ABSTRACT

Title of Thesis: DEVELOPMENT OF THE EPISODIC MEMORY NETWORK IN EARLY CHILDHOOD: INSIGHTS FROM GRAPH THEORETICAL ANALYSIS

Morgan Anna Botdorf, Master of Science, 2019

Thesis Directed By: Professor Tracy Riggins,

Department of Psychology

The hippocampal memory network has been identified in both children and adults and shown to be related to episodic memory ability. However, it remains unclear how its organization may differ across development, particularly during periods of large behavioral gains in memory ability. The goal of the present study was to utilize graph theoretical analysis to investigate the integration of the hippocampus within the memory network and segregation from other networks (i.e., fronto-parietal and cingulo-opercular attention networks) in the brain. Results indicated that with age, there was a general increase in connections between the hippocampus and both regions within the memory network and regions in other networks in the brain. These differences may contribute to improvements in memory typically observed in early childhood. Future analyses will examine relations with memory behavior and probe whether segregation is observed using other metrics, a sample of adult data, or other networks (e.g., sensorimotor).

DEVELOPMENT OF THE EPISODIC MEMORY NETWORK IN EARLY CHILDHOOD: INSIGHTS FROM GRAPH THEORETICAL ANALYSIS

by

Morgan Anna Botdorf

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Advisory Committee:

Professor Tracy Riggins, Chair
Professor Luiz Pessoa
Professor Donald J. Bolger
Professor Fengji Geng

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Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

Early childhood is a fascinating period for brain development, as it is thought to be characterized by changes in the organization of brain regions and the connections between them. Much thinking and empirical research has been devoted to understanding the nature of this important period in brain development, as these changes in organization likely precede or parallel behavioral changes in cognitive, motor, sensory, and social abilities.

Interactive specialization theory of brain and behavioral development

Several accounts have been proposed to explain the relation between brain and behavioral development. In terms of theoretical perspectives, early thinking proposed that brain and behavioral development occurred mostly within a maturational framework. In this view, maturation of specific brain regions (e.g., fusiform face area, dorsolateral prefrontal cortex) was thought to be responsible for age-related changes in a behavioral ability (e.g., facial recognition, cognitive control). Specifically, this theoretical account suggested that specific regions come "online," or become active, at a specified period in development and once "switched on," begin supporting specific sensory, motor, and cognitive abilities.

Although maturation plays a role in brain and behavioral development (Farah, Rabinowitz, Quinn, & Liu, 2000; Sowell et al., 2003), more recent theories have expanded their explanation of developmental changes to incorporate some complexities that are not addressed by the maturational perspective. These additions include consideration of the vast, intricate nature of the structural and functional connections

within the brain, and the acknowledgement that brain regions are not "offline" early in development and suddenly come "online", but are functional even during the prenatal period. One prominent theory that accounts for these complexities is the interactive specialization framework (Johnson, 2001). This viewpoint suggests that brain development stems from the organization and re-organization of interactions between brain regions. Early in development, specific brain regions are thought to be partially active and involved in a non-specialized array of processes, versus the specialized processes these regions support later in life. Within this framework, a developmental change in behavioral ability is thought to result from changes in the interactive connections between distinct regions of the brain as these structures become more specialized for certain tasks, activities, or domains (Johnson, 2001, 2011).

Support for interactive specialization theory

Empirical research has set out to test and provide support for the interactive specialization account of brain and behavioral development using both task-based and resting state functional magnetic resonance imaging (fMRI) methods. Research using task-based fMRI has suggested that this theoretical model offers important insights into cognitive development of processes including face processing (Joseph, Gathers, & Bhatt, 2011), problem solving and learning (Battista et al., 2018), and executive control (Durston et al., 2006). Based on findings from these studies, both progressive (i.e. increasing connectivity between regions) and regressive changes (i.e. decreasing connectivity between regions) are likely occurring within these task-related functional networks to support neurodevelopment of cognitive processes.

In addition to task-based studies, findings from research using resting state fMRI (rs-fMRI), a method which measures intrinsic activity occurring in the brain at rest (Biswal, Yetkin, Haughton, & Hyde, 1995), have been useful in testing the interactive specialization theory. Rs-fMRI has been identified as a promising method for gaining insight into the organization of brain networks during early childhood, specifically, as this type of scan does not require a child to complete a task, which reduces cognitive demands, and thus can be used with young children (Redcay, Kennedy, & Courchesne, 2007; Uddin, Supekar, & Menon, 2010; Vanderwal, Kelly, & Castellanos, 2013). This method operates on the idea that some regions of the brain tend to oscillate in synchrony, suggesting a history of co-activation that likely extends into periods when the brain is not at "rest" (e.g., during an attention task). This oscillating activity between regions has been shown to meaningfully organize into resting state networks of the brain (e.g., Fox et al., 2005). Studies that have used this and other task-free paradigms (such as passive viewing of low-level visual stimulation) methods to investigate how brain development supports age-related changes and differences in cognitive abilities, such as attentional control (Fair et al., 2007; Marek, Hwang, Foran, Hallquist, & Luna, 2015) or episodic memory (Riggins, Geng, Blankenship, & Redcay, 2016), provide support for the interactive specialization view, as they report changes in connectivity among regions of the brain throughout childhood that relate to changes in behavior.

