DEVELOPMENTAL NEUROPSYCHOLOGY, *24*(2&3), 641–668

Exploring Developmental Change in the Neural Bases of Higher Cognitive Functions: The Promise of Functional Magnetic Resonance Imaging

Joan Stiles, Pamela Moses, Alessandra Passarotti, and
Frederic K. Dick
Department of Cognitive Science
University of California—San Diego

Richard Buxton
Department of Radiology
University of California—San Diego

The dramatic changes in cognitive ability observed throughout childhood mirror comparably significant changes in the developing brain. Studies of animals provide important data on associations between the development of behavior and the neural substrate. However, understanding the development of brain–behavior relations for higher cognitive functions in humans requires direct, concurrent measurement of behavior and brain functions in the children themselves. To date, such data have been very limited. Recent developments in functional magnetic resonance imaging (fMRI) provide the opportunity to systematically explore the development of brain–behavior relations in children. In this article we consider the potential of fMRI to contribute to researchers' understanding of the development of brain–behavior relations. We begin with an overview of the basic imaging method. We then review work from our own laboratory that demonstrates systematic patterns of association between performance on visuospatial tasks and patterns of brain activation, and we compare our findings with those from other laboratories focused on other cognitive domains. Finally, we discuss the potential impact of functional imaging on researchers' understanding of core issues in cognitive and brain development.

Requests for reprints should be sent to Joan Stiles, Department of Cognitive Science, 0515, University of California—San Diego, 9500 Gilman Drive, La Jolla, CA 92093. E-mail: stiles@ucsd.edu

In a recent article celebrating the centennial of work in developmental psychology, John Flavell (2000) affirmed, perhaps somewhat tongue-in-cheek, that “there is most definitely a phenomenon called *cognitive development*, and it is an extremely rich, complex, and multifaceted process” (p. 8). Indeed, over the last several decades, tremendous progress has been made in understanding many aspects of cognitive development (e.g., Damon, 1998). Debate has focused on large issues, such as competence versus performance, stage-like versus continuous models of change, domain specificity, the emergence of expertise, the use and elaboration of strategies, and innate constraints. Each of these dialogues has had important and lasting effects on researchers’ thinking about how knowledge is acquired by the child.

One area that has received comparatively less attention is work focused on delineating the relationship between cognitive development and the development of the neural systems that mediate cognition. Much of what researchers know about the development of brain–behavior relations comes from three sources: animal studies, studies of atypical child populations, and a comparatively limited set of electrophysological (Electroencephalogram [EEG] and event-related potentials [ERP]) and metabolic (positron emission tomography [PET]) studies that directly measure brain–behavior relations. Animal models provide the best and most comprehensive data on mammalian brain development, and much of what has been learned from animal studies can be productively extrapolated to humans (e.g., Brown, Keynes, & Lumsden, 2001; Jacobson, 1991; Price & Willshaw, 2000). Nonetheless, understanding the processes that underlie the development of higher cognitive functions in human children will ultimately require data from studies on the children themselves. Studies of atypical child populations provide important data on how specific neuropathology can alter the normal course of cognitive development, but such work provides only indirect measures of the normal developmental course (e.g., Broman & Fletcher, 1999; Levin & Grafman, 2000). EEG and ERP have provided important data on the temporal parameters of brain function (e.g., Carver, Bauer, & Nelson, 2000; Carver et al., 2003; de Haan & Nelson, 1997; de Haan & Nelson, 1999; Mills, Coffey-Corina, & Neville, 1993; Mills, Coffey-Corina, & Neville, 1997; Molfese, Freeman, & Palermo, 1975; Nelson & de Haan, 1996; Nelson, Thomas, de Haan, & Wewerka, 1998; Taylor & Baldeweg, 2002), but spatial localization with measures of electrophysiology is poor. PET, which can be used to measure task-related brain metabolism, offers better spatial resolution, but it is an invasive methodology with limited utility in pediatric populations (Chugani, 1994; Chugani, Phelps, & Mazziotta, 1987; Müller, Rothermel, Behen, Muzik, Chakraborty, et al., 1997; Müller, Rothermel, Behen, Muzik, Mangner, et al., 1997). Thus, although answers to questions about the neural bases of cognitive development are crucial, means for obtaining data on the development of brain–behavior relations in typically developing children have been limited.

Over the past decade, advances in functional magnetic resonance imaging (fMRI) have introduced a new means for noninvasively measuring human brain activity. It is well established that neural activity increases metabolic demands in local areas of the brain, and this increase in metabolic demand is associated with an increase in local cerebral blood flow (CBF; Jueptner & Weiller, 1995). In the early 1990s, a number of investigative teams (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong et al., 1992; Ogawa et al., 1992) developed what is now called the blood oxygenation level dependent (BOLD) imaging technique, in which conventional MRI systems are adapted to be sensitive to local blood oxygenation changes that accompany activity-dependent blood flow changes. In the succeeding decade, literally hundreds of studies successfully used this noninvasive means of imaging human brain function to map associations between specific behaviors and brain activity in adults. More recently, this method has begun to be applied in studies of children and is proving to be a powerful and effective means of assessing developmental change in brain–behavior relations.

In this paper we consider the potential of fMRI to advance researchers' understanding of the development of brain–behavior relations. We begin with an overview of the basic methodology: the definition of the BOLD signal, a discussion of potential difficulties associated with using fMRI with pediatric populations, and a consideration of design issues relevant to the interpretation of developmental data. We then review findings from the small, but growing, body of work that has used fMRI to study pediatric populations. We begin by briefly summarizing the major findings from two studies of visuospatial processing conducted in our laboratory. These studies illustrate the utility of functional imaging for defining systematic developmental change in patterns of neural mediation associated with this basic cognitive ability. We then consider the relation of findings from our own work on visuospatial processing to those from pediatric studies in other domains; we also compare findings from studies on children to findings from studies of adults. In the final section of this article, we explore the issue of how data from pediatric functional imaging can be integrated with studies on cognitive and brain development. Specifically, we explore the role of fMRI in addressing questions about what differentiates cognitive functioning in children and adults, what is unique about the neural substrate during development, and how changes in cognition and the brain interact across development.

WHAT IS BOLD IMAGING?

In conventional MRI, a local signal is generated from an externally induced excitation and subsequent relaxation of hydrogen nuclei. Hydrogen protons, ubiquitous within the body, are spinning, charged particles with small magnetic fields perpendicular to their axes of rotation. In a strong magnetic field, such as the field created by a MRI scanner, protons align the axes of their individual magnetic fields with the dominant magnetic field. The application of an additional, radio frequency pulse tips the protons away from their alignment with the main field. As the protons relax back to their orientation with the dominant magnetic field after the radio frequency pulse, they generate a measurable signal. This signal serves as the basis for conventional anatomical MRI and, more recently, for fMRI. Anatomical imaging takes advantage of relative differences in signal intensity that derive from the distinct physical properties of the different tissues within the brain. Functional imaging capitalizes on changes in signal strength that arise from transient differences in the composition of blood oxygenation between different activity states.

fMRI was developed early in the last decade, after several research groups observed that the time constant with which the MRI signal decays increases slightly in active brain regions. This effect is thought to be due to local changes in blood oxygenation (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992). It is well established that the change in metabolic demands brought about by neural activity results in increased blood flow to localized areas of the brain (Jueptner & Weiller, 1995). However, for reasons that are still not well understood, the local increase in oxygen metabolism is much less than the increase in blood flow (Buxton, 1997). Consequently, during activation there is an increase in venous blood oxygenation and a decrease in deoxyhemoglobin. Deoxyhemoglobin is a paramagnetic substance that contributes to signal decay. Thus, a reduction in the local deoxyhemoglobin content has the effect of enhancing the local MR signal around the capillaries and venous vessels. This change in blood oxygenation level accompanying brain activity results in a detectable 1% to 5% increase in a local MR signal (when that signal is measured at 1.5 T). The slight but systematic increase in the local signal due to the BOLD effect is the basis for fMRI.

Methodological Considerations for Imaging Children

Although BOLD imaging offers a noninvasive means of examining the development of brain–behavior relations, it is not without complications. In both adults and children, the BOLD signal can be affected by a variety of factors that can alter the magnitude, distribution, or detectability of the signal. Among the most commonly cited are subject movement, vascular artifact, and task compliance. All of these factors, plus a variety of others related directly to developmental status, need to be considered when imaging children.

Physiological factors. In a recent review, Gaillard, Grandin, and Xu (2001) provided an excellent summary of physiological and behavioral differences between adults and children that might account for differences in activation not directly related to performance differences on the target task. A complete catalogue of these differences is beyond the scope of this paper; however, some of the differences noted by Gaillard et al. (2001) include the following: (a) Smaller head circumferences among children can affect the placement of children's heads within the magnetic field; (b) differences in skull thickness can enhance signal detection among children; (c) differences in cardiac and respiratory rates may introduce movement and thus noise in the child data; (d) both overall and regional differences in brain size, neuronal density, and synaptic exuberance can all affect brain physiology; and (e) developmental differences in cerebral blood flow and cerebral glucose metabolism can lead to differences in the blood flow that accompanies activation, thus affecting threshold considerations. Although all of the physiological factors need to be considered in imaging studies with children, and although data need to be interpreted with care, Gaillard et al. (2001) concluded that "fMRI provides a safe and reliable means for noninvasive identification of neural networks that underlie many cognitive processes during development" (p. 246).

