



Published in final edited form as:

J Cogn Neurosci. 2009 February ; 21(2): 316–332. doi:10.1162/jocn.2008.21028.

Development of Spatial and Verbal Working Memory Capacity in the Human Brain

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Abstract

A core aspect of working memory (WM) is the capacity to maintain goal-relevant information in mind, but little is known about how this capacity develops in the human brain. We compared brain activation, via fMRI, between children (ages 7–12 years) and adults (ages 20–29 years) performing tests of verbal and spatial WM with varying amounts (loads) of information to be maintained in WM. Children made disproportionately more errors than adults as WM load increased. Children and adults exhibited similar hemispheric asymmetry in activation, greater on the right for spatial WM and on the left for verbal WM. Children, however, failed to exhibit the same degree of increasing activation across WM loads as was exhibited by adults in multiple frontal and parietal cortical regions. Thus, children exhibited adult-like hemispheric specialization, but appeared immature in their ability to marshal the neural resources necessary to maintain large amounts of verbal or spatial information in WM.

INTRODUCTION

Working memory (WM) refers to the ability to maintain goal-relevant information in mind. WM is fundamental to higher cognitive functions, including reasoning and reading comprehension (Engle, Tuholski, Laughlin, & Conway, 1999; Just & Carpenter, 1992; Kyllonen & Christal, 1990; Daneman & Carpenter, 1980), and is linked to scholastic development (Hitch, Towse, & Hutton, 2001). Electrophysiological, lesion, and cooling studies with primates (Barone & Joseph, 1989; Quintana, Fuster, & Yajeya, 1989; Fuster, Bauer, & Jervey, 1985; Bauer & Fuster, 1976; Fuster & Alexander, 1971; Kubota & Niki, 1971) and functional neuroimaging studies with humans (Nystrom et al., 2000; Smith & Jonides, 1999; Courtney, Petit, Haxby, & Ungerleider, 1998; Jonides et al., 1993, 1998; Cohen et al., 1997; Manoach et al., 1997; Awh, 1996; Sweeney et al., 1996; Paulesu, Frith, & Frackowiak, 1993) (reviewed by Wager & Smith, 2003) provide convergent evidence that prefrontal and parietal cortices support the maintenance of information in WM in the absence of perceptual information. In delayed match-to-sample tasks in humans, such as the Sternberg WM task (Sternberg, 1966), reliable activations have been observed in dorsolateral prefrontal, ventrolateral prefrontal, premotor, and parietal cortices during the maintenance of information in WM after stimulus encoding and before stimulus response (Cabeza & Nyberg, 2000; D’Esposito, Ballard, Zarahn, & Aguirre, 2000; Haxby, Petit, Ungerleider, & Courtney, 2000;

Jonides et al., 1998). These studies have been performed with adults, and here we examined the development of the brain basis of WM in children.

The pattern and magnitude of brain activation during a WM task depends on the nature and the amount (or load) of information maintained in WM. Spatial and verbal information invoke, respectively, right-lateralized and left-lateralized activations in humans (Smith & Jonides, 1998, 1999; D'Esposito et al., 1998; McCarthy et al., 1994, 1996; Smith, Jonides, & Koeppe, 1996; Jonides et al., 1993). Maintaining larger amounts of information in WM leads to larger activation during WM tasks (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; Zarahn, Raskin, Abela, Flynn, & Stern, 2005; Jaeggi et al., 2003; Veltman, Rombouts, & Dolan, 2003; Jansma, Ramsey, Coppola, & Kahn, 2000; Nystrom et al., 2000; Postle, Berger, & D'Esposito, 1999; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999; Braver et al., 1997; Cohen et al., 1997; Manoach et al., 1997) until capacity limitations are reached (Jansma, Ramsey, van der Wee, & Kahn, 2004; Callicott et al., 1999). Increased activation for greater loads has also been observed specifically during WM maintenance (Narayanan et al., 2005; Leung, Gore, & Goldman-Rakic, 2002; Rypma, Berger, & D'Esposito, 2002). These brain activations during WM reflect neural processes essential for accurate maintenance of information: Greater magnitude of activation spanning the delay interval is associated with greater WM accuracy in healthy adults (Pessoa, Gutierrez, Bandettini, & Ungerleider, 2002).

Behavioral studies have documented an increase in WM ability from childhood to adulthood (Conklin, Luciana, Hooper, & Yarger, 2007; Gathercole, Pickering, Ambridge, & Wearing, 2004; Hitch et al., 2001; Chelonis, Daniels-Shawb, Blakea, & Paule, 2000; Kemps, De Rammelaere, & Desmet, 2000; Bjorklund, 1987). Cross-sectional functional neuroimaging studies of WM have shown similar distributions of brain activations in children and adults (Scherf, Sweeney, & Luna, 2006; Klingberg, Forsberg, & Westerberg, 2002; Nelson et al., 2000; Thomas et al., 1999; Casey et al., 1995). Development of WM has been associated with greater activation in frontal, parietal, and cingulate regions known to support WM performance in adults (Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006; Schweinsburg, Nagel, & Tapert, 2005; Klingberg et al., 2002; Kwon, Reiss, & Menon, 2002) and greater activation across this network has been related to improvements in children's performance (Ciesielski et al., 2006; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Nagel, Barlett, Schweinsburg, & Tapert, 2005; Klingberg et al., 2002).

In the present study, we compared activations between children ages 7–12 and adults ages 20–29 and focused on two major themes: (1) hemispheric specialization for verbal and spatial information and (2) WM capacity as measured by variation in load. Prior developmental WM imaging studies have examined performance on either verbal or spatial tasks. Here, we aimed to examine the development of hemispheric specialization by including both verbal and spatial tasks. Indeed, there has been only one study to date of verbal WM (VWM) development, and that study was performed with children only (precluding a comparison with adults) and was limited to an analysis of the frontal cortex with surface coils (Casey et al., 1995). Further, most prior developmental WM imaging studies have used complex WM tasks that sometimes included load as a manipulation, but also included other executive functions such as updating and ordering so that WM capacity (load) could not be examined independently from these executive functions. These studies examined WM in children 7 years or older on *n*-back tasks or variants of the *n*-back task (Ciesielski et al., 2006; Nagel et al., 2005; Schweinsburg et al., 2005; Kwon et al., 2002; Nelson et al., 2000; Thomas et al., 1999; Casey et al., 1995), and on WM tasks requiring sequential encoding and maintenance (Scherf et al., 2006; Klingberg et al., 2002), or maintenance and reordering (Crone et al., 2006). In the present study, we used a delayed match-to-sample, or Sternberg, WM design so that only load was manipulated across conditions (Figure 1). Including multiple loads allowed for examination of how activations

changed as a parametric function of the amount of information held in WM, and whether load-dependent change in brain function is similar in children and adults.

The dominant model of WM (Baddeley & Hitch, 1974) proposed that WM is composed of three main components: a central executive that acts as supervisory system and controls the flow of information to and from its two slave systems, the phonological loop, and the visuospatial sketchpad. The slave systems are short-term storage systems dedicated to verbal (phonological loop) or spatial (visuospatial sketchpad) content domains (Baddeley, 1992). The distinction between two domain-specific slave systems was motivated, in part, by experimental findings with dual-task paradigms in which performance of two simultaneous tasks requiring the use of verbal and spatial information was nearly as efficient as performance of each task individually. In contrast, carrying out two tasks simultaneously that used the same informational domain resulted in less efficient performance than performing the tasks individually.

Behavioral studies of WM development report less separation of verbal and spatial task domains in younger children. In one behavioral study, 8-year-olds demonstrated interference effects during WM whether the secondary task was from the same or a different domain (e.g., visuospatial interfered with verbal information), whereas 10-year-olds showed interference specific to the same domain (Hale, Bronik, & Fry, 1997). This indicates that VWM and spatial WM (SWM) systems are interdependent in young children, but approach adult-like independence by age 10. There is also some imaging evidence from a non-WM study indicating that other cognitive capacities shift from undifferentiated, bilateral processing toward hemispheric lateralization in children ages 7–14 years (Moses et al., 2002). These studies raise the possibility that children will not exhibit the strong hemispheric specialization shown by adults with VWM or SWM tasks.

By including both VWM and SWM tasks and by comparing children and adults directly, we were able to examine whether children exhibit the same hemispheric asymmetry as young adults. Our WM task design is a replication and extension of a study that examined cognitive decline associated with aging (Reuter-Lorenz et al., 2000). Imaging studies with healthy older adults have shown reduced asymmetry of activation in the prefrontal cortex (PFC) during SWM and VWM tasks. This reduced asymmetry of activation has been interpreted as recruitment of additional contralateral neural resources to compensate for age-related reductions in WM ability (Reuter-Lorenz et al., 2000). It is unknown whether children, who like older adults have reduced WM capacity compared to young adults, also exhibit reduced asymmetry.

