



PAPER

Developmental differences in prefrontal activation during working memory maintenance and manipulation for different memory loads

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Abstract

The ability to keep information active in working memory is one of the cornerstones of cognitive development. Prior studies have demonstrated that regions which are important for working memory performance in adults, such as dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and superior parietal cortex, become increasingly engaged across school-aged development. The primary goal of the present functional MRI study was to investigate the involvement of these regions in the development of working memory manipulation relative to maintenance functions under different loads. We measured activation in DLPFC, VLPFC, and superior parietal cortex during the delay period of a verbal working memory task in 11–13-year-old children and young adults. We found evidence for age-related behavioral improvements in working memory and functional changes within DLPFC and VLPFC activation patterns. Although activation profiles of DLPFC and VLPFC were similar, group differences were most pronounced for right DLPFC. Consistent with prior studies, right DLPFC showed an interaction between age and condition (i.e. manipulation versus maintenance), specifically at the lower loads. This interaction was characterized by increased activation for manipulation relative to maintenance trials in adults compared to children. In contrast, we did not observe a significant age-dependent load sensitivity. These results suggest that age-related differences in the right DLPFC are specific to working memory manipulation and are not related to task difficulty and/or differences in short-term memory capacity.

Introduction

Working memory, or the ability to temporarily store and manipulate information (Baddeley, 1992, 2003), has often been described as a driving force behind the development of cognitive control (Case, 1992; Hitch, 2002; Pascual-Leone, 1995). Behavioral studies have demonstrated that working memory functions generally continue to improve until late childhood/adolescence (Huizinga, Dolan & van der Molen, 2006; Luna, Garver, Urban, Lazar & Sweeney, 2004; van Leijenhorst, Crone & van der Molen, 2007). However, it is important to differentiate between online maintenance and manipulation of information, as these functions seem to follow different developmental trajectories (Conklin, Luciana, Hooper & Yarger, 2007; Gathercole, 1999, 2004). Within the context of the working memory model presented by Baddeley and colleagues (e.g. Baddeley, 2003), maintenance refers to the simple storage and rehearsal of information in short-term memory, whereas manipula-

tion involves complex operations on the information held in mind (i.e. executive control). A fundamental question in current research on cognitive development concerns the brain mechanisms that underlie the development of these different working memory functions.

In adults, most working memory tasks broadly activate the same fronto-parietal regions, including dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), and superior parietal cortex (Owen, McMillan, Laird & Bullmore, 2005; Wager & Smith, 2003). However, differences have been reported with respect to material type (i.e. verbal, spatial or object working memory) and process (i.e. simple storage versus manipulation). For example, simple verbal storage tasks are usually associated with more left lateralized activation than spatial or object tasks (Wager & Smith, 2003; Gruber, 2001). Tasks that involve executive processing are typically associated with more dorsal frontal and parietal activation than pure maintenance tasks (Curtis & D'Esposito, 2003; D'Esposito, Postle, Ballard & Lease,

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1999; Petrides, 2000; Sakai & Passingham, 2003; Smith & Jonides, 1999; Wager & Smith, 2003; Wagner, Maril, Bjork & Schacter, 2001). Maturation of lateral PFC and superior parietal cortex has been suggested to contribute to working memory development in childhood, such that increased activation in these areas is associated with an age-related increase in working memory performance (Ciesielski, Lesnik, Savoy, Grant & Ahlfors, 2006; Klingberg, Forssberg & Westerberg, 2002a; Kwon, Reiss & Menon, 2002; Olesen, Macoveanu, Tegner & Klingberg, 2007; Scherf, Sweeney & Luna, 2006; Schweinsburg, Nagel & Tapert, 2005). However, it is still not well understood how changes in lateral PFC and superior parietal cortex contribute to the development of different subcomponents of working memory.

Age differences in working memory performance have been explained in terms of processing speed, short-term memory capacity and the involvement of an executive control system allowing for the manipulation of information in mind (Case, 1992; Diamond, 2002; Hitch, 2002; Pascual-Leone, 1995; Pickering, 2001). It has been argued that working memory manipulation functions, which rely more strongly on the DLPFC, develop more slowly than maintenance functions, which rely more on ventral regions (e.g. Conklin *et al.*, 2007). This hypothesis was confirmed by a recent neuroimaging study (Crone, Wendelken, Donohue, van Leijenhorst & Bunge, 2006). In this study, children and young adults were asked to simply maintain a sequence of objects in short-term memory or to reverse the sequence of objects held in short-term memory, representing working memory manipulation processes. It was demonstrated that 8–12-year-old children may have difficulty with maintenance processes, but performance differences are much more pronounced when information needs to be manipulated in working memory (see also Diamond, 2002). Consistent with the suggested differential contribution of VLPFC and DLPFC to maintenance and manipulation processes, respectively, this study showed similar activation in left VLPFC in children and adults, but immature activation in right DLPFC in children, specifically for manipulation trials. Moreover, activation in right DLPFC, but not left VLPFC, was positively correlated with performance on manipulation trials. Therefore, it was proposed that left VLPFC and right DLPFC are important for different working memory components and follow separate developmental time courses.

The neuroanatomical distinction between manipulation and maintenance, however, has also received criticism. That is, in addition to manipulation processes, the involvement of DLPFC has also been observed for increasing short-term memory load, indicating that the DLPFC is also involved in maintenance processes (Narayanan, Prabhakaran, Bunge, Christoff, Fine & Gabrieli, 2005; Rypma, Prabhakaran, Desmond, Glover & Gabrieli, 1999; Veltman, Rombouts & Dolan, 2003). In agreement with these findings, prior developmental fMRI studies using a Sternberg paradigm (a prototypical

