# Longitudinal Working Memory Development Is Related to Structural Maturation of Frontal and Parietal Cortices

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## Abstract

■ Parallels between patterns of brain maturation and cognitive development have been observed repeatedly, but studies directly testing the relationships between improvements in specific cognitive functions and structural changes in the brain are lacking. Working memory development extends throughout childhood and adolescence and likely plays a central role for cognitive development in multiple domains and in several neurodevelopmental disorders. Neuroimaging, lesion, and electrophysiological studies indicate that working memory emerges from coordinated interactions of a distributed neural network in which fronto-parietal cortical regions are critical. In the current study, verbal working memory function, as indexed by performance on the Keep Track task, and volumes of brain regions were assessed at two time points in 79 healthy children and adolescents in the age range of 8–22 years. Longitudinal change in cortical and subcortical volumes was quantified by the use of Quantitative Anatomical Regional Change. Improvement in working memory was related to cortical volume reduction in bilateral prefrontal and posterior parietal regions and in regions around the central sulci. Importantly, these relationships were not explained by differences in gender, age, or intelligence level or change in intellectual abilities. Furthermore, the relationships did not interact with age and were not significantly different in children, young adolescents, and old adolescents. The results provide the first direct evidence that structural maturation of a fronto-parietal cortical network supports working memory development. ■

## INTRODUCTION

Cognitive development in childhood and adolescence is the result of a dynamic interaction between maturation and learning, and parallels between patterns of brain maturation and cognitive development have been observed (Lebel & Beaulieu, 2011; Gogtay et al., 2004). Still, aside from two notable exceptions focusing on general cognitive abilities (Shaw et al., 2006; Sowell et al., 2004), there is a lack of longitudinal studies directly linking cognitive functions and brain structure in development. In a large sample of children and adolescents, Shaw et al. (2006) found that the trajectory of change in the cerebral cortex, rather than the cortical morphology itself, was most closely related to the level of intelligence. The results indicated that children at different levels of intelligence had different cortical maturational trajectories, primarily in frontal regions, and that children with higher intelligence scores had a more plastic cortex. Sowell et al. (2004) tested the relationships between change in both behavioral performance and cortical structure in a group of children followed over 2 years and found that those who improved more in verbal intellectual ability had greater cortical thin-

ning in lateral dorsal frontal and parietal regions in the left hemisphere (LH). However, no previous studies have attempted to map change in specific cognitive functions directly to the maturation of specific brain networks. Here, we test the relationships between change in verbal working memory performance and change in cortical and subcortical volumes in a group of children and adolescents.

Working memory, conceptualized as a limited capacity multicomponent system for the temporary maintenance and manipulation of information (Baddeley, 2012), is an interesting candidate for testing the relationships between development of specific cognitive functions and structural brain maturation for several reasons. First, working memory performance is known to improve throughout childhood and adolescence (Conklin, Luciana, Hooper, & Yarger, 2007; Waber et al., 2007; Gathercole, Pickering, Ambridge, & Wearing, 2004; Luna, Garver, Urban, Lazar, & Sweeney, 2004) and to be predictive of scholastic attainment (Alloway & Alloway, 2010; Hitch, Towse, & Hutton, 2001). Second, working memory supports other cognitive processes by providing an interface between perception, long-term memory, and action (Baddeley, 2012) and is therefore of central importance for cognitive development in multiple domains. Third, deficits in working memory are observed in many neurodevelopmental

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disorders, including attention-deficit hyperactivity disorder and schizophrenia (Forbes, Carrick, McIntosh, & Lawrie, 2009; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). Finally, a large number of neuroimaging, lesion, and electrophysiological studies provide a tentative mapping of working memory onto a network of anatomical localizations (Sander, Lindenberger, & Werkle-Bergner, 2012; D'Esposito, 2007; Linden, 2007; Muller & Knight, 2006; Baddeley, 2003).

Functional imaging studies using a variety of tasks have implicated a distributed network of brain regions, including prefrontal and posterior parietal cortices as well as primary cortical areas, in working memory functions in both adults (Burzynska et al., 2011; Nagel et al., 2011; Collette et al., 2005; Owen, McMillan, Laird, & Bullmore, 2005; Gerton et al., 2004; Wager & Smith, 2003; Cabeza & Nyberg, 2000) and children and adolescents (O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008; Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Klingberg, 2006; Scherf, Sweeney, & Luna, 2006; Olesen, Nagy, Westerberg, & Klingberg, 2003; Klingberg, Forssberg, & Westerberg, 2002; Kwon, Reiss, & Menon, 2002). Overall, a general similarity of the cortical regions at work in children and adults is indicated (Thomason et al., 2009). Some studies have also found working memory recruitment of subcortical structures, including BG (Moore, Li, Tyner, Hu, & Crosson, 2013; Podell et al., 2012; Chang, Crottaz-Herbette, & Menon, 2007; Olesen, Nagy, Westerberg, & Klingberg, 2003), hippocampus (Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010), and cerebellum (Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006), possibly with diminishing contributions with age in development.

Throughout childhood and adolescence, the brain undergoes a multifaceted and regionally differentiated maturational process. Magnetic resonance imaging (MRI) studies have documented considerable developmental structural changes in cerebral cortex and subcortical and cerebellar structures (Tamnes et al., 2013; Brown et al., 2012; van Soelen et al., 2012; Sullivan et al., 2011; Tiemeier et al., 2010; Shaw et al., 2008; Lenroot et al., 2007) as well as volumetric increases and microstructural changes, as indexed by diffusion tensor imaging, in white matter (Lebel & Beaulieu, 2011; Tamnes, Østby, Fjell, et al., 2010; Westlye et al., 2010). It is thus reasonable to assume that developmental improvements in working memory functions are supported by the structural maturation of specific brain regions.

