CROSS-SECTIONAL DIFFERENCES IN BRAIN ACTIVITY SUPPORTING

WORKING MEMORY

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by

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Cross-sectional developmental studies have shown working memory (WM) to follow monotonic developmental trajectories through childhood into adolescence. In contrast, structural neuroimaging studies have shown that several brain regions, such as the prefrontal cortex (PFC), follow nonlinear developmental trajectories from birth through late adulthood. The present study sought to explore the relationship between functional activation in brain regions supporting WM and age throughout adolescence.

Forty-two healthy adolescents (aged 11 to 18) completed a delayed-response WM task while functional magnetic resonance imaging (fMRI) data were collected. Participants studied either one or six letters (3.5 seconds), remembered the items over a

delay (5 seconds), and then judged whether a single probe letter was in the studied set (within 2.5 seconds). An fMRI blocked design was used: four blocks per set-size and three trials per block. Additionally, the participants completed the Digit Span subtest from the Wechsler intelligence tests in order to obtain behavioral measures of WM.

Hierarchical regression analyses were used to evaluate linear and quadratic relationships between WM task-related signal-change per voxel and age while evaluating the potential mediating effects of WM indices (response time [RT], digit span forward, digit span backward). Linear relationships were found in right medial Brodmann's Area (BA) 6, right cerebellum, and left BA34 when the linear effects of gender, handedness, response time, digit span forward, and digit span backward were controlled for statistically. Thus, activation increased with age within these regions, but the linear trends were being suppressed by the covariates.

Activation on the WM task increased with age in right medial BA6 when the effects of WM indices, as measured in the present study, were removed. The separate relationship between WM capacity and right medial BA6 activation suppressed the detection of the relationship between right medial BA6 activation and age. The data support developmental, possibly maturational, changes in the role of medial PFC in WM that are independent of WM ability measures used in the present study. This finding has implications for broad theories about the development of WM and other cognitive abilities that allow for the identification of both normal and deviant developmental trajectories.

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LIST OF ABBREVIATIONS

BOLD – blood-oxygen-level dependence

DSB – raw Digit Span Backward scores from the WISC-IV/WAIS-III Digit Span subtest

DSF – raw Digit Span Forward scores from the WISC-IV/WAIS-III Digit Span subtest

DSS – Digit Span scaled scores

DLPFC – dorsolateral prefrontal cortex

DTI – diffusion tensor imaging

EF – executive function

EPI – echo planar imaging

fMRI – functional magnetic resonance imaging

G – gender

H - handedness

HDR – hemodynamic response

MPRAGE – magnetization prepared rapid acquisition gradient echo

PFC – prefrontal cortex

RT – response time

VLPFC – ventrolateral prefrontal cortex

WAIS-III – Wechsler Adult Intelligence Scale, Third Edition

WISC-IV – Wechsler Intelligence Scale for Children, Fourth Edition

WM – working memory

SECTION ONE
Main Findings

Introduction

      The present study explored the developmental trajectory of prefrontal cortex

(PFC) activity supporting working memory (WM) using functional magnetic resonance

imaging (fMRI). Cross-sectional developmental studies have shown WM performance,

based on cognitive testing, to follow monotonic developmental trajectories through

childhood into adolescence (see Best, Miller, & Jones, 2009; Fry & Hale, 1996;

Gathercole, Pickering, Ambridge, & Wearing, 2004; Kail & Salthouse, 1994; Luciana,

Conklin, Hooper, & Yarger, 2005; Span, Ridderinkhof, & van der Molen, 2004;

Swanson, 1999). Although WM performance improvements have been attributed to

increases in global capacity that occur with age, the underlying neural mechanisms

supporting proposed increases in capacity are not fully understood (Gathercole et al.,

2004; Luciana et al., 2005; Swanson, 1999). In contrast to global capacity predictions,

structural neuroimaging studies have shown that several brain regions follow nonlinear

developmental trajectories from birth through late adulthood (Giedd et al., 1999; Giorgio

et al., 2010; Gogtay et al., 2004). The nonlinear development of brain regions suggests

that cognitive improvements might result from more "qualitative" changes within cortical

structures (Gogtay et al., 2004; Johnson, 2001; Shaw et al., 2008; Span et al., 2004; Stuss

et al., 2005) rather than from more global "quantitative" changes in neural efficiency that

support an overall greater processing capacity (Gathercole et al., 2004; Kail & Salthouse,

1994).

      WM is a core cognitive construct that consists of a system of processes that allow

for the temporary maintenance and manipulation of information in the mind (Baddeley,

1

1981). WM is composed of multiple component processes (Baddeley, 1981; Miyake &

Shah, 1999). One multi-component model of WM includes a central executive function

that is responsible for the processes mediating encoding, manipulation, and retrieval

(Baddeley, 1981). This model also includes the phonological loop, mediating the storage

of verbal information, and the visuospatial sketchpad, mediating the storage of visual and

spatial information. Additionally, this model includes the episodic buffer, mediating the

integration of data into meaningful pieces (Baddeley & Logie, 1999; Repovs & Baddeley,

2006).

Thus, WM consists of both storage and manipulation processes (Baddeley, 1981;

Baddeley & Hitch, 1974). WM storage capacity has been shown to be limited (Brenner,

1940; Cowan, 2001; Luck & Vogel, 1997; Miller, 1955). Cowan (2001), for example,

suggested that WM capacity is limited to 4 +/-1 items regardless of the format (e.g.,

verbal or visual) of the stimuli being remembered. When the to-be-remembered

information exceeds these capacity limitations, however, WM executive processes can be

recruited to reorganize or chunk the information to fit within WM capacity limits (Cowan

2001; Miller, 1955). In addition to the reorganization of information into more

manageable chunks, executive processes can also be recruited for more complex tasks,

such as when the task requires the manipulation of computations or mental imagery

(Kozhevnikov, Motes, & Hegarty, 2007; Seyler, Kirck, & Ashcraft, 2003). The

integrated use of these component processes into overall WM ability is integral to higher

order cognitive processes, as has been demonstrated by correlations between measures of

WM and intelligence (Engle, Tuholski, Laughlin, & Conway, 1999), reasoning

(Carpenter, Just, & Shell, 1990; Goel & Grafman, 1995), problem-solving (Prabhakaran,

Narayanan, Zhao, & Gabrieli, 2000), and comprehension (Cain, Oakhill, & Bryant, 2004).

WM indices are often used to measure WM as a single construct (Miyake et al., 2000; St. Clair-Thompson & Gathercole, 2006) in order to distinguish WM from other executive functions (EF), such as inhibition and attention. However, the divergence of WM indices also has been demonstrated and provides further support that WM consists of unique underlying component processes (Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001; Schneider-Garces et al., 2009). In a latent variable analysis of verbal and visuospatial WM capacity, digit span forward was found to load onto a factor that included word span and letter span and thus was said to represent WM storage (Kane et al., 2004). Although, digit span forward as a measure of WM capacity is affected by the use of manipulation processes (i.e., "chunking", Cowan, 2001; Miller, 1955), digit span backward is considered to more heavily involve the recruitment of executive resources in order to reorganize the set of numbers (Wechsler, 2008), and digit span backward has been shown to correlate more strongly with measures of intelligence than digit span forward (Miyake & Shah, 1999; Wechsler, 2008). Finally, response time (RT) often has been used to index WM search and retrieval speed (Rypma & D'Esposito, 1999; Sternberg, 1966), and retrieval speed has been shown to increase with development and to be distinct from WM capacity (at least in young children, Cowan, Saults, Nugent, & Elliot, 1999).

Several measures of WM (such as RT on WM tasks and information manipulation) have been shown to improve along monotonic trajectories throughout childhood, adolescence, and into young adulthood, when many cognitive abilities seem to

peak (Cowan, Saults, & Elliot, 2002; Gathercole et al., 2004; Swanson, 1999). One explanation for the linear relationship between cognitive measures of WM and age is the global-capacity framework. This framework holds that general changes in cognitive transmission times throughout the lifespan control increases and decreases in overall processing capacity, including the changes in WM storage and manipulation capacity that occur (Bashore & Smulders, 1995; Fry & Hail, 1996; Salthouse, 1996). Thus, improvements on indices of WM, perhaps due to decreases in transmission times between WM and other relevant systems, may mediate age-related improvements in overall WM ability.

An additional explanation for the differential development of WM abilities is the neurocognitive-change framework. This framework holds that functional changes within brain regions control increases and decreases in modality-specific processing capacities (Pennington, 1994; Span et al.,1994), suggesting that WM storage and manipulation capacity changes throughout the lifespan occur with some degree of relative independence from other cognitive processes. The different developmental trajectories for storage and manipulation components of WM, for example, have been observed based on the complexity of the WM task. One study showed that a simple WM task, nonverbal face recognition, showed no significant improvement after age nine, but with more complex tasks (e.g., spatial self-ordered search), WM improvements were observed into adolescence (Luciana et al., 2005). Thus, global processing capacity improvements alone do not fully account for the changes in cognitive performance that occur throughout the lifespan. Developmental changes in cognitive abilities also may be linked to maturation of specific brain regions (Mountcastle, 1997; Paus, 2005; Stuss, 2006).

The identification of spatially distinct brain regions mediating WM component processes is also consistent with the neurocognitive-change framework. Neuroimaging studies using WM have shown that WM functions are tied to discrete brain regions (Baldo & Dronkers, 2006; D'Esposito, Postle, & Rypma, 2000; Klingberg, Forssberg, & Westerberg , 2002; Kwon, Reiss, & Menon, 2002; Owen, McMillan, Laird, & Bullmore, 2005; Rypma, 2006). The material being remembered, the complexity of the WM task (such as basic storage or goal-oriented manipulation), and the specific underlying WM process involved (such as the encoding, maintenance, or retrieval phase) lead to the differential use of regions within the PFC, parietal cortex, and other brain regions (Barby, Koenigs, & Gafman, 2010, Motes & Rypma, 2010; Owen et al., 2005, Rypma, 2006; Smith & Jonides, 1999). Based on the neurocognitive change framework, differential maturation rates in these regions would lead to different developmental trajectories for WM component processes.

Further support for the neurocognitive change framework has been generated by research on the anatomical development of the brain. Research on structural brain changes has shown that several regions follow nonlinear developmental trajectories from birth through late adulthood (Giedd et al., 1999; Giorgio et al., 2010; Gogtay et al., 2004; Johnson, 2001). For example, the gray matter volume of the PFC (and parietal cortex) follows a quadratic developmental trajectory; the gray matter volume of the PFC increases from birth, peaks around 12 years of age, and then begins to decrease (Giedd et al., 1999). This loss of gray matter volume has been hypothesized to be a function of neural pruning as neural circuits are refined (Giedd et al., 1999; Giorgio et al., 2010; Gogtay et al., 2004; Shaw et al., 2008). The region-specific maturation of the brain is not

consistent with global capacity increases but rather suggests that the different developmental changes in the function of specific brain regions underlie developmental changes in unique components of WM.

Previous cross-sectional studies exploring functional activation in the PFC during WM tasks found that age accounted for a significant portion of the differences in activation between groups of children, adolescents, and adults during visuospatial WM tasks (Klingberg et al., 2002; Kwon et al.2002). However, these studies identified increases in specific brain regions rather than global increases in activation. For example, Klingberg, Forssberg, and Westerberg (2002) found region-specific activation in the superior frontal, intraparietal, and occipital areas, with older children showing greater activation in the superior frontal regions. Additionally, Kwon, Reiss, and Menon (2002) found region specific activation in the DLPFC and superior frontal gyrus in children, which demonstrated that children activate similar brain regions during a WM task as adults. However, these studies classified participants into discrete cohorts of younger and older children and did not explicitly test for linear and nonlinear relationships, per se, between functional activation and age.

The present fMRI study sought to explore the relationship between functional activation in brain regions supporting WM and age throughout adolescence by testing for both linear and nonlinear activation changes as a function of age to generate support for current models of brain development. If the relationship between age and functional activation during a WM task follows a linear trajectory, support would be generated for the global-capacity framework. However, there is a discrepancy between cognitive and structural trajectories for which this framework does not account. Indeed, many brain

structures, such as cortical gray matter, follow a quadratic trend with region-specific peaks. Thus, if the relationship between neural activity supporting WM and age follows a non-linear (e.g., quadratic) developmental trajectory, support would be generated for the neurocognitve-change framework by suggesting that changes in function are based on different maturation rates of brain regions rather than global capacity improvements that occur with development.

Additionally, the present study examined the impact of various measures of WM as covariates. Percent signal-change has been shown to vary with task performance and other behavioral measures of individual differences (Gray, Chabris, & Braver, 2003; Motes, Biswal, & Rypma, 2010; Rypma & D'Esposito, 1999). Given that WM is comprised of multiple component processes, the effects of different indices of WM on brain activation patterns will be explored by evaluating mediation and suppression effects using different measures of WM processes. On the one hand, specific WM components might account for age-related changes in functional activation, thus allowing for the identification of WM functions undergoing change with brain development. On the other hand, statistically controlling for the WM indices might account for variability in the fMRI signal that is masking age-related activation changes, thus allowing for the identification of developmental changes in functional activation that are independent of the WM constructs measured but still related to the WM task. Thus, behavioral measures of WM aimed to capture performance, storage, and manipulation components of WM were included in the study in order the better understand the relationship between age and functional brain activation.

Method

Participants

Forty-two participants (age $M = 14$; range = 11 to 18; 17 females; 5 left-handed) participated in the study. However, the data from one participant (16-year-old right-handed male) were not included in the analyses due to artifact introduced during fMRI data acquisition. Participants were recruited through ongoing studies at both Children's Medical Center Dallas and the University of Texas at Dallas Center for BrainHealth, primarily through advertisements placed at these institutions, local middle schools, and the surrounding communities. All participants were prescreened for MRI contra-indicators and for medical, neurological, and psychiatric illness.

Procedure

All studies were approved by the University Institutional Review Board and were conducted according to the principles expressed in the Declaration of Helsinki. The benefits, risks, confidentiality, and other aspects of the studies were explained to the parents and a written description was provided. Prior to testing, written informed consent was obtained from each participant's legal guardian, and the adolescent provided their written assent.

WM Task. Participants completed a blocked-design, WM item recognition task while fMRI data were collected. Item recognition tasks have been used to study WM because the encoding, maintenance, and decision phases can be examined independently, and the set size can be manipulated to create sub- and supra-capacity WM sets (Motes, Kojori, Rao, Bennett, & Rypma, 2010; Rypma & D'Esposito, 1999; Sternberg, 1966).

Both a 1-letter condition and a 6-letter condition were used, with the 1-letter condition serving as the baseline condition and the 6-letter condition taxing the WM system.

Uppercase letters (B, F, G, H, J, L, M, N, Q, R, S, W, and X) were used as the encoding and probe stimuli, and adjacent letters in the English alphabet did not appear alphabetically. The background was black, and the letters were white. The encoding stimuli appeared on the upper half of the screen in a white rectangular box, and the probe stimuli appeared on the bottom half of the screen within a small white box; the outlines remained on the screen throughout the trials. If the probe stimulus matched a letter from the encoding stimuli, the participants were to press a single button. If the probe stimulus was not present in the encoding set, the participants were not to press the button (Figure 1). The use of a single button (rather than two buttons, one for "yes" and one for "no") was due to the single response criterion used across other tasks to ensure the tasks were easy enough for younger participants to successfully complete.

1 Letter Trial

| Encoding Phase (3.5s) | Maintenance Phase (5s) | Decision Phase (2.5s) |

6 Letter Trial

| Encoding Phase (3.5s) | Maintenance Phase (5s) | Decision Phase (2.5s) |
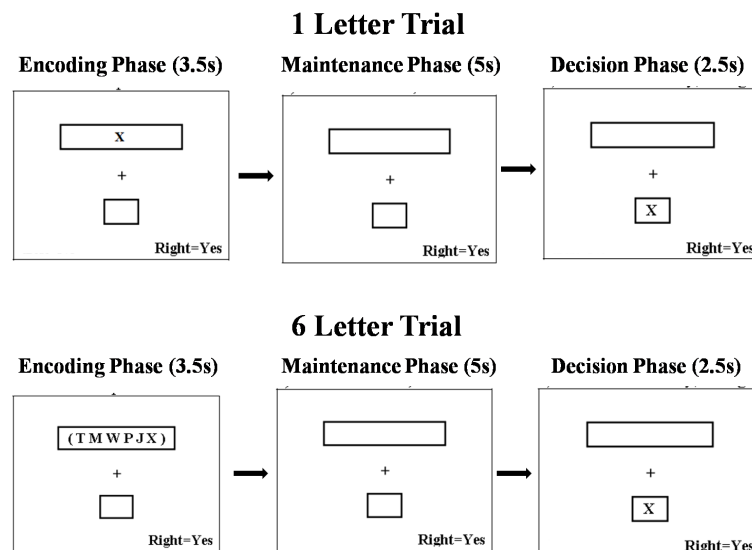
Figure 1. Examples of the 1-Letter trial and 6-Letter trial of the WM task.

For the 1-letter condition, the participants were to encode the one letter during an encoding phase (3.5 s), maintain this letter over a delay (5 s), and decide whether a single probe letter was in the studied set (2.5 s). For the 6-letter condition, the participants were to encode six letters during the encoding phase (3.5 s), maintain these letters over a delay (5 s), and then judge whether a single probe letter was in the studied set (2.5 s). A 1 s delay occurred between trials. An fMRI blocked design was used: four blocks per set-size and three trials per block. The 1-letter condition always appeared first. The completion of the WM task during the fMRI session varied given the differing protocols of each study; additionally, the order of the scans completed at the fMRI session may have varied as the protocols were adjusted to best accommodate each participant. RT (calculated for accurate responses only) was recorded for all trials in the 6-letter condition to be used as an index of WM, as RT has been said to measure search and retrieval speed on Sternberg WM tasks (Kirschen, Chen, & Desmond, 2010; Rypma & D'Esposito, 1999; Sternberg, 1966).

