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TARGET ARTICLE WITH COMMENTARIES AND RESPONSE

A shift from diffuse to focal cortical activity with development

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For commentaries on this article see Brown *et al.* (2006), Blakemore & Choudhury (2006) and Dick *et al.* (2006).

Abstract

Recent imaging studies have suggested that developmental changes may parallel aspects of adult learning in cortical activation becoming less diffuse and more focal over time. However, while adult learning studies examine changes within subjects, developmental findings have been based on cross-sectional samples and even comparisons across studies. Here, we used functional MRI in children to test directly for shifts in cortical activity during performance of a cognitive control task, in a combined longitudinal and cross-sectional study. Our longitudinal findings, relative to our cross-sectional ones, show attenuated activation in dorsolateral prefrontal cortical areas, paralleled by increased focal activation in ventral prefrontal regions related to task performance.

Introduction

How are behavioral changes during learning and development reflected in changes in the human brain? Functional magnetic resonance imaging provides us with an opportunity to explore these changes simultaneously. With this technology, researchers have begun to track cognitive and neural processes underlying learning and development. Recent imaging studies (e.g. Karni, Meyter, Jezzard, Adams, Turner & Ungerleider 1998; Brown, Lugar, Coalson, Miezin, Peterson & Schlaggar, 2005) suggest that these developmental changes may parallel aspects of adult learning. This study examines cortical changes with development from late childhood into early adolescence in the same individuals, to explicitly test how these processes are fine-tuned with experience during development (Johnson, 2002).

Evidence from neuroimaging studies of adult learning suggests that it is paralleled by a shift in the recruitment of cortical areas to those critical to task performance. One of the first functional imaging studies to track cortical changes with learning showed rapid changes in primary motor areas in human volunteers, with increases in the magnitude and extent of activation (Karni, Meyer, Rey-Hipolito, Jezzard, Adams, Turner & Ungerleider, 1995; Karni *et al.*, 1998). Changes occurred within a single session during motor sequence learning, with enhanced recruitment of motor cortex over successive weeks of training. Prolonged learning and continuing enhanced performance have further been associated with increased recruitment of prefrontal cortex (Muller, Kleinhans, Pierce, Kemmotsu & Courchesne, 2002). These cortical changes are thought to represent organization, associated with changes, development and consolidation of neural networks as new behavioral repertoires become established.

How are changes during development reflected in changes in cortical activity? Developmental neuroimaging studies suggest that development is supported by changes in patterns of brain activation, including enhancement of activation in critical areas, attenuation in others, and changes in the extent of activation as well as shifts in lateralization (e.g. Booth, Burman, Meyer, Trommer, Davenport, Parrish, Gitelman & Mesulam, 2004; Gaillard, Balsamo, Ibrahim, Sachs & Xu, 2003; Hertz-Pannier, Gaillard, Mott, Cuenod, Bookheimer, Weinstein, Conry, Papero, Schiff, Le Bihan & Theodore, 1997; Luna & Sweeney 2004; Nelson, Monk, Lin, Carver, Thomas & Truwit, 2000; Thomas, Hunt, Vizueta, Sommer, Durston, Yang & Worden, 2004).