Cross-sectional developmental studies have found age-independent associations between working memory performance and cortical thickness in frontal and parietal regions (Østby, Tamnes, Fjell, & Walhovd, 2011; Tamnes, Østby, Walhovd, et al., 2010), volume of the putamen (Pangelinan et al., 2011), and white matter microstructure in the superior longitudinal fasciculi (Østby et al., 2011; Vestergaard et al., 2011; Nagy, Westerberg, & Klingberg, 2004). The association fibers known collectively as the superior longitudinal fasciculi are the primary pathways providing bidirectional information transfer between the frontal and parietal cortices (Yeterian, Pandya, Tomaiuolo, & Petrides, 2012), and the latter results thus elaborate the evidence for the involvement of a fronto-parietal network in working memory. These age-independent associations are presumably partly mediated by variability in the pace of brain maturation (Jernigan, Baare, Stiles, & Madsen, 2011), but longitudinal studies are needed to directly test the relationships between working memory development and brain maturation.

This study addresses the following specific questions: (1) Is working memory development related to changes in cortical and subcortical volumes during childhood and adolescence? (2) Do these relationships interact with age? As no prior longitudinal studies have explored how working memory development relates to brain structure changes, we performed analyses both across the cortical surface and in a large number of subcortical structures. On the basis of the above-described functional imaging studies and studies showing gray-matter volume decreases in most regions in adolescence (Tamnes et al., 2013; Østby et al., 2009; Lenroot et al., 2007), we hypothesized that improvement in working memory performance would be associated with volume reduction in the network of prefrontal and posterior parietal cortices supporting working memory function as well as in BG structures. Furthermore, because cognitive development and brain maturation generally are more rapid at younger age, we tentatively also hypothesized that the relationships would vary with age and be stronger in children than in adolescents.

## METHODS

### Participants

The sample was drawn from the longitudinal research project "Neurocognitive Development" (Tamnes et al., 2013), University of Oslo. The study was approved by the Regional Committee for Medical and Health Research Ethics. Children and adolescents aged 8–19 years were recruited through newspaper ads and local schools. Written informed consent was obtained from all participants older than 12 years old and from a parent of participants under 16 years old. Oral informed consent was given by participants under 12 years old. At both time points, parents and participants aged 16 years or older completed screening for each participant with separate standardized health interviews to ascertain eligibility. Participants were required to be right handed; be fluent Norwegian speakers; have normal or corrected-to-normal vision and hearing; not have history of injury or disease known to affect CNS function, including neurological or psychiatric illness or serious head trauma; not be under psychiatric treatment; not use psychoactive drugs known to affect CNS functioning; not have had complicated or premature birth; and not have MRI contraindications. Additionally, all scans were evaluated by a neuroradiologist at both time points, and

participants were required to be deemed free of significant injuries or conditions.

At time point 1 (T1), 111 participants satisfied these criteria and had adequate processed and quality-checked MRI data. At time point 2 (T2), 18 participants did not want to or were unable to participate, two were not located, three had dental braces, three had a neurological or psychiatric condition, and six did not complete the behavioral assessment. Thus, the final sample for the current study included 79 children and adolescents (35 girls) with MRI and behavioral data from two time points. Mean age at T1 was 13.7 years ($SD$ = 3.4 years, range = 8.2–19.4 years), and mean age at T2 was 16.4 years ($SD$ = 3.4 years, range = 10.8–21.9 years). Mean interval between the two time points was 2.6 years ($SD$ = 0.2 years, range = 2.4–3.2 years). The length of the interval was not correlated with age ($r$ = −.15, $p$ = .198) and not different for girls and boys [$t(77)$ = 0.25, $p$ = .801].

## Behavioral Assessment

At both time points, verbal working memory was assessed by the Keep Track task (Figure 1) that was originally adapted from Yntema (1963) by Miyake et al. (2000), and previously modified for children and adolescents (Tamnes, Østby, Walhovd, et al., 2010). The task was administered using the E-Prime software (Schneider, Eschman, & Zuccolotto, 2002). Participants were first shown several target categories on the lower half of the computer screen. Sixteen words, including two or three exemplars from each of six possible categories (animals, clothing, colors, countries, fruit, and relatives), were then presented serially in a fixed pseudorandomized order for a duration of 2000 msec per word. The target categories remained on the screen during the trial. The task was to recall the last word presented in each of the target categories. Thus, the participants had to continuously select words belonging to the target categories and update their working memory representations. Immediately after each trial, participants were asked to recall these words, and the task administrator wrote down their responses and encouraged the participant to guess if an insufficient number of words were recalled. Participants first practiced on two trials with two and three target categories, respectively. The task itself consisted of four trials with three target categories, four trials with four target categories, and one trial with five categories, for a total of 33 words to be recalled. The proportion of the presented words of the target categories varied across trials and increased with the number of categories. The percentage of words recalled correctly was recorded at both time points. Change in working memory performance (score at T2 − score at T1) and annual change (change/scan interval) was then calculated. The change measures were not corrected for baseline values, as they may be associated because of systematic effects related to development.

Intelligence level was estimated at both time points by the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) that consists of the four subtests of vocabulary, similarities, block design, and matrix reasoning. Mean IQ at the two time points was 109.1 ($SD$ = 11.5, range = 82–141) and 112.2 ($SD$ = 10.6, range = 87–136), respectively. As the intelligence level estimates are adjusted for age according to norms and therefore not useful for indexing general cognitive development, we also calculated intellectual abilities scores that were not adjusted for age. This was done by first standardizing each of the subtest raw scores on both time points relative to the means and standard deviations at T1 and then calculating the mean of these four scores at each time point. Finally, we calculated change in the nonadjusted intellectual abilities and annual change.