Using graph theory to better understand brain and behavioral development

The intricacies of brain development highlighted in the interactive specialization perspective can be further characterized using computationally based approaches. One such method, known as graph theory, has proven particularly useful to further

understanding the intricate nature and changing organization of these task-related and resting state networks (Bullmore & Sporns, 2009, Supekar, Musen, & Menon, 2010; Wang, Zuo, & He, 2010). This method, which has been used extensively in other disciplines, including computer science and social network analysis, has recently increased in popularity within cognitive neuroscience as a method to understand and analyze networks of the brain. Graph theory views the brain as a graph composed of *nodes* (regions of interest) and *edges* (functional or structural connections). Research using graph theory to better understand the organization of the adult brain shows that the brain is organized in a non-trivial manner, characterized by modularity of activity into subnetworks (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Meunier, Lambiotte, Fornito, Ersche, & Bullmore, 2009; van den Heuvel, Stam, Boersma, & Hulshoff Pol, 2008; Wang et al., 2010).

Previous work in younger populations utilizing this method has highlighted the increased specialization of these subnetworks across development. Fair and colleagues (2007) utilized graph theory to examine the development of control subnetworks in children, adolescents, and adults. Results showed concurrent functional integration (increased long-range connectivity) and segregation (decreased short-range connectivity) occurring in the brain across development and that the organization of control subnetworks differs greatly between children and adults. While it was later determined that differences in motion between younger and older participants may have contributed to the differences in organization seen between age groups (see Power, Schlaggar, & Petersen, 2015), other, more recent, research has utilized graph theory and shown similar integration and segregation, though effects are attenuated relative to the original study

(Grayson & Fair, 2017; Fair et al., 2012b; Marek et al., 2015). These recent studies have suggested that while overall network structure appears to be more similar to adults than originally thought, there is still reorganization and refinement, involving integration and segregation processes, occurring within the brain. In general, these organizational changes through segregation and integration are thought to reflect neurodevelopmental events, such as synaptogenesis, pruning of synapses, and myelination of axons, occurring simultaneously throughout early development (Stiles & Jernigan, 2010). The concurrent processes of increased functional integration and segregation are thought to contribute to increased efficiency as well as functional specialization in the brain and provide important information regarding potential mechanisms of interactive specialization.

Moving from a focus on network level to subnetwork and node level analyses

Many of these developmental studies have focused on investigating whole-brain network level properties (e.g., modularity, global efficiency, small-world properties), which consider all nodes and edges in a graph (e.g., Fair et al., 2008; Supekar et al., 2009) to understand how integration and segregation may contribute to development of behavior. Overall, studies focused at the network level suggest that, in childhood, the developing brain is organized in a similar manner as in adults and that resting state networks previously revealed in adults are identifiable in children (de Bie et al., 2012; Cao et al., 2014; Gao et al., 2009; Muetzel et al., 2016; Supekar et al., 2009).

However, graph theoretical approaches can also be used to understand more about the fine-grained properties of a focused set of densely connected brain regions (subnetwork; e.g., reward processing subnetwork). In contrast to the approaches assessing global network metrics, research can assess subnetwork and node level properties to gain

deeper insight of specific processes, such as inhibitory control or social information processing, and potential factors that may affect their development. Although studies using this approach to focus on subnetworks are limited, several have shown it to be a useful and informative method (Joseph et al., 2012, Kinnison et al., 2012; Marek et al., 2015). For example, in a group of adults, Kinnison and colleagues (2012) focused on a subset of brain regions important to emotion and motivation and found that cortical-subcortical integration of these regions differed for reward versus threat conditions. Joseph et al. (2012) used a similar approach to study how the functional brain network for face processing changed in 5- to- 12-year-old children and found that connections among regions within the face-processing network increased with age. These studies suggest that this method may prove to be useful in understanding the changing nature of subnetworks supporting specific processes in childhood.

The proposed study

The proposed study utilized a graph theoretical approach focused on a distinct set of brain regions, subnetwork level properties, and node level properties to understand the development of regions thought to contribute to episodic memory (referred to as the hippocampal memory subnetwork; Vincent et al., 2006; Witte, Kerti, Margulies, & Flöel, 2014; Zhou et al., 2008). Memory is a cornerstone ability upon which we build knowledge of the world. Previous data from our lab and others has indicated that episodic memory shows rapid improvements in early childhood (i.e., between 4-7 years of age) (Drummey & Newcombe, 2002; Riggins, 2014; Sluzenski, Newcombe, & Kovacs, 2006), suggesting that important changes may be occurring in the brain during this period of development to support memory improvements.

