

When less is more: Thinner fronto-parietal cortices are associated with better forward digit span performance during early childhood

Morgan Botdorf & Tracy Riggins

Department of Psychology, University of Maryland, College Park, MD, USA.

Abstract

Although research shows that working memory improves during early childhood, it remains unclear how the fronto-parietal network of cortical regions, known to support this ability in adults, relates to changes in young children. Measures of cortical thickness may be useful in investigating this association as they reflect age-related differences in gray matter and have been proposed to support age-related improvements in other cognitive abilities, but have only sparingly been tested empirically in early childhood. The present study sought to investigate relations between cortical thickness and performance on a digit span task in 200 4- to 8-year-old children using both a priori defined regions of interest related to working memory (superior frontal cortex, middle frontal cortex, anterior cingulate cortex, superior parietal cortex) and whole brain analyses. Results indicated a significant association between cortical thickness in each a priori fronto-parietal region and performance on digit span, such that those with a thinner cortex recalled more items than those with a thicker cortex. Similar regions emerged from the whole brain analyses, as did several other regions not typically included in the fronto-parietal network. Results of a mediation analysis indicated that age-related differences in behavior were partially explained by variations in thickness of anterior cingulate cortex, suggesting a potentially important role for this structure during early childhood. Overall, these results suggest that in children as young as 4 years of age there are associations between working memory abilities and thickness in cortical areas known to support working memory in adults.

Keywords: cortical thickness, working memory, early childhood, structural MRI

Research Highlights

- Relations between age, digit span, and cortical thickness in children were assessed.
- Associations were assessed using both a priori regions and whole brain analyses.
- Cortical thickness in fronto-parietal regions related to digit span score.
- Anterior cingulate cortex mediated the association between age and digit span.
- Development of fronto-parietal regions relates to working memory in young children.

Introduction

Developmental research has shown that working memory (i.e., the ability to temporarily store and manipulate information) is both integral to successful learning in the classroom and an important predictor of academic success (Alloway & Alloway, 2010; Alloway, Gathercole, Willis, & Adams, 2004; Baddeley, 1992; Bull, Espy, & Wiebe, 2008). Improvements in working memory have been documented as early as 4 years of age (Gathercole, Pickering, Ambridge, & Wearing, 2004) and are thought to continue into early adulthood (Luciana, Conklin, Hooper, & Yarger, 2005; Luna, Garver, Urban, Lazar, & Sweeney, 2004).

Although models differ on how they characterize working memory (e.g., Baddeley & Hitch, 1974; Cornoldi & Vecchi, 2003; Cowan, 1999; Jonides et al., 2008; Logie, 2011), a widely accepted model that is supported by a wealth of research suggests that working memory consists of three core subcomponents: (1) the central executive, (2) visuospatial sketchpad, and (3) phonological store (Baddeley & Hitch, 1974). The visuospatial sketchpad and phonological store are involved in the processing and maintenance of visual and verbal information, respectively, and can be thought of as a short-term memory store (Baddeley, 1992). The central executive supports the manipulation and regulation of information in these stores. The visuospatial sketchpad and phonological store have been shown to reach maturity earlier than the central executive (Luciana et al., 2005). The phonological store, in particular, improves a great deal in childhood, such that the span for verbal information increases from 2 items to around 7 items by adulthood (Hulme, Muir, Thomson, & Lawrence, 1984). Research has shown that this component may be functioning as early as 2 years of age; however, it is around the age of 4 that accelerated changes typically occur (Gathercole, 1999), which then contribute to changes in working memory as a whole (Gathercole et al., 2004).

While it is clear that working memory and its subcomponents show improvements in early childhood, it is less clear how changes in the brain may support these behavioral improvements. A great deal of research has examined the neural correlates of working memory in adults using functional neuroimaging. Although many regions have been implicated in working memory, much research has highlighted the fronto-parietal network, including regions in frontal, parietal, and cingulate cortices, as being particularly important to working memory. Specifically, regions in this network tend to show functional activation during tasks assessing working memory (e.g., Burzynska et al., 2011; Bush et al., 1999; Cabeza & Nyberg, 2000; Casey et al., 1998). These findings of a fronto-parietal network are well established and reliable, as a meta-analysis of 189 studies examining the neural correlates of working memory in adults showed consistent bilateral activation of this network of regions (Rottschy et al., 2012).

