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Improved memory functioning and frontal lobe maturation between childhood and adolescence: A structural MRI study

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Abstract

Previous studies conducted by our group have provided evidence for age-related reductions in cortical thickness in dorsal frontal and parietal regions between childhood and adulthood, and gray matter volume increases of mesial temporal and anterior diencephalic structures. The purpose of this study was to describe neurobehavioral correlates of these brain maturational changes using morphometric analyses of brain magnetic resonance images (MRI) and two tests of cognitive abilities. Participants were 35 normal children roughly stratified by age (7 to 16 years) and sex (20 boys and 15 girls) and frontal and mesial temporal regions were anatomically defined in each subjects' MRI data. The California Verbal Learning Test–Children's Version and the Rey-Osterrieth Complex Figure test were used as measures of verbal and visuospatial memory and organizational abilities. Analyses designed to show regionally specific relationships between the brain and behavioral measures revealed interesting results. Specifically, frontal lobe gray matter thinning was more strongly predictive of delayed verbal memory functioning than was the mesial temporal lobe gray matter volume, and this relationship did not appear to be mediated by factors indexed in chronological age. Similar, but less regionally specific relationships were observed for measures of visuospatial memory abilities and frontal lobe maturation. Functional imaging studies in the literature consistently report activation in frontal regions in adults during retrieval tasks. The relationship between frontal lobe maturation and delayed recall observed here may be reflective of the children's development towards the more adult-like frontal lobe function revealed in the functional imaging studies. (*JINS*, 2001, *7*, 312–322.)

Keywords: Brain, Development, Childhood, Verbal memory, Visuospatial memory

INTRODUCTION

Studies of brain maturation using quantitative magnetic resonance imaging (MRI) have revealed evidence for brain development that continues well into adolescence. Specifically, *in vivo* findings of relatively stable brain volume with age-related changes in the gray and white matter components of the cerebrum between childhood and young adulthood have been reported by several researchers over the last few years (e.g., Casey et al., 1997; Caviness et al., 1996; Giedd et al., 1996a, 1996b, 1999; Jernigan et al., 1991b; Paus et al., 1999; Pfefferbaum et al., 1994; Reiss et al., 1996; Sowell & Jernigan, 1998; Sowell et al., 1999a, 1999b). These observations are probably related to the *post-mortem* findings of a protracted progression of myelination, particularly in frontal and parietal regions (Yakovlev & Lecours, 1967), which continues well into the 3rd decade of life, and large increases in perihippocampal myelination between the 1st and 2nd decades (Benes et al., 1994). Additionally, reductions in synaptic density have been reported to occur throughout adolescence in humans (Huttenlocher, 1979; Huttenlocher & de Courten, 1987), which could be related to *in vivo* findings of cortical volume reductions. These relatively late changes in brain morphology are likely related to children's maturing cognitive abilities during the same time period.

Few researchers have attempted to investigate the nature of brain–behavior relationships in normally developing chil-

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dren. Reiss et al. (1996) found positive relationships between brain volume and IQ in normal children that seemed to be influenced mostly by the amount of gray matter within the prefrontal region. Unfortunately, this finding does not shed light on relationships between maturational changes in the brain and changing cognitive abilities because IQ measures are, by definition, age-corrected. IQ and brain size relationships have also been observed in adult populations (Andreasen et al., 1993). Casey et al. (1997) found relationships between changing area measurements of the left and right anterior cingulate and improving attentional abilities in normal children. These relationships were not mediated by chronological age, suggesting that the changes in children's attentional abilities are due to changes in brain morphology more than to other factors indexed in chronological age (e.g., advancing education, environmental exposure). The specificity of the cingulate region in controlling attentional abilities, however, cannot be confirmed by this study. It is possible that other brain regions not measured are implicated in the changing cognitive ability as well.

Previous structural imaging studies have shown that some of the more dramatic developmental morphological changes in the brain are occurring in parietal, frontal (Giedd et al., 1999; Jernigan et al., 1991b; Sowell et al., 1999a, 1999b) and mesial temporal (Sowell & Jernigan, 1998) gray matter regions. As evidenced in neuropsychological studies, frontal brain regions tend to be associated with executive functions and organizational abilities (e.g. Levin et al., 1991), while mesial temporal regions (e.g., the hippocampus) are thought to mediate memory encoding functions (Squire, 1983). To our knowledge, relationships between improved memory functioning and organizational abilities and maturation in frontal and mesial temporal lobe (MTL) brain structures have not been addressed in the literature.

In the present study, two different neuropsychological tests were chosen to measure memory functions, and different indices from these tests were used to measure what was thought to be a relatively independent cognitive construct, organizational ability. While whole brain measurements, as well as tissue classification and detailed anatomical region segmentation were available for all subjects studied here, only the two brain regions thought to be most related to the cognitive functions of interest (frontal and MTL regions) were studied in the correlational analyses. The left and right hemispheres were measured separately for these structures. The experimental design chosen for this study, in which two brain regions (in each hemisphere) are analyzed, affords an examination of possible *a priori* cross-over effects in brain–behavior relationships in normally developing children, while minimizing Type I errors by keeping the number of statistical analyses to a minimum. We predicted that we would see localized relationships between the memory measures and the MTL, and between the organizational measures and the frontal lobe. We also expected spatial memory and organization might be more related to the right hemisphere and verbal memory and organization to be related to the left hemisphere.

METHODS

Research Participants

Thirty-five normal children and adolescents including 20 boys and 15 girls (see Table 1 for gender-by-age breakdown) were examined with structural MRI. All participants were recruited as normal controls for a large, multidisciplinary neurodevelopmental research center. As seen in Table 1, the sample was fairly well distributed across the age range and by sex. All of the children were right-handed and each was screened (via parent interviews and neurological examination) for neurological impairments and for any history of learning disability or developmental delay. Informed consent was obtained from all children and their parents.

