NeuroImage 64 (2013) 371–378

Contents lists available at SciVerse ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

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

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ARTICLE INFO

Article history:
Accepted 5 September 2012
Available online 12 September 2012

Keywords:
Preterm
Cerebellum
Language systems
Functional MRI
Resting state intrinsic connectivity contrast degree

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.

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

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.

☆ This work was supported by NS 27116.

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http://dx.doi.org/10.1016/j.neuroimage.2012.09.008

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)

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.

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

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 h 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).