Cerebral Cortex, 2017; 1–14

doi: 10.1093/cercor/bhx200
Original Article

ORIGINAL ARTICLE

Prefrontal Cortex Contributions to the Development of Memory Formation

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Abstract

The development of the brain, particularly the protracted maturation of the prefrontal cortex (PFC), supports the development of episodic memory. Yet how different regions of the PFC functionally mature to support age-related increases in memory performance remains unclear. We investigated the PFC contribution to subsequent memory (SM) of encoded visual scenes in children, adolescents, and young adults ($n = 83$). We identified distinct patterns of PFC activations supporting SM: regions in the lateral PFC showed positive SM effects, whereas regions in the superior and medial PFC showed negative SM effects. Both positive and negative SM effects increased with age. The magnitude of negative SM effects in the superior PFC partially mediated the age-related increase in memory. Functional connectivity between lateral PFC and regions in the medial temporal lobe (MTL) increased with age during successful memory formation. In contrast, functional connectivity between the superior PFC and regions in the MTL decreased with age, suggesting an age-related increase in the anti-correlation between these regions. These findings highlight the differential involvement of regions within the PFC supporting memory formation.

Key words: cognitive development, episodic memory, functional MRI, memory encoding, task-based functional connectivity

Introduction

The ability to form rich memories from past experiences is essential for everyday living and continues to develop throughout childhood and into adulthood (Bauer 2008; Ghetti and Angelini 2008; Ofen 2012; Ofen et al. 2016). Neuropsychological and functional neuroimaging evidence underscores the importance of the prefrontal cortex (PFC), particularly in supporting processes that result in rich mnemonic representations (Shimamura et al. 1995; Wheeler et al. 1997; Alexander et al. 2003; Blumenfeld and Ranganath 2007; Kim 2011). Neuroanatomical and structural imaging studies consistently show that the PFC undergoes protracted development (Rosenberg and Lewis 1995; Huttenlocher and Dabholkar 1997; Giedd et al. 1999; Benes 2001; Gogtay et al. 2004; Sowell 2004), and studies using functional neuroimaging techniques show an increase in PFC activation that supports the formation (Ofen et al. 2007; Ghetti et al. 2010) and retrieval (Ofen et al. 2012) of episodic memories. Although converging evidence underscores the critical role of the PFC in the development of episodic memory (Ofen 2012), the specific contributions of regions within the PFC to memory development are not fully understood. In this study, we used a subsequent memory (SM) paradigm to investigate the contributions of PFC to memory formation.

The SM paradigm has been widely used to investigate brain regions that support memory. Memory-related activation is determined by the significant difference in the blood oxygen level-dependent (BOLD) response between trials when the participant studied items they later remembered compared to those they later forgot (Dolan and Fletcher 1997; Fletcher et al.

1998; Paller and Wagner 2002; Kim et al. 2010; Kim 2011). Typically, such comparisons identify positive SM effects —"increased activation" when studying items that are later remembered compared to those that are later forgotten. Indeed, prior investigation of age-related differences in SM effects primarily focused on positive SM effects. However, a growing body of evidence suggests that positive SM effects constitute only part of the PFC contributions to memory, and the reverse effect, referred to as negative SM effects should also be carefully considered when evaluating the neural correlates of memory (Otten and Rugg 2001; Daselaar et al. 2004; Kim et al. 2010; Huijbers et al. 2013; de Chastelaine and Rugg 2014; Mattson et al. 2014). Negative SM effects can be the result of "increased deactivation" for remembered relative to forgotten items, and are commonly found in regions that are part of the default mode network (DMN), including the medial PFC (Buckner et al. 2008). Although increased negative SM effects are generally related to improved memory performance (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011, 2015; Mormino et al. 2012; Park et al. 2013; de Chastelaine and Rugg 2014), due to the fact that higher relative activation is associated with subsequent misses, the negative SM effects have also been referred to as unsuccessful memory (Huijbers et al. 2013), encoding failure (Kim et al. 2010), or subsequent forgetting (Otten and Rugg 2001; Kim 2011).

Negative SM effects within the PFC have been shown in studies across the adult lifespan, with some studies linking age differences in negative SM effects to memory performance (de Chastelaine et al. 2011; Park et al. 2013; de Chastelaine and Rugg 2014). Although these effects have been investigated in aging, little is known about possible age differences in negative SM effects across development from childhood through adulthood. Chai et al. (2014) evaluated age differences in SM effects in 4 DMN regions including one region within the PFC, the medial PFC. Negative SM effects were found in all DMN regions in young adults, but not in children, suggesting that negative SM effects support age-related enhancements in memory during development. While Chai et al. (2014) provided initial evidence linking negative SM effects to memory development, their investigation was limited, as it restricted the evaluation of these effects to one region in the PFC, rather than directly testing the relationship between age and memory-related deactivation in the full extent of the PFC. Thus, our first goal of this study was to evaluate whether, in addition to previously documented age-related increase in positive SM effects in the PFC, there is an age-related increase in negative SM effects.

Our second goal in this study was to more directly assess how age differences of SM effects in the PFC relate to age improvement in memory. Specifically, we were interested in evaluating whether age differences in SM effects mediate age improvement in memory. Although previous studies have identified regions within the PFC in which SM effects differed by age, they did not directly test how age differences in SM effects contribute to age differences in memory (Chiu et al. 2006; Ofen et al. 2007; Chai et al. 2010; Ghetti et al. 2010) thus not directly assessing whether PFC contributions to memory reflect age-dependent or age-independent individual differences. We tested whether age differences in SM effects explain a unique portion of age improvement in memory. Such a finding would provide direct evidence for the contribution of the PFC to memory development. We tested this possibility for both positive SM effects, which prior evidence linked to individual differences in memory performance (Chiu et al. 2006; Ofen et al. 2007) and negative SM effects, for which there is little evidence about how individual differences in activation relates to individual differences in memory or to age differences in memory. By testing whether age differences in positive or negative SM effects explain unique portion of age improvement in memory we aim to provide a more direct evidence for the PFC contribution to memory development.

Our third goal in this study was to assess age differences in the patterns of SM PFC functional connectivity. Extant research shows age differences in functional connectivity with the PFC across development and highlights the potential importance of such findings for the development of memory (Chai et al. 2014). Menon and colleagues (2005) first demonstrated the importance of functional connectivity in memory by showing increased coupling between the PFC and the medial temporal lobe (MTL) during memory encoding. While insightful, several limitations of this earlier report make it difficult to directly assess the contribution of PFC functional connectivity to memory development. Here, we evaluated age differences in memory-related functional connectivity of PFC regions showing either positive or negative SM effects. Prior evidence suggests an age-related increase in memory-related functional connectivity between PFC regions showing positive SM effects and MTL regions (Menon et al. 2005; Ofen et al. 2012). Little is known about the functional connectivity with PFC regions showing negative SM effects, or the possible age differences in these functional connectivity patterns and their potential relevance to memory development.

Taken together, in the present study, we characterized the PFC contribution to memory development using a SM paradigm, with fMRI data collected from 83 children, adolescents, and young adults. We assessed SM effects within the PFC and predicted age differences in both positive and negative SM effects. We tested whether age-related increases in SM effects explains a unique variance of the age improvement in memory. Finally, we assessed functional connectivity patterns with PFC regions showing age differences in positive or negative SM effects. By systematically exploring PFC contributions, we provide a more complete picture of the PFC supporting the development of memory.

Materials and Methods

Participants

Eighty-three participants ranging in age between 8 and 25 years (15.93 ± 5.08, mean ± SD, 42 females) were recruited from the community in Metro Detroit area. All participants were right-handed, had normal or corrected-to-normal vision and no history of psychiatric or neurological disorders. Participants provided informed consent as per a Wayne State University IRB-approved protocol. Data from 8 participants were excluded for the following reasons: incomplete data ($n = 3$), excessive movement ($n = 2$), task non-compliance (Miss Rate > 93%, $n = 2$), or IQ < 80 ($n = 1$). All participants were tested on IQ using the Kaufman Brief Intelligence Test—Version 2 (Kaufman and Kaufman 2004) and the relationship between IQ and age was examined. Supporting the validity of a cross-sectional comparison in this sample, individual differences in IQ (109.70 ± 11.93) were not correlated with age, $r81 = -0.05$, $P = 0.67$.