Interpreting the development of functional neural systems is challenging when adults outperform children, as they do on WM tasks. Activation differences may reflect not only development of WM systems but also other differences that arise from different levels of accuracy, such as error-monitoring and frustration. There is no true control for such fundamental developmental changes, but a parametric design allows for additional analysis between versions of the task in which participants are matched for accuracy. In the present study, by comparing activations in children and adults who performed with similar accuracy to one another at different load levels, we could determine whether any activation differences were strictly a function of performance accuracy.

METHODS

Participants

Healthy, right-handed, native English-speaking participants were recruited from Stanford University and the surrounding community and were paid for their participation. Adult participants gave informed consent, and parents and their children gave informed consent and

assent, respectively, as approved by the Stanford Institutional Review Board. Prior to scanning, children were acclimated to the scanner environment, and watched a 12-min video about the scanning process (prepared in-house by the authors for this study and other studies, at the Richard M. Lucas Center for Magnetic Resonance Spectroscopy and Imaging at Stanford University).

In order to reduce the fatigue of long functional scan sessions, SWM and VWM were scanned on two different days within a 2-week period. All children ($n = 16$) and adults ($n = 16$) were scheduled to participate in both the verbal and spatial fMRI experiments (mean child age = 9.8 years, range = 7.2–11.9; mean adult age = 22.8 years, range = 20–30). In a small number of cases, we only obtained useable data from a single session, due to participant dropout or technical problems associated with a scan session. Therefore, 27 participants completed both tasks, 28 participants completed the verbal task, and 32 participants completed the spatial task. Data from all participants who performed either the verbal (14 adults and 14 children) or the spatial (16 adults and 16 children) tasks were used in the analysis of load effects in each task. Data from a subset of participants who performed both verbal and spatial tasks (13 adults and 14 children) were used in the analysis of laterality effects, which required within-subject comparisons across tasks. All participants received practice on both the verbal and spatial tasks prior to scanning.

Behavioral Methods

During fMRI, visual stimuli were generated using Psy-Scope (Macwhinney, Cohen, & Provost, 1997) on a Macintosh G4 computer, and were back-projected onto a screen viewed through a mirror mounted above the participant's head. Participants indicated their responses on a button-pad interfaced to the PsyScope button box.

Each WM trial began with a central fixation cross, followed by presentation of successive encoding, maintenance, and retrieval phases (Figure 1). Participants were instructed to remember the information in the encoding display (either spatial locations defined by circles and rings, or letters, shown for 500 msec), maintain the information in mind over a delay period of either 100 msec (no maintenance) or 3000 msec (maintenance) while a fixation cross was shown, and then judge whether a test probe (either a spatial location or a letter), shown for 1500 msec, did or did not match the encoding display. For the spatial encoding displays, visual locations were indicated by one, three, or five target dots randomly arrayed across four invisible concentric circles centered around a fixation cross. At retrieval, participants saw a single outline circle either encircling or not encircling the location of one of the dots from the encoding display. For the verbal encoding displays, there were two, four, or six uppercase letters arranged in a concentric circle around a fixation cross. At retrieval, participants saw a single lowercase letter that was or was not one of the letters from the encoding display. For both verbal and spatial trials, participants pressed one of two buttons to indicate either a match or a mismatch between probe and target items (location or letter).

The experiment was a block design aimed at maximizing sensitivity to both load and maintenance and being brief enough to be comfortable for children. Experimental and control trials used equivalent stimulus sequences and motor response characteristics, but varied on both load and maintenance demands. Experimental blocks were those that included the 3000-msec maintenance delay between encoding and retrieval, whereas the control/baseline blocks were no maintenance blocks that included only a brief perceptual delay, 100 msec. The number of items presented in the encoding and retrieval phases was matched for experimental and control blocks at each load, but only one kind of letter was presented in the verbal control trials and only one target (black) location was presented in the spatial control trials. Thus, each control task matched each experimental task for perceptual and response factors, but not load. Each scan involved one kind of material with one load, and consisted of 72 trials (36

experimental, 36 control, 50% match in each condition) in pseudorandom order alternating between experimental and control blocks with 4 trials in each of 18 total blocks. Participants underwent SWM and VWM scans on different days in order to avoid fatigue and to minimize the possibility of cross-task interference.

SWM and VWM tasks were designed to be similar to one another. Different loads for spatial and verbal tasks were selected to equate difficulty across the tasks on the basis of pilot behavioral data. Task designs were similar to prior WM studies designed to identify activation related to WM maintenance (Reuter-Lorenz et al., 2000; Smith et al., 1996; Jonides et al., 1993). Therefore, SWM and VWM tasks used equivalent stimuli sequences, timing, and motor response characteristics. They differed only in the type of information held in mind, and across scans, differed in the number of items maintained.

Tasks were designed to minimize proactive interference between trials and to encourage phonological and spatial strategies in the verbal and spatial tasks, respectively. In order to control interference effects, letters or spatial locations on a given trial did not reappear on the next two trials. The probe letter was presented in lowercase in order to discourage template or perceptual matching and instead to encourage use of a phonological strategy. In order to verify that participants used a spatial strategy, there were two types of equally frequent spatial nonmatch trials: *near* nonmatches in which the probe ring was near (between 15° and 50° around a concentric circle) to one of the dots presented during encoding, and *far* nonmatches in which the probe ring was far (greater than 50° around a concentric circle) from any of the dots presented during encoding.

Behavioral Analyses

Behavioral accuracy (% correct) and speed of response (median reaction time, RT) were analyzed using repeated measures analyses of variance (ANOVA), correcting for nonsphericity, and *t* tests. Analyses were performed separately for verbal and spatial tasks, and for maintenance blocks and baseline blocks. Each analysis comprised a 2 × 3 ANOVA, with a between-subjects factor of group (children/adults) and a within-subjects factor of load (low/medium/high). Primary behavioral effects were examined using a 2 × 2 × 3 ANOVA (Distance × Group × Load) was performed for the spatial task to test the effect of the near–far spatial manipulation for non-match trials.

fMRI Acquisition Procedures

Magnetic resonance imaging was performed on a 3.0-T GE whole-body scanner. For each participant, ample padding was placed around the head and a bite bar (made of Impression Compound Type I, Kerr Corporation, Romulus, MI) was used to stabilize the head position and reduce motion-related artifacts during the scans. Twenty-three oblique axial slices were taken parallel to the AC–PC with 4-mm slice thickness, 1-mm skip. High-resolution T2-weighted fast spin echo structural images (TR = 3000 msec, TE = 68 msec, ETL = 12, FOV = 24 cm, 192 × 256) were acquired for anatomical reference. A T2*-sensitive gradient-echo spiral-in/out pulse sequence (Glover & Law, 2001) was used for functional imaging (TR = 1500 msec, TE = 30 msec, flip angle = 70°, FOV = 24 cm, 64 × 64). An automated high-order shimming procedure, based on spiral acquisitions, was used to reduce B0 heterogeneity (Kim, Adalsteinsson, Glover, & Spielman, 2002). Spiral-in/out methods have been shown to increase signal-to-noise ratio and BOLD contrast-to-noise ratio in uniform brain regions as well as to reduce signal loss in regions compromised by susceptibility-induced field gradients generated near air–tissue interfaces such as the PFC (Glover & Law, 2001). Compared to traditional spiral imaging techniques, spiral-in/out methods result in less signal dropout and greater task-related activation in PFC regions (Preston, Thomason, Ochsner, Cooper, & Glover, 2004). A high-resolution volume scan (124 slices, 1.2 mm thickness) was collected for every subject using

an IR-prep 3-D FSPGR sequence for T1 contrast (TR = 8.9 msec, TE = 1.8 msec, TI = 300 msec, flip angle = 15°, FOV = 24 cm, 256 × 192).

fMRI Analysis

fMRI data were analyzed using SPM99, SPM2 (Wellcome Department of Cognitive Neurology), and custom MATLAB routines. Preprocessing included correction for motion and signal drift. Functional images were normalized with participant-specific transformation parameters created by fitting gray matter segmented anatomical images to a single reference gray matter template image. Measured fMRI activation during the experimental blocks was compared to activation during the corresponding base-line blocks (maintenance > no maintenance). Regressors for the corresponding condition blocks were modeled as a boxcar function convolved with the canonical hemodynamic response function. Statistical analysis at the single-subject level treated each voxel according to a general linear model (GLM; Worsley et al., 2002). For both SWM and VWM, second-level analyses were performed by ANOVA to test for the main effects of group, load, and the interaction of Group × Load using a threshold of $p < .001$ (uncorrected for multiple comparisons), cluster size > 25. All reported activations were also significant at $p < .05$ false discovery rate.

Peak voxels of functional regions of interest (ROIs) that exhibited a significant Group × Load interaction were examined to characterize the interactions. We extracted mean parameter estimates from each participant's contrast image (maintenance > no maintenance) at each load level. Extracted values for each ROI were submitted to statistical analysis. Similar results were found when we performed comparable analyses with spheres surrounding the peak voxels.

