

NEUROLOGY

fMRI reveals novel functional neuroanatomy in a child with perinatal stroke

Damien A. Fair, Timothy T. Brown, Steven E. Petersen and Bradley L. Schlaggar

Neurology 2006;67;2246-2249

DOI: 10.1212/01.wnl.0000249348.84045.0e

This information is current as of August 17, 2007

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.neurology.org/cgi/content/full/67/12/2246>

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2006 by AAN Enterprises, Inc. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.



fMRI reveals novel functional neuroanatomy in a child with perinatal stroke

Abstract—Children who have experienced a perinatal stroke often develop normal language function, but the neurobiologic mechanisms underlying this plasticity remain unclear. In this study, we used fMRI to compare, at two ages, the functional neuroanatomy of a child with perinatal stroke with that of age-appropriate cohorts of typically developing children. Although the data for this child are similar to the control group, there are age-dependent differences.

NEUROLOGY 2006;67:2246–2249

Damien A. Fair, PA-C; Timothy T. Brown, PhD; Steven E. Petersen, PhD; and Bradley L. Schlaggar, MD, PhD

Children with perinatal stroke are capable of acquiring relatively normal language function after experiencing a cortical insult that in adults would often lead to devastating lifetime disabilities.¹ The phenomenon of this developmental plasticity has long been accepted, but its underlying neurobiologic mechanisms are not well characterized.

One prevailing idea is that the development of normal language in the presence of an early lesion is accomplished by the functional reorganization of homotopic regions in the contralateral hemisphere.² Other reports suggest intrahemispheric organization as well.³

Several factors may contribute to these discrepancies. Perinatal strokes show considerable variability in lesion etiology, onset, size, and location, making it difficult to obtain large homogeneous patient samples that provide adequate power suitable for study. Relatedly, at the behavioral level, individual differences in the rate and nature of language development exist even in the normal population.⁴

The main objective of the present work was to examine a strategy for identifying alternative functional neuroanatomic patterns of activity in children with perinatal stroke that contends with these con-

cerns. Ultimately, this strategy is intended to be applied to multiple subjects to assess common and individual effects in specific patients. However, for the purposes of this presentation, a case report is presented for one particular subject (PS1) who, despite a large posterior left middle cerebral artery (MCA) distribution perinatal infarct, is within average range for his age on standard neuropsychological measures including verbal and nonverbal IQ (tables E-1, E-2, and E-3 on the *Neurology* Web site at www.neurology.org).

Methods. For this report, 111 right-handed, typically developing subjects^{5,6} (48 males), along with PS1, performed event-related fMRI studies on a set of controlled and simple lexical processing tasks. The tasks (collapsed for this analysis) for PS1 and control subjects included verb, rhyme, and opposite generation (to both auditorily and visually presented words), reading, and repeating. PS1 was imaged at both 9.25 and 13.2 years of age.

As introduced above, to understand how the pattern of brain activation of PS1 statistically compares with that of appropriate control subjects, two age-appropriate subgroups were sampled from the 111 typically developing subjects for each age at which PS1 was scanned (figure E-1 and supplementary methods).

A complete description of similarities and differences between PS1 and the control subgroups required that parallel regions of interest (ROIs) be acquired from both the normal population and PS1. Previously published⁵ ROIs from typically developing children included age/performance-independent regions, where activity is the same despite differences in age and performance, and age-related regions, where activity changes with age independent of task performance (tables E-4 and E-5). Similar region sets were derived from PS1's own functional anatomic data: 1) regions statistically similar across both sessions (across-age regions) and 2) regions statistically different between sessions (between-age regions) (tables E-6 and E-7 and supplementary methods). For all ROIs, the activity magnitude from PS1 was compared with the distribution of activity magnitudes for the appropriate age-matched controls, presented as an absolute z score $[(\text{mean}_{\text{subject}} - \text{mean}_{\text{controls}})/\text{SD}_{\text{controls}}]$; hereinafter $|z|$.

Results. Imaging. For most ROIs, PS1's $|z|$ comparison with normal populations was relatively low (i.e., <2), suggesting that PS1 shows "normal" levels of activation in most regions. In the across-age ROIs, 44 of 49 had a $|z| < 2$ and in the age-/performance-independent ROI, 43 of 43 regions had a $|z| < 2$ (figure, A and C). A similar finding was observed for between age ROIs (in the first scan, 8 of 13 regions and in the second scan, 11 of 13 regions had a $|z| < 2$) and age-related ROIs (in the first scan, 34 of 38 and in the second scan, 36 of 38 had a $|z| < 2$).

A less frequent finding was that for some ROIs found in both hemispheres, PS1's $|z|$ comparison with the normal population was relatively high, suggesting reliable differ-

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the December 26 issue to find the link for this article.

