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Characterizing The Development Of Episodic Memory And Assessing The Reliability Of Fmri Measures

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CHARACTERIZING THE DEVELOPMENT OF EPISODIC MEMORY AND ASSESSING THE RELIABILITY OF FMRI MEASURES

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INTRODUCTION

The ability for humans to register information accurately in the memory system is crucial for everyday cognitive engagements and social interactions. The observation of dramatic improvements in memory capabilities from childhood to young adulthood led to interesting questions about how memory development happens and where it takes place. To answer these questions, there is no other place to look than into the human brain.

Over the past 30 years, advances in neuroimaging methodologies have led to a growing body of works investigating the development of memory systems, relying heavily on insights provided by functional (fMRI) and structural MRI measures (Ofen, 2012). Advances in neuroimaging methodologies have aided the mapping of distinct memory functions and their development to specific brain regions. For example, in a study investigating the development of two memory-related regions in the brain, Ofen and colleagues (2007) demonstrated that both the prefrontal cortex (PFC) and medial temporal lobe (MTL) play a role in memory formation in children and adults, but support differential developmental trajectories: the PFC supports the continued development of the memory strategy and executive control and the MTL supports the relatively stable function of binding different sources of information into a holistic representation. The characterization of age differences within regions in the PFC and MTL, including the hippocampus, continues to be a focus of research today.

While the continued developmental effect in the PFC supporting episodic memory development was replicated in independent studies (Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Ofen, Chai, Schuil, Whitfield-Gabrieli, & Gabrieli, 2012), questions remain about how specific regions of the PFC support memory formation. Moreover, as different brain regions function together as an integrated network, it is important to understand how the PFC couples with other

regions in the brain to support memory development. In Chapter 1, I will examine how PFC activation and functional connectivity develop to support episodic memory formation.

While there was a general consensus on the functional development of PFC supporting memory improvements from childhood to adulthood, similar investigations on the functional development of the MTL region have yielded apparently conflicting findings – the hippocampus was found to show age invariance in some studies (Ofen et al., 2012, 2007; Shing, Brehmer, Heekeren, Bäckman, & Lindenberger, 2016), but positive correlations in others (Chai, Ofen, Jacobs, & Gabrieli, 2010; DeMaster, Pathman, & Ghetti, 2013; Ghetti et al., 2010). As the hippocampus is a much smaller region compared to PFC and situates in an area that is prone to the fMRI signal loss, it is exceedingly important to apply analytical methods that are sensitive to its variability within this region. Furthermore, in addition to investigating hippocampal activation that contributes to memory development, the hippocampus should also be considered in the context of the greater memory-related network. In Chapter 2, I will investigate how hippocampal activation and functional connectivity develop to support memory formation.

Finally, in order to correctly characterize the activation and connectivity patterns of memory-related regions and understand their roles in memory development, establishing the reliability of fMRI measures is necessary, as reliability provides the upper bound for detecting true developmental effects. While excellent reliability has been shown for structural measures in key regions of the memory system, such as the hippocampus (Daugherty, Yu, Flinn, & Ofen, 2015; Wisse, Biessels, & Geerlings, 2014; Yushkevich et al., 2015), the reliability with fMRI in identifying memory-related regions remains fair at best (Bennett & Miller, 2010; Herting, Gautam, Chen, Mezher, & Vetter, 2018). With the field moving towards leveraging large open datasets for discovery science (Biswal et al., 2010) and increasingly adopting longitudinal methods for

understanding neural development (Braams, van Duijvenvoorde, Peper, & Crone, 2015; Ordaz, Foran, Velanova, & Luna, 2013; Peters, Van Duijvenvoorde, Koolschijn, & Crone, 2016), the ability to consistently identify target functional patterns using fMRI is crucial. In Chapter 3, I will examine the reliability in identifying the memory-related activation and connectivity with fMRI.

CHAPTER 1. DEVELOPMENT OF THE PREFRONTAL CORTEX

Introduction

The memory system undergoes continuous changes with age, and reliably characterizing these changes is the chief aim for many developmental scientists. Advances in neuroimaging methodologies, especially in fMRI, have led to an improved understanding of the neural substrate of memory development (Ofen, 2012). These findings support the notion that the brain activation identified in children are remarkably similar in localization as compared to those identified in adults. For example, in one study that employed an event-related design to assess age differences in memory-related activation predictive of subsequent memory, Ofen and colleagues (2007) identified differential developmental trajectories between activation in the PFC and the hippocampus, such that inferior frontal gyrus (IFG) showed increased activation with age.

Several subsequent studies replicated the findings by Ofen (2007), showing robust age-effects in IFG activation supporting both memory encoding and retrieval (DeMaster & Ghetti, 2013; Ofen et al., 2012). However, inconsistency in the developmental effects within different subregions of the PFC were evident upon closer examinations (Chai et al., 2010; DeMaster & Ghetti, 2013; Ghetti et al., 2010; Ofen et al., 2007; Paz-Alonso, Ghetti, Donohue, Goodman, & Bunge, 2008). As the PFC contains functionally heterogeneous subregions that support different cognitive functions, taking the fMRI analysis to the subregion level may paint a more complete picture of memory development in these regions.

The PFC is composed of structurally and functionally heterogeneous subregions that assume different roles in supporting memory processes (Badre & D'Esposito, 2009; Petrides, 2005). PFC subregions function in sync with other cortical and subcortical brain regions to support important functions such as memory formation. These memory-related regions can be identified by a widely-used subsequent memory paradigm, when these regions demonstrate what is known

as the subsequent memory effect (SME) (Dolan & Fletcher, 1997; Fletcher, Shallice, & Dolan, 1998; Kim, 2011; Kim, Daselaar, & Cabeza, 2010; Paller & Wagner, 2002). The SME is determined by the significant difference in the blood-oxygen-level-dependent (BOLD) response between trials participants later remembered compared to trials they later forgot. During memory formation, IFG and premotor cortex show increased activation for study items that are later remembered compared to those that are later forgotten (positive SME), whereas SFG and mPFC show increased deactivation for study items that are later remembered than those that are later forgotten (negative SME). Negative SME within the PFC have been demonstrated in studies across the adult lifespan, with some studies linking age differences in the strength of negative SME to memory performance (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2015; de Chastelaine & Rugg, 2014; Park, Kennedy, Rodrigue, Hebrank, & Park, 2013).

Although both positive and negative SMEs have been investigated in aging (de Chastelaine et al., 2015; de Chastelaine & Rugg, 2014; Park et al., 2013), little is known about possible negative SME in children and adolescents. While IFG has consistently shown age-related increases in activation during both memory encoding and retrieval, developmental effects within other subregions showing negative SME remain unclear. Thus, our first goal in this study is to understand age-related differences in both the positive and negative SME in different PFC subregions.

Furthermore, previous findings linking positive and negative SME with age are commonly confounded by the relationship between age and performance. Studies have identified regions within the PFC where brain activation show correlations with both age or memory performance (Chai et al., 2010; Chiu, Schmithorst, Brown, Holland, & Dunn, 2006; Ghetti et al., 2010; Ofen et al., 2007), yet it remains unclear how age-related differences in SME are related to age

improvements in memory performance. More specifically, it is unknown whether age-related differences in SME can explain a unique portion of variance in the age-related increase in memory performance. Therefore, our second goal in this study was to evaluate the link between age-related SME and age-related improvements in memory.

Lastly, given the role of PFC in global organization, it is important to assess its functional connectivity patterns and evaluate their associated developmental effects. Previous studies have shown age differences in the functional connectivity with PFC regions and have highlighted the potential importance of such findings for the development of memory (Chai, Ofen, Gabrieli, and Whitfield-Gabrieli 2014; Chai, Ofen, Gabrieli, and Witfield-Gabrieli 2014). For example, Menon and colleagues (2005) first demonstrated the importance of functional connectivity in memory by showing increased coupling between PFC and MTL during memory encoding, although several limitations of this earlier report prevent from directly assessing the contribution of PFC functional connectivity to memory development. Here, we used a subsequent memory paradigm and evaluated age differences in memory-related functional connectivity of PFC regions.

Current Study

In this study, we characterized the PFC contribution to memory development using a subsequent memory paradigm, with fMRI data collected from 83 children, adolescents, and young adults. We assessed SME within the PFC and predicted age differences in both positive and negative SME. We tested whether age-related increase in SME 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 SME. By systematically exploring PFC contributions, we provide a more complete picture of the PFC supporting the development of memory.

Methods

Participants

Eighty-three participants ranging in age between 8 to 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 eight 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 & 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, $r(81) = -.05$, $p = .67$.

Subsequent Memory Paradigm

We used an established visual subsequent memory paradigm, similar to what was described in previous publications (Ofen et al., 2007; Tang, Shafer, & Ofen, 2018). Specifically, the participants studied 120 indoor and outdoor scenes in the scanner and then completed a self-paced recognition test outside the scanner after the completion of the MRI session (120 old scenes intermixed with 80 new scenes). The stimuli set is comprised of 600 indoor or outdoor scenes from imaged used in prior studies (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Chai et al., 2010; Ofen et al., 2007), with additional images from the SUN Database (Xiao, Hays, Ehinger, & Torralba, 2013). The stimuli set was divided into 15 lists, each composed of 40 scenes (20 indoor and 20 outdoor scenes). During each visit, a participant was tested with a unique subset of the stimuli, with 3 lists during study and 2 additional lists (foils) only during recognition. Different

lists were assigned for participant visits in a pseudorandomized order. The assignment of lists as study or foil items was counterbalanced across participants, with a specific item equally likely to be included as study or foil items across participants. Each scene was presented for 3 s, followed by a 0.5 s fixation cross and a variable inter-trial interval ranging from 0 to 8 s. The inter-trial interval was used to increase fMRI measurement reliability (jitter sequence determined using optseq2, http://surfer.nmr.mgh.harvard.edu/optseq/). Scenes were presented in 3 consecutive runs, with 40 items in each run.

Participants were instructed to make an indoor/outdoor judgment for each scene using a two-button response box placed in their right hand and try their best to memorize the scenes for a subsequent recognition memory test. Accuracy of encoding judgment (response to whether it depicted an indoor or outdoor scene) and reaction time were recorded. Analyses of SME were restricted to the scenes that were properly attended during encoding, as indicated by an accurate encoding response. Approximately 15 minutes 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 and their neural correlates (Gutchess et al., 2005; Ofen et al., 2007), we also included a confidence judgment after the old-new judgment. After the “Old”/“New” judgement, participants were 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 they saw it, or any other detail 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). Based on the test outcome, trials were labeled as Hit or Miss whether they were later correctly recognized as "Old" (Hit) or incorrectly judged as "New" (Miss). After that, trials were further classified in two orthogonal ways, according to the or recognition confidence ("Sure"/"Not Sure") or the scene complexity (High/Low Complexity).

First, trials were classified based on the confidence rating given during the recognition test ("Sure"/"Not Sure"). Hit trials were further classified as Hit Sure (Hit_S) or Hit Not Sure (Hit_NS). Miss trials, however, were not further classified by the confidence rating because in both cases the response was incorrect, that is, a Miss trial represents an absence of memory formation, regardless of the subjective rating of the incorrect response during the recognition test. Moreover, by combining Miss trials regardless of confidence rating, we were able to compare an overall similar number of trials from both conditions of interest, diminishing the potential influence on our measurements from an influence of confounds due to imbalance of trial numbers. For the recognition memory test, foil scenes that were incorrectly identified as "Old" were labeled as False Alarm (FA). FA trials were further separated into FA Sure (FA_S) and FA Not Sure (FA_NS). In Chapter 1, we conducted analyses with trials divided by subsequent memory and confidence rating.

Second, trials were also classified based on the scene complexity (High/Low Complexity) of the indoor and outdoor images. The scene complexity was measured according to the number of unique object categories in the image, using the LabelMe toolbox (Russell, Torralba, Murphy, & Freeman, 2008). For example, four chairs in one image counts as one unique object category whereas a chair and a desk count as two unique objects. Scenes that have more than 4 unique object

categories were defined as high complexity (HC), and scenes that have less than 4 unique object categories were defined as low complexity (LC). In both the old and new scenes, half of the scenes selected were HC, and the other half were LC. For the encoding period, Hit and Miss trials were classified based on scene complexity into Hit High Complexity (Hit_HC), Hit Low Complexity (Hit_LC), Miss High Complexity (Miss_HC), and Miss Low Complexity (Miss_LC). For the recognition memory test, foil scenes that were incorrectly identified as "Old" were labeled as False Alarm (FA). FA trials were similarly categories into FA High Complexity (FA_HC) and FA Low Complexity (FA_LC). In Chapter 2 and 3, we conducted analyses with trials divided by memory and scene complexity.

MRI Data Acquisition

MRI data were acquired in a 3T Siemens Verio scanner at the Harper University Hospital in Detroit, MI. T1-weighted whole-brain structural 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. Thirty sagittal slices were collected parallel to the AC-PC plane (TR = 2000 ms, TE = 30 ms, flip angle = 90º, voxel size = 3.1 mm × 3.1 mm × 4 mm). Participants were scanned for three consecutive functional runs while performing in a subsequent memory paradigm, as described below. Each functional run consisted of 118 volume acquisitions and lasted for 3 minutes and 54 seconds.

Data Analysis

Behavior

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). For Chapter 1, we used 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's correlation. We also assessed participants' response times during the encoding task based on subsequent memory performance. Differences in mean response times were assessed using a repeated measures analyses of variance (ANOVA) with three levels (Hit_S, Hit_NS, and Miss), with age added as a covariate. Age differences in encoding response times across conditions were assessed using Pearson's correlations.

Preprocessing

Functional imaging data were analyzed with the SPM8 package (Wellcome Department of Imaging Neuroscience, London, UK). 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 1mm. The *Co-Planar Stereotaxic Atlas of the Human Brain* (Talairach & Tournoux, 1988) and MRIcron (Version Jun 6, 2013,

http://www.nitrc.org/projects/mricron) were used in conjunction to identify the anatomical locations and corresponding Brodmann areas for the peak coordinates that are reported for the analyses presented below.

Subsequent memory effect

Individual-level general linear models (GLMs) included three task-related regressors (Hit_S, Hit_NS and Miss) for each run. One error regressor and seven motion regressors (three 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 to 93 out of 120) and for the Miss (range: 15 to 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 (HRF). 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%), $r(81)$= -.58, $p < .001$. To minimize the influence of motion artifacts, we added one regressor per outlier volume into the GLM model (as identified by ART) (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 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)

SME 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 SME are reported at a voxel-level threshold of $p < .005$, cluster-level corrected at $p < .05$ 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 and colleagues (2016) (Cox, Reynolds, & Taylor, 2016). We further examined the nature of these positive and negative SME 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 SME and age- or performance-related effects, we first computed correlation *t* maps that assessed the relationship between SME and age, between SME and performance, using GLM models where both age and performance were included as covariates. Conjunction analyses were then performed with group-level SM maps and these 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) $\cap$ (Hit_S – Miss) $\propto$ age)]. A threshold of $p < .005$ was used for the SM *t* maps and a threshold of $p < .05$ was used for correlation *t* maps. The joint probability of the resulting double conjunction map was $p < .00025$ ($.005 \times .05$). 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 $p < .05$ using a Monte Carlo simulation implemented in 3dClustSim ($k = 43$ for double conjunction maps and $k = 10$ for triple conjunction maps). 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 SME across the whole brain in order to present a complete picture. The maps for positive and negative SME were cluster-level corrected at $p < .05$ as per a Monte Carlo simulation implemented in 3dClustSim ($p < .005$, $k = 1186$). In addition, the age- and performance-related SME were conducted using conjunction analyses as described before, cluster-level corrected at $p < .05$ (conjunctive $p < .00025$, $k = 183$).

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 & 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 & 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 SME 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 coordinates of each of these regions. We report results for PPI analyses including seed regions derived from all the clusters showing age differences in SME.

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 $p < .05$ 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 .57 ± .14 were correctly identified as “Old” (Hit), with .44 ± .15 classified as “Sure” (Hit_S), and .13 ± .08 classified as “Not Sure” (Hit_NS). The Hit_S rate

showed an increase with age ($r(81) = .46$, $p < .001$), while the Hit_NS rate showed a decrease with age ($r(81) = -.23$, $p = .04$). In contrast, a total of .43 ± .14 were incorrectly identified as "New" (Miss), and the Miss rate showed a decrease with age ($r(81) = -.34$, $p = .001$). Of the scenes used as foils during recognition, .26 ± .13 were incorrectly identified as "Old" (false alarm, FA), with .14 ± .11 classified as "Sure" (FA_S), and .12 ± .8 classified as "Not Sure" (FA_NS). Neither the FA_S rate ($p = .20$) nor the FA_NS rate ($p = .08$) showed significant correlations with age.

Recognition accuracy (Hit rate – FA rate) for responses classified as "Sure" (.31 ± .16) was higher than responses classified as "Not Sure" (.01 ± .06), $t(82) = 15.67$, $p < .001$. Moreover, recognition accuracy increased with age for responses classified as "Sure" ($r(81) = .54$, $p < .001$), but not for those classified as "Not Sure" ($p = .64$; Fig. 1.1). 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 (.52 ± .26), $p = .81$, suggesting that participants used similar criteria when making confidence judgments.

[Figure 1.1]

During the study phase, response times (RTs) did not differ between Hit_S (1.08s ± .29s), Hit_NS (1.06s ± .31s), and Miss (1.07s ± .28s) conditions, $F(2, 156) = .39$, $p = .63$. RTs for all trial types negatively correlated with age (Hit_S: $r(79) = -.24$, $p = .03$; Hit_NS: $r(78) = -.27$, $p = .01$; Miss: $r(79) = -.31$, $p = .004$). However, there was not an age by trial type interaction for RTs ($F(2, 156) = .88$, $p = .40$).

Imaging

Positive and negative SME within the PFC

Positive SME were observed in large bilateral clusters including regions in the precentral gyrus, inferior frontal gyrus (IFG), and middle frontal gyrus (MFG) (Table 1.1; Fig. 1.2). Negative SME 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 1.1; Fig. 1.2). 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 *p*s < .001; right IFG shown in Fig. 1.2A). Bilateral MFG/SFG showed significant deactivation compared to the baseline for Hit_S trials and Miss trials (all *p*s < .01; right SFG shown in Fig. 1.2B).

[Figure 1.2]

Positive and negative SME within the PFC increased with age

PFC regions that were associated with positive or negative SME and differences in age were identified by conjunction analyses performed on SM and correlation *t* maps. Age-related positive SME 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 ($r(81) = .46$, $p < .001$), but not by Miss trials ($p = .11$; Fig. 1.2C). In the left IFG, activation for Hit_S ($r(81) = .56$, $p < .001$) and Miss ($r(81) = .44$, $p < .001$) 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: $F(1, 81) = 6.31$, $p = .01$; left, $F(1, 81) = 8.20$, $p = .005$).

Age-related differences in negative SME 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 SME 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 ($r(81) = -.44$, $p < .001$) and medial frontal gyrus ($r(81) = -.31$, $p = .005$), but there were no age differences in the deactivation for Miss trials (ps > .14; Fig. 1.2D).

Negative SME in the PFC related to performance

PFC regions that were associated with positive or negative SME and increased with memory performance were identified by conjunction analyses performed on SM and correlation *t* maps. There were no positive SME that were uniquely associated with individual variability in memory performance. However, negative SME in bilateral SFG and medial frontal gyrus (BA 10/9) were related to individual differences in memory performance, such that the magnitude of deactivation for Hit_S trials increased with enhanced memory performance [$r(81) = -.40$, $p < .001$, parameter estimates extracted from peak cluster (right SFG, BA 10/9)], but the magnitude of deactivation for Miss trials did not ($p = .16$). We then conducted a triple conjunction analysis to identify PFC regions that showed SME 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. 1.3).

SME across the whole brain

For completeness, we also report regions, across the whole brain, that showed positive and negative SME (**A**), regions where SME correlated with age (**B**) and regions where SME correlated with memory performance (**C**) (Fig. 1.S1). Outside the PFC, positive SME were additionally identified in bilateral parahippocampal gyrus (PHG) and middle occipital lobe. Negative SME were additionally identified in bilateral supramarginal gyrus, inferior parietal lobule, precuneus, and anterior cingulate cortex. Age-related positive SME were additionally observed in bilateral superior parietal lobe, superior/middle occipital lobe, PHG, and fusiform gyrus. No age-related negative SME were observed outside the PFC. Performance-related positive SME were additionally identified in bilateral superior parietal lobe, bilateral inferior temporal gyrus, and left PHG. Performance-related negative SME were additionally identified in bilateral supramarginal gyrus, inferior parietal lobule, precuneus, and anterior/posterior cingulate cortex.

