Stronger Synaptic Connectivity as a Mechanism behind Development of Working Memory–related Brain Activity during Childhood

Fredrik Edin[1,2], Julian Macoveanu[1], Pernille Olesen[1], Jesper Tegnér[1,3,4], and Torkel Klingberg[1]

Abstract

■ The cellular maturational processes behind cognitive development during childhood, including the development of working memory capacity, are still unknown. By using the most standard computational model of visuospatial working memory, we investigated the consequences of cellular maturational processes, including myelination, synaptic strengthening, and synaptic pruning, on working memory-related brain activity and performance. We implemented five structural developmental changes occurring as a result of the cellular maturational processes in the biophysically based computational network model. The developmental changes in memory activity predicted from the simulations of the model were then compared to brain activity measured with functional magnetic resonance imaging in children and adults. We found that networks with stronger fronto-parietal synaptic connectivity between cells coding for similar stimuli, but not those with faster conduction, stronger connectivity within a region, or increased coding specificity, predict measured developmental increases in both working memory-related brain activity and in correlations of activity between regions. Stronger fronto-parietal synaptic connectivity between cells coding for similar stimuli was thus the only developmental process that accounted for the observed changes in brain activity associated with development of working memory during childhood. ■

INTRODUCTION

Working memory (WM), the ability to temporarily maintain visuospatial information in mind, is a key cognitive function that underlies other cognitive abilities such as complex reasoning, and undergoes significant maturation during childhood and adolescence (Gathercole, Pickering, Ambridge, & Wearing, 2004; Westerberg, Hirvikoski, Forssberg, & Klingberg, 2004; Fry & Hale, 2000; Baddeley & Hitch, 1974). Several maturational processes take place during that time, most importantly, the myelination of axons, the strengthening of synapses, and synaptic pruning (Bourgeois, Goldman-Rakic, & Rakic, 2000; Lamantia & Rakic, 1990; Rakic, Bourgeois, Eckenhoff, Zecevic, & Goldman-Rakic, 1986; Huttenlocher, 1979; Yakovlev & Lecours, 1967; Hubel & Wiesel, 1963). Anatomical and functional magnetic resonance imaging (fMRI) has been used to map structural and physiological changes associated with cognitive development during childhood (Olesen, Nagy, Westerberg, & Klingberg, 2003; Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002; Klingberg, Forssberg, & Westerberg, 2002; Casey, Giedd, & Thomas, 2000; Giedd et al., 1999; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). Despite the fact that interpretations of the developmental changes in brain activity have been made by referring to structural maturational processes (Bunge et al., 2002; Casey et al., 2000), it has actually not yet been demonstrated whether the maturational changes occurring at the cellular level really result in the gross changes in brain activity associated with cognitive development, nor has it been demonstrated how this process may occur. For example, how would myelination, which increases signal conduction velocity, affect macroscopic brain activity as measured with fMRI? Does synaptic pruning cause increases or decreases in brain activity? Here, by integrating computational modeling, with which we can predict the effects of structural changes on brain activity, and fMRI, with which we can learn which of the predicted changes in brain activity actually occur, we make the connection between structural changes and physiological development during the maturation of visuospatial WM (vsWM) in the adolescent.

The computational model that we use to make predictions about the development of macroscopic brain activity underlying vsWM relies on knowledge about the neuronal basis of vsWM. Specifically, electrophysiological experiments on behaving monkeys reveal sustained

[1]Karolinska Institutet, Stockholm, Sweden, [2]Royal Institute of Technology, Stockholm, Sweden, [3]Stockholm Bioinformatics Center, Stockholm, Sweden, [4]Linköping University of Technology, Sweden

neuronal activity during the delay period of vsWM trials (Funahashi, Bruce, & Goldman-Rakic, 1989). The activity is cue-specific so that different neurons code for objects at different angles in the visual field. In parallel with the characterization of vsWM-related activity on the neuronal level, progress in basic cortical physiology has produced a detailed description of cellular and synaptic characteristics of pyramidal cells and inhibitory interneurons (Douglas & Martin, 2004). These findings were recently incorporated in a biophysically based computational network model of vsWM activity (Wang, Tegnér, Constantinidis, & Goldman-Rakic, 2004; Tegnér, Compte, & Wang, 2002; Wang, 2001; Compte, Brunel, Goldman-Rakic, & Wang, 2000; Amit & Brunel, 1997), from which the model in this study was developed. The model has been able to explain several characteristics of the activity in the frontal cortex (Funahashi et al., 1989) during the performance of a WM task, as reviewed by Compte (2006). It reproduces a low but stable activity during the fixation period, as well as a higher and stable memory activity with physiological firing rates during the delay period. It also explains the decrease in delay-period activity in cells not coding for the presented visual stimulus. Furthermore, it has predicted differential connection strength between neurons depending on the degree of similarity of the stimuli that they encode. This has later been confirmed in experiments (Constantinidis, Franowicz, & Goldman-Rakic, 2001), indicating some predictive power of the model.

Unfortunately, the original version of the model only describes vsWM activity in one region of the frontal cortex, whereas vsWM studies in humans (Curtis, Rao, & D'Esposito, 2004; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998) and monkeys (Chafee & Goldman-Rakic, 1998, 2000) have found sustained delay activity associated with vsWM in several regions, most consistently in the superior frontal sulcus (SFS, presumably monkey area 8a) and the intraparietal sulcus (IPS, presumably monkey area 7ip). Therefore, in order to evaluate hypotheses about which neuronal developmental process accounts for the developmental improvement in vsWM, we extended the single-region vsWM computational network model to a two-region model. This allowed us to investigate hypotheses concerning strengthening of synapses, both within a region and between regions, as well as synaptic pruning and the velocity of signal conduction between regions. To compare the results of the model to experimental results, we translated the neuronal activity of the model into blood oxygenation level-dependent (BOLD) signals (Deco, Rolls, & Horwitz, 2004), the signals measured with fMRI.

