Alternative brain organization after prenatal cerebral injury: Convergent fMRI and cognitive data

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Abstract

The current study presents both longitudinal behavioral data and functional activation data documenting the effects of early focal brain injury on the development of spatial analytic processing in two children, one with prenatal left hemisphere (LH) injury and one with right hemisphere (RH) injury. A substantial body of evidence has shown that adults and children with early, lateralized brain injury show evidence of spatial analytic deficits. LH injury compromises the ability to encode the parts of a spatial pattern, while RH injury impairs pattern integration. The two children described in this report show patterns of deficit consistent with the site of their injury. In the current study, their longitudinal behavioral data spanning the age range from preschool to adolescence are presented in conjunction with data from a functional magnetic resonance imaging (fMRI) study of spatial processing. The activation results provide evidence that alternative profiles of neural organization can arise following early focal brain injury, and document *where* in the brain spatial functions are carried out when regions that normally mediate them are damaged. In addition, the coupling of the activation with the behavioral data allows us to go beyond the simple mapping of functional sites, to ask questions about how those sites may have come to mediate the spatial functions. (*JINS*, 2003, *9*, 604–622.)

Keywords: Brain development, fMRI, Pediatric brain imaging, Prenatal brain injury, Spatial development, Functional plasticity, Children

INTRODUCTION

The idea that the developing brain is plastic and capable of adaptive organization is not new. More than a century of animal work has documented both the dramatic effects of experience on brain development and the capacity of the developing brain to reorganize following experimental lesions (e.g., Goldman, 1971; Goldman et al., 1970; Greenough & Chang, 1988; Kennard, 1936, 1938, 1942; Kolb & Whishaw, 2000; Rosenzweig & Bennett, 1972;

Rosenzweig et al., 1962a, 1962b, 1968; von Melchner et al., 2000). The basic principles of brain plasticity have been shown to apply to humans as well. In the mid-19th century, Broca commented on the functional resilience of children with early brain injury in his review of a case of preserved language in a woman with congenital malformation of the anterior left hemisphere (LH) (Schiller, 1979). Subsequent clinical studies have documented functional sparing and/or recovery in children with early focal brain injury (e.g., Aram, 1988; Ashcraft et al., 1992; Dennis, 1980; Dennis & Kohn, 1975; Eisele & Aram, 1993; Gadian et al., 2000; Kohn & Dennis, 1974; Lenneberg, 1967; Vargha-Khadem et al., 1985, 1997; Woods & Carey, 1979). However, these studies are limited in that most human clinical

studies have focused exclusively on cognitive outcome. That is, on evaluating the degree of domain specific deficit in older patients whose injuries occurred early in life. Only a small number of studies (e.g., Aram, 1988; Aram & Eisele, 1994; Dennis & Kohn, 1975; Isaacs et al., 1996; Vargha-Khadem et al., 1997) have attempted to directly address questions about the development of brain-behavior relations following early focal brain injury. That is, to examine directly the process and course of development as it unfolds.

For more than a decade we have taken a prospective approach to studying the effects of early focal brain injury on behavioral and brain development. Our longitudinal approach has allowed us to begin to address the requisite set of questions that are essential to understanding both initial effects of brain injury and the course of developmental change that follows: (1) Is there *early* evidence of impairment? (2) Is the profile of impairment in early childhood the same as that observed in adults with similar injury? (3) Does the profile of deficit and ability change with development? (4) What is the relation between brain and cognitive development following early brain injury? Answers to all four of these questions are necessary for understanding the dynamics of human brain and cognitive development following early brain injury. The ultimate goal of our work is to define the developmental mechanisms that lead to the specific patterns of outcome observed in this population, and to ask not simply where the functions are carried out in the brain of a child with early injury, but how the alternative patterns of organization arise.

Most of our work thus far has focused on identifying profiles of behavioral change across development, beginning in the early preschool period and extending through adolescence. These data provide rich and detailed empirical accounts of the alternative profiles of cognitive development that can emerge in the wake of early brain injury, and provide critical information about both the range and limits of functional plasticity. They also suggest that there must be accompanying change in the organization of the neural substrate that supports the cognitive change. However, data documenting specific patterns of neural change are extremely limited; there is very little data on functional brain localization following early brain injury and even less documenting mechanisms of change. Functional imaging provides the means for addressing the critical question of what the alternative patterns of neural organization are.

The focus of studies in our laboratory has been on the development of a basic spatial cognitive function, spatial analysis. Spatial analysis involves the ability both to segment a pattern into a set of constituent parts, and to integrate those parts into a coherent whole. Children with focal brain injury manifest subtle, selective deficits in spatial analytic processing, and our work in this area has supplied answers to the first three questions outlined above, providing a clear definition of the behavioral side of the brain–behavior equation (see Stiles et al., 1998, for review). First, spatial deficits associated with early injury are detectable in the first years of life and they persist throughout childhood.

Second, the association between the specific spatial processing deficit and lesion location is consistent with profiles reported for adults. Specifically, in both adults (e.g., Arena & Gainotti, 1978; Delis et al., 1986; 1988; Gainotti & Tiacci, 1970; Lamb & Robertson, 1988, 1989, 1990; McFie & Zangwill, 1960; Piercy et al., 1960; Ratcliff, 1982; Robertson & Delis, 1986; Robertson & Lamb, 1988; Swindell et al., 1988) and children (e.g., Stiles et al., 1998), LH injury results in disorders of pattern segmentation, while right hemisphere (RH) injury affects integration. Third, children are able to compensate cognitively for their deficits in ways that adults cannot. Across the developmental period from preschool to adolescence, children present with milder deficits than are typically observed in adults, suggesting a degree of resiliency or plasticity that is not available to adults. While these findings are important and inform our understanding of the consequences of early injury on spatial cognitive development, they do not directly address the fourth and most critical question about the relation between brain and cognitive development. The key to addressing this question lies in functional neuroimaging.

The existing literature on functional brain imaging in children with focal brain injury is extremely limited, even when the full range of cognitive domains and imaging techniques is considered. Mills et al. (1994) reported on the association between early language and event related potential (ERP) responses in a small group of toddlers with pre- or perinatal focal brain injury. Poor linguistic ability was reported for children whose ERP activation was predominantly within the ipsilesional hemisphere. Children who showed a shift of activation to the contralesional hemisphere, showed a corresponding improvement in language ability. Müller and colleagues have used positron emission tomography (PET) to look at functional activation for language and motor function in children with early focal brain injury. Their studies of language in children with LH injury incurred before age 5 suggest that language organizes in homotopic regions of the contralesional RH (Müller et al., 1998a, 1998b, 1998c, 1998d, 1999). By contrast, motor functions localize to secondary rather than primary motor areas of the contralesional hemisphere (Müller et al., 1998b, 1998c). Graveline et al. (1998) reported patterns of activation in secondary motor and somatosensory areas of the contralesional hemisphere in hemispherectomized children, a finding that is consistent with Müller et al. (1998b, 1998c). Levin (1996) reported LH activation for a normally RH mediated spatial task in a teenager who suffered a right parietal skull fracture and a right temporal hemorrhage at age 7 months. Booth (1999, 2000) presented language and spatial tasks to six 9- to 12-year-old children who suffered focal brain injury within the 1st year of life (5 with LH injury, 1 with RH injury). Consistent with Müller (1998a, 1998b), activation in homotopic regions of the contralesional hemisphere was reported for language tasks. However, some activation was found in the ipsilesional hemisphere for all patients, and the degree of shift to the contralesional hemisphere appeared to be related to size of

lesion. Poor behavioral performance and minimal activation was reported for the spatial task.

The pediatric functional imaging studies summarized above suggest that, across a range of behavioral functions, the developing brain is capable of alternative organization in the wake of early injury. The current study was designed to use fMRI to document the alternative profiles of brain mediation that are associated with specific profiles of spatial cognitive deficit in children with focal brain injury. In the report that follows, we first highlight the critical findings from the longitudinal profiles of spatial processing in 2 children with focal brain injury. The data on which these profiles are based were collected over a decade of each child's development beginning in the late preschool period and extending into adolescence. The longitudinal data both document the presence of early specific spatial deficit, and define the complex interplay of deficit, compensation and development that is characteristic of children in this population. With these detailed spatial cognitive profiles in hand, we next turn to specific questions about the organization of the neural substrate that mediates the observed behaviors. We present an fMRI study of spatial analytic processing conducted with the 2 children from the focal lesion (FL) population as adolescents, and compare their data with that of a group of 20 typically developing children.

In contrast to the longitudinal data documenting developmental change in spatial processing, the imaging study was, of necessity, a study of *outcome*. fMRI is a comparatively new methodology that was unavailable in the early years of this longitudinal study. Further, imaging data is particularly sensitive to motion artifact thus making fMRI unsuitable for most types of cognitive studies with young children. These two factors led us to target the older children in our sample for our initial fMRI investigations, and to focus on documenting patterns of brain activation for spatial processing as they appear near the end of development. The imaging data reveal alternative patterns of neural activation for each child that both contrast with data from typically developing children and are consistent with the profiles of deficit evident in the longitudinal behavioral data. But more importantly, the comparison of data on developmental change in the typically developing children with data from the children with early focal brain injury suggests a hypothesis of how alternative patterns of organization for spatial functions can arise across the course of development.

THE DEVELOPMENT OF SPATIAL ANALYTIC PROCESSING IN TWO CHILDREN WITH EARLY FOCAL BRAIN INJURY

Two children were selected for this study: K.–LH, a male with prenatal injury to the LH, and M.–RH, a male with pre- or perinatal injury to the RH. The children were selected because they are representative of our larger FL population with regard to both the specifics of their neurological involvement (see neurological findings below) and in their profiles of longitudinal behavioral development. Further, they are children who have participated in the longitudinal study for more than a decade, and thus they are children for whom the longitudinal behavioral data are extensive.

