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Functional connectivity to a right hemisphere language center in prematurely born adolescents

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ABSTRACT

Prematurely born children are at increased risk for language deficits at school age and beyond, but the neurobiological basis of these findings remains poorly understood. Thirty-one PT adolescents (600–1250 g birth weight) and 36 T controls were evaluated using an fMRI passive language task and neurodevelopmental assessments including: the Wechsler Intelligence Scale for Children-III (WISC-III), the Peabody Picture Vocabulary Test-Revised (PPVT-R), the Comprehensive Test of Phonological Processing (CTOPP) and the Test of Word Reading Efficiency (TOWRE) at 16 years of age. Neural activity was assessed for language processing and the data were evaluated for connectivity and correlations to cognitive outcomes. PT subjects scored significantly lower on all components of the WISC-III ($p<0.05$) compared to term subjects, but there was no significant difference in PPVT-R scores between the groups. Functional connectivity (fcMRI) between Wernicke's area (left BA 22) and the right supramarginal gyrus (BA 40) was increased in preterm subjects relative to term controls ($p=0.03$), and the strength of this connection was inversely related to performance on both the PPVT-R ($R^2=0.553$, $p=0.002$), and the verbal comprehension index ($R^2=0.439$, $p=0.019$). Preterm adolescents engage a dorsal right hemisphere region for language at age 16 years. Those with the greatest cognitive deficits demonstrate increasing reliance on this alternate pathway.
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Introduction

Preterm birth represents a major pediatric public health problem in the United States and Europe today(Behrman and Stith Butler, 2007). The neurocognitive sequelae of preterm birth have been well described (Allin et al., 2008; Hack et al., 2009; Hille et al., 2007; Saigal and Doyle, 2008; Verrips et al., 2008), and the development of sophisticated magnetic resonance imaging (MRI) strategies has provided significant information about the impact of preterm birth on the developing brain. Preterm subjects have widespread structural and microstructural changes when compared to term control subjects in studies ranging from the newborn period to adolescence and young adulthood (Anjari et al., 2009; Dubois et al., 2008; Gimenez et al., 2008; Nagy and Jonsson, 2009; Skranes et al., 2009). In contrast to these presumptive markers of adverse outcome, functional MRI (fMRI) strategies from several investigators demonstrate the recruitment of alternative neural systems for language in the prematurely born (Ment et al., 2006b; Narberhaus et al., 2009; Nosarti et al., 2009; Rushe et al., 2004), and several recent reports suggest that cognitive outcomes for this vulnerable population may depend not only on the gestational age at birth but also on the maternal level of education (Hack et al., 2009; Weisglas-Kuperus et al., 2009). Functional connectivity (fcMRI), which assesses the functional organization of the developing brain, has been less well studied than other imaging strategies in the preterm population. By identifying those regions that activate together either during a particular task or at resting state, fcMRI may provide important information about the differential engagement of alternative neural systems in the developing preterm brain.

Abbreviations: BA, Brodmann's area; CTOPP, Comprehensive Test of Phonological Processing; fcMRI, Functional Connectivity Magnetic Resonance Imaging; fMRI, Functional Magnetic Resonance Imaging; FSIQ, Full Scale Intelligence Quotient; GLM, General Linear Model; PIQ, Performance Intelligence Quotient; PPVT-R, Peabody Picture Vocabulary Test-Revised; PT, Preterm; ROI, Region of Interest; SPM, Statistical Parametric Mapping; T, Term; TOWRE, Test of Word Reading Efficiency; VCI, Verbal Comprehension Index; VIQ, Verbal Intelligence Quotient; WISC-III, Wechsler Intelligence Scale for Children-III.

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Numerous cohort studies have revealed inferior educational outcomes in preterm subjects. At school entry, minor developmental impairment is diagnosed in 30–40% and major disabilities are found in almost 20% of preterm children (Allen, 2008; Larroque et al., 2008; Neubauer et al., 2008; Saigal and Doyle, 2008; Voss et al., 2007). Over half require special assistance in the classroom, 20% are in special education and 15% have repeated at least one grade in school (Aylward, 2005; Bhutta et al., 2002). Furthermore, although a majority of prematurely born neonates have recently been shown to become independent adults, the intellectual deficits of preterm subjects may persist through adolescence and young adulthood (Saigal et al., 2006).

