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Cortical Recruitment Patterns in Children Born Prematurely Compared with Control Subjects During a Passive Listening Functional Magnetic Resonance Imaging Task

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Abstract

Objectives—To use functional magnetic resonance imaging (fMRI) to test the hypothesis that subjects who were born prematurely develop alternative systems for processing language.

Study design—Subjects who were born prematurely (n = 14; 600–1250 g birthweight) without neonatal brain injury and 10 matched term control subjects were examined with a fMRI passive listening task of language, the Clinical Evaluation of Language Fundamentals (CELF) and portions of the Comprehensive Test of Phonological Processing (CTOPP). The fMRI task was evaluated for both phonologic and semantic processing.

Results—Although there were differences in CELF scores between the subjects born prematurely and control subjects, there were no significant differences in the CTOPP measures in the 2 groups. fMRI studies demonstrated that the groups differentially engaged neural systems known to process language. Children born at term were significantly more likely to activate systems for the semantic processing of language, whereas subjects born prematurely preferentially engaged regions that subserve phonology.

Conclusions—At 12 years of age, children born prematurely and children born at term activate neural systems for the auditory processing of language differently. Subjects born prematurely engage different networks for phonologic processing; this strategy is associated with phonologic language scores that are similar to those of control subjects. These biologically based developmental strategies may provide the substrate for the improving language skills noted in children who are born prematurely.

Magnetic resonance imaging (MRI) permits the investigation of structural aspects of the developing brain.^{1,2} Volumetric, diffusion tensor imaging, and magnetic resonance spectroscopy studies suggest that preterm birth is associated with significant alterations in corticogenesis, and several investigators have suggested that those cortical regions that subserve language are particularly vulnerable to the injury associated with preterm birth.^{3,4} In contrast, neural processing has been less well studied in subjects born prematurely, but may offer important insights into the functional aspects of brain development after preterm birth.⁵

Functional MRI (fMRI) is used extensively to study language processing in adults and children with known developmental disorders.^{6,7} Preliminary studies of auditory tasks in children who were born prematurely suggest the presence of aberrant systems for language at school age,^{5,8} yet recent neuropsychological studies document improvement in testing scores and school performance with time in children who were born prematurely.⁹⁻¹²

We previously reported in a study of almost 300 children born weighing 600 to 1250 g that the median Peabody Picture Vocabulary Test-Revised (PPVT-R) score, a standard measure for receptive vocabulary, increased from 88 at 3 years of age to 99 at age 8 years and that these children continue to enjoy academic success at middle school age.¹¹ We therefore hypothesized that children born prematurely develop auxiliary or alternative systems for the neural processing of common language tasks. To test this hypothesis, we compared brain activity associated with phonologic and semantic processing of language in children born prematurely who had no evidence for brain injury in the newborn period by means of ultrasound scanning with matched term control subjects at 12 years of age.

Methods

Subjects

Children provided written assent and parents provided written consent for the study. All scans were performed at Yale University School of Medicine. The preterm cohort consisted of 14 children with no evidence of intraventricular hemorrhage (IVH), periventricular leukomalacia, or both, normal findings on neurological examinations at age 12 years, and no contraindications to MRI study (ie, orthodontia or ventriculoperitoneal shunts) enrolled in the follow-up component of the Multicenter Randomized Indomethacin IVH Prevention Trial.^{13,14} The subjects in the preterm cohort were recruited for the fMRI study when they reached 12 years of age. These children are representative of the cohort from which they were selected in sex, handedness, full-scale intelligence quotient (FSIQ) scores, race/ethnicity, and maternal education. Eleven children born at term, aged 12 years, were recruited from the local community and group-matched with the preterm group for age, sex, and minority status. The scan of 1 child in the control group was excluded because of motion artifact, leaving scans of 10 term children in the control group available for analysis.

The assessments of neonatal health status and neurodevelopmental outcome have been previously described.¹⁵ Blinded assessment of intelligence was performed when the children were 12 years of age by using the Wechsler Intelligence Scale for Children-III.¹⁶ Children also underwent measures of language function, including CELF 3rd edition¹⁷ and the PPVT-R,¹⁸ the Test of Word Reading Efficiency (TOWRE),¹⁹ the Gray Silent Reading Test,²⁰ and 3 subtests from the Comprehensive Test of Phonological Processing (CTOPP).²¹ The CELF and the Gray Silent Reading Test measure the ability to understand spoken and written language, whereas the Phonemic Decoding Subtest of the TOWRE, and the subscales of the CTOPP measure phonologic processing in children and young adults. Phonology encompasses the encoding and processing of phonemes, the elemental sounds of speech, and phonological processing is critical for all aspects of language behavior.

fMRI Paradigms

The behavioral task used in the fMRI experiments was selected to help identify brain regions involved in the processing of spoken language; it consisted of a passive auditory listening task in which the children listened to 3 varying stimulus presentations of a children's story, both previously described and characterized in adult subjects.⁸

Stimulus 1

An audiotape of a female actress reading *The Ugly Duckling*²² was presented in its entirety during the scanning session, although it was broken into 6 segments, each 35 seconds long.

