Developmental Changes in Mental Arithmetic: Evidence for Increased Functional Specialization in the Left Inferior Parietal Cortex

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Arithmetic reasoning is arguably one of the most important cognitive skills a child must master. Here we examine neuro-developmental changes in mental arithmetic. Subjects (ages 8–19 years) viewed arithmetic equations and were asked to judge whether the results were correct or incorrect. During two-operand addition or subtraction trials, for which accuracy was comparable across age, older subjects showed greater activation in the left parietal cortex, along the supramarginal gyrus and adjoining anterior intra-parietal sulcus as well as the left lateral occipital temporal cortex. These age-related changes were not associated with alterations in gray matter density, and provide novel evidence for increased functional maturation with age. By contrast, younger subjects showed greater activation in the prefrontal cortex, including the dorsolateral and ventrolateral prefrontal cortex and the anterior cingulate cortex, suggesting that they require comparatively more working memory and attentional resources to achieve similar levels of mental arithmetic performance. Younger subjects also showed greater activation of the hippocampus and dorsal basal ganglia, reflecting the greater demands placed on both declarative and procedural memory systems. Our findings provide evidence for a process of increased functional specialization of the left inferior parietal cortex in mental arithmetic, a process that is accompanied by decreased dependence on memory and attentional resources with development.

Keywords: development, frontal cortex, mathematical, parietal cortex, reasoning

Introduction

Arithmetic reasoning is arguably one of the most important cognitive skills a child must master. Here we focus on an elementary and essential component of arithmetic reasoning — addition and subtraction. There has been a long history of research on the development of this type of simple quantification, which generally suggests an initial reliance on procedural knowledge and methods, such as counting followed by a gradual shift to retrieval from a network representation of arithmetic facts (Ashcraft, 1982). Ashcraft and Battaglia (1978) proposed that adults retrieve from memory the answer to a simple number problem (e.g. 3 + 4) through the activation of associative links between number combinations and solutions (Ashcraft and Battaglia, 1978). Most of the research done on the topic has followed the assumption that adults retrieve the results of simple calculation problems from a mental network (e.g. Ashcraft, 1982; Geary *et al.*, 1986; Miller *et al.*, 1984; LeFevre *et al.*, 1988; Rickard and Bourne, 1996). Research examining simple calculation performance in children, by contrast, has demonstrated that although as early as age 7 to 8 years there is some reliance on memory retrieval

of solutions, counting procedures and other reconstructive strategies are also prominently used (Groen and Parkman, 1972; Ashcraft *et al.*, 1984; Baroody *et al.*, 1984; Baroody, 1992). Thus, there appears to be a developmental shift from a flexible selection among a number of procedures by children to the use of a stable, invariant approach (i.e. fact retrieval from memory) by adults (Siegler and Shipley, 1995). Nevertheless, while there has been much research conducted on the ontogenetic progression of conceptual and procedural arithmetic knowledge (see Rittle-Johnson and Siegler, 1998, for a review), almost nothing is known about the neural basis of this developmental progress.

Much is already known about the way the brain processes arithmetic information in adults. Lesion studies, in particular, have been fundamental in elucidating the localization of arithmetic processes in the brain. For example, acalculia, the impaired ability to perform arithmetic calculations, often results from lesions to the (usually left) parietal cortex (Henschen, 1920; Benson and Weir, 1972; Grafman *et al.*, 1982; Warrington, 1982; McCarthy and Warrington, 1988; Rosselli and Ardila, 1989; Dehaene and Cohen, 1991; Lampl *et al.*, 1994; Takayama *et al.*, 1994; Tohgi *et al.*, 1995; Dehaene, 1997; Whalen *et al.*, 1997; Cohen *et al.*, 2000). These studies also have demonstrated that lesions to prefrontal (Fasotti *et al.*, 1992), frontoparietal (Cipolotti *et al.*, 1991) and subcortical structures, including the thalamus (Ojemann, 1974), are associated with impaired arithmetic reasoning.

Recently, a number of brain imaging studies of healthy adults have added to our knowledge of arithmetic processing (Roland and Friberg, 1985; Burbaud *et al.*, 1995, 1999, 2000; Rueckert *et al.*, 1996; Dehaene *et al.*, 1999; Kazui *et al.*, 2000; Gruber *et al.*, 2001; Menon *et al.*, 2000b,d, 2002; Rickard *et al.*, 2000). Across these studies, brain activation related to arithmetic tasks has been consistently reported in both the prefrontal and parietal cortex. In particular, the angular gyrus of the inferior parietal cortex has been identified as being a region specifically activated in response to increasing arithmetic complexity (Menon *et al.*, 2000d).

In this study, we investigate how brain activation during arithmetic calculation changes with age. We use a task involving addition and subtraction that is appropriate for our youngest (8 year old) subjects, yet it requires some effort on the part of the adolescent and young adult subjects. Seventeen subjects viewed arithmetic equations in the form '$a + b = c$' and were asked to judge whether the results were correct or not. Based on our previous imaging findings with adults (Menon *et al.*, 2000d) we hypothesized that age-related changes in activation would be observed in the prefrontal cortex and posterior parietal cortex, and that the intra-parietal region of

the posterior parietal cortex, in particular, would show increased functional specialization for mental arithmetic with development. In addition to identifying brain regions that show increases and decreases in activation with age, we examine the relationship between age and the gray matter density (GMD) in those regions, and provide for the first time data on the relationship between functional maturation and structural changes with age.

Materials and Methods

Subjects

Seventeen healthy, right-handed subjects (6 males and 11 females; ages 8.53–19.03 years; mean age 13.67) participated in the study after they (or their guardian) gave written informed consent. The lower age range for this study (8 years) was chosen as children at this developmental period are relatively facile at simple calculation, and memorization of addition and subtraction facts is commonly taught in school. Subjects had been recruited as typically developing controls for neurodevelopmental studies, and were screened for neurological, developmental and psychiatric disorders. The human subjects committee at Stanford University School of Medicine approved all protocols used in this study. Subjects were also assessed using the Wechsler Adult Intelligence Scale – 3rd edition (WAIS-III) or the Wechsler Intelligence Scale for Children – 3rd edition (WISC-III).
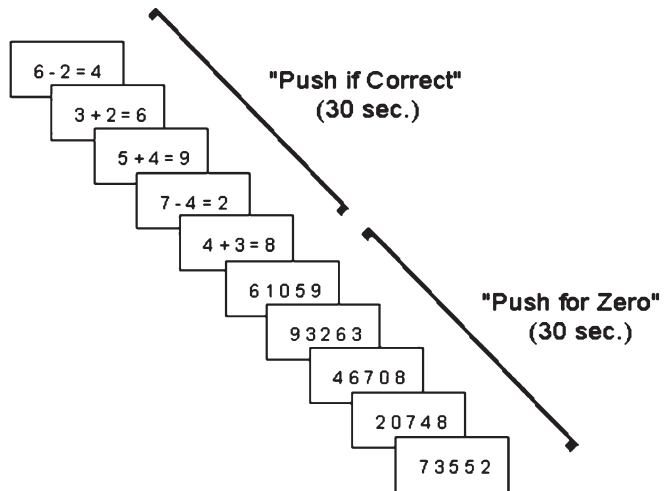
Arithmetic Task Experimental Design