In order to determine functional activation changes, an echo planar imaging (EPI) sequence was used to measure the blood-oxygenation-level dependent (BOLD) signal. As neural activity increases, there are increased metabolic demands, and these increased metabolic demands trigger a compensatory blood flow response to the brain region that brings oxygen-rich blood to the region (Ogawa & Lee, 1990). This hemodynamic response (HDR) leads to the change in the magnetic resonance signal by increasing the ratio of oxygenated to deoxygenated hemoglobin present in a single voxel, allowing for a stronger signal. However, the HDR does not happen instantaneously in response to a stimulus, as there is a slow building of increased oxygenation followed by a slow decline

in oxygenation after the task is complete (Figure 2). Thus, using a blocked fMRI design allows for the changes in HDR to be measured. Furthermore, the use of a 1-letter control condition rather than a resting state control condition allows the basic visual, motor, and attention demands to be parceled out from the increased WM demands that occur in the 6-letter condition.

Blocked Design and HDR Model
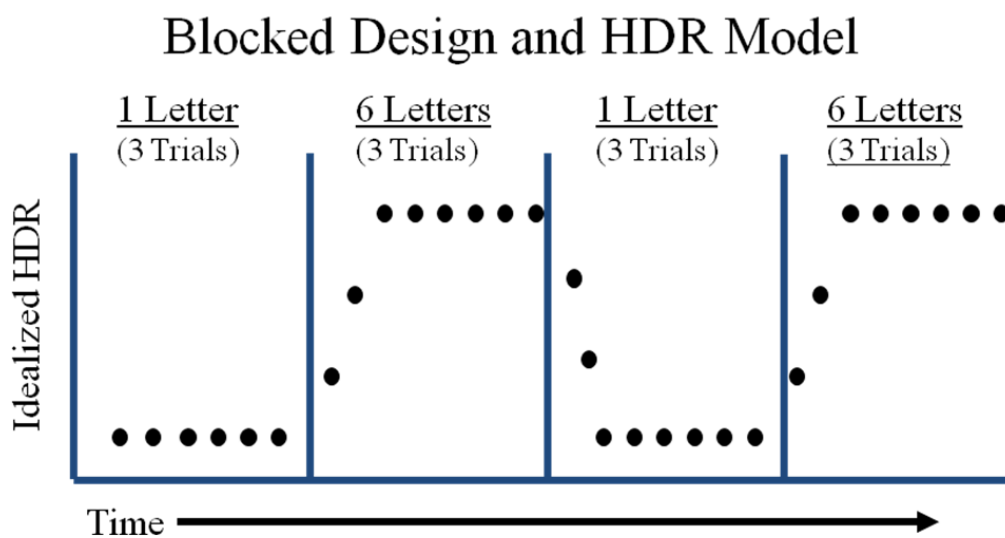
Figure 2. Visual depiction of the idealized HDR for an fMRI blocked design. Four blocks of 1-letter and 6-letters were used.

Digit Span. The impact of component processes underlying WM on the relationship between improvements in WM and age was explored by selecting indices of overall WM that have been shown to measure these different components. Research has suggested that span tasks capture different components of WM (Schneider-Garces et al., 2009). Digit span forward has been said to measure a basic capacity/storage component of WM limited by attention (Engle & Kane, 2004; Kane et al., 2006). Digit span backward, a task requiring a manipulation component, has been said to require the

recruitment of executive resources (Hale, Hoeppner, & Fiorell, 2002; Sattler, 2001; Wechsler, 2008). Thus, tasks measuring both span forward (an index of capacity) and span backward (an index of manipulation) were included. Participants completed the Digit Span subtest from either the Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV; Wechsler, 2004) or the Wechsler Adult Intelligence Scale, 3rd Edition (WAIS-III; Wechsler, 1997). Participants aged 11 through 16 completed the WISC-IV, and participants aged 17 through 18 completed the WAIS-III. Raw Digit Span Backward (DSB), raw Digit Span Forward (DSF), and scaled scores on the Digit Span subtest (DSS) were recorded for each participant.

Additionally, gender and handedness were treated as covariates to further control for related variability. Gender was considered in the behavioral analyses, and gender and handedness were considered in the fMRI analyses. Age was calculated in months, rather than years, to better capture the age-related variability within the sample of adolescents.

Image Acquisition

High-resolution anatomical images (MPRAGE; 1 mm isovoxel; sagittal; TE = 3.7 ms; flip angle = 12°) and functional images (EPI; voxel = 3.5 x 3.5 x 4 mm; 36 slices/volume; 147 volumes/run; TR = 2000 ms, TE = 30 ms; flip angle = 70°; matrix = 64x64; axial; inferior to superior interleaved) were collected on a Philips Achieva 3T scanner equipped with an 8-element, SENSE, receive-only head coil. Twelve "dummy" scans occurred at the beginning of each functional run to remove T1 saturation effects.

Image Analysis

The fMRI data were analyzed using AFNI software (Cox, 1996). For each participant, the data were corrected for slice-timing offset and motion, and then spatially

filtered with a Gaussian kernel (FWHM = 8 mm). The data for each voxel was scaled so that the deconvolution parameter estimates were expressed in terms of percent signal-change (i.e., $100 * y_t/My$, t= time point). These preprocessed BOLD time-series per voxel were deconvolved using modified linear regression with the regressor constructed by convolving a HDR model (a gamma-variate function; Cohen [1997] parameters b = 8.6, c = 0.547; max amplitude = 1.0) with a box-car task-reference function differentiating 6-letter trial blocks from 1-letter trial blocks (with 1s for time-points within 6-letter blocks and 0s for time-points within 1-letter blocks). This allowed for the estimation of percent signal-change during the 6-letter condition. Furthermore, regressors modeling linear and quadratic trends over the entire run and the motion correction parameters were also included in the regression model to remove these nuisance variables from the percent signal-change estimates. The resulting percent signal-change matrix (yielding percent signal-change per voxel for the 6-letter block relative to the 1-letter block) for each participant was spatially normalized to Talairach space via a 12-parameter affine transformation (Talairach & Tournoux, 1988; resampled to a 2 mm isovoxel resolution) and FSL's nonlinear warping algorithm was applied to improve registration (FMIRB Analysis Group; Woolrich et al., 2009).

Results

Behavioral Results

Indices of WM ability included RT (calculated as the mean RTs for accurate responses in which the target was present during the 6-letter condition; RTs two-and-a-half standard deviations above and below the mean were discarded), digit span forward (as a measure of WM capacity), and digit span backward (as a measure of WM

manipulation). Although accuracy was calculated (total correct responses/total possible

correct responses during the 6-letter condition) as an additional measure of performance,

accuracy was not used as a measure of performance due to a task ceiling effect; only six

participants performed worse than 93%.

Correlations between the behavioral measures were computed to examine the

degree to which the indices were measuring unique WM processes. Table 1 shows the

Table 1. *Correlations between covariates.*

	Digit Span Forward	Digit Span Backward	Age	Gender
Response Time	-.051	.119	-.362*	-.115
Digit Span Forward		.290	.204	.080
Digit Span Backward			.260	-.365*
Age				.053

*$p < .05$.

Pearson correlations between the three behavioral indices of WM: RT, digit span

forward, and digit span backward. Age and gender (coded as 0 = males and 1 = females)

also were included to determine if these sample characteristics were related to the WM

indices. None of the WM measures were strongly or significantly correlated with each

other. Although digit span forward and digit span backward were weakly correlated, $r =$

.29, the low correlation suggests that there is a substantial portion of unique variance for

each measure that justifies treating them separately in the analyses of the BOLD-age

relationships. The weak correlation this study found between digit span forward and digit

span backward is consistent with previous correlations between these two constructs on

the WAIS-IV ($r = .3$; Wechsler, 2008).

Analyses determining both linear and nonlinear relationships between age and

each index of WM were performed, as research has found that improvements in WM

ability on a variety of tasks follow monotonic developmental trajectories throughout

adolescence (Gathercole et al., 2004; Schneider-Garces et al., 2009). Additionally, each

index of WM, along with gender, was treated as a covariate in the analyses in order to

explore potential mediation and suppression effects on the relationships between each

index of WM and age.

RT linear effects. Hierarchical multiple regression was used to explore the

linear relationship between RT and age and the potential mediating and suppressing

effects of the covariates. Table 2 shows the results from the tests of linear relationships

between performance on the WM task and age. The results of a linear regression analysis

indicated that RT decreased as age increased ($r = -.362$, $p = .02$), indicating that search

and retrieval speed increased with age.

Table 2. *Hierarchical Multiple Regression Analyses Predicting the Linear Relationship between RT and Age with the Addition of Covariates*

	R^2	ΔR^2	ΔF	β_{age}	$df1$	$df2$	p
RT = Age	.131		5.876	-.362	1	39	.020*
Hierarchical Regression							
Reduced Model: G	.013		.525		1	39	.473
Full Model: G + Age	.140	.127	5.609	-.357	1	38	.023*
Hierarchical Regression							
Reduced Model: DSF	.003		.103		1	39	.750
Full Model: DSF + Age	.131	.129	5.637	-.367	1	38	.023*
Hierarchical Regression							
Reduced Model: DSB	.014		.555		1	39	.461
Full Model: DSB + Age	.179	.165	7.660	-.421	1	38	.009**
Hierarchical Regression							
Reduced Model G + DSF + DSB	.026		.268		3	37	.808
Full Model G + DSF + DSB + Age	.181	.155	6.807	-.416	1	36	.013*

Note. RT = response time; G = gender; DSF = digit span forward; DSB = digit span backward.
*$p < .05$, **$p < .01$.

Next, the impact of gender and WM behavioral indices was considered in order to determine if these covariates accounted for the relationship between RT and age. Three hierarchical linear regression analyses were conducted: each covariate (gender, digit span forward, digit span backward) was included in the reduced model (to remove variance in RT associated with these variables), and age was added to the full model to determine if age added to the regression model produced a significant increase in the variance accounted for. Last, a hierarchical regression analysis with all covariates entered into the reduced model was conducted. The results of these analyses revealed that none of the variables attenuated the relationship between RT and age. Across all of the models, when age was added to the full model, the change in proportion of variance accounted for (ΔR^2) was significant, indicating that age was accounting for a significant and unique proportion of the variance. Furthermore, the variance accounted for by age (β_{age} and ΔR^2) remained relatively constant over the different analyses and, in fact, increased when DSB and when all of the covariates were included in the models. Thus, these variables were having a slight suppression effect on the relationship between RT and age, and controlling for their influences revealed that RT is a unique index of the development of WM with age.

RT quadratic effects. Hierarchical multiple regression was used to evaluate the quadratic relationship between RT and age and the potential mediating and suppressing effects of the covariates. Table 3 shows the results from the tests of nonlinear relationships between performance on the WM task and age. The results of a hierarchical regression analysis indicated that the addition of a quadratic term to the relationship

between RT and age did not account for significantly more of the variance (ΔR^2) between

RT and age than the linear relationship alone.

Table 3. *Hierarchical Multiple Regression Analyses Predicting the Quadratic Relationships between RT and Age with the Addition of Covariates*

	R^2	ΔR^2	ΔF	$\beta_{age}{}^2$	df1	df2	p
Model 1							
Reduced Model							
Age	.131		5.876		1	39	.020*
Full Model							
Age^2	.195	.064	3.014	-3.314	1	38	.091$^+$
Model 2							
Reduced Model							
Age + G	.140		3.098		2	38	.057$^+$
Full Model							
Age + G + Age^2	.212	.072	3.374	-3.550	1	37	.074$^+$
Model 3							
Reduced Model							
Age + DSF	.131		2.876		2	38	.069$^+$
Full Model							
Age + DSF + Age^2	.196	.065	2.975	-3.339	1	37	.093$^+$
Model 4							
Reduced Model							
Age + DSB	.179		4.155		2	38	.023*
Full Model							
Age + DSB + Age^2	.281	.101	5.203	-4.309	1	37	.028*
Model 5							
Reduced Model							
Age + DSF + DSB + G	.181		1.983		4	36	.118
Full Model							
Age + DSF + DSB + + G + Age^2	.282	.102	4.959	-4.324	1	35	.032*

Note. RT = response time; G = gender; DSF = digit span forward; DSB = digit span backward.
*p <.05, ^+p < .1.

Next, the impact of gender and WM behavioral indices was considered in order

to determine if these covariates were suppressing the quadratic relationship between RT

and age. Three hierarchical regression analyses were conducted: each covariate (gender, digit span forward, digit span backward) along with age was included in the reduced model (to remove variance in RT associated with these variables), and age squared was added to the full model to determine if age squared added to the regression model produced a significant increase in the variance accounted for. Last, a hierarchical regression analysis with all covariates entered into the reduced model was conducted. The models including gender and digit span forward indicated that there was a quadratic trend present in the relationships between age and RT when the variance of these covariates was accounted for statistically (gender: $R^2_{reduced} = .140$, $R^2_{full} = .212$, $\Delta R^2 = .072$; digit span forward: $R^2_{reduced} = .131$, $R^2_{full} = .196$, $\Delta R^2 = .065$). However, the model that included digit span backward as a covariate showed that the model including the quadratic relationship between RT and age accounted for significantly more of the variance than the reduced model ($R^2_{reduced} = .179$, $R^2_{full} = .281$, $\Delta R^2 = .10$), thus suggesting that the linear effect of digit span backward suppressed the quadratic relationship between RT and age. Last, a hierarchical regression model with all covariates entered into the reduced model was conducted. As would be expected given the suppression effect of digit span backward, the model including the quadratic relationship between RT and age accounted for significantly more of the variance than the reduced model ($R^2_{reduced} = .181$, $R^2_{full} = .282$, $\Delta R^2 = .032$). Thus, these variables were having a slight suppression effect on the quadratic relationship between RT and age, and controlling for their influences revealed that improvements in performance on WM tasks across adolescence follow a monotonic curve, with more rapid improvements in retrieval speed occurring as adolescence progresses (Figure 3).
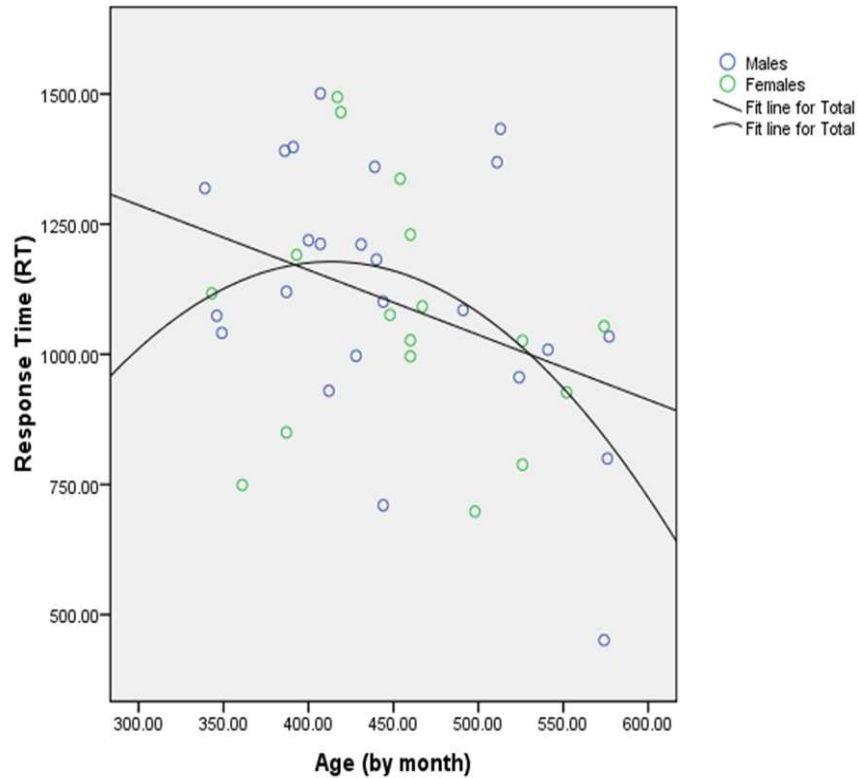
Figure 3. Graph of the relationship between RT and age ($R = .362$, $p = .020$). The addition of a quadratic term was significant when the linear effects of DSF, DSB, and G were controlled for ($\Delta R^2 = .102$, $p = .032$).

Digit span forward linear effects. Hierarchical multiple regression was used to explore the linear relationship between digit span forward and age and the potential mediating and suppressing effects of the covariates. Table 4 shows the results from the tests of linear relationships between WM capacity and age. The results of a linear regression analysis indicated that although digit span forward showed some improvement with age, the relationship was not significant ($r = .204$, $p = .202$).

Next, the impact of gender and WM behavioral indices was considered in order to determine if these covariates were suppressing the relationship between digit span

forward and age. Three hierarchical linear regression analyses were conducted: each

covariate (gender, RT, digit span backward) was included in the reduced model (to

remove variance in digit span forward associated with these variables), and age was

added to the full model to determine if age added to the regression model produced a

significant increase in the variance accounted for. Last, a hierarchical regression analysis

with all covariates entered into the reduced model was conducted. The results of these

analyses revealed that none of the variables suppressed the relationship between digit

span forward and age. Across all of the models, when age was added to the full model,

the change in proportion of variance accounted for (ΔR^2) was not significant. Thus, the

participants' basic WM capacity did not improve significantly as their age increased.

