Increased Brain Activity in Frontal and Parietal Cortex Underlies the Development of Visuospatial Working Memory Capacity during Childhood

Torkel Klingberg, Hans Forssberg, and Helena Westerberg

Abstract

■ The aim of this study was to identify changes in brain activity associated with the increase in working memory (WM) capacity that occurs during childhood and early adulthood. Functional MRI (fMRI) was used to measure brain activity in subjects between 9 and 18 years of age while they performed a visuospatial WM task and a baseline task. During performance of the WM task, the older children showed higher activation of cortex in the superior frontal and intraparietal cortex than the younger children did. A second analysis found that WM capacity was significantly correlated with brain activity in the same regions. These frontal and parietal areas are known to be involved in the control of attention and spatial WM. The development of the functionality in these areas may play an important role in cognitive development during childhood. ■

INTRODUCTION

The amount of information one can keep in working memory (WM) increases throughout childhood and early adulthood (Gathercole, 1999; Luciana & Nelson, 1998; Hale, Bronik, & Fry, 1997). This increase in WM capacity is thought to be important for the development of a wide range of cognitive skills, including reading and logical reasoning (Engle, Kane, & Tuholski, 1999; Fry & Hale, 1996; Hulme & Roodenrys, 1995). The changes in WM capacity coincide in time with several neuronal developmental processes, including a decrease in synaptic density (Bourgeois & Rakic, 1993; Huttenlocher, 1979), axonal elimination (LaMantia & Rakic, 1990), changes in global cerebral metabolism (Chugani & Phelps, 1986; Kennedy & Sokoloff, 1957), myelination (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999; Paus et al., 1999; Yakovlev & Lecours, 1967; Flechsig, 1920), and changes in catecholamine receptor structure and density (Lambe, Krimer, & Goldman-Rakic, 2000). However, there have been no studies measuring any of these maturational processes and correlating them with WM capacity in the same individuals.

Functional neuroimaging studies show that children activate similar areas as adults do during the performance of WM tasks (Nelson et al., 2000; Thomas et al., 1999; Casey et al., 1995). Data from WM studies including both adults and children is very limited (Thomas et al., 1999), and none have made any direct voxel-by-voxel comparisons of regional changes in brain activity with age. Moreover, it has proven difficult to design the tasks so that the different age groups perform at the same level during scanning. When performance during scanning varies between two groups, differences in brain activity between the same groups are difficult to interpret.

In the present study, we used a visuospatial WM task (Figure 1) that is sensitive for measuring developmental changes in WM capacity (Hale et al., 1997; Fry & Hale, 1996). Children between 9 and 18 years of age performed the task while their brain activity was measured with functional MRI (fMRI). By keeping the WM load low in the scanner version of the task, we intentionally created a ceiling effect in order to minimize interindividual differences in behavior during scanning. Differences in WM capacity was estimated outside the scanner. The WM-related brain activity was then analyzed to find correlations between brain activity and age, as well as between brain activity and WM capacity.

RESULTS

Accuracy during scanning was generally high, except in one subject where $d' = 0.03$, which was >3 *SD* from the mean of the other subject. This subject was therefore excluded from the analysis. After exclusion of this subject, the mean d' was 2.71 ($SD = 0.29$), with no correlation between accuracy during scanning and age ($r = .31$, $p = .30$). The mean reaction time during the WM tasks was 718 ($SD = 118$) msec, with a nonsignificant trend towards shorter reaction times in older children ($r = -.50$; $p = .08$).

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Areas activated as a main effect of WM, across all ages and across both Load 3 and Load 5, are shown in Figure 2a- b and listed in Table 1. These areas covered parts of the prefrontal cortex in the superior and middle frontal gyri and inferior and superior frontal sulci, cingulate cortex, and large parts of the parietal and occipital cortices. The following analyses were restricted to those areas in which a main effect of WM was seen.

