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Protracted development of executive and mnemonic brain systems underlying working memory in adolescence: a longitudinal fMRI study

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Abstract

Working memory (WM), the ability to hold information on-line to guide planned behavior, improves through adolescence in parallel with continued maturation of critical brain systems supporting cognitive control. Initial developmental neuroimaging studies with one or two timepoints have provided important though varied results limiting our understanding of which and how neural systems change during this transition into mature WM. In this study, we leverage functional magnetic resonance imaging (fMRI) longitudinal data spanning up to 9 years in 129 normally developing individuals to identify which systems demonstrate growth changes that accompany improvements in WM performance. We used a memory guided saccade task that allowed us to probe encoding, pure maintenance, and retrieval neural processes of WM. Consistent with prior research, we found that WM performance continued to improve into the early 20s. fMRI region of interest (ROI) analyses revealed developmental (1) increases in sensorimotor-related (encoding/retrieval) activity in visual cortex from childhood through early adulthood that were associated with WM accuracy and (2) decreases in sustained (maintenance) activity in executive regions from childhood through mid-adolescence that were associated with response latency in childhood and early adolescence. Together these results provide compelling evidence that underlying the maturation of WM is a transition from reliance on executive systems to specialized regions related to the domain of mnemonic requirements of the task leading to optimal performance.

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1. Introduction

Working memory (WM), the ability to maintain information online to guide planned voluntary behavior [1], is a core executive function. Although the rudiments of WM emerge in infancy and early childhood [2], developmental studies indicate that WM continues to improve into adolescence [3, 4, 5, 6, 7], with visuospatial WM in particular taking longer to develop than other types of WM (e.g., verbal [4]). The accuracy of WM has been found to improve late into the second decade of life [6], with load [8], and manipulation of the information exacerbating age effects [9].

WM requires an initial encoding of information, retaining the information on-line during a delay period, in some tasks requiring manipulation of the information, and finally retrieving this information to guide an executive response. These different epochs of WM have been found to be supported by partially overlapping brain systems. For example, frontoparietal systems have been found to be involved across epochs, whereas encoding is more specifically associated with sensory systems, while the maintenance period has been associated with prefrontal, and retrieval with motor systems [10, 11]. Investigating developmental brain changes that underlie improved WM can help disambiguate the unique roles of these systems in supporting WM precision and reliability. For instance, developmental improvements in WM performance may reflect mnemonic processing, relating to improvements in sensory representations in WM. In contrast, WM development may relate to executive processing, such that information is maintained in a more stable fashion due to developmental improvements in processes such as inhibitory control [6]. For example, findings of protracted development of WM performance hold across different delay lengths [6], suggesting that refinement of maintenance processes alone do not account for developmental improvements in behavior.

There have been several developmental studies of WM to date using fMRI, with mixed findings. Common across studies are findings of developmental changes in the function of DLPFC, as well as distributed brain regions, including parietal and visual cortex [12, 13, 14, 15, 16]. However, there have been several discrepancies in these studies as well, with varying patterns of DLPFC changes with age, including greater delay activity in children/adolescents than adults [12], greater delay activity in adults than children [13, 14, 15], as well as a U-shaped curve, with adolescents showing the greatest activity [12, 16].

These discrepant findings may be due to a range of methodological differences such as task requirements, ages examined, sample size and sampling variation inherent to cross-sectional designs. While these studies have primarily explored visuospatial WM, they have used a range of tasks, including N-back [17], object memory [9], and the memoryguided saccade (MGS) task [12, 16]. Further, some of these tasks require cognitive operations, such as manipulation of the contents of WM, that can lead to learning compensatory strategies such as verbal processing and inhibitory control that may be unrelated to WM per se [9, 8]. In the

present study, we used the memory guided saccade task (MGS), which does not include manipulation of information or the use of compensatory strategies; additionally, prior research has demonstrated that accuracy and reaction time on this task robustly improves with age (see Supplementary Figure 5 for task details). Furthermore, we applied an event-related analysis to separate developmental changes in activation of brain regions associated with encoding, maintenance, and retrieval components of WM; these components also help to distinguish mnemonic and executive processes [11], which has not previously been examined in adolescent development.

To integrate developmental change beyond age-related changes of WM-related behavior and brain function, we used a longitudinal design that included several observations per subject. There have been two prior studies using multiple time points to examine the development of WM, of which one had 2 time points for each participant [7], while the other had 1-3 time points per participant [18]. Both studies found that fronto-parietal activity was associated with current WM capacity, while basal ganglia regions were associated with future WM capacity [7, 18]. These studies are an important step in identifying within-individual developmental brain changes underlying working memory, which is critical to avoid limitations of cross-sectional studies by controlling for differences between individuals, representing “true” developmental change. However, they have a key limitation in that they utilize a two time-point follow-up design which doesn’t localize at which ages during development these changes occur, assuming these changes are constant across late childhood, adolescence, and early adulthood. In a previous longitudinal study using diffusion tensor imaging (DTI) from our laboratory [19], we developed a technique that uses specialized regression models and calculation of growth rates to identify at which ages active developmental change occurs and when these changes stop, i.e. maturation. We were able able to identify hierarchical patterns in brain development, with different regions maturing during childhood, adolescence, and early adulthood, respectively. Our study utilizes this approach in a large longitudinal sample, building on previous multiple time point studies to better characterize trajectories and individual differences in WM development and its underlying neural correlates.

2. Materials and Methods

2.1. Study Sample

129 participants (67 female) were studied in an “accelerated longitudinal design,” in which participants were enrolled at any age between 8 and 30, and returned for annual visits from that point (see Figure 1 for sample details). A total of 356 sessions with usable fMRI data (criteria detailed below) were available for analysis (mean = 2.8 visits/participant). All participants reported no past or current neurological or psychiatric disorders, no family history of these disorders in first-degree relatives and no contra-indications for scanning (such as claustrophobia or metal implants). All participants had intelligence quotient (IQ) tested using the Wechsler Abbreviated Scale of Intelligence (WASI) [20] and none had a full scale IQ of less than 80 (IQ at first visit: 114 ± 13). All participants gave informed consent and were compensated for their time. All experiments complied with the Code of Ethics of

the World Medical Association (1996 Declaration of Helsinki) and were approved by the Institutional Review Board at the University of Pittsburgh.

