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ORIGINAL ARTICLE

Functional Near-Infrared Spectroscopy Evidence for Development of Prefrontal Engagement in Working Memory in Early Through Middle Childhood

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Abstract

The neural underpinnings of working memory are hypothesized to develop incrementally across preschool and early school age, coinciding with the rapid maturation of executive function occurring during this period. This study investigates the development of prefrontal cortex function between the ages of 3 and 7. Children ($n = 68$) participated in a novel spatial working memory task while their middle and lateral prefrontal cortex (LPFC) was monitored using functional near infrared spectroscopy (fNIRS). We found increased activation of the LPFC when comparing working memory to rest. Greater LPFC increase was noted for longer compared with shorter delay periods. Increase in LPFC activation, accuracy, and response speed were positively correlated with child age, suggesting that developmental changes in prefrontal function might underlie effective development of executive function in this age range.

Key words: development, executive function, functional near infrared spectroscopy, prefrontal cortex, working memory

Introduction

Working memory, the ability to maintain information on line to support purposeful goal-driven behavior, is a core component of cognition (Baddeley 1992; Moscovitch 1992) that has a protracted development through childhood and adolescence (Luciana and Nelson 1998; Diamond 2002; Luna et al. 2004). As working memory develops from infancy to early childhood, children improve in working memory maintenance and manipulation abilities, but also begin to integrate working memory skills with other aspects of executive function. Previous work by Diamond et al. (1985, 1990) has shown that early elements of working memory are present by 8 months of age and these continue to fully develop throughout infancy. For instance, at 8 months, infants are able to complete Piaget's A-not-B task (Piaget 1936, 1951), which requires maintaining the location of a hidden object in working memory during a delay period, but only for a delay of 1–2 s. It is not until age 12–13 months that infants can manage 10-s delay without committing the "A-not-B error," which involves integration of working memory with simultaneously developing aspects of executive function, such as inhibitory control and cognitive flexibility (Diamond 2002).

Beyond the infancy period, multiple studies suggest that working memory skills increase with age. Luciana and Nelson (1998) have shown that spatial working memory, in concert with planning, pattern recognition, and set-shifting, improves across childhood, but has not reached adult levels by the age of 8. Gathercole et al. (2004) replicate this finding, showing that spatial working memory increases incrementally between the ages of 4 and 15 in a sample of over 700 children. Additionally, Luna et al. (2004) found significant improvements in working memory, particularly from age 8–15, with precision improving until the age of 19. Thus, it seems that working memory abilities emerge incrementally across childhood and adolescence, starting with basic perceptual and sensorimotor functions and developing toward the complex integration of other cognitive processes imperative in advanced adult functioning.

Studies of working memory have pointed to the lateral prefrontal cortex (LPFC) as a critical region for the neural basis of working memory and its development. In adults, functional magnetic resonance imaging (fMRI) (D'Esposito et al. 1995; Cohen et al. 1997; Courtney et al. 1998; Rypma et al. 1999), positron emission tomography (Jonides et al. 1993, 1997; Smith et al. 1995), and lesion studies (D'Esposito and Postle 1999; Müller and Knight 2006) indicate that this region is central to the multiple processes involved in working memory. Working memory has also been localized to the LPFC in nonhuman primates (Goldman and Rosvold 1970; Bauer and Fuster 1976; Sawaguchi and Yamane 1999). From birth through the school age, the prefrontal cortex undergoes structural and functional changes in gray and white matter volume (Giedd et al. 1999) and the number of synapses (Huttenlocher 1979; Petanjek et al. 2011) that persist into adulthood, which is hypothesized to underlie the rapid changes in cognitive development, occurring during this period (Diamond 1985; Goldman-Rakic 1987). One study (Luciana and Nelson 1998) employed the Cambridge Neuropsychological Test Automated Battery (Robbins et al. 1994), which is designed to isolate and test frontal lobe functions, to probe working memory development in a sample of 4- to 8-year-old children. The authors found that working memory, and its presumed underlying frontal lobe function, developed incrementally across the preschool and early school age period.

Several fMRI studies of brain activity during late childhood and adolescence have implicated increased use of the LPFC as working memory matures (Casey et al. 1995; Thomas et al. 1999; Nelson et al. 2000; Kwon et al. 2002; Crone et al. 2006; Scherf et al. 2006; Geier et al. 2009). Kwon et al. (2002) found that age was the most significant predictor of LPFC activation during a spatial working memory task. Investigating specific working memory skills individually, Geier et al. (2009) tested 8- to 12-year-old children in comparison to adolescents and adults on a task of spatial working memory maintenance. They found that while children, adolescents, and adults recruited a common network of regions including the LPFC, adults recruited the posterior parietal cortex during the long delay period while children recruited a more distributed circuitry, pointing to early imprecision of working memory processes in the child brain. Crone et al. (2006) also compared 8- to 12-year-old children with adolescents and adults in an investigation of working memory manipulation. Children failed to recruit the LPFC during manipulation, compared with maintenance, which points to the integrative development of working memory skills.