Interpreting developmental change: Issues of experimental design. A second area of concern in pediatric imaging is one that is familiar to investigators in cognitive development: specifically, the interpretation of age-related differences in task performance (Bookheimer, 2000; Casey, Davidson, & Rosen, 2002; Gaillard et al., 2001; Thomas & Casey, 1999). The goal of pediatric neuroimaging studies is to map developmental change in performance on a cognitive task to changes in the neural substrate. Documentation of developmental change, whether in behavior or brain activation, raises a range of theoretical and interpretative issues. Do differences reflect competence or performance, do differences index changes in strategy or the emergence of new abilities, are changes domain specific, or do they reflect change in more general cognitive processes, are differences the product of learning or maturation, and so forth. The task of reliably defining patterns of developmental change also raises a classic methodological issue: Are the tasks calibrated to avoid both floor and ceiling levels of performance and thus permit adequate assessment of behavior across the target age groups? The behavioral calibration problem finds a direct analog in the imaging data. It is well documented that moderately difficult tasks yield optimal levels of activation. Low levels of activation are associated both with tasks that are too simple, presumably reflecting lack of effort or task engagement (a ceiling effect) and with tasks that are too taxing, reflecting disengagement from the task (a floor effect; Just, Carpenter, Keller, Eddy, & Thulborn, 1996; Paulesu et al., 2000; Price & Willshaw, 2000; Raichle, Fiez, Videen, & MacLeod, 1994). The most tractable solution to the calibration problem for developmental neuroimaging studies is to begin with large-scale, multicondition behavioral studies that are specifically designed to provide detailed profiles of the development of the targeted cognitive function. Once the profile of cognitive development has been established, the most sensitive subset of the measures used to define those profiles can be adapted for the imaging studies. In addition to providing a solution to the calibration problem, the implementation of multicondition, within-subject imaging-task designs also has the critical advantage of minimizing the confounds associated with designs that rely on group differences in intensity or amount of activation as the primary measure of developmental change.

FUNCTIONAL NEUROIMAGING STUDIES WITH CHILDREN

Although the number of published pediatric functional imaging studies is still small, it is already becoming clear that this methodology offers a powerful tool for addressing questions about the relation between neural and behavioral development. As such, it is important to determine whether it is possible to identify prototypical patterns of change in brain activation that are associated with changes in behavior. One such pattern appears to be emerging from studies in our laboratory focused on the development of visuospatial processing. Specifically, across a range of visuospatial tasks, activation appears to become more spatially focused with development. This focusing of activation is accompanied by increasing proficiency on the associated spatial task.

Developmental Change in Global and Local Processing

The first study of visuospatial processing examined developmental changes in children's ability to process information at the global (whole) versus the local (part) levels of visually presented patterns. A wide array of animal, patient, and adult human imaging studies have demonstrated that the ventrolateral temporal–occipital region plays a critical role in processing visual pattern information. Furthermore, the two hemispheres differ in the kinds of information they process. Specifically, a right hemisphere (RH) advantage for global processing and a left hemisphere (LH) advantage for local processing have been consistently reported (Delis, Kiefner, & Fridlund, 1988; Delis, Robertson, & Efron, 1986; Fink et al., 1996; Kimchi & Merhav, 1991; Lamb, Robertson, & Knight, 1990; Martin, 1979; Martinez et al., 1997; Robertson, Lamb, & Knight, 1988; Sergent, 1982). Although studies of both human infants (Deruelle & de Schonen, 1991; Deruelle & de Schonen, 1995) and child patients with early LH or RH brain injury (Stiles, Bates, Thal, Trauner, & Reilly, 2002) suggest that this profile of lateralized differences in processing begins to emerge early in development, it is also clear that the development of visuospatial processing is far from complete in the first years of life. Indeed, there is evidence from behavioral studies that developmental change in visuospatial processing extends well into adolescence (Akshoomoff & Stiles, 1995a, 1995b; Dukette & Stiles, 1996, 2001; Newcombe & Huttenlocher, 2000; Roe, Moses, & Stiles, 1999).

In a study of late childhood/early adolescent development of visuospatial processing, Roe et al. (1999) used a hemifield design to examine lateralized differences in the speed of response to targets presented at the global or local level of hierarchically organized stimuli (e.g., a large triangle composed of small squares). Children ranged in age from 7 to 14 years. Across this broad age range, children show a slowly emerging and yoked pattern of faster reaction times and hemispheric lateralization. Younger children display an overall global advantage without distinct hemispheric differences for global or local processing. As they age, children show a critical shift from this more immature, bilateral (IB) processing pattern to a more mature, lateralized (ML) profile typical of adults (Martinez et al., 1997). The specific markers of this transition begin to emerge in the 12- to 14-year age range, and they include both more rapid processing of local level information and a coincident emergence of a LH advantage for local processing.

To further investigate changes in functional brain organization that accompany the developing profiles of lateralization observed at the behavioral level, we conducted an fMRI study adapted from Roe et al. (1999) that focused on a group of twenty 12- to 14-year-old children; that is, a group of children from the age range during the transition from an IB to a ML mode of processing takes place (Moses et al., 2002). Specifically, we compared patterns of task-related activation from two groups of children (IB and ML) in two separate imaging conditions. In one condition, children were instructed to attend to targets appearing at the global level; in the other condition, children were told to attend to targets at the local level. Children were assigned to either the IB or the ML group based on their performance on a hemifield reaction time task conducted outside the magnet prior to the imaging session. Children exhibiting the IB reaction time profile showed no evidence of processing differences for global versus local targets. These children demonstrated either no reaction time differences to stimuli presented to the RH or LH or consistently faster response to stimuli presented to the RH than to the LH, regardless of the target level. Children exhibiting the ML profile had faster responses to global forms presented to the RH and to local forms presented to the LH.

Analyses revealed patterns of functional activation that mirrored subjects' cognitive performance (see Figure 1). Specifically, children with an IB behavioral profile showed more functional activation during local analysis than during global analysis, and they displayed comparable amounts of activation in the RH and LH in both the global- and local-task conditions. In contrast, children in the ML group exhibited significantly more RH activation during global analysis and more LH activation during local analysis, a profile that mirrors the patterns of activation obtained in our earlier study of global local processing in adults (Martinez et al., 1997).

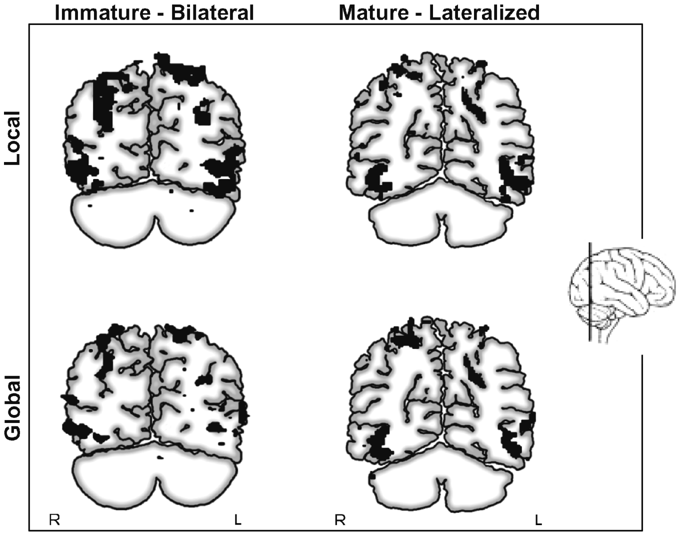

FIGURE 1 Functional activation patterns of two children from the immature, bilateral and mature, lateralized groups under attend-global and attend-local task conditions. Black regions represent sites of significant task-related blood oxygenation level dependent signal change. R = right hemisphere; L = left hemisphere.

The correspondence between children's reaction time performance and their functional activation is illustrated in the pair of graphs presented in Figure 2. Children exhibiting the IB profile were slower to analyze local-level shapes than global-level forms. Their inefficiency in local-level processing corresponds with greater activation during local analysis (compared to global processing). Further, spatial analysis appears to draw on both hemispheres regardless of the specific task: Children respond to global and local stimuli without adultlike lateralized reaction time advantages, and their functional activation is bilateral during global and local processing. Children exhibiting the ML profile process the local-level stimuli more quickly, such that they perform local and global analyses within the same time frame. As they do so, they show an allocation of processing that is more concentrated in one hemisphere or the other, according to the task.

Together the functional and behavioral data demonstrate that children's increased proficiency in visuospatial analysis coincides with a more focused pattern of functional activity at the neural level. Initially children appear to engage all available neural resources when confronted with the task of processing a visual pattern; thus the two hemispheres play comparable roles in mediating the analysis of both global and local information. However, as children become more efficient and effective processors of visual patterns, lateralized differences in processing emerge. These differences reflect the development of functional specialization within the hemispheres.