To illustrate directly the contrasting performance profiles associated with RH and LH injury, the two cases will be presented in parallel. The report is divided into three sections:

1. A review of the neurological, neuroanatomical and standardized neuropsychological data for each child is provided first.

2. That section is followed by presentation of the longitudinal spatial cognitive data for each child. This section is organized by task. It includes a summary of previously published group data from the larger sample of FL children and controls, followed by the data from each child. Findings presented in this section address issues raised by the first three questions outlined earlier.

3. The results of the fMRI study of spatial analytic processing are discussed last. This section begins with an overview of the results of our published studies of adults and typically developing children on a basic spatial processing task. Contrasting profiles of activation data from the two children with focal brain injury are then presented. These findings provide information relevant to the fourth question outlined above, specifically, the relation between brain and behavioral development.

Neurological, Neuroanatomical and Neuropsychological Findings

Neurological findings

Both of the children in this study presented with early neurological profiles that met the criteria for inclusion in the longitudinal study, and thus both are typical of the larger populations. Specifically, the children were selected on the basis of the presence of a single, unilateral brain lesion that was acquired prior to, or at birth. Location and size of the lesions were ascertained by neuroimaging procedures (MRI or CT scans). Individuals were excluded if there was evidence of multi-focal or diffuse brain damage, or if there was evidence of intrauterine drug exposure. Like the great majority of the children in the full sample, they were born full term. Finally, like the majority of children in the full population they score within the normal range on standardized IQ measures.

Child 1 (male): K.–LH. K.–LH is the product of a full term pregnancy. Beginning at 7 months gestation, his mother felt intermittent rhythmic kicking that lasted until birth and was later thought to be intrauterine seizures. K.–LH was born by C-section. His 1 and 5 min APGAR scores were 9 and 9. His weight at birth was 9 lb, 11 oz. K.–LH experienced right focal seizures beginning at 12 hours that lasted

3 days. He was placed on phenobarbital for control of seizures and continued on the medication for 1 year. A neonatal CT scan showed a left parietal cerebral infarction, judged to be prenatal in origin. He was kept in the neonatal ICU for 2 weeks. K.–LH is left-handed and showed mild right hemiparesis that has largely resolved. His sensory exam shows mild right stereognosis and graphesthesia.

Child 2 (male): M.–RH. M.–RH is the product of a full term pregnancy and uncomplicated delivery. The mother was confined to bed rest during the last 6 weeks of pregnancy for high blood pressure and toxemia. His 1 and 5 min APGAR scores were 8 and 9. His weight at birth was 8 lb, 2 oz, and he was discharged from the hospital after 36 hr. M.–RH's mother noted his left sided weakness at 5 months. He had seizures between 18 and 24 months. A CT scan at 30 months confirmed a right parietal infarction of presumed pre- or perinatal origin. M.–RH is right-handed, and has mild to moderate left hemiparesis with greater leg than arm involvement. His sensory exam is normal.

Neuroanatomical findings

Anatomical imaging data show that both K.–LH and M.–RH have frank lesions affecting primarily parietal areas. However, analyses of cerebral gray-to-white matter ratios also indicate white matter loss in regions posterior to the area of frank infarction (Moses, 1999). Thus the 2 children present interesting cases for this study of temporal–occipital lobe mediated spatial processing. Although the critical brain areas for spatial processing show indirect effects of the early lesions, the volume of cortical gray matter is minimally affected in both children. As reported below, the longitudinal behavioral data indicate specific, but subtle, deficits in spatial processes associated with these posterior temporal regions, providing suggestive evidence that the white matter abnormalities may affect neural processing in temporal areas.

K.–LH. Anatomical evaluation of K.–LH's structural MRI scans obtained at age 11 years shows the gray and white matter lesion in the anterior parietal, pericentral region of the LH (see Figure 1). The lesion removed the postcentral gyrus with the exception of the most superior aspect of the gyrus. The lesion also impinged upon the adjacent gray matter of the supramarginal gyrus posteriorly and marginally involves the precentral gyrus anteriorly. The lesion involved white matter underlying the supramarginal and superior temporal gyri. In this region, the lesion lies adjacent to the optic radiations and it is difficult to discern whether they are directly involved. Additionally, on visual inspection, the thalamus of the injured LH shows atrophy and the atrium of the left lateral ventricle is dilated. Within the cerebral lobes, the intact ipsilesional occipital lobe shows significant reduction in white matter volume. The gray matter within these regions is within the normal range (Moses, 1999; Moses et al., 2000b, 20000c). Measurement of the cross-sectional area of the corpus callosum is selectively reduced in the region of the posterior body that is typically comprised of fibers projecting from the parietal cortex (Moses et al., 2000a).

M.–RH. Anatomical evaluation of M.–RH's structural MRI scans obtained at age 17 indicated that his injury is restricted to the white matter of the right parietal lobe and to a lesser degree the frontal lobe (see Figure 2). This periventricular lesion affects the white matter of the postcentral, superior parietal, angular and supramarginal gyri in the parietal region. The lesion also extends superior and lateral to the anterior horn of the lateral ventricle into the frontal lobe where it involves the white matter of the precentral and inferior frontal gyri. In addition, the lesion marginally affects the superior and middle temporal gyri. The thalamus and optic radiations in the injured hemisphere appear visibly smaller than in the intact hemisphere. Measurement of the gray and white matter volumes of the intact occipital
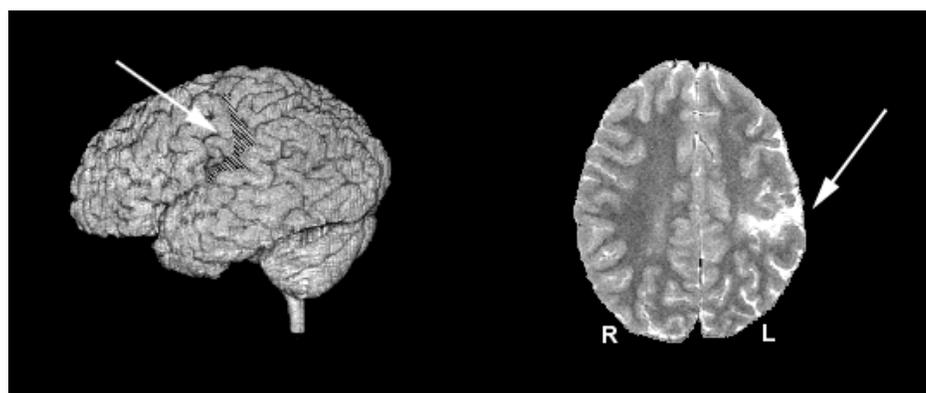

Fig. 1. Lateral and axial MRI views of K.–LH showing the location and extent of his brain lesion (adapted with permission from Moses et al., 2000a).
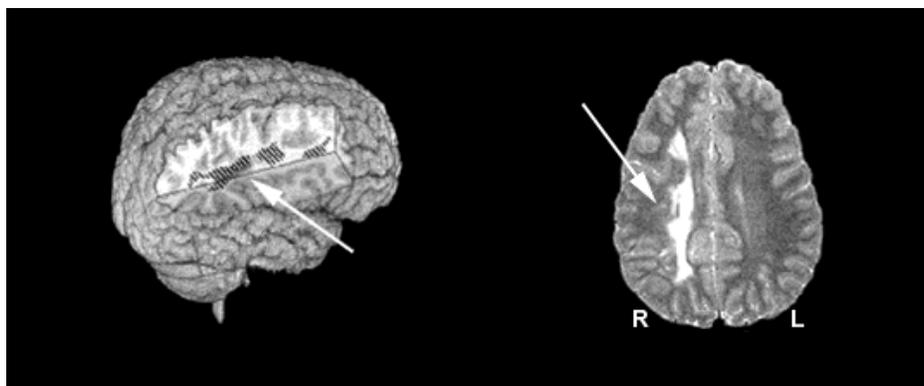
Fig. 2. Lateral and axial MRI views of M.–RH showing the location and extent of his brain lesion (adapted with permission from Moses et al., 2000a).

lobe shows an increase in the gray-to-white matter ratio. The cross-sectional area of the corpus callosum is reduced in size with the exception of the most anterior portion, the genu and rostrum (Moses et al., 2000a).

Neuropsychological findings

As part of the ongoing study of development in children with early focal brain injury a number of standardized neuro-psychological tests were administered periodically. In the sections that follow, longitudinal findings from IQ measures and the Beery Test of Visual Motor Integration (VMI) are presented. In addition, language and achievement test scores are provided, reflecting performance at a single time point near the child's imaging session. Language measures included the Expressive One Word Picture Vocabulary Test (EOWPVT) and the Peabody Picture Vocabulary Test–Revised (PPVT–R); achievement testing included three subtests of the Wide Range Achievement Test–Revised (WRAT–R): Reading, Spelling, and Mathematics.

K.–LH. On standardized tests of intelligence, K.–LH has scores within the normal range. Table 1 provides a summary of his scores on both Wechsler Intelligence Scales for Children (WISC) and the VMI. His WIS scores are consistent across the 4 to 11 year age range. He scored consistently higher on verbal than performance scales. Indeed, at ages 4 and 11 his verbal IQ (VIQ) was in the superior range, while his performance IQ (PIQ) was average. At ages 5 and 6, his VMI scores mirrored his PIQ. However, at 7 and 11, there was a significant decline in VMI performance that may reflect the changing demands on the VMI with age. Finally, Table 1 provides a summary of K.–LH's performance on language and achievement tests at age 12. Overall his performance on these measures placed him in the *average* to *high average* range.

