Morphometry and connectivity of the fronto-parietal verbal working memory network in development

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ABSTRACT

Two distinctly different maturational processes – cortical thinning and white matter maturation – take place in the brain as we mature from late childhood to adulthood. To what extent does each contribute to the development of complex cognitive functions like working memory? The independent and joint contributions of cortical thickness of regions of the left fronto-parietal network and the diffusion characteristics of the connecting pathway of the left superior longitudinal fasciculus (SLF) in accounting for verbal working memory performance were investigated, using a predefined regions of interest-approach. 108 healthy participants aged 8–19 years underwent MRI, including anatomical and diffusion tensor imaging (DTI), as well as cognitive testing using a digit span task. Radial diffusivity of the SLF, as well as cortical thickness of supramarginal gyrus and rostral middle frontal cortex, were negatively related to digit span forwards performance, independently of age. Radial diffusivity of the SLF was also negatively related to digit span backwards. A multi-modal analysis showed that cortical thickness and SLF microstructure were complementary in explaining working memory span. Furthermore, SLF microstructure and cortical thickness had different impact on working memory performance during the developmental period, suggesting a complex developmental interplay. The results indicate that cortical and white matter maturation each play unique roles in the development of working memory.

1. Introduction

What is happening in the developing brain that enables us to keep increasing amounts of information in mind? Is it the maturation of cortical regions, known to decrease in thickness as a result of processes like synaptic pruning? Or is it the development of white matter fibers in the pathways connecting those regions that ultimately enables us to hold ever increasing loads in mind as we grow older? Working memory, the ability to hold information in memory for short time periods for use in complex tasks (Baddeley, 1998), continues to develop throughout adolescence (Conklin, Luciana, Hooper, & Yarger, 2007; Gathercole, Pickering, Ambridge, & Wearing, 2004). Working memory is considered a tool for both the passive storage of information (short-term memory) and for manipulating and using that information while holding it in mind (Gathercole et al., 2004). While the working memory model has been mapped to the brain using functional magnetic resonance imaging techniques in numerous studies (D'Esposito et al., 1998),

evidence for the relationship between working memory function and the structural development of the brain is lacking.

A fronto-parietal network has been implicated in working memory, in studies using functional magnetic resonance imaging (fMRI), both for adults (D'Esposito et al., 1998; Salmon et al., 1996; van Asselen et al., 2006; Wager & Smith, 2003) and for children and adolescents (Casey et al., 1995; Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010; Klingberg, 2006; Kwon, Reiss, & Menon, 2002; Nelson et al., 2000; O'Hare, Lu, Houston, Bookheimer, & Sowell, 2008; Thomas et al., 1999; Thomason et al., 2009). This fronto-parietal network includes the dorso- and ventrolateral prefrontal and posterior parietal cortex (D'Esposito et al., 1998). In verbal working memory, the left supramarginal gyrus has also been implicated, owing to its involvement in phonological processing (Brahmbhatt, McAuley, & Barch, 2008; Crottaz-Herbette, Anagnoson, & Menon, 2004; Paulesu, Frith, & Frackowiak, 1993; Ravizza, Delgado, Chein, Becker, & Fiez, 2004; Rothmayr et al., 2007). Separating working memory tasks into simple storage capacity and complex working memory manipulation is thought to be reflective of the divide between the basic level "slave-systems" of the phonological loop/visuo-spatial sketch pad and the central executive component (Groeger, Field, & Hammond, 1999; Lezak, 1995; Wager & Smith, 2003). FMRI studies show different activity within the fronto-parietal network depending on the involvement

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of the central executive, typically with more activity in frontal regions (Wager & Smith, 2003). However, activations in parietal areas during complex working memory tasks, as well as activations in frontal regions during simple storage tasks (Wager & Smith, 2003) make it difficult to pinpoint an independent location of each of these processes within the fronto-parietal network.

The structural development of the cortical regions in this fronto-parietal network is characterized by thinning of the cortex throughout late childhood and adolescence, with frontal regions approaching adult maturity later than posterior regions (Gogtay et al., 2004; Shaw et al., 2008; Tamnes, Ostby, Fjell et al., 2010). The thinning of the cortex may be partly caused by pruning of synapses (Huttenlocher, 1984; Rakic, Bourgeois, & Goldman-Rakic, 1994), and this elimination of abundant synapses may lead to more efficient information processing. Increase in working memory capacity as seen during childhood and adolescence, has been hypothesized to be linked to the late cortical maturation of the frontal lobes, and to the development of the pathways connecting these areas (Conklin et al., 2007; Finn et al., 2010). The working together of different brain regions during cognitive tasks, such as working memory tasks, places demands on the communication between brain regions that are quite far apart. This communication, or signal transfer, relies among other properties on the size, density and myelination of long distance axons. Using diffusion tensor imaging (DTI), studies have shown a development in microstructural properties of white matter (Ashtari et al., 2007; Giorgio et al., 2008; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Tamnes, Ostby, Fjell et al., 2010). Histological studies have shown that myelination is a developmental characteristic within human white matter (Yakovlev & Lecours, 1967). DTI indices may be reflective of myelination, as well as other properties of fiber organization, as suggested by histological studies in both humans and animals (Bockhorst et al., 2008; Klawiter et al., 2011; Song et al., 2003, 2005). Furthermore, diffusion parameters have been related to developmental improvements in cognitive functions, including general intellectual abilities (Johansen-Berg, 2010; Nagy, Westerberg, & Klingberg, 2004; Tamnes, Ostby, Walhovd et al., 2010). Working memory performance is therefore likely to be dependent on white matter microstructural properties of pathways connecting cortical areas within the fronto-parietal network. The superior longitudinal fasciculus (SLF) is the main route connecting parietal and lateral prefrontal cortices (Petrides & Pandya, 2006), and relationships between diffusion parameters in this region and working memory performance have been reported in healthy adults (Burzynska et al., 2011), and in psychiatric disorders such as schizophrenia (Karlsgodt et al., 2008). Verbal and non-verbal working memory tasks have been found to be related to DTI measures in frontal regions and the SLF in development (Niogi & McCandliss, 2006; Olesen, Nagy, Westerberg, & Klingberg, 2003; Vestergaard et al., 2010).