Stimuli

A total of 240 stimuli were used across participants, based on stimuli sets used in prior studies (Ofen et al. 2007; Chai et al. 2010; Chai, Ofen, Gabrieli, and Whitfield-Gabrieli 2014). For the

purpose of counterbalancing, the stimuli set was divided into 6 lists, each composed of 40 scenes (20 indoor and 20 outdoor). Each participant was tested with a subset of the stimuli, using 3 lists during study and 2 additional lists during recognition (foils). The assignment of lists for study or recognition was counterbalanced across participants, with each participant allocated 1 of 6 pseudorandom list orders. Specific stimuli were equally likely to be included for study or recognition across participants.

Memory Paradigm

Participants studied 120 indoor and outdoor scenes while fMRI data were recorded. Scenes were presented in 3 consecutive runs with 40 presented in each run. Each scene was shown for 3 s followed by a 0.5 s fixation cross. Variable intertrial intervals (2–8 s) were used to increase fMRI measurement reliability (jitter sequence determined using optseq2, http://surfer.nmr.mgh.harvard.edu/optseq/). Participants were instructed to make an indoor/outdoor judgment for each scene using a 2-button response box placed in their right hand and to try their best to memorize the scenes for a subsequent recognition memory test. Accuracy of encoding judgment (correct response to whether it depicted an indoor or outdoor scene) and reaction time were recorded. Analyses of SM effects were restricted to the scenes that were properly attended during encoding, as indicated by an accurate encoding response. For 3 participants (one 8-year-old and 2 adults), button presses were not registered during memory encoding due to technical difficulties. An assessment of the remaining participants showed an overall very high accuracy in making indoor/outdoor judgments during memory encoding (0.95 ± 0.05). Therefore, although we did not have encoding responses for these 3 participants, we retained the imaging data by including all encoding trials in subsequent analyses.

Approximately 15 min after the completion of the imaging session, participants completed a self-paced recognition test outside the scanner. The recognition test included the 120 scenes studied during the scanning session, intermixed in a randomized order with 80 new scenes. Participants were instructed to respond "Old" if they thought they had seen the picture during memory encoding and "New" if they had not seen the picture. Because the level of confidence in old–new recognition judgments is an important factor for the observed age differences in memory (Ofen 2012) and their neural correlates (Gutchess et al. 2005; Ofen et al. 2007), we also included a confidence judgment after the old–new judgment. If an "Old" response was made, participants were then asked to indicate their confidence-level by answering "Sure" if they remember the scene (i.e., they remember anything specific about the scene, such as how it looked on the screen, what they were thinking of when the saw it, or any other details indicating vivid memory of when they studied the scene) or "Not Sure" if the scene just looks familiar (i.e., they think they have seen it, but they could not remember any specific detail from when they studied the scene). Participants were also asked to indicate whether they were "Sure" or "Not Sure" about their judgment of a scene as "New", based on how confident they were of their choice.

Encoding trials were labeled as Hit or Miss based on whether the scene presented in the trial was later correctly recognized as "Old" (Hit) or incorrectly judged as "New" (Miss). Hit trials were further classified as Hit Sure (Hit_S) or Hit Not Sure (Hit_NS) based on the "Sure"/"Not Sure" rating given during the recognition test. Foil scenes that were incorrectly identified as "Old" were labeled False Alarm (FA), and FA trials were further separated based on the "Sure"/"Not Sure" rating (FA Sure, FA_S; FA Not Sure, FA_NS). Trials that were labeled as Miss were not further separated by the confidence rating ("Sure" or "Not Sure"), because in both cases the response was incorrect—a Miss trial represents an absence of memory formation, regardless of the subjective rating of that incorrect response. Moreover, not separating Miss trials by the confidence rating allowed comparisons between overall similar numbers of trials across conditions of interest, diminishing the potential influence of imbalanced trial numbers on our measurement.

Behavioral Analysis

Recognition accuracy for responses classified as Sure was calculated by adjusting Sure Hit rates with Sure FA rates (Hit_S rate – FA_S rate). Similarly, recognition accuracy for responses classified as Not Sure was calculated by adjusting Not Sure Hit rates with Not Sure FA rates (Hit_NS rate – FA_NS rate). In all imaging analyses, we use the term memory performance when referring to the recognition accuracy for responses classified as Sure, as these responses were more likely to reflect real memory and less likely to reflect guessing. The relationship between age and recognition accuracy was assessed using a Pearson correlation. We also assessed participants' response times (RTs) during the encoding task based on SM performance. Differences in mean RTs were assessed using a repeated measures analyses of variance (ANOVA) with 3 levels (Hit_S, Hit_NS, and Miss), with age added as a covariate. Age differences in encoding RTs across conditions were assessed using Pearson correlations.

MRI Data Acquisition

MRI data were acquired in a 3 T Siemens Verio scanner at Harper University Hospital in Detroit, MI. T1-weighted whole-brain anatomy images were acquired using an MPRAGE sequence [192 sagittal slices, repetition time (TR) = 2200 ms, echo time (TE) = 4.26 ms, flip angle = 9°, field of view = 256 mm, 192 × 256 voxels, and voxel size = 1 mm × 0.5 mm × 1 mm]. Functional images were acquired using a T2*-weighted gradient-echo sequence (30 slices parallel to the AC–PC plane, TR = 2000 ms, TE = 30 ms, flip angle = 90°, voxel size = 3.1 mm × 3.1 mm × 4 mm). The memory encoding task was completed in 3 consecutive functional runs, each consisted of 118 volumes and lasted for 4 minutes and 2 seconds.

Imaging Analysis

Preprocessing

Functional imaging data were analyzed with the SPM8 package (Wellcome Department of Imaging Neuroscience). Images were motion-corrected, normalized to the Montreal Neurological Institute (MNI) template, and smoothed with an 8 mm full-width half-maximum Gaussian kernel. Additionally, we applied stringent criteria to screen the functional images with the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect/) and to identify outlier volumes. Specifically, an outlier volume was identified if (1) the global mean intensity of the volume was more than 3 SD from the mean volume intensity of the run, or (2) volume-to-volume difference of a composite motion parameter exceeded 1 mm. The "Co-Planar Stereotaxic Atlas of the Human Brain" (Talairach and Tournoux

1988) and MRIcron (Version 6 June 2013, http://www.nitrc.org/projects/mricron) were used in conjunction to identify the anatomical locations and corresponding Brodmann areas for the peak co-ordinates that are reported for the analyses presented below. Activation maps selected for figures were overlaid on a high resolution brain image displayed in 3-dimensional view using CARET 5.65 (http://www.nitrc.org/projects/caret) or in 2-dimensional view using MRIcron.

Individual and Group-Level SM Effects

Individual-level general linear models (GLMs) included 3 task-related regressors (Hit_S, Hit_NS, and Miss) for each run. One error regressor and 7 motion regressors (3 translational and rotational motion parameters, a composite motion parameter) were also included per run. To protect against potential differences that may be confounded with different numbers of trials across participants, we only included those for which we had at least 10 trials for the Hit_S (range: 13–93 out of 120) and for the Miss (range: 15–99 out of 120) conditions. Only one adolescent was excluded for having less than 10 trials.

Each encoding event was modeled as an impulse function and convolved with a canonical model of the hemodynamic response function. Temporal derivatives were included in the GLM to account for any temporal shifts in response to the stimuli (Friston et al. 1998). As commonly observed in developmental studies, the proportion of motion outliers out of total number of images decreased with age ($M = 9\%$, $SD = 11\%$), $r81 = -0.58$, $P < 0.001$. To minimize the influence of motion artifacts, we added one regressor per outlier volume into the GLM model (as identified by ART) (Chai et al. 2014). Individual-level analyses were limited with a brain mask created by summing the normalized cerebral spinal fluid, white, and gray matter images that were generated from segmenting individual T1-weighted image using SPM8.

