Development of Hippocampal Functional Connectivity During Childhood

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Abstract

The hippocampus is a medial temporal lobe structure involved in memory, spatial navigation, and regulation of stress responses, making it a structure critical to daily functioning. However, little is known about the functional development of the hippocampus during childhood due to methodological challenges of acquiring neuroimaging data in young participants. This is a critical gap given evidence that hippocampally-mediated behaviors (e.g., episodic memory) undergo rapid and important changes during childhood. To address this gap, the present investigation collected resting-state fMRI scans in 97 4- to 10-year-old children. Whole brain seed-based analyses of anterior, posterior, and whole hippocampal connectivity were performed to identify regions demonstrating stable (i.e., age-controlled) connectivity profiles as well as age-related differences in connectivity. Results reveal that the hippocampus is a highly connected structure of the brain and that most of the major components of the adult network are evident during childhood, including both unique and overlapping connectivity between anterior and posterior regions. Despite widespread age-controlled connectivity, the strength of hippocampal connectivity with regions of lateral temporal lobes and the anterior cingulate increased throughout the studied age range. These findings have implications for future investigations of the development of hippocampally-mediated behaviors and methodological applications for the appropriateness of whole versus segmented hippocampal seeds in connectivity analyses.

Introduction

The hippocampus is a medial temporal lobe structure important for a number of critical cognitive processes including, but not limited to, episodic memory, stress regulation, and spatial navigation (Eichenbaum & Cohen, 2014; Jacobson & Sapolsky, 1991). As such, investigations of the hippocampus and its development are important as they may provide unique insights into how neural substrates support cognition, affect, and behavior across the lifespan. For example, understanding the association between the maturation of neural circuitry and the developmental changes in cognitive capacities can inform our understanding of how stimuli are represented and processed in the brain (Casey et al. 2005; Nelson et al. 2006). Additionally, characterizing typical development allows for improvements in the ability to systematically predict, identify, and treat aberrant neural architectures early in life when their impact may have the greatest effects. Despite the broad applications for the investigation of hippocampal development, this area has received little exploration in humans.

To date, most studies investigating hippocampal development during childhood have assessed structural maturation, that is, changes in volume or morphometry. Many studies report ongoing volumetric changes in the hippocampus throughout childhood (Østby et al. 2009; Uematsu et al. 2012) and into adulthood (DeMaster et al. 2014; Giedd et al., 1996; Hu et al. 2013; Wierenga et al., 2014; Yang et al. 2013). Although there are some inconsistencies regarding the nature and timing of hippocampal structural development across the lifespan, converging evidence demonstrates structural maturation is evident throughout childhood. These developmental changes are not homogeneous across the structure, as some studies have shown that subregions (i.e., head, body, tail) of the hippocampus undergo differential developmental trajectories (Gogtay et al. 2006; Lin et al. 2013), which is likely due to the distribution and

development of subfields (CA1-4, dentate gyrus) along the longitudinal axis (Lavenex & Banta

Lavenex, 2013). Given the complex reciprocal relations between biological structure and

function, ongoing structural changes in the size and shape of the hippocampus may be paralleled

by functional changes. However, data that speak directly to functional changes during

development are sparse.

The extant literature examining functional development of the hippocampus has

predominantly focused on task-based activations (Chiu et al. 2006; Ghetti et al. 2010; Güler &

Thomas, 2013; Ofen et al. 2007; Ofen et al. 2012; Paz-Alonso et al. 2013; Paz-Alonso et al.

2008; Qin et al. 2014). Using task-based fMRI designs, researchers have demonstrated that

developmental changes in hippocampal activation (Ghetti et al. 2010) and in the coordinated

activity between the hippocampus and other cortical regions (i.e., connectivity) were linked to

the emergence of mature episodic memory abilities and other cognitive abilities (Ofen et al.

2012; Qin et al. 2014; for review, see Ghetti & Bunge, 2012). Mirroring structural development

during childhood, there is evidence from adults that hippocampal subregions are functionally

distinct (Poppenk et al. 2013; Poppenk & Moscovitch, 2011) and that these subregions show

qualitative changes in task-elicited functions during development (DeMaster et al. 2013;

DeMaster et al. 2014).

