

# The Impact of Early Childhood Lead Exposure on Brain Organization: A Functional Magnetic Resonance Imaging Study of Language Function

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## ABSTRACT

**OBJECTIVES.** The purpose of this work was to assess the long-term impact of childhood lead exposure on the neurosubstrate of language function and brain organization.

**METHODS.** Young adults from the Cincinnati Lead Study were recruited to undergo functional magnetic resonance image scanning while performing a verb generation task. These subjects have been followed from birth through early childhood with extensive documentation of lead exposure, neuropsychology, and behavior. Forty-two subjects provided useful imaging data. The locale, strength, and the correlation between brain language activation and childhood blood lead concentration were studied.

**RESULTS.** After adjusting for potential confounders, the activation in left frontal cortex, adjacent to Broca's area, and left middle temporal gyrus, including Wernicke's area, were found to be significantly associated with diminished activation in subjects with higher mean childhood blood lead levels, whereas the compensatory activation in the right hemisphere homolog of Wernicke's area was enhanced in subjects with higher blood lead levels.

**CONCLUSION.** This study indicates that childhood lead exposure has a significant and persistent impact on brain reorganization associated with language function.

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### Key Words

environmental pollutants, lead poisoning, neuroimaging, language development, pediatric research

### Abbreviations

fMRI—functional magnetic resonance imaging  
CLS—Cincinnati Lead Study  
EPI—echo planar imaging  
BOLD—blood oxygen level-dependent  
SES—socioeconomic status  
IQ—intelligence quotient  
ROI—region of interest

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CHILDHOOD LEAD EXPOSURE is inversely associated with intellectual abilities, academic achievement, and psychomotor development.<sup>1-4</sup> Even low-level lead exposure can negatively impact a wide range of cognitive functions, such as attention, language, memory, cognitive flexibility, and visual-motor integration based on various types of neuropsychological and neurobehavioral testing.<sup>5-8</sup> However, because of the nature of the research methodology, previous studies were unable to directly localize functional changes in the brain. The underlying mechanism by which lead disrupts brain function in children, especially for low lead concentrations that do not produce noticeable physical signs, remains poorly understood.

Language, a unique human neurocognitive function, is often the earliest marker for the presence of a developmental or acquired neurologic disorder. The association between lead exposure and language function disorder has been studied extensively in cognitive research.<sup>9-12</sup> In the present study, we used functional MRI (fMRI) and investigated the impact of early childhood lead exposure on the cortical organization of language in young adults who experienced a wide range of lead exposure levels during development. Measurement of language activation patterns in various brain regions of these young adults was expected to help us to localize the deleterious effects on language function and language reorganization associated with lead exposure. We hypothesize that lead exposure during childhood significantly influences brain development and organization of language function. Further, compensatory brain language functional reorganization is expected as a consequence of the subtle brain insult associated with childhood lead exposure.

## METHODS

### Subjects

Forty-five young adults with documented childhood lead exposure from the Cincinnati Lead Study (CLS) were recruited for the study. The CLS, a birth cohort recruited from 1979 to 1984, enrolled pregnant women who lived in neighborhoods with high rates of childhood lead poisoning. The pregnant women were excluded if

they were known to be addicted to drugs, diabetic, or had any known neurologic or psychiatric malady. Infants were excluded if their birth weight was <1500 g or if genetic or other serious medical issues were present at birth.

These subjects have been followed from birth through early childhood with extensive documentation of lead exposure, social and medical history, intellectual attainment, neuromotor function, academic achievement, and behavior.<sup>9-13</sup> Blood lead concentrations were determined on a quarterly basis from birth until 5 years of age and again at 5.5, 6.0, and 6.5 years. The mean childhood blood lead concentration, beginning at 3 months and continuing through 78 months of age, was considered to be more representative of the average exposure of the population and, thus, was chosen as our lead level of interest in the study. It should be noted that results similar to that reported later in this study were found in similar brain regions for many of the other age time points. Table 1 briefly summarizes the demographic information of the subjects and the social, family, and individual factors that may potentially confound the association between outcome and exposure in our study. Each subject completed a urine screening for drugs of abuse at the time of imaging. All positive results ( $N = 22$ ) indicated the presence of cannabinoids. Because marijuana was the only drug detected and used with any frequency in this sample, it was the only drug tested for potential confounding effect, although potentially other drugs might also affect the brain function. All 45 of the subjects finished the verb generation task successfully. However, 3 subjects were removed from the analysis because of excessive head motion (1), data corruption (1), or a significant missing demographic record (1). Therefore, only 42 subjects' results remained for statistical analysis ( $N = 42$ ; 22 males; mean childhood blood lead level =  $14.18 \pm 6.52 \mu\text{g/dL}$ ; range: 4.77–31.06  $\mu\text{g/dL}$ ).

