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# Network Specialization During Adolescence: Hippocampal Effective Connectivity in Boys and Girls

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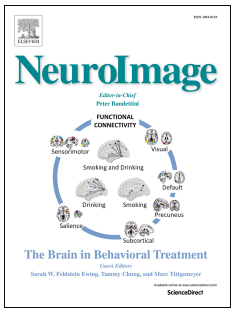


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# Network specialization during adolescence: Hippocampal effective connectivity in boys and girls

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**Abstract**

Adolescence is a complex period of concurrent mental and physical development that facilitates adult functioning at multiple levels. Despite the growing number of neuroimaging studies of cognitive development in adolescence focusing on regional activation patterns, there remains a paucity of information about the functional interactions across these participating regions that are critical for cognitive functioning, including memory. The current study used structural equation modeling (SEM) to determine how interactions among brain regions critical for memory change over the course of adolescence. We obtained functional MRI in 77 individuals aged 8 to 16 years old, divided into younger (ages 8-10) and older (ages > 11) cohorts, using an incidental encoding memory task to activate hippocampus formation and associated brain networks, as well as behavioral data on memory function. SEM was performed on the imaging data for four groups (younger girls, younger boys, older girls, and older boys) that were subsequently compared using a stacked model approach. Significant differences were seen between the models for these groups. Younger boys had a predominantly posterior distribution of connections originating in primary visual regions and terminating on multi-modal processing regions. In older boys, there was a relatively greater anterior connection distribution, with increased effective connectivity within association and multi-modal processing regions. Connection patterns in younger girls were similar to those of older boys, with a generally anterior-posterior distributed network among sensory, multi-modal, and limbic regions. In contrast, connections in older girls were widely distributed but relatively weaker. Memory performance increased with age, without a significant difference between the sexes. These findings suggest a progressive reorganization among brain regions, with a commensurate increase in efficiency of cognitive functioning, from younger to older individuals in both girls and boys, providing insight into the age- and gender-specific processes at play during this critical transition period.

Keywords: Adolescent development, structural equation modeling, brain networks, gender, functional magnetic resonance imaging

## 1. Introduction

One of the most significant chapters in human development is the transition from childhood to adolescence (Blakemore et al., 2010; Paus et al., 2008). During this period, individuals show significant maturation of cognitive abilities, including processing speed, working memory, abstract reasoning, and response inhibition (Bunge and Wright, 2007; Luna et al., 2004), affording the ability to better attend to relevant information. Only recently have the neurophysiological mechanisms underlying these distinct behavioral changes begun to be uncovered. Human functional neuroimaging has provided a new avenue of study via the visualization and measurement of brain structure and function over the course of adolescent development (Blakemore, 2012; Casey et al., 2005).

The complexity of this transformative stage contains many avenues for disruption, and it is little wonder, therefore, that this period brings with it a surge of psychiatric illnesses, in particular disorders of mood (Paus et al., 2008). The groundwork for this process is actually laid perinatally, as a surge of gonadal hormones drives the initial organization of neural networks; a second surge of these hormones at puberty then serves to fully develop and activate these previously-constructed networks (Schulz et al., 2009). This time frame is therefore a critical window for the study of brain network reorganization.

Rapid adoption of neuroimaging techniques has generated a large and continually growing number of studies seeking to understand the changes occurring in the brain during adolescence (Bennett and Rypma, 2013; Ernst et al., 2015; Mills and Tamnes, 2014), and yet relatively few have focused on how brain regions work *in concert*, influencing one another, to perform these elaborate functions. This knowledge gap may be due to the enormous complexity of the task: the functional interactions among a broad set of brain regions are not only continually changing over time, but changes to one brain region cause changes to others, whether they are directly or indirectly connected (Bressler and Mcintosh, 2007). Formal functional network analyses are therefore invaluable to meet this challenge. Such analyses examine the

brain as a network, defined as a set of elements (or nodes, which in the current context are brain regions) and the pairwise interaction between these elements (Stanley et al., 2013). Functional network analyses are a way to represent and interrogate the brain's complexity either at the whole level (e.g., whole brain graph analysis) (Bullmore and Sporns, 2009) or by focusing on a selected number of brain regions/nodes (e.g., Structural equation modeling (SEM) and dynamic causal modeling (DCM) (Frässle et al., 2015; McIntosh and Gonzalez-Lima, 1994).

The formal interaction among nodes, generally quantified via covariance metrics, can be done with two types of assessment: "functional connectivity" and "effective connectivity". Whereas the former is based strictly on correlations among brain regions, the latter conveys information on directionality via the influence of one node over another (Friston, 2002, 2011, 1994). A well-established statistical method for evaluating effective connectivity is structural equation modeling (SEM), pioneered in neuroimaging by McIntosh and Gonzales-Lima (McIntosh and Gonzalez-Lima, 1994). SEM can be performed as a hypothesis-driven approach constrained by *a priori* structural anatomical knowledge (typically derived from macaque anatomy) to quantify the influence of brain regions on one another. The advantages of SEM lie in the fact that it uses statistical evidence from observed data, as well as residuals that are otherwise not measured, to test specific hypotheses (Friston, 2011); it does so by comparing observed and modeled variance-covariance data structures (Guye et al., 2008). Effective connectivity approaches thus provide a deeper understanding of the interactions within the brain than functional connectivity approaches, more effectively bridging the divide between network structure and function (Mashal et al., 2012; McIntosh, 2000). Indeed, SEM has previously been used to investigate a variety of aspects of adolescence, including the development of brain structure (Giedd et al., 2007), the interaction of executive function and risk taking (Romer et al., 2011), and the genetics of cortical variability, specifically cortical thickness (Schmitt et al., 2009).

Absent from studies of developmental effective connectivity is the investigation of brain networks central to learning, memory, and emotion. The hippocampal complex is particularly critical to these functions, serving as a core component within a hierarchy of processing centers, with information flowing to and from a wide array of cortical regions via the entorhinal cortex (Amaral et al., 2014; Canto et al., 2008; Schultz and Engelhardt, 2014). This extensive network of brain regions, the communication of which is centered around and converges upon the hippocampus (Mišić et al., 2014), is critical for the sensing, encoding, integrating, and storage of life experiences (Davachi, 2006). Mature cognitive processing, and in particular the formation of memories, is thought to be driven by the intricate coordination of brain rhythms among distributed neural regions (Colgin, 2016). The hippocampus may thus serve as a point of convergence, or functional hub (Mišić et al., 2014), that is involved in a wide array of cognitive functions, including the binding together of information from multiple brain areas to form coherent memories. Emerging evidence suggests that this process is driven by the coupling of different frequencies (Axmacher et al., 2010), which develops over the course of adolescence (Cho et al., 2015). The ability to effectively integrate experiential information into memory may in fact augment executive functioning (Murty et al., 2016), facilitating the transition from procedure-based to memory-based strategies for problem solving (Qin et al., 2014).