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Developmental changes in patterns of brain activation may be conceptualized as a shift in patterns of activation from diffuse to more focal, or a fine-tuning of relevant neural systems (Johnson, 2002). Here, the shift to focal activation may represent increases in the magnitude or extent of activation in regions critical to task performance, similar to changes seen in adult learning (Bunge, Dudukovic, Thomason, Vaidya & Gabrieli, 2002; Casey, Trainor, Orendi, Schubert, Nystrom, Cohen, Noll, Giedd, Castellanos, Haxby, Forman, Dahl & Rapoport, 1997; Casey, Thomas, Davidson, Kunz & Franzen, 2002; Gaillard, Hertz-Pannier, Mott, Barnett, LeBihan & Theodore, 2000; Hertz-Pannier *et al.*, 1997; Holland, Plante, Weber Byars, Strawsburg, Schmithorst & Ball, 2001; Luna, Thulborn, Munoz, Merriam, Garver, Minshew, Keshavan, Genovese, Eddy & Sweeney, 2001; Monk, McClure, Nelson, Zarahn, Bilder, Leibenluft, Charney, Ernst & Pine, 2003; Moses, Roe, Buxton, Wong, Frank & Stiles, 2003; Nelson, McClure, Monk, Zarahn, Leibenluft, Pine & Ernst, 2002; Schlaggar, Brown, Lugar, Visscher, Miezin & Petersen, 2002; Tamm, Menon & Reiss, 2002; Turkeltaub, Gareau, Flowers, Zeffiro & Eden, 2003). The shift from diffuse activation may represent attenuation of activation in other, less critical, cortical areas, either in the number of regions activated or in the extent of activated tissue (Brown *et al.*, 2005; Bunge *et al.*, 2002). Although these changes may mirror aspects of adult learning, the time window of this shift is longer, with changes spanning years rather than hours or weeks.

To date, the developmental observations described above have relied on cross-sectional samples (e.g. Brown *et al.*, 2005) or even comparisons across studies (e.g. Casey, Cohen, Jezzard, Turner, Noll, Trainor, Giedd, Kaysen, Hertz-Pannier & Rapoport, 1995; Cohen, Forman, Braver, Casey, Servan-Schreiber & Noll, 1994). However, cross-sectional analyses may falsely suggest changes over time through confounds that are accidentally introduced into the study design, such as a time scale that is related to the variable of interest (Kraemer, Yesavage, Taylor & Kupfer, 2000). This may be particularly noteworthy in studies of development, as maturation and learning are related to age. Furthermore, cross-sectional data introduce significant noise in neuroimaging studies given the large individual variability in brain structure during development (Caviness, Kennedy, Richelme, Rademacher & Filipek, 1996) and as such may result in type II errors, both in functional and structural studies.

In the current study, our primary objective was to track cognitive and brain development from late childhood into early adolescence in the same individuals. We hypothesized that there would be a developmental shift in activation patterns from diffuse to more focal, where activation in cortical regions critical to task performance would increase in magnitude or extent, and activation in less critical regions would attenuate. Changes in the extent of activation during performance of a target detection task were investigated using whole-brain voxelbased analyses, while changes in critical areas were investigated using a second, region-of-interest (ROI) analysis. Based on previous cross-sectional studies, we hypothesized that the magnitude of activation would increase in inferior prefrontal cortex, as activation of this region has previously been shown to correlate with performance on our task (Durston, Thomas, Yang, Ulug, Zimmerman & Casey, 2002). Furthermore, we hypothesized that activation magnitude in other less critical prefrontal regions would decrease. These hypotheses test theoretical issues related to how cognitive and neural systems are fine-tuned with development (Johnson, 2002). A second objective of this study was to evaluate the added value of a longitudinal approach, by comparing a within-subject to a between-subjects design.

Methods

Subjects

A total of 21 scans were collected from 14 subjects. Seven subjects (three male) participated in two fMRI sessions, on average 2.1 (0.6) years apart, when they were 9.0 (1.2) and 11.0 (1.2) years of age (group 1 at time 1 and 2). A second group of seven subjects (three male) participated in the study once, when they were on average 12.1 (2.0) years of age (group 2). Average age was not significantly different between group 1 at time 2 and group 2 ($t = 1.2$, $p = .25$) nor was Tanner-based pubertal stage different for group 1 at time 2 and group 2 (mean = 1.7 (1.1) and 2.6 (1.2), respectively, $t = 1.0$, $p = .32$). For each subject, written assent and parental informed consent were obtained. The procedure was approved by the institutional review board at Weill Medical College of Cornell University.