Stimulus 2

This was the same children's story, but with all phonemes of the story randomized in time. The story was read by the same actress and with the same prosody as the original story. This version was designed to contain the same acoustic spectral frequencies, phonemes, prosody, and duration as the original story, but phonemic randomization was intended to destroy the linguistic structure enabling semantic comprehension of speech. Images acquired while the children listen to stimulus 1 compared with those acquired with stimulus 2 should therefore identify the differential brain activity needed for semantic processing of this children's story.

Stimulus 3

For this component, the randomized story was low-pass filtered as previously described. This version had the same prosody and duration as the first 2 stimuli, but no phonemic content. Comparing images acquired when the children listened to stimulus 2 with images acquired when they listened to stimulus 3 provided the differential brain activity associated with the phonologic processing of the story.

Stimulus 4

This stimulus was 35 seconds of rest to allow comparison of all the language-related tasks with a common baseline.

Stimulus Presentation

The audiotaped stimuli were delivered through MR compatible headphones. Portions of the 4 stimuli were presented sequentially in an alternating sequence. Each was presented as separate segments (35 seconds long) in each of the 3 experimental runs (each run 9 minutes 20 seconds). The segments were presented sequentially within each story throughout the scanning session, but the order of presentation of the 3 types of stimuli was pseudo-randomized within runs and counterbalanced across runs.

The children were told that they would be listening to a story through the headphones. They were instructed to listen to the story closely and to try to understand and remember what they heard. After the scanning session, they were asked 10 multiple-choice questions about the content of the story to assess their comprehension of the task.

Image Acquisition

Images were acquired on a Siemens Sonata 1.5 Tesla scanner (Siemens AG, Munich, Germany) equipped with high-speed gradients (maximum amplification, 40mT/m; slew rate, 200 mT/m/sec). Head positioning in the magnet was standardized with the canthomeatal line. For each subject, an anatomic image for localization of functional acquisition was obtained by using these parameters: 2D FSE with 3-mm slices acquired in the sagittal plane, TR = 7200, TE = 17/75, nex = 1, FOV = 20, and a 256-by-160 matrix (scan time, 5:17 minutes).

In all subjects, 18 axial-oblique slices, 7 mm thick with a 0-mm gap, were acquired oriented parallel to the anterior commissure-posterior commissure line (AC-PC) line and adjusted superiorly/inferiorly to provide whole brain coverage. Functional images were obtained with a gradient echo, echo-planar imaging pulse sequence. For all tasks, TR = 2000 msec, TE = 60, 80-degree flip angle, single excitation per image, 22-by-22 cm field of view, a 64-by-64 matrix,

and 3.4-by-3.4mm in-plane resolution; a total of 300 echo planar images were acquired for each slice per run.

Data Analysis

Data were motion-corrected with SPM-99,²³ smoothed with a Gaussian filter with FWHM = 6.25mm,²⁴ and aligned to reference T1 anatomic scans collected in the same planes as the functional scans. These anatomic scans were then registered to the individual subject's 3-dimensional (3D) scan, which in turn was registered to a 3D reference volume on which the results were displayed. The transformation matrices for all these steps were applied directly to the fMRI results to build composite maps in the reference 3D space, by using a mutual information algorithm.²⁵

Statistical Methods

Demographic, neurologic, and cognitive data were analyzed by using standard chi-square analyses for categorical data, and non-parametric Wilcoxon rank sum tests for continuous-valued data. Pearson correlations were used to compare behavioral and fMRI data.

fMRI data were analyzed in 3 stages. In stage I, for each subject, functional images (Beta maps) were computed for all 3 tasks (implicitly defining the stimulus 4 rest condition) by using general linear modeling (GLM). These Beta maps were used in stage II for group region of interest (ROI) analysis in the common brain reference space. Contrast maps comparing the preterm group minus the term group were thresholded at $P < .01$ corrected (cluster 200).²⁶ For the semantic (story minus scrambled condition) and the phonologic (scrambled minus low-pass), contrasts were used to generate ROIs in the common brain reference space.