2.2. Task

For this study, participants performed a variant of the memory-guided saccade (MGS) task [21, 22]. In this task, a participant maintains fixation and is presented with a peripheral cue stimulus in an unexpected location, which the participant is instructed to saccade to. Saccading to the cue is a variant of the typical MGS, where fixation is retained, in order to equate demands with younger participants whose inhibitory control system is immature and have difficulty retaining fixation with a competing stimulus [23]. This constitutes the encoding epoch. After the stimulus disappears, the participant returns their gaze to fixation during a varied delay period where this information is sustained defining the maintenance epoch. Once fixation is extinguished this indicates to the subject to generate a saccade to the remembered location defining the retrieval epoch. See Supplementary Figure 5 for task illustration.

Participants performed 3 runs of the MGS task, each containing 20 trials, evenly split into short (1.5s)/long (3s) encode periods, and short (1.5s)/long (9s) delay periods, followed by a 1.5s retrieval period. Fixation between trials was jittered between 1.5-15s.

2.3. Eye Movement Analysis

Eye-movement data were analyzed and scored using inhouse scripts in R [24]. Saccades were identified using a velocity algorithm using a 20 degree/s criterion, and blinkrelated artifacts were identified and corresponding trials discarded. Each eye movement trial was scored for performance accuracy (correct, incorrect, or dropped due to blinks or instrument error). A run within a session was excluded if there were less than 10 correct trials out of 20; further, a session was excluded if it contained less than 20 correct trials across runs. Across included sessions, there was 9.3 ± 6.8 trials dropped (range 0-32). Primary measures of interest were latency, measured as the time from the end of the delay (fixation disappears) to the onset of the memory-guided saccade, and accuracy, measured as the difference in degrees between the MGS and the target position, relative to the initial encoding saccade.

2.4. fMRI Acquisition and Preprocessing

Acquisition details are described elsewhere [23], but briefly standard fMRI and high-resolution anatomical images were obtained on a 3T scanner. Participants were initially acclimated in a “mock scanner” to familiarize with the environment and reduce head motion. Participants performed three runs of the MGS task (each run contains 229 volumes, length=5’43”); they also performed four functional runs of an antisaccade task in the same session (25 minutes total), which are reported on separately [23].

fMRI data were preprocessed using a standard pipeline using FSL (FMRIB, Oxford, UK) and AFNI (NIH, Bethesda, MD) software. fMRI data were initially converted from raw DICOM images to NIFTI format, followed by application of slice time correction, rigid-body motion correction, nonlinear deformation to template (Montreal Neurological Institute; MNI) via intermediate highresolution anatomical image while resampling to 3mm isotropic

voxels, and temporal/spatial (5mm) smoothing. Voxelwise data were normalized to 10000 × global median, an alternative to voxel-wise normalization for calculating percent signal change. Structural and functional data were manually inspected to ensure data integrity, including artifacts due to motion.

2.5. fMRI Analysis

Individual fMRI data were analyzed using a general linear model (GLM) in AFNI. Correct, error, and dropped trials were modeled using a gamma function, with separate regressors for each task epoch (cue, delay, target), and baseline signal drift entered as covariates. Volumes with motion were addressed by censoring a volume and its preceding volume, if the derivative value of the volumes motion had a Euclidean norm above 1mm, to minimize potential confounds [25, 26]; motion parameter estimates were not included as covariates, as this approach has been shown to be ineffective relative to censoring alone [26]. Sessions were excluded if more than 20% of volumes were discarded (0.6 ± 1.8%, range 0-14.8%); a majority of sessions had no excluded volumes (70.6%). Contrasts for each epoch were generated by including only correct trials and were contrasted implicitly with the fixation baseline.

2.6. Regions Associated with WM

A cross-sectional sample (n=72, 34 female) was used for voxelwise analyses to identify regions of interest (ROIs) to use in the longitudinal analyses and avoid circularity (based on the first scan from individuals with 1 or 2 scans). A one-sample t-test was performed on individual contrast maps for each task epoch. Maps from each epoch were combined through a conjunction analysis, with a voxelwise threshold of $p<0.001$, clustered at 9 voxels, corresponding to a corrected $p<0.05$ level, as determined by AFNI's Alphasim program. Results revealed the canonical widely distributed circuitry engaged in WM (see Supplementary Figure 8). There were regions of overlap across epochs but unique systems were identified. Encoding and retrieval showed extended engagement of sensorimotor regions while maintenance showed extended engagement of prefrontal and subcortical regions. 41 regions were included in the ROI analysis, names and abbreviations listed below (full details in Supplementary Table 3). Theses included Cerebellum (Left (L), Right (R), Vermis), L/R Basal Ganglia (Caudate, Putamen, Pallidum), L/R Thalamus, L/R frontal (Dorsolateral Prefrontal Cortex (DLPFC), Ventrolateral Prefrontal Cortex (VLPFC), Frontal Eye Fields (FEF)), Supplementary Motor Area (SMA), preSMA, L/R Anterior Insula, Cingulate (Anterior (Ant), Middle (Mid), Posterior (Post)), L/R parietal (Inferior Parietal Lobule (IPL), Superior Parietal Lobule (SPL), Precuneus), R Supramarginal Gyrus/Superior Temporal Gyrus (SMG/STG), L/R Middle Temporal Gyrus (MTG), R Inferior Temporal Gyrus (ITG), and L/R occipital (Primarly Visual Cortex (V1), Medial Visual Assocation Cortex (Med_VAC), Lateral Visual Assocation Cortex (Lat_VAC), Fusiform).