Research has also investigated regions supporting the development of working memory ability in school-aged children (> 8 years) and adolescents. Results of these studies typically parallel those found in adults, showing activation in frontal, parietal, and cingulate regions during working memory tasks, although levels of activation may differ relative to adults (Casey, Tottenham, Liston, & Durston, 2005; Klingberg, Forssberg, & Westerberg, 2002; Luciana & Nelson, 1998; Nelson et al., 2000). Additionally, developmental studies have shown that working memory activation may be more widespread in children than adults as more regions are recruited to carry out processes that later become specialized in late adolescence and adulthood (Geier, Garver, Terwilliger, & Luna, 2009). For example, some research points to cingulate regions as being especially important to working memory in early childhood relative to adulthood (Kharitonova, Winter, & Sheridan, 2015).

Although the aforementioned studies have provided a foundation for understanding the neural underpinnings of working memory in school-aged children and adolescents, the methods employed are difficult to implement in studies of younger (i.e., preschool-aged) children. Specifically, the requirement of concurrently remaining still and performing a task in the scanner is particularly challenging for young children. To begin to examine neural correlates in younger children, researchers have turned to other methods, such as structural MRI (e.g., Sowell et al., 2004; Tamnes et al., 2013). In these studies, behavioral measures of working memory are obtained and then related to structural images obtained during short scanning sessions where the children are simply required to remain still (and often allowed to watch a movie to enhance compliance). One advantage of this approach over studies using functional activation is that it not only identifies regions showing brain-behavior relations, but also addresses potential neurobiological mechanisms that may underlie these associations, such as synaptic pruning and increased myelination. However, the exact relation between these processes and the measures derived from structural MRI (i.e., cortical thickness, gray matter volume) is still debated. Although these changes in the brain are complex in nature, they are thought to begin between the ages of 4 and 6 years, continue throughout adolescence, and result in decreases in cortical gray matter (Brown & Jernigan, 2012). Thinning of gray matter during childhood is particularly characteristic of the maturation of frontal and parietal lobes, regions that are important to working memory in adults and children (Brown & Jernigan, 2012; Sowell et al., 2004).

Studies have started to investigate relations between maturation of cortical regions and behavioral differences in working memory in children. Thus far, research has suggested that decreases in cortical gray matter, as measured using cortical thickness, may be important for the development of working memory (e.g., Bathelt, Gathercole, Johnson & Astle, 2017; Darki &

Klingberg, 2015; Faridi et al., 2015; Kharitonova, Martin, Gabrieli, & Sheridan, 2013; Østby, Tamnes, Fjell, & Walhovd, 2011; Tamnes et al., 2013) as well as general executive function (e.g., Shaw et al., 2006; Sowell, Delis, Stiles, & Jernigan, 2001; Tamnes et al., 2010). This association between cortical thickness and working memory has been shown for multiple cortical regions, including those in the fronto-parietal network (e.g., superior parietal cortex, rostral middle frontal cortex; Kharitonova et al., 2013; Østby et al., 2011; Tamnes et al., 2013).

However, the majority of the aforementioned studies include a wide age range (e.g., 8-22 years, Tamnes et al., 2013) and few include individuals younger than 7 years (cf. Kharitonova et al., 2013), and none younger than 5 years. Of the studies that have included children younger than 7 years of age (i.e. Bathelt et al., 2017, Darki & Klingberg, 2015; Kharitonova et al., 2013), the mean age is typically around 9 or 10 years, and these studies only include a handful of 5-, 6-, or 7-year-old children. This is a problematic gap given that early childhood (i.e. 4-6 years of age) may be a time when important cortical changes and improvements in working memory are occurring. Furthermore, this is a time when many children transition to school and working memory becomes critical for successful learning. A deeper understanding of cortical changes implicated in working memory would potentially inform interventions for children who are at risk for memory impairments.

In summary, the present study aimed to explore relations between working memory and regions in the fronto-parietal network in a large cross-sectional sample focused on early childhood (4-8 years old). Digit span was used to assess working memory. This task likely predominantly taps the phonological subcomponent of working memory, the development of which impacts working memory in early childhood (Alloway et al., 2004). We hypothesize that a thinner cortex in fronto-parietal regions would relate to better digit span performance. We

explore these relations by utilizing both a priori defined regions of interest (ROIs) included in the fronto-parietal network and whole brain vertex-by-vertex analyses. The a priori ROIs allow us to test specific regions known to be important to working memory in adults and older children, while the whole brain analyses allows us to supplement our findings and explore whether additional regions outside this network are related to working memory. The present study will allow for a further understanding of the neural basis of differences in working memory during early childhood, a period of time when both cortical and working memory development have been shown to occur.