In addition, activations were compared between children performing the lowest load WM tasks and adults performing the highest load WM tasks so that activations could be compared at similar levels of behavioral accuracy. These second-level analyses were performed by two-sample t tests between the groups for the maintenance > no maintenance contrast images at their respective loads.

Laterality

In the subset of participants who performed both SWM and VWM scans, an analysis was performed to test the main effects of material, collapsed across all loads. Laterality indices (LIs), which are quantitative measures of hemispheric asymmetry of activation, were obtained for each age group. LI is typically calculated using the equation $LI = (R_{vx} - L_{vx}) / (R_{vx} + L_{vx})$, where R_{vx} is the number of voxels in the right hemisphere, and L_{vx} is the number of voxels in the left hemisphere. Positive numbers indicate predominately right-sided activation and negative numbers indicate predominately left-sided activation. Because statistically weighted voxel counts have recently been shown to be a superior approach to LI estimation (Branco et al., 2006), LI values were also calculated by weighted LI (wLI) quantification, wherein suprathreshold voxels were multiplied by their effect sizes. Thus, R_{vx} and L_{vx} in the equation above were replaced by $R_{vx}' = R_{vx} \times R_s$ and $L_{vx}' = L_{vx} \times L_s$, respectively, where R_s and L_s are the mean effect sizes in right and left hemispheres, respectively. Two-tailed t tests were used to test differences in LI and wLI between groups. Additionally, regression analysis was used to test the association between age and LI in children.

Estimation of Factors Associated with BOLD-related Confounds

To exclude that a lower signal-to-noise ratio may confound reported differences between groups or across loads, an analysis of the residual-error variance estimate of the GLM (ResMS) between groups and within groups across loads was performed. The ResMS map reflects the discrepancy between GLM estimates and the time-course BOLD data, and thus, is a measure of all sources of measurement noise after detrending, including BOLD-related noise as well

as the goodness of GLM fit. To obtain noise estimates for each subject, the ResMS map was converted to a percent variance map by dividing it by the square of the Beta map that corresponded to the time-series constant signal. The Beta map was used to scale the ResMS map to exert normalized influence on the group mean. An average and standard deviation map was obtained for all subjects in a group, and mean values were obtained using an all-brain mask. Significances of between-group differences at each load, and within group between load differences were determined by two-tailed *t* tests.

The translational movement during each scan was calculated in millimeters and the rotational motion in radians, based on the SPM99 parameters for motion correction of the functional images in each subject.

RESULTS

Behavioral Data

Primary behavioral effects were examined using a $2 \times 2 \times 3$ ANOVA of Material (M) \times Group (G) \times Load (L) for accuracy across maintenance trials (Table 1). Four significant effects were identified as a result of this analysis: (1) Adults were more accurate than children; (2) Participants were less accurate at higher loads; (3) Differences between groups were greatest at the highest load (G \times L interaction); and (4) Accuracy declined more for SWM than VWM as a function of load (L \times M interaction). Further analyses are summarized by material type.

Spatial Working Memory—For SWM maintenance trials, adults (\bar{x} = 91.6%) were more accurate than children (\bar{x} = 71.9%) [$F(1, 30) = 45.6, p < .001$]. All participants were less accurate with greater loads [main effect of load, $F(2, 60) = 36.06, p < .001$] (Figure 2). Importantly, there was a Group \times Load interaction [$F(2, 60) = 7.21, p < .01$], reflecting the fact that the difference between adults and children grew across increasing loads. For the baseline (no maintenance) condition, adults were more accurate than children [$F(1, 30) = 7.06, p < .05$], and there was a trend that participants were less accurate with greater load [main effect of load, $F(2, 60) = 3.15, p = .06$]. The Group \times Load interaction for the baseline condition was not significant ($p > .3$).

For correct SWM maintenance trials, adults (median 862 msec) were faster to respond than children (median = 1098 msec) [$F(1, 30) = 33.94, p < .001$]. Participants slowed as load increased [main effect of load, $F(2, 60) = 70.45, p < .001$], and there was no Group \times Load interaction ($p > .3$).

The near–far spatial manipulation was examined by submitting accuracy and RT to two separate $2 \times 2 \times 3$ ANOVAs of D distance (near–far) \times G \times L for maintenance nonmatch trials. Adults were more accurate [$F(1, 30) = 14.35, p \leq .001$] and faster [$F(1, 30) = 25.29, p < .001$] than children. Participants were less accurate [$F(2, 60) = 10.75, p < .001$] and slower [$F(2, 60) = 8.33, p < .01$] with greater loads. Critically, participants were less accurate [$F(1, 30) = 14.61, p \leq .001$] and slower [$F(1, 60) = 27.06, p < .001$] for near than far nonmatch retrieval trials. The D \times L interaction was significant for both accuracy [$F(2, 60) = 6.43, p < .01$] and RT [$F(2, 60) = 12.34, p < .001$]. For both measures, performance on the near trials dropped off more steeply than on far trials as load was increased. The D \times G \times L interaction was nonsignificant for accuracy, but was significant for RT [$F(2, 60) = 4.51, p < .05$]. For both groups, the smallest RT difference between near and far trials occurred at the low load level and increased for the middle load. For adults, this difference continued to increase as load increased, but for children, the difference between near and far RT was reduced slightly in the high load as compared to the middle load.

Verbal Working Memory—For VWM maintenance trials, adults ($\bar{x} = 92.3\%$) were more accurate than children ($\bar{x} = 75.7\%$) [$F(1, 26) = 26.27, p < .001$]. Participants were less accurate with greater loads [main effect of load, $F(2, 52) = 21.04, p < .001$]. Importantly, there was a Group \times Load interaction [$F(2, 52) = 6.96, p < .01$], reflecting the fact that the difference between adults and children grew across increasing loads. For the baseline (no maintenance) condition, adults were more accurate than children [$F(1, 26) = 6.57, p < .05$]. The main effect of load, and the Group \times Load interaction, were not significant for the baseline condition ($p > .7, p > .8$, respectively).

For correct VWM maintenance trials, adults ($x = 816$ msec) were faster to respond than children ($x = 1084$ msec) [$F(1, 26) = 33.96, p < .001$]. Participants were slowed as load increased [main effect of load, $F(2, 52) = 21.14, p < .001$], and there was no Group \times Load interaction ($p > .1$).

Performance Matching—Accuracy for experimental trials was similar between children performing on the lowest loads and adults performing on the highest loads for the spatial task [children, 85.1%, adults 86.6%; $t(15) = 0.47, p = .65$] and for the verbal task [children 84.7%, adults 89.1%; $t(13) = 1.13, p = .27$]. Median RT was similar for children performing the lowest load and adults performing the highest load in the SWM task [children 1007 msec, adults 937 msec; $t(15) = 1.67, p = .11$], but adults remained significantly faster than children for the verbal task when performing the highest and lowest loads, respectively [children 1037 msec, adults 873 msec; $t(13) = 3.38, p = .002$].

fMRI Results

Adults and children exhibited greater activation for maintenance trial blocks than for the no-maintenance baseline blocks in many regions for both the verbal and spatial tasks, including areas in the bilateral inferior frontal gyrus (IFG), the middle frontal gyrus (MFG), the cingulate cortex, and the parietal cortex (Figure 3).

When activations in adults and children were compared directly, adults exhibited greater activation in large regions of the frontal, parietal, and temporal lobes, basal ganglia, and cerebellum during both VWM and SWM tasks (Table 2). Children demonstrated greater activation than adults only in portions of the parahippocampal gyrus and in a punctate region of the right middle frontal cortex during the VWM task, and several regions of the occipital lobe during the SWM task (Table 3).

The influence of load on activation was examined separately in adults and children for verbal and spatial tasks (Table 4). Adults exhibited increasing activation as a function of greater load in bilateral prefrontal and parietal cortices. Children exhibited fewer regions responding to load on the spatial task, and neither prefrontal nor parietal areas were among those regions that exhibited significant load-dependent activations. Children exhibited load-dependent frontal and parietal activations for the verbal task, although these were smaller in volume than those in adults.

There were 16 regions that exhibited Group \times Load interactions, including bilateral frontal and parietal regions. ROI analyses showed that the significant interactions were due to a disproportionate influence of load on adult activation, such that greater loads were associated with linearly increasing activations. In contrast, children exhibited small growths of activation across loads, and often no reliable growth at all (Figure 4).

For adults, activation increased significantly with WM load in 15 of 16 interaction regions ($p \leq .001$ for 14 regions, $p < .05$ for the occipital cortex). The region of exception was the insula, where a significant decrease in activation across loads was observed in adults as

compared to no observed reduction in children ($p < .001$). By contrast, for children, activation increased significantly ($p < .05$) with WM load in only 6 of these 16 interaction regions (Figure 4). At the lowest loads, group differences were not significant in 12 out of 16 ROIs ($p < .01$). At the middle loads, adults exhibited greater activation than children in all eight SWM regions and in six of eight VWM regions ($p < .01$). At the highest loads, adults exhibited significantly greater activation than children in all 16 ROIs ($p < .01$). These results provide further evidence that activation differences between groups increased with WM load.