In stage II of analysis, the Beta weights from these ROIs computed in the first stage were used as the measurement data (Y) on which an analysis of covariance model was run. The tasks were treated as a fixed effect in this model, and group effects (premature, full-term) were treated as the covariate with interaction terms to examine whether there was a differential effect of group across these tasks. The test for no interaction examines the null hypothesis that the effect of these tasks is similar in both the full-term subjects and premature subjects. The hypothesis test is performed by examining the F-statistics with the full model, including the interaction terms and the reduced model without the interaction term. Significant interaction effects in this analysis indicate there is an effect of group that then allows for direct contrast to be made to investigate the factors contributing to the effects observed.

In stage III, to accommodate for the effect of cognitive impairment and possible influences of age at scan, percent BOLD signal change adjusted for verbal IQ and age at scan were calculated for these ROIs, to determine those regions that remained significant.

The Talairach coordinate system was defined on the reference 3D brain²⁷ so that results could be reported by using both the Brodmann classification scheme²⁸ and the Talairach coordinate system.

All maps are shown at $P < .005$ corrected,²⁶ and the data from the semantic subtraction (ie, images acquired while the children listen to stimulus 1 [story] compared with those acquired with stimulus 2 [scrambled]) are shown in Figure 1. Data from the phonologic subtraction (ie, images acquired as the children listened to stimulus 2 [scrambled] with images acquired as they listened to stimulus 3 [low-pass filtered]).

All P values in this report are of the 2-sided type.

Results

Subject Population

There were no significant differences in the number of male subjects, non-white or Hispanic children, or years of maternal education. None of the mothers had less than a high school education. (Table I; available at www.jpeds.com)

Demographic and cognitive data for the subjects demonstrate no significant differences in growth parameters or number of right-handed subjects in the study groups. (Table II; available at www.jpeds.com) All analyses were initially performed on right-handed subjects only; because there were no significant differences in any of our analyses on the basis of handedness, analyses presented include all study children. Verbal IQ, performance IQ, full scale IQ, and PPVT-R scores were all significantly lower for the preterm subjects when compared with term control subjects ($P = .040$, $.017$, $.025$, and $.047$, respectively). One child in the preterm group and no control subjects had a verbal IQ score <70 .

There were significant differences between preterm subjects and control subjects on all measures that tap into the understanding of language and sight word recognition, including the 3 CELF scores ($P = .049$, $.016$, and $.021$), the Gray Silent Reading Score ($P = .015$), and the sight word efficiency subtest of the TOWRE ($P = .041$; Table III) In contrast, there were no significant differences between the preterm subjects and control subjects on the 3 subtests of the CTOPP ($P = .195$, $.943$, and $.158$).

A short post-fMRI session questionnaire to determine comprehension of the children's story revealed no significance difference in the test scores between groups.

fMRI Results

The main effect contrast maps for semantic processing for the preterm and term subjects are shown in Figure 1, A and B, respectively, and demonstrate significantly different BOLD signal changes for the 2 study groups.

Percent BOLD signal change adjusted for verbal IQ and age at scan were calculated for these ROIs, and those regions that remained significant are shown in Figure 1, C. Both preterm and term subjects deactivated the left inferior parietal lobule (IPL, Brodmann's area [BA] 40) and right inferior frontal gyrus (IFG, BA 46) during semantic processing, but in both cases the deactivation was significantly greater in the term subjects compared with that in the preterm group ($P = .0035$ and $.011$, respectively). Similarly, although both groups activated the left middle temporal gyrus (MTG, BA 21), left angular gyrus (AG, BA 39), and posterior cingulate gyrus (pCingG) during semantic processing, the BOLD signal changes were significantly greater for the term control subjects ($P = .0042$, $.0043$, and $.003$, respectively). Talairach coordinates for these regions of interest are shown in Table IV (available at www.jpeds.com).

BOLD maps for phonologic processing for the preterm and term study groups are shown in Figure 2, A and B, respectively. In contrast to maps for semantic processing, the preterm subjects exhibited strongly positive BOLD signals in the left MTG/STG (BA 21/BA 22), the right anterior middle temporal gyrus (aMTG, BA 38), and the left parahippocampal gyrus (paHG; $P < .005$ for all), whereas the term control subjects demonstrated widespread frontal and occipital deactivation during phonologic processing in this passive listening task, as shown in Figure 2, B.

The percent BOLD signal changes for phonologic processing adjusted for verbal IQ and age at scan are shown in Figure 2, C. These data demonstrate significant positive activation in the left MTG/STG (BA 21/22), left paHG, pCingG, and right aMTG (BA38) for the preterm group,

whereas in these 4 regions a negative BOLD signal is found for the term control subjects ($P = .0008, .0009, .0032$, and $.0001$, respectively). In both the left and right occipital gyrus (OG), the term subjects demonstrated significant deactivation, whereas the preterm subjects exhibit mixed deactivation/activation BOLD signals ($P = .0025$ and $.0043$, respectively). Finally, although both the preterm and term subjects deactivated the anterior cingulate gyrus during phonologic processing, the adjusted negative BOLD signal was far greater in the term group ($P = .0002$).