Methods

Participants

A total of 200 4- to 8-year-old children participated in the present study, which is part of an ongoing longitudinal investigation examining brain and memory development in early childhood. Of these, 189 children underwent scanning and yielded T1 scans for processing (6 children did not undergo scanning because they refused to enter the scanner, 1 did not keep their scan appointment, 2 were born premature, and 2 had difficulty understanding English). Three of the acquired T1 scans were deemed unusable due to motion artifact. Thus, the final sample used in analyses of cortical thickness included 186 (89 male, 97 female) 4- to 8-year-old children (average age at time of scan 6.26 years, $SD = 1.47$). Breakdown of participants by age and sex was as follows: 46 4 year olds (23 male), 39 5 year olds (17 male), 41 6 year olds (26 male), 29 7 year olds (12 male), and 31 8 year olds (11 male). Younger age groups were oversampled to ensure enough useable data would be available and because they were being followed longitudinally.

Procedure

Parents gave informed consent and children over the age of 7 years gave written assent to participate in the study. Children visited the laboratory twice for a behavioral and neuroimaging session. During the behavioral session, participants completed a forward digit span task and intelligence measure. In addition, several other cognitive tasks were administered, but are not discussed in this paper. Approximately one week later, children returned to the lab for a structural MRI scan.

Measures

Forward Digit Span. Working memory was measured using a forward digit span task (Wechsler, 1974). This task measures the number of items a child can maintain in working memory. Based on the definitions discussed above and prior research, this task draws most heavily on the phonological component of working memory as it does not involve manipulation of information, but instead maintenance of verbal information (Alloway et al., 2004). As such, this task serves as an index of working memory and has been shown to be a useful predictor of school performance, including children's mathematical ability (Bull & Scerif, 2001). It has also been widely used in clinical settings and has been shown to be associated with attentional deficits, including ADHD (e.g. Karatekin & Asarnow, 1998). Furthermore, the simplicity of the task allows it to be used in preschool as well as school-aged children (Gathercole & Adams, 1993).

In the forward digit span task, the experimenter read aloud digits to the participant, and participants were instructed to listen to the sequence of the digits and then repeat them aloud in a forward manner. Digits were presented at a rate of one digit per second. Participants first

completed four practice trials of two-digit sequences to ensure comprehension. The task began with two digits per sequence at level one and increased by one digit per level for a maximum of eight digits per sequence at level seven. There were four sequences of digits for each level. If the child correctly recalled the digit sequence for two out of four trials in a level, they moved to the next level. If this criterion was not reached, the task ended. A participant's digit span score was measured as the proportion of correct sequences recalled out of the total possible number of sequences.

Intelligence. Indices of general intelligence (IQ) were obtained using subtests from age-appropriate standardized IQ tests (Wechsler Intelligence Scale for Children Fourth Edition, or WISC, and the Wechsler Preschool and Primary Scale of Intelligence, or WPPSI). Scaled scores from the block design subtest were obtained for use as covariates in analyses including working memory performance to control for general differences in IQ. Eight children were not administered the IQ test at this assessment period and were not included in analyses using IQ.

MRI Acquisition

Participants completed training in a mock scanner before MR data acquisition in order to become acclimated to the scanning environment and receive motion feedback. Additionally, head movement was minimized during scan acquisition using padding around the participants' heads. In some cases, if these efforts to obtain high quality scans were unsuccessful, families were invited back to the lab on another day to attempt the MRI scan again. Participants were scanned in a Siemens 3.0-T scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions, Erlangen, Germany) using a 32-channel coil. Structural data were collected using a high-resolution T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence consisting

of 176 contiguous sagittal slices (.9 mm isotropic; 1900 ms TR; 2.32 ms TE; 900 ms inversion time; 9° flip angle; pixel matrix = 256 × 256).

MRI Analysis

Images were analyzed using FreeSurfer Version 5.1.0, a standard automatic segmentation program (surfer.nmr.mgh.harvard.edu; Fischl, 2012; Fischl et al., 2002). Use of FreeSurfer has been validated in children as young as 4 years of age (Ghosh et al., 2010). Boundary lines separating gray/white and pial surfaces were visually inspected to ensure accuracy. Specifically, two independent editors inspected the boundaries of each slice for errors, including slices where the pial boundary contained portions of the skull and slices where the gray/white matter boundary extended into or beyond the skull. If errors lasted for more than 7 slices, editors corrected these errors first by changing the watershed value within FreeSurfer and then by editing manually, if necessary (Ducharme et al., 2016). Edits were made on approximately 35% of the sample and typically involved fewer than 20 slices per subject. An experienced reviewer (MB) completed a final quality check. Cortical thickness was calculated by measuring the distance from the gray/white matter boundary to the pial boundary (Fischl & Dale, 2000).