Subtraction images first were created by subtracting the brain activity during the baseline task from the mean activity during the WM tasks. One subtraction image was created for each subject. The subtraction images were then used in a second-level analysis where age was used as a covariate to find values in these subtraction images that correlated with age. A positive correlation with age was found bilaterally in the superior frontal sulcus, in the intraparietal and superior parietal cortex, and in the left occipital cortex (Table 1; Figure 2c- d and Figure 3). In statistical terms, this correlation is an interaction between the effect of age and the effect of WM. All of these areas were also significantly activated when accuracy during scanning (d' from each subject) was used as a confound, that is, when variance in brain activity that could be attributed to differences in performance during scanning was removed prior to correlation with age. A tendency towards a negative interaction was found in the right inferior frontal sulcus (Table 1). As described in the Introduction, such interaction could possibly be explained by the trend of negative correlation between reaction time and age. We therefore included reaction times as a confound, that is, removed variance due to differences in reaction times before analyzing the effect of age. However, including reaction times as a confound only marginally influenced this effect, decreasing the overall significance of the cluster from $p = .08$ to $p = .11$. In a different analysis, we investigated the interaction between WM load and age (difference between Load 5 and Load 3 was correlated with age). No such significant interaction was found.

WM capacity was measured outside the scanner and used as a covariate in the same way as the effect of age was analyzed. Correlation between WM capacity and WM activity was found in the left superior frontal sulcus and in the left intraparietal cortex (Figure 2e- f; Table 1), thus confirming that the correlation between age and WM related activity was due to the age trends in WM capacity.

To exclude that there was a lower signal-to-noise ratio in the images from younger subjects, a ''control-subtraction'' was done. Because there were more visual stimuli in the baseline task than in the Load 3 WM task (five circles vs. three circles), subtraction of Load 3 from baseline would presumably show an effect of this difference in visual stimulation. When brain activity during Load 3 was subtracted from baseline task, a large, significant activation of primary visual cortex and surrounding early visual areas showed up. However, no interaction was found between activity in this area and age ($p = .98$, using the same thresholds as in the analysis of interaction between WM and age). This lack of interaction between visually induced activity and age confirmed that the interactions between WM-induced activity and age were not due to a generally lower signal-to-noise ratio in younger children.

To investigate if there was an age-related trend in the amount of cortex activated, we performed a separate statistical analysis of the main effect of WM in each single subject. Significant clusters were identified ($z > 3.09$; cluster size > 45), and the total number of voxels in these clusters were counted for each subject and correlated with age. However, there were no age-related trends in the amount of cortex activated ($r = .09$, $p = .76$).

DISCUSSION

A positive correlation between age and WM-related brain activity was found in several areas, including the cortex

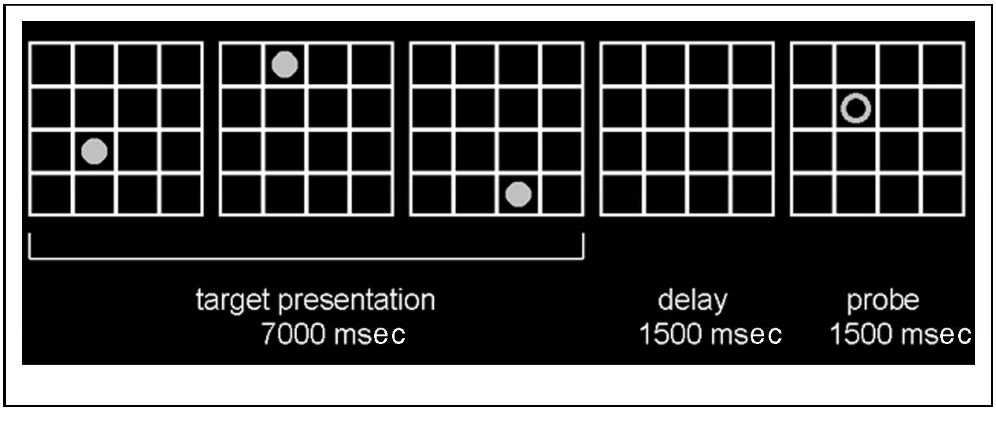

Figure 1. Working memory task performed during scanning. The subjects were asked to remember the location of red circles that were presented sequentially in a 4 × 4 grid. After a 1500-msec delay, a circle appeared and the subjects pressed a button if the circle was in the same location as any of the dots. Two versions of this task was given during scanning: one with three circles to remember and one with five. In the baseline condition, subjects watched as green circles were presented sequentially in either of the four corner boxes (top-left, top-right, bottom-left, or bottom-right). After a 1500-msec delay, a green circle appeared in the middle of the grid and the subjects pressed the button.