maintenance task) illustrated that increasing load has a similar effect on activation in lateral PFC and parietal cortex as manipulation demands (Thomason, Race, Burrows, Whitfield-Gabrieli, Glover & Gabrieli, 2009; O'Hare, Lu, Houston, Bookheimer & Sowell, 2008). For example, Thomason and colleagues (2009) demonstrated that when load increased, adults showed increasing activation in parietal and frontal regions (including right DLPFC) relative to children. These findings suggest that the developmental patterns in DLPFC could be attributed to task difficulty (reflected by an increased number of errors or larger reaction times), rather than manipulation processes *per se*. For example, children might have more difficulty than adults remembering a longer list and remembering a list in the reverse order. Related to this, activation differences might represent a difference in short-term memory capacity, which subserves both storage and processing functions (Case, Kurland & Goldberg, 1982; Daneman & Carpenter, 1983; Just & Carpenter, 1992). In agreement with this hypothesis, it has been demonstrated that individuals with a high capacity show a monotonical increase of fronto-parietal activation, while activation levels off for individuals with a low capacity (Nyberg, Dahlin, Stigsdotter & Backman, 2009). Moreover, a positive correlation has been found between capacity and fronto-parietal activation in 9–18-year-old children (Klingberg *et al.*, 2002a). Thus, the inability of children to increase DLPFC activation during both manipulation processes and storage/rehearsal processes with increased load might be related to a smaller short-term memory capacity. However, an alternative explanation suggests that besides maintenance, these Sternberg tasks were capturing executive functions. More specifically, executive functions might have been needed to maintain information in mind when capacity limits were reached (Rypma *et al.*, 1999; Rypma, Berger & D'Esposito, 2002; Thomason *et al.*, 2009), or when response processes involved searching memory content and matching (Veltman *et al.*, 2003).

In the present study, we investigated the development of working memory in relation to increasing load and manipulation demands in a single verbal working memory paradigm. We examined how developmental differences within DLPFC, VLPFC, and superior parietal cortex are related to (a) the ability to manipulate information in working memory and (b) the ability to maintain information in mind under increasing memory load. We obtained behavioral and fMRI data for 11–13-year-old children and 18–25-year-old adults. The age selection was based on prior research showing that 11–13-year-old children are able to perform working memory tasks with varying loads, while there is also still a rapid increase in performance and associated brain activation between late childhood and adulthood. We used an event-related design to isolate delay period activation from activation related to encoding and response processes (Crone *et al.*, 2006; Curtis & D'Esposito, 2003). During the delay period, participants were asked to either maintain a sequence

of objects in short-term memory or to reverse the objects (i.e. working memory manipulation). To test the differential effects of load versus manipulation demands, maintenance and manipulation trials were presented in sequences of three, four or five objects. With respect to activation in DLPFC, we formulated two hypotheses: the first hypothesis (the manipulation hypothesis) states that DLPFC activation is directly related to manipulation processes. According to this hypothesis, children will fail to recruit DLPFC for manipulation relative to maintenance trials (similar to Crone *et al.*, 2006), but they will show a similar activation profile as adults for increasing load. Accordingly, we expected to find age \times condition interactions, but no age \times load interactions. In contrast, the second hypothesis (the difficulty hypothesis) states that DLPFC activation is associated with task difficulty and/or short-term memory capacity. According to this hypothesis, adults will show increased activation for manipulation relative to maintenance trials, as well as for increasing load. In both cases, the increased activation should be absent in children, resulting in age \times condition as well as age \times load interactions. Developmental differences were also investigated for left superior parietal cortex, which has also shown developmental differences in working memory manipulation (Crone *et al.*, 2006) and for left VLPFC, which was thought to be more specifically involved in maintenance processes (D'Esposito *et al.*, 1999; Smith & Jonides, 1999; Wagner *et al.*, 2001). Based on prior results, we expected VLPFC to have a more mature pattern of activation (Crone *et al.*, 2006).

Method

Participants

Fifteen children (ages 11–13, $M_{\text{age}} = 12.5$, 10 female) and 15 adults (ages 19–25, $M_{\text{age}} = 22.0$, eight female) participated in the current study. One adult was excluded from further analyses because she performed at chance level in the manipulation task. A chi-square analysis confirmed that gender distribution did not differ between age groups, $\chi^2(1, N = 29) = 0.83, p = .36$. Prior to enrollment, participants were screened for psychiatric or neurological conditions, history of head trauma, and history of attention or learning disorders. Parents of the children filled out the Child Behavior Checklist (CBCL; Achenbach, 1991) to screen for psychiatric symptoms. All participants scored below clinical levels on all subscales of the CBCL. All participants completed the WISC or WAIS intelligence subscales similarities and block design (Wechsler, 1991, 1997). A one-way ANOVA indicated that age groups did not differ in estimated IQ, $F(1, 27) = 0.64; p = .43$. All participants gave written informed consent for participation in the study. Parents of children that participated in the study gave written informed consent as well. Adults received financial compensation for participation. Children received a gift

and their parents received monetary compensation for travel costs. The experiment was approved by the Central Committee on Research Involving Human Subjects in the Netherlands.

Task and procedures

On the day of the scan session, all participants were familiarized with imaging procedures using an MRI mock scanner. Next, participants were trained on the working memory task. The task involved a modified version of the verbal working memory task that was previously used by Crone and colleagues (Crone *et al.*, 2006), with the addition of a parametric manipulation of load. The task is referred to as 'verbal working memory' because participants were explicitly instructed to use a verbal strategy. The visual stimuli consisted of two sets of 150 black and white pictures of simple objects taken from the Max Planck Institute's picture database (<http://www.mpi.nl>). Before the scanning session, participants were shown all objects that were used in the task and they were asked to name each object out loud. They were instructed that there was no right or wrong answer, but they should name the objects with one- or two-syllable words. Thus, prior to scanning participants were familiar with all objects in the scanning session (see Crone *et al.*, 2006, for a similar procedure).