Integration and segregation in the memory subnetwork

Multiple lines of evidence suggest that the hippocampus is a structure that is critical for episodic memory (Davachi, Mitchell, & Wagner, 2003; Eichenbaum, 2004; Ghetti & Bunge, 2012; Scoville & Milner, 1957; Squire, 1992), a type of long-term memory for events and the details that surround them. One of these lines of evidence includes whole-brain seed-based analyses, which compare connectivity in a seed region to all other voxels in the brain, including regions within and outside the memory subnetwork. Using this method, Riggins et al. (2016) and Blankenship et al. (2017) used the hippocampus as a seed region and reported that the hippocampal memory subnetwork can be identified in children as young as 4 years of age. Furthermore, developmental differences were found between connectivity within the memory subnetwork and its association with episodic memory, such that stronger connectivity within the subnetwork was related to better memory performance in older children, whereas stronger connectivity between the hippocampus and regions outside of the defined subnetwork was related to memory performance in younger children (Riggins et al., 2016).

These intriguing findings were interpreted within the interactive specialization framework, as the authors hypothesized that the hippocampus may become functionally integrated with regions that are part of the memory subnetwork in adults and segregated from regions outside of the memory subnetwork to support improvements in memory. However, this hypothesis was not directly tested, as seed-based methods fall short when attempting to understand this functional integration and segregation because this approach does not formally assess the role of the hippocampus relative to other subnetworks in the brain. In order to fully grasp and understand changes across age in the

integration and specialization of the hippocampus within the hippocampal memory subnetwork, graph theoretical methods are necessary.

Advantages of graph theory

Graph theory allows for the characterization of the differing role of the hippocampus within the memory subnetwork relative to other subnetworks in the brain with age. This method quantitatively assesses the importance of the hippocampus within the memory subnetwork and determines whether it can be described as a "hub", a node characterized by a high number of connections. Many studies have outlined the quantitative importance of hubs within and between subnetworks (Power, Schlaggar, Lessov-Schlaggar, Petersen, 2013; Jeong et al., 2001). Most importantly, this method allows for the examination of how age impacts development of the memory subnetwork, specifically the role of the hippocampus within this subnetwork.

In addition to its usefulness in understanding the role of the hippocampus within the subnetwork, this method allows for visualization of the subnetwork and a deeper understanding of the organization underlying it, as graph theory has the added benefit of providing information regarding connections between all nodes in the subnetwork. This may also allow for the identification of regions that may serve a similarly high status as the hippocampus within the subnetwork.

Hypotheses

In sum, the proposed study aims to address the contribution of age to integration and segregation of the hippocampus within the memory subnetwork by examining age-related differences in subnetwork and node level graph theoretical metrics (within-

module degree *z*-score and participation coefficient) in a sample of 4- to- 8-year-old children. If the development of the hippocampal memory network operates through an interactive specialization framework, the hippocampus should become increasingly functionally integrated with the memory subnetwork (Hypothesis 1) and segregated from other subnetworks (Hypothesis 2) over the age range assessed. Hypothesis 1 will be tested by examining age-related differences in the within-module degree associated with the hippocampus. If this hypothesis is supported with the proposed dataset, the within-module degree will increase with age, which would indicate an increase in connections between the hippocampus and regions within its subnetwork. Hypothesis 2 will be tested by examining age-related differences in the participation coefficient. If this hypothesis is supported, the participation coefficient will decrease over the age range, indicating that the hippocampus' connections with regions outside of this subnetwork decrease as it becomes a more central hub in the memory subnetwork.

Given that interactive specialization theory suggests that brain development proceeds with integration and segregation of subnetworks, understanding this delicate balance within the hippocampal memory subnetwork is critical to understanding both the continuous evolution of this subnetwork and its impacts on memory, as disruption of this balance can lead to impairment.

Chapter 2: Methods

Participants

A total of 137 typically developing children ages 4- to 8-year-old (*M* = 6.50, *SD* = 1.48) were included in the current study. Data came from a larger longitudinal investigation examining brain and memory development in early childhood. To ensure eligibility in the study, parents completed questionnaires indicating that children were full-term, native English speakers, free of neurological conditions, and able to undergo MRI scanning. Children were recruited from the Baltimore-Washington DC metropolitan area through the Infant and Child Studies Consortium, flyers to schools, and word of mouth.

Procedure

Parents provided written consent and children over the age of 7 years provided written assent to participate in the study. Participants under the age of 7 years provided verbal assent.

MRI Data Acquisition

Children completed training in a mock scanner before MR data acquisition in order to become acclimated to the scanner environment and receive motion feedback. Additionally, head movement was minimized using padding around the head. Children were scanned in a Siemens 3.0-Tesla scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions, Erlangen, Germany) using a 32-channel coil.

Structural data were collected using a high-resolution T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence consisting of 176 contiguous sagittal slices (.9

mm isotropic; 1900 ms TR; 2.32ms TE; 900ms inversion time; 9° flip angle; pixel matrix= 256 × 256). Functional data was also collected in the same scan session. Participants completed a 7 minute and 6 second task-free scan where they passively viewed a series of evolving abstract shapes referred to as *Inscapes* (similar to a screen saver; Vanderwal et al., 2017; Vanderwal, Kelly, Eilbott, Mayes, & Castellanos, 2015) presented via E-Prime version 2.0 (Psychology Software Tools, Pittsburgh, PA). Inscapes was utilized, as it did not contain a task, but was still engaging enough to ensure participants, particularly children, did not fall asleep. Functional data for children were collected with the following scan parameters: 210 EPI volumes consisting of 36 oblique interleaved slices with a 3.0mm x 3.0mm x 3.5mm voxel size; 2000 ms TR; 24 ms TE; 3 mm slice thickness; 70 degree flip angle; 192 mm field of view, and 64 x 64 voxel matrix.

