

Brain Basis of Developmental Change in Visuospatial Working Memory

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Abstract

■ Although brain changes associated with the acquisition of cognitive abilities in early childhood involve increasing localized specialization, little is known about the brain changes associated with the refinement of existing cognitive abilities that reach maturity in adolescence. The goal of this study was to investigate developmental changes in functional brain circuitry that support improvements in visuospatial working memory from childhood to adulthood. We tested thirty 8- to 47-year-olds in an oculomotor delayed response task. Developmental transitions in brain circuitry included both quantitative changes in the recruitment of necessary working memory regions and qualitative changes in the specific regions recruited into the functional working memory circuitry. Children recruited limited activation from core working memory re-

gions (dorsal lateral prefrontal cortex [DLPFC] and parietal regions) and relied primarily on ventromedial regions (caudate nucleus and anterior insula). With adolescence emerged a more diffuse network (DLPFC, anterior cingulate, posterior parietal, anterior insula) that included the functional integration of premotor response preparation and execution circuitry. Finally, adults recruited the most specialized network of localized regions together with additional performance-enhancing regions, including left-lateralized DLPFC, ventrolateral prefrontal cortex, and supramarginal gyrus. These results suggest that the maturation of adult-level cognition involves a combination of increasing localization within necessary regions and their integration with performance-enhancing regions. ■

INTRODUCTION

By late childhood, the gross architecture of the human brain is largely developed (Caviness, Kennedy, Bates, & Makris, 1996) and children have acquired proficiency with essential cognitive skills. In adolescence, brain maturation continues in the form of increasing myelination and synaptic pruning (Gogtay et al., 2004; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999; Huttenlocher, 1990; Yakovlev & Lecours, 1967), as does the ability to cognitively control behavior (Luna & Sweeney, 2004). Although the acquisition of skills in childhood appears to involve functional specialization within brain regions, little is known about the neural changes that support adolescents' increasing cognitive efficiency. Our previous work suggests that the maturation of response inhibition through adolescence is supported by the functional integration of more locally specialized brain regions (Luna & Sweeney, 2004; Luna, Thulborn, et al., 2001). Although acquisition of cognitive abilities appears to be supported by increasing specialization, an additional process of integration among specialized regions might support the developmental transition into mature, adult-level performance.

The goal of this study was to investigate whether similar kinds of functional reorganization in the brain supports improvements in working memory, a skill that continues to develop into late adolescence (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Kwon, Reiss, & Menon, 2002; Zald & Iacono, 1998). Working memory is a complex system that represents an interface between memory, attention, and perception, and is defined as the ability to hold task-relevant information in mind long enough to use it to attain a task-relevant goal (Baddeley, 1998). Based on our previous work, we propose that early acquisition of working memory requires functional specialization within brain regions that support visuospatial organization (e.g., parietal regions), maintenance of representations (e.g., dorsolateral prefrontal cortex [DLPFC]), and the ability to act on those representations (e.g., premotor regions). On the other hand, adult-level working memory performance involves both specialization within these necessary regions and efficient functional integration among these regions.

Adults performing visuospatial working memory (VSWM) tasks recruit a widely distributed circuitry including the ventrolateral prefrontal cortex (VLPFC), DLPFC, medial prefrontal regions, striatum, posterior parietal cortex, middle temporal gyrus, and cerebellum (D'Esposito, Postle, Ballard, & Lease, 1999; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Fuster, 1997;

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Sweeney et al., 1996). Each of these regions has been implicated in supporting different components of working memory, including encoding, maintaining, and manipulating task-relevant information and preparing task-relevant responses. However, little is known about which of these regions is necessary to VSWM and which are recruited to simply enhance performance. A developmental model could provide insight about the relative contribution of these regions. Necessary VSWM regions would be active across all ages, whereas supplemental performance-enhancing regions might become integrated with increasing age and performance levels.

Only a handful of studies have investigated developmental changes in the functional neuroanatomy supporting working memory in children and adolescents. These studies have found that, like adults, young children recruit a broad network of regions during VSWM tasks, which includes prefrontal and parietal regions (Olesen, Nagy, Westerberg, & Klingberg, 2003; Klingberg, Forssberg, & Westerberg, 2002; Kwon et al., 2002; Nelson et al., 2000; Thomas et al., 1999). Several of these studies have found differences in the extent of activation within these common regions when children and adults were compared (Nelson et al., 2000; Thomas et al., 1999; Casey, Cohen, Jezzard, Turner, & Noll, 1995). In the few studies that compared children and adolescents, researchers found a linear increase in prefrontal and parietal activation that correlated with age (Klingberg et al., 2002; Kwon et al., 2002). These results have been interpreted to show that efficient adult-like performance on VSWM tasks is dependent upon local computations within the prefrontal and parietal regions and on the communication between these areas.

This interpretation rests on a fundamental assumption that developmental changes in brain circuitry are primarily *quantitative*. Our results from a study of developmental changes in response inhibition circuitry indicate that there are also *qualitative* changes in brain circuitry that support the transition to adult-level performance in adolescence and additional qualitative changes that occur as adolescents mature into adults (Luna, Thulborn, et al., 2001). In the current study, we were interested in evaluating whether similar qualitative changes in functional brain circuitry support developmental improvements in VSWM. We investigated the neural basis of developmental change in VSWM as children progress through adolescence and acquire adult-level working memory performance. We used the oculomotor delayed response (ODR) task to study developmental changes in the network of regions recruited by children, adolescents, and adults to support VSWM. In the ODR task, also referred to as the memory-guided saccade (MGS) task, participants execute a saccade to a spatial location based *only* on the memory of the location of a previously presented visual target. Performance in the MGS task was compared to that in

a baseline visually guided saccade (VGS) task in which participants fixate a stimulus as it moves across several spatial locations. Contrasting these two tasks allowed us to identify working memory related activity while controlling for visual processing and eye movement related activity.

Our previous behavioral results using these oculomotor tasks with a sample of 245 individuals showed that children reach adult-level control in the VGS task in middle childhood; however, there are two developmental stages in the refinement of working memory skills during the transition from childhood to adulthood (Luna, Garver, et al., 2004). First, the ability to plan and execute a saccade based on a remembered location seems to improve until the age of 14 when it stabilizes and becomes indistinguishable from adult performance. Second, the quality of the mental representation of the target location continues to improve until the age of 19, allowing individuals to make more accurate final resting saccades in the task. At age 19, all VSWM skills, as measured in these oculomotor tasks, have reached adult levels.

In addition to being highly developmentally sensitive, oculomotor tasks have additional advantages for investigating developmental changes in the neural circuitry. First, the encoding and response demands of the task occur within the same modality, preventing individuals from having to translate visual information into articulatory or manual responses, an integrative process that may have its own independent developmental trajectory. Second, the MGS task does not introduce any competing information during the delay period, which allows participants to maintain their representations of the spatial locations without interference and which may also have an independent developmental trajectory. Finally, these oculomotor tasks are quite neuroanatomically tractable because they have been used to identify both single delay-dependent cells in monkeys (Hikosaka & Wurtz, 1983) and entire cortical networks that support VSWM in humans (Brown et al., 2004; Curtis, Rao, & D'Esposito, 2004; Postle, Berger, Taich, & D'Esposito, 2000; Sweeney et al., 1996).