[Figure 1.S1]

Negative SME in the PFC mediated age-related increase in memory

Using mediation analysis, we further examined whether negative SME 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 SME in the SFG with a medium effect size ($\kappa^2 = .15$), see Fig. 1.3. Confidence intervals for the indirect effect did not contain zero and the Sobel test determined that the indirect effect between age and memory performance through negative SME in the right SFG was significantly different than zero (indirect effect 95% standardized CI: [.05, .27], Sobel test $p = .01$).

[Figure 1.3]

To rule out the effects of RTs in assessing the relationship between SME, age, and memory performance, we included RTs as covariates in the mediation analysis. We tested two 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 as a covariate (two participants without RT data were excluded). The results indicated that age-related differences in memory performance was mediated by the negative SME in SFG/MFG after controlling for differences in RTs (original model, CI: [.05/.27], $p = .012$; additional model (1) with mean RTs for both Hit_S and Miss trials, CI: [.07/.31], $p = .009$; additional model (2) with the mean RT difference, CI: [.06/.30], $p = .008$).

Negative SME 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 response time during a cognitive task (Garrett et al., 2013; McIntosh et al., 2010; Simmonds et al., 2007). For example, the pattern of activation in the SFG/MFG region was related to the *intra-individual coefficient of variability* (ICV = σ_{RT}/μ_{RT}), in a Go/No-Go task with young children (Simmonds et al., 2007; Fig. 1.4). Specifically, individual differences in SFG/MFG activation were related only to the ICV of No-Go 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 SME and the ICV. Interestingly, we found that negative SME in SFG/MFG correlated with the ICV of subsequent Hit_S trials ($r(79) = .27$, $p = .01$), 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 relation was found between

negative SME and the ICV of subsequent Miss trials (p = .61); nor were relations found between positive SME and the ICV of either subsequent Hit_S trials or subsequent Miss trials, ps > .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. 1.4A). A PPI analysis with another positive SM seed in the right IFG (BA45/44; MNI Coordinates: 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. 1.4B). In contrast, a PPI analysis with a negative SM seed in the right SFG (BA 10/9; MNI Coordinates: 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. 1.4C). A PPI analysis with another negative SM seed in the medial frontal gyrus (BA 10; MNI Coordinates: 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. 1.4D).

[Figure 1.4]

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 SME. In addition, we also identified age-related increases in PFC negative SME. Importantly, the negative SME in the superior portion of the PFC partially mediated the relationship between age and memory performance, suggesting that age-related improvement in memory performance are related to greater decrease in the BOLD response relative to baseline for remembered compared to forgotten items. Finally, we found that the distinct regions showing age-related increases in either positive or negative SME have unique patterns of functional connectivity. Interestingly, PFC regions where we identified positive SME showed age-related increases in PFC-MTL connectivity, whereas PFC regions where we identified negative SME showed age-related increases in the anti-correlation between PFC and MTL. These findings are further discussed below.

Positive and negative SME within the PFC increased with age

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

Age-related increases in positive SME 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, three 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 strategic control processes (Ofen, 2012; Ofen, Yu, & Chen, 2016; Shing et al., 2010; Yu et al., 2018).

Age-related differences in negative SME 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 SME 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 SME may be related to memory decline in older adults. For example, using an incidental memory task, Park et al. (2013) demonstrated that greater negative SM predicted better memory performance. In addition, 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 SME 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; de Chastelaine et al. 2015). Taken together, these findings show that reductions in negative SME

within the PFC are found in both young children and older adults, and that negative SME in general serve as an important neural correlate of memory formation across the lifespan.

Negative SME in SFG partially mediated the relationship between age and memory

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

The relationship between negative SME and memory performance has not been previously shown in children, but has been reported in studies examining memory during young, middle and late adulthood (de Chastelaine et al., 2015, 2011; de Chastelaine & Rugg, 2014; Duverne, Motamedinia, & Rugg, 2009; Miller et al., 2008; Mormino et al., 2012; Park et al., 2013). De Chastelaine & Rugg (2014), Mormino et al. (2012), and Park et al. (2013) reported positive relationships between the strength of the negative SME, averaged across all ROIs showing negative SME, 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 & Rugg (2014) and Park et al. (2013) showed that only negative SME 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, Gordon, Smallwood, Smith, & Schooler, 2009; Maillet & Rajah, 2014b, 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 & Rajah, 2014a; Maillet & 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 & Rajah, 2016). In addition, this region has also been linked to the active suppression of memory in both children and young adults (Paz-Alonso, Bunge, Anderson, & Ghetti, 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 (McIntosh et al., 2010, 2014; Simmonds et al., 2007). In our current study, we found that increased negative SME in the superior PFC correlated with more consistency in RTs for subsequent Hit_S trials. It is therefore possible that the level of negative SME 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 SME. Specifically, PFC regions that were identified by age-related increases in positive SME showed age-related increases in PFC-MTL connectivity, whereas PFC regions that were identified by age-related increases in negative SME 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 SME regions in the PFC 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, Boyett-Anderson, & Reiss, 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 two 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 to 9. Paralleling these behavioral findings, increased functional connectivity between the lateral prefrontal cortex (IFG/MFG) and the hippocampus were 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, Sheridan, Kam, Hinshaw, & D'Esposito, 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.

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 parahippocampal gyrus 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 (Anticevic et al., 2012; Chadick & Gazzaley, 2011; Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010), whereas DMN regions show positive functional connectivity with other DMN regions and anti-correlation with task-positive regions (Anticevic et al., 2012; Chadick & Gazzaley, 2011). 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, & Witfield-Gabrieli, 2014) and task-positive vs. task-negative networks (Barber, Caffo, Pekar, & Mostofsky, 2013). These findings may reflect the presence of maturation processes that are observed as the inverse coupling of these two 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 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 SME. Positive SME have been demonstrated previously and likely influence memory through age-related increase in intentional cognitive control. To our knowledge, this is the first report of age-related increases in negative SME. 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 SME 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.

CHAPTER 2. MEMORY FORMATION AND THE DEVELOPMENT OF THE HIPPOCAMPUS

Introduction

Memory undergoes protracted development from childhood to adulthood. In the previous chapter, we have demonstrated developmental effects in the PFC supporting memory improvements from childhood to adulthood, consistent with previous studies (Ghetti & Bunge, 2012; Ofen, 2012). However, investigations on the functional development of the hippocampus portrays a far less clear picture. Studies on the developmental effects of the hippocampus contributing to memory development have yielded mixed results: the function of the hippocampus and its adjacent cortices have been found to show age invariance in some cases (Ofen et al., 2012, 2007; Shing et al., 2016), but positive correlations with age in others (Chai et al., 2010; DeMaster et al., 2013; Ghetti et al., 2010).

An important consideration when characterizing the involvement of the hippocampus is that its structure is heterogeneous, and its connectivity patterns differ drastically along the anterior-posterior axis (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Poppenk et al., 2008; Strange, Witter, Lein, & Moser, 2014). It has been shown that the granularity of encoded information increases systematically along the hippocampal long axis: anterior hippocampus preferentially encodes higher-order information, constructing memory gist, whereas posterior hippocampus preferentially encodes lower-order spatial and sensorimotor information, registering memory details (Lisman et al., 2017; Poppenk et al., 2013, 2008). In rodents, the most ventral region of the hippocampus, which is congruent to the primate anterior hippocampus, has a representational field 10 times larger than the most dorsal region, which is congruent to the primate posterior hippocampus (Kjelstrup et al., 2008). In addition, studies of humans and non-human primates have demonstrated relative segregation between anterior and posterior portions of the hippocampus,

such that anterior and posterior regions project to medial and lateral bands of the entorhinal cortex respectively, which are sparsely interconnected (Fanselow & Dong, 2010; Poppenk et al., 2013). Given the functional distinctions between hippocampal subregions, it is likely that the anterior and posterior hippocampus facilitate different aspects of encoding through their differential connections with the cortex.

To characterize the functional heterogeneity of the anterior and posterior hippocampus and their contributions to memory development, it is important to use methods that are sensitive and specific to the variability within this region. Functional studies on the development of the hippocampus to date, with the exception of a recent study (Geng, Redcay, & Riggins, 2019), either did not specifically segment the hippocampus from the whole brain, or utilized a probabilistic atlas for segmenting the hippocampus. Moreover, when the focus is assessing anterior compared to posterior hippocampal contributions in developmental studies, the hippocampus was commonly segmented using a predefined boundary, based on a priori determined y-coordinates (e.g., y = -21 as the boundary between anterior and posterior hippcoampus on the AAL hippocampal ROI; Tzourio-Mazoyer et al., 2002). Such a one-size-fits-all approach has been demonstrated in other applications to risk reducing the validity and sensitivity of hippocampal measures (Sandstrom et al., 2006; Wenger et al., 2014; Wisse et al., 2014). Poorly-constructed ROIs may misrepresent the signals from individual hippocampi, leading to the mixing of signals of different subregions or contamination from signals of the white matter and ventricles. These misrepresentations would greatly reduce the validity and reliability of measurements of hippocampal activations (Sandstrom et al., 2006). To fully understand the developmental trajectory of hippocampal subregions, it is ideal to assess their levels of activation with ROIs specified for each individual by leveraging

common anatomical expertise, as can be afforded with reliable manual segmentation of high-resolution MRI.

In addition to addressing a methodological issue for the measurement of hippocampal-specific contributions to memory development, the role of the hippocampus in the context of a larger functional network needs to be considered. Few previous studies have examined how patterns of functional connectivity with the hippocampus and surrounding medial temporal cortices differ from childhood to adulthood (Menon et al., 2005; Ofen et al., 2012; Tang et al., 2018). These few studies have consistently shown increased functional connectivity with age between medial temporal cortices and the PFC. When examined at rest, both young children (ages 4 to 10; Blankenship et al., 2017) and adults (Kahn, Andrews-Hanna, Vincent, Snyder, & Buckner, 2008; Poppenk & Moscovitch, 2011; Qin et al., 2016) display different patterns of connectivity with the anterior hippocampus as compared to the posterior hippocampus. Specifically, anterior hippocampus show more functional connectivity with anterior and ventrolateral temporal cortices, while posterior hippocampus show more functional connectivity with medial prefrontal cortex, lateral parietal cortex, posterior cingulate, and retrosplenial cortices (Kahn et al., 2008; Poppenk & Moscovitch, 2011; Qin et al., 2016). In young children, hippocampal functional connectivity with the cortex show largely overlapping developmental effects between anterior and posterior subregions, yet subtle differential developmental effects exist between hippocampal subregions and several frontal and temporal regions (Blankenship et al., 2017; Geng et al., 2019). While these studies provide insight into the development of connectivity patterns of hippocampal subregions in children, how connectivity patterns of hippocampal subregions develop from childhood to adulthood remains largely unknown. In addition, when examining the functional connectivity of the hippocampus, previous studies have demonstrated differential developmental patterns when

memory outcome was taken into consideration compared to when it was not (task-based vs task-free design; Geng et al., 2019). It is therefore important to characterize hippocampal functional connectivity during performance of a memory task both with and without taking into account differential connectivity patterns based on subsequent memory outcomes.

In this study, we investigated hippocampal activation and functional connectivity with a subsequent memory paradigm in a developmental sample with functional MRI. For improved validity of signal measurement in hippocampal subregions, we defined individual hippocampal ROIs with manual segmentation of high-resolution T2-weighted scans. Within these individually defined anterior and posterior hippocampus ROIs, we conducted several analyses, with the main goal of assessing age differences in subsequent memory-related hippocampal activations and in whole-brain hippocampal functional connectivity patterns. We conducted two separate whole-brain anterior and posterior hippocampal connectivity analyses, first without taking into account subsequent memory outcomes and second by directly assessing subsequent memory-related connectivity patterns. In the first analysis, we predicted an overall similar connectivity patterns of anterior and posterior hippocampal regions, however, by contrasting the anterior versus posterior hippocampal connectivity, we would identify differential connectivity of these regions similar to that identified in prior studies (Kahn et al., 2008; Poppenk & Moscovitch, 2011; Qin et al., 2016). In the second analysis, we also predicted an overall similar connectivity patterns of anterior and posterior hippocampal regions, but a direct comparison may identify differential connectivity with the medial PFC. This prediction is based on findings of strong modulation by memory outcome of connectivity between anterior hippocampus and the medial PFC (Preston & Eichenbaum, 2013; van Kesteren, Fernandez, Norris, & Hermans, 2010). Finally, and critical to our main aim, we assessed age effects in subsequent memory-related differential connectivity of anterior and

posterior hippocampal regions. Based on previous studies showing age-related differences in memory-related functional connectivity of posterior hippocampus and the PFC (Menon et al., 2005; Ofen et al., 2012; Tang et al., 2018), we predicted age differences in posterior hippocampal regional connectivity with the PFC. Taken together, with this large sample and across a wide age range, we aimed to characterize age differences in hippocampal reginal activation and connectivity patterns supporting memory performance. We predicted minimal age differences in subsequent memory activations. In contrast, we predicted that assessing regional hippocampal connectivity will allow us to identify robust age differences, hence underscoring the importance of functional connectivity in assessing the neural basis of memory development.

Methods

Participants

We obtained behavior and MRI data from 96 participants ages 8 to 25 (16.06 ± 4.73, 53% female). Participants were recruited from the Metro Detroit area, were right-handed, had normal or corrected-to-normal vision, and had no history of psychiatric or neurological disorders. Participants provided informed consent or assent as per a Wayne State University IRB-approved protocol and were compensated for their time spent in this study. Prior to the MRI session, the participants underwent extensive mock scanner training so that they were comfortable with the MRI environment. Data from additional 18 participants (14 children and 4 adolescents, 44% female) were collected but were excluded from the current analysis due to excessive head motion (average framewise displacement > 0.8 mm or any single framewise displacement > 6 mm).

MRI Data Acquisition

The T1-weighted and T2*-weighted data acquisition sequences are exactly as described in Chapter 1. In addition, a T2 high-resolution proton density-weighted turbo spin echo (PD-TSE)

sequence was included to obtain high resolution images for the hippocampus. Images were acquired in the coronal plane perpendicular to the long axis of the hippocampus with voxel time = 7150 ms, flip angle = 120º, pixel bandwidth = 96 Hz/pixel, voxel size = 0.42 mm x 0.42 mm x 2 mm (30 slices), TE = 17 ms, repetition limited field of view = 280 mm x 512 mm.

Data Analysis

Hippocampal manual segmentation and the generation of regions of interest

To accurately capture the signals in hippocampal subregions, we followed an established protocol to segment the hippocampus into head, body, and tail from contiguous slices obtained from the T2 high-resolution scan (Daugherty et al., 2015). Three raters (AMD, RF, and QY) segmented bilateral hippocampi ($0.4 \times 0.4 \times 2$ mm^3, coronal) with high reliability, as indicated by two-way mixed intraclass correlation coefficients [$ICC(2) \geq 0.85$ for left and right hemisphere separately, and $ICC(2) \geq 0.90$ for total bilateral measures; Shrout & Fleiss, (1979)]. The manual segmentation protocol was detailed in Daugherty et al. (2015) and the segmentation process was conducted in Analyze v11.0 (Biomedical Imaging Resource, Mayo Clinic College of Medicine, Rochester, MN, USA; See Fig. 2.1, left for a manually segmented hippocampus overlaid on top of the T1 structural image of that participant). Manual segmentation masks were then realigned and resampled to match individual functional images using in-house bash and MATLAB (Mathworks, Natick, MA, USA) scripts. Anterior and posterior hippocampal ROIs were constructed separately for left and right hippocampus per participant. The anterior hippocampal ROI was defined as the manually demarcated hippocampal head, while the posterior hippocampal ROI was defined as the manually demarcated hippocampal body and tail combined. Individual hippocampal ROIs were normalized to the MNI space after first-level univariate analysis (See below). To visualize the manually segmented ROIs, anterior and posterior hippocampal ROIs were averaged across all

participants to generate a coverage map (Fig. 2.1, right). Based on the coverage map, we observe that these ROIs respected the boundaries between anterior and posterior hippocampus and between hippocampus and surrounding brain structures.

[Figure 2.1]

Univariate fMRI analyses

Functional MRI data were analyzed with the SPM12 package (Wellcome Department of Imaging Neuroscience, London, UK) in MATLAB. Images were motion-corrected and smoothed with an 8 mm kernel. A GLM was constructed for each participant, including encoding trials for three separate runs.

For each run, individual-level analyses included regressors of interest with respect to subsequent memory outcomes. Regressors were modeled as subsequent hits and subsequent misses separately for high and low complexity scenes (Chai et al., 2010) to reduce possible differences related to scene complexity, which was not a focus of this investigation. Additionally, a single regressor was modeled for scenes with incorrect or no encoding (indoor/outdoor) responses to reduce possible differences due to encoding trials that were not sufficiently attended by the participant. Each encoding trial was modeled as an impulse function, convolved with a canonical model of the hemodynamic response function. Temporal derivatives were included for all conditions. For each run, 7 motion parameters were included, and outlier volumes were controlled, by including covariates calculated through the Artifact Detection Tools (ART; http://www.nitrc.org/projects/artifact_detect/; an outlier is defined as global mean intensity > 3 SD or framewise motion > 1 mm).

To measure the level of neural response to the subsequent memory task and the level of neural response specifically supporting encoding success, we computed 3 contrasts of interest in

each individual: (1) all Hits (vs implicit baseline), (2) all Misses (vs implicit baseline), and (3) Hit > Miss. Individual contrast maps and statistical maps (SPM *t*) were generated for each contrast, and together with individual hippocampal ROIs, were subsequently normalized to the MNI space.

To understand the effects of memory outcome (Hit vs Miss), hippocampal subregion (anterior vs posterior), and hemisphere (left vs right) on hippocampal activation, we extracted parameter estimates of the hippocampus for all combinations of these three factors, leading to 8 (2 × 2 × 2) variables. We excluded all data from a participant if any of the 8 extracted values from the participant were above 3 standard deviations from the mean of the respective variable. This exclusion criteria resulted in analyses for activations to be conducted within 92 participants. We conducted two ANOVAs. First, we examined memory-related activation across all participants by including the 8 extracted parameter estimates as dependent variables (DVs), and memory outcome (Hit vs Miss), subregion (anterior vs posterior), and hemisphere (left vs right) as independent variables (IVs), with no covariates included. After determining the overall effect of hippocampal subregions, we conducted an additional ANOVA with age as a covariate to examine age differences and approximate developmental effects in the hippocampus.

Functional connectivity fMRI analyses

We next investigated the patterns of functional connectivity in anterior and posterior hippocampus. First, we investigated the functional connectivity of anterior and posterior hippocampus during memory encoding regardless of memory outcome. Then we identified memory-related connectivity patterns across all participants. After that, we addressed the main question of this paper by investigating age effects in differential memory-related functional connectivity patterns between anterior and posterior hippocampus. Seeds of anterior and posterior hippocampal ROIs were generated based on individually demarcated tracing performed on high

resolution T2 images. Whole-brain connectivity maps with these individually defined anterior and posterior hippocampal ROIs were generated using the CONN toolbox (http://www.nitrc.org/projects/conn).

To facilitate the processing of the functional data in the CONN toolbox, we created an additional preprocessing stream where functional images and individual hippocampal ROIs were preprocessed similarly as the univariate analysis but were normalized to the MNI template prior to the first-level analysis. We modeled each trial as 3 s blocks to ensure stability in the connectivity estimation and included the same conditions as in the univariate analyses, with a main focus on memory outcome (Hit vs Miss). We extracted time-series data from bilateral anterior and posterior hippocampus, controlling for signals in the white matter, CSF, and for motion-related covariates (using the ART motion covariates as detailed above in the section describing the univariate analysis). We applied linear detrending and a high-pass filter of .008 Hz to the data. Seed-based connectivity analyses were conducted on the first-level in all four hippocampal seeds.

For group-level analyses, we created several sets of models. First, we assessed the patterns of anterior and posterior hippocampal functional connectivity during memory encoding irrespective of subsequent memory outcome. We further tested possible differential functional connectivity between anterior and posterior hippocampal ROIs during memory encoding irrespective of subsequent memory outcome. Second, we examined the patterns of anterior and posterior hippocampal functional connectivity that were directly related to encoding success by assessing differential connectivity patterns in Hit compared to Miss trials, hence referred to as memory-related functional connectivity. In these analyses, we examined separately memory-related functional connectivity with anterior and posterior hippocampus and further tested possible differential memory-related functional connectivity between anterior and posterior hippocampus.