The organization of the investigations aiming to connect the structural and functional development of vsWM was as follows: From the general observation that synaptic pruning, synaptic strengthening, and myelination take place during development, five specific hypotheses were put forth, each describing in detail a single aspect of structural development. Thus, the effect of each structural change could be studied in isolation. The developmental change of each hypothesis could be modeled by a simple change of a single parameter in the network model. For each hypothesis, we produced a ''child'' version and an ''adult'' version of the network, differing only in the parameter change relating to that specific hypothesis. The ''adult'' version of the network was common to all hypotheses. Simulations were performed with each of the networks, and the difference between characteristics of the simulated BOLD activity in the ''child'' and ''adult'' networks of each hypothesis was the prediction from that hypothesis. In order to test the prediction of the model, we let a group of children and a group of adults perform a vsWM task while the delay-phase BOLD activity was measured. In this way, we could conclude which of the hypotheses could accurately predict experimentally measured developmental changes in brain activity relating to vsWM and which could not.

METHODS

To make the logical structure of the study easier to grasp, the more technical parts concerning modeling and fMRI data acquisition have been moved to the Supplemental Methods section.

Computational Model: General Overview

The structure of the vsWM network model that we created is shown in Figure 1A and B. The network contains two interconnected regions, each consisting of a population of 128 pyramidal cells (P) and a population of 32 inhibitory interneurons (I). Every cell codes for an angle in the visual field. The two regions are replicas of the frontal region network in Tegnér et al. (2002), and like that model, this model also consists of Hodgkin–Huxley type cells with ion channels and input–output relations matching those of real layer II/III neurons. The regions are connected only through their pyramidal cells. Interregional connections have a conduction delay (Ferraina, Pare, & Wurtz, 2002), whereas all other connections are instantaneous. There exists a topography in the connection strength between pyramidal cells within or between two regions, as indicated by the *connection curve* (Figure 1B), a key term in this text as several of the developmental hypotheses are expressed as changes in this curve. The curve shows that cells with similar preferred angles are strongly connected, whereas cells with dissimilar preferred angles are weakly connected (Constantinidis et al., 2001).

Simulations (Figure 1C) showed that the model accounts for several characteristics of the delay-phase neural activity in the vsWM tasks (Chafee & Goldman-Rakic, 1998; Funahashi et al., 1989). As in previous, single-region

versions of the model, model neurons showed the experimentally observed stable resting activity during the intertrial interval as well as stable, spatially localized and physiologically realistic mnemonic firing rates during the delay phase. The model also reproduced the decrease in activity in cells not coding for the memory during the delay phase. The activity in the two simulated regions was very similar, which is in agreement with single-unit recordings from the frontal and parietal cortices in the macaque (Chafee & Goldman-Rakic, 1998).

To be able to compare simulations from the model with experimental results, we translated the electrical activity of the network into a corresponding BOLD signal (Deco et al., 2004; Figure 1D). Total synaptic current (Attwell & Iadecola, 2002), as given by the sum of the absolute values of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), NMDA (N-methyl-D-aspartic acid), and GABA (γ-aminobutyric acid) components, with a standard hemodynamic response function (Friston et al., 1998). We confirmed that the use of spiking activity (Mukamel et al., 2005) or only excitatory synaptic activity as a basis for the BOLD signal did not affect our results. The neural basis of the BOLD signal has been discussed by Attwell and Iadecola (2002).