The study was conducted under the ethical guidelines of the Cincinnati Children's Hospital Medical Center and the University of Cincinnati institutional review boards. A certificate of confidentiality was obtained from the National Institutes of Health. All of the subjects gave

TABLE 1 Demographic Information for the Study Cohort ( $N = 42$ )

No.	Variables	Range	Mean	SD
1	Mean PbB, $\mu\text{g/dL}$	4.77–31.06	14.18	6.52
2	Age, y	20–23	21	1
3	Gender		Female/male = 20/22	
4	FSIQ	56–105	86.7*	11.39
5	IQ-SPC	11–40	20.6*	7.78
6	Gestational age, wk	37–42	39.79	1.50
7	Birth weight, g	2770–4260	3102	356
8	Subjects' marijuana usage		Test positive/negative = 22/20	

Abbreviations: PbB, mean blood lead level in childhood from month 3 to month 78; FSIQ, full-scale IQ at age 7 years; IQ-SPC, IQ for special language factor (total IQ score for subject, below 100).

written informed consent after the nature and possible consequences of the studies were explained.

### The Language Task and Experimental Paradigm

The fMRI experimental paradigm followed a standard block periodic design in which “test” period was interleaved with “control” period. The test interval consisted of a 30-second period of verb generation task to collect language activation data. During each test period, a series of nouns were presented to the subject once every 5 seconds. The subject was instructed to silently generate verbs associated with each noun presented. For example, if the noun “ball” was presented, the subject should generate the verbs “throw,” “kick,” or “hit.” The subject was instructed to think about these verbs silently instead of saying them aloud to avoid unnecessary motion artifact. The details of this task have been based on and documented in detail in previous studies.<sup>14,19</sup>

Bilateral finger tapping was used as the control task during each 30-second resting period. This task was designed to control for the auditory prompt used in the verb generation task, to distract subject from unintentionally continued engagement in the verb generation task during rest interval, and to provide activation of motor strip as reference data for each subject.

At the beginning of each experiment, a 30-second dummy scan was conducted to allow the magnetization to reach magnetic equilibrium. Five cycles of test and control data were subsequently collected. In each of these 30-second periods, 24 image slices were collected once every 3 seconds. Therefore, there are 110 time points of data collected in 5 minutes and 30 seconds for the language task imaging. The initial 10 images during the dummy scan were discarded with 100 time points of data remaining for the following data analysis.

### Image Acquisition

All of the images were acquired on a 3.0 T Bruker Biospec 30/60 MRI scanner (Bruker BioSpin MRI, Inc, Billerica, MA). A 3-plane gradient echo scan was performed to provide a reference for the alignment and localization of the brain followed by a shim procedure to optimize a homogeneous magnetic field. A T2\*-weighted gradient-echo echo planar imaging (EPI) sequence was used during the subsequent functional sessions (repetition time/echo time: 3000/38 milliseconds; field of view: 25.6 × 25.6 cm; matrix: 64 × 64; slice thickness: 5 mm; and flip angle: 90°). The whole-brain high-resolution T1-weighted anatomic data set was obtained using a modified driven equilibrium Fourier transform pulse sequence with the following parameters: repetition time/echo time: 15.7/4.3 milliseconds; inversion time: 550 milliseconds; field of view: 19.2 × 25.6 × 16.0 cm; matrix: 256 × 192 × 128; and imaging time: 14 minutes, 40 seconds).

### Data Processing and Analysis

Image reconstruction, postprocessing, and group statistical analysis were performed with custom software (Cincinnati Children’s Hospital Imaging Processing Software) written in Interactive Data Language (Research Systems Inc, Boulder, CO).