Correlation of fMRI Signals and Cognitive Measures

Because previous research has demonstrated correlations between BOLD signal and IQ in similarly aged children,²⁹ we tested the hypothesis that changes in BOLD signal would correlate with language measures and performed correlation analyses between the Non-Word Repetition test of the CTOPP, an auditory phonologic measure, and our auditory fMRI phonologic processing BOLD signal changes for the study children. Although we found significant correlations between BOLD signal changes in language regions for the term study subjects (Table V; available at www.jpeds.com), these correlations were not significant for the preterm group.

Subgroup Analyses

To test the hypothesis that the preterm children with the lowest verbal IQ scores may have significantly altered the results for the preterm children as a whole, we eliminated those 4 preterm subjects with verbal IQ scores <85 and repeated our analyses. These data demonstrated no significant difference in verbal IQ and full scale IQ scores between the preterm and term control study subjects ($P = .211$ and $.104$, respectively). In contrast, when we compared the BOLD signal changes for the ROIs aforementioned, we found no significant differences between the analyses comparing the 10 preterm subjects with 10 term control subjects and those comparing the original 14 preterm subjects with 10 control children. Specifically, there were no significant changes in those analyses in which the ROIs were covaried by verbal IQ and age at scan for either semantic or phonologic subtractions.

When examining the relatively “IQ-matched” preterm and term subject analysis, both preterm subjects and term subjects deactivated the left IPL and right IFG during semantic processing. Similar to the larger group, however, in both cases the deactivation was significantly greater in the term subjects compared with the preterm group ($P = .0038$ and $.013$, respectively). Furthermore, although both study groups activated the left MTG, left AG, and posterior cingulate gyrus during semantic processing, the BOLD signal changes were significantly greater for the term control subjects ($P = .0049, .013$, and $.006$, respectively).

Similarly, the percent BOLD signal changes for phonologic processing adjusted for verbal IQ and age at scan demonstrate significant positive activation in the left MTG/STG (BA 21/22), left paHG, and right aMTG (BA38) for the preterm group, whereas in these 4 regions a negative BOLD signal is found for the term control subjects ($P = .0007, .0021$, and $.0002$, respectively). In both the left and right OG and the pCingG, the term subjects demonstrated significant deactivation, whereas the preterm subjects exhibited mixed deactivation/activation BOLD signals ($P = .0070, .0111$, and $.0036$, respectively). Finally, although both the preterm and term subjects deactivated the anterior cingulate gyrus during phonologic processing, the adjusted negative BOLD signal is far greater in the term group ($P = .0003$).

Discussion

While using fMRI strategies for the processing of a passive listening task, we demonstrated that children born prematurely and matched term control subjects engage neural systems

subserving language very differently at age 12 years. During comprehension of the coherent spoken story, preterm and term control subjects engaged similar cortical regions, but the BOLD signals for the preterm group were significantly less than those for the term controls for semantically tuned areas recruited during performance of this task. In contrast, preterm subjects recruited a different array of neural systems than term control subjects during phonologic processing in the randomized phonemic version of this passive listening task. Neurocognitive and language testing of the study subjects detected no significant differences in phonologic processing skills in the 2 groups of children at school age, although a marginally poorer performance was suggested by some tests. These fMRI data, however, do suggest the engagement of a broader network of neural systems for auditory phonologic processing of language in the preterm group.

Examination of BOLD signal changes associated with semantic processing demonstrated activation of classic language areas in both the term control and preterm subjects—the left MTG, the left AG, the posterior cingulate gyrus, and the right IFG.³⁰ However, the typical language areas that were activated in both groups were found to have significantly lesser magnitudes of activation in the preterm group.

The left MTG has been frequently associated with the storage of higher-level semantic representations,^{31,32} and children with higher accuracy on neurocognitive tasks of semantic function have been shown to have greater activation of the left MTG than those “poorer performers” with low semantic testing scores.³³ That is the pattern seen in the current experiment also. In addition, the left AG and posterior cingulate gyrus are believed responsible for understanding concrete words compared with more abstract ones with weak semantic associations, and several investigators have postulated that the right IFG is recruited to conduct a broad semantic search for novel words.^{32,34,35} Activation during a variety of semantic processing tasks has been shown to increase with both age and skill in not only the left MTG, but also the left AG and the right IFG.^{32,33,36}

Negative BOLD signal changes were detected in the LIPL and LIFG in this fMRI subtraction for semantic processing. By using a reading task, Frost has shown that high-imageable words reduce activation in the IFG but increase BOLD signal in both the MTG and AG.³⁷ Furthermore, decreases in BOLD signal in the left IPL suggest a shift in baseline neural activity from this region traditionally responsible for phonologic processing to those critical to semantic processing in the developing brain.³⁸