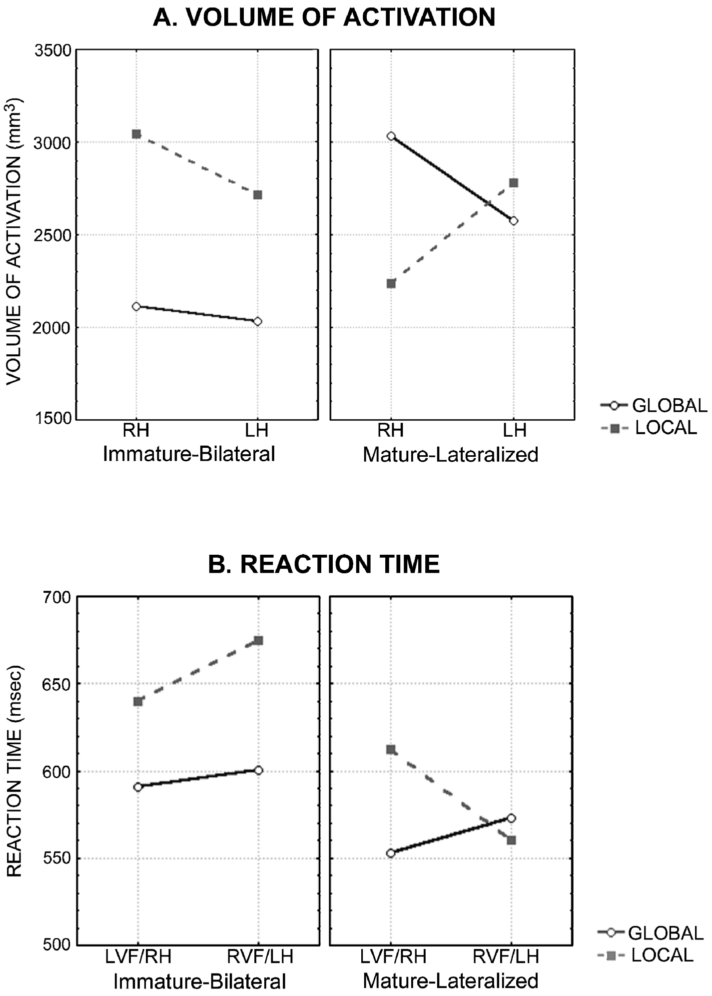

FIGURE 2 A. Functional activation: mean volume of activation in the right and left hemisphere (RH, LH) regions of interest under global and local task conditions. B. Cognitive performance: mean reaction times for global and local analysis of hierarchical forms presented in the left and right visual hemifields (LVF/RH, RVF/LH). Reprinted from Moses et al., 2002 with permission from Elsevier Science.

Developmental Change in Face and Location Processing

A second example of tasks that reflect more distributed functional activation in children than in adults in the visuospatial domain was provided by a study of face and location processing (Passarotti et al., 2003). A large number of animal studies and adult imaging studies have demonstrated that the mammalian visual system is divided into two anatomically and functionally separate systems (Courtney, Ungerleider, Keil, & Haxby, 1996; D'Esposito et al., 1998; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Haxby, Horwitz, Ungerleider, & Maisog, 1994; Kanwisher, McDermott, & Chun, 1997; Postle, Zarahn, & D'Esposito, 2000; Ungerleider & Mishkin, 1982). Within the inferior temporal–occipital lobes, the ventral system is involved in processing object properties and contains cells specialized for processing shape, color, texture, and orientation. The dorsal system, located in occipital–parietal lobes, is involved in spatial processes, such as detecting and processing the movement, location, and direction of an object (Desimone & Ungerleider, 1989). Haxby et al. (1994) provided one of the first demonstrations of a double dissociation in dorsal and ventral processing in humans in his positron emission tomography–regional cerebral blood flow (PET–rCBF) study of face processing and location processing. Specifically, face-identity was associated with bilateral rCBF increases within the fusiform gyrus of the inferior temporal–occipital cortex. This area has also been identified in a number of subsequent face-processing studies and has thus been termed the "fusiform face area" (FFA) (Gauthier, Tarr, et al., 2000; Kanwisher et al., 1997; Kanwisher, Stanley, & Harris, 1999; Wojciulik, Kanwisher, & Driver, 1998). By contrast, the location-matching task was associated with bilateral activation of the dorsal occipital, superior parietal, and intraparietal sulcus cortex (Haxby et al., 1994).

Developmental studies of face processing have shown that even young infants can process faces and may even show adultlike configural processing biases (Cohen & Cashon, 2001). Nevertheless, although it is clear that rudimentary abilities may exist very early in life, face processing undergoes rapid and dramatic change during the first years of life. Indeed, there is considerable evidence that face processing develops in a gradual and quantitative manner throughout childhood (Taylor, McCarthy, Saliba, & Degiovanni, 1999). The role of experience in the development of face processing is still a matter of debate (for a review, see Gautheir & Nelson, 2001; see also de Haan & Nelson, 1997; de Schonen & Mathivet, 1989; Gauthier, Tarr, et al., 1999; Johnson & Morton, 1991; Mazoyer et al., 1999). Although faces have been considered stimuli for which at least some initial specialization may be innate (de Schonen & Mathivet, 1989; Farah, 1996; Johnson & Morton, 1991), recent studies suggest that experience may play an important role in establishing the neural system for face processing (e.g., Gauthier, Tarr, et al., 1999).

Children's ability to process information about location also undergoes orderly change with development. Systematic change in memory for spatial location has been observed throughout the preschool period (Huttenlocher, Newcombe, & Sandberg, 1994; Newcombe, Huttenlocher, Drummey, & Wiley, 1998) and well into the school years (Newcombe & Huttenlocher, 2000). Furthermore, there is evidence of dramatic improvement in spatial working memory from the age of 4 years through adolescence (Luciana & Nelson, 1998). Somewhat surprisingly, functional imaging studies of dorsal-stream processes in children 8 to 11 years of age suggest adultlike patterns of activation. Recent studies by Nelson et al. (2000) and Thomas et al. (1999) reported similar patterns of activation for adults and children on spatial n-back tasks. Similarly, Booth et al. (2000) reported no major differences between child and adult patterns of activation in a mental rotation task.

In our face- and location-processing task, 16 adults and 12 children (ages 10–12 years) were shown three black-and-white male faces (two reference faces, followed by a target) presented sequentially in 1 of 12 possible locations on the screen. On separate imaging runs, the participants matched either faces or locations. In the face-matching task, participants decided whether the third face (the target) matched either of the two previous faces, independent of their location. In the location-matching task, they decided whether the target face appeared in the same location as either of the previous two, independent of their identity.

We compared adult and child patterns of activation with three functionally defined regions of interest. For the face-matching task, significant clusters of activation obtained from the averaged adult data served as the first region of interest; this region of interest corresponded with the typical medial fusiform face area. The remaining two regions of interest reflected significant clusters of activation based on the child data that lay outside the region of interest identified from the adult data: One was lateral to adult-determined region of interest, and one was anterior to it. For the location data, all of the activation in both the child and adult samples could be captured in the same posterior parietal region of interest.

The activation data from the face-processing task with adult subjects replicated findings from earlier studies indicating bilateral activation of the middle fusiform gyrus (with greater RH than LH activation). Children showed activation in the region of interest. But they also showed more widespread, lateral, middle fusiform, and anterior fusiform activation. Further, while children showed more activation overall in the RH than in the LH, the pattern of greater distribution of activation was observed in both hemispheres. As can be seen in Figure 3, the group patterns of activation for the face task show that although there was medial and lateral fusiform activation across all ages, the distribution of activation within both the RH and the LH differs for children and adults. With regard to the location-matching task, we found clusters of activation in parietal regions of interest both for children and adults (Figure 3). However, whereas the parietal activation for adults was much greater in the RH than in the LH, activation for children was bilateral and symmetrically distributed across the hemispheres.

In summary, the two studies of visuospatial processing demonstrated developmental changes in the localization of functional activity into the teenage years. The major findings from these studies suggest a number of specific profiles of

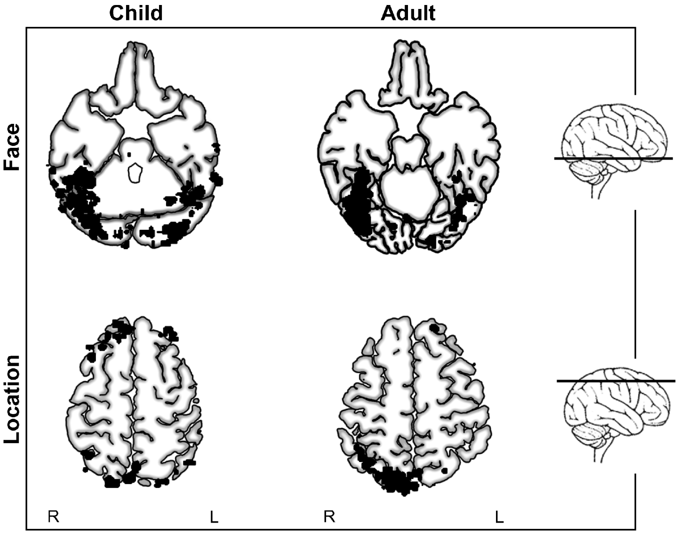

FIGURE 3 Functional activation pattern for adults and children on the face-matching and location-matching tasks. R = right hemisphere; L = left hemisphere.

developmental change in the brain systems that mediate visuospatial function. In all three of the visuospatial processing tasks included in these studies, children activated the same general brain regions as adults, but the patterns of activation differed with age. The differences involved either shifts in patterns of lateralization or changes in the distribution of activation within a hemisphere. In the global–local processing task, the immature pattern of activation was bilateral and failed to show the differentiated patterns of lateralization typical of adults. A similar developmental pattern was observed on the location-matching task. Specifically, whereas adults had much greater activation in the RH than in the LH, children's activation was bilateral and symmetrically distributed across the hemispheres. For face processing a different profile emerged. The total amount of activation across the medial and lateral fusiform regions of interest combined was nearly identical for adults and children. However, the distribution of activation within each hemisphere differed significantly with the participants' age. Whereas adult activation was primarily localized within the medial fusiform, children had significantly less activation medially, and greater activation in lateral and anterior areas. Both of these patterns suggest a focusing of activation that may reflect increasing processing efficiency or expertise with development. It is important to ask whether these kinds of developmental profiles are unique to visuospatial processing or whether they have also been observed in studies focused on other domains.

