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Neural Correlates Of Episodic Memory Formation In Children And Adults

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NEURAL CORRELATES OF EPISODIC MEMORY FORMATION IN CHILDREN AND ADULTS

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DEDICATION

I dedicate this to my teachers, friends and family

without whom it was impossible for me to complete my thesis work

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INTRODUCTION

Episodic memory refers to the kind of memory that is usually vivid in detail, containing rich contextual information of time and space. When recalling past events, such as a dinner last week, or a trip to Paris years ago, individuals can utilize episodic memories to mentally travel in time and space and re-experience these events (Tulving, Terrace, & Metcalfe, 2005). The ability to effectively form and later recall episodic memories is one of the most important aspects that differentiates human from many other animal species, which is crucial for everyday living.

Some researchers have suggested that episodic memory forms around the age of four and continues to develop into adulthood (Perner & Ruffman, 1995; Tulving et al., 2005). Children could effectively retain factual knowledge at a very young age, but show inadequate capacity in registering contextual details and spontaneously utilizing memory strategies to guide memory formation (Sander, Werkle-Bergner, Gerjets, Shing, & Lindenberger, 2012; Schneider, Knopf, & Stefanek, 2002; Tulving et al., 2005). Previous research investigating memory encoding and retrieval in children and adolescents has shown that the formation of vivid memories increases markedly with age, but the formation of vague or familiarity-based memories only increases slightly with age (Billingsley, Smith, & McAndrews, 2002; Brainerd, Holliday, & Reyna, 2004). The behavioral evidence demonstrates that the ability to encode vivid contextual information into holistic episodic experiences likely improves with age.

Episodic memory formation is supported by different brain regions and their critical contribution to memory formation is illustrated in cases where such function is lost. Patients with lesions in the medial temporal lobe (MTL), show marked deficits in forming memories of important life events (Tulving et al., 2005). In the cases of H.M. and others, who suffered from damages in the MTL, normal cognitive abilities and working memory functions remained intact.

However, they could not form memories of events they experienced beyond the last few minutes and showed no recollection of significant life events after the MTL was damaged (Schmolck, Kensinger, Corkin, & Squire, 2002; Tulving et al., 2005). Evidence from functional neuroimaging research also show that brain activation in the MTL is linked to successful memory formation, such that higher magnitude of activation in the MTL predicts better subsequent memory performance (Ofen et al., 2007; Schacter & Wagner, 1999; Stern et al., 1996). These pieces of evidence highlight the crucial role of the MTL in episodic memory formation.

Several studies have investigated the developmental trend in the MTL and showed mixed results (Chai, Ofen, Jacobs, & Gabrieli, 2010; DeMaster & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Gogtay et al., 2006; Ofen et al., 2007; Poppenk & Moscovitch, 2011). While some found that the MTL as a whole showed no age-related differences supporting memory formation (Ofen et al., 2007), others showed age-related structural and functional effects in the subregions of the MTL (Chai et al., 2010; DeMaster & Ghetti, 2013; Ghetti et al., 2010; Gogtay et al., 2006; Poppenk & Moscovitch, 2011). These subregions of the MTL may show differential developmental patterns to support episodic memory of detailed information (Chai et al., 2010; DeMaster & Ghetti, 2013; Ghetti et al., 2010). More research is needed to further delineate the developmental trajectory for the different subregions of the MTL.

Other than the MTL, the prefrontal cortex (PFC) also plays an important role supporting memory formation. Patients with PFC lesions show subtle but evident deficits in episodic memory (Wheeler, Stuss, & Tulving, 1997). While they demonstrate close-to-normal performance in structured encoding tasks that requires minimal strategy use and in tasks free of distractors, they exhibit marked deficit in free recall tasks that require subjective organization and attentional control (Alexander, Stuss, & Fansabedian, 2003; Shimamura, Jurica, Mangels, Gershberg, &

Knight, 1995; Swick & Knight, 1996; Thompson-Schill et al., 2002; Wheeler et al., 1997). It is hypothesized that during memory formation, the PFC engages in spontaneous adoption of memory strategies and orients the person to task-related stimuli (Blumenfeld & Ranganath, 2007).

Research on the functions of the PFC generally agrees upon its continued development from childhood to adulthood (Ghetti et al., 2010; Ofen et al., 2007). However, these developmental effects supporting memory formation and retrieval show inconsistency within different regions of the PFC (DeMaster & Ghetti, 2013; Ghetti et al., 2010; Ofen et al., 2007; Paz-Alonso, Ghetti, Donohue, Goodman, & Bunge, 2008). Importantly, the PFC is not an anatomically homogenous region, but is composed of distinct subregions that support varying levels of sophistication in information processing (Badre & D'Esposito, 2009; Fuster & Bressler, 2012; Petrides, 2005). Previous research has shown functional shift along anterior-posterior and dorsal-ventral axes in the PFC for older adults, highlighting the importance to further investigate the developmental pattern of the subregions in the PFC in children and young adults (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Grady, McIntosh, & Craik, 2003).

The PFC and MTL function together to support memory formation (Fernández & Tendolkar, 2001; Grady et al., 2003; Summerfield et al., 2006). In general, the PFC is associated with strategy use and attentional control, while the MTL is associated with encoding item and contextual information (Shing et al., 2010; Summerfield et al., 2006). Tractography analysis shows that the PFC directly projects to the anterior MTL through uncinate fasciculus, and this tract shows continued increase in anatomical integrity from children to adults (Catani & Thiebaut de Schotten, 2008; Lebel & Beaulieu, 2011; Lebel et al., 2012; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). However, few studies investigated the functional connectivity (FC) pattern between the PFC and MTL in the context of memory development (Menon, Boyett-Anderson, & Reiss, 2005;

Ofen, Chai, Schuil, Whitfield-Gabrieli, & Gabrieli, 2012; Paz-Alonso, Gallego, & Ghetti, 2013; Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005). Although the majority of these studies showed increased FC between the PFC and MTL, the specific regions that showed such effects vary from one study to the other (Menon et al., 2005; Ofen et al., 2012; Ranganath et al., 2005). Additional analysis is needed to systematically investigate the FC between subregions of the PFC and MTL in a developmental context.

In sum, episodic memory formation is supported by both the PFC and MTL. While it seems that the developmental patterns of the PFC and MTL are established in previous literature, more detailed analysis revealed that the developmental patterns for the subregions, and FC of these two regions remain unclear. In the following section, we separately review the functional and developmental patterns for these subregions and identify gaps in the literature.

Subregions in the MTL Supporting Memory Formation

The MTL supports episodic memory formation, and activation in the MTL predicts memory success in both children and adults (Ghetti et al., 2010; Ofen et al., 2007). The MTL consists of many subregions, including (anteriorly to posteriorly) perirhinal cortex (PRC), entorhinal cortex (ERC), hippocampus, and parahippocampal gyrus (PHG) (Eichenbaum, Yonelinas, & Ranganath, 2007). Structural and functional differences exist along the long axis of the MTL. It is suggested that more anterior portion of the MTL, especially the PRC is linked to encoding item-related information, whereas more posterior portion of the MTL, such as the PHG is linked to encoding context-related information. The hippocampus serves to bind item and contextual information together to support rich episodic memory formation (Davachi, 2006; Staresina & Davachi, 2008; Staresina, Duncan, & Davachi, 2011). Using an incidental memory task, previous research has shown that PRC activation is related to memory formation of specific

items, whereas hippocampal activation is related to memory formation of associated color or task information (Staresina & Davachi, 2008). In another experiment, neural correlates of item and context information were differentiated using fractal images (Wang, Yonelinas, & Ranganath, 2013). These fractal images were artificially juxtaposed to create the item/context differentiation, with one smaller and more focal, whereas the other bigger and in the background. With this design, they found that the PRC showed more activation supporting item memory formation, whereas the PHG showed more activation supporting contextual memory formation. Taken together, during episodic memory formation, the ERC and PHG in the MTL support item and contextual information, and the hippocampus binds multiple pieces of information together.

Within the hippocampus, anatomical and functional differentiation exist along its long axis. Structurally, anterior and posterior hippocampus show sparse direct anatomical connection with each other and they project separately to anterior and posterior MTL (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). Functionally, anterior hippocampus is more likely to encode semantic gist or schema-related information, while posterior hippocampus is more likely to encode scene details, especially details with a spatial component (Poppenk et al., 2013). Comparative studies from the animal literature show that ventral and dorsal hippocampus in rats, roughly corresponding to anterior to posterior hippocampus in human, the size of the encoded spatial region decreased from a magnitude of 10 mm to 1 mm (Kjelstrup et al., 2008). Evidence from human imaging research shows that, anterior hippocampus supports global pathway finding and judgments related to episodic experiences, whereas posterior hippocampus responds more to spatial details, such as the positions of individual landmarks and local environmental features (Baumann, Chan, & Mattingley, 2010; Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch,

2012; Xu, Evensmoen, Lehn, Pintzka, & Håberg, 2010). During memory formation, posterior hippocampus is more likely to bind detailed information to form coherent episodic memory.

Given the importance of the hippocampus in supporting episodic memory formation, it is crucial to investigate the developmental pattern of this region. Previously, cross-sectional studies examining the differences in the whole hippocampal volume from childhood to adulthood have yielded inconsistent results (Giedd et al., 1996; Suzuki et al., 2005). For example, Giedd et al. (1996) found a hippocampal volume increase in females between the age of 4 and 18, but Suzuki et al. (2005) found a volume increase in males between the age of 13 and 21. Recent evidence, however, suggests potential differential developmental patterns when the anterior and posterior portion of the hippocampus are investigated separately (Gogtay et al., 2006; Poppenk & Moscovitch, 2011). Using a longitudinal sample from age 4 to 25, Gogtay et al. (2006) showed that the volume of the anterior hippocampus decreases with age, the volume of the posterior hippocampus increases with age, and the volume of the posterior tail of the hippocampus decreases with age. When investigating the relationship between hippocampal size and memory, it is generally found that that larger posterior hippocampal volume and relatively smaller anterior hippocampal volume correlated with better episodic memory performance (Maguire et al., 2000; Poppenk & Moscovitch, 2011). Similarly, DeMaster, Pathman, Lee, and Ghetti (2013) using two groups, children and adults, found that adults have smaller right hippocampal head, but larger right hippocampal tail compared to children. They also found that smaller right hippocampal head and bigger hippocampal body correlated with better episodic memory performance in adults, whereas bigger left hippocampal tail correlated with better memory performance in children. These pieces of evidence suggest that analyzing the developmental effects separately for the anterior and posterior hippocampus is crucial for further clarification.

Recent functional neuroimaging research shows differential developmental effects in different regions of the MTL. Ghetti et al. (2010) utilized a source memory paradigm to test episodic memory of children from different age groups (8 year olds, 10-11 year olds, 14 year olds, and young adults). The participants viewed line drawings in red or green and were required to make judgments whether the objects "can be found in a house", or were "alive". They were not explicitly told to remember the color information associated with the drawings, but were later tested for both the memory of line drawings and associated colors. While there were no significant differences in correctly recognizing the line drawings between age groups, there were significant increase for the memory of the color information with age. Importantly, fourteen year olds and adults showed activation in the hippocampus and posterior PHG that differentiated between remembering and forgetting the color information, whereas such differentiation was not observed in younger children. These results show that the ability to register detailed episodic memory information increases with age and this ability may be supported by subregions of more developed hippocampus and PHG.