To identify whether functional development of the PFC supports memory formation, we first computed individual-level contrasts for positive (Hit_S > Miss) and negative (Miss > Hit_S) SM effects and entered these contrasts into a group-level GLM model (one-sample *t*-test) with both age and recognition accuracy included as continuous linear covariates. We then restricted these *t*-maps to the PFC using an anatomical mask that included superior, middle, inferior, medial PFC, and precentral gyrus, as defined in the AAL atlas (Tzourio-Mazoyer et al. 2002). Positive and negative SM effects are reported at a voxel-level threshold of $P < 0.005$, cluster-level corrected at $P < 0.05$ as per a Monte Carlo simulation implemented in 3dClustSim ($k = 482$; http://afni.nimh.nih.gov/afni). The Monte Carlo simulation was restricted to the PFC mask and was performed using smoothing estimates of the group-level residuals obtained from 3dFWHMx (http://afni.nimh.nih.gov/afni). The updated version of 3dClustSim and the 3dFWHMx tool with the autocorrelation function (-acf option) was implemented using the group-level residual maps to circumvent the issues reported by Eklund *et al.* (2016) (Cox et al. 2016). We further examined the nature of these positive and negative SM effects as a function of trial type by extracting average parameter estimates separately for Hit_S and Miss trials from the significant clusters and comparing the extracted estimates to the implicit baseline with one-sample *t*-tests.

To identify PFC regions that showed SM effects and age- or performance-related effects, we first computed correlation *t*-maps. These assessed the relationship between SM effects and age, and between SM effects and performance, using GLM models where both age and performance were included as covariates. Conjunction analyses were then performed using group-level SM and correlation *t*-maps. For example, the positive SM *t* map was inclusively masked by corresponding correlation *t* map to determine areas of overlap between positive SM and age effects [(Hit_S – Miss) ∩ ((Hit_S – Miss) ∝ age)]. A threshold of $P < 0.005$ was used for the SM *t*-maps and a threshold of $P < 0.05$ was used for correlation *t*-maps. The joint probability of the resulting double conjunction map was $P < 0.00025$ (0.005×0.05). We then performed a triple conjunction to determine if there were any PFC regions showing memory, age- and performance-related effects, [e.g., (Hit_S – Miss) ∩ ((Hit_S – Miss) ∝ age) ∩ ((Hit_S – Miss) ∝ memory performance)]. Conjunction maps were cluster-level corrected at $P < 0.05$ using a Monte Carlo simulation implemented in 3dClustSim ($k = 43$ for double conjunction maps and $k = 10$ for triple conjunction maps). The 3dClustSim C(p, alpha) value for the triple conjunction map restricted to the PFC mask fell below 1. As a result, cluster threshold of the triple conjunction map was set to $k = 10$. The Monte Carlo simulation was restricted to the PFC mask and performed using smoothing estimates of the group-level residuals obtained from 3dFWHMx. While the focus of our current investigation is within the PFC, we additionally examined SM effects across the whole brain in order to present a complete picture. The maps for positive and negative SM effects were cluster-level corrected at $P < 0.05$ as per a Monte Carlo simulation implemented in 3dClustSim ($P < 0.005$, $k = 1186$). In addition, the age- and performance-related SM effects were conducted using conjunction analyses as described before, cluster-level corrected at $P < 0.05$ (conjunctive $P < 0.00025$, $k = 183$).

Mediation Analysis

To further examine the relationship between age, brain, and memory performance, we conducted a mediation analysis. This allowed us to determine if age-related differences in performance can be explained by memory-related BOLD responses. In creating the mediation model, we considered age as the driving factor of neural development (X), memory performance as the outcome of the development (Y), and the brain activity as the mediating variable (M). The strength of the mediation was measured by an indirect effect between X and Y through M, where possible values for the indirect effect were estimated by a bootstrapping procedure [Preacher and Hayes 2008; 5000 resamples to generate 95% a bias-corrected confidence interval (CI)]. To increase the validity of our mediation analysis, joint significance testing was implemented in determining if the indirect effect was significant. First, the CI was examined for the exclusion of zero, which indicates that the total effect from X to Y has been significantly reduced by M (Preacher and Hayes 2008). Second, a Sobel test was performed. The Sobel test compares the indirect effect to the null hypothesis that no indirect effect exists (the path coefficient of X to Y through M is zero).

Functional Connectivity Analysis

We further characterized PFC contributions to the development of memory by evaluating age-related differences in the whole-brain functional connectivity with the PFC regions whose positive and negative SM effects differed by age. Age-related differences in PFC functional connectivity during memory formation were evaluated using seed-based psychophysiological interaction (PPI) analyses. Seed regions for PPI analyses were defined as 6-mm radius spheres created around the peak co-ordinates from each of these regions. We report results for PPI analyses including seed regions derived from all the clusters showing age differences in SM effects.

Individual-level PPI analyses similarly included motion parameters and additional regressors for the outlier time points that were identified, as previously described. Group-level *t*-tests were performed with age entered as a covariate. Correlation *t*-maps were computed to assess the positive relationship between task-based connectivity (Hit_S > Miss) and age. Conjunction maps were created to identify regions where memory-related functional connectivity with the seed region of interest also showed age-related differences. Final conjunction maps were cluster-level corrected at $P < 0.05$ using Monte Carol simulations implemented in 3dClustSim (k ranged from 164 to 175, depending on the residuals in the group-level model being investigated).

Results

Behavior

Of the studied scenes, a total of 0.57 ± 0.14 were correctly identified as "Old" (Hit), with 0.44 ± 0.15 classified as "Sure" (Hit_S), and 0.13 ± 0.08 classified as "Not Sure" (Hit_NS). The Hit_S rate showed an increase with age ($r81 = 0.46$, $P < 0.001$), while the Hit_NS rate showed an decrease with age ($r81 = -0.23$, $P = 0.04$). In contrast, a total of 0.43 ± 0.14 were incorrectly identified as "New" (Miss), and the Miss rate showed a decrease with age ($r81 = -0.34$, $P = 0.001$). Of the scenes used as foils during recognition, 0.26 ± 0.13 were incorrectly identified as "Old" (false alarm, FA), with 0.14 ± 0.11 classified as "Sure" (FA_S), and 0.12 ± 0.8 classified as "Not Sure" (FA_NS). Neither the FA_S rate ($P = 0.20$) nor the FA_NS rate ($P = 0.08$) showed significant correlations with age.

Recognition accuracy (Hit rate – FA rate) for responses classified as "Sure" (0.31 ± 0.16) was higher than responses classified as "Not Sure" (0.01 ± 0.06), $t82 = 15.67$, $P < 0.001$. Moreover, recognition accuracy increased with age for responses classified as "Sure" ($r81 = 0.54$, $P < 0.001$), but not for those classified as "Not Sure" ($P = 0.64$; Fig. 1). To assess whether confidence judgment differed by age, we examined participants' "Sure" and "Not Sure" classification using the FA responses which are not confounded by prior exposure. The likelihood of making a "Sure" response did not correlate with age (0.52 ± 0.26), $P = 0.81$, suggesting that participants used similar criteria when making confidence judgments.

During the study phase, RTs did not differ between Hit_S (1.08 s ± 0.29 s), Hit_NS (1.06 s ± 0.31 s), and Miss (1.07 s ± 0.28 s) conditions, $F_{2,156} = 0.39$, $P = 0.63$. RTs for all trial types negatively correlated with age (Hit_S: $r79 = -0.24$, $P = 0.03$; Hit_NS: $r78 = -0.27$, $P = 0.01$; Miss: $r79 = -0.31$, $P = 0.004$). However, there was not an age by trial type interaction for RTs ($F_{2,156} = 0.88$, $P = 0.40$).

Imaging

Positive and Negative SM Effects within the PFC

Positive SM effects were observed in large bilateral clusters including regions in the precentral gyrus, inferior frontal gyrus (IFG), and middle frontal gyrus (MFG) (Table 1; Fig. 2). Negative SM effects were observed in a large cluster including regions in the bilateral superior frontal gyrus (SFG, peak at right SFG), MFG, and medial frontal gyrus (Table 1; Fig. 2). We separately extracted parameter estimates for Hit_S and Miss trials in each cluster and compared the parameter estimates for Hit_S trials to the baseline. Bilateral IFG showed significant activation for Hit_S trials compared to the baseline (all Ps < 0.001; right IFG shown in Fig. 2A). Bilateral MFG/SFG showed significant deactivation compared to the baseline for Hit_S trials and Miss trials (all Ps < 0.01; right SFG shown in Fig. 2B).