Imaging plays an important role in understanding the neurobiology underlying the cognitive deficits of preterm children. When compared to term control subjects, preterm subjects have global and regional decreases in cortical gray and deep gray matter, less myelinated white matter, smaller corpus callosal areas and significant ventriculomegaly (Allin et al., 2004; Boardman et al., 2007; Huppi et al., 1998; Inder et al., 1999, 2005; Mewes et al., 2006; Peterson et al., 2003). Diffusion tensor imaging (DTI) provides information about the microstructure of the developing brain through measures such as fractional anisotropy (FA). FA increases with increasing myelination, axonal diameter and fiber bundle packing. Widespread decreases in FA have been reported in PT children compared to term controls in studies ranging from infancy through young adulthood (Anjari et al., 2007, 2009; Skranes et al., 2007) and DTI parameters have been shown to significantly correlate with cognitive and motor outcomes for the prematurely born (Constable et al., 2008; Counsell et al., 2008; Skranes et al., 2009).

More recently, studies using fMRI have identified differences in the brain areas activated during language and executive tasks in preterm children when compared to term control subjects, and preliminary studies investigating fcMRI in preterm subjects during the newborn period and at school age suggest that, when compared to term control subjects, preterm subjects exhibit different patterns of connectivity between brain areas both at rest and during a functional task (Doria et al., 2008, 2009; Fransson et al., 2007; Gozzo et al., 2009; Smyser et al., 2009). Resting state literature suggests that functional connectivity is at least partially anatomically determined, but the role of these alternative pathways remains poorly understood.

In order to test the hypothesis that the alternative neural connections found in prematurely born subjects at adolescence may be associated with cognitive measures including language skills, the connectivity between language regions during an fMRI language task was investigated in preterm and term subjects by correlating the strength of the differential connections with language measures. Wernicke's area, in the left superior temporal gyrus (left Brodmann's area 22), was chosen as a reference region for functional connectivity analysis based on findings from a previous study showing significant differences in functional connectivity levels between eight year old preterms and terms. Functional connectivity to Wernicke's area was evaluated in other primary language regions in the left hemisphere and their right-sided homologues.

Because intraventricular hemorrhage, periventricular leukomalacia and low-pressure ventriculomegaly have been associated with adverse cognitive outcomes in the prematurely born (Ment et al., 1996), our *a priori* hypothesis was tested in preterm subjects who were free of these lesions in both neonatal cranial ultrasound studies and magnetic resonance images at age 16 years.

Methods

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

Subjects

The preterm cohort consisted of children who were enrolled in the follow-up MRI component of the Multicenter Randomized Indomethacin IVH Prevention Trial at Yale University School of Medicine and Brown University (Ment et al., 1994). Only those preterm children who lived within 200 miles of the Yale MRI Research Facility were eligible for this protocol. From a potential pool of 191 preterm subjects, 43 preterm children provided written assent, parental written consent, and participated in a scanning session. Of these 43, data from 12 were removed from analysis because of the presence of intraventricular hemorrhage, ventriculomegaly or periventricular leukomalacia (11) or excess motion artifact on MRI (1). Term control children were recruited from the local communities of the study children. They were group-matched to the PT children for age, sex, and minority status. Forty-two term children provided written assent, parental written consent and participated in a scanning session. Of these 42, data from 6 were removed from analysis because of excess motion artifact (4) or because of poor performance on the in magnet assessment designed to evaluate the subjects' understanding of the in magnet task (2). Thus, of the 85 total children who participated in the scanning session, 67 were eligible for analysis, with a total of 5 subjects removed from analysis due to excess motion artifact. There was no difference in motion artifact between the groups ($p = 0.38$). Mothers were interviewed at the time of enrollment as to their level of educational attainment.