As summarized above, while previous research found no age-related differences during memory formation when examining MTL function as a whole (Ofen et al., 2007), more recent efforts have found evidence for age-related differences in MTL subregions (Chai et al., 2010; Ghetti et al., 2010). Both Chai et al. (2010) and Ghetti et al. (2010) demonstrated that activation of posterior PHG during the encoding of detailed scene information increased with age. Additionally, Ghetti et al. (2010) also found such age-related effects in the hippocampus. However, it is important to note that in Ghetti et al. (2010), participants viewed line drawings of objects while performing semantic tasks, and were later tested for the memory of their color information, as a proxy of the memory for detailed episodic information. In Ofen et al. (2007) and Chai et al. (2010),

however, participants viewed indoor and outdoor scenes and were later tested for the recognition memory of these scenes. As episodic memory typically involves mentally travelling to a specific space back in time, the indoor and outdoor scenes used in Ofen et al. (2007) and Chai et al. (2010) provide more ecological validity than the line drawings as used in Ghetti et al. (2010). However, in Chai et al. (2010), the authors first identified a region of interest (ROI) in the posterior MTL that showed more activation when *viewing* high complexity scenes compared to *viewing* low complexity scenes. Afterwards they extracted memory-related activation separately for high- and low-complexity scenes based on this ROI to examine age-related differences. This approach, although insightful, restricts the search space within the regions that show differential activation for *viewing* these scenes, but does not identify regions that only show differential activation for *remembering* high complexity versus low complexity scenes. This first aim of the current study is to examine the subregions in the MTL that show differential activation supporting the memory of high and low complexity scenes and the second aim is to examine the developmental effects of these memory-related activation.

Perceptual Regions Supporting Memory Formation

Episodic memory is usually rich in temporal and spatial detail, involves a mental image of an event, and commonly includes an indoor or outdoor "scene" that is associated with the event (Hassabis & Maguire, 2007; Tulving, 2002). Several brain regions have been linked to scenes processing, including the parahippocampal place area (PPA), retrosplenial cortex (RSC) and transverse occipital cortex (TOS). These regions show activation when the participants were viewing or imagining scenes (Epstein, Higgins, Jablonski, & Feiler, 2007). One study used transcranial magnetic stimulation (TMS) to establish a causal link between brain regions and their

perceptual functions by temporarily disrupting the function of TOS (Dilks, Julian, Paunov, & Kanwisher, 2013). They found that participants with TOS functions suppressed showed significant performance decrease for a difficult scene categorization task, but not for an equally difficult object categorization task. The activation of these scene perception regions also showed modulation by memory and personal experiences (Epstein et al., 2007). When participants viewed images of familiar and unfamiliar locations, the PPA, RSC and TOS showed stronger activation for familiar locations compared to unfamiliar locations. These findings support the view that scene perception regions can also support the formation of scene-related memory.

Scene perception skills emerge relatively early in life (Brown & Campione, 1972). Children develop adult-like schematic representations for scenes as young as their first grade, but the ability to effectively process unstructured scenes and memorize landmark details continues to develop until adolescence (Brown & Campione, 1972; Doherty & Pellegrino, 1985; Mandler & Robinson, 1978). Neuroimaging studies examining the development trajectory of scene perception regions show that the size and selectivity of the PPA increase from children to adults (Golarai et al., 2007). Importantly, the increase in size correlates with scene recognition memory, such that larger PPA is related to better memory performance. These results show that, although scene perception skills emerge early in life, scene specific brain regions continue to develop supporting more detailed scene encoding.

As shown in previous studies, the size of the PPA increases with age and is known to support better episodic memory formation, especially for indoor and outdoor scenes (Golarai et al., 2007; Köhler, Crane, & Milner, 2002). Yet to our knowledge, how individual PPA supports episodic memory formation has not been explored in a developmental context. Given the behavioral findings that the abilities to perceive and memorize scenes improve with age, it is

expected that the PPA will show age-related differences supporting scene perception and memory formation. The third aim of the current study is to explore how the activation in individual PPA supports both the perception and memory processes.

Subregions in the PFC Supporting Memory Formation

As previously mentioned, the PFC plays an important role regulating attention and memory strategies. Neural activation supporting memory formation has been consistently found in both dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC) (Eichenbaum et al., 2007; Kim, 2011; Simons & Spiers, 2003). In these regions, the activation is greater for items that are later remembered compared to items that are later forgotten. However, memory formation is also linked to a deactivation in a wide range of brain regions (Daselaar, Prince, & Cabeza, 2004; Otten & Rugg, 2001). In those regions the magnitude of the deactivation is greater for later remembered items compared to later forgotten items. Typically these regions overlap with the well-characterized default mode network (DMN) (Buckner, Andrews-Hanna, & Schacter, 2008). The DMN, a network typically including posterior cingulate cortex (PCC), lateral parietal lobule, and medial PFC (mPFC), shows a characteristic deactivation during external oriented tasks. The magnitude of the deactivation in these regions is modulated by task difficulty and have been linked to performance in both episodic and working memory tasks (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014a; Mckiernan, Kaufman, Kucera-Thompson, & Binder, 2003). A recent study further demonstrated different recruitment of these region by age, such that more memory-related deactivation was found in adults compared to children (Chai et al., 2014a).

Related to the DMN but much less discussed is the superior portion of PFC (SupPFC; BA10/9), a region that show robust FC to DMN nodes during resting-state (Fox et al., 2005;

Huijbers et al., 2013; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), and similar deactivation supporting memory formation (Daselaar et al., 2004; Huijbers et al., 2013; Kim, 2011; Otten & Rugg, 2001; Wagner & Davachi, 2001). In fact, given its functional and spatial affinity to midline DMN structures, it is considered part of the DMN by a number of studies (Buckner, 2013; Buckner et al., 2008; Power et al., 2011; Sylvester et al.). Previous studies have shown age-related differences in the anticorrleated effect in the vicinity of the SupPFC (Chai, Ofen, Gabrieli, & Whitfield-Gabrieli, 2014b), but how SupPFC functionally connects to other parts of the brain has never been explored in a developmental context. Recently published aging research has also identified the SupPFC as part of the task-negative network, deactivating more during task compared to resting state (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2014; de Chastelaine & Rugg, 2014). It has been demonstrated that the deactivation in SupPFC support both episodic and semantic memory formation for young and old adults (de Chastelaine et al., 2014; de Chastelaine & Rugg, 2014; Park, Kennedy, Rodrigue, Hebrank, & Park, 2013). Old adults showed reduced SupPFC deactivation compared to younger adults, and this reduction has been linked to poor memory performance (de Chastelaine et al., 2014; Park et al., 2013), for a review see Maillet and Rajah (2014). These findings suggest that SupPFC deactivation is critical for memory formation across life span.

Previous research has shown that PFC exhibited protracted maturation from childhood to adulthood. Evidence from longitudinal structural imaging studies indicates that both PFC and parietal cortex show continued cortical thinning into adulthood (Gogtay et al., 2004; Sowell et al., 2003; Sowell et al., 2002). Functional imaging studies using cross-sectional samples have identified differential activation patterns in the PFC supporting the formation of episodic memory, source memory, and monitoring false memory in children and adults (Ghetti et al., 2010; Ofen et

al., 2007; Paz-Alonso et al., 2008). While age-related increase in PFC activation has been shown unequivocally in tasks related to attentional control and working memory formation (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Geier, Garver, Terwilliger, & Luna, 2009; Klingberg, Forssberg, & Westerberg, 2002; Thomason et al., 2009; Wendelken, Baym, Gazzaley, & Bunge, 2011), developmental effects for the formation of long-term memory have not been consistently reported in different subregions of PFC. For example, age-related differences supporting memory formation and retrieval have been found in the DLPFC (Ghetti et al., 2010; Ofen et al., 2007), VLPFC (Ghetti et al., 2010; Paz-Alonso et al., 2008) and anterior PFC (DeMaster & Ghetti, 2013; Paz-Alonso et al., 2008).

The discrepancies between these findings are likely due to different experimental designs. In Ofen et al. (2007), the participants were explicitly instructed to memorize indoor and outdoor scenes while making an "indoor"/"outdoor" judgments. The memory of these scenes was tested afterwards as part of the plan. In Ghetti et al. (2010), however, the researchers adopted an incidental memory paradigm, and the memory for both the item and color of these line drawings were examined subsequently in a surprise memory test. A lack of explicit instruction during the memory encoding process could lead to a difference in task expectations. Adults may be more likely to expect a recall test after the encoding session, which could confound the age-related findings in the PFC. Based on this concern, we adopted an intentional memory formation task. The forth aim of the study is to examine age-related memory activation in the PFC, including the DLPFC and VLPFC, during intentional memory formation.

Previous studies show that memory-related deactivation support memory formation in the PFC, and medial/parietal nodes of the DMN (Chai et al., 2014a; Daselaar et al., 2004; Otten & Rugg, 2001). More robust deactivation has been found in the DMN for adults compared to children

(Chai et al., 2014a), but age-related effects for lateral PFC deactivation has not been investigated. Very recent studies identified deactivation in the SupPFC that supported memory formation in both young and old adults (de Chastelaine et al., 2014; Park et al., 2013). They further demonstrated that young adults showed more effective deactivation compared to old adults to support better memory performance. Age-related effects for deactivation in children, however, have never been tested. Thus, the fifth aim of the current study is to investigate how the SupPFC supports memory formation in children and adults and the sixth aim is to examine the developmental effects of the SupPFC supporting memory formation.

Development of Connectivity between the PFC and MTL

During memory formation, PFC guides MTL to efficiently encode relevant episodic information. Structurally, the ventral and orbital part of PFC were known to project directly to anterior MTL through the uncinate fasciculus (Catani & Thiebaut de Schotten, 2008). This tract shows continued increase in white matter integrity from young children to adults (Lebel & Beaulieu, 2011; Lebel et al., 2012; Lebel et al., 2008). Functionally, there are a paucity of studies that investigated developmentally memory-related connectivity pattern in the PFC relating to memory (Menon et al., 2005; Ofen et al., 2012; Paz-Alonso et al., 2013; Ranganath et al., 2005). One study using a block design found that the FC between left ERC and left DLPFC increased with age during memory encoding (Menon et al., 2005). Another study used a mental rotation working memory task and tested subsequent memory of the items (Ranganath et al., 2005). They found more FC between the hippocampus and orbitofrontal cortex for subsequently remembered compared to subsequently forgotten items. Another prior research tested memory retrieval of indoor and outdoor scenes for young children and adults (Ofen et al., 2012). They found that FC

between the hippocampus and VLPFC increased with age for both true and false memory. Recently, one research investigated the FC pattern for children and adults using a Deese/Roediger-McDermott (DRM) false memory paradigm (Paz-Alonso et al., 2013). In this paradigm, participants were presented with a set of words during encoding, and tested with a set of words combining those shown before (old), words not shown but semantically related (critical lures), and words that are not semantically related (unrelated lures). The results showed that in adults compared to children, there were stronger hippocampus to parietal lobe and hippocampus to DLPFC coupling supporting true memory in adults compared to children, and stronger hippocampus to VLPFC coupling in children compared to adults.