Finally, to test possible age differences in the patterns of hippocampal subregion functional connectivity, we estimated the differential memory-related functional connectivity patterns between anterior and posterior hippocampus, including age as a covariate of interest and controlling for covariates that were not a target of this investigation: head motion (indexed by average framewise displacement) and recognition accuracy. These last sets of models were the target models of our study providing specificity in assessing age differences in differential memory-related functional connectivity between anterior and posterior hippocampus. All models were thresholded at $p < .005$ voxel level and corrected at $p < .05$ FDR. For visualization purposes, we extracted and plotted the parameter estimates of all significant clusters based on the results of group-level analyses.

Results

Behavior

For the subsequent memory paradigm, participants were highly accurate during the encoding task, classifying the pictures as depicting an indoor or outdoor scene (.95 ± .06). The accuracy for the encoding task did not differ by age ($r(83) = -.17$, $p = .11$). Participants' recognition accuracy, defined as the difference between the hit rate (rate of correctly recognizing a studied scene as "old" out of the number of studies scenes) and the false alarm rate (the rate of falsely accepting foils as "old" out of the number of foil scenes), was .32 ± .15 overall. Consistent with prior reports, recognition accuracy significantly increased with age ($r(94) = .46$, $p < .001$, Fig. 2.2).

[Figure 2.2]

Imaging

Hippocampal Subregion Activations Relating to Encoding Success

Given the inconsistency in characterizing developmental effects in hippocampal activations supporting subsequent memory in previous studies, we defined hippocampal ROIs based on manual segmentation of high-resolution hippocampal images, a method that provides more robust delineation of hippocampal subregions. We first investigated whether activations in bilateral anterior and posterior hippocampus supported encoding success and then examined whether activations in hippocampal subregions were modulated by age.

We extracted parameter estimates for Hit and Miss conditions from the anterior and posterior subregions separately for left and right hippocampus and conducted a memory outcome (Hit vs Miss) × subregion (anterior vs posterior) × hemisphere (left vs right) ANOVA. Four participants with univariate outliers in their extracted values were excluded from the analysis. We identified a main effect of memory outcome in both anterior and posterior hippocampus ($F(1, 91) = 60.41$, $p < .001$), such that significant SME (Hit > Miss) were found in all 4 hippocampal ROIs (left anterior: .98 ± 1.51, posterior: .98 ± 1.31; right anterior: 1.22 ± 1.89, posterior: 1.21 ± 1.36; all ps < .001) (Fig. 2.3A-B).

In addition, we identified two main effects in overall activation, regardless of memory outcome. First, we identified a main effect of subregion ($F(1,91) = 260.52$, $p < .001$), such that posterior hippocampus showed overall higher activation than anterior hippocampus (anterior: .65 ± 1.52, posterior: 2.82 ± 1.45, $t(91) = 16.14$, $p < .001$). Second, we identified a main effect of hemisphere ($F(1,91) = 21.67$, $p < 0.001$), such that the right hippocampus showed higher activation than the left hippocampus (left: 1.49 ± 1.36, right: 1.98 ± 1.50, $t(91) = 4.66$, $p < .001$). We also observed an interaction between memory outcome and hemisphere ($F(1,91) = 7.35$, $p = .008$), such

that SME observed in the right hippocampus were higher compared to those in the left hippocampus (left: .99 ± 1.34, right 1.22 ± 1.50, $t(91) = 2.71$, $p = .008$). Overall, these findings were consistent with previous studies and highlighted the role of both anterior and posterior hippocampus in supporting encoding success. Furthermore, the results pointed to stronger activation in posterior hippocampus and in right hippocampus, with activations in right hippocampus more directly linked to encoding success.

Next, we investigated possible age differences in hippocampal activations that support encoding success across subregions and hemispheres. Similar as before, we conducted a memory outcome (Hit vs Miss) × subregion (anterior vs posterior) × hemisphere (left vs right) ANOVA and included age as a covariate. Age was unrelated to hippocampal activation ($F(1,90) = 2.18$, $p = .14$), and did not interact with effects of memory outcome ($F(1,90) = 1.85$, $p = .18$), subregion ($F(1,90) = .08$, $p = .78$), or hemisphere ($F(1,90) = 3.07$, $p = .08$) (Fig. 2.3C-D). In this model when age was included, memory outcome was not significant ($F(1,90) = .71$, $p = .40$), but there were significant main effects of subregion ($F(1,90) = 22.05$, $p < .001$) and hemisphere ($F(1,90) = 8.89$, $p = .004$).

[Figure 2.3]

Hippocampal Functional Connectivity

To characterize the patterns of functional connectivity with anterior and posterior hippocampus and how age and memory outcome modulate this pattern, we conducted several connectivity analyses using the CONN toolbox. Since there were no significant hemisphere × subregion or hemisphere × memory outcome interactions, we elected to conduct group-level connectivity analyses combining results from left and right hippocampus in order to increase the

statistical power to identify the patterns of functional connectivity in anterior and posterior hippocampus.

Hippocampal functional connectivity irrespective of memory outcome

We first investigated patterns of functional connectivity during memory encoding regardless of subsequent memory outcome, separately for anterior and posterior hippocampal ROIs. We identified similar patterns of functional connectivity for both regions (Fig, 2.4A-B). Anterior and posterior hippocampus showed positive functional connectivity with IFG, lateral and middle temporal lobe, and midline structures. Anterior and posterior hippocampus showed negative functional connectivity with middle/superior frontal gyrus and inferior parietal lobule ($p < .05$, FDR corrected for all subsequent analyses; red: positive functional connectivity, blue: negative functional connectivity).

While the pattern of functional connectivity was visually similar between hippocampal subregions, we identified significant differences in the patterns of connectivity between anterior and posterior hippocampus when directly contrasting their respective connectivity maps. We observed that anterior, compared to posterior hippocampus, showed relatively higher functional connectivity with regions in the anterior temporal lobe, orbitofrontal, inferior frontal gyrus, and premotor cortex. In contrast, posterior, compared to anterior hippocampus, showed relatively more functional connectivity with regions in the medial and lateral frontal lobe, inferior parietal lobule, precuneus, and occipital lobes (Fig. 2.4C, $p < .05$, FDR corrected for all subsequent analyses; red: functional connectivity anterior > posterior hippocampus, blue: functional connectivity posterior > anterior hippocampus). These findings obtained when investigating functional connectivity patterns during encoding irrespective to subsequent memory outcome are in line with prior findings obtained when investigating differential anterior/posterior connectivity during rest in both

adults (Kahn et al., 2008; Poppenk & Moscovitch, 2011; Qin et al., 2016) and children (Riggins, Geng, Blankenship, & Redcay, 2016). The degree to which differential anterior posterior connectivity patterns were directly related to memory outcome, however, can only be assessed if analyses included direct measures that were gathered with respect to subsequent memory outcome. Thus, we next carried out analyses to assess potentially different roles the functional connectivity of hippocampal subregions played in memory formation by employing measures of differential functional connectivity with subsequent memory outcome.

[Figure 2.4]

Hippocampal functional connectivity related to memory outcome

Patterns of anterior and posterior hippocampal functional connectivity that were linked to subsequent memory outcome were computed by assessing differential functional connectivity of these regions between the Hit and Miss trials. Overall, anterior and posterior hippocampus showed lower memory-related functional connectivity to precuneus, middle temporal gyrus, and inferior parietal lobule during Hit compared to Miss trials (Fig. 2.5A-B; purple: lower functional connectivity). The regions that showed a reduction in memory-related functional connectivity resemble those in the default mode network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008).

[Figure 2.5]

We next identified regions that showed differential memory-related functional connectivity with anterior compared to posterior hippocampus. Only one region was identified with this analysis, located within the medial PFC (mPFC). Specifically, we identified a relatively lower memory-related functional connectivity of anterior compared to posterior hippocampus with the mPFC (Fig. 2.5C). Follow-up analyses demonstrated low functional connectivity between anterior

hippocampus and mPFC specifically for Hit trials. In contrast, high functional connectivity was observed between anterior hippocampus and mPFC for Miss trials, and between posterior hippocampus and mPFC for both Hit and Miss trials (Fig. 2.5D). Thus, memory-related functional connectivity was observed between anterior hippocampus and mPFC due to lower functional connectivity between these regions for Hit trials, indicating reduced coactivation between these regions being beneficial to memory formation. Overall, with these analyses we identified fairly similar patterns of memory-related functional connectivity of anterior and posterior hippocampus, with differential memory-related functional connectivity found in the mPFC.

Hippocampal functional connectivity with age

We next turned to examine age differences in differential memory-related functional connectivity of anterior and posterior hippocampus. To achieve this, we created additional connectivity analyses which modeled connectivity patterns per subregion by memory outcome, including age as a covariate of interest and controlling for covariates of non-interest (head motion and recognition accuracy). We identified several regions that showed differential memory-related functional connectivity with anterior and posterior hippocampus that were modulated by age. These included regions in the IFG, superior frontal gyrus (SFG), postcentral gyrus, and occipital lobe. In each of these regions, we extracted the parameter estimates for the connectivity effects to assess their specific relations with age.

Anterior and posterior hippocampus showed differential age effects in their memory-related functional connectivity with regions in the PFC (Fig. 2.6A-B). Anterior hippocampus showed age invariance in memory-related functional connectivity with IFG ($r(94) = -.09$, $p = .39$) and SFG ($r(94) = .04$, $p = .69$). However, posterior hippocampus showed an age-related increase in memory-related functional connectivity with IFG ($r(94) = .29$, $p = .004$), but an age-related

decrease in memory-related functional connectivity with SFG ($r(94) = -.25$, $p = .01$). Overall, posterior hippocampus showed a pattern of memory-related functional connectivity with the PFC that may be reflecting a dynamic shift across development. With an increase of age, memory-related functional connectivity between posterior hippocampus and SFG decreased, whereas memory-related functional connectivity between posterior hippocampus with IFG increased. These effects may represent the utilization of differential memory strategies supporting encoding success across development.

[Figure 2.6]

Memory-related functional connectivity of the anterior and posterior hippocampus differed by age also with regions in the occipital lobe and precentral gyrus (Fig. 2.6C-D). Posterior hippocampus showed age invariance in its memory-related functional connectivity with regions in the postcentral gyrus ($r(94) = .06$, $p = .56$) and occipital lobe ($r(94) = .11$, $p = .27$). In contrast, anterior hippocampus showed an age-related decrease in functional connectivity with the postcentral gyrus ($r(94) = -.27$, $p = .009$), and non-significant trend in age-related decrease in functional connectivity with occipital lobe ($r(94) = -.14$, $p = .18$). Overall, these findings suggest that children compared to adults evince higher memory-related functional connectivity of the anterior hippocampus with visual and sensorimotor regions.

Discussion

In this study, we examined the activation and connectivity patterns of anterior and posterior hippocampus that supported memory formation and evaluated age differences therein. Both anterior and posterior hippocampus showed robust SME that were relatively stable from age 8 to 25 years. Hippocampal subregions exhibited differential functional connectivity during memory encoding irrespective of memory outcomes, such that anterior hippocampus showed stronger

functional connectivity with inferior frontal gyrus and lateral temporal cortex, while posterior hippocampus showed stronger functional connectivity with medial and superior frontal lobe, inferior parietal lobe, precuneus, and occipital lobe. Both anterior and posterior hippocampal regions showed lower memory-related functional connectivity with key regions in the default mode network, including precuneus, middle temporal gyrus, and inferior parietal lobule. In addition, we identified differential memory-related functional connectivity between anterior and posterior hippocampus with the mPFC, specifically a relative lower functional connectivity between anterior hippocampus and mPFC relating to encoding success. Differential memory-related functional connectivity of anterior and posterior hippocampus with several cortical regions was modulated by age. Overall, these age differences in connectivity patterns suggest a shift in memory-related functional connectivity between posterior hippocampus and regions in the PFC, as well as reduced degrees of memory-related functional connectivity between anterior hippocampus and occipital and precentral cortical regions.

Our findings of robust SME in the anterior and posterior hippocampus and their relative stability across age are consistent with some of the previous findings utilizing subsequent memory paradigms with either pictorial or verbal stimuli that showed age invariance in hippocampal activations (Ofen et al., 2007; Shing et al., 2016). In other studies, researchers have identified age differences in hippocampal subsequent memory activations; yet these effects were not systematically assessed with respect to the anterior versus posterior delineations of the hippocampus. Examination of these age differences in SME reported in previous studies suggests that they are localized in the specific regions in anterior or posterior regions of the hippocampus (DeMaster & Ghetti, 2013; Ghetti et al., 2010). Here, we attempted to investigate age differences in subsequent memory activations systematically, parsing the hippocampus to anatomically

defined anterior and posterior subregions. The strength of our approach is that we extracted fMRI signals from anterior and posterior hippocampal ROIs that were generated based on manual demarcation of these regions on specialized high-resolution hippocampal structural MR images (0.4 × 0.4 mm in-plane resolution) using a valid and reliable protocol (Daugherty et al., 2015). This approach may have allowed us to account for more of the individual differences in structural features in anterior and posterior hippocampus and resulted in higher fidelity in representing fMRI signals in these regions in children and across the age range investigated here. In sum, our findings are consistent with the notion that there is relative stability in hippocampal activations supporting subsequent memory across age between middle childhood and young adulthood.

Patterns of functional connectivity with hippocampal subregions over a wide age range from children to adults were not reported in prior studies. Although we identified overall similarity in the patterns of functional connectivity of the anterior and posterior hippocampus during the encoding of scenes in preparation for a later recognition test, there were also marked differences when those patterns were directly contrasted. Anterior, compared to posterior, hippocampus showed more functional connectivity with inferior PFC and anterior temporal lobe, whereas posterior, compared to anterior, hippocampus showed more functional connectivity with the medial and superior frontal gyrus, inferior parietal lobule, precuneus, and occipital lobe. These differential functional connectivity effects during a memory task are consistent with previous studies showing differential functional connectivity with the hippocampus during rest in both children and adults (Blankenship et al., 2017; Kahn et al., 2008; Poppenk & Moscovitch, 2011; Qin et al., 2016). Together, these findings suggest that differential functional connectivity patterns along the long axis of the hippocampus may serve as an intrinsic feature that persists with age and across different task demands.

Next, to understand how patterns of anterior and posterior hippocampal functional connectivity support encoding success, we computed the whole-brain hippocampal functional connectivity during the encoding of scenes that were subsequently remembered (Hits) compared to those that were subsequently forgotten (Misses). We computed these subsequent memory-related functional connectivity patterns separately for anterior and posterior hippocampus and also assessed the difference in these patterns in direct contrast of the patterns for anterior and posterior hippocampus. We identified lower functional connectivity of both anterior and posterior hippocampus with several cortical regions in the DMN, including medial PFC cortex, inferior parietal lobule, and precuneus. In addition, when considering brain regions where anterior and posterior hippocampal connectivity differed to support encoding success, we observed differential memory-related functional connectivity of anterior compared to posterior hippocampus with the medial PFC, where decreased functional connectivity between anterior hippocampus and medial PFC was indicative of successful memory encoding. This finding is consistent with prior findings of strong modulation by memory outcome of connectivity between anterior hippocampus and the medial PFC (Preston & Eichenbaum, 2013; van Kesteren et al., 2010). Thus, an overall reduced connectivity of anterior compared to posterior hippocampus with medial PFC is indicative of selective subsequent memory-related modulation of functional connectivity between these regions and a possible differentiation of hippocampal functional connectivity with one of the DMN regions. Overall, extensive literature has highlighted the importance of the DMN in memory and other cognitive processes (Buckner et al., 2008; Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Christoff et al., 2009; Maillet & Rajah, 2016). During engaging cognitive tasks, regions in the DMN generally show reduced activation compared to rest, and has been suggested to engage in the suppression of mind wandering and unrelated thoughts to facilitate task performance (Christoff

et al., 2009; Maillet & Rajah, 2016). To support encoding success, it is likely that the hippocampus ramps up to promote information binding, whereas the DMN "quiets down" to suppress mind wandering and attentional shift. The mPFC, in particular, shares reciprocal structural connections with anterior hippocampus and serves as a main hub for the DMN (Buckner et al., 2008; Poppenk et al., 2013). Effective reduction in functional connectivity between anterior hippocampus and mPFC may be especially relevant for encoding success. Together, the findings that reduced functional connectivity between the hippocampus and DMN supports memory formation are consistent with previous research relating effective memory-related deactivation in the DMN to successful memory encoding (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014; Tang et al., 2018) and highlight a push-and-pull type of relations between hippocampus and DMN regions.

To address the main question of the study, which is to understand how differential functional connectivity between anterior and posterior hippocampus supports memory development, we examined regions in the brain whose differentiation of connectivity with hippocampal subregions differed by age during successful memory encoding. We identified regions including IFG, SFG, postcentral gyrus, and calcarine sulcus that showed such effects. Specifically, memory-related functional connectivity between posterior hippocampus and SFG decreased with age, whereas memory-related functional connectivity between posterior hippocampus and IFG increased with age. Memory-related functional connectivity between anterior hippocampus and both visual and sensory regions decreased with age.

Previous studies on differential hippocampal functional connectivity in young children have demonstrated a shift in the connectivity patterns between the hippocampus and PFC. For example, in children ages 4 to 8 years undergoing a subsequent memory task, differential functional connectivity between hippocampal subregions and IFG increased in older compared to

younger children (Geng et al., 2019). In another resting state study with children ages 4 and 6 years, anterior hippocampus showed positive functional connectivity with SFG in 6-year-olds, but negative functional connectivity for 4-year-olds (Riggins et al., 2016). The varying level of engagement between posterior hippocampus and different PFC subregions found in the current study can be understood in the context of the PFC facilitating strategy use. During memory formation, the PFC supports spontaneous use of elaborative mnemonic strategies, and the volume of dorsolateral regions of the PFC has been shown to mediate age-related increases in strategy use in a memory task (Yu et al., 2018). It is therefore possible that the shifting connectivity pattern between the hippocampus and PFC subregions underlie changes in the utilization of memory strategies. Alternatively, the simultaneous increase and decrease in the functional connectivity between PFC subregions and the hippocampus can be understood in the context of correlation and anti-correlation. In our previous study investigating the development of positive and negative SME in the PFC (Tang et al., 2018), we have identified an age-related increase in positive functional connectivity between medial temporal lobe (MTL) and IFG, but an age-related increase in negative functional connectivity, or anti-correlation between MTL and SFG. The current findings showing age-related increase in memory-related functional connectivity between posterior hippocampus and IFG but age-related decrease in memory-related functional connectivity between posterior hippocampus and SFG mirrored our previous findings, suggesting a dynamic shift in long-range functional connections between subregions of the hippocampus and subregions of the PFC.

In addition to the above-mentioned age effects in differential functional connectivity with posterior hippocampus, memory-related functional connectivity between anterior hippocampus and visual and sensory regions decreased with age. Consistent with the model of the anterior hippocampus supporting gist-based encoding in adults, the observed decrease in functional

connectivity between anterior hippocampus and visual/sensory regions from childhood to adulthood may suggest functional maturation with diminished detail-oriented processing. Together, these findings where the hippocampus show disengagement from irrelevant task highlight a potential developmental increase in the functional specialization along the long axis of the hippocampus.

In sum, we systematically investigated the development of activation and connectivity patterns of the hippocampus from middle childhood to adulthood. We found that while the level of activation in the hippocampus remained relative stability with age, anterior and posterior hippocampus showed distinct connectivity patterns supporting encoding success, which showed robust modulation by age. The age-related increase in differential functional connectivity with the hippocampus suggests an increased specialization of the hippocampus along its long axis and a shift in positive and negative functional connections with the neocortex to support effective memory encoding. Although we utilized stringent methods to examine hippocampal development with a relatively large sample size, our ability to characterize the signals in the hippocampus is limited by the resolution of the fMRI scans. Studies with high-resolution fMRI scans may be able to provide better understanding for the developmental effects in the hippocampus in the future. Furthermore, given the functional distinctions of hippocampus subfields and their potential developmental effects (Daugherty, Bender, Raz, & Ofen, 2016), future studies may examine the developmental patterns of different hippocampal subfields in children to provide a clearer picture of the development of the hippocampus.