Neurodevelopmental assessment

Blinded assessment was performed at 16 years of age in a separate session from the fMRI scan using the Wechsler Intelligence Scale for Children-III (WISC-III) (Wechsler, 1991), the Peabody Picture Vocabulary Test-Revised (PPVT-R) (Peabody, 1981), the Comprehensive Test of Phonological Processing (CTOPP) (Wagner et al., 1999) and the Test of Word Reading Efficiency (TOWRE) (Torgesen et al., 1999). The WISC-III is an intelligence test with scores assessing full scale intelligence quotient (FSIQ), performance IQ (PIQ), verbal IQ (VIQ) and the verbal comprehension index (VCI). The VCI score is derived from four subscales: vocabulary, similarities, information and comprehension. The PPVT-R is designed to assess receptive vocabulary, while the CTOPP provides measures of phonologic awareness, phonological memory, and rapid naming.

Task paradigm during fMRI scanning

We employed an event-related cue-target identity task that required a match/mismatch judgment between pictures and words that were presented acoustically and/or in printed form on each trial. Responses were made via a button press. Between 8 and 10 runs were completed per subject. This task is described in detail in Frost et al. (2009).

fMRI data analysis

Preprocessing

All data were converted from Digital Imaging and Communication in Medicine (DICOM) format to Analyze format using XMedCon (http://xmedcon.sourceforge.net/). During the conversion process, the first four images at the beginning of each of the ten functional series were discarded to enable the signal to achieve steady-state, leaving 109 measurements for analysis. Images were first slice time corrected using sinc interpolation and then motion corrected using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Runs

with linear motion in excess of 1.5 mm or rotation greater than 2° were discarded. All voxels with signal less than 5% of the maximum were set to zero, drift removal (up to 3rd order) and temporal Gaussian smoothing (standard deviation = 1) were then performed on the time-course of each voxel. Finally, the global time-course was regressed out.

Registration to a common reference space

To take individual subject data into a common reference space, three registrations were calculated within the Yale BioImage Suite software package (http://www.bioimagesuite.org) (Duncan et al., 2004). The first was a linear registration between the individual subject's raw functional data and that subject's T1 anatomical image collected at the same slice locations. The T1 anatomical image was then linearly registered to the individual's 1 mm isotropic MP-Rage anatomical image. Finally, a non-linear registration was computed between the individual's MP-Rage anatomical image and the Colin27 Brain (Holmes et al., 1998) in order to transform data into the standardized space defined by the Montreal Neurological Institute (MNI). The inverse transformation from the MNI space to the individual functional space was also computed.

Functional connectivity maps

A reference region in Wernicke's area was defined anatomically on the MNI reference brain as the posterior portion of left BA 22 with center of mass Talairach coordinates of −54,−36,10 [consistent with Gozzo et al. (2009)], 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. 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 Wernicke's area in terms of Gaussian variables, which was then spatially smoothed (6 mm diameter Gaussian).

Regions of interest analyses

Three *a priori* regions of interest (ROIs), shown in Fig. 1, were defined as those areas that showed significant differences in activation levels between 8 year old preterms and terms in a previous study (Gozzo et al., 2009). These were anatomically delineated regions defined to include the inferior portion of the left supramarginal gyrus (left BA 40), the inferior portion of the right supramarginal gyrus (right BA 40) and the homologue of Broca's area (right BA 44/45). Talairach coordinates of center of mass and volumes (mm^3) for these regions are given in Table 1. For all three regions, the inverse transformation from the MNI space to the individual functional space was also computed.

Of note, the children in the 8 year old study from which the ROIs were taken performed a different in magnet task than that employed for the 16 year old subjects.

Statistical analyses

Demographic and cognitive data were analyzed using standard chi-squared statistics for categorical data, and nonparametric Wilcoxon rank sum tests for continuous-valued data. Individual general linear models were run with connectivity data for each of the three designated ROI as the dependent variable to determine the contribution of group (PT vs. T) to regional connectivity. The independent variables included group, age at scan and gender as well as the group-by-gender interaction term.