M.–RH. On standardized IQ tests, M.–RH scored within the normal range. Table 2 provides a summary of his scores on both WIS and the VMI. M.–RH's scores on the IQ tests

provide a consistent pattern of performance across the 5 to 15 year range. He scored within the average range on both the VIQ and PIQ scales. M.–RH's scores on the VMI were very consistent across the 7 year testing period. His VMI scores were, however, somewhat lower that his PIQ scores.

Table 1. Standardized test scores for K.–LH.

Longitudinal Test Scores for K.–LH on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the Wechsler Intelligence Scale for Children (WISC–R)

Age at test	Test	Verbal IQ	Performance IQ	Full scale IQ
4,01	WPPSI	120	107	115
6,05	WISC–R	105	96	101
11,08	WISC–R	120	102	113

Longitudinal test scores for K.–LH on the Beery-Buktenica Developmental Test of Visual–Motor Integration (VMI)

Age at test	Raw score	Standard score	Percentile	Age equivalent
5,02	10	94	34th	4,10
6,00	12	93	32nd	5,06
7,01	12	82	12th	5,06
11,00	15	69	2nd	6,06

Language and achievement test scores for K.–LH at age 12

Test	Standard score	Percentile	Grade equivalent
Peabody Picture Vocabulary–Revised	121	92nd	
Expressive One-Word Vocabulary Test	106	66th	
WRAT–R*: Reading	107	68th	8th
WRAT–R: Spelling	119	90th	11th
WRAT–R: Arithmetic	98	45th	7th

*Wide Range Achievement Test–Revised

Table 2. Standardized test scores for M.–RH.

Longitudinal test scores for M.–RH on the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the Wechsler Intelligence Scale for Children (WISC–R)

Age at test	Test	Verbal IQ	Performance IQ	Full scale IQ
5,09	WPPSI	96	104	100
8,00	WISC–R	90	95	91
12,08	WISC–R	103	102	102
15,06	WISC–R	106	93	100

Longitudinal test scores for M.–RH on the Beery-Buktenica Developmental Test of Visual–Motor Integration (VMI)

Age at test	Raw score	Standard score	Percentile	Age equivalent
6,04	12	88	21st	5,06
8,01	14	85	16th	6,02
11,01	17	83	13th	7,06
13,01	19	84	14th	8,09

Language and achievement test scores for M.–RH at age 15

Test	Standard score	Percentile	Grade equivalent
Peabody Picture Vocabulary–Revised	111	77th	
Expressive One-Word Vocabulary Test	96	40th	
WRAT–R*: Reading	90	25th	8th
WRAT–R: Spelling	102	55th	8th
WRAT–R: Arithmetic	114	82nd	Above 12th

*Wide Range Achievement Test–Revised

Table 2 provides a summary of M.–RH's performance on language and achievement tests at age 15. Overall his performance on all of these measures placed him in the average range.

Longitudinal Profiles of Spatial Analytic Processing: Deficits and Development

In this section, K.–LH's and M.–RH's data from a series of longitudinally administered spatial tasks is presented. The section is organized by task and the tasks are ordered in an age-based chronology from youngest to oldest. Each task is designed to assess the child's ability to analyze a spatial array and to probe for deficits in either encoding or integrative abilities. For each task, data from the two children is compared with that of larger groups of children with RH or LH injury, as well as age-matched controls. On each task, both children present profiles of deficit that are observed in the larger sample of children with RH or LH brain injury, respectively.

Block construction in the preschool period

In the block construction task, children are presented with simple block models (e.g., a line or an arch) and asked to copy them. The task thus requires the child to define and reproduce the parts of the model construction, and to integrate those parts to form an accurately organized whole. Typically developing children show systematic developmental change between 24 and 48 months, reaching ceiling performance by about age 4 years (Stiles & Stern, 2001). Children in the lesion groups show systematic patterns of deficit (Stiles et al., 1996; Vicari et al., 1998). Children with LH injury initially show delay, producing simplified constructions. By 4 years, children begin to produce accurate copies of the target constructions, but the procedures they use are greatly simplified compared to age-matched controls.[1] This dissociation between product and process persists at least through age 6. Children with RH injury are also initially delayed, and produce only simplified constructions. At 4 years, their constructions are more complex, but poorly configured, and at this time, the procedures they use to generate these ill-formed constructions are complex and comparable to age-matched controls. By age 6, their performance changes. They are able to accurately copy the target constructions, but like their LH injured peers, they now use simple procedures. This study suggests that there is impairment in spatial processing following early injury, and compensation with development. However, the prolonged use of simplified spatial construction procedures suggests persistent deficits.

K.–LH's performance on the block construction task at age 4 closely mirrored that of other children with LH injury. Specifically, his copies were accurate (see Figure 3A), but they were constructed using simple, less efficient procedures (see Figure 3B). Unfortunately, the block task was introduced into the longitudinal study when M.–RH was too old to participate.

Memory for hierarchical forms in the school-age period

In this task, children are shown hierarchical forms and then asked to reproduce them from memory. As reported by Delis (1986), adults with LH injury have difficulty reproducing the local level elements, while patients with RH injury had difficulty with the global level of structure (see Figure 4). Data from the child FL population mirror findings from adult patients (Stiles et al., 1998). Specifically, while typi-

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[1]Construction process was scored using a 3-point scale. Process I involved the use of simple repetitive relations, with new elements extending in one direction (e.g., a stack *or* a line). Process II involved the use of more than one type of relation or direction, but produced in sequence (e.g., first a stack and then a line; right half of a line, and then the left). Process III involved the flexible use of multiple relations in which the child shifts back and forth between different kinds of relations and different parts of the block construction (e.g., the addition of blocks to the stack or line is intermixed). Note that Process I or II may be efficient for producing simple constructions, however, Process III is typically the most effective means of generating the complex constructions.
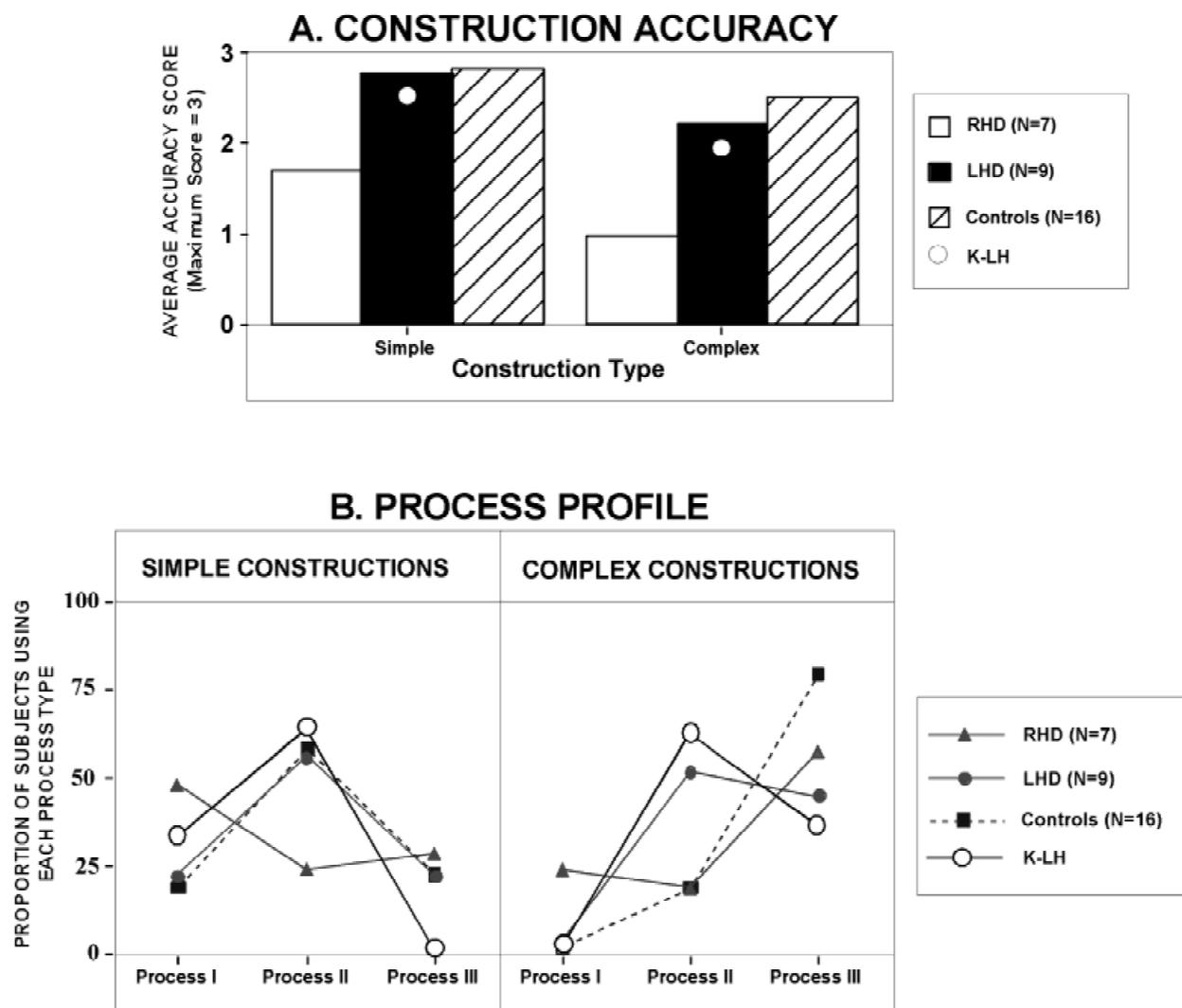
A. CONSTRUCTION ACCURACY

B. PROCESS PROFILE

Fig. 3. Comparison of K.–LH's performance on the block construction task relative to larger groups of children with RH or LH lesions, and normal 4-year-old controls: (A) Performance on the product based measure for the simple and complex stimuli (K.–LH's performance is indicated by the open dot marked on the bar indicating the group performance for 4-year-old children with LH injury). (B) Distribution of process scores for the simple and complex constructions for the three groups, plus K.–LH (see Footnote 1 for description of process scoring).

cally developing children as young as age 4, are able to accurately reproduce both the global and local levels of the hierarchical forms (Dukette & Stiles, 2001), children with RH injury are significantly less accurate in reproducing the global pattern level, while children with LH injury are less accurate with the local level. Figure 5A summarizes the results from a sample of 47 5- to 10-year-old children (RH injury $N = 13$, LH injury $N = 14$, controls $N = 20$) on the memory for hierarchical forms task (Stiles et al., 2002). Overall accuracy improves with age, but patterns of differential impairment persist throughout the school-age period.