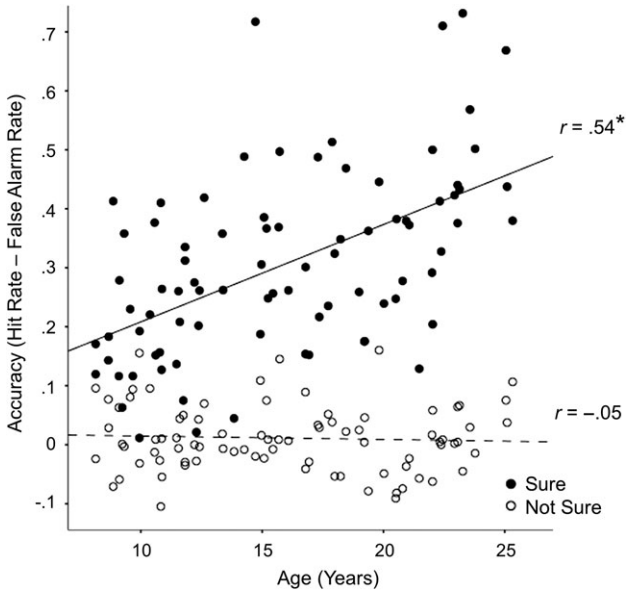

Figure 1. Recognition accuracy by confidence and age. Recognition accuracy (Hit rate – False Alarm rate) for high-confidence (Hits with "Sure" responses) scenes increased with age, $r81 = 0.54$, $P < 0.001$ (denoted with *), but recognition accuracy for low-confidence (Hits with "Not Sure" responses) scenes did not, $r81 = -0.05$, $P = 0.64$.

Table 1. Positive and negative SM effects in the PFC

Hemi.	Regions	BA	MNI co-ordinates			t-values	Number of voxels
			x	y	z		
Positive SM effects							
R	IFG	44/6	40	8	28	7.71	1701
		45/44	44	32	12	5.80	
L	IFG	44/6	−44	6	26	6.76	2819
		45/44	−44	28	16	6.41	
		47	−34	32	−16	4.67	
	Precentral gyrus	6/4	−48	−4	58	4.51	
Negative SM effects							
R	MFG/SFG	10/9	24	54	22	7.95	7196
		9	24	44	40	6.43	
L	Medial frontal gyrus	10	4	48	6	5.95	
	SFG	10	−28	50	−2	4.89	
		9	−24	54	24	3.17	
	MFG	9	−40	40	28	4.63	

PFC regions showing positive (Hit Sure > Miss trials) and negative (Miss > Hit Sure trials) SM effects. The significance threshold is $P < 0.05$, corrected. Hemi., hemisphere; BA, Brodmann Area; R, right; L, left.

Positive and Negative SM Effects within the PFC Increased with Age

PFC regions that were associated with positive or negative SM effects and differences in age were identified by conjunction analyses performed on SM and correlation *t*-maps. Age-related positive SM effects were identified in bilateral IFG (BA 45/44) and right precentral gyrus (BA 6) (Table 2). In the right IFG, age-related increases were driven by increased activation for Hit_S trials ($r81 = 0.46$, $P < 0.001$), but not by Miss trials ($P = 0.11$;

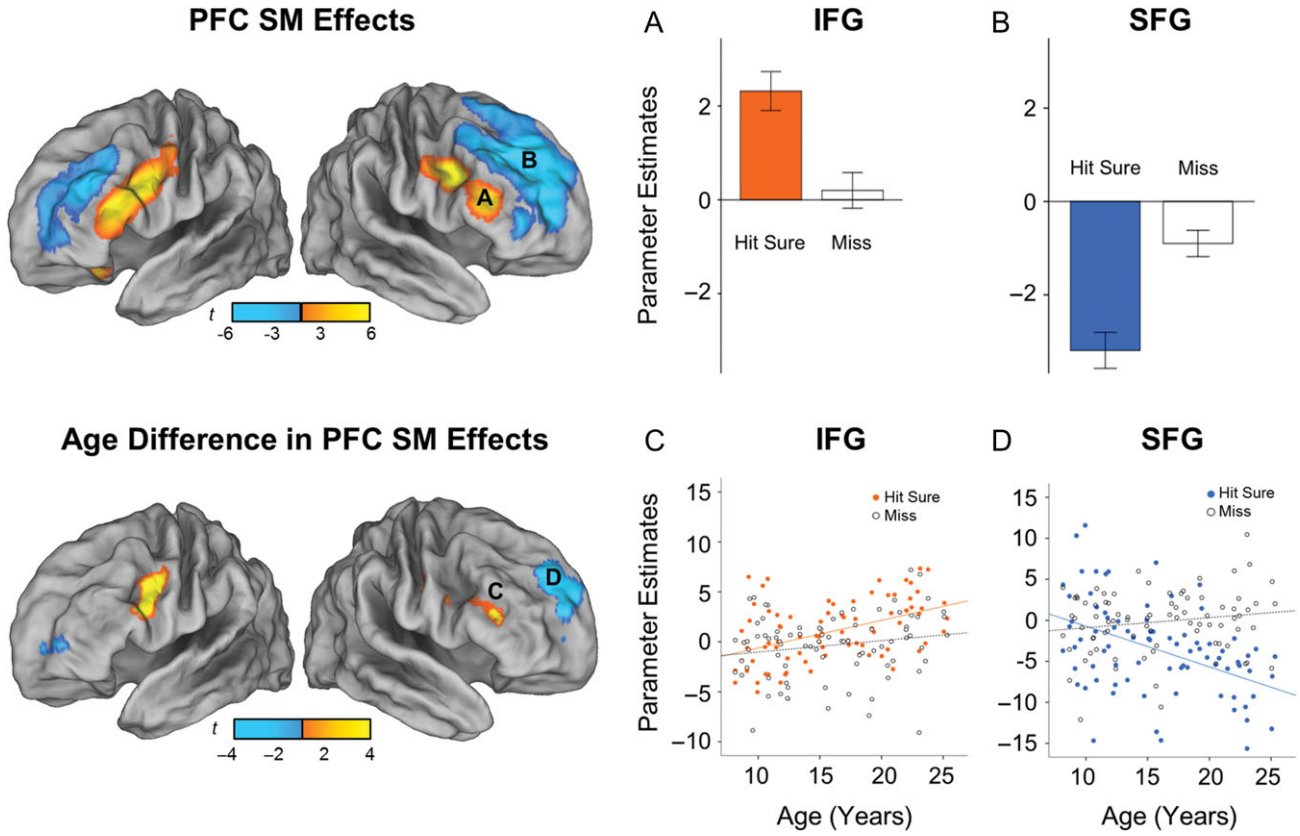

Figure 2. PFC regions showing positive and negative SM effects and age-related differences in these SM effects. (*A*) Positive SM effects (shown in red) were observed in bilateral IFG. (*B*) Negative SM effects (shown in blue) were observed in bilateral SFG. (*C*) Positive SM effects in bilateral IFG increased with age (shown in red). (*D*) Negative SM effects in bilateral SFG and medial PFC increased with age (shown in blue). The significance threshold for the *t*-maps shown on the left is $P < 0.05$, corrected.

Table 2. PFC regions showing overlapping SM and age-related effects

Hemi.	Regions	BA	MNI co-ordinates			*t*-values		Number of voxels
			x	y	z	Main effect	Correlation with age	
Age-related positive SM effects								
R	IFG*	44/6	44	6	26	6.32	1.74	128
	Precentral gyrus	6	50	−4	34	3.26	2.02	
R	IFG*	45/44	44	32	12	5.80	2.02	166
L	IFG*	44/6	−44	6	26	6.76	2.29	397
Age-related negative SM effects								
R	SFG*	10/9	22	54	24	7.55	1.68	610
		8/9	22	46	38	6.27	1.78	
R/L	Medial frontal gyrus*	10	4	48	6	5.95	1.72	176
L	SFG*	10	−22	54	−2	3.62	1.70	
	MFG	10	−34	52	4	3.20	1.67	

PFC regions involved in memory development. "Age-related positive SM effects" = (Hit Sure – Miss) inclusively masked by (Hit Sure – Miss) ∝ Age. "Age-related negative SM effects" = (Miss – Hit Sure) inclusively masked by (Miss – Hit Sure) ∝ Age. The significance threshold is $P < 0.05$, corrected. *Denotes the co-ordinates used as seeds for functional connectivity analyses. Hemi., hemisphere; BA, Brodmann Area; R, right; L, left.