CHAPTER 3. RELIABILITY IN IDENTIFYING MEMORY-RELATED REGIONS WITH FMRI

Introduction

In fMRI studies, the level of neural activity was approximated by measurable changes in the blood oxygen-level dependent (BOLD) signals in different regions of the brain. While this technique has proven to be instrumental in understanding the neural substrate of a range of cognitive behaviors, many factors can influence the ability to capture the true signal, raising questions regarding the reliability of fMRI measures. As the reliability of fMRI measures provides an upper bound for its validity, quantifying the reliability, ideally prior to conducting relevant analyses, becomes necessary.

Group-level and Individual-level Reliability

To systematically examine the reliability within the context of fMRI experiments, we recognize two kinds of reliability: group-level reliability and individual-level reliability. The group-level reliability refers to the level of consistency that is observed on the group averages of a measure of interest, be it performance measures or the group-level activation maps. On the other hand, individual-level reliability refers to the level of consistency that is observed on the data of each individual, e.g., performance measures or the activation maps of a participant across different visits.

Previous studies have shown clear distinctions between group-level and individual-level reliability using fMRI. FMRI results on a group level has shown to be highly replicable – systematic investigations have demonstrated an excellent group-level test-retest reliability across a wide range of cognitive tasks conducted with fMRI (reliability measured with inter-class correlation, or ICC, between .88 and .98; Plichta et al., 2012; Raemaekers et al., 2007). For cross-

sectional datasets that are prevalent in developmental research, group-level analyses and their variants are commonly used. To investigate age-related differences between children and adults, individual-level contrast maps are combined across multiple participants in a group-level GLM model, with age as either a grouping variable or a covariate. With a reasonably large sample size, fMRI has been shown to reliably identify memory-related regions, showing consistent activation across the PFC and MTL regions (Kim, 2011; Spaniol et al., 2009). In addition, reliable age differences during memory encoding and retrieval have been demonstrated and replicated. For example, IFG activation showed an age-related increase in supporting memory formation, as replicated across studies from different labs (DeMaster et al., 2013; Ghetti et al., 2010; Ofen et al., 2007; Tang et al., 2018). These results provide initial evidence for high *group-level* reliability using fMRI and, by association, lend support for investigating the developmental effect with cross-sectional designs.

While cross-sectional designs have proven instrumental in providing information on developmental differences in the brain, they may not adequately characterize true developmental effects, or *changes* within individuals (Herting et al., 2018; Maxwell & Cole, 2007). In contrast, longitudinal studies, with children and adults measured at multiple time points, afford the unique opportunity to characterize individual developmental changes while separating between-subject factors that influence observable differences. In order for individual-level comparisons with fMRI to be valid, measurements at *each time point* need to demonstrate a reasonable level of reliability.

While it is our desire that the fMRI measures obtained in one person at one time point would be highly consistent with the measures obtained on the same person the next time, this might not necessarily be the case. In a review of 13 fMRI studies that reported individual-level reliability of task-based fMRI in adults, the reliability index ICC averaged to .5 across all studies, suggesting

that the individual-level reliability falls in the "fair" range (Bennett & Miller, 2010). On a whole-brain level, the individual-level reliability is even lower, with a median in the "poor" range (Bennett & Miller, 2013; Caceres, Hall, Zelaya, Williams, & Mehta, 2009). Given the increasing prevalence of openly-available longitudinal datasets and a push towards a data-driven discovery science (Biswal et al., 2010; Herting et al., 2018), it is extremely necessary to understand the extent to which we can rely on individual level fMRI data to provide replicable results.

Although many have studied the reliability in fMRI under a range of cognitive and social paradigms, few have concentrated on the reliability of a memory task (Bennett & Miller, 2013; Brandt et al., 2013; Clément & Belleville, 2009; Harrington, Tomaszewski Farias, Buonocore, & Yonelinas, 2006; Putcha et al., 2011; Towgood et al., 2015). Of these few, the majority of studies were reported with samples of healthy older adults or with clinical/subclinical population (e.g., people with mild cognitive impairment, Alzheimer's, or epilepsy). For healthy adults, studies using a memory paradigm have found the test-retest reliability to be "poor to fair". For example, one study investigated one-month apart individual-level reliability with a novelty encoding paradigm, where they compared the level of activation in a sample of 15 young adults when they viewed blocks of novel items compared to when they viewed blocks of repeating items (Brandt et al., 2013). They found that the reliability of fMRI results in key memory regions to be "poor to fair" across the whole brain (ICCs ≤ 0.45) and "poor" in the MTL (ICC between 0 and .19). In another study with event-related episodic recognition task, a mean ICC of .30 was found across the whole brain (Bennett & Miller, 2013). These results call into questions the reliability in identifying memory-related regions using fMRI. To determine possible causes for a less than optimal level of reliability in identifying memory-related regions using fMRI, I outline the factors that may impact reliability in the next section.

Factors Impacting fMRI Reliability

Field strength

The ability to detect the BOLD signal from noise depends on an adequate signal-to-noise ratio (SNR) for the fMRI scan. Differences in the SNR between scans can significantly impact the comparability (Bennett & Miller, 2013; Raemaekers et al., 2007). In general, a larger field strength translates into higher SNR and is therefore more desirable for fMRI studies. For example, relative to a 1.5-Tesla magnet, a 3-Tesla magnet affords a 60% to 80% increase in the ability to identify significant effects (Hoenig, Kuhl, & Scheef, 2005). However, as the field strength increases, so do the artifacts induced by susceptibility and physiological noise (Bennett & Miller, 2010). For these reasons, a field strength between 3 and 7 Tesla is recommended for fMRI studies.

Motion

Although motion is a factor that is largely dependent on the participant rather than the experimenter, it has been shown to drastically reduce test-retest reliability. Motion alone can account for 20% to 23% total inter-session variance, as shown by previous studies (Gorgolewski, Storkey, Bastin, Whittle, & Pernet, 2013). With the same participant measured at multiple time points, either an increase of motion at one time point or a steady reduction of motion across multiple time points can seriously affect the interpretability of observed differences. In order to reduce the impact of motion in all time points, proactive mock scanner training is recommended and aggressive "data scrubbing" should be employed in the analytical pipeline (Bennett & Miller, 2013; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

Experimental design

In reliability studies, participants perform the same task multiple times, and the underlying brain activity can be influenced by a range of factors, including task demand, task performance,

task familiarity, and strategy use (Bennett & Miller, 2013; Herting et al., 2018). Previous research has shown large differences when estimating the reliability from different experimental tasks (Gorgolewski, Storkey, Bastin, Whittle, Wardlaw, et al., 2013; Plichta et al., 2012; Vetter et al., 2017). For example, differences in ICC were found between cognitive and emotional tasks (Gorgolewski, Storkey, Bastin, Whittle, Wardlaw, et al., 2013; Plichta et al., 2012; Vetter et al., 2017) and between different experimental paradigms targeting the same construct (Harrington et al., 2006).

While comparing different experimental paradigms is beyond the scope of this study, a commonly used and widely-validated experimental paradigm should be adopted for a reliability study. As participants will be performing the same task multiple times, it is expected that tasks that involve deception or omission of information, such as an accidental memory encoding task, where participants were not told about the follow-up recognition test until after encoding was completed, would not work for multiple visits. In addition, as the participants become more familiar with the task and its content, their performance increases. A reliability study, on memory especially, requires unique but counterbalanced stimuli for each visit.

Contrast types

For reliability studies of the same experimental paradigm, differences in the choice of fMRI contrast can drastically affect the reliability estimates. For example, in a study using fMRI to assess the reliability of functional activation of prosaccades and antisaccades (against the implicit baseline), reliability for a task vs. baseline contrast showed excellent reliability (ICC = .88), but the reliability for the main contrast of interest, antisaccades vs. prosaccades, showed only fair reliability (ICC = .43) (Raemaekers et al., 2007). In general, contrasts against implicit baseline yield higher reliability compared to contrasts with more effective controls (Aron et al., 2006;

Bennett & Miller, 2013). In conducting reliability experiments, researchers are often at liberty in choosing certain fMRI contrasts than others. However, without systematically considering specific contrasts, the comparison between two ICC values is meaningless. Therefore, when conducting reliability analyses, it is informative to report the reliability for a basic contrast, e.g., task vs. baseline, and a more effectively controlled contrast.

Time gaps between visits

To establish the reliability of fMRI measures, it is assumed that the underlying construct being measured by fMRI does not change over time. To examine the reliability in a developmental context, it is important to recognize that children learn new skills and adopt different cognitive strategies as they mature, and the stability for their brain functions is only temporary. Previous study investigating the onset of specific memory strategies in children as young as 6 demonstrated an abrupt "switching on" of strategy utilization within a 6-month span (Schneider, Kron, Hünnerkopf, & Krajewski, 2004). Newly developed skills and strategies could lead to completely different neural responses compared to previous time points, the equivalent of performing a different task (Church, Petersen, & Schlaggar, 2010). These differences may negatively impact the reliability of fMRI measures, if the developmental changes were incorrectly included as evidence for a lack of reliability. One previous reliability study (with a time gap of 3.5 years) found higher overall test-retest reliability for adults and adolescents compared to children, who showed poor reliability in all predefined ROIs (Koolschijn, Schel, de Rooij, Rombouts, & Crone, 2011). The observed low reliability could reflect factors intrinsically different about children, or it could reflect the misattribution of meaningful developmental changes within the 3.5-year gap as "unreliability". Therefore, for a fair estimation of reliability in young children, a shorter time gap between assessments is preferred. Although an optimal length of the time gap remains unknown,

for datasets aimed at estimating test-retest reliability, shorter intervals between few weeks to a month is preferable (Herting et al., 2018).

Methods for Quantifying fMRI Reliability

In quantifying test-retest reliability in fMRI measures, the intra-class correlation, or ICC was most widely used (Bennett & Miller, 2010; Caceres et al., 2009; Herting et al., 2018). ICC quantifies the reliability by calculating the ratio of between-subject variance to total variance. For test-retest reliability studies in fMRI, a two-way random model with absolute agreement, ICC(2), was commonly used. ICC(2) assumes that these assessments in the reliability study were random samples from a population of possible assessments, rather than considering the assessments as the only assessments, as in ICC(3) (Caceres et al., 2009; Shrout & Fleiss, 1979). ICC(2) is therefore more generalizable and more stringent than ICC(3).

An ICC value reflects the percentage of variance explained by between-subject variance and can be used to quantify the consistency in observed values between visits. Since it is a relative ratio between 0 and 1 (theoretically), it can be used to compare across different studies. Conventionally, ICC less than .4 indicates poor reliability; ICC between 0.41 to 0.59 indicates fair reliability, between 0.6 and 0.74 indicates good reliability, and between .75 and 1 indicates excellent reliability (Cicchetti, 2001).

For behavior measures, one ICC value can be calculated with an n (participants) x k (visits) matrix of values for that behavior measure. For whole-brain fMRI measures, one ICC value can be calculated per each voxel, with an n (participants) x k (visits) matrix of the values of that voxel, to quantify its reliability. A whole-brain ICC map can be generated by running the ICC calculation through all voxels in the brain (Caceres et al., 2009). Alternatively, a variant of ICC can be used to quantify the consistency in observed values in a range of voxels (ICCv; Caceres et al., 2009;

Raemaekers et al., 2007; Towgood et al., 2015). This method takes an m (voxels) x k (visits) matrix to derive one ICC measure to quantify the consistency in the values of these voxels between visits, which could be used to estimate the reliability between two individual-level or two group-level statistical maps.

Reliability of Functional Network

While functional activation in fMRI is commonly used to understand cognition, the patterns of brain functional connectivity, or inter-region coactivation, serve as a complementary descriptor for brain function activation. The changes of functional connectivity between key memory regions in response to task demands provide important information for understanding the neural substrate of memory formation and memory development. Previous studies have highlighted the relevance of functional connectivity between the PFC and the MTL regions in supporting episodic memory function, and some further demonstrated an age-related increase in the functional connectivity strength supporting memory improvements (Menon et al., 2005; Ofen et al., 2012; Tang et al., 2018). However, to our knowledge, the reliability of memory-related functional connectivity patterns has not been examined. Therefore, in addition to examining the reliability of functional activation identifiable by the fMRI, we are also interested in investigating the reliability in identifying functional connectivity patterns during a memory task.

Memory Paradigm for Assessing fMRI Reliability

To assess the reliability of fMRI specifically for memory, a suitable paradigm that consistently activates memory-related regions should be selected. The subsequent memory paradigm, as I have used in previous studies (described in Chapters 1 and 2), serves as a good candidate. The subsequent memory paradigm can be used to identify memory-related brain regions, by directly contrasting BOLD signals for remembered versus forgotten items (Dolan & Fletcher,

1997; Fletcher et al., 1998; Kim, 2011; Kim et al., 2010; Paller & Wagner, 2002). This paradigm has been shown effective in identifying memory-related regions across the lifespan, and its pictorial version works well with children (Ghetti et al., 2010; Maillet & Rajah, 2014a; Ofen, 2012). According to previous studies in adults, scene stimuli exhibit higher test-retest reliability compared to verbal stimuli (Brandt et al., 2013; Towgood et al., 2015). Therefore, a subsequent memory paradigm with scene stimuli is ideal for a reliability study.

Current Study

To determine the reliability of fMRI in identifying memory-related regions in children and adults, we scanned 24 participants at two different visits, approximately one month apart. We utilized a subsequent memory paradigm (as described in Chapter 1), where participants viewed indoor and outdoor scenes in the scanner and their memory of these scenes were tested after the scan. Given the influence of contrast choice on test-retest reliability, we considered two complimentary ones, (1) Task – Baseline and (2) Hit – Miss. We calculated both group-level and individual-level reliability of the functional activation based on these contrasts. We tested if age modulates test-retest reliability. Next, we explored group-level and individual-level reliability in the pattern of functional connectivity with three key memory regions, IFG, PHG, and the hippocampus.

Since the stimuli were carefully counterbalanced, I expect good reliability in the behavioral data. For functional activation, I expect similar group-level results for both visits. In addition, I expect good individual-level reliability in cortical regions, and fair reliability in subcortical regions. Based on previous literature (Koolschijn et al., 2011), I expect age effects in individual-level reliability. For functional connectivity, I similarly expect good reliability for IFG and PHG, but not for hippocampus.

Methods

Participants

Twenty-four participants ranging in age between 8 to 20 years were recruited from the community in Metro Detroit area. All participants were right-handed, had normal or corrected-to-normal vision with no history of psychiatric or neurological disorders. For child participants, their parents provided informed consent and they provided assent as per a Wayne State University IRB-approved protocol. In order to assess the reliability of fMRI in identifying the memory-related regions, all participants completed two fMRI visits, approximately one month apart. An additional four participants were excluded from the study due to incomplete data, technical difficulties, or excessive motion.

Subsequent Memory Paradigm

The subsequent memory paradigm is conducted similarly as described in Chapter 1. For the reliability study, the participants studied and were tested on different stimuli lists between two visits. For the encoding portion of the subsequent memory paradigm, we registered the reaction time (RT) for the indoor/outdoor response of each trial. For memory recognition, we quantified the rate at which participants correctly (Hit) or incorrectly (False Alarm, FA) recognized an image as previously studied.

MRI Data Acquisition

The T1-weighted and T2*-weighted data acquisition sequences are the same as described in Chapter 1. All participants included in this study underwent one structural scan and three consecutive functional runs for both of their visits, with exactly the same sequences.

Data Analysis

Behavior

Similar to what was described in Chapter 1, after memory recognition, encoding trials were categorized by memory outcome into Hit and Miss, whereas for the recognition memory test, foil were categories into FA and correct rejection (CR). As scene complexity is not a focus of the reliability study, we modelled but did not contrast between different levels of complexity in subsequent analyses. Memory performance was measured by the sensitivity index d' (z(Hit) – z(FA)) for both Visit 1 and Visit 2. We also quantified the average reaction time (RT) separately for Hit and Miss conditions.

Preprocessing

The functional data were preprocessed similarly as Chapter 1. Functional imaging data were analyzed with the SPM12 package (Wellcome Department of Imaging Neuroscience, London, UK). All functional images were motion-corrected, normalized to the Montreal Neurological Institute (MNI) template, and smoothed with an 8 mm full-width half-maximum Gaussian kernel. We similarly 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.

Functional activation

Univariate analyses were conducted to generate individual-level contrast maps, as described in Chapter 2. We generated two contrasts of interest, (1) task performance (Task – Baseline) and (2) subsequent memory (Hit – Miss) for each participant visit. Group-level analyses were conducted for each visit by combining individual-level contrast maps of all participants with

a one-sample *t*-test. After that, group-level effects of two visits were visualized, with *t*-values at Visit 1 plotted against *t*-values at Visit 2 (Raemaekers et al., 2007).

To quantify the reliability between two visits, we calculated the intravoxel ICC (ICCv) related to task performance and subsequent memory based on group maps of the corresponding contrasts. For functional activation, ICC values were calculated voxel-wise using the ICC_maps function from the ICC toolbox (Caceres et al., 2009), based on individual-level *t*-maps from both visits (Gorgolewski, Storkey, Bastin, Whittle, Wardlaw, et al., 2013). We measured two-way random ICC (absolute agreement) as follows:

$$ICC\ (2,\ 1) = (BMS - EMS) / (BMS + (k - 1)\ EMS + k(JMS)/n)$$

where BMS denotes between-subject mean square variance; EMS denotes residual mean square variance; and JMS denotes between judge mean square.

To determine the reliability of functional activation was modulated by age, we calculated ICCv for each individual and tested if there were age-related differences. In a complimentary analysis, we subdivided the sample into two groups (24 younger and 24 older) and calculated reliability maps for both task performance and subsequent memory contrasts in each age group.

Functional connectivity

Similar to what was described in Chapter 2, we conducted functional connectivity analyses with the CONN toolbox (http://www.nitrc.org/projects/conn). We modeled each trial as a 3-s block and included the same conditions as in the univariate analyses. We selected bilateral regions of interest (ROIs) including IFG, posterior PHG and the hippocampus from a 132-node Harvard-Oxford atlas, as implemented in the CONN toolbox. The mean time course from each ROI was calculated, while controlling for signals in the white matter, CSF, and for motion-related covariates

(using the ART motion covariates as detailed in Chapter 1). We applied linear detrending and a high-pass filter of .008 Hz to the data.

Whole-brain connectivity maps were generated for these anatomically-defined ROIs per each condition and participant visit, using a weighted-GLM approach. Individual contrast maps (task performance and subsequent memory) were combined on a group level for each visit using a one sample *t*-test. As the results for ROIs from left and right hemispheres were highly symmetrical, we reported findings based on three ROIs on the right hemisphere. Similar to functional activation, we generated group-level *t*-maps per contrast and per visit. We generated reliability maps for each contrast by calculating two-way random ICCs.

Results

Reliability of Performance Measures

All participants included in the subsequent analyses visited the imaging center twice (Age at Visit 1, mean ± SD: 13.31 ± 3.11), and the two visits were 30.26 ± 3.04 days apart. In order to examine whether participants performed consistently in the subsequent memory task between Visit 1 and Visit 2, we extracted the memory performance (d') for each participant visit and conducted several analyses. First, we compared group averages of memory performance of the two visits and found no statistical differences (Visit 1: .84 ± .42, Visit 2: .88 ± .52; $t(23) = .51$, $p = .62$, Fig. 3.1). Next, we examined the individual-level reliability of memory performance between two visits with the reliability index (ICC). We observed good test-retest reliability between the two visits (ICC = .62, 95% CI: [.30 .82]). As we were interested in probing possible age differences in test-retest reliability, we additionally calculated the reliability index for memory performance after regressing out the age-related variance. We obtained a slightly attenuated reliability when age was controlled (ICC = .55, 95% CI: [.19 .78]), with little evidence of an effects on test-retest reliability.

We also tested the reliability for the reaction time (RT), separately for both Hit and Miss conditions, given the significant difference in RTs between conditions, as described in Chapter 1. We found overall good test-retest reliability in RT for both conditions (ICC of RTs for Hit condition = .66; ICC of RT for Miss condition = .62).

[Figure 3.1]

To assess if the order of presentation influenced the reliability of memory performance, we calculated separately the d' for each of the three runs and conducted reliability analyses for each run. Since testing was conducted with images from all encoding runs, it was not possible to separate the FA rate by each run. We therefore approximated the FA rate for each run with the overall FA rate to calculate d'. We found that the ICC for run 1 (ICC = .43, CI: [.03 .71]) was numerically lower than for both run 2 (ICC = .57, CI: [.22 .79]) and run 3 (ICC = .58, CI: [.24 .80]), although the statistical significance cannot be determined due to the high confidence interval between the ICC measures.