K.–LH's performance on this task reflects the pattern observed for other children with LH injury. At age 5, he had difficulty with the local elements, but by age 8 his performance was improved (see Figure 5B). M.–RH first participated in the task at age 9. His performance at that time was very similar to other RH children of that age. While he was able to produce recognizable forms, he still made mistakes that reflect a subtle global-level processing deficit (see Fig. 5C).

The Rey-Osterrieth Complex Figure: Copy and memory in the school-age to adolescent periods

The Rey-Osterrieth Complex Figure (ROCF; see Figure 6) is a complex pattern that has been used for years to evaluate spatial planning in adults. The figure is organized around a central rectangle that is symmetrically divided by vertical, horizontal, and diagonal bisecting lines; additional pattern details are positioned within and around the core rectangle. The most advanced strategy for copying the ROCF is to
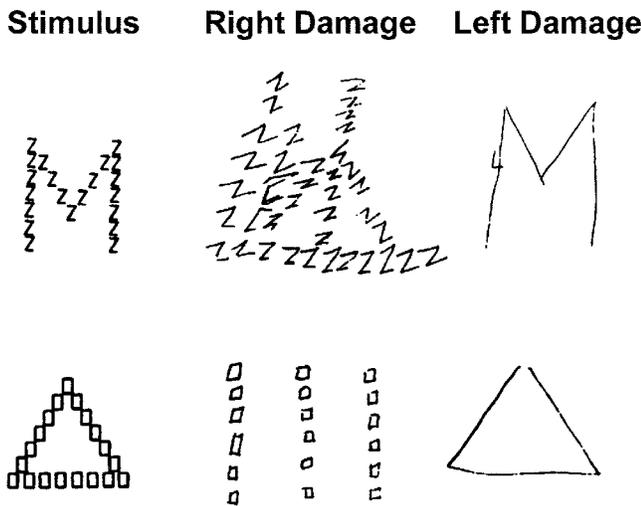
Stimulus   Right Damage   Left Damage

Fig. 4. Examples of the memory reproductions generated by 2 adult stroke patients in a study of memory for hierarchical forms (Delis et al., 1986). The patient with LH injury had difficulty reproducing the local level elements; while the patient with RH injury had difficulty with the global level form (reprinted with permission from Delis et al., 1986).

begin with the core rectangle and bisectors, and then add details. However, this strategy also places great demands on spatial processing. Akshoomoff and Stiles (1995a; 1995b) have shown that typically developing children do not regularly use this advanced copying strategy until 12 years. Children at age 6 to 7 years use piecemeal strategies drawing each small subdivision separately. Older children use progressively larger subunits (quadrants, halves), until finally, by about age 12, organization centers around the core rectangle.

Longitudinal data collected were over an 8-year period (age 6–14 years) from 10 children with LH injury and 10 with RH injury. Children were asked to copy the Rey form with the model present, and then after a 5-min delay, asked

to reproduce it from memory. Using both a copy and a memory task provide interesting profiles of deficit and development (Akshoomoff et al., 2002). On the copying task, children with both RH and LH injury performed worse than age-matched controls. Deficits were most evident among the youngest children (age 6–7) in the lesion groups, however, differences between LH and RH groups were not striking. With development, performance improved considerably, such that by 9 to 10 years the children were able to produce reasonably accurate copies of the ROCF. However, analysis of how they generated the figure showed that both groups continued to use the most immature, piecemeal processing strategies. These data thus mirror the pattern of performance in the block construction task, with improvement in the products of spatial construction, but persistent deficit indexed by process. Although the ROCF copy task data failed to differentiate the lesion groups, the memory task data from the older children did. The memory and copy reproduction of children with RH injury were similar in terms of both content and the process by which the figures were produced. In both tasks they produced detailed figures, using an immature, piecemeal strategy. By contrast, the memory reproductions of the LH group differed dramatically along both dimensions. Specifically, while the children in the LH group used an immature, piecemeal strategy when copying the Rey form, their memory reproductions were organized around the core rectangle, reflecting the adoption of an advanced processing strategy. Their continuing deficit in local level processing was evident in the lack of detailed elements produced in the memory task.

The longitudinal pattern of developmental improvement in product, and deficit in process was observed for both K.–LH and M.–RH. Figure 7 shows a longitudinal series of ROCFs produced by K.–LH and M.–RH on the copying task. For both children, the overall quality of the reproduction improved with age, but the processing strategy did not. Like the larger sample of children with focal brain injury, few differences between the 2 children are notable in the
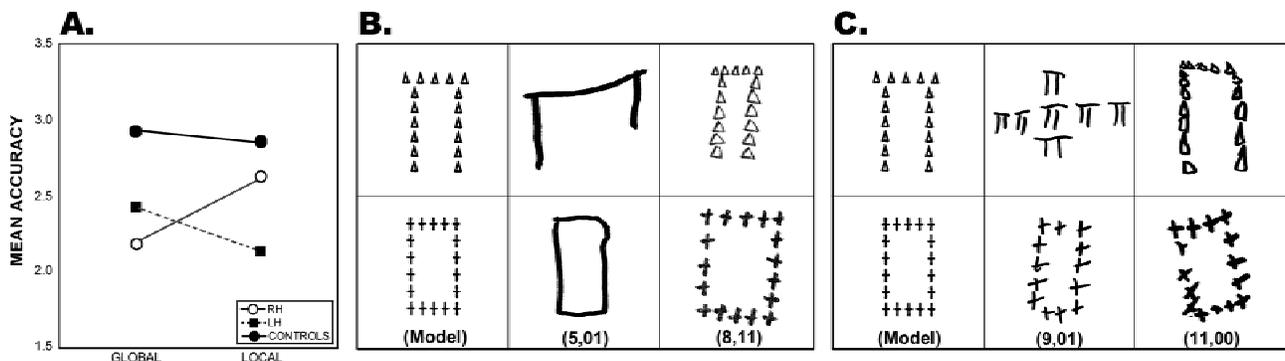