Development Change in Lateralization of Activation Patterns for Nonspatial Tasks

The increase in relative asymmetry of activation with increasing behavioral expertise or functional maturation has been observed in several recent developmental studies of both affect processing and attention. Thomas et al. (2001) compared patterns of activation for facial affect processing in 11-year-old children and in adults. They found that in behavioral testing completed outside the magnet, the children were less accurate in categorizing facial expressions than were the adults. Examination of the activation data revealed that whereas adult activation was strongly lateralized to the left amygdala, children's activation was more bilaterally distributed.

A number of recent developmental studies of language processing suggest there is a shift from bilateral to strongly left-lateralized processing on a variety of tasks. Gaillard et al. (2000) reported both overall greater levels of activation in left inferior frontal cortex (Broca's area) in a group of 8- to 13-year-olds (as compared to adults) performing a covert verbal fluency task. In addition, children showed significantly greater RH activation. Holland et al. (2001) reported similar findings for children using a verb-generation task. Specifically, although both adults and 7- to 18-year-old children showed LH dominance in activation on this task, children also showed significant RH activation, and the degree of left lateralization increased with age.

The tendency for lateralization of functional activation to increase with chronological age or expertise is echoed in the infant ERP studies of Mills et al. (1993; 1997). Infants and toddlers with below-average productive vocabularies showed bilateral P100 and N200-500 responses, whereas children in the same age group with above-average vocabularies tended to show left-lateralized responses. Conboy and Mills (2001) have extended these results by studying a group of 20- to 22-month-old Spanish–English bilingual infants who were more dominant in one of the two languages. P100 responses to known versus unfamiliar words presented in the dominant language were lateralized to the LH, whereas responses in the nondominant language were bilateral. These results suggest that relative expertise, and not simple functional maturation, drives the change in relative hemispheric dominance.

Lateralized shifts in activation have also been observed on tasks involving cognitive control and attention. Bunge, Dudokovic, Thomason, Vaidya, and Gabrieli (2002) reported that on behavioral tasks, 8- to 12-year-old children were more susceptible to interference and less able to inhibit inappropriate responses than adults. These behavioral differences were reflected in two quite different developmental profiles in the activation data. Response-suppression tasks revealed lateralized differences in activation for adults and children. Specifically, successful interference suppression among children was associated with left ventrolateral prefrontal activation, whereas successful suppression among adults was associated with right ventrolateral prefrontal activation. During response inhibition, children showed significantly lower overall activation than adults, and they activated a more limited set of brain regions than adults. Specifically, whereas both children and adults activated posterior parietal, temporal, and occipital regions, only adults showed significant activation in ventrolateral and dorsolateral frontal areas. However, another study of response inhibition did reveal lateralized differences among children and adults. Rubia et al. (2001) compared activation profiles of adolescent boys (*M* age = 15 years) to those of adults. Adults showed activation in the infero-lateral frontal lobes (more in the right than in the left) and in the left middle frontal lobe. The adolescents showed activation in the right infero-lateral frontal lobe, but they exhibited very little LH activation in either the infero-lateral or the middle frontal lobe. In addition, the adolescents showed activation in the right inferior frontal cortex and in the right caudate. These patterns might reflect a shift, with age, in the distribution of activation from subcortical to cortical brain areas, a shift that accompanies progressively more bilateral mediation of function at the cortical level.

Develomental Change in the Distribution of Activation for Nonspatial Tasks

The pattern of developmental change in the distribution of functional activation within a hemisphere found in our study of face processing also has parallels in other domains. In some cases, the shift reflects the kind of consolidation of activation observed in our visuospatial studies; in others, it is observed in developmental shifts in the magnitude of activation within a region. Gaillard et al. (2000) reported that on studies of verbal fluency, children showed 60% to 70% more activated pixels than adults did ($r > .7$). Booth et al. (2000) reported a development shift in activation in 9- to 12-year-olds on a sentence comprehension task. Although adults and children activated similar brain networks, the distribution of activation differed. Specifically, children had greater activation in inferior occipital areas than adults did suggesting children use an imagery-based strategy.

According to two different studies on basic attention processes, children showed a higher percentage of signal change in the same activated regions (dorsolateral prefrontal cortex) than did adults in both n-back and go/no-go tasks (Casey et al., 1995; Casey et al., 1997). On a parametric variant of the task, children showed increased dorsolateral prefrontal cortical activation at a lower level of task difficulty than did adults (Casey et al., 1998; Casey, Giedd, & Thomas, 2000), suggesting that at least some of these increases may be due to less efficient or more effortful processing in children.

Finally, the shift in activation within a particular region, with age or expertise, is echoed in the facial affect study of Thomas et al. (2001), referred to earlier. Here, the authors showed that children's responses to fearful versus neutral faces in the left amygdala was opposite that of adults; whereas adults showed more left amygdala activation for fearful than for neutral faces, the children showed more activation in the *same* area for neutral than for fearful faces.

CHANGE IN PATTERNS OF NEURAL ACTIVATION AMONG ADULTS

These findings raise interesting questions about the nature of the changes observed in the activation profiles over development. Do they reflect change in neural maturation, change in cognitive ability, or cognitive change interacting with long-term neural reorganization and development? In considering this question, it is useful to compare our results with findings from other imaging studies on expertise-related differences in activation in adults.

Most closely related to the developmental studies are the studies of Gauthier and colleagues (Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997; Gauthier, Behrmann, & Tarr, 1999; Gauthier & Nelson, 2001; Gauthier, Skudlarski, Gore, & Anderson, 2000; Gauthier & Tarr, 1997; Gauthier, Tarr, et al., 1999; Gauthier, Tarr, et al., 2000; Gauthier, Williams, Tarr, & Tanaka, 1998), who compared the activation profile for face perception with those of other object classes (cars, birds, and "greebles") whose recognition or categorization required a high level of expertise and significant, long-term training or exposure to multiple exemplars. "Object experts" (car buffs, bird watchers, and adults trained in greeble recognition) showed activation in a functionally-defined fusiform face area comparable to face processing, whereas nonexperts appeared to use a more distributed network of fusiform areas. Such results are reminiscent of both the developmental difference in face processing reported by Passarotti et al. (2003) and the changes in profiles of activation to local level stimuli reported by Moses et al. (2002).

Studies of bilingual adults who learned their second language at different points in their development also suggest that information may be processed differently if it is acquired at different points in development or to differing degrees of proficiency. Chee, Hon, Lee, and Soon (2001) used a semantic judgment task to compare fMRI activation in Mandarin–English bilinguals adults. One group was almost equally fluent in both languages, and another was Mandarin-dominant. Chee et al. found that proficient language use evoked a more focused profile of activation in traditional "language areas," whereas use of a later- or less-thoroughly-learned language engaged a greater extent of activation in the same areas, with a more bilateral distribution. These results paralleled the earlier PET and fMRI studies of Perani et al. (1996) and Dehaene et al. (1997) in French, English, and Italian. However, it is difficult in these three studies to disentangle the effect of expertise and maturation, as the adults who were more dominant in one language tended to have begun learning their less-dominant language later in life. To address this confound, Perani et al. (1998) compared highly proficient Italian–English bilingual adults who began to study English relatively late in life to Catalan–Spanish bilingual adults, who used both languages extensively from early childhood. When comparing these groups to each other and to a group of less-proficient bilinguals on the same language comprehension tasks, Perani found that expertise, and not age of acquisition, determined whether language organization would be more focal and left-lateralized or more diffuse and bilateral. The association of proficiency or processing efficiency with a more process-dependent, lateralized profile of activation echoes the results of Moses et al. (2002), who found that increasing local-processing efficiency leads to hemispheric functional segregation.

WHAT IS UNIQUE ABOUT DEVELOPMENT?

Although data from both adult and child studies suggest a pattern of increasing localization of brain activation as subjects become more proficient at a task, it is important to consider whether (or to what extent) the developmental data and the data from adults reflect the same kinds of underlying change in the neural substrate. One notable difference in the data from the child and adult studies is the time scale over which change in activation profiles has been observed. For adults, substantial change is often observed over periods of weeks or months. By contrast, developmental shifts in localization of activation emerge over periods of months or years. One could argue that initial acquisition of any complex cognitive ability is a protracted process, and that the slower change in the consolidation of activation among children is simply the reflection of their more slowly changing level of mastery. By this account, the mechanisms of change in neural processes associated with mastery of a skill would be preserved over development, and the differential timing is attributed to differences in cognitive proficiency at different ages. However, such an account assumes that the processes involved in mastering a cognitive task are the same at different ages. Cognitive development studies suggest that this may not be the case. Further, there are studies suggesting that the neural processes that mediate cognitive change may differ substantially during development. These issues are considered next.

Is Cognition Different During Development?