Raw EPI data were reconstructed using the multiecho phase reference scan to correct for Nyquist ghosting and geometrical distortion artifacts.<sup>20</sup> The reconstructed EPI-fMRI time series were then corrected for baseline drift using a quadratic baseline correction algorithm on a pixel-by-pixel basis. Motion artifacts were corrected using a pyramid iterative coregistration algorithm.<sup>21</sup> The images were then transformed into Talairach coordinate<sup>22</sup> for the subsequent group analysis.

The fMRI data were first postprocessed with a general linear model<sup>23</sup> to relate the time series with brain activation on a pixel-by-pixel basis. For each subject, a Pearson’s correlation coefficient between brain activation and time course was calculated for each pixel, and then a  $z$  score was derived from the coefficient by Fisher’s  $z$  transformation. During the group analysis, a 1-sample  $t$  test was performed for each pixel across all of the subjects to test the significance of the pixel in the group. After transforming  $t$  statistics to  $z$  score, a statistical parametric map (composite  $z$ -score map) can be generated to identify brain regions with the most significant contrast between language task and control task for the entire group. This was a random-effect analysis that accounted for the intersubject variance. A cluster method was used to improve specificity and adjust for the inflated  $\alpha$  from multiple comparisons.<sup>24</sup> Monte Carlo simulation performed on the data set showed that a cluster of 3 and nominal  $z = 3$  would lead to a corrected  $P < .001$ .

We also conducted a random-effect group analysis to test the association between blood oxygen level–dependent (BOLD) signal activation and mean childhood blood lead levels accounting for likely confounders. This analysis involved the following steps: (1) the brain activation in response to verb generation task was first studied independently for its relationship with childhood lead exposure by pixelwise simple linear regression analysis with a corrected  $P < .05$  (cluster = 9 based on Monte Carlo simulation); (2) because the lead exposure might be associated with other factors that could also contribute to the modification of BOLD signal patterns, 6 such variables, including subjects family’s socioeconomic status (SES), subjects’ full-scale intelligence quotient (IQ), birth weight, gender, drug (marijuana) usage, and gestational age, were pretested separately for their potential confounding influence to language function. After adding a putative confounder into the otherwise simple linear regression between BOLD and mean childhood blood lead level, the change of regression coefficient ( $\beta$ ) for lead exposure was calculated on a pixel-by-

pixel basis to evaluate the influence of the corresponding variable. This testing was conducted within the cortical areas that had been tested to correlate significantly with childhood blood lead level as determined in the previous step. The variable was kept for subsequent final multivariate analysis if adding this variable caused >20% of the pixels within the predetermined ROI to have over a 10% change in the  $\beta$  value; (3) the final step of this group analysis was to perform a multiple regression analysis to evaluate the main effect of early childhood lead exposure on language function at young adulthood with all of the significant or marginally significant confounders. Because IQ has always been a major index in the literature for lead behavioral studies, we took an extra step to determine if adding IQ to the 4-term regression (BOI.D versus blood lead, with birth weight and marijuana as confounders) would appreciably alter the exposure effect. Because the result was negative, IQ, together with gender, SES, and gestational age, was discarded.

## RESULTS

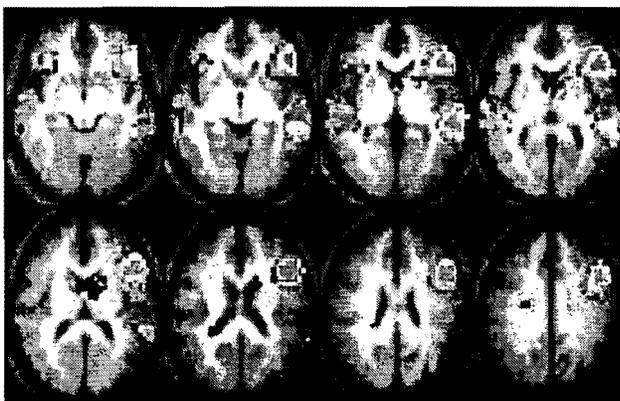
Figure 1 presents a statistical parametric map (composite z-score map) that represents the significant language activation (nominal  $z = 3$ ; cluster = 3; corrected  $P < .001$ ) across the entire subject group in our study after correction for multiple comparisons. The functional areas for language reported previously using the verb generation task<sup>19,21</sup> are all activated in our C.I.S. cohort: Broca's area (BA 44 and BA 45) at the left inferior frontal gyrus and Wernicke's area (BA 21 and BA 22) at the left superior temporal gyrus and the left middle temporal gyrus, as well as some homologues that are located contralaterally in the right hemisphere. A strong left hemispheric dominance of frontal and temporal language activation is also observed in this composite map.