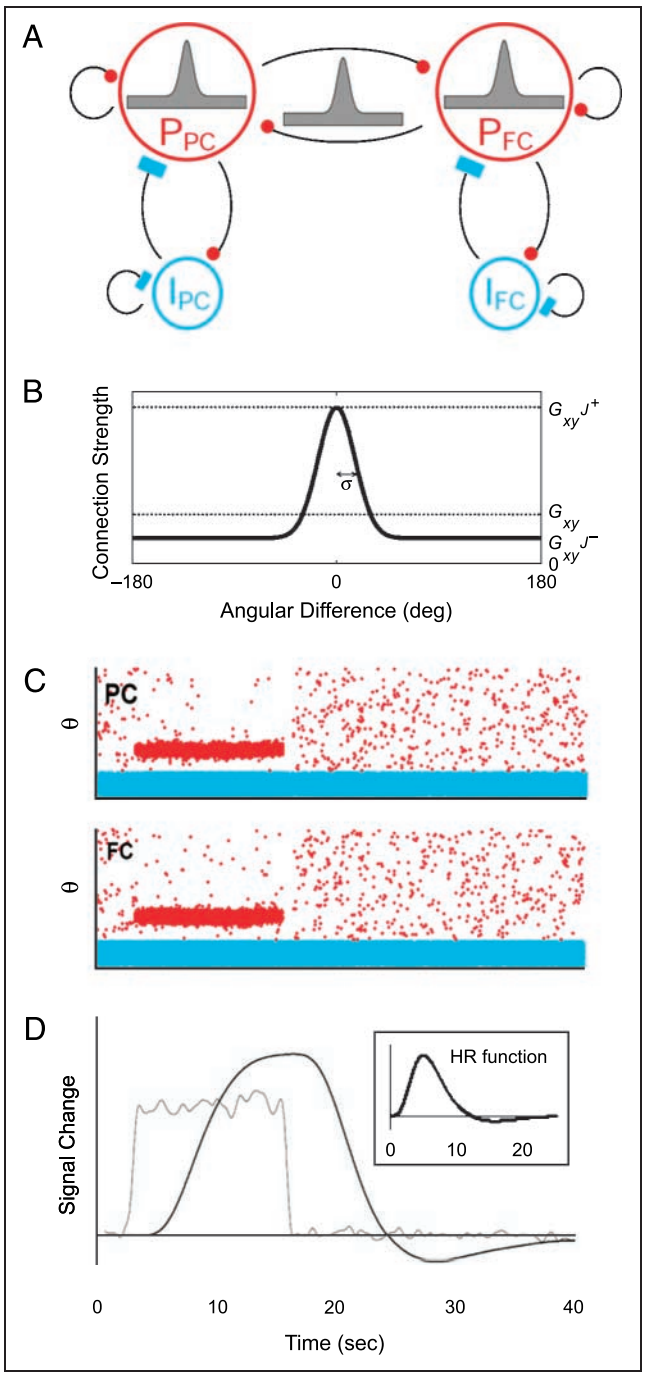

Figure 1. The two-region network. (A) The vsWM network with a frontal cortical (FC) and a parietal cortical (PC) region. Each region consists of a pyramidal cell population (P) and an inhibitory interneuron (I) population, both connected internally and with the other population. Interregional connections are purely excitatory. The gray curves are connection curves (see B). (B) The connection curve indicates how the connection strength between two pyramidal cells within or between two regions depends on the difference in their preferred angle. In the model, the connection curve has the shape of a Gaussian curve on top of a box. G_{xy} is the mean connection strength from area y onto area x. $G_{xy}J^+$ is the height of the connection curve, and σ is the standard deviation of the Gaussian curve. To regulate the shape of the connection curve while preserving total connection strength (area under curve), changes in σ or J^+ are compensated by changes in J^-. (C) Network simulation of the WM trial. Dots represent action potentials. Pyramidal cells are aligned according to stimulus specificity. Cue stimuli enter both regions as a current into pyramidal cells coding for the stimulus. Memory for the position ($0° \leq \theta < 360°$) of a visual cue is retained during the delay phase through localized persistent activity. At selection, a current causes memory activity to return to the baseline. (D) By convolving the network synaptic currents (thin) with a standard hemodynamic response (HR) function (Friston et al., 1998, inset), a simulated BOLD signal was obtained (Deco et al., 2004, thick). Red = pyramidal cells; blue = inhibitory interneurons.

Developmental Hypotheses

Having established the computational model with which we can predict the effect of our developmental hypotheses on the BOLD signal, we are now in a position to describe these. Based on the three known neuronal developmental changes, we put forth a total of five hypotheses (Figure 2A). The first two hypotheses are exclusively related to strengthening of synapses whereas the following two are related to both synaptic strengthening and pruning. All four are expressed as changes in the neuronal connection curve. Finally, the fifth hypothesis is related to myelination. The five hypotheses will now be described in order.

The first hypothesis (H1) modeled a developmental strengthening of connections *within* a region by increasing the mean frontal and parietal intraregional connection strengths G_{ff} and G_{pp} (terms in this subsection are explained in Figure 1B and the Supplementary Methods section). The second hypothesis (H2) tested a strength-