There is a lack of knowledge about the joint contribution of cortical and white matter maturation in explaining age-related improvements in working memory. Temporal synchronicity in the development of cortex and the underlying white matter has been proposed, but recent studies have shown that the developmental patterns are fundamentally different and that the relationship between them in development are modest (Tamnes, Ostby, Fjell et al., 2010). Thus, a fundamental question is whether white matter maturation contributes to performance independently of cortical maturation, and vice versa. Answering this will help increasing our understanding of the principles of neurocognitive development, disentangling the contributions of two partly separable neurodevelopmental events Approaches so far have combined fMRI and DTI (Olesen et al., 2003), correlating fractional anisotropy (FA), measuring the degree of directionality of water diffusion, with activation in fronto-parietal regions (Olesen et al., 2003), pointing to the

possibility of structural connections being a driving force behind utilization of the working memory network on the cortical level. No working memory studies have so far utilized a combination of measures of morphometry of cortical maturation and microstructural properties of connectivity, in spite of general agreement that structural maturational processes must have functional consequences. Hence, we investigate whether white matter microstructural properties of the SLF and cortical thickness are important for working memory development independently of each other. Further, we test whether white matter microstructural properties on the one hand, and cortical thinning on the other, play different roles at different times during working memory development. This could give us a unique glimpse into the steps that are taken by developing brains towards adult functioning.

Specifically, the objectives of the present study are:

1) In a sample of children and adolescents, to investigate the relationships between verbal working memory (simple and complex digit span) performance and (a) cortical thickness within parietal and lateral prefrontal regions within the left hemisphere, (b) diffusion parameters (fractional anisotropy (FA) and radial diffusivity (RD)) of the SLF in the left hemisphere and (c) the relative contributions of cortical thickness and SLF variables to explaining working memory when seen together in the same analysis.

2) To investigate developmental changes in the relative contributions of DTI measures and cortical thickness in explaining working memory performance, by performing similar analyses as in (1c), separately for three age groups within the 8–19 age span.

We hypothesized that cortical thickness in regions within the left fronto-parietal network (superior parietal, inferior parietal, supramarginal, caudal middle frontal, rostral middle frontal, pars opercularis and pars triangularis) would correlate with working memory performance independently of age, as would microstructural properties (FA and RD) of the SLF. Based on previous results from a partly overlapping sample (Ostby, Tamnes, Fjell, & Walhovd, 2011; Tamnes et al., 2011; Tamnes, Ostby, Walhovd et al., 2010), we expected the correlations with cortical thickness and RD to be negative, while correlations with FA would be positive. Further, we hypothesized that cortical maturation and fiber tract development would contribute uniquely to working memory performance, as they are likely reflective of two distinct neurodevelopmental processes. Both of these processes may have a bearing on working memory development through more mature cortical processing, and speeded and efficient communication between frontal and parietal areas. Dividing the sample into age groups was done in order to investigate the changing patterns of white matter versus cortical contributions to working memory performance across development. At least two developmental patterns could potentially be revealed through this analysis: on the one hand, white matter development is a continuing process throughout late adolescence and early adulthood, and could play a greater part in the oldest adolescents by providing increased speed of communication between relatively more mature cortical regions, thus primarily refining the network. On the other hand, connecting the regions within the fronto-parietal network could be more important earlier in development, in order for the cortical regions to come into play in predicting individual differences in working memory performance.

2. Materials and methods

2.1. Sample

108 children and adolescents (53 males) aged 8–19 years (M = 13.89, SD = 3.46) participated in the study. The distribution of sex and age in three age groups is shown

Table 1
Characteristics of three age groups in terms of sex, WASI IQ scores and Digit Span scores.

	Age groups					
	8–11		12–15		16–19	
N	36 (19M/17F)		37 (18M/19F)		35 (16M/19F)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Age	9.91 (1.13)	8.17–11.75	13.90 (1.17)	12.00–15.92	17.97 (1.05)	16.00–19.67
Full scale IQ (WASI)	106.53 (11.00)	82–127	108.16 (10.70)	91–141	112.14 (10.53)	91–132
Digit span forwards	7.81 (1.45)	5–12	9.08 (2.14)	5–15	10.00 (2.20)	6–14
Digit span backwards	5.1 (1.2)	3–8	5.9 (2.0)	4–12	7.4 (1.5)	5–11

in Table 1. The sample was recruited through newspaper advertisements, and local schools and workplaces, and constitutes the first part of an ongoing longitudinal project at the Center for the Study of Human Cognition at the University of Oslo. The study was approved by the Regional Ethical Committee of South Norway. Written informed consent was obtained from all participants older than 12 years of age and from a parent/guardian of volunteers under 18 years of age. Oral informed consent was obtained from all participants under 12 years of age. Participants had no self- or parent-reported history of neurological or psychiatric disorders, chronic illness, premature birth, learning disabilities, or use of medicines known to affect nervous system functioning. They were further required to be right-handed, speak Norwegian fluently and have normal or corrected to normal hearing and vision. Among the initial 116 children and adolescents who met the inclusion criteria, 4 had no useable MRI scans due to movement artifacts. All participants' scans were examined by a neuroradiologist, which led to the exclusion of one additional participant. Of the 111 remaining participants, 3 participants did not complete the DTI sequence, which resulted in a final sample of 108. There was no correlation between sex and age ($r = -.07$, $p = .453$, females coded as 1, males as 2). Participants were tested using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), and all participants scored above 80 on full scale IQ ($M = 108.91$, SD = 10.90, range: 82–141). The distribution of WASI full-scale IQ in three age groups is shown in Table 1. There was no difference in IQ between males ($M = 110.00$, SD = 11.94) and females ($M = 107.85$, SD = 9.79; t [106] = −1.023, $p = .309$).