To test the significance of the relationship between

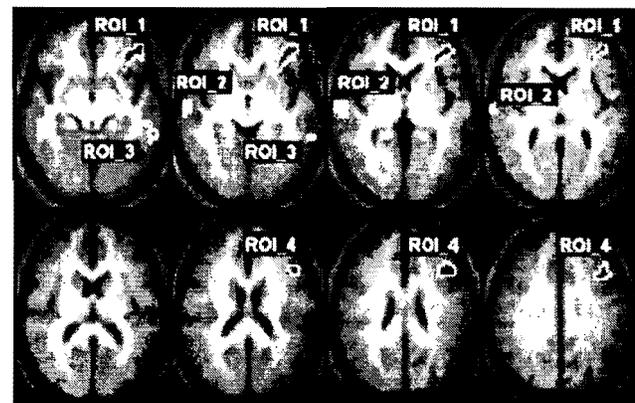
mean childhood blood lead levels and brain language activation, we conducted multivariable regression analysis, controlling for significant potential confounders. As shown in Fig 2, many cortical areas demonstrate significant association (corrected  $P < .01$  based on Monte Carlo simulation with cluster = 9) between language activation (in  $z$  score) in the brain and mean childhood blood lead level after adjusting for the 2 significant confounding factors (subjects' birth weight and marijuana consumption) as shown using the partial correlation coefficient coded in color and overlaid on the structural images. The color of light blue represents higher correlation, and dark blue represents lower correlation. For comparison, the cortical areas that have a significant simple correlation coefficient between brain activation and mean childhood blood lead level are outlined by the white lines.

As shown in Table 2, the highlighted areas in Fig 2 represent 4 separate regions of interest (ROIs). ROI\_1 and ROI\_4 correspond with brain regions in the left frontal cortex, and ROI\_2 and ROI\_3 correspond with right temporal lobe and left temporal lobe, respectively. The influence of the confounding factors can be inferred from the difference between the size of brain regions that exhibit significant correlation with lead exposure before (total pixel number,  $n = 119$ ) and after the confounders were controlled for ( $n = 81$ ). However, the inclusion of the 2 confounders in the multivariate analysis does not change the loci for these ROIs (except for the slight change in ROI\_4).

A closer examination of Fig 2 shows that, in some areas in the left inferior and middle frontal gyrus (BA 46, 47, 9, and 10), which are adjacent to Broca's area for speech generation, and in some other areas in the left middle temporal gyrus (BA 21), a region typically involved in language and auditory processing, the brain



**FIGURE 1**  
Composite fMRI activation map for the verb generation task, showing  $z$  score statistics in young adults with childhood lead exposure ( $n = 42$ ). Most highly activated areas include left inferior frontal gyrus, left medial temporal gyrus, and right medial temporal gyrus. The orientation of the images follows radiologic convention.



**FIGURE 2**  
Composite partial  $\beta$  map. The pixels with significant correlation between brain activation and lead level with confounders taken into account are coded with color and overlaid on anatomical image. The regions that have significant correlation between activation and lead level without taking confounders into consideration are demonstrated with white lines.

TABLE 2 Individual ROI

ROI	Corresponding Cortical Regions	Corresponding Brodmann Areas	Range of z Coordinate	Without Confounders		With Confounders <sup>a</sup>	
				Focus (x,y,z)	Size (Pixels)	Focus (x,y,z)	Size (Pixels)
ROI_1	left frontal	46,47,10	5+ to -10	(-38,43,5)	63	(-49,43,6)	37
ROI_2	right temporal	22,42	0+ to +10	(58,-13,0)	31	(58,-13,0)	27
ROI_3	left temporal	21	5+ to +10	(-58,-41,-5)	76	(-58,-41,-5)	70
ROI_4	left frontal	46,9	20+ to +30	(-38,3,30)	25	(-34,19,31)	16
					Total: 134		Total: 81

<sup>a</sup>ROI numbers include subjects with low or no lead consumption.

activation levels are inversely correlated with mean childhood blood lead level after adjustment for the 2 significant confounders. The activation levels in some areas in the right superior/middle temporal gyri (BA22 and 42), contra lateral to the traditional Wernicke's area, which is usually regarded as being responsible for speech perception, is positively correlated with mean blood lead level after adjustment for significant confounders (Fig 2).