In order to examine whether children exhibited load-dependent growths of activation in other brain regions different than adults, we performed a separate analysis of load-dependent activations in children. Regions exhibiting load-dependent growths of activation in children (Table 4) were selected as functional ROIs, and we examined load-dependent adult activations in those children-defined ROIs. In all of these regions, adults exhibited comparable or greater growths of load-dependent activation than children even though the ROI had been defined by the children's activations.

Activation Differences Persist when Performance is Matched

A direct comparison of activation was made between children (at the lowest load) and adults (at the highest load) performing with equal accuracy to identify differences attributable to age independent of performance (Figure 5A and B). This revealed large regions of frontal and parietal cortices that were more active in the adults despite the equal accuracy of performance.

Lateralization

To investigate if there was a group-related difference in the lateralization of the spatial and verbal information activation, we performed a separate statistical analysis of the main effect of material (or WM domain) in the 14 children and 13 adults who performed both the spatial and verbal tasks. There was greater activation for SWM than VWM tasks in both groups across a large extent of the right hemisphere, covering areas of the inferior parietal lobule, the visual association area of the occipital lobe, and premotor regions in the frontal lobe (Figure 6). There was greater activation for verbal than spatial tasks in both groups in the left IFG and MFG, including BA 44, and regions of the left temporal lobe (Figure 6). Effect-size weighted laterality indices (wLIs) of the volumes of activation from group random effects analyses were similar in the adults and children, with both groups exhibiting right-lateralized activation for the SWM task [adult wLI = 0.53, child wLI = 0.52, $t(26) = 0.36$, $p = .78$], and left-lateralized activation for the VWM task [adult wLI = -0.89, child wLI = -0.95, $t(26) = 0.33$, $p = .8$]. Additionally, results in children and adults were similar for the non-effect-weighted LIs. Again, both groups exhibited right-lateralized activation for the SWM task [adult LI = 0.48, child LI = 0.48, $t(26) = 0.07$, $p = .96$], and left-lateralized activation for the VWM task [adult LI = -0.88, child LI = -0.94, $t(26) = 0.33$, $p = .8$]. A post hoc analysis of activation maps at the individual-subject level showed that no significant age-related laterality effects were present within the children either. In children, age was not found to be significantly correlated with wLI for SWM > VWM ($r = -.053$, $p = .86$), or with wLI for VWM > SWM ($r = .028$, $p = .93$).

BOLD-related Confounds

Residual error of the GLM (ResMS)—There were no significant differences in residual variance from the GLM between spatial low and middle loads [for children, $t(30) = 0.29$, $p = .77$; for adults, $t(30) = 0.14$, $p = .89$], spatial middle and high loads [for children, $t(30) = 0.39$, $p = .70$; for adults, $t(30) = 0.74$, $p = .47$], or spatial low and high loads [for children, $t(30) = 0.12$, $p = .91$; for adults, $t(30) = 0.89$, $p = .38$]. There were also no differences between verbal low and middle loads [for children, $t(26) = 0.24$, $p = .81$; for adults, $t(26) = 0.13$, $p = .90$], verbal middle and high loads [for children, $t(26) = 0.74$, $p = .47$; for adults, $t(26) = 0.43$, $p = .67$], or verbal low and high loads [for children, $t(26) = 0.57$, $p = .57$; for adults, $t(26) = 0.58$,

$p = .57$] for noise. There were significant differences in residual variance from the GLM (ResMS) between children and adults at each load in the spatial tasks ($p = .02$ for low, middle, and high loads). There were no significant differences between groups in ResMS at each load in the verbal tasks, but the p values approached significance ($p = .09$ low and middle loads; $p = .1$ at high load). These results indicate that ResMS value differences did not change across loads.

Motion—Children and adults did not differ significantly in translational or rotational motion parameters in either the SWM task ($ps > .19$) or the VWM task ($ps > .09$).

DISCUSSION

We examined the influence of two factors on the development of the brain organization of WM in children, the content of information (verbal or spatial) and the amount of information (load). The content of information in WM had similar influences on children and adults, with verbal content yielding greater left-hemisphere activation and spatial content yielding greater right-hemisphere activation. The amount of information, or WM load, resulted in strikingly dissimilar fMRI and behavioral responses in children and adults. Both groups made more errors and took longer to respond as WM load increased, providing behavioral evidence that the higher loads were taxing WM capacity. The children, however, had a disproportionate growth in errors as a function of load. Similarly, activation differences between children and adults were greatly influenced by load. Adults exhibited steep increases in activation as load increased in many brain regions associated with WM, including the lateral PFC and the parietal cortex. Children exhibited far less increase in activation across loads. Thus, children had a severe WM capacity limitation relative to adults manifest as both a disproportionate acceleration of errors and a disproportionate failure to engage WM circuitry in proportion to WM loads.

In general, our findings are consistent with prior imaging studies of WM development. First, there was a general similarity of the locations of activation in children and adults. Second, adults exhibited greater activation than children. The present study goes beyond prior studies by (1) comparing children and adults on VWM, (2) examining both VWM and SWM in children, and (3) examining behavior and activation at multiple loads that allow for parametric comparisons between groups. One study examined activation in children ages 9–18 at two SWM loads, but comparisons are difficult to make because that study examined most effects as a continuous function of age (Klingberg et al., 2002). In that study, one activation in the superior frontal cortex was compared between younger (ages 9–12) and older (ages 13–18) children, and there were main effects of group and load, but no interaction. Thus, our findings comparing children ages 7–12 and adults differ in observing both behavioral and activation differences that powerfully interacted with development. A future study that includes children, adolescents, and adults in a single design may clarify the transition from immature to mature WM systems.

Hemispheric specialization is a hallmark of the organization of mental functions in the adult human brain, with left-hemisphere specialization for verbal functions and right-hemispheric specialization for visuospatial functions. At one time, it was hypothesized that hemispheric specialization develops slowly from equipotential hemispheres (Lenneberg, 1967), but subsequent behavioral and EEG studies have shown that even infants express a degree of hemispheric specialization (Holowka & Petitto, 2002; Best, Hoffman, & Glanville, 1982; Molfese, Freeman, & Palermo, 1975). Hemispheric specialization has also been described in prior fMRI studies of either SWM (Thomas et al., 1999) or VWM (Casey et al., 1995) development. However, no prior developmental fMRI study of WM compared hemispheric specialization quantitatively. Here, we compared spatial and VWM within-subjects and found that hemispheric asymmetry of activation in children and adults was left-lateralized for verbal

processes and right-lateralized for spatial processes. The degree of lateralized activation was quantitatively similar for children and adults, and was not correlated with age within children. In this respect, our findings differ from a report that children ages 7–14 shift from bilateral processing toward hemispheric lateralization in a study of global versus local processing (Moses et al., 2002). This suggests that the development of hemispheric lateralization is process-specific. In the present study, under these task conditions, the magnitude of hemispheric specialization was equal in children ages 7–12 and in young adults.

Our lateralization findings also differ from what has been reported in studies of aging adults with similar tasks. Functional neuroimaging studies with healthy older adults have revealed reduced prefrontal activation asymmetry relative to young adults, and the reduced asymmetry has been interpreted as recruitment of additional contralateral neural resources to compensate for age-related reductions in WM ability (Reuter-Lorenz et al., 2000). Although the children had reduced WM ability relative to the young adults in the present study, they did not exhibit any decrease (or increase) in hemispheric asymmetry of activation as has been observed in aging. This difference between children and older adults is noteworthy because the present study with children used a paradigm very similar to that which did find reduced asymmetry of PFC activation for both VWM and SWM in older adults (Reuter-Lorenz et al., 2000). A direct contrast between children and older adults will be needed to confirm the idea that, for PFC contributions to WM, development from childhood to adulthood is marked by consistent hemispheric asymmetry, whereas development from younger to older adulthood is marked by a change in hemispheric asymmetry.

The most striking difference between children and adults in the present study was the far larger WM capacity exhibited by adults by both behavioral and brain measures. As WM capacity was taxed by greater amounts of information, adults appeared to respond by recruiting relevant brain regions in frontal and parietal cortices with increasing intensity. The recruitment of these resources allowed for about a 10% decrease in accuracy across increasing WM loads for adults. As WM capacity was taxed by greater loads of information, children appeared unable to recruit the same brain regions with increasing intensity. Perhaps as a consequence, children exhibited a 30% decrease in accuracy across increasing WM loads. Thus, performance and activation differences between children and adults were smallest when WM was least taxed, and greatest when WM was most taxed.

We examined the possible role of developmental differences in accuracy by an analysis in which children and adults were equated for accuracy by comparing activations at the low load for children and the high load for adults. Despite similar accuracy rates for children and adults in this comparison, the adults exhibited greater activation in frontal and parietal regions. Matching by accuracy cannot equate the processes engaged by children and adults, but such matching suggests that developmental differences could not be accounted for simply by correlates of accuracy, such as increased error monitoring and frustration that may accompany higher error rates. Critically, similar developmental differences were found whether we compared adults and children performing the same tasks (at different levels of accuracy) or performing at the same levels of accuracy (on different tasks).