The Desikan-Killiany Atlas, which includes 34 gyral-based cortical regions, was used for cortical parcellation (Desikan et al., 2006). Total gray matter volume was also extracted using FreeSurfer (Fischl et al., 2002) and was used as a control variable to ensure that effects were not driven by overall differences in gray matter, and instead were specific to the regions assessed. Because of concerns that FreeSurfer might provide an imprecise measure of gray matter, we compared gray matter calculations obtained from FreeSurfer to those obtained by another more robust method (see Tillman et al., 2017). Gray matter calculations were similar using both

methods so we elected to use FreeSurfer's calculations to keep all brain analyses within the same toolbox.

Regions of Interest

Based on previous functional research in adults and children indicating a fronto-parietal network of core regions important to working memory, we included four a priori ROIs: superior frontal cortex (SFC), middle frontal cortex (MFC), superior parietal cortex (SPC), and anterior cingulate cortex (ACC) (Figure 1, Panel A). ROIs were created by averaging cortical thickness values of the areas that comprised these regions. SFC was created by averaging left and right hemisphere values for SFC. MFC was created by averaging values for left and right rostral MFC. SPC was created by averaging values for left and right SPC. Finally, ACC was created by averaging left and right hemisphere values for rostral and caudal ACC.

Statistical Analysis Plan

Covariates. Sex, total gray matter volume, and age were included as covariates in all analyses. IQ was used as a covariate in all analyses including memory to ensure that results were specific to memory and were not simply the result of differences in general intelligence.

Correction for Multiple Comparisons. Since four regions were assessed, alpha levels were adjusted for multiple comparisons using a Bonferroni correction. $P_{\text{corrected}} < .05$ indicates significance values that satisfy the threshold imposed by this correction ($p < .0125$). In analyses examining effects of lateralization, 8 tests were conducted, thus $P_{\text{corrected}} < .05$ indicates significance values that satisfy the threshold imposed by this correction ($p < .006$).

Behavioral Analyses. Behavioral data were first analyzed to investigate the association between age and performance on digit span. Specifically, a linear regression was run entering

digit span score as the dependent variable, age as the independent variable, and IQ and sex as covariates.

MRI Analyses. MRI data were analyzed to investigate the associations between age and cortical thickness in each region using a series of linear regressions. Specifically, thickness of each specified ROI was entered as the dependent variable, age was entered as the independent variable, and total gray matter volume and sex were entered as covariates.

Associations between digit span and cortical thickness of each ROI were then examined with linear regressions entering digit span score as the dependent variable, cortical thickness of each specified ROI as the independent variable, and sex, IQ, and total gray matter volume as covariates. Significant associations between cortical thickness and digit span were then probed using regression analyses assessing the effect of hemisphere to determine if results were specific to one hemisphere or the other.

Age was not included as a covariate in the aforementioned analyses as we were interested in investigating associations related to age rather than age-independent relations (i.e., individual differences). However, follow-up regression analyses adding age as a covariate were also run to understand whether associations exist irrespective of age.

After identifying associations between age and digit span score, age and cortical thickness, and cortical thickness and digit span score, a mediation model was tested in order to statistically assess whether performance on the digit span task was due (at least in part) to age-related differences in cortical thickness. Separate models were tested with age as the predictor, each ROI as the mediator, and digit span score as the dependent variable. Hayes' SPSS PROCESS macro (Hayes, 2013) was used to test the mediation models. This method uses

bootstrapping to calculate confidence intervals for the indirect effect. Confidence intervals that do not include zero indicate a significant mediation model where age indirectly affects digit span score via the specified ROI.

Whole Brain Vertex-by-Vertex Analyses. Following analyses with the a priori defined ROIs, whole brain vertex-by-vertex analyses were carried out using the QDEC program within FreeSurfer. These analyses were run to support results obtained with the a priori ROIs and to ensure that important regions were not missed. Smoothing was applied with a 10mm FWHM Gaussian kernel. General linear models were used to test the association between digit span score and cortical thickness controlling for IQ and total gray matter volume. One analysis was run for each hemisphere. A Monte Carlo Simulation was used to correct for multiple comparisons and estimate cluster size limits (Hagler, Saygin, & Sereno, 2007). A threshold of $p < .05$ was considered significant.

Results

Behavioral Data

Relations between age and digit span. Participants varied in their performance on the digit span task with scores ranging from 0.29 to 1.00 ($M = 0.64$, $SD = 0.16$). To examine associations between age and digit span, a linear regression was conducted. Results indicated a significant effect that explained 32.20% of the variance in digit span (adjusted $R^2 = 0.32$, $F(3,177) = 28.28$, $p < .001$). Age was a significant predictor of digit span score ($\beta = 0.57$, $p < .001$) even after controlling for effects of sex ($\beta = -0.01$, $p = .87$) and IQ ($\beta = 0.03$, $p = .65$), such that increases in age were associated with better digit span performance (see Supplementary Figure S1).

