population are shown in Table 1. The preterm subjects weighed between 600 and 1250 grams at birth, with a mean birth weight of 974.6 ± 163.2 grams and mean gestational age of 28.2 ± 1.8 weeks. Sixteen percent of the subjects developed bronchopulmonary dysplasia.

Demographic data of the term and preterm cohorts are presented in Table 2. There were no significant differences between the preterm and term cohorts in gender, age at scan, number of right-handed subjects, percentage of non-white subjects, subjects who receive special therapeutic services or subjects whose mothers had less than a high school education.

Results of cognitive testing for the language pathway correlations are presented in Table 3. Preterm subjects scored significantly lower than term subjects on the WISC-III performance IQ (p =0.05), but there were no other significant differences in WISC-III or PPVT scores. Similarly, preterm subjects performed comparably to term subjects on the Rapid Naming Composite score, which is composed of Rapid Digit Naming and Rapid Letter Naming tasks. The Phonological Awareness Composite score, made up of tasks involving Blending Nonwords and Segmenting Nonwords, showed significant deficits in preterm subjects compared to term controls (p=0.008).

Intrinsic connectivity contrast degree analyses

The ICC-d analysis for this group of subjects revealed a single cluster of increased intrinsic connectivity, higher network measure of degree, in the left cerebellum for the preterm subjects when compared to term controls (p < 0.05). This included aspects of the inferior and superior semilunar, simple, biventer and quadrangular lobules, as shown in Figure 1.

This cluster was robust to threshold as ICC-d analysis using a range of thresholds between r=0.15 to r=0.35 showed similar connectivity differences.

Seed-based connectivity analyses

When the study groups were compared, seed-based analyses from the L cerebellar region of increased ICC-d demonstrated stronger negative connectivity (anticorrelations) to both the left and right inferior frontal gyri (IFG) for the preterm group compared to the term controls ($p < 0.05$ for both), as shown in Figure 2.

Whole brain seed-based analyses from the L cerebellar ROI showed no other patterns of differential connectivity for the preterm subjects compared to the term controls.

Correlational analyses

Since both the left and right IFG are known to subserve semantic language, we tested the hypotheses that the L cerebellar to IFG connections would be significantly correlated with semantic language tasks for the preterm subjects but not term controls at young adulthood. These correlations, shown in Figure 3, demonstrate that both the L cerebellar to L IFG and L cerebellar to R IFG connections are significantly positively correlated with the PPVT scores for the preterm subjects ($r = 0.454$, $p = 0.05$ and $r = 0.555$, $p = 0.01$, respectively). Similarly, although the L cerebellar to L IFG connection did not correlate with the verbal comprehension index (VCI) for the preterm group, we found a positive correlation between the L cerebellum and the R IFG ($r = 0.472$, $p = 0.04$) for the preterm subjects.

Two influential points were detected for each of the two preterm PPVT-R correlations, and these points differ depending on the measures being analyzed. For the correlation between the L cerebellar – L IFG connection and the PPVT-R score for the preterm subjects, the r value declines from 0.454 to 0.401. For the correlation between the L cerebellar – R IFG connection and the PPVT-R score for the same subject group, the r value decreases from 0.555 to 0.226. Overall, however, the direction of the correlations is confirmed when the analyses are completed without the influential points.

In contrast, while there were no positive correlations between the L cerebellar to R IFG connection and either PPVT or VCI scores for the term controls, we found a significant negative correlation for the L cerebellar to L IFG connection for VCI ($r = -0.504$, $p = 0.03$) and a trend for a negative correlation between this connection and PPVT-R scores ($r = -0.441$, $p = 0.06$). Of note, an outlier was detected for each of the two term PPVT-R correlations. When the outlier was removed from the correlation between the L cerebellar – L IFG connection and the PPVT-R score for the term controls, the measures became more negatively correlated ($r = -0.517$, $p = 0.028$). Likewise, when the outlier was removed from the correlation between the L cerebellar – R IFG connection and the PPVT-R score for the same subject group, although not significant, the measures also became more negatively correlated, ($r = -0.360$, $p = 0.14$).

Finally, there were no correlations between the L cerebellar connection to the L or R IFG and phonologic testing scores for either the preterm subjects or term controls.

Discussion

Employing a voxel based, task-free measure of resting state intrinsic connectivity contrast degree, these data demonstrate for the first time that preterm subjects have different functional connectivity in the cerebellum and that this region of altered connectivity is differentially connected to systems for language even at young adulthood. Preterm subjects with no evidence for severe brain injury exhibited a significant increase in resting state intrinsic connectivity in the left cerebellar hemisphere.