Fig. 5. (A) Mean accuracy scores for the memory reproduction task by three groups of 5- to 10-year-old children: RH, $N = 13$, LH, $N = 13$, controls, $N = 20$. Controls were equally accurate on global and local levels of pattern structure. Children with RH injury were selectively impaired in reproducing the global level, while children with LH injury were most impaired in reproducing local level pattern elements. (B) Memory reproductions for K.–LH at ages 5,01 and 8,11. (C) Memory reproductions for M.–RH at ages 9,01 and 11,00.
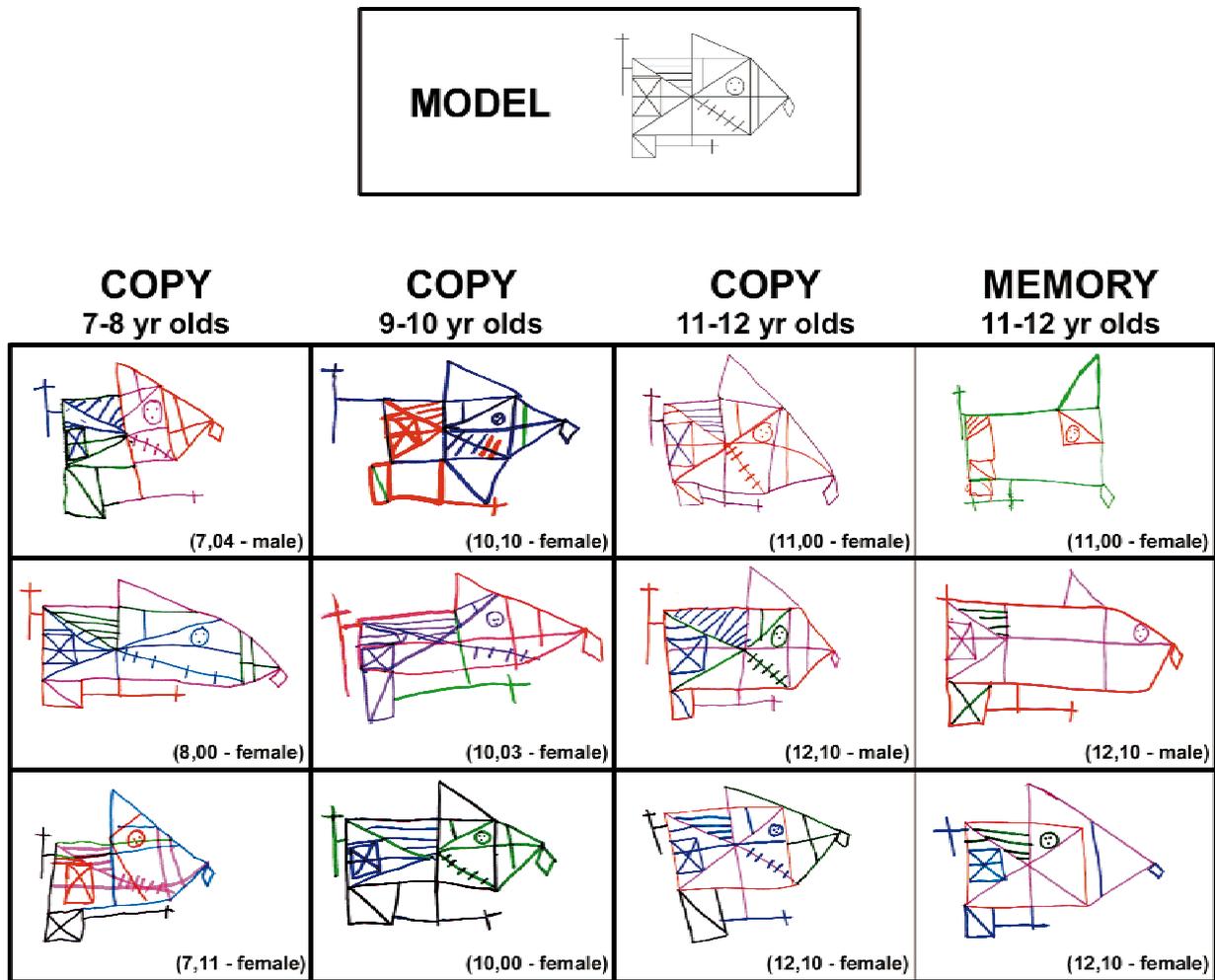
Fig. 6. Examples of Rey-Osterrieth Complex Figures by typically developing children. Copies are presented for 7- to 12-year-olds. In addition the 5-min memory reproduction is provided for the 11- to 12-year-olds.
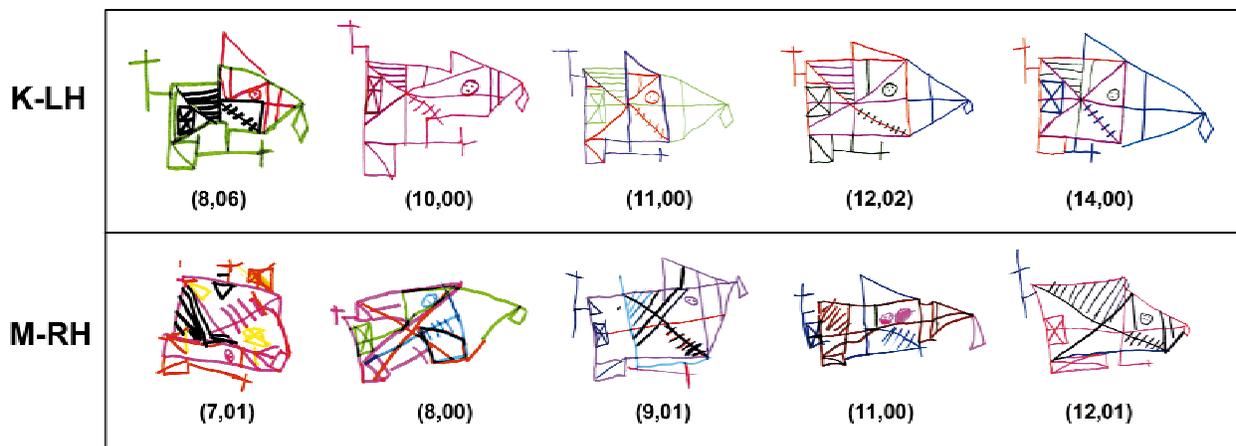

Fig. 7. Longitudinal series of Rey-Osterrieth Complex Figures obtained in the copying condition for the two children with focal brain injury. Copies from K.–LH cover the age period from 8,06 to 14,00. Copies for M.–RH range from 7,01 to 12,01.

copy data. However, striking differences were evident in their memory task reproductions. Figure 8A shows K.–LH's performance on the copy and memory task at age 11. The drawing sequence for each figure is indicated by the differ-

ent colors. The first frame of each series shows the first elements drawn (depicted in blue), the second shows the addition of the next elements added (green), and the final elements are shown in red in the third frame. K.–LH's copy
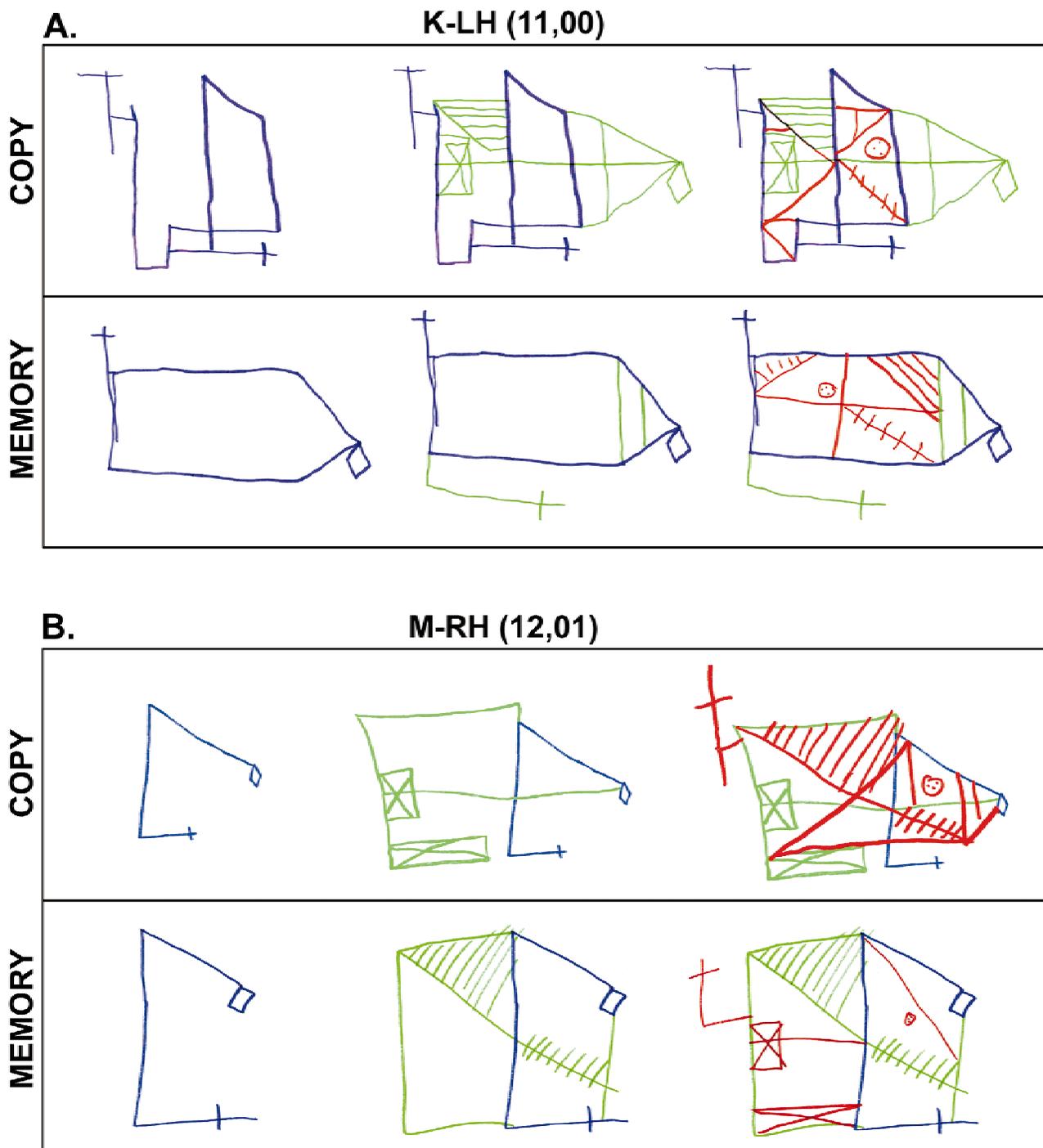

Fig. 8. The drawing sequences for the copy and memory conditions of the Rey-Osterrieth complex figure for K.–LH (age 11,00), and M.–RH (age 12,01). The order of element production is indicated by the color of the elements produced. For each condition, blue indicates the first lines produced, green indicates the second set of lines, and red the final lines added to the drawing. Note that K.–LH's approach to drawing the figure was very different in the copy and memory conditions. His copy strategy was much more fragmentary than his strategy at memory. By contrast, M.–RH's performance was quite similar over the copy and memory conditions.

reproduction was generated in a fragmented and piecemeal fashion, with no sense of the core rectangle. However, in his memory reproduction it is clear that he encoded and was able to reproduce the larger rectangular structure, thus demonstrating a mature processing strategy. However, he failed to produce many pattern details. By contrast, M.–RH's approach to the copy and memory tasks was similar (see Figure 8B). He provided rich detail in both drawings, but his processing strategy was fragmentary and immature.

Summary of the longitudinal data on spatial cognitive development

The longitudinal data for both K.–LH and M.–RH provide evidence for both the early onset of spatial processing deficits and the persistence of those deficits throughout the school years. However, the patterns of deficit for the two children are quite different, and each reflects the profiles for the larger groups of children with RH or LH injury. Also notable from these data is the relatively mild nature of the deficits and the capacity of the children to develop compensatory strategies for mastering different tasks. For both children, standardized measures of IQ place them within the normal range for both VIQ and PIQ. Interestingly, while performance on the VMI appears to be affected for both children across the longitudinal testing period, the largest decrement in performance for both children appear in early adolescence, perhaps reflecting the limits on their capacity to compensate for their visuospatial deficits. While these data provide a good deal of information on both nature of early visuospatial deficit following early focal brain injury and the longitudinal profiles of developmental and compensatory change that follow, they provide little information about the neural systems that support visuospatial processing in the wake of early injury. This question is addressed in the next section.

fMRI Studies of Spatial Analytic Processing

Behavioral studies of spatial analytic processing provide well-defined profiles of development and deficit in children with focal brain injury. A logical next step is to use fMRI to address questions about neural correlates of spatial behavior. In our studies of adults (Martinez et al., 1997) and of typically developing 12- to 14-year-old children (Moses et al., 2002), we used both visual hemifield reaction time (RT) and fMRI to document typical patterns of developmental change in brain activation patterns associated with global–local processing. The tasks, which used hierarchical forms as stimuli (see Figure 4), were designed with two separate experimental conditions, one in which participants attended to the global level of the stimulus pattern, and one in which they attended to the local level. Presenting stimuli to either the left or right visual hemifield during the RT task made possible the selective assessment of the efficiency with which the two cerebral hemispheres processed information presented at the global or local level.