MRI Data

Relations between age and cortical thickness. Results indicated that age was a significant predictor of cortical thickness for all regions (SFC, ACC, SPC), except MFC (Figure 1, Panel B; Table 1).

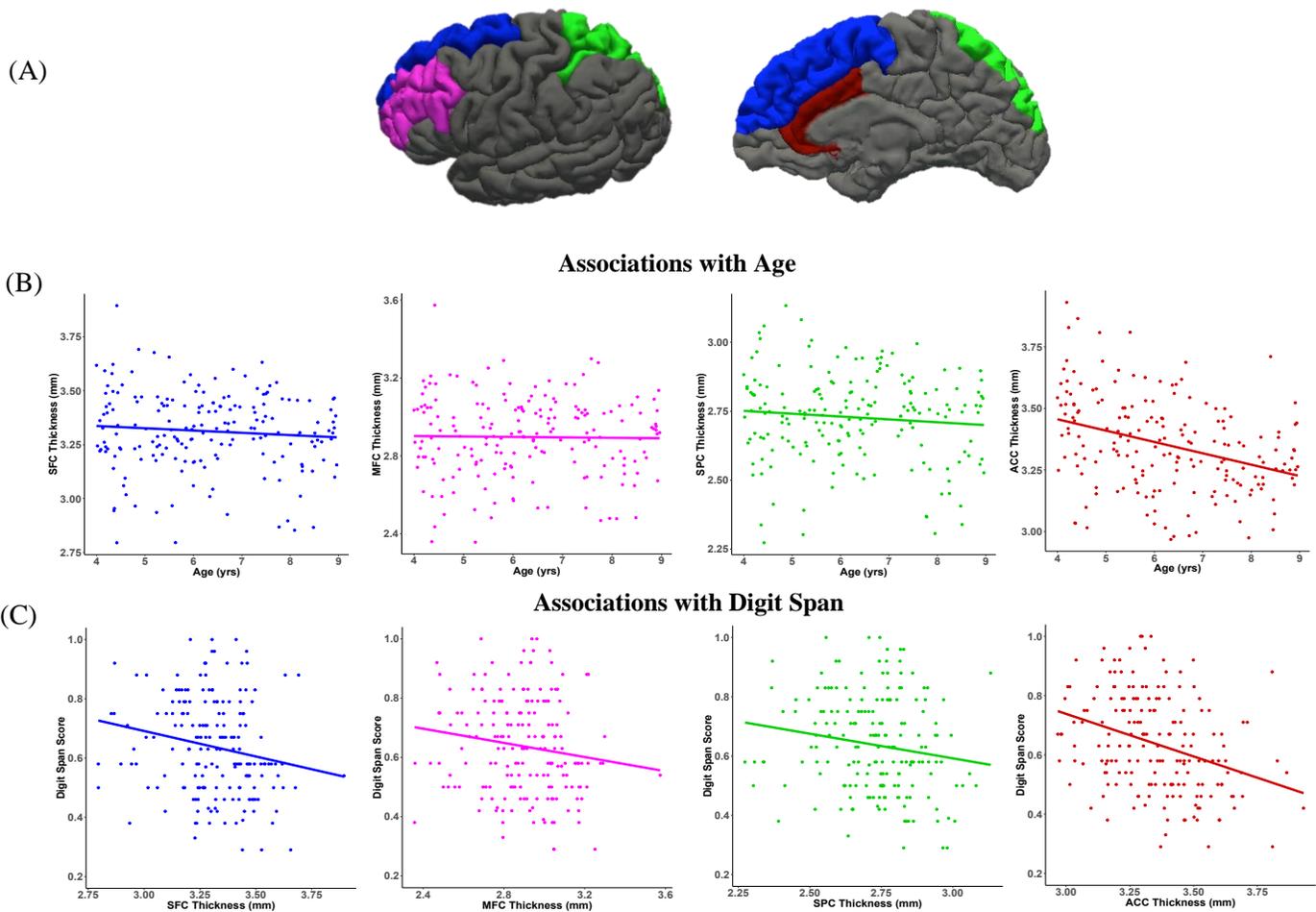


Figure 1. Panel A shows the location of superior frontal cortex (blue), middle frontal cortex (pink), superior parietal cortex (green), and anterior cingulate cortex (red). Panel B shows associations between age and thickness of each ROI. Panel C shows associations between thickness of each ROI and digit span score.