Table 1. Areas Activated during WM Tasks and Correlation between Age and Activity

Area	*Coordinates* *x*	*y*	*z*	*t* Value
Areas activated during performance of the WM tasks				
Superior frontal sulcus				
Right	22	−8	60	8.67
	20	10	64	6.29
Left	−26	0	56	10.93
	−38	6	60	5.11
Middle frontal sulcus				
Right	42	2	28	7.99
	44	26	40	7.62
Left	−50	4	32	9.97
	−52	30	32	6.42
Frontal operculum				
Right	38	20	−8	7.64
Left	−46	18	−8	7.13
Cingulate cortex	4	12	48	8.97
	0	26	36	8.50
	0	38	36	7.87
Caudate nucleus				
Right	6	4	8	4.01
Inferior and intraparietal cortex				
Right	22	−72	56	11.32
	42	−42	44	8.85
Left	−24	−68	60	14.50
	−44	−46	48	10.29
Correlation between WM-related activity and age				
Positive correlations				
Superior frontal sulcus				
Right	30	0	52	4.72
Left	−24	−4	52	4.48
	−28	6	60	2.83
Superior and intraparietal cortex				
Right	22	−64	48	4.75
Left	−26	−60	60	4.65
Middle occipital gyrus				
Left	−32	−72	16	3.55
Negative correlations				
Inferior frontal sulcus				
Right	42	4	40	2.90*

Table 1. (*continued*)

Area	*Coordinates* *x*	*y*	*z*	*t* Value
Correlation between WM-related activity and WM capacity				
Positive correlations				
Superior frontal sulcus				
Left	−26	4	60	3.59
Intraparietal cortex				
Left	−36	−76	44	5.83
Inferior parietal cortex	−50	−46	56	2.90**

For all clusters $p < .05$ corrected for multiple comparison, except $^{*}p = .08$; $^{**}p = .13$.

in the superior frontal sulcus and intraparietal sulcus, bilaterally. In a second analysis, a positive correlation between WM capacity and WM activity was found in the left superior frontal and left intraparietal areas. This second analysis suggests that the interaction between brain activity and age in these areas was due to the increases in WM capacity with age.

The positive correlation between WM capacity and brain activity is contrary to the results of some prior imaging studies that have associated improved performance as a result of training with lower activity in prefrontal areas (Klingberg & Roland, 1998; Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Raichle et al., 1994). The tasks where frontal activity decreased, however, can presumably become automatic with training, which is not the case with WM tasks. In general, lower prefrontal activity associated with superior performance (Haier et al., 1988) could be due to shorter reaction times, and thus less time on task (Poldrack, 2000; D'Esposito et al., 1997). Higher accuracy can also be associated with less prefrontal activity related to error detection and error correction. In the present study, however, interindividual differences in behavior during scanning were minimized. The increased activity with higher age therefore represents a developmental trend in the relationship between behavior and brain activity.

The anatomy and functionality of the frontal and parietal areas will first be commented on, before discussing the possible mechanism underlying the interaction between age and WM activity.

Functions of the Superior Frontal Sulcus

Correlation between age and WM activity was found in the cortex lining the superior frontal sulcus, extending anteriorly from the intersection of the superior frontal sulcus and precentral sulcus. Several previous studies of visuospatial WM have also reported activation at this location (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Postle & D'Esposito, 1999; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Sweeney et al., 1996; Smith et al., 1995; Jonides et al., 1993). In addition to spatial WM tasks, visual but nonspatial WM tasks activate this region (Postle & D'Esposito, 1999; Klingberg, 1998; Cohen et al., 1997). Several studies have further characterized the temporal dynamics of activity in this area and found that it exhibits sustained activity during the delay period when information is held in WM (Rowe et al., 2000; Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997). The activity thus resembles the delay-specific activity, which is generally considered to be the hallmark of WM activity in electrophysiological studies of WM in macaques (Funahashi, Bruce, & Goldman-Rakic, 1989; Fuster & Alexander, 1971).