## MRI Acquisition

Imaging data were collected at Oslo University Hospital, Rikshospitalet, using a 12-channel head coil on a 1.5-T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The sequences used for morphometry analysis were a minimum of two repeated 160 slices of sagittal T1-weighted magnetization prepared rapid gradient-echo sequences (repetition time [TR] = 2400 msec, echo time [TE] = 3.61 msec, time to inversion = 1000 msec, flip angle = 8°) per participant in each visit. To increase the signal-to-noise ratio, the runs
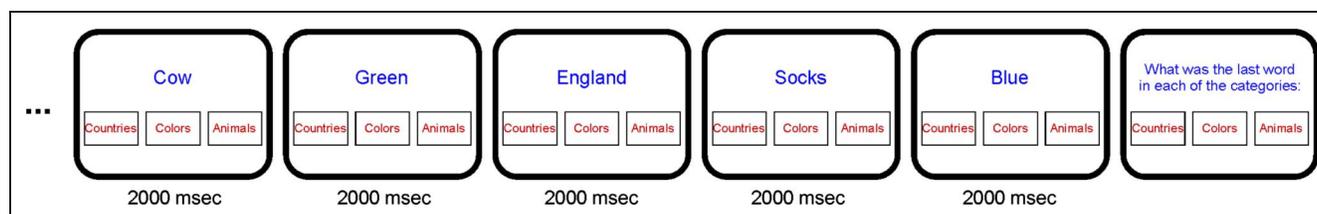


**Figure 1.** Keep Track task. Schematic illustration of the verbal working memory task, showing the last part of a single trial. At the beginning of each trial, participants were shown several target categories on the lower half of the computer screen. Sixteen words were then presented serially, whereas the target categories remained on the screen. Immediately after each trial, participants were asked to recall the last word presented in each of the categories, and the task administrator registered the responses. After two practice trials, the task consisted of four trials with three categories, four trials with four categories, and one trial with five categories.

were averaged during preprocessing. The protocol also included a 176-slice sagittal 3-D T2-weighted turbo spin-echo sequence (TR = 3390 msec, TE = 388 msec) and a 25-slice coronal FLAIR sequence (TR = 7000–9000 msec, TE = 109 msec) to aid the neuroradiological examination. The same scanner and pulse sequences were used at both time points.

## MRI Analysis

Image processing and analyses were performed at the Multimodal Imaging Laboratory, University of California, San Diego. The raw data were reviewed for quality and automatically corrected for spatial distortion because of gradient nonlinearity (Jovicich et al., 2006) and $B_1$ field inhomogeneity (Sled, Zijdenbos, & Evans, 1998). The two image volumes for each participant were coregistered, averaged to improve the signal-to-noise ratio, and resampled to isotropic 1-mm voxels. Volumetric segmentation (Fischl, Salat, et al., 2004; Fischl et al., 2002) and cortical surface reconstruction (Fischl & Dale, 2000; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999) and parcellation (Desikan et al., 2006; Fischl, van der Kouwe, et al., 2004), using the FreeSurfer software package (version 5.1.0; Martinos Center for Biomedical Imaging, Boston, MA), were used to quantify the volumes of brain regions. The surface-based stream has been validated via histological (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003), and the subcortical procedure has been shown to be statistically indistinguishable from manual raters (Fischl et al., 2002). The subcortical segmentation and surface reconstruction and parcellation procedures are run automatically but require supervision of the accuracy of spatial registration and tissue segmentations. All volumes were inspected for accuracy, and minor manual edits were performed on most participants, usually restricted to removal of nonbrain tissue included within the cortical boundary.

Longitudinal changes in brain structure measures were quantified using the Quantitative Anatomical Regional Change (Holland, Brewer, Hagler, Fennema-Notestine, & Dale, 2009; Holland & Dale, 2011; Holland, McEvoy, & Dale, 2012), as described in detail elsewhere (Tamnes et al., 2013). In brief, the longitudinal percentage volume outcome measure of change was calculated by directly registering the T1 scan to the T2 scan, as it is reasonable to assume that there is less motion distortion with older age in developmental samples. However, the processing scheme uses an explicitly inverse-consistent registration approach (Holland & Dale, 2011); Quantitative Anatomical Regional Change essentially eliminates longitudinal image processing bias by combining forward and reverse image registrations and provides a powerful volumetric change biomarker compared with other state-of-the-art processing schemes (Holland et al., 2012). To ease interpretation of the results, the direction of all effects was inversed in the surface illustrations. Furthermore, the

image segmentation (Fischl et al., 2002) was used to obtain percentage volume change estimates in subcortical structures. Labels from the T2 images were used to extract average change for each region, and annual percentage volume change from T1 was calculated before statistical analyses.

## Statistical Analyses

Statistical analyses were performed by the use of FreeSurfer 5.1 (surfer.nmr.mgh.harvard.edu/) and IBM SPSS Statistics 20.0. Analyses of the behavioral data were performed with descriptive statistics, $t$ tests, correlation analyses, and ANOVA. Longitudinal change in cortical and subcortical volumes was calculated as percentage change and is reported elsewhere (Tamnes et al., 2013).

Cortical analyses across the surface were performed with general linear models (GLMs), as implemented in FreeSurfer. First, we tested the statistical significance of the effects of change in working memory performance on cortical volume change, with gender, age, and scan interval included as covariates of no interest. Second, to additionally control for differences in general cognitive abilities, the analysis was repeated with intelligence level at T1 as an additional covariate. Third, to control for general cognitive development, the first analysis was repeated with change in intellectual abilities as an additional covariate. For the surface analyses, corrections for multiple comparisons were performed by means of simulation-based clusterwise correction as implemented in FreeSurfer (Hagler, Saygin, & Sereno, 2006; Hayasaka & Nichols, 2003). Cluster size limits were estimated with synthesized $Z$ Monte Carlo simulations (Forman et al., 1995) using a method based on AFNI's AlphaSim (Ward, 2000), with 10.000 iterations per analysis with an initial cluster-forming threshold of $p < .05$ (two-tailed). A clusterwise corrected $p < .05$ was regarded significant. Mean percentage volume change was then extracted from each significant cluster, and annual change was calculated. To describe and illustrate the effect sizes within these cortical clusters, we performed multiple regressions on annual change in each clusters, with gender, age, and annual change in working memory performance as independent variables, and also plotted the relationships residualized for gender and age. Note that the betas for annual change in working memory in these multiple regressions are inflated because they are based on already-identified significant clusters from the previous surface-based analyses.