The comparison between groups matched for accuracy or latency, despite overall group differences in performance, has been made in other imaging studies. For example, patients with schizophrenia sometimes exhibit reduced prefrontal cortical activation on WM tasks, but that activation difference disappears when patients and controls are compared for different task conditions that equate task performance (Jansma et al., 2004; Perlstein, Carter, Noll, & Cohen, 2001). In these cases, activation was directly related to performance irrespective of group. Another study examined the development of activations associated with single-word reading, and compared subsets of children (the best-performing children) and adults (the worst-

performing adults) equated for response latency (Schlaggar et al., 2002). Although some developmental activation differences were eliminated when comparing performance-equated groups, other activation differences persisted. Thus, the reading study and the present WM study converge by finding that developmental differences in brain functions are not simply consequences of performance differences, but rather reflect a fundamental difference between children and adults in functional brain organization.

There are several factors that can complicate interpretation of developmental differences in functional neuroimaging. First, children have sometimes been reported to exhibit greater movement during scanning, but movement was measured and did not differ between children and adults in the present study. Second, the use of the SPM canonical hemodynamic function could be less suitable for children than adults. For example, children may exhibit more BOLD variance than adults even on a simple breath-holding task (Thomason, Burrows, Gabrieli, & Glover, 2005). We examined the residual variance associated with the GLM for adults and children, and found that the model was, indeed, a less good fit for some children, but found that the difference between children and adults did not change as a function of load. This finding is similar to that reported for a study of the development of face and scene processing in the brain (Golarai et al., 2007). In that study, differences between children and adults in activations were not changed significantly when subgroups of adults and children were equated for residual variance.

A third complicating factor, common to behavioral and neuroimaging studies, pertains to differences in performance between participants of different ages. Behavioral development inherently involves changes in performance. In the present study, adults were faster and more accurate than children in all conditions, and disproportionately more accurate than children when performing with higher WM loads. There were, however, a number of important similarities between patterns of behavioral performance in children and adults. First, children and adults had similar increases in response times (slopes) as a function of load for both the verbal and spatial tasks. Second, children and adults exhibited worse performance on spatial nonmatch trials that were near (and thus more difficult to reject) than far from the target location. This supports the idea that both groups were using a similar spatial strategy for the SWM task, rather than an alternative strategy such as template matching. Nevertheless, there were substantial differences in performance. One major difference was that children had slower response times. In general, slower response times are associated with more time on task, and therefore, potentially greater activations as a function of longer task performance. Because adults had greater activations than children, it appears unlikely that response times per se accounted for differences between adults and children.

Although WM loads were increased in consistent steps of two additional items per load, behavioral and neuroimaging evidence suggests a qualitative distinction between smaller WM loads of two or three items and larger WM loads. A large behavioral literature indicates that there is a short-term memory capacity of about four items on tasks of immediate recall (Cowan, 2001). In the present study, the addition of a delay between study and test may further diminish that capacity. Thus, children and adults may have been able to perform the low-load condition largely on the basis of a short-term memory store. For the higher loads, additional control or executive functions may be necessary to maintain information in mind when it exceeds short-term memory capacity. Convergent functional neuroimaging evidence has shown that a WM load of three letters recruits a limited left-hemisphere circuit, whereas a WM load of six letters recruits an extensive bilateral frontal and parietal circuit (Rypma et al., 1999). Thus, the present results may reflect a distinction between a limited short-term memory capacity that is similar in children at this age and adults, and more extensive neural circuit that supports WM capacity beyond the short-term memory store and that is markedly different in adults and children.

Several limitations of the present study may be rectified in future studies. The block design precludes isolation of encoding, maintenance, and retrieval operations, and also precludes separate analyses of correct and incorrect trials. Both of these concerns can be addressed in an event-related design. Further, the children made significantly more errors in the easy baseline condition, although they only performed 6% worse than adults and there was no interaction between load and group in either the verbal or spatial baseline task. Nevertheless, it will be useful to understanding the basis of this performance difference.

Limited mental and neural WM capacity in children has broad consequences in cognitive performance, including problem solving and text comprehension in which it is advantageous to have much information in mind. Although a delayed WM task for letters and spatial locations may be surprisingly demanding, it is not a task that involves manipulation of information in WM or complex relations among thoughts. Thus, the present study reveals large developmental differences in the neural basis of WM capacity under relatively simple circumstances. A fundamental question for future research will be to understand at the cellular level what neural changes account for the growth of WM capacity from childhood to adulthood.

Acknowledgments

We thank Silvia Bunge for helpful recommendations and acknowledge Paul Mazaika, Jarrett Rosenberg, Bryan Knowles, Tessa Johung, Jeff Cooper and Mike Fleming for their time and technical contributions. These studies were supported by MH071996, MH61426, and RR09784.

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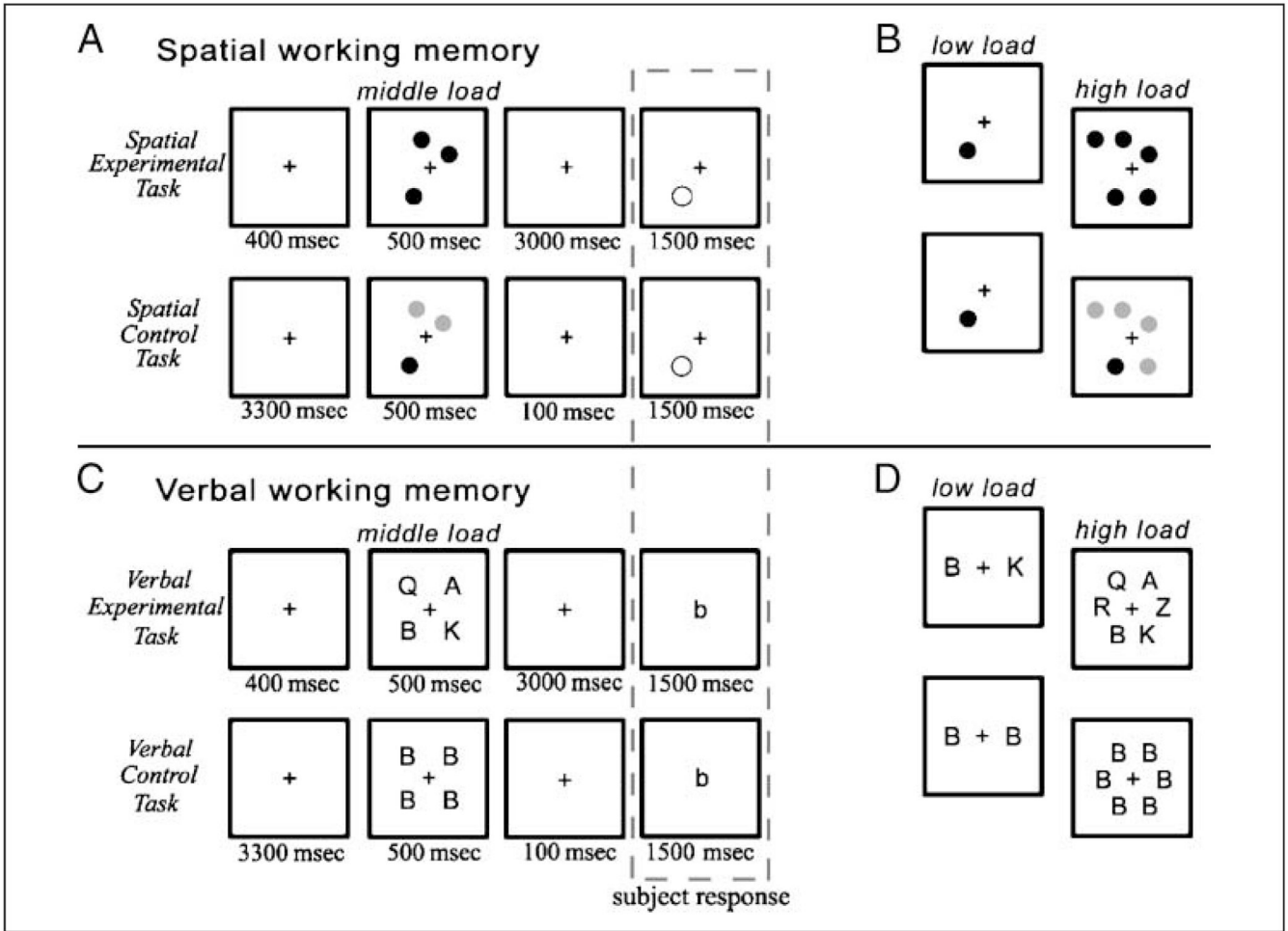


Figure 1. Examples of spatial and verbal trials

(A) Sequence of events in a spatial trial with a three-location load, with experimental task (WM maintenance) above and control task (no WM maintenance) below; participant response period is shown with dashed lines. (B) Examples of encoding displays in one- and five-dot spatial load conditions. (C) Sequence of events in a verbal trial with a four-letter load with experimental task (WM maintenance) above and control task (no WM maintenance) below; participant response period is shown with dashed lines. (D) Examples of encoding displays in two- and six-letter verbal load conditions.