Fig. 2*C*). In the left IFG, activation for Hit_S ($r81 = 0.56$, $P < 0.001$) and Miss ($r81 = 0.44$, $P < 0.001$) trials both significantly correlated with age. To verify that the correlations with age were significantly different between Hit_S and Miss trials, a repeated measures ANOVA with trial type (Hit_S and Miss) as an independent variable and age as a covariate was performed on the average parameter estimates from both left and right IFG clusters. The correlations with age were different for Hit_S versus Miss trials in both the right and left IFG, as indicated by significant trial type by age interactions, (right: $F_{1,81} = 6.31$, $P = 0.01$; left, $F_{1,81} = 8.20$, $P = 0.005$).

Age-related differences in negative SM effects were identified bilaterally in SFG (right BA 10/9/8; left BA 10), medial frontal gyrus (BA 10), and left MFG (BA 10). To determine whether age-related increase in negative SM effects were driven by age differences in response to hits or misses, we extracted the average

parameter estimates in each functional cluster separately for Hit_S and Miss trials and correlated them with age. There was an age-related increase in the magnitude of deactivation for Hit_S trials in the right SFG ($r81 = -0.44$, $P < 0.001$) and medial frontal gyrus ($r81 = -0.31$, $P = 0.005$), but there was no age differences in the deactivation for Miss trials (Ps > 0.14; Fig. 2D).

Given our approach to separately conduct conjunction analyses for positive and negative SM effects to investigate the age effects in the PFC, it is possible that regions showing opposite directions in SM effects were not captured by our original analyses. To investigate if any additional PFC regions showed different SM patterns with age, we generated t-maps of SM effects in the PFC separately for children ($n = 31$; ages 8–12) and adults ($n = 30$; ages 18–25). At a liberal threshold ($P < 0.01$, $k = 50$), both children and adults showed positive SM effects in the IFG and negative SM effects in the MFG/SFG (see Supplementary Table S2; Supplementary Fig. S2). No region showed the opposite patterns of SM effects between the 2 age groups.

Negative SM Effects in the PFC Related to Performance

PFC regions that were associated with positive or negative SM effects and increased with memory performance were identified by conjunction analyses performed on SM and correlation t-maps. There were no positive SM effects that were uniquely associated with individual variability in memory performance. However, negative SM effects in bilateral SFG and medial frontal gyrus (BA 10/9) were related to individual differences in memory performance (see Supplementary Table S1; Supplementary Fig. S1, shown in blue), such that the magnitude of deactivation for Hit_S trials increased with enhanced memory performance [$r81 = -0.40$, $P < 0.001$, parameter estimates extracted from peak cluster (right SFG, BA 10/9)], but the magnitude of deactivation for Miss trials did not ($P = 0.16$). We then conducted a triple conjunction analysis to identify PFC regions that showed SM effects and correlated with both age and individual differences in memory performance. Only one region was identified in this triple conjunction analysis, the right SFG (BA 10/9, Fig. 3).

SM Effects across the Whole Brain

For completeness, we also report regions, across the whole brain, that showed positive and negative SM effects (*A*), regions where SM effects correlated with age (*B*) and regions where SM effects correlated with memory performance (*C*) (see Supplementary Table S3; Supplementary Fig. S3). Outside the PFC, positive SM effects were additionally identified in bilateral parahippocampal gyrus (PHG) and middle occipital lobe. Negative SM effects were additionally identified in bilateral supramarginal gyrus, inferior parietal lobule, precuneus, and anterior cingulate cortex. Age-related positive SM effects were additionally observed in bilateral superior parietal lobe, superior/middle occipital lobe, PHG, and fusiform gyrus. No age-related negative SM effects were observed outside the PFC. Performance-related positive SM effects were additionally identified in bilateral superior parietal lobe, bilateral inferior temporal gyrus, and left PHG. Performance-related negative SM effects were additionally identified in bilateral supramarginal gyrus, inferior parietal lobule, precuneus, and anterior/posterior cingulate cortex.

Negative SM Effect in the PFC Mediated Age-Related Increase in Memory

Using mediation analysis, we further examined whether negative SM effect in the region identified in the triple conjunction analysis uniquely contributed to the relationship between age and memory performance. We found that the relationship between age and memory performance was partially mediated by the negative SM effect in the SFG with a medium effect size ($\kappa^2 = 0.15$), see Figure 3. CIs for the indirect effect did not contain zero and the Sobel test determined that the indirect effect between age and memory performance through negative SM effect in the right SFG was significantly different than zero (indirect effect 95% standardized CI: [0.05, 0.27], Sobel test $P = 0.01$).

To rule out the effects of RTs in assessing the relationship between SM effects, age, and memory performance, we included RTs as covariates in the mediation analysis. We tested 2 additional mediation models: (1) with mean RTs for both Hit_S and Miss trials included as covariates or (2) with the mean RT difference between Hit_S and Miss trials included as a covariate (2 participants without any RT data were excluded). The results indicated that age-related differences in memory performance was mediated by the negative SM effect in SFG/MFG after controlling for differences in RTs (original model, CI: [0.05/0.27], $P = 0.012$; additional model (1) with mean RTs for both Hit_S and Miss trials, CI: [0.07/0.31], $P = 0.009$; additional model (2) with the mean RT difference, CI: [0.06/0.30], $P = 0.008$).

Negative SM Effect in the PFC Correlated with Variability in RTs During Successful Memory Encoding

Recent evidence suggests that the activation of specific brain regions known to be involved in inhibitory processes may be related to the variability in RT during a cognitive task (Simmonds et al. 2007; McIntosh et al. 2010; Garrett et al. 2013). For example, the pattern of activation in the SFG/MFG region was related to the

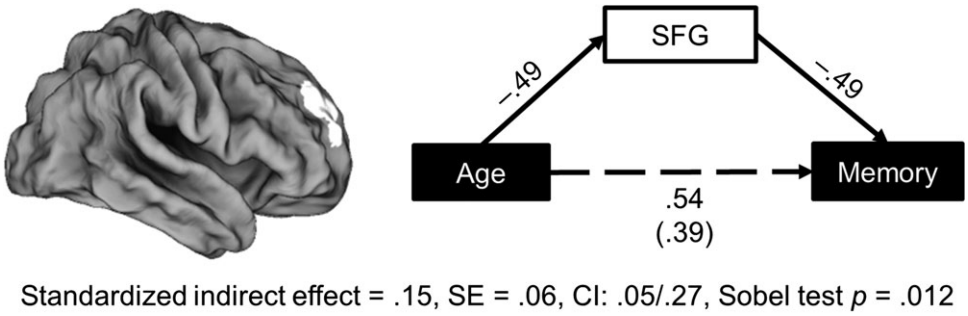

Figure 3. Negative SM effect in right SFG mediates the relationship between age and memory performance. SM effects in the right SFG (shown in white, left panel) mediated the effect of age on memory performance (right panel). Age was directly related to improved memory performance, but it was also indirectly related to performance through negative SM in the right SFG. Joint significance testing showed the indirect effect was significant as the CI did not contain zero and the Sobel test showed the indirect effect was significantly different from zero. All paths in the model are significant at $P < 0.001$ and numbers for each path are the standardized Beta weights. SE, standard error.