The experiment began with a 30 s rest epoch followed by six alternating 30 s experimental and control epochs. During the rest epoch, subjects passively viewed a blank screen. Each experimental epoch consisted of five trials in which two-operand addition or subtraction equations (randomly intermixed) with either a correct or an incorrect resultant (e.g. $1 + 2 = 3$ or $5 - 2 = 4$) were presented. Equations were chosen such that the result never added up to more than nine, so that correct answers were always single digit. Sixty percent of the results were correct and required a button press and the other 40% were incorrect. Of the incorrect-resultant trials, half of the equations had resultants that were one more than the correct answer, and the other half had resultants one less than the correct answer. Subjects were instructed to respond with a key press only if the resultant of the arithmetic equation was correct. Each control epoch consisted of five trials in which a string of five single digits (e.g. '6 1 2 3 4' or '5 2 0 3 1') was presented (see Fig. 1). Subjects were instructed to respond with a key press only when a zero appeared in the string of digits. Equal numbers of button presses were required for experimental and control trials. During experimental epochs the instruction 'Push if Correct' was displayed for the entire length of the epoch, in order to remind the subjects of the task they were to perform. During the control epochs the instruction 'Push for 0' was displayed during the entire length of the epoch. All experimental and control stimuli were presented for 5250 ms, with an inter-stimulus interval (ISI) of 750 ms.

Behavioral Data Analysis

Due to equipment failure, behavioral data could not be obtained for one of the 17 subjects. For the remaining 16 subjects, the relationships between age and reaction time (RT) and accuracy (percentage of correct responses) to experimental and control trials were examined using Pearson correlations.

fMRI Acquisition

Images were acquired on a 1.5 T GE Signa scanner with Echospeed gradients using a custom-built whole head coil that provides a 50% advantage in signal-to-noise ratio over that of the standard GE coil (Hayes and Mathias 1996). A custom-built head holder was used to prevent head movement. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 2 s using a T_2^*-weighted gradient echo spiral pulse sequence: $T_R = 2000$ ms, $T_E = 40$ ms, flip angle = 89° and 1 interleave (Glover and Lai, 1998). The field of view was 240 mm and the effective in-plane spatial resolution was 4.35 mm.

Figure 1. Schematic of task design, showing blocks of experimental and control trials.

To aid in localization of functional data, a high resolution T_1-weighted spoiled grass gradient recalled (SPGR) three-dimensional magnetic resonance imaging (MRI) sequence with the following parameters was used: $T_R = 24$ ms; $T_E = 5$ ms; flip angle = 40°; 24 cm field of view; 124 slices in sagittal plane; 256 × 192 matrix; acquired resolution = 1.5 × 0.9 × 1.2 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9 mm spatial resolution. Structural and functional images were acquired in the same scan session.

The task was programmed using Psyscope (Cohen *et al.*, 1993) on a Macintosh (Sunnyvale, CA) notebook computer. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a 'CMU Button Box' microprocessor (http://poppy.psy.cmu.edu/psyscope) connected to the Macintosh. Stimuli were presented visually at the center of a screen using a custom-built magnet compatible projection system (Resonance Technology, CA).

Image Preprocessing

Images were reconstructed, by inverse Fourier transform, for each of the 225 time points into 64 × 64 × 18 image matrices (voxel size: 3.75 × 3.75 × 7 mm). fMRI data were pre-processed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm). Images were corrected for movement using least-square minimization without higher-order corrections for spin history, and normalized to stereotaxic Talairach coordinates (Talairach and Tournoux, 1988). Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4 mm Gaussian kernel to decrease spatial noise.

Statistical Analysis of fMRI Data

Statistical analysis was performed on individual and group data using the general linear model (GLM) and the theory of Gaussian random fields as implemented in SPM99 (Friston *et al.*, 1995). First, data from each subject were modeled voxel-wise, using a GLM that included the experimental and control conditions. Confounding effects of fluctuations in global mean were removed by proportional scaling where, for each time point, each voxel was scaled by the global mean at that time point. The data were high-pass filtered (cut-off frequency 0.5 cycles/min) to remove low-frequency signal drifts and low-pass filtered, by temporal smoothing with a canonical hemodynamic response function, to enhance the temporal signal to noise ratio. Contrast images corresponding to (experimental trials) *minus* (corresponding control trials) were then generated for each subject. These contrast images were entered into a group-level random effects analysis, using a GLM with age as a covariate of interest. Voxel-wise *t*-scores from the regression analysis were transformed to normally distributed *Z*-scores. Significant clusters of activation were determined using a height threshold of $P < 0.01$ ($Z > 2.33$) and an extent threshold of $P < 0.05$, with corrections for multiple comparisons at the cluster-level

(Poline *et al.*, 1997). Activation foci were superposed on high-resolution T_1-weighted images and their locations interpreted using known neuroanatomical landmarks (Mai *et al.*, 1997; Duvernoy and Bourgouin, 1999).

Structural and Functional Changes with Age

To investigate whether age-related changes in brain activation are associated with anatomical changes, we examined structural changes within the fMRI-activation clusters identified in the previous section. There were two sets of clusters — one that showed age-related increases in functional activation and a second set that showed age-related decreases in functional activation. Within these functional-activation clusters we used regression analysis to examine age-related changes in GMD. The normalized T_1-weighted images, created during the functional image pre-processing, were segmented (Ashburner and Friston, 2000), modulated by the spatial normalization parameters to correct for true gray matter volume, and the resultant gray matter images were smoothed using a Gaussian kernel. For each subject, gray matter intensities were globally normalized to 1 and voxel-wise intensities were averaged across all voxels in the functional-activation cluster. A parallel analysis also examined changes in fMRI activation in these clusters. For this purpose, voxel-wise t-scores were averaged across all voxels in the cluster. GMD without volume correction was also examined. The image pre-processing was identical to the volume gray matter images, with the exception that the images were not modulated by their normalization parameters. Results from the GMD analyses were nearly identical to the volume-corrected analyses and are not presented here.