A mean activation value (mean z score) was calculated across all of the pixels in each of the 4 regions (as defined in Table 2) for each subject. Figure 3 A and B show the scatter plots, along with the partial correlation coefficient (partial *R*), of the mean brain activation within the corresponding ROI versus the mean childhood blood lead concentration across subjects for ROI\_1 (BA46, BA47, and BA10; partial *R* = -0.32; *P* < .04) and ROI\_2 (BA22 and BA42; partial *R* = 0.35; *P* < .03), respectively. The correlation between the mean activation versus mean childhood blood lead concentration is also significant for ROI\_3 (BA21; partial *R* = -0.31; *P* < .05) but not for ROI\_4 (BA46 and BA9; partial *R* = -0.30; *P* = .08).

DISCUSSION

Consistent with our hypothesis and existing literature, we found a significant inverse association of mean childhood blood lead level with brain activation in the left frontal gyrus and left middle temporal gyrus, regions traditionally associated with semantic language function (ROI\_1 and ROI\_3 in Figs 2 and 3A). The diminished activation in these regions in subjects with higher childhood blood lead level suggests that lead exposure during early childhood disrupts development of the normative neural substrates of language and leaves a long-term impact on the functional neuroanatomy of language. However, the observation that these young adults still use conventional brain circuitry in support of the verb generation task, as shown in Fig 1, indicates that the effect of lead exposure on the neural substrates of language is significant but not as severe as that observed with more dramatic brain injuries, for example, stroke or brain trauma, at least not for our cohort with low-to-moderately elevated childhood blood lead levels.

We also found a positive correlation between childhood mean blood lead level with brain activation in the

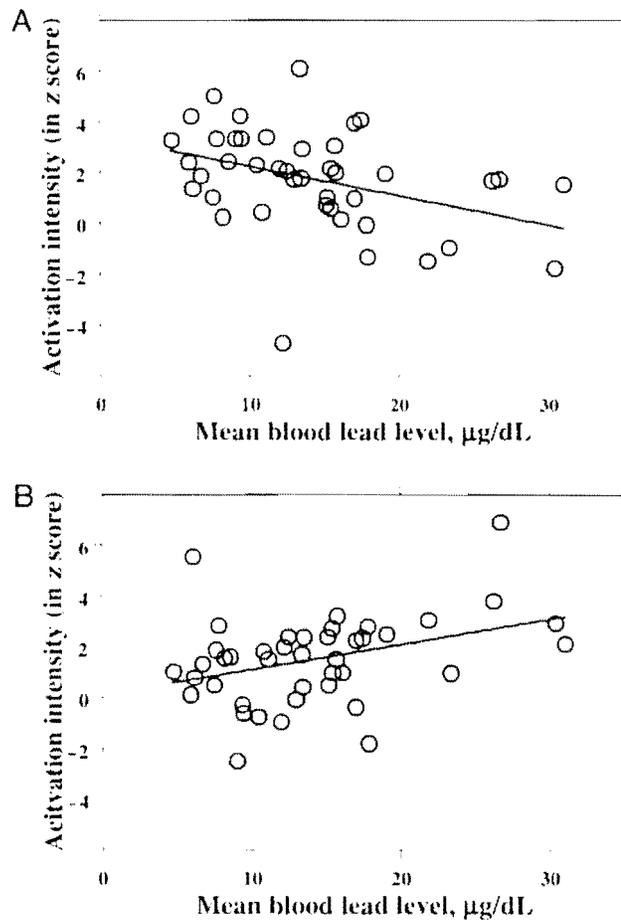


FIGURE 3  
 A, Multivariate linear regression of brain activation in left inferior frontal gyrus (ROI\_1) versus childhood mean blood lead level adjusted for our confounders. Partial *R* = -0.32, *P* < .03. B, Multivariate linear regression of brain activation in right middle temporal gyrus (ROI\_2) versus childhood mean blood lead level adjusted for our confounders. Partial *R* = 0.35, *P* < .03.