Working memory neurodevelopment in infancy, in the context of the A-not-B task (Piaget 1936, 1951), has been investigated during electroencephalogram (EEG) recording. Successful task performance, with increasingly longer delays between 7 and 12 months longitudinally and cross-sectionally, was correlated with increased fontal EEG power, the likely position of the LPFC, and increased anterior/posterior EEG coherence (Bell and Fox 1992). At 8 months, frontal EEG power and coherence at 6–9 Hz is also associated with individual differences in task success in both reaching (Bell and Fox 1997) and nonreaching (eye movement) (Bell 2001) versions of the task. One study (Bell and Wolfe 2007) addressed the changes in EEG power and coherence from infancy to early childhood using age appropriate working memory tasks. At 8 months, working memory was associated with increased EEG power and coherence across the entire scalp, while working memory was associated only with frontal EEG power and anterior/posterior coherence at 4.5 years. The authors argue that these data provide evidence for more diffuse to focal frontal specialization of working memory from infancy to early childhood, a pattern also noted by Geier et al. (2009) during late childhood through adolescence.

Other studies have focused upon longitudinal brain changes that might predict later working memory abilities. Tamnes et al. (2013) found that improvement in working memory at 2-year follow-up was specifically related to LPFC cortical volume reduction in a longitudinal study of 8- to 22-year-old children. Ullman et al. (2014) conducted a study with similar longitudinal methods, in children as young as 6, and found that LPFC activation at T1 was related only to concurrent working memory abilities, but did not predict working memory ability at follow-up. Instead T2 working memory ability was predicted by structure and activation of the basal ganglia and thalamus at T1. These studies have pointed to the importance of understanding functional changes in the dorsolateral prefrontal cortex that occur during development to support incremental improvement in working memory behavior (accuracy and reaction time) and integration of working memory with other aspects of executive function. However, despite well-designed longitudinal studies in older children, very little research has been conducted to examine neural correlates of working memory performance before 6 years of age. This has led Bell and Wolfe (2007) to conclude that "the paucity of brain–behavior research in preschool children is disturbing because early childhood is a time when many advances are being made in working-memory abilities" (p. 24). This dearth of brain–behavior working memory research in young child population is likely due to challenges of employing neuroimaging techniques below the age of 7.

Recent studies have employed the emerging technique of functional near infrared spectroscopy (fNIRS) (Jobsis 1977) to investigate cortical activation during working memory in 3- to 4-year olds (Buss et al. 2014) and 5- to 6-year olds (Tsujimoto et al. 2004). fNIRS is a technique well suited for this age group because it is noninvasive, allows children to complete tasks in a sitting position, and is less sensitive to movement than other imaging methodologies (Aslin and Mehler 2005; Cutini and Brigadoi 2014). Buss et al. (2014) found increased activation during working memory maintenance in both the frontal and parietal cortex during a change detection task using fNIRS. This effect was higher in the parietal cortex, and slightly higher in the right LPFC, for 4- versus 3-year olds. Tsujimoto et al. (2004) found that 5- to 6-year-old child activation of the LPFC was equal to adults during a simple task of remembering the positions of shapes in a visual array. The magnitude of activation increased for both 5- to 6-year olds and adults depending on memory load (i.e., the number of shapes in the array); however, no developmental change from 5 to 6 years was investigated. This leaves a gap in the developmental brain literature during the preschool and early school age period (age 3–7), which has often been cited as one of the most intensive periods for executive function development (Welsh et al. 1991; Diamond 2002; Carlson 2005; Marcovitch and Zelazo 2009). LPFC activation underlying working memory, however, has yet to be studied across the full 3- to 7-year age range.

Thus, the goals of the current study were 2-fold. First, we used fNIRS, which offers increased spatial resolution compared with EEG measurement (Aslin and Mehler 2005), to probe the development of LPFC function supporting working memory during the preschool to early school age period (ages 3–7). Based on the research of Luciana and Nelson (1998) who found incremental advancement in working memory abilities during this period, we hypothesized escalation in working memory across age in conjunction with increased LPFC activation. Second, we examined the effects of working memory maintenance on LPFC activation.

Based upon neurophysiological studies in animals (Fuster 1973; Funahashi et al. 1993) and fMRI human studies (Rowe et al. 2000; Curtis and D'Esposito 2003; Geier et al. 2009) suggesting that information is retained by sustained delay activity in the LPFC and parietal regions, we hypothesized that LPFC activation would be greater for long, compared with short, working memory delays in preschool to school age children.

Materials and Methods

Subjects

Subjects included in analyses were 68 3- to 7-year-old children (mean = 4.98 years, SD = 1.22, range = 3.0–7.83) (To allow for maximum variability in age for the purposes of developmental hypotheses, all analyses were calculated using subjects age in months [mean = 59.75, SD = 14.60, range = 36.0–94.0].) recruited through local advertising. Thirty-nine male and 29 female subjects were identified by their parent/guardian as 44% Caucasian, 50% African American, 4% Asian, and 2% Native American. An additional 4 children who were tested, but did not complete the task, were excluded from analyses. All subjects were reported by their parents to have no psychiatric diagnoses and to have no lifetime history of severe psychiatric diagnoses in any first-degree relative. A parent or legal guardian provided written informed consent for each child subject. All recruitment and experimental procedures were approved by the local Institutional Review Board.