From the Departments of Psychology (T.T.B., S.E.P.), Neurology (D.A.F., T.T.B., S.E.P., B.L.S.) Radiology (S.E.P., B.L.S.), Department of Anatomy and Neurobiology (S.E.P., B.L.S.), and Pediatrics (B.L.S.), Washington University School of Medicine, St. Louis, MO.

This work was supported in part by the Washington University Chancellor's Fellowship and UNCF * Merck Graduate Science Research Dissertation Fellowship (D.A.F.) and by NIH NSADA (B.L.S.), NS32979 (S.E.P.), NS41255 (S.E.P.), NS46424 (S.E.P.), The McDonnell Center for Higher Brain function (S.E.P., B.L.S.), and The Charles A. Dana Foundation (B.L.S.).

Disclosure: The authors report no conflicts of interest

Received April 19, 2006. Accepted in final form September 5, 2006.

Address correspondence and reprint requests to Damien Fair, PA-C, Department of Neurology, Campus Box 8111, Washington University School of Medicine, 660 S. Euclid Avenue, St. Louis, MO 63110; e-mail: damien.fair@wustl.edu

2246 Copyright © 2006 by AAN Enterprises, Inc.

Downloaded from www.neurology.org at Washington University on August 17, 2007

Copyright © by AAN Enterprises, Inc. Unauthorized reproduction of this article is prohibited.

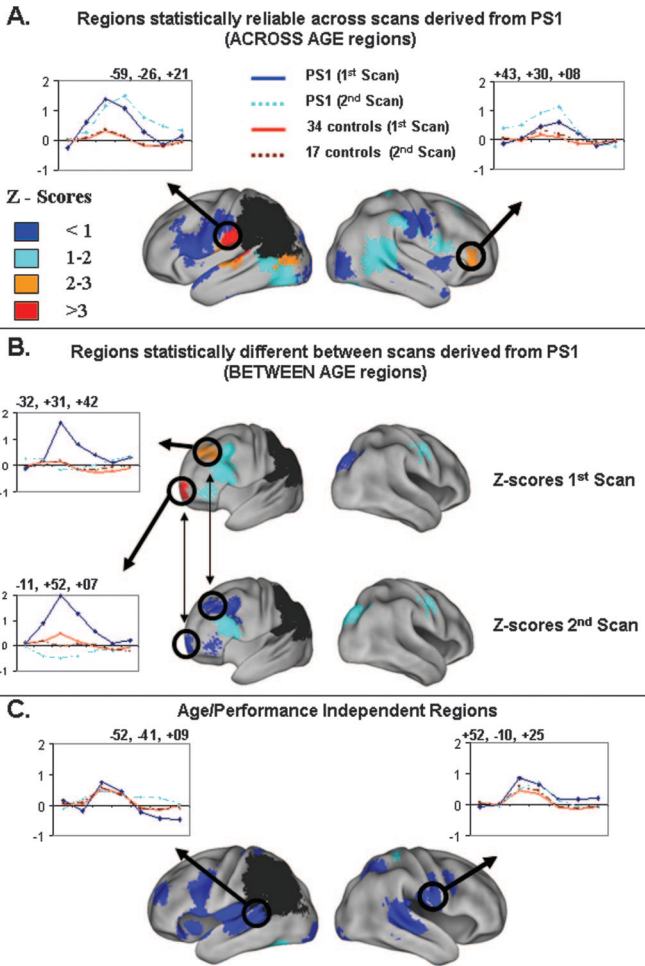


Figure. Lateral views of three region sets and selected time courses (lesion is in black). Each region is color coded by absolute z score values (blue: $|z| < 1$; light blue: $1 > |z| < 2$; orange: $2 > |z| < 3$; red: $|z| > 3$). Time courses for PS1 and control cohorts are divided by scan (blue, solid line = PS1 at first scan; light blue, dotted line = PS1 at second scan; dark red solid line = age-bracketed cohort first scan; light red, dotted line = age-bracketed cohort at second scan). (A) Regions statistically reliable across scans derived from PS1 (across-age regions). Two of the five regions with $|z|$ scores > 2 are highlighted. One of these regions is located in the right anterior inferior frontal gyrus, and the other is located perilesionally, near the left supramarginal gyrus. (B) Regions statistically different between scans derived from PS1 (between-age regions). Two of the 13 regions with $|z|$ scores > 2 at one or both scan sessions are highlighted. Both of these regions are located in the frontal lobe distant from the lesion in the ipsilateral hemisphere (the hemispheres are slightly rotated for viewing). (C) Age-/performance-independent regions. Within this region set, no regions were found with $|z|$ scores > 2 . Two regions are highlighted. One region is located perilesionally in the ipsilateral hemisphere, and the other is in the contralateral hemisphere near the presumptive mouth sensorimotor cortex.

ences between PS1 and controls. Of these differences, several regions showed increased activation at the two ages. In the across-age image, five such regions were identified (table). The only region with a $|z| > 3$ was located peril-

esionally, near the left supramarginal gyrus (figure, A). Another ROI that deviated from the normal distribution was located in the right anterior inferior frontal gyrus (figure, A, and figure E-2).