"intraindividual coefficient of variability" (ICV = σ_{RT}/μ_{RT}), in a Go-NoGo task with young children (Simmonds et al. 2007; Fig. 4). Specifically, individual differences in SFG/MFG activation were related only to the ICV of NoGo trials, but not to the ICV of Go trials. Given this link between brain activation and response variability, we tested if activation differences in the PFC regions correlated with individual response variability during memory formation. We calculated the ICV per each trial type per participant, and assessed the correlation between both positive and negative SM effects and the ICV. Interestingly, we found that negative SM effect in SFG/MFG correlated with the ICV of subsequent Hit_S trials ($r79 = 0.27$, $P = 0.01$), such that more effective deactivation in SFG/MFG during memory formation was related to more consistency (i.e., less variability) in reaction times. No such

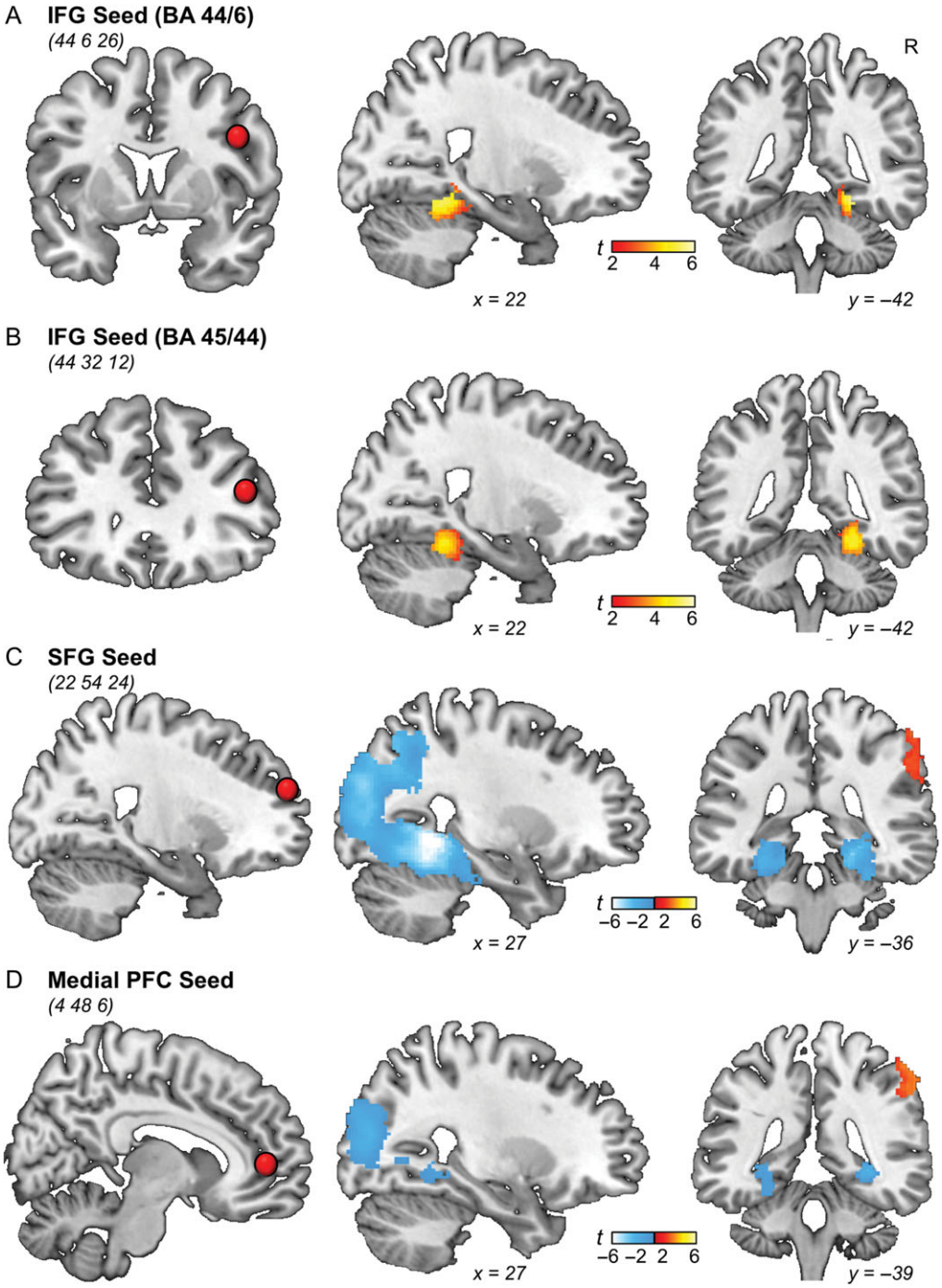

Figure 4. PFC regions showing age-related differences in the functional connectivity linked to memory formation. (*A* and *B*). Age-related increase in the functional connectivity between IFG and PHG (shown in red). (*C*) Age-related increase in functional connectivity between SFG and IPL (shown in red), as well as age-related increase in anti-correlated functional connectivity between SFG and PHG (shown in blue). (*D*) Age-related increase in functional connectivity between medial PFC seed and IPL (shown in red), as well as age-related increase in anti-correlated functional connectivity between medial PFC and PHG (shown in blue). The significance threshold for the *t*-maps shown is $P < 0.05$, corrected.

relation was found between negative SM effect and the ICV of subsequent Miss trials ($P = 0.61$); nor were relations found between positive SM effects and the ICV of either subsequent Hit_S trials or subsequent Miss trials, $Ps > 0.10$.

Functional Connectivity with PFC During Successful Memory Formation Increased with Age

To investigate the development of PFC networks important for memory formation, we performed conjunction analyses using seed-based functional connectivity and correlation *t*-maps (see Table 2 for the seed regions). No regions survived the significance threshold for the left hemisphere seeds (left IFG, BA 44/6; left SFG, BA 10). A PPI analysis with a positive SM seed in the right IFG (BA 44/6) identified an age-related increase in the functional connectivity with right PHG (BA 37/36) and right lingual gyrus (BA 19) (Table 3; Fig. 4A). A PPI analysis with another positive SM seed in the right IFG (BA 45/44; MNI Co-ordinates: 44 32 12) identified an age-related increase in the functional connectivity with right PHG (BA 37/36) and left superior/middle occipital gyrus (BA 19/18) (Table 3; Fig. 4B). In contrast, a PPI analysis with a negative SM seed in the right SFG (BA 10/9; MNI Co-ordinates: 22 54 24) identified an age-related increase in the functional connectivity with the right inferior parietal lobule (IPL, BA 40) and supramarginal gyrus (SMG, BA 40), and the opposite pattern of connectivity (an age-related increase in anti-correlated functional connectivity) with bilateral PHG (BA 37/36) and middle occipital gyrus (BA 19) (Table 3; Fig. 4C). A PPI analysis with another negative SM seed in the medial frontal gyrus (BA 10; MNI Co-ordinates: 4 48 6) identified an age-related increase in the functional connectivity with right IPL (BA 40), and the opposite pattern of functional connectivity with bilateral PHG (BA 37) and middle occipital gyrus (BA 19/18) (Table 3; Fig. 4D).

To assess whether differences in memory performance influenced age-related differences in functional connectivity, we conducted additional PPI analyses including only a subset of participants that were selected, such that performance in this subset was comparable across age (correlation between age and memory performance: $P = 0.54$; age and number of Hit_S trials: $P = 0.55$; age and number of Miss trials: $P = 0.67$; $n = 59$). Consistent with our primary PPI analyses, we found that for the seed located in the IFG (BA 44/6), there was an age-related increase in the functional connectivity to the PHG and middle occipital lobe ($P < 0.00025$, $k = 10$; see Supplementary Table S4; Supplementary Fig. S4). Similarly, for the seed located in the SFG (BA 10/9), there was an age-related increase in the functional connectivity to the IPL, and an age-related increase in negative functional connectivity to the PHG and middle occipital lobe ($P < 0.00025$, $k = 10$; see Supplementry Table S4; Supplementary Fig. S4). Overall, the findings obtained from a sample, where memory outcomes were controlled showed similar connectivity patterns compared to the findings obtained with all participants.