Behavioral Task

Children were seated at a touch-screen computer at a child-sized desk for a spatial working memory task. They were introduced to a cartoon monkey and told that this monkey likes to hide his bananas in trees. Their job was to remember in which tree the monkey hid his bananas. Six palm trees were presented on the screen for the duration of each trial (see Fig. 1). For each trial, the monkey first appeared, holding his bananas, on one of the six trees (2 s). This was followed by either a long (6 s) or short (2 s) delay period in which the monkey disappeared, requiring the child to hold his location in working memory. After the delay period, red question marks appeared on the screen (3 s) prompting children to touch the tree in which the bananas were hidden. The trial was followed by a 1-s interstimulus interval in which a smiley face was presented at the center of the screen.

Four trials of each type (long/short) were presented sequentially to create long and short working memory blocks. Thus, long blocks contained 4 trials in which the child was required to hold the location of the bananas in working memory for 6 s and the short blocks contained 4 trials in which the child was required to hold the location of the bananas in working memory for 2 s. Three of each long and short blocks were interleaved and presented with a 6-s rest period between each block. The full duration of the task was 5 min 33 s. Before task participation, children completed a practice version of the task in order to ensure task familiarity and comfort with the touch screen. Children were asked to repeat the practice version until they scored a minimum of 80% correct trials.

fNIRS Measurement and Analysis

As previously described by Perlman et al. (2014), noninvasive optical imaging was performed with a CW6 real-time fNIRS system (Techen, Inc., Milford, MA, USA). In this study, a total of 4 light source emitter positions each containing a 690-nm (12 mW) and 830-nm (8 mW) laser light and 8 detectors were used. The intersensor distance was 3.2 cm. Sensors were mounted into a custom-built head cap constructed from neoprene and silicone, which was comfortably worn by the participant. Additionally, children were allowed to select an animal hat that was placed on top of the head cap. Three-meter long fiber optic cables connected the head cap to the fNIRS system, which was positioned behind the participant in the back of the room. For each participant, the fNIRS head cap was positioned according to the international 10–20 coordinate system with the middle of the probe at position FpZ as shown in Figure 2. The probe extended over Brodmann area 10 (ventrolateral prefrontal cortex) and area 46 (dorsolateral prefrontal cortex) on each hemisphere. Once the fNIRS instrument was securely and comfortably placed upon the subject's head, they were seated at a child size desk. Upon the desk was a touch-screen computer, designed to present the task and record responses. One experimenter was seated at the desk next to the subject in order to guide him/her through the task. A second experimenter remained behind the subject in order to control and monitor the fNIRS instrument. On average, the total fNIRS setup time to place the head cap was around 5 min.

During the study, the fNIRS data were collected at a sample rate of 10 Hz through a custom-built data acquisition interface as described by Abdelnour and Huppert (2009). This software allowed fNIRS signals (oxy- and deoxyhemoglobin) to be visualized in real-time during collection. The operator was also able to add comments to the data in real time to indicate subject events such as motion or distractions. The timing for the stimulus presentation through the Eprime (Psychology Software Tools, Sharpsburg, PA, USA) program was recorded in sync with the fNIRS data through an analog signal from the computer port.

Analysis of fNIRS data was collected using an iteratively whitened weighted least-squares regression model and canonical

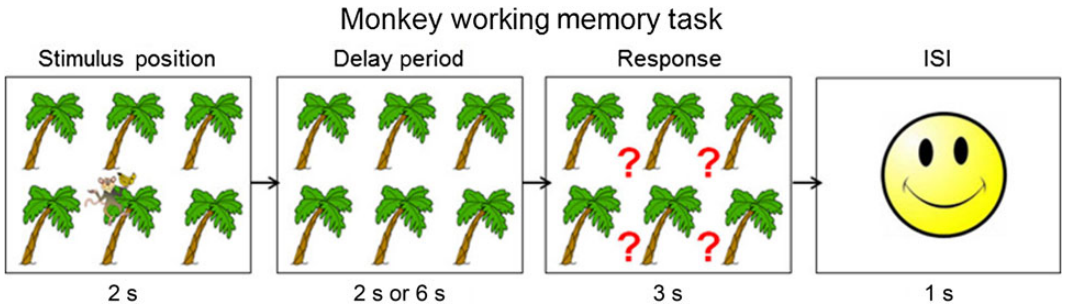

Figure 1. A single trial of the working memory task. Subjects were instructed to remember the tree in which the monkey hid his bananas during the delay period.

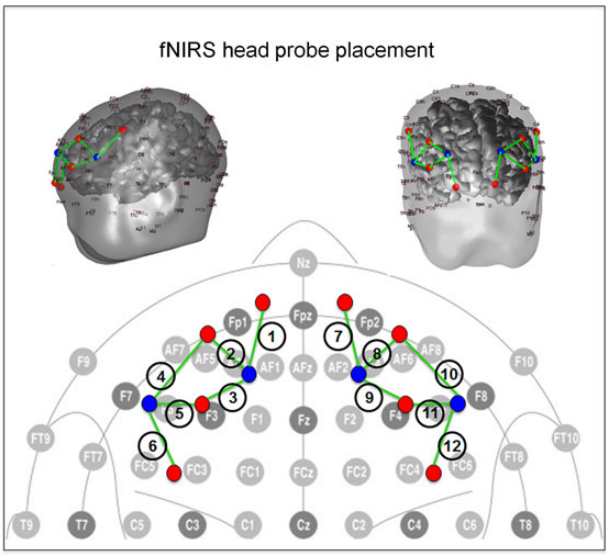

Figure 2. A schematic of the fNIRS cap layout design including international 10/20 coordinates.