Results

Cognitive Assessment

The mean (M) and standard deviations (SDs) for the IQ scores were as follows: full-scale IQ, M = 111, SD = 11.86; verbal IQ, M = 112.24, SD = 13.87; performance IQ, M = 107.94, SD = 13.69. Regression correlation analyses showed no significant relationships between IQ and age, or between IQ and behavioral performance on the trials.

Relation between Age and Behavioral Performance

Accuracy was 100% for all but three subjects, and the lowest accuracy was 87% (Fig. 2). Accuracy was not correlated with age in the experimental ($r = 0.424$, $P = 0.10$) or in the control trials ($r = 0.140$, $P = 0.60$). In contrast, there was a significant negative correlation between reaction time and age in both the experimental ($r = -0.678$, $P < 0.01$) and the control trials ($r = -0.815$, $P < 0.001$). A direct comparison of reaction time versus age slopes in the experimental and control trials revealed no significant differences [$F(1,14) = 0.0009$; $P = 0.97$].

Relation between Age and Brain Activation

Significant positive correlations between age and activation (increased activation with age) emerged in two clusters in: (i) the left lateral occipital-temporal (LOT) cortex, including the left posterior inferior and middle temporal gyrus (BA 37/21), and left middle and inferior occipital gyri (BA 37/21); and (ii) the left supramarginal gyrus (SMG, BA 40) and left anterior intraparietal sulcus (BA 7), as shown in Table 1, and Figures 3 and 4.

Significant negative correlations between age and activation (decreased activation with age) were observed in five clusters in: (i) left and right superior frontal gyrus (BA 8) and middle frontal gyrus (BA 9/46), left inferior frontal gyrus (BA 11/47), and cingulate cortex (BA 24/32); (ii) bilateral basal ganglia including caudate, putamen and globus pallidus, nucleus ac-

cumbens, ventral pallidum, thalamus, and the substantia nigra; (iii) left medial temporal lobe, including the hippocampus and parahippocampal gyrus; (iv) brainstem; and (v) left anterior insula and frontal operculum, as shown in Table 1 and Figures 3 and 5.
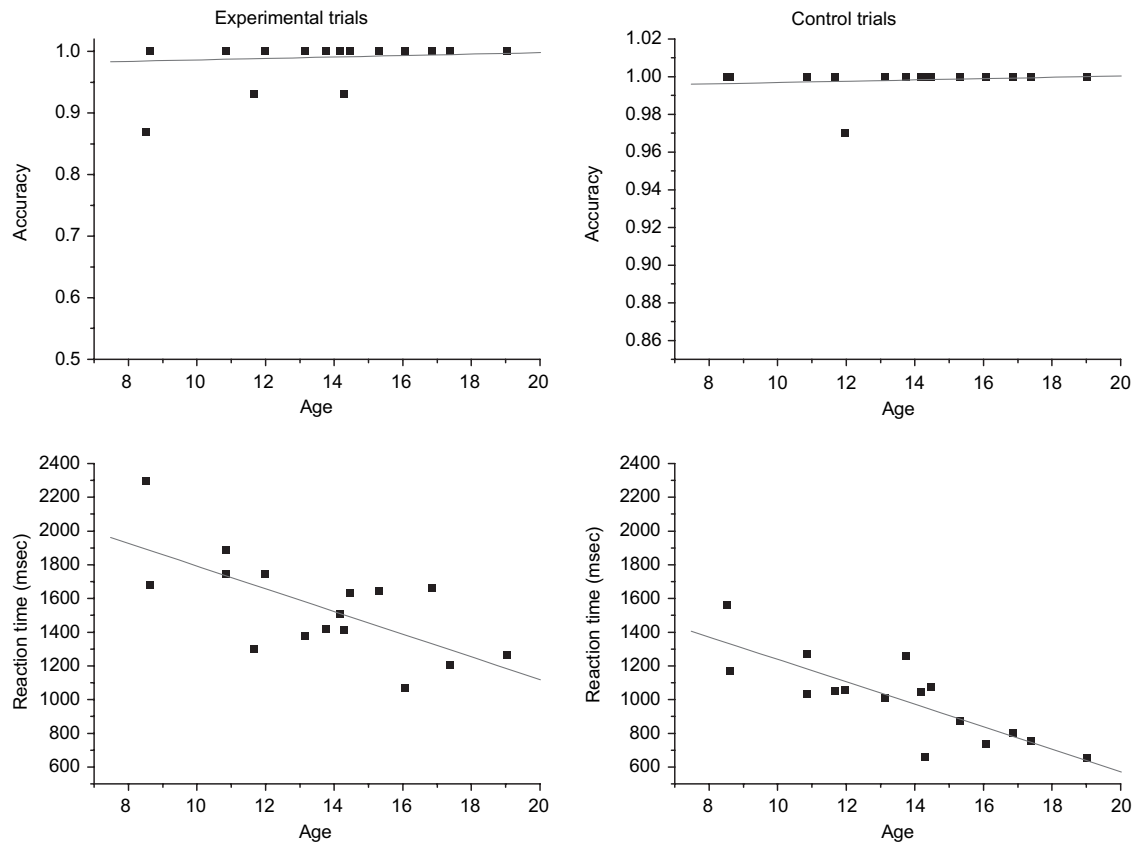
Relation between Brain Activation, Brain Structure and Age

We examined structural and functional changes in the two clusters, identified in Table 1, which showed increases in task-related activation with age. The relationship between GMD and age was first examined. No correlation was found between age and GMD in either left SMG cluster ($r = 0.15$, $P = 0.56$) or the left LOT cluster ($r = -0.24$, $P = 0.35$) (see Fig. 4*B*). A parallel analysis examined changes in task-related activation in these same clusters. Within the two clusters that showed age-related increases in activation, average t-scores showed significant changes with age: left LOT cluster ($r = 0.75$, $P < 0.0001$) and in the left SMG cluster ($r = 0.88$, $P < 0.0001$). These results confirm that age-related increases in functional activation do not arise from changes in GMD with age.