Successful and efficient performance of any higher cognitive task requires the marshaling and integration of a wide range of cognitive resources. For example, the visuospatial tasks described earlier engage perception, attention, memory, and decision processes, in addition to the spatial analytic processes. Efficient spatial analysis relies on the ability to both engage and integrate this array of skills. This means that, for adults, mastering a new task requires the application of well-learned skills to a new problem space. However, for children, the component skills necessary to master the new task are still developing. Improvement in visual acuity does not reach asymptote until the early school-age period (Mauer & Lewis, 2001); the ability to engage and shift attention continues to improve in a monotonic fashion through mid-adolescence (Schul, Townsend, & Stiles, 2003); and children's capacity for selective attention (Barrett & Shepp, 1988; Enns & Cameron, 1987; Lane & Pearson, 1982; Shepp, Barrett, & Kolbet, 1987) and working memory (Gathercole, 1998; Zald & Iacono, 1998) is still developing during the school-age years. These data suggest that engaging and integrating the component skills necessary to master the target task constitutes a much larger, more demanding, and, in some ways, qualitatively different problem for children than for adults. For example, in the global–local task, younger children were slower to process local-level shapes than global ones, and they showed greater activation during local processing than global processing. As children's reaction times for local processing decreased, the LH bias for local processing began to emerge. Additionally, a behavioral face- and location-matching task study (using a paradigm similar to the one in Study 2) by Paul, Passarotti, and Stiles (2003) showed no differences in speed of processing in children and adults. However, when Paul et al. (2003) increased task demands by introducing a task-switching component, children were significantly slower than adults. If task demands indeed influence the extent to which activation is distributed in children, it should be possible to experimentally alter patterns of activation by manipulating the task parameters. A study is currently in progress to examine the effects of altering task demands on the activation patterns of children and adults.

Although our functional studies did not specifically examine the effects of strategy differences on functional activation, it is likely that children's changing strategies also played a role in the more extensive functional activation exhibited by children. Previous studies, designed to examine developmental change in the strategies children use to solve visuospatial problems, have shown that both the range of available strategies and children's ability to implement efficient strategies improve with age (Akshoomoff & Stiles, 1995a, 1995b; Stiles & Stern, 2001). In our studies' tasks, improvement in children's performance may reflect a transition from reliance on a variety of simple, but inefficient, strategies to the use of a single, more effective strategy. In this case, consistent use of a single, efficient strategy may streamline performance and strengthen neural connections within a pathway, and this may result in more focal activation.

Are Neural Organization and Function Different During Development?

The data documenting significant developmental change in cognition might, by itself, account for the shifting patterns of activation observed in our fMRI studies.

However, it is equally clear from previous studies of brain development that there are important changes in the structure and organization of the brain that parallel the cognitive shifts. Moreover, there is substantial evidence that experience plays a critical role in directing the course and content of those neurodevelopmental changes. Thus, changes in cognitive ability may well interact with and affect the development of the neural substrate.

Postnatal human brain development is a protracted process, with changes in total brain volume, myelination, metabolism, vascularization, cerebral blood flow, cortical gray volume, and synaptic connectivity all extending well into adolescence. With the exception of total brain volume and myelination, which increase montonically with development, each of these major processes follows a developmental profile characterized by initial exuberance and followed by the pruning, or scaling back, of neural elements. The cycle of exuberance and pruning unfolds in different brain regions at different points in development, with sensorimotor systems developing earliest and frontal lobe regions last (e.g., Chugani et al., 1987; Huttenlocher & Dabholkar, 1997; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Yakovlev & Lecours, 1967). Experience plays an important role in the unfolding of these developmental cycles of exuberance and pruning (e.g., Black & Greenough, 1986; Crair, Gillespie, & Stryker, 1998; Greenough, 1993; Hubel, Wiesel, & LeVay, 1977; Katz, Weliky, & Crowley, 2000; Shatz, 1994). Greenough (1993) described this kind of cyclic neurological change as “experience expectant.” He suggested that it reflects the processes of adaptation necessary for the developing nervous system to utilize the sorts of environmental information that are ubiquitous and essential for basic information processing. That is, for the brain to develop normally, it must receive certain critical kinds of input (e.g., pattern input for vision, sound variation for audition, or coordinated muscle activity for the motor system). In that sense, brain development is experience-expectant. Greenough contrasted this kind of experience-expectant neurological change with a second kind of change, which he termed “experience dependent” because it reflects the acquisition of information that is unique to the individual. This kind of change tends to be localized to brain regions processing specific information types. He called the experience dependent change the neurological basis of learning. Indeed, many of the adult studies discussed earlier were designed to look specifically at the effects of explicit training on brain organization and involved more localized brain regions, thus reflecting this kind of experience-dependent learning.

Figure 4 illustrates the contrast between experience-expectant and experience-dependent change for one particular marker of brain development, synaptic density. To examine the importance of input on brain organization, animals in these experiments (rats) were reared in two quite different environmental contexts. One group was reared in a complex environment with many different objects arranged in constantly changing configurations, and in the company of a large number of companions. Animals in the second group were reared in isolation in wire

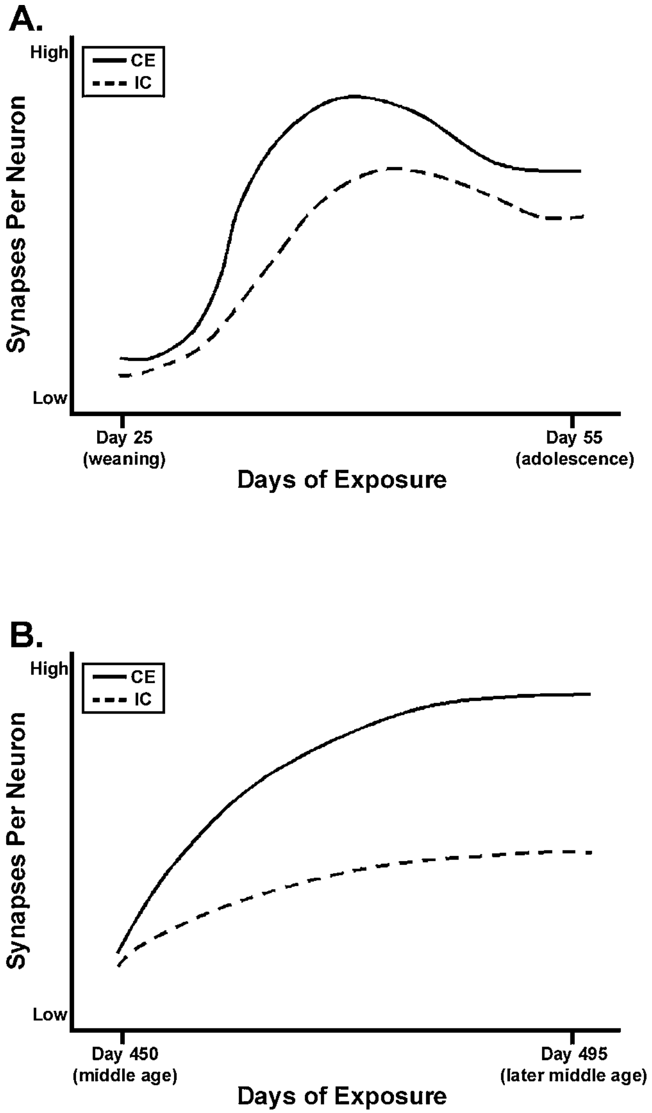

FIGURE 4 A. Effects of exposure to complex environment (CE) or individual cage (IC) for young rats. B. Effects of exposure to complex environment (CE) or individual cage (IC) for adult rats. Adapted from Figures 1.6 and 1.8 from Black & Greenough, 1986. Reprinted with permission from the publisher.

laboratory cages. The developmental component of the experiment is represented across panels A and B; the data from juvenile rats is shown in A, and the data from adults is shown in B. For each graph, synaptic density is indicated on the x-axis, and duration of exposure to the environmental condition on the y-axis. There are two important points to note from these data. First, environmental context affects synaptic density regardless of the age of the animal; input matters at every age. Second, the profile of change in synaptic density over time is qualitatively different depending on the age of the animal. Exposure to identical environmental conditions, whether impoverished or complex, results in different profiles of synaptic density, depending on age. That is, effect of experience on the neural substrate differs with age, suggesting that there are features of the neural context that are unique to the developing organism.

How do these findings relate to the question of interpreting patterns of developmental change in neural activation? The data on experience-expectant and experience-dependent change demonstrate that the developmental context within which learning occurs matters. Although experience-dependent changes are clearly an important component of change in patterns of activation for both adults and children, data on experience-expectant changes suggest that factors uniquely associated with the developing brain may make separate contributions to the change in profiles of neural activation for children. Note that the available data on synaptic exuberance and pruning in humans (Huttenlocher & Dabholkar, 1997; Huttenlocher et al., 1982) show region-specific differences in the timing of these events. Thus, the specific effects of experience-expectant neurodevelopmental processes on patterns of brain activation may well differ depending on the brain regions under study and the age of the children. The studies of visuospatial processing discussed earlier involve ventral–temporal regions. Although there are no human data on synaptic density from this brain region, data from occipital regions indicate that synaptic exuberance peaks during the first year of life and begins a slow decline that extends into middle adolescence (Huttenlocher et al., 1982). Thus, data from the visuospatial task with 10- to 12-year-olds may reflect processes associated with late neurodevelopmental synaptic pruning (i.e., the tail of the curve in Figure 4A). By contrast, synaptic exuberance peaks in the frontal lobe in middle childhood (Huttenlocher & Dabholkar, 1997) and then begins to decline. Thus, studies of attention or language processing focused on frontal lobe functioning in middle childhood may reflect the effects of both synaptic exuberance and pruning (see the peak of the curve in Figure 4A).