regressors of the stimulus task as described by Barker et al. (2013). In brief, this model uses iterative auto-regressive (AR) filtering to remove serial correlations in the residual of the model. Our previous work has shown that this model greatly reduces the false-discovery rate due to both serially correlated noise (e.g., drift and systemic physiology) and due to motion artifacts. The AR model is estimated by a Bayesian information criteria (BIC) search of AR model order to whiten the residual of the linear regression model (e.g., $Y = X\beta$; where X is the design matrix based on the canonical response model). The AR coefficients are used to construct a linear whitening filter (S^{-1}), which is applied to both sides of the regression model and iteratively solved (e.g., $S^{-1} \cdot Y = S^{-1} \cdot X\beta$). The canonical design model (X) was based on the first-order convolution of the standard hemodynamic response function basis from SPM8 (Friston et al. 1994). Robust regression methods are used to estimate the model parameters (β) using a further iterative procedure to reduce the influence of statistical outliers. In particular, our previous work had shown that both "shift" and "spike" types of motion artifacts showed strong studentized errors after AR filtering and thus their influence on the model estimates was reduced by this approach. This procedure was repeated for each independent fNIRS optical density channel. No additional filtering or motion correction was preformed prior to the regression analysis. In this analysis, all NIRS channels and time points are included in the analysis, although outliers (e.g., those differing from the normally distributed distribution after AR whitening) are automatically downweighted according to the bi-square weighting function within the robust regression algorithm. Thus, this approach does not require preprocessing to remove data or NIRS channels from analysis.

The brain activity model parameters (β) were then input into a second-level random-effects ANOVA analysis as described in Abdelnour and Huppert (2011). Based on the placement of fNIRS probe relative to the international 10–20 coordinate system, the sensitivity of the optical measurements to the underlying brain was modeled based on the brain anatomy of an age-matched child's MRI data who participated in a previous study (Perlman and Pelphrey 2010, 2011). This template MRI structural image was segmented into skin, skull, cerebral spinal fluid, and brain tissue layers as previously described by Abdelnour et al. (2009). A Monte Carlo implementation (Fang and Boas 2009) of the optical diffusion approximation was used to simulate the optical "forward" model from this template which describes the sensitivity of each measurements to the underlying brain. The forward models for both 690 and 830 nm sets of measurements were estimated using background optical scattering and absorption coefficients provided in (Strangman et al. 2003). These 2 wavelength models were then combined into a spectroscopic forward model (L) by combining with the extinction coefficients of the Beer–Lambert law as described in by Li et al. (2004). Note, this procedure incorporates the differential pathlength and partial volume terms in the modified Beer–Lambert equation via the use of the Monte Carlo sensitivity models. The forward models for each subject are then incorporated into a single mixed random-effects ANOVA model, which additionally included cofactors based on the behavioral terms.

Given a set of behavioral parameters $\{a, b\}$ for the subjects $\{1, 2. . .n\}$ and the optical forward model $\{L\}$, the group-level ANOVA model is described by the expression

$$\begin{bmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{bmatrix} = \begin{bmatrix} L_1 & L_1 & 0 & \cdots & & a_1 \cdot L_1 & b_1 \cdot L_1 \\ L_2 & 0 & L_2 & & & a_2 \cdot L_2 & b_2 \cdot L_2 \\ & \vdots & & \ddots & & \vdots & \vdots \\ L_n & & & & L_n & a_n \cdot L_n & b_2 \cdot L_n \end{bmatrix} \cdot \begin{bmatrix} \beta_{\text{Group}} \\ \Delta\beta_1 \\ \vdots \\ A_{\text{Group}} \\ B_{\text{Group}} \end{bmatrix}$$

where β_{Group} describes the group effect and $\Delta\beta$ is the individual effect terms (Abdelnour and Huppert 2011). The terms A_{Group} and B_{Group} (etc.) model the cofactored effect (age). A hierarchical statistical model and a restricted maximum likelihood (ReML) cost function was used was used to estimate the model parameters (Abdelnour et al. 2010). The effective degrees of freedom for the underdetermined linear model was estimated using the Welch–Satterwaite method, which estimates the degrees of freedom from the structure of the data residual after fitting. The random-effects image reconstruction method utilizes the idea that it's more robust and self-consistent to do a single image reconstruction using all the data (all subjects) compared with solving multiple inverse models for each subject independently and then combining the results in a second step. This method was first introduced for magnetoencphalography (MEG) and electroencephalography (EEG) within the SPM software program (Mattout et al. 2006) and was adapted for use in the fNIRS model (Abdelnour and Huppert 2011). This group-level and ReML methods have been described and validated with simulation and comparison to fMRI in previously published work (Abdelnour et al. 2009, 2010; Abdelnour and Huppert 2011).