Behavioral Measures

Most children were given the California Verbal Learning Test for Children (CVLT–C; Delis et al., 1994) and the Rey Osterrieth Complex Figure (ROCF) as part of a battery of tests administered by a large multidisciplinary neurodevelopmental research center. On some occasions, children were not given the CVLT–C ($n = 2$) or the ROCF ($n = 4$) because of testing time constraints. Inclusion criteria insured that the behavioral data were collected within 4 months of the imaging session. Thus, 3 children were omitted from the statistical analyses in which brain and ROCF measures were compared because the time between MRI and administration of the ROCF was greater than 4 months. Two children were omitted from statistical analyses comparing CVLT–C and brain measures for the same reason. The final sample of children included in the analyses for the CVLT–C was 31, and 28 children were studied with the ROCF.

The CVLT–C involves the oral presentation of two "shopping" lists (List A and List B) with 15 words in each list. The test was administered to each child using the following standardized procedure: Each participant was given five consecutive trials to learn List A with a test of immediate recall after each administration. The next trial presentation was an interference list (List B), followed by an immediate re-

Table 1. Age-by-sex breakdown

Age	Male	Female
7 years	1	1
8 years	3	2
9 years	3	2
10 years	1	2
11 years	2	3
12 years	3	1
13 years	1	2
14 years	3	1
15 years	1	1
16 years	2	0

call of the first list. The participant was then asked to recall the first list again in a delayed free recall condition and then in a delayed cued recall condition. After a 20-min delay, each participant was asked to recall the words from the first list. Finally, the participant was given a yes–no recognition test in which he/she was asked to respond "yes" only to words from the first list. Words on the recognition list included all of the List A words, some of the List B words, and other distracter words from various semantically or nonsemantically related categories.

While many measures can be obtained from the CVLT–C, only two were examined in this study. First, the total of words recalled from the five learning trials was thought to be the best available measure from the CVLT–C to tap the children's ability to *organize* and learn information. Participants' tendency to cluster words in semantic categories to aid in memory performance is measured with the CVLT–C, and this measure is traditionally thought to tap frontal, organizational abilities. However, scores on the CVLT–C semantic clustering ratio did not change in the age range studied here, and were not at the level observed in young adult normative samples (Delis et al., 1987) even in the oldest adolescents studied here. Thus, while it may be a good measure of frontal organizational ability in adults, it does not appear to be the best measure in children and adolescents.

The children's score on the long delay free recall was thought to be the best measure of children's *memory* ability. However, the measure of delayed recall was highly correlated with the measure of total words recalled across the five learning trials, as would be expected given that the more words children learn, the more they can remember after a delay (baseline effects). Since our intent was to capture two separate aspects of memory functioning, namely, organization and learning factors on the one hand, and retention of learned information on the other, a new measure of delayed recall was computed by removing variance in that measure attributable to recall performance at Trial 5. It was hoped that this new measure, CVLT–C delayed recall residual score, would provide a purer measure of retention *per se*.

The ROCF test was individually administered to each child. First, the child was asked to copy the ROCF from a stimulus card using colored pens. The examiner handed the child a new colored pen each minute in a prescribed order and there was no time limit. On completion of the copy, the examiner removed the stimulus card and the participant's copy and placed a blank sheet of paper on the desk. The participant was then asked to draw as much of the figure as he or she could remember, and again, the examiner gave the subject a new colored pen each minute in the same order as in the copy presentation. After approximately 30 min in which the participant performed other neuropsychological tests, each participant was asked to draw the figure again from memory using the same procedure as in the immediate recall condition.

A qualitative scoring system (Taylor, 1959) was used to obtain measures of accuracy for the copy and recall conditions for the ROCF. This scoring system consists of judging the adequacy of the drawing on 18 units (specific details or areas of the figure) with 2 possible points for each unit. This score provides an index of how well the participant reproduces the design. The 18-unit scoring system was chosen because it is widely used, and interrater reliability has been established (Tupler et al., 1995). Meyers and Meyers (1995) criteria for scoring with the 18 unit system were used because they provide more detailed scoring descriptions than are available with Taylor's (1959) original scheme.

Akshoomoff and Stiles (1995) created a developmentally appropriate scoring system for the ROCF that is a modification of the Planning Measure of the Boston Quantitative Scoring System (BQSS; Stern et al., 1993). Specifically, they assessed how children proceeded with their drawings once they began (referred to as a *progression strategy*), and each drawing could be classified into four categories depending on which strategy was relied upon to organize and complete the figure. Akshoomoff and Stiles (1995) found that older children tended to use a more integrated approach in their progression strategy than did the younger children.

The two measures from the ROCF used in this study were the children's progression strategy score at copy, which was thought to tap their ability to efficiently *organize* information. Unfortunately only a subgroup of children were administered a delayed recall condition for the ROCF, thus a measure of delayed retention was not available for 9 participants. Analyses were conducted on the reduced sample size for this measure ($n = 19$). The zero-order correlation between the children's delayed recall accuracy and their progression scores at copy was high, again, suggesting that the two primary measures were not independent. As with the CVLT–C, the high correlation between the two measures suggests that variability in delayed recall is strongly influenced by factors contributing to organization and new learning. A new measure was computed by removing the variability in the delayed recall score that was attributable to accuracy at copy. This new measure was thought to be the best available measure of spatial memory retention.

