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# White matter structural connectivity and episodic memory in early childhood

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ABSTRACT

Episodic memory undergoes dramatic improvement in early childhood; the reason for this is poorly understood. In adults, episodic memory relies on a distributed neural network. Key brain regions that supporting these processes include the hippocampus, portions of the parietal cortex, and portions of prefrontal cortex, each of which shows different developmental profiles. Here we asked whether developmental differences in the axonal pathways connecting these regions may account for the robust gains in episodic memory in young children. Using diffusion weighted imaging, we examined whether white matter connectivity between brain regions implicated in episodic memory differed with age, and were associated with memory performance differences in 4- and 6-year-old children. Results revealed that white matter connecting the hippocampus to the inferior parietal lobule significantly predicted children's performance on episodic memory tasks. In contrast, variation in the white matter connecting the hippocampus to the medial prefrontal cortex did not relate to memory performance. These findings suggest that structural connectivity between the hippocampus and lateral parietal regions is relevant to the development of episodic memory.

## 1. Introduction

Remembering a past event and the specific spatiotemporal context in which the event occurred is a hallmark of episodic memory. Early childhood marks an important developmental period for episodic memory, as substantial growth in this ability is observed. Many studies have shown robust age differences between 4- and 6-year-old children, with 4-year-olds performing worse than 6-year-olds on tasks that require relational memory, i.e., memory linking multiple items (Drummey and Newcombe, 2002; Lloyd et al., 2009; Newcombe et al., 2014; Ngo et al., 2017; Sluzenski et al., 2006), or memory for contextual details (Bauer et al., 2012; Riggins, 2014; Riggins et al., 2015; Riggins and Rollins, 2015). The enhancement in episodic memory during childhood is thought to rely, at least in part, on complex and dynamic developmental changes in the brain, in an interplay with social and other cognitive factors (Riggins, 2012). Understanding the neural bases of episodic memory development requires investigation of the relation among key regions of episodic memory, including the hippocampus, the parietal cortex, and the prefrontal cortex. The goal of our study was to better understand this interaction by examining the structural connectivity among these brain areas via white matter pathways.

In the last two decades, there have been substantial efforts in characterizing the developmental profiles of white matter pathways in the brain. Convergent findings from cross-sectional (e.g., Bonekamp et al., 2007; Lebel et al., 2008; Loenneker et al., 2011; Moon et al., 2011; Qiu et al., 2010; Rollins et al., 2010; Sadeghi et al., 2014) and longitudinal studies (e.g., Krogsrud et al., 2016; Lebel and Beaulieu, 2011; Simmonds et al., 2014) show a protracted timeline of white matter development from early childhood until adulthood, with differential maturational rate across white matter tracts (reviewed in Lebel et al., 2017). It is believed that the information transmission properties of any given white matter tract can be predicted by the function of the gray matter regions that it connects (Maunsell and van Essen, 1983; Passingham et al., 2002). Thus, it is likely that specific white matter pathways connecting brain regions implicated in episodic memory should play a role in age-related improvements in memory performance in children. The focus of this paper is to examine such relations.

An essential role of the hippocampus is to construct relational memories by binding together multiple elements of an event to form a cohesive episode (Backus et al., 2016; Cohen and Eichenbaum, 1993; Horner and Doeller, 2017). Developmental changes in hippocampal structure and function relate to improvement in episodic memory in

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school-aged children (e.g., DeMaster et al., 2013; DeMaster and Ghetti, 2013; Ofen et al., 2007; reviewed in Ghetti and Bunge, 2012). Gray matter volume of the hippocampal head predicts children's ability to recall contexts in which events occur, but this relation only exists in 6-year-olds, not in 4-year-old children (Riggins et al., 2015). A recent study using resting state functional connectivity in 4- and 6-year-olds showed that the hippocampal-cortical network supporting episodic memory varies with age, such that with age, the hippocampus becomes more functionally integrated with cortical regions associated with the adult-like memory network (Riggins et al., 2016). Thus, age-related differences in the hippocampus and its functional connectivity with cortical regions contribute to the rapid memory improvements exhibited in young children. However, the role of structural connectivity has not been investigated.

### 1.1. Memory-related cortical regions

The inferior parietal lobe (IPL) has been strongly linked to episodic memory in adults, yet its precise role remains controversial. A large number of fMRI studies have reported activations in the IPL during episodic memory retrieval. For instance, it is more active during retrieval of studied, versus unstudied items, and during source, as compared to item memory judgments (reviewed in Cabeza et al., 2008). Despite the consistency of neuroimaging findings, evidence from patients with lesions to the IPL suggests that its role in episodic memory is quite nuanced. Patients with bilateral IPL lesions are not amnesic; rather, they exhibit normal performance on many episodic memory tasks (Berryhill et al., 2009; Haramati et al., 2008; Simons et al., 2010). However, these same patients show diminished detail, and vividness of recollection when recalling autobiographical memories based on a cue (Berryhill et al., 2007). They also consistently show decreases in subjective aspects of recollection (Drowos et al., 2010; Hower et al., 2014; Simons et al., 2010). Most recently, it was reported that unilateral IPL lesions can cause deficits in cued recall (Ben-Zvi et al., 2015).