The third finding was the presence of age-related changes in regions unique to PS1 that generally normalize over time. Five left hemisphere regions, derived from PS1's between-age image, showed differences at the first scan ($|z| > 2$), whereas only two regions showed differences at the second scan ($|z| > 2$) (figure, B, and figure E-2). A similar finding was observed for the age-related regions (table).

Behavior. PS1's performance (accuracy and reaction time) during scanning was compared with the same normal cohorts. The analysis revealed considerable similarity for accuracy (first scan, $z = 0.38$; second scan, $z = -0.55$; across scans, $z = 0.07$). For reaction time, PS1 was different from the cohort group only at the first scan (first scan, $z = 3.5$; second scan, $z = -1.38$; across scans, $z = 1.37$).

Discussion. We examined a method that uses a normative database of typically developing children and adults, so that single-subject fMRI data can be examined probabilistically. Similar in concept to a previously published approach,⁷ the strategy described here accounts for normal variability and developmental trajectory in the brain's functional organization and allows individual patterns of activation related to disparate lesions to be assessed in a normative context. Employing this strategy across multiple subjects with varying brain injuries will also permit a better understanding of alternate developmental outcomes that are based on differences in the etiology, onset, size, and location, and, ultimately, the consequence of clinical interventions.

Specifically, we examined the functional neuroanatomy of lexical processing tasks in PS1, a patient with normal psychometric scores, despite an extensive left posterior hemisphere lesion acquired perinatally. Even with the loss of several regions that are typically involved in the tasks described here, PS1 manages to perform the tasks well at age 9 and again at age 13. Over the two scanning sessions, evidence from PS1 revealed mostly similarities in functional anatomic activation with some differences found in *both* hemispheres corresponding to 1) increased activation in some regions, which are also active in the age-matched controls, and 2) age-related changes in regions unique to this subject that generally normalize over time. Because of the significant difference between PS1 and controls for reaction time at the first scan, it is possible that some of these transient regions are related to performance differences. For example, a region located in the medial frontal/anterior cingulate ($-11, 52, 7$) cortex lies in close proximity (1.5-cm vector distance) to a performance-related region previously defined in normal subjects.⁵

Overall, the results suggest at least two compensatory mechanisms, one that uses the upregulation of activity in selected, typically involved regions and another that uses, at least in part, the recruitment of novel, but transient "scaffolding" regions.

Table Regions with absolute z scores greater than 2

	x	y	z	Location	z Score	
PS1s across age regions						
Left						
	-59	-26	21	Parietal	3.4	
	-8	-23	39	Med. par./post. cing.	2.2	
	-55	-17	12	Occipital/temporal	2.1	
	-50	-71	7	Occipital/temporal	2.5	
	-45	-26	-28	Occipital/temporal	2.1	
Right						
	43	30	8	Frontal	2.5	
Age/performance-independent regions						
Left						
	none					
Right						
	none					
	x	y	z	Location	1st scan z score	2nd scan z score
PS1s between age regions						
Left						
	-32	31	42	Frontal	2	-0.6
	-14	38	8	Med. front./ant. cing.	2.6	-1.1
	-11	52	7	Med. front./ant. cing.	3.1	-0.4
	-3	-40	50	Med. front./ant. cing.	2.7	-2.1
	-2	-83	33	Occipital/temporal	-0.6	-2.4
Right						
	none					
Age-related regions						
Left						
	-18	55	8	Frontal	3.5	-0.1
	-12	-42	12	Med. par./post. cing.	2.4	-0.3
	-5	-41	29	Med. par./post. cing.	1.5	-2.4
	-41	-85	7	Occipital/temporal	2.3	0.9
	-37	7	-18	Occipital/temporal	-1.1	2.8
Right						
	14	-39	30	Med. par./post. cing.	2.8	-1.4

The changes that take place in the task-related functional anatomy in PS1 have implications regarding the neurobiologic mechanisms that underlie this process. Theories that are based on the hypothesis that reorganization (either homotopic or ipsilateral) supports the acquisition of normal language in the setting of perinatal stroke would largely predict an addition of regions that “take over” the functions that are lost to the lesion and retention of these additions over time. However, in PS1, most regions that change with age show increased activity in disparate regions compared with controls at an early age that decrease to baseline over time. The remain-

ing differences are upregulations of regions that are normally involved in these tasks.