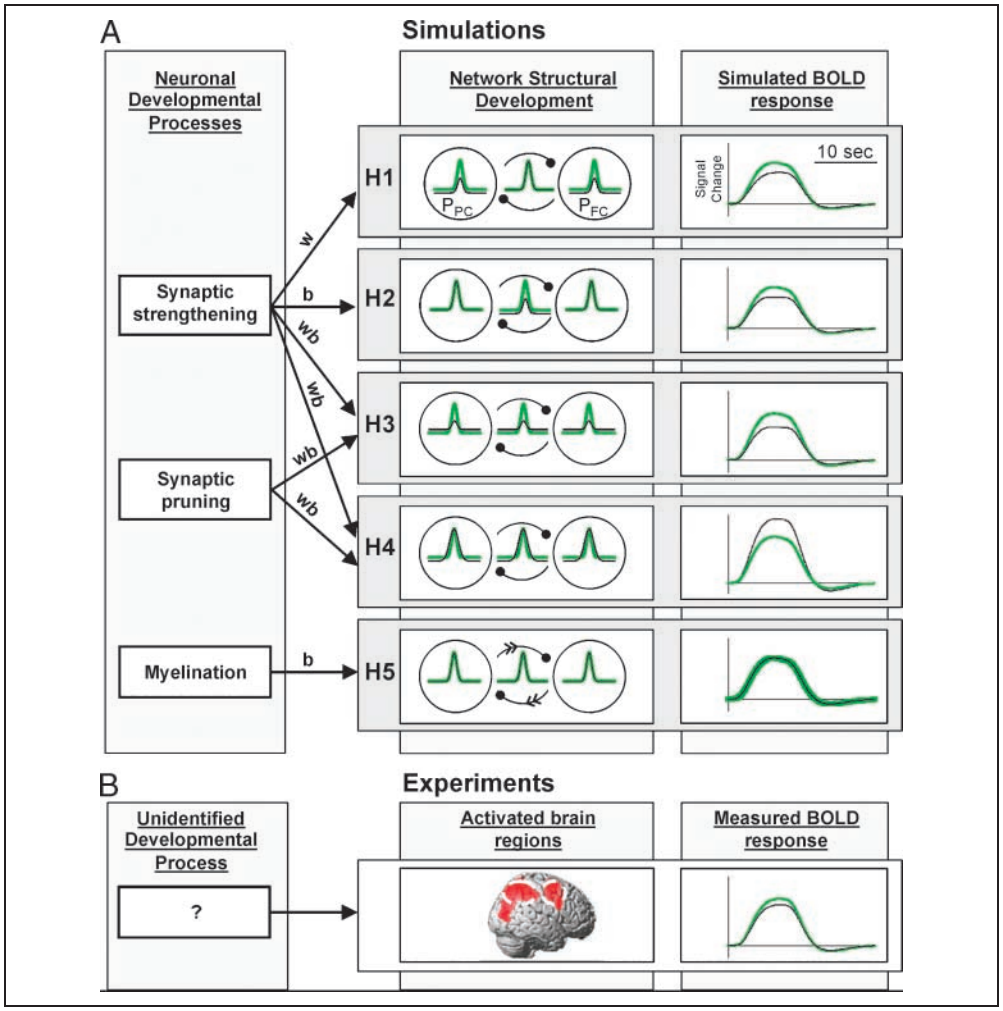

Figure 2. The logical structure of the study. (A) Simulations. Based on three known neuronal developmental processes (column 1), we put forth five hypotheses (H1–H5) regarding the structural development of the vsWM network (column 2). For each hypothesis, ''child'' (black) and ''adult'' (green) versions of the network were created. The strengths of connections within a region are indicated by the connection curves inside the circles (which represent the parietal and frontal pyramidal cell populations), whereas the curves between the circles show connection curves between regions. Finally, predictions from the hypotheses regarding the development of the vsWM maintenance-related BOLD signal were obtained through simulation (column 3). H1: greater connection strength within regions. H2: greater connection strength between regions. H3: higher contrast. H4: higher specificity. H5: faster signal conduction velocity (indicated by the arrows). In the hypotheses, structural development occurs at connections within (w) and/or between (b) regions. (B) Experiments. To find which of the developmental processes that can predict the development of vsWM maintenance-related BOLD signals, fMRI data were collected from children and adults during the performance of a vsWM task. Column 2 shows pooled adult and child delay-phase activity. Consistent with the model, frontal and parietal regions (encircled) were significantly activated. Column 3 shows the delay-phase BOLD signal in each group separately, averaged across bilateral SFS and IPS regions (arbitrary units).

ening of connections *between* two regions by increasing the mean interregional connection strengths G_{fp} and G_{pf}.

Hypotheses 3 and 4 (H3, H4) modeled development as synaptic remodeling leading to a redistribution of synapses without changing total connection strength. This could occur through the simultaneous pruning of silent synapses and strengthening of active synapses, so H3 and H4 are related to both synaptic strengthening and pruning. Two changes are possible: increasing J^+ leads to a higher contrast in the neuronal response, and decreasing σ leads to a sharper connection curve with higher neuronal coding specificity. An increased contrast means that the difference in activity between neurons coding for the stimulus and neurons with unrelated activity will be greater. An increased specificity means that, in order to activate the neuron, stimuli must be more similar to the preferred stimulus of that neuron than was previously the case; hence, the activity of the neuron provides more specific information about the identity of the stimulus. An early example of these phenomena is Hubel and Wiesel's study showing how cells in the visual cortex first receive widespread inputs, but that elimination results in neuronal responses having higher contrast and greater specificity (Hubel & Wiesel, 1963). Later, Rainer and Miller (2000) found increased specificity in the monkey prefrontal cortex as a result of visual training. Thus, the third hypothesis (H3) represented a higher contrast by increasing J^+, and the fourth hypothesis (H4) represented increased neuronal specificity by decreasing σ.

The third developmental process, myelination, continues throughout adolescence (Yakovlev & Lecours, 1967) and is usually thought to improve cognitive processing by increasing action potential conduction velocity. Therefore, to model the effect of myelination, we designed a model (H5) with increased action conduction velocity between the two cortical regions. To test

the hypotheses, we designed one ''adult'' and five ''child'' networks (Figure 2A, column 2). The ''child'' networks each instantiated one of the hypothesized developmental changes, but they were otherwise identical to the ''adult'' network.

Subjects and vsWM Task

To test the predictions made by the developmental hypotheses expressed in the computational model, we measured brain activity with fMRI in a group of 13 children (10 boys, 13.1 ± 0.5 years) and 11 adults (4 men, 23 ± 3 years) while they performed a vsWM task. Behavioral data were successfully collected from 10 of the children and 9 of the adults. Significant effects of task and group, and the interaction between these factors, were calculated using a repeated-measures analysis of variance (ANOVA). To get more reliable results for the interaction effects, additional data were included in the ANOVA. These data were collected outside the scanner from 18 adults (8 men, 23.7 ± 1.9 years) and 9 children (6 boys, 12 ± 0.9 years). Thus, the main performance analysis was based on data from 27 adults (11 men, 23.3 ± 2.4 years) and 19 children (13 boys, 12.7 ± 0.9 years).The children were recruited from a school in Solna, Sweden. The adults were recruited through an advertisement on the hospital Web site and through friends. All subjects were healthy and right handed. Written consent was obtained from all subjects and from the parents of the children. The study was approved by the ethical committee at Karolinska Institutet.