right hemisphere homologs of Wernicke's area, as shown in ROI\_2 (Figs 2 and 3B). This suggests that a compensatory mechanism may be at work at the level of the neural circuitry supporting language. As language begins to emerge in early childhood, there is a documented trend toward increasing focus of language-related activity in the left temporal and frontal lobe regions in normally developing children.<sup>19,23</sup> If these regions are not available either because of impaired connectivity or

reduced neuronal capacity, the brain deploys new areas to replace the lost capacity for language normally subserved by these preferred neural circuits.<sup>26</sup> Regions of positive correlation between lead exposure level and later language activation that occur in the right temporal lobe (ROL\_2 in Fig 2) correspond closely with the location of Wernicke's area (BA22) in the left hemisphere. This is consistent with previous neuroimaging studies describing the impact of developmental and/or acquired lesions, for example, tumor,<sup>27</sup> epilepsy,<sup>28</sup> stroke,<sup>29</sup> and dyslexia,<sup>30</sup> on language functional development. The neuroplasticity observed in the present study is consistent with our understanding about language function reorganization: the brain attempts to compensate for injury to regions that are structurally and functionally dedicated to language by recruiting support from other cortical regions. The engagement of the analogous right hemisphere temporal lobe in the compensation process provides evidence for a dormant language circuit in the nondominant hemisphere. This is a hypothesis that has been proposed and supported by other fMRI language studies.<sup>11,12</sup>

One possible explanation for these findings is that lead exposure during early childhood specifically impedes brain regions that are undergoing rapid development to support nascent language capabilities. This might result in language delays in children exposed to lead during the preschool years. Later in childhood as these children enter kindergarten and are taught to read, write, and form complete sentences, demand for neural support of language skills accelerates, forcing the brain to compensate for the injury suffered during preschool years. Dormant, contralateral language circuits in the right hemisphere with similar cytoarchitecture are capable of subserving language functions when recruited for this purpose when formal education begins in the classroom. However, it should be noted that the compensatory alternative pathway does not necessarily yield equivalent performance to that achieved using the normative cortical circuitry for the same function. The degree to which this compensation mechanism is able to meet the demand for the development of language function is assumed to be associated not only with the type of insults, but also with the timing, duration, and intensity of the insult requiring further investigation.

## CONCLUSIONS

This fMRI study offers a new insight into the neural substrates of semantic language function that are selectively influenced by lead exposure during childhood. Elevated childhood lead exposure exerts a substantial influence on the cortical organization of semantic language function in young adulthood, demonstrated by a selective, deleterious effect on normal language areas with concomitant recruitment of contralateral regions, resulting in striking, exposure-dependent patterns of re-

cruitment for language function. These imaging data provide further confirmation of the adverse consequences of environmental lead exposure on cognitive abilities.

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## REFERENCES

1. Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect*. 2005;113:894-899
2. Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL. The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati Lead Study Cohort following school entry. *Neurotoxicol Teratol*. 1993;15:37-44
3. Bellinger DC, Stiles KM, Needleman HL. Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. *Pediatrics*. 1992;90:855-861
4. Needleman HL, Schell A, Bellinger D, Leviton A, Alford EN. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *N Engl J Med*. 1990;322:83-88
5. Ris MD, Dietrich KN, Succop PA, Berger OG, Bornschein RL. Early exposure to lead and neuropsychological outcome in adolescence. *J Int Neuropsychol Soc*. 2004;10:261-270
6. Baghurst PA, McMichael AJ, Tong S, Wigg NR, Vimpani GV, Robertson EF. Exposure to environmental lead and visual-motor integration at age 7 years: the Port Pirie Cohort Study. *Epidemiology*. 1995;6:104-109
7. Bellinger D, Hu H, Titlebaum L, Needleman HL. Attentional correlates of dentin and bone lead levels in adolescents. *Arch Environ Health*. 1994;49:98-105
8. Stiles KM, Bellinger DC. Neuropsychological correlates of low-level lead exposure in school-age children: a prospective study. *Neurotoxicol Teratol*. 1993;15:27-35
9. Wang CL, Chuang HY, Ho CK, et al. Relationship between blood lead concentrations and learning achievement among primary school children in Taiwan. *Environ Res*. 2002;89:12-18
10. Ferguson DM, Horwood LJ. The effects of lead levels on the growth of word recognition in middle childhood. *Int J Epidemiol*. 1993;22:891-897
11. Mayfield SA. Language and speech behaviors of children with undue lead absorption: a review of the literature. *Speech Hear Res*. 1983;26:362-368
12. Campbell TF, Needleman HL, Riess JA, Tobin MJ. Bone lead levels and language processing performance. *Dev Neuropsychol*. 2000;18:171-186
13. Dietrich K, Bearer CE, Kalm R, et al. Long-term adverse neurobehavioral consequences of low-level exposure to environmental toxins: an update of the Cincinnati Children's Environmental Health Center [abstract]. *Epidemiology*. 2004;15:S90
14. Binder JR. Neuroanatomy of language processing studied with functional MRI. *Clin Neurosci*. 1997;4:87-94
15. Binder JR, Frost JA, Hammeke TA, Cox RW, Rao SM, Prieto T.