Although task-based fMRI investigations are effective for studying the neural correlates

of specific hippocampally-mediated processes (e.g., memory), they are limited by the nature of

the experimental design (e.g., visual versus auditory stimuli), task difficulty, and the cognitive

process being studied (e.g., memory versus spatial awareness). Thus, these studies alone do not

provide sufficient evidence regarding the development of the full hippocampal network, limiting

the extent to which conclusions can be drawn about functional development of the hippocampus

more broadly. One method for overcoming these limitations is the use of task-independent or resting-state functional connectivity MRI (hereafter rs-fcMRI). Rs-fcMRI, first identified by Biswal and colleagues (1995), measures spontaneous low-frequency oscillations of brain activity while an individual lies passively in the scanner. Correlations in these low frequency oscillations are thought to be indicative of a history of co-activation, where regions demonstrating temporal coherence at rest are proposed to be the same regions that show coordinated activity during a task (Biswal et al. 1995; Power et al. 2014). Therefore, rs-fcMRI permits the investigation of complex brain networks unconstrained by experimental paradigms. Moreover, given the lack of cognitive demands during scanning, rs-fcMRI makes these networks identifiable in populations who may find task demands too challenging (e.g., children, clinical patients, and older adults) (Power et al. 2010; Uddin et al. 2010; Vanderwal et al. 2013).

Rs-fcMRI has been successful in characterizing mature hippocampal memory networks in adults. Vincent et al. (2006) evaluated voxelwise whole-brain hippocampal connectivity using an anterior hippocampal seed to identify parietal regions uniquely connected to the hippocampal memory network and the visuo-spatial integration network and documented, across four independent datasets (total N=47), a hippocampal network including medial prefrontal, posterior cingulate, and bilateral posterior parietal cortices. Others have also supported these findings and further identified hippocampal connectivity with the cerebellum, temporopolar cortex, lateral temporal cortex, striatum, anterior cingulate, angular gyrus, precentral gyrus, middle prefrontal gyrus, and superior frontal gyrus (Poppenk & Moscovitch, 2011; Uddin et al. 2010; Witte et al. 2014; Zhou et al. 2008). Critically, on-going age-related changes in hippocampal network connectivity has been associated with individual differences in memory ability in aging adults (Salami et al. 2014). Finally, there is evidence from adults that anterior and posterior segments of

the hippocampus show differential functional connectivity throughout the cortex (Poppenk & Moscovitch, 2011). Despite our knowledge of hippocampal connectivity in adults, little is known about the developmental changes that occur to reach this "mature" state.

Although no study to date has examined the hippocampal resting-state network in children, previous research has used rs-fcMRI to analyze other network architectures during childhood. Pediatric investigations of resting-state connectivity have recently been used to predict performance differences on behavioral tasks (Barber et al. 2013; Langeslag et al. 2013; Zhong et al. 2014), identify aberrant connectivity between patient populations (Alexander-Bloch et al. 2010; Lynch et al. 2013; Yu-Feng et al. 2007), determine general principles of network development (Fair et al. 2009; Supekar et al. 2009), and elucidate age-related differences in connectivity from subcortical regions (i.e., amgdala, Gabard-Durnam et al. 2014).

These studies highlight the usefulness of rs-fcMRI as a technique to examine functional development of structures, such as the hippocampus, where large gaps remain in our understanding. First, there is minimal research characterizing hippocampal networks in pediatric populations, leaving it unknown whether the network is similar or different than the adult network. Second, no study to date has investigated the early development of these hippocampal networks, especially during early to middle childhood (4-8 years). In fact, few resting-state studies (e.g., de Bie et al. 2012; Gabard-Durnam et al. 2014; Smyser et al. 2010) have examined network properties in awake, non-sedated children under 7 years (for review of resting-state studies in sleeping children, see (Graham et al. 2015). These are significant gaps in the literature given known changes in hippocampal structure (e.g., DeMaster et al., 2014), the rapid development of hippocampally-mediated behaviors during childhood (Bauer & Fivush, 2013; Riggins, 2014; Sluzenski et al. 2006), and evidence of ongoing processes of neural

reorganization throughout adolescence and adulthood (Fair et al. 2009; Supekar et al. 2009; Purves & Lichtman, 1985) that has been proposed to influence episodic memory during childhood (Riggins, Geng, Blankenship, & Redcay, 2016; Riggins, Blankenship, Mulligan, Rice, & Redcay, 2015). Failure to understand the normal developmental trajectory of the hippocampus and its connections limits our ability to understand the mechanisms driving individual differences and age-related improvements in hippocampally-mediated cognitive and affective capacities and disorders.