The vsWM task (Figure 3) was adapted with the E-prime software (Psychology Software Tools, Pittsburgh, USA) from a previous study where it was used to successfully isolate vsWM maintenance-specific activity in the SFS and IPS (Rowe et al., 2000). An easy task was chosen so that both children and adults would perform at a high level. All trials started with a fixation cross and a 3-sec intertrial interval. For vsWM trials, three blue dots appeared for 0.5 sec, followed by a delay phase of 12 sec, during which items were maintained in vsWM. After the delay, a line crossed the location of one of the previously presented dots for 0.5 sec, and subjects had to click on the intersection between the line and the dot with a nonmagnetic fiber-optic trackball (Current Designs, Philadelphia, USA). Performance was measured as the distance between the dot and the response location. Distracter trials were identical to vsWM trials, except for the additional presentation of three yellow dots for 0.15 sec during the delay. The distracters appeared after 3, 6, or 9 sec of the 12-sec delay period. In control trials, designed to control for brain activity related to motor and visual functions, a line crossed the screen for 0.5 sec, followed by a delay of 12 sec. After the delay, a blue dot appeared and the task was to click on this circle. For both vsWM and control trials, the maximum response time was 6 sec.

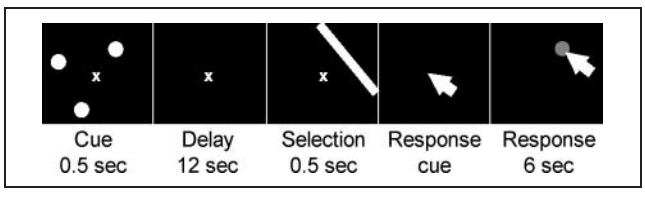

Figure 3. The vsWM task used in scanning and behavioral experiments. Subjects fixated on the X. After an initial intertrial interval, a cue consisting of three blue dots was presented, which subjects were instructed to maintain in memory during the 12-sec-long delay period. At selection, a line appeared which crossed the position of one of the previously presented cue dots. At response, subjects had to click at that position.

Brain Imaging: Analysis of Mean BOLD Signal

The generalized linear model of fMRI time-series was applied using SPM2 (www.fil.ion.ucl.ac.uk/spm/software/spm2/) to statistically analyze the developmental changes in mean BOLD signal (Friston et al., 1995). Hemodynamic response functions in children and adults have previously been shown to be comparable (Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). On the other hand, Thomason, Burrows, Gabrieli, and Glover (2005) reported that children had higher variability in the BOLD signal. To test the possibility of unequal variances, we performed a two-tailed F test with significance level $\alpha = .05$ after correction for multiple comparisons (critical values $F_{low} = 0.930$ and $F_{hi} = 1.076$) on the dataset used for the correlation analysis (see the next section for details about this dataset): $F_{pfc} = 0.942$, $F_{ppc} = 1.026$. Effective degrees of freedom $df_{old} = 3762$, $df_{young} = 3764$. The F ratios were within the critical values, and thus, were not significant.

In addition to the region-of-interest analysis of BOLD activity in the superior frontal and intraparietal regions included in the model, we also used an exploratory analysis to investigate differences in delay-related brain activity in every voxel of the frontal and parietal cortices. Clusters and voxels were considered as significant if $p < .05$, corrected for multiple comparisons. Corrections for multiple comparisons were based on the theory of Gaussian random fields (Worsley et al., 1996). Coordinates for localization of the activations were displayed in the MNI 152 space. For all statistical analyses of extracted voxel data, values that were more than 2 *SD* from the mean were excluded. Fixed-effect analyses were performed to create single-subject contrast images (Friston et al., 1998) of delay activity. Brain activity related to the delay during the vsWM trial was compared to brain activity during the delay in the control trials. For each subject, one image was created for the delay contrast. To allow inferences to the population, random-effects analyses were applied to the contrast images from the single-subject analyses. The main effect analy-

ses of activity related to the delay-phase (i.e., the mean BOLD signal) consisted of one-sample t tests applied on the linear combination of parameter estimates stored in the contrast images. Interactions between group and event-related activity were analyzed using a two-sample t test on the contrast images.

Computational Model and Brain Imaging: Analysis of Fronto-parietal BOLD Correlations

Pearson's product–moment coefficient of correlation between frontal and parietal BOLD signals was calculated with MATLAB 6.5 (The Mathworks, Natick, USA). The coefficient was transformed into an approximately normally distributed Fisher z-score with variance $\sigma_z^2 = (\mathrm{df}-2)^{-1}$, where df is the effective degrees of freedom (Neter, Kutner, Nachtsheim, & Wasserman, 1996). Because the slow dynamics of the hemodynamic response function introduces autocorrelations between BOLD signal measurement values at nearby time points, the correlation coefficient is measured with less certainty than if measurements had been independent. This leads to a reduction in df, from $n - 1$ to $(n - r)/\sqrt{2\pi w^2}$ (Friston et al., 1995). Here, n is the number of BOLD signal values and $w = 1.42$ is the smoothing factor, which is the standard deviation of a Gaussian curve fitted to the hemodynamic response, 2.84 sec, divided by the time between measurements, 2 sec. Lastly, r is the number of effects modeled. In this case, $r = 1$ (the mean BOLD signal).

For the simulated hypotheses, four simulations were made for each of the ''adult'' and ''child'' networks corresponding to a developmental hypothesis, and t tests were performed on the Fisher-transformed correlations to test whether there were significant differences between ''child'' and ''adult'' networks.

To obtain correlations between experimentally measured BOLD signals, time-series of BOLD data were extracted from the SFS and IPS from each subject. In order to maximize the task-related signal and minimize noise, we allowed the anatomical location where data were extracted to vary slightly from subject to subject so that we could find the voxel with maximum task-related activity within the SFS and IPS in each subject. If no task-related activity was found within the region for a particular subject and session (using a liberal threshold of $p < .3$ and cluster size > 90), no data were extracted from that session. The application of the liberal threshold served to further enhance signal-to-noise ratio. An equal number of sessions were excluded from each group.