How Do Cognitive and Neural Development Interact?

One final point that should be emphasized is that the patterns of change observed in the studies of cognitive and brain development are not independent.

When Greenough (1993) discussed developmental change in the neural substrate as experience expectant, he meant specifically that the development of typical patterns of brain organization requires specific kinds of input. That is, input, in the form of sensory information or behavior, has specific modulatory effects on the stabilization or retraction of synaptic connections in the developing brain. Indeed, the importance of understanding the interaction between experience and brain organization is not limited to development; it extends into adulthood. Experience-dependent learning also specifies the relationship between the animal's experience and the organization of the brain. The effects of experience-dependent learning are more localized, reflecting specific learning of new information, but they nonetheless reflect interaction between the experience and the brain.

The evidence for the interaction between experience and brain development comes from both animal studies and studies of clinical human populations. Numerous animal studies have demonstrated the effects of deprivation on the development of brain systems (e.g., Rosenzweig & Bennett, 1972; Rosenzweig, Krech, Bennett, & Diamond, 1962); specifically, cortical regions that fail to receive appropriate input at critical points in development organize differently than regions that receive typical input. Conversely, studies of animals with early brain lesions have demonstrated the capacity of the developing neural system to form alternative patterns of organization to retain critical functions that would normally have been mediated by damaged brain regions (e.g., Sur, Angelucci, & Sharma, 1999; Sur, Pallas, & Roe, 1990). Studies of clinical populations confirm that this profile of early brain plasticity applies to humans as well. Electrophysiological and neuroimaging studies of congenitally deaf or blind individuals have shown that cortical regions deprived of normal sensory input acquire alternative functions (Neville, 1990; Finney, Fine, & Dobkins, 2001). For example, Neville has shown that primary auditory cortex of congenitally deaf adults responds to visual stimulation. Brain imaging studies of blind individuals who read Braille have documented responsiveness to tactile stimulation in occipital regions (Cohen et al., 1997). Studies of children with early focal brain injury provide a substantial base of evidence that the developing human brain is capable of considerable neural and cognitive compensation. Longitudinal studies of children with pre- or perinatal stroke have shown patterns of both early deficit and substantial development of higher cognitive functions, despite destruction of brain regions that are critical for those functions in adults (Stiles, 2000; Stiles, Bates, Thal, Trauner, & Reilly, 1998).

CONCLUSIONS

It is clear from these studies of patient populations that the developing human brain is responsive to input and can exhibit substantial developmental plasticity in its organization. However, as discussed in the introductory sections of this article, neither the animal studies nor the studies of pathological development in clinical populations can provide a window into the development of higher cognitive functions in typically developing children. Do normally developing brains exhibit the same capacity to respond differentially to input? Is the capacity to respond flexibly to input a critical feature of human brain development? What is the relationship between levels of cognitive and brain development? Does task difficulty or learning affect the engagement of neural systems? fMRI studies provide the opportunity to address critical issues in brain–behavior development. This work is in the very early stages, and there is, as yet, very little child imaging data available. At this point, it is critical to look to related areas of research to guide and constrain hypotheses. From the animal studies, we have identified the possibility that developmental changes in activation profiles might be affected by the large, uniquely developmental processes of exuberance and pruning that affect large cortical networks, the vascular system, metabolism, and so forth. Drawing from other studies on cognitive development, we have focused on tasks and behaviors that are known to change in specific and well-documented ways across a target age range. Indeed, we have identified changes in activation patterns that relate meaningfully to known changes in cognitive development. The studies reviewed here suggest that activation becomes increasingly consolidated as the child develops and as the child becomes more proficient at the task. This finding is consistent with all of the developmental findings we have used to guide our work. These data constitute a first step in exploring the relationships between cognitive development and developmental change in the neural substrate. The principle of functional consolidation of activation as one defining characteristic of neuroimaging data linking cognitive and brain development is a reasonable and conservative one. Others are sure to follow.

ACKNOWLEDGMENTS

This work was supported by the National Institute of Child Health and Human Development Grant R01-HD25077, the National Institute of Neurological Disorders and Stroke Grant P50-NS22343, and the National Institute of Deafness and Communicative Disorders Grant P50-DC01289. We thank the parents and children for their participation in the studies described in this article.

REFERENCES

Akshoomoff, N. A., & Stiles, J. (1995a). Developmental trends in visuospatial analysis and planning: I. Copying a complex figure. *Neuropsychology, 9,* 364–377.

Akshoomoff, N. A., & Stiles, J. (1995b). Developmental trends in visuospatial analysis and planning: II. Memory for a complex figure. *Neuropsychology, 9,* 378–389.

Bandettini, P. A., Wong, E. C., Hinks, R. S., Tikofsky, R. S., & Hyde, J. S. (1992). Time course EPI of human brain function during task activation. *Magnetic Resonance in Medicine, 25,* 390–397.

Barrett, S. E., & Shepp, B. E. (1988). Developmental changes in attentional skills: The effect of irrelevant variations on encoding and response selection. *Journal of Experimental Child Psychology, 45,* 382–399.

Black, J. E., & Greenough, W. T. (1986). Induction of pattern in neural structure by experience: Implications for cognitive development. In M. E. Lamb, A. L. Brown, & B. Rogoff (Eds.), *Advances in developmental psychology* (Vol. 4, pp. 1–50). Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.

Bookheimer, S. Y. (2000). Methodological issues in pediatric neuroimaging. *Ment Retard Dev Disabil Res Rev, 6,* 161–165.

Booth, J. R., MacWhinney, B., Thulborn, K. R., Sacco, K., Voyvodic, J. T., & Feldman, H. M. (2000). Developmental and lesion effects in brain activation during sentence comprehension and mental rotation. *Developmental Neuropsychology, 18,* 139–169.

Broman, S. H., & Fletcher, J. (1999). *The changing nervous system: Neurobehavioral consequences of early brain disorders.* New York: Oxford University Press.

Brown, M., Keynes, R., & Lumsden, A. (2001). *The developing brain.* New York: Oxford University Press.

Bunge, S. A., Dudukovic, N. M., Thomason, M. E., Vaidya, C. J., & Gabrieli, J. D. (2002). Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron, 33,* 301–311.

Buxton, R. B., & Frank, L. R. (1997). A model for the coupling between cerebral blood flow and oxygen metabolism during neural stimulation. *Journal of Cerebral Blood Flow and Metabolism, 17,* 64–72.

Carver, L. J., Bauer, P. J., & Nelson, C. A. (2000). Associations between infant brain activity and recall memory. *Developmental Science, 3,* 234–246.

Carver, L. J., Dawson, G., Panagiotides, H., Meltzoff, A. N., McPartland, J., Gray, J., et al. (2003). Age-related differences in neural correlates of face recognition during the toddler and preschool years. *Developmental Psychobiology, 42*(2)*,* 148–159.

Casey, B. J., Cohen, J. D., Jezzard, P., Turner, R., Noll, D. C., Trainor, R. J., et al. (1995). Activation of prefrontal cortex in children during a nonspatial working memory task with functional MRI. *NeuroImage, 2,* 221–229.

Casey, B. J., Davidson, M., & Rosen, B. (2002). Functional magnetic resonance imaging: Basic principles of and application to developmental science. *Developmental Science, 5,* 301–309.

Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology, 54,* 241–257.

Casey, B. J., Thomas, K. M., Welsh, T. F., Berkowitz, A., Forman, S. D., Eccard, C. H., et al. (1998). A developmental fMRI study of ventral and dorsal prefrontal organization [Abstract]. *Society for Neuroscience Abstracts, 24,* 494–410.

Casey, B. J., Trainor, R. J., Orendi, J. L., Schubert, A. B., Nystrom, L. E., Giedd, J. N., et al. (1997). A developmental functional MRI study of prefrontal activation during performance of a Go-No-Go task. *Journal of Cognitive Neuroscience, 9,* 835–847.

Chee, M. W., Hon, N., Lee, H. L., & Soon, C. S. (2001). Relative language proficiency modulates BOLD signal change when bilinguals perform semantic judgments. Blood oxygen level dependent. *NeuroImage, 13,* 1155–1163.

Chugani, H. T. (1994). Development of regional brain glucose metabolism in relation to behavior and plasticity. In G. Dawson et al. (Eds.), *Human behavior and the developing brain* (pp. 153–175). New York: Guilford.

Chugani, H. T., Phelps, M. E., & Mazziotta, J. C. (1987). Positron emission tomography study of human brain functional development. *Annals of Neurology, 22,* 487–497.

Cohen, L. B., & Cashon, C. H. (2001). Do 7-month-old infants process independent features or facial configurations? *Infant & Child Development, 10,* 83–92.

Cohen, L. G., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., Dambrosia, J., et al. (1997). Functional relevance of cross-modal plasticity in blind humans. *Nature, 389,* 180–183.

Conboy, B., & Mills, D. (2001, April). *Two languages, one developing brain: Effects of vocabulary size on bilingual toddlers' event-related potentials to auditory words*. Paper presented at the meeting of the Society for Research in Child Development, Minneapolis, MN.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex, 6,* 39–49.

Crair, M. C., Gillespie, D. C., & Stryker, M. P. (1998). The role of visual experience in the development of columns in cat visual cortex. *Science, 279,* 566–570.