As mentioned above, studies investigating the differential FC between subregions of the MTL and PFC in children and adults have yielded inconsistent results. Only one earlier study examined FC between MTL and PFC for episodic memory formation (Menon et al., 2005). As this study utilized a block design, it did not allow for the direct comparison for the FC between remembered versus forgotten trials. Using an event-related design, the age-related differences in the FC between the subregions of the MTL and PFC will be more readily delineated. The seventh aim of the current study is to analyze the FC between subregions of the MTL and PFC during episodic memory of indoor and outdoor scenes and determine how the FC differs by age.

Current Study

In the current study, we investigate how the development of subregions in the PFC and MTL support episodic memory formation and how the connectivity pattern of the PFC and MTL regions differs by age. We utilized a group of participants ages 8 to 25 performing an episodic memory task. The participants studied indoor and outdoor scenes in the scanner and their memory

of these scenes were tested afterwards. By back sorting their encoded trials as Hits or Misses, the contrasts were created between different kinds of trials to investigate the brain regions supporting memory formation.

Previous studies have shown that MTL subregions such as hippocampus and PHG support the memory formation of episodic details (Davachi, 2006; Staresina & Davachi, 2008; Staresina et al., 2011). As high complexity scenes have significantly more details embedded in the images compared to low complexity scenes, it is expected that hippocampus and PHG will show more activation for remembering high complexity scenes compared to low complexity scenes. Additionally, because the ability to encode detailed information has shown an age-related increase as reviewed before, it is expected that the activations in these regions will also show an age-related increase.

Relatedly, because the ability for complex scene memory improves with age (Brown & Campione, 1972; Doherty & Pellegrino, 1985; Köhler et al., 2002; Mandler & Robinson, 1978), and the PPA region has been linked to the processing and memory formation of scenes, it is expected that functionally defined PPA region will show age-related increase supporting memory formation of complex scenes.

During intentional memory formation, we expect both the DLPFC and VLPFC to show activation supporting memory formation. We expect the SupPFC to show deactivation supporting memory formation. Furthermore, given the role of the DLPFC in supporting the ability to spontaneously apply memory strategies and regulate attention, and children's apparent lack of these abilities (Blumenfeld & Ranganath, 2007; Shing et al., 2010), it is expected that the DLPFC will show significantly more activation for adults compared to children. Because adults are more skilled at utilizing memory strategies and regulating attention to facilitate complex information

binding, we predict that the DLPFC and hippocampus/PHG will show more FC to facilitate the formation of holistic episodic experiences.

Besides the memory-related activation, previous research has hinted that the SupPFC shows memory-related deactivation during memory formation. Evidence from aging literature demonstrates less effective deactivation in the SupPFC for old adults compared to young adults during memory formation (de Chastelaine et al., 2014). Because less optimal memory performance has been observed in both children and old adults (Shing et al., 2010), we predict that children, similar to old adults, will show less effective deactivation in the SupPFC.

We thus hypothesize that during memory formation, we will observe 1) more activation in the hippocampus and PHG supporting memory formation of high complexity scenes compared to low complexity scenes 2) age-related increase of activation in the hippocampus and PHG supporting memory formation of high complexity scenes 3) age-related increase of activation in the PPA supporting memory formation 4) age-related increase of activation in the DLPFC 5) age-related increase of the FC between the DLFPC and hippocampus/PHG 6) deactivation in the SupPFC in both children and adults 7) age-related increase for deactivation in the SupPFC.

METHODS

Participants

Ninety-one participants, ages 8 to 25 years were recruited from the community in Metro Detroit area and provided informed consent as per a Wayne State University IRB-approved protocol. All participants were right-handed, had normal or corrected-to-normal vision, with no history of psychiatric or neurological disorders. Three participants were excluded for not completing the functional portion of the study. In addition, one adult and one child were excluded for excessive motion, one adolescent and one child for abnormal memory performance, and another adolescent for IQ below normal range. Data are presented for 83 participants (42 females, mean age = 15.71 ± 5.18). The IQ of the participants were assessed using Kaufman Brief Intelligence Test and are in the normal range (mean = 109.70 ± 11.93). IQ also did not show a significant correlation with age (r = -.05, p = .67).

Subsequent Memory Paradigm

Participants studied 120 indoor and outdoor scenes in the scanner. They were instructed to memorize these scenes for a later memory test. During this study phase, participants judged whether each picture depicted an indoor or outdoor scene, and indicated their judgment using a two-button response box. They were instructed to press one button with their right index finger to indicate an indoor scene or another button with their right middle finger to indicate an outdoor scene. Each scene was presented for 3 s followed by a 0.5 s of fixation across. Variable intertrial intervals (2–8 s) were used to increase fMRI measurement reliability (jitter sequence determined using optseq2, http://surfer.nmr.mgh.harvard.edu/optseq/).

Immediately following the scan session, participants completed a self-paced recognition test with 120 old and 80 new (foils) scenes. During the testing phase, participants first judged whether they were shown the scenes before in the study phase (Old) or not (New). Next they indicated whether they "really remembered" the scenes (Sure) or whether the scenes just "looked familiar" (Not Sure). Participants were instructed to make a "Sure" response if they had a vivid, clear memory of studying a scene and could recall specific episodic information like what the picture looked like on the screen, what they were thinking about at the time or anything that made the memory distinct. In contrast, a "Not Sure" response was made if participants knew they had studied the scene, but could not recall details of that experience.

Parahippocampal Place Area (PPA) Localizer

To functionally define PPA and other scene-sensitive regions, participants performed a one-back localizer task while viewing pictures of scenes and common objects. They were shown four blocks of scenes and four blocks of objects. Every block contained 14 items, lasting for 1s each. The localizer task lasted 4 minutes and 10 seconds and the order was counterbalanced for even and odd participant numbers.

MRI data acquisition

MRI data were acquired in a 3T Siemens Verio scanner. T1-weighted whole-brain anatomy images were acquired using a MP-RAGE sequence: 192 sagittal slices, repetition time (TR) = 2200 ms, echo time (TE) = 4.26 ms, flip angle = 9 °, field of view = 256 mm, 192 x 256 voxels, and voxel size = 1mm x 0.5 mm x 1mm. Functional images were acquired using a T2*-weighted gradient-echo sequence: 30 slices parallel to the AC-PC plane, TR = 2000 ms, TE = 30 ms, flip

angle = 90 º, voxel size 3.1mm x 3.1mm x 4mm. For the current task, we acquired three consecutive functional runs, each consisting of 118 volumes and lasting 4 minutes and 10 seconds.

Behavioral Analysis

Each scene showed in the study phase was labeled as a Hit or Miss based on if the participant correctly identified the scene or not later in the testing phase. A Hit trial was further labeled based on the recognition confidence as Sure or Not Sure. All studied scenes were sorted into three categories: Hit Sure (Hit_S), Hit Not Sure (Hit_NS), or Miss. Each foil shown during the testing phase was labeled as a False Alarm (FA) if the participant incorrectly identified the scene as old. These responses were similarly categorized into FA Sure (FA_S) and FA Not Sure (FA_NS).

Besides categorizing Hit and Miss trials by recognition confidence, these trials were also categorized, in a separate analysis, based on scene complexity. Scene complexity was calculated according to the number of unique object categories in a scene, using the LabelMe image toolbox (Russell, Torralba, Murphy, & Freeman, 2008). Scenes that have more than four unique object categories were defined as high complexity (HC) scenes, and scenes that have less than four unique object categories were defined as low complexity (LC) scenes. In both the old and new scenes, half of them were HC scenes, and the other half were LC scenes. Using the complexity information, Hit and Miss trials were categorized into Hit High Complexity (Hit_HC), Hit Low Complexity (Hit_LC), Miss High Complexity (Miss_HC), and Miss Low Complexity (Miss_LC). FA trials during retrieval were similarly categories into FA High Complexity (FA_HC) and FA Low Complexity (FA_LC).

To make sure scenes that were not properly attended are excluded from these categories, any scene with no response recorded (indicating that participants were not responding within the time window allowed for a response) or with an incorrect response was marked as "Error". The button presses for three participants (one 8-year-old child and two adults) were not registered due to technique difficulties. Given the observed high overall compliance (M = .95, SD = .05) in making indoor/outdoor judgments during scanning, we retained the data from these three participants assuming that they studied all the scenes.

Imaging Analysis

Functional imaging data were analyzed with SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Images were motion corrected, normalized to the Montreal Neurological Institute (MNI) template, and smoothed with smoothed with an 8 mm full-width half-maximum Gaussian kernel.

To account for motion in the developmental sample, we applied stringent criteria to the functional images with the Artifact Detection Tools (ART; www.nitrc.org/projects/artifact_detect/) to identify outlier scans. An outlier scan was identified if (1) the global mean intensity of the scan was more than 3 SD from the mean image intensity of the run, or (2) scan-to-scan difference of composite motion parameter exceeded 1 mm.

A first-level general linear model (GLM) analysis was performed. Three parameters, Hit_S, Hit_NS and Miss were included as regressors of interest. The Error trials, seven motion parameters (3 translational, 3 rotational and 1 composite motion parameter) and the vectors for outlier scans were included as regressors of non-interest. Each outlier scan was represented by a single vector in the GLM, with a 1 at the onset of the outlier scan and 0s elsewhere. The temporal derivatives of

the task-related regressors (Hit_S, Hit_NS, Miss, and Error) were included in the GLM model. A canonical HRF was used for participants of all ages. The GLM analysis was conducted within the space defined by an individual binary mask. Each individual mask was constructed from segmented anatomy image.

Imaging analysis for the MTL. To investigate how MTL activation is modulated by scene complexity for scene perception and memory formation, we conduct three contrasts. First, we generated a contrast comparing viewing HC scenes to viewing LC scenes for each individual, regardless of memory outcome (HC > LC). Second, we generated SM contrasts separately for HC (Hit_HC > Miss_HC) and LC scenes (Hit_LC > Miss_LC). Then these contrasts were combined into a group-level analysis with a one-sample t-test. We report the group-level findings with a conventional threshold of $p < .005$ with 50 contiguous voxels. To compare SM effects between HC and LC scenes, we also conducted a paired t-test combining individual differences between the SM effects for HC scenes and SM effects for LC scenes (SM effects for HC scenes > SM effects for LC scenes) in a group level analysis. As this analysis is based on a double subtraction effects of both the SM effects and the complexity effect, we adopted a liberal voxel-level threshold of $p < .05$.

To identify the scene-sensitive region of PPA, we contrasted Scenes > Objects for each individual and combined these contrasts into a group-level analysis with a one-sample t-test. We identified the group-level PPA by locating the peak coordinates within posterior PHG (left x y z = -24 -44 -8, $t = 20.54$, $p < 10^{-12}$; right x y z = 24 -42 -8, $t = 19.00$, $p < 10^{-12}$). Subsequently, we identified individual PPA by the peak coordinates within 6mm radius from the group PPA peaks in both hemisphere. For three individuals, there was no identifiable PPA activation at a liberal

threshold of $p < .05$. These participants were excluded from the subsequent PPA analyses. For all other individuals, their PPA showed stronger activation when viewing scenes compared to viewing objects (*t* values left: $M = 5.48$, $SD = 1.69$; right: $M = 5.62$, $SD = 1.52$).