Subcortical analyses were performed with multiple regressions on annual percentage volume change in each structure, with gender, age, and annual change in working memory performance as independent variables. The following structures were tested separately for each hemisphere: accumbens, amygdala, caudate, cerebellar cortex, hippocampus, pallidum, putamen, and thalamus. The subcortical analyses were Bonferroni-corrected by a factor of 16 (reflecting the number of subcortical

structures included), roughly corresponding to a corrected alpha of $p < .003$.

Finally, to test if the relationships between working memory development and brain maturation varied with age, we performed multiple regressions on annual volume change in brain regions that showed significant effects for the total sample, with Sex, Age, Annual Working Memory Change, and the interaction term of Annual Working Memory Change × Age as independent variables. We also split the sample in three groups according to age at T1 and performed partial correlations between annual working memory change and annual brain volume change, with gender and age as covariates.

## RESULTS

### Behavioral Results

Mean accuracy score on the Keep Track task at T1 was 66.8% ($SD$ = 13.8%, range = 30.3%–93.9%), and at T2, it was 74.2% ($SD$ = 10.0%, range = 48.5%–93.9%; Figure 2A). Mean annual change in working memory performance was 2.8% ($SD$ = 4.6%, range = −8.4% to 12.4%), which was highly significant [$t(78) = 5.37, p < 10^{-6}$]. This improvement was not significantly different for girls (2.9, $SD$ = 4.1) and boys [2.7, $SD$ = 5.0; $t(77) = 0.26, p = .793$]. Furthermore, annual change in working memory performance was negatively correlated with age ($r = -.52, p < 10^{-5}$; Figure 2B). Quadratic and smoothing spline models (Fjell et al., 2010) were not distinguishable from the linear model (AIC, $\Delta_I < 1$), indicating that the degree of improvement in working memory performance decreased linearly over the investigated age range. We then split the sample in three groups according to age at T1: children ($n$ = 27, 8.2–11.6 years old), young adolescents ($n$ = 28, 12.0–15.9 years old), and old adolescents ($n$ = 24, 16.0–19.4 years old). Annual change in working memory performance was significant in childhood [mean = 5.4%, $t(26) = 6.34, p < 10^{-6}$] and early adolescence [mean = 2.4%, $t(27) = 3.02, p = .006$] but not in late adolescence [mean = 0.3%, $t(23) = 0.42, p = .681$].

A one-way between-group ANOVA showed that there was a significant difference in Annual Change in Working Memory performance for the three age groups [$F(2, 76) = 9.47, p < 10^{-3}$], and post hoc comparisons using the Tukey HSD test indicated that the child group was significantly different from both adolescent groups ($p < 10^{-3}$ and $p = .026$, respectively) but that the adolescent groups did not differ significantly ($p = .184$).

Mean annual improvement in the intellectual abilities measure, unadjusted for age, was highly significant [$t(78) = 11.01, p < 10^{-17}$] and showed a strong negative correlation with age ($r = -.74, p < 10^{-14}$). Partial correlation, controlling for age and sex, showed that annual change in working memory performance was not significantly related to change in intellectual abilities ($r = .12, p = .319$) or to intelligence level at T1 ($r = -.08, p = .508$).

### Cortical Analyses

The relationships between working memory development and cortical maturation were tested with GLMs of the effects of change in working memory performance on change in cortical volume point-by-point on the surface, with gender, age, and scan interval included as covariates. Simulation-based clusterwise correction for multiple comparisons was employed. The results revealed three significant clusters in each hemisphere (Figure 3, Table 1), all showing negative associations, indicating that the degree of improvement in working memory performance was related to the degree of cortical volume reduction. First, effects were observed bilaterally in prefrontal clusters covering large parts of the superior frontal and rostral middle frontal gyri and the frontal poles. Second, effects were seen in clusters around the central sulci extending into the caudal middle frontal gyrus in the LH and into the supramarginal and superior temporal gyri in the right hemisphere (RH). Third, bilateral clusters were observed encompassing substantial parts of the superior and inferior parietal cortices and in the RH additionally extending down into the lateral occipital region.