Anatomical Analyses

Three whole-brain image series were collected for each participant. The first was a gradient-echo (SPGR) T1-weighted series with TR = 24 ms, TE = 5 ms, NEX = 2, flip angle = 45° field of view of 24 cm, section thickness of 1.2 mm, no gaps. The second and third series were a fast spin-echo (FSE) acquisition yielding two separate image sets: TR = 3000 ms, TE = 17 ms, ET = 4 and TR = 3800 ms, TE = 102 ms, ET = 8; for both sets the field of view was 24 cm, section thickness 4 mm, no gaps (interleaved). Imaging time for all three series totaled approximately 30 min. Figure 1 displays representative spatially registered T1-weighted (left), T2-weighted (middle) and proton density-weighted (right) images.

Image Analysis

The image-analytic approach is similar to that used in our previous anatomical studies (Jernigan et al., 1990, 1991a,

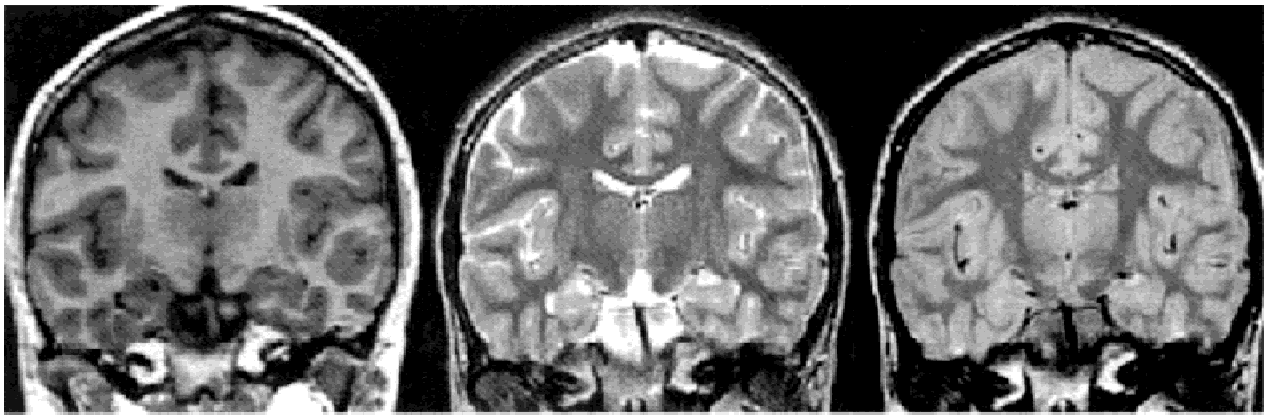

Fig. 1. Representative images from the standard 3-D and fast spin-echo protocols. Left: 3-D gradient-echo (SPGR) T1-weighted series with TR = 24 ms, TE = 5 ms, NEX = 2, flip angle = 45°, field of view of 24 cm, section thickness of 1.2 mm, no gaps. Middle: coronal section, TR = 3000 ms, TE = 17 ms, ET = 4; Right: spatially registered coronal section TR = 3800 ms, TE = 102 ms, ET = 8; for both sets field of view was 24 cm, section thickness 4 mm, no gaps (interleaved).

1991b), but represents a significant elaboration of these methods as described below, and reported elsewhere (Jernigan et al., 2001). Trained anatomists who were blind to participant diagnosis, age, sex, or any other identifying information subjected each image dataset to the following image analysis procedures: (1) interactive isolation of intracranial regions from surrounding extracranial tissue, (2) three-dimensional digital filtering of the matrix of pixel values representing brain voxels to reduce inhomogeneity artifact, (3) reslicing of the volume to a standard orientation, (4) tissue segmentation using semi-automated algorithms, and (5) neuroanatomical region-of-interest analysis.

Brain was first isolated from extracranial areas in the image, that is, from surrounding tissue that was in some instances contiguous with brain tissue and similar in signal value. This process results in a new volume within which the positions of brain voxels are coded, that is, a mask. The reproducibility of the stripping method was assessed by performing the stripping operations independently on six pairs of image volumes and comparing the within-pair discrepancies. Each pair represented 2 FSE volumes obtained on different occasions in the same individual. Discrepancies in brain volume were small, ranging from .03% to 1.25% with a mean of .54%.

Filtering is applied to reduce nonbiological signal drift across the field of view, which is presumably due to field inhomogeneity and susceptibility effects. A three-dimensional, high-pass filter is applied, with two iterations, separately to the "stripped" proton density weighted and T2-weighted FSE image volumes. First, a roughly cubic near-neighbor averaging filter is applied to produce a smoothed dataset; then the original volume is divided by the smoothed dataset on a voxel-by-voxel basis; and finally each voxel value is multiplied by the mean voxel value of the original dataset. The dimensions of the cubic smoothing filter were chosen by subjective evaluation of the results obtained with a series of filter sizes and were set at approximately 30 mm. That is, the set of voxels averaged to create each voxel value in the smoothed dataset spans 33 voxels in the *X* and *Y* directions, and 7 voxels in the *Z* direction (i.e., it measures $31 \times 31 \times 28$ mm). In constructing the smoothed datasets, near-neighbor averages are produced only for positions within the volumes coded as brain. Similarly, only the values for near-neighbors that are also brain voxels are averaged. This method is a 3D elaboration of the 2D filtering method used in our previous anatomical studies.