Correlations between functional connectivity and language measures

For the region of interest that showed significant differences in connectivity to Wernicke's in PT compared to T, R BA 40, general linear models were run with language measures including standard scores for PPVT-R, VCI, the WISC-III vocabulary subscore, the CTOPP and the TOWRE as the dependent variables. The independent variables were strength of connection, age at scan, gender, group, maternal education (4 levels) and the R BA 40 connectivity-by-group interaction term. In addition to main effects, interactions between the strength of connection and gender and group were examined. Where significant strength of connection by group effects were observed, secondary analyses were run for each group separately with language measure as the dependent variable and strength of connection, age at scan, gender and maternal education as independent variables.

Scatter plots showing the relationship between cognitive variables and connectivity were made. To assess the effects of leverage in these plots, robust regressions were performed for each analysis.

Correlations between connectivity and perinatal variables

The relationship between connectivity data (described below) and neonatal variables was assessed in the preterm group using a general linear model. Perinatal variables included gender, birth weight, randomization to indomethacin vs. placebo, bronchopulmonary dysplasia (Tooley, 1979) and maternal education in four levels (<high school, high school graduate, some college, and college

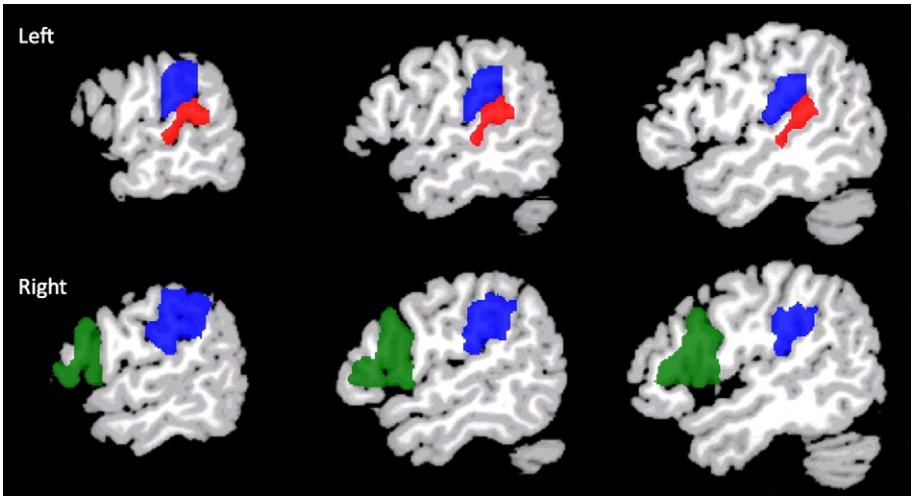

Fig. 1. Anatomic ROIs where connectivity to left Wernicke's area (red) was assessed. Left and right BA 40 are shown in blue, and the ROI in right BA 44/45 is green.

Table 1
Talairach coordinates for connectivity from Wernicke's area (−54,−36,10).

Brodmann's areas (BA)	Talairach coordinates	Volume (mm^3)
Left BA 40	40, −53,−33	8122
Right BA 40	40, 56, −30	12443
Right BA 44–45	46, 15, 14	20874

graduate). GLM also was used to investigate the contribution of maternal education to connectivity from L Wernicke's area to R BA 40 for all study subjects.

All statistical analyses were performed using SAS 9.1.3, and all *p*-values are two-sided.

Results

Subjects and neurodevelopmental assessment

Thirty-one preterm children and 36 term controls participated in this study. Perinatal data for preterm children are described in Table 2. As shown in Table 3, there were no significant differences between the preterm and term groups in the number of males, minority status, special services received or handedness. There were differences between the groups in maternal education ($p=0.03$) and participant age at the time of scan ($p=0.04$). Although preterm adolescents scored significantly lower than term controls on FSIQ, VIQ, VCI, PIQ and TOWRE, there were no significant differences in the PPVT-R, CTOPP or WISC-III vocabulary scores for the groups.