2.7. Longitudinal Analysis

All data was included for behavioral analyses. A longitudinal-only sample (n=57, 33 female, 259 sessions, 4.5 scans/subject, mean age at first visit 16.1 ± 3.7, mean age at last visit 21.2 ± 4.3) was used to characterize developmental changes in brain activitation in ROIs defined by the cross-sectional sample. We excluded participants with data <10 or >30 due to low

power at these ages (2 participants). Voxelwise analyses were also run in the longitudinal sample to confirm ROI results, identify additional regions changing with development, and to generate whole-brain movies depicting age-related change. These images and movies from these analyses are thresholded at a $p<0.05$ with no cluster threshold to confirm results from regional analyses and illustrate continuous change.

Our group analysis methods in the study were similar to those described in a previous longitudinal white matter study from our lab [19]. Briefly, we used linear mixedeffects regression, where fixed effects represent the average growth trajectory in the sample while random effects account for individual variability around mean growth parameters [27], implemented in R using the lme4 package [28]. Natural spline growth curve models were used, and optimal number and spacing of splines were obtained using an iterative algorithm, with the most parsimonious model selected based on Bayesian Information Criterion (BIC). For each analysis, outliers were identified by removing each time point from the model, refitting and predicting the missing time point, then calculating prediction error; those exceeding 2.5 standard deviations from the mean were excluded. Model significance was assessed by using a loglikelihood test to compare to a lower-level null model with the effect of interest removed. We additionally evaluated significance of the intercept after controlling for an inverse effect of age, which was used instead of a linear effect due to the inverse curve being shown to better represent developmental changes [6]. In analyses where multiple ROIs are examined, a Holm correction for multiple comparisons was used [29]; this is similar to a Bonferroni correction but less stringent, since the threshold becomes more lenient with each significant region. Further, in analyses of homologous left and right regions, if one met for Holm correction, the other was evaluated at a lower threshold of $p<0.05$ in reporting results. Timing and stages of development were calculated using bootstrapping and prediction as described previously in detail [19]. We additionally evaluated brain-behavior interactions, first by controlling for an inverse effect of age, and second by examining stages of interaction of brain and behavior, as described previously in detail [19].

2.8. Confounding Variables

In addition to our primary analyses, we examined the effect of confounding variables on our data.

2.8.1. Time Point—We examined potential confounding effects of time point, which may represent practice effects or familiarity. Although sessions are 1 year apart, which would make practice effects less likely, given the implicit collinearity between age and time point, we ran a few analyses to rule out this possibility. We examined the effect of time point using an inverse effect, assuming effects would be greatest in the earlier scans, controlling for the spline age model. Confounding effects were found to be negligible; details can be found in the Results section.

2.8.2. IQ—Regression analysis found an association between IQ and inverse effect of age (1.2 points/year, p=3.0e-07). This effect was driven by the adult portion of the sample; when excluding subjects ≥18 at first time point, there effect no longer reaches significance (p=0.051). This suggests that the adult portion of the sample may be skewed towards higher

IQ. However, we revisited our primary findings and added IQ as a confounder, and confounding effects were found to be negligible; details can be found in the Results section.

2.8.3. Dropped Trials and Censored Volumes—Mixed models examining the association of dropped trials and inverse effect of age was significant (p=5.7e-06). Of note, this was no longer significant after excluding participants younger than 13 (p=0.11), indicating this effect was driven by a greater number of dropped trials in children. Further, censored volumes were also significantly associated with age (p=2.7e-10), such that there were less volumes excluded with increasing age. As with IQ, we revisited our primary findings and with dropped trials and censored volumes as a confounder, with negligible effects on significance. We have included details from these analyses in the Results.

2.8.4. Differences Between Cross-Sectional and Longitudinal Groups—We characterized the two samples (cross-sectional for ROI definition, longitudinal for other analyses) based on several variables (race, sex, socioeconomic status/SES, IQ, WM performance) to assess whether there were differences between the samples. Proportion tests revealed no differences in race (p=0.28) or sex (p=0.46). T-tests showed no differences in IQ (p=0.80) or SES (0.33). Mixed models showed no difference in latency (p=0.060) or precision (p=0.31). Further details can be seen in Supplementary Table 2 and Supplementary Figures 1, 2, 3 and 4.

3. Results

Subjects performed a variant of the MGS where they were required to retain in WM an initial saccade to a visual stimulus and after a varied delay period, generate a saccade to the remembered location. We constructed developmental models of change for behavior and fMRI activation using flexible spline growth curves, with omnibus p-values obtained using log-likelihood tests of lower level models. We identified stages of development by calculating predicted growth rates across development and obtaining variation in these growth rates using bootstrapping and prediction from lower level models; maturation time indicates the final age after which significant growth is no longer seen.

3.1. Development of WM Performance

We found robust developmental changes in both accuracy and latency measures of WM performance (precision error: p=2.5e-07; latency: p<1e-15) (see Supplementary Figure 6). In both cases, we found improvements in saccade precision error and latency from childhood (8.1y) continuing into the third decade (maturation time: precision error=20.0y, latency=23.8y).

3.1.1. Confounding Variables—We examined potential confounding effects of time point, which may represent practice effects or familiarity. No significant effect was seen for precision error (p=0.66). There was a significant effect for latency (p=0.029), such that individuals were slightly faster with repeated measurements, although this effect was vastly smaller than age effects. We then re-examined our age models, controlling for an inverse effect of time point. Both precision error and latency remained significant, and maturation

times were nearly identical (precision: p=7.1e-06, maturation age=19.9y; latency: p<1e-15, maturation age=23.6y), suggesting that practice effects/familiarity did not effect our data.

Controlling for IQ, age models remained significant for precision error (p=4.7e-06) and latency (p<1e-15). Conversely, controlling for age models, IQ was not significantly associated with precision error (p=0.10) or latency (p=0.27).