Each trial started with a 250 ms fixation cross, followed by three, four, or five objects presented sequentially in the center of the screen (i.e. the parametric manipulation of load). Each object was shown for 850 ms interleaved with 250 ms fixation screens. After the last object was presented, the instruction 'forward' or 'backward' was presented for 500 ms. On forward trials, participants were instructed to remember the objects in the presented order during the following 6000 ms delay. These trials are referred to as 'maintenance trials'. On backward trials, participants were instructed to remember the objects in the reverse order during the following 6000 ms delay. These trials are referred to as 'manipulation trials'. Participants were explicitly instructed to name the objects internally during the delay period. After the delay period, one of the target objects was presented for 2850 ms with the instruction to choose number 1, 2, 3, 4, or 5, representing the location of the target object in the forward or backward sequence. Here, participants had to indicate whether the object was presented first, second, third, fourth or fifth in the forward or backward sequence. They could respond by pressing a button on a left or right response box with their left middle finger (number 1), left index finger (number 2), right index finger (number 3), right middle finger (number 4) or right ring finger (number 5). Inter-stimulus intervals, in which a fixation cross was presented, were jittered between trials based on an optimal sequencing program designed to maximize the efficiency of recovery of the blood oxygenation level-dependent (BOLD) response (Dale, 1999).

The task consisted of three runs of 30 trials each, in which 15 maintenance and 15 manipulation items were intermixed. In one run, the trial sequences consisted of three objects to be memorized ('load 3'), in a second run, the trial sequences consisted of four objects ('load 4'), and in a third run the trial sequences consisted of five objects ('load 5'). The order of runs was counterbalanced across participants. There were six different versions of the task, in which the order of maintenance and manipulation trials was determined by the optimal sequencing program (Dale, 1999). In these six versions, sequences consisted of a different combination of objects.

Prior to scanning, participants practiced the task to obtain proficiency. During this practice period, they were presented with one block of four maintenance trials, one block of four manipulation trials and three blocks of eight trials in which maintenance and manipulation trials were mixed. The first mixed task block consisted of sequences of three objects, the second block consisted of sequences of four objects and the third block consisted of sequences of five objects.

FMRI data acquisition

Scanning was performed with a standard whole-head coil on a 3-Tesla Philips Achieva MRI system (Best, The Netherlands). A total of 222 (load 3), 241 (load 4) and 260 (load 5) T2*-weighted whole-brain EPIs were acquired, including two dummy scans preceding each scan to allow for equilibration of T1 saturation effects (TR = 2.2 sec; TE = 30 msec, flip angle = 80 degrees, 38 transverse slices, $2.75 \times 2.75 \times 2.75$ mm [+ 10% inter-slice gap]). Visual stimuli were projected onto a screen that was viewed through a mirror at the head end of the magnet. After the functional runs, a high-resolution EPI scan and a T1-weighted anatomical scan were obtained for registration purposes (EPI scan: TR = 2.2 msec; TE = 30 msec, flip angle = 80 degrees, 84 transverse slices, $1.964 \times 1.964 \times 2$ mm; 3D T1-weighted scan: TR = 9.717 msec; TE = 4.59 msec, flip angle = 8 degrees, 140 slices, $.875 \times .875 \times 1.2$ mm, FOV = $224.000 \times 168.000 \times 177.333$). All anatomical scans were reviewed and cleared by a radiologist. No anomalous findings were reported.

FMRI data analysis

Data analysis was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIBs Software Library, <http://www.FMRIB.ox.ac.uk/fsl>; Smith, Jenkinson, Woolrich, Beckmann, Behrens, Johansen-Berg, Bannister, De Luca, Drobniak, Flitney, Niazy, Saunders, Vickers, Zhang, De Stefano, Brady & Matthews, 2004). The following pre-statistics processing was applied: motion correction (Jenkinson, Bannister, Brady & Smith, 2002); non-brain removal (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 8.0 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering

(Gaussian-weighted least-squares straight line fitting, with $\sigma = 50.0$ s). Functional scans were registered to high-resolution EPI images, which were registered to T1 images, which were registered to standard MNI space (Jenkinson & Smith, 2001; Jenkinson *et al.*, 2002).

In native space, the FMRI time-series were analyzed using an event-related approach in the context of the General Linear Model with local autocorrelation correction (Woolrich, Ripley, Brady & Smith, 2001). Within each run (for load 3, load 4 and load 5), cue period, delay period, and target/response period were modeled separately. Each effect was modeled on a trial-by-trial basis as a concatenation of square-wave functions: the cue period started with the presentation of the first memory item and lasted until the last memory item disappeared (3050 ms, 4150 ms, or 5250 ms); the delay period started with the instruction and lasted until the target item appeared (6500 ms); and the target/response period started with the presentation of the target item and lasted until the participant made a response (≤ 2850 ms). Delay- and target/response periods of maintenance and manipulation trials were modeled separately. If present, erroneous trials were included in the model (delay- and target/response periods separately), but excluded from the contrasts of interest. Hence, there were either five or seven square-wave functions (i.e. cue, delay maintenance, target maintenance, delay manipulation, target manipulation, delay error, target error). Each of these square-wave functions was convolved with a canonical hemodynamic response function and its temporal derivative. The model was high-pass filtered (Gaussian-weighted least-squares straight line fitting, with $\sigma = 50.0$ s).

Because we were specifically interested in maintenance and manipulation processes, the contrasts of interest only involved delay period activation. Region of interest (ROI) analyses were performed to investigate differences between children and adults in DLPFC activation, as well as activation in other regions that were related to working memory in prior research; VLPFC and superior parietal cortex (SPC) (e.g. Crone *et al.*, 2006). The locations of the regions of interest were functionally defined using a whole-brain delay > fixation contrast (i.e. combined across maintenance and manipulation for all loads) for children and adults together, masked by anatomical regions from the Harvard-Oxford cortical atlas (FMRIB.ox.ac.uk/fsl/data/atlasdescriptions.html#ho). The whole-brain contrast was thresholded at $p < .001$, uncorrected. The VLPFC ROI was defined by delay > fixation activation that fell within the opercular part of the left inferior frontal gyrus, the DLPFC ROIs were defined by activation that fell within the middle frontal gyri, and the SPC ROI was defined by activation that fell within the left superior parietal cortex. Because there was no delay period activation in the right inferior frontal gyrus and right superior parietal cortex, we did not create a functional ROI for the right VLPFC and right SPC. For each of the four remaining ROIs (right DLPFC, left DLPFC, left VLPFC, and left SPC), mean

z-values were calculated for load 3, load 4 and load 5 'maintenance versus fixation' and 'manipulation versus fixation' contrasts for each participant (using Featquery; FMRIB.ox.ac.uk/fsl/feat5/featquery.html). These values were *z*-transformed parameter estimates (averaged across the ROI), which indicate how strongly the mean signal of the ROI fits the waveforms of the explanatory variables (i.e. the delay-period maintenance and manipulation regressors). Finally, the mean *z*-values were entered in a repeated measures ANOVA with load (load 3, load 4, and load 5) and condition (maintenance and manipulation) as within-subjects variables and with age group (children and adults) as a between-subjects factor.