In addition, we suspected that the reliability of memory performance may be impacted by the peculiarity of the scanner environment. To assess if the reliability performing the subsequent memory task differed in the scanner compared to in a conventional lab environment, we conducted the same test-retest reliability experiment in a sample of 10 young adults in the lab. We found that the ICC value for performing the task in a conventional lab environment was fair (ICC = .4).

Reliability of fMRI Activation Maps

Group-level reliability

Next, we examined whether we can identify, on a group level, similar patterns of activation in participants undergoing a subsequent memory tasks using fMRI. Given the influence of different

contrasts on the reliability measures, we hereby considered two contrasts: task performance (Task – Baseline) and subsequent memory (Hit – Miss). We first evaluated group-level activation similarities during task performance between two visits. Overall, we observed very similar activation maps across two visits (Figure 3.2; $p < .01$, 100 contiguous voxels for visualization purposes). For both visits, we found task-related activation in inferior frontal, lateral occipital, and superior parietal gyri. We also found task-related deactivation in several regions of the DMN, including medial prefrontal cortex, inferior parietal lobe, and superior frontal gyrus.

[Figure 3.2]

Next, we focused on the subsequent memory contrast and evaluated if we can identify reliable SME in the current sample. Furthermore, we evaluated if the patterns of SME were consistent between the two visits. Consistent with previous literature on the subsequent memory task, we identified canonical SME in several key brain regions (Kim, 2011; Ofen et al., 2007; Tang et al., 2018). Specifically, we identified positive SME (Hit > Miss) in IFG, PHG, and middle occipital lobe. We identified negative SME (Miss > Hit) in superior frontal gyrus, medial prefrontal cortex, and inferior parietal lobe.

In order to examine if group-level activation maps differed between two visits for both task performance and subsequent memory contrasts, we extracted per voxel *t*-values for each group map and plotted the values at Visit 2 against that of Visit 1 (Fig 3.3). To quantify the reliability between the two group maps, we calculated the ICCv values for each contrast. We observed good to excellent voxel-wise reliability for task performance (ICCv = .91) and subsequent memory (ICCv = .70) contrasts.

[Figure 3.3]

To examine potential age effects on the group-level reliability across the two visits, we separated the dataset by the median age of the current sample (13 years old) and calculated the ICC maps of both contrasts separately for younger (age: 10.71 ± 1.46, [8.12, 12.71], 6M:6F, Fig 3.4) and older (age: 15.83 ± 2.05, [13.02, 20.18], 6M:6F, Fig 3.5) participants. For both younger and older participants, we found good reliability in IFG, PHG, and middle occipital lobe for both task performance and subsequent memory contrasts, similar to the findings based on the full sample. In addition, the reliability of the hippocampus was good in the task performance contrast, but remained poor in the subsequent memory contrast for both age groups.

[Figure 3.4]

[Figure 3.5]

Individual-level reliability

Next, we investigated test-retest reliability on the individual level, first of the task performance contrast and then of the subsequent memory contrast. For each contrast, we generated whole-brain reliability maps by calculating per-voxel ICC values between two visits and then thresholded the reliability maps by ICC > .6 (Fig. 3.2, right panel). For task performance, good reliability was found in several cortical regions, including bilateral IFG, PHG, lateral occipital lobe, cuneus, and posterior regions of the hippocampus (ICC > .6). In contrast, poor test-retest reliability was found in subcortical regions (ICC < .4) (Fig 3.2, upper right). For the subsequent memroy contrast, good reliability was observed in bilaral IFG, right PHG, and bilateral lateral occipital lobe (ICC > .6), whereas the hipppocampus showed poor reliability in the subsequent memory contrast (ICC < .4) (Fig 3.2, lower right).

As we were interested in age effects in the reliability of fMRI activation, for each contrast we computed an intravoxel reliability value (ICCv) for each individual and correlated the per-individual ICCv values with age. We found no age effects in the reliability for the Task – Baseline contrast ($r(22) = 0.02$, $p = 0.93$), but a trending age effect for the Hit – Miss contrast ($r(22) = 0.35$, $p = 0.09$) (Fig. 3.6).

[Figure 3.6]

Reliability of fMRI Connectivity

Lastly, in addition to examining the reliability of functional activation patterns with fMRI, we also examined the reliability of functional connectivity patterns. We calculated for each participant functional connectivity patterns with three seed-based ROIs (IFG, PHG, and the hippocampus), for both task performance and subsequent memory contrasts. We first examined group-level functional connectivity patterns of each of these three seed-based ROIs for both contrasts and both visits. Then we calculated a whole-brain reliability map assessing the similarity of the connectivity patterns for both contrasts.

We tested the reliability of seed-based functional connectivity patterns between two visits, when participants performed an encoding task (Task – Baseline), irrespective of subsequent memory of the encoded scenes. For the task performance contrast, group-level connectivity patterns based on the IFG seed ROI showed consistent patterns between visits in large areas of the cortex bilaterally (Fig. 3.7, top panel). We observed good reliability for the connectivity patterns across visits in distributed regions in frontal and partial cortices, but not in lateral occipital lobe or visual cortex (Fig. 3.7, top panel, right). As for the MTL, connectivity patterns based on the PHG seed ROI appeared similar between the two visits, with good reliability (ICC > .6) observed with both IFG and posterior/visual cortices (Fig. 3.7, middle panel). Finally, although connectivity

patterns based on the hippocampus seed ROI appeared similar in the two visits, these patterns evinced relatively lower reliability between the two visits (Fig. 3.7, bottom panel).

[Figure 3.7]

To understand the reliability of connectivity patterns that specifically relates to subsequent memory, we further investigated functional connectivity patterns for the subsequent memory contrast (Hit – Miss). Interestingly, we found little evidence of consistency in subsequent memory-related functional connectivity between the two visits for any of the three seed-based ROIs tested. Instead, only subtle and non-consistent functional connectivity effects were identified across these three regions (Fig. 3.8, left two panels). Across all ROIs, the connectivity effects specific to subsequent memory demonstrated poor reliability (Fig. 3.8, right panel).

[Figure 3.8]

Discussion

In this study, we investigated the reliability for performance and fMRI measures based on a commonly used subsequent memory task. We found that memory performance was very similar between two visits and demonstrated good reliability. We observed good to excellent group-level reliability on the fMRI activation. In addition, good individual-level reliability was observed in IFG and PHG regions for both the task performance (Task – Baseline) and subsequent memory (Hit – Miss) contrast, but not in the hippocampus for the subsequent memory contrast. Within our sample, we found ICC to not significantly differ by age. For functional connectivity patterns, we observed good reliability with IFG and PHG regions for task performance, but not with the hippocampus. Surprisingly, low reliability was observed for all functional connectivity patterns of the subsequent memory contrast. These findings are further discussed below.

From the behavior data of this study, we observed a consistent level of task performance between two visits. Group averages of memory performance did not differ between Visit 1 and Visit 2. In addition, we observed good individual-level reliability in memory performance (ICC = .62) and reaction time (ICC between .62 to .66). The level of reliability in our behavior result was in line with other cognitive and emotional studies investigating the reliability for behavior measures in and out of the scanner (Hedge, Powell, & Sumner, 2018; Van Den Bulk et al., 2013).

While performance measures suggested a certain level of correspondence between Visit 1 and Visit 2, it also highlighted the fact that a big portion of variance (about 40%) cannot be explained by the between-subject variance. There are multiple possible explanations for this observation. First, while we try to equate the stimuli between two visits, each participant studied different lists for the two visits. There is a likelihood that, while the overall memorability of the stimuli was equivalent between two visits, differences in stimuli-specific effects exist on an individual level, leading to the observed difference in individual memory performance. Second, the performance of participants could be influenced by other, domain-general factors, effectively rendering the participants to be in different cognitive states between visits. Examples for these factors include a range of variables that were not controlled in this study, such as sleep, concentration, and motivation. The variance of memorability and cognitive states could cause individual differences in memory performance between visits, even if these differences were not evident, perhaps even "cancelled out" on the group level.

In addition, the relatively modest reliability for this commonly-used subsequent memory task may be in the nature of its design. In a recent paper investigating the reliability of a range of widely-validated behavioral tasks, including Flanker, Stroop, and go/no-go tasks, Hedge et al., (2018) found that the reliability for the critical contrast in these tasks (e.g., RT of the incongruent

condition – RT of the congruent condition for the Stroop task) to be modest, with an ICC between .36 to .76. In theorizing this unexpected finding, the authors argued that well-established behavioral tasks, in order to provide higher differentiability between different groups (e.g., clinical and control groups), will by design produce low between-subject variance in favor of larger effect size (differences between groups). Statistically, the between-subject variance appears in the denominator in the calculations of *t*- or *F*- statistics, but it appears as the numerator in the ICC formula. Therefore, valid behavioral tasks likely by design have low individual-level reliability, as they generate low between-subject variance, which boosts the effect size for discovering between-group differences, but simultaneously reduces the reliability when the focus is on individual differences measures.

For fMRI data, we found overall good to excellent group-level reliability in functional activation and connectivity. These findings are consistent with previous studies showing high reliability in group-level activation across different experimental paradigms with fMRI (Aron et al., 2006; Plichta et al., 2012; Raemaekers et al., 2007). We can therefore infer that, when we average the functional activation for a fMRI paradigm with a reasonable number of participants, we can reliably establish the activation pattern for this paradigm. Since cross-sectional designs usually center around comparing different age groups or utilize a group-based model with age as a covariate, the findings of high reliability in group-level reliability lend support for the reliability of cross-sectional designs. On the other hand, when we investigated individual-level reliability, we found that, it is overall much attenuated compared to the group-level reliability. Good reliability is found in large areas of the cortex, but not in the subcortical regions. While good reliability was demonstrated in IFG, PHG, and the hippocampus for the task contrast, hippocampus showed poor reliability for the subsequent memory contrast, suggesting that memory-related

activation in the hippocampus may be unreliable on an individual level. Previous studies investigating the reliability of memory-related fMRI activation generally found low reliability in the hippocampus (Brandt et al., 2013; Clément & Belleville, 2009, but see Putcha et al., 2011). The accumulating evidence provides a cautionary note on the extent to which researchers should interpret memory-related effects in the hippocampus.

Although we hypothesized age differences in test-retest reliability with fMRI, based on one previous study that reported higher reliability in adults compared to children in a performance monitoring task (Koolschijn et al., 2011), we observed no such effect in this sample. Several possible explanations may account for these differences between studies. First, different paradigms were used in the two studies – in this study a subsequent memory paradigm was used, and in the other, a performance monitoring task with significant motor components. It is therefore possible that age effects do not exist when assessing the reliability of subsequent memory effects. Second, in this study we carefully controlled for factors like movement, which is known to generate spurious effects in developmental studies. Controlling for movement may have removed possible spurious age effects in reliability estimates. Third, we aimed to assess reliability that is not compounded by possible changes within individuals due to development and therefore kept a relatively short time gap between two visits. This is in contrast to the prior report that included a 3.5-years gap between visits. In fact, our current findings of a lack of age effects in reliability provide a critical evidence to contextualize and increase the validity of the interpretations made by Koolschijn and colleagues (2011), such that lower reliability in children can be taken as evidence of developmental changes. Taken together, our findings suggest it is possible that there are no systematic age differences in the reliability in identifying memory-related activation with fMRI.

For functional connectivity, we observed good group-level reliability for all selected ROIs. The IFG and PHG overall showed very similar group-level functional connectivity patterns between visits. However, good individual-level reliability in the functional connectivity with IFG was found in large areas of the fronto-parietal regions, but not in the occipital lobe; good individual-level reliability in the functional connectivity with PHG was found in inferior frontal gyrus and the occipital lobe, but not with superior frontal gyrus or interior parietal lobe. These findings suggest that although IFG and PHG are functionally connected regions (given their inclusion of each other in their connectivity map), the reliability of their functional connectivity pattern may reflect fundamental functional differences.

Although we found good reliability for the functional connectivity of the Task – Baseline contrast for all ROIs, we observed poor reliability of the Hit – Miss contrast. The reliability of functional connectivity measures observed is largely consistent with the literature, such that good reliability was found in baseline functional connectivity (Laumann et al., 2017; Zuo & Xing, 2014), whereas poor reliability was found with task-based functional connectivity (e.g., ICC between .21 to .36 for the connectivity patterns with three network hubs; Noble et al., 2017). Relatedly, the difference between two highly-correlated measures has shown to be less reliable than either measure considered alone (Hedge et al., 2018). By subtracting two condition, idiosyncrasy in the individual measurements is cancelled out. But this in turn increased the relative contributions of measurement error as compared to the now lower between-subject variance, which leads to lower observed reliability (See Fig. 4 in Hedge et al., 2018). Together, these findings call for additional caution specifically in interpreting functional connectivity findings that target subsequent memory effects. In our study, while we found prominent effects when comparing Task and Baseline, the difference in functional connectivity patterns between Hit and Miss conditions was not found. It

is possible that while the tasks generate small but detectable perturbations to the network, the different connectivity patterns between Hit and Miss conditions was too subtle to detect.

CONCLUSIONS

The overarching goal for my dissertation work is to characterize functional correlates in the brain that contribute to memory development. I used functional MRI measures obtained from a large sample of children and adults and focused my investigation on two key brain regions involved in memory, the PFC and the hippocampus. With this approach, I identified regional effects within the PFC and the hippocampus, adding new insights to previous efforts in characterizing functional correlates that contribute to memory development. However, a critical aspect that has not been systematically examined in fMRI studies of memory development is the reliability of the measures typically used. This is a critical consideration, particularly as the researchers in the field will be moving towards utilizing longitudinal study designs, assessing within-individual changes in functional correlates with memory over development. Thus, a particularly innovative focus of my dissertation work is to quantify the reliability of fMRI measures in identifying memory-related brain regions, in order to provide the context as to how developmental effects identified by fMRI studies should be interpreted. Below I summarize the main findings in my dissertation work. I then present my attempt at integrating the findings across studies. The importance of considering reliability in interpreting fMRI findings is discussed, highlighting current limitations and pointing to what I believe are fruitful avenues to generalize this work.

Several important new findings have emerged from the investigation of functional correlates of memory development. As for the contributions of the PFC to memory development, I showed in Chapter 1 that PFC subregions differentially support memory formation, with IFG showing memory-related activation and superior frontal gyrus showing memory-related deactivation. Interestingly, both memory-related activation and deactivation showed age effects, and memory-related deactivation in superior regions of the PFC mediated the relationship between

age and memory performance. Finally, PFC subregions showed dynamic age increases in their functional connectivity with MTL regions.

Focusing on the contribution of the hippocampus to memory development, I investigated how hippocampal subregions support memory formation and evaluated age differences therein in Chapter 2. I found robust subsequent memory effects which were relatively stable from ages 8 to 25 years in both anterior and posterior regions of the hippocampus. In addition, hippocampal subregions showed differential connectivity patterns during task performance, such that anterior hippocampus showed stronger functional connectivity with inferior frontal gyrus and lateral temporal cortex, while posterior hippocampus showed stronger functional connectivity with several DMN regions and the visual cortex. Additionally, I demonstrated age- and memory-related functional connectivity effects between PFC and hippocampal subregions.

In Chapter 3, I assessed the critical aspect of reliability in the fMRI measures of subsequent memory that are the basis of previous research, including the findings described here in Chapters 1 and 2. I investigated test-retest reliability of behavior and fMRI measures. On a group level, we observed good to excellent reliability for behavior measures and for fMRI activation. On an individual level, good test-retest reliability was observed for activation in both task performance and subsequent memory contrasts in IFG and PHG, but not in the hippocampus for the subsequent memory contrast. During the memory task (when Hit and Miss conditions were combined), we observed connectivity patterns with IFG, PHG and the hippocampus that were similar between visits. Reliability for the functional connectivity with the hippocampus was limited. Finally, when considering the patterns with respect to the subsequent memory contrast (contrasting Hit and Miss conditions), the reliability for functional connectivity was relatively low for all ROIs.

The findings presented in this dissertation highlight the consistency in findings obtained in different samples from different studies. Considering all three studies described in this dissertation, we found robust subsequent memory effects in both our full sample of 83 children and adults (age: 15.93 ± 5.08, 8 to 25) and in our reliability sample of 24 participants, most of which children and adolescents (age: 13.31 ± 3.11, 8 to 20) (Fig 3.2, bottom panel; Fig 4.1). In both samples, we found memory-related activation in large areas of the superior parietal lobe, occipital lobe, and PHG. We also found memory-related activation in the IFG with our full sample and in small clusters of the IFG with our smaller and comparatively younger reliability sample (Fig 3.2, bottom panel; Fig 4.1). In addition, we found remarkable consistency in memory-related deactivation in several DMN regions, including inferior parietal lobe, mPFC, and precuneus. Critically, replicating our findings in Chapter 1, we identified memory-related deactivation in superior regions of the PFC in the reliability dataset. Comparing to the individual ICC map, the regions where we found memory effects overlap with regions where we demonstrated acceptable test-retest reliability (Fig 4.1, top panel), including lateral occipital cortex, parahippocampal gyrus, inferior frontal gyrus, medial prefrontal cortex, and superior frontal gyrus. Similarly, regions where we found age differences are within, or adjacent to, regions where we observed good reliability.

On the other hand, subsequent memory activation in the hippocampus did not reveal age effects, but there were age- and performance-related effects in hippocampal functional connectivity with several cortical regions. The relatively low reliability in the activation and connectivity measures from the hippocampus constrain the interpretations of findings from the hippocampus. The low test-retest reliability in hippocampus fMRI measures likely contribute to the inconsistencies among the findings obtained in developmental studies (Chai et al., 2010; DeMaster et al., 2013; Ghetti et al., 2010; Ofen et al., 2012, 2007; Shing et al., 2016).

Another important aspect in characterizing the neural correlates of memory formation is assessing the functional connectivity patterns associated with successful memory formation. An open question in the developmental work aimed to characterize functional correlates that account for memory development is to understand the role of age differences in functional connectivity supporting memory development. Or framed more specifically, does functional connectivity between key memory-related regions, including the PFC and the MTL account for age differences in memory. Here, we provide additional evidence highlighting the central role of functional connectivity between PFC and MTL regions during memory formation, and that there is an age-related increase in the functional connectivity between these two regions. These results were further supported by good reliability in task-related functional connectivity with IFG and PHG (Fig. 4.2). While we identified good reliability in task-related functional connectivity, we found low reliability when considering the functional connectivity for the subsequent memory contrast in all the ROIs. The lack of reliability specific to the subsequent memory contrast could be due to the limited sensitivity in functional connectivity network to detect differences between closely-related conditions.

There are several limitations in our current studies. First, while we have a relatively large sample size for the cross-sectional sample (n = 83), our sample size for the reliability study is comparatively small (n = 24). As the reliability estimate and its confidence interval is strongly affected by sample size, a bigger sample size is likely to yield more accurate estimate of the reliability characteristics. Second, while we adopted a commonly used subsequent memory paradigm for these studies and the stimuli were counterbalanced between different participants and different visits, the intrinsic memorability of the stimuli for each participant visit may be different. These differences in the memorability of the stimuli could reduce the reliability across all studies.

Systematic quantification and norming of stimuli by memorability could help increase the reliability of the paradigm. Third, for the reliability study, we conducted the test-retest within a month. As the reliability appears to be only modest, it is interesting to test the reliability in shorter time frames, e.g., a week, or even an hour, to see if we observe higher reliability for shorter time gaps. Shorter gaps such as an hour will further help us understand if fMRI reliability is affected by the day-to-day fluctuations of cognitive states. Furthermore, additional analyses could be conducted, for example, comparing the between-run or split-half reliability can provide an upper bound for maximumly expected reliability.