Table 3. PFC regions showing age-related differences in the functional connectivity linked to memory formation

Seed regions	Hemi.	Regions	BA	MNI co-ordinates			*t*-values		Number of voxels
				x	y	z	Main effect	Correlation with age	
IFG (BA 44/6; MNI co-ordinates: 44 6 26)									
Age-related increases in FC									
	R	PHG	37/36	24	−44	−14	5.55	1.95	265
		Lingual/fusiform gyrus	19	18	−52	−12	4.47	1.69	
IFG (BA 45/44; MNI co-ordinates: 44 32 12)									
Age-related increases in FC									
	R	PHG	37/36	24	−44	−16	4.75	2.29	381
	L	Superior occipital gyrus	19/7	−24	−84	28	4.20	1.78	176
		Middle occipital gyrus	19	−32	−80	22	3.89	1.75	
		Cuneus	19/18	−20	−90	32	3.79	1.69	
SFG (BA 10/9; MNI co-ordinates: 22 54 24)									
Age-related increases in FC									
	R	Inferior parietal lobule	40	58	−34	56	3.33	2.03	318
		Supramarginal gyrus	40	58	−44	38	3.27	1.75	
Age-related increases in anti-correlated FC									
	R	PHG	37/36	28	−48	−6	6.60	3.84	16 317
		Middle occipital gyrus	19	36	−78	16	5.88	4.70	
	L	Middle occipital gyrus	19	−40	−78	2	5.93	2.95	
		PHG	37	−26	−50	−6	5.76	4.59	
Medial frontal gyrus (BA 10; MNI co-ordinates: 4 48 6)									
Age-related increases in FC									
	R	Inferior Parietal Lobule	40	64	−32	42	4.54	1.86	494
Age-related increases in anti-correlated FC									
	R	PHG	37	30	−44	−4	4.41	2.03	4521
		Middle Occipital Gyrus	19/18	22	−88	10	4.40	2.28	
	L	Middle Occipital Gyrus	19/18	−24	−78	10	4.39	3.00	
		PHG	37	−30	−48	−6	3.93	2.51	

Brain regions involved in memory development that are functionally connected to PFC regions where SM effects differed by age. "Age-related increases" *in FC* = FC (Hit Sure − Miss) inclusively masked by FC (Hit Sure − Miss) ∝ Age. "Age-related increases in anti-correlated" *FC* = FC (Miss − Hit Sure) inclusively masked by FC (Miss − Hit Sure) ∝ Age. The significance threshold is $P < 0.05$, corrected. Hemi., hemisphere; BA, Brodmann Area; FC, functional connectivity; R, right; L, left.

Discussion

The goal of the present investigation was to characterize PFC contributions to memory development. Consistent with prior findings, we identified age-related increases in PFC positive SM effects. In addition, we also identified age-related increases in PFC negative SM effects. Importantly, the negative SM effect in the superior portion of the PFC partially mediated the relationship between age and memory performance, suggesting that age-related improvement in memory performance is related to a greater decrease in the BOLD response for remembered compared to forgotten items. Finally, we found that the distinct regions showing age-related increases in either positive or negative SM effects have unique patterns of functional connectivity. Interestingly, PFC regions where we identified positive SM effects showed age-related increases in PFC-MTL connectivity, whereas PFC regions where we identified negative SM effects showed age-related increases in the anti-correlation between PFC and MTL. These findings are further discussed below.

Positive and Negative SM Effects within the PFC Increased with Age

Consistent with previous research, we identified positive SM effects bilaterally in regions within the dorsolateral (BA 46) and ventrolateral (BA 44/45) PFC (Blumenfeld and Ranganath 2007; Ofen et al. 2007; Kim 2011; Huijbers et al. 2013) and negative SM effects bilaterally in regions within superior (BA 8/9) and medial (BA 10) PFC. Although negative SM effects have been consistently found during memory formation in adults in studies spanning more than a decade (Otten and Rugg 2001; Daselaar et al. 2004; Huijbers et al. 2013), this is the first study showing age differences in these effects from childhood to young adulthood. Both positive and negative SM effects increased with age.

Age-related increases in positive SM effects were found in ventrolateral PFC (bilateral BA 44/6 and right BA 45). These regions are in close proximity to regions identified in previous reports of age-related differences in the neural correlates of memory formation (e.g., Ofen et al. 2007; Ghetti et al. 2010). Thus, 3 independent studies examining functional maturation in the neural correlates of memory formation point to the involvement of the ventrolateral PFC, particularly the IFG. This region has been consistently identified in studies of cognitive control (for a review, see Banich and Depue 2015), and age-related increase in IFG contribution to memory may reflect age-related improvement in aspects of memory that rely more strongly on attentional and cognitive control processes (Shing et al. 2010; Ofen 2012; Ofen et al. 2016).

Age-related differences in negative SM effects were found in the superior (right BA 8/9, left BA 10) and medial (BA 10) PFC. With the exception of Chai et al. (2014a) who demonstrated differences in negative SM effects in DMN regions between groups of children, adolescents, and young adults, these effects have not been thoroughly examined during development. Findings from investigations of the neural correlates of memory in adults, however, suggest that age differences in negative SM effects may be related to memory decline in older adults (de Chastelaine et al. 2011; Park et al. 2013; de Chastelaine and Rugg 2014). For example, using an incidental memory task, Park et al. (2013) demonstrated that greater negative SM predicted better memory performance, and compared to younger adults, older adults showed reduced deactivation in negative SM regions, including the superior PFC, IPL, and precuneus. The findings of decreased magnitude of negative SM in older adults mirror our current findings showing a reduction of these effects in children, and in both studies, reductions in the effects were related to less efficient memory formation. Moreover, age-related negative SM effects appear to be generalizable to memory formation across stimulus modality, as these effects have been identified when testing associative memory with either scenes (Park et al. 2013) or word pairs (de Chastelaine et al. 2011, 2015). Taken together, these findings show that reductions in negative SM effects within the PFC are found in both young children and older adults, and that negative SM effects in general serve as an important neural correlate of memory formation across the lifespan.

Negative SM Effect in SFG Partially Mediated the Relationship Between Age and Memory

Additional support for the importance of negative SM effects to age-related memory improvement comes from our mediation analysis, where we identified one region in the superior PFC (BA 10/9), where the SM effect partially mediated the relationship between age and memory performance. Unlike negative SM effects, positive SM effects were not related to the differences in memory performance. This null finding is difficult to interpret, yet given that we identified negative SM effects related to memory performance and that a region showing negative SM effects mediated the relationship between age and behavior, it is intriguing to speculate that negative SM effects offer a unique and complementary contribution to memory development.

The relationship between negative SM effects and memory performance has not been previously shown in children, but has been reported in studies examining memory during young, middle and late adulthood (Miller et al. 2008; Duverne et al. 2009; de Chastelaine et al. 2011, 2015; Mormino et al. 2012; Park et al. 2013; de Chastelaine and Rugg 2014). De Chastelaine and Rugg (2014), Mormino et al. (2012), and Park et al. (2013) reported positive relationships between the strength of the negative SM effects, averaged across all ROIs showing negative SM effects, and memory performance. In addition, findings from de Chastelaine et al. (2011), Duverne et al. (2009), and Miller et al. (2008) converge to show that when activation to remembered items in right SFG occurs in older and/or low-performing adults, it is negatively related to memory performance. Furthermore, and consistent with our null finding regarding positive SM and memory performance, both de Chastelaine and Rugg (2014) and Park et al. (2013) showed that only negative SM effects were related to behavior.

Recent studies implicate regions in the superior PFC in processes related to task-unrelated thoughts (TUTs), mind wandering, and thoughts about environmental distractions (Anderson et al. 2004; Christoff et al. 2009; Maillet and Rajah 2014a, 2016). Indeed, during memory formation, TUTs are negatively correlated with memory performance and frequently show an age-related difference between young and older adults (Maillet and Rajah 2014b; Maillet and Schacter 2016). Moreover, regions in the superior PFC (BA 6/8/9) are involved in both TUTs and subsequent forgetting, supporting the notion that this region may be involved in failure to regulate TUTs, which then leads to subsequent forgetting (Maillet and Rajah 2016). In addition, this region has also been linked to the active suppression of memory in both children and young adults (Paz-Alonso et al. 2013). These recent findings highlight the involvement of the superior PFC in thought regulation and memory control, and further

suggest that its development is highly relevant to the maturation of episodic memory.

Providing further support for the involvement of superior PFC regions in the suppression of TUTs, we identified a significant effect between more effective deactivation in the superior PFC region and less variability in RTs during successful memory encoding. Variability in RTs may reflect individual differences in the ability to effectively engage in thought suppression. Several previous studies have linked activation in brain regions known to support inhibitory processes to lower variability in RTs (Simmonds et al. 2007; McIntosh et al. 2010, 2014). In our current study, we found that increased negative SM effects in the superior PFC correlated with more consistency in RTs for subsequent Hit_S trials. It is therefore possible that the level of negative SM effects in superior PFC during memory formation indicates more effective suppression of TUTs, allowing more attention to be directed to facilitate memory formation.

Functional Connectivity During Successful Memory Encoding Increased with Age

Using PPI analyses, we demonstrated that age-related differences in the functional connectivity between the PFC and regions in the MTL differed based on whether the PFC regions showed positive or negative SM effects. Specifically, PFC regions that were identified by age-related increases in positive SM effects showed age-related increases in PFC-MTL connectivity, whereas PFC regions that were identified by age-related increases in negative SM effects showed an age-related decrease in PFC-MTL connectivity (i.e., increased PFC-MTL anti-correlation with age). We also identified an age-related increase in the connectivity between the right superior PFC and lateral parietal cortex.