2.2. Working memory assessment

Participants were given the strings of numbers identical to those in the Digit Span subtest of the Norwegian version of WISC-III (Wechsler, 1992) as part of a larger battery of cognitive tests. Participants were orally presented with strings of numbers of increasing length, and were in the first part of the test required to repeat the digits in the same order (digit span forwards, DSF), and in the second part of the task they were asked to repeat them in the reversed order (digit span backwards, DSB). Strings of digits of increasing length were presented. The length of the digit strings were increased after every two strings. The stop criterion was two wrong answers within a pair of equal length. One point was given for each correctly repeated string of digits. The sum scores of DSF and DSB were used in the present study, as theoretically, they should be reflective of different aspects of working memory. The DSF is believed to be more dependent on simple storage span, as held in the phonological loop, while the DSB task is thought to be more reflective of executive control of working memory. The mean scores for three non-overlapping age groups are shown in Table 1.

2.3. MRI acquisition

Imaging data were collected using a 12 channel head coil on a 1.5-Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The pulse sequences used for the morphometric analyses were two 3D T1-weighted (MP-RAGE) scans, with the following parameters: TR/TE/TI/FA = 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 192. Each scan took 7 min, 42 s. Each volume consisted of 160 sagittal slices with voxel sizes 1.25 mm × 1.25 mm × 1.20 mm. This sequence was chosen in order to optimize signal-to-noise ratio relative to time in the scanner. Each MP-RAGE was visually inspected, and only scans deemed to have no or minimal movement artifacts were included in analyses. The two MP-RAGEs were averaged to increase the signal-to-noise-ratio. Where there were problems achieving two high quality scans due to motion artifacts, only one scan was used in the analysis. This was the case for 23.1% of the participants, of whom most (72%) were below 12 years of age.

Diffusion-weighted images were acquired using a single-shot twice refocused spin echo planar imaging pulse sequence with 30 diffusion sensitized gradient directions and the following parameters: TR/TE = 8200 ms/82 ms, b value = 700 s/mm^2, and voxel size = 2.0 mm × 2.0 mm × 2.0 mm, with a total scanning time of 11 min, 21 s. This sequence is optimized to minimize eddy current- induced image distortions (Reese, Heid, Weisskoff, & Wedeen, 2003). The sequence was repeated in 2 successive runs with 10 non-diffusion-weighted images ($b = 0$) in addition to 30 diffusion-weighted images collected per acquisition. The two acquisitions were acquired in the same session, and were combined during post-processing to increase signal-to-noise ratio. Each volume consisted of 64 axial slices.

2.4. Morphometric analysis

All datasets were processed and analyzed at the Neuroimaging Analysis Lab, Center for the Study of Human Cognition, University of Oslo, with additional use of computing resources from the Titan High Performance Computing facilities (http://hpc.uio.no/index.php/Titan) at the University of Oslo. Cortical thickness was estimated using FreeSurfer 4.0.5 (http://surfer.nmr.mgh.harvard.edu/fswiki) by means of an automated surface reconstruction procedure (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Fischl, Sereno, & Dale, 1999; Fischl, Sereno, Tootell, & Dale, 1999; Segonne et al., 2004). Briefly, a representation of the gray/white matter boundary was reconstructed (Dale et al., 1999), using intensity and continuity information from the entire MR volume in segmentation and deformation procedures. Minor manual editing of vessels and dura was routinely performed, according to FreeSurfer guidelines. The cortical maps produced are not restricted to the voxel resolution of the original data and are thus capable of detecting sub millimeter differences between groups (Fischl & Dale, 2000). The technique has been validated via histological (Rosas et al., 2002) as well as manual measurements (Kuperberg et al., 2003). Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum of approximately 15 mm and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns. This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortions, resulting in a measure of cortical thickness for each person at each point on the reconstructed surface. Using FreeSurfer, each hemisphere was parcellated into 33 brain regions, of which 7 frontal and parietal regions within the left hemisphere were selected as regions of interest (ROI). These were: superior parietal cortex, inferior parietal cortex, supramarginal gyrus, caudal middle frontal cortex, rostral middle frontal cortex, pars opercularis and pars triangularis. The cortical ROIs are shown in Fig. 2. In accordance with previous findings with largely overlapping samples (Ostby et al., 2009; Tamnes, Ostby, Fjell et al., 2010), all 7 ROIs showed age effects, as shown in Supplementary Table 1 and Supplementary Fig. 1. For use in follow-up analyses of the specificity of the fronto-parietal network in verbal working memory, relationships with all 33 parcellations were analyzed. The parcellations can be seen in Supplementary Fig. 2.