The region where we observed a significant correlation was located close, although slightly superior and anterior, to previously reported activations associated with voluntary eye movements. Eye-movement-related activity is generally found along the anterior wall of the precentral sulcus (Corbetta et al., 1998; Luna et al., 1998; Paus, 1996; Fox, Fox, Raichle, & Burde, 1985). Furthermore, in the present study, the number of stimuli per trial, and thus presumably the number of saccades, was, on average, higher during the baseline condition (five dots) than in the WM conditions (three and five dots, respectively); therefore, the activation in the WM tasks in this study was presumably not due to saccadic eye movements. Courtney et al. (1998) suggested that activity underlying visuospatial WM is topographically separate from that produced by voluntary saccades. In their study, eye-movement-related and WM-related activities overlapped in the intersection of the superior frontal sulcus and the precentral sulcus. However, the eye movement- related activity extended inferiorly along the precentral sulcus, while the WM-related activity extended anteriorly along the superior frontal sulcus, consistent with the location of the WM-related activity in the present study and with eye-movement-related activity in other studies (Corbetta et al., 1998; Paus, 1996; Fox

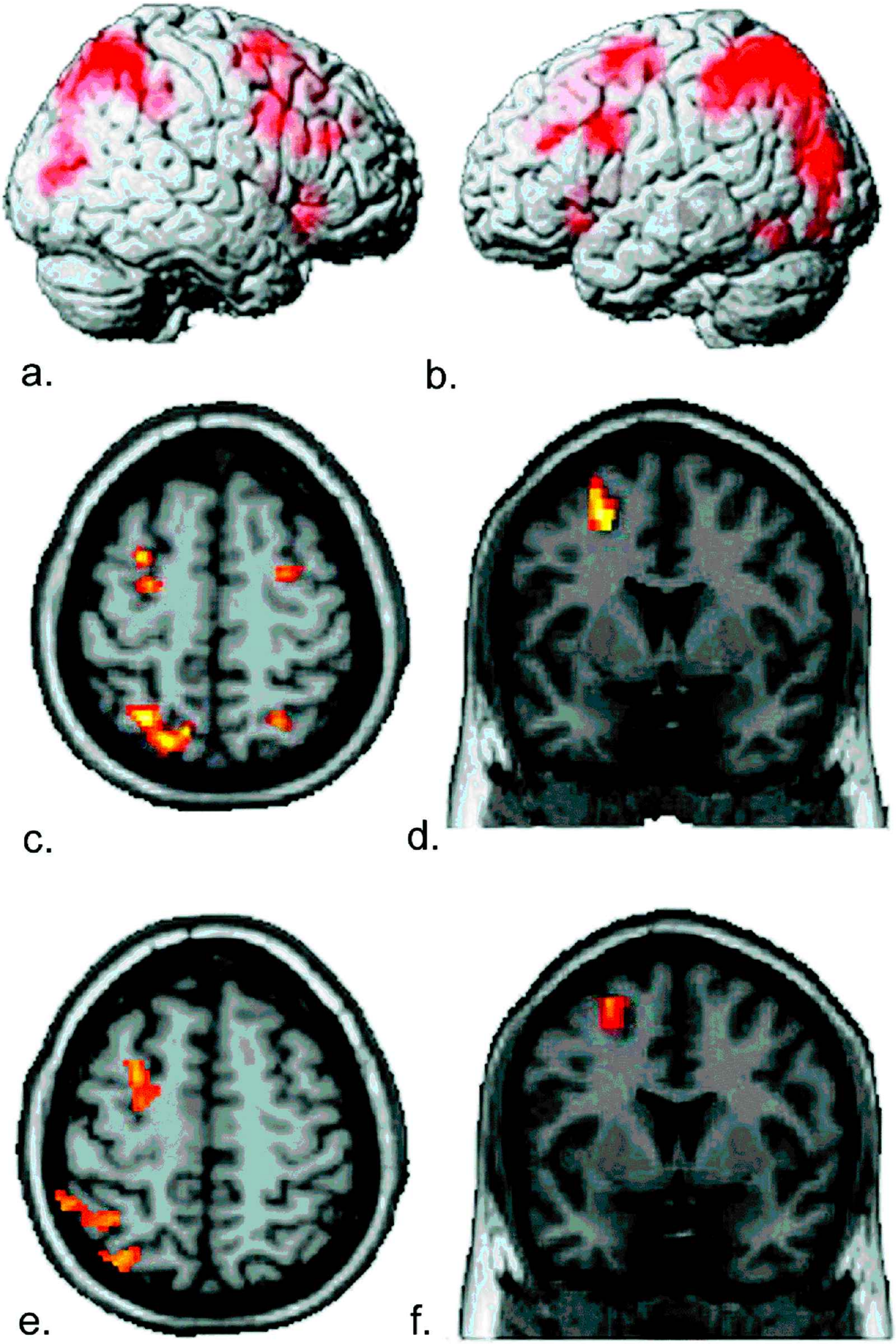

Figure 2. BOLD responses during the WM tasks. (a, b) Main effect of WM in the right (a) and left (b) hemisphere. (c, d) Areas showing a correlation between WM activity and age: (c) horizontal section showing activity bilaterally in the superior frontal sulcus and intraparietal sulcus; (d) coronal section showing activity in the left superior frontal sulcus. (e, f) Areas showing a correlation between WM capacity and WM-related activity: (e) horizontal section showing the left superior frontal sulcus and left inferior- and intraparietal cortex; (f) coronal section showing activity in the left superior frontal sulcus.

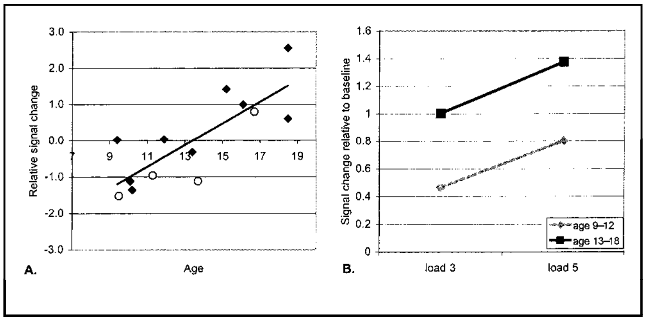

Figure 3. BOLD responses in the superior frontal cortex. (A) Relative signal change plotted against age. ✦ = boys; ○ = girls. (B) Activation in the two versions of the WM tasks; Load 3 and Load 5, for younger and older children.

et al., 1985). Nonetheless, a later study could not reproduce the topographical separation of activity related to eye movements from that related to WM (Postle, Berger, Taich, & D'Esposito, 2000). If the same area is activated by both WM and eye movement, it would be analogous to the results suggesting that top-down attention and eye movements activate the same anatomical area (Corbetta et al., 1998).