Successful phonological processing is critical to the effective processing of spoken and written language. Examination of activity associated with phonological processing demonstrated significantly differential patterns of activation in the preterm group when compared with the term control group. Although the term control subjects exhibited large areas of deactivation throughout both hemispheres, the preterm subjects significantly activated those regions known to subserve both phonologic and semantic aspects of processing of language, the left STG and MTG, respectively.^{38,39}

Numerous neuroimaging studies that use rhyming tasks to identify regions subserving phonological processing in children have revealed activation of both the LSTG and LMTG, although the LMTG, as aforementioned, has been implicated in semantic processing also.^{37,38,40-43} Similarly, in a phonologic task of words and non-words, the posterior cingulate gyrus was activated by words more significantly than by non-words.⁴⁴ In contrast, both the aMTG and the left parahippocampal gyrus, also engaged by the preterm subjects during the phonologic task, have traditionally been thought to be responsible for semantic processing of language.⁴⁵ Taken as a whole, these data may suggest an interpretation of phonologic deficit in the preterm group that is commonly seen in children with language disorders.⁶ Indeed, behavioral

research with language-impaired populations indicates that children with relatively poor phonological processing will tend to rely on lexical-semantic information to compensate for these deficits.⁷ The engagement of putatively semantic regions (MTG, AG) in preterm children on the phonologic task may reflect this tendency.

Studies exploring the functional organization of language in children born prematurely are limited. Rushe examined phonologic processing in 6 male subjects with a very low birth weight who had thinning of the corpus callosum and compared them to term control subjects.⁵ Despite no difference in task performance scores for the 2 groups, increased activation in the frontal region and decreased occipital activation was noted in the preterm subjects, which suggests the development of compensatory systems in the preterm brain. Similarly, in our previous study using the current task with subjects born prematurely and matched term control subjects at age 8 years, the BOLD patterns of activation for the semantic condition for the preterm group mimicked those found for phonologic processing in the term control subjects.⁸

The limitations of this study include the small sample size, the paucity of information available concerning fMRI signal changes in subjects born prematurely, and the limited number of tests administered that assess phonological processing. The BOLD signal for fMRI is in part dependent on cerebral blood flow, and preterm infants have been shown to experience alterations in cerebral blood flow and autoregulation in the newborn period.⁴⁶ Although there has been no correlation reported between resting cerebral blood flow and later neurologic outcome,⁴⁷ BOLD signal changes in subjects born prematurely remain largely unexplored.

It is well known that different brain regions mature at different rates,^{48,49} and recent fMRI studies suggest that the developing brain undergoes significant changes in functional organization with increasing age and skill.^{32,33,36} The neurobehavioral sequelae of preterm birth represent 1 of the major pediatric public health problems of our time,^{10,50} however the functional effect of injury and recovery in the developing brain remains largely unexplored. Our data suggest that, at age 12 years, children born prematurely who had no evidence of brain injury in the newborn period engage alternative neural systems to process auditory language compared with those found in term control subjects. Future research will determine whether these alternative neural systems provide the substrate for the improving language skills of children born prematurely or reflect phonological processing deficits.

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References

1. Inder TE, Wells SJ, Mogridge NB, Spencer C, Volpe JJ. Defining the nature of the cerebral abnormalities in the premature infant: a qualitative magnetic resonance imaging study. *J Pediatr* 2003;143:171–9. [PubMed: 12970628]
2. Maalouf EF, Duggan PJ, Counsell SJ, Rutherford MA, Cowan FM, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm neonates. *Pediatrics* 2001;107:719–27. [PubMed: 11335750]
3. Isaacs E, Lucas A, Chong WK, Wood SJ, Johnson CL, Marshall C, et al. Hippocampal volume and everyday memory in children of very low birth weight. *Pediatr Res* 2000;47:713–20. [PubMed: 10832727]
4. Nosarti C, A-A MHS, Frangou S, Stewart A, Rifkin L, Murray RM. Adolescents who were born very preterm have decreased brain volumes. *Brain* 2002;125:1616–23. [PubMed: 12077010]