In the present study, we measured brain activity with functional magnetic resonance imaging (fMRI) as children, adolescents, and adults performed the working memory and sensorimotor control tasks. We were especially interested in evaluating differences in functional neural circuitry that support the two developmental stages of improvement in working memory performance as children progress through adolescence. We hypothesized that: (1) regions that are *necessary* for VSWM, including the prefrontal (VLPFC and DLPFC) and posterior parietal regions, would be active in all three age groups. However, these core regions might be recruited to different degrees across the age groups with adults showing the most robust and localized recruitment of the necessary regions. (2) As children progress into adolescence and reach adult-level VSWM performance,

they will show increasing functional integration of more specialized cortical networks involved in recognition, maintenance, response preparation, and executive control. Finally, (3) adults will show activation across a network of very specific and localized regions that are necessary for VSWM together with sufficient regions that allow for more consistent and efficient performance. For example, adults may recruit regions that enhance encoding mechanisms, rehearsal strategies, monitoring one's own task performance, and maintaining task-attentive vigilance.

METHODS

Participants

The participants in this study included children (age 10–13), adolescents (age 14–17), and adults (age ≥ 18) from the Greater Pittsburgh area. These age groups were picked to maximize behavioral differences that were predicted to be supported by overlapping, but different, cortical networks. Our previous developmental findings suggest that the ability to prepare and execute a saccade to a remembered location in the MGS task is still improving before age 14 and that the level of detail of the spatial representation for the remembered location continues to improve until age 19 (Luna, Garver, et al., 2004).

All of the participants were right-handed, healthy individuals as determined through interview with participants and/or their guardians. Participants were excluded if they themselves or a first-degree relative (parent or sibling) had ever been diagnosed with meningitis, encephalitis, epilepsy, diabetes, a head injury with loss of consciousness, a learning disability, a psychiatric disorder, a history of drug or alcohol abuse, or

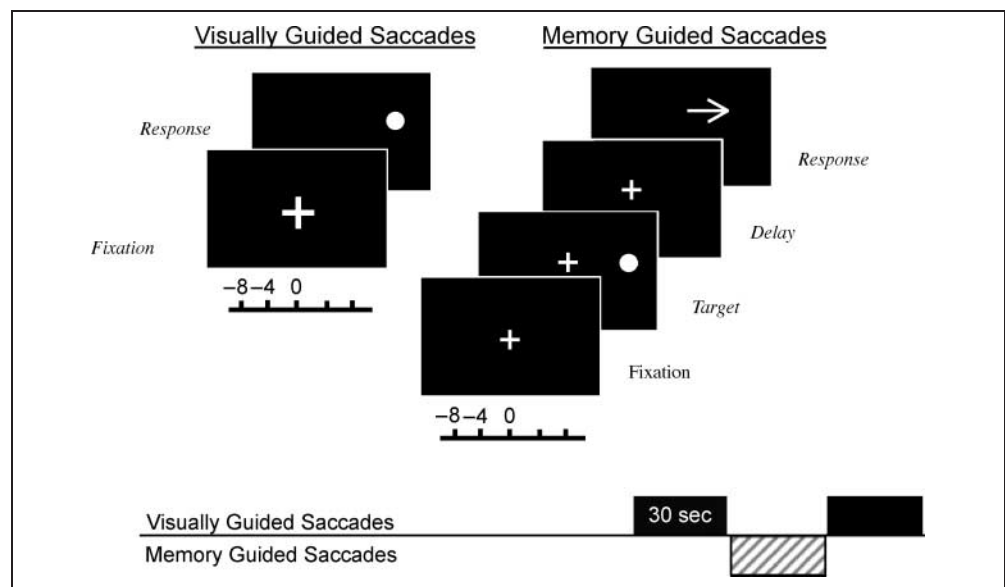
an eye movement abnormality such as strabismus or amblyopia. The sample included 9 children ($M = 11.2$ years, $SD = 1.3$ years), 13 adolescents ($M = 15.7$ years, $SD = 1.2$ years), and 8 adults ($M = 29.5$ years, $SD = 10.6$ years). An additional 16 participants were eliminated due to excessive head movement (8 children, 2 adolescents), equipment malfunction (2 children), sleeping during the task (2 children), and refusal to complete the entire experiment (1 child, 1 adolescent). Participants and/or their legal guardians provided informed consent prior to participating in the study. All the experimental procedures complied with the Code of Ethics of the World Medical Association (1964 Declaration of Helsinki) and the standards of the University of Pittsburgh Internal Review Board.

Procedure

The experiment consisted of two tasks in which the participants made saccades to specific target locations. In the MGS task, participants had to (1) remember the spatial location of a briefly presented peripheral target, (2) hold the location information in mind during a delay period, and (3) look at that location upon presentation of a cue (see Figure 1). In the VGS sensorimotor baseline task, participants executed saccades to a location upon presentation of a cue without the spatial working memory demand.

In the two weeks prior to participating in the fMRI experiment, participants performed both the MGS and VGS tasks in our eye movement laboratory (Luna, Garver, et al., 2004). Eye movement activity was not monitored in the scanner but was presumably similar to the behavioral performance measured in the laboratory, as has been reported in other studies (Kastner, Weerd, Desimone, & Ungerleider, 1988). The impact of the pre-MRI session on

Figure 1. Examples of visually guided control and memory-guided test trials. Arrow indicates the correct location of saccade to remembered location. The size of the fixation crosshair indicated the task block.



the behavioral responses during the scanning session was also presumably similar across the three age groups as the target locations in the behavioral and scanning sessions were different, preventing participants from developing long-term representations of the specific target locations. In the fMRI paradigm, participants performed 10.5 alternating 30-sec blocks of the two tasks, beginning with the VGS task.

Visually Guided Saccade Baseline Task

During VGS blocks, participants were instructed to maintain fixation and then to look at each target as it appeared in one of the same four locations ($\pm 4^\circ$ and $\pm 8^\circ$) that were used in the MGS task. In the behavioral paradigm used outside the scanner, there were six target locations ($\pm 10^\circ$, $\pm 20^\circ$, and $\pm 30^\circ$). The fixation and target stimuli in the VGS task included white circles that subtended 1.0° of visual angle. The target moved every 750 msec to one of the potential locations for a total of 40 trials per 30-sec block in the fMRI experiment (see Figure 1). The direction of the moving target was unpredictable except that it always returned to fixation following each peripheral location. When a 30-sec VGS block finished, subjects were signaled to begin the MGS block with a central fixation circle that reduced in size from 1° of visual angle to 0.5° of visual angle.