The current investigation examined whole-brain seed-based hippocampal connectivity in a sample of 97 4- to 10-year-old children. We sought to identify regions demonstrating stable connectivity profiles (i.e., age-constant connectivity) as well as age-related differences in connectivity. Lastly, given evidence of functional and structural distinctions along the longitudinal axis (i.e., anterior and posterior regions in humans, ventral and dorsal segments in rodents) (DeMaster et al. 2014; Evensmoen et al. 2013; Fanselow & Dong, 2010; Kahn et al. 2008; Poppenk et al. 2013; Poppenk & Moscovitch, 2011; Strange et al. 2014; Zeidman et al. 2014), we also investigated unique connectivity of anterior and posterior regions of the hippocampus.

2. Methods

2.1 Participants

Participants in the current study were drawn from three investigations of functional and structural brain development during childhood (ages 4 to 10 years). Inclusionary criteria were as follows: no MR contraindications and no history of developmental disorders or previous brain injury. All studies were approved by the University of Maryland Institutional Review Board. Parents provided informed consent and children over 7 years provided written assent to

participate. Participants included in the present report were selected from a larger sample
(N=187) based on: no movement exceeding 3 mm or degrees from the previous volume, no
reports of sleeping during the functional scan, >5 minutes of usable scan data after censoring (see
below), and no gross structural abnormalities. If an individual participated in more than one
study, the scan with the least amount of motion was included (n=5). When motion was
comparable, scans occurring at under-represented ages were included (n=1). As seen in Figure 1,
this resulted in a sample of 97 children (M=6.68 years, SD=1.42, range=4.02-10.81 years; 58.8%
female; 48.5% White, 23.7% African American/Black, 12.4% Multi-Racial, 3.1% Other, and
12.4% did not report; 11.3% identified as Hispanic/Latino with 14.4% choosing not to disclose;
total household income ranged from <$20,000 - >$100,000 per year). Three participants included
in the final sample were born premature at 27, 33, and 36 weeks[1]. Handedness data were
available for 93 individuals, only 13 of which reported being left-handed[2]. Participants in one
contributing study (n=43) were recruited for an investigation of the effects of maternal
depression on childhood development; of the 43 children, 27 were offspring of depressed
parents[3]. Because history of parental depression was not screened for and thus not able to be
controlled for in the other contributing studies, these participants were included in the present
analyses.

[Figure 1]

2.2 Data Acquisition

All participants completed a 30-60 minute mock scanner training immediately before MR
data acquisition in order to become acclimated to the scanner environment and receive motion

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[1] There were no significant differences in results when premature participants were excluded.
[2] There were no significant differences in results when left-handed participants were excluded.
[3] There were no significant differences in results when offspring of depressed parents were excluded.

feedback. Participants were scanned in a Siemens 3.0-T scanner (MAGNETOM Trio Tim

System, Siemens Medical Solutions, Erlangen, Germany) using a 12-channel coil. Before

resting-state data collection, participants watched approximately 2-10 minutes of an animated

film of their choice or a slideshow of still color photographs of animals in order to minimize any

potential anxiety during scan set-up. All participants completed a 6-minute resting-state scan

where they viewed the same video of abstract shapes (similar to a screen saver). In adults, this

method does not elicit significant differences in hippocampal connectivity in comparison to a

standard fixation resting-state scan, providing preliminary evidence that a non-canonical resting-

state scan may be used to tap the hippocampal network without eliciting significantly altered

connectivity (see Supplementary Material, Greicius et al., 2003; Riggins et al., 2016; Vanderwal,

Kelly, Eilbott, Mayes, & Castellanos, 2015). Functional data were collected with the following

scan parameters: 180 EPI volumes consisting of 36 oblique interleaved slices with a 3.0 x 3.0 x

3.0 mm voxel size; 2s TR; 24ms TE; 3mm slice thickness; 90° flip angle; 64x64 pixel matrix.