From the identified maximum voxels, we defined one parietal and one frontal region of interest with 3 mm radii, extracted the time-series of BOLD values from within this VOI, and used the eigenvector of that data for further analysis. Altogether, a total of 5323 BOLD signal values from 25 sessions (with 213 time points per session) from nine adults and 5326 BOLD signal values from 25 sessions from nine children were included in the analysis. A fixed-effect analysis was performed by pooling BOLD signal values to calculate a single correlation coefficient for every group. The degrees of freedom were calculated as described above in order to take the autocorrelation between time points into account. The Fisher-transformed z-score was then calculated, and a one-sided normal test was performed to test for significant group difference in z-score. We used a one-sided test because the developmental effects of the correlation coefficient in the model were either positive or not significant.

RESULTS

Increased Mean BOLD Signal Supports H1–H3

In the third column of Figure 2A, the simulated BOLD curves of all five ''child'' networks (black) are compared to the ''adult'' network (green). Of the five hypotheses—which were described in the Methods section—stronger synaptic connections (H1, H2) and increased contrast (H3) resulted in a developmental increase of the BOLD signal, whereas increased specificity (H4) caused a decrease in the BOLD signal, and an increased conduction velocity (H5) had no effect.

To assess the robustness of the simulated developmental effects on the mean BOLD signal, we developed five additional versions of the computational model with perturbed parameter values of the ''child'' and ''adult'' networks (Supplemental Tables 1 and 2). We changed synaptic locations, reduced the pyramidal cell model to a single-compartment model, and removed all ion channels except for the spike-producing Na^+ and K^+ channels. In addition, we changed the absolute height and width of the ''adult'' connection curve. In summary, despite the considerable parameter changes, all tested parameter configurations produced the same relative differences between ''child'' and ''adult'' mean BOLD signal as those shown in the third column of Figure 2A. Furthermore, we confirmed that using only excitatory synaptic currents or total spiking activity, instead of total synaptic currents, as a basis for the BOLD signal (Mukamel et al., 2005; Attwell & Iadecola, 2002) did not affect our results.

We next compared the predicted BOLD activity to the delay-phase BOLD activity measured with fMRI. Delay activity was extracted from maxima in the SFS and IPS in both hemispheres (Figure 2B, column 2). Although previous imaging studies have been performed on the development of vsWM-related BOLD activity, the delay-phase activity has not been previously isolated. We therefore conducted an experiment to measure this activity in SFS and IPS. A more comprehensive analysis of all imaging results relating to the development of vsWM from this experiment can be found in Olesen et al. (2006). An ANOVA with the behavioral data showed

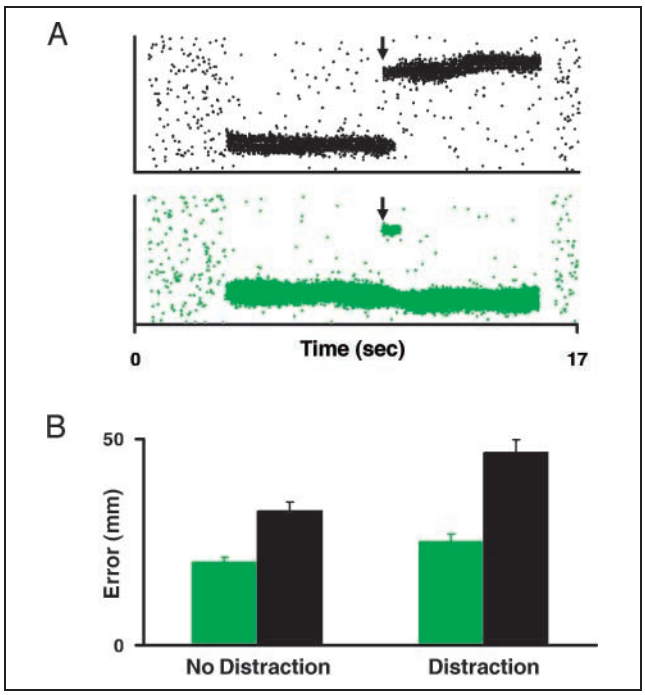

Figure 4. vsWM performance and distractibility in experiments and simulations. (A) Perturbing currents were injected into the somata of cells located 180° away from the cue (arrows). Frontal region pyramidal cell activity is shown. Each dot represents an action potential. (B) Adults were significantly more accurate than children on the basic WM task (''No Distraction''). In separate trials (''Distraction''), distracting dots were presented during the delay period. The distracter impaired performance significantly more for children than for adults. Performance was measured as the error in millimeters between cue and response locations. Error bars: *SEM*. Green = adult; black = child.

that the adults were significantly more accurate on the vsWM task ($p < .001$; Figure 4B, ''No distraction''), confirming previous findings (Gathercole et al., 2004). An additional two-way ANOVA with fMRI data showed greater activity in adults than in children [$F(1, 44) = 4.52, p < .05$], but found no interaction between age and region [$F(1, 44) = 0.89, p = .35$], which is consistent with the presupposed symmetric structure of the computational model. Figure 2B, column 3, shows the measured delay activity, averaged across bilateral SFS and IPS regions, for the adult and child groups.