A persistent issue of concern for the interpretation of developmental neuroimaging results is the role of sexual dimorphism. The hippocampus is well-established as a brain region with distinctive sex-specific properties, and thus has been extensively studied in this context, particularly in animal models (Fester and Rune, 2015; McCarthy and Arnold, 2011). Furthermore, the hippocampus not only serves a critical role in memory, but is implicated as a potential point of vulnerability to disorders of mood and cognition, particularly in response to early life stress (Chen and Baram, 2015). Studies examining human hippocampal volumes have mixed results, with several early studies finding that the hippocampus is larger in females compared to males (when corrected for overall brain size) (Cahill, 2006), yet a

meta-analysis in humans did not found any volumetric distinctions between sexes (Tan et al., 2016). In contrast, investigations of developmental *trajectories* can provide deeper understanding of this process, as hippocampal volumes significantly increase in females but not males over the course of puberty (Satterthwaite et al., 2014).

Furthermore, sex differences in the development of white matter connections among regions are also present, as boys show a steeper increase in white matter volumes than girls over the age range from 6 to 17 years (De Bellis, 2001), with evidence from myelin-transfer ratios suggesting that increases in white matter in males are predominantly due to increased axonal diameter whereas increases in girls are more likely due to increased myelin content (Perrin et al., 2009). These differences also extend to the network level, as previous work has found differences in intra- and inter-hemispheric white matter connectivity between young girls and boys (Ingalhalikar et al., 2014), with stronger intrahemispheric connections in boys and stronger interhemispheric connections in girls.

Taken together, these studies provide evidence that the structure of the hippocampus and its associated anatomical connections undergo significant remodeling during adolescence. The concomitant developmental changes of influences among functional connections within this brain network remain unknown. In this paper, we explore the nature of these changes, with particular emphasis on the maturation of the influences of individual regions on each other. Furthermore, as adolescence is a period typified by distinct trajectories based on gender, it is important to compare and contrast developmental changes of girls and boys. The goal of this study was therefore to determine potential sexual dimorphism in the effective connections associated with the hippocampal activation in boys and girls 8-16 years old. For this, we sought to determine the architecture of hippocampal directional connections, where we hypothesized, boys would show a delayed evolution of the network with respect to girls, given their later onset of adolescence neural development (Brenhouse and Andersen, 2011). In addition,

given that previous work suggests that with maturation comes a posterior to anterior shift in the strength of connections, we hypothesized that boys would display characteristics of a more posteriorly distributed network compared to girls.

## 2. Methods

### 2.1. Subjects

The study included 77 participants aged 8 to 16 years old (33 females). In order to compare by groups, participants were divided into two cohorts based on the median distribution of age (age = 10.5) (Sowell et al., 1999): Younger (ages 8-10; N = 42 (19 Females, 23 Males; mean age 9.48 +/- 0.59)) and older (age 11-16, N = 35 (14 Females, 21 Males; mean age 12.94 +/- 1.39)). Pubertal age (adrenal (PDSA) and gonadal (PDSG) was calculated based on the Tanner stages (Tanner and Whitehouse, 1976). The work described herein was done in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study was approved by the Institutional Review Board of the University of California Irvine, and all volunteers provided their assent and their parents provided written informed consent prior to participation.

### *2.2. Imaging*

#### *2.2.1. Equipment*

Scanning was performed on a Phillips 3.0 Tesla scanner (Best, the Netherlands), using a sensitivity encoding (SENSE) 32-channel head coil at the Neuroscience Imaging Center at UC Irvine.

#### *2.2.2. Imaging acquisitions*

Anatomical images were acquired using a 3D T1-weighted MPRAGE sequence with a

SENSE reduction factor of 2.4 (TR/TE = 8/3.7 ms, FA=8°, scan duration of 586 s) with 1mm isotropic resolution. Full brain coverage was achieved with a matrix size 256x204, 208 slices.

Functional images were acquired using a T2* weighted single shot interleaved EPI sequence (flip angle =64°, TE=30ms, SENSE reduction factor of 2.5) with 3 x 3.11 x 3 mm resolution and a TR of 2.5 s. During each scanning run 160 images were acquired corresponding to 6 minutes 40 seconds. Whole brain coverage was achieved with a matrix size of 64x61, 51 slices (FOV 19.2x19.2x15.3 cm).

*2.2.3. Behavioral paradigm during functional imaging*

The study employed a task of incidental memory encoding, the Behavioral Pattern Separation Task – Object Version (BPS-O) (Stark et al., 2013) to investigate the development of the hippocampal network during adolescence. We used a version of the BPS-O that has been slightly modified for fMRI scanning in children.
This task had two basic components: an "incidental encoding" task using landscape pictures, and a "baseline" task, using a visual discrimination paradigm. The effectiveness of this task in hippocampal formation activation has been fully explored and validated (Stark and Squire, 2001).

All subjects were trained on both tasks prior to scanning, using a laptop computer and the same four-button response pad that was used during the fMRI acquisition.

For the hippocampal task, subjects were presented a series of six unique scenic landscape pictures (selected from the National Geographic library), randomly shown ten times for two seconds each (total time = two minutes). They were instructed to press the left button (using their dominant hand) when presented with a scene containing an animal; they were instructed to press the right button when no animal was present.

For the baseline task, subjects were presented with two squares of differing opacity (against a noisy background) and instructed to select the brighter of two squares. Selection was made with the same button box, with the dominant index finger choosing the left box and the dominant middle finger selecting the right box. Opacity differences changed with each button press, becoming more similar with correct responses. Competency on the visual discrimination task was ensured when the participants correctly performed the task 10 consecutive times.

### *2.2.5. Scanning session*

While in the scanner, the subjects performed these two tasks in a block design, with three different block types, each 30-seconds in duration: familiar landscape images (images that were previously seen in the pre-scanning training session), novel images (new to the subject and never repeated), and the baseline (visual discrimination) task. Each block type was presented four times, for a total of twelve blocks. The blocks were presented in random order, and counterbalanced across participants. No rest period occurred between blocks. Blocks with scenic images (familiar or novel) consisted of 12 images presented for 2.5 seconds each. For the baseline blocks, the subjects were presented with the same translucent squares on a noisy background; the magnitude of differences of brightness between the two blocks was varied throughout the task to maintain a specific accuracy level of 80%, as selected by the subjects.