Memory-guided Saccade Task

Each trial began with the onset of a central target that participants fixated for 1000 msec. The fixation and target stimuli were white circles that subtended 0.5° and 1.0° of visual angle, respectively. During that cue period, a peripheral target was presented for 75 msec in one of four locations ($\pm 4^\circ$ and $\pm 8^\circ$ from fixation) in the horizontal plane. This was different from the behavioral paradigm used outside the scanner in which there were six target locations ($\pm 9^\circ$, $\pm 18^\circ$, and $\pm 27^\circ$) that covered a larger extent of the visual field. Participants were instructed to avoid looking at the peripheral target but to remember its location. Then participants fixated a central target and remembered the spatial location of the target throughout a 4925-msec delay period. The offset of the central target at the end of the delay period cued subjects to saccade to the remembered location in the absence of sensory guidance. Participants had 1500 msec to execute a saccade and fixate that point. There were a total of four MGS trials in a 30-sec block for a total of 40 trials in the fMRI experiment. In order to control for the number of executed saccades, the MGS task required two saccades every 7.5 sec (one to the remembered location and one back to central fixation) in comparison to one saccade every 750 msec in the VGS task. This ensured that activation occurring during the MGS was not attributable to purely oculomotor factors.

The stimuli in the scanner were displayed on a rear projection screen located inside the MR scanner and viewed by the participants from an angled mirror fixed to the head coil. Immediately prior to the scanning session, participants were trained for 20 min in a mock scanner that simulated the noise and confinement of an actual MR scanner.

Data Acquisition

The neuroimaging data were collected using a 3.0-Tesla Signa whole-body MR scanner (General Electric Medical Systems, Milwaukee, WI). Gradient-echo, echo-planar imaging was performed using a commercial head radio-frequency coil. The acquisition parameters included: TE = 25 msec; TR = 5.0 sec; single shot; full k -space; 128×64 acquisition matrix with an FOV = 40×20 cm. Twenty-three 3-mm-thick oblique slices with a 2-mm gap were aligned to the base of the genu and splenium of the corpus callosum generating $3.125 \times 3.125 \times 5$ mm voxels, which covered the entire cortex and cerebellum. A three-dimensional volume spoiled gradient-echo (SPGR) pulse sequence with 124 slices (1.5 mm) was used to acquire the structural images in the axial plane.

The raw fMRI data were analyzed using Functional Imaging Analysis Software Computational Olio (Eddy, Fitzgerald, Genovese, Mockus, & Noll, 1996). Images were corrected for three-dimensional head motion by aligning each volume in the time series to the volume obtained in the middle of the acquisition. Participants who moved more than 5 mm (1 voxel) were not included in the analyses. Prior to the creation of functional activation maps, each subject's images were (1) smoothed with a 5.6-mm full-width half-maximum filter, which, given the original voxel size, was optimal for maximally improving the signal-to-noise ratio while minimally reducing resolution, and (2) shifted 5 sec, which adjusts for the peak activation of the BOLD response function (Cohen et al., 1997). Each individual map was then spatially normalized into Talairach space using anatomical markers and resampled into 3-mm isotropic voxels.

Data Analyses

Behavioral Data

Saccadic reaction time (latency), in milliseconds, and accuracy, as defined by error in degrees of visual angle from target location, were measured in both tasks. Saccadic accuracy was measured from (1) the first saccade following the cue, which in the MGS task reflects both ability to prepare and to execute a voluntary response based on a remembered spatial location, and (2) from the final resting position after the final saccade was made to the desired target location, which reflects the detail of the remembered spatial representation. One-way ANOVAs with the factor of age group

(children, adolescents, adults) were used to analyze differences in the accuracy and reaction time measures for each task. Post hoc comparisons between groups were evaluated using Tukey's HSD tests. Oculomotor data from two adolescents and two adult participants were not included in these analyses due to experimenter error.

fMRI Data

Because it is not clear whether the group differences would be manifest as differences in terms of the "organization of activation" (extent) within the entire functional network or in the "magnitude" of percent change across the two tasks, we looked for both kinds of differences. First, group differences in the organization of activation were evaluated across a series of a priori-defined ROIs known to support adult working memory. Second, group differences in the magnitude of percent signal change were evaluated throughout the whole brain on a voxelwise basis.

Individual participant task-related brain activity was computed in two ways. First, functional activation maps were generated for each subject by performing paired two-tailed *t* tests on the raw activations of each voxel. The *t* statistic critical value was set at 4.0 because it is sufficiently high to control for Type I error in a single subject with our particular scanner and single-shot, echo-planar pulse sequence. These *t* maps were used to evaluate the extent of activation in a series of 22 a priori-defined ROIs for each participant. These ROI-based measures of activation were then submitted to Spearman's rho correlational analyses to assess the relation between individual behavioral performance and extent of activation.

Second, another set of functional activation maps were generated for each subject computing the mean percent signal change across the tasks in each voxel. Differences in the organization of network activation were evaluated by computing a mean image of the average percent signal change in each voxel for each age group. Within each age group mean image, the significance of activation was estimated by computing voxelwise *t* tests to determine if the average percent signal change was significantly different from zero. Only voxels that were significantly different from zero at $p < .001$, which in each group represented a *t* value of 3.82, were used to determine the proportion of total active voxels in each a priori-defined ROI in each age group (No. of active voxels within an ROI/No. of total active voxels across all ROIs).

Twenty-two a priori ROIs were defined anatomically in each hemisphere using Analysis of Functional Neuro-Images software (AFNI; Cox, 1996) (see Table 1). ROIs were drawn on the SPGR of a representative subject that had been normalized to Talairach coordinates and then the size and shape of ROIs were adjusted to

Table 1. Anatomically Defined ROIs in Each Hemisphere

<i>Region</i>	<i>ROI</i>
Frontal	Inferior precentral sulcus (Inf PCS)
	Frontal eye fields (FEF)
	Supplementary eye fields (SEF)
	Pre-supplementary motor area (pre-SMA)
	Dorsal lateral prefrontal cortex (DLPFC)
	Pars opercularis
	Anterior cingulate (AC)
Insula	Anterior insular cortex (Ant Insula)
Parietal	Intraparietal sulcus (IPS)
	Angular gyrus
	Supramarginal gyrus (SMG)
	Precuneus
	Posterior cingulate (PC)
Temporal	Inferior temporal gyrus (ITG)
	Middle temporal gyrus (MTG)
	Superior temporal gyrus (STG)
	Fusiform gyrus
Occipital	Interoccipital sulcus (IOS)
Subcortical	Basal ganglia (BG)
	Thalamus
Cerebellum	Lateral cerebellum

assure that each individual's anatomic ROI was included and that no ROIs overlapped. The mask of anatomically defined ROIs was then applied to a mean percent signal change map for each age group. The criteria for delineating the prefrontal, anterior insula, AC, posterior cingulate cortex (PC), posterior parietal, precuneus, IPS, IOS, BG, thalamus, and lateral cerebellum ROIs are explained elsewhere (Luna, Thulborn, et al., 2001). The temporal lobe gyri, including the superior, middle, inferior, and fusiform gyri, were defined using anatomical landmarks.