Lateralized differences in RT were then compared to differences in activation between the hemispheres during the fMRI versions of the tasks.

In both tasks, participants were shown a series of hierarchical forms, and on separate blocks of trials, asked to identify targets at *either* the global or local level. In the RT study, stimuli were presented centrally, or to the right or left visual half-fields (RVF, LVF), and the subject's task was to detect which of two targets was present at the attended level. RT and accuracy for targets presented selectively to the LVF/RH or RVF/LH were used to evaluate lateralized differences in global or local processing. In the fMRI study, the participants counted the number of times a predesignated target appeared in a rapid series of centrally presented stimuli. A region of interest (ROI) analysis was used to evaluate activation in lateral temporal–occipital regions under different task conditions.[2]

The results of these studies of adults and typically developing children suggest systematic, yoked profiles of developmental change in the patterns of behavior and brain activation (BA). Among adults, consistent lateralized differences in RT and BA were found (Figure 9A). RTs to global targets presented to the RH/LVF were significantly faster than to local targets; the reverse pattern was found for targets presented to the LH/RVF, but the difference was less robust. Patterns of BA mirrored the RT findings. The RH showed greater activation than the LH in global processing condition, while the LH showed greater activation than the right during local analysis.

The children could be categorized as demonstrating one of two distinct RT/activation profiles (Figure 9, B and C). Based upon developmental findings from a separate hemi-

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[2] *fMRI task and image acquisition:* For the task presented during image acquisition, 12 hierarchical forms were presented for 50 ms each with a 500 ms intertrial interval. Stimuli were presented in four 40-s blocks, which alternated with five 40-s blocks of a control task. During the control task children passively observed a square color field which filled the field of view and changed between shades of gray at the same rate of presentation as the hierarchical forms. Each trial began and ended with the control task for a total run time of 6 min.

Functional images were acquired on a GE 1.5T Signa magnet using a single-shot EPI sequence (TE = 40 ms, TR=5000 ms, flip angle = 90°, FOV = 240 mm, 64 × 64 matrix, 74 repetitions). Twenty coronal 5 mm thick slices were acquired beginning at the occipital pole and extending to the anterior temporal pole. For anatomical localization the EPI images were superimposed on a set of whole-brain T_1-weighted 3D MPRAGE images (TE = 5.2 ms, TR = 10.7 ms, flip angle = 10°, FOV = 240 mm, 256 × 256 matrix, 1.5-mm thickness).

Image analysis: Activation maps were created by correlating the time course of the blood oxygen level dependent (BOLD) signal for each voxel with a trapezoidal reference waveform. Voxels that correlated positively with a Bonferroni corrected *p* value <.01 were retained in the functional maps. ROIs in the right and left hemispheres were delimited for analysis by tracing the lateral temporal–occipital regions on the structural images in three slices in the coronal plane, perpendicular to the AC–PC plane. The posterior boundary of the ROI transected the base of the anterior occipital sulcus. On the lateral surface of the brain a horizontal projection from the point immediately posterior to the transverse temporal gyrus through the temporal–occipital region formed the superior division. Medially, the ROI was bounded by a line that projected midway to the calcarine fissure. From this midpoint the line projected to the fundus of the collateral sulcus. The ROI maps were then overlaid on the activation maps and the volume of correlated activation within the ROI was derived.
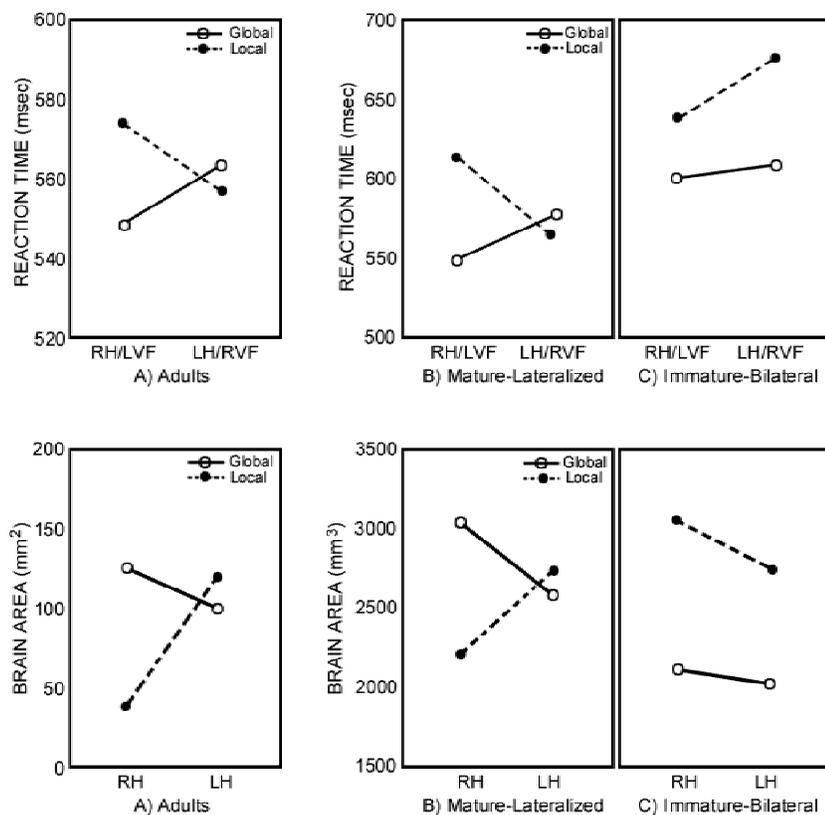
Fig. 9. Quantitative representation of the extent of brain activation (measured in mm^3) and hemifield RT data for adults and the two groups of normal control children (from Moses et al., 2002). The data from children in the 12 to 14 year age range are divided according to performance on the RT task into two distinct performance groups. (A) Data from adults shows greater RH BA for global and greater LH BA for local. (B) Data from the child group reflecting a mature–lateralized profile. (C) Data from the other child group reflecting an immature–bilateral profile (reprinted with permission from Moses et al., 2002).

field RT study of global–local processing in a large sample of 8- to 14-year-old children (see Roe et al., 1999), two patterns of performance were identified in the children in the imaging study. Specifically, the performance of 8 children was identical to that of adults for both RT and BA (Figure 9B, Figure 10B), specifically it was lateralized to the left during local processing, and to the right for global processing. The remaining 12 children showed an immature response pattern. In the RT task they showed an overall global advantage and no lateralized difference; their imaging data showed bilateral activation for both tasks, with a tendency toward greater RH activation overall (Figure 9C, Figure 10A). These findings indicate a close link between RT and activation, and suggest that a changing pattern of neural activation accompanies the cognitive shift toward greater proficiency and increased lateralization of local processing.

fMRI and RT profiles for K.–LH and M.–RH on the global–local processing task

Our examination of the neural correlates of global–local processing in K.–LH and M.–RH included the same measures of hemifield RT and functional BA, as well as the same image acquisition and analysis procedures used with the typically developing children.

K.–LH. K.–LH was 13 years old when he participated in the fMRI study. His performance on the hemifield RT

task followed the pattern observed for the developmentally more immature group of normal controls. Specifically, he showed an overall global RT advantage and no evidence of lateralized difference for either global or local processing (see Figure 11B). His activation patterns during the fMRI task yielded a somewhat different pattern of lateralization (see Figure 11A). For both the global and local task conditions, K.–LH's activation was strongly asymmetrical, and localized primarily within the RH (see Figure 11C). Unlike either group of typically developing children, he showed very little activation in the temporal–occipital ROI of the LH. This profile suggests that in the wake of early injury to the LH the normally bilaterally distributed processing of spatial pattern information was strongly localized to the RH.