Structural data were collected using a high-resolution T1 magnetization-prepared rapid gradient-

echo (MPRAGE) sequence consisting of 176 contiguous sagittal slices ($1.0 \times 1.0 \times 1.0$ mm

voxel dimensions; 1900 ms TR; 2.52ms TE; 900ms inversion time; 9° flip angle; pixel matrix=

256 x 256).

2.3 Pre-processing

Functional data were slice time corrected in the Analysis of Functional Neuroimages

(AFNI) software package (Cox, 1996), aligned to the first volume using rigid-body motion

correction using Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/),

coregistered with the skull-stripped anatomical (SPM8; Wellcome Trust Centre for

Neuroimaging, London, UK), and bandpass filtered at $.009 < f < .08$. Timepoints where the

Euclidean distance of the derivative from the 6 motion parameters exceeded 1mm were excluded, along with the previous volume, using censor files. Given convention that resting-state networks can be identified with 5 minutes of useable resting data (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), participants who had less than 5 minutes of useable resting data (*n*=8) after censoring were excluded from analyses (*M*= 356.56 seconds, *SD* =6.85 seconds, 314 – 360 seconds; average number of volumes censored = 1.72). Nuisance regression included 18 regressors: 5 CSF and WM timeseries (left/right lateral ventricle, left/right hemisphere white matter, corpus callosum)[4], 6 motion parameters and their 6 temporal derivatives, as well as baseline, linear, quadratic, and cubic drift. Average hippocampal timeseries were extracted from the nuisance-regressed and filtered data in native space (see below). Data were normalized with a nonlinear transformation algorithm (ANTs) to a 4.5-8.5 year-old symmetrical MNI Child Template (Fonov et al. 2011), selected to minimize age-related differences in image registration, then smoothed using a 6mm Gaussian kernel within a whole-brain mask. Whole brain connectivity analyses were run using 3dDeconvolve. The resulting R^2 values were converted to Pearson's r and then to z-scores using a Fisher's r-to-z transformation. Individual subjects' z-scored connectivity maps were entered into the group analysis. To control for multiple comparisons, we generated 10,000 Monte Carlo simulations using AFNI's 3dClustSim with an uncorrected voxel-wise threshold of p=.001, resulting in cluster extent k>25 for $p_{corrected}$<.05.

2.4 Mask generation

To ensure precise extraction of hippocampal and nuisance timeseries, individual native-space masks were generated from each participant's T1-weighted anatomical scan using an

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[4] Two individuals' lateral ventricles were too small to reliably include as a mask. For these two individuals, nuisance regression was completed without lateral ventricle timeseries.

automatic segmentation procedure in Freesurfer (surfer.nmr.mgh.harvard.edu). Resulting

segmentations were visually inspected[5], aligned with the structural and functional data,

resampled to functional resolution, and converted to binary masks. Only resampled voxels which

resulted in 100%, 80%, 90%, or 50% inclusion were retained in final masks for bilateral white

matter, bilateral lateral ventricles, bilateral hippocampi, and corpus callosum, respectively. Each

subject's bilateral hippocampal mask was split into anterior and posterior segments by

identifying the last coronal slice that the uncal apex was visible, a standard anatomical landmark

(Poppenk & Moscovitch, 2011; Weiss et al. 2005). Final masks were visually inspected to ensure

anatomical precision.