We then examined structural and functional changes in the five clusters, identified in Table 1, which showed decreases in task-related activation with age. No significant age-related GMD changes were present in four of the five clusters: basal ganglia cluster ($r = -0.20$, $P = 0.44$), left medial temporal lobe cluster ($r = 0.30$, $P = 0.25$), brainstem cluster ($r = -0.01$, $P = 0.96$), and the left insula/frontal operculum cluster ($r = 0.32$, $P = 0.20$) (see Fig. 5*B*). There was a significant increase in GMD with age in the left superior frontal gyrus cluster ($r = 0.51$, $P = 0.04$), A parallel analysis examined changes in task-related activation in these same clusters. The average t-scores showed significant decreases with age in all five clusters: left superior/middle frontal gyrus cluster ($r = -0.82$, $P < 0.0001$), basal ganglia cluster ($r = -0.77$, $P < 0.0003$), left medial temporal lobe cluster ($r = -0.78$, $P < 0.0002$), brainstem cluster ($r = -0.76$, $P < 0.0004$) and left insula/frontal operculum cluster ($r = -0.80$, $P < 0.0001$). These results indicate that age-related decreases in functional activation are not associated with GMD changes in any region.

Discussion

Our study provides evidence for significant changes in neural responses underlying the development of mental arithmetic in children and adolescents. During two-operand addition or subtraction trials, for which accuracy was comparable across age, there are both increases and decreases in activation with age, suggesting disparate levels and trajectories of functional maturation in particular brain regions. Older subjects demonstrated more activation in the left SMG and adjoining intra-parietal sulcus. This brain area has been consistently implicated in mental arithmetic processing across a number of lesion, positron emission tomography and fMRI studies (Levin *et al.*, 1996; Eliez *et al.*, 2001; Rivera *et al.*, 2002). Older subjects also demonstrated more activation in the left LOT, an area thought to important for visual word and symbol recognition (Hart *et al.*, 2000; Price and Devlin, 2003, 2004; Cohen and Dehaene, 2004; Kronbichler *et al.*, 2004). Younger subjects showed greater activation in the prefrontal cortex, including the dorsolateral prefrontal cortex (comprising BA 46 and 9 in the SFG and MFG) and ventrolateral prefrontal cortex (comprising BA 44, 45 and 47 in the IFG) as well as anterior cingulate cortex. Taken

Figure 2. Correlation between age and (*A*) accuracy (top row) and (*B*) reaction time (bottom row) on mental arithmetic trials (left column) and the corresponding control trials (right column).

together, these findings suggest a process of increased functional specialization of the left posterior parietal cortex with age, with decreased dependence on working memory and attentional resources.

Our results provide new information about potential influences on age-related changes in brain activation, and help to further constrain the interpretation of our findings. The age-related functional activation changes were clearly stronger than age-related GMD changes in the same regions, and suggest that the age-related functional changes appear to be a consequence of maturing neural systems, rather than specific changes in gray matter within each region. There are additional explanations for the GMD results. Sowell *et al.* (2003) reported age-related decreases in GMD within some of the regions examined in this study. Our sample may have failed to capture regional declines in GMD because of confounding influences of arithmetic ability and sulcal–gyral variability. Low GMD and increased sulcal–gyral variability in the parietal lobe has been reported in individuals with Turner syndrome who exhibited depressed parietal activation for addition tasks and poor math performance (Molko *et al.*, 2003). Surprisingly, the only age-related GMD finding was an increase in the superior and middle frontal cortex. Experience and expertise has been shown to increase GMD in jugglers (Draganski *et al.*, 2004) and cab drivers (Maguire *et al.*, 2003). The finding of increased GMD in the midst of decreases in task-related activation indicates that more efficient processing may result in part from structural maturation in these prefrontal regions. Interestingly, GMD differences were observed only in PFC regions that are known
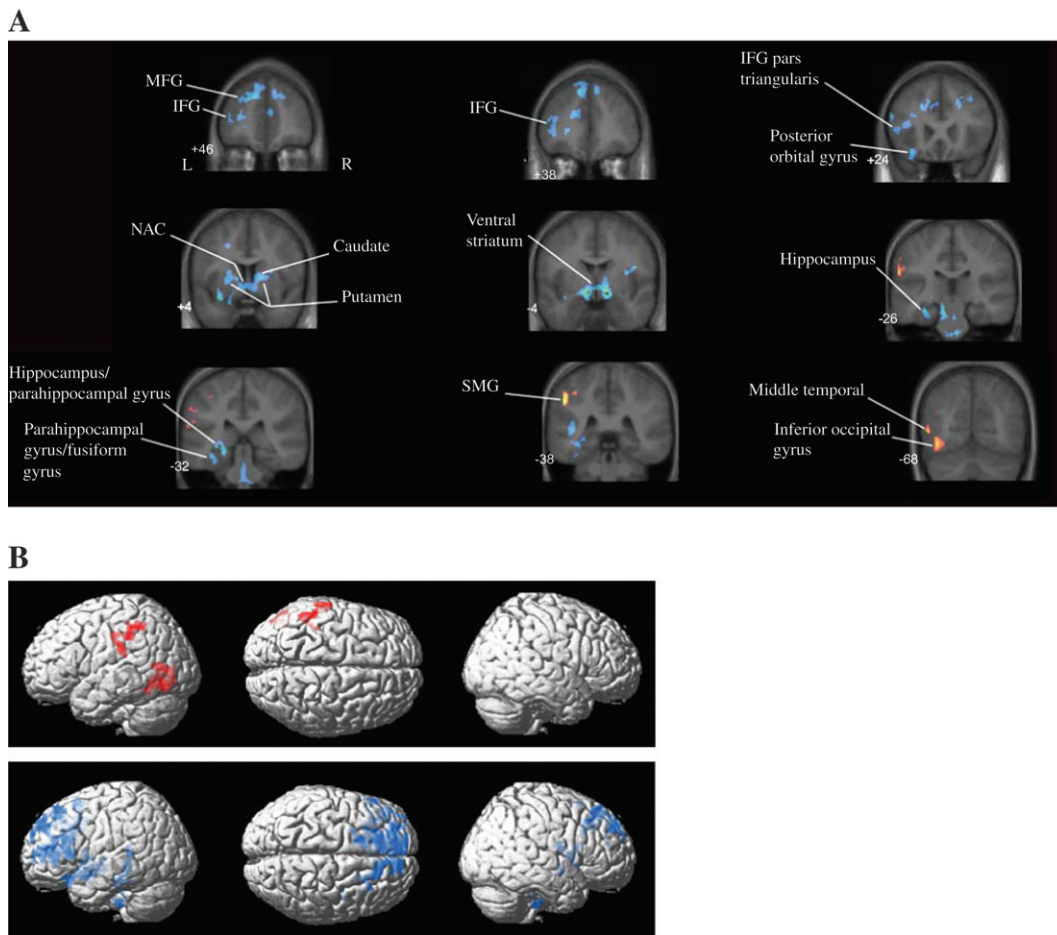
to subserve control and inhibitory functions. It is therefore likely that the pattern of observed changes is related to the development of more automatized task performance.