Paradigm

All subjects performed a target detection task while in the MRI environment. The task was to press a button in response to a string of visually presented stimuli, but to avoid responding to a rare non-target. Stimuli were cartoon characters, with a cat character serving as the non-target (Davidson, Horvitz, Tottenham, Fossella, Watts, Ulug & Casey, 2004; Durston *et al.*, 2002). Two variations of the same task were used with different cartoon characters and a slightly different task design in the

second version (Davidson *et al.*, 2004). In both sessions, 25% of trials were non-target trials. All trials lasted 4.0 s and included two functional scans. The use of a rapid mixed-trial design allowed us to include only correct trials in the imaging analyses (see Durston *et al.*, 2002).

Functional imaging analysis

Functional scans were EPI BOLD images, acquired in 24 slices in either axial or coronal direction on a 1.5 T GE Signa scanner (TR = 2000, TE = 40, 64 × 64, 4 to 6 mm slice thickness, 3.125 x 3.125 mm in-plane resolution). Analysis of functional images has been described in detail elsewhere (Durston *et al.*, 2002), and involved motion correction, image smoothing (2 mm) and cross-registration of data. Whole-brain, voxelwise between-group analyses were performed for activation patterns associated with both target and non-target trials (longitudinal comparison: group 1 at time 1 vs. group 1 at time 2; cross-sectional comparison: group 1 at time 1 vs. group 2; and control comparison: group 1 at time 2 vs. group 2) with multiple comparison correction using $p < .0001$ and 3 or more contiguous voxels (Forman, Cohen, Fitzgerald, Eddy, Mintun & Noll, 1995). In order to further investigate developmental changes in magnitude of activation within regions involved in performance of this task, a region-based follow-up analysis was performed. Here, a fixed effects analysis of variance was performed on functional imaging data from group 1 at the first time point, comparing non-target to target trials. For each trial type, two 2-second scans were included in the analyses taken at the peak of the haemodynamic response (4 and 6 s after stimulus presentation). Regions of three or more contiguous voxels ($p < .01$) were identified (Forman *et al.*, 1995). The map of regions of interest that was generated was binarized and used as a mask in the analysis of the scans from the second time point for group 1 and group 2, allowing us to compare the magnitude of activation within regions. Signal change was defined on an individual basis as percent change for non-target from target trials, in order to compare signal change between groups.

Results

Behavioral

Longitudinal results

For the longitudinal comparison, subjects were tested at two time points, 2 years apart (mean ages 9 and 11 years). Mean reaction time (RT) on target detection trials decreased for all subjects from time 1 to time 2 (638 (80) ms and 432 (49) ms respectively, $t = 5.8$, $p < .001$). Overall accuracy for detecting targets did not change significantly (93.5 (6.1)% and 98.2 (4.7)%, respectively, $t = 1.6$, $p = .14$), although the number of children performing at ceiling (100% accurate detection) significantly increased from 28 to 86% of the sample ($\chi^2 = 4.7$, $p < .04$). A decrease in accuracy on non-target trials as a function of time failed to reach significance (89.0 (7.2)% at time 1 and 80.4 (8.3)% at time 2, $t = 2.0$, $p = .061$).

Cross-sectional results

For the cross-sectional comparison, the data from time 1 were compared to data from a second set of subjects, with mean age of group 1 at time 2. Reaction time on target trials was faster for group 2 (512 (109) ms) than group 1 (638 (80) ms) ($t = 2.5$, $p < .030$), but changes in accuracy on both target and non-target trials were not significant (ACC on target trials was 93.5 (6.1)% for group 1 and 96.4 (5.1)% for group 2, $t = 1.0$, $p = .35$; the number of subjects at ceiling was 28% and 57%, respectively, $\chi^2 = 1.2$, $p = .28$; ACC on non-target trials was 89.0 (7.3)% and 83.9 (13.4)%, respectively, $t = 0.9$, $p = .40$). There were no significant differences in performance between group 1 at time 2 and group 2.