Controlling for dropped trials, age models remained significant for precision error (p=1.4e-05) and latency (p<1e-15). Conversely, controlling for age models, dropped trials was not significantly associated with precision error (p=0.17) or latency (p=0.28).

We also compared WM measures between the crosssectional and longitudinal samples. There were no significant differences for precision error (p=0.31) or latency (p=0.060).

3.2. Development of Functional Specificity

We modeled longitudinal results separately for fMRI activation during WM epochs (encoding, maintenance, and retrieval) on ROIs defined in a separate cross-sectional sample to avoid circularity. Developmental models were generated as described above with behavioral data; due to a large number of ROIs, Holm correction was employed to correct for multiple comparisons. Summary of significant findings can be seen in Table 1.

3.2.1. Encoding/Retrieval activity—Encoding and retrieval shared age related increases predominantly in visual areas (BA17/18) from childhood into the third decade (see Figure 2); similar developmental increases were seen during encoding in right ITG. We found fluctuating trajectories in the mid-cingulate during encoding (decrease 10.2-12.4, increase 12.8-14.4, decrease 17-19.1) and in DLPFC during retrieval (L: increase 12.6-14.7, decrease 15.4-17.8, increase 19.3-23.3, decrease 25.2-28.3; R: increase 10.2-13.2, decrease 14.3-17.7, increase 19.3-20.9).

A widely distributed WM circuitry was engaged across all ages. The encoding period reliably engaged visual areas (V1, Med_VAC, Lat_VAC, Fusiform), parietal cortex (IPL, SPL), premotor regions (FEF, preSMA), R ITG, and L DLPFC. The retrieval period showed activation in cortical and subcortical regions similar to encoding including: visual and parietal regions (V1, Med_VAC, Lat_VAC, Fusiform, IPL, SPL, Precuneus, R SMG/STG). Additionally, subcortical regions were also engaged during retrieval (Cerebellum, Pallidum, Putamen).

3.2.2. Maintenance activity—Results demonstrated age-related *decreases* in maintenance activity across several regions, including Anterior Cingulate, Anterior Insula, IPL, Pallidum, and Putamen. Similar decreases were seen in right DLPFC (p=0.0061), although this did not survive correction for multiple comparisons (see Figure 3). Only the FEF and preSMA were significantly engaged across all ages.

3.2.3. Confounding Variables—Although confounding variables had negligible effects in the behavioral data, we also examined them in the fMRI data to ensure results remained significant. We examined time point, IQ, dropped trials, and censored volumes due to

motion. These variables had negligible effects on the data (see Supplementary Table 1 for details).

3.2.4. Voxelwise analyses—We additionally ran voxelwise analyses to confirm ROI results and explore additional regions whose activity changed with development. Results were consistent with the findings described above (see Supplementary Figure 7), including developmental increases of encoding and retrieval activity in visual cortex, and decreases of maintenance activity in prefrontal, parietal, and subcortical regions. Further, these analyses lent greater sensitivity, revealing additional regions that change with development, as well as additional patterns of development in regions whose activity was suppressed during WM processing (detailed results can be seen in Supplementary Table 4). Finally, these analyses were used to create whole-brain movies highlighting age-related changes in WM-associated brain activity (see SI for details).

3.3. Relation of function to behavior

We further explored the ROIs detailed in Supplementary Table 3 in the longitudinal sample to study brainbehavior associations, both controlling for age as well as examining how these associations change with development (See Figure 4). After controlling for age, precision error was negatively related to encoding activity in V1 (Left: p=0.00048; Right: p=0.0084), such that greater activity was associated with greater accuracy. Latency showed an interaction between the brain-behavior association and age for the maintenance epoch during childhood and adolescence; these effects were specifically seen in Anterior cingulate (stages = 10.2-11.5 (neg), 12.4-14.2 (pos), p=3.5e-05) and Anterior Insula (Left: stages = 10.2-12 (neg), 13.1-14.6 (pos), p=0.00025; Right: stages = 10.9-12.4 (pos), p=0.042), such that greater utilization in childhood resulted in faster responding, while in adolescence it resulted in slower responding; for R anterior insula, even in childhood it was associated with slower responding.

4. Discussion

This is the first longitudinal fMRI study with greater than three time points used to identify brain systems changing during the transition from childhood to adulthood as WM improves and stabilizes. We confirmed that WM performance improved with age, showing asymptotic growth through adolescence [6] that continued into the third decade of life. Specifically, correct WM responses were evident across all ages but the precision of the saccade to the remembered location improved and its latency continued to decrease into the twenties. That is, the basic ability to generate a WM-guided oculomotor response is already developed, but improvements in speed and precision of a response continue to develop into adulthood. The Memory-Guided Saccade (MGS) task is distinct from prototypical WM tasks that require manipulation of information during the delay period [1] in that it taps specifically into the delay-dependent neural processes that underlie the ability to retain a representation on-line without requiring additional cognitive demands that may affect interpretation of neural activity associated with maintaining these representations [30, 6]. Findings of protracted development are especially notable because the MGS task does not have extra cognitive demands known to be developmentally sensitive, such as needing to remember additional

items [8], performing operations on the contents of WM [9], or resilience in the face of distractors [15].

4.1. Roles of DLPFC and FEF

Just as children are capable of the basic ability to generate a WM response, canonical regions involved in WM are engaged across all ages. These regions include parietal and visual cortical regions, as well prefrontal, premotor and subcortical regions [31, 32], with much of this circuitry being recruited to a similar extent across ages. While many studies emphasize the role of DLPFC in WM maintenance [31, 32], we found this was only engaged earlier in development, and not used by adulthood. This is in agreement with a recent adult study showing that lesions to DLPFC did not affect MGS performance [33]. As we already noted, previous developmental studies of WM have found inconsistent directionality of DLPFC effects with age [12, 13, 14, 15, 16], likely secondary to a range of methodological differences such as task demands and ages examined. Another discrepancy may be based on contrast; adults show increased DLPFC activity for more difficult trials, whereas children do not show this difference [9, 8], suggesting that they require more effort to perform at a similar level, and that differences may be related more to difficulty than specific WM processes. Children and early adolescents also engaged parietal, subcortical and insula regions, which were not used by adults during maintenance and may participate as a compensatory mechanism.