Finally, group differences in the magnitude of activation across the whole brain were evaluated by submitting the individual participant percent signal change maps to a voxelwise fixed-effects ANOVA with age group as the between-subjects independent factor. This ANOVA generated an age group main effect statistical image that indicated voxels where one group showed a significantly larger percent signal change across tasks. To correct for the large number of statistical comparisons, the group main effect image was clustered using criteria from a Monte Carlo simulation. To achieve

$p < .001$ significance, the simulation required 5 contiguous voxels all with an F value ≥ 5.77 . In order to interpret the regions generated in the main effect image, we also computed voxelwise post hoc linear contrasts on the percent signal change maps comparing adults to adolescents, adults to children, and adolescents to children.

RESULTS

Behavioral Data

Table 2 shows the mean saccadic reaction time and accuracy in degrees of visual angle from the target for both the VGS and MGS tasks. There were no age group differences during the VGS task in the saccadic reaction time, $F(2,24) = 0.5$, ns , or in saccadic accuracy, $F(2,24) = 0.7$, ns . However, the age groups tended to differ in their saccadic reaction times in the MGS task, $F(2,24) = 2.8$, $p = .08$. Tukey's post hoc comparisons determined that none of the groups were significantly slower to make an MGS saccade. The age groups also tended to differ in the accuracy of the initial saccade, $F(2,24) = 2.9$, $p = 0.08$. Tukey's post hoc comparisons determined that the children tended to be less accurate by 1.6° visual angle than were the adolescents, $p = .06$, but were not different from the adults. Finally, the age groups were not different in the accuracy of their final saccades during the MGS task, $F(2,24) = 1.8$, ns .

In order to investigate the relationship between behavioral performance and age in a more continuous fashion, an inverse curve-fitting regression was performed on each behavioral measure (Luna, Garver, et al., 2004). The accuracy of the initial saccade tended to increase with age during the MGS task, $F(2,25) = 3.7$,

$p = .07$, $r^2 = .128$. Participants' initial saccades tended to be more accurate (closer to the target) in the MGS task with increasing age. The accuracy of the final saccade increased significantly with age during the MGS task, $F(2,25) = 5.4$, $p < .05$, $r^2 = .176$. Participants' final saccades were more accurate (closer to the target) in the MGS task with increasing age. Neither saccadic reaction time nor accuracy of the initial saccade significantly improved with age.

fMRI Data

Organizational Commonalities in VSWM Networks

The region-of-interest (ROI)-based analyses revealed that all three groups recruited the following core set of regions during the working memory task (greater than 1.0% of their total activation): right DLPFC, right anterior cingulate (AC), bilateral anterior insula, right superior temporal gyrus (STG), right interoccipital sulcus (IOS), and right basal ganglia (BG). Table 3 shows the proportion of the total significant activation accounted for by each ROI for each age group.

Organizational Differences in VSWM Networks

Despite the fact that all three groups recruited a common set of regions, the extent to which each of these regions was recruited into a functional working memory network varied by age. Figure 2 shows the proportion of total significantly active voxels in these common regions for each age group. Some of the common regions showed a *decreasing* network contribution across the age groups. The extent of the bilateral anterior insula activation steadily decreased across the age groups, with children recruiting the strongest insular activation (34% of total activation), followed by the adolescents (31%), and finally, the adults (9%). Similarly, children recruited the largest amount of BG activation (30%), whereas the adolescents and adults recruited much less (4% and 3%, respectively). Conversely, several of the common regions showed an *increasing* network contribution across the age groups. The right AC gradually increased across the age groups from 1% of the total activation in the children, to 4% in the adolescents and 19% in the adults. The right IOS showed a similar increase in contribution across the three age groups. The relative contributions of the right and left DLPFC showed different patterns of change across the three age groups (see Figure 2). The left DLPFC contribution increased greatly across the three age groups from 0% of the total activation in the children, to 2% in the adolescents and 13% in the adults. The pattern of developmental change was much different in the right DLPFC. Children (2%) and adults (5%) recruited less than half the activation in the right DLPFC as compared to adolescents (13%). Finally, the proportion of right STG activation was also

Table 2. Saccadic Reaction Time and Accuracy by Task and Age

	Children <i>n</i> = 9	Adolescents <i>n</i> = 13	Adults <i>n</i> = 8
<i>VGS Control Task</i>			
Saccadic RT	232.6 (23.5)	218.3 (26.5)	232.6 (30.5)
Saccadic Accuracy	1.9 (0.6)	1.8 (0.5)	2.0 (0.3)
<i>MGS Test Task</i>			
Saccadic RT	461.7 (71.3)	406.5 (44.1)	406.9 (64.9)
Saccadic Accuracy— Initial	4.8* (0.8)	3.2 (0.6)	3.8 (1.1)
Saccadic Accuracy— Final Resting	3.5 (1.1)	3.0 (0.7)	2.7 (0.7)

*Cell contents contain mean (SD) reaction time (msec) and error in degrees of visual angle from target.

Children > Adolescents, $p < .10$.

Table 3. Proportion of Total Active Voxels Accounted for by Each ROI in Each Age Group during the Spatial Working Memory Task

ROI	Children		Adolescents		Adults	
	Right	Left	Right	Left	Right	Left
<i>Frontal Regions</i>						
FEF	0.00	0.03	6.58	3.10	0.00	0.00
Inferior PCS	0.68	0.51	6.02	1.21	9.15	4.65
Pre-SMA	0.00	0.00	3.00	1.63	0.08	0.00
SEF	0.00	0.00	3.20	0.55	0.18	0.00
DLPFC	1.85	0.25	12.66	1.99	5.10	13.40
Pars Opercularis	1.80	0.59	0.84	0.01	0.80	1.90
Anterior Cingulate	1.06	0.98	4.40	0.73	18.95	1.45
<i>Insular Cortex</i>						
Anterior Insula	16.25	17.40	13.18	18.01	4.38	5.00
<i>Parietal Regions</i>						
IPS	0.08	0.00	1.95	1.63	0.18	0.00
Precuneus	0.01	0.62	0.05	0.25	0.00	0.00
SMG	1.89	0.00	0.80	2.13	3.20	15.00
Angular Gyrus	0.00	0.00	0.00	0.65	0.03	0.00
Posterior Cingulate	0.00	0.00	0.40	0.25	0.03	0.00
<i>Temporal Regions</i>						
STG	5.11	0.80	1.21	0.01	6.70	2.20
MTG	2.97	1.45	1.17	0.09	0.70	0.23
ITG	0.00	0.08	0.04	0.21	0.00	0.00
Fusiform	2.61	0.29	0.06	0.00	0.00	0.00
<i>Occipital Regions</i>						
IOS	1.67	0.01	2.46	3.37	3.60	0.25
<i>Subcortical Regions</i>						
Basal Ganglia	17.37	12.63	2.71	1.48	2.48	0.05
Thalamus	3.29	4.11	0.88	1.10	0.18	0.05
Lateral Cerebellum	0.47	2.84	0.00	0.00	0.00	0.13

FEF = frontal eye fields; PCS = precentral sulcus; SMA = supplementary motor area; SEF = supplementary eye fields; DLPFC = dorsal lateral prefrontal cortex; IPS = intraparietal sulcus; SMG = supramarginal gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; IOS = interoccipital sulcus.

similar in children (5%) and adults (7%), but much less in adolescents (1%).