The seed-based connectivity analysis revealed stronger anti-correlations between the cerebellum and right temporal and frontal language regions for the preterm group. Previous studies have demonstrated such anticorrelations can be related to cognitive function, and our findings support this work.(Hampson et al., 2010; Kelly et al., 2008) To ensure that such anti-correlations did not arise simply from the global mean removal step of preprocessing, (Chai et al., 2012; Murphy et al., 2009) we also performed this analysis without global mean removal and still observed a stronger anticorrelation between the left cerebellum seed and the same right frontal/temporal regions in the preterm group relative to the control group although without this correction the subtraction maps did not survive correction for multiple comparisons.

Our data show significant positive correlations between well-described semantic language measures and seed-based connectivity analyses from this ICC-d-region of interest to the inferior frontal gyri bilaterally for the preterm subjects at young adulthood, suggesting engagement of an alternative cerebellar pathway for language in the prematurely-born. In contrast, the negative correlation for the term subjects suggests that those with the greatest cognitive need are engaging this presumptive auxiliary pathway. Language has been shown to be parcellated into ventral and dorsal pathways.(Friederici, 2009; Hickok and Poeppel, 2007; Saur et al., 2008) As demonstrated in numerous fMRI and microstructural studies, the ventral pathway, composed of the inferior frontal gyrus, middle temporal lobe, angular gyrus/interior parietal lobule, hippocampus with parahippocampal gyrus and anterior cingulate is bilateral and supports higher level, semantic language comprehension. In contrast, the left-dominant dorsal pathway is largely responsible for phonology and the phonologic memory loop. As described by Saur, the dorsal pathway connects the superior temporal lobe and premotor cortices in the frontal lobe by means of the superior longitudinal fasciculi. Preterm subjects typically perform at levels similar to term controls on measures of phonologic testing but exhibit “catch up” growth for semantic language measures, although the mechanism for this phenomenon remains largely unknown. (Luu et al., 2011; Luu et al., 2009) It is of particular interest, therefore, that we noted significant correlations in the L cerebellar – IFG connectivity and semantic testing scores but none for those measures assessing phonology.

Although the role of cerebellar function in fMRI language studies not requiring appendicular movement has only been recently interrogated, (Stoodley, 2012; Stoodley and Schmahmann, 2009) damage to the right cerebellar hemisphere has long been known to result in language deficits,(Schmahmann et al., 2009) and subjects with cerebellar surgery frequently suffer cerebellar mutism in the post-operative period. (Ellis et al., 2011) The neuroanatomical connections between the cerebral cortex and cerebellar hemispheres are contralateral, (Marien et al., 2001; Murdoch, 2010) and most fMRI language tasks in typically developing subjects activate the right cerebellar hemisphere. (Stoodley, 2012; Stoodley and Schmahmann, 2009)

That our preterm subjects exhibit increased resting state intrinsic connectivity in the left cerebellar hemisphere is a novel departure from published work in control young adults, but not unsurprising when both functional and microstructural studies in preterm subjects at school age, adolescence and young adulthood are considered. Cerebellar neural networks have been detected in preterm subjects as early as 27 weeks gestational age,(Smyser et al., 2010) and both functional and diffusion tensor imaging studies demonstrate that preterm subjects typically engage auxillary right hemisphere neural systems for language – even when there are no differences in testing scores.(Mullen et al., 2010; Myers et al., 2010;

Nosarti et al., 2009) If the predominant cortical-cerebellar connections are crossed,(Krienen and Buckner, 2009) then one would hypothesize engagement of the left cerebellum for language in the prematurely-born. Of note, the recent work of Perani(Perani et al., 2011) suggests that language is bilateral in term neonates at age 2 days, suggesting that the persistent engagement of the R cerebral hemisphere and thus the L cerebellum for language represents failure of pruning in the prematurely-born.