Results

Behavioral Performance

All behavioral data were calculated as a proportion of trials in which the subject responded by touching the screen. Subjects responded to approximately 85% (SD = 18%) of short delay trials and 84% (SD = 15%) of long delay trials. Reaction time was negatively correlated with age ($r(66) = -0.61$, $P < 0.001$). Older children were quicker to respond than younger children. When broken down by long and short delay periods, age was related to reaction time for both long ($r(66) = -0.54$, $P < 0.001$) and short ($r(66) = -0.56$, $P < 0.001$) delay conditions. Accuracy was high on this task (mean = 86%, SD = 19%) and correlated positively with age ($r(66) = 0.33$, $P < 0.01$). When broken down by long and short delay periods, age was related to accuracy for both long ($r(66) = 0.32$, $P < 0.01$)

and short ($r(66) = 0.29$, $P < 0.05$) delay conditions. Overall, subjects had significantly higher accuracy on short delay trials than long delay trials ($t_{(67)} = -2.95$, $P < 0.01$).

fNIRS Results

Neural Activity Contrast Between Working Memory Conditions and Rest

The NIRS data were analyzed using the general linear model and reconstructed to brain activation images as detailed in the previous section. The statistical contrast of the activation pattern for each of the optical measurement pairs is shown in Figure 3 for the contrast between working memory and rest blocks. The optical measurements pairs on the right hemisphere located around the international 10–20 coordinate of AF4 (channel 7) and AF6 (channel 8) which correspond to approximately Brodmann areas 10 and medial 46 right showed significant ($P < 0.05$; corrected) activations in oxyhemoglobin contrast between both the short and long working memory blocks versus rest blocks (Fig. 3). NIRS channels around F3, F5, and FC5 (channels 3, 5, and 6, respectively) on the left frontal cortex showed significantly higher ($P < 0.05$) activation during the working memory blocks compared with the rest blocks (approximately Brodmann areas lateral 46 and 44) for the group results. Deoxyhemoglobin activation maps (Fig. 3) showed a larger number of regions significantly increased between the working memory and rest blocks.

Based on the activation maps for each optical measurement pair and the optical sensitivity model constructed from the age-matched MRI template image, estimates of brain activity can be reconstructed to provide better visualization of the NIRS results. The reconstructed brain image from the group of subjects is shown in Figure 4 for the contrast between the short and long working memory and rest blocks. Although NIRS image reconstruction is ill-poised (e.g., mathematically unable to yield a single unique solution), this provides a qualitative projection of the channel-based data. In agreement with the channel-based results, we found activation in the left dorsal prefrontal cortex (approximately BA 10/46) was greater for working memory blocks compared with rest blocks. The longer working memory block showed greater activity in both the right medial frontal (approximately Brodmann areas 10 and medial 46 right) and left lateral frontal (approximately Brodmann areas lateral 46 and 44) compared with the shorter duration working memory task ($P < 0.05$).

Development of Neural Working Memory across Age

In Figure 5, we show the evoked time-courses for the two working memory conditions from the average of all significant ($P < 0.05$ based on the sum of the short and long memory contrast) NIRS channels on the left and right sides of the probe. The time-courses are shown for the average of the participants in the lower and upper groups of a median split by age. The younger group (dotted lines) trended towards lower activation amplitudes for both memory conditions compared with the older group (solid lines) but this was not significant ($P > 0.05$) between the two groups over the time window of 10–30 and 10–40 s for the short and long conditions respectively. This difference was strongest for the long working memory condition on the left side of the probe ($t_{(66)} = 1.46$; NS).

To further investigate this, we examined the effect of age as a continuous covariate instead of the median split within the group-level model as previously described. Consistent with the median split results, older children showed greater activation in this region during working memory conditions. We found that age was positively correlated with changes in oxygenated hemoglobin ($r_{(66)} = 0.26$, $P = 0.003$, two-tailed), but not significantly with changes in deoxygenated hemoglobin ($r_{(66)} = -0.15$, *NS*, two-tailed), during the combined short and long working memory blocks in comparison to the rest blocks over the region of interest in the left LPFC identified as significant ($P < 0.05$) from the age-covariate image reconstruction analysis and shown in Figure 5. The right side of the figure includes a scatter plot of the mean amplitude of oxyhemoglobin contrast from this region of interest and age for each of the 68 subjects for long and short working memory conditions. As shown in Figure 6, the correlation of age with the long working memory condition was slightly stronger then the short condition although this difference was not significant.

Discussion

This study complements the existing longitudinal literature on working memory neuro development (Tamnes et al. 2013;