MRI Preprocessing

Task-free fMRI data was preprocessed using the Data Processing Assistant for Resting-State fMRI Advanced Edition (DPARSF-A, version 3.1) toolbox (Yan & Yu-Feng, 2010). This toolbox performs the following preprocessing steps: removal of the first 4 volumes, slice time correction, head motion correction, realignment of functional data, coregistration of T1-weighted data to the functional data, regression of nuisance variables, and spatial smoothing (Gaussian kernel FWHM = 5 mm). ICA was also used on smoothed data to remove motion components (Pruim et al., 2015). Six toolboxes, including ANTs, Brainsuite, Robex, AFNI, FSL, and SPM, were used for brain extraction (Tillman et al., 2018).

Data were normalized to MNI space using nonlinear transformation algorithm (ANTs, Avants et al., 2011). Child data was normalized to a 4.5- to 8.5-year-old symmetrical MNI child template (Fonov et al., 2011). This child template was used to minimize age-related differences in registration of images. Finally, temporal bandpass filtering was applied to normalized data in AFNI (Cox, 1996).

Given the serious effects movement can have on resting state and task-free analyses (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Power, Schlaggar, & Petersen, 2015; Satterthwaite et al., 2013; Van Dijk, Sabuncu, & Buckner, 2012), precautions were taken to mitigate effects of motion. Volumes with more than 0.3 mm of framewise movement were censored from analyses. Additionally, the immediately surrounding volumes were censored. Only children with ≥ 4 minutes of data were included in analyses. Mean framewise displacement (FD) was also calculated and used as a covariate in analyses (Power et al., 2012; Van Dijk et al., 2012). Associations between motion (i.e., mean FD) and age were assessed to ensure that motion was not driving effects, and age-related effects reflect meaningful differences changes in brain activity.

Node and Network Construction

Coordinates from previous data were used to construct the subnetworks. Separate masks were created for regions "within" the hippocampal memory subnetwork and regions "outside" of the memory subnetwork. All nodes were created using 3D spheres with a radius of 4mm.

Within-subnetwork regions were defined using coordinates from previous functional and anatomical research. Specifically, coordinates came from a meta-analysis of functional studies showing regions activated during retrieval of information in adult

participants (Spaniol et al., 2009). Given that the hippocampus is not always included in fMRI studies, and because we wanted to have precise coordinates for this region since it was used as a main node of interest in the network analysis, coordinates from a separate meta-analysis were used to define hippocampal nodes (Chen et al., 2016). It's important to note that the hippocampus is a functionally heterogeneous structure that can be divided along its longitudinal axis into an anterior and posterior section (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). In turn, both anterior and posterior hippocampus were included in the network. However, only anterior hippocampus was analyzed as this was used as the seed region in previous connectivity analyses (Blankenship et al., 2017; Riggins et al., 2016; Vincent et al., 2016). In total, 22 regions were included in the within-subnetwork mask. (Table 1).

Table 1. Within-subnetwork regions included in the graph.

	Hemisphere	Region	x	y	z
1	R	Anterior Hippocampus	24	-14	-20
2	L	Anterior Hippocampus	-24	-14	-20
3	R	Posterior Hippocampus	26	-34	-4
4	L	Posterior Hippocampus	-26	-34	-4
5	L	Superior Parietal Lobule, Precuneus, Inferior Parietal Lobule	-35	-64	48
6	L	Inferior Frontal Gyrus, Middle Frontal Gyrus, Precentral Gyrus	-39	49	-2
7	L	Middle Frontal Gyrus, Anterior Cingulate, Superior Frontal Gyrus	-6	37	33
8	L	Cingulate Gyrus	-5	-38	36
9	L	Inferior Frontal Gyrus, Insula	-33	24	-11
10	R	Inferior Parietal Sulcus	33	-70	46
11	R	Superior Parietal Lobule	47	-48	54
12	L	Caudate	-12	11	-1
13	R	Caudate	11	13	-8
14	R	Middle Frontal Gyrus	37	52	8
15	R	Inferior Frontal Gyrus	34	27	-20
16	L	Middle Temporal Gyrus	-67	-39	-10
17	L	Superior Frontal Gyrus	-24	60	10
18	L	Parahippocampal Gyrus	-13	-36	0
19	R	Angular Gyrus	46	-52	28
20	R	Superior Frontal Gyrus	45	35	28
21	L	Superior Frontal Gyrus	-12	50	-14
22	R	Insula	34	21	1

Note. R = right, L = left.