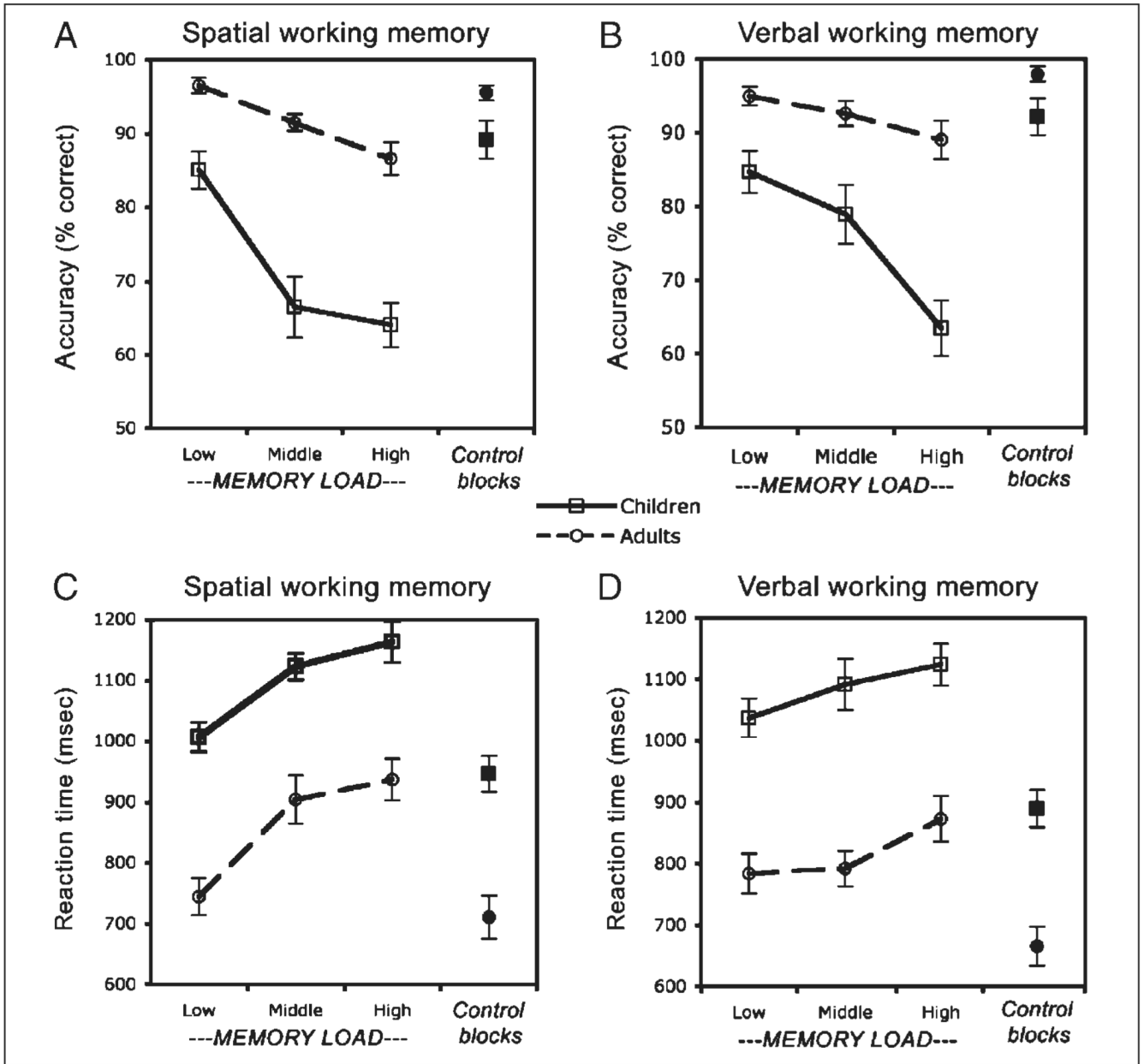


Figure 2. Performance by children (solid lines, squares) and adults (broken lines, circles) as a function of WM load

(A) Percent correct for spatial trials, showing children as less accurate, and a Group \times Load interaction. Control blocks, which did not differ by load, are shown as averaged single points for all loads at right in all panels. (B) Percent correct for verbal trials, showing children as less accurate and a Group \times Load interaction. (C) Mean of median RTs for correct spatial trials, showing slower times for greater loads, and children as slower, but no interaction. (D) Mean of median RTs for correct verbal trials, showing slower times for greater loads, and children as slower, but no interaction. *SEM* denoted by brackets.

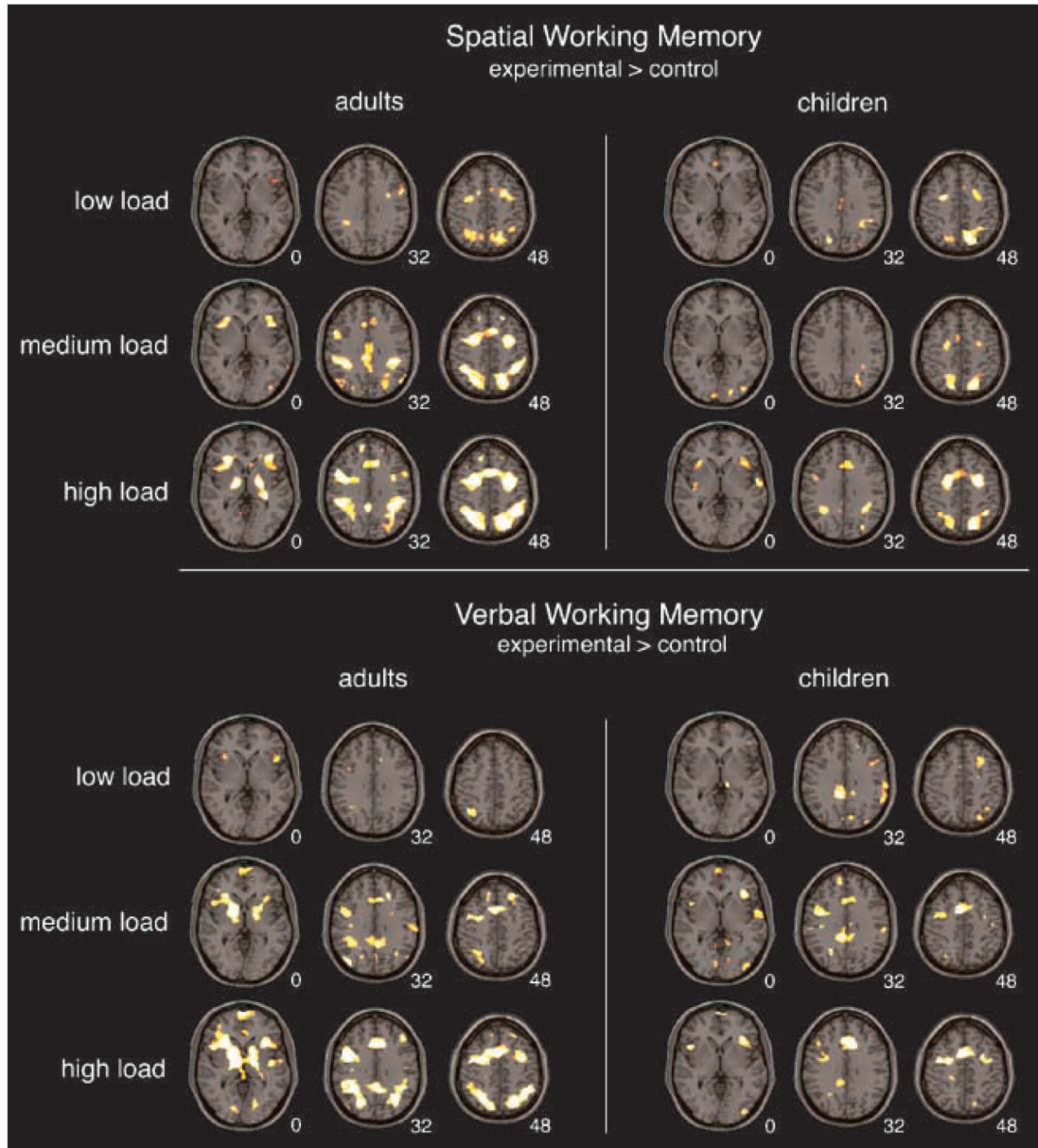


Figure 3. Activations as a function of load for adults (left) and children (right) for spatial (upper panel) and verbal (lower panel) WM maintenance. Activations ($p < .001$, uncorrected) are displayed on a standard MR on axial slices at $z = 0, +32, +48$. Left side of each image is the left side of the brain.