Numerous avenues of investigation suggest that preterm birth alters the developmental program of the cerebellum,(Limperopoulos et al., 2007; Tam et al., 2011) and smaller cerebellar volumes have been significantly correlated with poor neurological performance at 2 years corrected age. (Lind et al., 2011) There is rapid expansion of the cerebellum during the third trimester of gestation, (Limperopoulos et al., 2005a; Limperopoulos et al., 2005b) a time at which most very low birth weight preterm subjects have already been delivered, and volumetric studies at school age and young adulthood demonstrate not only decreased cerebellar volumes in preterm subjects compared to term controls(Parker et al., 2008) but also evidence for crossed cerebellar atrophy for preterms with hemispheric injury. (Limperopoulos et al., 2007; Limperopoulos et al., 2005b; Tam et al., 2011) Of note, because they are at grave risk for neurodevelopmental handicap, (Woodward et al., 2009) premature infants receive special services including speech, language and other developmental intervention following hospital discharge (Milgrom et al., 2010; Spittle et al., 2010) and may experience significant alterations in corticogenesis across developmental time periods(Gimenez et al., 2008) likely due to the increased use of targeted developmental pathways. Early intervention has been shown to promote corticogenesis and improve testing scores in preclinical models for neonatal brain injury, (Faverjon et al., 2002) and also to increase fractional anisotropy values, a measure of axonal coherence, in preterm neonates exposed to early intervention therapy.(Als et al., 2004; Milgrom et al., 2010) Finally, although there are no published reports of the influence of early intervention on cerebellar development in preterm subjects, constraint-induced movement therapy has been shown to increase cerebellar activation contralateral to the affected hemisphere in adult ischemic stroke patients,(Murayama et al., 2011) suggesting plasticity of cerebellar neural networks in response to intervention.

The strengths of our study include the utilization of a voxel level whole-brain measure of intrinsic resting state connectivity, the ICC-d, and the detailed prospective, longitudinal characterization of the cohort. Limitations include the sample size and the lack of both advanced imaging in the neonatal period and cerebellar volumetric measurements at age 20 years. It is probable that some of the preterm subjects had subtle white matter injury undetectable with neonatal cranial ultrasonography. Furthermore, although we detected two influential points for each of the two preterm connectivity – PPVT-R correlations, we have no reason to believe that they are outliers. Indeed, the two influential points differ depending on the measures being analyzed. Finally, although the r values decrease secondary to fewer subjects in the analyses, the direction of our correlations is confirmed when the analyses are completed without the influential points.

Twenty years after the insult of preterm birth, prematurely-born subjects continue to show impaired performance on multiple aspects of neuropsychological testing in addition to alterations in the functional organization of their brains. Our data provide the first evidence that left cerebellar systems underlie language function in adolescents born preterm. Moreover, the correlations between semantic test performance and L cerebellar – IFG connectivity in our preterm population are consistent with the bi-lateralization of the ventral semantic pathway in typically developing subjects. These suggest increased utilization of the right hemisphere – left cerebellar pathway in preterm subjects, and are consistent with the adaptive connectivity that characterizes the developing preterm brain. Future studies will explore the neurobiological basis of these results.

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ABBREVIATIONS

BA	Brodmann area
BW	Birth weight
CSF	Cerebral-spinal fluid
CTOPP	Comprehensive test of phonologic processing
fcMRI	Functional connectivity
fMRI	Functional MRI
FSIQ	Full scale IQ
ICC-d	Intrinsic connectivity contrast degree
IFG	Inferior frontal gyrus
PIQ	Performance IQ
PT	Preterm
PPVT-R	Peabody Picture Vocabulary Test - Revised
ROI	Region of interest
VCI	Verbal comprehension index
VIQ	Verbal IQ
VLBW	Very low birth weight

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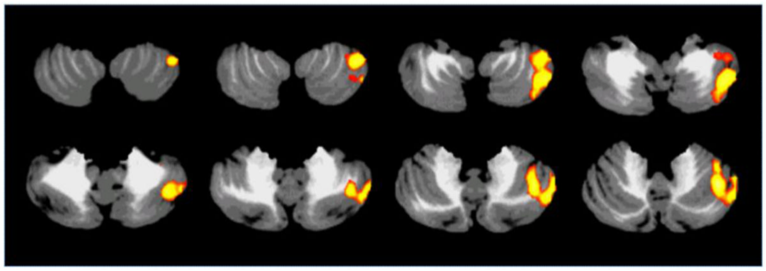

Figure 1.
Cerebellar region showing group differences (preterm – term) in local tissue connectivity as measured by the network measure degree (p<0.05 corrected). This left cerebellar region was subsequently used as a seed region-of-interest (ROI) for ROI-to-whole-brain connectivity analysis.