Several regions were selectively recruited within the age groups. Children selectively recruited the right

fusiform and the left lateral cerebellum. Only adolescents activated the right frontal eye field (FEF), the left pre-supplementary motor area (pre-SMA), bilateral supplementary eye fields (SEF), bilateral intraparietal sulcus (IPS), and left IOS. Only adolescents and adults drew upon the left DLPFC and the left supramarginal gyrus (SMG). There were no regions in the adult ROI network that were not also active in either the children or adolescents.

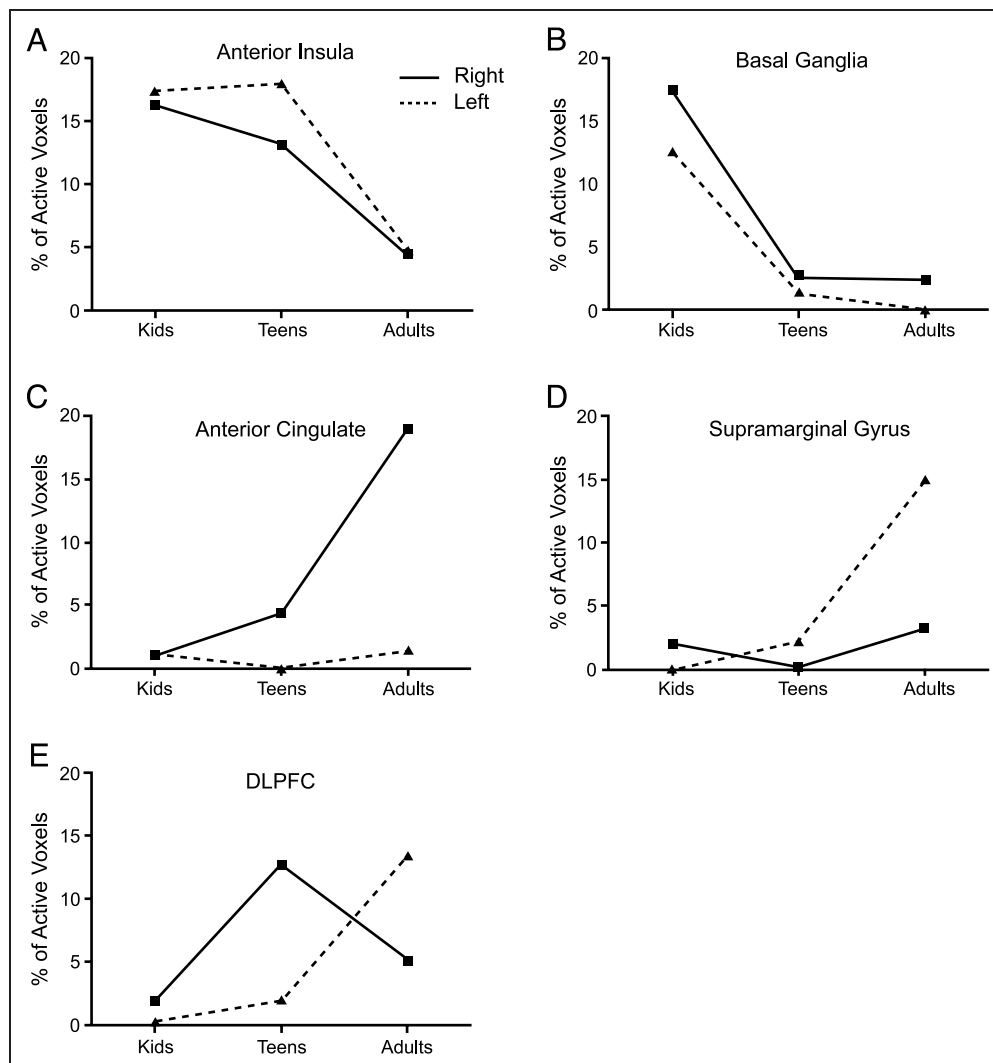
Some of these age group differences in the extent of activation were supported by additional correlational analyses measuring the degree of association between age and the ROI-based activations. Extent of activation in several of the ROIs increased significantly with age, including the right DLPFC ($p_1 = .339, p < .005$), bilateral inferior precentral sulcus (PCS) ($p_1 = .314, p < .05$), SMG ($p_1 = .336, p < .05$), IOS ($p_1 = .323, p < .05$), and precuneus ($p_1 = .430, p < .005$).

The voxelwise analysis of variance (ANOVA) contrasting percent signal change across the two tasks and three age groups revealed age group differences in the magnitude of activation across each group's functional working memory network. Table 4 reports the regions that showed significant differences in magnitude of activation. The linear contrasts reveal that adults showed stronger magnitude responses than adolescents and children in primarily left prefrontal regions, including the left superior frontal gyrus (SFG), left postcentral gyrus, left DLPFC, and right anterior insula (see Figure 3B). Additionally, adults showed greater percent signal change than children in a more dorsal region of the left DLPFC, right inferior PCS, and left SMG. Adolescents showed stronger activation than both children and adults in premotor regions (pre-SMA and SEF) and the right posterior parietal cortex. Adolescents also showed stronger activation than the children in the left SFG and DLPFC and than the adults in the right thalamus. Children showed stronger percent signal changes than both adults and adolescents bilaterally in the rostral AC, anterior insula, caudate nuclei, thalamus, and throughout the temporal lobe in the superior, middle, inferior, and fusiform gyri. Finally, children showed stronger magnitude responses than adolescents in the right inferior PCS and bilaterally in the lateral cerebellum.

Brain-Behavior Relations

Associations between behavioral performance and brain activation were evaluated by submitting the ROI-based activations from all the individual participant t maps to one-tailed Spearman's rho correlational analyses with the two measures of saccade accuracy from the MGS task. Several regions were positively related to the degree of error in participants' saccades. In other words, participants who relied more heavily on these regions were *less accurate* and tended to saccade farther away from the target locations. Activation in the IOS and the

Figure 2. Proportion of total activation in six commonly activated ROIs across all three age groups. The anterior insula and BG (A, B) showed decreases in total network activation across the age groups in both hemispheres. The AC and SMG (C, D) showed increases across the age groups. The DLPFC showed an increasing overall network contribution across the age groups in the left hemisphere, but peaked during adolescence in the right hemisphere (E).



pre-SMA ($p_1 = .400, p < .025$) were related to larger errors in the accuracy of the first saccade. Other regions were negatively correlated with the degree of error in participants' saccades. Activation in the posterior parietal areas, including the precuneus and IPS, was related to more accurate saccades ($p_1 = -.355, p < .05$). Neither activation in the right DLPFC ($p_1 = .192, ns$) nor in the left DLPFC ($p_1 = .005, ns$) predicted the accuracy of participants' initial saccades. In terms of accuracy of the last saccade, bilateral activation in the BG ($p_1 = .433, p < .025$), fusiform gyri ($p_1 = .451, p < .025$), the FEF ($p_1 = .363, p < .05$), and pre-SMA ($p_1 = .458, p < .025$) were associated with larger errors from the target locations. Only activation in the bilateral SMG ($p_1 = -.345, p < .05$) was related to more accurate final resting saccades.