Damon, W. (1998). *Handbook of child psychology: Cognition, Perception, and Language* (5th ed., Vol. 2). New York: Wiley.

de Haan, M., & Nelson, C. A. (1997). Recognition of the mother's face by six-month-old infants: A neurobehavioral study. *Child Development, 68,* 187–210.

de Haan, M., & Nelson, C. A. (1999). Brain activity differentiates face and object processing in 6-month-old infants. *Developmental Psychology, 35,* 1113–1121.

Dehaene, S., Dupoux, E., Mehler, J., Cohen, L., Paulesu, E., Perani, D., et al. (1997). Anatomical variability in the cortical representation of first and second language. *Neuroreport, 8,* 3809–3815.

Delis, D. C., Kiefner, M. G., & Fridlund, A. J. (1988). Visuospatial dysfunction following unilateral brain damage: Dissociations in hierarchical hemispatial analysis. *Journal of Clinical & Experimental Neuropsychology, 10,* 421–431.

Delis, D. C., Robertson, L. C., & Efron, R. (1986). Hemispheric specialization of memory for visual hierarchical stimuli. *Neuropsychologia, 24,* 205–214.

Deruelle, C., & de Schonen, S. (1991). Hemispheric asymmetries in visual pattern processing in infancy. *Brain and Cognition, 16,* 151–179.

Deruelle, C., & de Schonen, S. (1995). Pattern processing in infancy: Hemispheric differences in the processing of shape and location of visual components. *Infant Behavior & Development, 18,* 123–132.

de Schonen, S., & Mathivet, E. (1989). First come, first served: A scenario about the development of hemispheric specialization in face recognition during infancy. *Cahiers de Psychologie Cognitive, 9,* 3–44.

Desimone, R., & Ungerleider, L. G. (1989). Neural mechanisms of visual perception in monkeys. In H. Goodglass & A. R. Damasio (Eds.), *Handbook of Neuropsychology* (Vol. 2, pp. 267–299). New York: Elsevier.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K., & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Cognitive Brain Research, 7,* 1–13.

Dukette, D., & Stiles, J. (1996). Children's analysis of hierarchical patterns: Evidence from a similarity judgment task. *Journal of Experimental Child Psychology, 63,* 103–140.

Dukette, D., & Stiles, J. (2001). The effects of stimulus density on children's analysis of hierarchical patterns. *Developmental Science, 4,* 233–251.

Enns, J. T., & Cameron, S. (1987). Selective attention in young children: The relations between visual search, filtering, and priming. *Journal of Experimental Child Psychology, 44,* 38–63.

Farah, M. J. (1996). Is face recognition "special"? Evidence from neuropsychology. *Behavioural Brain Research, 76,* 181–189.

Fink, G. R., Halligan, P. W., Marshall, J. C., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1996). Where in the brain does visual attention select the forest and the trees? *Nature, 382*(6592), 626–628.

Finney, E. M., Fine, I., & Dobkins, K. R. (2001). Visual stimuli activate auditory cortex in the deaf. *Nature Neuroscience, 4,* 1171–1173.

Flavell, J. H. (2000). The history and future of cognitive development research. In K. Lee (Ed.), *Childhood Cognitive Development: The essential readings* (pp. 8–29). Malden, MA: Blackwell.

Gaillard, W. D., Grandin, C. B., & Xu, B. (2001). Developmental aspects of pediatric fMRI: considerations for image acquisition, analysis, and interpretation. *NeuroImage, 13,* 239–249.

Gaillard, W. D., Hertz-Pannier, L., Mott, S. H., Barnett, A. S., LeBihan, D., & Theodore, W. H. (2000). Functional anatomy of cognitive development: fMRI of verbal fluency in children and adults. *Neurology, 54,* 180–185.

Gathercole, S. E. (1998). The development of memory. *Journal of Child Psychology & Psychiatry & Allied Disciplines, 39,* 3–27.

Gauthier, I., Anderson, A. W., Tarr, M. J., Skudlarski, P., & Gore, J. C. (1997). Levels of categorization in visual recognition studied using functional magnetic resonance imaging. *Current Biology, 7,* 645–651.

Gauthier, I., Behrmann, M., & Tarr, M. J. (1999). Can face recognition really be dissociated from object recognition? *Journal of Cognitive Neuroscience, 11,* 349–370.

Gauthier, I., & Nelson, C. A. (2001). The development of face expertise. *Current Opinion in Neurobiology, 11,* 219–224.

Gauthier, I., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). Expertise for cars and birds recruits brain areas involved in face recognition. *Nature Neuroscience, 3,* 191–197.

Gauthier, I., & Tarr, M. J. (1997). Becoming a "Greeble" expert: exploring mechanisms for face recognition. *Vision Research, 37,* 1673–1682.

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform "face area" increases with expertise in recognizing novel objects. *Nature Neuroscience, 2,* 568–573.

Gauthier, I., Tarr, M. J., Moylan, J., Skudlarski, P., Gore, J. C., & Anderson, A. W. (2000). The fusiform "face area" is part of a network that processes faces at the individual level. *Journal of Cognitive Neuroscience, 12,* 495–504.

Gauthier, I., Williams, P., Tarr, M. J., & Tanaka, J. (1998). Training "greeble" experts: a framework for studying expert object recognition processes. *Vision Research, 38,* 2401–2428.

Greenough, W. T. (1993). Experience and brain development: An update. In M. H. Johnson (Ed.), *Brain development and cognition: A reader*. Oxford, England: Blackwell.

Haxby, J. V., Horwitz, B., Ungerleider, L. G., & Maisog, J. M. (1994). The functional organization of human extrastriate cortex: A PET–rCBF study of selective attention to faces and locations. *Journal of Neuroscience, 14,* 6336–6353.

Holland, S. K., Plante, E., Weber Byars, A., Strawsburg, R. H., Schmithorst, V. J., & Ball, W. S., Jr. (2001). Normal fMRI brain activation patterns in children performing a verb generation task. *Neuroimage, 14,* 837–843.

Hubel, D. H., Wiesel, T. N., & LeVay, S. (1977). Plasticity of ocular dominance columns in monkey striate cortex. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences, 278,* 377–409.

Huttenlocher, J., Newcombe, N., & Sandberg, E. H. (1994). The coding of spatial location in young children. *Cognitive Psychology, 27,* 115–148.

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology, 387,* 167–178.

Huttenlocher, P. R., de Courten, C., Garey, L. J., & Van der Loos, H. (1982). Synaptogenesis in human visual cortex—evidence for synapse elimination during normal development. *Neuroscience Letters, 33,* 247–252.

Jacobson, M. (1991). *Developmental neurobiology* (3rd ed.). New York: Plenum.

Johnson, M. H., & Morton, J. (1991). *Biology and cognitive development: The case of face recognition*. Cambridge, MA: Blackwell.

Jueptner, M., & Weiller, C. (1995). Review: Does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *NeuroImage, 2,* 148–156.

Just, M. A., Carpenter, P. A., Keller, T. A., Eddy, W. F., & Thulborn, K. R. (1996). Brain activation modulated by sentence comprehension. *Science, 274,* 114–116.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neuroscience, 17,* 4302–4311.

Kanwisher, N., Stanley, D., & Harris, A. (1999). The fusiform face area is selective for faces, not animals. *Neuroreport, 10,* 183–187.

Katz, L. C., Weliky, M., & Crowley, J. C. (2000). Activity and the Development of the Visual Cortex: New Perspectives. In M. S. Gazzaniga (Ed.), *The New Cognitive Neuroscience* (pp. 199–221). Cambridge, MA: MIT Press.

Kimchi, R., & Merhav, I. (1991). Hemispheric processing of global form, local form, and texture. *Acta Psychologica, 76,* 133–147.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences, USA, 89,* 5675–5679.

Lamb, M. R., Robertson, L. C., & Knight, R. T. (1990). Component mechanisms underlying the processing of hierarchically organized patterns: Inferences from patients with unilateral cortical lesions. *Journal of Experimental Psychology: Learning, Memory, & Cognition, 16,* 471–483.

Lane, D. M., & Pearson, D. A. (1982). The development of selective attention. *Merrill-Palmer Quarterly, 28,* 317–337.

Levin, H. S., & Grafman, J. (2000). *Cerebral reorganization of function after brain damage.* New York: Oxford University Press.

Luciana, M., & Nelson, C. A. (1998). The functional emergence of prefrontally-guided working memory systems in four- to eight-year-old children. *Neuropsychologia, 36,* 273–293.

Martin, M. (1979). Local and global processing: The role of sparsity. *Memory & Cognition, 7,* 476–484.

Martinez, A., Moses, P., Frank, L., Buxton, R., Wong, E., & Stiles, J. (1997). Hemispheric asymmetries in global and local processing: Evidence from fMRI. *Neuroreport, 8,* 1685–1689.

Mauer, D., & Lewis, T. L. (2001). Visual acuity and spatial contrast sensitivity: Normal development and underlying mechanisms. In C. A. Nelson & M. Luciana (Eds.), *Handbook of developmental cognitive neuroscience* (pp. 237–251). Cambridge, MA: MIT Press.

Mazoyer, N., de Schonen, S., Quinton, O., Crivello, F., Reutter, B., & Mazoyer, B. (1999). Functional anatomy of face processing in two-month-old alert children. *NeuroImage, 9,* S346.