The tissue classification procedure is an interactive, supervised process. Operators manually designate the positions of three sets of tissue samples, one for each of the target tissues (gray, white, and CSF). The goals are to obtain samples in standard anatomical locations, within regions of homogeneous tissue, and to avoid artifacts and tissue abnormalities (such as ischemic damage). Samples are selected in locations that appear to be homogeneous and free of signal abnormalities both in the section to be sampled and in the adjacent sections. In most cases the operators select samples in six gray matter locations (bilaterally in the caudate nucleus, putamen, and the pulvinar of the thalamus); in four white matter locations (bilaterally in the suprasylvian white matter at the level of the pulvinar, and in similar locations at the level of the caudate/putamen); and in four locations within CSF-filled structures (two samples are taken within the frontal horns, and two more posterior samples are taken at approximately the level of the trigones of the cerebral ventricles). The sample voxel values are then analyzed using simple regression techniques to separate first all brain parenchymal voxels from CSF voxels, and then gray matter voxels from white matter voxels. The regression coefficients obtained in these simple analyses are then applied to classify each voxel within the volume as most similar to CSF, gray matter, or white matter. Interoperator reliability of total tissue volumes for independent tissue classification by two anatomists was estimated using 11 brain datasets, and was .92 for white matter, .95 for gray matter, and .99 for CSF.

In order to facilitate anatomical region definition, resectioned datasets were aligned to a standardized stereotactic space defined relative to the decussations of the anterior and posterior commissures and the structural midline. This improved the reliability of boundary determination, facilitated reference to standard brain atlases, and made it possible to identify small structures more consistently. Registration of the T1-weighted and spin-echo datasets was accomplished so that registered sections from all three datasets were available to the operators when attempting to resolve anatomical boundaries. Anatomists circumscribed regions on tissue-segmented images. Standardized rules were applied for delineating a set of subcortical structures and cortical regions.

The primary hemispheric cortical structural measures of interest in this study were frontal cortical gray matter and MTL gray matter (including the hippocampus, parahippocampal gray matter and the amygdala), though many other regions of interest were defined for each participant. Each structure was measured independently for the left and right hemispheres. Interrater reliability for the frontal gray matter region was estimated to be .99, and for the MTL region it was estimated to be .95 (both for combined left and right hemisphere measures).

Frontal designation

In the 4-mm coronal tissue segmented sections, the frontal lobe region was separated from the parietal lobe by drawing through the central sulcus. Anterior to the coronal slice containing the long columns of the fornix (see Duvernoy, 1991), all cortical gray matter superior to the temporal lobe (Sylvian fissure) was designated as frontal lobe, excluding the insula.

MTL designation

The MTL region is separated from temporal neocortex by drawing through the collateral sulcus. The MTL region extends anteriorly through all sections containing the temporal stem. No MTL may be defined in sections posterior to the colliculi and to the posterior extent of the pulvinar.

Sample tissue segmented images are presented in Figure 2 with frontal lobe gray matter highlighted in black in the top row, and the mesial temporal lobe gray matter regions highlighted in black in the bottom row. Note that only a few of the numerous sections containing MTL and frontal lobe gray matter are presented here for illustrative purposes.

Statistical Analyses

First, effects of age and sex on the behavioral measures of interest were estimated in multiple regression analyses.

Because a large component of the volume variability in cortical gray matter is related to brain size variability, the effects of cortical thinning are difficult to detect unless such variability is controlled. Thus, we created new residual scores where irrelevant variance attributable to total brain volume was subtracted from the gray matter region of interest. These new residual scores were used as estimates of cortical thinning, and regression analyses were conducted to assess for effects of age and sex on these variables. The association between the primary anatomical measures (frontal and MTL)

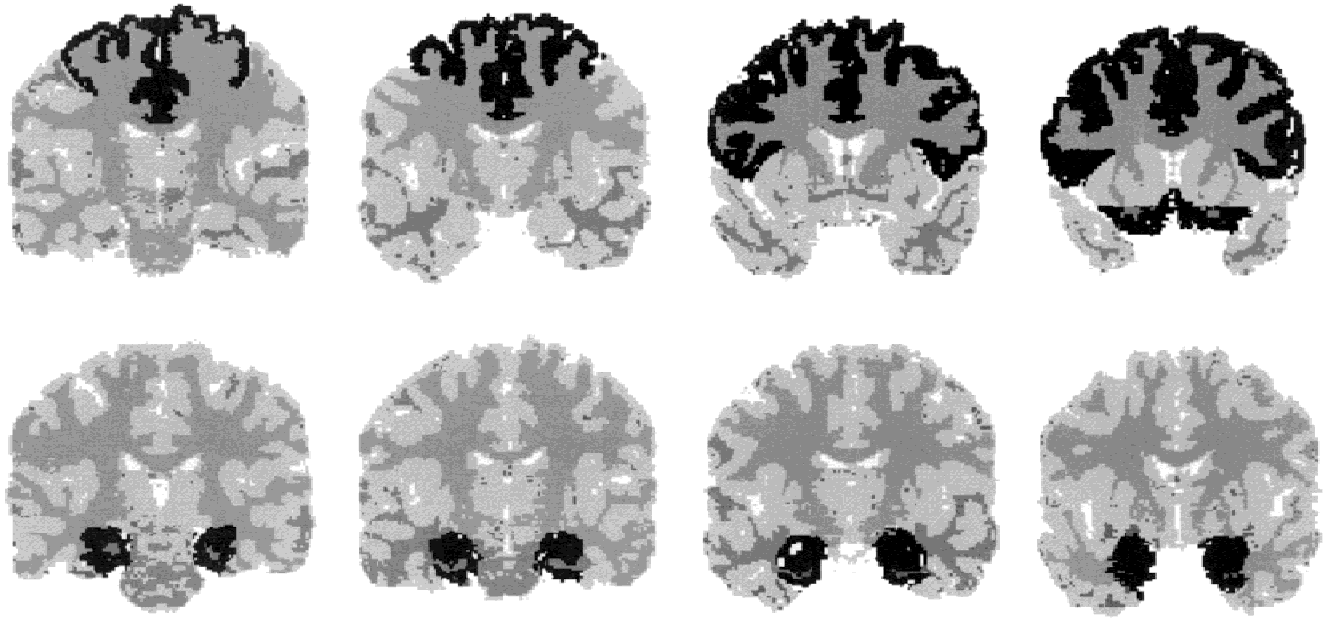

Fig. 2. Sample tissue segmented images with segmented gray matter within the defined frontal lobe highlighted in black in the top row, and the MTL gray matter highlighted in black in the bottom row. Nonfrontal/MTL gray matter is light gray and white matter is darker gray. Note that only four of the approximately forty-two, 4-mm resliced sections were chosen for presentation of each structure.