ROI analyses

As shown in Table 4, the right supramarginal gyrus, BA 40, was significantly more functionally connected to Wernicke's area in preterms than in terms ($p=0.025$). There was a trend ($p=0.058$) in the difference between groups in functional connectivity from left supramarginal gyrus to Wernicke's area. In contrast, there was no difference between groups in connectivity from Wernicke's area to the right homologue of Broca's area, BA 44–45($p=0.84$).

In addition, since 25 subjects (13 PT and 12 term controls) took part in both the 8 year old connectivity study from which the ROIs were taken, the connectivity analysis for L Wernicke's area to R BA 40 was repeated with the 42 cross-sectional non-longitudinal subjects; a trend significance was noted for greater connectivity in the PT group ($p=0.06$).

Connectivity-cognition relationships

There was a significant effect of the strength of the connection between Wernicke's area and right BA 40 on PPVT-R scores ($R^2=0.357$, $p=0.02$), a significant effect of group on PPVT-R scores ($p=0.024$) and a significant interaction between strength of connection and group ($p=0.009$). A significant effect of maternal education ($p=0.002$) also was found, indicating the important and independent effect of several factors. To explore the interaction between strength of connection and group in predicting PPVT-R scores, separate general linear model analysis was performed for each group. As shown in Table 5, the strength of the connection to right BA 40 had a significant effect on PPVT-R scores in the preterm group ($R^2=0.553$, $p<0.002$), but not in the term controls (Table 6). For the preterm group, there was an effect of maternal education ($p=0.02$) but no main effects of age at scan or gender. These results were confirmed using a robust regression analysis evaluating the impact of connectivity to the PPVT-R score ($p<0.001$ for both adjusted and unadjusted analyses).

A scatter plot showing the relationship between the strength of this connection in the preterm subjects and their PPVT-R scores is provided in Fig. 2, top panel. This figure shows that a stronger connectivity between Wernicke's area and right BA 40 in preterm subjects was associated with decreasing performance on the PPVT-R.

In addition, there was a significant group-by-region effect for the strength of the connection between Wernicke's area and right BA 40 on VCI scores ($R^2=0.391$, $p=0.01$), trend effects for both group and ROI on VCI scores ($p=0.07$ and $p=0.096$, respectively), and a main effect of maternal education ($p<0.001$). Group-specific general linear models revealed that the strength of the connection to right BA 40 had a significant effect on VCI scores in the preterm group ($R^2=0.439$, $p=0.019$, Table 5), but not in the term controls (Table 6). Neither age at scan nor gender were significant predictors in the preterm subjects, while maternal education was statistically significant ($p=0.031$). As shown in the middle panel of Fig. 2, greater connectivity between these regions was associated with decreasing VCI scores for the preterm group.

In contrast, there were no significant effects of the strength of the connection between Wernicke's area and right BA 40 on either the CTOPP or the TOWRE scores ($p\geq0.8$ for both).

Because the vocabulary subtest of the WISC-III assesses a similar language function as the PPVT-R, a *post-hoc* analysis was performed to test the hypothesis that this language measure would also correlate with connectivity between Wernicke's area and right BA 40. A significant effect of the strength of this connection on vocabulary

Table 2
Perinatal data for preterm subjects.

	N (%)
Number	31
Male	19 (61)
Gestational age (weeks)	27.7 ± 2.0
Birth weight (g)	933.1 ± 189.3
Randomized to indomethacin	17 (55)
Antenatal steroids	11 (35)
Bronchopulmonary dysplasia	9 (29)
Necrotizing enterocolitis	4 (13)

Table 3
Demographic and cognitive data for study children.

