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Hippocampal functional connectivity and episodic memory in early childhood☆

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ABSTRACT

Episodic memory relies on a distributed network of brain regions, with the hippocampus playing a critical and irreplaceable role. Few studies have examined how changes in this network contribute to episodic memory development early in life. The present addressed this gap by examining relations between hippocampal functional connectivity and episodic memory in 4- and 6-year-old children ($n = 40$). Results revealed similar hippocampal functional connectivity between age groups, which included lateral temporal regions, precuneus, and multiple parietal and prefrontal regions, and functional specialization along the longitudinal axis. Despite these similarities, developmental differences were also observed. Specifically, 3 (of 4) regions *within* the hippocampal memory network were positively associated with episodic memory in 6-year-old children, but negatively associated with episodic memory in 4-year-old children. In contrast, all 3 regions *outside* the hippocampal memory network were negatively associated with episodic memory in older children, but positively associated with episodic memory in younger children. These interactions are interpreted within an interactive specialization framework and suggest the hippocampus becomes functionally integrated with cortical regions that are part of the hippocampal memory network in adults *and* functionally segregated from regions unrelated to memory in adults, both of which are associated with age-related improvements in episodic memory ability.

1. Introduction

The hippocampus is critical for episodic memory in adults (e.g., Aggleton and Brown, 2006; Cabeza and Nyberg, 2000; Davachi et al., 2003; Eichenbaum et al., 2007; Ranganath et al., 2004; Scoville and Milner, 1957; Yonelinas et al., 2005; see Spaniol et al., 2009 for review). Developmental changes in hippocampal structure and function have been shown to be related to improvement in episodic memory in school-aged children and adolescents (e.g., DeMaster et al., 2014; DeMaster and Ghetti, 2012; Ghetti et al., 2010; Ofen et al., 2007; Østby et al., 2012; see Ghetti and Bunge, 2012 for review). Overall, these studies suggest positive correlations exist between hippocampal volume and delayed recall and that changes in hippocampal function (as measured by task-based fMRI) contribute to age-related improvements in episodic memory. However, relatively little is known about how the hippocampus is related to memory development earlier in life. This gap is particularly unfortunate since behavioral studies have consistently identified early childhood (4–6 years) as a time of rapid improvement in episodic memory (e.g.,. Bauer et al., 2012; Drummey and Newcombe, 2002; Sluzenski et al., 2006; Riggins, 2014). Theoretical arguments have been made proposing how developmental changes in the hippocampus may be related to the development of episodic memory ability during early childhood (e.g., Jabès and Nelson, 2015; Lavenex and Lavenex, 2013; Riggins, 2012; Serres, 2001), however, this association has not been empirically examined in human children. This gap is likely due to the multiple challenges associated with acquiring functional neuroimaging measures in young children. To overcome these challenges and address this gap in the literature, the present research examined relations between resting-state functional connectivity and behavioral measures of

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episodic memory ability assessed outside the scanner in 4- and 6-year-old children.

1.1. Episodic memory development during early childhood

Behavioral studies examining development of episodic memory in children collectively suggest that early childhood is an important time of change. Specifically, several studies suggest that the ability to recall contextual details associated with events shows striking improvement between 4 and 6 years of age (e.g., Bauer et al., 2012; Drummey and Newcombe, 2002; Sluzenski et al., 2006, for review see Riggins, 2012). For instance, a recent longitudinal study examined rates of change in 4- to 10-year-old children's ability to recall both individual items (i.e., novel facts, such as bananas grow in bunches called hands) and contextual details associated with these items (i.e., from whom the fact was learned, a puppet or experimenter) across a 1-week delay (Riggins, 2014). Results revealed that whereas memory for items increased linearly between 4 and 10 years of age, memory for contextual details associated with these items showed accelerated change between 5 and 7 years of age.

Such empirical findings from controlled laboratory-based studies fit well with reports of children's ability to recall events from their own lives (i.e., autobiographical memories). For example, another longitudinal investigation examined 4- to 13-year-old children's ability to recall their earliest memories across a 2-year period (Peterson et al., 2011). Results indicated minimal consistency in the memories reported in 4- to 6-year-old children (either in the specific events recalled or the details of these events), but that consistency increased dramatically after this period. Based on these findings, the authors argued memories in early childhood are particularly fragile and especially prone to forgetting (see Bauer, 2015 for similar argument). However, the role of the hippocampus and associated networks in these changes remain relatively unstudied.