Table 4. *Hierarchical Multiple Regression Analyses Predicting the Linear Relationship*
between DSF and Age with the Addition of Covariates

	R^2	ΔR^2	ΔF	β_{age}	$df1$	$df2$	p
DSF = Age	.041		1.688	.204	1	39	.202
Hierarchical Regression							
Reduced Model: G	.006		.249		1	39	.620
Full Model: G + Age	.046	.040	1.589	.200	1	38	.215
Hierarchical Regression							
Reduced Model: RT	.003		.103		1	39	.750
Full Model: RT + Age	.042	.039	1.564	.213	1	38	.219
Hierarchical Regression							
Reduced Model: DSB	.064		3.574		1	39	.066
Full Model: DSB + Age	.102	.018	.747	.138	1	38	.393
Hierarchical Regression							
Reduced Model							
G + RT + DSB	.129		1.821		3	37	.160
Full Model							
G + RT + DSB + Age	.135	.006	.264	.091	1	36	.611

Note. RT = response time; G = gender; DSF = digit span forward; DSB = digit span
backward.

Digit span forward quadratic effects. Hierarchical multiple regression was used to evaluate the quadratic relationship between digit span forward and age and the potential mediating and suppressing effects of the covariates. Table 5 shows the results from the tests of nonlinear relationships between WM capacity and age. The results of a hierarchical regression analysis indicated that the addition of a quadratic term to the relationship between digit span forward and age did not account for significantly more of the variance (ΔR^2) between digit span forward and age than the linear relationship alone.

Table 5. *Hierarchical Multiple Regression Analyses Predicting the Quadratic Relationships between DSF and Age with the Addition of Covariates*

	R^2	ΔR^2	ΔF	β_{age}^2	$df1$	$df2$	p
Model 1							
Reduced Model							
Age	.041		1.688		1	39	.202
Full Model							
Age^2	.044	.003	.103	.669	1	38	.750
Model 2							
Reduced Model							
Age + G	.046		.921		2	38	.407
Full Model							
Age + G + Age^2	.050	.004	.144	.806	1	37	.706
Model 3							
Reduced Model							
Age + RT	.042		.834		2	38	.442
Full Model							
Age + RT + Age^2	.046	.004	.139	.814	1	37	.712
Model 4							
Reduced Model							
Age + DSB	.102		2.149		2	38	.131
Full Model							
Age + DSB + Age^2	.102	.000	.005	-.146	1	37	.945
Model 5							
Reduced Model							
Age + DSB + RT + G	.135		1.405		4	36	.252
Full Model							
Age + DSB + RT + + G + Age^2	.135	.000	.010	-.231	1	35	.920

Note. RT = response time; G = gender; DSF = digit span forward; DSB = digit span backward.

Next, the impact of gender and WM behavioral indices was considered in order to determine if these covariates suppressed the quadratic relationship between digit span forward and age. Three hierarchical regression analyses were conducted: each covariate (gender, RT, digit span backward) along with age was included in the reduced model (to remove variance in digit span forward associated with these variables), and age squared was added to the full model to determine if age squared added to the regression model produced a significant increase in the variance accounted for. Last, a hierarchical regression analysis with all covariates entered into the reduced model was conducted. The results of these analyses revealed that none of the variables suppressed the relationship between digit span forward and age squared. Across all of the models, when age squared was added to the full model, the change in proportion of variance accounted for (ΔR^2) was not significant. Thus, age was not found to be a significant linear or nonlinear predictor of basic WM capacity (Figure 4).
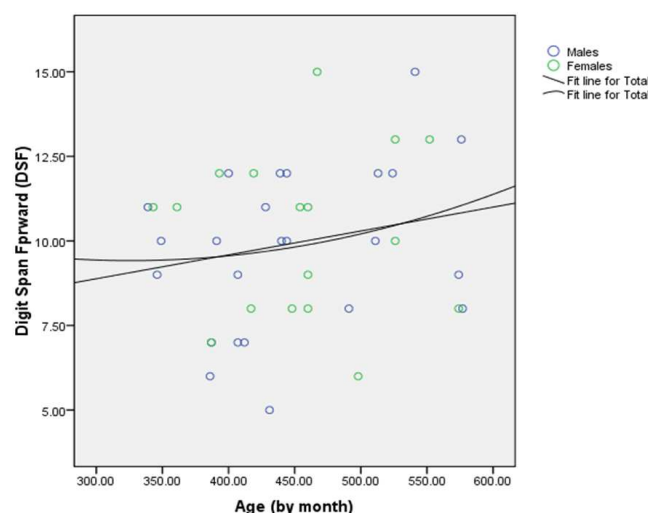

Figure 4. Graph of the relationship between DSF and age (R = .204, p = .202). The addition of a quadratic term was not significant (ΔR2 = .003, p = .750).

Digit span backward linear effects. Hierarchical multiple regression was used to explore the linear relationship between digit span backward and age and the potential mediating and suppressing effects of the covariates. Table 6 shows the results from the tests of linear relationships between WM manipulation and age. The results of a linear regression analysis indicated that although digit span backward showed some improvement with age, the relationship was not significant ($r = .260$, $p = .10$).

Table 6. *Hierarchical Multiple Regression Analyses Predicting the Linear Relationship between DSB and Age with the Addition of Covariates*

	R^2	ΔR^2	ΔF	β_{age}	$df1$	$df2$	p
DSB = Age	.068		2.831	.260	1	39	.100
Hierarchical Regression							
Reduced Model: RT	.014		.555		1	39	.461
Full Model: RT + Age	.120	.106	4.561	.349	1	38	.039*
Hierarchical Regression							
Reduced Model: DSF	.084		3.574		1	39	.066
Full Model: DSF + Age	.126	.042	1.835	.210	1	38	.183
Hierarchical Regression							
Reduced Model: G	.133		5.991		1	39	.019*
Full Model: G + Age	.211	.078	3.775	.280	1	38	.059
Hierarchical Regression							
Reduced Model							
G + RT+ DSF	.244		3.974		1	37	.015*
Full Model							
G + RT+ DSF + Age	.317	.073	3.859	.296	1	36	.057[+]

Note. RT = response time; G = gender; DSF = digit span forward; DSB = digit span backward.
*$p < .05$, [+]$p < .1$

Next, the impact of gender and WM behavioral indices was considered in order to determine if these covariates suppressed the relationship between digit span backward and age. Three hierarchical linear regression analyses were conducted: each covariate (gender, digit span forward, RT) was included in the reduced model (to remove variance

in digit span backward associated with these variables), and age was added to the full

model to determine if age added to the regression model produced a significant increase

in the variance accounted for. The results of these analyses revealed that the linear

effects of RT suppressed the relationship between digit span backward and age ($R^2_{reduced} =$

.014, $R^2_{full} = .120$, $\Delta R^2 = .106$). Last, a hierarchical regression analysis with all covariates

entered into the reduced model was conducted. Although the addition of age accounted

for a marginally significant portion of the variance ($R^2_{reduced} = .244$, $R^2_{full} = .317$, $\Delta R^2 =$

.073), the result of the analysis revealed that the linear effects of the covariates accounted

for significantly more of the variance in digit span backward than age ($R^2 = .244$, $p =$

.015); the covariates predicted linear changes in age more robustly than digit span

backward. Thus, linear changes in age do not significantly predict changes in WM

manipulation, unless the linear effects of RT are controlled for.

Digit span backward quadratic effects. Hierarchical multiple regression was

used to evaluate the quadratic relationship between digit span backward and age and the

potential mediating and suppressing effects of the covariates. Table 7 shows the results

from the tests of nonlinear relationships between WM manipulation and age. The results

of a hierarchical regression analysis indicated that the addition of a quadratic term to the

relationship between digit span backward and age did not account for significantly more

of the variance (ΔR^2) between digit span backward and age than the linear relationship

alone.

Next, the impact of gender and WM behavioral indices was considered in order

to determine if these covariates suppressed the quadratic relationship between digit span

backward and age. Three hierarchical regression analyses were conducted: each

Table 7. *Hierarchical Multiple Regression Analyses Predicting the Quadratic Relationships between DSB and Age with the Addition of Covariates*

	R^2	ΔR^2	ΔF	$\beta_{age}{}^2$	df1	df2	P
Model 1							
Reduced Model							
Age	.068		2.831		1	39	.100
Full Model							
Age^2	.126	.059	2.548	3.174	1	38	.119
Model 2							
Reduced Model							
Age + G	.211		5.096		1	39	.011
Full Model							
Age + G + Age^2	.249	.037	1.825	2.548	1	38	.185
Model 3							
Reduced Model							
Age + DSF	.126		2.743		1	39	.077$^+$
Full Model							
Age + DSF + Age^2	.179	.053	2.379	3.017	1	38	.131
Model 4							
Reduced Model							
Age + RT	.120		2.584		1	39	.089$^+$
Full Model							
Age + RT + Age^2	.219	.100	4.724	4.301	1	38	.036*
Model 5							
Reduced Model							
Age + DSF + RT + G	.317		4.175		4	36	.007*
Full Model							
Age + DSF + RT + G + Age^2	.374	.057	3.207	3.320	1	35	.082$^+$

Note. RT = response time; G = gender; DSF = digit span forward; DSB = digit span backward.
*$p < .05$, $^+p < .1$.

covariate (gender, digit span forward, RT) along with age was included in the reduced model (to remove variance in digit span backward associated with these variables), and age squared was added to the full model to determine if age squared added to the regression model produced a significant increase in the variance accounted for. Only the

model that included RT as a covariate showed that the model including the quadratic relationship between digit span backward and age accounted for significantly more of the variance than the reduced model ($R^2_{reduced}$ = .120, R^2_{full} = .219, ΔR^2 = .1), thus suggesting that the linear effect of RT suppressed the quadratic relationship between digit span backward and age. Last, a hierarchical regression analysis with all covariates entered into the reduced model was conducted. Despite the suppression of the quadratic relationship between digit span backward and age by RT, the addition of age squared to the full model revealed a trend ($R^2_{reduced}$ = .317, R^2_{full} = .374, ΔR^2 = .057). Thus, after controlling for the linear effects of RT, there was a nonlinear component to the relationships between WM manipulation and age (Figure 5).
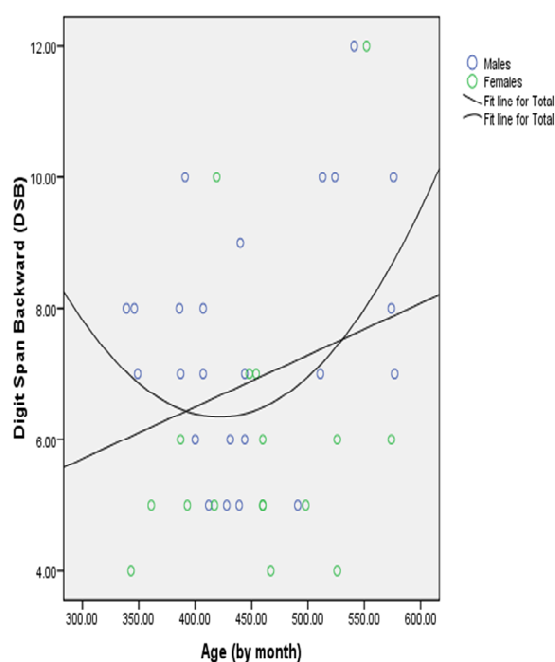

Figure 5. Graph of the relationship between DSB and age (R = .260, p = .100). The addition of a quadratic term was significant when the linear effects of RT were controlled for ($\Delta R2$ = .120, p = .039).

fMRI Results

      To test the hypothesis that functional activation in brain areas implicated in WM, such as the PFC, have a quadratic relationship with age, whole brain voxel-wise hierarchical regression was used (see Appendix B, Figure 10).   Using hierarchical regression allowed for both the linear effects (with the reduced model) as well as any quadratic effects (with the full model) in brain regions supporting WM to be explored. To control for Type I error due to multiple comparisons, the results were cluster-thresholded based on Monte-Carlo simulations (AlphaSim software; Ward, 2000) so that surviving clusters were significant with a family-wise $\alpha = .05$, for that analysis, and a voxel-level $\alpha = .005$.   Clusters of ≥ 146 voxels were significant with a family-wise $\alpha = .05$, based on the simulations (1000 iterations for a dataset having 191,679 voxels [2 mm isovoxel], smoothness = 8 mm FWHM, cluster = pairs of voxels having a connectivity radius < 3.47 mm, thus having connecting faces, edges, or corners at the resampled voxel size).

      Linear effects. Hierarchical multiple regression was used to explore the linear relationship between percent signal-change and age and the potential mediating and suppressing effects of the covariates. The results of a linear regression analysis indicated that no clusters survived the thresholding criteria.

      Next, to reduce the variance, the impact of gender, handedness, and WM behavioral indices (RT, digit span forward, digit span backward) was considered to determine if these covariates accounted for (mediated) or detracted from (suppressed) the linear relationship between percent signal-change and age. Hierarchical regression revealed three clusters where percent BOLD signal-change increased as age increased

when the linear effects of the covariates were controlled for statistically: right medial

BA6 (peak t = 5.528, B_{age} = .005, cluster size = 292), right cerebellum (peak t = 4.465,

B_{age} = .002, cluster size = 282), and left BA34 (peak t = 4.347, B_{age} = .002, cluster size =

164); Table 8; Figure 6). Given that right medial BA6 has been implicated in WM tasks

(Owen et al., 2005; Rypma, 2006; Schneider-Garces et al., 2009), the impact of each

covariate on the relationship between percent signal-change and age was systematically

explored in this region.

Table 8. *Descriptive Statistics for Clusters showing a Significant Linear Relationship between Percent Signal-Change and Age with Covariates.*

Anatomical Structure	Coordinates (RAI mm) of voxels with highest t-value within cluster			B_{age}	Cluster size
	x	y	z		
Right medial BA6	-3	-1	+58	.005	292
Right Cerebellum	-41	+59	-34	.002	282
Left BA34	+13	-5	-12	.002	164

Note. Clusters are significant at $p < .05$.

Right Cerebellum   Left BA34   Right BA6
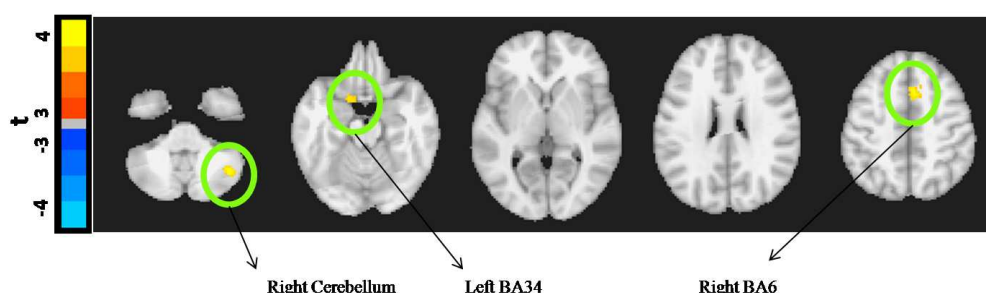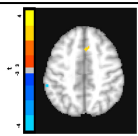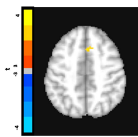
Figure 6. Brain regions showing a linear relationship between percent signal-change and age with covariates controlled. Red to yellow voxels illustrate positive correlations, where age increases were associated with higher signal-change. Data were cluster thresholded with cluster α = .05 and voxel α = .005.

Next, the unique impact of potential sample characteristics and WM behavioral indices was considered in order to determine the individual suppression effect of each covariate on the independent relationship between percen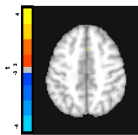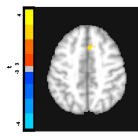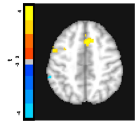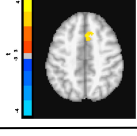t signal-change and age. Table 9 shows the increases in right medial BA6 activation that occurred with age when the linear effects of covariates suppressing this relationship were removed. First, a linear

Table 9. *Hierarchical Multiple Regression Analyses Predicting the Linear Relationship between Percent Signal-Change and Age with the Addition of Covariates*

	peak t	peak B_{age}	R^2	Cluster size	Right Medial BA6
BOLD = Age	2.977	.003	.226	17	
Sample Covariates BOLD = G + H + Age	2.983	.004	.142	25	
RT as a Covariate BOLD = G + H + RT + Age	2.993	.004	.143	22	
DSB as a Covariate BOLD = G + H + DSB + Age	4.721	.005	.209	67	
DSF as a Covariate BOLD = G + H + DSF + Age	4.438	.003	.145	156*	
All Covariates BOLD = G + H + RT + DSB + DSF +Age	5.528	.005	.429	292*	

Note. Equations listed are full models. Coordinates (RAI mm) of clusters: x = -3, y = -1, z = +41. G = gender; H = handedness; RT = response time; DSF = digit span forward; DSB = digit span backward.
*Clusters greater than 146 are significant at $p < .05$.

regression analysis between percent signal-change and age showed no significant regions

of activation. Next, four hierarchical linear regression analyses were conducted: sample

differences (gender/handedness) and WM behavioral indices (RT, digit span forward, and

digit span backward) were included in the reduced model as covariates (to remove error

variance associated with these variables), and age was included in the full model to

determine if age added to the regression model produced a significant increase in the

variance accounted for. The regression analyses controlling for gender/handedness, RT,

and digit span backward were not significant. However, when digit span backward was

added to model, the hierarchical regression analysis revealed a significant linear

relationship between percent signal-change and age (peak $t = 4.438$, $B_{age} = .003$, cluster

size = 156), indicating that the linear relationship between digit span forward and percent

signal-change had suppressed the linear relationship between percent signal-change and

age. Last, all covariates (gender/handedness, RT, digit span forward, and digit span

backward) were added to the model, and the removal of the linear effects of these

variables revealed the significant relationship between percent-signal change and age

(peak $t = 5.528$, $B_{age} = .005$, cluster size = 292; Figure 7).