**Figure 2.** Working memory development. (A) Spaghetti plot of percentage of words recalled correctly on the Keep Track task by age (years). (B) Annualized change in working memory performance by age at T1. Improvement in working memory performance was negatively correlated with age ($r = -.52, p < 10^{-5}$) and decreased linearly over the investigated age range.
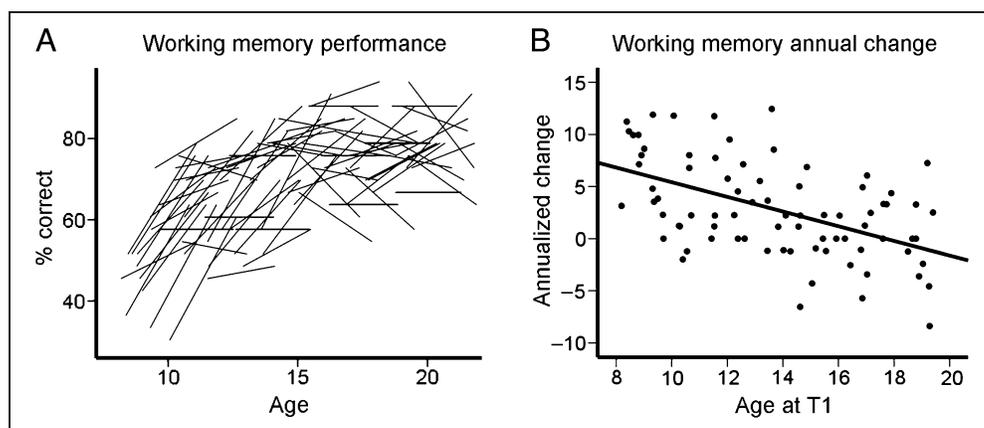
**Figure 3.** Working memory development and cortical maturation. GLMs were used to test the relationship between change in working memory performance and change in cortical volume, with sex, age, and scan interval included as covariates. The results were corrected for multiple comparisons by a simulation-based clusterwise correction. Uncorrected *p* values within the significant clusters are shown. Three clusters in each hemisphere showed negative associations, indicating that working memory improvement was related to cortical volume reductions. No relationships were seen in the opposite direction.
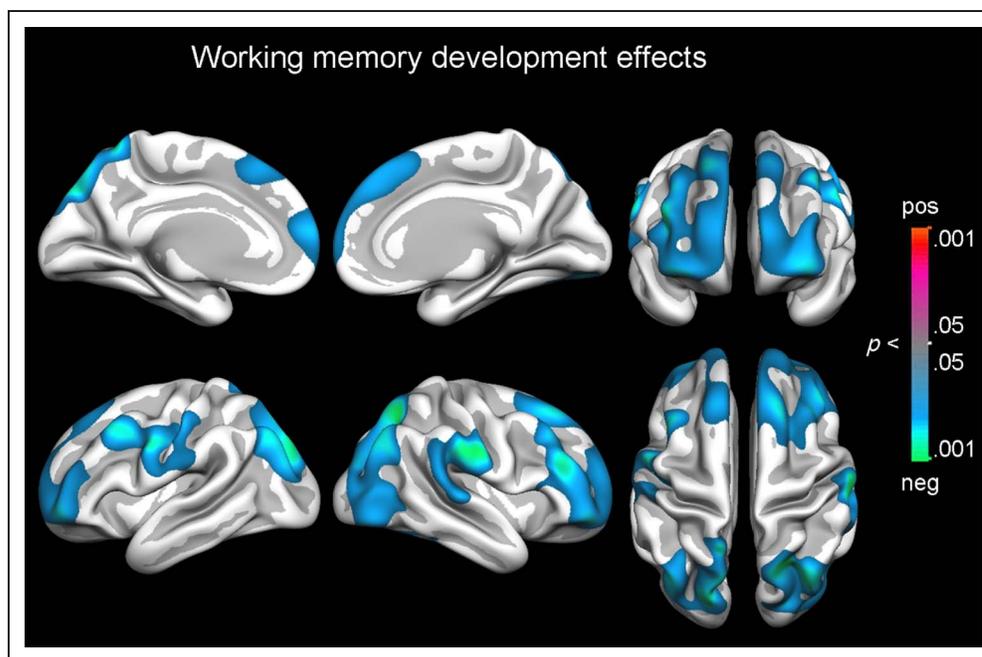
To characterize the strength of these relationships, we performed multiple regressions on the mean annual percentage change in each of the cortical clusters, with gender, age, and annual change in working memory performance as independent variables (Table 2), and made partial regression plots of the unique effects of change in working memory performance (Figure 4). The partial correlations ranged from −.23 to −.27. To test the specificity of the associations in these clusters, we performed multiple regressions with annual change in each cluster as a dependent variable and gender, age, annual percentage cortical volume change over the whole of either LH or RH, and annual change in working memory performance as independent variables. Still, significant negative unique relationships between working memory change and cortical change was seen in five of the six clusters (prefrontal LH was only marginally significant: *p* = .051). Finally, we performed a hierarchical multiple regression

on annual change in working memory performance, with gender and age entered into the model in the first block and annual percentage volume change in each of the six clusters entered stepwise in the second block. Only the parietal RH cluster had a unique prediction value ($\beta = -0.24$, $t = -2.38$, $p = .020$).

To test whether the observed relationships between working memory development and cortical maturation were influenced by differences in general cognitive abilities, we repeated the above point-by-point surface GLM analysis with intelligence level at T1 included as an additional covariate. The results showed virtually identical clusters (Figure 5A). Next, to test if the relationships were specific for working memory development and not explained by general cognitive development, a GLM analysis was performed with change in intellectual abilities as an additional covariate together with gender, age, and scan interval. Again, the results showed largely identical

**Table 1.** Clusters Showing Significant Relationships between Working Memory Development and Cortical Maturation

| Cortical Cluster | Annotation Max Vertex | Cluster Size (mm²) | MNI Coordinates Max Vertex (x, y, z) | Clusterwise p | Confidence Limits for Clusterwise p |
|---|---|---|---|---|---|
| Prefrontal LH | Rostral middle frontal | 4621.5 | −36, 53, −7 | .0006 | .0003−.0009 |
| Prefrontal RH | Rostral middle frontal | 8506.4 | 43, 34, 22 | .0001 | .0000−.0002 |
| Central LH | Precentral | 3324.3 | −56, −1, 36 | .0136 | .0121−.0151 |
| Central RH | Postcentral | 2858.7 | 58, −16, 29 | .0405 | .0380−.0430 |
| Parietal LH | Superior parietal | 5579.3 | −22, −86, 29 | .0001 | .0000−.0002 |
| Parietal RH | Superior parietal | 8432.4 | 21, −60, 51 | .0001 | .0000−.0002 |

Sex, age, and scan interval were included as covariates of no interest, and simulation-based clusterwise correction for multiple comparisons was employed. All clusters showed negative associations.