In contrast, we found premotor regions were engaged during maintenance across ages, specifically preSMA and FEF. FEF is known to play a role in the executive control of eye movements and WM [34, 11, 35], and is recruited to a greater degree when WM is necessary to guide responding [36]. Lesions to FEF, in contrast to DLPFC, do undermine MGS performance [33]. Taken together, these findings suggest that while FEF is central to WM across development, children and young adolescents must use additional regions in order to accurately maintain stimuli in WM.

4.2. Mnemonic and Executive Processing

We found that even at the earliest ages and throughout our sample there was evidence of engagement of a core widely distributed circuitry across WM epochs. Developmental changes were evident in both sensory and executive regions known to be critical in WM [11], which has not been previously studied in adolescent development.

First, we found that what changed through development into adulthood was predominantly an increase in the engagement of visual cortical regions that continued into the early 20s for both encoding and retrieval. This finding is consistent with the Sensorimotor Hypothesis of WM [37] that highlights the role of visual cortex in providing optimal storage of visuospatial information while prefrontal regions support the executive aspect of generating a voluntary response. This proposal is supported by studies using multivariate analyses of fMRI data showing that the stimulus characteristics stored in WM are encoded exclusively in visual cortex [38, 39, 40, 41]. Importantly, activity in visual cortical regions during encoding was associated with accuracy across development (after controlling for age), suggesting that

developmental improvements in WM are predominantly underlied by enhanced integration of systems specific to the task, namely visuospatial processing.

Second, we found that executive regions involved in maintenance aspects of WM showed attenuation which became less engaged through childhood. Further, we found an interaction between age, maintenance-related activity, and latency, such that greater activity in children was associated with faster responding, but greater activity in adolescents was associated with slower responding. This suggests that greater engagement may reflect immature processing at older ages.

4.3. Comparision to Prior Studies

As detailed above, there have been several prior studies using fMRI to study the development of brain systems underlying WM, with varying findings across these studies. These discrepant findings may be due to a range of methodological differences such as task requirements, fMRI contrasts, regions studied, ages examined, sample size and sampling variation inherent to cross-sectional designs. We addressed all of these limitations: we used a WM task with minimal cognitive demands, separately examined task components, examined a broad range of regions via a conjunction analysis across epochs, and studied a large range of individuals from childhood through adulthood with several time points.

There have also been two studies to date using fMRI obtained at multiple time points to study WM development [7, 18], up to 2 and 3 time points per participant, respectively. Both studies highlighted the role of prefrontal/parietal cortex and the basal ganglia, with the former associated with current WM capacity and the latter with future WM capacity. Of note, although the latter study does not indicate how many participants had 3 time points, both studies used a two time point approach whereby change from time 1 to time 2 was measured. This approach assumes changes are constant across late childhood, adolescence, and early adulthood, whereas prior studies have shown non-linear changes across development. To address this limitation, we developed a technique that uses specialized regression models and calculation of growth rates to identify at which ages active developmental change occurs and when these changes stop, i.e. maturation [19]. In our previously published DTI study [19], we were able able to identify hierarchical patterns in brain development, with different regions maturing during childhood, adolescence, and early adulthood, respectively. As described above, we similarly found specific regions matured during adolescence, others during early adulthood.

Another key improvement is the large number of time points per participant in our study. Although longitudinal data controls for between-subject variance, functional imaging is still susceptible to within-subject variance from several sources, such as motivation, arousal, and head motion. With the current dataset, we were able to use quality control methods to identify outlier time points within-participants, further reducing variance and leading to more robust models. Although in this study we did not explore non-linear within-individual trajectories, this may be a useful approach in further studies.

Finally, the large amount of longitudinal data included, combined with within-individual quality control methods, make this the most robust longitudinal study of WM to date. This

allowed us to look at more regions than previous studies. In addition to regions previously seen, this additional robustness likely contributed to revealing developmental patterns in regions not typically implicated in previous studies.

4.4. Conclusions

In this study, we showed that developmental changes in working memory (WM) behavior and underlying neural processes are protracted through adolescence into early adulthood. Increases in encoding/retrieval activity in visual cortex into the early 20's were seen which corresponded with increases in WM accuracy, and decreases in maintenance activity in prefrontal/subcortical regions into mid-late adolescence were seen which corresponded with decreases in latency. Associations between WM-associated brain activity and performance suggest that accuracy is related to mnemonic processing while latency is related to executive processing, with distinct developmental profiles for each. These findings suggest that initially in childhood WM is primarily supported by executive processing, with maturation WM becomes reliant less on executive processes as specialized regions are integrated enhancing mnemonic processes leading to greater accuracy and faster responding. Understanding the qualitative transitions in brain processing underlying the normative development of working memory is critical for discerning the nature of abnormal development such as in psychopathology as well as informing basic science regarding the role of different brain systems underlying WM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Protracted development of working memory and underlying neural processes into 20's
- Increases in encoding/retrieval activity in visual cortex
- Decreases in maintenance activity in prefrontal/subcortical regions
- Association of precision error and encoding activity reflecting mnemonic processing
- Association of latency and maintenance activity reflecting executive processing