The importance of accounting for performance differences across age has been noted in several recent developmental neuroimaging studies (Gaillard *et al.*, 2001; Klingberg *et al.*, 2002; Kwon *et al.*, 2002; Schlaggar *et al.*, 2002). Of particular concern is that an observed increase or decrease in brain activity may be due to performance differences rather than functional maturation with age. Because accuracy remained comparable across age, we are able to examine age-related changes in brain activation that are due to maturation of functional systems involved in mental arithmetic, unconfounded by the effects of changes in task accuracy. Accuracy levels reached asymptotic levels by age 8–10 in the experimental trials as well as the corresponding control trials; moreover, a direct comparison showed that accuracy versus age slopes in the experimental and control trials were not different. Reaction times showed significant changes with age in both the experimental and control trials. However, a direct comparison showed that the reaction times versus age slopes in the experimental and control trials were not significantly different, and that there was a difference only in the intercept, as shown in Figure 2. These findings validate our imaging results, in that they confirm that the children are just slower to react overall, even when they have no cognitive difficulty whatsoever executing the task. While these results clearly exclude the possibility that the developmental effects observed in our study are due to differences in accuracy, the effect of reaction time

Table 1
Brain areas that showed significant positive or negative correlations with age during mental arithmetic ($P < 0.01$, corrected at the $P < 0.05$ level for multiple comparisons)

Comparison	Area	No. of voxels in cluster	Z_{max}	Peak coordinates
Increases with age (older > younger)	L lateral occipital-temporal cortex, including inferior and middle occipital gyrus (BA 19/37), inferior and middle temporal gyrus (BA 37/21)	431	3.87	−53, −68, 7
	L supramarginal gyrus (BA 40), intra-parietal sulcus (BA 7)	292	4.02	−51, −37, 46
Decreases with age (younger > older)	L and R superior and middle frontal gyri (BA 9/46/8), L inferior frontal gyrus (BA 11/47), L SMA (BA 6), L ACC (BA 24/32)	2818	4.09	−16, 59, 19
	L and R basal ganglia, including caudate, putamen, globus pallidus, nucleus accumbens, ventral striatum and pallidum, substantia nigra and thalamus	1481	4.72	−10, −4, −5
	L medial temporal lobe, including hippocampus, and parahippocampal gyrus and fusiform gyrus	344	4.47	−32, −33, −2
	L and R brainstem	256	4.29	−10, −20, −17
	L insula, frontal operculum	246	4.12	−32, 1, −13

For each significant cluster, region of activation, number of voxels activated, maximum Z-score and location of peak are shown.
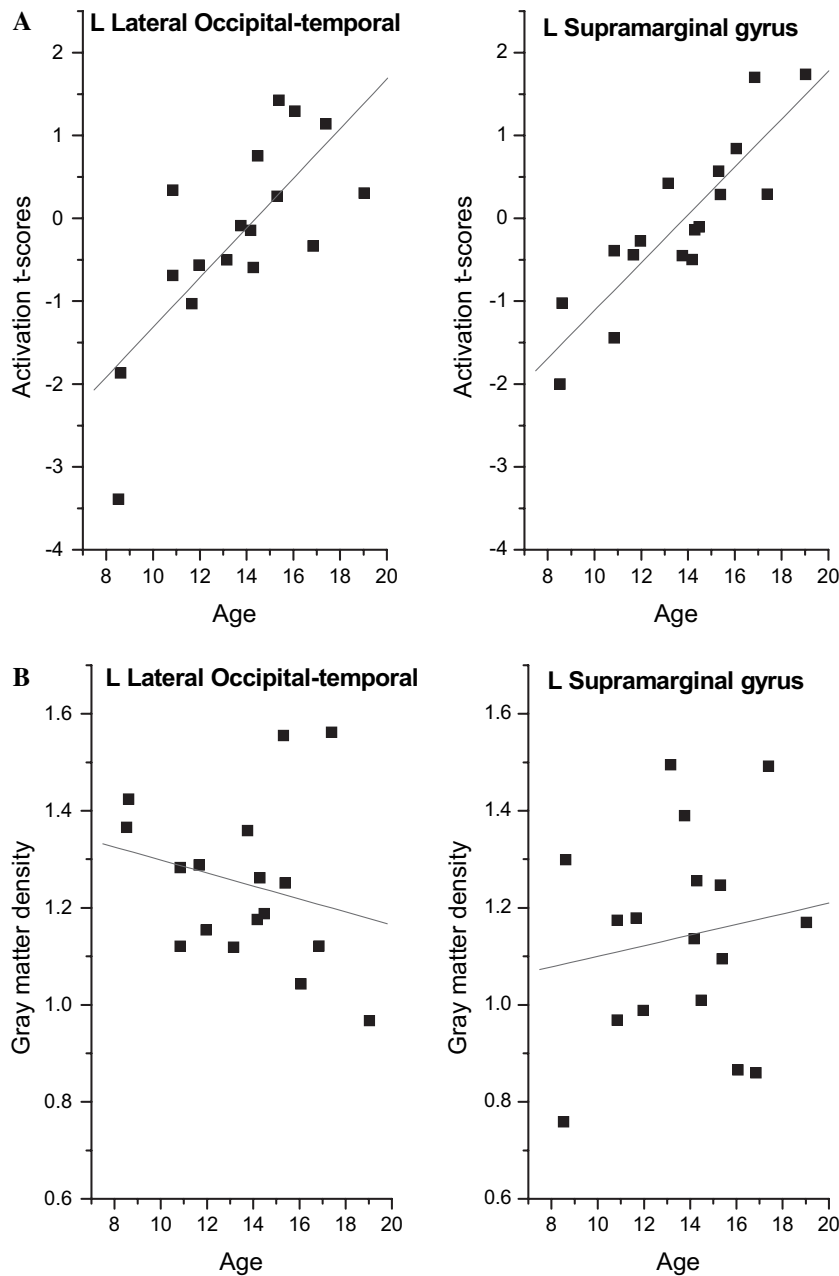