**Table 2.** Working Memory Development Effects on Change in Cortical Clusters

| Cortical Cluster | Sex | | Age | | Working Memory Development | | Model | |
|---|---|---|---|---|---|---|---|---|
| | β | t (p) | β | t (p) | β | t (p) | $R^2$ | F (p) |
| Prefrontal LH | −0.07 | −0.63 (.532) | −0.37 | **−2.93** (.005) | −0.27 | **−2.08** (.041) | .11 | **3.10** (.032) |
| Prefrontal RH | −0.05 | −0.49 (.622) | −0.33 | **−2.56** (.012) | −0.28 | **−2.21** (.030) | .09 | 2.60 (.058) |
| Central LH | −0.20 | −1.86 (.067) | −0.13 | −1.04 (.301) | −0.30 | **−2.32** (.023) | .10 | **2.85** (.043) |
| Central RH | −0.08 | −0.72 (.473) | 0.20 | 1.63 (.108) | −0.29 | **−2.38** (.020) | .19 | **5.72** (.001) |
| Parietal LH | −0.16 | −1.45 (.151) | 0.11 | 0.85 (.398) | −0.29 | **−2.35** (.021) | .15 | **4.42** (.006) |
| Parietal RH | −0.11 | −1.09 (.280) | 0.18 | 1.47 (.145) | −0.29 | **−2.38** (.020) | .18 | **5.54** (.002) |

Multiple regression analyses on annual volume change, with gender, age, and annual change in working memory performance as independent variables.
**Bold**: $p < .05$.

clusters (Figure 5B). In summary, the relationships between working memory improvement and cortical volume reductions were not explained by differences in either intelligence level or change in intellectual abilities.

### Subcortical Analyses

The relationships between working memory development and maturation of subcortical structures were tested with multiple regressions on the annual percentage volume change, with sex, age, and annual change in working memory performance as independent variables. The following subcortical structures were tested separately for the LH and RH: accumbens, amygdala, caudate, cerebellar cortex, hippocampus, pallidum, putamen, and thalamus. There were no corrected (or uncorrected [$p < .05$]) significant relationships between change in working memory performance and change in any of the subcortical structures.

### Age Interactions

To test whether the relationships between working memory development and brain maturation interacted with age, we performed multiple regressions on the mean annual percentage volume change in each of the six cortical clusters, with sex, age, annual working memory performance change, and the interaction term of Annual



**Figure 4.** Relationships between working memory change and cortical change. Partial regression plots were obtained from multiple regression analyses on the annual percentage volume change in each of the six cortical clusters, with gender, age, and annual change in working memory performance as independent variables. The plots show working memory change against volume change (both in z scores), and the linear fit lines correspond to the partial correlations, controlled for gender and age.
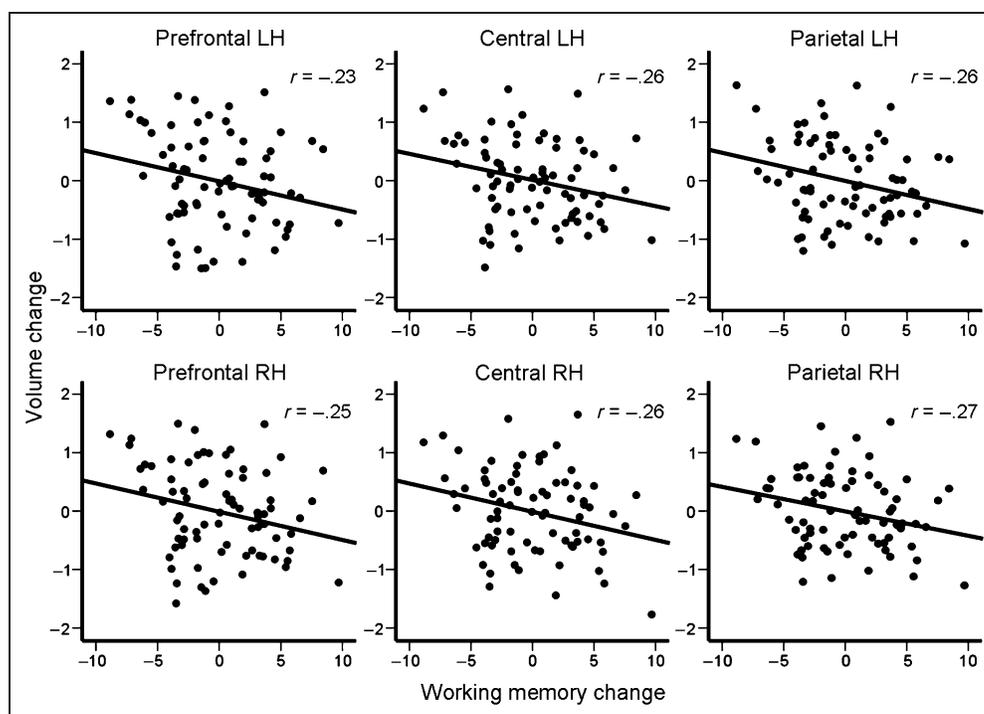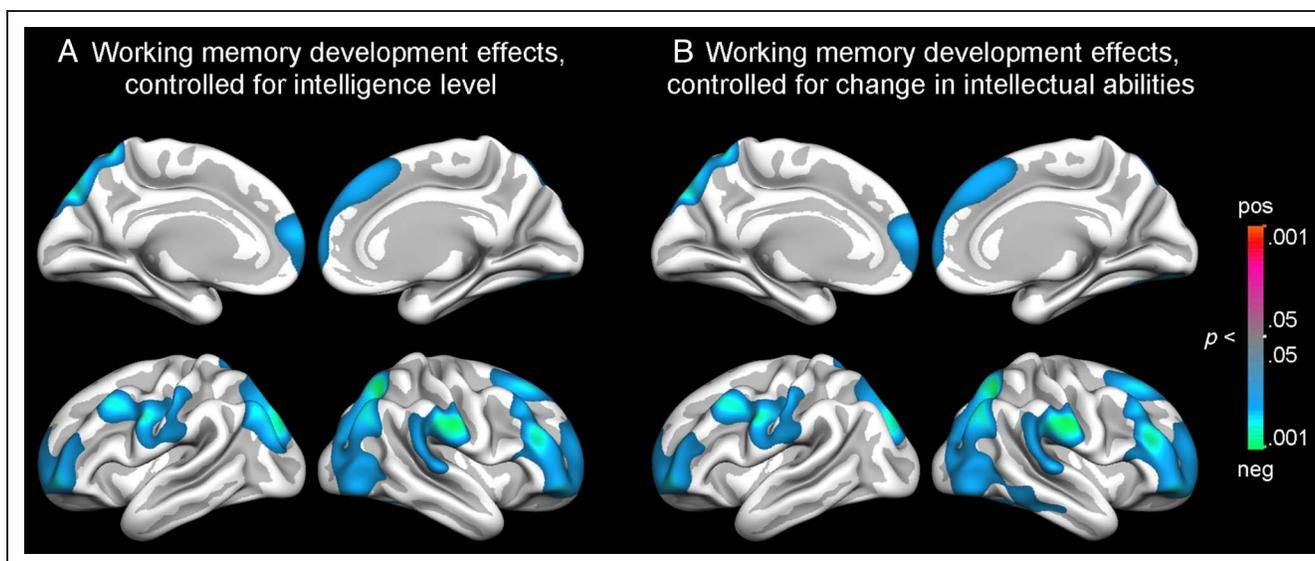
**Figure 5.** Specific working memory development and cortical maturation relationships. To test if the observed relationships between working memory development and cortical maturation (Figure 2) were influenced by differences in general cognitive abilities or general cognitive development, GLMs were used to test the statistical significance of the effects of change in working memory performance on change in cortical volume, with gender, age, scan interval, and additionally, (A) intelligence level at T1 or (B) change in intellectual abilities included as covariates. The results were corrected for multiple-comparison simulation-based clusterwise correction and showed virtually identical effects in the analysis without these additional covariates. The relationships between working memory improvement and cortical volume reductions were thus not explained by differences in either intelligence level or change in intellectual abilities.