A theory more consistent with these observations has recently been highlighted in the developmental literature.⁸ This theory, termed interactive specialization, suggests that cognitive functions are mediated by a constellation of interconnected regions, and that the response properties of these regions are determined by the activity-dependent connections within this constellation. Through normal development, the response properties of such interconnected regions will likely change as they interact and compete with each other to acquire their mature roles.

Thus, for a particular task, the contribution of any given region across age may be reduced, increased, or remain the same.

This interaction-driven theory also anticipates, as previously discussed,^{9,10} that normal developmental mechanisms will interact with early-onset pathology to yield an atypical adult functional neuroanatomy. If the balance of regional competition is altered by removal of one or more of the competing regions, as is the case for perinatal stroke, an alternate organization and developmental time course would ensue that would largely depend on the timing, location, and size of the stroke. The potentially idiosyncratic alternate organizations may explain, in part, the inconsistent findings found throughout the literature in regards to the ipsilateral vs homotopic reorganization debate.^{2,3}

The presence of multiple sorts of changes in a single individual (PS1) presented here is consistent with the interactive activation view; however, future work that employs this strategy across multiple subjects will be necessary to solidify this conclusion (or not) and more generally advance our understanding of how these changes support developmental plasticity.

Acknowledgment

The authors thank the participants in this study, as well as Mark McAvoy and Avi Snyder for neuroimaging application development and David Van Essen and his colleagues for the use of CARET for figures.

References

1. Bates E. Plasticity, localization, and language development. Broman SH, Fletcher JM, eds. *The changing nervous system*. New York: Oxford University Press, 1999:214–253.
2. Muller RA, Rothermel RD, Behen ME, et al. Brain organization of language after early unilateral lesion: a PET study. *Brain Lang* 1998; 62:422–451.
3. Liegeois F, Connelly A, Cross JH, et al. Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. *Brain* 2004; 127:1229–1236.
4. Bates E, Dale PS, Thal D. Individual differences and their implications for theories of language development.: Fletcher J, MacWhinney B, eds. *Handbook of child language*. Oxford: Basil Blackwell; 1995:96–151.
5. Brown TT, Lugar HM, Coalson RS, et al. Developmental changes in human cerebral functional organization for word generation. *Cereb Cortex* 2005;15:275–290.
6. Schlaggar BL, Brown TT, Lugar HM, et al. Functional neuroanatomical differences between adults and school-age children in the processing of single words. *Science* 2002;296:1476–1479.
7. Turkeltaub PE, Flowers DL, Verbalis A, et al. The neural basis of hyperlexic reading: an FMRI case study. *Neuron* 2004;41:11–25.
8. Johnson MH. Functional brain development in humans. *Nat Rev Neurosci* 2001;2:475–483.
9. Moses P, Stiles J. The lesion methodology: contrasting views from adult and child studies. *Dev Psychobiol* 2002;40:266–277.
10. Webster MJ, Ungerleider LG, Bachevalier J. Development and plasticity of the neural circuitry underlying visual recognition memory. *Can J Physiol Pharmacol* 1995;73:1364–1371.

ACTIVATE YOUR ONLINE SUBSCRIPTION

At www.neurology.org, subscribers can now access the full text of the current issue of *Neurology* and back issues to 1999. Select the “Login instructions” link that is provided on the Help screen. Here you will be guided through a step-by-step activation process.

Neurology online offers:

- Access to journal content in both Adobe Acrobat PDF or HTML formats
- Links to PubMed
- Extensive search capabilities
- Complete online Information for Authors
- Examinations on designated articles for CME credit
- Access to in-depth supplementary scientific data

fMRI reveals novel functional neuroanatomy in a child with perinatal stroke

Damien A. Fair, Timothy T. Brown, Steven E. Petersen and Bradley L. Schlaggar

Neurology 2006;67;2246-2249

DOI: 10.1212/01.wnl.0000249348.84045.0e

This information is current as of August 17, 2007

Updated Information & Services	including high-resolution figures, can be found at: http://www.neurology.org/cgi/content/full/67/12/2246
Supplementary Material	Supplementary material can be found at: http://www.neurology.org/cgi/content/full/67/12/2246/DC1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): fMRI http://www.neurology.org/cgi/collection/fmri Neonatal http://www.neurology.org/cgi/collection/neonatal All Cerebrovascular disease/Stroke http://www.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke Infarction http://www.neurology.org/cgi/collection/infarction Plasticity http://www.neurology.org/cgi/collection/plasticity Childhood stroke http://www.neurology.org/cgi/collection/childhood_stroke
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/misc/Permissions.shtml
Reprints	Information about ordering reprints can be found online: http://www.neurology.org/misc/reprints.shtml