Table 1

Summary of regression analyses for age predicting thickness in each ROI (N = 186)

Predictor variables	SFC	MFC	ACC	SPC
	β	β	β	β
Sex	0.26*	0.22*	0.24*	0.22*
Total Gray Matter Volume	0.35*	0.39*	0.04	0.47*
Age	-0.19*	-0.13	-0.39*	-0.23*
Adj. R^2	0.12	0.13	0.17	0.20
F	9.48*	10.02 *	13.24*	15.93*

* $P_{\text{corrected}} < .05$, † $p < .05$

Relations between digit span and cortical thickness. Results indicated that thickness of each region (SFC, MFC, ACC, SPC) was a significant predictor of digit span score. For all regions, individuals with a thinner cortex in the specified area performed better than those with a thicker cortex (see Table 2). Panel C of Figure 1 depicts associations between cortical thickness in each region and digit span score.

Follow-up analyses investigating lateralization of these effects indicated that both right and left hemispheres of SFC and ACC were significant predictors of digit span. Right and left MFC were significant predictors of digit span, but associations did not survive corrections for

multiple comparisons. Finally, right SPC was a significant predictor of digit span, whereas left SPC was not (see Supplementary Table S1).

Table 2

Summary of regression analyses for thickness in each ROI predicting digit span (N = 178)

Predictor variables	SFC	MFC	ACC	SPC
	β	β	β	β
IQ	0.06	0.05	0.10	0.05
Sex	0.13	0.12	0.14	0.12
Total Gray Matter Volume	0.20*	0.21†	0.10	0.22*
ROI	-0.24*	-0.21*	-0.35*	-0.22*
Adj. R^2	0.06	0.04	0.12	0.05
F	3.66*	2.94†	7.19*	3.14†

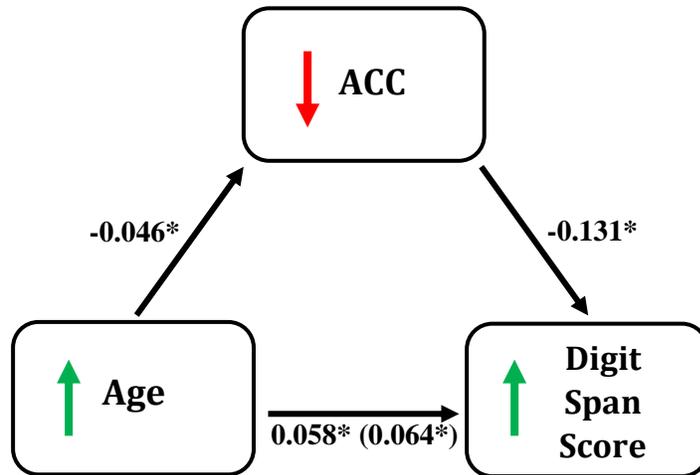
* $P_{\text{corrected}} < .05$, † $p < .05$

Follow-up analyses adding age as a covariate indicated that SFC, MFC, and ACC remained significant predictors of digit span score even after controlling for age ($\beta = -0.15$ - - 0.14 , $ps < .05$). In contrast, after controlling for effects of age, SPC was no longer a significant predictor of digit span score ($p = .19$).

Does cortical thickness mediate relations between age and digit span? Significant mediation was observed for the model with ACC as the mediator. Specifically, there was a significant indirect effect of age on digit span score through ACC thickness, ($b = 0.006$,

SE=0.0027, CI = [0.0011, 0.0116]) (Figure 2). The mediation models with SFC (CI = [-0.0011, 0.0044]), MFC (CI = [-0.0025, 0.0027]), and SPC (CI = [-0.001, 0.004]) were not significant.

Standardized regression coefficients are also presented in Figure 3.



Indirect effect: 0.006 (Bootstrap SE = 0.0027), 95% CI [0.0011, 0.0116]

Figure 2. Standardized regression coefficients for the relation between age and digit span score as mediated by ACC thickness. The standardized regression coefficient in parentheses represents the total effect of age on digit span score, * $p < .05$.

Whole brain vertex- by-vertex analysis

Clusters showing a significant association between digit span score and cortical thickness are presented in Figure 3. Results indicated eight significant clusters in right hemisphere (Table 3) and six significant clusters in left hemisphere (Table 4). Each of these associations was negative indicating that a thinner cortex in these regions is associated with better digit span performance.