Mills, D. L., Coffey-Corina, S. A., & Neville, H. J. (1993). Language acquisition and cerebral specialization in 20-month-old infants. *Journal of Cognitive Neuroscience, 5,* 317–334.

Mills, D. L., Coffey-Corina, S., & Neville, H. J. (1997). Language comprehension and cerebral specialization from 13 to 20 months. *Developmental Neuropsychology, 13,* 397–445.

Molfese, D. L., Freeman, R. B., & Palermo, D. S. (1975). The Ontogeny of Brain Lateralization for Speech and Nonspeech Stimuli. *Brain & Language, 2,* 356–368.

Moses, P., Roe, K., Buxton, R. B., Wong, E. C., Frank, L. R., & Stiles, J. (2002). Functional MRI of global and local processing in children. *Neuroimage, 16,* 415–424.

Müller, R. A., Rothermel, R. D., Behen, M. E., Muzik, O., Chakraborty, P. K., & Chugani, H. T. (1997). Plasticity of motor organization in children and adults. *Neuroreport, 8,* 3103–3108.

Müller, R. A., Rothermel, R. D., Behen, M. E., Muzik, O., Mangner, T. J., & Chugani, H. T. (1997). Receptive and expressive language activations for sentences: A PET study. *Neuroreport, 8,* 3767–3770.

Nelson, C. A., & de Haan, M. (1996). Neural correlates of infants' visual responsiveness to facial expression of emotion. *Developmental Psychobiology, 29,* 577–595.

Nelson, C. A., Monk, C. S., Lin, J., Carver, L. J., Thomas, K. M., & Truwit, C. L. (2000). Functional neuroanatomy of spatial working memory in children. *Developmental Psychology, 36,* 109–116.

Nelson, C. A., Thomas, K. M., de Haan, M., & Wewerka, S. S. (1998). Delayed recognition memory in infants and adults as revealed by event-related potentials. *International Journal of Psychophysiology, 29,* 145–165.

Neville, H. J. (1990). Intermodal competition and compensation in development: Evidence from studies of the visual system in congenitally deaf adults. *Annals of the New York Academy of Sciences, 608,* 71–87; discussion 87–91.

Newcombe, N., Huttenlocher, J., Drummey, A. B., & Wiley, J. G. (1998). The development of spatial location coding: Place learning and dead reckoning in the second and third years. *Cognitive Development, 13,* 185–200.

Newcombe, N. S., & Huttenlocher, J. (2000). *Making space: The development of spatial representation and reasoning.* Cambridge, MA: MIT Press.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., et al. (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Sciences, USA, 89,* 5951–5955.

Passarotti, M. M., Paul, B. M., Bussiere, J. R., Buxton, R. B., Wong, E. C., & Stiles, J. (2003). The development of face and location processing: A fMRI study. *Developmental Science*.

Paul, B., Passarotti, A. M., & Stiles, J. (2003). *Face and location processing: A developmental perspective*. Manuscript in preparation.

Paul, B. M., Stiles, J., Passarotti, A. M., Bavar, N., & Bellugi, U. (2002). Face and place processing in Williams syndrome: Evidence for a dorsal-ventral dissociation. *Neuro Report, 13*(a), 1115–1119.

Paulesu, E., McCrory, E., Fazio, F., Menoncello, L., Brunswick, N., Cappa, S. F., et al. (2000). A cultural effect on brain function. *Nature Neuroscience, 3,* 91–96.

Perani, D., Dehaene, S., Grassi, F., Cohen, L., Cappa, S. F., Dupoux, et al. (1996). Brain processing of native and foreign languages. *Neuroreport, 7,* 2439–2444.

Perani, D., Paulesu, E., Galles, N. S., Dupoux, E., Dehaene, S., Bettinardi, V., et al. (1998). The bilingual brain: Proficiency and age of acquisition of the second language. *Brain, 121,* 1841–1852.

Postle, B. R., Zarahn, E., & D'Esposito, M. (2000). Using event-related fMRI to assess delay-period activity during performance of spatial and nonspatial working memory tasks. *Brain Research Protocols, 5,* 57–66.

Price, D. J., & Willshaw, D. J. (2000). *Mechanisms of cortical development.* New York: Oxford University Press.

Raichle, M. E., Fiez, J. A., Videen, T. O., & MacLeod, A.-M. K. (1994). Practice-related changes in human brain functional anatomy during nonmotor learning. *Cerebral Cortex, 4,* 8–26.

Robertson, L. C., Lamb, M. R., & Knight, R. T. (1988). Effects of lesions of temporal–parietal junction on perceptual and attentional processing in humans. *Journal of Neuroscience, 8,* 3757–3769.

Roe, K., Moses, P., & Stiles, J. (1999). Lateralization of spatial processes in school aged children. *Journal of Cognitive Neuroscience,* 41(Suppl.).

Rosenzweig, M. R., & Bennett, E. L. (1972). Cerebral changes in rats exposed individually to an enriched environment. *Journal of Comparative & Physiological Psychology, 80,* 304–313.

Rosenzweig, M. R., Krech, D., Bennett, E. L., & Diamond, M. C. (1962). Effects of environmental complexity and training on brain chemistry and anatomy: A replication and extension. *Journal of Comparative & Physiological Psychology, 55,* 429–437.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., et al. (2001). Mapping motor inhibition: Conjunctive brain activations across different versions of go/no-go and stop tasks. *NeuroImage, 13,* 250–261.

Schul, R., Townsend, J., & Stiles, J. (2003). The development of attentional orienting during the school-age years. *Developmental Science, 6*(3), 262–272.

Sergent, J. (1982). The cerebral balance of power: Confrontation or cooperation? *Journal of Experimental Psychology: Human Perception & Performance, 8,* 253–272.

Shatz, C. J. (1994). Role for spontaneous neural activity in the patterning of connections between retina and Lgn during visual system development. *International Journal of Developmental Neuroscience, 12,* 531–546.

Shepp, B. E., Barrett, S. E., & Kolbet, L. L. (1987). The development of selective attention: Holistic perception versus resource allocation. *Journal of Experimental Child Psychology, 43,* 159–180.

Stiles, J. (2000). Neural plasticity and cognitive development. *Developmental Neuropsychology, 18,* 237–272.

Stiles, J., Bates, E. A., Thal, D., Trauner, D., & Reilly, J. (1998). Linguistic, cognitive, and affective development in children with pre- and perinatal focal brain injury: A ten-year overview from the San Diego longitudinal project. In C. Rovee-Collier, L. P. Lipsitt, & H. Hayne (Eds.), *Advances in infancy research* (pp. 131–163). Stamford, CT: Ablex.

Stiles, J., Bates, E. A., Thal, D., Trauner, D. A., & Reilly, J. (2002). Linguistic and spatial cognitive development in children with pre- and perinatal focal brain injury: A ten-year overview from the San Diego longitudinal project. In M. H. Johnson, Y. Munakata, & R. O. Gilmore (Eds.), *Brain Development and Cognition: A Reader* (Vol. 2, pp. 272–291). Malden, MA: Blackwell.

Stiles, J., & Stern, C. (2001). Developmental change in spatial cognitive processing: Complexity effects and block construction performance in preschool children. *Journal of Cognition & Development, 2,* 157–187.

Sur, M., Angelucci, A., & Sharma, J. (1999). Rewiring cortex: The role of patterned activity in development and plasticity of neocortical circuits. *Journal of Neurobiology, 41,* 33–43.

Sur, M., Pallas, S. L., & Roe, A. W. (1990). Cross-modal plasticity in cortical development: Differentiation and specification of sensory neocortex. *Trends in Neurosciences, 13,* 227–233.

Taylor, M. J., & Baldeweg, T. (2002). Application of EEG, ERP and intracranial recordings to the investigation of cognitive functions in children. *Developmental Science, 5,* 318–334.

Taylor, M. J., McCarthy, G., Saliba, E., & Degiovanni, E. (1999). ERP evidence of developmental changes in processing of faces. *Clinical Neurophysiology, 110,* 910–915.

Thomas, K. M., & Casey, B. J. (1999). Functional MRI in Pediatrics. In C. T. W. Moonen & P. A. Bandettini (Eds.), *Functional MRI.* Berlin, Germany: Springer-Verlag.

Thomas, K. M., Drevets, W. C., Whalen, P. J., Eccard, C. H., Dahl, R. E., Ryan, N. D., et al. (2001). Amygdala response to facial expressions in children and adults. *Biological Psychiatry, 49,* 309–316.

Thomas, K. M., King, S. W., Franzen, P. L., Welsh, T. F., Berkowitz, A. L., Noll, D. C., et al. (1999). A developmental functional MRI study of spatial working memory. *NeuroImage, 10,* 327–338.

Ungerleider, L. G., & Mishkin, M. (1982). Two cortical visual systems. In D. J. Ingle, & M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of visual behavior* (pp. 549–586). Cambridge, MA: MIT Press.

Wojciulik, E., Kanwisher, N., & Driver, J. (1998). Covert visual attention modulates face-specific activity in the human fusiform gyrus: fMRI study. *Journal of Neurophysiology, 79,* 1574–1578.

Yakovlev, P. I., & Lecours, A. R. (1967). The myelogenetic cycles of regional maturation of the brain. In A. Mankowski (Ed.), *Regional development of the brain in early life* (pp. 3–69). Philadelphia: Davis.

Zald, D. H., & Iacono, W. G. (1998). The development of spatial working memory abilities. *Developmental Neuropsychology, 14,* 563–578.