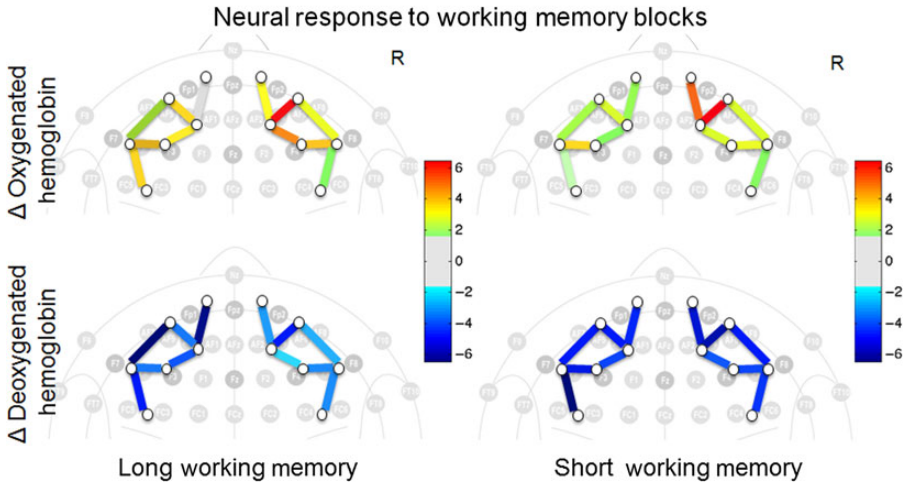

Figure 3. Brain activity contrast for the group-level hemoglobin signals during the working memory blocks minus the rest blocks. The color of each line indicates the *T*-statistic for the comparison of the 2 conditions in the general linear model for each fNIRS source–detector pair. The approximate locations of the closest international 10–20 coordinates to the fNIRS probe are shown. Oxy- and deoxyhemoglobin signals are shown in top and bottom panels, respectively.

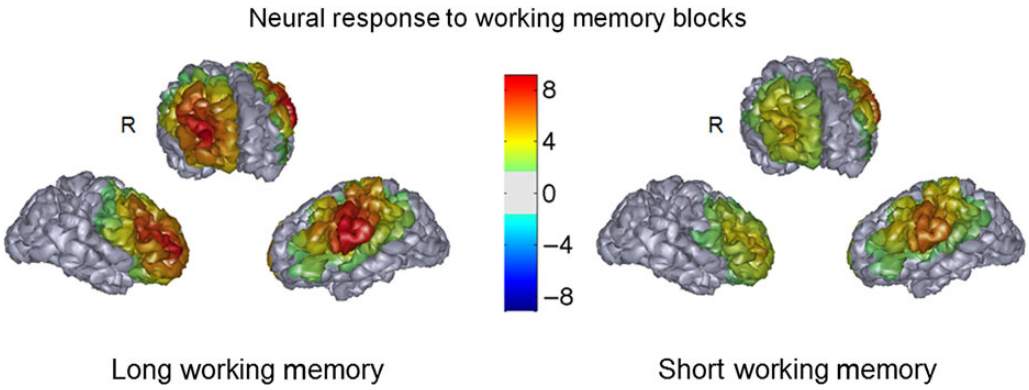

Figure 4. Reconstructed images of brain activity for the oxyhemoglobin contrast of the long and short working memory blocks minus rest. Colors represent *T*-statistic for the comparison of the 2 conditions (working memory, rest) in the general linear model. FNIRS data were reconstructed and displayed using an age-matched template of a brain for visualization purposes.