and the four critical behavioral measures were assessed for zero-order correlations. Where significant zero-order relationships were observed, age was added as an additional predictor of the behavioral measure in multiple regression analyses. In these analyses, the regression coefficient for the anatomical measure would reflect how much of the variance in the behavioral measure was uniquely associated with the change in brain morphology (i.e., not mediated by other factors indexed by chronological age). This step in the analysis was essential because the main goal of the study was to establish direct links between brain morphology and cognitive ability. A simple correlation between brain morphology and behavior could occur simply because both variables are related to chronological age.

Finally, localization hypotheses were tested. In each regression equation, the score on the behavioral measure of interest was used as the dependent variable and the left and right frontal and MTL regional gray matter residuals were entered as the independent variables. In this way, it could be determined how much of the variance in the dependent behavioral measure was uniquely associated with the change in brain morphology in each of the specific brain regions.

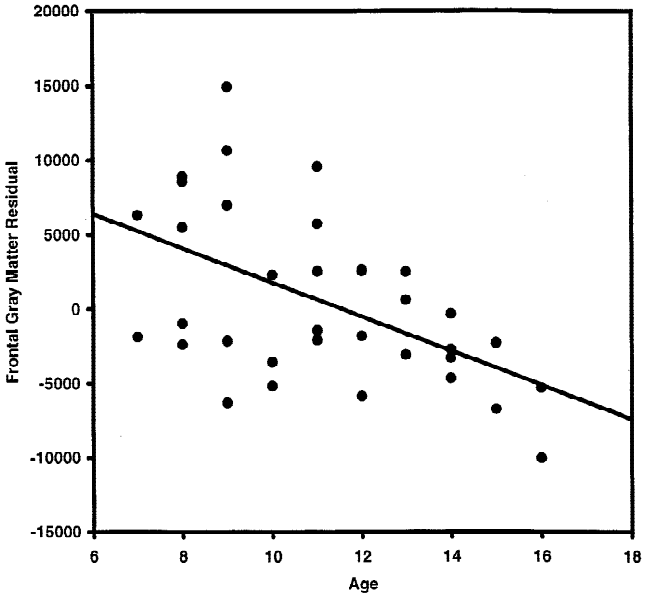

Fig. 3A. Scatterplot representing the age effect for frontal cortical gray matter residual.

RESULTS

Behavioral Measures

Only data from children who were given the CVLT–C within 4 months of their brain imaging session were used in these analyses ($n = 31$). Regression analyses predicting children's overall learning ability (List A Trials 1–5) with age and sex indicate that both boys and girls improve on this measure with increasing age ($\beta = .63$, $p < .001$), and the girls are significantly better than the boys at learning the list of words ($\beta = .34$, $p < .05$). Similar age effects are observed in children's recall of the words over a long delay (residualized for initial learning effects), with significant improvement with increasing age ($\beta = .41$, $p < .05$); but gender effects were not significant.

Only data from children who were given the ROCF within 4 months of their brain imaging session were included in these analyses ($n = 28$). Children's organizational ability on the ROCF, as measured by their Progression Strategy score in the copy condition, was significantly predicted by age ($\beta = -.59$, $p < .05$), but not sex. Note that lower Progression Strategy scores reflect a more integrated and mature organizational approach to copying the figure. Age effects for the delayed recall measure (residualized for copy performance) on the ROCF did not reach significance and there were no gender effects. It should be noted, however, that this test had reduced statistical power with only 19 participants in the analysis.

Brain Measures

Age and gender effects for left and right frontal and mesial temporal lobe gray matter residuals (correcting for total brain volume) were assessed using the larger sample of children ($n = 31$) who all received the CVLT–C within 4 months of image acquisition. As no difference was observed in age effects for the left and right hemisphere measures, they were combined to simplify the statistical analyses. Multiple regression analyses (using age and gender to predict gray matter volume) revealed volume reduction with increasing age in the MTL residual score ($\beta = -.40$, $p < .05$) and in frontal lobe gray matter residual score ($\beta = -.48$, $p < .01$). Gender effects in MTL volumes were observed ($\beta = .347$, $p < .05$) indicating that the girls had larger MTL volumes (relative to brain size) than the boys. Figures 3A and 3B display the age effects for the frontal lobe and MTL residuals respectively.

Brain–Behavior Relationships

Zero-order correlations

Results from left and right hemisphere measures of frontal and MTL gray matter for brain–behavior analyses were virtually identical and thus were combined to simplify the statistical analyses. The first step in these statistical analyses was to assess for zero-order correlations between the two memory retention measures and the two primary brain measures, and for correlations between the two organizational measures and the two brain measures. The results of these analyses are given in Table 2. Note the different sample sizes for the different statistical tests reflect the total number of participants who had scores for the behavioral measure of interest.