Imaging

Longitudinal findings

The longitudinal whole-brain, voxel-based comparison revealed regions in dorsolateral prefrontal cortex, extending into surrounding cortex that decreased in activation between time 1 and time 2 (total extent was 35 voxels at $p < .0001$, maximally active voxels in BA 8/9 at −34, 27, 43 and −49, 10, 43). For regions of maximal change see Figure 1. For the longitudinal ROI analysis, several cortical regions showed significant change in the magnitude of MR signal change from time 1 to time 2 (see Table 1). Most regions displayed either a decrease in activation (e.g. dorsolateral prefrontal regions) or no change from time 1 to time 2 (e.g. primary motor cortex). The only region where activation increased between time 1 and time 2 was in the right inferior frontal gyrus (see Figure 2).

Cross-sectional findings

The cross-sectional whole-brain, voxel-based comparison also revealed prefrontal regions that decreased in activation between time 1 and time 2, although the extent was less (extent was 11 voxels at $p < .0001$, maximally

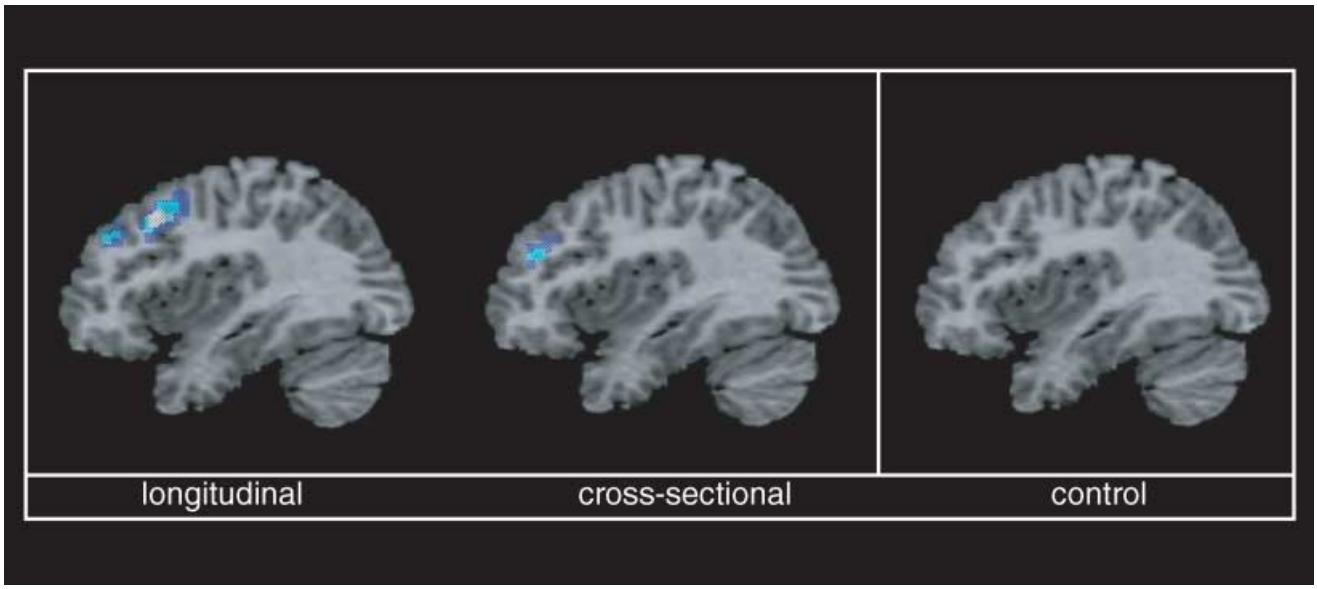

Figure 1 *Two-dimensional renderings of prefrontal decreases in cortical activation with development, overlayed on a standard subject's brain from the longitudinal and cross-sectional whole-brain analyses (p < .0005). As a control, the comparison of group 1 at time 2 to group 2 is also shown.*

Table 1 *Areas showing change for non-target vs. target trials. BA = Brodmann Area, L = left, R = right, B = bilateral.* * p < .05