Figure 3. (A) Brain areas that showed significant increases and decreases in activation with age on mental arithmetic trials ($P < 0.01$, corrected at the $P < 0.05$ level for multiple comparisons). The red color scale shows areas of activation that are positively correlated with age, while the blue color scale shows areas of activation that are negatively correlated with age. (B) Surface rendering of significant increases (top) and decreases (bottom) in activation for mental arithmetic trails.

is more complex. If a region is activated by both experimental and control tasks, then the similarity of reaction time slopes suggests that age-related changes may be more directly related to functional maturation. If, on the other hand, a region is activated only by the experimental task, it is not possible to determine whether the age-related changes are related to reaction time changes or functional maturation.

While there was no difference in accuracy across age on these mental arithmetic problems, reaction time was negatively correlated with age. The age-related differences in reaction time observed in our study may be tied to changes in white matter development. It has been well documented that structural maturation of fiber tracts in the human brain, including an increase in the diameter and myelination of axons, occurs across development throughout childhood and adolescence (Giedd *et al.*, 1999; Paus *et al.*, 1999). Our findings are consistent with Kwon *et al.* (2002), who found that even on simple 'control' tasks, which younger subjects were performing
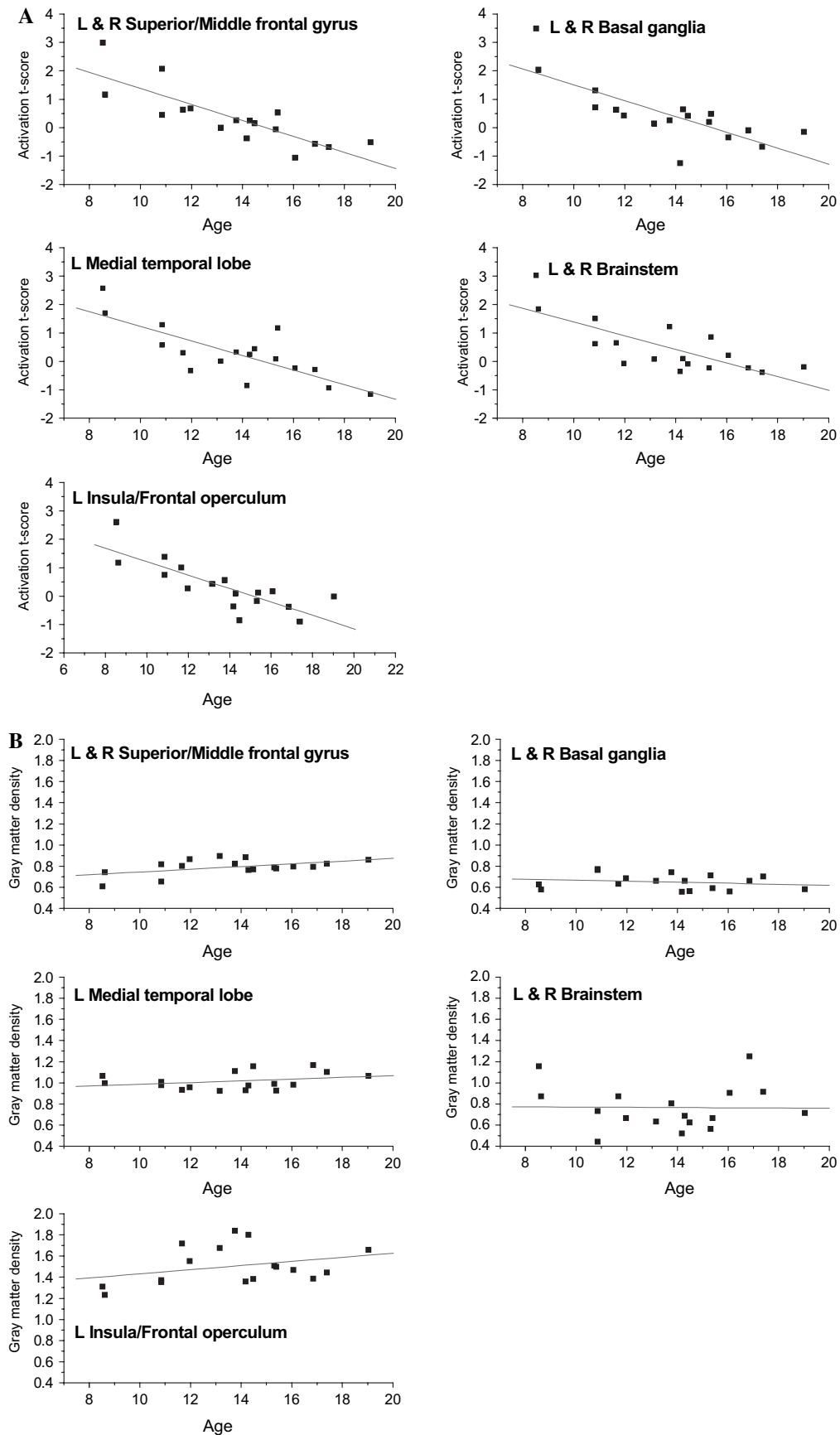
Figure 4. Contrasting functional and structural changes with age in the two clusters (see Table 1) that showed age-related increases in activation. (*A*) Age-related increases in brain responses in the left supramarginal gyrus and the left lateral occipital-temporal cortex. The *t*-scores representing mental arithmetic related activation (experimental trials minus the corresponding control trials) were averaged across voxels in each of the two clusters that showed age-related increases in activation (see Table 1). (*B*) In these functional-activation clusters, no changes in gray matter density were observed.

as well as older subjects, reaction time continued to decrease with age; moreover, the slopes of reaction time versus age were almost identical for the simple control task and more complex cognitive tasks, just as we found here.

