CORTICAL RECRUITMENT PATTERNS IN CHILDREN BORN PREMATURELY COMPARED WITH CONTROL SUBJECTS DURING A PASSIVE LISTENING FUNCTIONAL MAGNETIC RESONANCE IMAGING TASK

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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. *(J Pediatr 2006;149:490-8)*

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

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

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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 edition[17] 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