Working Memory Change × Age as independent variables. The interaction term was not significant ($p < .05$) for any of the cortical clusters. To characterize the stability of the relationships across age, we performed partial correlations between annual working memory performance change and annual change in the cortical clusters, controlling for sex and age, in the three age groups (as described above; Table 3). The coefficient strengths at different ages were generally similar, although the relationships were weakest for the youngest group in all clusters. The relationships increased somewhat in strength in the central and parietal

clusters in early adolescence and in the prefrontal clusters in late adolescence. However, the Fisher $z$-transformed partial correlation coefficients were not significantly different in the three age groups, and these tendencies should therefore be interpreted with caution.

## DISCUSSION

The present longitudinal MRI study examined associations between working memory development and cortical and subcortical structural maturation in children and

**Table 3.** Associations between Working Memory Development and Change in Cortical Clusters in Subgroups of Children, Early Adolescents, and Late Adolescents

| Cortical Cluster | Childhood (n = 27, 8.2–11.6 Years Old) | Early Adolescence (n = 28, 12.0–15.9 Years Old) | Late Adolescence (n = 24, 16.0–19.4 Years Old) |
| --- | --- | --- | --- |
| | r | r | r |
| Prefrontal LH | −.18 | −.23 | **−.44** |
| Prefrontal RH | −.26 | −.26 | **−.44** |
| Central LH | −.24 | −.34 | −.37 |
| Central RH | −.25 | −.38 | −.32 |
| Parietal LH | −.14 | **−.40** | −.41 |
| Parietal RH | −.20 | **−.40** | −.36 |

Partial correlations between annual change in working memory performance and annual volume change, controlled for sex and age. Note that none of the correlations were significantly different in the three age groups.

**Bold**: $p < .05$.

adolescents. There were three main findings: (1) The degree of improvement in verbal working memory performance decreased linearly over the investigated age range (8–22 years); (2) working memory development was related to cortical volume reduction in widespread frontal and parietal regions, overlapping a fronto-parietal network active in working memory tasks; and (3) these relationships did not significantly interact with age. It is poorly understood how structural maturation of the brain brings about gradual improvements in specific cognitive functions during childhood and adolescence. Two previous studies have directly investigated the relationships between general cognitive abilities and structural brain maturation (Shaw et al., 2006; Sowell et al., 2004), but the current study is the first to demonstrate that cortical maturation is associated with the longitudinal development of working memory function.

The results revealed three cortical regions in each hemisphere where the extent of improvement in verbal working memory performance was related to the degree of volume decrease. The largest effects were seen in bilateral prefrontal and posterior parietal regions, and additional effects were found in regions around the central sulci. Crucially, these associations were demonstrated independently of gender, age, intelligence level, and change in intellectual abilities. Overall, the anatomical localizations of the effects correspond well with previous cross-sectional fMRI (Thomason et al., 2009; O'Hare et al., 2008; Klingberg et al., 2002) and structural/microstrucural (Østby et al., 2011; Vestergaard et al., 2011) findings in developmental samples, although it should be noted that the precise locations vary somewhat across studies. The observed associations were highly symmetrical across the two hemispheres. Using fMRI, Thomason et al. (2009) found that children and adults exhibited similar hemispheric asymmetries in brain activation, with greater activation in the LH for verbal working memory and greater RH activation for spatial working memory. There are several possible reasons for why we did not observe any leftward lateralization. Whereas Thomason et al. (2009) used relatively simple delayed match-to-sample tasks, we used a more complex task that might, to a greater degree, depend on domain-general neural networks (Chein, Moore, & Conway, 2011). Furthermore, our analyses might not be sensitive to hemispheric effects, as cortical volume change rates in development in most regions are comparable and likely highly correlated across hemispheres (Tamnes et al., 2013). In summary, the current study corroborates the conclusion that a fronto-parietal network supports working memory function and critically extends this by demonstrating that structural maturation of these cortical regions is related to the development of working memory.