Several important future directions are intriguing and motivate my ongoing and future research efforts. Apart from investigating developmental effects in memory, I have additionally examined the effect of aging on memory, in the form of mild cognitive impairment (Hayes et al., 2017), and have started to explore relevant themes in lifespan development of memory (Pruitt et al., under review). Another exciting avenue for my future research that have begun, while focusing on fMRI measures, is to explore cross-modal correspondence between findings from the fMRI and findings from intracranial EEG (iEEG). We were fortunate to have tested several patients with epilepsy, who underwent the subsequent memory paradigm with fMRI and were later monitored with iEEG. iEEG provides unparalleled spatial and temporal resolution, and using this technique, we have recently demonstrated that the spatiotemporal propagation of PFC activity and activity flow between PFC regions support memory formation in children (Johnson, Tang, Yin, Asano, & Ofen, 2018). In the future, building on the findings from this dissertation, I aim to corroborate fMRI and iEEG measures to further the investigation into the development of the memory system and to determine cross-modal reliability. Finally, based on information we obtained so far on

healthy children and adults, I hope to devise ways to define the healthy brain in the memory context, to differentiate between healthy and unhealthy brain functions, and to aid diagnosis and treatment.

APPENDIX

Table 1.1 Positive and negative SME in the PFC

Hemi.	Regions	BA	MNI Coordinates			*t* Values	Number of Voxels
			x	y	Z		
Positive SME							
R	Inferior Frontal Gyrus	44/6	40	8	28	7.71	1701
		45/44	44	32	12	5.80	
L	Inferior Frontal Gyrus	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 SME							
R	Middle/Superior Frontal Gyrus	10/9	24	54	22	7.95	7196
		9	24	44	40	6.43	
	Medial Frontal Gyrus	10	4	48	6	5.95	
L	Superior Frontal Gyrus	10	-28	50	-2	4.89	
		9	-24	54	24	3.17	
	Middle Frontal Gyrus	9	-40	40	28	4.63	

Prefrontal cortex regions showing positive (Hit Sure > Miss trials) and negative (Miss > Hit Sure trials) SME. The significance threshold is $p < .05$, corrected. Hemi., hemisphere; SM, subsequent memory; BA, Brodmann Area; MNI, Montreal Neurological Institute; R, right; L, left.

Table 1.2 PFC regions showing overlapping SM and age-related effects

Hemi.	Regions	BA	MNI Coordinates			*t* Values		Number of Voxels
			x	y	z	Main Effect	Correlation with Age	
Age-related Positive SME								
R	Inferior Frontal Gyrus *	44/6	44	6	26	6.32	1.74	128
	Precentral Gyrus	6	50	-4	34	3.26	2.02	
R	Inferior Frontal Gyrus *	45/44	44	32	12	5.80	2.02	166
L	Inferior Frontal Gyrus *	44/6	-44	6	26	6.76	2.29	397
Age-related Negative SME								
R	Superior Frontal Gyrus *	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	Superior Frontal Gyrus *	10	-22	54	-2	3.62	1.70	
	Middle Frontal Gyrus	10	-34	52	4	3.20	1.67	

Prefrontal cortex regions involved in memory development. ***Age-related Positive SME*** = (Hit Sure – Miss) inclusively masked by (Hit Sure – Miss) ∝ Age. ***Age-related Negative SME*** = (Miss – Hit Sure) inclusively masked by (Miss – Hit Sure) ∝ Age. The significance threshold is $p < .05$, corrected. * denotes the coordinates used as seeds for functional connectivity analyses. Hemi., hemisphere; SM, subsequent memory; BA, Brodmann Area; MNI, Montreal Neurological Institute; R, right; L, left.

Table 1.3 PFC regions showing age-related differences in the functional connectivity linked to memory formation

Seed Regions	Hemi.	Regions	BA	MNI Coordinates			*t* Values		Number of Voxels
				x	y	z	Main Effect	Correlation with Age	
IFG (BA 44/6; MNI Coordinates: 44 6 26)									
Age-related increases in FC									
	R	Parahippocampal Gyrus	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 Coordinates: 44 32 12)									
Age-related increases in FC									
	R	Parahippocampal Gyrus	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 Coordinates: 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	

Table 1.3 Continued

Seed Regions	Hemi.	Regions	BA	MNI Coordinates			*t* Values		Number of Voxels
				x	y	z	Main Effect	Correlation with Age	
Age-related increases in anti-correlated FC									
	R	Parahippocampal Gyrus	37/36	28	-48	-6	6.60	3.84	16317
		Middle Occipital Gyrus	19	36	-78	16	5.88	4.70	
	L	Middle Occipital Gyrus	19	-40	-78	2	5.93	2.95	
		Parahippocampal Gyrus	37	-26	-50	-6	5.76	4.59	
Medial frontal gyrus (BA 10; MNI Coordinates: 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	Parahippocampal Gyrus	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	
		Parahippocampal Gyrus	37	-30	-48	-6	3.93	2.51	

Brain regions involved in memory development that are functionally connected to PFC regions where SME 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 $p < .05$, corrected. Hemi., hemisphere; SM, subsequent memory; BA, Brodmann Area; MNI, Montreal Neurological Institute; FC, functional connectivity; R, right; L, left.

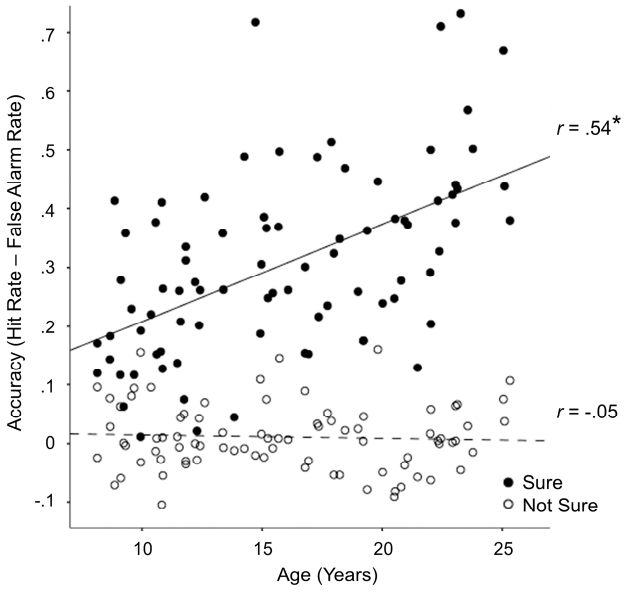

Figure 1.1 Adjusted recognition accuracy by confidence and age. Recognition accuracy (Hit rate – False Alarm rate) for high-confidence (Hits with "Sure" responses) scenes increased with age, $r(81) = .54, p < .001$, but recognition accuracy for low-confidence (Hits with "Not Sure" responses) scenes did not, $r(81) = -.05, p = .64$.

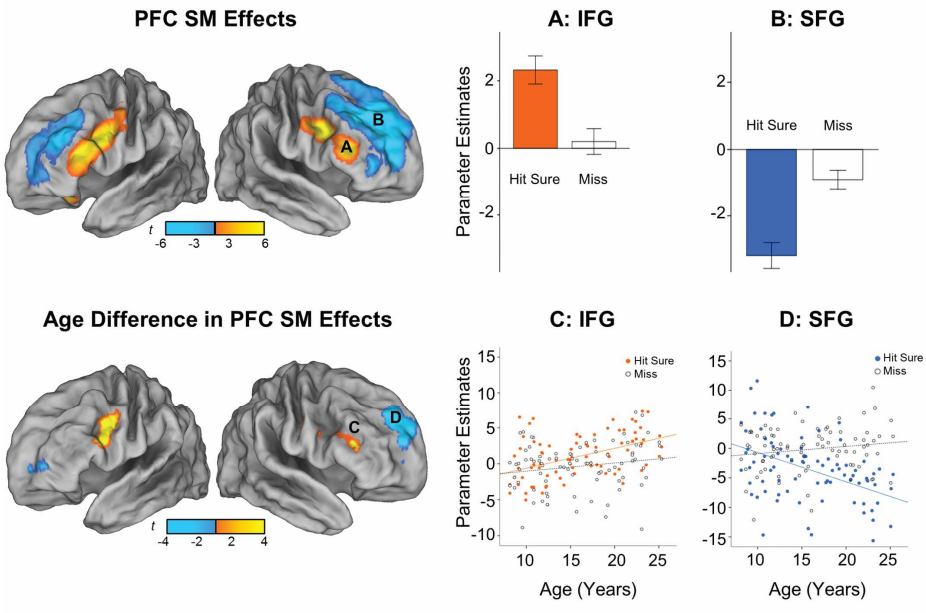

Figure 1.2 PFC regions showing positive and negative subsequent memory (SM) effects and age-related differences in these SME. **A.** Positive SME (shown in red) were observed in bilateral IFG. **B.** Negative SME (shown in blue) were observed in bilateral SFG. **C.** Positive SME in bilateral IFG increased with age (shown in red). **D.** Negative SME in bilateral SFG and medial PFC increased with age (shown in blue). The significance threshold for the *t* maps shown on the left is $p < .05$, corrected. IFG, inferior frontal gyrus; SFG, superior frontal gyrus.

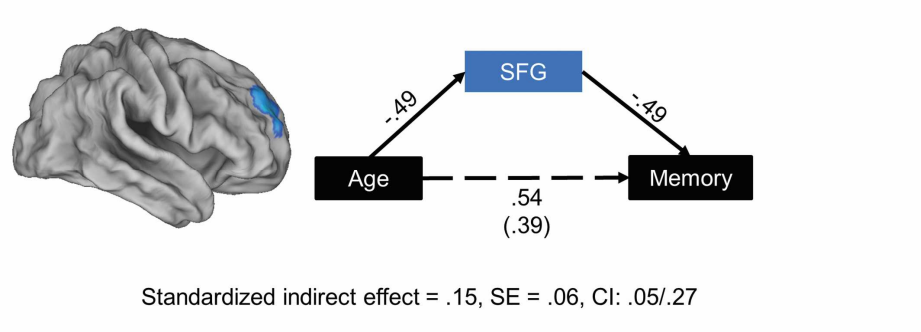

Figure 1.3 Negative SME in right SFG mediates the relationship between age and memory performance. SME in the right SFG (shown in white, left panel) mediated the effect of age on memory performance (right panel). Age was directly related to improved memory performance, but it was also indirectly related 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 $p < .001$ and numbers for each path are the standardized Beta weights. SE, standard error; CI, confidence interval.

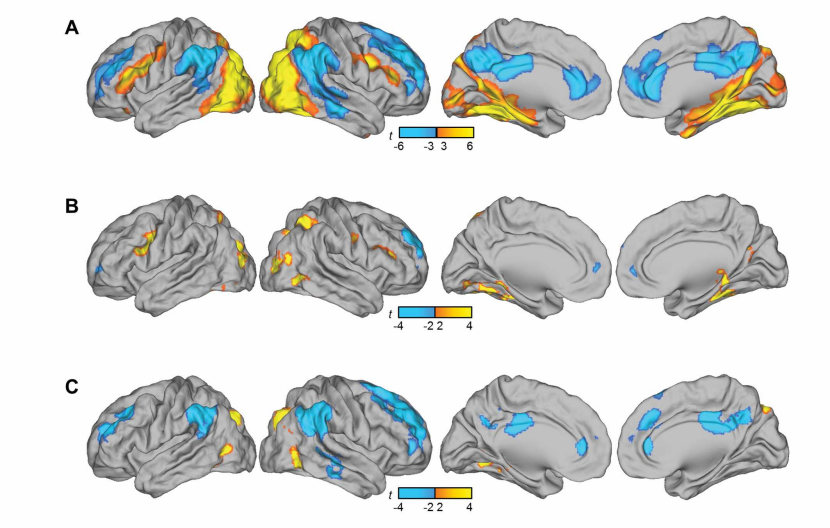

Figure 1.S1 Brain regions showing positive and negative subsequent memory (SM) effects (**A**), age-related SM effects SM effects (**B**), and performance-related SM effects (**C**). Positive SM effects were shown in red, and negative SM effects were shown in blue. Conjunction analyses were used to identify regions that showed SM effects that differ by age and performance. The significance threshold for the *t* maps shown is $p < .05$, corrected.

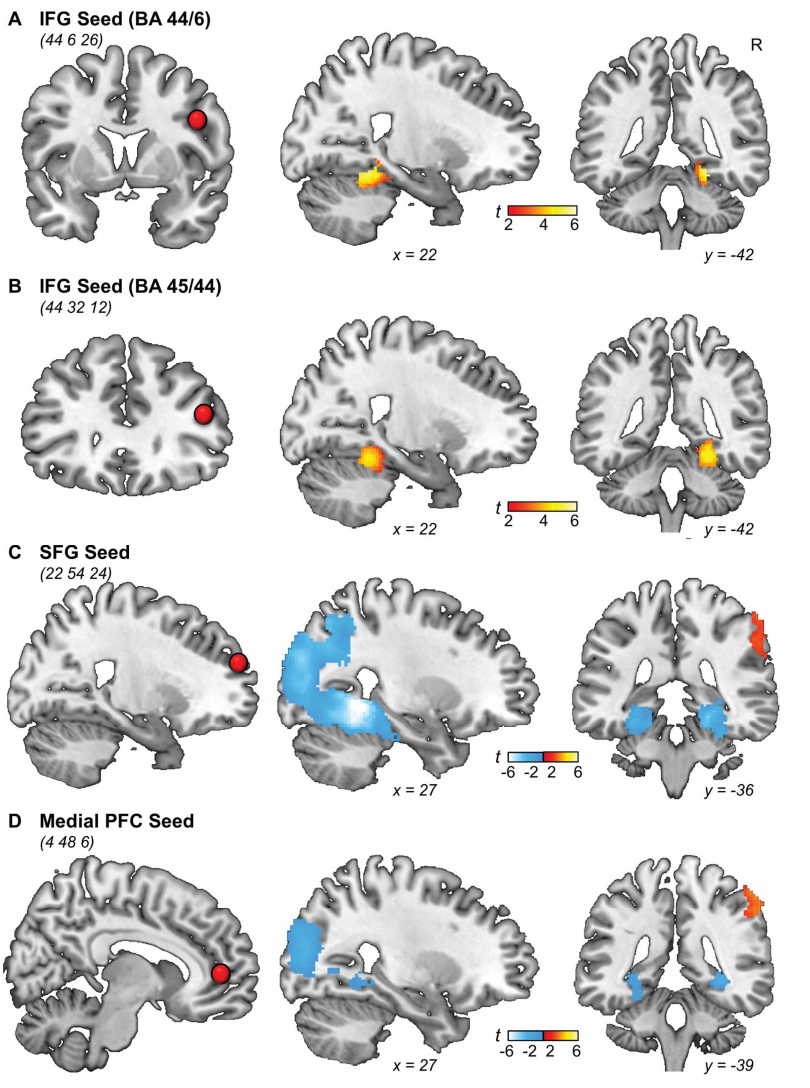

Figure 1.4 PFC regions showing age-related differences in the functional connectivity linked to memory formation. **A and B.** Age-related increase in the functional connectivity between IFG and PHG (shown in red). **C.** Age-related increase in functional connectivity between SFG and IPL (shown in red), 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 $p < .05$, corrected. IFG, inferior frontal gyrus; SFG, superior frontal gyrus; PHG, parahippocampal gyrus; IPL, inferior parietal lobule.

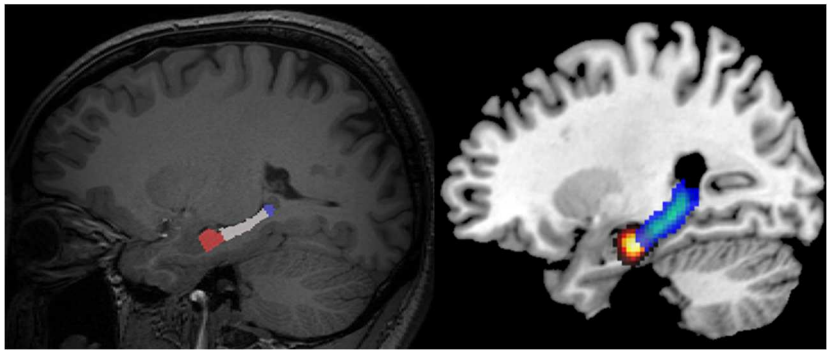

Figure 2.1 Segmentation of the hippocampus and construction of hippocampal regions of interest. Left: Manually segmented hippocampal head (red), body (white), and tail (blue) from one participant, based on a T2 high-resolution hippocampal scan (not shown), overlaid onto the T1 structural scan of this participant. Right: A coverage map showing the average anterior (red) and posterior (blue) hippocampal ROIs across all participants.

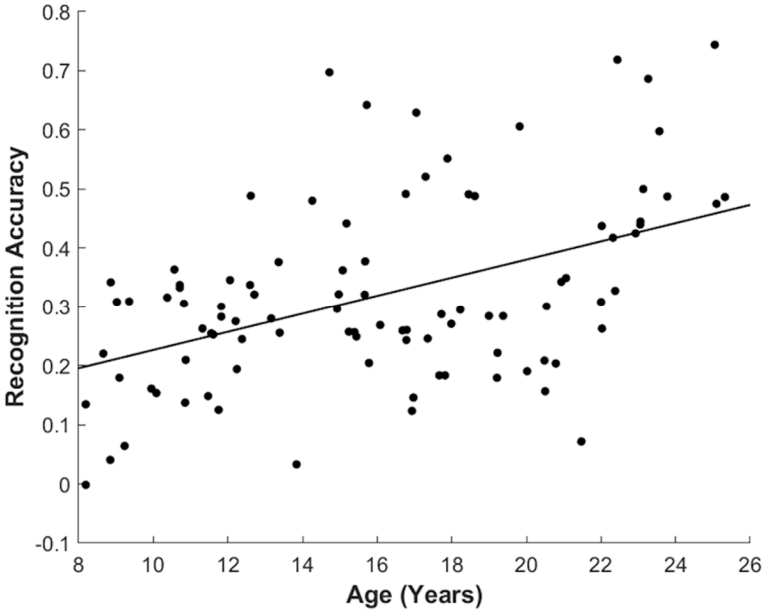

Figure 2.2 Recognition accuracy by age. Across all participants, recognition accuracy (Hit rate – False Alarm rate) showed significant increase with age ($r(94) = .46$, $p < .001$)).

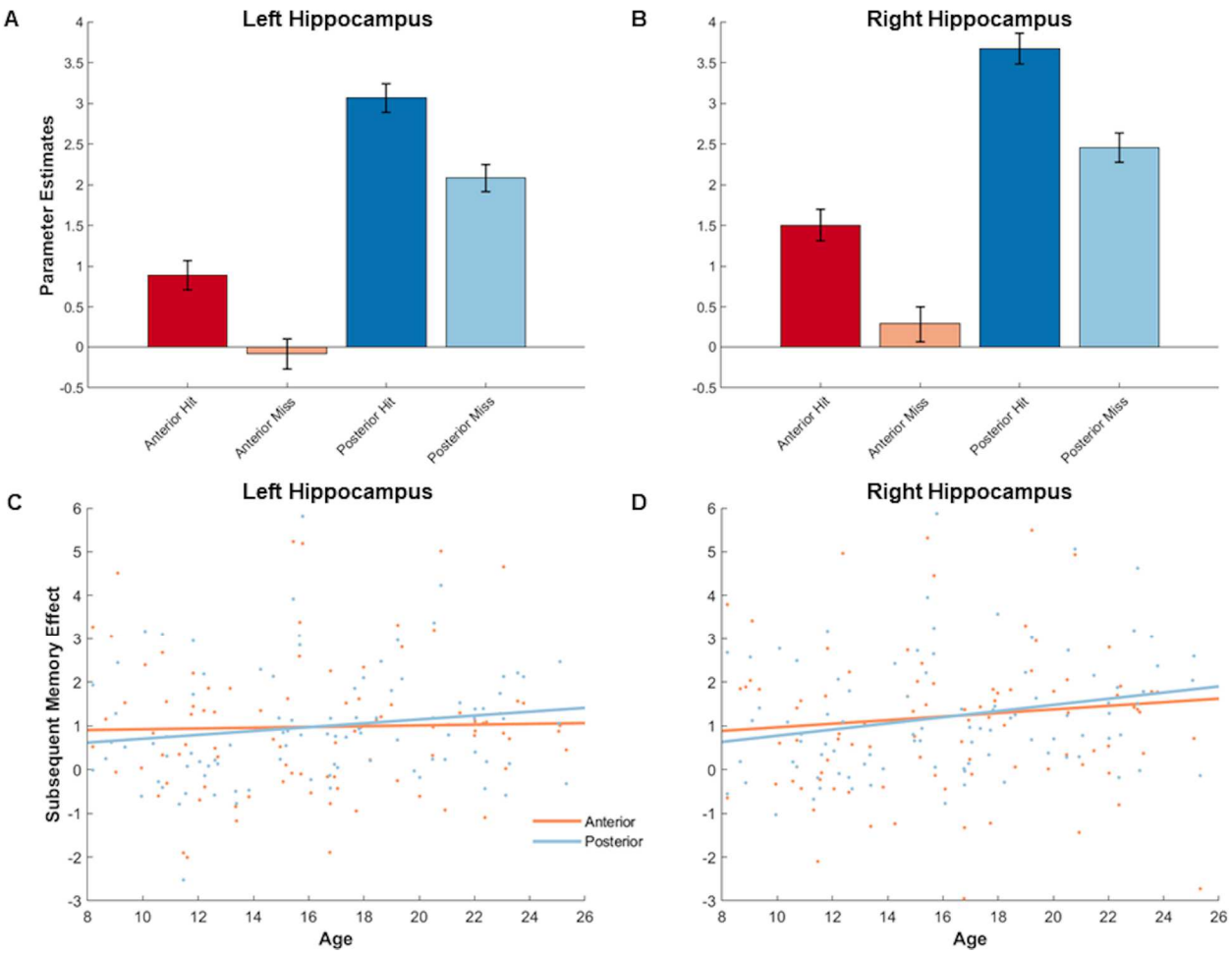

Figure 2.3 Hippocampal activations and SME. Top: Hippocampal activations showed a main effect of subregion (posterior hippocampus > anterior hippocampus), hemisphere (right hippocampus, **B** > left hippocampus, **A**), and an interaction between memory outcome and hemisphere (SME in the right hippocampus > SME in the left hippocampus; all *p*s < .01). Bottom: Hippocampal activations did not show age effects. There were also no interactions between age and memory outcome, between age and subregion, or between age and hemisphere (all *p*s > .08; left hippocampus shown in **C**; right hippocampus shown **D**).