To create a mask of regions outside of the memory subnetwork, coordinates from previous research investigating functional resting state networks in adults were used (Fair et al., 2009). These regions were originally derived from a meta-analysis on control-demanding tasks and are defined as part of the fronto-parietal and cingulo-opercular attention networks. These were treated as separate subnetworks when creating graphs and calculating metrics, but as a single subnetwork (the “outside” subnetwork) when discussing results. A total of 18 regions were included in the subnetwork of regions

outside the memory subnetwork (11 regions from the fronto-parietal network and 7 regions from the cingulo-opercular network, Table 2). Both of these networks were chosen to ensure that there were a similar number of regions outside of the memory subnetwork as there were within the memory subnetwork.

Table 2. Between-subnetwork regions included in graph.

	Hemisphere	Region	x	y	z
1	L	Dorsolateral Prefrontal Cortex	-43	22	34
2	R	Dorsolateral Prefrontal Cortex	43	22	34
3	L	Frontal	-41	3	36
4	R	Frontal	41	3	36
5		Midcingulate Cortex	0	-29	30
6	L	Inferior Parietal Lobule	-51	-51	36
7	R	Inferior Parietal Lobule	51	-47	42
8	L	Intraparietal Sulcus	-31	-59	42
9	R	Intraparietal Sulcus	30	-61	39
10	L	Precuneus	-9	-72	37
11	R	Precuneus	10	-69	39
12	L	Anterior Prefrontal Cortex	-28	51	15
13	R	Anterior Prefrontal Cortex	27	50	23
14	L	Anterior Insula, Frontal Operculum	-35	14	5
15	R	Anterior Insula, Frontal Operculum	36	16	4
16	L	Dorsal Anterior Cingulate, Medial Superior Frontal Cortex	-1	10	46
17	L	Thalamus	-12	-15	7
18	R	Thalamus	10	-15	8

Note. Regions 1-11 are part of the fronto-parietal network and 12-18 are part of the cingulo-opercular network. R = right, L = left.

Once each network mask was created, it was resampled to functional space and time courses from each ROI were extracted using the 3dROIstats command in AFNI.

Network Analysis

A correlation matrix using Pearson's correlation, a commonly used metric in network analysis, was constructed to model the pairwise comparisons between the time series of each node. Because no a priori hypotheses were made regarding the direction of information, graphs were defined as undirected. Edges were weighted, as opposed to unweighted (i.e., consisting of binary weights of 0 and 1) so as to retain continuous connectivity information. It is important to note that the metrics included in the present study do not take into account this continuous information, but rather only take into account whether there was a connection or not. However, future analyses will be conducted with this data to assess strength of associations in addition to number of associations.

Next, an adjacency matrix was created and data were thresholded to set negative correlations to zero (Rubinov & Sporns, 2010). While negative correlations were removed, weak correlations were retained. Although some research suggests that weak correlations may be indicative of noise, in this young sample, the correlations were on average very weak ($\sim r < .3$) so it was not practical to remove these correlations. Furthermore, weak correlations in this sample may be interesting as they may also be indicative of distributed weak connections that become more focal in nature later in development. In the adjacency matrix, a value greater than zero indicated a connection between nodes, while zero indicated the absence of a connection. Regions were then given a community assignment of inside (1) or outside (fronto-parietal: 2; cingulo-opercular: 3) the memory subnetwork.

Data analyses were carried out in R using the program igraph (Csardi & Nepusz, 2006), which requires the input of the adjacency matrix and community assignments. The importance of the hippocampal nodes were characterized using a method proposed by Guimerà and Amaral (2005) that takes into account both a node's connection within the subnetwork as well as to other subnetworks. This method uses the within-module degree *z*-score and the participation coefficient metrics. The within-module degree is a within module version of degree centrality, where a node with many connections to other nodes within its subnetwork receives a high degree. The within-module degree *z* score of node *i* is

$$z_i = \frac{K_i - \overline{K}_{Si}}{\sigma_{K_{Si}}}$$

where K_i is the number of links of node *i* to other nodes in its subnetwork S_i, $\overline{K}_{Si}$ is the average of *K* over all the nodes in S_i, and σ_{KSi} is the standard deviation of *K* in S_i. This metric allows for quantifying the importance of a particular node and its integration within a subnetwork. A degree of 2.5 or greater denotes a node as a hub (Jin, Jeong, Seol, Kwon, & Chung, 2013; Power et al., 2013). In this case, it was used to quantify the importance of the left and right hippocampus within the memory subnetwork.

The participation coefficient is used to assess the distribution of a node's connections between subnetworks and can be thought of as a measure of segregation. The participation coefficient of node *i* is

$$P_i = 1 - \sum_{S=1}^{N_M} \left(\frac{K_{is}}{K_i}\right)^2$$

where K_{is} is the number of links of node *i* to nodes in subnetwork *S* and K_i is the total number of links of node *i*. If a node is denoted as a hub, this metric can further identify

the node as a provincial or connector hub based on its connection with other networks in the brain. A high participation coefficient close to one would indicate that the hippocampus is a connector hub, meaning it is well connected with other networks. A low participation coefficient close to zero would indicate that the hippocampus is linked exclusively to nodes within its subnetwork and labels a hub as a provincial hub (Guimerà & Amaral, 2005). It is important to point out that these metrics assess the number of connections rather than the strength of connections.