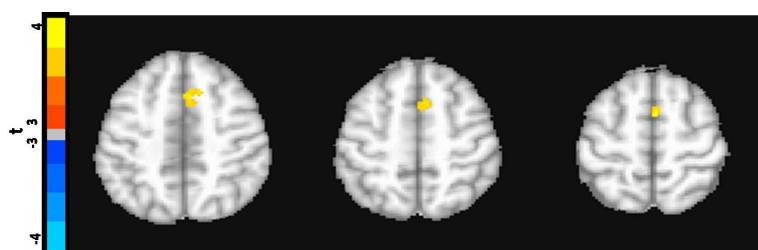
Figure 7. Linear relationship between medial right BA6 and percent signal-change and age. The
linear effects of G, H, RT, DSF, and DSB were controlled for (peak t = 5.528, B = .005, cluster
size = 292). Red to yellow voxels illustrate positive correlations, where age increases were
associated with higher signal-change. Data were cluster thresholded with cluster α = .05 and
voxel α = .005.

Thus, digit span forward's relationship with both percent signal-change and age served as the primary suppressing factor of the relationship between percent-signal change and age. However, the cluster size was largest when all of the covariates were included (cluster size = 292), suggesting that each covariate contributed a unique suppressing effect.

To illustrate the suppression effect of the covariates on the linear relationship between percent signal-change and age in right medial BA6, percent signal-change in the peak voxel in this region was obtained for each participant. A scatter-plot of percent signal-change and age was made. Next, age was regressed on the covariates (gender/handedness, RT, digit span forward, digit span backward) and percent signal-change was regressed on the covariates (gender/handedness, RT, digit span forward, digit span backward) to remove the effects of these variables. The resulting residuals were saved, and a scatter-plot of percent signal-change and age without the effects of the covariates was made. The resulting scatter-plot illustrates the independent relationship between age and percent signal-change in right medial BA6 after removing the effects of the covariates (Figure 8).

Quadratic effects. Hierarchical multiple regression was used to determine the additional contribution of age squared on percent signal-change. A full model that included age squared as a quadratic predictor variable was added to the reduced model in order to determine if age squared accounted for significantly more of the variance between percent signal-change and age than the linear model alone. However, no clusters showing a quadratic relationship between percent signal-change and age survived the thresholding criteria. Next, the unique impact of potential sample characteristics and WM behavioral indices was considered in order to determine if these covariates
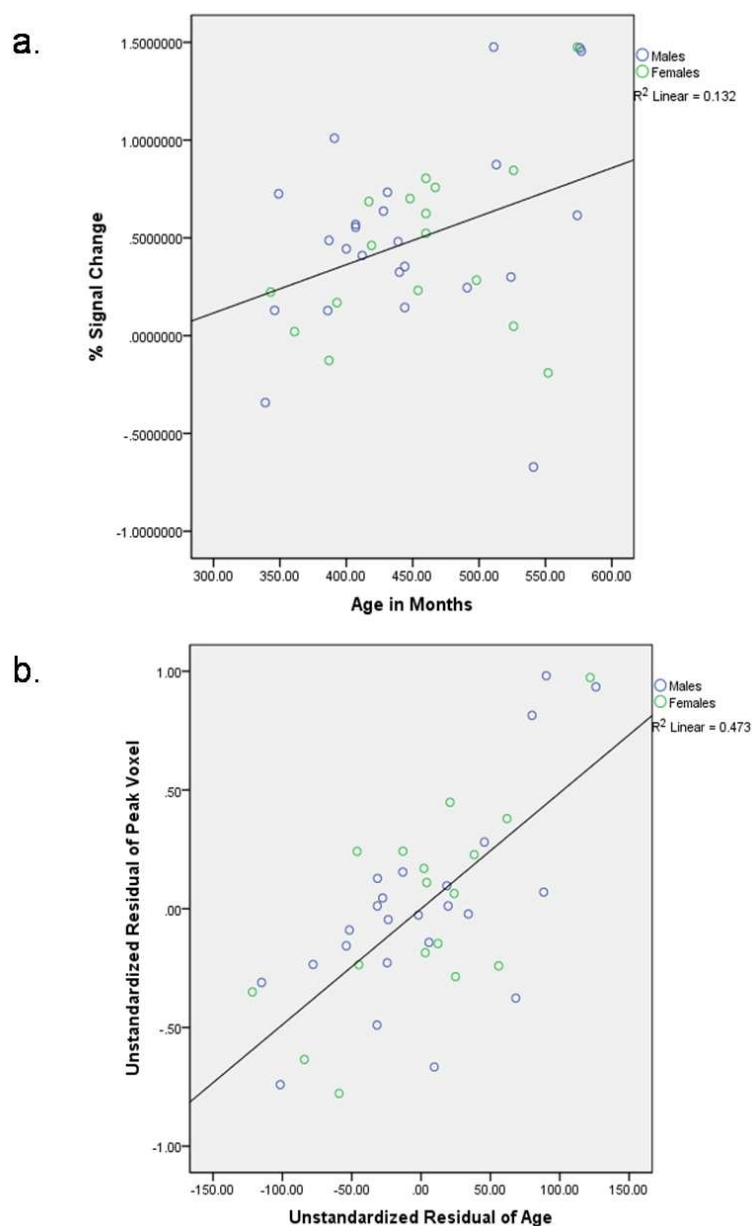
Figure 8. Illustration of the effect of the covariates on the relationship between percent signal-change and age. Percent signal-change was measured in the peak voxel in right medial BA6, and age was expressed in months. The top scatter-plot (a) shows the relationship between percent signal-change and age. The bottom scatter-plot (b) shows the relationship between percent signal-change and age after removing the shared variance between gender, handedness, RT, digit span forward, and digit span backward.

suppressed a potential quadratic relationship between percent-signal change and age. Hierarchical regression did not reveal any significant clusters showing a relationship between percent-signal change and age squared, indicating that the linear effects of the covariates were not suppressing a potential nonlinear relationship between percent signal-change and age. The results of the hierarchical regression analysis revealed no evidence for a quadratic relationship between percent BOLD signal-change, indicating that activation changes in brain regions supporting WM do not follow a quadratic trend with age across adolescence.

Discussion

This study sought to explore the relationship between functional activation in brain regions supporting WM and age throughout adolescence. After the effects of different measures of WM were controlled for statistically, the results indicated linear age-related functional activation patterns in right medial BA6. This finding is consistent with existing research that suggests BA6 is a critical brain region underlying WM ability in both children and adults (Klingberg et al, 2002; Kwon et al., 2002; Owen et al., 2005; Rypma, 2006; Schneider-Garces et al., 2009), and this region is considered part of the dorsolateral prefrontal cortex (DLPFC)/anterior pre-motor region recruited for the completion of complex WM tasks requiring an executive function component, such as the manipulation of information (Kirschen et al., 2010; Rypma & D'Esposito, 1999). Furthermore, although BA6 is part of the pre-supplementary motor area, this region is consistently activated in a variety of executive function tasks (Crosson et al., 1999) and has been shown to serve a possible "executive" role in preparedness for response selection (Petit, Courtney, Ungerleider, & Haxby, 1998).

The analyses also revealed linear increases in activation with age in the right cerebellum and left BA34. Although these regions are not typically considered integral to WM processes, both regions have recently gained attention for their impact on memory-related networks. The superior cerebellum has been implicated in cerebro-cerebellar networks activated during verbal working memory tasks (Chen & Desmond, 2005; Crottaz-Herbette, Anagnoson, & Menon, 2004; Kirschen et al., 2010; Stoodley & Schmahmann, 2009). BA34 is considered part of the parahippocampal gyrus and has been implicated in intentional and unintentional forgetting neuroimaging tasks (Wylie, Fox, & Taylor, 2007).

Relationship between WM Component Processes and Age

The shared and unique linear relationships between individual WM measures and age were explored using hierarchical regression analyses, and the results of the behavioral analyses were consistent with past research that has shown monotonic improvements on cognitive measures of WM across adolescence (Fry & Hail, 1996; Gathercole et al., 2004; Luciana et al., 2005). RT improved significantly with age, and digit span backward improved significantly with age when the linear effects of RT and digit span forward were removed. The lack of mediation effects between the WM indices indicates that both search and retrieval speed (as measured by RT) and WM manipulation (as measured by digit span backward) each share a unique relationship with age. Furthermore, the improvement in search and retrieval speed and WM manipulation that occurred with age followed a curved monotonic trajectory (having both linear and quadratic components). A quadratic relationship between WM search and retrieval speed and age emerged only when the linear effects of all covariates were statistically

controlled for, and a quadratic relationship between WM manipulation and age emerged when the linear effects of WM performance and age were controlled for statistically. The curved monotonic relationships between both WM performance and WM manipulation with age suggests that overall improvements in these WM component processes occur more rapidly as adolescence progresses. However, basic WM capacity, as measured by digit span forward, did not improve significantly with age, either along a linear or nonlinear trajectory. Basic WM abilities have been shown to be developed by age nine (Luciana et al., 2005), which could account for the failure to find developmental changes in WM capacity.

The inclusion of behavioral measures of WM allowed for the unique developmental trends of individual WM components to be explored. WM consists of both capacity/storage and manipulation processes (Baddeley, 1981; Baddeley & Hitch, 1974). The results showed that WM capacity, as measured by digit span forward, was developed by age 11, as changes in this process were not observed across adolescence. However, WM manipulation processes that more heavily involve the recruitment of executive resources, as measured by digit span backward, improved throughout adolescence, with more rapid changes occurring in late adolescence. The separate developmental trajectories of these WM behavioral indices supports the existence of unique underlying component processes that contribute to overall WM ability (Miyake, Friedman, Rettinger, Shah, & Hegarty, 2001; Schneider-Garces et al., 2009). Finally, response time often has been used to index WM search and retrieval speed (Rypma & D'Esposito, 1999; Sternberg, 1966). Consistent with previous research, search and retrieval speed was found to increase with development (Cowan, Saults, Nugent, &

Elliot, 1999). However, this study also found a nonlinear component to the decrease in RT with age, suggesting that greater improvements in search and retrieval speed occur later in adolescence.

Relationship between Right Medial BA6 Activation and Age

Just as mediation and suppression effects between each WM behavioral index were evaluated, the effects of WM capacity (digit span forward), WM search and retrieval speed (RT), and WM goal-oriented manipulation (digit span backward) on the relationship between functional activation during the WM task and age were explored. The results showed that functional activation increased in right medial BA6 as age increased during a supra-capacity load WM task. However, this linear trend was apparent only after statistically controlling for the effects of WM component processes on functional activation. The combination of the unique relationships between these covariates and functional activation in right medial BA6 obscured the relationship between age and right medial BA6, although WM capacity seemed to have the strongest suppressing influence.

The linear relationship between percent BOLD signal-change and age was not explained by individual improvements in WM component processes (i.e., were not statistically mediated by the WM measures), suggesting that age increases contribute independently to heavier recruitment of this region during WM tasks. Despite the significant relationship between improvements on behavioral measures of WM (such as RT and digit span backward) and age, the behavioral improvements do not account for the increase in right medial BA6 activation that occurs with age.

These results further support the multi-component model of WM (Baddeley & Logie, 1999; Repovs & Baddeley, 2006). The digit span forward and digit span backward tasks captured two central features of WM, both capacity/storage and manipulation processes (Baddeley, 1981; Baddeley & Hitch, 1974).   Additionally, these two components impacted the relationship between percent signal-change and age in different ways. The impact of manipulation processes did not affect the relationship between activation and age in right medial BA6, suggesting that manipulation processes and age are not related in right medial BA6. However, variability in storage capacity processes suppressed the relationship between activation and age in right medial BA6 with both basic WM storage capacity and age individually accounting for increases in right medial BA6 activation.

Global-Capacity Framework versus Neurocognitive-Change Framework

Another objective of the present study was to explore how changes in brain activation across adolescence fit into present models of brain development. The global-capacity framework holds that general changes in transmission times throughout the lifespan control increases and decreases in overall processing capacity, including the changes in WM storage and manipulation capacity that occur (Bashore & Smulders, 1995; Fry & Hail, 1996; Salthouse, 1996). The linear relationships between BOLD signal-change and age were consistent with this model. However, linear relationships were restricted to three brain regions (i.e., right medial BA6, right cerebellum, and left BA34), and not more widespread as one might think with "global" capacity changes. The analyses failed to show that the age-related increases in percent signal-change in right medial BA6 were accounted for by age-related increases in performance, WM storage, or

WM manipulation. It is possible that the effects of other, unmeasured, WM processes obscured the relationship between amplitude increases and age in other brain regions. It is possible, for example, that BA6 mediates changes that occur in attention. Rather than simply being active during the motor response phase of WM response selection, BA6 has been found to be active throughout the entire WM task, suggesting that BA6 plays a role in attentional preparedness (Haxby, Petit, Ungerledier, & Courtney, 2000; Petit et al., 1998). It is also possible that the age-related changes are accounted for by a fundamental process undergoing change with development. Kail and Salthouse (1994), for example, have argued that developmental changes in processing speed account for developmental changes in a host of cognitive functions, including WM. Thus, an independent measure of global processing speed might account for age-related changes in these regions and more broadly throughout the brain.

Despite the support generated for the global-capacity framework, this study's findings do not preclude the possibility that independent neurocognitive changes occur throughout development as well. The neurocognitive-change framework suggests that individual brain structures and functions are responsible for specific cognitive improvements/declines (Pennington, 1994; Span et al.,1994). Recent fMRI research that explored differences in brain regions recruited during a visuo-spatial WM task between children (aged 10-13), adolescents (aged 14-17), and adults (>18) found support for the use of different networks that occurs with development. The results indicated that the adolescent group activated DLPFC and premotor regions significantly more than the child group, indicating a shift to more specialized and efficient WM networks similar to those observed in the adult group (Scherf, Sweeney, & Luna, 2006); furthermore,

neuroimaging research exploring WM has identified networks differentially activated dependent on WM load and WM component processes recruited (Barby, Koenigs, & Gafman, 2010; Motes & Rypma, 2010; Rypma, 2006; Smith & Jonides, 1999). Although the present study found linear, rather than nonlinear, relationships between brain activation and age, it is possible that global processing speed increases account for the increased specialization and efficacy of identified brain networks underlying WM tasks (Fry & Hale, 1996; Motes et al., 2010).

Limitations

One of the limitations of this study is sample size. While relatively large for an fMRI study with adolescents, a larger sample would minimize within-group error. Furthermore, the age range of this study (11 to 18) may not have been wide enough to capture the full maturational trajectory of PFC development and thus obscured potential nonlinear relationships between functional activation and age that parallel gray matter volume loss. Individual participant characteristics such as intelligence, gender, and pubertal status are potential confounds. Future studies exploring percent signal-change activation and age across adolescence would benefit from including a measure of puberty status (e.g., onset of menstruation for females and hair growth for males, hormone samples) and a broad measure of IQ. Furthermore, a longitudinal, rather than a cross-sectional, study would also minimize individual differences.

Future studies could also include more measures. A longer version of the current WM task, such as using more blocks (rather than four), would assist in countering in the participants' high accuracy achievement by making the task more challenging; furthermore, lengthening the task would improve the reliability of the signal-change

estimate. Additionally, the use of a resting state condition would be beneficial in order to further differentiate brain activation between the 6-letter condition and baseline. Additional behavioral measures of WM could be added to further evaluate the impact of WM component processes on functional activation changes with age. To measure WM capacity, the Operation Span (OPSAN; Turner & Engle, 1989) and Reading Span (RSPAN, Daneman & Carpenter, 1983) could be used to differentiate between verbal and visuo-spatial components of WM. To measure WM manipulation, the use of n-back tasks could be used (Owen et al., 2005). Furthermore, the addition of measures of processing speed, such as Symbol Search and Coding subtests from the WISC-IV/WAIS-IV (Wechsler 2004; Wechsler 2008) and the DSVT (adapted from the Digit–Symbol Coding Task from the WAIS-III for use in fMRI scanners; Rypma et al., 2006) could be included to better ascertain whether linear improvements in amplitude are due to global increases in overall processing capacity.

Future Directions

Although a linear relationship between percent signal-change and age across adolescence in right medial BA6 was found, the underlying mechanisms responsible for this unique relationship warrant further exploration. An extension of this study could include measures aimed at achieving convergent validity for measuring the WM construct. While psychometrically sound behavioral measures of WM exist, it remains unclear if these measures adequately access brain regions believed to underlie overall WM ability. Including additional behavioral measures, and developing additional WM tasks to be completed during fMRI data acquisition, would assist in this endeavor.

Furthermore, convergent validity studies would further the understanding of the impact that component WM processes have on overall WM ability.

To further evaluate the current models of brain development, white matter tracking through the use of diffusion tensor imaging (DTI; Giorgio et al., 2010; Giedd, 2004) could be included along with fMRI. Global transmission speed increases have been linked to white matter tracts and could perhaps underlie WM improvements (Filley, 2010; Turken et al., 2008). Additionally, the synthesis of white matter data and functional activation data would further the understanding of complex brain-behavior relationships.

Continued knowledge of the developmental trajectory of brain regions supporting WM in healthy children and adolescents will inform educational strategies and curriculums by targeting WM development throughout critical educational phases. Additionally, given that WM difficulties have been observed in a variety of childhood and adolescent disorders (Attention-Deficit/Hyperactivity Disorder: Sheridan, Hinshaw, & D'Esposito, 2007; developmental disorders: Alloway, Rajendran, & Archibald, 2009; bipolar disorder: Bearden et al., 2007; depressive disorders: Franklin et al., 2010), the ability to identify WM deficits at a neural level could impact future identification and treatment of these disorders.