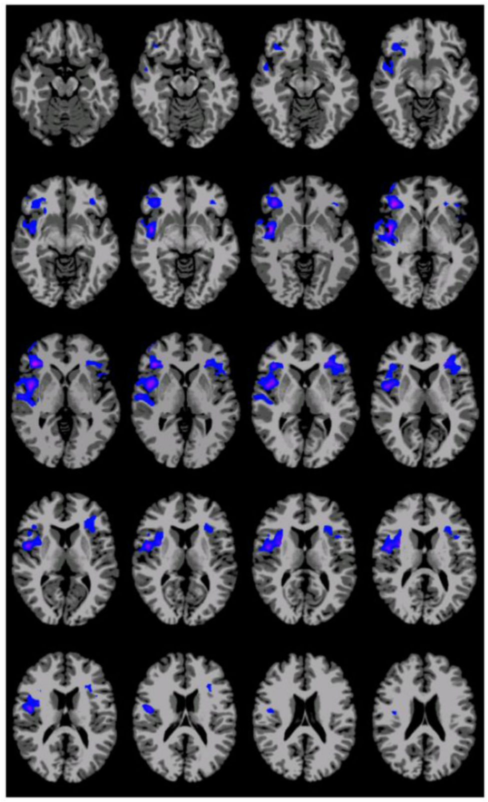

Figure 2.
Map showing group differences (preterm – term, $p<0.05$) in connectivity from the left cerebellar seed-to-whole-brain analysis. Stronger negative connectivity (anticorrelations) to both the left and right inferior frontal gyri (IFG) and right temporal cortex are observed for the preterm group compared to the term controls.

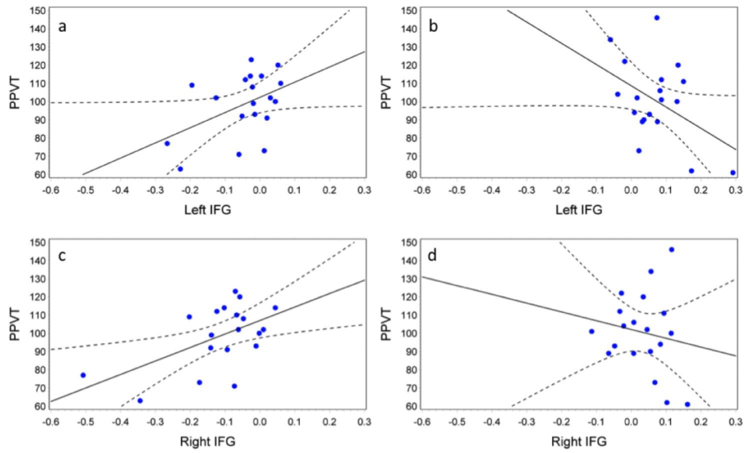

Figure 3.

Plot illustrating the relationship between PPVT score and cerebellar-to-left IFG connectivity for preterms (a) and for term controls (b), and cerebellar-to-right IFG connectivity for preterm subjects (c) and term controls (d). Both the L cerebellar to L IFG (panel a) and L cerebellar to R IFG (panel c) connections are significantly positively correlated with the PPVT scores for the preterm subjects ($r = 0.454$, $p = 0.05$ and $r = 0.555$, $p = 0.01$, respectively). In contrast, there was a trend negative correlation for the L cerebellar to L IFG connection for PPVT score (panel b: $r = -0.441$, $p = 0.06$) for the term controls. There was no correlation between the L cerebellar to R IFG connection and PPVT score for the term subject group (panel d: $r = -0.159$, $p = 0.52$). The solid lines represent the regression lines; the dashed lines are the 95% confidence limits of the mean.

Table 1

Preterm Neonatal Data

N	19
Male, N (%)	11(57.9)
Birth weight, grams, mean ± SD	974.6±163.2
Gestational age, weeks, mean ± SD	28.2±1.8
Bronchopulmonary dysplasia, N (%)	3 (15.8)
Necrotizing enterocolitis, N (%)	1 (5.3)
Retinopathy of prematurity, N (%)	5 (27.8)

Table 2

Demographic Data for the Study Subjects

	Preterm N=19	Term N=19	p value
Male, N (%)	11 (58%)	9 (47%)	0.52
Age at scan, Years ± SD	20.1±0.9	19.7±1.1	0.21
Right-handed, N (%)	16 (84%)	18 (95%)	0.30
Non-white, N (%)	3 (16%)	5 (26%)	0.43
Special services	4 (21%)	2 (11%)	0.38
Maternal education less than high school, N (%)	7 (37%)	5 (26%)	0.49

Table 3

Cognitive Data

	Preterm	Term	p value
Wechsler Intelligence Scale for Children – III (WISC)			
Full Scale IQ	91.74±12.4	100.44±18.7	0.10
Verbal IQ	91.58±11.6	97.06±17.5	0.27
Verbal comprehension index	92.26±11.3	96.78±16.7	0.34
Performance IQ	93.97±13.9	104.39±18.9	0.05
Peabody Picture Vocabulary Test - Revised (PPVT)			
PPVT	98.58±17.2	100.47±21.9	0.77
Comprehensive Test of Phonological Processing (CTOPP)			
Rapid Naming Composite Score	103.47±21.5	97.00±14.0	0.28
Phonological Awareness Composite Score	80.76±12.3	91.32±10.0	0.008