### *2.2.6. Data Processing and Analysis*

Structural imaging parcellation was performed using the FreeSurfer Imaging Analysis Suite (http://surfer.nmr.mgh.harvard.edu/). Briefly, this process involves affine registration to a common atlas, removal of non-brain tissue, intensity normalization, automated delineation of gray/white and gray/cerebrospinal fluid borders, and parcellation of cortical regions based on gyral and sulcul structures. Several regions-of-interest (ROIs) were then isolated for each subject, the selection

of which is described in section 2.2.7. Functional imaging analysis was performed using the Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Preprocessing steps included despiking, volume regularization, removal of nuisance and motion signals through use of ANATICOR (regressors: 6 Motion, mean cerebrospinal fluid (CSF), 15 mm radius kernel for local white matter erosion and CSF), and spatial smoothing using a 5mm FWHM smoothing kernel. Next, high-resolution anatomical images were co-registered to functional data using align_epi_anat. The fMRI time series were converted to percent signal change for inter-subject comparisons of beta coefficients, which were then entered into the general linear model using a block design, contrasting scene visualization (novel stimuli) against the baseline, thus generating T-statistic and beta coefficient maps for the Novel vs. Baseline condition, created in subject space and corrected using a family wise error threshold (FWE: $\alpha < 0.05$). Of note, the current study focused on the Novel vs. Baseline contrast; in previous work it was found that this condition generated the most robust activation of the medial temporal lobe (Stark and Squire, 2001). Cluster analysis was performed using the radius of activation for contiguous voxels, using Monte Carlo Methods (AFNI: 3dclustsim) with an uncorrected p-value threshold of $\alpha < 0.001$.

### *2.2.7. Region-of-interest analysis*

Volumes of activation were determined for each FreeSurfer region for all subjects. First, brain regions that were activated in at least 50% of subjects were identified, isolating 18 FreeSurfer labels. Regions that serve similar functions (e.g. pericalcarine and lateral occipital brain regions) were combined into regions of interest, generating a total of eleven ROIs covering cognitive domains ranging from primary sensory to multimodal and limbic regions. The regions included are summarized in Table 1. For each SEM ROI, a representative time series was derived from the peak voxel as we have done previously (Walsh et al., 2008). The regional time series from each subject in a particular group (young males, young females,

older males, older females) were then averaged and used as input to generate the effective connectivity model, using structural equation modeling (described in section 2.2.8.).

Table 1. Regions of interest used in Structural Equation Models

| **SEM Region** | **FreeSurfer Label** |
|---|---|
| Primary Visual | Pericalcarine<br>Lateral occipital |
| Secondary Visual | Inferior temporal<br>Fusiform<br>Lingual |
| Temporal Association | Superior temporal<br>Middle temporal<br>Bankssts |
| Entorhinal Cortex | Entorhinal |
| Hippocampus | Hippocampus |
| Cuneus/Precuneus | Cuneus<br>Precuneus |
| Superior Parietal | Superior parietal |
| Inferior Parietal | Inferior parietal<br>Supramarginal |
| Cingulate | Posterior cingulate |
| Orbitofrontal | Lateral orbitofrontal |
| Inferior Frontal | Pars opercularis |

### *2.2.8. Structural Equation Modeling*

We built structural equation models using AMOS (v. 19.0.0), as we have performed previously (Dick et al., 2010; Walsh et al., 2008). The process first involves the generation of an initial anatomical model, based on known connections among the active regions during this task, focusing mostly on feed-forward connections (Barbas, 2000), progressing from sensory to association, multimodal, and then limbic regions. As any change in a particular connection will change the entire network, an iterative process that may add or remove connections is then performed where the differences between the current model and the empirical data are minimized. In this way, backward connections are subsequently added if such connections help to improve the fit of the model.

The SEM modeling involved the following steps:

1. Constraining the model with anatomical connections;
2. Generating the variance-covariance matrix for each group (younger girls, younger boys, older girls, older boys), based on the average time series;
3. Solving the equations simultaneously to obtain path coefficients. For this, we performed an iterative maximum likelihood method to minimize differences between predicted and observed covariance matrices using goodness-of-fit statistics ($X^2$ distribution). Positive connection weights indicate that greater activity in the region of origin predicted greater activity in the target region, whereas negative connection weights indicated that greater activity in the region of origin predicted reduced activity in the target region.

*2.2.9. Statistical analysis*

Goodness of fit of the structural equation models was assessed using a $X^2$ test as well as the Root Mean Square Error of Approximation (RMSEA). Differences between the models were calculated using the "stacked model" approach (McIntosh and Gonzalez-Lima, 1994). In this assessment, a pair of groups (i.e., younger girls vs. younger boys) was simultaneously fit to the same model, testing the null hypothesis that the path coefficients between the two groups do not differ. Significant differences between the models were determined using a $X^2$ difference test.

Behavioral measures were compared pairwise (in accordance with the SEM comparisons) between four subgroups (1) younger boys vs. older boys, 2) younger girls vs. older girls, 3) younger girls vs. younger boys, and 4) older girls vs. older boys) using the Wilcoxon Rank Sums test, assessed for a correlation with age (in months) using Spearman's rho, and assessed via Levene's test for differences in variance between groups.

### *2.3. Memory Assessment*

#### *2.3.1. Behavioral Task*

Given that there were relatively fewer participants at the upper end of the age range, we used a near-identical BPS-O task on a larger cohort of 219 individuals (age range 8 – 16 years, including the scanned participants) in order to more fully investigate the developmental trends associated with this tasks. These behavioral measures were taken outside of the scanner, just as was done for the scanned cohort. These biological markers may be more sensitive to developmental changes, with changes to neural architecture potentially lagging behind changes in behavior. Notably, this also served to verify that the task used to activate the hippocampal network in the MRI scanner is indeed sensitive to incidental encoding in children, as the stimulus paradigm used in the scanner does not directly test incidental encoding.

For this task performed outside the scanner, participants are first presented a series of 96 color photographs of everyday objects on a white background, and are asked to perform an indoor/outdoor judgment for each object via a button press with their dominant hand (32 items total, 2 s each, self-paced ISI). We refer to this series as the "study phase" of the experiment. During the next "test phase", subjects perform a surprise recognition memory task, identifying each item via button press as “Old”, “Similar”, or “New” (96 items total—32 repeated items, 32 lure items, and 32 foil items; 2 s each, self-paced ISI). This surprise recognition memory task is not performed in the scanner. One-third of the images in the test phase were exact repetitions of images presented in the study phase (targets); one-third of the images were new images not previously seen (foils); and one-third of the images were similar to the those seen during the study phase, but not identical (lures). Behavioral pattern separation performance (BPS score) was calculated as the difference between the rate of “Similar” responses given to the lure items minus “Similar” responses given to the foils (to correct for response biases). Thus, if a

participant has poor pattern separation performance, their BPS score will be low because they have made fewer "Similar" responses to lure trials (i.e., typically making more "Old" responses).