Results

Behavioral results

Performance was examined in terms of accuracy (quantified as the percentage of correct responses within each condition) and response time (RT) on correct trials. All significant effects survived Greenhouse-Geisser correction in case of violations of the sphericity assumption.

Accuracy

To test for task and age differences in accuracy, a repeated measures ANOVA was performed with load (load 3, load 4, and load 5) and condition (maintenance and manipulation) as within-subjects variables and with age group (children and adults) as a between-subjects factor. This ANOVA confirmed that accuracy decreased with increasing load, $F(2, 54) = 89.95, p < .001; \eta^2 = .77$, and for manipulation trials relative to maintenance trials, $F(1, 27) = 105.76, p < .001; \eta^2 = .80$ (Figure 1). Repeated contrasts showed that participants performed better at load 3 trials compared to load 4 trials, $F(1, 27) = 79.39, p < .001; \eta^2 = .75$, and at load 4 trials compared to load 5 trials, $F(1, 27) = 19.26, p < .001; \eta^2 = .42$. Children performed less accurately than adults, $F(1, 27) = 10.79, p < .005; \eta^2 = .29$. The age difference was not significantly affected by load and/or condition, $F(1, 27) = 3.14, p = .09; \eta^2 = .10$ (age \times condition interaction), $F(2, 54) = 1.12, p = .33; \eta^2 = .04$ (age \times load interaction), $F(2, 54) = 0.79, p = .46; \eta^2 = .03$ (age \times load \times condition interaction), and there was no significant interaction between load and condition effects, $F(2, 54) = 2.13, p = .13; \eta^2 = .07$.

To compare the present results with those presented by Crone and colleagues (2006), we also examined isolated condition effects by performing group comparisons for each load separately. These analyses showed that there was a significant age by condition interaction at load 3, $F(1, 27) = 5.06, p < .05; \eta^2 = .16$, indicating that children performed disproportionately worse for manipulation trials compared to maintenance trials. At loads 4 and 5,

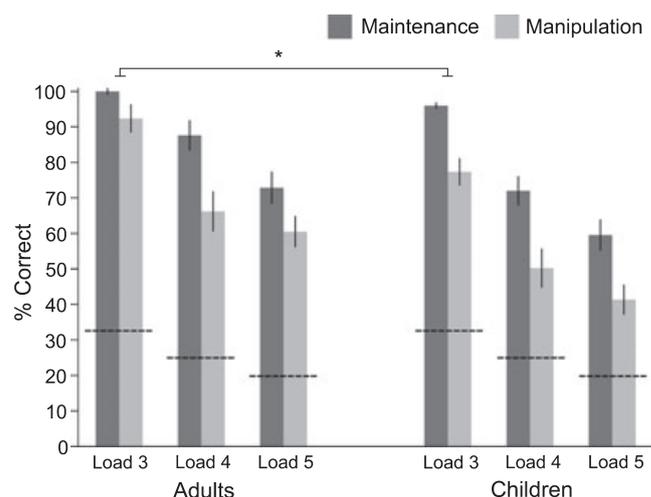


Figure 1 Accuracy as indicated by the percentage of correct trials for each condition and each age group. All participants performed well above chance level (dotted lines), but children performed worse than adults. At load 3, these effects were more pronounced for the manipulation condition.

children performed less accurately than adults, $F(1, 27) = 6.27, p < .05; \eta^2 = .19$ (load 4), $F(1, 27) = 9.34, p = .005; \eta^2 = .26$ (load 5), but there were no significant age by condition interactions, $F(1, 27) = 0.003, p = .95; \eta^2 < .001$ (load 4), $F(1, 27) = .79, p = .38; \eta^2 = .03$ (load 5). Next, we tested for isolated maintenance effects by analyzing only the forward trials in loads 3, 4 and 5 runs. Even though there was no significant age by load interaction when all loads were entered in the ANOVA, $F(2, 54) = 2.12, p = .13; \eta^2 = .07$, a direct comparison between load 3 and load 4 resulted in a significant age by load interaction, $F(1, 27) = 4.33, p < .05; \eta^2 = .14$.

Response times

A similar load (load 3, load 4, and load 5) \times condition (maintenance and manipulation) \times age group (children and adults) repeated measures ANOVA was performed for mean RTs on correctly performed trials. This analysis resulted in a main effect of condition, $F(1, 27) = 56.15, p < .001; \eta^2 = .68$, showing that participants were slower on manipulation trials than on maintenance trials ($M_{\text{manipulation}} = 1,608.21 \text{ ms}, SE = 37.70$; $M_{\text{maintenance}} = 1,361.86 \text{ ms}, SE = 39.37$) and a main effect of load, $F(2, 54) = 40.14, p < .001; \eta^2 = .60$, showing that participants performed slower when load increased ($M_{\text{load3}} = 1,286.82 \text{ ms}, SE = 37.16$; $M_{\text{load4}} = 1,543.48 \text{ ms}, SE = 45.61$; $M_{\text{load5}} = 1,624.82 \text{ ms}, SE = 41.67$). Repeated contrasts revealed that participants performed better at load 3 trials compared to load 4 trials, $F(1, 27) = 51.39, p < .001; \eta^2 = .66$; the comparison between load 4 and load 5 trials was close to significance, $F(1, 27) = 4.08, p = .054; \eta^2 = .13$. Consistent with prior reports, there were no significant age differences and no significant interactions with age, $F(1, 27) = 2.50, p = .13; \eta^2 = .09$ (main effect of age), $F(2, 54) = 1.67, p = .20; \eta^2 = .06$ (age \times