APPENDIX A
Detailed Literature Review

The purpose of the present study is to explore the developmental trajectory of PFC activity supporting WM using functional magnetic fMRI. WM, the overall process of temporarily holding and reorganizing information in the mind, is an integral aspect of cognitive development. WM has been found to contribute to a range of higher order abilities, such as reasoning (Carpenter et al., 1990) and comprehension (Cain et al., 2004), and WM has been implicated as an important component of fluid intelligence (Engle, Tuholski, Laughlin, & Conway, 1999; Wechsler, 2008). Additionally, WM deficits have been associated with several childhood and adolescent disorders (Alloway et al., 2009; Bearden et al., 2007; Sheridan et al., 2007). Thus, given the central role of WM in cognitive development, understanding the brain mechanisms that mediate WM will advance theories of WM.

Cross-sectional developmental studies have shown WM, based on cognitive testing, to follow monotonic developmental trajectories through childhood into adolescence (Best et al.,2009; Gathercole et al., 2004; Kail & Salthouse, 1994; Luciana et al., 2005; Span et al., 2004; Swanson, 1999). These WM improvements have been attributed to increases in global capacity that occur with age. The underlying neural mechanisms supporting this proposed increase in capacity, however, are not fully understood (Gathercole et al., 2004; Luciana et al., 2005; Swanson, 1999).

Despite these cognitive findings, brain structural changes in regions known to support WM, such as the PFC, follow a different developmental trajectory. Research on

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structural brain changes has shown that several regions follow nonlinear developmental trajectories from birth through late adulthood. For example, the gray matter volume of the PFC follows a quadratic developmental trajectory; the gray matter volume of the PFC increases from birth, peaks around 12 years of age, and then begins to decrease. This volume loss has been hypothesized to be a function of neural pruning as neural circuits are refined (Giedd et al., 1999; Giorgio et al., 2010; Gogtay et al., 2004). The nonlinear development of brain regions suggests that cognitive improvements might result from more "qualitative" changes within cortical structures (Gogtay et al., 2004; Shaw et al., 2008; Span et al., 2004; Stuss et al.,2005), rather than from more global "quantitative" changes supporting an overall greater processing capacity (Gathercole et al., 2004; Kail & Salthouse, 1994).

The discrepancy in the developmental trajectories between measured cognitive changes and brain structure changes mediating WM raises questions about the functional role of the PFC in supporting WM. The cognitive developmental data suggest that linear increases in WM ability might be explained by global capacity increases; however, the anatomical data suggest that improvements in WM might be due to qualitative functional changes in regions, such as the PFC, that support WM ability. Indeed, this discrepancy between the cognitive and anatomical changes suggests that the PFC functional activity supporting WM might change monotonically with age, consistent with the cognitive data, or might change nonlinearly with age, consistent with the anatomical data.

A better understanding of the developmental trajectory of brain regions supporting WM in healthy children and adolescents will advance theories about WM development that will inform educational strategies and curriculums that can target WM

development throughout critical educational phases. Additionally, the advancement of theories about WM development could have broad implications for the treatment of WM difficulties in children and adolescents. WM difficulties have been observed in a variety of childhood and adolescent disorders, such as attention-deficit/hyperactivity disorder (Sheridan et al., 2007), developmental disorders (Alloway et al., 2009) bipolar disorder (Bearden et al., 2007), and depressive disorders (Franklin et al., 2010). Thus, given the central role of WM to higher order cognition and its critical role in cognitive development, understanding the brain mechanisms that mediate WM can aid in the testing and development of models of WM and higher-order cognition. The goal of the present study is to analyze fMRI data from preadolescents and adolescents collected during a WM task to examine the developmental trajectory of PFC functional activity supporting WM.

WORKING MEMORY (WM)

Working memory (WM) is a core cognitive construct that describes the processes of temporarily maintaining, manipulating, and reorganizing information in the mind (Baddeley, 1981). WM is a component of executive function (EF), which is a broad construct describing the cognitive processes responsible for goal-oriented mental control, such as WM, attention, inhibition, and set-shifting (Best et al., 2009). Correlations between WM and measures of intelligence illustrate its central role in higher-order cognitive processes (Engle et al., 1999). Indeed, without this basic ability to maintain and manipulate information, complex processes such as reasoning, comprehension, and decision-making would be difficult (Carpenter et al., 1990; Owen, McMillan, Laird, & Bullmore, 2005).

WM is composed of multiple component processes (Miyake & Shah, 1999). One multi-component model of WM includes a central executive (responsible for the encoding, manipulation, and retrieval processes), the phonological loop (responsible for the maintenance of auditory information), the visuospatial sketchpad (responsible for the maintenance of visual and spatial information), and the episodic buffer (responsible for the integration of data into meaningful pieces; Baddeley & Logie, 1999; Repovs & Baddeley, 2006). Thus, WM encompasses both storage and manipulation processes (Baddeley, 1981; Baddeley & Hitch, 1974). WM storage capacity has been shown to be limited (Brenner, 1940; Cowan, 2001; Luck & Vogel, 1997). Cowan (2001), for example, has argued for the capacity limits of 4 +/-1 items regardless of the format (e.g., verbal or visual) of the stimuli being remembered. When the to-be-remembered information exceeds these capacity limitations, however, WM executive processes can be recruited to reorganize or chunk the information to fit within capacity limits (Cowan 2001; Miller, 1955). In addition to the reorganization of information into more manageable chunks, additional executive processes can also be recruited for more complex tasks, such as when the task requires the manipulation of computations or mental imagery (Kozhevnikov et al., 2007; Seyler et al., 2003).

WM as a Core Cognitive Construct

The ability to manipulate information in WM is integral to higher order cognitive processes, as has been demonstrated by correlations between measures of WM and intelligence (Engle et al., 1999). WM (as a latent variable derived from an 11 measure battery, $N = 133$), for example, has been shown to be a moderate predictor ($r = .49$) of fluid intelligence (derived from the Culture Free Intelligence Test [CFIT; Cattell, 1949]

& the Raven's Standard Progressive Matrices Test [Raven's Matrices; Raven, Raven, & Court, 2003]); whereas simple storage has been shown to correlate weakly with fluid intelligence ($r = .12$). Additionally, WM is measured as a component of the WAIS-IV (Wechsler, 2008). Factor analysis has shown that some subtests (such as Digit Span and Arithmetic) consistently load onto a single factor that is believed to measure WM (Wechsler, 2008). This factor captures the storage capacity (Digit Span Forward), manipulation (Digit Span Backward), and integration (Arithmetic) components of WM.

The integral role that WM plays in overall intellectual abilities has been complemented by research showing the essential involvement of WM in reasoning (Carpenter et al., 1990; Goel & Grafman, 1995), problem-solving (Prabhakaran et al., 2000), and comprehension (Cain et al., 2004). WM ability (as a latent variable derived from performance on the Tower of Hanoi puzzle [Hinz, 1989], $N = 45$), for example, has been shown to discriminate high performers from fair performers on the Raven's Matrices (Carpenter et al., 1990), where Raven's Matrices (Raven et al., 2003) served as a measure of nonverbal reasoning ability due to the complexity, nonverbal format, and requirement to manipulate novel information (Marshalek, Lohman, & Snow, 1983; Snow, Kyllonen, & Marshalek, 1984). In computer models derived from the participants' performance, the abilities for goal-maintenance and the capacity to remember items for rule formulation were disabled, and the differences in performance on the Raven's Matrices were eliminated. Thus, WM appeared to contribute to higher-level cognition both through global processes, such as goal-maintenance, and through local processes, such as the storage and manipulation of stimuli necessary for problem-solving.

COGNITIVE DEVELOPMENT

The integral role of WM in both intelligence and higher-order cognitive processes highlights the importance of WM in normal development. Measures of cognitive performance have revealed that WM improves throughout childhood, adolescence, and into young adulthood, when many cognitive abilities seem to peak (Gathercole et al., 2004) and that cognitive abilities, including WM, steadily decline into late adulthood (Kail & Salthouse, 1994; Park et al., 2002). Two theories have been proposed to explain these changes in cognitive performance throughout childhood, adolescence, and late adulthood: 1) the global-capacity framework, which suggests that a single global factor, such as increased processing speed, results in an overall greater processing capacity for cognitive abilities (Bashore & Smulders, 1995) and 2) the neurocognitive-change framework, which suggests that individual brain structures and functions are responsible for specific cognitive improvements/declines (Pennington, 1994; Span et al.,1994). The global-capacity framework holds that general changes in transmission times throughout the lifespan control increases and decreases in overall processing capacity, including the changes in WM storage and manipulation capacity that occur. The neurocognitive-change framework, however, holds that functional changes within brain regions control increases and decreases in modality-specific processing capacities (Baddeley, 2003), suggesting that WM storage and manipulation capacity changes throughout the lifespan occur with some degree of relative independence from other cognitive processes. Additionally, it is likely that these two models are not mutually exclusive and may in fact be integrated; linear capacity improvements could

occur in some brain regions while nonlinear functional changes could occur in other brain regions.

Primary support for the global-capacity framework has come from cross-sectional and longitudinal studies of changes in processing speed. The global-capacity framework uses processing speed as the global mechanism underlying improvements and declines in cognitive abilities across the lifespan because processing speed has been shown to mediate the age-related variations in cognitive performance (Fry & Hail, 1996; Salthouse, 1996). Kail and Salthouse (1994), for example, used the normative data of over 6000 individuals between the ages of 6 and 80 to evaluate the effects of age on processing speed, measured by the Visual Matching Test from the Woodcock-Johnson Tests of Cognitive Ability (Woodcock, McGrew, & Mather, 1990). The results indicated that between the ages of 6 and 20 processing speed increased linearly, between the ages of 20 and 40 processing speed remained relatively constant, and between the ages of 40 and 80 processing speed declined. When speed of processing was statistically controlled for, the age-related variations in cognitive performance, as measured by the Raven's Matrices (Raven et al., 2003) were reduced. This finding suggests that processing speed as a global mechanism is responsible for the improvements and decline in cognitive performance across the lifespan.

Processing speed as the global mechanism underlying changes in cognitive capacity has been further supported by evaluations of processing speed as a mediator of age-related changes in other cognitive abilities (Fry & Hale, 1996; Kail, 1991). In one study, the relationship between processing speed, WM, and performance on the Raven's Matrices (Raven et al., 2003) as a way to understand the development of general fluid

intelligence was evaluated (Fry & Hale, 1996). The participants ($N = 214$, aged 7 to 19)

completed four measures of processing speed, four measures of WM, and the Raven's

Matrices. Path analysis indicated that processing speed mediated improvements in WM,

and WM, in turn, mediated improvement on the Raven's Matrices. The authors proposed

a developmental cascade model of intelligence, in which age-related improvements in

processing speed led to improvements in WM, which in turn led to gains in fluid

intelligence. Thus, according to the global-capacity framework, brain mechanisms

underlying processing speed underlie cognitive development by leading to overall

improvements in processing capacity.

Although several studies have supported the global-capacity framework, research

on the complexity of the component processes that underlie cognitive abilities has

provided support for a neurocognitive-change framework (Span et al., 2004). Stuss

(1992) first proposed that a cognitive supervisory system develops in a hierarchical

fashion, with more complex cognitive processes emerging as specific brain regions

mature. This model suggested that individual modules manage routine tasks, and that as

the tasks became more complex, a "supervisory system" is needed to integrate processing

across modules. Stuss et al. (2005), for example, recently found support for this model in

a study of RT in patients with frontal lesions ($n = 38$) and age-matched controls ($n = 38$).

All participants completed two RT tasks, the Simple RT (push button 1 when the letter

"A" appears) and the Choice RT (push button 1 when "A" appears and push button 2

when any other letter appears); the Choice RT task required greater attention. The results

indicated that both Simple RT and Choice RT were impaired in the superior medial lesion

group ($n = 8$; $p = .02$, $p = .07$, respectively), but that the left dorsolateral frontal lesion

group (n = 10) and the inferior medial lesion group (n = 14) were also significantly slower than controls on the Choice RT task (p = .01, p = .07, respectively). This finding suggested that different brain regions were integral to the efficient completion of complex functions, as different PFC regions were implicated when greater attention was required. The authors used this finding to support the theory that a PFC-mediated supervisory system is recruited as demands on EFs, such as attention, increase.

Furthermore, research has raised questions about the ubiquity of processing speed as a mediator of changes in cognitive abilities across the lifespan (Span et al., 2004). Tasks measuring response selection, response inhibition, WM, adaptive control, and processing speed were given to children (mean age: 9.2; n = 22), adolescents (mean age: 15.4; n = 17), adults (mean age: 24.1; n = 21), and seniors (mean age: 68.7; n = 19). As expected, mean response latency was longer in the children, adolescent, and senior groups than in the adult group on all tasks. However, when processing speed was statistically controlled, the age-related performance differences on the response selection, response inhibition, WM, and adaptive control tasks disappeared for the children and adolescents when compared to the adults. The seniors, however, performed significantly worse than the adults on all tasks even after controlling for processing speed. Although global processing speed may help explain developmental improvements in children and adolescents, this finding suggests that additional mechanisms, such as the changes in underlying brain regions, need to be considered in the study of cognitive performance changes across the lifespan.

The research supporting the neurocognitive-change framework suggests that global processing capacity improvements alone do not account for the changes in

cognitive performance that occur throughout the lifespan, as cognitive abilities seem to be linked to specific brain regions that a supervisory system integrates into a network (Paus, 2005; Stuss, 2006). It is possible that the different maturational trajectories of different brain regions support the development and utilization of different cognitive processes (Mountcastle, 1997). Thus, understanding the individual developmental trajectories of specific cognitive functions, such as WM, will assist in understanding the relationship between cognition and brain function throughout the lifespan.

Executive Function (EF) Development

Research on the development of EF throughout childhood and adolescence has shown that performance improves along a linear trajectory (Best et al., 2009; Cepeda, Kramer, & Gonzalez de Sather, 2001; Huizinga, Dolan, & van der Molen, 2006), consistent with the global-capacity framework. EF is considered to be a set of abilities that use goal-oriented mental control, such as attention, inhibition, set-shifting, and WM (Miyake et al., 2000; St. Clair-Thompson & Gathercole, 2006) to solve complex problems. Given the high correlations between these cognitive processes, these abilities are often studied as a single construct (Best et al., 2009). The underlying processes supporting the monotonic improvements in cognitive performance, however, are not fully understood, but again, these changes are consistent with the global-capacity framework.

Cepeda, Kramer, and Gonzalez de Sather (2001) found that linear increases in EF components during childhood, adolescence, and into young adulthood could be explained by increases in global processing capacity. The participants ($N = 152$, aged 7 to 82) completed measures of processing speed (e.g., Digit Copying), WM (e.g., Backward Digit Span from the WAIS-R [Wechsler, 1981]), and executive control (e.g., a novel set-

switching task that required participants to identify either the integer that appeared or the number of integers that appeared). An inverse U-shaped function was found for RT on the set-shifting task across the lifespan; however, linear improvements in RT on both the processing speed and WM tasks were found until 20 years of age. Furthermore, for the subjects between the ages of 7 and 24, 84% (R^2=.876) of the age-related variance of RT could be accounted for by improvements in processing speed and WM. Although this finding suggests that an increase in global processing speed can account for EF improvements, the individual components of EF were not considered separately.

In contrast, although Huizinga et al. (2006) found that improvements in EF (as defined by WM, shifting, and inhibition components) continued to develop linearly into young adulthood, the individual EF components followed different developmental trajectories, more consistent with the neurocognitive-change framework. The participants (70 7-year-olds, 108 11-year-olds, 111 15-year-olds, and 94 21-year-olds) completed the Wisconsin Card Sorting Task (WCST; Grant & Berg, 1948) and the Tower of London (ToL; Shallice, 1982) task, two commonly used measures of EF. Using confirmatory factor analysis, WM and shifting were found to be the two factors that best explained overall improvements on these two measures of EF that occurred with age. Furthermore, shifting ability increased from 7 to 15 years of age but not from 15 to 20 years of age; therefore, the ability to shift between different sets of information seemed to be stable after age 15. In contrast, WM consistently improved from 7 to 21 years of age, suggesting that WM continues to develop and improve into young adulthood. The different developmental trajectories of the EF components suggest that a single global

factor may not fully account for observed developmental improvements in cognitive abilities.

WM Development

Similar to developmental improvements observed in EF, the findings on improvements in WM that occur with development have been mixed in their support for the global-capacity framework versus the neurocognitive-change framework. Although improvements in WM performance throughout childhood and adolescence seem to follow a linear trajectory (Gathercole et al., 2004; Luciana et al., 2005; Swanson, 1999), as would be suggested by the global-capacity framework, more qualitative changes in the brain regions underlying these improvements that occur with age are suggested when the complexity of the WM task is considered (Best et al., 2009). This suggests that although cognitive abilities generally improve along linear trajectories, differences in the onsets and rates of change occur, supporting the neurocognitive-change framework.