#### *2.3.2. Statistical analysis*

Whole-group correlations between age and BPS-O were determined by Pearson correlation coefficient. Age group and sex differences were assessed using a 2 (age group) by 2 (sex) ANOVA with *post hoc* tests as needed. The influence on age and gender on PDSA scores was assessed using a standard least squares analysis.

## 3. Results

### *3.1. Subjects*

PDSA and PDSG ages were significantly different between younger and older cohorts ($p < 0.0001$). There was no significant difference in PDSA or PDSG scores between younger boys and girls, or between older boys and girls; of note, however, is that among older subjects, girls approached significantly higher PDS scores than boys ($p < 0.07$). Furthermore, there was a significant interaction between age*sex for the PDSA scores ($p < 0.01$) and PDSG scores ($p < 0.03$), reflecting slower pubertal development in boys as compared to girls.

### *3.2. Behavioral performance*

Pair-wise comparisons between subgroups of age and sex (e.g., younger boys vs. younger girls) found no significant difference in performance on the BPS-O task (all $p > 0.05$) (Younger boys = $38.2 \pm 26.1$ (Mean, $\pm$ SD); Younger girls = $35.8 \pm 20.8$; Older boys = $32.7 \pm 35.6$; Older girls = $45.9 \pm 9.4$), and no significant correlation was found between age in months and performance on the BPS-O task for both girls and boys (all $p > 0.05$). This lack of difference may be due to the age distribution of these subjects; this cohort had a smaller proportion of subjects at the older age

range. Furthermore, a test for equivalence of variance (Levene's test) between the four subgroups found a significant difference in variances ($p = 0.0181$), with older girls having the lowest variance.

As noted in the methods section, we further tested a larger cohort of participants in order to more fully investigate the ability of the BPS-O to measure incidental encoding in children. Among this group ($N = 219$), there was a significant, albeit weak, positive correlation between child age and BPS-O scores (Pearson correlation coefficient = 0.21, $p = 0.001$). Consistent with these findings, the older age group performed significantly better when contrasting all subjects by age group, as scores on the BPS-O were significantly higher in the older age group (Older = 45.8 ± 18.9 (mean ± SD); Younger = 37.3 ± 21.7; $p = 0.003$); there were no significant differences when contrasting sex differences (Females = 41.7 ± 18.6; Males 40.1 ± 22.9; $p = 0.672$) or age by sex interactions ($p = 0.596$) (Figure 5).

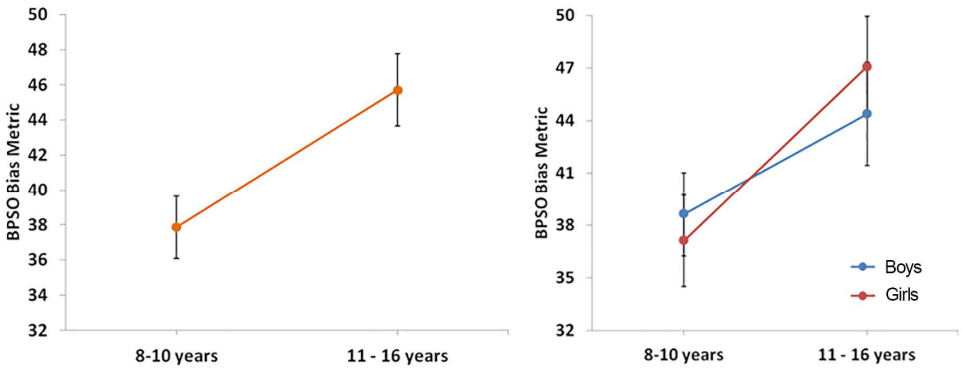


Figure 5. Plot of BPSO Bias Metric for all subjects (orange), as well as for girls (red) and boys (blue) as a function of age. Performance on the BPSO increased significantly with age ($p = 0.003$); no differences were found when contrasting females and males.

### *3.3 Functional activation*

Significant levels of activation were detected throughout the brain, including the hippocampus proper, frontal regions (orbitofrontal, inferior frontal, precentral gyrus), temporal regions (superior, middle, and inferior temporal gyri and

entorhinal cortex), parietal regions (superior and inferior parietal, precuneus, and postcentral), occipital (lingual gyrus, fusiform gyrus, lateral occipital cortex, pericalcarine area, cuneus), insula, cingulate cortex (posterior cingulate and isthmus), and subcortical regions (thalamus, caudate, and putamen) (Figure 1).

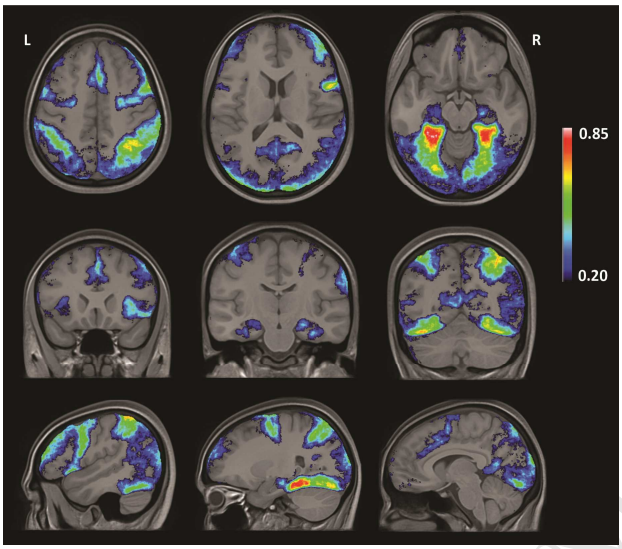


Figure 1. Group activation map for fMRI task, showing regions of brain activation common among subjects. Activation is presented as a proportion of subjects with significant activation at a given voxel, with hot colors representing greater overlap of activation among subjects. The task was effective at activating a broad network of brain regions including hippocampus and entorhinal cortex, as well as bilateral orbitofrontal and lateral frontal regions, temporal regions (superior, middle, and inferior), parietal regions (superior and inferior parietal, precuneus, and postcentral), occipital (lingual gyrus, fusiform gyrus, lateral occipital cortex, pericalcarine area, cuneus), insula, cingulate cortex (posterior cingulate and isthmus), and subcortical regions (thalamus, caudate, and putamen).