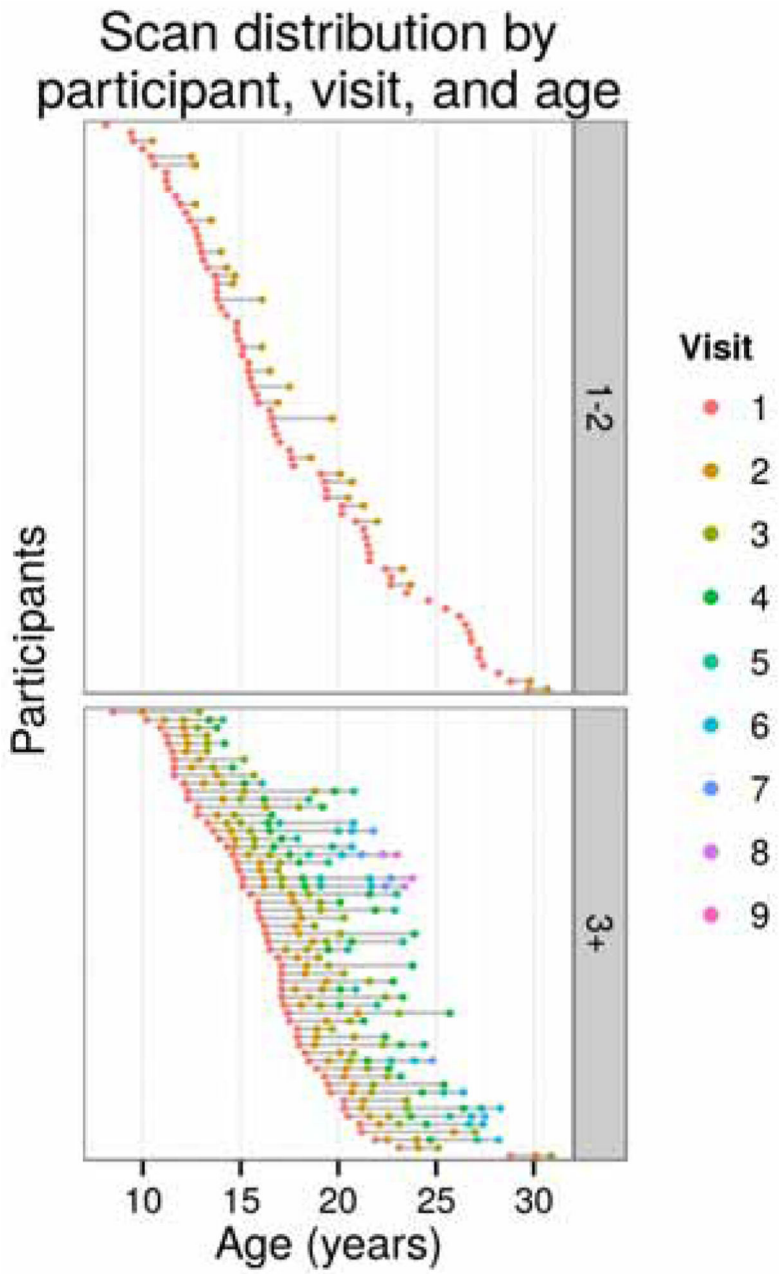

Figure 1:

Distribution of ages and scans in study sample. Each point represents a time point; color represents year of study (up to 9) as indicated in the legend. Time points belonging to the same individual are connected by lines.