Several tasks involving "top-down" or "voluntary control" of attention have found activation at an almost identical superior frontal site as in visuospatial WM tasks (Hopfinger, Buonocore, & Mangun, 2000; Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Corbetta et al., 1998). In these tasks, the subject is cued about the location of a future target or searches for a particular known target. The subject thus needs to keep a representation of the target or its location in WM in a similar way as information is kept on-line in WM tasks. Top-down attention and WM could thus be overlapping concepts, with overlaps in the underlying brain activity, as have also been suggested previously (Kastner & Ungerleider, 2000; Desimone & Duncan, 1995).

Functions of the Intraparietal Cortex

The inferior and intraparietal cortex shares many functional characteristics with the superior frontal cortex: It is active during visuospatial WM tasks (Rowe et al., 2000; Postle & D'Esposito, 1999; Courtney et al., 1998; Sweeney et al., 1996; Smith et al., 1995; Jonides et al., 1993) and shows sustained activity during the delays in the WM tasks (Rowe et al., 2000; Cohen et al., 1997). The intraparietal cortex is also active in tasks demanding voluntary control of visual attention (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Hopfinger et al., 2000; Kastner et al., 1999) and has sustained activity during the cue period in such tasks (Corbetta et al., 2000; Hopfinger et al., 2000; Kastner et al., 1999).

Although the functional parcellation of the intra- and inferior parietal cortex is unclear at this point, this intra/inferior parietal region can be separated from an area in the temporo-parietal junction (about 15 mm above the AC- PC line), which is not involved in top-down control but is involved in orienting (Corbetta et al., 2000; Downar, Crawley, Mikulis, & Davis, 2000) and arousal (Coull, Nobre, & Frith, 2001). Intraparietal and inferior parietal cortex is active in a wide range of tasks demanding WM and control of attention. Several studies comparing different types of stimuli within the same session have found evidence of activity in the inferior and intraparietal cortex that is independent of the modality of the stimuli (Bushara et al., 1999; Coull & Frith, 1998; Klingberg, 1998; Klingberg, Roland, & Kawashima, 1996). A possible supramodal function would be especially interesting in light of the present results, since development of functionality in a supramodal area could explain the increase in WM capacity and the improvement in control of attention, which both occur across different sensory modalities.