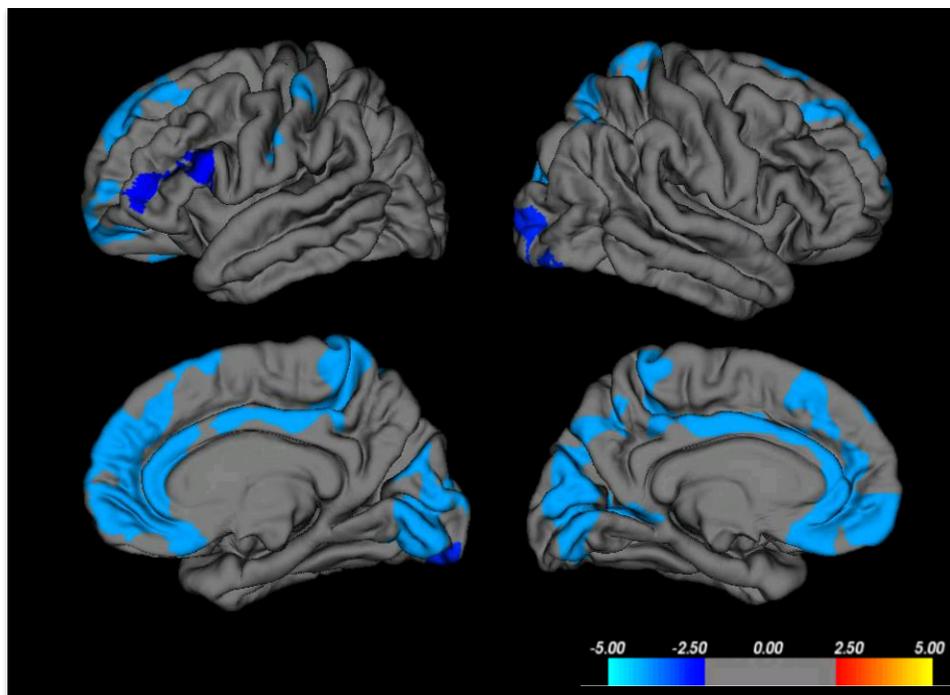


Figure 3. Results of whole brain vertex-by-vertex analyses showing clusters of significant associations between cortical thickness and digit span score.

Table 3

Right hemisphere clusters indicating a significant association between digit span score and cortical thickness

Region	Hemisphere	Cluster Size (mm ²)	x	y	z
Lingual	right	1232.41	4.7	-83.6	0.4
Rostral Anterior Cingulate	right	1093.07	7.4	36.1	7.3
Inferior Parietal	right	558.33	33.3	-66.2	32.5
Paracentral	right	502.03	13.6	-35.7	58.4
Superior Frontal	right	485.32	8.7	39.5	29
Lateral Occipital	right	336.70	40.7	-66.2	5.7
Middle Temporal	right	320.47	51.8	-36.1	-3.4
Transverse Temporal	right	288.25	43.6	-21.2	4.9

Note. Coordinates are in Talairach space and represent the maximum vertex.

Table 4

Left hemisphere clusters indicating a significant association between digit span score and cortical thickness

Region	Hemisphere	Cluster Size (mm ²)	x	y	z
Medial Orbitofrontal	left	3972.40	-9.2	44.6	-11.2
Cuneus	left	3858.32	-4.4	-74.8	20.8
Postcentral	left	1314.04	-39.6	-24.7	53.2
Superior Frontal	left	1202.52	-13.6	50.8	25.7
Rostral Middle Frontal	left	865.92	-38.6	43.7	1.7
Lateral Occipital	left	740.33	-22.5	-93.4	5.9

Note. Coordinates are in Talairach space and represent the maximum vertex.

Discussion

Our results indicate that variations in cortical thickness in frontal, parietal, and cingulate cortices relate to age-related differences in working memory during early childhood.

Specifically, results from analyses including a priori ROIs show that thickness in each ROI (SFC, MFC, ACC, SPC) was negatively associated with performance on the digit span task, such that children with a thinner cortex in each of the regions performed better on the task than

children with a thicker cortex. These findings are consistent with research in older children and adolescents (e.g., Tamnes et al., 2013), which found associations between thinning in prefrontal and parietal cortices and working memory performance. Furthermore, the relation between SPC and digit span is similar to research by Kharitonova et al. (2013), which showed the same association using a forward digit span task in 5- to 10-year-old children. The association with MFC is consistent with research by Østby et al. (2011), which showed an association between this region and forward digit span in 8- to 19-year-old children and adolescents. Analyses investigating specificity of effects with regards to hemisphere suggested that there was no specificity for SFC or ACC as both right and left hemispheres of these regions were significant predictors of digit span. However, results with SPC did suggest specificity as right, but not left, SPC was a significant predictor of digit span. Neither right nor left MFC survived corrections for multiple comparisons.