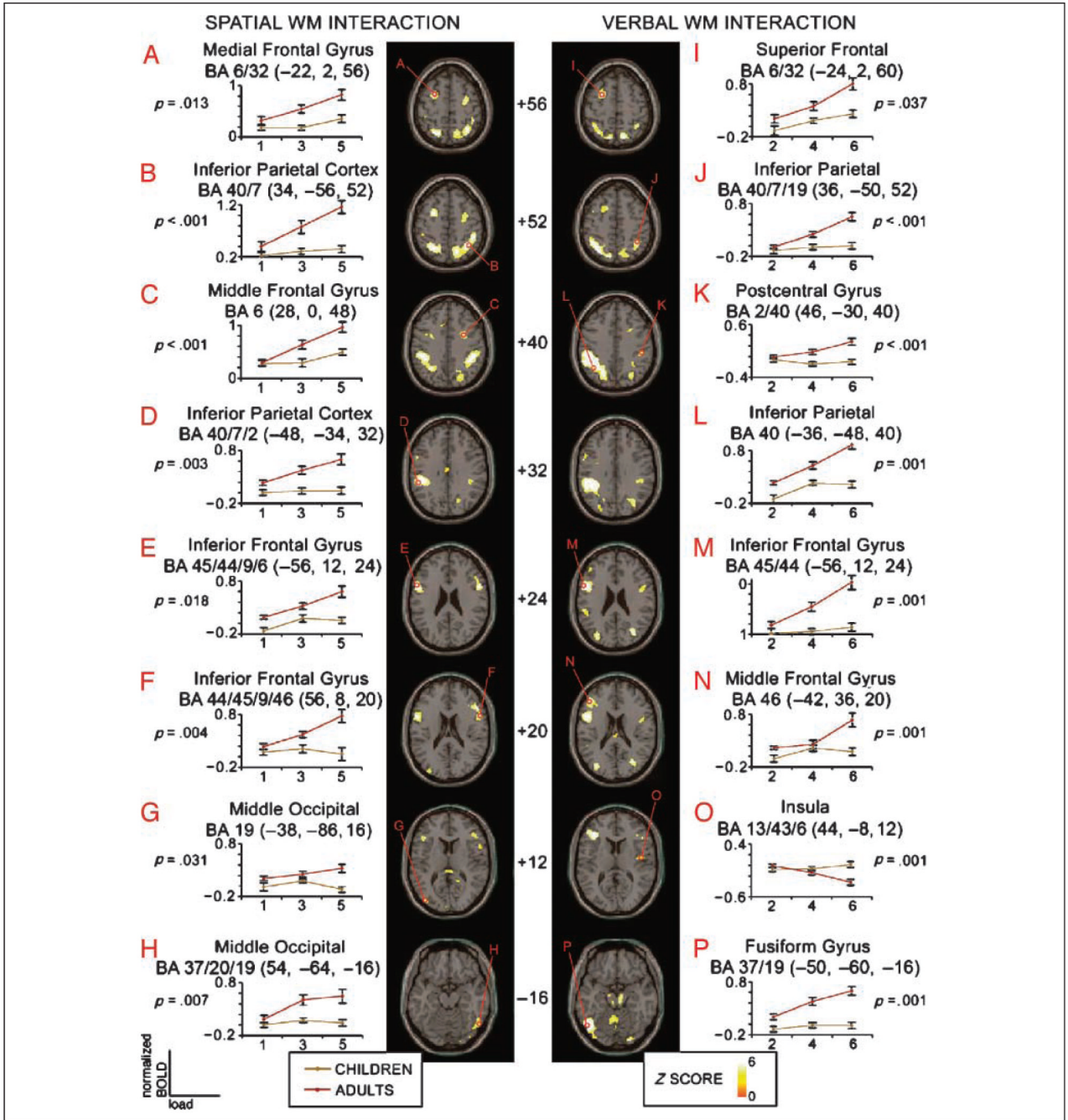


Figure 4. Group \times Load spatial and verbal interactions

Activations ($p < .001$, uncorrected) are displayed on a standard magnetic resonance (MR) on axial slices. Peak contrast values (experiment > control) were extracted for every participant, averaged within each group, across memory loads, and are plotted as line graphs adjacent to activation pictures. Coordinates are in MNI space. *SEM* denoted by brackets.

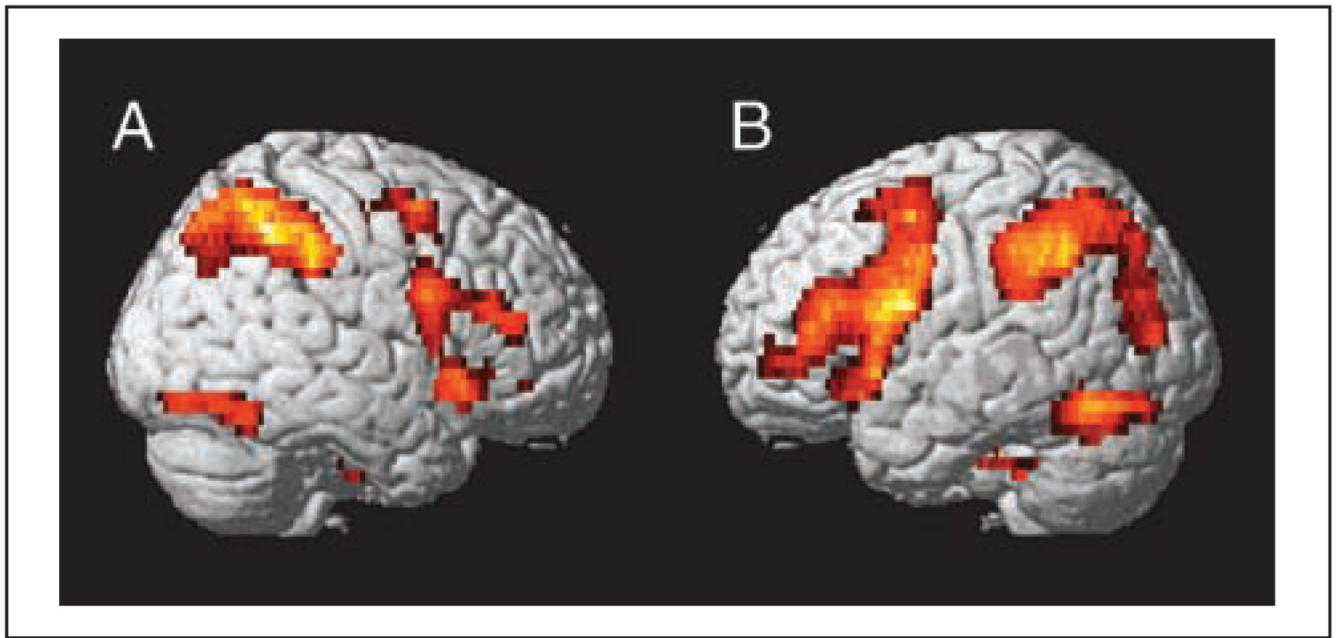


Figure 5. Lateral renderings of mixed load, accuracy-equated analyses

(A) Regions of greater activation for adults at highest SWM load compared to children at lowest SWM load ($n = 32$). (B) Regions of greater activation for adults at highest VWM load compared to children at lowest VWM load ($n = 28$). Comparisons are significant at $p < .001$, uncorrected.