2.5. Diffusion data analysis

DTI analyses were performed using FSL (http://www.fmrib.ox.ac.uk/fsl/index.html) (Smith et al., 2004; Woolrich et al., 2009). The initial steps of the analyses, whereby a common white matter skeleton is derived for use in group analyses, was done with a sample overlapping the present (Tamnes, Ostby, Walhovd et al., 2010). This sample included the current study's participants, as well as 60 adults aged 20–30 years, described in detail elsewhere (Tamnes, Ostby, Walhovd et al., 2010). The inclusion of an adult sample in the creation of the mean FA skeleton is unlikely to cause very deviant results, as comparisons between 8–10-year-olds and 20–30-year-olds have shown minimal differences in the organization of main tracts (Westlye et al., 2010). Initially, each of the 60 DTI volumes was affine registered to the T2-weighted $b = 0$ volume using FLIRT (Jenkinson & Smith, 2001). This corrected for motion between scans and residual eddy-current distortions. In order to preserve the orientation information after motion correction, we reoriented each volume's B matrix by applying the corresponding transformational matrix from the motion-correction procedure. After removal of non-brain tissue (Smith, 2002), FA, eigenvector and eigenvalue maps were computed. The FA volumes were then skeletonized and transformed into a common space as employed in TBSS (Smith et al., 2006, 2007). Briefly, all volumes were nonlinearly warped to the FMRIB58_FA template by use of local deformation procedures performed by FNIRT, a nonlinear registration toolkit using a b-spline representation of the registration warp field. Next, a mean FA volume of all subjects (aged 8–30 years) was generated and thinned to create a mean FA skeleton representing the centers of all common tracts. The mean skeleton was thresholded at FA > 0.25 to reduce the likelihood of partial voluming in the borders between tissue classes, yielding a mask of 108,005 WM voxels. Individual FA values were warped onto this mask by searching perpendicular from the skeleton for maximum FA values. The same steps of analyses were performed, this time using RD (radial diffusion) instead of FA values. In order to obtain DTI

measures from white matter tracts, binary masks based on a probabilistic tractography atlas (the Johns Hopkins University (JHU) white-matter tractography atlas) (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005), as provided in FSL, were created with a probability threshold of 5%. The relatively liberal threshold was chosen to accommodate inter-subject variation in gross WM fiber architecture. Voxels intersecting both the skeleton and the TOIs were used in subsequent regional analyses. The superior longitudinal fasciculus (SLF) was chosen as region of interest, and a 3D-rendeing of this tract is shown in Fig. 2. The age effects on SLF RD and FA were as expected based on previously published results with a largely overlapping sample (Tamnes, Ostby, Fjell et al., 2010), as displayed in Supplementary Table 1. For use in follow-up analyses of the specificity of the fronto-parietal network in verbal working memory, all tracts in both hemispheres, as well as the commissural tracts (Forceps major and Forceps minor) were selected for analyses, as shown in Supplementary Fig. 3A. Because the SLF is so large, smaller ROIs were also used to delineate the extent of parietal and frontal involvement, as compared to temporal lobe white matter involvement. Individual binary masks based on the WM areas from FreeSurfer, based on the same regions as the cortical parcellations, were created and mean FA and RD values from the overlap between the FA skeleton generated in TBSS and the WM labels were calculated. Voxels intersecting both the skeleton and the WM areas underlying the original 7 cortical ROIs as well as four regions within the temporal lobe were used in the analyses. Examples of some of these white matter parcellations are shown in Supplementary Fig. 3B. These white matter parcellations do not cover the parts of SLF that go through the deep white matter, but may represent end points of the major tracts.

2.6. Statistical analyses

2.6.1. Preliminary analyses
The effects of sex were investigated using multivariate analysis of covariance, with sex as between-subjects factor and age as covariate. These analyses were completed for each set of variables: working memory test scores (DSF and DSB), cortical thickness ROIs, SLF FA, and SLF RD.

2.6.2. Objective 1 – age-independent relationships between brain morphometry/connectivity and working memory performance
The relationships between brain characteristics and working memory performance were investigated using regression analyses with each of the digit span variables (DSF and DSB) as dependent variables, and cortical thickness ROIs/SLF FA/RD together with age as predictor variables in turn. The significance threshold was Bonferroni-corrected for multiple comparisons in three sets of analyses: analyses with cortical ROIs was corrected for 7 ROIs ($p < .007$), SLF analyses were corrected for 2 DTI measures (FA and RD), and working memory analyses (behavioral only) was corrected for 2 working memory scores (DSF and DSB) ($p < .025$). Where there were statistically significant relationships between brain variables and digit span scores, the regression analyses were repeated with IQ as an additional predictor variable, in order to test whether the relationships were specific to working memory. Further, to investigate cortical and white matter tract contributions to working memory performance relative to each other, regression analyses were performed using working memory scores as dependent variables, and one cortical ROI, SLF diffusion variables and age as simultaneous predictor variables. These analyses were done for cortical ROIs and SLF variables that showed a statistically significant relationship with digit span forwards or backwards. In order to investigate the anatomical specificity of the results, partial correlations controlling for age were calculated between Digit Span scores and each of the remaining 26 FreeSurfer parcellations in the left hemisphere, and the 33 parcellations of the right hemisphere. Also, major tracts in both hemispheres were correlated with Digit Span scores while controlling for age, as were the 7 white matter regions in each hemisphere that correspond to the fronto-parietal cortical ROIs and four temporal lobe regions. No correction for multiple comparisons were employed in these follow-up analyses, as the focus here was to compare the original analyses with the non-theory-driven relationships elsewhere. Hence, the analyses could yield results that would normally not survive corrections, but could nevertheless serve as a test of the appropriateness of the original, theory-driven selection of ROIs.