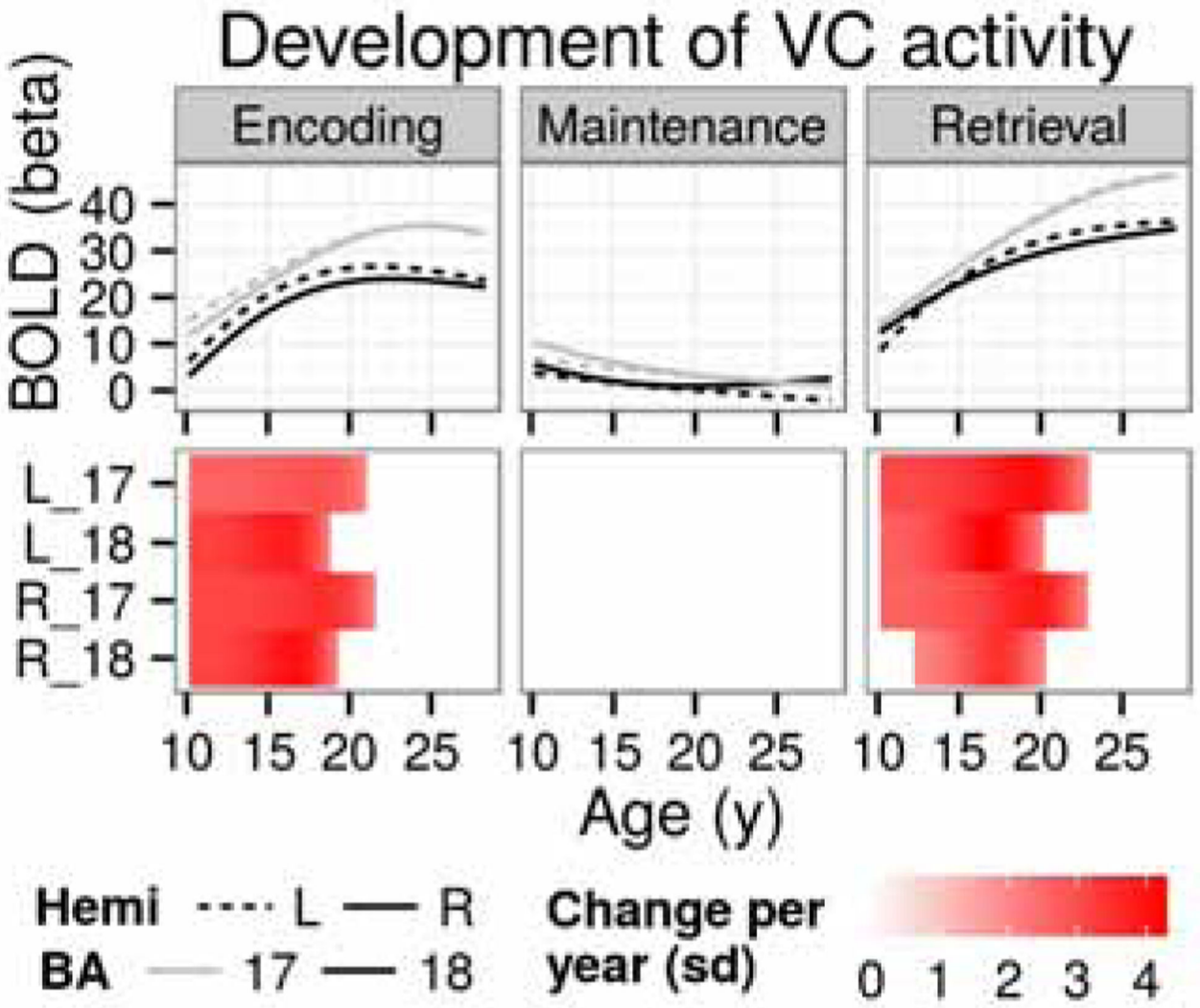

Figure 2:

Plots showing fMRI activation in visual cortex (VC; BA 17/18) during encoding (left), maintenance (middle), and retrieval (right), highlighting developmental increases during encoding and retrieval into early adulthood. Analyses in longitudinal dataset with ROIs drawn from the cross-sectional dataset. Lines indicates spline model fit (color indicates Brodmann Areas, with gray=17 and black=18, and line type indicates hemisphere, with left=dashed and right=solid). Heat plot beneath highlights developmental stages, with active change occurring during shaded periods.

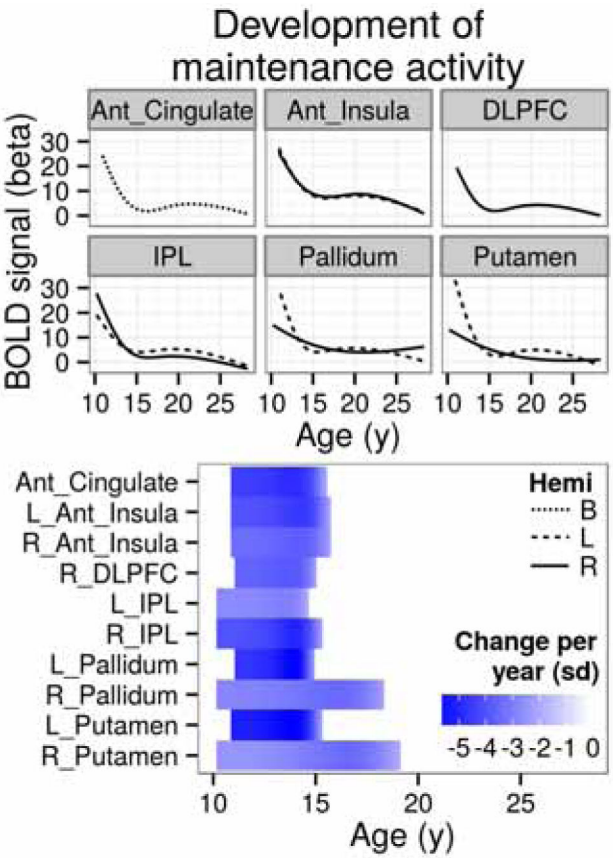

Figure 3:

Plots showing developmental decreases in fMRI activation during maintenance into mid-late adolescence. Analyses in longitudinal dataset with ROIs drawn from the cross-sectional dataset. Lineplot panels indicate spline fits in separate regions, with line type inside the panels showing hemisphere (left=dashed, right=solid, bilateral=dotted). Heat plot beneath highlights developmental stages, with active change occurring during shaded periods.