2.5 Motion

Motion has been shown to have significant deleterious effects on resting-state analyses

(Power et al. 2012; Power et al. 2015; Power et al. 2014; Satterthwaite et al. 2012; Van Dijk et

al. 2012). To mitigate any potential effects of motion on our results, we took a number of

precautions. (1) Only participants who showed no more than 1 voxel (3mm) of framewise

movement throughout the entire scan were included. (2) Volumes demonstrating >1mm of

framewise movement were censored in addition to the previous volume. (3) Similar to the

approach reported by Gabard-Durnam et al. (2014) and suggested by Van Dijk et al. (2012) and

Power et al., (2012), mean absolute framewise displacement (FD), calculated as the mean

Euclidean distance between successive volumes: $d_i = $

$\sqrt{(x_{i+1} - x_i)^2 + (y_{i+1} - y_i)^2 + (z_{i+1} - z_i)^2 + (\alpha_{i+1} - \alpha_i)^2 + (\beta_{i+1} - \beta_i)^2 + (\gamma_{i+1} - \gamma_i)^2}$ was

calculated for each individual and included in all analyses as a covariate. (4) To ensure that

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[5] In the case of obvious under- or over- inclusions, Freesurfer hippocampal segmentations were manually
edited ($n=8$)

differences in movement did not account for our observed age-related effects, we demonstrated

that age (in months) did not significantly correlate with mean FD (r=-0.096, *p*=.348), number of

censored timepoints (r=-0.035, *p*=.733), or maximum framewise displacement (r=-0.030,

p=0.773) (Figure 2).

Despite stringent motion inclusion criteria for such a young, movement-prone sample,

our motion inclusion criteria are liberal by standards in the adult literature. Therefore, to identify

regions which may have a greater likelihood of displaying false-positives in our primary

analyses, we performed follow-up *t*-tests assessing differences in anterior, posterior, and whole

hippocampal connectivity between median-split high and low motion groups (low motion:

M=0.09, *SD*=0.02, range=0.05-0.13; high motion: *M*=0.18, *SD*=0.06, range=0.13-0.40;

Supplementary Tables 5-8). The output of these analyses was assessed for overlap with all

significant regions reported below.

[Figure 2]

2.6 Age controlled analysis

In order to identify regions of hippocampal connectivity that were relatively stable

throughout the age range being investigated, we ran an ANCOVA controlling for mean absolute

displacement and age (in months), testing against 0, using the 3dttest++ function in AFNI.

2.7 Age dependent analysis

To identify regions where hippocampal connectivity differed linearly with age, we ran an

ANCOVA using the AFNI function 3dttest++ with age (in months) as the predictor, controlling

for mean absolute displacement. Age was significantly correlated with whole bilateral

hippocampal connectivity with global signal (r=0.223, p=0.028), but not white matter (r=-0.056,

p=0.584) or CSF (r=0.041, p=0.695) (Figure 3). Mean FD was not significantly correlated with

whole bilateral hippocampal connectivity with global signal (r=0.101, p=0.326), white matter

(r=0.018, p=0.858) or CSF (r=-0.105, p=0.311) (Figure 3). Together, this suggests that observed

age-related differences in hippocampal connectivity may be driven by meaningful (i.e., non-

nuisance) changes in global brain activity. One possibility is that age-related increases in

hippocampal-global signal connectivity may reflect ongoing changes in the hippocampus'

integration with large-scale brain networks. To explore this possibility and determine how age-

related changes in hippocampal connectivity may be associated with developmental changes in

the involvement of the hippocampus in global brain networks, separate exploratory whole-brain

connectivity analyses were conducted with regions of age-related increases in hippocampal

connectivity as seed regions of interest.

[Figure 3]

2.8 Hippocampal subregion analysis

Given evidence that the hippocampus is a functionally heterogeneous structure (Poppenk

et al. 2013; Poppenk & Moscovitch, 2011; Strange et al. 2014), and evidence that subregions

show developmental change with age (DeMaster et al. 2013; DeMaster et al., 2014; Gogtay et al.

2006), we supplemented our bilateral whole hippocampal seed analyses with age-dependent and

age-controlled analyses of anterior and posterior hippocampal connectivity, as described above

(2.6, 2.7). We employed two complimentary methods to qualitatively and quantitatively assess

patterns of anterior and posterior hippocampal connectivity (see Gabard-Durnam et al. 2014 for a

similar approach). The first approach, a masking technique, was employed to highlight regions

qualitatively that differed in connectivity between anterior and posterior subregions in the

primary analyses described above (2.6, 2.7). This method was conducted by masking the

thresholded (at $p<10^{-15}$ for age-controlled, and $p<.05$ for age-dependent) results of the analyses

of separate anterior and posterior connectivity. Regions of map overlap (i.e., regions of

connectivity with anterior and posterior connectivity) were removed to highlight regions of

overlapping or unique anterior and posterior connectivity. The second approach employed a

paired-samples *t*-test that tested for regions of statistically different anterior versus posterior

connectivity. Together these methods provide complementary indices of regionally-specific

hippocampal connectivity: the masking method provides a qualitative summary of regions with

statistically significant anterior or posterior connectivity without making claims regarding

whether or not a region is more highly connected to one subregion or the other whereas the

statistical approach provides a direct quantitative comparison to test for regions with statistically

different anterior versus posterior connectivity.