2.6.3. Objective 2 – developmental differences in relationships between brain morphometry/connectivity and working memory
The relationships between brain variables and working memory were assessed for three age groups: 8–11 years, 12–15 years and 16–19 years. The IQ and digit spans scores of the three age groups are shown in Table 1. The brain variables that showed Bonferroni-corrected significant relationships with working memory in the analyses in Section 2.6.2 were chosen for further developmental analyses. Regression analyses were performed using working memory scores as dependent variables, and one cortical ROI, one SLF variable and age as simultaneous predictor variables. Statistical significance testing of these age group differences in brain–behavior relationships was done by computing partial correlations (DSF/DSB with cortical ROIs while partialling out age and SLF FA or RD, and DSF/DSB with SLF FA or RD while partialling out age and cortical ROI) and testing them pair wise (two age groups at a time) using t-tests of Fisher's z-transformed correlations.

3. Results

3.1. Sex differences

Multivariate analyses of variance were performed with sex as between-group variable, age as covariate, and sets of working memory variables, cortical thickness variables, FA or RD, as dependent variables. These analyses revealed no overall main effect of sex on neither working memory performance ($F = .178$, $p = .837$), cortical thickness ROIs ($F = 1.078$, $p = .383$), SLF FA ($F = .791$, $p = .376$) nor SLF RD ($F < .001$, $p = .998$). Sex was therefore not included in further analyses.

3.2. Development of working memory

The effect of age on working memory performance is displayed in graphs in Fig. 1. Positive age relationships were found for both digit span forwards ($F[1,108] = 33.933$, $p < .001$, $\beta = .49$, $R^2 = .34$) and Digit Span Backwards ($F[1,108] = 47.330$, $p < .001$, $\beta = .56$, $R^2 = .31$). The two measures of working memory correlated .26 ($p = .007$) when partialling out age.

3.3. Relationships between brain variables and working memory

3.3.1. Digit span forwards
Regression analyses with cortical ROIs and age as predictor variables, and DSF as dependent variable, revealed negative relationships between simple working memory span and thickness of supramarginal gyrus and rostral middle frontal cortex, as shown in Table 2. Inferior parietal cortex and caudal middle frontal cortex showed significant relationships at an uncorrected $p < .05$, but were not included in further analyses. SLF RD, but not FA, was related to DSF performance (negatively). The ROIs (cortical and SLF) that were significantly related to DSF are indicated in Fig. 2a. In order to test the specificity of the results, regression analyses were then performed with DSF performance as dependent variable, and age, IQ and each of the brain variables as predictors. For the cortical ROIs, these analyses revealed mainly the same results: supramarginal: $\beta = -.32$, $p = .004$; rostral middle frontal: $\beta = -.29$, $p = .005$. SLF RD showed about the same relationship with DSF performance after correcting for IQ: SLF RD: $\beta = -.24$, $p = .017$.

The independence of cortical ROIs versus SLF microstructure in explaining DSF performance was then tested using regression analyses with each of the two cortical ROIs together with SLF RD and age as predictor variables. One cortical variable was entered together with age and SLF RD in each of the analyses. The results are presented in Table 3. All brain variables remained significant when tested together in pairs of one cortical thickness variable and SLF RD ($p < .05$), and each measure provided comparable predictive power, as shown by partial standardized βs in the range of $-.24$ to $-.33$.

3.3.2. Digit span backwards
In the regression analyses with DSB as dependent variable, and age and brain variables as predictor variables, only RD of the SLF showed a significant relationship (standardized partial $\beta = -.23$, $p = .018$), while thickness of the pars triangularis showed a tendency at uncorrected $p = .019$ (standardized partial $\beta = -.24$), as shown in Supplementary Table 3 and Fig. 2b. SLF RD was then entered as predictor variable together with age and IQ. This analysis showed mainly the same result: SLF RD: $\beta = -.23$, $p = .017$.

3.3.3. Age group analyses of brain–behavior relationships
Regression analyses with DSF as dependent variable, and each of the two cortical ROIs, SLF RD and age as predictor variables, were performed with each of the three age-groups (as describedin

Table 2
Relationships between brain variables and digit span forwards.

	F^a	p	R^2	β age	p age	β ROI	p ROI[b]
Cortical thickness							
Superior parietal	19.046	<.001	.27	.32	.008	−.23	.068
Inferior parietal	20.012	<.001	.28	.30	.014	−.27	.030
Supramarginal	23.412	<.001	.31	.27	.014	−.34	**.002**
Caudal middle frontal	19.619	<.001	.27	.42	<.001	−.19	.041
Rostral middle frontal	22.707	<.001	.30	.31	.003	−.30	**.003**
Pars opercularis	18.591	<.001	.26	.43	<.001	−.15	.103
Pars triangularis	19.041	<.001	.27	.39	<.001	−.18	.069
White matter diffusion properties							
Superior longitudinal fasciculus FA	19.190	<.001	.27	.41	<.001	.18	.060
Superior longitudinal fasciculus RD	20.996	<.001	.29	.35	.001	−.25	**.013**

[a] Results of regression analyses with digit span forwards as dependent variable and age and brain variables (cortical thickness and superior longitudinal fasciculus fractional anisotropy (FA) and radial diffusivity (RD)) as predictor variables.
[b] Significant relationships (Bonferroni-corrected) in bold.

Table 3
Cortical ROIs and SLF RD and age as simultaneous predictors of digit span forwards.