Highly significant relationships between frontal lobe gray matter thinning and both verbal and spatial memory were

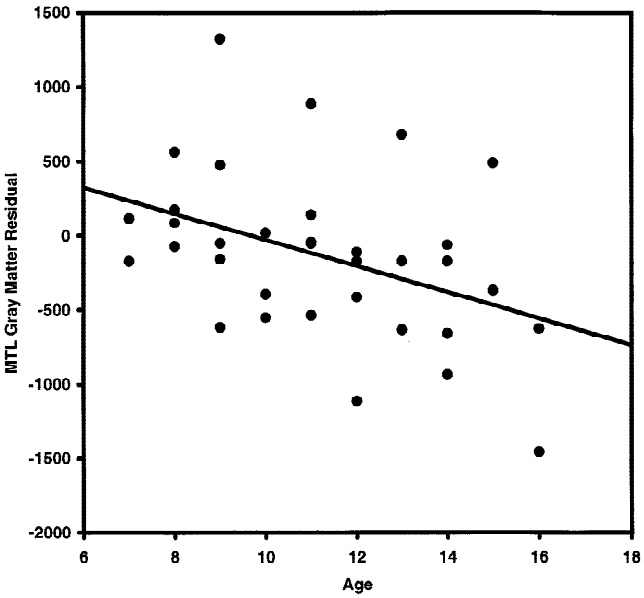

Fig. 3B. Scatterplot representing the age effect for MTL cortical gray matter residual.

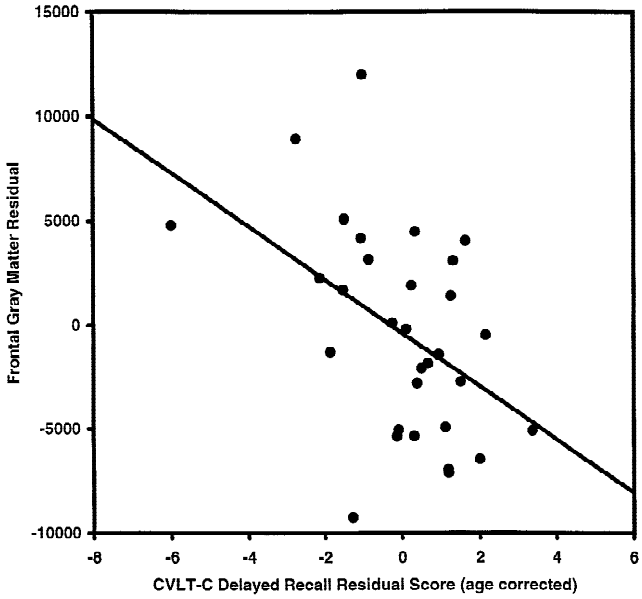

Fig. 4A. Scatterplot representing the correlation between frontal cortical residual (residualized for chronological age) and CVLT–C delayed recall score (residualized for initial learning and age).

observed ($r = -.56$, $p = .001$; $r = -.50$, $p = .03$, respectively). In other words, the children with thinner frontal cortex performed better on the memory tests. A significant relationship between spatial memory and the MTL was also observed ($r = -.53$, $p = .02$). No relationships were observed between the organizational and the brain measures.

Age-mediated effects in brain behavior relationships

Regression analyses were next conducted to assess whether the relationship between frontal cortical changes and delayed verbal and spatial retention was mediated by their correlations with chronological age. In this analysis, age and the frontal residual measure were used to predict first, the children's delayed memory retention score on the CVLT–C, and then their delayed spatial memory residual score for the ROCF. Interestingly, the relationship between frontal lobe cortical thinning and delayed verbal memory retention remained significant ($\beta = -.488$, $p = .011$), and age was no longer a significant predictor ($\beta = .14$, $p = .444$), despite the variables' strong zero-order age relationships. A similar pattern was observed for the spatial memory measure where frontal gray matter thinning was at trend-level significance as a predictor of this measure ($\beta = -.53$, $p = .080$) even when the factors indexed in chronological age were statistically controlled. Finally, the same type of analysis was conducted to see if the relationship between MTL and delayed ROCF recall was mediated by shared variance with chronological age. Once again, the brain morphological variable was at trend-level significance as a predictor of the children's delayed spatial recall ($\beta = -.49$, $p = .053$), and age did not significantly contribute to the prediction ($\beta = .09$, $p = .720$). Figure 4A illustrates the relationship between the frontal gray matter residual and verbal memory, and Figure 4B illustrates the frontal–spatial memory relationship. Note that the effects of age were statistically removed from the brain and behavioral measures for these graphs so that the effects independent of chronological age could be visualized.

Regional specificity

Analyses were next conducted to assess for regional specificity of the unexpected, but interesting, finding of a relationship between frontal cortex volume and delayed recall abilities. In a regression analysis, both frontal and MTL re-

Table 2. Tests for zero-order brain–behavior relationships

Measure	MTL gray residual	Frontal lobe gray ratio
CVLT–C Trials 1–5	$r = -.09$, $p = .62$ ($n = 31$)	$r = -.14$, $p = .47$ ($n = 31$)
ROCF Copy Progression	$r = .11$, $p = .59$ ($n = 28$)	$r = -.05$, $p = .81$ ($n = 28$)
CVLT–C Delayed Recall Residual	$r = -.22$, $p = .25$ ($n = 31$)	$r = -.56$, $p = .001$ ($n = 31$)
ROCF Delayed Recall Residual	$r = -.53$, $p = .02$ ($n = 19$)	$r = -.50$, $p = .03$ ($n = 19$)