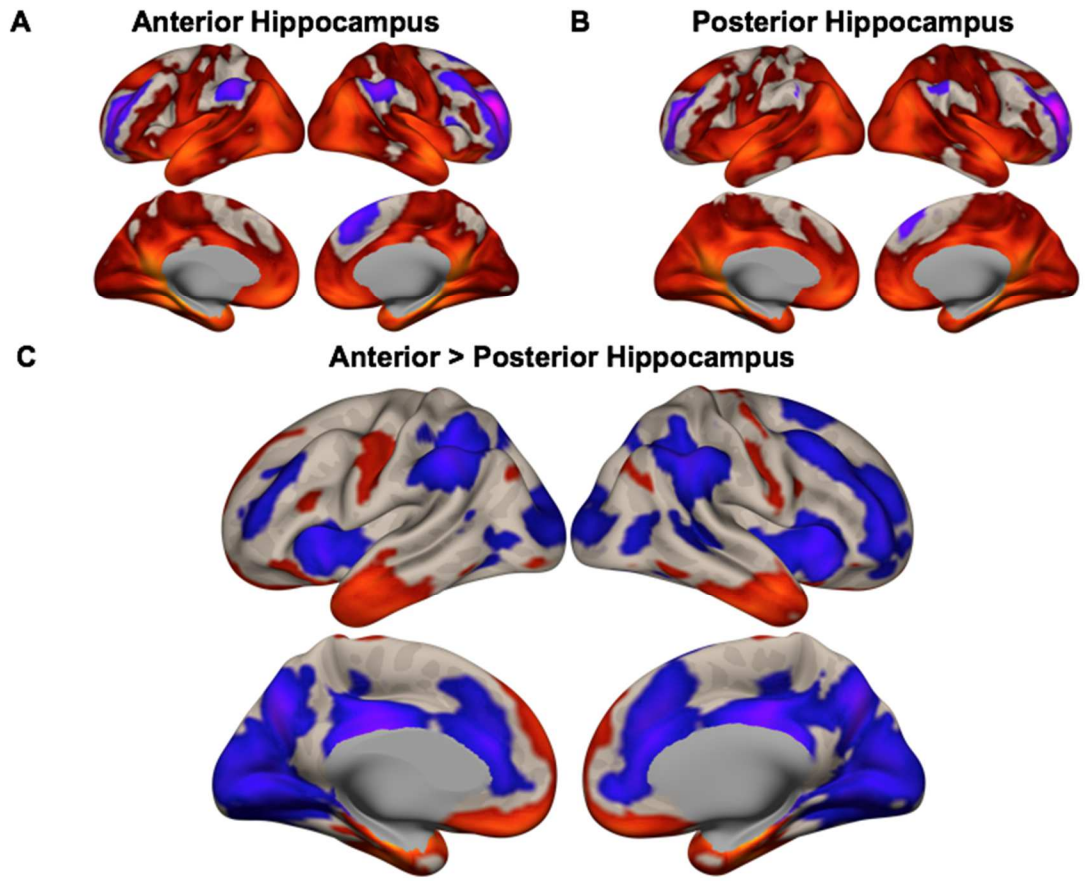

Figure 2.4 Functional connectivity with the hippocampus irrespective of memory outcome. Similar patterns of functional connectivity during memory encoding were identified for anterior (**A**) and posterior hippocampus (**B**) (red: positive functional connectivity; blue: negative functional connectivity; $p < .05$, FDR corrected). Differential patterns of functional connectivity with multiple cortical regions were identified when directly comparing functional connectivity of anterior and posterior hippocampal subregions (**C**; red: higher functional connectivity with anterior compared to posterior hippocampus; blue: higher functional connectivity with posterior compared to anterior hippocampus; $p < .05$, corrected).

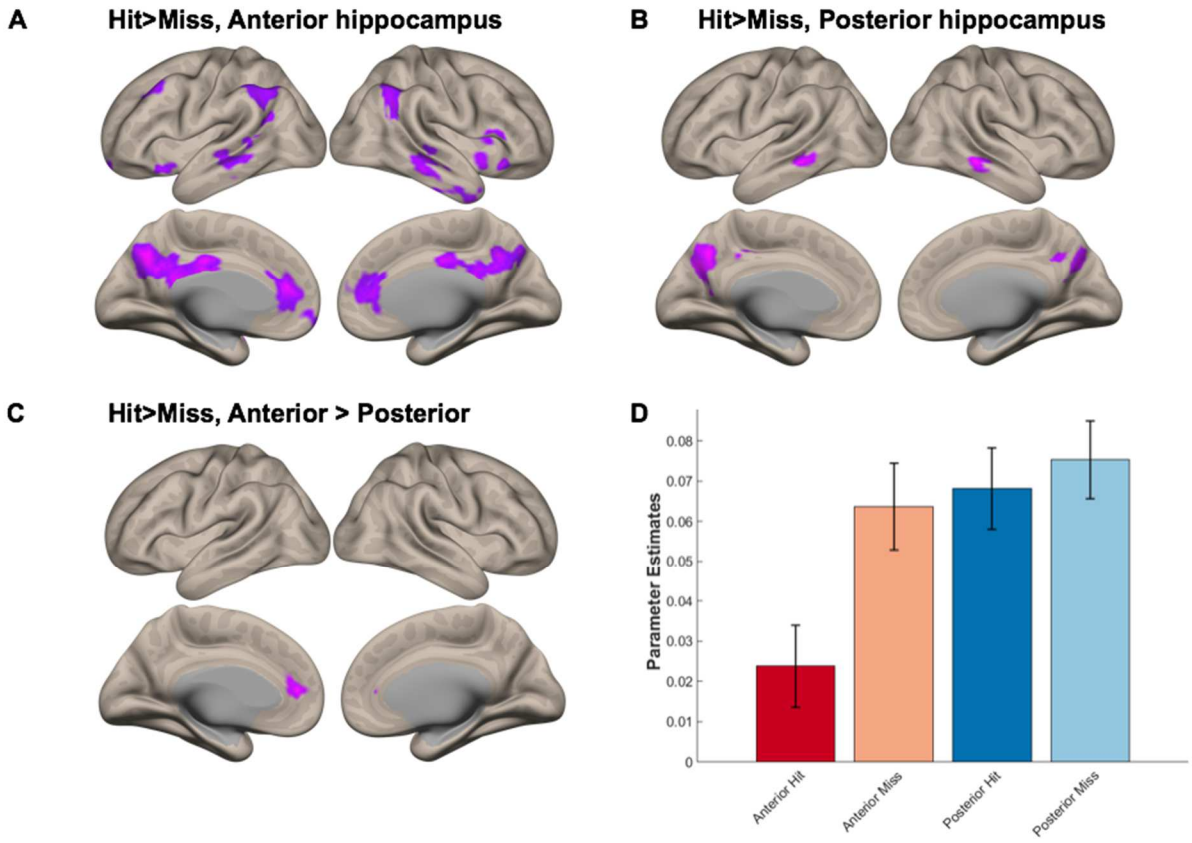

Figure 2.5 Memory-related functional connectivity with hippocampus. Anterior (A) and posterior (B) hippocampus showed lower memory-related functional connectivity to the precuneus and middle temporal lobe (purple: lower functional connectivity; $p < .05$, corrected). Compared to posterior hippocampus, anterior hippocampus showed lower memory-related functional connectivity to the mPFC region (**C**; $p < .05$, corrected), and this effect was driven by lower functional connectivity between anterior hippocampus and mPFC for Hit trials (**D**).

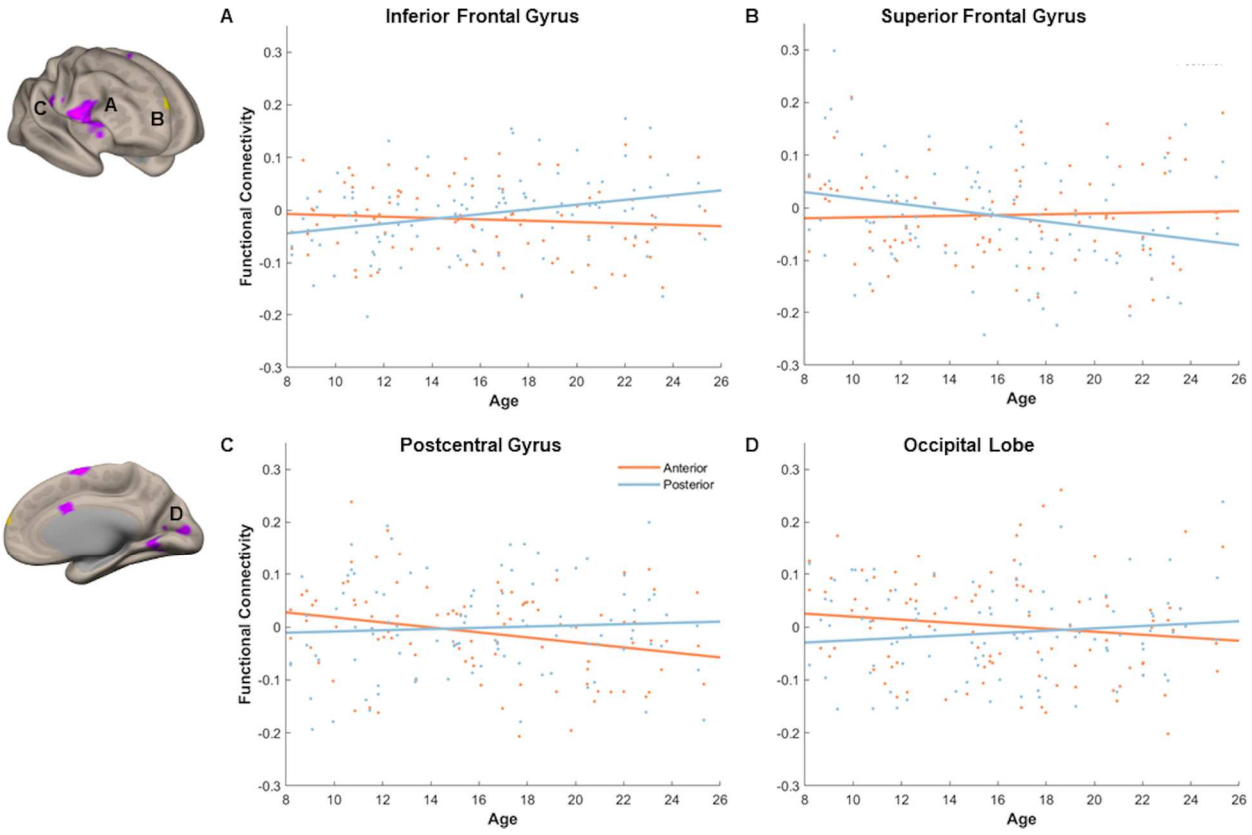

Figure 2.6 Age modulated differential memory-related functional connectivity between anterior and posterior hippocampus in the inferior frontal gyrus (**A**), superior frontal gyrus (**B**), postcentral gyrus (**C**), and occipital lobe (**D**). With an increase of age, posterior hippocampus showed a dynamic shift in its functional connectivity pattern with subregions in the prefrontal cortex, whereas anterior hippocampus showed decreased functional connectivity to sensory and visual regions.

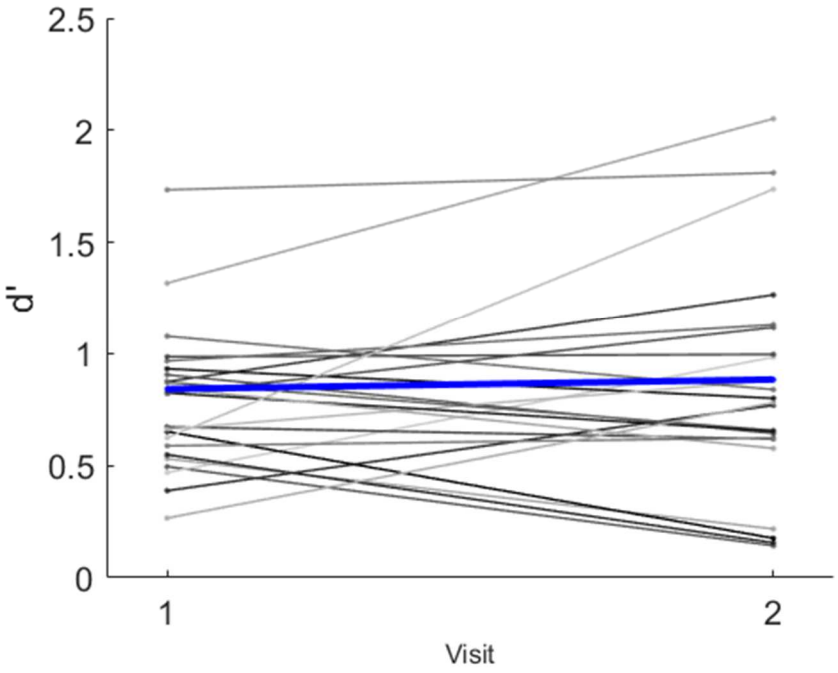

Figure 3.1 Memory performance (d') for Visit 1 and Visit 2. We observed no difference in group averages of memory performance between the two visits (Visit 1: .84 ± .42, Visit 2: .88 ± .52, $t(23)$ = .51, p = .62). Blue line indicates group means for both visits. Good reliability was found in individual memory performance between Visit 1 and Visit 2 (ICC = .62).

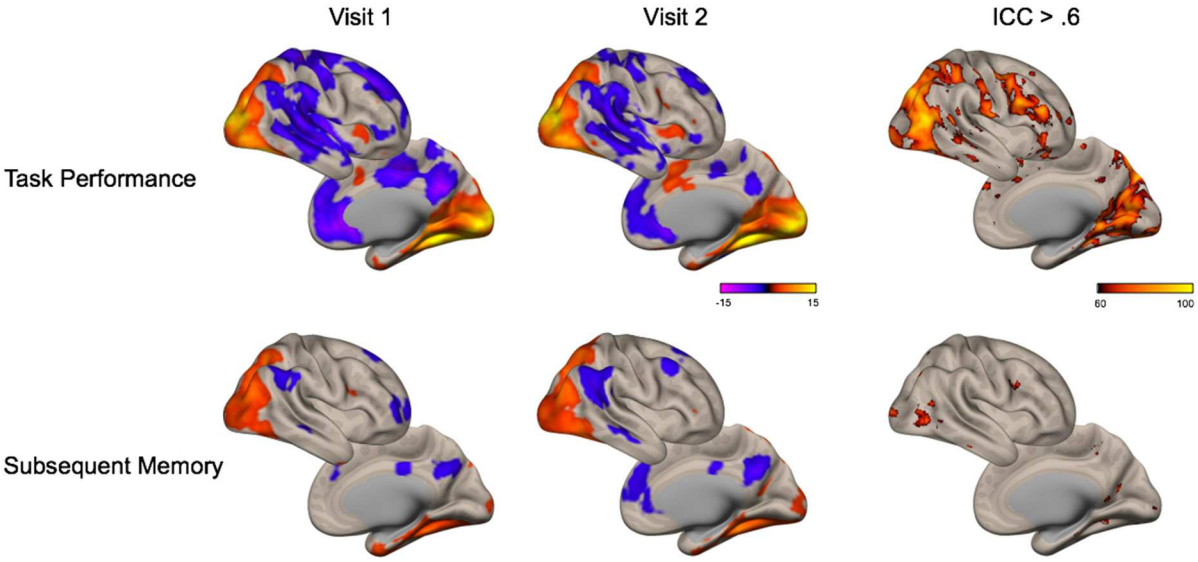

Figure 3.2 Patterns of activation for task performance (Task – Baseline; top panel) and subsequent memory (Hit – Miss; bottom panel) during two visits (p < .01, 100 contiguous voxels for visualization purposes) and the respective reliability maps for both conditions

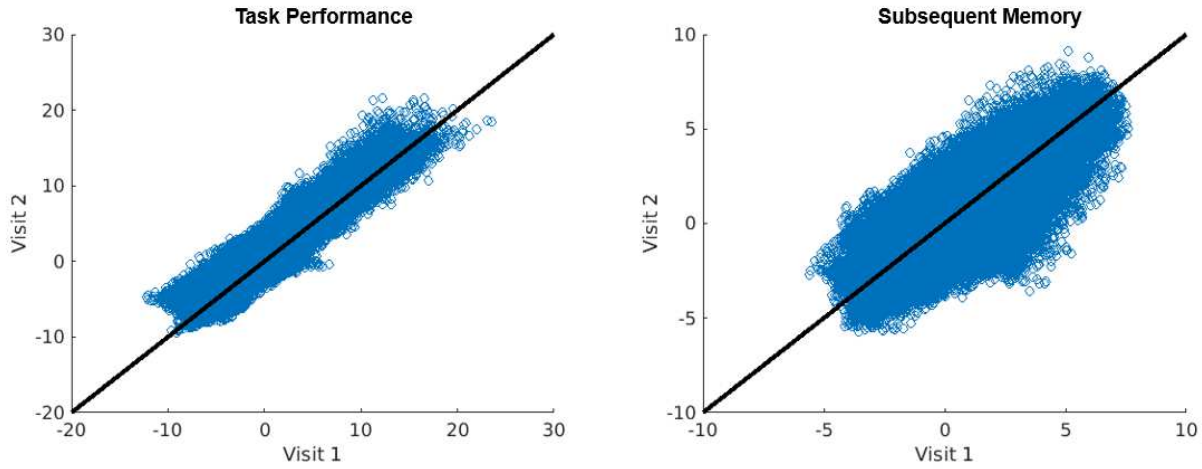

Figure 3.3 Comparing *t*-values from group maps of Visit 1 and Visit 2 for task performance (ICCv = .91, left panel) and subsequent memory (ICCv = .70, right panel) contrasts.