We also performed an exploratory analysis using SPM2 to investigate differences in delay-related brain activity in every voxel of the frontal and parietal cortices. We found that adults showed higher activity than children in the right middle frontal gyrus and intraparietal cortex, whereas there were no regions in which children showed higher BOLD activity than adults. The location of this frontal region corresponds to an anterior frontal activation, presumably Brodmann's area 46. This indicates that the relative difference between adult and child delay activity does not depend on the particular location of measurements in the frontal and parietal lobe. In conclusion, the results from measurements of the mean BOLD signal were predicted by H1 and H2: stronger intra- and interregional synaptic connections, and H3: increased contrast, but not by H4: increased specificity or H5: increased conduction velocity.

Increased Interregional Correlation of BOLD Signal Supports H2–H3

H1, H2, and H3 were the only hypotheses that were consistent with the developmental increase in mean BOLD signal. To distinguish between these three hypotheses, we analyzed interregional correlations, based on the idea that brain activity in regions that are strongly connected should be correlated. By performing repeated simulations, we could statistically confirm that the ''adult'' network had a higher interregional correlation of the BOLD signal than the ''child'' network for both H2 and H3 (difference in Fisher z-score, Δ, was 0.59, $p < .001$, $n = 8$ for H2 and $\Delta = 0.48$, $p < .05$, $n = 8$ for H3). Changing local connection strength (H1, $p = .23$, $n = 8$) or increasing neuronal conduction velocity (H5, $p = .15$, $n = 8$) produced no difference, whereas increasing specificity (H4, $\Delta = -0.35$, $p < .05$, $n = 8$) led to a decreased interregional correlation. We then calculated group differences in correlations from the measured BOLD time-series data. We found that adults had a significantly higher correlation coefficient, ρ, between frontal and parietal activities ($\rho_{adult} = 0.42$, $\rho_{child} = 0.37$ and $\Delta = 0.06$, $p < .05$). This confirmed the prediction made by H2: stronger interregional synaptic connections, and H3: increased contrast, but did not confirm H1: stronger intraregional synaptic connections (or H4: increased specificity and H5: increased conduction velocity).

H2–H3 Predict Human Distractibility

Lastly, to assess the predictive capacity of the H2–H3 network models, we investigated their mnemonic performance by testing whether memory-related activity was affected by a perturbing current (Figure 4A). Activities in the ''child'' networks H2 and H3 (and H1) were less stable than the ''adult'' activity (whereas H4 and H5 ''child'' networks were not), which is consistent with the finding that adult subjects show a greater resistance to distracters (Figure 4B). This result serves as an independent validation of the results from the investigations of mean BOLD signal and interregional BOLD signal correlations as discussed previously.

Conclusion—Synaptic Strengthening behind Developmental vsWM Improvement

To conclude, we found that three types of changes—increased intraregional connectivity (H1), increased interregional connectivity (H2), and increased contrast (H3)—could predict the developmental increase in delay-phase BOLD activity in the frontal and parietal lobes, as

well as the superior performance of adults on the vsWM task. Of these hypotheses, H2 and H3 also predicted the developmental increase in the interregional correlation of activity. Thus, H2 and H3 were the only mechanisms that were supported by the experimental data.

Although slightly different, in both H2 and H3, synaptic strengthening causes an increase in the interregional connection strength between cells coding for similar stimuli. The impact of a change in strength of a connection going from cell i to cell j is high if cell i has high activity, whereas it is low if the activity in cell i is low. Therefore, synaptic strengthening in H2 and H3 has a major impact on vsWM-related activity, as it causes an increased connection strength between those cells in the network having the highest activity (those coding for the stimulus). By the same token, synaptic pruning has a low effect on mnemonic activity because the decrease in synaptic strength occurs in connections from cells with low activity. We therefore conclude that it is the strengthening of fronto-parietal synapses, rather than synaptic pruning, that constitutes the most important cellular maturational process underlying the improvement of vsWM.

DISCUSSION

In the present study, we have used a new approach in order to evaluate how developmental processes taking place on the neuronal level can be directly related to the maturation of WM and associated changes in brain activity. Deco et al. (2004) have developed a similar approach comparing modeling and fMRI, but their approach is slightly different in that they propose new models which can account for a previously observed phenomenon, whereas we use modeling to make predictions about unknown phenomena (the BOLD signal characteristics had never been measured before). Thus, by expressing neuronal developmental changes in a computational model that represents our current knowledge about the mechanisms underlying the delay-phase activity studied in vsWM tasks, we could predict the effect of these changes on the magnitude and correlation of delay-phase activity in two vsWM-related brain regions. We found that one developmental change accounted for the observed increase in vsWM-related brain activity, namely, synaptic strengthening, which results in increased synaptic connection strength between cells in SFS and IPS with similar coding preferences. Other potential maturational processes, such as pruning and myelination, could not account for the observed developmental changes in brain activity.

The conclusion reached in this study could be affected either by discrepancies between the model and the human brain or by an incomplete model of the neurovascular coupling function. The feasibility of the latter has been supported in two recent articles. Logothetis et al. (2001) reported a correlation coefficient of .72 between the local field potential and the BOLD signal, and of .67 between multiunit activity and the BOLD signal. Mukamel et al. (2005) showed that a convolution between either spiking activity or local field potential and a linear hemodynamic response function was a good predictor of BOLD activity. By excluding time periods when there was no neural activity in the brain area under investigation—such periods, by definition, result in zero correlation without implying poor predictability—they were able to show even higher predictive power of the spiking activity, with a correlation coefficient of .81, and reaching .9 during the most informative time periods.