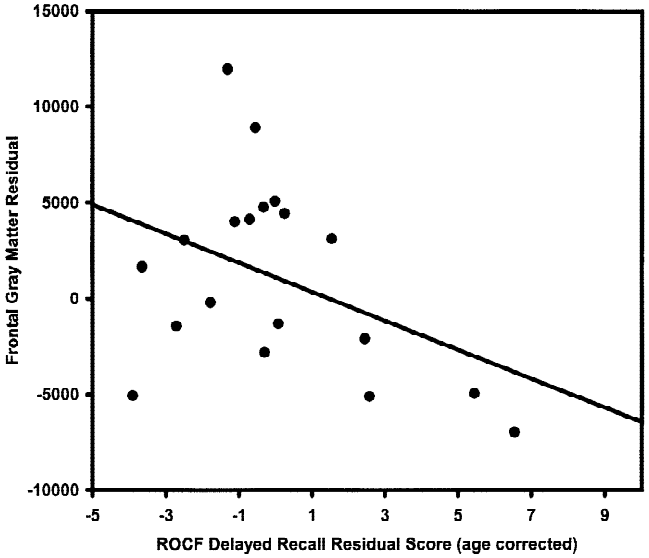

Fig. 4B. Scatterplot representing the correlation between frontal cortical volume (residualized to remove effects of chronological age) and ROCF delayed recall score (residualized for initial learning and age).

sidual scores were used to predict the children's delayed verbal memory retention score. It should be noted that this is a particularly stringent statistical test because the two brain variables are intercorrelated ($r = .61$) which would tend to attenuate observable independent relationships. Nonetheless, the frontal lobe was a strong predictor of CVLT–C delayed memory retention ($\beta = -.68$, $p = .002$), and the predictive value of the MTL residual was greatly reduced ($\beta = .20$, $p = .307$) in this test. Neither the frontal nor the MTL gray matter residual score was predictive of spatial memory when both were entered into the same regression equation, but the smaller sample size also reduced statistical power for this test. The results of this analysis are summarized in Table 3.

Follow-up brain–behavior analyses

Follow-up analyses were conducted after the unexpected, but interesting relationship between delayed verbal memory abilities and frontal lobe maturation was observed. The goal was to disambiguate factors more related to retention and factors more related to retrieval in the verbal delayed recall scores.

Retrieval

In order to measure *retrieval* ability that was less confounded with the children's retention abilities, a new residual measure was constructed from the CVLT–C measures. Specifically, the variance in the scores reflecting the children's ability to discriminate list from nonlist words in a recognition task (which required retention but placed little demand on retrieval abilities) was statistically removed from their scores on the Long-Delay Free Recall measure. Thus, the shared retention variability between Discriminability and Long-Delay Free Recall was statistically removed, leaving a new residual score that was thought to be a purer measure of retrieval.

Retention

In order to measure *retention* ability over a delay that was less confounded with the ability to retrieve stored information, another residual score was computed. For this score, the variability attributable to Short-Delay Free Recall was removed from the Long-Delay Free Recall score. Arguably, both Short- and Long-Delay Free Recall have strong retrieval components, thus residualizing the Long-Delay Free Recall score by Short-Delay Recall would theoretically remove the measures' shared retrieval variance, and leave behind a "forgetting" score, which was relatively independent of retrieval abilities. The "forgetting" score was thought to be the best measure of retention (lack of forgetting) over a delay period.

Brain–behavior relationships for retrieval

Post-hoc statistical analyses indicated that the new *retrieval* score was significantly positively correlated with age ($r = .529$, $p = .002$). This score was also highly negatively correlated with the frontal gray matter residual score ($r = -.559$, $p = .001$) indicating that more mature (thinner) frontal cortex is predictive of better retrieval. Once age was added into the regression equation as an additional predictor of retrieval ability, frontal gray matter was still a significant predictor of that measure ($\beta = -.395$, $p = .026$), and the effects of age were only marginally significant ($\beta = .336$, $p = .055$).

To assess for regional specificity of the relationship between brain maturation and retrieval abilities, the same analyses were conducted using the MTL as a predictor of retrieval abilities. The zero-order correlation between the new retrieval score and the MTL residual score was also signifi-

Table 3. Regional specificity analysis

Score	Frontal	MTL
CVLT–C Delayed Recall Residual Score ($n = 31$)	$\beta = -.68$, $p = .002$	$\beta = .20$, $p = .307$
ROCF Delayed Recall Residual Score ($n = 19$)	$\beta = -.28$, $p = .304$	$\beta = -.35$, $p = .119$

cant ($r = -.388$, $p = .031$). Once age was used as an additional predictor of the new retrieval score, the MTL residual was no longer significant in its predictive power ($\beta = -.189$, $p = .292$), but the independent contribution of age was still significant ($\beta = .444$, $p = .018$).

Brain–behavior relationships for retention

Similar analyses were conducted to assess for relationships between brain maturation and *retention* abilities using the new residual retention score from the CVLT–C. Correlational analyses indicated that the children's retention scores were not significantly correlated with chronological age, but the new retention score was marginally correlated with the frontal residual score ($r = -.336$, $p = .065$) and not the MTL residual.

DISCUSSION

Interesting findings resulted from the planned statistical analyses in this study. Specifically, frontal lobe thinning, bilaterally, was found to be significantly related to verbal memory abilities. Further analysis revealed that the relationship between frontal thinning and improved ability to retain and retrieve verbal information was statistically independent from, thus not mediated by, the variables' shared variance with chronological age. Similar results were observed for the spatial memory measure. There is evidence that frontal lobe maturation is specifically related to improving memory functioning; the mesial temporal lobe measure was not predictive of the behavioral measures when included with the frontal measure in the regression analyses, particularly for the verbal memory test. This indicates that there is some anatomical specificity to the relationship between improved memory functioning and brain maturation.