If a node is not considered a hub, it can still be classified based on its participation coefficient or *P*. Specifically, *P* close to zero indicates that all connections of a node are within its own subnetwork. $P < 0.625$ indicates that at least 60% of a node's connections are within its subnetwork. *P* between 0.62 and 0.8 denotes a node as a non-hub connector, which means that the node has at least half of its connections within the subnetwork. Finally, a node with $P > 0.8$ indicates that a node is not clearly part of any subnetwork (Guimerà and Amaral, 2005).

Statistical Analysis

Right and left hippocampus were included as the nodes of interest in the following analyses. The within-module degree and participation coefficient were computed for the right and left hippocampus. To assess associations with age, bivariate correlations between each metric for the hippocampal nodes and age were computed to examine how associations differed throughout early childhood. Significant correlations were followed up with linear regressions to determine if associations remained after taking into account effects due to motion. Specifically, the within-module degree or participation coefficient was entered as the dependent variable, age was entered as the

independent variable, and mean FD was entered as a covariate to ensure that results were not simply due to differences in motion.

Finally, the within-module degree and participation coefficient were assessed relative to one another. Specifically, the average within-module degree was assessed to determine whether the hippocampus could be considered a hub (i.e., a node of degree 2.5 or higher). Next, if this criterion was met, the participation coefficient was used to determine what type of hub the hippocampus is (i.e., provincial hub or connector hub). If this criterion was not met, the participation coefficient was used to determine what type of non-hub node it was.

Chapter 3: Results

Descriptive statistics for graph theoretical metrics are presented in Table 3. Mean FD was also assessed and was at a level consistent with current publication in the literature ($M = 0.19$, $SD = 0.08$). Bivariate correlations between graph theoretical metrics, age, and mean FD are presented in Table 4.

Table 3. Descriptive statistics for graph theoretical metrics.

	Within-module degree (*z*-score)		Participation coefficient (*P*)	
Node	Mean	SD	Mean	SD
Right hippocampus	0.08	.95	0.55	.06
Left hippocampus	0.22	.85	0.54	.08

Table 4. Bivariate correlations between age, mean FD, and graph theoretical metrics.

	1	2	3	4	5	6
1. Age	0					
2. Mean FD	-.04	0				
Within-module degree						
3. R Hippocampus	.23**	.004	0			
4. L Hippocampus	.12	-.01	.11	0		
Participation coefficient						
5. R Hippocampus	.16	.25**	.07	.11	0	
6. L Hippocampus	.18*	.13	-.02	.29**	.62**	0

Note. *$p < .05$, **$p < .01$. R = Right, L = Left.

There was a significant bivariate correlation between the within-module degree associated with the right hippocampus and age (r = 0.23, p = .008) (Figure 1). Results of a linear regression indicated that associations with age (b = 0.15, SE = 0.05, p = .008) held after controlling for the effects of mean FD (b = 0.15, SE = 0.97, p = .876). Although there were associations with age, the within-module degree did not reach the threshold of 2.5 so the right hippocampus cannot be considered a hub. No significant relations between age and the within-module degree associated with the left hippocampus were observed (p > .05).

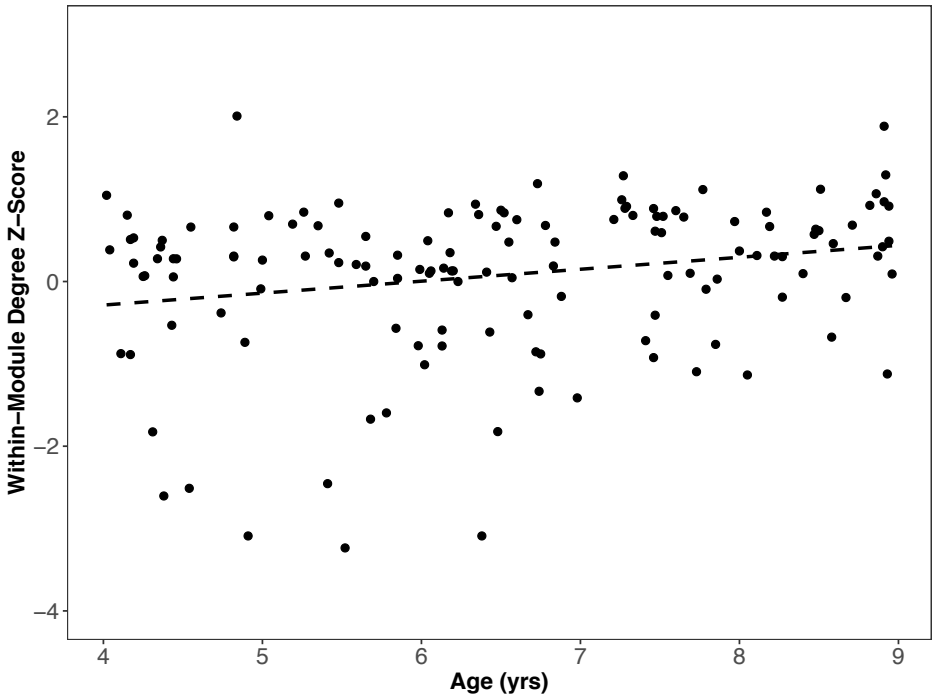

Figure 1. Association between age and the within-module degree z-score associated with the right hippocampus.