- Human brain language areas identified by functional magnetic resonance imaging. *J Neurosci*. 1997;17:353–362
16. Petersen SE, Fox PT, Posner MI, Mintun M, Raichle ME. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature*. 1988; 331:585–589
  17. Benson RR, Logan WJ, Cosgrove GR, et al. Functional MRI localization of language in a 9-year-old child. *Can J Neurol Sci*. 1996;23:213–219
  18. Benson RR, FitzGerald DB, LeSueur LL, et al. Language dominance determined by whole brain functional MRI in patients with brain lesions. *Neurology*. 1999;52:798–809
  19. Holland SK, Plante E, Byars AW, Strawsburg RH, Schmithorst VJ, Ball WS Jr. Normal fMRI brain activation patterns in children performing a verb generation task. *Neuroimage*. 2001;14: 837–843
  20. Schmithorst VJ, Dardzinski BJ, Holland SK. Simultaneous correction of ghost and geometric distortion artifacts in EPI using a multiecho reference scan. *IEEE Trans Med Imaging*. 2001;20: 535–539
  21. Thevenaz P, Unser M. A pyramid approach to subpixel registration based on intensity. *IEEE Trans Image Process*. 1998;7: 27–41
  22. Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain*. New York, NY: Thieme Medical Publishers, Inc; 1988
  23. Worsley KJ, Liao CH, Aston J, et al. A general statistical analysis for fMRI data. *Neuroimage*. 2002;15:1–15
  24. Xiong J, Gao JH, Lancaster JL, Fox PT. Clustered pixels analysis for functional MRI activation studies of the human brain. *Hum Brain Mapp*. 1995;3:287–301
  25. Szafarski JP, Holland SK, Schmithorst VJ, Byars AW. fMRI study of language lateralization in children and adults. *Hum Brain Mapp*. 2006;27:202–212
  26. Lidsky TL, Schneider JS. Lead neurotoxicity in children: basic mechanisms and clinical correlates. *Brain*. 2003;126:5–19
  27. DeVos KJ, Wylie E, Geckler C, Kotagal P, Comair Y. Language dominance in patients with early childhood tumors near left hemisphere language areas. *Neurology*. 1995;45:349–356
  28. Saltzman-Benaiah J, Scott K, Smith ML. Factors associated with atypical speech: representation in children with intractable epilepsy. *Neuropsychologia*. 2003;41:1967–1974
  29. Thulborn KR, Carpenter PA, Just MA. Plasticity of language-related brain function during recovery from stroke. *Stroke*. 1999;30:749–754
  30. Shaywitz SJ, Shaywitz BA, Pugh KR, et al. Functional disruption in the organization of the brain for reading in dyslexia. *Proc Natl Acad Sci U S A*. 1998;95:2636–2641
  31. Schmithorst VJ, Holland SK, Plante E. Cognitive modules utilized for narrative comprehension in children: a functional magnetic resonance imaging study. *Neuroimage*. 2006;29: 254–266
  32. McClelland JL, Rogers TT. The parallel distributed processing approach to semantic cognition. *Nat Rev Neurosci*. 2003;4: 310–322

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