3. Results

Age-controlled analyses for whole hippocampus, anterior, and posterior regions, are

presented first, followed by age-dependent analyses.

3.1 Age-controlled analyses

3.1.1 Whole bilateral hippocampus

At a cluster-corrected threshold of $p_{corrected} < .05$, most cortical gray matter was positively

correlated with the hippocampal seed, with highest correlations occurring in bilateral hippocampi

(k=59,737). To explore these results in greater depth, the voxel-wise threshold was reduced until

regions of the largest cluster segregated into distinct regions (to $p < 10^{-15}$), which largely

resembled the hippocampal-parietal memory network identified in adults at rest by Vincent et al,

(2006). This hippocampal network included, but was not limited to (see Table 1 for entire list of

included regions), regions of medial prefrontal cortex (mPFC) extending caudally through the

cingulate cortex, angular gyrus extending anteriorly into supramarginal gyrus and through the

temporal pole, the precuneus, and left dorsolateral prefrontal cortex (Figure 4). Additional

regions include bilateral precentral gyrus, midline subcortical structures, bilateral cerebellum,

bilateral insula, and bilateral orbital cortex. There were no regions of significant negative

hippocampal connectivity.

[Figure 4]

3.1.2 Anterior bilateral hippocampus

At the reduced voxelwise threshold ($p<10^{-15}$) an anterior hippocampal network emerged,

similar to previous reports in adults (e.g., Poppenk & Moscovitch, 2011; Vincent et al. 2006) and

the whole hippocampal seed described above, including mPFC, bilateral angular gyri, precuneus,

anterior and posterior cingulate, bilateral orbital cortex, bilateral temporal poles, midline

subcortical structures, and cerebellum. (Table 2; Figure 4). No clusters of anterior connectivity

(k>10) were absent from the whole hippocampal map, suggesting that regions of whole

hippocampal seed connectivity may be largely driven by anterior subfields. No regions

demonstrated significant negative connectivity.

3.1.3 Posterior bilateral hippocampus

At the reduced voxelwise threshold, regions demonstrating age-controlled connectivity

with the posterior hippocampus included: cingulate cortex, bilateral precentral gyri, angular

gyrus extending into supramarginal gyrus, and down through the temporal pole, and cuneus

(Table 3; Figure 4), all regions previously reported in adults (Poppenk et al. 2013; Poppenk &

Moscovitch, 2011). The posterior hippocampus demonstrated connectivity that was not present

in analyses with the whole hippocampal seed, including connectivity with bilateral lingual gyrus,

a large cluster centered in the left inferior parietal lobe and extending into the superior and

middle temporal gyri, bilateral precuneus and superior cuneus, right cerebellum, and isolated

regions of anterior and mid-cingulate. There were no regions of significant negative connectivity.

3.1.4 Unique age-controlled connectivity between anterior and posterior seeds

Whereas most regions of age-controlled connectivity overlapped between the anterior and

posterior seeds, a number of regions showed unique connectivity with each subregion (Figure

3B). As described above, two methods were used to characterize regions of unique anterior

versus posterior connectivity. Using the masking approach, regions of unique anterior

hippocampal connectivity included: ventromedial prefrontal cortex, medial prefrontal cortex,

bilateral orbital cortex, left dorsolateral prefrontal cortex, a large cluster extending from inferior

temporal gyrus through fusiform gyrus and down through the temporal pole, posterior cingulate,

a region of precuneus, (Figure 4). Regions of unique posterior hippocampal connectivity

included a large posterior region extending from precuneus through cuneus, lingual gyrus, and

down through the cerebellum, a large temporoparietal region extending from through left inferior

parietal lobule, angular gyrus, and supramarginal gyrus down through superior and middle

temporal gyri, right middle temporal gyrus, isolated regions of anterior, middle, and posterior

cingulate cortex, bilateral regions of superior insular cortex, and regions of cerebellum (Table 4;

Figure 4).