	Preterm	Term	*p* value
Number	31	36	
Male	19 (61%)	15 (42%)	0.14
Right-handed	26 (84%)	35 (97%)	0.08
Minority	13 (42%)	13 (36%)	0.89
Full scale IQ	92 ± 17	108 ± 17	0.003
Verbal IQ	95 ± 18	107 ± 16	0.02
Verbal comprehension index	96 ± 17	107 ± 16	0.02
WISC subtest: vocabulary	8.9 ± 4.0	10.6 ± 2.8	0.17
Performance IQ	90 ± 17	107 ± 18	0.001
PPVT-R	98 ± 22	107 ± 23	0.16
TOWRE: standard score	89 ± 11	97 ± 14	0.03
CTOPP: rapid naming composite	97 ± 16	101 ± 14	0.36
Special services	8 (25%)	3 (8%)	0.10
Age at scan (years)	16 ± 0.3	16 ± 0.4	0.04
Maternal education			
<High school graduate	4 (13%)	1 (3%)	0.03
High school graduate	13 (42%)	13 (36%)	
Some college	9 (29%)	7 (19%)	
College graduate	5 (16%)	15 (42%)	

Table 4
Connectivity to left Wernicke's region (least square means).

BA Regions	Preterm	Term	*p* value
Left BA 40	0.148 ± 0.01	0.126 ± 0.01	0.058
Right BA 40	0.099 ± 0.01	0.077 ± 0.01	0.025
Right BA 44–45	0.016 ± 0.01	0.018 ± 0.01	0.838

Data covaried for age at scan, gender and group-by-gender interaction.

Table 5
GLM for connectivity to R BA 40 and cognitive measures for preterm subjects.

Cognitive measures	R^2	p value
PPVT-R	0.553	0.002
VCI	0.439	0.019
WISC subtest: vocabulary	0.502	0.004

Data covaried for age at scan, gender and maternal education.

scores was detected ($R^2 = 0.425$, $p = 0.02$), along with an effect of group on vocabulary scores ($p = 0.005$), a significant interaction between strength of connection and group ($p = 0.001$), and a main effect of maternal education ($p < 0.001$). Group-specific general linear models were performed and revealed that the strength of the connection to right BA 40 had a significant effect on vocabulary scores in the preterm group ($R^2 = 0.502$, $p = 0.004$, Table 5), but not in the term controls ($R^2 = 0.23$, $p = 37$, Table 6). Neither age at scan nor gender were significant, but maternal education was important in the preterm group ($p = 0.035$) and the term group ($p = 0.009$). As shown in the bottom panel of Fig. 2, greater connectivity between these regions was associated with decreasing vocabulary scores for the preterm group ($R^2 = 0.502$, $p = 0.004$, Table 5).

Exploratory analyses of perinatal risk factors

Exploratory analyses were performed to examine those factors that have been associated with microstructural changes in the preterm brain. These included gender, age at scan, birth weight, randomization to early indomethacin, bronchopulmonary dysplasia and levels of maternal education. Regression analysis suggested that, in the presence of gender, age at scan, birth weight and randomization to indomethacin, both bronchopulmonary dysplasia and level of maternal education (model $R^2 = 0.408$, $p = 0.04$ and 0.03, respectively) contributed to connectivity between Wernicke's and right BA 40. In this analysis, increasing years of maternal education was inversely related to connectivity between these two regions.

Although perinatal data are not available for the term control group, a second GLM investigating the impact of maternal education on connectivity between Wernicke's and right BA 40 for the term controls demonstrated that, in the presence of age at scan and gender, there was a trend for maternal education ($p = 0.07$).

Discussion

Preterm birth and, by extension, the longterm neurocognitive sequelae of the prematurely born represent major public health problems in the United States today. Thus, understanding the influence of birth at an early gestational age on brain development becomes a priority for neonatologists and neuroscientists alike. The development of sophisticated neuroimaging strategies has facilitated this goal, and we report alterations in neural connectivity for language in preterm adolescents when compared to term controls.

Preterm subjects exhibited increased connectivity from Wernicke's region to a dorsal right hemisphere language region: right BA 40. The strength of this connection was inversely related to performance for the preterm adolescents on three well-standardized semantic tasks: the PPVT-R, the VCI and the WISC-III vocabulary subtest. Microstructural findings have been reported in preterm neonates with respiratory difficulties (Anjari et al., 2009), and our analyses suggest that adolescents with neonatal BPD exhibit greater connectivity from Wernicke's area to right BA 40. Further, maternal education is a major predictor of cognitive outcome in preterm subjects at young adulthood (Weisglas-Kuperus et al., 2009), and those subjects whose mothers had the lowest levels of education have the greatest connectivity between Wernicke's and R BA 40 in our analyses. This supports our finding that this pathway is used most by those with the lowest testing scores.