To assess how PPA activation supports scene perception and memory formation for scenes of different levels of complexity, we constructed ROIs as 6 mm spheres centered on individual PPA peaks and extracted parameter estimates averaging across these ROIs from the three previously defined contrasts (HC>LC; SM for HC scenes; SM for LC scenes). To test if activation of PPA show a developmental effect, these parameter estimates were correlated with age.

Imaging analysis for the PFC. Contrasts for positive SM (Hit_S > Miss) and negative SM (Miss > Hit_S) effects were created at the individual level and were entered into a group-level analysis. To identify the age-related and performance-related SM effects, age and recognition accuracy were entered as linear covariates into a group-level model. As we focus on the PFC in this part of analysis, activations maps were computed within a PFC mask, which includes anatomically defined superior, middle, inferior, medial PFC and precentral gyrus as implemented in the Wake Forest University PickAtlas tool (http://www.fmri.wfubmc.edu/). The SM effects were reported at a voxel-level threshold of $p < .005$, cluster-level corrected at $p < .05$ ($p < .005$; $k = 151$) as per a Monte Carlo simulation implemented in AlphaSim (http://afni.nimh.nih.gov/afni).

To examine brain regions where SM effects differed by age, we conducted several conjunction analyses. First, we generated correlation maps that showed positive and negative SM effects differed by age: (Hit_S > Miss) $\propto$ age and (Miss > Hit_S) $\propto$ age. These correlation maps were generated at a voxel-level threshold of $p < .05$. After that, we computed conjunction maps masking these age-correlated maps by their corresponding SM maps. Specifically, we computed

conjunction activation maps for brain regions that (1) increased activation with age within positive SM effects: ((Hit_S > Miss) ∝ age) ∩ (Hit_S > Miss), (2) increased deactivation with age within negative SM effects: ((Miss > Hit_S) ∝ age) ∩ (Miss > Hit_S). The conjunction maps were cluster-level thresholded at $p < .05$ based on their conjunctive p value, with the extent threshold determined by AlphaSim (conjunction $p < .00025$, $k > 29$). For ease of illustration, we combined age-related conjunction effects of both Map (1) and Map (2). The resultant maps depict increase of positive SM effects as positive (red), and increase of negative SM effects as negative (blue).

Functional connectivity analysis. To investigate the age-related differences in FC with the PFC, we conducted several psycho-physiological interaction (PPI) analyses. First, seed regions were created as 6 mm spheres centered on the peak coordinates according to previously identified age-related conjunction effects. We identified bilateral DLPFC (±44, 6, 26), right interior frontal gyrus (IFG; 44, 32, 12), right SupPFC (22, 54, 24), and right medial PFC (mPFC, -34, 52, 4), which showed age-related increase in their activity as regions of interest (ROIs). Then, individual-level PPI effects contrasting Hit_S > Miss were generated using these ROIs as seed regions. These individual effects were entered into a group-level analysis to identify both positive and negative PPI effects. Age was used as a linear covariate to identify developmental differences in the PPI effects. These group level PPI maps survived a voxel-level threshold of $p < .005$, and a cluster-level threshold of $p < .05$ ($p < .005$; $k = 250$) as per a Monte Carlo simulation implemented in AlphaSim.

RESULTS

Behavioral Analysis

Of the scenes shown during the study phase, 57 ± 14% were correctly identified as old in the recognition test (Hit). Of the scenes used as foils during the recognition test, 26 ± 13% were incorrectly identified as old (False Alarm, FA). When recognition of scenes was considered by scene complexity, 30 ± 8 % of the old scenes were Hits of high-complexity scenes (Hit_HC) and 28 ± 8% were Hits of low-complexity scenes (Hit_LC). On the other hand, 29 ± 13 % of the new scenes were FA of HC scenes (FA_HC), 31 ± 13 % were FA of LC scenes (FA_LC). Across all participants, recognition accuracy was higher for HC compared to LC scenes ($t(82) = 2.80$, $p < .01$). Recognition accuracy for both HC and LC scenes increased with age (HC: $r(81) = .38$, $p < .001$; LC: $r(81) = .26$, $p < .05$) (Fig. 1).

Next the recognition of scenes was considered by recognition confidence or "sureness". Of the old scenes, 44 ± 15% were Hits with "Sure" responses (Hit_S) and 13 ± 8% were Hits with "Not Sure" responses (Hit_NS). Of the foils, 14 ± 11% were FAs with "Sure" responses (FA_S), and 12 ± 8 % were FAs with "Not Sure" responses (FA_NS).

Recognition accuracy rates were calculated separately by the recognition confidence (Hit rates of high-confidence and low-confidence corrected by their respective FA rates). Recognition accuracy was higher for high-confidence judgements ($M = .31$, $SD = .16$) compared to low-confidence ones ($M = .01$, $SD = .06$; $t(82) = 15.67$, $p < .001$), with recognition accuracy for low-confidence judgments not significantly different from zero ($t(82) = 1.82$, $p = .07$). Recognition accuracy increased with age for high-confidence judgments ($r(81) = .54$, $p < .001$), but not for low-confidence judgments ($r(81) = -.05$, $p = .64$; Fig. 2).

To assess whether there are age-related differences in the distribution of recognition responses across confidence levels, we calculated the proportion of FA_S out of all FA trials (FA_S/FA). This measure allows us to assess individual implicit bias towards high-confidence judgements without being exposed to the stimuli. Participants were fairly balanced in assigning high or low levels of confidence when incorrectly endorsing a new scene as old, which does not differ from 50% (proportion FA_S/FA: M = 52%, SD = 26%; $t(81) = .56$, $p = .58$). Critically, there were no age-related differences in the proportion of high or low confidence judgements ($r(80) = .03$, $p = .81$), suggesting that the distribution between high and low confidence recognition judgments was similar across age.

Imaging

SM effects by complexity in the MTL. Overall, activation for later remembered compared to later forgotten scenes were found along the long axis of bilateral MTL (Fig 3A, 3B). When we compared the SM effects between HC and LC scenes, we found more activation in both the anterior MTL (PRC and ERC) and posterior MTL (PHG) as identified within an anatomically defined MTL mask ($p < .05$; Fig. 4).

Age-related increase for SM effects was observed in anterior MTL for HC scenes (Fig. 3C). This region overlaps with the PRC and ERC, regions related to the encoding of item-related information. On the other hand, age-related increase for SM effects was observed in posterior MTL for LC scenes. This region spans across posterior hippocampus and pPHG and is related to the encoding of context-related information.

Individual PPA analysis. We found that the PPA was sensitive to scene complexity, showing more activation when the participants were viewing HC scenes, compared to viewing LC

scenes. Sensitivity to scene complexity increased significantly with age for left PPA ($r(79) = .23$, $p < .05$), but not for right PPA ($r(79) = .24$, $p = .06$). PPA activation supporting memory formation was also modulated by scene complexity. PPA activation for SM of HC scenes increased with age (left: $r(79) = .25$, $p < .05$; right: $r(79) = .19$, $p = .09$), but PPA activation for SM of LC scenes did not (left: $r(79) = .21$, $p = .06$; right: $r(79) = .21$, $p = .06$).

Positive and negative subsequent memory (SM) effects within the PFC. Across all participants, positive SM effects (Hit_S > Miss) were observed in bilateral large clusters spanning the dorsolateral PFC (DLPFC, BA 46/6), inferior frontal gyrus (IFG, BA 45/44), and smaller bilateral clusters in the ventral lateral PFC (VLPFC, BA 47/11; Fig. 5A, Table 1). Negative SM effects were observed bilaterally in a large superior PFC cluster extending over to the medial frontal gurus (SupPFC, BA10/9; Fig. 5A, Table 1).

To determine the nature of these positive and negative SM effects, we separately extracted parameter estimates for Hit_S and Miss trials from the functionally identified clusters. Parameter estimates are extracted with respect to the baseline. Bilateral DLPFC/IFG and VLPFC showed positive SM effects, with more activation compared to baseline for both Hit_S, and Miss trials. As expected by the positive SM effects, based on which these regions were identified, the activation was stronger for Hit_Sure compared to Miss trials (Fig. 5B, 5C). In contrast, regions that exhibited negative SM effects (bilateral SupPFC) showed deactivation compared to baseline, during both Hit_Sure and Miss trials. As expected by the negative SM effect, based on which these regions were identified, the magnitude of deactivation was larger for Hit_S compared to Miss trials (Fig. 5).

Positive and negative SM effects in PFC increased with age. To identify PFC regions where SM effects increased with age, conjunction analyses were conducted to show age-effects

within both positive and negative SM regions. From the analysis we identified bilateral DLPFC (BA 46/6), and right IFG (BA 45/44), shown in red, where positive SM effects increased with age (Fig. 6A, Table 2). We also identified right SupPFC (BA 10/9), right aPFC (BA 10), mPFC (BA32), and left aPFC (BA10), shown in blue, where negative SM effects increased with age (Fig. 6A, Table 2).

To further characterize these age-related SM effects, parameter estimates were extracted separately for Hit_S and Miss trials for above identified clusters. The parameter estimates for both type of trials were correlated with age. Results showed that the activation for Hit_S trials in the right DLPFC correlated with age (r = .46, p < .001), but activation for Miss trials did not (r = .18, p = .11; Fig. 6B). Similarly, activation for Hit_S trials in the right IFG correlated with age (r = .34, p < .01), but activation for Miss trials did not (r = .13, p = .25; Fig. 6C). For left DLPFC, both activation for Hit_S trials (r = .56, p < .001), and activation for Miss trials correlated with age (r = .44, p < .001), but the correlation coefficient is significantly larger for Hit_S trials than Miss trials (p < .05, one tailed). Deactivation for Hit_S trials in right SupPFC correlated with age (r = -.44, p < .001), but deactivation for Miss trials did not (r = .16, p = .14; Fig. 6D). Deactivation for Hit_S trials in mPFC correlated with age (r = -.31, p < .01), but deactivation for Miss trials did not (r = .04, p = .73).

FC for age-related SM regions. To investigate how SM regions functionally connected with other brain regions, we conducted PPI analyses using bilateral DLPFC, right IFG, right SupPFC, and mPFC as seed regions. Across all participants, right DLPFC showed positive FC with visual association cortex, including bilateral middle occipital lobe and posterior parahippocampal gyrus (pPHG; Fig. 7). Right DLPFC showed negative FC with DMN-related regions, including right middle/SupPFC and bilateral inferior parietal regions. The majority of

voxels in the inferior parietal cluster were within inferior parietal lobule (IPL; left: 42.8%, right: 65.2%) as identified with SPM Anatomy toolbox (Eickhoff et al., 2005).

The other two positive SM regions in PFC showed similar FC with other brain regions. Left DLPFC showed positive FC with bilateral middle occipital lobe and calcarine sulcus, negative FC with left IPL, left inferior temporal lobe and temporal pole. Right IFG showed positive FC with bilateral middle occipital lobe, calcarine sulcus, and bilateral pPHG, negative FC with bilateral IPL, left middle and superior temporal gyrus and bilateral precuneus.