Statistically comparing patterns of anterior and posterior connectivity revealed more

localized effects than the masking approach. Regions demonstrating statistically significant

greater anterior (versus posterior) connectivity included bilateral anterior hippocampus extending

rostrally to the amygdala and laterally through anterior middle temporal gyrus and fusiform

gyrus, ventromedial prefrontal cortex, posterior cingulate cortex, bilateral paracentral lobule,

bilateral precentral gyrus, and right orbitofrontal cortex (Table 5; Figure 4). Regions

demonstrating statistically significant greater posterior (versus anterior) connectivity included:

bilateral inferior parietal lobule extending laterally to supramarginal gyrus and angular gyrus;

precuneus extending into cuneus, lingual gyrus, and cerebellum; bilateral insular cortex

extending into bilateral putamen and thalamus; anterior and middle cingulate cortex; bilateral

straight gyrus; bilateral dorsolateral prefrontal cortex; and left caudate (Figure 4).

3.2 Age-dependent analyses

3.2.1 Whole bilateral hippocampus

The bilateral whole hippocampal seed showed significant age-related increases in

connectivity with bilateral temporal cortex and right piriform area (Figure 5A; Table 6). No

regions demonstrated significant age-related decreases in connectivity. Regions of age-dependent

connectivity with the whole hippocampal seed reflect the intersection of age-dependent

connectivity in anterior and posterior seeds; therefore, follow-up investigation of the whole-brain

connectivity of these seeds is included below.

[Figure 4]

3.2.2 Anterior bilateral hippocampus

Similar to results of whole hippocampal connectivity, the anterior hippocampal seed only

demonstrated age-related increases in connectivity, in regions isolated to left temporal lobe and

right piriform cortex (Figure 5A; Table 7). Separate exploratory whole-brain connectivity

analyses were conducted with regions of age-related increases in anterior hippocampal

connectivity as seeds. Results indicated that the region of left superior temporal gyrus is part of

the somatomotor network (Yeo et al., 2011; Supplementary Figure 2B); the regions of left

middle temporal and the right piriform cortex did not clearly belong to any full network at a

threshold of $p<10^{-15}$, but displayed some connectivity with regions associated with the default mode network (Raichle, 2015; Supplementary Figure 2A and C, respectively).

3.2.3 Posterior bilateral hippocampus

The posterior hippocampal seed showed age-related increases in connectivity with left angular gyrus at the temporoparietal junction, right middle temporal gyrus, and left anterior cingulate cortex (Figure 5A; Table 8). Separate exploratory connectivity analyses were run for each of these regions to determine brain networks with which they may be associated. All three of these regions demonstrated clear connectivity with the entire extent of the default mode network, but with greatest connectivity with regions adjacent to the seeds. That is, the left angular gyrus demonstrated greatest connectivity to DMN parietal regions (Supplementary Figure 3A), the right middle temporal gyrus seed demonstrated greatest connectivity to DMN temporal regions (Supplementary Figure 3B, and the anterior cingulate region demonstrated greatest connectivity to frontal regions (Supplementary Figure 3C).

3.2.4 Unique age-related differences in connectivity between anterior and posterior seeds

The masking approach revealed no intersecting regions of age-related anterior or posterior hippocampal connectivity. However, there were also no regions of statistically significant age-related differences in connectivity between anterior and posterior subregions. Closer inspection of these results reveals that this apparent contradiction in results is due to similar age-related increases in connectivity with both anterior and posterior segments, with this age-related association only reaching statistical significance for one subregion in the individual statistical tests (i.e., 3.2.2 & 3.2.3). Taken together, these results indicate considerable

anterior/posterior overlap in age-related connectivity (see section 4.1.1 for discussion of the interpretation of overlapping connectivity).