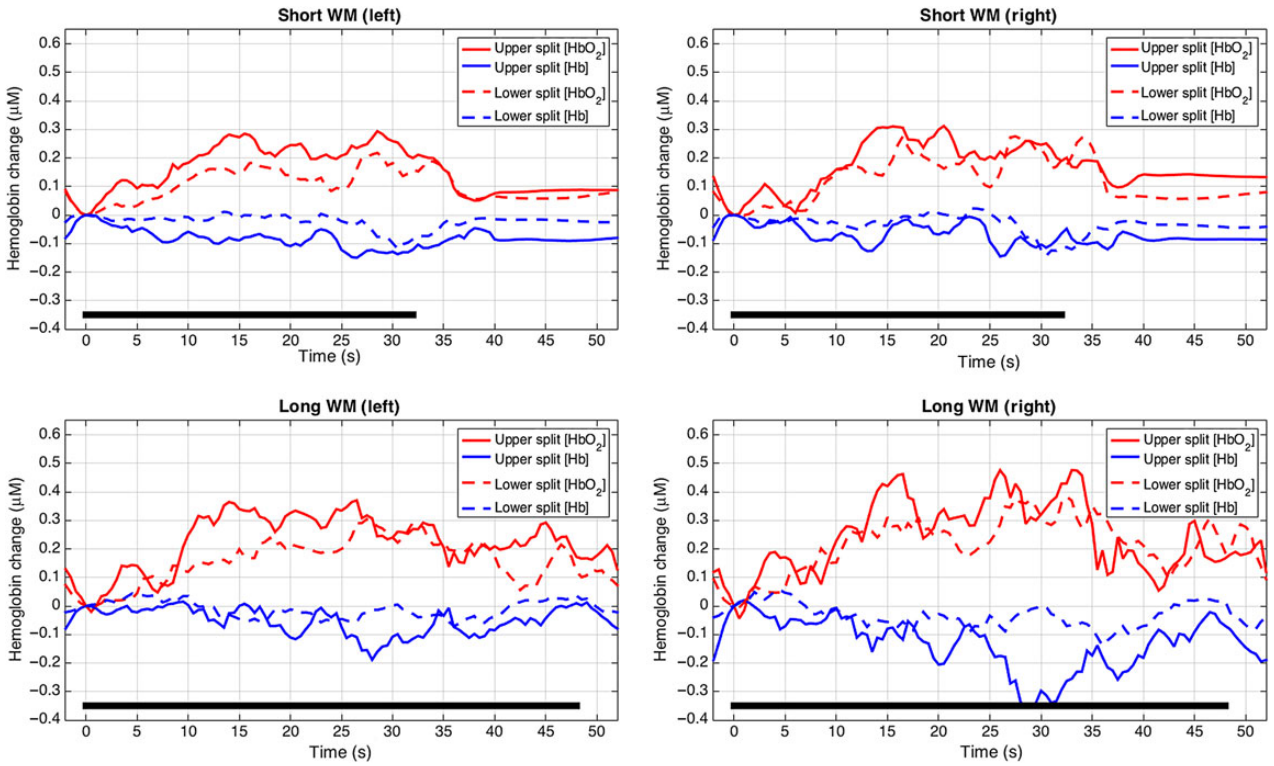

Figure 5. The group averaged time-course of the evoked oxy- (red) and deoxyhemoglobin (blue) responses are shown for the lower and upper groupings of subjects from a median split on age. The data are shown from the average of all significant ($P < 0.05$) channels on the left and right sides of the probe.

Ullman et al. 2014) and is among the first to measure LPFC activation underlying working memory before the ages of 6–7 from a cross-sectional perspective. We found that LPFC function increased from 3 to 7 years during spatial working memory maintenance. These results imply that the neural mechanisms supporting working memory develop incrementally throughout the preschool and school age in concert with improved behavioral performance (speed and accuracy).

We hypothesized that spatial working memory abilities, along with underlying LPFC function, would increase from 3 to 7 years. Across all subjects, we found that the LPFC was significantly more active during spatial working memory compared with rest. Further, we examined age-related changes using subjects' age in months as a continuous variable rather than separating children into groups based on their age in years. This method allowed for increased variability in age-related analyses, finding that older children engaged the LPFC more during working memory than younger children. Age was also correlated with decreased reaction time and greater accuracy, during working memory, which implies behavioral efficiency accompanying neurodevelopment. Previous research at the behavioral level has suggested that the foundation of school-age spatial working memory skills are in place at the age of 4, but continue to develop between the ages of 5 and 8, which is interpreted as evidence for the emergence of LPFC function during this period (Luciana and Nelson 1998). Structural studies of

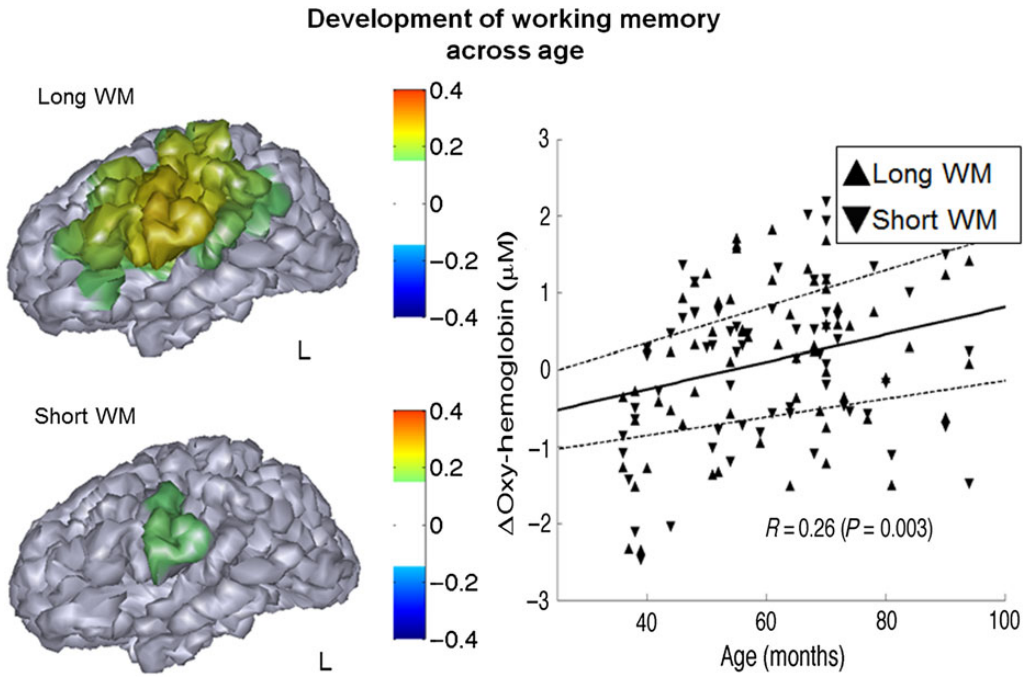

Figure 6. Map of brain regions correlated ($P < 0.05$) with age in a group-level ANOVA regression model. Scatter plots of the mean oxyhemoglobin from regions of interest and age for each subject is pictured at right. Positive correlation is observed between age and the oxyhemoglobin contrast of the long and short working memory blocks and rest in the left LPFC. The solid line shows the linear fit of the correlation (linear) model and 1 standard deviation from the fit to the short and long WM data.

brain development support this interpretation, finding increasing gray matter volume in the prefrontal cortex from age 4 through adolescence (Giedd et al. 1999). Increase in the number of prefrontal synapses continue until approximately age 7 (Huttenlocher 1979), showing further support for preschool and early school age as a significant period for executive function-related neural development.