To determine the developmental effects of the FC with positive SM regions, we correlated the PPI effects of these regions with age. Right DLPFC showed an age-related increase in positive FC with bilateral superior parietal lobe (SPL) and left pPHG. Right DLPFC also showed age-related increase in negative FC with left middle occipital lobe (Fig. 8). In contrast, left DLPFC showed age-related increase in positive FC with precentral and postcentral gyrus, and SPL (Fig. 8). No age-related increase in negative FC was found with the set threshold. Finally, right IFG showed age-related increase in positive FC with frontal and temporal lobes, including right precentral gyrus, right DLPFC and putamen, left middle temporal sulcus, anterior MTL, and PHG. No age-related increase in negative FC was found.

For negative SM regions, right SupPFC showed positive FC with DMN-related regions, including right IPL and right superior temporal lobe (Fig. 9). Right SupPFC also showed negative FC with large clusters in visual association regions, including bilateral middle occipital lobe, pPHG and retrospenial cortex (Fig. 9). In addition, mPFC showed positive FC with bilateral IPL, bilateral supramarginal gyrus, right insula and putamen. mPFC showed negative FC with bilateral pPHG and middle occipital lobe.

When the developmental effects of FC with these negative SM regions were analyzed, right SupPFC showed age-related increase in positive FC with several DMN regions, including bilateral IPL, precuneus, anterior cingulate gyrus and SupPFC (Fig. 10). Right SupPFC showed age-related increase in negative FC with visual association cortex including bilateral middle occipital lobe and pPHG (Fig. 10). In addition, mPFC showed age-related increase in positive FC with left precentral gyrus and several DMN regions, including bilateral medial frontal gyrus, anterior cingulate cortex, right superior frontal gyrus. mPFC showed age-related increase in negative FC with visual association cortex including bilateral middle occipital lobe, lingual gyrus, and pPHG.

DISCUSSION

In this study, we analyzed developmental effects for PFC and MTL regions that are linked to memory formation. We found that (1) both anterior and posterior MTL showed more activation supporting SM of complex scenes. (2) Anterior MTL showed a developmental effect supporting SM for more complex scenes, whereas posterior MTL showed a developmental effect supporting SM for less complex scenes. (3) PPA, a scene-sensitive region in the MTL showed an age-related increase to support better memory formation, especially for complex scenes. (4) DLPFC activation showed age-related increase to support SM. (5) DLPFC showed positive FC with posterior MTL regions. (6) SupPFC showed deactivation supporting SM. (7) SupPFC deactivation show an increase with age.

First of all, we examined if the MTL showed a regional difference supporting SM of scenes with different levels of complexity. We have previously hypothesized that more activations would be found in the PHG for the SM of HC scenes, as the PHG supports encoding of detailed information that can be found in HC scenes. We found that both anterior and posterior MTL showed more activation supporting SM of more complex scenes. The anterior MTL cluster overlaps with the PRC and ERC, whereas the posterior MTL cluster overlaps with posterior PHG. The results confirmed this hypothesis, showing more SM effects in posterior PHG for HC scenes, but in addition, more activation in both the PRC and ERC. Previous research has demonstrated that these regions are related to encoding item-related information (Eichenbaum, Yonelinas, & Ranganath, 2007). By definition, there are more unique object categories in HC scenes, hence more item-related information to encode. In this case, it is essential for the PRC and ERC to register multiple key items from a complex scene to ensure proper memory formation.

Second, we examined the SM effects of HC scenes to identify which regions in the MTL showed a developmental difference. We previously hypothesized that the hippocampus and PHG would show age-related increase supporting memory formation of high complexity scenes. However, we observed that anterior MTL showed increased activation supporting better memory of HC scenes. This anterior MTL cluster overlaps with the PRC and ERC. Similar to previous interpretations, the finding that the age-related anterior MTL activation is related to the SM of more complex scenes is consistent with its function to encode item-related information. The ability to quickly identify and register prominent items in complex scenes may increase with age and lead to better SM. On the other hand, we observed more age-related activation in posterior MTL for less complex scenes. This region overlaps with posterior hippocampus and posterior PHG. This result was surprising at first. But as we come to understand, for less complex scenes, there are likely fewer unique items for them to be identifiable. It is thus crucial that participants pay attention to the subtle differences in the background, or the contextual information. A lot of LC scenes, including empty rooms, waves, and mountains can be very similar to others within the same category. In the absence of prominent items in the scene, the participants need to rely on the refined analysis of the contextual information, and are also in need of more efficient binding of different pieces of information. Here we observed more activation with age in posterior hippocampus and the PHG that may suggest more processing and more effective binding of the detailed contextual information.

Third, we examine if the PPA exhibit a developmental effect supporting scene perception and memory formation. Consistent with our hypothesis, we found that the PPA showed a developmental difference in scene sensitivity. Adults compared to children showed more differential activation in the PPA when viewing HC scenes compared to viewing LC scenes. In

addition, the PPA showed an age-related increase to predict memory formation, and the effect is stronger for complex scenes. Previous research have shown that PPA is specialized in scene perception and activates when the participants process indoor and outdoor scenes, whether the scenes are real, imagined, or computer-generated (Nasr et al., 2011). Research exploring the developmental effects of perception regions show that the ability to better process scenes continue to develop from childhood to adulthood, likely due to the growing size of PPA (Golarai et al., (2007), but see Scherf, Behrmann, Humphreys, & Luna (2007). Previous research also found that posterior PHG, a region that significantly overlaps with the conventional PPA region, showed increasing positive SM with age for more complex scenes, but not for less complex scenes (Chai, Ofen, Jacobs, & Gabrieli, 2010). Our results are consistent with previous findings showing developmental effects in both scene perception and scene memory for more complex stimuli. Taken together, these findings suggest that the PPA supports the basic level of scene perception and memory early in childhood, but in order to support more complex scene perception and memory processes, the PPA likely undergoes continued development through to adulthood.

Besides MTL, PFC plays a critical role in memory formation by contributing to strategy use and attentional control. Previous research has confirmed that PFC show continued development into adulthood (Ghetti et al., 2010; Ofen et al., 2007), but these studies have used a ROI approach, which restricted the analysis to few specific PFC regions. In the current analysis, we systematically examined all the regions in the PFC to determine if they show a developmental effect. We have hypothesized that activation in the DLPFC would show an age-related increase. Using a conjunction analysis, we indeed identified an age-related increase in positive SM effects for DLPFC (Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Ofen et al., 2007). The DLPFC region identified overlaps with the premotor cortex, a region that is reported in a meta-analysis showing

strong SM effects during memory formation (Kim, 2011). It is suggested that this region, together with SPL, exert top-down attentional control, and are crucial in selective encoding of task-related stimuli (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Kim, 2011; Uncapher & Wagner, 2009). DLPFC and SPL have been shown in resting-state connectivity studies to be part of the dorsal attention network (DAN; Power et al., 2011; Vincent et al., 2006). The current study indeed found that FC between DLPFC and SPL, between DLPFC and visual association regions increased with age, suggesting that adults compared to children exert more attentional control in visual attention to facilitate selective encoding of scene information.

We hypothesized that there should be age-related increase for in the FC between DLFPC and hippocampus/PHG. In our current study, we first identified an age-related SM effect in a relatively anterior portion of IFG. This region showed FC with visual association regions including middle occipital lobe and pPHG. In addition, the FC between IFG and bilateral pPHG increased with age. Although IFG is topographically more ventral to DLPFC, these findings suggest that this region, similar to DLPFC, likely facilitates selective encoding of prominent features with inputs from visual association regions. Adults compared to children are more efficient in utilizing memory strategy to select these features to support better memory formation.

Aside from identifying positive SM effects within the PFC, we also identified negative SM effects in several PFC regions including bilateral SupPFC and left aPFC. We hypothesized that these regions would show more deactivation for remembered verses forgotten scenes in both children and adults, which is confirmed by our current results. Although the deactivation in the PFC is much less discussed, these effects were consistently found during memory formation in research spanning more than a decade (Daselaar, Prince, & Cabeza, 2004; Huijbers et al., 2013; Otten & Rugg, 2001). This effect was sometimes referred to as the subsequent forgetting (SF)

effect to emphasize the relationship between the activation of this region and poor memory outcome (Daselaar et al., 2004; Kim, 2011; Otten & Rugg, 2001). Kim (2011), identified in a meta-analysis that more activation in the SupPFC and frontal pole regions is related to SF, which is consistent with our current findings. When we extracted parameter estimates separately for Hit_S and Miss trials in our current study, it became clear that when participants were attending to the encoding scenes, SupPFC showed more deactivation compared to baseline, although more deactivation was observed for later remembered than later forgotten scenes. Thus we adopted the term "negative SM effects" to highlight the deactivating nature of the SupPFC.

While negative SM effects have rarely been discussed in memory developmental literature, evidence in aging studies has started to shed light on these effects (de Chastelaine et al., 2014; de Chastelaine & Rugg, 2014; Park et al., 2013). Overall, it was shown that negative SM effects were stronger in young adults than older adults, regardless of scenes or words as the encoding stimuli (de Chastelaine & Rugg, 2014; Park, Kennedy, Rodrigue, Hebrank, & Park, 2013). Importantly, the strength of negative activation is closely related to memory performance (de Chastelaine & Rugg, 2014; Park et al., 2013). For example, using an incidental memory task for scenes, Park et al. (2013) demonstrated that higher level of deactivation of these negative SM regions predict better memory performance for middle aged and older adults. In addition, older adults compared to younger adults showed reduced deactivation in negative SM regions, including IPL, precuneus and SupPFC. Their finding showing reduced level of negative SM effects in older adults mirrored our current finding showing reduced level of SupPFC deactivation in children. In both cases, the lack of SupPFC deactivation is related to less efficient memory formation. Relatedly, in a meta-analysis Maillet & Rajah (2014) identified apparent over-recruitment in middle/SupPFC during memory formation in the aging population. This over-recruitment, as they and others have

suggested, is in fact due to an ineffective deactivation in these PFC regions for older adults. Combining the results from both developmental and aging memory research, we reason that that effective deactivation in SupPFC is critical in supporting memory formation across life span.

Limitations

While we infer neural developmental changes in our current study, we are cognizant that the design of this experiment is cross-sectional in nature, which does not provide a direct proof for the existence of such changes. Here we compared the neural substrate for memory formation between children and adults ages 8 to 25 and showed age-related differences in the MTL, PFC and their FC. While it is rational to infer that these brain regions will likely show such changes from children to adults, the research design limits our ability to make such claims. We are currently collecting data for the follow-ups with the same participants and these data would stronger such claims in the future.

In addition, our current analysis was conducted using age as a linear variable to assess memory development. This approach, combined with a relatively large sample size for imaging studies, increased the power to detect developmental differences. Yet, this approach assumes a linear or close-to-linear developmental trajectory for neural development. As previous research has demonstrated, there can be a rapid non-linear development in memory-related brain regions during middle childhood, especially in the DLPFC and VLPFC (Ghetti et al., 2010). Our research method does not allow us to zoom in on the developmental trajectory during middle childhood, but instead allowed us to identify the developmental trajectory across a longer life span.