5. Rushe TM, Rifkin L, Stewart AL, Townsend JP, Roth SC, Wyatt JS, et al. Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. *Devel Med Child Neurol* 2001;43:226–33. [PubMed: 11305398]
6. Shaywitz SE, Shaywitz BA, Fulbright RK, Skudlarski P, Mencl E, Constable RT, et al. Neural systems for compensation and persistence: young adult outcome of childhood reading disability. *Biol Psychiatry* 2003;54:25–33. [PubMed: 12842305]
7. Shaywitz BA, Shaywitz SE, Pugh KR, Mencl E, Fulbright RK, Skudlarski P, et al. Disruption of posterior brain systems for reading in children with developmental dyslexia. *Biol Psychiatry* 2002;52:101–10. [PubMed: 12114001]
8. Peterson BS, Vohr BR, Kane M, Whalen DH, Schneider KC, Katz KH, et al. A functional MRI study of language processing and cognitive outcome in prematurely born children. *Pediatrics* 2002;110:1153–62. [PubMed: 12456913]
9. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics* 2005;116:333–41. [PubMed: 16061586]
10. Hack MB, Flannery DJ, Schluchter M, Cartar L, Borawski E, Klein N. Outcomes in young adulthood for very-low-birth-weight infants. *N Engl J Med* 2002;346:149–57. [PubMed: 11796848]
11. Ment LR, Vohr BR, Allan WA, Katz KH, Schneider C, Westerveld M, et al. Change in cognitive function over time in very low-birth-weight infants. *JAMA* 2003;289:705–11. [PubMed: 12585948]
12. Saigal S, Stoskopf B, Streiner DL, Boyle M, Pinelli J, Paneth N, et al. Transition of extremely low-birth-weight infants from adolescence to young adulthood. *JAMA* 2006;295:667–75. [PubMed: 16467235]
13. Ment LR, Oh W, Ehrenkranz RA, Philip AGS. Low dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics* 1994;93:543–50. [PubMed: 8134206]
14. Ment LR, Oh W, Ehrenkranz RA. Low dose indomethacin and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr* 1994;124:951–5. [PubMed: 8201485]
15. Vohr BR, Allan WA, Westerveld M, Schneider C, Katz KH, Makuch RW, et al. School age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. *Pediatrics* 2003;111:e340–6. [PubMed: 12671149]
16. Wechsler, D. Wechsler Intelligence Scale for Children. 3rd. New York: The Psychological Corporation Harcourt Brace Co; 1991.
17. Semel, E.; Wiig, EH.; Secord, WA. Clinical Evaluation of Language Fundamentals. 3rd. New York: The Psychological Corporation Harcourt Brace & Company; 1995.
18. Peabody. Peabody Picture Vocabulary Test-Revised. Circle Pines, NM: American Guidance Service; 1981.
19. Torgesen, JK.; Wagner, RK.; Rashotte, CA. TOWRE: Test of Word Reading Efficiency. Austin, Texas: PRO-ED; 1999.
20. Wiederholt, JL.; Blalock, G. Gray Silent Reading Tests. Austin, Texas: PRO-ED; 2000.
21. Wagner, RK.; Torgesen, JK.; Rashotte, CA. The Comprehensive Test of Phonological Processing. Austin, Texas: PRO-ED; 1999.
22. Jerrard, J. The ugly duckling: fairy tale treasury. Lincolnwood, IL: Lincolnwood Publications International; 1993.
23. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magn Reson Med* 1996;35:346–55. [PubMed: 8699946]
24. Souten A, Papademetris X, Constable RT. Spatial resolution, signal-to-noise ratio, and smoothing in multi-subject functional MRI studies. *Neuroimage* 2006;30:787–93. [PubMed: 16343951]
25. Studholme C, Constable RT, Duncan JS. Accurate alignment of functional EPI data to anatomical MRI physics based distortion model. *IEEE Trans Med Imag* 2001;19:1115–27.
26. Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintum MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. *Magn Reson Med* 1995;33:636–47. [PubMed: 7596267]

27. Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain. New York: Thieme Medical Publishers; 1988.
28. Damasio, H. Human brain in computerized images. 2nd. New York: Oxford University Press; 2005.
29. Schmithorst VJ, Holland SK. Functional MRI evidence for disparate developmental processes underlying intelligence in boys and girls. *Neuroimage*. 2006e-publication
30. Price CJ. The anatomy of language: contributions from functional neuroimaging. *J Anat (Lond)* 2000;197:335–59. [PubMed: 11117622]
31. Booth JR, Burman DD, Meyer JR, Gitelman DR, Parrish TB, Mesulam MM. Modality independence of word comprehension. *Hum Brain Mapping* 2002;16:251–61.
32. Chou TL, Booth JR, Burman DD, Bitan T, Bigio JD, Lu D, et al. Developmental changes in the neural correlates of semantic processing. *Neuroimage*. 2005e-publication ahead of print
33. Blumenfeld HK, Booth JR, Burman DD. Differential prefrontal-temporal neural correlates of semantic processing in children. *Brain Lang*. 2005e-publication
34. Binder JR, Westbury CF, McKiernan KA, Possing ET, Medler DA. Distinct brain systems for processing concrete and abstract concepts. *J Cogn Neurosci* 2005;17:905–17. [PubMed: 16021798]
35. Sabsevitz DS, Medler DA, Seidenberg M, Binder JR. Modulation of the semantic system by word imageability. *Neuroimage* 2005;27:188–200. [PubMed: 15893940]
36. Brown TB, Lugar HM, Coalson RS, Miezin FM, Petersen SE, Schlaggar BL. Developmental changes in human cerebral functional organization for word generation. *Cerebral Cortex* 2005;15:275–90. [PubMed: 15297366]
37. Frost SJ, Mencl WE, Sandak R, Moore DL, Rueckl JG, Katz L, et al. Functional magnetic resonance imaging study of the tradeoff between semantics and phonology in reading aloud. *NeuroReport* 2005;16:621–4. [PubMed: 15812320]
38. Burton MW, LoCasto PC, Krebs-Noble D, Gullapalli RP. A systematic investigation of the functional neuroanatomy of auditory and visual phonological processing. *Neuroimage* 2005;26:647–61. [PubMed: 15955475]
39. Gitelman DR, Nobre AC, Sonty S, Parrish TB, Mesulam MM. Language network specializations: an analysis with parallel task designs and functional magnetic resonance imaging. *Neuroimage* 2005;26:975–85. [PubMed: 15893473]
40. Chee MW, O'Craven KM, Bergida R, Rosen BR, Savoy RL. Auditory and visual word processing studied with fMRI. *Hum Brain Mapping* 1999;7:15–28.
41. Shaywitz BA, Shaywitz SE, Pugh KR, Fulbright RK, Skudlarski P, Mencl WE, et al. The functional neural architecture of components of attention in language-processing tasks. *Neuroimage* 2001;13:601–12. [PubMed: 11305889]
42. Simos PG, Papanicolaou AC, Breier JI, Wheless JW, Constantinou JE, Gormley WB, et al. Localization of language-specific cortex by using magnetic source imaging and electrical stimulation mapping. *J Neurosurg* 1999;91:787–96. [PubMed: 10541236]
43. Simos PG, Breier JI, Fletcher JM, Foorman BV, Castillo EM, Papanicolaou AC. Brain mechanisms for reading words and pseudowords: an integrated approach. *Cereb Cortex* 2002;12:297–305. [PubMed: 11839603]
44. Binder JR, Medlar DA, Desai R, Conant LL, Liebenthal E. Some neuropsychological constraints on models of word naming. *Neuroimage* 2005;27:677–93. [PubMed: 15921937]
45. Hoenig K, Scheef L. Mediotemporal contributions to semantic processing: fMRI evidence from ambiguity processing during semantic context verification. *Hippocampus* 2005;15:597–609. [PubMed: 15884095]
46. Kluckow M. Low systemic blood flow and pathophysiology of the preterm transitional circulation. *Early Hum Dev* 2005;81:429–37. [PubMed: 15935920]
47. Baenziger O, Mueller AM, Morales CG, Jaggi JL, Duc G, von Siebenthal K, et al. Cerebral blood flow and neurological outcome in the preterm infant. *Eur J Pediatr* 1999;158:138–43. [PubMed: 10048611]
48. Dobbing J, Sands J. Quantitative growth and development of human brain. *Arch Dis Child* 1973;48:757–67. [PubMed: 4796010]

49. Huttenlocher P, Dabholkar A. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol* 1997;387:167–78. [PubMed: 9336221]
50. Saigal S, Pinelli J, Hoult L, Kim MM, Boyle M. Psychopathology and social competencies of adolescents who were extremely low birth weight. *Pediatrics* 2003;111:969–75. [PubMed: 12728073]

Glossary

AG	Angular gyrus
aMTG	Anterior middle temporal gyrus
CELF	Clinical Evaluation of Language Fundamentals
CTOPP	Comprehensive Test of Phonological Processing
fMRI	Functional magnetic resonance imaging
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
IVH	Intraventricular hemorrhage
MTG	Middle temporal gyrus
OG	Occipital gyrus
paHG	Parahippocampal gyrus
PPVT-R	Peabody Picture Vocabulary Test-Revised
PVL	Periventricular leukomalacia
ROI	Region of interest
STG	Superior temporal gyrus
3D	Three-dimensional
TOWRE	Test of Word Reading Efficiency

Figure 1. Beta maps ($P < .005$ corrected) illustrate the main effect of semantic processing for the preterm (A) and term (B) groups. During the semantic processing condition, preterm subjects have decreased BOLD signal in the regions of the left MTG (BA 21) and STG (BA 22; $P < .005$ for all]. In contrast, although semantic processing by the term control subjects results in a pattern of widespread deactivation in the IFG (BA 46) bilaterally, the left IPL (BA 40) and the pCingG, a positive BOLD signal is found in both the left MTG (BA 21) and the left AG (BA 39; $P < .005$ for all). C, Percent signal change in specific ROIs in this condition for the 2 groups when the data are covaried by verbal IQ and age at scan.