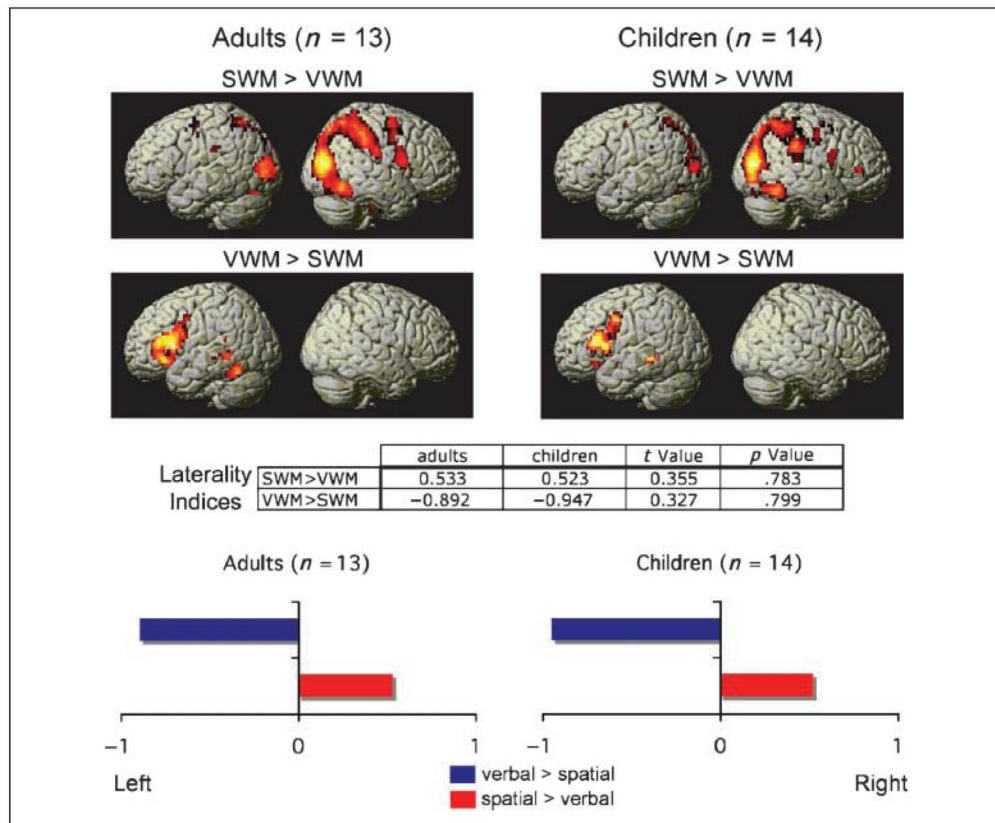


Figure 6. Lateral renderings of the main effect of material-type
 SWM > VWM (top two panels) and VWM > SWM (bottom two panels) confirm lateralization effects are present for both groups. Comparisons are significant at $p < .001$, uncorrected. Positive laterality index values denote rightward lateralization. SWM = spatial WM; VWM = verbal WM.

Table 1
 $2 \times 2 \times 3$ Analysis of Variance for Material (M) \times Group (G) \times Load (L) for the Maintenance Conditions

Source	df	F	Partial Eta Squared	Sig.
<i>Between Subjects</i>				
Group (G)	1	34.148**	0.577	.001
Error	25	(387.18)		
<i>Within Subjects</i>				
Load (L)	2	41.76**	0.626	.001
Material (M)	1	4.09	0.141	.054
L \times G	2	8.58**	0.255	.001
M \times G	1	2.03	0.075	.167
L \times M	2	3.65*	0.127	.033
L \times M \times G	2	2.68	0.097	.078
Error (L \times M)	50	(55.98)		

Mean square errors in parentheses.

* $p < .05$.

** $p < .001$.

Table 2
Regions of Significantly Greater Activation in Adults Compared to Children for Spatial and Verbal Tasks

	BA	x	y	z	Volume	Z Score
<i>Spatial</i>						
Frontal						
Inferior	L45*/44/9/6	-55	13	21	581	5.62
Inferior	R9*/44/45/46	57	9	22	539	4.75
Medial	L6*/52/9	-22	6	51	631	5.01
Middle	R6	32	3	51	390	4.64
Inferior	R47*/38	44	15	-7	71	3.6
Inferior	L47*/13	-32	21	-8	65	4.18
Parietal						
Inferior	L40*/1/2	-48	-31	31	1612	5.91
Inferior	R40*/7	44	-34	50	1783	5.46
Occipital						
Middle	R37*/19/18/20	48	-66	-7	405	4.7
Middle	L19*/37/18/17	-51	-68	-7	345	4.76
Middle	L19*/39/7/31	-38	-83	19	199	4.57
Temporal						
Middle	R19*/39	46	-77	19	126	3.89
Subcortex						
Lentiform Nucleus	R Globus Pallidus*/Putamen	16	4	0	440	4.29
Lentiform Nucleus	L Globus Pallidus*/Putamen/Caudate Head	-16	0	4	502	4.24
Caudate	L Caudate/Thalamus	-18	-7	19	47	3.96
Thalamus	R Ventral Thalamus/Caudate/Putamen	10	-9	15	64	3.88
Cerebellum						
Anterior Lobe	L Dentate	-12	-50	-21	85	3.68
<i>Verbal</i>						
Frontal						
Inferior	L45*/44	-55	13	21	1030	5.13
Inferior	R45*/46/44	48	35	2	663	4.48
Middle	R6	36	8	51	7	3.4

	BA	x	y	z	Volume	Z Score
Superior	L6*/32/8	-24	7	55	255	4.88
Parietal						
Inferior	L40*/2	-44	-29	38	4766	6.1
Temporal						
Fusiform	R37*/19/20	-50	-59	-11	744	6.55
Fusiform	R37*/20/18	44	-46	-18	851	5.06
Subcortex						
Lentiform Nucleus	L Globus Pallidus*/Putamen/Caudate/Ventral Thalamus	24	-14	-6	1937	4.79
Limbic						
Cingulate	R Cingulate Gyrus	10	-6	26	46	3.78
Cerebellum						
Anterior Lobe	L Dentate	-16	-46	-25	29	3.56

Coordinates are given in Talairach and Tournoux convention. BA = Brodmann's area.

* Location of peak coordinate.

Table 3
Regions of Significantly Greater Activation in Children Compared to Adults for Spatial and Verbal Tasks

	BA	x	y	z	Volume	Z Score
<i>Spatial</i>						
Occipital						
Lingual	L19 [*] /18/30	-18	-54	-1	74	3.74
Cuneus	L18	-2	-93	12	12	3.73
Lingual	R19 [*] /30/18	16	-48	2	59	3.68
Cuneus	R19	8	-88	27	7	3.48
<i>Verbal</i>						
Limbic						
Parahippocampus	L30 [*] /18	-28	-52	3	78	3.77
Frontal						
Middle	R11	22	50	-13	5	3.52

Coordinates are given in Talairach and Tournoux convention. BA = Brodmann's area.

* Location of peak coordinate

Table 4
Regions of Significant Load-related Increases in Activation for Both Age Groups in Spatial and Verbal Tasks

	BA	x	y	z	Volume	Z Score
<i>Spatial—Adult Participants (n = 16)</i>						
Frontal						
Middle	L6*/32	-26	2	44	2057	5.78
Inferior	R44*/45/9	53	8	14	155	4.84
Inferior	L47*/13/46	-30	21	-8	396	4.58
Inferior	R47*/11	22	33	-8	49	3.42
Inferior	R47*/13	34	29	-5	94	3.6
Middle	R46*/10	44	32	17	91	3.92
Medial	L6	-6	3	55	12	3.44
Parietal						
Precuneus	R7*/40	16	-62	47	1811	5.46
Precuneus	L7	-20	-59	55	1289	5.38
Temporal						
Inferior	R20*/37	53	-57	-14	106	4.46
Fusiform	L37	-48	-57	-11	27	3.45
Subcortex						
Lentiform	L Medial Globus Pallidus	-16	-6	-6	42	4.13
Lentiform	R Medial Globus Pallidus	14	-6	-6	10	3.37
<i>Verbal—Adult Participants (n = 14)</i>						
Frontal						
Inferior	L47*/13/32/6/9	-32	19	-4	7790	6.9
Inferior	R47*/13	36	17	-8	815	5.85
Inferior	R44*/45	50	9	18	213	4.17
Parietal						
Inferior	L40*/7	-36	-47	39	1866	6.28
Precuneus	R7*/40	16	-66	44	1761	5.56
Temporal						
Fusiform	L37*/19	-42	-59	-11	293	4.91
Cerebellum						

	BA	x	y	z	Volume	Z Score
Anterior Lobe	R Culmen	28	-56	-24	5	3.64
Posterior Lobe	R Declive	28	-61	-20	6	3.61
Posterior	L Declive	-18	-61	-20	5	3.35
<i>Spatial—Children Participants (n = 16)</i>						
Limbic						
Cingulate	L24*/32/6	-20	-4	44	427	4.26
Occipital						
Lingual	L18*/19	-14	-68	-3	18	3.31
Lingual	R19*/18	18	-66	0	76	3.41
Lingual	L18	-18	-76	4	28	3.23
Cerebellum						
Posterior Lobe	R Pyramis	26	-60	-27	17	3.68
Subcortex						
Insula	L Insula	-46	6	11	6	3.15
<i>Verbal—Children Participants (n = 14)</i>						
Frontal						
Middle	R6*/32/9	26	4	44	2873	5.89
Middle	R46	48	40	20	286	4.85
Inferior	L47*/13	-30	21	-8	123	4.3
Middle	L46	-46	30	21	85	3.16
Superior	L10	-26	49	1	34	3.95
Parietal						
Precuneus	R7	18	-66	47	1016	5.69
Precuneus	L7	-20	-70	40	751	5.07
Subcortex						
Insula/Inferior	R47*/13/45	34	21	-1	280	5.04
Occipital						
Lingual	L18*/19	-12	-66	-3	198	4.27
Lingual	R18*/19/23/17	14	-68	0	55	3.34
Cuneus	L18	-22	-85	19	27	3.19

	BA	x	y	z	Volume	Z Score
Cerebellum						
Anterior Lobe	R Culmen	10	-63	-7	5	3.29

Coordinates are given in Talairach and Tournoux convention. BA = Brodmann's area.

* Location of peak coordinate.