Which specific biological processes produce cortical reductions in adolescence remain poorly understood, as estimates of the extent and time course of these processes generally rely on extrapolation from the very limited postmortem material and from the data acquired in other species (Brown & Jernigan, 2012). There is however evidence for at least two concurrent processes. First, apparent cortical reductions are likely influenced by increased caliber and myelination of axons coursing within and near the lower cortical layers (Benes, Turtle, Khan, & Farol, 1994; Benes, 1989; Yakovlev & Lecours, 1967). Second, there is evidence for true regressive changes in the form of simplification or elimination of neuronal processes and synapses (Petanjek et al., 2011; Huttenlocher & Dabholkar, 1997; Bourgeois & Rakic, 1993). These, and other biological processes, presumably contribute to increased processing specialization and efficiency and could thus underlie working memory development.

No associations were found between working memory development and volume change in subcortical structures. Different subcortical structures have been implicated in working memory in developmental samples, including caudate, putamen, hippocampus, and cerebellum (Pangelinan et al., 2011; Finn et al., 2010; Ciesielski et al., 2006; Olesen et al., 2003), but associations in specific subcortical regions are less consistently observed than fronto-parietal cortical effects. Notably, the possible role of the hippocampus and related medial-temporal lobe structures in working memory is also a debated issue (Jeneson & Squire, 2012). We recently found that, although significant volumetric maturation was evident for most subcortical structures, the cortical changes were markedly greater (Tamnes et al., 2013; see also Sullivan et al., 2011). Thus, relatively smaller changes have been found for subcortical structures, and these changes were not associated here with improvement in verbal working memory performance.

An issue of interest is whether the relationships between brain maturation and working memory development are quantitatively or even qualitatively different at different ages. However, in the current data, the associations between working memory improvement and fronto-parietal cortical volume reductions did not significantly interact with age. We also observed generally similar relationships across age groups, although somewhat weaker—but not significantly different—correlations were seen in the youngest group. Brain maturation is regionally differentiated, for example, with cortical maturation in general progressing in a posterior-to-anterior order with relatively late maturation of prefrontal regions (Tamnes et al., 2013; Shaw et al., 2008; Gogtay et al., 2004), and different regions could thus be expected to support working memory development in varying degrees in childhood and early and late adolescence. Furthermore, networks of brain activity show both integration (added or strengthened long-range connections) and segregation (lost or weakened short-range connections) in development (Fair et al., 2007), possibly reflecting a shift either from a predominantly local organization in children to a more distributed architecture in adults (Dosenbach et al., 2010; Fair et al., 2009, 2010) or from diffuse to more focal activation patterns (Uddin, Supekar, & Menon, 2010). The

implications of reorganization on a function network level on structure–behavior relationships across age are however not clear. In an elegant longitudinal fMRI study, Finn et al. (2010) found that pFC was recruited as expected during a verbal working memory task in both early and late adolescence, but the hippocampus was additionally recruited in early adolescence. Structural and functional studies with larger numbers of participants at different ages and with younger children are thus warranted to explore this issue further.

## Limitations and Future Directions

We measured verbal working memory performance using the Keep Track task, which requires participants to constantly renew their representations of words and which has been regarded as mainly a measure of working memory content updating and monitoring (Miyake et al., 2000). However, it also requires categorization and selection of relevant incoming information, as participants are asked to remember only words belonging to target categories. The task is thus not optimized for isolating specific cognitive processes. Much work remains in the mapping of the neural correlates of discrete working memory operations, although evidence suggests that at least some operations are functionally and neuroanatomically dissociated (Bledowski, Rahm, & Rowe, 2009). However, results from a recent meta-analysis of 36 fMRI studies that examined executive processes of working memory suggest that two frontal regions are recruited across diverse task demands (Nee et al., 2013). One region was located in the superior frontal sulcus and was especially sensitive to spatial content, whereas the other region was located in the midlateral pFC and showed sensitivity to nonspatial content. Nee et al. (2013) suggest that the dorsal–ventral distinction between location-based "where" information and identity-based "what" information that has been applied to working memory maintenance (Levy & Goldman-Rakic, 2000) also applies to executive processes of working memory. However, others claim that many of the operations that work on the contents of working memory are not specific but that working memory instead emerges from interactions between higher sensory, attentional, and mnemonic functions (Bledowski, Kaiser, & Rahm, 2010). To further explore these topics, future studies on the relationships between working memory development and brain maturation should employ tasks designed to measure multiple specific cognitive operations.

The method used for the quantification of longitudinal morphometric change has been shown to be highly sensitive (Tamnes et al., 2013; Holland & Dale, 2011; Fjell et al., 2009), but because it quantifies change in any direction, only volumetric estimates are obtained. Developmental changes in cortical volume are known to arise through a complex interplay of several distinct facets of anatomy, including thickness, surface area, and degree of gyrification (Mills, Lalonde, Clasen, Giedd, & Blakemore, in press;

Raznahan et al., 2011; White, Su, Schmidt, Kao, & Sapiro, 2010), and longitudinal studies are thus needed to explore the specific links between these various morphometric changes and the development of cognitive functions. Future studies should also include more time points to better map group-level developmental processes.

An intriguing question is whether imaging data can improve our predictions of scholastic achievement and the identification of children at risk of poor outcome. A recent longitudinal fMRI study of participants aged 6–16 years found that working memory activation in the posterior parietal cortex improved the prediction of arithmetical performance 2 years later compared with behavioral measures alone (Dumontheil & Klingberg, 2012). Encouragingly, accumulating evidence indicates that working memory can be improved by extended training and that such training is associated with changes in brain activity in frontal and parietal cortices and BG and with changes in dopamine receptor density (Jolles, van Buchem, Rombouts, & Crone, 2012; Klingberg, 2010). Future studies should investigate if working memory training affects structural maturation of this brain network and whether morphometric measures predict real-world scholastic outcomes.

## Conclusion

The results from this study provide the first longitudinal evidence that structural maturation of a fronto-parietal cortical network supports working memory development. Although two previous longitudinal studies have demonstrated associations between general cognitive abilities and structural brain maturation, the current results map developmental change in a more specific cognitive function directly to structural change in distributed frontal and parietal cortical regions, overlapping a fronto-parietal network known to be active in working memory tasks.

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