Adolescence is a time of significant cortical maturation, and the present studies expand and extend our previous work investigating the impact of preterm birth on the developing brain. Earlier fMRI studies from this cohort have shown that preterm children recruit right hemisphere regions in response to a passive listening task at age 12 years (Ment et al., 2006a), and our recent fcMRI analyses suggest increased connectivity to right hemisphere language regions at age 8 years (Gozzo et al., 2009). At 8 years, however, there were no significant cognitive correlates in this cohort, while at 16 years we identified a similar increased right-sided connectivity, now correlating significantly to poor cognitive task performance. Recent descriptions of language systems in typically developing adults and children suggest the engagement of a ventral pathway for semantic processing and a dorsal system for phonologic needs (Hickok and Poeppel, 2007; Saur et al., 2008). This study reports the engagement of the dorsal right hemisphere language center for semantic tasks and increased use of this putative phonologic connection for semantic processing by those subjects with the greatest semantic deficits.

Recent studies of functional connectivity in typically developing children reveal age-dependent patterns of cortical maturation. Resting state networks are present in infancy (Fransson et al., 2009), and the maturation of neural networks continues throughout adolescence and young adulthood (Fair et al., 2007, 2008). As maturation progresses, the developing brain increases the strength of connections that exist in spatially remote regions in an anterior–posterior direction to create highly cohesive functional circuits, while simultaneously reducing the strength of connections between adjacent regions and contralateral homologues (Fair et al., 2009; Stevens et al., 2009; Supekar et al., 2009). Further, although preliminary data from adolescents with dyslexia suggest that abnormalities in functional connectivity may correlate with cognitive measures, the neurocognitive correlates of maturing cortical connections are as yet unknown (Wolf et al., 2009).

The limitations of this study include the small sample size, incomplete voxel-based morphometric and diffusion tensor data for the cohort and the lack of serial functional connectivity studies over time. The subjects we report are part of a well-studied cohort with neuroimaging available from the earliest postnatal hours. Although MRI investigations were not available in the newborn period for these subjects, sequential evaluation with a variety of imaging modalities has documented their progress in terms of cognitive performance, volumetric differences, cortical activation and microstructural alterations in normal cortical development over time. Although recent data in adult subjects suggest a correlation between structure and function, we had neither complete volumetric data nor diffusion tensor imaging in this cohort of adolescents. Further, although a subset of subjects in the current report participated in our previous functional connectivity report of 8 year old preterm subjects and term controls, two factors prevent the report of a longitudinal analysis: the selection of a different language task for the 16 year old cohort, and the unavailability of study subjects secondary to both orthodontic appliances and geographic availability. The use of fMRI to evaluate functional connectivity in adolescents is an emerging technology with little known yet about those complex factors such as maternal education which contribute to the findings we report.

Table 6
Correlations for connectivity to R BA 40 and cognitive measures for term subjects.

Cognitive measures	R^2	p value
PPVT-R	0.167	0.746
VCI	0.213	0.411
WISC subtest: vocabulary	0.229	0.370

Data covaried for age at scan, gender and maternal education.