The discrepancy between K.–LH's performance on the hemifield RT task and the brain activation data is somewhat puzzling. One possible, and admittedly speculative, explanation comes from the neuroanatomical data. K.–LH's MR images show visible atrophy of the left thalamus. While much of this atrophy is likely attributable to his anterior parietal lesion of cortical somatosensory areas, it is possible that thalamic visual pathway was also affected (see von Melchner et al., 2000, for an experimental example of thalamic rerouting of visual information in ferrets). If the left visual thalamus was damaged early in development, it is possible that much of the visual input to the posterior cortical region may pass through the right thalamus. Data from the hemifield RT tasks are typically assumed to reflect the functioning of separate and equally efficient retinothalamic
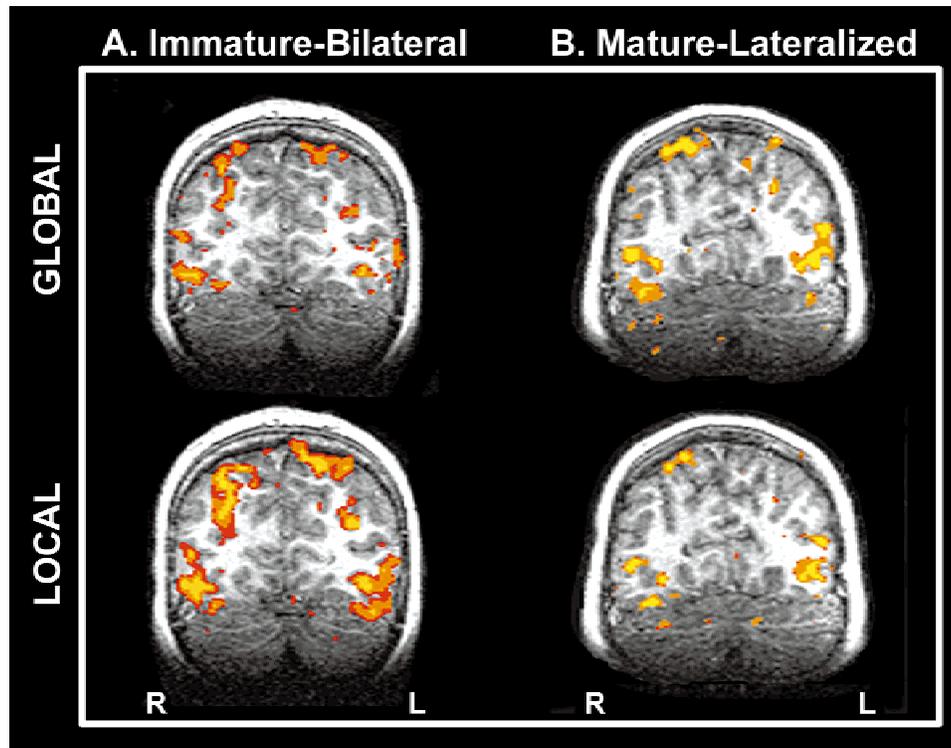
Fig. 10. Brain activation data from representative subjects from the two groups of normal control children in the attend global and the attend local processing condition (Moses et al., 2002). The activation data mirrors the quantitative profiles described for the children using the (A) immature, and (B) mature processing strategies (reprinted with permission from Moses et al., 2002).

input pathways to the cortical visual areas of the two hemispheres. In the case of early left thalamic damage, the stimuli presented to the two visual fields may not be directed selectively to the contralateral visual hemispheres as intended by the hemifield task design, rather information from both fields may be directed primarily to the RH. Further, the brain activation data suggests that both global and local level processing are organized predominantly within the uncompromised RH of this child with early LH brain injury.

M.–RH. M.–RH was 15 years old when he participated in the fMRI study. His performance on the hemifield RT task diverged from either of the patterns observed in typically developing children. Specifically, while he showed an overall global RT advantage, he also had a RT advantage for both global and local processing for stimuli presented to the RVF/LH (see Figure 12B). Thus in the behavioral study, this child with RH injury showed a consistent advantage for stimuli presented to the LH. M.–RH's activation patterns during the fMRI task were consistent with his hemifield RT data (see Figure 12A). For both global and local task conditions, M.–RH's activation was strongly asymmetrical, and localized primarily within the LH (see Figure 12C). Again, unlike either group of typically developing children, he showed very little activation in the ROI of the RH. This profile presents a complementary profile to that of K.–LH, and suggests that in the wake of early injury to the RH the

normally bilaterally distributed processing of spatial pattern information was localized primarily within the LH.

DISCUSSION

The current study focused on the development of visuospatial processing following early injury. The data presented here document alternative patterns of brain activation following early injury, and, in combination with the data on developmental change in activation patterns for typically developing children, suggest a specific account of how alternative patterns of brain organization could emerge in the wake of early injury. The longitudinal behavioral profiles of spatial analytic processing in the 2 children with early focal brain injury provide consistent evidence for both specific deficit and developmental change. Data from both K.–LH and M.–RH followed closely the profiles of deficit and development observed in the data from larger groups of children with early LH or RH injury. The 2 children presented with different patterns of spatial analytic deficit, but both showed the pattern of immaturity in processing spatial information that is characteristic of children with early focal brain injury. The brain activation data provide insight into the relation between brain and behavioral development following early injury. In each case, processing of both global and local level pattern information is strongly lateralized to the contralesional hemisphere, documenting the
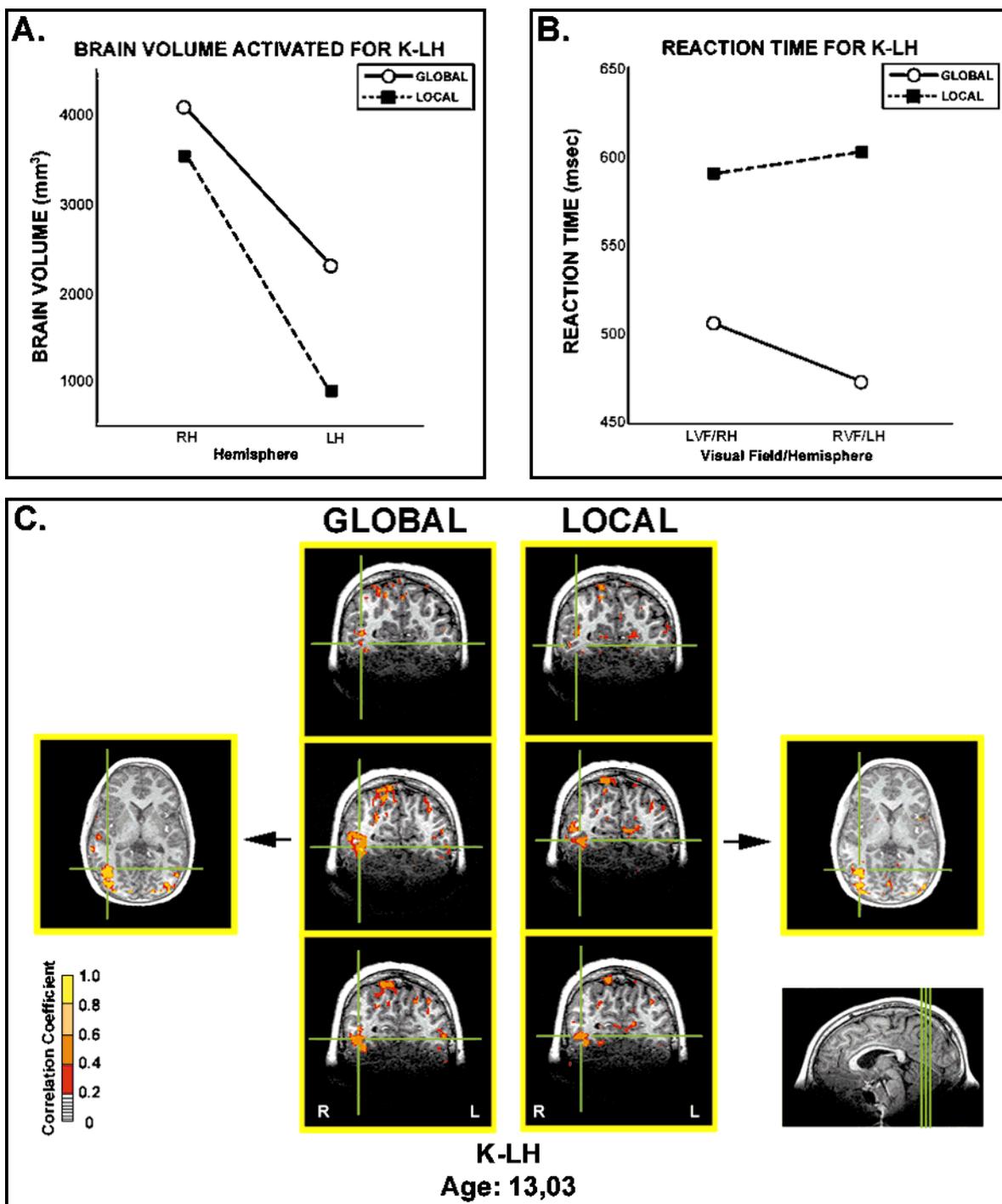
Fig. 11. Quantitative representation of K.–LH's data from the fMRI and hemifield RT study are shown in A and B; image data are shown in C. (A) K.–LH showed strongly right lateralized profiles of activation (measured as brain volume, mm^3) for both the attend global and the attend local processing conditions. (B) K.–LH showed no lateralized differences on the hemifield RT task. (C) Brain activation data from K.–LH for the attend global and the attend local processing conditions. The activation data illustrates the strong RH pattern of activation for both test conditions. The three coronal slices indicate the anterior and posterior extent of the ROI used in this study.