	F	p	R^2	β age	p age	β cortical ROI	p cortical ROI[b]	β SLF RD[a]	p SLF RD[b]
Digit span forwards									
Supramarginal	18.466	<.001	.35	.14	.241	−.33	**.002**	−.24	**.014**
Rostral middle frontal	17.955	<.001	.34	.18	.112	−.29	**.004**	−.24	**.014**

[a] SLF RD, superior longitudinal fasciculus, radial diffusivity.
[b] Significant relationships in bold.

Table 4
Age group analyses with cortical ROIs and SLF RD.

	8–11-year-olds		12–15-year-olds		16–19-year-olds	
	β^a cortical ROI	β^a SLF RD	β cortical ROI	β SLF RD	β cortical ROI	β SLF RD
Digit span forwards						
Supramarginal	−.16	.12	−.17	−.39[*]	−.53[*]	−.16
Rostral middle frontal	−.20	.17	−.23	−.44[*]	−.44[*]	−.18

[a] βs from two brain variables from regression analyses performed within each of three age groups, with DSF as dependent variable, and age, one cortical ROI and radial diffusivity (RD) of superior longitudinal fasciculus (SLF) as predictor variables. Only the regressions in the two oldest age groups were significant ($p < .05$).
[*] $p < .02$.

Section 2.1), and the results are shown in Table 4. For the youngest age group (8–11 years), none of the individual brain variables were significant. In the middle group (12–15 years), only SLF RD was a significant predictor of performance. In the oldest group (16–19 years), only the cortical ROIs were significant predictors of DSF performance. t-tests of Fisher's z-transformed correlations revealed a significant difference between DSF-SLF correlations of .13 (partialling out supramarginal thickness) and .18 (partialling out rostral middle frontal thickness) in the youngest age group and −.40 (partialling out supramarginal thickness) and −.44 (partialling out rostral middle frontal thickness) in the middle group. No other differences were significant, although a difference between the youngest age group ($r = −.17$) and the oldest ($r = −.55$), of correlations between DSF and thickness of supramarginal thickness (while partialling out SLF RD) showed a tendency towards significance ($p = .072$).
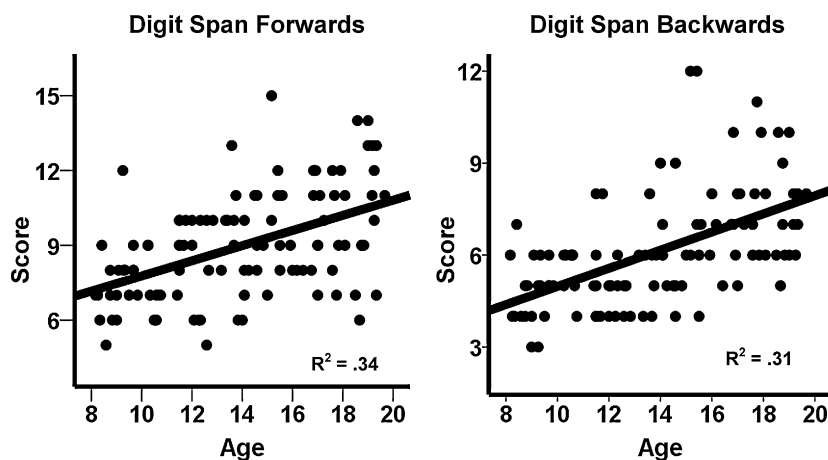

Fig. 1. Scatter plots showing the relationships between age (on the x axes) and Digit Span performance (on the y axes).
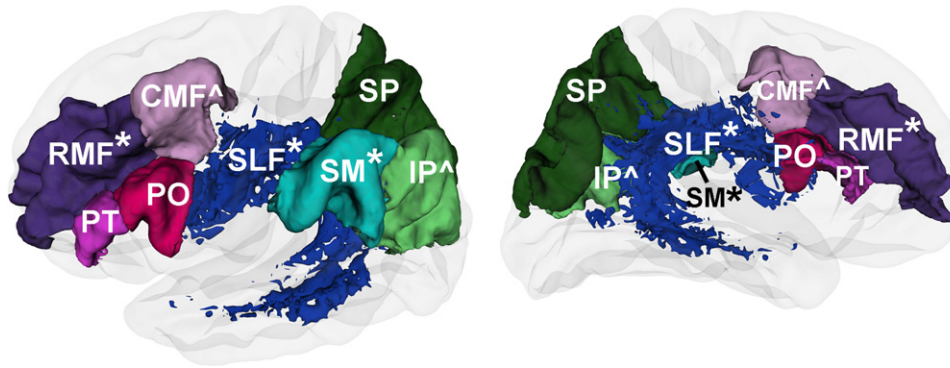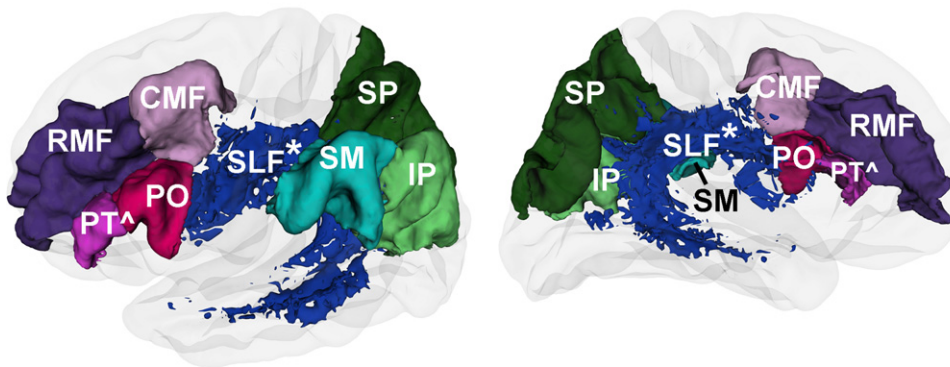
(A) Digit Span Forwards