Table 1 Delay-related activation across age groups, loads and conditions

Cluster	Cluster size	Peak voxel			
		Z	x	y	z
Bilateral Supplementary Motor Cortex, Middle Frontal Gyrus, Superior Frontal Gyrus, Precentral Gyrus, Postcentral Gyrus, Supramarginal Gyrus	6435	5.19	-2	4	66
Right Postcentral Gyrus, Supramarginal Gyrus	377	3.94	48	-34	58
Right Precentral Gyrus, Postcentral Gyrus	338	3.82	56	-6	34
Right Posterior Cingulate, Precuneus, Lingual Gyrus	325	4.72	32	-44	2
Bilateral Superior Parietal Lobule, Lateral Occipital Cortex, Superior Division, Precuneus Cortex	209	4.01	10	-70	58
Left Posterior Cingulate, Precuneus, Lingual Gyrus	168	4.55	-20	-46	10
Left Middle Frontal Gyrus, Inferior Frontal Gyrus (Pars Triangularis)	162	3.90	-42	32	24
Right Caudate	160	3.79	22	26	12
Right Frontal Pole, Middle Frontal Gyrus	124	4.16	40	44	26
Right Caudate	101	3.74	18	-14	24
Right Cerebellum	85	3.83	22	-62	-28
Left Caudate	37	3.50	-16	28	10
Left Caudate	18	3.48	-16	-14	26
Left Inferior Frontal Gyrus (Pars Triangularis)	18	3.42	-38	32	6
Frontal Operculum Cortex, Insular Cortex	10	3.29	-38	22	2

load interaction), $F(1, 27) = 0.67, p = .42; \eta^2 = .02$ (age \times condition interaction), $F(2, 54) = 0.04, p = .97; \eta^2 = .001$ (age \times load \times condition interaction).

FMRI results

To investigate whether immature activation patterns in DLPFC (e.g. Crone *et al.*, 2006; O'Hare *et al.*, 2008; Thomason *et al.*, 2009) were primarily reflecting manipulation processes (the manipulation hypothesis) or were due to task difficulty or capacity differences (the difficulty hypothesis), we performed ROI analyses, primarily targeted at DLPFC. In addition, we performed similar analyses for other regions within the fronto-parietal working memory network: left VLPFC, and superior parietal cortex (Crone *et al.*, 2006). ROIs were identified using a whole-brain contrast examining delay > fixation activation across conditions and age groups masked by FSL anatomical regions. An overview of the whole-brain activation for this contrast at $p < .001$ is reported in Table 1 and Figure 2. All brain coordinates are reported in MNI atlas space. The results reported below are displayed in Figure 3. All significant effects survived Greenhouse-Geisser correction in case of violations of the sphericity assumption.

DLPFC

Clusters of activation were found in both hemispheres. Although the right DLPFC ROI was slightly more superior than in the study by Crone *et al.* (2006), the activation pattern in this region was very similar. Right DLPFC showed a main effect of condition, $F(1, 27) = 41.90, p < .001; \eta^2 = .61$, but no significant main effect of load, $F(2, 54) = 2.40, p = .10; \eta^2 = .08$, or load by condition interaction, $F(2, 54) = 2.44, p = .10; \eta^2 = .08$. Left DLPFC showed a main effect of condition as well, $F(2, 54) = 39.25,$

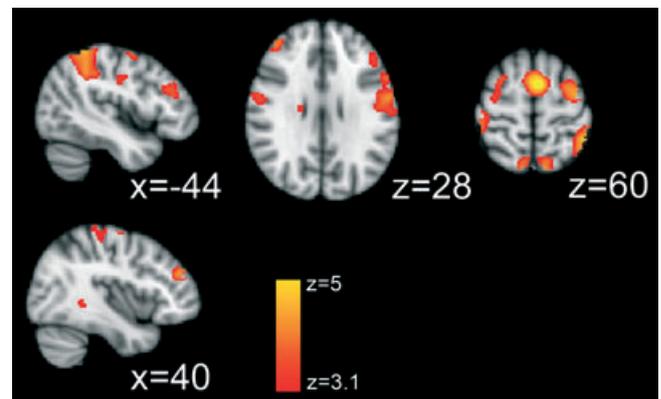


Figure 2 Delay-related activation collapsed across age groups, loads, and conditions, and overlaid on a standard anatomical image. Activation is thresholded at $p < .001$, uncorrected. The left of the image is the right of the brain.

$p < .001; \eta^2 = .59$, but in contrast to right DLPFC, it also showed a main effect of load, $F(2, 54) = 4.08, p < .05; \eta^2 = .13$, and a load by condition interaction, $F(2, 54) = 6.45, p < .005; \eta^2 = .19$. Neither of the regions showed a significant main effect of age, $F(1, 27) = 0.15, p = .70; \eta^2 = .006$ (right DLPFC) and $F(1, 27) = 1.52, p = .23; \eta^2 = .05$ (left DLPFC). However, the three-way interactions between age, load, and condition were significant, $F(2, 54) = 6.95, p < .005; \eta^2 = .21$ (right DLPFC) and $F(2, 54) = 7.91, p = .001; \eta^2 = .23$ (left DLPFC).

Two sets of post-hoc comparisons were carried out to test for age-related differences of condition irrespective of load, and of load irrespective of manipulation demands. The first set of post-hoc comparisons was performed at each load separately. We focused on age by condition effects, reflecting increased activation for manipulation > maintenance in adults relative to children. At load 3, there was a significant age by condition interaction in right DLPFC, $F(1, 27) = 6.22, p < .05; \eta^2 = .19$, but not