1.2. Hippocampal development during early childhood

Based on the known importance of the hippocampus for episodic memory in adults, it has been proposed that changes in hippocampal function during early childhood are related to observed improvements in episodic memory (Jabès and Nelson, 2015; Lavenex and Lavenex, 2013; Riggins, 2012; Serres, 2001). Neuroanatomical data from non-human primates suggest that developmental changes in synaptic connectivity within the hippocampus continue throughout early childhood (i.e., until 5–7 years of age, Jabès et al., 2010; Lavenex and Lavenex, 2013; Serres, 2001). Because circuitry in the dentate gyrus is critical for adult-like memory formation, its protracted developmental profile suggests that adult-like memory formation in humans may not be expected until the end of early childhood (Serres, 2001). Protracted development of the hippocampus may account for behavioral memory phenomena such as poor recall of contextual details in younger compared to older children and infantile or childhood amnesia (i.e., adults' inability to recall autobiographical memories from very early in life).

To date, only one previous study has examined relations between hippocampal structure and episodic memory in early childhood (Riggins et al., 2015). In this study, associations between episodic memory and volume of subregions (head, body, tail) of the hippocampus were examined in 4- and 6-year-old children. Results revealed significant positive relations between episodic memory and volume of anterior regions of the hippocampus in both the left and right hemispheres for 6- but not 4-year-old children. These results suggested not only that relations between the hippocampus and episodic memory show significant developmental differences during early childhood, but they may be specific to certain subregions. These findings are consistent with results from fMRI studies in school-aged children (i.e., 8 years of age and older) that also suggest that changes in anterior hippocampal regions may be particularly relevant for episodic memory development (Ghetti et al., 2010; Maril et al., 2010; Paz-Alonso et al., 2008). However, relations between hippocampal *function* and memory behavior in early childhood (i.e., 3–6 years) were not addressed. Acquiring data addressing hippocampal function in children this young is challenging as typical task-based methods require children to remain motionless in the scanner while performing challenging memory tasks and likely accounts for why this question has not been explored previously.

1.3. Hippocampal functional connectivity at rest

One method that can be utilized to overcome the challenge of acquiring functional neuroimaging data from young children is task-free or resting-state functional connectivity MRI (rs-fcMRI). Previous research in adults has demonstrated that correlated patterns of intrinsic, spontaneous, low-frequency oscillations in brain activity can be detected in the absence of a specific task (Biswal et al., 1995; Fox and Raichle, 2007). These patterns, referred to as resting-state networks, are organized in functionally-relevant ways, as regions of these networks are typically co-activated during tasks designed to elicit distinct cognitive, social, or perceptual processes (Smith et al., 2009). The ability to identify brain networks independent of a task offers a significant advantage in the study of brain organization in development, particularly in young children, because the cognitive burden of performing a task while remaining motionless is eliminated (Casey et al., 2005; Uddin et al., 2010, for empirical examples see Emerson and Cantlon, 2012; Fareri et al., 2015; Gabard-Durnam et al., 2014). Moreover, use of rs-fcMRI has some particular advantages over traditional task-based approaches in that it (1) shifts focus to development of the entire network supporting memory and (2) results are independent of task-specific cognitive demands.

In adults, rs-fcMRI maps have been shown to reveal the full distribution of memory-related regions, as they coincide with regions showing activation across a variety of task-based memory studies (Vincent et al., 2006). Specifically, rs-fcMRI maps show robust correlations between BOLD signal in the hippocampus and several parietal regions (including precuneus, posterior cingulate, retrosplenial cortex, and bilateral inferior parietal lobule) as well as medial prefrontal regions. These regions are also often identified as the Default Mode Network (DMN), a network of regions that is preferentially active when individuals are not focused on tasks that demand external attention (e.g., when individuals are remembering past events, envisioning future events, or considering the perspectives of others, Buckner et al., 2008; Raichle et al., 2001). In addition, this network has been shown to be spatially distinct from other networks identified by different seed regions, such as the motion-sensitive MT complex (Vincent et al., 2006). Finally, specialization has also been shown along the longitudinal axis of the hippocampus, as functional connectivity maps differ between anterior and posterior hippocampal seed regions (Kahn et al., 2008; Poppenk and Moscovitch, 2011). Together, these studies report greater connectivity between the anterior hippocampus and lateral temporal regions (including the temporal poles), and greater connectivity between the posterior hippocampus and multiple regions including, frontal, parietal, posterior cingulate, and retrosplenial cortices. In addition, these rs-fcMRI studies suggest greater involvement of *posterior* regions of the hippocampus in episodic memory in adults, given its connectivity with multiple cortical areas known for their role in memory (e.g., frontal and parietal cortices).

Inter-subject variability in hippocampal network connectivity in adults has been shown to be related to variability in performance on episodic memory tasks. Specifically, connectivity between