It has been previously proposed that increased working memory abilities are related to LPFC functional development from early childhood to adolescence (Luciana and Nelson 1998; Tamnes et al. 2013; Ullman et al. 2014). Our study is now among the first to provide neurodevelopmental evidence of age-related progression in this aspect of executive function in children ages 3–7. Tsujimoto et al. (2004) did not find evidence for differences in LPFC activation during working memory when comparing 5- to 6–year olds and did not examine change across the 5- to 6-year-old age range. Buss et al. (2014) were the first to use fNIRS to examine developmental change in working memory-related LPFC activation, but did so during a narrow developmental window (3–4 years). The study found increased activation in the parietal cortex during a change detection task, with support for a similar, but slightly weaker, effect in the LPFC. The paradigms of that study and the current study differed in that Buss et al. (2014) manipulated working memory load by varying the amount of objects in the visual array, while our study manipulated working memory maintenance by containing only a single object in the visual array with variation in delay time. While both studies found a similar effect in the LPFC, manipulation of the object amount was particularly well suited for the increased parietal activation noted in the Buss study, as numerical manipulation has been previously linked to the parietal cortex in the preschool age range (Cantlon et al. 2006). We focused our interests specifically on development of the LPFC, replicating Buss et al. (2014) findings of increased LPFC activation from age 3 to 4 and extending these findings from a developmental perspective by demonstrating that these neural mechanisms improve incrementally across the full age range of 3–7 years.

Supporting our second hypothesis, we found evidence for modulation of LPFC activation as a function of working memory maintenance. That is, the LPFC was more active for blocks of delay periods that were long (6 s) than it was for delay periods that were short (2 s). This finding is consistent previous fNIRS studies investigating working memory load, a related category to maintenance. Tsujimoto et al. (2004) found that varying of working memory load led to increased LPFC activation in 5- to 6-year-old children while Buss et al. (2014) found that 4–year olds showed a more robust response to memory load manipulation relative to 3-year olds. Geier et al. (2009) investigated working memory maintenance, using fMRI, and found that children as young as 8 years recruited the LPFC to support extended delay trials. Thus, the results of our study are in line with others, but are novel in that they show that differential LPFC activation supporting working memory maintenance is present in children as young as 3 years (Luciana and Nelson 1998; Diamond 2002; Geier et al. 2009). Increased LPFC activation during the long delay period may relate to increased neural support for working memory requirements or to the need to integrate working memory with other cognitive demands associated with the task (e.g., attention, cognitive load). Indeed, the correlation with age was slightly stronger and more diffuse for the long than the short working memory condition; however, this effect was not statistically significant. Increased correlation between age and working memory during long blocks may point to the integration of working memory with other aspects of executive function throughout childhood (Diamond 1985; Luciana and Nelson 1998; Geier et al. 2009). Future studies are planned to examine connectivity between the frontal and parietal cortices as a function of development in working memory, and its integration with other aspects of executive function, motivation, and emotion, across early and middle childhood.

Our study is among the first to employ the emerging neuroimaging method of fNIRS as a technique for measuring the development of executive function in preschool and early school age children. Until recently, the challenges of lying motionless for long periods of time during fMRI made it nearly impossible to examine the development of hemodynamic brain function across this age period. Along with a child-friendly probe of working memory ability (a cartoon game) and an interactive testing format (a touch-screen computer), we were able to employ this method, which is less sensitive to motion than other neuroimaging techniques, and more spatially specific than EEG, to assess working memory in a population that is traditionally challenging to test. The results of our study stand to make a contribution to the growing body of fNIRS studies examining multiple aspects of executive function during childhood in typically (Schroeter et al. 2004; Moriguchi and Hiraki 2009) and atypically (Weber et al. 2005; Schmitz et al. 2006; Jourdan Moser et al. 2009; Schecklmann et al. 2010; Inoue et al. 2012) developing populations. Longitudinal fNIRS (Moriguchi and Hiraki 2011), combined with innovative behavioral measures, has the potential to elucidate neural correlates of executive function from birth through adolescence and adulthood and to contribute to the growing body of longitudinal neuroimaging working memory studies (Tamnes et al. 2013; Ullman et al. 2014) by reaching a younger age group. Further, we emphasize the novel and age-appropriate experimental paradigm, combined with fNIRS data collection, that can serve as a developmentally sensitive probe for researchers who may be interested in deficits in executive function in various child clinical populations (e.g., ADHD, autism spectrum disorders).

Though the results of our study are compelling, some limitations must be acknowledged. fNIRS is a region-of-interest-only technique that is only capable of measuring hemodynamic changes in the cortical surface. Thus, additional subcortical regions of the working memory neural circuit (e.g., hippocampus) were not included in our measurements, nor are we able to investigate connectivity between these regions and the LPFC. Additionally, due to the young age of our subjects, we were not able to include conditions or working memory load in addition to maintenance or increase working memory manipulation across the task. Our findings are among the first to suggest that the LPFC develops functionally across the 3- to 7-year age range to enable processing of working memory. These findings stand to make an important contribution to the understanding of functional development of the PFC.

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