Fronto-parietal networks have been suggested to underlie WM in macaques (Friedman & Goldman-Rakic, 1994; Quintana & Fuster, 1993). In humans, the inferior and intraparietal cortex is often co-activated, as well as correlated, with areas in the superior and middle frontal gyri during tasks demanding WM and top-down attention (Klingberg, O'Sullivan, & Roland, 1997). Recordings of electrical activity also show that frontal and posterior association cortices increase coherence during the delay period in WM tasks (Sarnthein, Petsche, Rappelsberger, Shaw, & von Stein, 1998). Taken together, this suggests that performance of visuospatial WM tasks will not only depend on local computations within these areas, but will also depend on the communication between them.

Possible Mechanisms Underlying the Age-Related Changes

There are several maturational processes that coincide in time with the increase in WM capacity. Myelination is of particular interest because the inferior parietal cortex, where we found an interaction between activity and age, is among the last brain regions to myelinate (Yakovlev & Lecours, 1967; Flechsig, 1920). This late myelination includes intracortical neuropil, as well as radial fibers and tangential fibers entering the supragranular layer. Myelination of the parietal fibers would presumably increase transmission speed locally within the parietal cortex, as well as effect the communication between the parietal and frontal cortices. Myelination could thus enhance cortico-cortical excitation and metabolism in a fronto-parietal network. The functional relevance of this would be a fronto-parietal activity that is more stable during WM delays and cue periods and thus is more resistant to interference. The superior frontal sulcus is not among the last regions to myelinate, but the correlation of activity and age could possibly be secondary to the development of the intraparietal cortex, which, in this particular task, forms a network with cortex in the superior frontal sulcus.

Synaptic and axonal pruning is another possible contributor to the interaction between brain activity and age. There is an overproduction of connections and synapses early in life, with a pruning of the connections that are not used (Bourgeois & Rakic, 1993; LaMantia & Rakic, 1990; Huttenlocher, 1979). Less competition with input from other areas could leave the fronto-parietal communications more stable. Therefore, although the total number of synapses decreases, the connections related to WM would be more active during performance of WM tasks. Yet, another possibility is that the activities in the frontal and parietal areas were effected by developmental changes outside the superior frontal and parietal areas. One example would be increased input to the fronto-parietal network from a more anterior prefrontal area that was inconsistently located between individuals and therefore did not show up in the group analysis.

Conclusions

This study found a positive correlation between age-related increases in WM capacity and brain activity in the superior frontal and intraparietal cortex. Future studies, using verbal tasks or more complex problem-solving tasks, might show other or additional areas where activity changes with age. The present study suggests that the relationship between WM capacity and brain activity is positive, that is, with higher activity in older children, presumably because this is associated with a more stable and interference-resistant delay activity.

The areas where we observed a developmental trend are known to be involved in a wide range of functions that demand visuospatial WM and control of attention. The parietal area is, furthermore, one of the last in the brain to myelinate and is involved in a wide range of tasks requiring attention and WM. The development of functionality in these areas may therefore be an important contributor to the development of cognitive abilities during childhood.

METHODS

Subjects

Fourteen healthy volunteers participated in the study. After exclusion of one subject (see Results), the 13 remaining participants (4 girls, 9 boys) were aged 9.4-18.5 years (mean 13.4). The study was approved by the local ethics committee.

Tasks

WM Tasks During Scanning

This task is illustrated and described in Figure 1. Two versions of the WM tasks were used: one with three targets and one with five targets. In order to have the same overall time for the target presentation period, there were longer delays between the stimuli during the presentation period in the three-target version than in the five-target version and the baseline task.

Baseline Task

Five green, filled circles were presented sequentially. After a 1500-msec delay, a green unfilled circle appeared in the middle of the grid. The subjects were instructed to look at each of the green filled circles as they appeared and always press the button when the unfilled green circle appeared. The control condition was thus designed to control for visual stimulation, eye movements, and motor output.

WM Task Outside the Scanner

The task was similar to the scanning task in that circles were presented sequentially in a 4 × 4 grid. However, after the delay, the subject indicated, by using a computer mouse, each of the locations where targets had appeared. The number of targets varied from three to nine, with two trials on each level. The total number of correctly indicated locations in all trials on all levels was taken as our measurement of the individuals WM capacity. The WM capacity was later used as a covariate in the analysis of fMRI data.