There was a significant bivariate correlation between the participation coefficient associated with the left hippocampus and age (r = 0.18, p = .038) (Figure 2). Results of a

linear regression indicated that associations with age (b = 0.009, SE = 0.004, p = 0.031) held after controlling for the effects of mean FD (b = 0.13, SE = 0.08, p = 0.103). No significant relations between age and the participation coefficient associated with the right hippocampus were observed (p > .05).

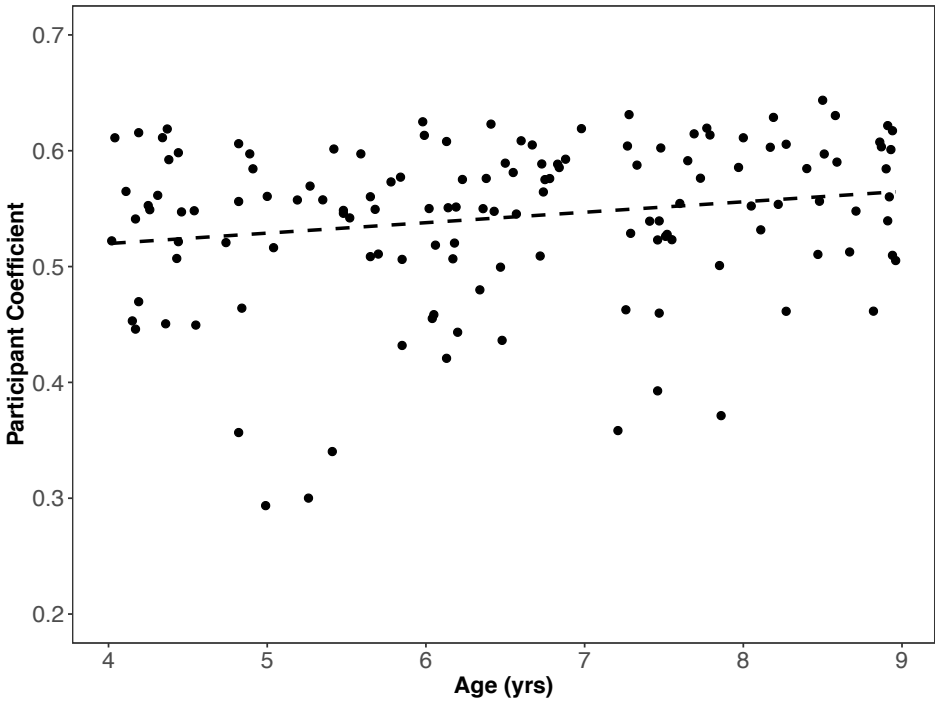

Figure 2. Association between age and the participation coefficient associated with the left hippocampus.

Post-hoc assessments of network structure suggested that modularity, a measure of the degree to which nodes in a graph organize into subnetworks, was low (M = - 0.01, SD = 0.07).

Chapter 4: Discussion

In this study, the role of the hippocampus within the memory network was assessed during early childhood when large gains in memory are typically observed. Results indicate a positive association between both the within-module degree and the participation coefficient associated with the hippocampus across the age range assessed, and these effects were not due to differences in motion between younger and older children.

Within-subnetwork connections

The within-module degree associated with the right hippocampus was positively associated with age, which suggests that connections between this hemisphere of the hippocampus and all regions within the memory subnetwork increase in number between 4 and 8 years of age. These results support the hypothesis that the hippocampus becomes increasingly connected with regions within its subnetwork in early childhood, and suggests an increased integration of the hippocampus within the memory subnetwork. Increased integration of the hippocampus in consistent with an interactive specialization view of brain development underlying the behavioral development of memory. Specifically, this region is likely becoming increasingly specialized for memory processing as changes occur in its connections to regions in its subnetwork.

Between-subnetwork connections

The participation coefficient associated with the left hippocampus also showed a positive association with age. These results do not support the proposed hypothesis that connections between the hippocampus and regions outside the memory subnetwork

would decrease with age as the hippocampus becomes increasingly segregated from regions outside its subnetwork. Instead, they suggest that, in addition to an increase in connections within the hippocampal memory subnetwork, there is also an increase in between-subnetwork connections of the left hippocampus to regions outside the memory subnetwork, specifically those included in the fronto-parietal and cingulo-opercular subnetworks.

One possible explanation for the increase in between-subnetwork connections is that the hippocampus is increasing its connections to regions that are important for attention, as memory and attention are intricately related processes. Indeed, in addition to its importance for attention, development of prefrontal regions is important to the development of episodic memory (Ghetti & Bunge, 2012; Ofen et al., 2007). Although contributions of prefrontal regions tends be greater in older children and adolescents, research shows that in young children, developmental changes are occurring in prefrontal regions (Brown & Jernigan, 2012; Sowell et al., 2004), which may impact their functional and structural connectivity with the hippocampus and influence development of memory processes. In turn, it is possible that the hippocampus is increasing its connections, specifically to regions within the fronto-parietal subnetwork, as these regions become increasingly important for memory.