Improvements in visuospatial, verbal, and complex WM tasks also have been found to be linearly related to age (Gathercole et al., 2004; Swanson, 1999), as would be expected in the global-capacity framework. Gathercole et al. had over 700 children between the ages of 4 and 15 complete tasks from the Working Memory Test Battery for Children (Pickering & Gathercole, 2001). All three components of WM were found to be highly correlated with age (visuospatial WM, $r^2 = .979$; verbal WM, $r^2 = .971$; complex WM, $r^2 = .969$). Similarly, Swanson (1999) had 778 participants between the ages of 6 and 76 complete four WM tasks: two verbal WM tasks (auditory digit sequence and semantic association) and two visuospatial WM tasks (mapping/directions and visual matrix). Regardless of the modality, WM performance increased linearly with age, from

6 to 20 years of age. These two studies provide evidence for the global-capacity framework, as improvements in overall processing capacity might contribute to the improved ability to store and manipulate information as seen in the overall improvement in WM performance.

When the complexity of the WM task has been considered, however, the strength of the linear relationship between age and WM performance has differed, thus suggesting that qualitative changes in WM ability may occur with age, as suggested by the neurocognitive-change framework (Luciana et al., 2005). Luciana et al. (2005) had participants ($N = 133$, grouped as 9-10 year olds, 11-12 year olds, 13-15 year olds, 16-17 year olds, and 18-20 year olds) complete four WM tasks (nonverbal face recognition memory, spatial delayed response, spatial working memory, and spatial self-ordered search). The results indicated that the simplest of tasks, nonverbal face recognition, showed no significant improvement with age and thus seemed to be fully developed by age 9. However, as the tasks became more complex, WM improvements were observed into adolescence (e.g., spatial location of an object showed improvement until age 12 and the ability to self-organize showed improvement until age 16). This study suggests that different WM abilities emerge at different ages; it is possible that nonlinear brain develop underlies WM improvements, thus supporting the neurocognitive-change framework.

The cross-sectional developmental studies have shown WM improvements to follow monotonic developmental trajectories through childhood into adolescence, but studies also have shown differences in the onsets and rates of these changes for specific WM component processes (Luciana et al., 2005; Stuss et al., 2004). Thus, these data have provided mixed support for the global-capacity and neurocognitive-change

frameworks. Cognitive models, however, are indirect measures of brain function, and attempts at more direct measures of the development of the brain bases supporting WM have come through structural and functional neuroimaging and lesion studies (D'Esposito et al., 2000; Owen et al., 2005; Rypma, 2006). Indeed, a better understanding of the relationship between the structural and functional changes in the brain and WM improvements may clarify the cognitive findings.

<div align="center">**BRAIN-BASES OF WM**</div>

Brain-bases of WM in Adults

Through the use of both neuroimaging and lesion studies, the PFC has been identified as having a key role in mediating WM functions (Figure 9; D'Esposito, Postle, & Rypma, 2000; Owen et al., 2005; Rypma, 2006). Furthermore, different brain regions have been shown to be differentially activated depending on WM component-process required, such as whether the task requires simple storage or more complex manipulation of information (Smith & Jonides, 1999), consistent with a hierarchical model of brain organization (Badre, 2008; Petrides, 2005; Stuss & Benson, 1987).

Different brain regions are activated depending on WM demand and the necessary recruitment of additional executive resources (Dove, Rowe, Brett, & Owen, 2001; Levy & Rakic, 2000; Owen et al., 2005). Owen, McMillan, Laird, and Bullmore (2005) performed a meta-analysis of studies using the *n*-back task to evaluate WM. The *n*-back task requires participants to hold a series of information in the mind for an undetermined length of time and to recall a specific piece of information presented *n*-tasks ago. Given the complex nature of this task, the brain regions impacting different stages of the WM process can be explored. This meta-analysis identified the

ventrolateral prefrontal cortex (VLPFC; BAs 44, 45, 47) as being activated in the most

routine tasks (e.g., ordered information) that require basic storage and maintenance

(additionally, see Levy & Rakic, 2000; Rypma, 2006). However, the meta-analysis

showed that the DLPFC (BAs 9, 46) tends to become active as tasks became more

complex, such as when tasks required additional attention, selection, comparison, or

judgment (additionally, see Dove et al., 2001; Rypma, 2006). As tasks

increase in complexity and begin to require the coordination of multiple processes (e.g.,

maintenance, manipulation, and attention simultaneously), the orbitofrontal cortex (BAs

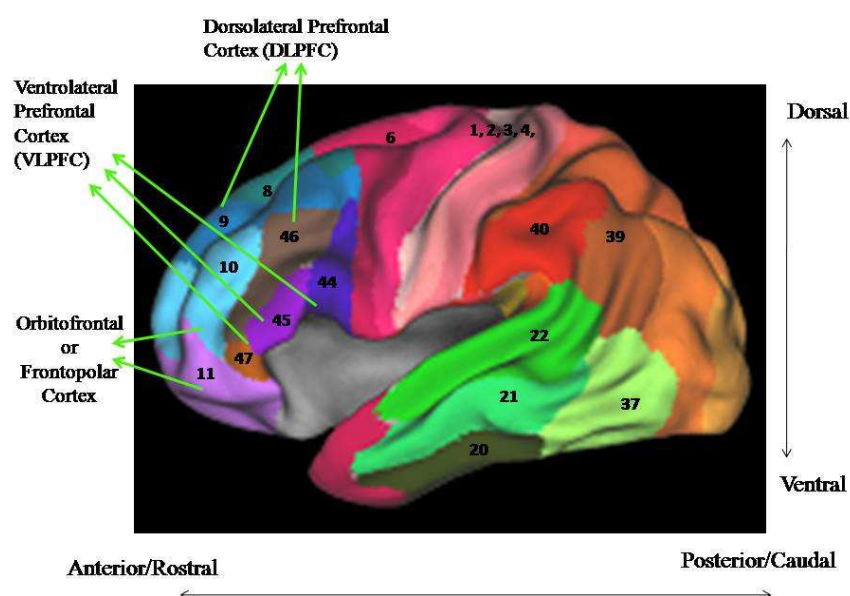10 and 11) also becomes involved (Barby et al., 2010).

Figure 9. Major anatomical subdivisions of the human brain. Brodmann's Areas (BAs), particularly those relevant to the frontal lobe, are numbered. The BAs conventionally considered to make up the DLPFC, VLPFC, and the orbitofrontal/frontopolar cortex are shown.

Additionally, the involvement of different PFC regions varies depending on the specific underlying WM processes involved, such as during the encoding, maintenance, and retrieval phases (D'Esposito et al., 2000; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). Motes and Rypma (2010), for example, used a partial-trial WM task as a way to differentiate the PFC activity throughout a WM task. For the full-trial version of this task, participants were asked to encode 2 or 6 letters, maintain the letters over a delay, and judge whether the letters appeared in a probe set. For the partial-trial version of this task, the participants engaged in various combinations of the encoding and maintenance phases. By completing the partial-trials, differences in brain activity during these three distinct phases of WM could be better ascertained. The results indicated that the PFC was involved during the encoding phase for both the 2 and 6 letter sets, however the PFC was more active during the maintenance phase for the supra-capacity set (6 letters) than for the sub-capacity set (2 letters). This suggests that additional PFC activation during supra-capacity WM tasks may represent the recruitment of additional executive resources rather than route WM maintenance (Rypma & Prabhakaran, 2009). The evidence that WM is supported by multiple PFC regions further supports the neurocognitive-change framework

Thus, the complexity of the WM task (such as basic storage or goal-oriented manipulation) as well as the specific underlying WM process involved (such as the encoding, maintenance, or retrieval phase) leads to the differential use of regions within the PFC (Motes & Rypma, 2010; Owen et al., 2005). Although performance on WM tasks seems to follow a monotonic developmental trajectory with age (Gathercole et al., 2004; Luciana et al., 2005), the neuroimgaging and lesion studies suggest that specific

brain-regions mediate specific components and processes of WM. Thus, WM improvements might not be due to global brain changes associated with global capacity increases but rather to local qualitative changes in the functional activation underlying WM processes that occurs with development.

Brain-Bases of WM in Children and Adolescents

Although few studies have been conducted to look at the brain-bases of WM in children and adolescents, the early studies show that similar brain regions that underlie WM in adults also underlie WM in children. Thomas et al. (1999) compared brain activation in six children (aged 8-10) and six adults (aged 19-26) and found that similar brain regions were activated during a visuospatial WM task (participants visually searched an array of boxes for a dot and indicated which box the dot had appeared in *n*-trials back). These brain regions included the right DLPFC, right superior frontal gyrus, and bilateral inferior parietal cortex, although quantitative differences in functional activation were not evaluated between the children and the adults. Similarly, Nelson et al. (2000) studied brain activation in a group of children (N = 9, aged 8-11) during a comparable visuospatial WM task and found a similar activation pattern. Specifically, the brain regions activated during the task were the right DLPFC, bilateral superior frontal gyrus, and right inferior parietal cortex. Again, this study did not explore quantitative functional activation differences in these regions between the children and adult groups. However, these studies are significant because they laid the foundation for the interest in functional activation supporting WM throughout development.

More recently, cross-sectional studies have found that age accounted for a significant portion of the differences in activation between groups of children,

adolescents, and adults during visuospatial WM tasks. Klingberg, Forssberg, and Westerberg (2002) had participants ($N = 13$, aged 9 to 18) complete a visuospatial WM task (required participants to remember the location of either 3 or 5 sequentially shown dots in a 4 X 4 matrix of boxes and press a button after a delay to indicate if a probe dot appeared in a remembered location) while fMRI data was collected. A general linear model was used to evaluate the main effect of activation during the WM task and age. This analysis revealed a positive correlation between activation and age in the bilateral superior frontal sulcus (considered part of the PFC; right side: $t = 4.72$, $p < .05$; left side: $t = 4.48$, $p < .05$) and in the intraparietal/superior parietal cortex (the parietal cortex has been implicated in spatial tasks; right side: $t = 4.75$, $p < .05$; left side: $t = 4.65$, $p < .05$). Similarly, Kwon, Reiss, and Menon (2002) collected fMRI data from participants ($N = 23$; n aged 7-12 = 8, n aged 13-17 = 8, n aged 18-22 = 7) during a 2-back WM task. Multiple linear regression analyses were applied to the data to examine the individual contributions of age and performance to functional activation. This analysis revealed that significant age-related activation changes occurred across subjects during the WM task after performance measures (response time and accuracy) were held constant (left PFC peak t-score: $p = .091$; right PFC peak t-score: $p = .001$). This result shows that age is a significant linear predictor of functional activation changes in brain areas, such as the PFC, that underlie WM tasks.

These studies suggest that functional specialization of brain regions contribute to improvements in WM performance and provide further support for the neurocognitive-change model. However, the nature of qualitative changes in brain regions requires further exploration as these studies only considered linear relationships between

performance and functional activation supporting WM with age. Given the nonlinear

development of brain regions (see Giedd et al., 1999; Gogtay et al., 2004), more complex

relationships, such as quadratic models based on Giedd et al.'s 1999 study that found a

quadratic relationship between PFC gray matter volume and age, warrant further

exploration.

<div align="center">**CORTICAL DEVELOPMENT**</div>

Although cognitive measures show that WM (and other cognitive processes) tend

to steadily improve with development from childhood through adolescence, structural

imaging data show that the human brain follows a nonlinear developmental pattern

(Gogtay et al., 2004; Johnson, 2001). Cortical brain regions follow heterochronic

development, with individual brain regions each following individual developmental

trajectories accounted for by bursts of synaptic development followed by neural pruning

that occur at different periods of development.

Synaptogenesis and Neural Pruning

Human brain development involves neuronal proliferation, neuronal migration,

neuronal differentiation, synaptogenesis, and synapse elimination (Gazzaniga, Ivry, &

Mangun, 2008). At birth, the human brain is anatomically fully developed – including

the cortex and its cortical layers observed in adulthood – aside from complete

myelination. The process of brain development begins during the first quarter of

gestation through the process of neuronal proliferation, which refers to the genesis of the

cells that will make-up the cerebral cortex. This process is followed by neuronal

migration, as the new neurons travel farther and farther outward to form the cortex; the

first neurons to develop form the deepest cortical layers, and the last neurons to develop

form the outermost cortical layers. Up until this point, all neurons are identical.

However, after about five to six weeks of gestation, the dividing neurons become

differentiated dependent on their respective gestational ages.

Synaptogenesis is the formation of the synapses of neurons that occurs most

rapidly prenatally and in the first few months after birth. Because synapses are

responsible for the transmission of electrical signals, the primary way that neurons

communicate with each other, synapse connections are an integral factor in optimal brain

functioning (Gazzaniga et al., 2008). Research has shown that the peak density of

synapses varies depending on the brain region (Huttenlocher, 1990; Huttenlocher &

Dabholkar, 1997). However, neural pruning, or synapse elimination, occurs well into

adolescence. Neural pruning is thought to increase the optimal functioning of the human

brain by eliminating redundant or unnecessary neurons (Hua & Smith, 2004).

Although synaptogenesis significantly slows after about 15 months of life, the

overall volume of the brain continues to increase throughout adolescence (Giedd et al.,

1999). This continued increase in volume occurs in both the gray and white matter

structures, and this growth is likely a result of continued dendritic branching, increased

myelination, and the addition of glial cells (De Bellis et al., 2001.) However, despite the

importance of synapse development, this stage of brain growth slows long before humans

function at their optimal cognitive ability. Thus, understanding the differences between

the development of gray and white matter structures will shed light on the development

of complex cognitive abilities.

Gray Matter Development

Gray matter brain regions gain volume rapidly during the first few years of life and then begin to slowly lose volume with age throughout preadolescence and adolescence (Jernigan, Trauner, Hesselink, & Tallal, 1991; Johnson, 2001; Sowell et al., 2004). Gray matter refers to the layers of the brain where the cell bodies are, and these cells cluster together to form cortical structures (such as the PFC, temporal lobe, parietal lobe, occipital lobe, and their respective gyri); the high density of cell bodies leads to their grayish hue in comparison to other brain structures (Gazzaniga et al., 2008). The acquisition of gray matter is likely a result of synaptogenesis initially and glial development thereafter. The loss of gray matter that occurs throughout adolescence is somewhat more complex. The predominant explanation for the gray matter loss is that it is likely a result of neural pruning and the refinement of cortical pathways (Cowan, Fawcett, O'Leary, & Stanfield, 1984; Huttenlocher & Dabholkar, 1997; Sowell & Jernigan, 1998). However, the refinement of MRI acquisition and analysis has allowed several studies to demonstrate robust gray matter volume changes that support this theory of neural pruning and refinement (Giedd et al., 1999; Giorgio et al., 2010; Gogtay et al., 2004; Shaw et al., 2008). Interestingly, this acquisition and loss of gray matter during development is not a linear or uniform process. Regions responsible for primary functions (such as the visual cortex) undergo this process earlier, whereas brain regions responsible for higher order functions (such as the PFC) undergo this process later (Gogtay et al., 2004). The changes in brain volume seem to parallel cognitive abilities, with higher order processes such as reasoning, planning, and inhibition slowly emerging and maturing throughout adolescence

Giedd et al. (1999) found that cortical structures follow a heterochronic developmental pattern, with different brain structures following unique growth curves. The longitudinal study had participants ($N = 149$, 89 male, 60 female; aged 4.2 to 21.6) undergo MRI scans every two years for up to eight years. The data were analyzed using a combination of techniques that allow individual growth patterns to be detected with both cross-sectional and longitudinal data. The results indicated that, as expected, the volume of white matter increased linearly with age, with no significant differences in this growth between various cortical structures; the volume of white matter seemed to increase slightly more in males. Overall, the net increase in white matter volume from age 4 to 22 was 12.4%. In contrast, the changes in gray matter volume varied by region and seemed to occur in a nonlinear fashion. In the frontal lobe, gray matter volume increases seemed to follow a quadratic trend, with the peak gray matter volume for females occurring at 11 years and the peak volume for males at 12.1 years; after this peak, the gray matter volume in the PFC began to decrease, resulting in a net loss during this age span. The gray matter volume of the parietal lobe followed a similar pattern, with the maximum size occurring at 10.2 years for females and 11.8 years for males. The temporal lobe gray matter, although following the same nonlinear pattern, did not peak until 16.7 years in females and 16.5 years in males. Unlike the other cortical brain structures, the gray matter in the occipital lobe seemed to follow a linear path, with a steady increase in volume in both sexes with age.

The heterochronic developmental pattern of the cortex, with different brain structures following unique growth curves, is a pattern that seems consistent with the neurocognitive-change framework (Shaw et al., 2008; Sowell, Thompson, Holmes,

Jernigan, & Toga, 1999; Thatcher, Walker, & Giudice, 1987.) Furthermore, it seems that volume changes in the gray matter of the primary visual and auditory centers (located primarily in the occipital lobe) precedes the development of higher order executive functions, such as WM, associated with frontal lobe function. The authors infer that neural pruning, or a refinement of the neural pathways, might be responsible for the net loss of gray matter in the frontal cortex that occurs during adolescence. Indeed, although the adolescent brain has the most gray matter volume around age 11 or 12, it might not be at its most efficient stage of development, as that likely occurs after neural pruning.

The studies exploring the changes in gray matter volume with development consistently find that the phylogenetically older brain regions, such as the lower-order sensiomotor regions, complete development earlier, while high-order (and evolutionarily newer) cortical regions, such as the PFC, do not complete develop until well into adolescence (Giorgio et al., 2010; Gogtay et al., 2004; Shaw et al., 2008; Sowell et al., 1999). This hierarchical development provides further support for the neurocognitive-change framework, as the brain regions responsible for higher-order processes, such as reasoning and decision-making, rely on the integration of lower-order processes. However, further exploration of the structural cortical changes associated with development and functional activation changes that underlie cognitive tasks, such as WM, is needed.

White Matter Development

In contrast to gray matter volume, the volume of white matter seems to increase linearly throughout adolescence and into young adulthood (Giorgio et al., 2010; Giedd, 2004); this increase in white matter volume could serve as a mechanism underlying the

increase in global processing capacity as suggested by the global-capacity framework.