The medial prefrontal cortex (mPFC) is also believed to play an important role in episodic memory. In rodents, an axonal pathway connecting the mPFC to the hippocampus is critical for several forms of memory including the classic Morris water maze (Goto and Grace, 2008; Wang and Cai, 2008). This evidence has led to the proposal that the mPFC takes inputs from the hippocampus about the past and combines this with information about the current context to predict adaptive responses (reviewed in Euston et al., 2012). Less is known about the functional significance of hippocampal-mPFC structural connectivity in humans, although it is known that such connectivity exists. Theories about the frontal lobe in episodic memory have focused on its role in retrieval strategy and control. For instance, functional connectivity between the hippocampus and PFC has been related to mnemonic control in adults (Benoit and Anderson, 2012). It has been proposed that age-related improvements in episodic memory depend on the development of strategic processes mediated by portions of the prefrontal cortex (DeMaster and Ghetti, 2013; Shing et al., 2008). However, little is known about whether structural connectivity between the hippocampus and mPFC relates to the improvements of episodic memory in early childhood.

Taken together, the interactions between the hippocampus and the IPL, as well as between the hippocampus and the mPFC, are likely to play a key role in the development of episodic memory in young children. To better understand the interplay among these regions, it is important to examine the underlying structural connectivity among these regions, given that developmental changes in white matter connectivity are crucial aspects of cognitive development (reviewed in Ghetti and Bunge, 2012). To our knowledge, no study has linked age-related changes in white matter connectivity and memory performance during early childhood, an imperative developmental period for episodic memory development.

### 1.2. Current study

The goal of the current study was to examine the relation between white matter connectivity of the hippocampus and specific cortical regions hypothesized to be related to episodic memory enhancement during early childhood. Specifically, we focused on the children ages four and six, which marks a critical transition from fragile to robust episodic memory (Lloyd et al., 2009; Riggins, 2014; Sluzenski et al., 2006). The currently study had two aims: (1) to test age-related differences in the macrostructure and microstructure of white matter connectivity among brain regions implicated in episodic memory in four- and six-year-olds; and (2) to relate variations in hippocampal-cortical white matter connectivity to episodic memory performance.

We administered the Children's Memory Scale (CMS; Cohen, 1997), as well as an Episodic Memory task developed to test young children (Riggins et al., 2015; Riggins and Rollins, 2015). The CMS is a standardized and well-known measure of episodic memory (e.g., Willford et al., 2004; Jack et al., 2009), which provides a "gross" measure of episodic memory. The Episodic memory task is a lab-based task designed to specifically probe context details surrounding an event, tapping memory for what happened and where it happened. We collected diffusion-weighted imaging data in the same group of children and employed probabilistic tractography to examine macro- and microstructural properties of white matter connecting key brain regions shown to support episodic memory. These regions included the hippocampus, the inferior parietal lobule, and the medial prefrontal cortex. In addition, we delineated a control tract (hippocampus – primary visual cortex), which should not be associated with memory functions.

Furthermore, we conducted an exploratory analysis to examine whether memory performance related to two major limbic pathways: the fornix and the uncinate fasciculus, both of which have been implicated in memory functions (fornix: reviewed in Douet and Chang, 2014; uncinate fasciculus: reviewed in Olson et al., 2015). The fornix is the largest efferent pathway from the hippocampus and projects from the posterior hippocampus to the septal area, mammillary bodies, and portions of the hypothalamus, and has long been linked to episodic memory (e.g., Metzler-Baddeley et al., 2011; Mielke et al., 2012; Oishi et al., 2011; Sexton et al., 2010; Tsivilis et al., 2008; Zhuang et al., 2013, reviewed in Douet and Chang, 2014). The uncinate fasciculus connects the anterior temporal lobe, as well as perirhinal and entrorhinal cortex and possibly portions of the anterior hippocampus to lateral and orbitofrontal prefrontal cortex. It has also been linked to memory functions in older children (ages 7–11: Wendelken et al., 2015) and adults (Alm et al., 2016; reviewed in Von Der Heide et al., 2013 and Olson et al., 2015). Given these findings, we tested whether variations in the macrostructure or microstructure of the fornix and uncinate relates to episodic memory performance using probabilistic tractography.

To preview, we found that, although no age differences emerged across the white matter connectivity measures, the microstructure of the white matter connecting the hippocampus to the inferior parietal lobule predicted children's episodic memory performance. All other tracts examined did not relate to memory performance.

## 2. Methods

### 2.1. Participants

The sample in this report included 29 4-year-old (19 females; $M_{month}$ = 53.14 ± 3.73; range = 48.00–59.00) and 23 6-year-old children (14 females; $M_{month}$ = 77.35 ± 3.19; range = 73.00–83.00). Of these, DTI data from 5 children were excluded due to incomplete scans ($n$ = 4) and excessive head motion ($n$ = 1). The final sample included 47 (24 4-year-old and 23 6-year-old children). The racial break down was as follow: 53.84% Caucasian, 9.62% African American, 3.85% Native American or Native Alaskan, and 32.69% undisclosed/unreported or wished to not disclose. The majority of the children's