DISCUSSION

The goal of this study was to investigate both qualitative and quantitative changes in the functional neural circuit-

ry that underlies developmental changes in VSWM. Although the pattern of behavioral differences in this sample was more limited compared to that found in the larger sample from which these participants were selected (Luna, Garver, et al., 2004), developmental improvements were observed in the ability to plan and execute a saccade to a remembered location and in the ability to sufficiently encode the target. Participants from all three age groups performed the working memory task well, however, children tended to be less accurate than adolescents in their ability to plan and execute the initial saccade. The ability to sufficiently encode the target, as measured by the accuracy of the final resting saccade, increased across the entire age range.

Quantitative and qualitative changes in functional brain circuitry were observed across the three age groups. Quantitative changes primarily occurred in a set of six core regions that were consistently recruited by all three age groups during the working memory task despite differences in performance. These regions included the right DLPFC, right AC, bilateral anterior

Table 4. Regions of Significant Activity for Main Effect of Group

Group	Hemisphere	Anatomical Region	Brodmann's Area	Talairach Coordinates			Max F	Contrasts
				x	y	z		
Children	Left	Precuneus	7	-5	-54	56	7.62*	C > T, C > A
	Right	Inf PCS	6	32	12	41	6.85*	C > T
	Left	AC	24	-6	-7	30	8.67*	C > T, C > A
	Right	AC	33	3	11	24	7.73*	C > T, C > A
	Left	Caudate	*	-10	15	19	8.99**	C > T, C > A
	Right	Caudate	*	11	13	5	8.95*	C > T, C > A
	Right	Caudate Tail	*	29	-44	13	11.43**	C > T, C > A
	Left	Ant Insula	*	-23	25	9	13.68***	C > T, C > A
	Right	Ant Insula	*	38	23	7	9.49**	C > T, C > A
	Left	Thalamus	*	-14	-28	9	5.90*	C > T, C > A
	Right	Thalamus	*	17	-11	5	9.40**	C > T, C > A
	Left	MTG	21	-58	-46	6	7.46*	C > T, C > A
	Right	MTG	22	60	-33	3	7.11*	C > T, C > A
	Left	STG	22	-49	-35	6	7.92*	C > T, C > A
	Right	STG	13/22	45	-20	6	11.93**	C > T, C > A
	Right	STG	22	51	0	2	13.01**	C > T, C > A
	Left	ITG	37	-52	-72	1	7.62*	C > T, C > A
	Right	Fusiform	37	37	-67	-13	15.33***	C > T, C > A
	Left	Fusiform	37	-25	-45	-15	10.15**	C > T, C > A
	Left	Lat Cerebellum	*	-17	-53	-20	9.90**	C > T
Right	Lat Cerebellum	*	24	-49	-28	7.35*	C > T	
Adolescents	Left	SFG	6	-21	1	63	7.25*	T > C
	Left	DLPFC	8	-31	38	41	6.34*	T > C
	Left	Pre-SMA	6	-4	11	64	12.97**	T > C, T > A
	Right	SEF	6	23	-3	63	7.11*	T > C, T > A
	Right	IPL	40	39	-47	50	9.64**	T > C, T > A
	Right	Thalamus	*	17	-11	5	9.40**	T > A
Adults	Left	SFG	6	-18	1	71	11.69**	A > C, A > T
	Left	Postcentral gyrus	5	-21	-40	71	12.80**	A > C, A > T
	Left	DLPFC	8	-31	38	41	6.34*	A > C
	Right	Inf PCS	6	39	0	40	6.93*	A > C
	Left	SMG	40	-54	-54	33	7.26*	A > C
	Left	DLPFC	9	-41	37	26	7.38*	A > C, A > T
	Right	Ant Insula	*	35	-4	-4	11.07**	A > C, A > T

AC = anterior cingulate; Ant = anterior; DLPFC = dorsal lateral prefrontal cortex; Inf PCS = inferior precentral sulcus; IPL = inferior parietal lobule; ITG = inferior temporal gyrus; Lat = lateral; MFG = middle frontal gyrus; SEF = supplementary eye fields; FEF = frontal eye fields; SMA = supplementary motor area; SMG = supramarginal gyrus; SFG = superior frontal gyrus; STG = superior temporal gyrus; A = adults; T = adolescents; C = children.

* $p < .01$.