The findings showing age-related increases in functional connectivity between positive SM PFC regions and the MTL is consistent with a previous report showing an increase in functional connectivity with age between the PFC (left MFG, BA unreported) and the MTL (entorhinal cortex) regions during memory formation (Menon et al. 2005). Our findings are also consistent with previous studies showing age-related differences in the functional connectivity between the PFC and the MTL during memory retrieval (Ofen et al. 2012). Increased functional connectivity between the PFC and the MTL has also been identified in 2 longitudinal investigations. Qin and colleagues (2014) examined age-related changes in brain activity associated with memory-based arithmetic and found increased employment of memory-based strategies for solving arithmetic problems across a period of 14 months in children ages 7–9. Paralleling these behavioral findings, increased functional connectivity between the lateral prefrontal cortex (IFG/MFG) and the hippocampus was observed for the second compared to the first visit. Similarly, in a longitudinal study of working memory development, reduced PFC-MTL functional connectivity for low-load trials and increase functional connectivity for high-load trials were observed on the second visit (Finn et al. 2010). Our finding, when taken in conjunction with these earlier reports, suggests that the maturation of a task-related functional coupling between the PFC and MTL plays a role in the development of high-level cognitive processing.

To the best of our knowledge, this is the first report of age-related differences in the functional connectivity for negative SM effects during development. The connectivity findings showing increased coupling with age between superior PFC (BA 9) and another DMN region (IPL/SMG) during memory formation, likely reflects the improved ability to suppress internal thoughts and task-unrelated stimuli, as this function has been attributed to a number of overlapping DMN regions (Buckner et al. 2008; Cabeza et al. 2008; Uncapher and Wagner 2009; Anticevic et al. 2010, 2012; Chadick and Gazzaley 2011; Andrews-Hanna 2012).

In addition to age-related increased in positive connectivity between superior PFC and IPL/SMG, we also identified the opposite pattern, an age-related increase in negative functional connectivity, or anti-correlation, between superior PFC and regions in the posterior MTL (PHG) and the occipital cortex. Anti-correlation between these networks is not surprising given that previous research has demonstrated that, during cognitive tasks, regions that belong to the task-positive network show positive functional connectivity with other task-positive regions (Spreng et al. 2010; Chadick and Gazzaley 2011; Anticevic et al. 2012), whereas DMN regions show positive functional connectivity with other DMN regions and anti-correlation with task-positive regions (Chadick and Gazzaley 2011; Anticevic et al. 2012). Furthermore, age-related increases in the strength of the anti-correlation is consistent with previous findings on the development of resting state networks (Chai, Ofen, Gabrieli, and Witfield-Gabrieli 2014) and task-positive versus task-negative networks (Barber et al. 2013). These findings may reflect the presence of maturation processes that are observed as the inverse coupling of these 2 large-scale networks. Taken together, the current findings of an age-related increase in functional connectivity within the network, and increased anti-correlation between networks, suggest that these networks operate in concert, guiding attention and mental resources to support effective memory formation.

In this study, we focused our investigation on age-related differences in the PFC, a region that was identified in prior research to demonstrate age differences in SM effects. Moreover, in line with prior reports, we investigated age differences in a specific type of memory that has previously shown robust age differences —memory for detailed information, which we measure through the rate of Hit_S responses (Ofen et al. 2007; Ghetti and Angelini 2008; Ghetti et al. 2010). As expected, we observed an age-related increase in recognition accuracy for Hit_S trials. Investigating the neural correlates that give rise to age differences in this measure cannot easily be dissociated from the fact that younger participants tend to have fewer Hit_S trials. It is thus possible that some of the effects we report represent differences in the power to detect neural correlates during the encoding of Hit_S trials.

Although making inferences about age differences in PFC activation as the neural correlates underlying age differences in memory performance is inherently difficult, we note that we have taken several steps to mitigate the potential limitations of our investigation. First, we ensured that participants with less than 10 trials per condition were excluded (only 1 adolescent was excluded). Even among the youngest participants (ages 8–12; $n = 31$), the average number of Hit_S trials was 40.77 $\pm$ 15.51, which is comparable to the number of Hit_S trials in adults, 58.83 $\pm$ 15.01 (age > 18; $n = 30$). The variance in memory outcome measures was consistent with previous fMRI studies based on similar tasks (Ofen et al. 2007; Chai et al. 2010).

Second, in the analyses for SM effects, we included both age and adjusted memory accuracy as covariates in the same model. In the PPI analyses, we additionally confirmed the age-related effects in the functional connectivity with a selective sample of participants where age did not correlate with memory performance (i.e., there were no relations between age and either adjusted memory accuracy, the number of Hit_S trials, or the number of Miss trials, $Ps > 0.54$). With these analyses, we found age differences in the respective outcome measures that

persisted after controlling for performance. These results suggest that our main findings of age differences in PFC contributions to memory formation are not merely the result of age differences in performance.

Lastly, support for our approach can be construed from the localization of the effects documented in our findings. Our rationale is that, if age differences in the number of trials influenced age differences in SM effects, the influence we argue, is more likely to generate global rather than localized age differences in SM effects. And if the number of trials were to generate a global bias on the estimation of SM contrast values (Hit_S – Miss), we would observe a significant correlation between these contrast values and the number of trials across the brain. It would follow that, since the number of Hit_S trials varied with age, we might also observe age differences in contrast values in regions not considered to support memory formation. However, this was not the case. The age effects we reported were localized, and in regions that have been previously reported to support memory formation. To illustrate this point, we added a region of interest outside regions typically reported to support memory formation as a control check. We extracted SM contrast values within an anatomically defined region of interest in the bilateral calcarine sulci, and correlated those values with several variables of interest, including the number of Hit_S trials, the number of Miss trials, and age. SM contrast values from the calcarine sulci did not correlate with any of these variables (*Ps* > 0.38). These findings further demonstrate the localization of our age effects and provide additional support to the notion that age differences in the number of trials minimally affected the interpretation of age differences in PFC contributions to memory formation.

Although the results from both developmental and aging memory research converge to suggest that effective deactivation in the superior PFC is important in supporting successful memory formation, we must note that the available findings we reviewed, and our own investigation are limited in that they were based on cross-sectional samples. Although data from cross-sectional samples may shed light on how variables of interest differ over time, these differences must be interpreted cautiously due to potential confounds from a number of other variables also changing over time (Maxwell and Cole 2007). True age-related change can be more strongly inferred from longitudinal samples, where the variables of interest can be isolated from other variables that are time-variant. Future research using longitudinal studies is needed to corroborate the findings from cross-sectional investigations of the neural correlates of memory formation.

In conclusion, the present findings underscore that the functional maturation of the PFC is likely an important factor contributing to memory development. We identified age-related increases in both positive and negative SM effects. Positive SM effects have been demonstrated previously and likely influence memory through age-related increase in intentional cognitive control. To the best of our knowledge, this is the first report of age-related increases in negative SM effects. Although speculative, we consider that these age effects may be associated with successful memory formation as they are important for age-related increases in effective thought suppression and reduction in the processing of task-irrelevant stimuli. The importance of these effects is bolstered by the fact that the negative SM effect in the superior PFC partially mediated age-related increase in memory performance. Lastly, we identified complementary age-related effects when examining PFC functional connectivity patterns, reinforcing the notion that successful memory formation relies on specialized functional coupling between the PFC and regions in the MTL, and more broadly, on functional maturation of integrated, but reciprocal brain networks.

Supplementary Material

Supplementary data are available at *Cerebral Cortex* online.

Funding

This work was supported by funds available from the National Institute of Mental Health R01MH107512, and the Institute of Gerontology at Wayne State University to NO.

Notes

The authors wish to thank 2 anonymous reviewers for helpul comments on an earlier version of this manuscript, Naftali Raz and Jeske Damoiseaux for helpful discussions on this paper, Amanda Hardwick, Raphael Serota David Brush, and Carson Miler Rigoli for assistance with data collection, and to the families and children who participated in this study. *Conflict of Interest*: None declared.

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