(B) Digit Span Backwards

Fig. 2. Regions of the fronto-parietal network and superior longitudinal fasciculus. 3D-renderings of FreeSurfer-derived cortical regions of interest and the superior longitudinal fasciculus in the left hemisphere, shown in lateral (left column) and medial (right column) view. Note that the figure displays the whole SLF, while only voxels overlapping the TBSS-derived skeleton is included in analyses. Significant relationships with Digit Span performance are indicated with * (corrected for multiple comparisons) and ^ (uncorrected $p < .05$), for digit span forwards in (A) and Digit Span Backwards in (B). SP, superior parietal cortex; IP, inferior parietal cortex; SM, supramarginal gyrus; SLF, superior longitudinal fasciculus; CMF, caudal middle frontal cortex; RMF, rostral middle frontal cortex; PT, pars triangularis; PO, pars opercularis.

3.3.4. Structural specificity of brain–behavior relationships, and hemispheric lateralization

The question of how unique the relationships between working memory scores and brain variables are to the fronto-parietal network and connecting pathways, was investigated by looking at the brain–behavior relationships across all cortical regions and tracts, in both hemispheres. Partial correlation coefficients between DSF or DSB and cortical thickness, while partialling out the effect of age, in all 33 FreeSurfer parcellations in each hemisphere, are displayed in Supplementary Table 3. In Supplementary Fig. 4, the correlations between DSF and the 33 parcellations in the left hemisphere are ranked in ascending order (from the strongest negative to the strongest positive correlations). Ranking the correlations showed that the 7 originally chosen ROIs were among the 14 strongest correlations of the 33, with mostly other frontal and parietal regions also among the 14 highest correlations. Analyses also showed correlations of similar magnitude in the right hemisphere, although not entirely symmetrical to the left hemisphere regions. Inferior parietal cortex, caudal middle frontal and rostral middle frontal cortex, and pars orbitalis were among the highest correlations in both hemispheres. DSB was generally weakly correlated with left hemisphere cortical thickness, with two ventrolateral prefrontal regions showing the highest negative correlations (Pars orbitalis: $r = -.24$; Pars triangularis: $p = -.23$). Weak correlations were seen with the right hemisphere regions. Because the strongest relationships between DTI indices and working memory in the main analyses were with RD, follow-up analyses were done with RD tracts and white matter parcellations. The DTI results from all tracts,

as shown in Supplementary Table 4, showed that although the left SLF RD showed the strongest correlation with both DSF and DSB, the left inferior longitudinal fasciculus (in the case of DSF) and left cingulum parahippocampus gyrus (in the case of DSB) showed relationships of equal magnitude. This makes it relevant to ask whether the relationship with the SLF is mainly driven by its temporal lobe fraction. Correlations between DSF and RD within white matter in the same regions as the cortical regions of the fronto-parietal network, as well as temporal regions, were therefore calculated, and are displayed in Supplementary Table 5. Here, the strongest correlations were in the parietal ROIs (up to $-.30$), followed by temporal regions (up to $-.26$), then frontal regions (up to $-.19$). Weak correlations were found in the tracts and white matter ROIs of the right hemisphere.

4. Discussion

There were two novel findings in the present study: (1) verbal working memory (storage and to a lesser extent manipulation) was related to structural properties of cortical regions within the fronto-parietal network and connecting pathways during childhood and adolescence, and (2) regional cortical thickness and SLF microstructure were complementary in explaining working memory performance in childhood and adolescence. The effects were most pronounced for storage capacity (DSF), where the supramarginal gyrus and rostral middle frontal cortex, as well as radial diffusivity in the SLF, were related to performance. Working

memory manipulation capacity (DSB) was related to radial diffusivity in the SLF.

4.1. Neurodevelopment of verbal working memory

Both working memory tasks were related to age in our sample, as expected based on age norms (Wechsler, 1992) and previous developmental studies (Gathercole et al., 2004). Older adolescents could keep longer strings of digits in mind, and could reverse the order of longer digit strings than could younger children. More interestingly, the hypothesized involvement of cortical thinning in regions within the left hemisphere fronto-parietal network in working memory performance was confirmed in the simple storage span condition (DSF). Here, two of the seven predefined regions were predictive of performance, while additionally two regions showed a similar tendency. This confirms that structural cortical development of parietal and lateral prefrontal regions is related to working memory performance, extending the findings from fMRI studies (Casey et al., 1995; Finn et al., 2010; Klingberg, 2006; Kwon et al., 2002; Nelson et al., 2000; O'Hare et al., 2008; Thomas et al., 1999; Thomason et al., 2009). The supramarginal gyrus was one of the regions most predictive of performance, which is in accordance with this region's role in verbal processing (Brahmbhatt et al., 2008; Crottaz-Herbette et al., 2004; Paulesu et al., 1993; Ravizza et al., 2004; Rothmayr et al., 2007).

In the complex span task (DSB), the results were much weaker. One possible reason could be that task performance in the manipulation condition was more vulnerable to effects of extraneous variables such as fatigue, distraction and employment of different strategies, making it a more diverse measure than the purer storage span task. Nevertheless, caution must be taken when concluding on the present results, as the two tasks to varying degrees were related to cortical thickness of fronto-parietal regions. Only one ROI, cortical thickness of the pars triangularis, was related to complex working memory performance independently of age, and only at an uncorrected significance level, thus making conclusions about its involvement uncertain. However, the pars triangularis is part of Broca's area, and fMRI studies have demonstrated the importance of this area in working memory, thought to reflect the articulatory support processes of encoding and rehearsal (Henson, Burgess, & Frith, 2000; Kwon et al., 2002). This makes it possible that the relationship between DSF and the pars triangularis could be based on the additional use of rehearsal of the digits when preparing for reversing them. Thus, this relationship must await future replications.