					Change at time 2 (%)	
Area	BA	Side	Talairach	Max F	Longitudinal	Cross-sectional
Primary motor	4	L	(−40, −16, 60)	86.48	0.00	0.00
Medial frontal gyrus	10	L	(−12, 50, 11)	39.29	−0.03	0.04
Middle frontal gyrus		R	(14, 36, 36)	19.21	−0.02	0.08
		L	(−31, 34, 37)	24.56	0.01	–
Precentral gyrus	4/6	R	(55, −19, 60)	28.19	−0.20*	−0.06
Superior frontal gyrus	6	R	(46, 16, 61)	31.13	−0.46*	0.04
Anterior cingulate gyrus	24	B	(−6, 3, 28)	42.68	0.01	0.06
Posterior cingulate gyrus	30	B	(0, −44, 16)	17.45	−0.22*	−0.03
Superior temporal gyrus	22	R	(60, −29, 11)	21.85	−0.14*	−0.20*
Inferior frontal gyrus	47	R	(42, 12, −8)	13.41	0.08*	0.14*

active voxel in BA 9 at –36, 30, 18). For regions of maximal change see Figure 1. For the cross-sectional ROI comparison, a less consistent pattern was observed where a number of regions that displayed a reduction in activation in the longitudinal analysis, now displayed no clear change (see Table 1). However, activation in primary motor cortex remained unchanged between the two groups, and the region in right inferior frontal gyrus displayed an increase in activation.

A control comparison of group 1 at time 2 vs. group 2 revealed no significant changes ($p < .0001$) (see Figure 1).

Correlations between behavioral and imaging measures

Signal change in the ROI in the right ventral prefrontal region was correlated with accuracy on non-target trials ($r = –0.56$, $p < .029$) (see Figure 3), where subjects having the most difficulty withholding a response to non-targets activated this region more during those trials where a response was *correctly* withheld. The correlation was present in both the longitudinal and cross-sectional analyses ($r = –0.73$, $p < .016$ for the longitudinal analysis; $r = –0.57$, $p < .054$ for the cross-sectional analysis). A positive correlation between MR signal change and age in this region did not exceed trend level ($r = 0.52$, $p = .083$) (see Figure 3). The correlation between signal change and accuracy maintained significance, even when controlling for age.[1]

[1] Five outliers were excluded from these analyses distributed across all groups.

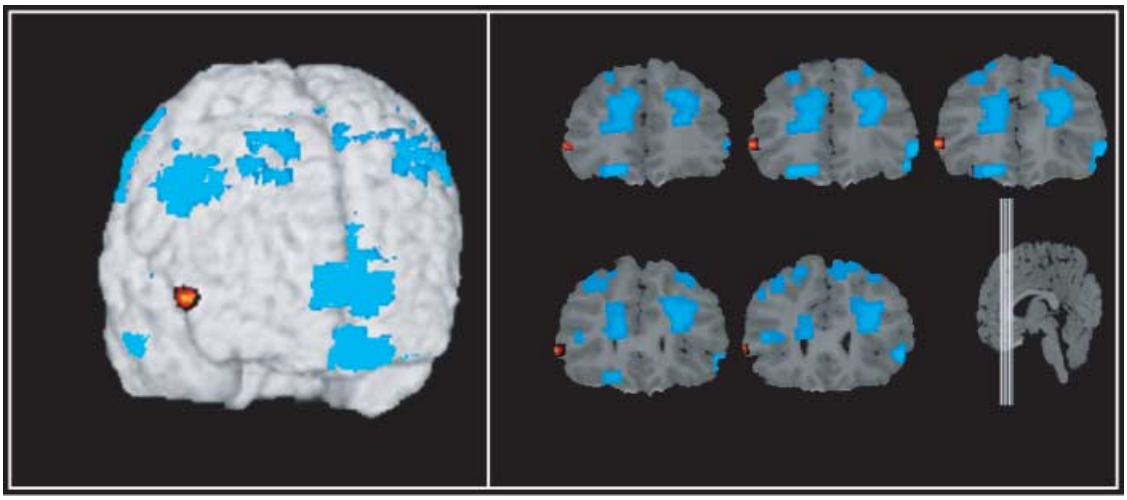

Figure 2 *Change in patterns of cortical activation with development. Cortical regions displaying increased (in red) or unchanged or reduced (in blue) activation at time 2 compared to time 1 of the longitudinal comparison (liberal threshold at* p < *.05 to show the extent of change).*