** $p < .001$.

*** $p < .0001$.

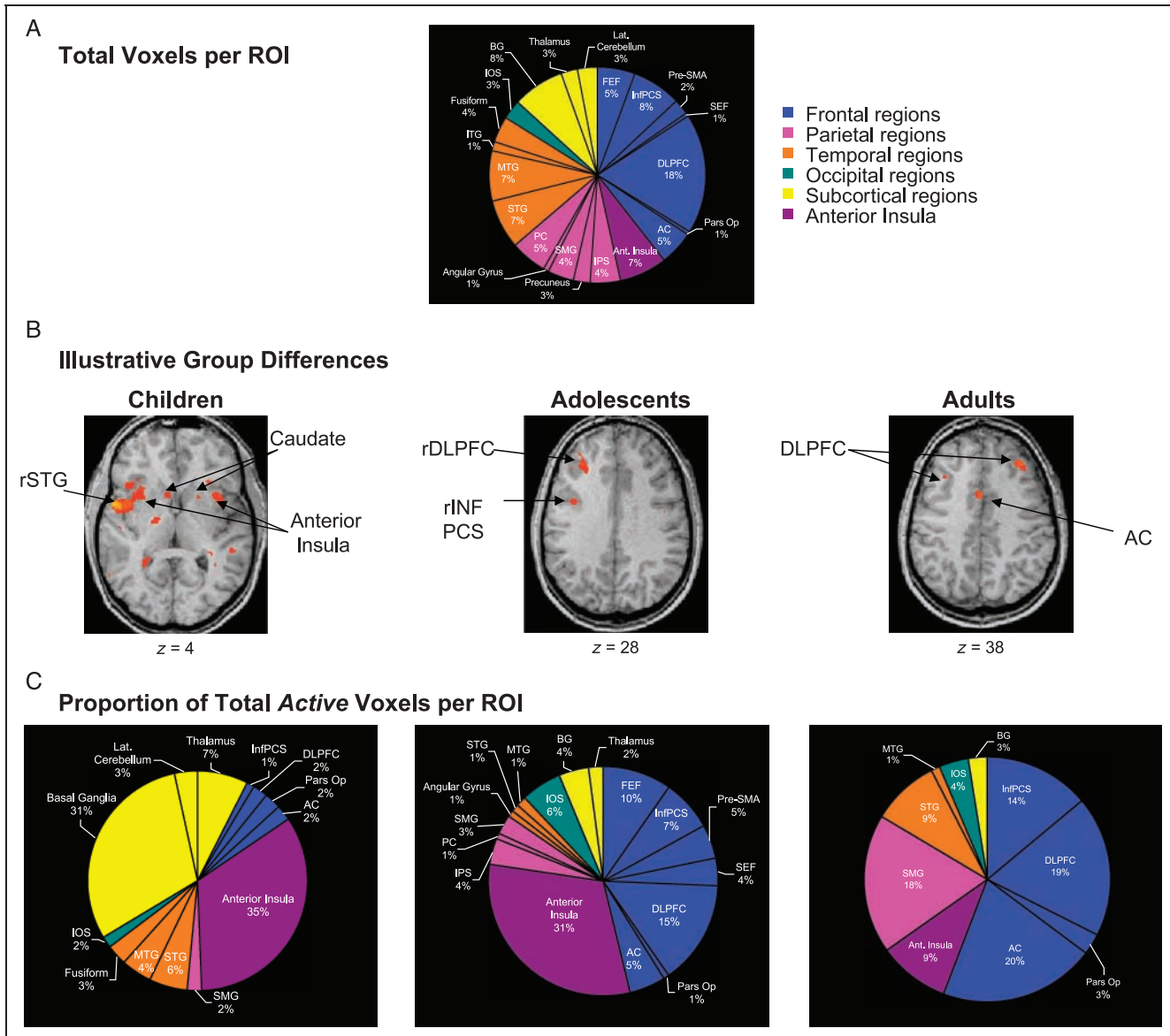


Figure 3. Imaging results from both magnitude and extent of activation analyses. (A) Proportion of total number of voxels in each ROI submitted to extent of activation analyses in all groups (see Table 1 for names of ROIs). (B) Each group image represents illustrative differences in both the magnitude and extent of activation in the group-averaged percent signal change functional maps. Children showed stronger activation bilaterally in the caudate nucleus, the thalamus, and the anterior insula. Adolescents showed the strongest right DLPFC activation, and adults showed concentrated activation in the left prefrontal and posterior parietal regions. (C) Group differences in the extent of activation as measured by the proportion of total *active* voxels in each ROI for each age group. Despite the fact that the proportion of total voxels in the extent of activation analyses was consistent across the age groups, the groups showed large differences in the proportion of total *active* voxels across the ROIs.

insula, right STG, right BG, and right IOS. Contrary to predictions, this common set of regions did not include inferior parietal areas or the cortical eye fields. The finding that all three age groups recruited this set of core regions indicates how essential they are in VSWM networks. The quantitative differences are interpreted to reflect development within these local regions and in their collaborations with other regions. Qualitative differences in functional brain circuitry also accompanied the transitions from childhood to adolescence and

adolescence to adulthood. These qualitative differences are interpreted to reflect the early recruitment of compensatory regions and later refinement of functional connectivity among necessary and sufficient regions.

VSWM Networks in Childhood

Despite the minimal group differences in performance, children recruited overlapping but different VSWM networks compared to both adolescents and adults. In

addition to the core regions, children recruited the thalamus, regions throughout the medial and lateral temporal lobes, and the left lateral cerebellum.

The quantitative differences in children's reliance on ventromedial regions during the working memory task were dramatic. There was a large decrease in caudate and thalamus activation from childhood to adolescence. Other developmental neuroimaging studies have reported a similar early reliance on the BG in childhood (Casey, Davidson, et al., 2004). Although the local connectivity within the BG continues to mature into adolescence (Sowell et al., 1999), children relied heavily on the caudate nuclei to support their VSWM performance. At the same time, children were limited in their ability to recruit the cortical regions to which the caudate projects and that are so important for VSWM. For example, children recruited much less DLPFC, inferior parietal, premotor, and AC activation during the working memory task than did either the adolescents or adults. Other developmental neuroimaging experiments of VSWM have found similar limitations in children's abilities to recruit the right DLPFC (Olesen et al., 2003; Klingberg et al., 2002; Kwon et al., 2002). The less extensive DLPFC activation in children may result from a limitation in both the localized computations within the DLPFC, because of insufficient synaptic pruning, and in less developed connections between the DLPFC and caudate nuclei (Olesen et al., 2003; Yakovlev & Lecours, 1967). These results suggest that as brain maturation occurs throughout frontal-striatal circuitry, there is a developmental shift toward more reliance on prefrontal regions and less reliance on the BG.

Children also recruited much less inferior parietal activation, especially in the SMG, that is consistently recruited by adults across VSWM studies. Instead, children's parietal activation was concentrated in the precuneus. This finding is consistent with other developmental neuroimaging studies of VSWM (Nelson et al., 2000; Thomas et al., 1999). The recruitment of the precuneus may reflect children's limited access to inferior parietal regions, which are not necessary for VSWM but may be responsible for more sophisticated levels of working memory performance in adulthood.

Children were qualitatively different from adolescents and adults in their recruitment of regions in premotor areas, the ventral temporal cortex, and the lateral cerebellum. Children failed to recruit the premotor regions, including the SEF and FEF, which are part of a frontostriatal loop that controls voluntary saccadic eye movements (Hikosaka, Takikawa, & Kawagoe, 2000). This finding indicates that the functional integration of response preparation and execution circuitry is still immature in childhood when the ability to plan and execute a saccade to a remembered location is still improving.

Children exhibited unique recruitment of the fusiform and lateral cerebellum. Children's recruitment of the fusiform, which facilitates encoding and recognition of

visual objects (Haxby, Petit, Ungerleider, & Courtney, 2000), could reflect a more object-based encoding strategy of the spatial target. Additional support for this interpretation comes from our finding that reliance on the fusiform was actually related to less accurate encoding of the target stimuli. This early use of the fusiform to support VSWM could be related to developmental differences in the maturation of the ventral "what" and dorsal "where" visual pathways. The dorsal stream, which is more useful for encoding spatial information, reportedly develops along a more protracted developmental timeline than does the ventral stream (for review, see Johnson, Mareschal, & Csibra, 2001). Our results are consistent with the notion that children compensate for an underdeveloped dorsal pathway by relying on the ventral pathway to encode visual spatial stimuli.

Children were also unique in their recruitment of the lateral cerebellum. In previous neuroimaging studies using motor learning tasks with both children and adults, left lateral cerebellar activation was associated with unskilled performance (Van Mier & Petersen, 2002). As participants acquired skill in the task, this cerebellar activation decreased, leading researchers to argue that the left lateral cerebellum might be involved in error detection and correction. This is consistent with other models of the "cognitive" cerebellum that attribute it with a role in motor planning and the ability to keep track of movement errors (Thach, 1998). The recruitment of the left lateral cerebellum in childhood may reflect limitations in access to premotor and inferior parietal regions that support efficient planning, execution, and correction of MGSs.

VSWM Networks in Adolescence

Despite minimal differences in behavioral performance, adolescents demonstrated both quantitative and qualitative differences from children and adults in VSWM circuitry. In addition to the core regions, adolescents primarily recruited bilateral premotor regions and right-lateralized inferior parietal regions.