Recent functional imaging studies provide evidence that the frontal lobes are involved in the active encoding and retrieval of episodic memory in adults. Tulving and his colleagues in several studies using positron emission tomography (PET) reported strong right hemisphere frontal activations during effortful retrieval of recently studied material (e.g., Kapur et al., 1995; Nyberg et al., 1995; Tulving et al., 1994). Fletcher et al. (1998) found similar results. Findings of right prefrontal activation during retrieval of information from episodic memory have occurred whether verbal or spatial stimuli have been used, and whether auditory or visual materials were used in the study conditions. It is possible that results from the functional imaging studies are related to our findings of improved memory functioning specifically related to frontal lobe maturation. Note that relatively circumscribed regions have been implicated for memory in the functional imaging studies (e.g., left inferior prefrontal cortex for encoding, right prefrontal for retrieval), which are much more anatomically specific than the total frontal lobe measure described here. Nonetheless, we did find robust correlations with our relatively large region of interest that were specific to frontal and not MTL regions. Future studies will focus on the relationships between more circumscribed anatomical regions within the frontal lobe and memory functioning.

The question as to whether the residualized delayed verbal memory score used in this study actually measured the children's memory retention or their memory retrieval abilities is of considerable importance when speculating about the relationship between these findings and findings in the adult PET literature. The significant zero-order correlations for both the retention and retrieval scores with frontal lobe maturation suggest that our new residual scores may not actually represent distinct aspects of delayed recall abilities. However, in simultaneous multiple regression analyses where both retention and retrieval scores were used to predict the frontal gray matter residual, only the retrieval measure remained significant ($\beta = -.506$, $p = .006$) in the presence of the retention score ($\beta = -.131$, $p = .447$). Thus, it seems likely that the relationship observed between frontal cortical thinning and the original retrieval score was carried by a retrieval "factor." Clearly, many factors play a role in efficient retrieval, but the functional imaging work suggests that some factors rely more heavily on frontal structures than others (Buckner et al., 1998; Schacter et al., 1997). More detailed cognitive assessments and developmental fMRI studies will be needed to address these critical issues.

A priori hypotheses predicting positive relationships between mesial temporal lobe gray matter volume and memory functioning on the CVLT–C and the ROCF were not strongly supported with these data. In this study, the children's visuospatial, but not verbal, memory functioning was correlated with MTL volume, although this finding was not regionally specific. MTL structures correlated negatively with chronological age, rather than the expected increase in volume with age described in our earlier report (Sowell & Jernigan, 1998) where we studied a greater age span. It is possible that maturational changes in MTL structures continue into adulthood, are nonmonotonic in nature, and perhaps are in part related to pubertal factors. Speculations that development in the MTL would be specifically related to improved memory performance in this sample were based on adult lesion studies (e.g., Zola-Morgan et al., 1986) and *in vivo* MRI studies in adults with memory impairment (e.g., Jernigan & Ostergaard, 1993) that suggest that MTL structures play a specific role in encoding. However, evidence from the developmental literature shows that, while children's recognition abilities may already be near peak levels by 8 years of age (for a discussion, see Schneider & Pressley, 1989), their retrieval abilities improve considerably over this age range (7–16 years). This suggests that there may be little maturational change in encoding ability during this age range that could have resulted in the relatively weak MTL–memory relationship observed here.

Further predictions were made in this study about the relationship between verbal and spatial organizational abilities and maturation in the frontal lobes. These hypotheses were also not supported with these data. While the frontal lobe gray matter did significantly decrease in volume in this

age range, relationships between the children's ability to organize spatial and verbal information and maturation in the frontal lobes were not confirmed. It is possible that the measures chosen here did not adequately represent the construct (organizational and planning ability) that has so frequently been associated with frontal lobe functioning in the literature (e.g., Levin et al., 1991). Disambiguating organization and new learning is difficult in young, healthy individuals. While the clinical neuropsychological tests used here have been validated in clinical populations, they may not be ideal tools for measuring brain–behavior relationships during normal development. On the other hand, it is possible that the constructs were measured adequately, but that the development of planning ability during this stage of brain maturation relies on developing connections between high-level sensory input systems (i.e., visual input pathways not directly measured in these morphometric analyses) and frontal organizational regions. If so, our global frontal lobe measure may not have been sufficiently sensitive to localized changes underlying this type of cognitive maturation.

On a related note, material specific hypotheses regarding hemispheric differences in the relationship between verbal and spatial abilities were not supported. Again, it is possible that the anatomical regions circumscribed were too large and heterogeneous to tap these functional relationships on a hemispheric level, or that the behavioral measures used were not sufficiently specific.

Differences in sample size could confound our ability to compare directly the results from the verbal and spatial brain–behavior analyses. However, fewer participants were examined with the ROCF delayed recall analyses and these were the measures that were significantly related to MTL maturation in the zero-order analyses, not the CVLT measures available for more of the participants. Perhaps a more specific relationship between the ROCF scores and the MTL measure (relative to the frontal measure) would have been observed if the sample size were larger in the simultaneous multiple regression analyses. Future studies with larger samples will be needed to address this limitation to the study.

Overall, the results from this study provide interesting insights into the functional significance of regionally specific brain maturation. While the initial predictions were not strongly supported with these data, robust relationships between delayed memory abilities and brain maturation in the frontal lobes were observed with two different neuropsychological tests of memory functioning. Relationships between improving learning and memory abilities and brain maturation have not previously been studied using structural MRI in a normative sample in this age range. The functional imaging studies in adults provide interesting insights as to the possible significance of the structural changes in frontal cortex observed in children. While PET studies have been the primary methodology used to establish frontal lobe activations during memory tasks in adults, this invasive procedure is rarely used for the study of normal children. However, less invasive functional magnetic resonance imaging (fMRI) is becoming widely available. Future developmental studies using fMRI to assess functional brain–behavior relationships during memory tasks might provide additional insights into how children progress towards more adult-like frontal lobe functioning.

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