

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 20's. 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.

Introduction

Working memory (WM), the ability to maintain information online to guide planned voluntary behavior (Baddeley, 1992), is a core executive function. Although the rudiments of WM emerge in infancy and early childhood (Diamond et al., 1994), developmental studies indicate that WM continues to improve into adolescence (de Luca et al., 2003; Demetriou et al., 2002; Luciana et al., 2005; Luna et al., 2004; Ullman et al., 2014), with visuospatial WM in particular taking longer to develop than other types of WM (e.g., verbal (Demetriou et al., 2002)). The accuracy of WM has been found to improve late into the second decade of life (Luna et al., 2004), with load (Thomason et al., 2009), and manipulation of the information exacerbating age effects (Crone et al., 2006).

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 informa-

tion 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 (Emrich et al., 2013; Postle et al., 2000). 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 (Luna et al., 2004). For example, findings of protracted development of WM performance hold across different delay lengths (Luna et al., 2004),

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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 (Geier et al., 2009; Klingberg et al., 2002; Kwon et al., 2002; Olesen et al., 2007; Scherf et al., 2006). 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 (Geier et al., 2009), greater delay activity in adults than children (Klingberg et al., 2002; Kwon et al., 2002; Olesen et al., 2007), as well as a U-shaped curve, with adolescents showing the greatest activity (Geier et al., 2009; Scherf et al., 2006).

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 (Burzynska et al., 2011), object memory (Crone et al., 2006), and the memory-guided saccade (MGS) task (Geier et al., 2009; Scherf et al., 2006). 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 (Crone et al., 2006; Thomason et al., 2009). 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 (Postle et al., 2000), 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 (Ullman et al., 2014), while the other had 1–3 time points per participant (Darki and Klingberg, 2014). Both studies found that fronto-parietal activity was associated with current WM capacity, while basal ganglia regions were associated with future WM capacity (Ullman et al., 2014; Darki and Klingberg, 2014). 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 (Simmonds et al., 2014), 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 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.

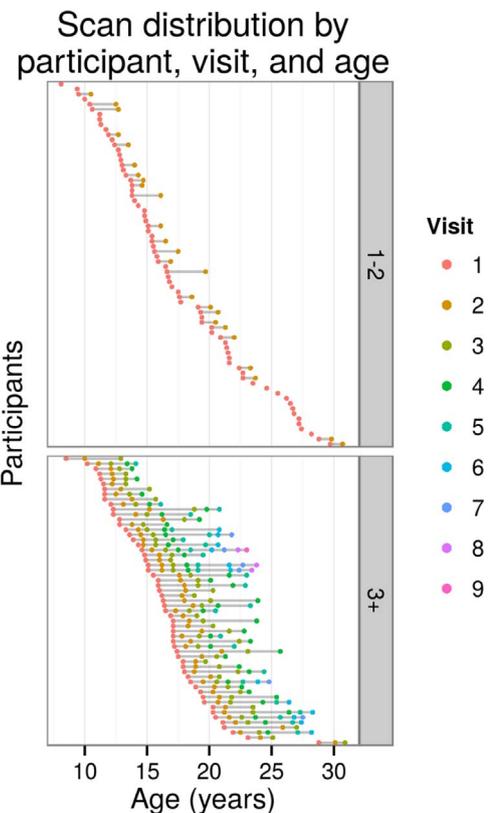


Fig. 2. Distribution of ages and scans in study sample. Each point represents a time point; color represents year of study (up to 9) as indicated in the legend. Time points belonging to the same individual are connected by lines.

Materials and methods

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 Fig. 2 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) (Wechsler, 1999) 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.

Task

For this study, participants performed a variant of the memory-guided saccade (MGS) task (Hikosaka and Wurtz, 1983; Funahashi et al., 1989). 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

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