### *3.4. Connectivity Analysis*

As there was no laterality between left and right hemispheres, analyses were collapsed across hemispheres. Models for each group were achieved with at least 40% of variance explained for each node with inputs. A good fit was obtained for all models (see below, all p-values > 0.05), indicating that the hypothesized model should be retained; results for each group are presented in Figure 2. Results for each

group as well as qualitative descriptions are presented below.

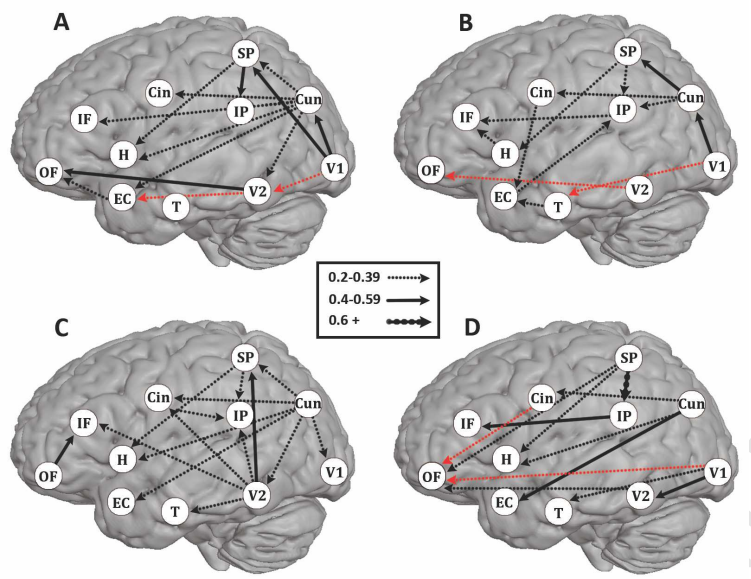


Figure 2. Effective connections present in each group: (A) younger girls, (B) older girls, (C) younger boys, and (D) older boys. Connections are presented by effective connectivity strength: low (0.2 – 0.39), medium (0.4 – 0.59), and high (0.6 and above); black arrow are positive effective connections, red arrows are negative effective connections. Patterns of connectivity are notable for relatively high density, posterior distribution in younger boys, an anteriorly shifted pattern of connectivity in older boys (relative to younger boys) with multiple inputs to orbitofrontal regions, an anterior-posterior distribution in younger girls (similar to older boys) but with more balanced distribution, and an anteriorly shifted pattern of connectivity with overall lower density. OF = orbitofrontal, IF = inferior frontal, H = hippocampus, EC = entorhinal cortex, T = temporal association, Cin = cingulate, SP = superior parietal, IP = inferior parietal, V2 = secondary visual, V1 = primary visual, Cun = cuneus/precuneus.

Effective connectivity in younger boys: The model associated with younger boys ($X^2$ = 34.782, degrees of freedom (df) 25, p = 0.092, root mean square error of approximation (RMSEA) = 0.052, comparative fit index (CFI) = 0.972, is notable for two reasons: a) a high density of connections among nodes of the model; b) a relatively posterior distribution, with a predominance of connections among visual regions targeting parietal and frontal association and multi-modal regions with weak connections to limbic regions (including hippocampus and entorhinal cortex). There is also a notable influence of orbitofrontal onto inferior frontal cortex.

Effective connectivity in older boys: Whereas the effective connections in the model for older boys ($X^2$ = 20.775, df = 16, p = 0.187, RMSEA = 0.046, CFI = 0.987) showed only a slight decrease in density of connections, its distribution showed an anterior shift relative to younger boys. That is, there was a decrease in effective connections within sensory (visual) areas and an increase in effective connections from sensory and association regions onto more anterior multi-modal and regions (especially those converging in the orbitofrontal regions).

Effective connectivity in younger girls: The model associated with younger girls ($X^2$ = 31.306, df = 31, p = 0.451, RMSEA = 0.008, CFI = 0.999), had remarkable parallels to the model seen in older boys. For example, the density of connections was similar among the sensory and association and multimodal regions. However, whereas the model in older boys show multiple inputs converging into the orbitofrontal region, the model for younger girls did not, and instead showed a more balanced distribution of effective connections among brain regions.

Effective connectivity in older girls: The model associated with older girls ($X^2$ = 33.351, df = 26, p = 0.152, RMSEA = 0.044, CFI = 0.97), showed several particularities. First, the density of effective connections was lower than any of the other groups. Second, there is a clear anterior shift in which visual areas have a low density of connections and interconnectivity between limbic regions and between limbic and multimodal regions is maximal. Of note, this is the only group that showed efferent connections from entorhinal cortex and hippocampus to non-limbic cortical regions.

### *3.5. Statistical assessment of differences between models*

Comparisons of network models between groups using the "stacked model" revealed significant differences in the pattern of interactions between age and sex. Specifically, there was a significant difference between younger boys and older boys

($X^2$ = 115.9, degrees of freedom (df) 22, p = 9.63e-15), and younger girls and older girls ($X^2$ = 115.96, df = 20, p < 1.0e-15). There was also a significant difference with respect to sex, younger girls vs. younger boys: ($X^2$ 206.5 = df = 21, p < 1.0e-15), and older girls vs. older boys ($X^2$ = 103.1, df = 18, p = 5.87e-14).

### *3.6. Qualitative comparisons among groups*

Critical similarities and differences were seen when contrasting groups by both age and sex. Table 2 lists connections (effective connectivity > 0.3) present in both younger and older age groups (panel A), as well as those that were similar between boys and girls (panel B).