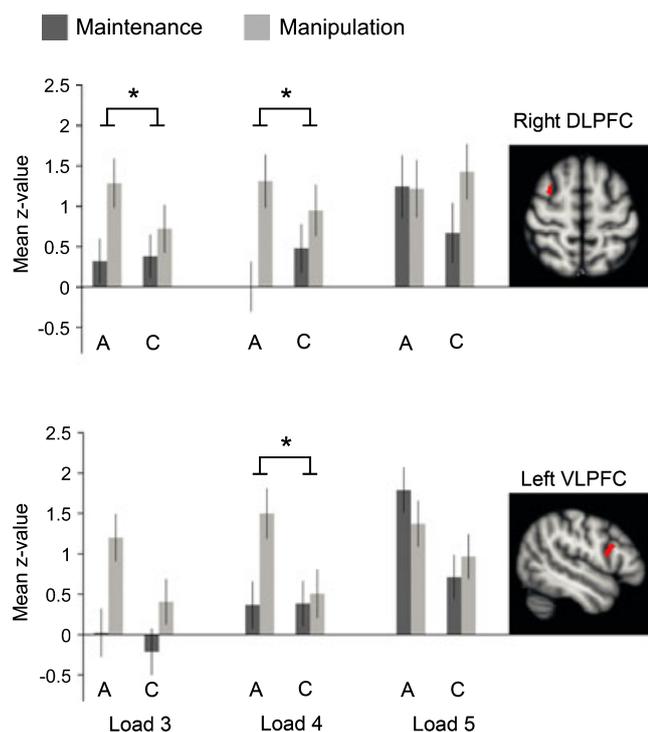


Figure 3 Delay-related activation in left VLPFC (-50, 10, 20) and right DLPFC (32, 6, 58) for adults (A) and children (C). The left of the image is the right of the brain. Age group by condition interactions are indicated with *. Neither of the regions showed an age group by load interaction.

in left DLPFC, $F(1, 27) = 3.11, p = .09; \eta^2 = .10$. At load 4, the interaction was significant for both regions, $F(1, 27) = 8.31, p < .01; \eta^2 = .24$ (right DLPFC), and $F(1, 27) = 16.45, p < .001; \eta^2 = .38$ (left DLPFC). Finally, at load 5 neither of the regions showed a significant age by condition interaction $F(1, 27) = 3.22, p = .08; \eta^2 = .11$ (right DLPFC), $F(1, 27) = 2.31, p = .14; \eta^2 = .08$ (left DLPFC), or a significant main effect of condition, $F(1, 27) = 2.76, p = .11; \eta^2 = .09$ (right DLPFC), $F(1, 27) = 1.67, p = .21; \eta^2 = .06$ (left DLPFC). The second set of post-hoc comparisons was performed for maintenance trials separately. These analyses revealed main effects of load, $F(2, 54) = 3.99, p < .05; \eta^2 = .13$ (right DLPFC), and $F(2, 54) = 8.03, p = .001; \eta^2 = .23$ (left DLPFC), but no significant interaction effects between age and load, $F(2, 54) = 1.89, p = .16; \eta^2 = .07$ (right DLPFC), and $F(2, 54) = 1.96, p = .15; \eta^2 = .07$ (left DLPFC). Taken together, we found age \times condition interactions (specifically at the lower loads), but no age \times load interactions, which is in line with the manipulation hypothesis.

VLPFC

For VLPFC, a cluster of activation was found in the left hemisphere only. In this cluster, there was more activation for increasing load, $F(2, 54) = 7.04, p < .005; \eta^2 = .21$, and for manipulation trials relative to maintenance trials, $F(1, 27) = 19.50, p < .001; \eta^2 = .42$. The difference between manipulation trials and maintenance trials

decreased with increasing load, $F(2, 54) = 13.02, p < .001; \eta^2 = .33$ (load \times condition interaction). In general, activation was higher in adults, $F(1, 27) = 4.71, p < .05; \eta^2 = .15$, but the age effects depended on the interaction between load and condition, $F(2, 54) = 9.65, p < .001; \eta^2 = .26$ (age \times load \times condition interaction).

Again, two sets of post-hoc comparisons were carried out. The first set of post-hoc comparisons showed that at load 3, activation was increased for manipulation trials relative to maintenance trials, $F(1, 27) = 35.15, p < .001; \eta^2 = .57$, but there was no significant age by condition interaction, $F(1, 27) = 3.42, p = .08; \eta^2 = .11$. In contrast, at load 4 the age by condition interaction was significant, $F(1, 27) = 10.24, p < .005; \eta^2 = .28$. Finally, the age by condition interaction at load 5 was close to significance, $F(1, 27) = 4.18, p = .051; \eta^2 = .13$. The second set of post-hoc comparisons, performed for maintenance trials separately, showed a main effect of load, $F(2, 54) = 13.85, p < .001; \eta^2 = .34$, but no significant interaction between age and load, $F(2, 54) = 2.44, p = .10; \eta^2 = .08$.

Right DLPFC versus left VLPFC

To examine whether age effects in right DLPFC and left VLPFC were significantly different, we conducted a region (right DLPFC and left VLPFC) \times load (load 3, load 4, and load 5) \times condition (maintenance and manipulation) \times age group (children and adults) repeated measures ANOVA. As predicted, there was a region by load by condition interaction, $F(2, 54) = 4.46, p < .05; \eta^2 = .14$, suggesting that VLPFC and DLPFC contributed differently to working memory processes. The ANOVA, however, did not reveal significant region by age interactions, $F(1, 27) = 2.17, p = .15; \eta^2 = .07$ (region \times age interaction), $F(2, 54) = 0.21, p = .82; \eta^2 = .008$ (region \times age \times load interaction), $F(1, 27) = 0.12, p = .73; \eta^2 = .005$ (region \times age \times condition interaction), $F(2, 54) = 0.13, p = .88; \eta^2 = .005$ (region \times age \times load \times condition interaction). Thus, even though the activation patterns of left VLPFC and right DLPFC were different, the age effects were not statistically different when tested against each other. It is possible that this is the result of a power limitation, but it could also indicate that the regions operate in a highly interconnected way.

Superior parietal cortex

A cluster of activation was found in the left hemisphere superior parietal cortex only. In this cluster, activation was increased for increasing load, $F(2, 54) = 4.72, p < .05; \eta^2 = .15$, and for manipulation trials relative to maintenance trials, $F(1, 27) = 37.96, p < .001; \eta^2 = .59$. The difference between manipulation trials and maintenance trials decreased with increasing load, $F(2, 54) = 3.94, p < .05; \eta^2 = .13$ (load \times condition interaction). Activation was higher in adults, $F(1, 27) = 6.15, p < .05; \eta^2 = .19$. However, the interaction effects between age and load and/or condition failed to reach significance,

$F(2, 54) = 0.57, p = .57; \eta^2 = .02$ (age \times load interaction), $F(1, 27) = 0.06, p = .81; \eta^2 = .002$ (age \times condition interaction), $F(1, 27) = 2.79, p = .07; \eta^2 = .09$ (age \times load \times condition interaction).