Assessing within- and between-subnetwork connections

Results assessing the status of the left and right hippocampal nodes indicate that neither region had a within-module degree of 2.5 or higher over the age range assessed so these regions cannot be considered a hub. However, in the right hippocampus, the within-module degree is trending towards this threshold so it may reach the status of a hub in

older children when memory is more fully developed. Although these nodes cannot be considered a hub, they can be classified based on their participation coefficient. When data were examined as a group, the mean participation coefficient for the right and left hippocampus was 0.55 and 0.54, respectively. This suggests that the hippocampus is a peripheral node and that the majority of its connections are within the memory subnetwork even in young children.

Mechanisms supporting increasing connections

Although they cannot be assessed directly, the likely mechanisms underlying both increasing within- and between-subnetwork functional connections are synaptogenesis, neurogenesis, and increases in dendritic complexity (synaptic elaboration). Each of these neurodevelopmental processes promotes synapse formation and occurs in parallel to the process of pruning, which removes synapses that are not used or not needed. This process of pruning would likely support a decrease in hippocampal functional connections; however, given the young age of the participants in the study, it is possible that higher levels of processes promoting synapse formation are occurring relative to processes removing synapses. These structural changes in the brain are known to be highly important to changes in function and the organization of the brain (Stiles & Jernigan, 2010; Tau & Peterson, 2010).

With these neurodevelopmental processes in mind, along with the fact that the hippocampus is a highly connected structure and is important for an array of processes (e.g., working memory, decision making, empathy), it is possible that there is a general increase in connections between the hippocampus and regions distributed throughout the brain in this age range through the aforementioned processes. In support of this notion, an

exploratory examination of the group adjacency matrix (not reported in results) suggested that many of the hippocampus' connections were low-level correlations ($r < 0.2$) so it may be diffusely connected to many regions in the brain. These connections may be pruned later on in childhood, as they are not needed. To rule out this hypothesis in future research, it may be beneficial to threshold correlations by removing weak correlations from the networks. In addition, it would be beneficial to assess both the strength of connections and number of connections within the same study.

Limitations and Future Research

These results provide important information to our understanding of connectivity of the hippocampal memory subnetwork in young children. However, there were several limitations associated with the present study. As with any project utilizing network analysis, multiple decisions needed to be made throughout the course of the study, which could have impacted the results. Many of these decisions were related to establishing the network and include, but are not limited to, selecting nodes, defining nodes, and establishing the size and number of nodes. Although the majority of these decisions were made based on prior research; unfortunately, there are few standards in the field to provide guidance in making these decisions. Network analysis methods have been used extensively in other disciplines; however, they have only recently been used in cognitive neuroscience so it is reasonable there are not standards. Thus, research should work towards establishing standards, as network analysis is a powerful tool that is useful to providing a deeper understanding of the organization of the brain.

In the present study, nodes were given an a priori community assignment based on theory and prior research in adults. An alternative way to define the community

assignment of a network is to use a data driven approach and allow the toolbox (i.e., igraph) to perform a community detection procedure. Given the decision to use an a priori community assignment, we were not concerned with maximizing modularity (a measure of network structure), as is the case when utilizing community detection. However, upon performing post-hoc assessments of modularity, it became apparent that modularity was low, which suggests limited network structure. Moving forward, this limited network structure may be a cause for concern. Future research would benefit from utilizing functionally defined brain regions distributed throughout the whole brain and allowing the toolbox to perform community detection on the data. An alternative possibility would be to utilize a tool, such as NeuroSynth (Yarkoni, Podrack, Nichols, Essen, & Wagner, 2012), which can utilize meta-analyses to generate a mask of specific functionally activated regions in the brain. This may be a more precise way to ensure that important regions for memory and attention are not missed and would likely result in more robust network structure.

Given that the data were cross-sectional in nature, we can only hypothesize that change is occurring and can only discuss differences in network structure. Future research will utilize longitudinal data to investigate changes in these metrics rather than age-related differences across different participants. This will allow for a better understanding of the developmental trajectory of the hippocampus. Although vast developments in memory are occurring in early childhood, brain development extends well into adolescence, as does memory, so changes are likely still occurring in the memory network throughout adolescence. Therefore, assessing these metrics in older

children and adolescents and adults will also provide a more thorough understanding of the development of the hippocampal memory subnetwork in childhood.

Finally, the purpose of the present study was to lay the groundwork for understanding functional connections between the hippocampus and both regions within and outside of its subnetwork. However, what is of utmost importance is whether these differences in functional connections translate to differences in memory ability. Therefore, a next step will be to investigate the relation between these metrics and behavioral differences in episodic memory.

Conclusions

Overall, the present study highlights an increase in connections between the hippocampus and both regions within its memory subnetwork and regions distributed across other subnetworks in the brain. These changes in the number of hippocampal connections likely contribute to improvements in memory abilities or the emergence of new memory abilities. These findings add important information to the dearth of research on brain regions and networks supporting memory during early childhood, a period characterized by rapid development. They also lay the groundwork for addition analyses investigating the network structure of the memory network in early childhood.

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