Table 2. Similar connections between younger and older cohorts (effective connectivity > 0.3)

| **A.** | | | | |
|---|---|---|---|---|
| | **Origin** | **Target** | **Younger** | **Older** |
| **Girls** | Primary visual | Cuneus/precuneus | 0.427 | 0.416 |
| | **Cuneus/precuneus** | **Cingulate** | 0.309 | 0.337 |
| | Superior parietal | Hippocampus | 0.331 | 0.391 |
| **Boys** | **Cuneus/precuneus** | **Cingulate** | 0.353 | 0.315 |
| | Cuneus/precuneus | Entorhinal cortex | 0.326 | 0.484 |
| | Superior parietal | Inferior parietal | 0.385 | 0.724 |
| **B.** | | | | |
| | **Origin** | **Target** | **Girls** | **Boys** |
| **Younger** | **Cuneus/precuneus** | **Cingulate** | 0.309 | 0.353 |
| | Superior parietal | Hippocampus | 0.331 | 0.322 |
| | Superior parietal | Inferior parietal | 0.385 | 0.548 |
| **Older** | **Cuneus/precuneus** | **Cingulate** | 0.337 | 0.315 |

Notably, both girls and boys had similar connections in younger and older groups predominantly originating in cuneus and parietal regions and terminating in parietal, cingulate, and hippocampal/entorhinal complex. When comparing boys to girls, the younger group had numerically more similar connections than the older group. A conspicuous connection that was consistently seen between the younger and older cohorts, as well as the girl and boy cohorts, was the cuneus/precuneus to cingulate (shown in bold). Table 3, in contrast, lists the connections that were different between the younger and older age groups (defined as values greater than 0.3 in one group but not the other).

Table 3. Differences in effective connections between age groups

| **A.** | | | | |
|---|---|---|---|---|
| | **Origin** | **Target** | **Younger** | **Older** |
| **Girls** | Secondary visual | Entorhinal cortex | -0.39 | -0.078 |
| | Cuneus/precuneus | Hippocampus | 0.354 | 0.143 |
| | Superior parietal | Inferior parietal | 0.548 | 0.27 |
| | Entorhinal cortex | Orbitofrontal | 0.306 | -0.06 |
| | Secondary visual | Orbitofrontal | 0.447 | -0.32 |
| | Primary visual | Superior parietal | 0.435 | 0.119 |
| **Boys** | Orbitofrontal | Inferior frontal | 0.444 | 0.079 |
| | Secondary visual | Cingulate | 0.366 | -0.031 |
| | Secondary visual | Superior parietal | 0.403 | 0.127 |
| **B.** | | | | |
| | **Origin** | **Target** | **Younger** | **Older** |
| **Girls** | - | - | - | - |
| **Boys** | Inferior parietal | Inferior frontal | 0.127 | 0.445 |
| | Primary visual | Secondary visual | 0.12 | 0.418 |
| | Primary visual | Orbitofrontal | 0 | -0.312 |
| | Superior parietal | Orbitofrontal | 0 | 0.393 |

This comparison is remarkable for the fact that girls had several more connections present in the younger but not the older group (Figure 3, panel A), particularly the input into the orbitofrontal cortex. In contrast, there were several connections that were present in older but not younger boys (Figure 3, panel B), including input into the orbitofrontal cortex; girls showed no connections that were present in the older but not younger groups.

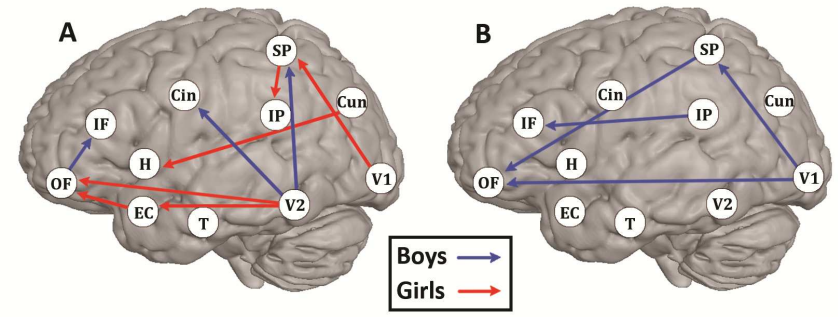


Figure 3. Effective connections present (> 0.3) in (A) younger but not older subjects, and (B) older but not younger subjects. Red arrows = girls, blue arrows = boys. Among girls, there were several connections present in younger but not older girls; in contrast, there were no connections present in older girls that were not present in younger girls. Among boys, differences are less stark, but there are more anterior-posterior, ventral, long-range

connections present in older boys that were not present in younger boys. OF = orbitofrontal, IF = inferior frontal, H = hippocampus, EC = entorhinal cortex, T = temporal association, Cin = cingulate, SP = superior parietal, IP = inferior parietal, V2 = secondary visual, V1 = primary visual, Cun = cuneus/precuneus.

There were also several differences seen when contrasting the presence (strength > 0.3) of connections in girls as compared to boys (Table 4). Among younger subjects, there were several connections that were strong in girls but not in boys. In contrast, there were only a few connections that were strong in younger boys but not younger girls. This is not true in the older subjects, however, where the number of strong connections is similar in both groups.

Table 4. Effective Connections Different Between Sexes

| A. | | | | |
|---|---|---|---|---|
| | **Origin** | **Target** | **Girls** | **Boys** |
| **Younger** | Primary Visual | Cuneus/precuneus | 0.427 | 0.277 |
| | Cuneus/precuneus | Entorhinal Cortex | 0.215 | 0.326 |
| | Secondary Visual | Entorhinal Cortex | -0.39 | 0.091 |
| | Cuneus/precuneus | Hippocampus | 0.354 | 0.237 |
| | Orbitofrontal | Inferior Frontal | 0.103 | 0.444 |
| | Entorhinal Cortex | Orbitofrontal | 0.306 | 0 |
| | Secondary Visual | Orbitofrontal | 0.447 | 0.144 |
| | Primary Visual | Superior Parietal | 0.435 | 0 |
| | Secondary Visual | Cingulate | 0 | 0.366 |
| | Secondary Visual | Superior Parietal | 0 | 0.403 |
| **Older** | Primary Visual | Cuneus/precuneus | 0.416 | 0.172 |
| | Cuneus/precuneus | Entorhinal Cortex | 0.032 | 0.484 |
| | Superior Parietal | Hippocampus | 0.391 | 0.246 |
| | Inferior Parietal | Inferior Frontal | 0.228 | 0.445 |
| | Superior Parietal | Inferior Parietal | 0.27 | 0.724 |
| | Secondary Visual | Orbitofrontal | -0.32 | 0.223 |
| | Primary Visual | Secondary Visual | 0.11 | 0.418 |
| | Cuneus/precuneus | Superior Parietal | 0.442 | 0.151 |
| | Primary Visual | Orbitofrontal | 0 | -0.312 |
| | Superior Parietal | Orbitofrontal | 0 | 0.393 |

Furthermore, it is interesting to compare older boys and younger girls, which shows a similar pattern of connectivity with respect to the anterior-posterior axis, i.e., predominance of connections from basic visual processing onto more anterior multi-modal and limbic areas. However, boys tended to have more dorsal/parietal connections, whereas girls tended to have more ventral/temporal connections (Figure 4).