Microstructural properties of the SLF were related to of working memory performance in both tasks, confirming the importance of structural connectivity for working memory performance in development. The results are in accordance with previous studies with adults (Burzynska et al., 2011) as well as children (Vestergaard et al., 2010). Also in accordance with previous findings (Tamnes, Ostby, Walhovd et al., 2010; Vestergaard et al., 2010), radial diffusivity was a stronger predictor of cognitive performance than FA in development. The importance of white matter pathways for efficient working memory performance is thought to reflect the need for speeded communication between the frontal and parietal regions in the network, since these regions are far apart and must work together in close harmony. One of the underlying biological processes in white matter development through adolescence is myelination, whereby axons get insulated and able to conduct action potentials at greater speeds (Lebel et al., 2008; Yakovlev & Lecours, 1967). Radial diffusivity indexes the degree to which water molecules travel in the direction perpendicular to the main diffusion direction, and this has been hypothesized to be more reflective of myelination. Support for the role of myelination in the RD measure comes from studies with mouse and rat models (Bockhorst

et al., 2008; Song et al., 2003, 2005), as well as a combined ex vivo DTI and histological study of multiple sclerosis patients where degree of demyelination correlated with radial diffusivity (Klawiter et al., 2011). The idea of the importance of reduced RD, and possibly increased myelination, for cognitive development is compelling. Still, care should be taken when considering underlying biological processes that are not directly measured by DTI or structural MRI. Other processes, such as axonal alignment, axonal density and axon circumference (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010) must be kept in mind as well.

As both cortical and white matter maturation are processes that take place in the brains of children and adolescents, the question of their respective impact relative to each other on development of working memory function arises. In the fMRI study by Olesen et al. (2003), FA in frontal and parietal white matter regions was correlated with blood oxygenation level dependent (BOLD) signal in a frontal region, pointing to the possibility of increased structural connectivity being the driving force behind cortical activation. In the present study, white matter microstructural properties and cortical thickness were complementary in accounting for individual differences in working memory performance. This underscores the importance of both cortical and structural connectivity maturational processes within the fronto-parietal network of working memory. This is the first time the question of joint contributions of cortical and white matter properties to working memory function in development has been approached using MRI morphometry and DTI in combination.

4.2. Brain developmental patterns within the fronto-parietal network and working memory performance

The age-group analyses suggested that the importance of white matter microstructure and cortical thickness for working memory performance was different across age: SLF relationships were found mainly in the 12–15 age group, while cortical thickness relationships were found in the oldest age group (16–19). Thus, it may be that the influence of structural connectivity and cortical thickness on working memory performance follows different age trajectories. This remains speculative, though, as statistical comparisons between the age groups yielded few significant differences. This could be because the sample sizes were too small, leaving it an open question whether these group differences are reflective of true developmental patterns or random group differences in brain measures.

The SLF and nearby white matter microstructure has previously been linked to working memory development in other studies (Burzynska et al., 2011; Karlsgodt et al., 2008; Olesen et al., 2003; Vestergaard et al., 2010), but the study by Niogi and McCandliss (2006) did not find any relationship between SLF microstructure and verbal working memory. Their sample was under 10 years of age, and thus their results are in line with the lack of SLF relationships in the youngest age group in our study. This points to the importance of including wide age ranges in developmental studies, and to consider developmental variability.

4.3. Working memory and brain development – beyond the fronto-parietal regions

The focused approach of selecting a limited number of ROIs allowed for structure–function relationships to be found, without the strict criteria for correcting for multiple comparisons that would go with a whole-brain analysis. Still, the role of these regions may not be unique. As some studies show, regions outside the fronto-parietal network may also be of importance in working memory (Chang, Crottaz-Herbette, & Menon, 2007; Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006; Finn et al., 2010; Geier,

Garver, Terwilliger, & Luna, 2009; O'Hare et al., 2008). The results of the analyses with all cortical regions of the left hemisphere revealed that the 7 ROIs were among the 14 highest correlation coefficients of a total of 33 regions in the analysis, pointing to some regional specificity. The results also showed relationships between DSF and regions of the right hemisphere of comparable magnitude to the left hemisphere results, as well as relationships with other white matter regions and tracts. Thus, these extended analyses point to the possibility of other networks and regions being important for working memory performance in development as well. Caution must be taken when considering these results, as correction for multiple comparisons was not employed.

4.4. Limitations

The operationalization of SLF, through the use of a probabilistic atlas, might not capture all of the connections between frontal and parietal areas, and may include connections that go elsewhere, for instance into the temporal lobe. Also, the current results are cross-sectional, and genuine effects of development may only be captured in a longitudinal design.

4.5. Conclusion

The present study found evidence for the importance of macro- and microstructural brain maturation for working memory performance in children and adolescents. Both cortical thickness and microstructural properties of the superior longitudinal fasciculus, thought to connect frontal and parietal regions, accounted for working memory performance independently of age. The unique contribution of the cortical and white matter variables in explaining working memory indicates that working memory development results from the joint sum of different neurobiological maturational events. These findings underscore the importance of considering multiple measures of brain maturation in the effort of understanding the neurobiological basis of cognitive development.

Conflict of interest

The authors declare no competing financial interests.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuropsychologia.2011.10.001.

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