White matter refers to the axons of neurons, sheathed in myelin, that form tracts

throughout the brain and connect structures; the myelin causes the axons to appear white

(Gazzaniga et al., 2008). Thus, the increases in white matter are likely a result of

increases in myelination; when myelin sheaths the axon tracts connecting brain regions,

the brain regions can communicate with each other faster and more efficiently (Filley,

2010). More specifically, this steady increase in the volume of white matter throughout

adolescence is most profound in the frontal lobe and corpus callosum (Barnea-Goraly et

al., 2005; Gogtay et al., 2004; Perrin et al., 2008). In the 2010 study conducted by

Giorgio et al., the DTI data revealed a relatively steady increase in white matter volume

with age, with only a slight difference in trajectory between the four brain lobes.

Increases in white matter volume were observed in the frontal lobe and corpus callosum,

and in parts of the arcuate fasciculus and corticospinal tract. As the volume of white

matter in these critical regions increases, higher order cognitive processes become more

refined; indeed, increases in white matter support overall processing capacity

improvements in cognitive processes as suggested by the global-capacity framework.

IMPLICATION OF BRAIN-BEHAVIOR RELATIONSHIPS

When both the structural brain changes and cognitive improvements related to

development are considered, there are three possible predictions: linear increases in white

matter volume could lead to increases in cognitive capacity as suggested by the global-

capacity framework; regional heterchronicity in gray matter volume could lead to

qualitative changes in brain function as suggested by the neurocognitive-change

framework; both increases in cognitive capacity and regional hereochronicity occur and

thus suggest an integration of the two models. Although the gray matter volume in the PFC reaches its maximum size around 11 or 12 years of age, the subsequent decrease in gray matter is likely a result of neural pruning and refinement. The neural pruning eliminates inefficient or unused pathways, while highly-used and effective pathways remain. These structural changes may result in the qualitatively different use of brain regions while engaging in cognitive tasks. Although performance on cognitive measures, such as measures of WM, may improve as a result of capacity increases, it is possible that structural brain changes may also contribute to this observed improvement as suggested by the neurocognitive-change framework.

Thus, the relationship between brain structures and behavior may be more complex than linear activation patterns. Efforts have been made to link cognitive functions to specific anatomical regions and to track the relationships between changes in behaviors and their respective underlying brain structures throughout development (Lenroot & Giedd, 2006). Although cognitive processes seem to improve linearly, as supported by the global-capacity framework, there is a discrepancy between cognitive and structural trajectories that this framework does not account for; indeed, many brain structures, such as cortical gray matter, follow a quadratic trend with region-specific peaks.

APPENDIX B
Rationale, Aims, and Hypotheses

RATIONALE

The discrepancy in the developmental trajectories between structural changes in brain regions mediating WM and performance on cognitive measures opens the question of what changes occur in PFC functional activity supporting WM with development. Cross-sectional developmental studies of cognitive performance show that cognitive abilities, including WM, follow monotonic developmental trajectories through childhood into adolescence. Although these cognitive improvements in WM have been explained by increases in global capacity that occur with age, the underlying mechanisms supporting this proposed increase in capacity are not fully understood

Cross-sectional and longitudinal research on the development of cortical brain regions mediating WM functions reveals the heterochronicity of brain development. Specifically, gray matter volume in the PFC seems to follow a quadratic developmental trajectory, with the peak in gray matter volume occurring around 12 years of age; this suggests that the PFC may undergo qualitative changes in functional activation that underlie WM improvement as suggested by the neurocognitive-change framework. Indeed, this discrepancy suggests that the functional changes within the PFC that support WM may be more complex than linear increases or decreases in activation, and could possibly follow the same quadratic changes seen in gray matter volume. This finding suggests that the improvements in WM with age are not simply a result of improved processing capacity, but could reveal qualitative changes in PFC function that occur with age.

Establishing the relationship between PFC functional activity supporting WM and improvements in WM ability will fill an existing gap in the literature that does not fully account for the differences between developmental anatomical changes and performance on cognitive measures of WM. fMRI research will allow developmental models that integrate functional activation to be tested. Furthermore, by understanding how the development of the human brain drives performance during integral cognitive tasks, such as WM, a more holistic perspective of brain-behavior relationships will emerge. This understanding of the brain's development and its relationship with cognitive tasks will drive future research to better identify, understand, and treat cognitive atypicalities in childhood and adolescence.

AIMS AND HYPOTHESES

Aim: Using functional activation and whole-brain analysis, this study seeks to find the model that best accounts for age-related variability in PFC functional activation during a WM task. A linear regression model will be used to explore the strength of the linear relationship between functional activation and age, and a quadratic term will be added to the regression model to explore the strength of the quadratic relationship with age in order to consider potential nonlinear changes in functional activation (Figure 10).

Hypothesis 1: Functional activation in brain areas implicated in WM, such as the PFC, will have a quadratic relationship with age, based on findings that structural changes in gray matter volume in the PFC also have a quadratic relationship with age. This hypothesis will be tested using a whole brain-analysis to identify the brain regions where there are significant changes in the amplitude of the BOLD signal related to age. Hierarchical regression will be used after controlling for the linear effects of age, the
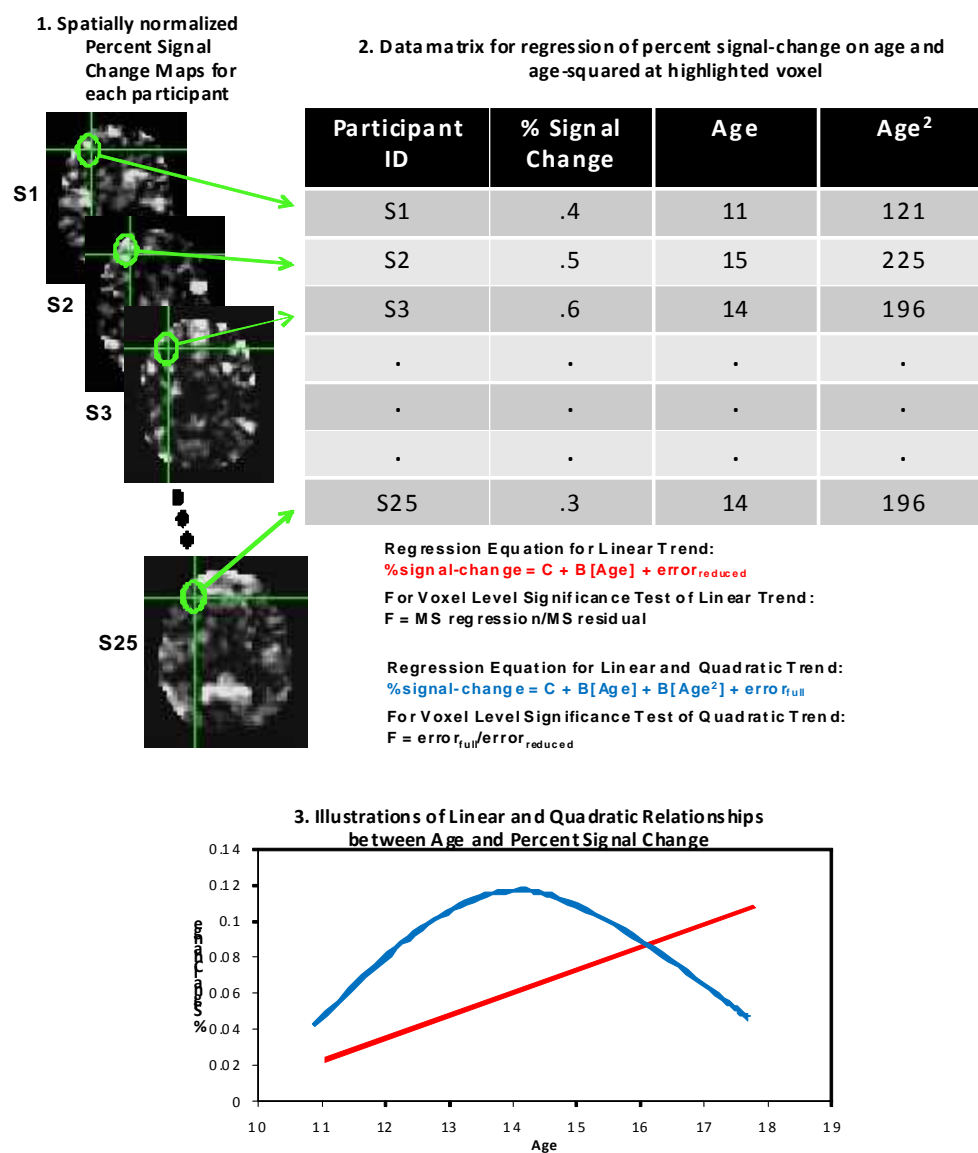
Figure 10. Example of linear and quadratic relationships between functional activation in brain regions supporting WM and age.

effects of gender, and the effects of performance (accuracy, capacity [derived from accuracy], and RT]). BOLD signal-change estimates will be regressed on linear and quadratic models of the age of the participants while performance variables, gender effects, and handedness are held constant. It is predicted that the quadratic model will account for significantly more of the variance (as measured by the F-value) in BOLD signal-change than the linear model, thus suggesting that qualitative functional changes in the PFC occur throughout adolescence.

Hypothesis 2: Changes in performance will have a linear relationship with age, given that WM improvements are observed with age. Capacity will be the primary measure of performance; however, the effects of RT and accuracy will be explored as well. The performance variables will be tested with the same hierarchical modeling used to test Hypothesis 1 (see Appendix D for an explanation of the performance variables used).

Exploratory Aim: The synthesis of the cognitive changes, as measured by performance measures, and the functional changes in brain regions, as measured by BOLD signal-change, will be attempted.

APPENDIX C
Description of the Samples

A cross-sectional design including both retrospective and novel data was used. Although the data constitute a sample of convenience from two studies, all participants completed the same fMRI WM task and the Digit Span subtest from the WISC-IV/WAIS-III as controls for both studies. The completion of the WM task during the fMRI session varied given the differing protocols of each study; additionally, the order of the sessions may have varied as the protocols were adjusted to best accommodate each participant. Data were collected from 42 participants (age $M = 14$ years; range = 11 to 18 years; 17 females; 5 left-handed). However, the data from one participant (16-year-old right-handed male) were not included in the analyses due to errors in fMRI data acquisition (Figure 11).
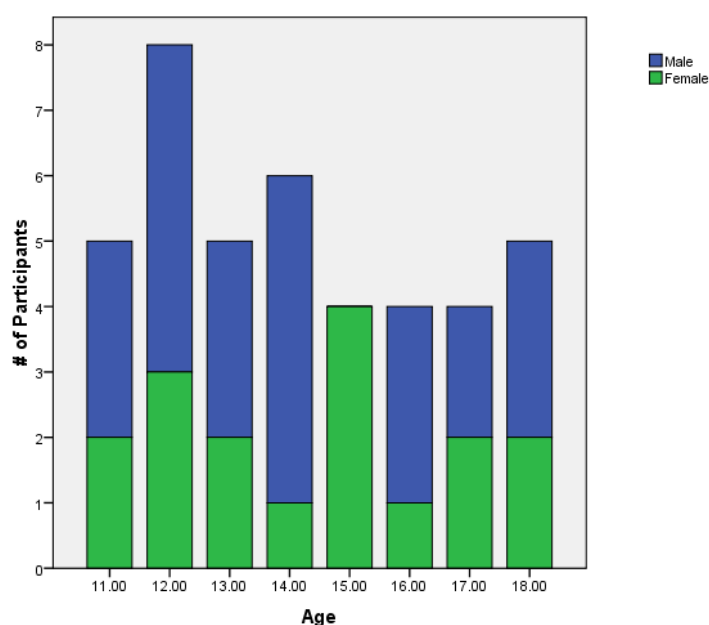

Figure 11. Frequency counts for age and gender of participants included in the study (N = 41).

STUDY ONE

An fMRI Study of Amygdala Activation at Pre- and Post-Antidepressant Treatment Among Adolescents with Major Depressive Disorder

　　Purpose. This study sought to explore brain activation differences in adolescents before and after antidepressant treatment (fluoxetine) compared to healthy controls using fMRI. The principal investigator was Rongrong Tao, M.D., Assistant Professor at the University of Texas Southwestern Medical Center at Dallas and Child Psychiatrist at Children's Medical Center Dallas. The study was approved by the Institutional Review Board at the University of Texas Southwestern Medical Center, and the study was conducted according to the principles expressed in the Declaration of Helsinki.

　　Participants. Twenty-one healthy adolescents (aged 11-18; 13 males, 8 females; 3 left-handed) completed the fMRI WM task as part of their participation in this study as controls. These participants were recruited through Children's Medical Center Dallas through the distribution of fliers to potentially qualifying participants. The inclusion criteria for the control participants required that they be between the ages of 11 and 18, currently attending school, in good general medical health, of normal intelligence (i.e. IQ>80 based on the WISC-IV if concerns about intelligence became apparent), no evidence of a past or present psychiatric disorder, and no reported psychiatric disorders in any first-degree relatives. The exclusion criteria for the control participants required they had not been taking psychotropic medications for the past four weeks, had no concurrent medical condition that would interfere with the study or harm the participant, had no contraindications to MRI scanning (e.g., metallic objects such as braces), and that no females could be pregnant or lactating. At the baseline fMRI scan, the benefits, risks,

confidentiality, and other aspects of the study were explained to the parents and a written description of the study was provided. Prior to testing, written informed consent was obtained from each participant's legal guardian, and the adolescent provided their written assent. During baseline fMRI scans, participants completed the WM task, and these data were used in the present study.

STUDY TWO

Middle School Brain Years Project

Purpose. This study sought to explore the effects of Strategic Memory and Reasoning Training (SMART), a curriculum developed by Sandra Bond Chapman, Ph.D. and Jacquelyn Gamino, Ph.D. at the University of Texas at Dallas to help adolescents with ADHD on critical thinking skills and academic performance in middle school youth. In addition to receiving the SMART intervention, a portion of participants in this study underwent neuropsychological, EEG, and fMRI evaluations pre- and post-SMART intervention; the brain imaging component of this study was led by Michael Motes, Ph.D. The study was approved by the Institutional Review Boards at the University of Texas Southwestern Medical Center and the University of Texas at Dallas, and the study was conducted according to the principles expressed in the Declaration of Helsinki.

Participants. As part of the fMRI task battery, 21 participants (aged 11-17; 12 males, 11 females; 2 left handed) completed the WM task. These participants were recruited from Dallas-area schools through the distribution of fliers; some participants were recruited through the SMART study and some participated as neurotypical controls. Inclusion criteria for these participants required that they be between the ages of 11 and 18, currently attending school, in good general medical health, of normal intelligence (i.e.

IQ>70 WASI, Wechsler, 1999), and no self-reported history of a past or present

psychiatric disorder. The exclusion criteria for these participants required that they were

not currently taking psychotropic medications, had no concurrent medical condition that

would interfere with the study, had no contraindications to MRI scanning (such as

metallic objects such as braces), and that no females could be pregnant or lactating. At

the baseline fMRI scan, the benefits, risks, confidentiality, and other aspects of the study

were explained to the parents and a written description of the study was provided. Prior to

testing, written informed consent was obtained from each participant's legal guardian,

and the adolescent provided their written assent. During the baseline fMRI scans, these

participants completed the WM task which was used in the present study.

APPENDIX D
Additional Data Analyses/Results

COMPARISON OF PARTICIPANTS

Digit Span Scaled (DSS) Scores

Given that the participants were recruited from two different studies (see Appendix C), efforts were made to ensure that the two groups had comparable cognitive skills and thus could be treated as a single sample. The Digit Span subtest from the WISC-IV (Wechsler, 2004) was used for all participants aged 11 through 16, and the WAIS-III (Wechsler, 1997) was used for all participants aged 17 through 18. Scaled scores normalized by age were calculated for each participant and were used as a rough measure of cognitive performance.

An independent samples *t* test was performed to evaluate whether there was a statistically significant difference in DSS scores from the WISC-IV/WAIS-III between the participants from the Depression Study and the MSBY Study. The test was not significant at $\alpha = .05$, $t(39) = 1.297$, $p = .202$. Participants from the Depression Study ($M = 10$, $SD = 2.83$) did not perform significantly different than participants from the MSBY Study ($M = 9$, $SD = 3.28$), and thus could be treated as a cohesive group in terms of cognitive WM skills (Figure 12).