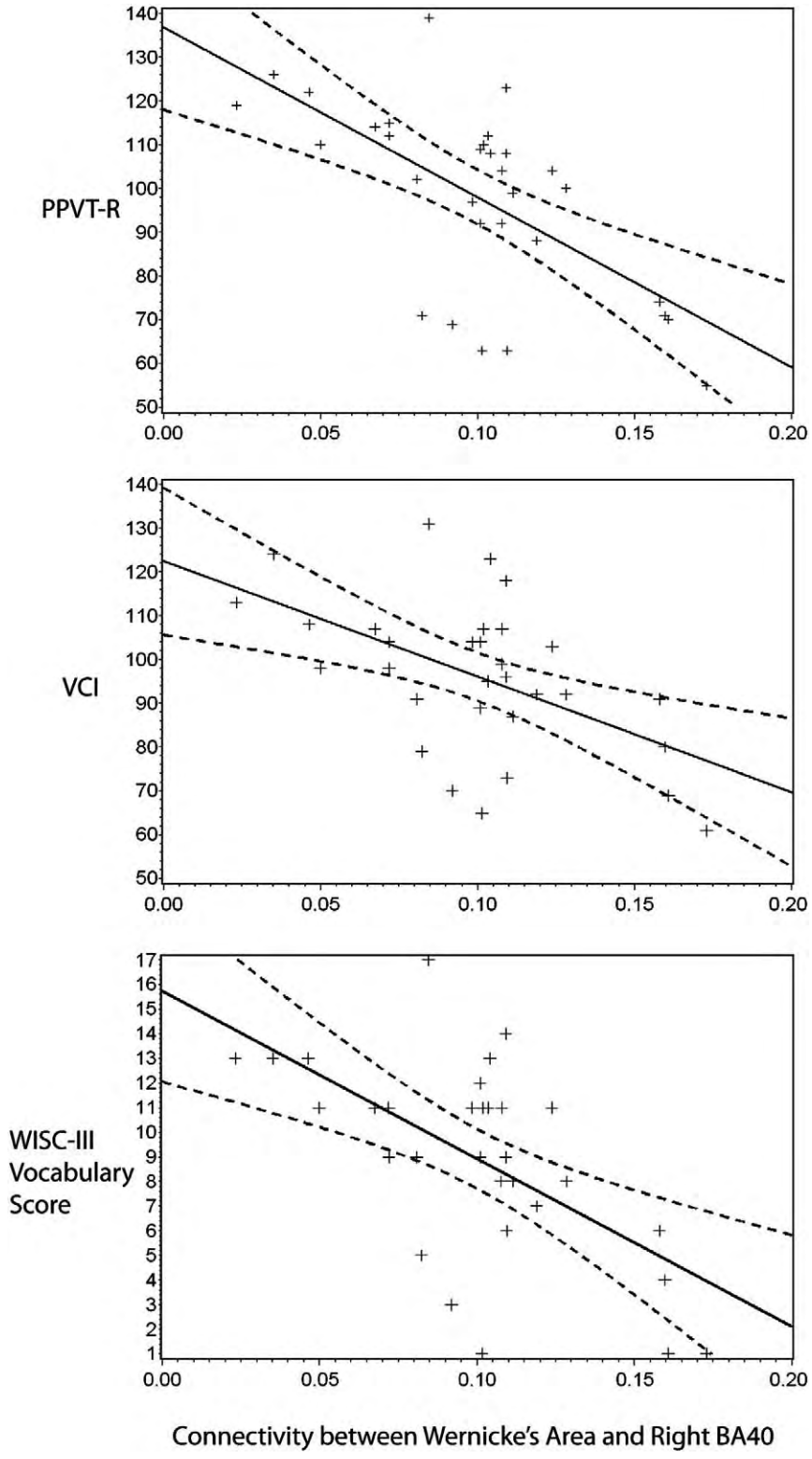

Fig. 2. Scatterplots depict connectivity-cognitive relationships in the preterm subjects. The strength of connection between Wernicke's area and the ROI in right BA 40 was inversely related to scores on the PPVT-R (top plot, $y = 137 - 388\ x$), the VCI (middle plot, $y = 122 - 264\ x$) and the vocabulary score of the WISC-III (bottom plot, $y = 16 - 68\ x$).

Preterm birth results in alterations in connectivity in the developing brain. The engagement of an auxiliary right hemisphere language region in those preterm children with the greatest cognitive need suggests that longitudinal studies must be done. The connectivity to right BA 40 may represent either a delay in cortical maturation in the prematurely born, or the recruitment of alternate circuits for language in the developing preterm brain.

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