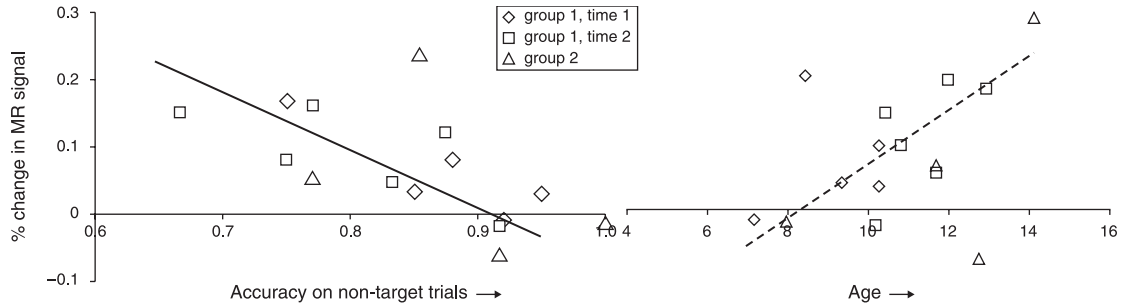

Figure 3 *Significant correlation for activation in ventral prefrontal cortex with accuracy on non-target trials (left;* p < *.03), and trend level correlation with age (right;* p = *.08).*[1]

Discussion

In the current study, we show a developmental shift in patterns of cortical activation from diffuse to focal activity, illustrating that with development, regions uncorrelated with task performance are recruited less. This change was associated with enhanced detection of targets in a cognitive control task, as evidenced by faster reaction times, near-ceiling performance in detection of targets, but no improvement in ability to override a response to non-targets. The only region to show an increase in activation across development during performance of this task was in ventral prefrontal cortex. Here, activation correlated with accuracy on non-target, nogo trials, suggesting that this region is related to successful task performance. These results suggest that even though the number of false alarms did not improve, there was a shift within the pattern of cortical activation that paralleled enhanced responding to targets. Activation decreased in other prefrontal cortical regions, although this was not true of primary motor cortex, where activation remained unchanged when comparing target versus non-target trials (i.e. motor responses versus no response). Taken together, these findings suggest differential development across sensorimotor and association cortex, at least in the context of performance of this task.

Behaviorally, target detection improved as indexed by improved reaction time and an increase in the number of subjects at ceiling accuracy. A decrease in accuracy on non-target trials failed to exceed trend level, most likely due to the relatively small number of subjects included in this study. Interestingly, there was a significant negative correlation between accuracy on non-target trials and activation in ventral prefrontal cortex, accompanied by a trend-level *positive* correlation between age and

activation in this region (see Figure 3). This suggests that at this developmental stage, subjects may in fact be responding more impulsively, related to their faster response on target detection trials and therefore need more top-down control in overriding a response to a non-target. Interestingly, this ties in with anecdotal evidence of increases in impulsive and risk-taking behavior in adolescence, and illustrates the complexity of the relationships between development, performance and brain activation patterns.

In this study, we combined whole-brain analyses with ROI analyses, allowing us to address both changes in the extent of activation (whole-brain analyses), and changes in activation magnitude (ROI analyses). The longitudinal whole-brain analysis revealed decreases in activation extent in regions in dorsolateral prefrontal cortex, where activation was not correlated to performance on this task. In contrast, the ROI analysis showed an increase in the amplitude of activation in the only region where performance and activation were correlated. This suggests an attenuation of activation in areas not critically involved in the task, and a corresponding increase in magnitude of activation in key areas. As such, these data support a shift from more diffuse to focal cortical activation with development. The increase in magnitude of activation in key areas is similar to changes seen in adult learning, and may represent reorganization in cortical areas, perhaps allowing for more efficient processing (Ungerleider, Doyon & Karni, 2002). However, the time window in the current study is much longer, spanning years rather than hours or weeks. The whole-brain comparisons investigating the extent of changes in activation did not reveal enhanced activity in regions in right ventral prefrontal cortex, possibly due to the limited sample size.