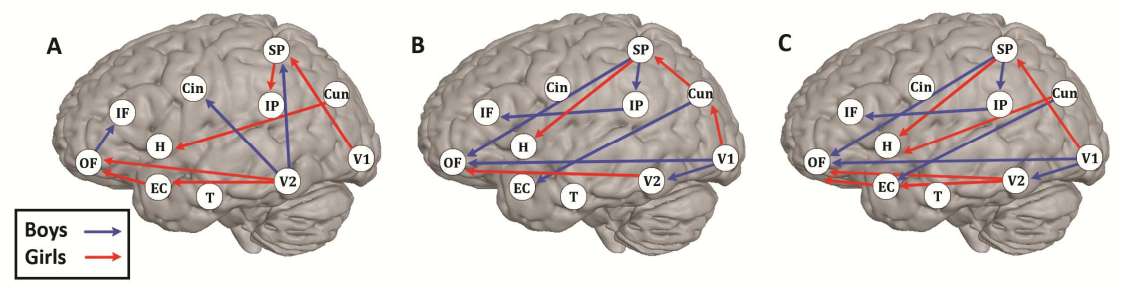


Figure 4. Effective connection differences by sex, visualized as those present (> 0.3) in one group but not the other, contrasting (A) younger subjects, and (B) older subjects, and (C) younger girls and older boys. Red arrows = girls, blue arrows = boys. Among younger subjects (A), there are notably more connections in girls than boys; this disparity is not as great in older subjects (B). When comparing younger girls and older boys (C), there is a similar anterior-posterior distribution of connections, but boys have a much more dorsal distribution, whereas girls have a much more ventral distribution. OF = orbitofrontal, IF = inferior frontal, H = hippocampus, EC = entorhinal cortex, T = temporal association, Cin = cingulate, SP = superior parietal, IP = inferior parietal, V2 = secondary visual, V1 = primary visual, Cun = cuneus/precuneus.

Taken together, maps for each group could suggest a reorganization among and between brain regions from the transition from pre-puberty to adolescence. Specifically, the density of connections progressively simplified as the burden shifted from posterior sensory regions to a preponderance of cognitive-limbic connectivity with respect to maturation from younger boys to older boys/younger girls to older girls. In concert, the behavioral measures provide evidence for concomitant functional maturation of this system, as evidenced by a tendency towards an increased performance with age as well as a clear decrease in the variance of scores with maturation.

## 4. Discussion

This study investigated the development of effective networks activated during a well-characterized hippocampus-associated task during the transition from childhood to adolescence in both boys and girls. Using SEM, we identified the directional interactions among multiple brain regions activated by an incidental encoding task. The major findings of the study are: (a) Whereas certain

relationships between regions were similar between younger and older subjects, others showed clear differences when contrasting these two groups of children; (b) Many of these changes were sex-specific, highlighting the influence of sex on brain processes and their evolution during this critical transition period; and (c) measures of memory performance increase with age, suggesting a commensurate increase in the efficiency of memory processing with maturation. These results provide significant insight into the development of the implicit encoding network, evidenced by a shift of connection strengths that are dominated by basic visual processing towards those of higher-level multi-modal processing.

### *4.1. Both* persistent *and* changing *effective connections are associated with development*

A main finding of this study is that several connections found to be different between younger and older subjects were specifically represented by those terminating on more rostral brain regions critical for learning and adaptive behavior (e.g., orbitofrontal cortex (Roberts, 2006)). Indeed, it should be of little surprise that differences were found between these brain networks, as adolescence is a period of great physical and mental change. This critical chapter is marked by a surge of hormones that drive a complex, multi-faceted process involving the concurrent development of social and cognitive behaviors and sexual maturation to facilitate reproduction and functioning (Choudhury et al., 2006).

The current findings suggest an initial extensive engagement of multiple regions, which subsequently decreases in concert with increased skill, as has been shown for expertise in motor skills (Milton et al., 2007). The neurophysiological processes driving these changes are due to many factors, including experience (Bell et al., 2010; Murty et al., 2016). Somewhat counter-intuitively, certain brain processes that occur more regularly often display a higher degree of pruning, as this

"habitualized" activity allows for a streamlining that requires fewer neuronal connections; in contrast, associations requiring constant updating do not undergo as robust pruning (Teicher et al., 1995).

Furthermore, white matter pathways, critical for proper communication among regions throughout the brain network, show progressive maturation over the course of adolescence, and alterations in this development are associated with changes in cognitive performance (Simmonds et al., 2014a). Maturation of structural connectivity can also be seen at the network level, as evidenced by increases in strength and efficiency of connections over this time frame (Hagmann et al., 2010). There is also a distinct association between structural and functional metrics (Hagmann et al., 2010), with functional connections shifting in strength, topology, and organization at adolescence (Stevens, 2016), effectively maturing towards an adult-like state (Marek et al., 2015). However, with these changes come risk, as shifts in the balance among brain regions may contribute to the increased incidence of mood disorders seen during this time (Casey et al., 2010).

Mechanistically, these network changes are likely mediated, at least in part by pruning, the process of remodeling involving the overproduction and subsequent loss of synapses, predominantly at excitatory synapses on dendritic spines (Brenhouse and Andersen, 2011). The GABAergic system, known to show great changes over the course of adolescence (Caballero and Tseng, 2016), is particularly important for neuronal and functional plasticity during this time (Afroz et al., 2016; Kilb, 2012), mediating the shifting balance of excitatory/inhibitory circuits throughout the brain. Furthermore the development of white matter during adolescence (Eluvathingal et al., 2007; Muftuler et al., 2012) is associated with improved cognitive performance (Tamnes et al., 2010). Interestingly, this process of synaptic remodeling and myelin development has been shown to occur in a generally posterior-anterior fashion (Krogsrud et al., 2016; Simmonds et al., 2014b), which is in line with the progressive anterior shift of connections seen between the younger and older cohorts in the current study.

Another pattern of remodeling found recurring throughout studies of adolescence is an initial change in one direction followed by subsequent change in the opposite direction (i.e., back towards baseline), often described as a U-shaped curve (upright or inverted). This pattern, for example, is seen for total (Lenroot et al., 2007) and regional brain volumes (Paus et al., 2008), dendritic spine density (Petanjek et al., 2011), and the pruning of steroid receptors during development (Brenhouse and Andersen, 2011). It is interesting to speculate that such a U-shaped developmental trajectory may be represented in the current study, if one views these cohorts along a continuum of maturation (based on the earlier onset of developmental changes in girls (Brenhouse and Andersen, 2011)), beginning with a relatively sparse network in younger boys, progressing to more connections present in older boys and younger girls, and in turn ending with relatively sparse networks in older girls.