CONCLUSION

In sum, we used a subsequent memory paradigm to investigate the neural correlates of episodic memory development with a cross-sectional sample of 83 children and adults, ages 8 to 25. We found age-related increase in subsequent memory activation in both anterior and posterior subregions of the MTL. Furthermore, there was an age-related increase in activation supporting memory formation of complex scenes in a functionally defined scene-sensitive region in the posterior MTL. This region also predicted better memory for complex scenes. Furthermore, we found age-related increase in both DLPFC activation and SupPFC deactivation supporting better memory formation. Finally, the functional connectivity between DLPFC and posterior MTL that increased with age. These findings suggest that the functional development of the MTL and PFC and their connectivity contributes to age-related improvement in memory development.

APPENDIX

Table 1. *Positive and Negative SM Effects in PFC*

Regions	BA	MNI Coordinates			Peak T Value	Number of Voxels
		x	y	z		
Positive SM Effects in PFC (Hit Sure > Miss)						
R DLPFC	44/6	40	8	28	7.71	1701
R IFG	46/45	44	32	12	5.80	
L DLPFC	44/6	-44	6	26	6.76	2819
L IFG	46/45	-44	28	16	6.41	
L VLPFC	47/11	-34	32	-16	4.67	
R VLPFC	47/11	28	34	-10	4.56	206

Table 1 Continued

Regions	BA	MNI Coordinates			Peak T Value	Number of Voxels
		x	y	z		
Negative SM Effects in PFC (Miss > Hit Sure)						
R SupPFC		10/9	24	54	22	7.95	7196
R IFG/Insula		44	48	16	4	4.15	248

Both positive and negative effects reported at $p < .05$ corrected.

Table 2. *Age-related Positive and Negative SM Effects in PFC*

Regions	BA	MNI Coordinates			Peak T Value	Number of Voxels
		x	y	z		
Age-related Positive SM Effects in PFC (Hit_S > Miss ∩ Hit_S > Miss with Age)						
L DLPFC	6/9	-44	6	26	6.76	397
R DLPFC	6/9	44	6	26	6.32	128
R Precentral Gyrus	6	50	-4	34	3.26	
R IFG	46/44	44	32	12	5.80	166

Table 2 Continued

Regions	BA	MNI Coordinates			Peak T Value	Number of Voxels
		x	y	z		
Age-related Negative SM Effects in PFC (Miss > Hit_S ∩ Miss > Hit_S with Age)						
R SupPFC	10/9	22	54	24	7.55	610

Both positive and negative effects reported at $p < .05$ corrected.

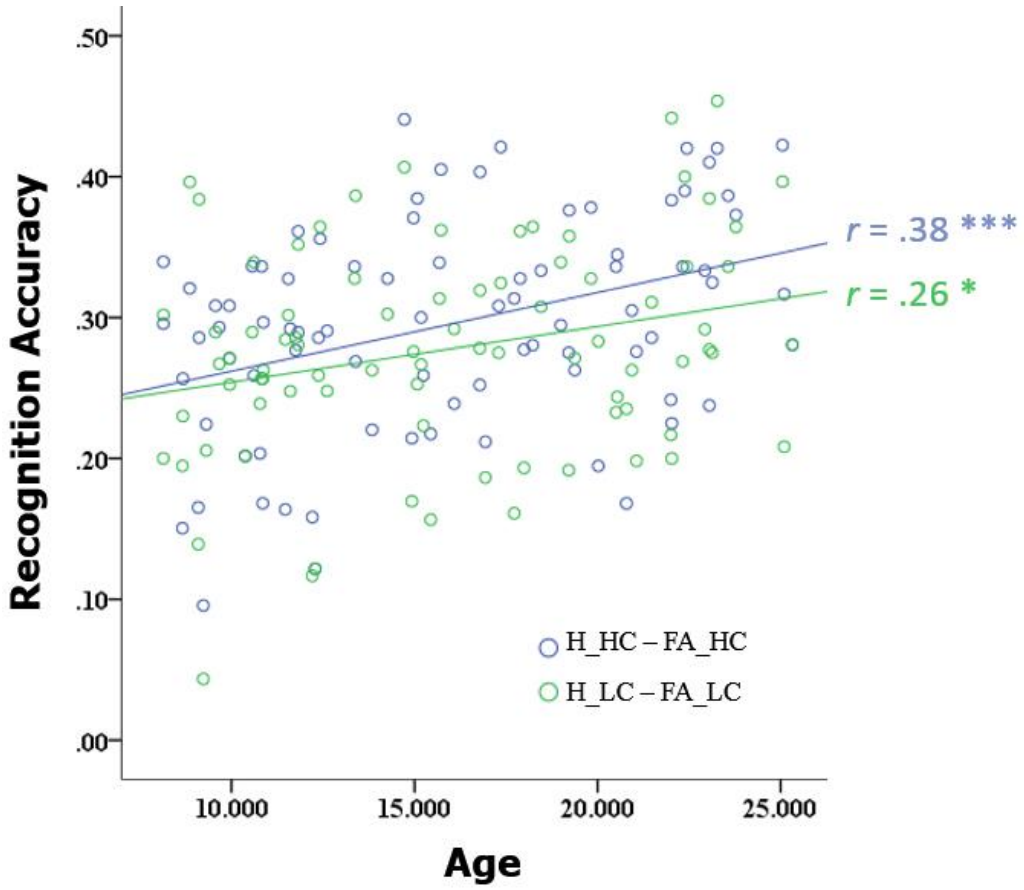

Figure 1. Recognition accuracy by scene complexity and age. Recognition accuracy increased with age for both high-complexity ($r(81) = .38$, $p < .001$) and low-complexity scenes ($r(81) = .26$, $p < .05$).

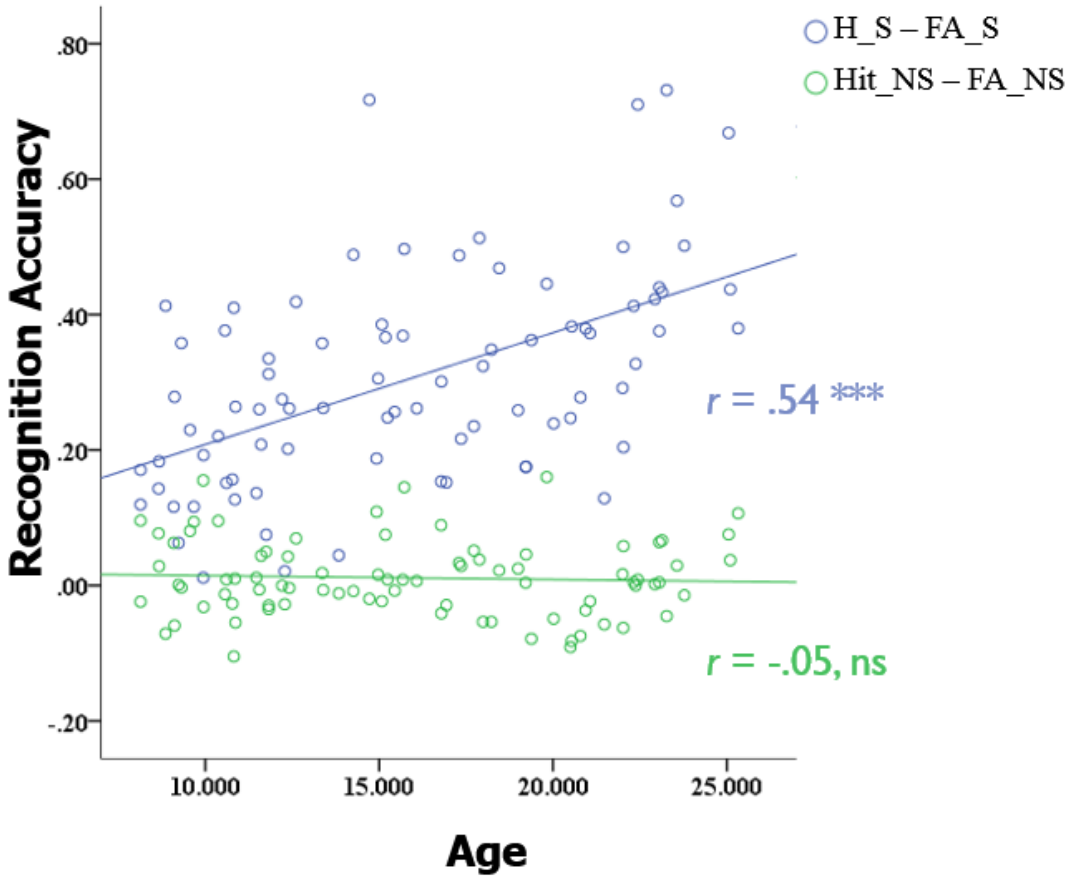

Figure 2. Recognition accuracy by recognition confidence and age. Recognition accuracy for high-confidence ("sure") scenes increased with age ($r(81) = .54$, $p < .001$), but recognition memory for low-confidence ("not sure") scenes did not increase with age ($r(81) = -.05$, $p = .64$).

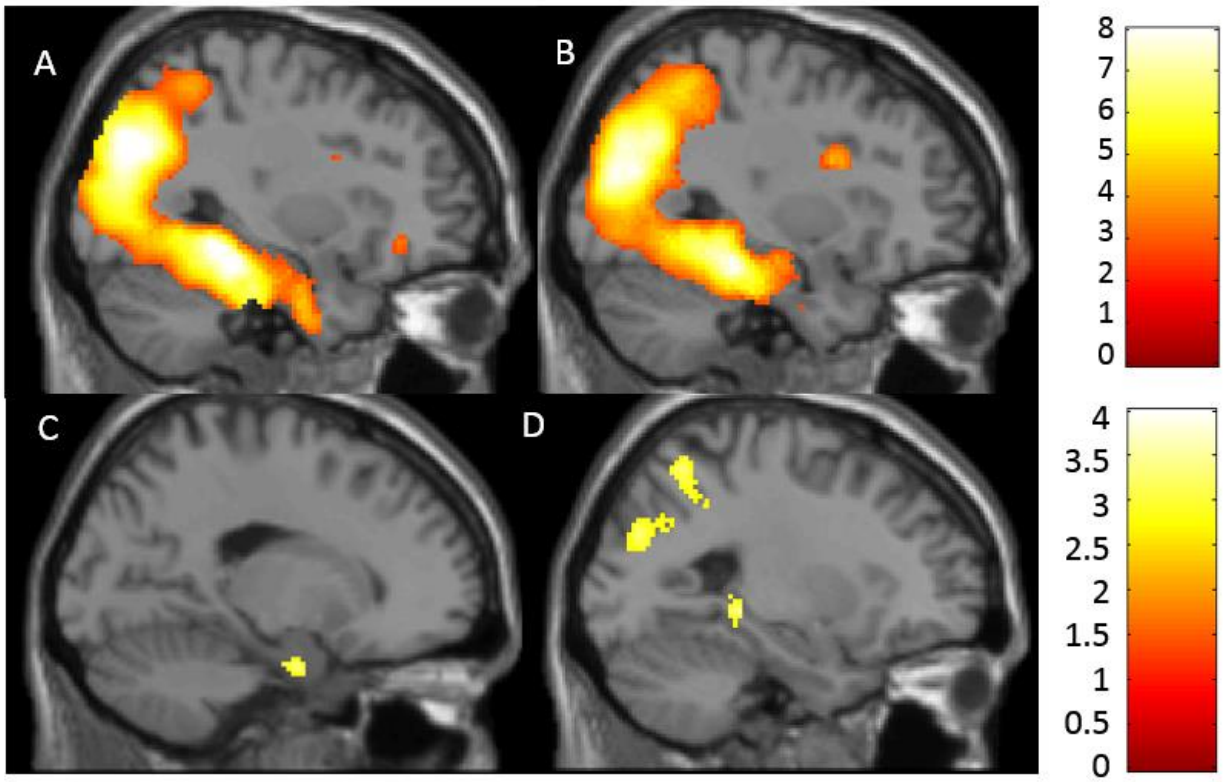

Figure 3. Subsequent memory effects and age-related effects. Subsequent memory effects for high- (**A**) and low-complexity scenes (**B**) showed activation along the long axis of the MTL. Subsequent memory effects for high-complexity scenes showed age-related effects in anterior MTL (**C**) whereas SM effects for LC scenes showed age-related effects in posterior MTL (**D**).