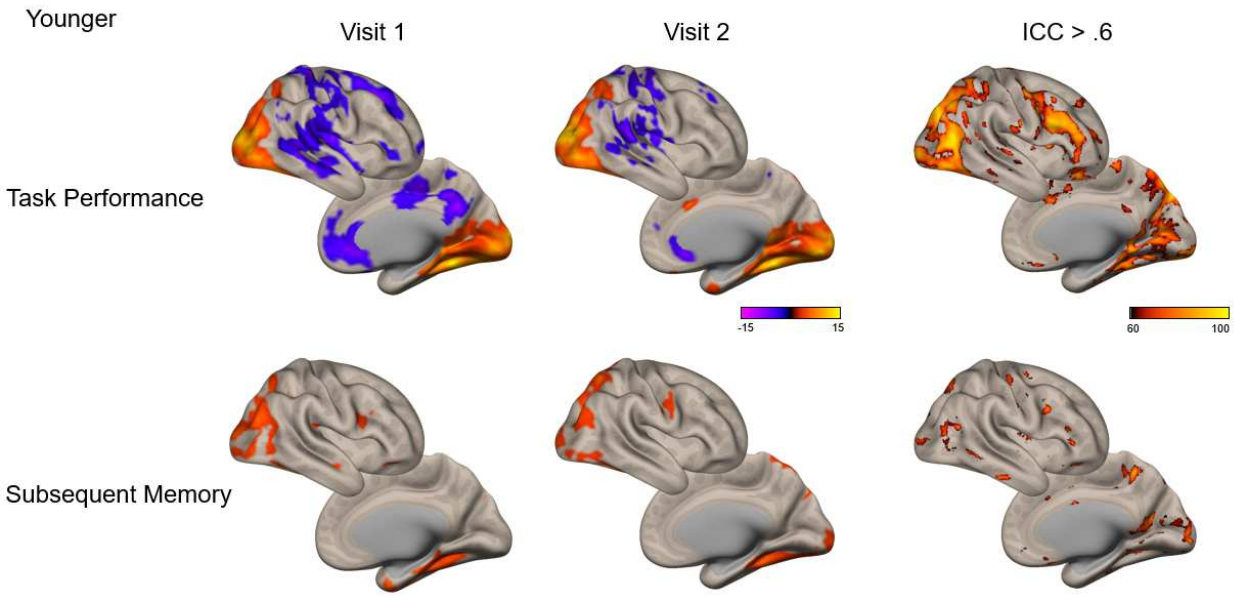

Figure 3.4 Patterns of activation for task performance (top panel) and subsequent memory (bottom panel) for young participants (< 13 years old) during two visits ($p < .01$, 100 contiguous voxels for visualization purposes) and the respective reliability maps for both conditions

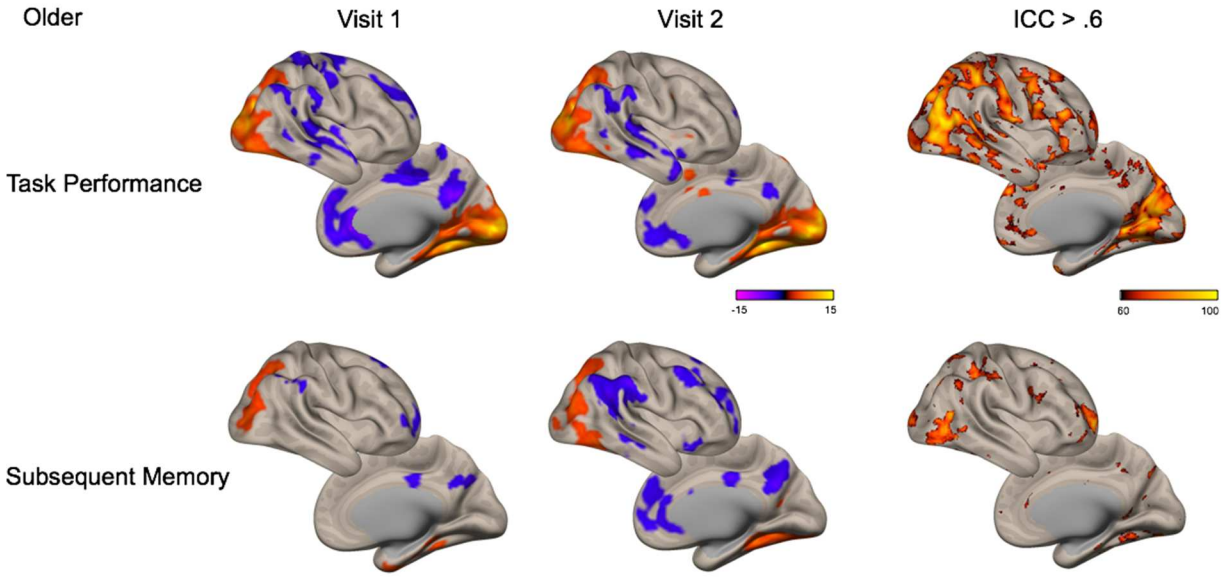

Figure 3.5 Patterns of activation for task performance (top panel) and subsequent memory (bottom panel) for older participants (>13 years old) during two visits ($p < .01$, 100 contiguous voxels for visualization purposes) and the respective reliability maps for both conditions

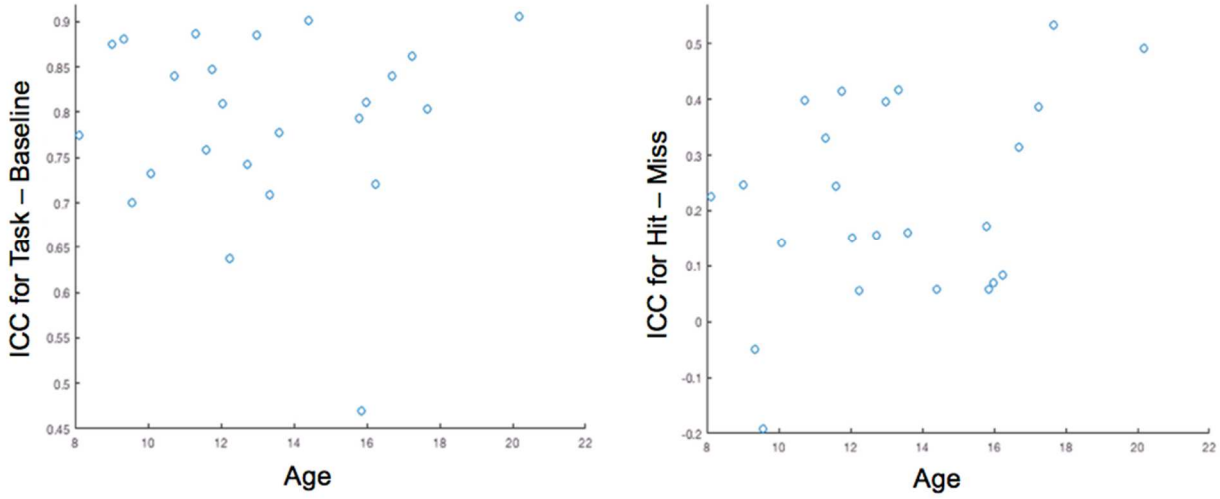

Figure 3.6 Individual intravoxel reliability (ICCv) correlating with age for Task – Baseline contrast ($r(22) = 0.02$, $p = 0.93$, left) and Hit – Miss contrast ($r(22) = 0.35$, $p = 0.09$, right).

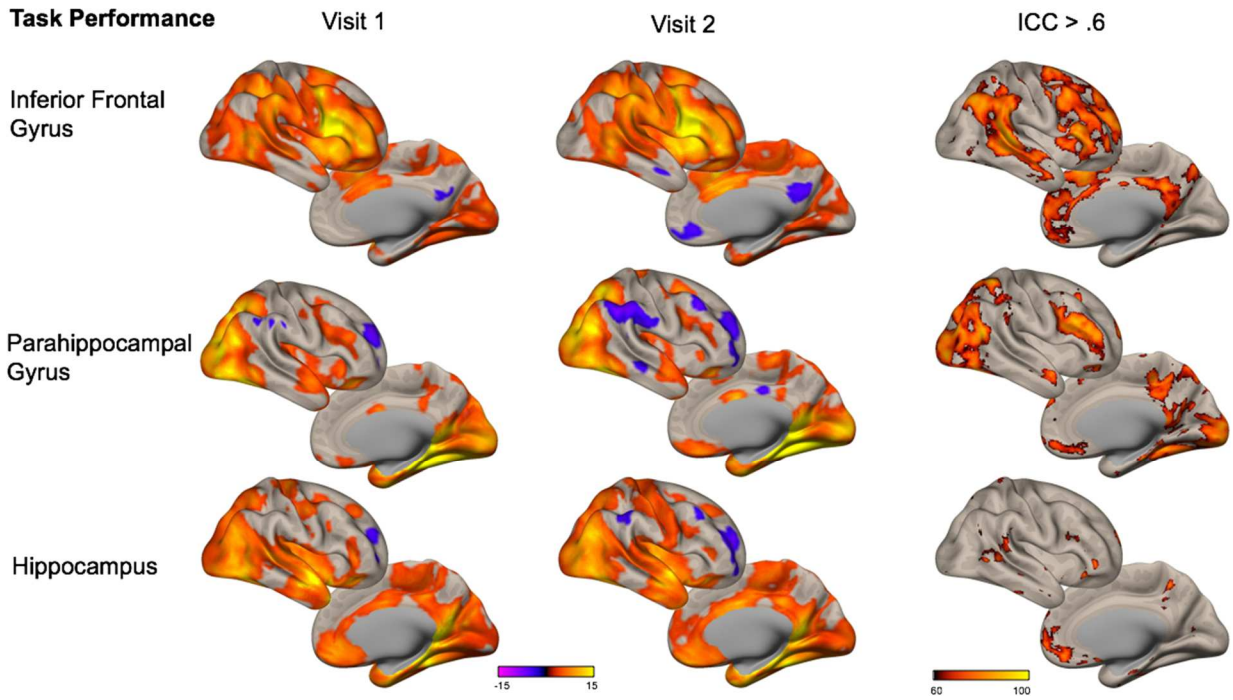

Figure 3.7 Functional connectivity patterns with three ROIs for the task performance contrast and their respective reliability maps

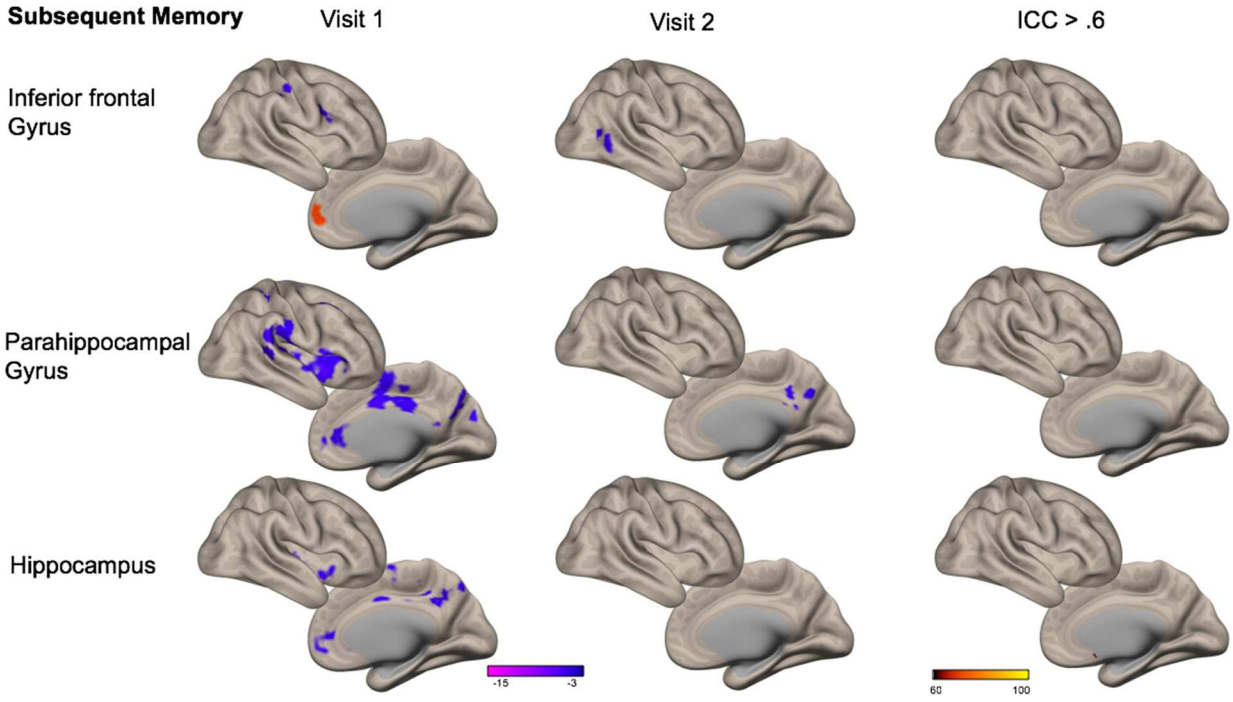

Figure 3.8 Functional connectivity patterns with three ROIs for the subsequent memory contrast and their respective reliability maps

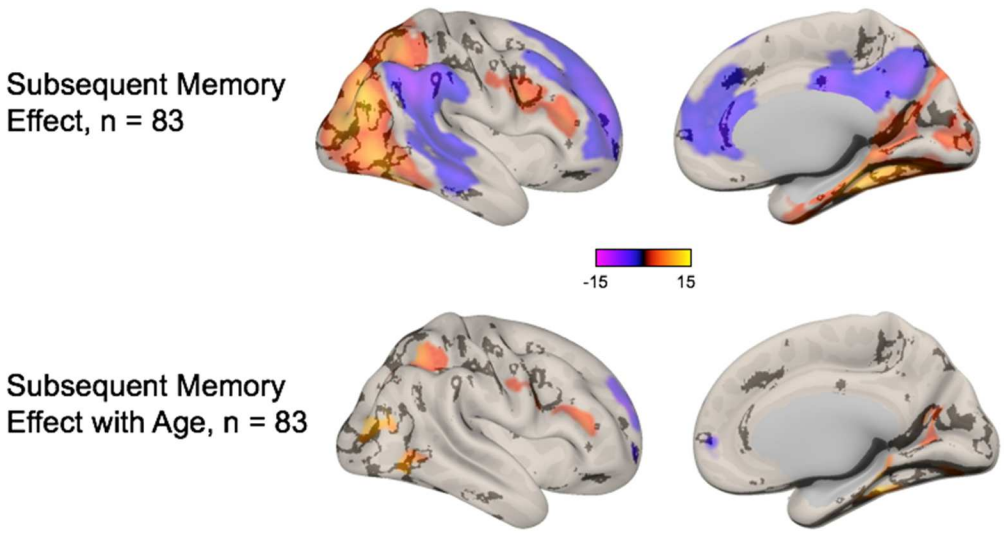

Figure 4.1 Subsequent memory effects (top panel) and age-related subsequent memory effect (bottom panel), as identified by the experiment with full sample (n = 83). The images were overlaid by a mask outlining areas showing acceptable reliability (ICC > .4), as identified by the reliability study (n = 24).

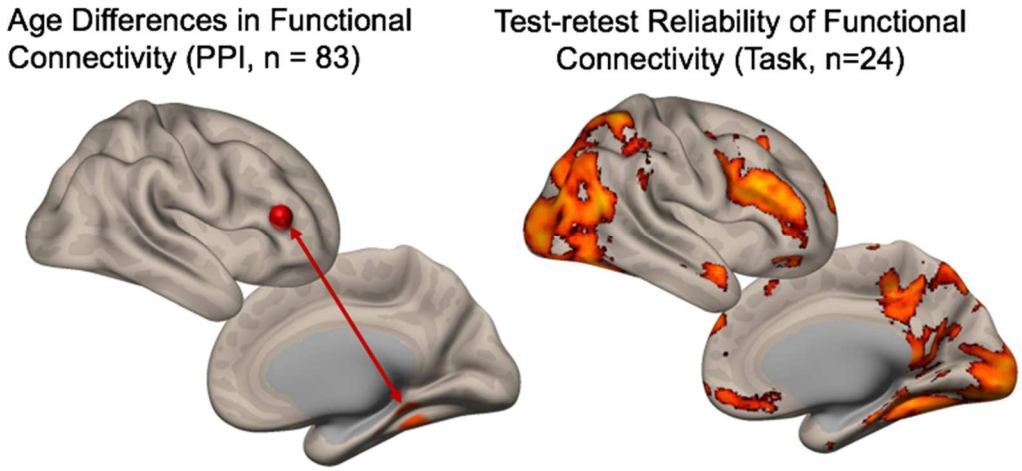

Figure 4.2 Functional connectivity between PFC and PHG in the full sample using the psychophysiological interaction (PPI) method (left panel) and the reliability of functional connectivity patterns with PHG (right panel)

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ABSTRACT

CHARACTERIZING THE DEVELOPMENT OF EPISODIC MEMORY AND ASSESSING THE RELIABILITY OF FMRI MEASURES

by

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Major: Psychology

Degree: Doctor of Philosophy

The ability to remember past events is critical for everyday life and showed robust improvement over development from childhood to adulthood. With advances in noninvasive neuroimaging methods such as functional MRI in recent years, research efforts have been focused on identifying neural correlates underpinning developmental gains in memory performance. In my dissertation work, using a widely-validated subsequent memory paradigm, I aim to characterize functional MRI correlates of memory development. Specifically, I focused my investigation on identifying age differences in the functional patterns of two brain regions critical for memory, the prefrontal cortex and the hippocampus. Focusing on the prefrontal cortex (Chapter 1), I found memory-related activation in inferior frontal gyrus and memory-related deactivation in superior frontal gyrus. Both regions demonstrated developmental effects, but only memory-related deactivation in superior prefrontal cortex mediated the relationship between age and memory performance. The prefrontal cortex showed dynamic developmental effects in its functional connectivity with the medial temporal lobe, including parahippocampal gyrus. Focusing on the hippocampus (Chapter 2), I found that both anterior and posterior hippocampus supported memory formation, with effects that are relatively stable from ages 8 to 25 years. Differential developmental

patterns were found for the functional connectivity between hippocampal subregions and prefrontal/visual cortices, suggesting increased functional specialization along the long axis of the hippocampus. Lastly, I tackled critical yet often neglected concerns over the reliability in identifying neural correlates of memory with fMRI (Chapter 3). I estimated the reliability of subsequent memory effects using an independent reliability dataset (n=24, ages 8 to 20 years), with similar focus on the prefrontal cortex and the hippocampus. Good to excellent test-retest reliability was observed on the group-level contrast, corresponding to group-level analyses with a cross-sectional design. On the individual level, good reliability was observed in cortical regions including the prefrontal cortex and parahippocampal gyrus, but not in the hippocampus. Collectively, through critical evaluation and rigorous analyses, I have made important contributions to the field by providing novel insights into how traditionally-defined "memory-regions" dynamically support memory development on a granular, subregion level. In addition, my work has contributed in establishing the much-needed boundaries to the extent to which fMRI measures can be applied to answer important questions in memory development.

AUTOBIOGRAPHICAL STATEMENT

Education

Wayne State University, Michigan — 2012-Present

Pursuing a Doctor of Philosophy

University of Auckland, New Zealand — 2008-2011

Bachelor of Arts, Psychology

University of Electronic Science and Technology of China — 2004-2008

Bachelor of Engineering, Electronics

Professional Appointments

Wayne State University, Michigan

Graduate Research Assistant — 2016-Present

Wayne State University, Michigan

Graduate Teaching Assistant — 2012-2016

Select List of Peer-Reviewed Publications

Tang, L., Shafer, A. T., & Ofen, N. (2018). Prefrontal Cortex Contributions to the Development of Memory Formation. *Cerebral Cortex*, *28*(9), 3295-3308.

Johnson, E. L., **Tang, L.**, Yin, Q., Asano E., & Ofen, N. (2018). Direct brain recordings reveal prefrontal cortex dynamics of memory development. *Science Advances*, *4*(12), 1-13.

Ofen, N., **Tang, L.**, Yu, Q., & Johnson, E. L. (2018). Memory and the developing brain: From description to explanation with innovation in methods. *Developmental Cognitive Neuroscience*, *36*(4).

Progovac, L., Rakhlin, N. V., Angell, W., Liddane, R., **Tang, L.**, & Ofen, N. (2018). Neural correlates of syntax and proto-syntax: evolutionary dimension. *Frontiers in Psychology*, *9*(3).

Yu, Q., McCall., D. M., Homayouni, R., **Tang, L.**, Chen Z, Schoff D., Nishimura M., Raz S., & Ofen, N (2018). Age-associated increase in mnemonic strategy use is linked to prefrontal cortex development. *Neuroimage*, *181*(7), 162-169.

Hayes, J. M., **Tang, L.**, Viviano, R., van Rooden, S., Ofen, N., & Damoiseaux, J. S. (2017). Subjective memory complaints are associated with brain activation supporting successful memory encoding. *Neurobiology of Aging, 60*(12), 71-80.

Goetz, S. M. M.*, **Tang, L.***, Thomason, M. E., Diamond, M. P., Hariri, A. R., & Carré, J. M. (2014). Testosterone rapidly increases neural reactivity to threat in healthy men: a novel two-step pharmacological challenge paradigm. *Biological Psychiatry, 76*(4), 324-331 (* *equal contribution*).