The qualitative differences in adolescent's reliance on the anterior insula and the AC were impressive. Like children, adolescents recruited more than three times the insula activation compared with adults and much less activation in the AC. Both the anterior insula and the AC reportedly play a role in maintaining cognitive control. The anterior insula has been generally associated with cognitive control in neuroimaging studies of both children (Bunge et al., 2002; Casey, Thomas, Davidson, Kunz, & Franzen, 2002) and adults (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000; Garavan, Ross, & Stein, 1999). The AC has been specifically associated with conflict monitoring (Carter et al., 1998), error correction (Kerns et al., 2004), and controlling voluntary saccades (Paus, 1993). These developmental differences indicate that the transition from adolescence to adult-

hood is marked by a change in the distribution of activation across these cognitive control regions. Weak access of the AC prior to adulthood may limit the use of self-monitoring and error-correcting processes that support organized and efficient task performance.

The other remarkable quantitative difference in adolescents' functional circuitry was the sharp increase in right DLPFC activation from childhood. Previous VSWM studies have found similar increases in DLPFC activation from childhood to adolescence (Olesen et al., 2003; Klingberg et al., 2002; Kwon et al., 2002). Adolescents' extensive and diffuse activation in the DLPFC clustered around two loci, a dorsal locus and a separate ventral locus. Surprisingly, adults showed a decrease in right DLPFC activation compared with adolescents. This finding is consistent with other studies of nonspatial working memory tasks (Casey, Cohen, et al., 1995). Adults activated a more localized portion of the DLPFC that overlapped with the dorsal, but not ventral, locus of activation in the adolescents. This finding explains why an increasing extent of activation within the right DLPFC was not related to increased accuracy. Although participants became more accurate in their final resting saccades with age, the extent of activation in the right DLPFC actually got smaller. This pattern of increasing localization within cortical regions is consistent with other studies of cognitive and brain development (Casey, Giedd, & Thomas, 2000). The contribution of the DLPFC to working memory skills may be increasingly refined well into adulthood as a result of developing local specialization within the DLPFC that occurs with continued synaptic pruning and myelination.

With adolescence emerged the functional integration of the oculomotor response preparation and execution circuitry. Unlike the children, the adolescents incorporated several premotor regions into their VSWM networks. However, the distribution of activation across these premotor regions continued to develop from adolescence to adulthood. Adolescents showed distributed activation throughout the premotor regions, but adults had concentrated activation in the inferior PCS. These results indicate that although the transition into adolescence is marked by the integration of prefrontal circuitry, additional functional specialization and localization of this circuitry mark the transition into adulthood.

Unlike children, adolescents were able to access both superior and inferior parietal regions to support their working memory performance. Adolescents recruited regions in the IPS, precuneus, SMG, angular gyrus, and posterior cingulate. As with the premotor regions, adolescents recruited more distributed activation throughout the parietal cortex than did the adults, who showed more localized recruitment of the SMG that was primarily left lateralized. Focused activation of the SMG was related to more accurate final resting saccades, indicating more detailed encoding of the spatial targets. Part of the

developmental transition from adolescence to adulthood in the VSWM circuitry involves increasing specialization in both prefrontal and posterior parietal regions.

VSWM Networks in Adulthood

Adults recruited the most locally specialized VSWM networks. In addition to the core regions, adults recruited a set of left-lateralized regions, including the DLPFC, the pars opercularis in the VLPFC, and the SMG. These findings indicate that the adult VSWM circuitry is more functionally specialized for maintaining cognitive control, planning and preparing appropriate motor responses, and encoding and maintaining visuospatial stimuli.

There was a fourfold increase in AC activation from adolescence to adulthood. In fact, adults relied more heavily on the right AC than on any other region. They recruited a caudal portion of the AC (BA 24/31) that has been specifically linked to facilitating a state of preparedness for selecting memory-guided oculomotor responses (Petit, Courtney, Ungerleider, & Haxby, 1998). This recruitment of the AC reflects the most efficient and sophisticated use of regions related to preparing and organizing saccadic behavior.

Adults were unique in their strong reliance on the left DLPFC, the pars opercularis in the VLPFC, and the SMG. These left-lateralized regions have been identified as part of the phonological loop that supports subvocal verbal rehearsal processes in working memory (Baddeley, 1998). Kwon et al. (2002) found a similar developmental difference when children and adults performed a VSWM task. They argued that this increasing left hemisphere activation may be associated with the developing ability to recode visual stimuli into phonological form for use in more sophisticated verbal rehearsal strategies. The ability to verbally recode visuospatial stimuli is significantly related to the development of VSWM (Pickering, Gathercole, Hall, & Lloyd, 2001) and appears to develop as a rehearsal strategy in late childhood that continues to improve through adolescence (Halliday & Hitch, 1988). Although we did not interview participants about their rehearsal strategies, our neuroimaging results suggest that the adults may have been implementing a verbal rehearsal strategy to help organize and maintain focus in their task performance.

Limitations and Future Directions

The pattern of behavioral differences in this sample was more limited compared to that found in the larger sample from which these participants were selected (Luna, Garver, et al., 2004). Unlike in the larger sample, children were not reliably different from adults on the accuracy of their initial saccade. This could be due to the inclusion of older adults, which undermined their superior

performance. However, the two oldest adults were *more* accurate on average and the correlational analyses revealed that participants' accuracy on the final resting saccade, which indicates the ability to sufficiently encode the target stimuli, increased with age. It seems more likely that the lack of behavioral differences between the adults and children resulted from insufficient power due to the small sample sizes. An optimal developmental design would permit the effects of age to be evaluated as a continuous variable when considering developmental changes in behavior and in patterns of brain activation. We maximized our ability to observe developmental differences in both brain activation and behavior by considering the effects of age both categorically and continuously. Viewing age as a continuous variable in future studies in a larger sample will provide a strong approach to confirm our findings. Our ongoing studies include larger sample sizes with a more constrained adult age range.

Conclusions

Developmental changes in the VSWM circuitry include: (1) *quantitative changes* that reflect the refinement of local connectivity and computations within essential working memory regions, such as the DLPFC, AC, and caudate nuclei; and (2) *qualitative changes* that reflect the refinement of functional connectivity among more distal regions, such as the incorporation of premotor, VLPFC, and inferior parietal regions. Synaptic pruning and myelination, which continue through childhood and adolescence, refine both local and distal connections. Such maturational changes may help establish and maintain these quantitative and qualitative patterns of developmental change. Furthermore, as these developmental transitions are occurring, both children and adolescents appear to compensate for less integrated functional connectivity or less specialized computations within a region by relying on regions that play a much smaller role in the adult network.

Acknowledgments

The research reported in this article was supported by National Institutes of Mental Health (NIMH) grants MH067924 and MH01727 to Beatriz Luna and HD35469 to John Sweeney as well as a Young Investigator Award from the National Alliance for Research in Schizophrenia and Depression to Beatriz Luna. We thank Joel Welling, for consulting with us about analyzing the fMRI data; the staff in the Laboratory of Neurocognitive Development, for their help with this project; and our study participants, for making this research possible.

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The data reported in this experiment have been deposited with the fMRI Data Center (www.fmridc.org). The accession number is 2-2006-120R4.

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