Increased activation with age was observed in the left parietal cortex, notably in the left SMG and adjoining intra-parietal sulcus. Lesions to this brain region are known to significantly disrupt performance in a number of mental arithmetic tasks, including simple addition and subtraction (see Kahn and Whitaker, 1991, for a review). Furthermore, these regions also consistently show activation in functional imaging studies of arithmetic reasoning (Warrington, 1982; Takayama *et al.*, 1994; Burbaud *et al.*, 1995; Levin *et al.*, 1996; Rueckert *et al.*,

1996; Dehaene, 1997; Dehaene *et al.*, 1999; Menon *et al.*, 2000d; Gruber *et al.*, 2001; Simon *et al.*, 2002). Indeed, using a task similar to the one used in the present study, Menon *et al.* (2000d) identified the left SMG and angular gyrus as key brain areas involved in numerical computation. We also detected increased activity with age in the adjoining angular gyrus, but this increase was not significant at the conservative (spatially corrected) thresholds used in our study. Simon *et al.* (2002) examined the topographical layout of a number of parietal lobe functions, including calculation, attention and language in adults, and have provided new evidence for specialization of the SMG gyrus and adjoining anterior IPS in arithmetic calculation. The precise locus of parietal lobe

Figure 5. Contrasting functional and structural changes with age in the five clusters (see Table 1) that showed age-related decreases in activation. (*A*) Age-related decreases in brain responses were observed in the left superior frontal gyrus, left insula/frontal operculum, ventral striatum, medial temporal lobe, including hippocampus and the brain stem. (*B*) In these same clusters, no changes in gray matter density were observed. Other details as in Figure 4.

regions that showed age-related increases in activation in our study is consistent with findings from the Simon *et al.* study. Taken together, our findings suggest that with age, children and adolescents develop increased functional specialization for mental arithmetic in focal regions of the left inferior parietal cortex. At first glance, this finding may appear to be inconsistent with one we previously reported for 'perfect performers' using a similar arithmetic calculation task (Menon *et al.*, 2000c). In that study, we found that subjects who had 100% accuracy on the task (compared to those having <100% accuracy) showed significantly *less* activation in the left angular gyrus. While the current study suggests that activity in the left parietal cortex increases with age, which presumably is also associated with functional optimization, it is important to note that the 'performers' in the previous report (Menon *et al.*, 2000c) were adult college students, who would constitute a group of 'very optimized', expert performers, as opposed to the subjects in the present developmental study. Other possibilities for the discrepancy include: (i) developmental increases in the angular gyrus are gradual; and (ii) relationship between performance and activation in this region is a nonlinear one, with increased activation to a certain level of performance, and decreased activation with further consolidation and expertise.

The only other brain region that showed increased activation with age was the left LOT cortex. This region has been implicated in a number of cognitive–symbolic functions, including graphic–verbal conversions (Sevostianov *et al.*, 2002) as well as the abstract categorization of visually presented alphabetic symbols (Gros *et al.*, 2001). It has been suggested that this region may be involved in passing lexical representations of arithmetic symbols to the parietal cortex in a format that facilitates numerical calculation and computation (Pinel *et al.*, 2001). Lesion studies have shown that damage to these temporal-parietal-occipital areas in the left hemisphere can result in a disturbance in symbolic reasoning, including those leading to deficits in the performance of simple mental arithmetic (Luria, 1966; Martins *et al.*, 1999; Jung *et al.*, 2001). Our findings suggest that efficient engagement of this distributed neural network increases with age.

Our findings may also shed light on the current debate about the presence of a visual word form area (VWFA) in the same region. While some have argued that the so-called VWFA is specialized for processing visual words and pseudo-words (Mechelli *et al.*, 2003) or the perception and sequencing of letters (Cohen *et al.*, 2002; McCandliss *et al.*, 2003; Cohen and Dehaene, 2004) others have maintained that this area also subserves a number of tasks that do not engage visual word form processing, such as naming colors, naming pictures, reading Braille, repeating auditory words and making manual action responses to pictures of meaningless objects (Price and Devlin, 2003). The peak of our LOT cluster was at $y = -68$, 8 mm from the 'average' (but within the range, '$y = -43$ to -70') identified as being 'VWFA proper' by Cohen *et al.* (2002). And although it is more posterior than any of the 18 studies reviewed in Price and Devlin (2003), it is within 8 mm of the most posterior y-coordinate reported there as well. Our finding of increased of increased activation of the left LOT with age suggests that the VWFA area may also be responsible for mapping symbolic information during arithmetic processing, suggesting that this area is not unique to visual word form processing.

Although reliance on fact retrieval is thought to increase with age, we did not see increased activation with age in frontal regions known to be associated with retrieval. We believe this has to do with the differences in the nature of the retrieval required in our mental arithmetic task. Studies reporting prefrontal retrieval-related activation tend to require high levels of controlled retrieval in which subjects were required to remember lists of words or pictures that were recently learned (e.g. Velanova *et al.*, 2003). The mental arithmetic task used in our study, on the other hand, requires more automatic, long-term fact retrieval — a process that appears to primarily engage the parietal cortex. Consistent with the argument that the right PFC may be more closely related to controlled and effortful retrieval, it was the younger subjects who showed greater activation in this region. Such an interpretation is also supported by lesion studies showing that left posterior, not frontal, lesions are particularly prone to produce impairments in arithmetic fact retrieval.

Decreased activation with age was observed in the prefrontal cortex, including bilateral superior and middle frontal gyrus, and left inferior frontal gyrus and frontal operculum. In adults, these regions are reliably activated across several different types of mental arithmetic tasks (Burbaud *et al.*, 1995; Rueckert *et al.*, 1996; Dehaene *et al.*, 1999; Kazui *et al.*, 2000; Rickard *et al.*, 2000; Gruber *et al.*, 2001; Rivera *et al.*, 2002), and they appear to subserve auxiliary functions related to calculation. For instance, Menon *et al.* (2000d) observed a main effect of rate of stimulus presentation in the prefrontal cortex, while the main effect of calculation difficulty was found in the SMG and the angular gyrus. Similarly, two other studies found that similar bilateral prefrontal cortical regions are activated during calculation as well as during non-mathematical tasks (Gruber *et al.*, 2001; Simon *et al.*, 2002), suggesting that these regions are not specific to mental arithmetic, but rather play a more general supporting role in these tasks. As in our previous study (Menon *et al.*, 2000d), it has also been reported that exact calculation predominantly elicited activation of the left dorsal angular gyrus, and furthermore suggested that the more complex the calculation tasks were (i.e. those requiring compound calculation, where direct retrieval of simple table facts is not sufficient to solve the problem), the more they activated left inferior frontal areas known to be associated with linguistic as well as working memory functions (Gruber *et al.*, 2001). Thus, the negative correlation between age and activation in the prefrontal cortex observed in our study may be due to the fact that younger subjects require comparatively more working memory and/or allocation of attentional resources to complete the task of calculating the arithmetic equations, which are presumably less automatic than they are for older subjects. Taken together, these results provide evidence for maturation of prefrontal cortex functions that contribute to the development of mental arithmetic skills, a finding consistent with a considerable body of behavioral research which has shown a direct relationship between mental arithmetic performance and working memory capacity, especially in children (Siegel and Ryan, 1989; Wolters *et al.*, 1990; Logie *et al.*, 1994; Adams and Hitch, 1997; McLean and Hitch, 1999; Klein and Bisanz, 2000).