Figure 2. Beta maps ($P < .005$ corrected) illustrate the main effect of phonologic processing for the preterm (A) and term (B) groups. The preterm subjects exhibit strongly positive BOLD signals in the left MTG/STG (BA 21/BA 22), the right aMTG (BA 38), and the left paHG ($P < .005$ for all), whereas the term control subjects demonstrate widespread frontal and occipital deactivation during phonologic processing in this passive listening task ($P < .005$ for all regions shown, including the anterior cingulate gyrus, left occipital gyrus (OG, BA 19), right OG, posterior cingulate, and right aMTG). C, Percent signal change in specific ROIs in this condition for the 2 groups covaried by verbal IQ and age at scan.

Table I

Neonatal data for the study subjects

	Preterm	Term	<i>P</i> value
Number	14	10	
Number of males	7 (50%)	6 (60%)	.63
Birth weight (g)	919.9 ± 154.9	3367.3 ± 385.3	<.0001
Gestational age (weeks)	27.9 ± 1.5	39.6 ± 1.1	<.0001
Non-white	4 (29%)	4 (40%)	.57
Hispanic	2 (14%)	3 (30%)	.36
Maternal education (years)	13.1 ± 1.5	15.0 ± 3.3	.25

Table II

Demographic and cognitive data

	Preterm (n = 14)	Term (n = 10)	P value
Age at scan (years)	12.3 ± 0.5	12.3 ± 0.7	.92
Height (cm)	148.8 ± 7.3	152.4 ± 13.2	.55
Weight (kg)	44.3 ± 9.8	57.6 ± 28.2	.22
Number right-handed	12 (86%)	8 (80%)	.72
WISC-III			
Verbal IQ	95.6 ± 20.5	114.6 ± 19.2	.040
Performance IQ	86.6 ± 20.4	111.4 ± 19.9	.012
Full-scale IQ	90.1 ± 20.3	114.0 ± 20.4	.017

Table III

Measures of language processing

	Preterm (n = 14)	Term (n = 10)	P value
CELF			
Receptive language	92.3 ± 18.5	111.3 ± 17.0	.049
Expressive language	88.7 ± 20.6	111.2 ± 12.6	.016
Total score	89.4 ± 19.9	111.3 ± 13.4	.021
Gray Silent Reading			
Silent reading quotient	87.3 ± 18.5	113.8 ± 18	.015
TOWRE			
Sight word efficiency	96.0 ± 4.5	108.0 ± 12.8	.041
Phonemic decoding	96.8 ± 10.7	106.9 ± 16.5	.084
CTOPP			
Rapid digit naming *	9.2 ± 1.6	10.2 ± 2.9	.195
Nonword repetition *	10.0 ± 1.6	10.3 ± 2.7	.943
Rapid letter naming *	9.3 ± 2.5	10.8 ± 3.5	.158
Rapid name comp.	95.3 ± 11.8	103.0 ± 18.6	.142
P PVT-R			
P PVT-R	93.6 ± 20.4	112.9 ± 19.3	.038

* Subtest standard score with a mean of 10 and SD of 3.

Table IV
Talairach coordinates for the regions of interest

Brain region	Brodmann's region	Talairach coordinates (x,y,z)
<i>Semantics</i>		
Left IPL	BA 40	44,-38,41
Left MTG	BA 21	-52,-19,-13
Left AG	BA 39	-22,-65,39
pCingG		-12,-55,19
Right IFG	BA 46	42,35,11
<i>Phonology</i>		
aCingG	BA 32	-9,43,3
Left OG	BA 19	-41,-78,20
Left STG/MTG	BA 21/22	83,-19,6 and 37, 14,-28
Left paHG		-31,-34,-11
pCingG		-15,-61,11
Right OG	BA 19	37,-71,24
RaMTG	BA 38	-55,-27,10 and -55, -53,13

Table V
Correlation of the Non-Word Repetition Score with BOLD signal changes for phonologic processing

	Preterm		Term	
	R value	P value	R value	P Value
Cingulate	−0.10506	.758	−0.23128	.520
RaMTG	0.03702	.914	−0.61573	.058
LMTG/STG	−0.34847	.294	−0.67932	.031
ROG	−0.18057	.595	−0.56189	.091
LOG	−0.30751	.358	−0.39431	.260
PCingG	−0.08846	.796	−0.21444	.552
LpaHG	0.13000	.703	−0.36537	.299