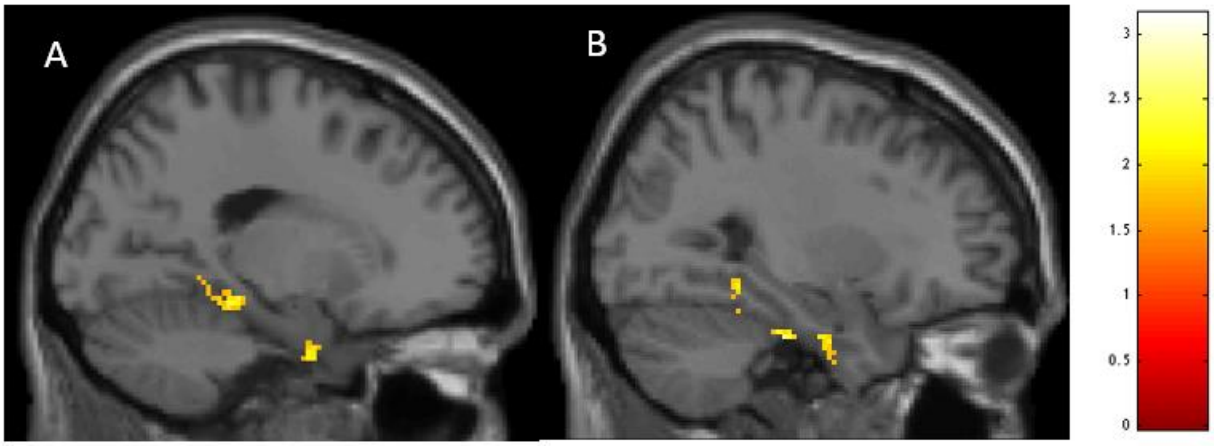

Figure 4. Difference of SM effects between subsequent memory of high-complexity and low-complexity scenes. More activation in both the anterior and posterior MTL supported subsequent memory of high-complexity scenes compared to low-complexity scenes ($p < .05$).

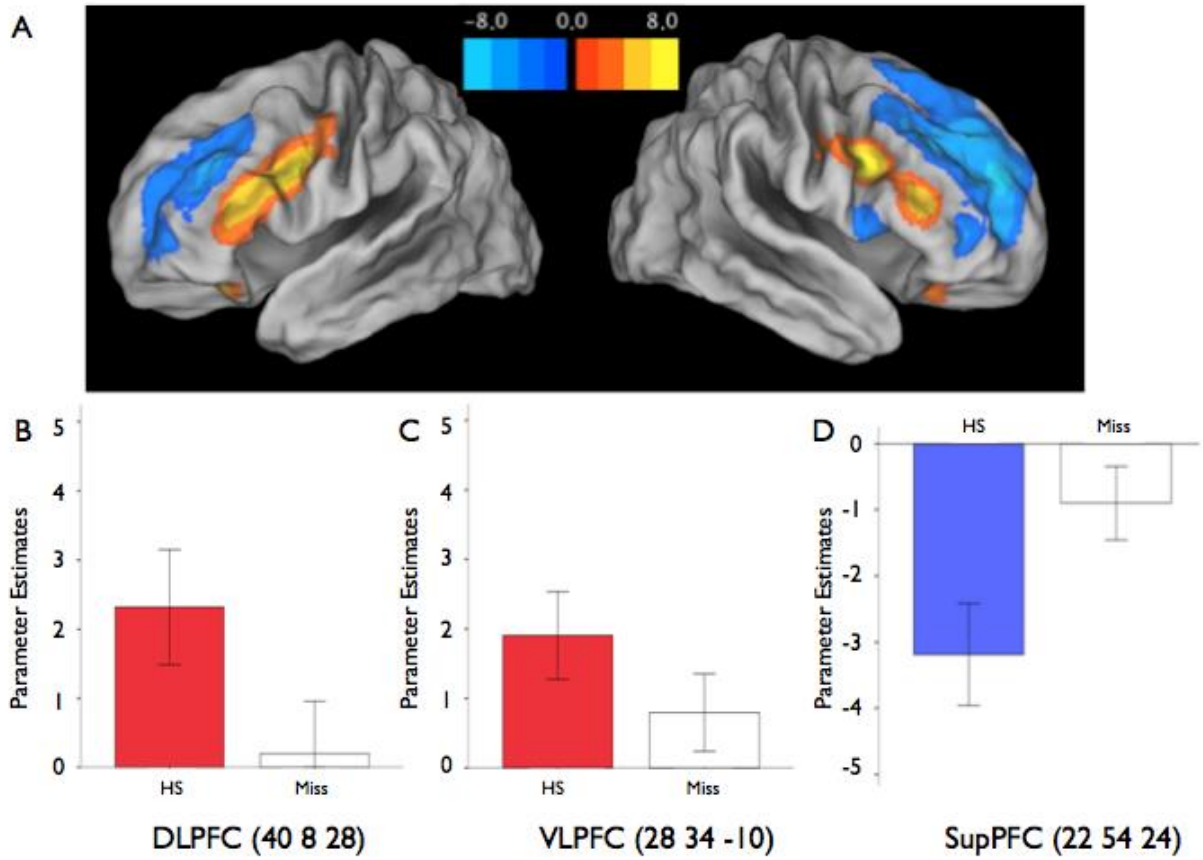

Figure 5. PFC regions showing positive and negative SM effects. **A.** Positive SM effects were observed in bilateral DLPFC and VLPFC (Hit Sure > Miss, parameter estimates shown in **B, C**, right hemisphere). Negative SM effects were observed in bilateral SupPFC (Miss > Hit Sure, parameter estimates shown in **D**, right hemisphere).

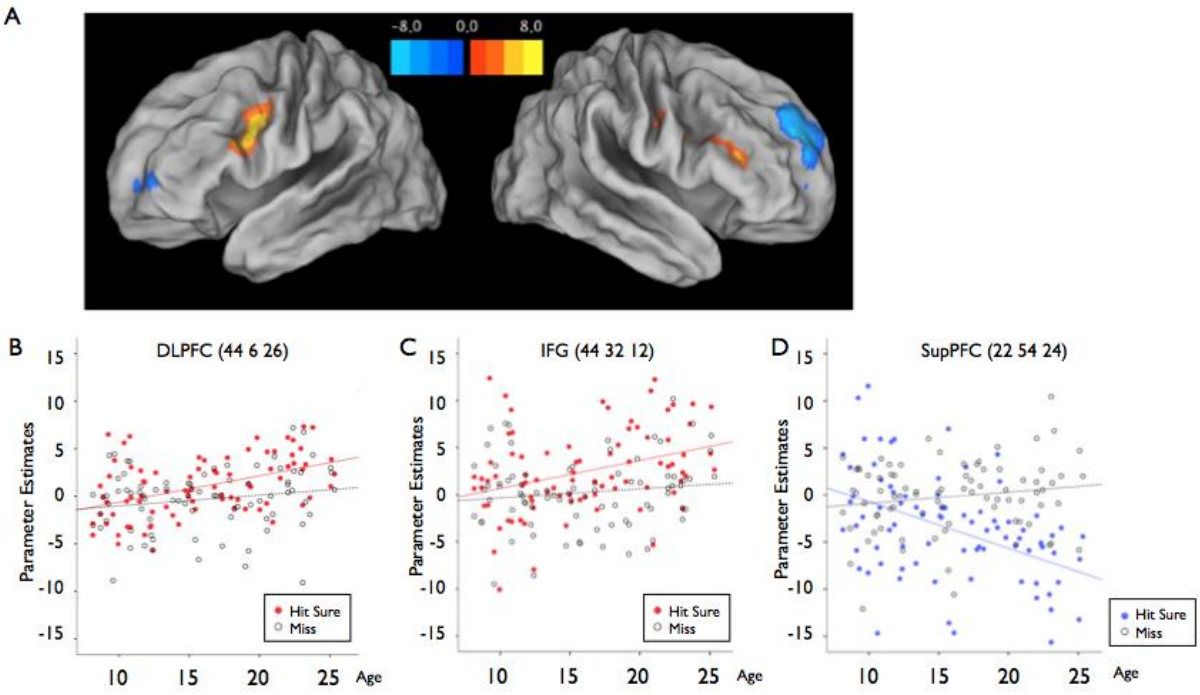

Figure 6. Age-related SM effects in the PFC **A.** Bilateral DLPFC, right IFG, right SupPFC and left aPFC showed age-related positive and negative SM effects ($p < .05$ corrected). Activation for Hit Sure trials increased with age in right DLPFC (**B**, $r = .46$, $p < .001$) and left IFG (**C**, $r = .34$, $p < .01$), but activation for Miss trials did not ($ps > .05$). **D.** Magnitude of deactivation for Hit Sure trials in right SupPFC increased with age ($r = -.31$, $p < .01$), but magnitude of deactivation for Miss trials did not ($r = .04$, $p = .73$).

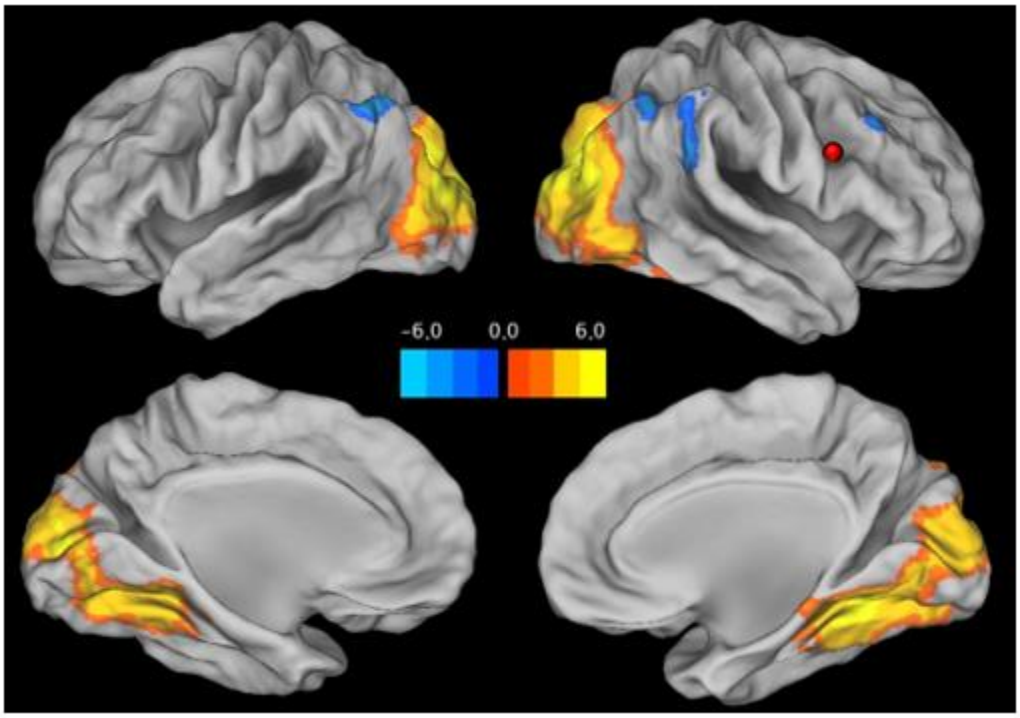

Figure 7. Brain region that showed functional connectivity with right DLPFC. DLPFC showed positive functional connectivity with visual association cortex in the occipital and temporal lobe. DLPFC showed negative functional connectivity with regions in the default-mode network, including the inferior parietal lobule.