It should be noted that the finding of decreased recruitment of the prefrontal cortex with age stands in apparent opposition to the maturational pattern of the brain, given the ample existing evidence that the frontal cortex is the last to develop (Huttenlocher, 1990; Segalowitz and Davies, 2004). Indeed,

other developmental studies report a pattern of increased recruitment of the frontal cortex with age for skills such as word reading (e.g. (Simos *et al.*, 2001; Schlaggar *et al.*, 2002; Turkeltaub *et al.*, 2003), response inhibition (Booth *et al.*, 2003) and working memory (Kwon *et al.*, 2002). We believe that one difference between these findings and our own is that the function being played by the prefrontal cortex with respect to simple arithmetic calculation is an *auxilliary*, rather than a primary one. Because with development, as discussed earlier, reliance on counting and other reconstructive strategies is gradually replaced by more automatic memory retrieval, it follows that reliance on prefrontal executive processes such as working memory, interference control and strategic planning should accordingly decrease.

Younger children also showed greater activation in the left hippocampus and parahippocampal gyrus. Interestingly, decreases were also observed in the dorsal basal ganglia, including the caudate and putamen. Both the hippocampus and the parahippocampal gyrus are known to play a major role in retrieval of facts and rules from memory (Squire *et al.*, 2004). Additionally, it also is possible that since the parahippocampal gyrus mediates convergence of high-level input from visual association cortex into the hippocampus (Suzuki and Amaral, 1994), this allows for persistence of representations in short-term memory (Eichenbaum, 2000). The increased activation seen in this region in younger subjects may reflect the greater recruitment of medial temporal lobe resources to sustain appropriate memory representations. The greater medial temporal lobe activation in younger subjects also may reflect generalized novelty effects. With increased experience and exposure, medial temporal lobe activations may decrease as stimuli appear less novel (Menon *et al.*, 2000e). The basal ganglia are known to be critical for procedural memory (Ghilardi *et al.*, 2000), i.e. memory for procedures and habits, and this region also plays a role in maintenance of information in working memory (Menon *et al.*, 2000a). Furthermore, the medial temporal lobe and dorsal basal ganglia memory systems are known to engage the prefrontal cortex, which plays a role in the executive and control processes involved in declarative and working memory. All of these three regions showed greater activation in children. Parallel increases in the hippocampus and basal ganglia activation in children have also been recently reported in a task involving overriding a learned action in favor of a new one (Casey *et al.*, 2002). Taken together, these findings provide evidence for the greater involvement of and greater reliance on memory functions subserved by the hippocampus and the basal ganglia in our younger participants. It is possible that greater activation of these areas in children reflects immature memory functions required for mental arithmetic. Furthermore, these regions may compensate for the lack of appropriate functional specialization of the parietal cortex during mental arithmetic. Such a view is consistent with our finding of parallel age-related increases in left parietal cortex.

Finally, an intriguing finding of our study involves a set of ventral basal ganglia regions that showed decreased activation with age. This includes the left substantia nigra, ventral striatum, nucleus accumbens and ventral pallidum. There have been numerous studies implicating these regions as part of a dopaminergic system (Schultz, 1997; Gardner and Vorel, 1998; Ashby *et al.*, 1999; Breiter and Rosen, 1999; Everitt *et al.*, 1999; Kalivas and Nakamura, 1999; Knutson *et al.*, 2000; Thomas *et al.*, 2000; Fried *et al.*, 2001; Rilling *et al.*, 2002) that plays a key role in reward and reinforcement and are also important in the development of motivated behaviors and habit formation (Haber, 2003). Interestingly, when we examined (unpublished) data from a separate three-operand arithmetic task, we found no such age-related changes in activation. Our results suggest that the two-operand equations, on which the children performed well, were relatively more rewarding to the younger subjects. Such a view is consistent with the hypothesis that positive affect is associated with increased brain dopamine levels, which in turn helps to improve cognitive functioning (Ashby *et al.*, 1999). Alternatively, or perhaps simultaneously, increased dopamine neurotransmission may be involved in learning, reinforcement of behavior, attention and sensorimotor integration (Koepp *et al.*, 1998). We are among the first to report developmental changes in these mesencephalic structures during cognitive processing (see also Casey *et al.*, 2002). These results were unexpected, and warrant further investigation with appropriate experimental designs.

One interesting issue concerns the direction of the fMRI signal changes that drive the observed age-related correlations. Positive correlations, for example, between age and brain responses may arise a combination of three factors: (i) increased experimental task-related activation in older subjects; (ii) increased control task-related activation in younger subjects; or (iii) suppressed responses, i.e. deactivation *vis-à-vis* a low-level baseline (Greicius *et al.*, 2003) in younger subjects. We found that the positive correlations observed in our study arose in part from increased experimental task-related activation in older subjects, typically aged 14 and above. The decreased experimental task-related activation in the younger subjects may arise from either increased control task-related activation in younger subjects, or from increased deactivation in younger subjects. Future studies will use additional control conditions, including a passive baseline 'rest' condition, to tease out the relative contributions of these factors to the observed developmental changes. Similar considerations apply to developing a better understanding of the observed negative correlations as well. The neural processes underlying activation and deactivation in imaging studies are poorly understood (Logothetis, 2003). Nevertheless, it is clear that there are significant developmental differences in the functional properties of brain regions that are recruited during mental arithmetic.

Our study provides evidence for specific neurodevelopmental changes in mental arithmetic. Because basic arithmetic reasoning is one of the most fundamental cognitive skills that children need to master, the implications of our findings are potentially wide-ranging. It is through examination and elucidation of the unfolding of complex distributed networks involved that we can begin to understand the typical development of arithmetic reasoning, and to develop methods for understanding disorders such as developmental dyscalculia.

Notes

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