Procedure

The WM capacity of each subject was tested before scanning. Subjects received additional training on the scanner version of the WM task before entering the scanner. All stimuli were presented on a computer using E-prime software (Psychology Software Tools). During scanning, the subjects watched the stimuli on a screen via a mirror mounted on the head coil. The subjects responded by pressing a button with their right index finger. Responses were collected using a button-response unit connected to the computer controlling the stimuli. Head movements were restricted by wedge-formed pillows on both sides of the head and an additional adhesive tape over their forehead. During scanning, 30-sec epochs of baseline task and WM tasks were alternated, with the order counterbalanced between the two runs. Each run lasted 5 min.

MR Scanning

Images were acquired using a 1.5-T GE Signa scanner. T2*-weighted, gradient echo, spiral echo-planar images were acquired with TR = 2500 msec, TE = 70, flip angle = 85°, 18 axial slices, 5.0 mm slice thickness, 220 × 220 mm FOV, 64 × 64 grid, resulting in voxels that were 3.4 × 3.4 × 5.0 mm. For each subject, 240 volumes were acquired during two 5-min sessions. T1-weighted spinecho images, FOV=220 × 220 mm, 256 × 256 grid, were acquired in the same position as the functional images and used for anatomical normalization of the functional images. Total time in the scanner was less than 35 min for most subjects.

Data Analysis

The data were analyzed with SPM99 (Welcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). Motion during scanning was estimated by six parameters (three translations, three rotations), which were used to realign the functional images to the first image in the series, and later used as confounds in the statistical analysis. The T1-weighted images were normalized to Talairach space using a template from the Montreal Neurological Institute. The parameters from this normalization were then used to normalize the functional images, which were subsampled to a voxel size of 2 × 2 × 4 mm and then smoothed with an isotropic Gaussian kernel of 6.0 mm.

There were two different version of the WM task, one with three and one with five stimuli. However, in the present analysis, these two conditions were analyzed together relative to the baseline task. To identify areas involved in the WM tasks, a fixed-effects model was used, including all images from all subjects. The main effect of WM was estimated by a general linear model. Low frequency ($<1/120$ Hz) drifts in the signal were removed by including cosine basis functions as confounds in the model. The six parameters describing head movement during scanning were also included as confounds, as was the effect of scanning session.

To identify age-related changes in activity, a so called ''random-effects'' model was used. For each subject, the main effect of WM was estimated with a general linear model removing low-frequency drifts, motion-correlated signals, and session effects as described above. An image was then formed for each subject, describing the estimated mean activity during WM tasks, as compared to the baseline task. A correlation was then made between age (or WM capacity) and voxel values in these images describing estimated mean activity during the WM tasks.

Estimating the Effect of Removing Motion-Related Signals

Removal of signal correlated with head motion, as described above, could potentially in itself introduce age-related differences in signal detection (Josephs & Henson, 1999). To evaluate the effect of removing motion-correlated signals, we first formed a vector Y, with ones and zeros describing the on- off pattern of WM and control condition. Motion-correlated variance was then removed from Y using multiple regression analysis. The residuals from Y were then bandpassed using the same bandpass filter that was applied to the functional data. The bandpassed data was then Fourier-transformed, and the energy was calculated as the sum of the power spectrum. This energy is a measurement of the signal-to-noise of the image (Josephs & Henson, 1999) and was calculated for each individual and then correlated with age. There was no significant correlation between age and energy ($r = -.18$; $p = .55$), demonstrating that the removal of signals correlated with head motion did not introduce any age-related bias.

Estimating Age-Related Differences in Brain Size

From the 4 × 4 matrix containing the normalization parameters, the linear scaling factor in the x, y, and z directions, were identified from each subject and then correlated with age. No significant correlation between age and brain size was found: (X: $r = -.05$; $p = .87$; Y: $r = .34$; $p = .26$; Z: $r = .09$; $p = .76$). This is consistent with previous investigations showing that the total brain size does not increase during the time between ages 9 and 18 (Reiss, Abrams, Singer, Ross, & Denckla, 1996).

Reprint requests should be sent to Torkel Klingberg, Karolinska Institute, Department of Neuropediatrics, Astrid Lindgrens Children's Hospital Q2:07, 171 76 Stockholm, Sweden, or via e-mail: torkel.klingberg@neuro.ki.se.

The data reported in this experiment have been deposited in the fMRI Data Center (http://www.fmridc.org). The accession number is 2-2001-1123Y.

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