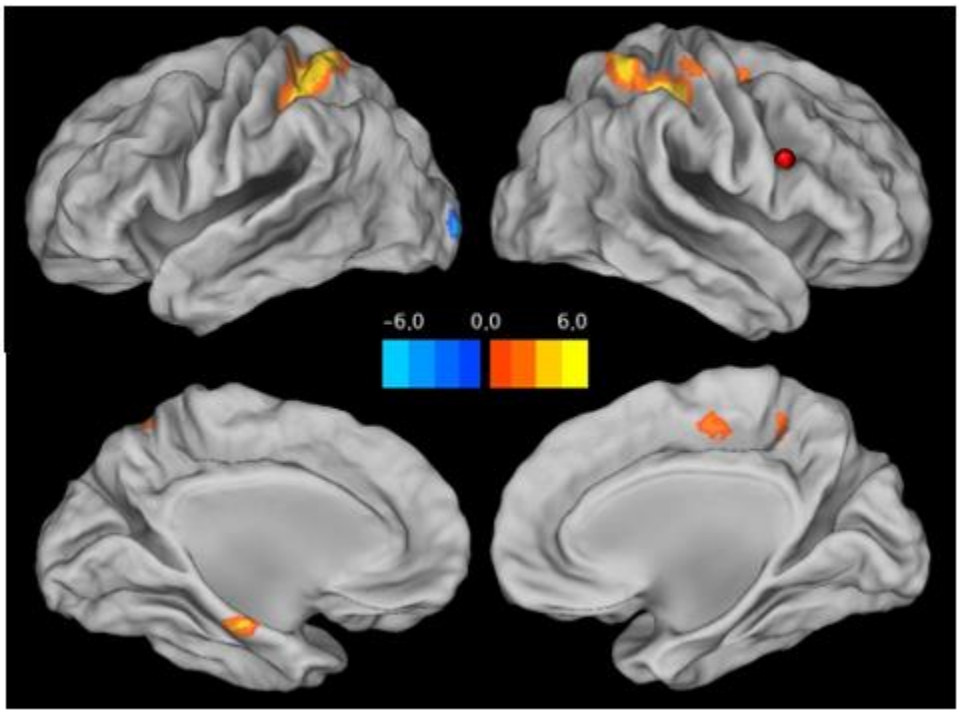

Figure 8. Brain regions that showed developmental differences in the functional connectivity with DLPFC. DLPFC showed age-related increase in positive functional connectivity with dorsal attention network and left pPHG. DLPFC showed age-related increase in negative functional connectivity with left lower level visual regions.

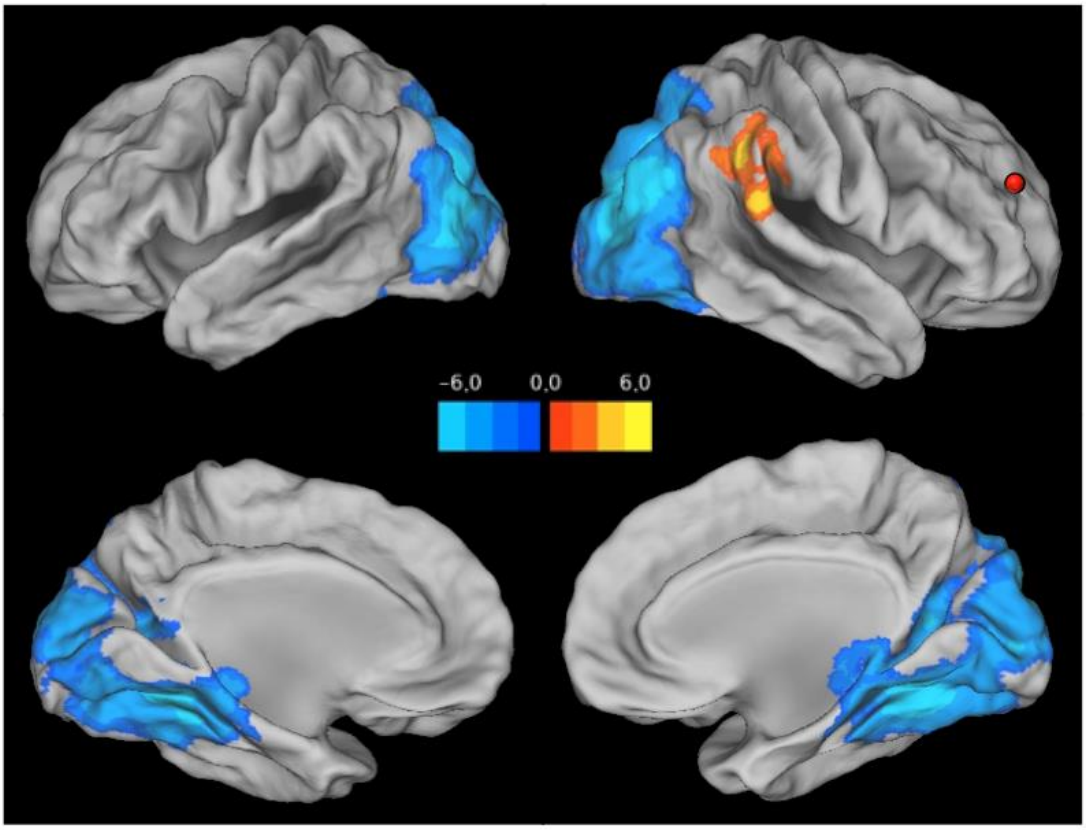

Figure 9. Brain region that showed functional connectivity with SupPFC. SupPFC showed positive functional connectivity with inferior parietal lobule, but negative functional connectivity with visual association cortex.

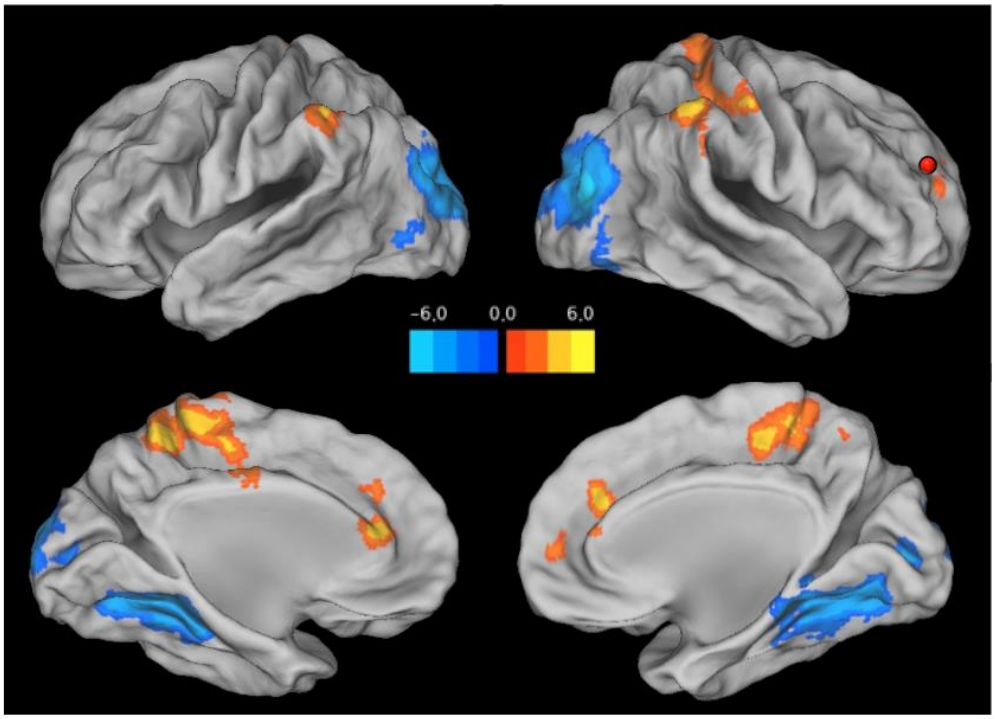

Figure 10. Brain regions that showed developmental differences for the functional connectivity with SupPFC. SupPFC showed age-related increase in positive FC with several regions in the default mode network, including inferior parietal lobule, precuneus, and medial PFC. SupPFC showed age-related increase in negative FC with visual association cortex.

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ABSTRACT

NEURAL CORRELATES OF EPISODIC MEMORY FORMATION IN CHILDREN AND ADULTS

by

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Major: Psychology

Degree: Master of Arts

The medial temporal lobe (MTL) and prefrontal cortex (PFC) are two key brain regions that support episodic memory formation in both children and adults, but the functional developmental of these regions remains unclear. In this study, we investigated the development of neural correlates of episodic memory formation using functional MRI with a subsequent memory paradigm, administered to a cross-sectional sample of 83 children and adults. We found that MTL subregions showed an age-related increase in activation supporting memory formation of complex scenes. In addition, a functionally defined scene-sensitive region in the posterior MTL also showed similar increase and predicted better memory for complex scenes. Within the PFC we found age-related increase in both activation and deactivation that support memory formation. Finally, we found age-related increase in the functional connectivity between dorsal lateral PFC and posterior MTL regions. Taken together, these findings suggest that the continued functional development of the MTL and the PFC is crucial for age-related improvements in memory.

AUTOBIOGRAPHICAL STATEMENT

Education

Wayne State University, Michigan 2012-Now

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, Electronic Science and Technology

Professional Appointments

Wayne State University, Michigan

Graduate Teaching Assistant 2012-Now

Selective Publications & Presentations

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 contriution).

Tang, L., Miller Rigoli C. G., Patel I., Adapa N., Yu Q. J., Ofen N. (2014). Developmental differences in the anterior and posterior medial temporal lobe during memory formation, *Organization of Human Brain Mapping*, Hamburg, Germany

Daugherty A. M., Bender A. R., **Tang, L.**, Raz N., Ofen N. (2014). Differential Age-Related Decrease in Hippocampal Subfield Volume from Childhood to Late Adulthood, *Organization of Human Brain Mapping*, Hamburg, Germany