In sum, this developmental pattern can be described as an overall "simplification" of the hippocampal network with maturation. These findings are consistent with previous work that shows a progressive shift from local toward more distributed, long-range processing over the transition from childhood to adolescence (Fair et al., 2009). This reorganization facilitates more effective integration of information, evidenced by increases in signal variance, which is related to behavioral measures (McIntosh et al., 2008).

In contrast to these changes, several connections showed little to no differences between younger and older subjects. These connections originated in and terminated on regions critical for visuospatial processing and/or working memory. Specifically, interactions with the medial occipitoparietal regions (cuneus and precuneus) were remarkably stable with age. The cuneus/precuneus are classically viewed as important to visual information processing and integration (Cavanna and Trimble, 2006; Vanni et al., 2001). These regions also seem to be involved in autobiographical (episodic) memory (Addis et al., 2004), and have been shown to deactivate with encoding and activate with retrieval (Bonnì et al., 2015).

Interestingly, they also appear to be involved in the determination of old versus new information (Donaldson et al., 2010), which is an integral, albeit implicit, part of the current study task.

Furthermore, one region, the cingulate gyrus, showed little changes to its input. The cingulate gyrus is important in the processing of emotional salience and the regulation of attentional focus (Leech and Sharp, 2014), a likely core component of the current study task. Interestingly, this region, along with the precuneus, have been shown to have particularly vigorous increases in signal variability during adolescence, highlighting their role as hubs critical for functional integration at the global level (Misić et al., 2010). Indeed, graph theoretical metrics have found these regions to be central components of anatomical and functional brain networks, as evidenced by their highly efficient, centralized connectivity (Hagmann et al., 2008). Interestingly, one connection that was consistently seen between the younger and older cohorts, as well as the girl and boy cohorts, was the cuneus/precuneus to cingulate. However, it should be noted that, in this context, it is not completely clear if there is any biological significance to this finding, as caution suggests that it could be due to limitations of topological anatomical parcellation. That is, since there are not absolute landmarks to delimit posterior cingulate and precuneus, our ROIs could be mixed with both regions (at least in some cases).

The lack of differences between young and old suggests that these areas are both critical to the task and are well developed early in the course of development, involved in core functions that are relatively constant over this phase of life. This is substantiated by the fact that these regions are located more posteriorly, in brain areas that tend to mature early in the course of development (Simmonds et al., 2014a).

### *4.2. Sexual dimorphism in hippocampal network development*

The other main finding of the current study is that hippocampal network development also differed between girls and boys. Specifically, younger girls had a clear predominance of influence from basic visual processing (primary and secondary visual) to multi-modal and limbic regions. For younger boys, the pattern was more mixed; while they also showed influence of basic visual processing (albeit from secondary but not primary visual regions), there was much more influence from cuneus/precuneus onto the core memory regions (hippocampus and entorhinal cortex) as well as a somewhat surprising influence of orbitofrontal onto inferior frontal cortex.

Among older subjects, girls had a continued but simplified pattern of influence from basic visual processing onto more anterior multi-modal and limbic regions. Interestingly, older boys showed a pattern of influence similar to younger girls in that there were multiple influences from basic visual processing onto multi-modal regions; this is consistent with the ideas that boys are likely somewhat behind girls with respect to network development, but tend to reach similar networks over time. A notable difference, however, is the significant influence from dorsal parietal regions in older boys relative to younger girls, which showed more influences among ventral temporal regions. Furthermore, girls had noticeably more negative connections in among ventral regions. This may indicate a degree of inhibition from one region to another, which then serves the purpose of efficiently engaging the dorsal stream. Alternatively, this may indicate that activations between these regions are out of phase, potentially due to changes in the speed of connectivity. Taken together, these results thus provide evidence that sex-dependent developmental changes among this network are region-specific.

Previous studies have consistently found differences between the genders with respect to brain morphology. For example, there is a clear trend of different developmental trajectories between girls and boys during adolescence. Girls have an

earlier peak in brain volumes over the course of development (Lenroot et al., 2007), although differences in the peak time of regional gray matter volumes appear to depend on cortical region (Giedd et al., 2006). White matter volumes appear to increase to a greater extent in boys relative to girls during childhood and adolescence (De Bellis, 2001), postulated to be due to testosterone-mediated increases in axonal caliber (Perrin et al., 2008). The current findings are consistent with the existence of developmental differences between the sexes.

### *4.3. Improved memory processing with age*

Consistent with our initial hypothesis, we found a significant correlation between performance on the BPS-O memory task and age. Older children showed enhanced ability to successfully identify similar objects from identical objects suggesting developmental improvement in pattern separation. This suggests that this task is effective at tracking the development of incidental encoding during adolescence. The BPS-O task assesses the ability to discriminate similar items from items that have been viewed previously. Pattern separation enables newly encoded items to be dissociated from similar and previously stored events and is thought to be a key component of episodic memory (Yassa and Stark, 2011). In adults, performance on this pattern separation is dependent on intrinsic hippocampal connections (Bakker et al., 2008; Yassa et al., 2010) as well as limbic networks, especially the fornix and cingulum, that interconnect the hippocampus with other brain regions underlie such episodic memory processes (Bennett et al., 2015)

The observation of age related improvement in pattern separation suggests a functional consequence of the increased efficiency during the development of this brain network. Consistent with this, we also found a difference in the variance of performance on the BPS-O task among scanned participants, with younger boys having the largest variance, and older girls having the smallest variance. This suggests an evolution in the nature of cognitive processing with maturation, with an increase in the efficiency of performance at this task. It is particularly interesting to

interpret these findings in the context of the increased efficiency of effective connectivity seen with the task over the course of development. Taken together, these findings provide insight into the mechanistic underpinnings of cognitive development with adolescence.

### *4.4. Conclusion*

In the current study, we focused on an incidental encoding task that involves the hippocampus formation and associated brain regions as a means to investigate a relatively understudied brain network underlying spatial and episodic memory that is also intimately involved in numerous sensory and cognitive processes (Eichenbaum and Cohen, 2014). The hippocampal formation develops along a specific trajectory that is distinct from that of, for example, amygdala or frontal cortex (Avishai-Eliner et al., 2002). It is likely that the developmental, sex-specific changes we discuss herein differ across nodes and networks, yet the principles we uncover are germane to the adolescent development of multiple brain networks (Casey et al., 2016).

These results provide unique insight into the complex interactions occurring within the brain over the course of adolescence, demonstrating a clear progression towards a simplified, streamlined network over the course of aging.

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