With regard to the biological plausibility of the cortical model, it should be noted that an important assumption of the model is that the two regions only interact through their pyramidal cells. This assumption most likely is an oversimplification, as excitatory cells could make long-range connections to inhibitory cells. However, a study of the effect of cooling either the prefrontal cortex or the posterior parietal cortex on the activity of the other region suggests that net connections are excitatory (Chafee & Goldman-Rakic, 2000). Therefore, a nonspecific strengthening of connections onto excitatory and inhibitory cells alike should generate the same change in mean BOLD signal as was seen in the present study. Similarly, the interregional correlations between BOLD signals are not expected to be affected by the omission of interregional excitatory connections to inhibitory cells, because it is still the case that activity in strongly connected regions will be correlated.

The frontal and parietal regions identified in this study were previously shown to be active during the delay period in vsWM tasks (Curtis et al., 2004; Rowe et al., 2000; Courtney et al., 1998). Other fMRI studies of vsWM comparing children and adults (Bunge et al., 2002; Klingberg et al., 2002; Casey et al., 2000) were also compatible with our data, although none of these isolated the delay-specific activity simulated in the model. Especially noteworthy is the increased fronto-parietal connection strength found in this study which is compatible with a previous study showing a higher correlation between area 8 and the posterior part of the IPS in correct than incorrect trials (Sakai, Rowe, & Passingham, 2002).

Apart from the developmental processes dealt with in this study, it is possible that other processes—such as the development of the dopamine system—could improve WM as well. The strength of connection between an upstream and a downstream neuron is defined as the influence that a unit change in the activity of the upstream neuron has on the downstream neuron. Although maturation of synapses is the most natural mechanism whereby interregional connections could be strengthened, there are also other ways to achieve this. Modulatory neurotransmitters such as dopamine might act by changing effective connection strengths between active

cells. Dopamine levels are increased during WM tasks (Watanabe, Kodama, & Hikosaka, 1997), and blocking of the dopamine D1 receptor can increase the signal-to-noise ratio of the delay-phase activity, that is, the activity of delay-phase pyramidal neurons tuned to the angle of the stimulus increases, whereas the activity of the neurons with other preferred directions decreases (Williams & Goldman-Rakic, 1995). Moreover, dopamine innervation of the prefrontal cortex declines during adolescence in the primate (Rosenberg & Lewis, 1995), suggesting a possible functional increase in the contrast (H3) of interregional connections through a developmental change in D1 stimulation. However, several effects of dopamine on the properties of prefrontal layer III pyramidal cells have been reported (Gonzalez-Burgos et al., 2002), and their interrelationship and relative importance is still unknown. Further research is therefore needed before any reliable predictions can be made on how dopamine modulation of WM-related brain activity changes during development.

Our modeling did not suggest any effect of myelin on brain activity levels. This might seem inconsistent with previous studies suggesting the importance of myelination in general (Giedd et al., 1999; Klingberg et al., 1999; Paus et al., 1999; Sowell et al., 1999) and, more specifically, a connection between fronto-parietal myelination and WM maturation (Nagy, Westerberg, & Klingberg, 2004; Olesen et al., 2003). However, from a dynamical system's point of view, it is not surprising that changes in conduction velocity did not affect the activity during the delay period. The mnemonic activity is a stable state in the network (a fixpoint of the system). Although the change in conduction velocity could possibly have caused the mnemonic activity to synchronize (oscillate around the fixpoint, a known possible effect of incorporating conduction delays into dynamical systems), which could, in turn, have affected the mean neuronal firing rate in the network, this was not seen (data not shown). Indeed, the most natural assumption would be that because the network has reached a stable state—meaning that the mean activity level in the network is approximately the same between reasonably proximal time points—the incoming synaptic activity experienced by a neuron would be approximately the same regardless of whether this activity originated 6 or 12 msec before. It is, however, possible that myelination could cause a decreased action potential failure rate (Zhou & Chiu, 2001), and the effect of myelination could thus be to increase the influence that a change in the activity of the upstream neuron has on the downstream neuron, that is, an increase in connection strength. Finally, we must stress that the absence of an effect of conduction velocity on delay-phase activity does not mean that myelination is unimportant for vsWM. Indeed, conduction velocity might be very important for other processes related to vsWM rather than maintenance, for example, encoding.

We do not rule out that several of the mechanisms described above could interact during development. In fact, building on the work in the present study, a recent study by Macoveanu et al. (2006) shows that although specificity on its own does not improve vsWM capacity, specificity and increased mean connection strength or increased contrast have a synergistic effect on capacity. However, in separate simulations, we have seen no interaction between conduction velocity and interregional connection strength on interregional synchrony or mean activity levels (data not shown). It is possible that the combination of increased specificity and stronger connections or contrast could lead to stronger but more focused activity during development, as has been observed during cognitive development other than vsWM (Casey, Galvan, & Hare, 2005). However, we did not test this explicitly in this study.

Lastly, it is possible that the mechanisms we have identified as important for development are more generally valid for determining interindividual differences in WM capacity. The link between delay-related activity in the intraparietal cortex and vsWM capacity that we found by studying developmental changes has also previously been identified within the context of interindividual variability in vsWM capacity among adult subjects (Olesen, Westerberg, & Klingberg, 2004; Todd & Marois, 2004).

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Reprint requests should be sent to Torkel Klingberg, Pediatric Neurology, Department of Woman and Child Health MR Center, Karolinska Institutet, SE-171 76 Stockholm, Sweden, or via e-mail: torkel.klingberg@ki.se; or to Jesper Tegnér, Computational Biology, Department of Physics, Linköping University of Technology, SE-581 53 Linköping, Sweden, or via e-mail: jespert@ifm.liu.se.

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