Performance-matched analyses

Finally, to exclude the possibility that age differences in neural activation were confounded by performance differences, a direct comparison was made between children at load 3 trials and adults at load 4 trials. Behavioral results showed that, if anything, adults performed less accurately than children, $F(1, 27) = 4.12, p = .052; \eta^2 = .13$, and there was no significant age by condition interaction for accuracy scores, $F(1, 27) = .29, p = .60; \eta^2 = .01$. In addition, there was no significant RT difference between age groups, $F(1, 27) = 1.84, p = .19; \eta^2 = .06$, or age by condition interaction, $F(1, 27) = .64, p = .43; \eta^2 = .02$. ROI analyses, however, revealed that the age by condition interaction in right DLPFC was still highly significant, $F(1, 27) = 13.03, p = .001; \eta^2 = .33$. In addition, left DLPFC and superior parietal cortex also showed significant age by condition interactions, $F(1, 27) = 7.16, p < .05; \eta^2 = .21$ (left DLPFC) and $F(1, 27) = 4.65, p < .05; \eta^2 = .15$ (superior parietal cortex). For the VLPFC this interaction did not reach statistical significance $F(1, 27) = 3.39, p = .08; \eta^2 = .11$.

Summary of fMRI findings

In summary, except for right DLPFC, all regions showed a main effect of load and a main effect of condition. In contrast, right DLPFC showed a main effect of condition but not of load. Moreover, bilateral DLPFC and left VLPFC showed an interaction between load, condition and age. Post-hoc tests indicated that there were interactions between condition and age at load 3 (right DLPFC) and load 4 (right DLPFC, left DLPFC, left VLPFC) that were characterized by increased activation for manipulation compared to maintenance for adults relative to children. A second set of post-hoc tests revealed that there were no significant interactions between load and age for any of the regions.

Discussion

The goal of the present study was to test the developmental differences in neural activation for increasing load versus manipulation demands. This question was inspired by prior reports, which demonstrated immature DLPFC activation in children for manipulation relative to maintenance conditions (Crone *et al.*, 2006), but also for increasing load (Thomason *et al.*, 2009). By examining load and manipulation demands in a single design, we investigated whether immature activation patterns in prior studies were primarily reflecting manipulation processes (i.e. the manipulation hypothesis) or were due

to task difficulty and/or differences in short-term memory capacity subserving both maintenance and manipulation processes (i.e. the difficulty hypothesis).

A whole-brain analysis (for children and adults together) showed delay-related activation in a fronto-parietal circuit, including bilateral DLPFC, left VLPFC, left SPC, bilateral lateral occipital cortex, bilateral anterior cingulate cortex, and bilateral supplementary motor area. Activation was more extended in the left hemisphere, consistent with a left hemisphere dominance in storage and rehearsal within verbal working memory tasks (Gruber, 2001). However, dorsal frontal activation was found in both hemispheres. Activation in dorsal areas is generally found for working memory tasks that involve executive processing relative to tasks that involve simple storage of information in short-term memory (Wager & Smith, 2003).

Region of interest (ROI) analyses were performed to investigate group differences in activation of DLPFC, VLPFC and SPC (Crone *et al.*, 2006). Consistent with prior findings, we found age-related behavioral improvements in working memory and functional changes within VLPFC and DLPFC activation patterns. At the lowest load (load 3), the findings are in agreement with prior results by Crone *et al.* (2006). That is, 11–13-year-old children performed less accurately than adults, but performance differences were disproportionately larger for manipulation trials than for maintenance trials. Behavioral effects were accompanied by activation differences in right DLPFC. That is, right DLPFC activation for manipulation relative to maintenance trials was larger in adults than in children. No significant age differences were present in left VLPFC and left DLPFC at load 3. The replication of prior findings for these regions sets the stage for examining the effects of increasing load.

Behaviorally, we found that increasing load and manipulation instruction had additive detrimental effects on performance, suggesting that performance was independently affected by the task conditions. In general, children performed less accurately than adults. In contrast to the age by condition interaction that was found for load 3, adults performed similarly to children at loads 4 and 5. In addition, an age by load interaction was found when contrasting load 3 and load 4 maintenance trials, indicating that performance differences were disproportionately larger for load 4 maintenance trials than for load 3 maintenance trials. Together, these results indicate that age-related performance differences were present in specific contrasts for working memory manipulation (load 3 manipulation versus maintenance) and increasing load (load 4 maintenance versus load 3 maintenance).

Neuroimaging results showed age-related differences in activation patterns for all lateral PFC ROIs. In right DLPFC, the activation pattern was characterized by group differences for manipulation versus maintenance at load 3 and load 4. In agreement with the hypothesis that group differences in right DLPFC were specific to the manipulation condition and not related to task

difficulty and/or differences in short-term memory capacity, we did not find significant interactions between increasing load and age group. Thus, although both manipulation demands and increasing load had detrimental effects on performance, we found only age \times condition interactions and no age \times load interactions. Moreover, age differences in activation persisted when performance was matched between children and adults (by comparing children's load 3 trials with adults' load 4 trials), indicating that the observed age differences were not simply related to differences in performance between children and adults. Taken together, these results are consistent with the hypothesis that right DLPFC is important for working memory manipulation, which is a process that becomes additionally engaged over childhood (Diamond, 2002; Conklin *et al.*, 2007; Crone *et al.*, 2006). Interestingly, at load 5 there was no significant age by condition effect and no main effect of condition, indicating that the adult group did not show significant activation for manipulation compared to maintenance trials either. In line with the idea that the mean memory capacity in adults is about four items (Cowan, 2001), some participants reported having used strategies to memorize sequences of five objects. This strategy use, which is also some type of manipulation, may explain the increased DLPFC activation at load 5 maintenance trials (Bor & Owen, 2007; Bunge, Ochsner, Desmond, Glover & Gabrieli, 2001; Jolles, Grol, van Buchem, Rombouts & Crone, 2010; Rypma *et al.*, 1999; Rypma *et al.*, 2002; Wendelken, Bunge & Carter, 2008).