ACC was the only region to mediate the relation between age and digit span suggesting that with increases in age, the thickness of the cortex thins, which then in turn impacts working memory performance. Although the effect size was small, these results raise the question of why this region, in particular, is important to explaining age-related differences in working memory in this young age group. ACC is undoubtedly important to working memory, but it is not thought to be as critical to this process as frontal regions are thought to be. However, different regions of the cortex may differentially impact working memory throughout development. Since ACC showed the strongest association with age, this region may be developing particularly rapidly during this time period and may contribute to more general improvements in cognition. It may also be that ACC is part of a wider network of activation, typically seen in functional studies of children (Geier et al., 2009). These networks become more specialized with age, resulting in

improvements in cognitive processes, such as working memory (Casey et al., 1995; Durston et al., 2006). Adding to this interpretation, results from a study by Kharitonova and colleagues (2015) indicated that ACC showed more activation in 6-year-old children relative to adults across all difficulty levels of a working memory capacity task. Therefore, in our young age group, ACC may be more important to working memory than in adulthood when the neural network supporting this process is more specialized in nature.

Significant mediation was not observed for SFC, MFC, or SPC suggesting that associations between these ROIs and digit span reflect individual differences rather than age-related differences. Similarly, after holding age constant, cortical thickness in both SFC and MFC still significantly predicted digit span score suggesting that associations exist irrespective of age. These associations, specifically in frontal regions, are consistent with prior research showing relations between individual differences in the structure of the cortex and digit span performance (Østby et al., 2011). Individual differences in cortical thickness may reflect multiple influences, as many factors have been shown to affect cortical development, including, but not limited to socioeconomic status (Luby et al., 2013), vitamin and mineral deficiency (Georgieff, 2007), and prenatal stress (Lou et al., 1994). Furthermore, some research indicates that genetics could contribute to the thickness of these regions (Schmitt et al., 2008). Although a sizeable body of research suggests that the development of the cortex is influenced by many factors, empirical support for these claims is often lacking. A ripe avenue for future research would be to focus on identifying specific factors that impact the structure of the cortex, particularly during early childhood.

In addition to relations with working memory performance, our results also indicated age-related differences in the thickness of SFC, SPC, and ACC such that older children had a

thinner cortex than younger children. These results are consistent with findings by Sowell and colleagues (2004) and Brown and Jernigan (2012), both of which showed thinning occurring in frontal and parietal regions in early childhood. Although the exact processes underlying this decrease in gray matter are not known, we can infer that it is likely due to a combination of pruning of inefficient synapses and increased myelination, both of which are thought to support the development of cognitive processes in childhood (Brown & Jernigan, 2012; Giedd et al., 1999). Age was not associated with MFC thickness. It is possible that MFC follows a different, potentially more protracted, developmental trajectory relative to the other regions. Fittingly, research has shown that frontal regions mature later in childhood relative to other cortical regions (Casey, Giedd, & Thomas, 2000). Therefore, it is possible that the developmental trajectory of thinning would be captured in an older age group not included in this study.

Results from the whole brain vertex-by-vertex analyses support the results from the a priori analyses by indicating clusters of significant associations between digit span and thickness in SFC, MFC, and ACC. In addition to these regions, several regions not included in the fronto-parietal network emerged supporting the notion highlighted above and in previous research that working memory in young children likely relies on a network of regions distributed throughout the brain (Casey et al., 1995; Durston et al., 2006; Geier et al., 2009). Although the fronto-parietal network may be the core set of regions implicated in working memory in children, regions from other networks may also serve important roles, as connections between regions are refined for processing.

Our large sample of preschool and school-aged children fills an important gap in the literature as previous research has only sparingly focused on this age range and no study has included children younger than 5 years of age. This systematic focus on early childhood allowed

us to further understand how changes that may be occurring in the cortex may parallel behavioral changes in working memory. In addition, our inclusion of cingulate regions along with frontal and parietal regions allowed us to focus on specific regions that are implicated in working memory in adults, while our whole brain vertex-by-vertex analyses allowed us to elucidate other brain regions that may not be typically included as core regions important for working memory in adults. The results of our study underscore the importance of studies utilizing multiple approaches when studying structural brain and cognitive development in early childhood.

Although our cross-sectional study is the first to include preschool-aged children, it is important that future research replicate these results with longitudinal data to better aid in our understanding of specific developmental mechanisms contributing to behavioral changes in working memory. Additionally, the digit span task used in this study likely predominantly taps the phonological store, the development of which contributes to working memory development. Although digit span is a well-known task used extensively in clinical as well as research settings, a task or battery of tasks that involves the manipulation of information in working memory and also assesses both spatial and verbal working memory would be beneficial to determining whether the present results extend to working memory tasks across domains.

Overall, our results suggest that in early childhood, there are associations between working memory ability, assessed via digit span, and thickness in cortical regions known to support working memory in adults. Specifically, results suggest that these associations are present in children as young as 4 years of age and that ACC may be an important region underlying the development of working memory. These findings provide a basis for further investigations into associations between cortical structure and development of other higher order cognitive processes (e.g., episodic memory) in early childhood.

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