The reported shift in cortical patterns of activity is likely related to experience-driven maturational processes in the developing human brain that include both regressive and progressive events (Casey, Tottenham, Liston & Durston, 2005). Histologic studies have shown that new growth of dendrites and synaptic connections occur mainly during infancy and early childhood, with the excess synaptic connections being eliminated during later childhood and adolescence (Huttenlocher, 1979, 1990; Zecevic & Rakic, 2001). The exuberant connections that occur during infancy may form the anatomical basis of neural plasticity and certain types of learning (Huttenlocher, 1990). As such, pruning of neurons and elimination of connections later in development may reflect maturation in the developing human brain. These processes are believed to result in more efficient processing by increasing signal to noise in the system, in turn allowing for the strengthening of relevant connections, such as in the case of long-term potentiation (LTP). The shift in cortical activation observed in the current study may reflect the functional consequence of such maturation, but provide only an indirect index of suggested processes.

A number of pediatric structural MRI studies are consistent with these findings at an anatomical level, showing changes in cortical and subcortical volumes with development (Caviness *et al.*, 1996; Giedd, Snell, Lange, Rajapakse, Casey, Kozuch, Vaituzis, Vauss, Hamburger, Kaysen & Rapoport, 1996; Giedd, Blumenthal, Jeffries, Castellanos, Liu, Zijdenbos, Paus, Evans & Rapoport, 1999; Jernigan, Trauner, Hesselink & Tallal, 1991; Reiss, Abrams, Singer, Ross & Denckla, 1996; Sowell, Thompson, Holmes, Jernigan & Toga, 1999; Sowell, Thompson, Holmes, Batth, Jernigan & Toga, 1999; Sowell, Peterson, Thompson, Welcome, Henkenius & Toga, 2003). Increases in cortical gray matter volumes during childhood are followed by decreases during adolescence (Caviness *et al.*, 1996; Giedd *et al.*, 1999; Reiss *et al.*, 1996; Sowell *et al.*, 1999). These changes may in part reflect the ongoing neuronal regressive events, such as pruning and the elimination of connections. Cortical white matter has been shown to continue developing throughout adolescence and into adulthood, as evidenced by increases in volume and density (Giedd *et al.*, 1999; Paus, Zijdenbos, Worsley, Collins, Blumenthal, Giedd, Rapoport & Evans, 1999). Changes in cortical white matter pathways during this window of development have been confirmed using diffusion tensor imaging (DTI) techniques that provide greater detail on integrity of white matter fiber tracts, likely reflecting regularity and myelination of these tracts (e.g. Klingberg, Vaidya, Gabrieli, Moseley & Hedehus, 1999). More recently, these changes have been linked to enhanced cognitive performance (Liston, Watts, Tottenham, Davidson, Niogi, Ulug & Casey, 2005), illustrating the subtle interplay between neuroanatomical and cognitive maturation.

Both the longitudinal and cross-sectional whole-brain analyses revealed decreases in extent of activation in dorsolateral prefrontal cortex, in areas not critical to task performance. However, the number of affected voxels was greater for the longitudinal comparison. Importantly, a control comparison comparing the two groups of the same age (group 1 at time 2 and group 2) showed no significant differences (see Figure 1). Both the longitudinal and cross-sectional ROI comparisons showed increased activation in right inferior prefrontal cortex. However, the longitudinal comparison revealed additional reduction of activation in cortical regions, not as evident in the cross-sectional comparison. As such, these results confirm that studies tracking development within individuals are more sensitive to subtle developmental changes than cross-sectional comparisons.

We believe this study represents an important step in mapping the neural basis of brain maturation in the context of cognitive development within individuals. The use of longitudinal functional MRI showed a shift in patterns of cortical activation in development, consistent with activity becoming less diffuse and more focal, and related to enhanced cognitive performance.

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