Additionally, correlations between DSS and other sample characteristics were explored. DSS was highly correlated with both DSF ($r = .804$, $p < .001$) and DSB ($r = .739$, $p < .001$), as would be expected given that DSS is an aggregate of these scores. Thus, DSS was not treated as a covariate of an independent measure of intelligence in this study given its high correlation with DSF and DSB. Furthermore, a linear regression

analysis was performed to evaluate whether there was a statistically significant

correlation between DSS scores and age. The regression analysis was not significant (r =

.140, p = .383), indicating that variability in this aggregate measure of WM was not

related to age.
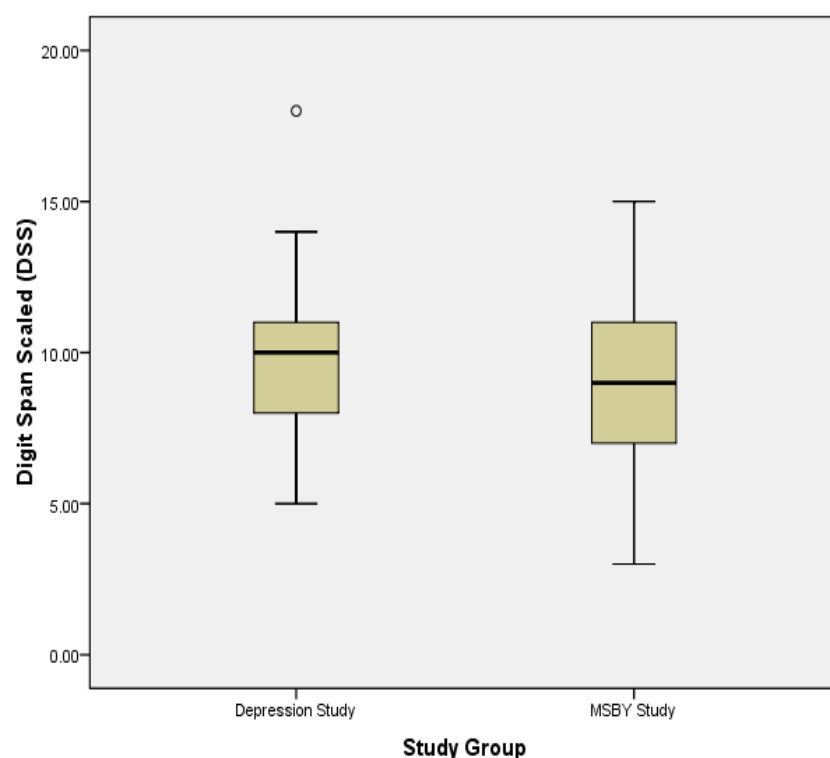
Figure 12. Descriptive graph of Digit Span scaled scores in the two samples.

Gender Differences

An exploration of gender was conducted to determine if gender differences were

present across the behavioral measures. An independent samples *t* test was performed to

evaluate whether there was a statistically significant difference in DSS scores from the

WISC-IV/WAIS-III between males and females. The test was not significant at α = .05,

$t(39) = 1.204$, $p = .236$. Thus, males and females did not vary significantly on the rough

measure of cognitive ability used (DSS). An independent samples t test was performed

to evaluate whether there was a statistically significant difference in RT between males

and females. The test was not significant at $\alpha = .05$, $t(39) = .724$, $p = .473$. Thus, males

and females did not vary significantly on their search and retrieval speed on the WM task.

An independent samples t test was performed to evaluate whether there was a statistically

significant difference in DSF scores between males and females. The test was not

significant at $\alpha = .05$, $t(39) = -.499$, $p = .620$. Thus, males' and females' digit span did

not vary significantly. An independent samples t test was performed to evaluate whether

there was a statistically significant difference in DSB scores between males and females.

The t test was significant at $\alpha = .05$, $t(39) = 2.448$, $p = .019$, indicating that the males

performed significantly better than the females on DSB. However, the significant

relationship between gender and DSB can be explained by three females' low scores on

the DSB task which skewed the relationship between gender and age in favor of males.

When the three females' low scores were dropped from the analysis, the t test was no

longer significant at $\alpha = .05$, $t(36) = 1.682$, $p = 1.01$. Overall, males and females did not

vary significantly on the complex WM ability.

BEHAVIORAL MEASURES

In addition to the behavioral Digit Span task (DSF, DSB), indices of performance

on the WM task performed in the scanner (RT and accuracy) were also recorded. RT was

calculated as the mean RTs on correct trials during the 6-letter condition; RTs two-and-a-

half standard deviations above and below the mean were discarded as outliers. The range

of RTs indicated that this was a robust measure of performance on the WM task ($M =$

1098 ms, range = 451ms to 1501 ms). However, although accuracy was calculated (total correct responses/total possible correct responses during the 6-letter condition), accuracy was not used as a measure of performance due to a task ceiling effect. Only six participants performed worse than 93% accuracy ($M = 92\%$, range = 67% to 100%). Furthermore, capacity estimates were derived from accuracy in the 6-letter condition using Cowan's K (Cowan, 2001): K = (hit rate + correct rejection rate) – 1 X N; where N = set size (6). However, given that only 12 trials were completed in the task, capacity estimates at the ceiling and also perfectly correlated with accuracy ($r = 1$). Thus, only RT was used an index of performance on the fMRI WM task.

ADDITIONAL fMRI ANALYSES

A whole-brain analysis revealed a linear relationship between percent BOLD signal-change and age in the right medial BA6. However, no clusters showing a quadratic relationship between percent signal-change and age survived the thresholding criteria. Thus, attempts were made to improve statistical power. However, even with the use of the following analyses, no support was found a significant quadratic relationship between percent BOLD signal-change and age.

Group Level

Whole brain *t*-test. To determine the functional activation patterns in brain areas implicated in WM, such as the PFC, voxel-wise hierarchical regression was used. Using hierarchical regression allowed for both the linear effects of age (with the reduced model) as well as any quadratic effects of age (with the full model) in brain regions supporting WM to be explored. A whole-brain *t*-test was used to identify voxels where the mean percent signal-change estimates were significantly greater than zero (family-

wise α = .05 and a voxel-level α = .005; Figure 13). Next, only voxels showing positive activation were considered, and these regions were further restricted to the cortex by applying a mask of the cortical strip to the identified regions. The resulting functional activation mask was used in the analyses in order to restrict the number of voxels and thus reduce the number of comparisons (i.e., voxel-wise *t* tests). To control for Type I errors, the results were cluster-thresholded based on Monte-Carlo simulations (AlphaSim software; Ward, 2000) so that surviving clusters were significant with a family-wise α = .05 and a voxel-level α = .005. Clusters of ≥ 49 voxels were significant with a family-wise α = .05, based on the simulations (1000 iterations for a dataset having 11,558 voxels [2 mm isovoxel], smoothness = 8 mm FWHM, cluster = pairs of voxels having a connectivity radius < 3.47 mm, thus having connecting faces, edges, or corners at the resampled voxel size).

In order to determine if a significant relationship between percent signal-change and age emerged with the use of this functional mask, a full model that included age squared as a quadratic predictor variable was added to the reduced mode that included age. However, no clusters survived the thresholding criteria. Even when the linear effects of the covariates were removed (G, H, RT, DSF, and DSB), no clusters survived the thresholding criteria.
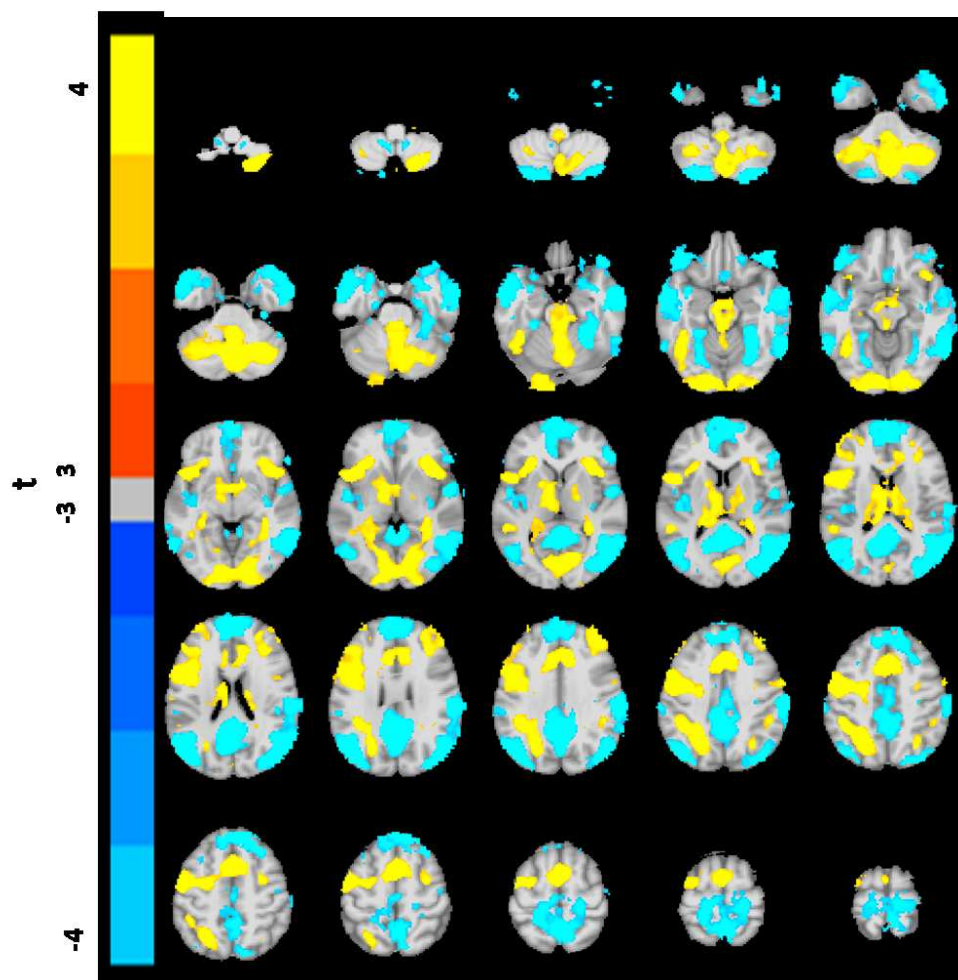
Figure 13. Results of a whole brain t-test. The voxel-wise one-sample t-test compared the mean percent signal-change estimates to zero. Red to yellow voxels illustrate positive correlations, where age increases were associated with higher signal-change, and blue to cyan voxels illustrate negative correlations, where age increases were associated with lower signal-change.. Data were cluster thresholded with cluster α = .05 and voxel α = .005.

Regions of Interest (ROI) analysis. Based on previous research identifying the parietal cortex and anterior/inferior regions of the PFC as underlying WM (Awh et al., 1995; Baldo & Dronkers, 2006; Rypma et al., 1999), hierarchical regression analyses were restricted to brain regions (ROIs) thought to underlie WM. ROIs were drawn to

isolate the DLPFC (BAs 6, 9, 46), VLPFC (BAs 44, 45, 47), parietal cortex (BA 7), and inferior parietal cortex (BAs 39, 40; Figure 14). By restricting the analysis to predetermined brain regions, the number of voxels (and thus the number of necessary t-tests) was reduced.
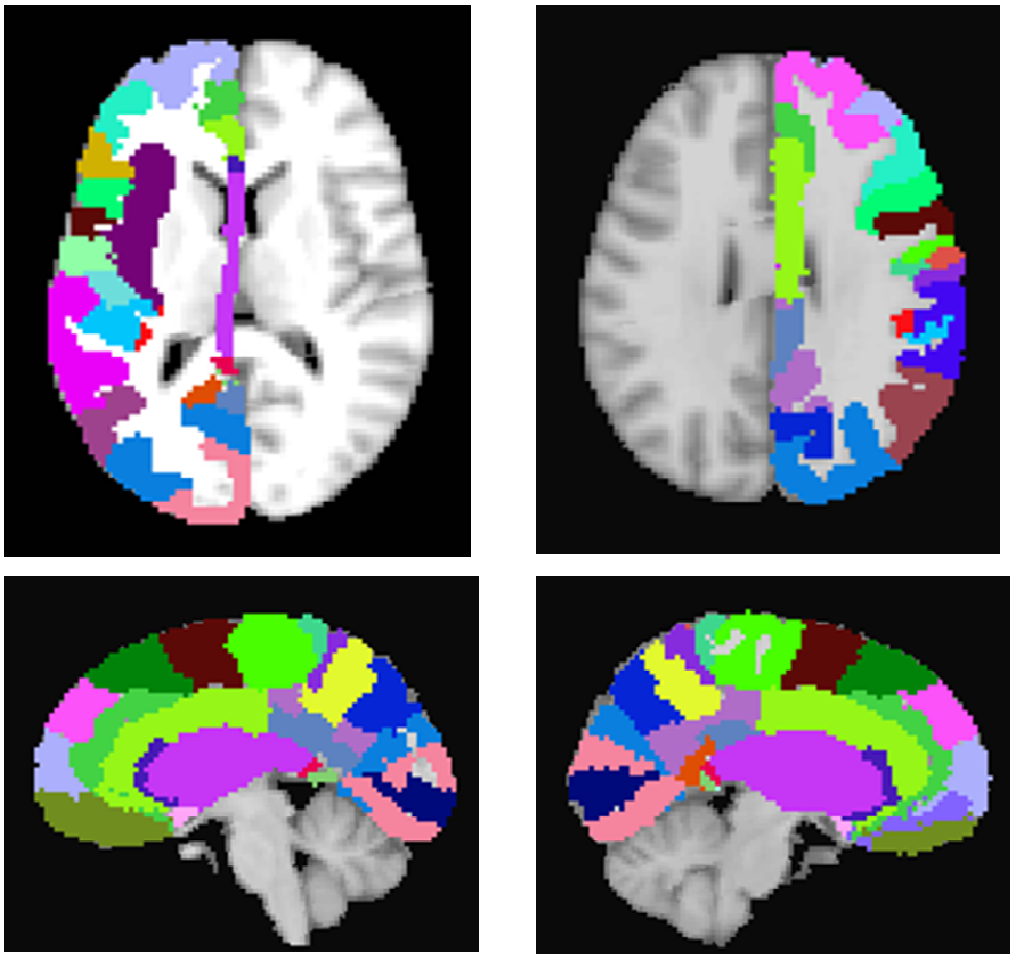

Figure 14. ROIs approximating Brodmann's Areas.

The mean percent signal change within the ROI during the 6-letter condition was calculated for each participant. Hierarchical linear regression was used to compare variance reduction by the reduced regression model (where percent signal-change = C +

B[Age] + error$_{reduced}$) to a full regression model (where percent signal-change = C +

B[Age] + B[Age^2] + error$_{full}$) in each ROI to assess whether there was a significant

quadratic relationship between BOLD and age. However, a significant relationship

between age squared and percent signal-change was not found in any of the ROIs.

Additionally, even when all covariates (G, H, DSF, DSB, and RT) were controlled for, a

significant quadratic relationship between percent BOLD signal-change and age was not

found (see Table 10).

Table 10. *Hierarchical Multiple Regression Analyses Predicting the Quadratic Relationship between Percent Signal-Change and Age with the Addition of Covariates*

ROI	R^2	ΔR^2	ΔF	$\beta_{age}{}^2$	$df1$	$df2$	p
Left BA6	.242	.002	.081	-.607	1	34	.777
Right BA6	.115	.000	.002	-.104	1	34	.964
Left BA7	.152	.002	.089	-.671	1	34	.767
Right BA7	.114	.021	.807	2.067	1	34	.375
Left BA9	.164	.001	.049	-.494	1	34	.826
Right BA9	.031	.003	.094	.739	1	34	.761
Left BA39	.095	.003	.106	-.757	1	34	.747
Right BA 39	.106	.000	.013	-.263	1	34	.910
Left BA 40	.146	.002	.085	-.657	1	34	.461
Right BA 40	.087	.012	.434	-1.538	1	34	.515
Left BA 41	.309	.000	.000	.017	1	34	.993
Right BA 41	.183	.024	.980	2.187	1	34	.329
Left BA 45	.102	.017	.628	-1.836	1	34	.434
Right BA 45	.245	.002	.078	.594	1	34	.782
Left BA 46	.169	.006	.254	-1.123	1	34	.617
Right BA 46	.100	.005	.174	-.967	1	34	.679
Left BA 47	.074	.007	.241	1.155	1	34	.627
Right BA 47	.296	.000	.003	-.112	1	34	.957

Note. All values reported are for the full model (BOLD = Age + G + H + RT + DSF + DSB + Age^2). RT = response time; G = gender; DSF = digit span forward; DSB = digit span backward.

One-way ANOVA. In addition to the planned hierarchical regression analyses, a one-way analysis of variance was performed to evaluate the relationship between percent signal-change and age across the whole brain. The independent variable, age, was broken into three groups: young participants (comprised of the 14 youngest participants), middle participants (comprised of the next oldest 14 participants), and old participants (comprised of the 13 oldest participants). The ANOVA yielded no significant clusters (clusters ≥146 voxels, family-wise $\alpha = .05$), which indicated that there was no regions of activation that significantly differed between the three age groups.

Image Level

Smoothing: Gaussian kernels. Gaussian kernels are applied to the BOLD data in order to evenly distribute the error across a predetermined space (based on the smoothing kernel width) and improve the signal-to-noise ratio (AFNI software; Cox, 1996). Although a conventional Gaussian kernel is 8mm, the most effective smoothing parameter for individual data sets is unknown. Thus, the data were re-analyzed using two additional Gaussian kernels in order to see if the whole-brain hierarchical regression analysis exploring both the linear and quadratic relationships between age and percent signal-change was significant. However, neither a 5mm Gaussian kernel or a 12mm Gaussian kernel revealed any brain regions that showed significant quadratic relationship with age.

Removal of poor performers. A qualitative evaluation of the data revealed that one participant achieved only 67% ACC. Thus, this participant was dropped from the analysis. However, the hierarchical regression analysis did not reveal any significant

clusters indicating a quadratic relationship between percent BOLD signal-change and age.

Removal of poorly registered images. A qualitative evaluation of the data revealed that one participant's functional data did not align well with her anatomical data, which could result in voxel-loss at the group level. Thus, this participant was dropped from the analyses. However, the hierarchical regression analysis did not reveal any significant clusters indicating a quadratic relationship between percent BOLD signal-change and age.

Removal of participants who moved in the scanner. Although motion correction parameters were applied, each participant's data was evaluated to identify participants who moved their heads more than 1 mm; head movements during data acquisition can create noise in the BOLD signal estimates. Three participants were identified who moved more than 1 mm, and these participants were dropped from the analyses. However, the hierarchical regression analysis did not reveal any significant clusters indicating a quadratic relationship between percent BOLD signal-change and age.

SECTION THREE
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