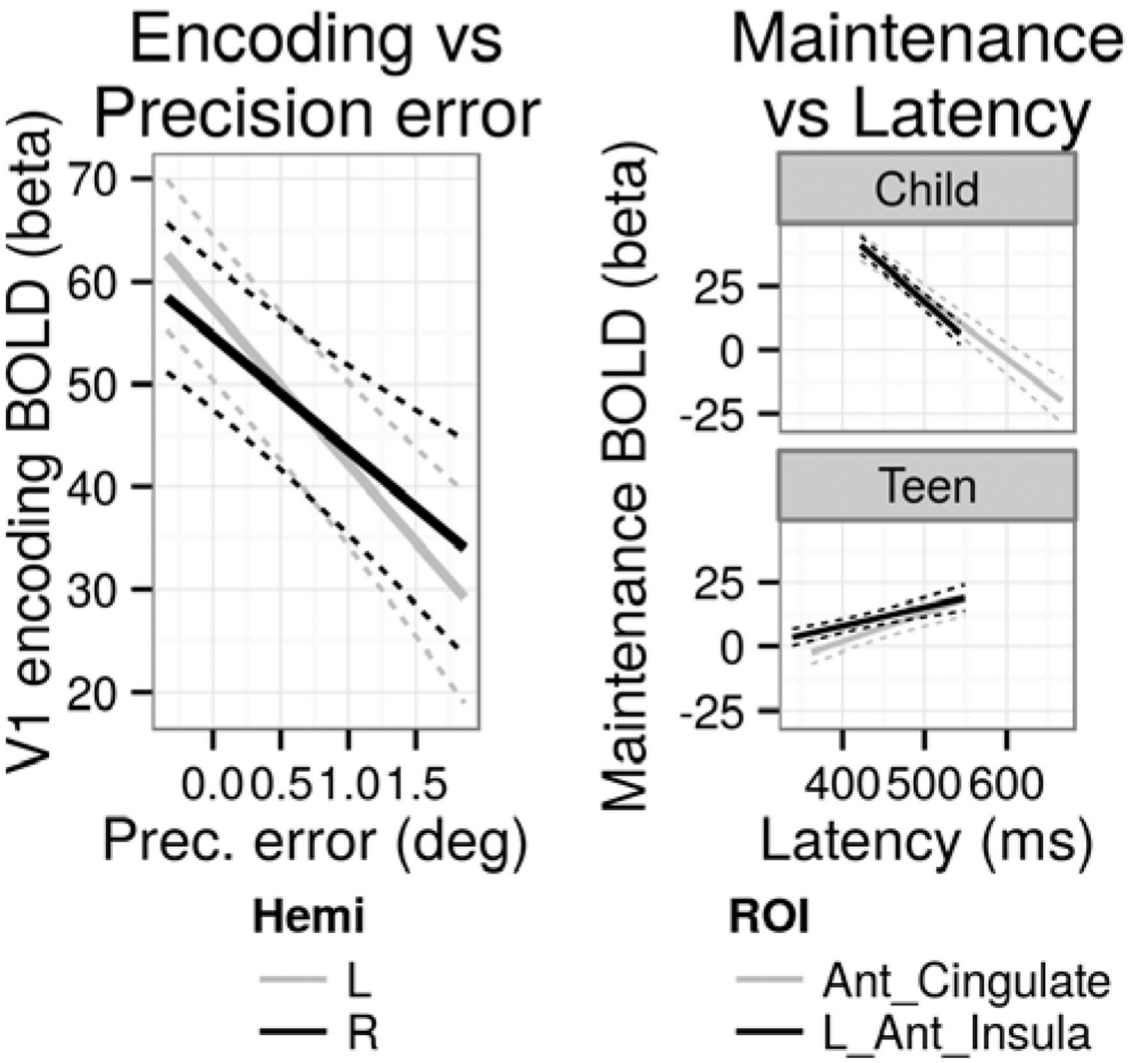

Figure 4:

Left: Interaction of precision error and fMRI activation in visual cortex in both right (black) and left (gray) hemispheres during encoding, after controlling for age. Right: Interaction of age and latency with fMRI activation in Anterior Cingulate (gray) and the Left Anterior Insula (black) during maintenance; panels indicate developmental stage (left=child, right=teen, age ranges indicated in text). Analyses in longitudinal dataset with ROIs drawn from the cross-sectional dataset. Solid line indicates spline model fit and dashed lines indicate 1 standard deviation from fit line, derived from bootstrapping.

Table 1:

ROIs showing significant activity after controlling for age, or showing age effects, separated by epoch.

		Label	BA	Active across ages (p)	Changes with age (p)	Inc or Dec	Matur-ation age (y)
Enc	L	V1	17	1.7e-11	0.0061	Inc	21.0
	R	V1	17	1.2e-12	0.00075	Inc	21.6
	L	Med_VAC	18	7.0e-11	0.0031	Inc	18.8
	R	Med_VAC	18	3.0e-11	0.00078	Inc	19.3
	R	ITG	20/37	1.6e-06	0.0011	Inc	19.7
	B	Mid_Cing	23		5.2e-05	Mix	19.1
	L	Lat_VAC	19	4.3e-07			
	R	Lat_VAC	19	3.2e-08			
	L	Fusiform	19/37	3.5e-05			
	R	Fusiform	19/37	2.0e-04			
	L	IPL	40	8.9e-05			
	R	IPL	40	0.0013			
	L	SPL	7	2.2e-07			
	R	SPL	7	3.6e-06			
	L	DLPFC	9/46	0.00082			
	B	PreSMA	6	0.00019			
	L	FEF	6	2.0e-05			
	R	FEF	6	0.00011			
Mnt	L	IPL	40		1.0e-05	Dec	14.8
	R	IPL	40		0.00048	Dec	15.7
	R	DLPFC	9/46		0.0061	Dec	15.0
	B	Ant_Cing	24/32		4.3e-05	Dec	15.5
	L	Ant_Ins			1.0e-05	Dec	15.7
	R	Ant_Ins			0.00048	Dec	15.3
	L	Pallidum			1.3e-06	Dec	14.9
	R	Pallidum			0.0086	Dec	18.3
	L	Putamen			2.6e-07	Dec	14.3
	R	Putamen			0.0076	Dec	19.1
	B	PreSMA	6	0.00011			
	L	FEF	6	0.00048			
	R	FEF	6	0.00013			
Rtr	L	V1	17	3.0e-15	3.1e-05	Inc	23.0
	R	V1	17	1.5e-15	0.00016	Inc	22.9
	L	Med_VAC	18	3.2e-14	0.00021	Inc	20.6
	R	Med_VAC	18	4.6e-12	0.0029	Inc	20.3
	L	DLPFC	9/46		0.00011	Mix	28.3
	R	DLPFC	9/46		0.0015	Mix	20.9
	L	Lat_VAC	19	0.00060			

	Label	BA	Active across ages (p)	Changes with age (p)	Inc or Dec	Matur-ation age (y)
R	Lat_VAC	19	5.1e-05			
L	Fusiform	19/37	8.2e-07			
R	Fusiform	19/37	0.00038			
L	IPL	40	0.024			
R	IPL	40	0.00094			
L	SPL	7	0.0032			
R	SPL	7	0.00018			
L	Precuneus	5/7	0.0012			
R	Precuneus	5/7	0.00021			
R	SMG/STG	40/42	0.0014			
L	Cerebellum		3.4e-06			
R	Cerebellum		2.0e-05			
L	Pallidum		0.00047			
R	Pallidum		0.0048			
L	Putamen		0.00019			
R	Putamen		0.0012			

Analyses in longitudinal dataset with ROIs drawn from the cross-sectional dataset. P-values listed for significant models; when age effects are significant, notes whether age-related changes are increases (Inc), decreases (Dec), or a mix of both, as well as maturation age, the last age where significant developmental change is seen. Enc=encoding, Mnt=maintenance, Rtr=retrieval. ROI label abbreviations in methods.