capacity of the developing brain to establish alternative patterns of neural mediation for this basic cognitive function. In the child with LH injury, activation was lateralized within the temporal–occipital regions of the RH during both the

global and local task conditions. In the child with RH injury, activation in both conditions was localized primarily to the intact LH. Thus, these data confirm the general finding from both the cognitive literature and the growing body
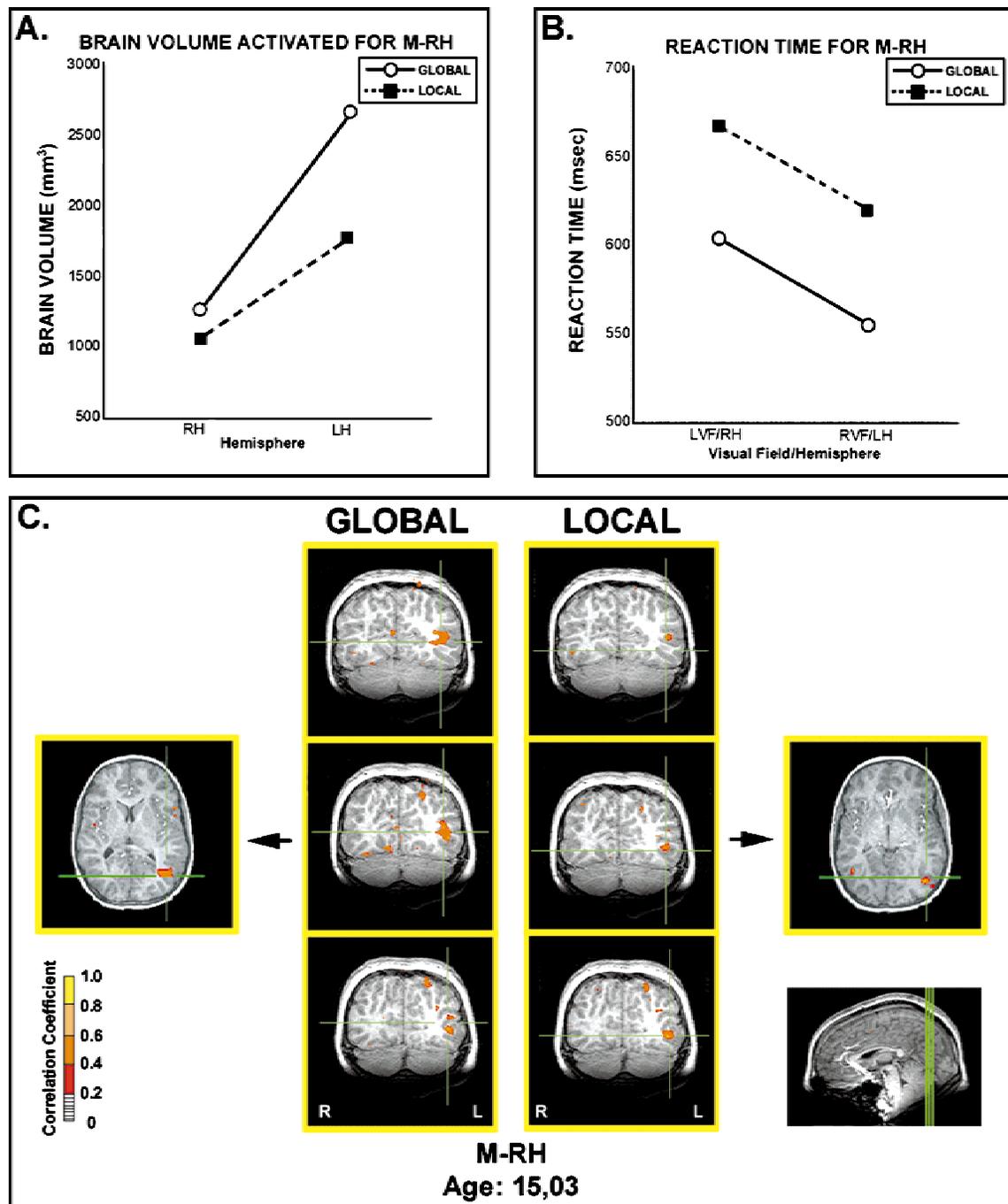
Fig. 12. Quantitative representation of M.–RH's data from the fMRI and the hemifield RT study are shown in A and B; image data are shown in C. (A) M.–RH showed a strongly left lateralized profiles of activation (measured as brain volume, mm³) for both the attend global and the attend local processing conditions. (B) M.–RH showed a strong RVF/LH advantage for stimuli presented in either the attend global or the attend local condition. (C) Brain activation data from M.–RH for the attend global and the attend local processing conditions. The activation data illustrates the strong LH pattern of activation for both test conditions. The three coronal slices indicate the anterior and posterior extent of the ROI used in this study.

of neuroimaging literature that alternative patterns of brain organization can emerge in the wake of early focal brain injury. This study is the first to document change in functional brain organization for neural systems that mediate spatial analytic processing.

In addition to addressing the general question about *whether* alternative patterns of organization can arise following early brain injury, this study raises an important second question, which is *how* do the alternative patterns of brain activation arise in these children with early focal brain

injury? While the longitudinal data documenting the specific patterns of change in neural activation is not yet available for the children in this population, a comparison of the "outcome" activation data for the children with early focal brain injury with that of typically developing groups of children provides insight into how alternative profiles of neural organization might emerge. In our study of typically developing 12- to 14-year-olds, two groups of children were distinguished on the basis of their performance on the hemifield RT study of global–local processing. The differences in RT performance that distinguished the two groups were also reflected in their differential patterns of brain activation. Specifically, the developmentally less mature group's behavior was characterized by a global processing advantage and bilateral RT profile, and strongly bilateral fMRI activation on both the global and local tasks. By contrast, the developmentally more mature group's behavior was characterized by comparably efficient processing on the global and local tasks, and a strongly left lateralized pattern of fMRI activation for the local processing task and right lateralized activation for the attend global task.

These findings suggest that, with development, both processing strategies and profiles of brain mediation change. Initially, while local processing is more effortful than global processing, the brain systems marshaled to carry out the task of *either* global or local processing are the same. This suggests that children initially adopt a less efficient, resource intensive strategy for processing spatial information. With development, spatial processing becomes both more efficient and more specialized. Thus, as local processing gradually becomes as efficient as global processing, the patterns of brain mediation change and become more highly specialized, particularly for local processing. In short, processing strategy and patterns of brain activation are highly coupled, in that developmental changes in spatial processing strategy are mirrored in changes in brain activation patterns.

Given the importance of change in processing strategy across the normal course of development, it is crucial to recall that the persistence of immature processing strategies was an important marker of cognitive deficit in the FL population. This was observed repeatedly in the longitudinal data on tasks such as block modeling and the ROCF, where the products of children's spatial processing efforts improved, but the processing strategies did not change. It should be noted, however, that the strategies adopted by the children in the FL population were not abnormal and are not, themselves, the source of their deficits. Rather they reflect strategies characteristic of younger children. The spatial deficits observed in this population are specific to the child's ability to encode pattern detail in the case of children with LH injury, or to integrate elements into organized wholes in the case of children with RH injury. However, deficits in either aspect of spatial analysis appear to impact the child's ability to develop and execute flexible and efficient spatial processing strategies. The children's failure to develop more mature strategies may arise because the development of

those strategies requires the kind of hemispheric specialization of the spatial encoding and integrative functions that typically accompanies the normal developmental shift to more efficient and flexible strategies.

Together these findings from the typically developing children and the children with focal brain injury provide insight into the question of how the alternative patterns of brain organization for visuospatial processing might arise in the wake of early brain injury. One plausible interpretation of the key differences in processing that underlie the mature and immature strategies is that mature strategies *selectively* engage specialized visuospatial processing systems, while immature strategies require the marshalling of *all available* spatial processing resources. Accordingly, for typically developing children, marshalling all available visuospatial processing resources should result in bilateral activation of the temporal–occipital system. In the typical course of development the more efficient and selective mature processing strategies emerge, and they should be accompanied by greater specificity in patterns of activation. Indeed, brain activation data from our study of typically developing children confirm both of these patterns. Activation patterns for children with immature processing strategies were bilateral for both the global and local tasks, while children with mature processing strategies had more selective, lateralized activation patterns. For the children with focal brain injury, marshalling all available resources would result in activation of the more limited pool of resources in the contralesional hemisphere. Note also, however, that although the resource pool is limited, this strategy also creates a situation in which the noninjured hemisphere would assume the role of mediating both global and local processing. When resources are reduced, in these cases by focal brain damage, the capacity for specialization would be diminished, immature processing strategies would persist, and processing of both global and local information would continue to be carried out in a single hemisphere. The brain activation data from both of the FL children in the current study confirm this pattern.

It should be emphasized that the evidence for a developmental shift toward a more mature, selective spatial processing strategy should be separated from the question of whether or not the hemispheres exhibit an early advantage for global or local processing. That is, although early in development typically developing children may not be able to selectively engage the LH and RH systems, it could still be the case that the RH is a better global level processor and the LH a better local level processor. Indeed, evidence that children with early RH or LH injury exhibit differential profiles of deficit from the first years of life, confirms the idea that the hemispheric biases for global and local level processing must be present very early in development. Thus, while the single contralesional hemisphere may come to, or perhaps more accurately persist in, mediating both global and local processing, it may well lack the full range of spatial analytic processing resources available to even an immature intact, bilateral system. The early lateralization

of global–local processing biases coupled with the engagement of an immature strategy for processing visuospatial information would account for the patterns of both deficit and development observed in our children with early focal brain injury.

Finally, while the current study focused on the development of spatial analytic processing following early brain injury, the typical developmental course for the neural systems that mediate other cognitive abilities may differ, and the factors that mediate alternative patterns of brain organization for those systems may not be the same as those observed for visuospatial processing. Thus, documentation of change across a range of cognitive and behavioral domains is critical. Indeed, the small amount of available fMRI data suggests that activation profiles will differ depending on neural system and task demands (see Müller et al., 1998b). In addition, it is clear that different cognitive domains exhibit differing degrees of behavioral resilience and these differences may be reflected in the range or extent of organizational diversity exhibited in the activation data. For example, in our study of behavioral development in the FL population, measures of language and spatial processing provided different answers to the question of initial deficit, mapping to adult profiles of deficit, and change over time (see Stiles et al., 1998 for review). In contrast to the patterns for spatial processing, language deficits were evident early but the specific features of deficit did not map well to the adult profile. Further, children showed considerable improvement over time, achieving normal levels of performance by age 7 (Bates, 1999; Bates et al., 1997; Reilly et al., 1998). These differences in behavior must reflect differences in the capacity of the neural system to respond flexibly to early injury and to develop alternative patterns of neural organization. Specification of patterns of change in neural activation for a wide range of tasks and domains will be critical to our understanding of the extent and limits on the capacity of the neural system to develop alternative patterns of functional organization following early brain injury.

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