Contrary to predictions, left VLPFC was not only engaged for increasing load; this region was also sensitive to manipulation conditions, specifically at the lower loads. At load 4, these effects were more pronounced for adults than for children. With respect to the proposed role of the VLPFC in maintenance processes (D'Esposito *et al.*, 1999; Smith & Jonides, 1999; Wagner *et al.*, 2001), the increased activation for manipulation trials compared to maintenance trials could be related to higher demands on maintenance capacity (e.g. for the storage of intermediate stages of a manipulation process; Just & Carpenter, 1992). The age differences could then be interpreted in terms of a limited-capacity theory, which posits that maximum capacity is reached first for manipulation trials and earlier for children than for adults. Alternatively, it is possible that the differential roles of VLPFC and DLPFC to maintenance and manipulation processes are less clear than previously reported. In the current data set, the statistical tests did not reveal differential developmental effects of left VLPFC and right DLPFC when tested against each other. The similarity of activation profiles suggests that the regions function in a highly connected way. In the current study, developmental differences were particularly evident for prefrontal regions (see also van den Bos, Guroglu, van den Bulk, Rombouts & Crone, 2009), but the performance-matched analyses also revealed differences in the superior parietal cortex (in agreement with Crone *et al.*, 2006).

Taken together, all ROIs (right DLPFC in particular) showed an interaction between condition and age for at least one of the loads. This interaction was characterized by increased activation for manipulation relative to maintenance in adults compared to children. None of the regions showed age-dependent load sensitivity. These findings are consistent with the hypothesis that the ability to manipulate information held in mind shows a more protracted development than simple maintenance of information. Although the neural effects were not accompanied by a significant age by condition effect on performance (except at load 3), several prior studies have demonstrated that mature performance is reached later for working memory tasks with high executive demands compared to tasks with low executive demands (Conklin *et al.*, 2007; Gathercole, 1999; Luciana, Conklin, Hooper & Yarger, 2005; Luciana & Nelson, 2002). For example, Conklin and colleagues (2007) demonstrated that performance on backward span tasks and self-ordered search tasks (which involve strategy use, updating of information in working memory and monitoring of performance) stabilized later than performance on simple maintenance tasks such as forward digit span and forward spatial span. Tasks that involve maintenance as well as inhibition or switching processes also show a longer developmental trajectory (Diamond, 2002). In contrast, it has been argued that the ability to maintain information in short-term memory (without manipulation) develops early and shows little improvement after the preschool years (Diamond, 1995, 2002).

Nonetheless, in the present study there were group differences for performance on maintenance trials as well. These results do not necessarily contradict prior findings. One explanation for the group differences on maintenance trials relates to improvements in the speed of processing. Several studies have illustrated that age-related improvements in verbal memory span could be predicted from speed of word repetition, which is closely related to processing speed (e.g. Cowan, Wood, Wood, Keller, Nugent & Keller, 1998; Fry & Hale, 2000; Kail, 2007). Case and colleagues (1982) demonstrated that when speed of word repetition was equated between children and adults, word span (i.e. the number of words a participant can hold in short-term memory) was no longer significantly different between groups. A second possible explanation for the performance differences on maintenance trials relates to memory for temporal order. Whereas online maintenance of single items may be fully developed around age 12, memory for the order of items might show further improvements in adolescence (McCormack, Brown, Vousden & Henson, 2000). Future experiments can test these hypotheses by varying word length and examining error patterns on a serial recall task.

In summary, the results of the present study indicate that developmental differences in DLPFC activation are specific to working memory manipulation functions and are not related to task difficulty and/or differences in short-term memory capacity. Besides the contribution to

developmental questions, these results might have important implications for the dual process theory, emphasizing that working memory is not a unitary system. It should be noted that we did not find strong evidence for differential developmental activation profiles in DLPFC, VLPFC, and superior parietal cortex. It is possible that the absence of a significant region \times age interaction is the result of the relatively small sample size for this purpose, resulting in reduced power. The interaction between load, condition and region, however, supports the hypothesis that the regions contribute differently to working memory sub processes. Future studies with larger sample sizes and more age groups are needed to inform us about the possibility of differential developmental trajectories of these regions. In addition, future research should specifically test for the relations between VLPFC, DLPFC and parietal regions, for example using functional connectivity analyses (Fair, Dosenbach, Church, Cohen, Brahmabhatt, Miezin, Barch, Raichle, Petersen & Schlaggar, 2007; Narayanan *et al.*, 2005; Wendelken *et al.*, 2008) and diffusion tensor imaging (Olesen, Nagy, Westerberg & Klingberg, 2003). Finally, one important remaining question concerns the malleability of working memory functions (e.g. Bunge & Wright, 2007). For example, prior studies have shown that working memory functions can be trained (Klingberg, Fernell, Olesen, Johnson, Gustafsson, Dahlström, Gillberg, Forssberg & Westerberg, 2005; Klingberg, Forssberg & Westerberg, 2002b; Holmes, Gathercole & Dunning, 2009) and one of the questions for future studies is whether this can also result in increased recruitment of VLPFC and DLPFC (Jolles *et al.*, 2010; Olesen, Westerberg & Klingberg, 2004). Alternatively, children may increase in performance because they engage a different neural network (Luna, 2004; Qin, Carter, Silk, Stenger, Fissell, Goode & Anderson, 2004). Understanding these differences will be of great importance in the future, as they may eventually help tailor education programs (Diamond, Barnett, Thomas & Munro, 2007; Gathercole, Lamont & Alloway, 2006).

Acknowledgements

SARBR and EAC are supported by grants from the Netherlands Organization for Scientific Research (NWO, VIDI grant nos 91786368 and 45207011). This work was also supported by the LUF Gratama stichting (EAC). The authors thank Joram van Driel, Eveline Warmerdam, and Cesco Willemse for their help with the data collection.

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Received: 6 April 2010

Accepted: 4 August 2010