3.2.5 High versus low motion groups

There were no regions of age-dependent hippocampal connectivity that differed between participants in the high versus low motion groups. Similarly, no regions of age-controlled anterior, whole, or anterior versus posterior connectivity overlapped (k>15) with regions differing in hippocampal connectivity between participants in the high versus low motion groups (Supplementary Tables 5-7). However, there were regions of posterior connectivity that differed between participants in the high and low motion groups that overlapped with the age-controlled posterior hippocampal connectivity map (see Section 3.2.3). Regions of overlap included: a large region centered in the left thalamus extending laterally into the surrounding white matter and inferiorly to the subhippocampal white matter, a region of white matter superior to the left hippocampus, a region at the junction of the left fusiform gyrus and the cerebellum, a medial region of the right posterior hippocampus, the right thalamus, and the pons (Supplementary Figure 4). Age-controlled posterior connectivity in these regions should be interpreted with caution as they may have a particularly high susceptibility to Type I errors induced by participant motion.

4. Discussion

The present study investigated developmental changes in hippocampal resting-state networks during early to middle childhood (4 to 10 years). Results revealed that the hippocampus is a highly connected subcortical structure, showing connectivity with diffuse cortical and subcortical regions. Despite widespread connectivity during childhood, age-related increases in the magnitude of connectivity were evident in a number of regions. Moreover,

overlapping and unique profiles of connectivity were evident between anterior and posterior segments of the hippocampus, providing converging evidence of functional distinctions along the longitudinal axis. These findings provide some of the first measures of the development of hippocampal functional networks in childhood. The maturation of hippocampal connectivity may signal developmental changes in the efficiency or specificity of neural processing within hippocampal networks and may influence behavioral changes throughout childhood.

4.1. Age-Controlled Analyses

Age-controlled analyses, at a conservative threshold, demonstrated a hippocampal network consistent with resting-state findings in adults, including regions of the medial prefrontal cortex, cingulate cortex, and lateral parietal cortex. This pattern of results suggests that the functional connections between the hippocampus and distributed cortical and subcortical regions are apparent early in development (i.e., at least by 4 years of age). Connectivity with the whole hippocampal seed appeared to be an additive map composed of signals generated from anterior and posterior segments. Specifically, using a masking approach, the anterior hippocampus accounted for the observed whole hippocampal connectivity with mPFC and anterolateral middle temporal gyrus, whereas posterior hippocampus accounted for the observed connectivity with the more posterior portions of the middle temporal gyrus extending through the supramarginal and angular gyri.

These effects differed in the statistical approach, which indicated that although significant connectivity may exist, neither anterior nor posterior connectivity was significantly more connected to the most posterior portions of the middle temporal gyrus through the angular gyrus. This may be attributed to high correlation between anterior and posterior timeseries and/or the current method for selecting statistical thresholds in the masking technique. In fact, the statistical

approach suggested much more localized regions of anterior versus posterior connectivity, with anterior hippocampus projecting to medial prefrontal cortex and anterior middle temporal lobes, and the posterior hippocampus projecting to middle cingulate, bilateral insular cortex, cuneus, and inferior parietal lobule. These results are largely consistent with previous reports of the anterior hippocampus projecting to more anterior regions (e.g., mPFC) and posterior hippocampus projecting to cingulate cortex and parietal regions (Poppenk et al. 2013). However, despite these consistencies, the present investigation provides new evidence that during development the anterior hippocampus demonstrates connectivity with posterior cingulate. This finding may suggest more diffuse or less segregated patterns of connectivity during childhood – an established developmental pattern (e.g., Durston et al., 2006, Fair et al., 2009, Supekar, Musen, & Menon, 2009), which has been previously undocumented in the hippocampal network due to the limited research on this network in children.

4.1.1. Overlapping Connectivity

Despite the fact that functional specificity is known to exist along the longitudinal axis of the hippocampus (Poppenk et al. 2013), significant overlapping anterior and posterior connectivity was observed in age-controlled analyses in regions not previously reported as overlapping in adults. It is plausible that, in childhood, anterior and posterior regions are functionally connected to overlapping regions of cortex, as similar overlap in subregion connectivity has been demonstrated in the developing amygdala (Gabard-Durnam et al. 2014) and the adult hippocampus (Poppenk et al. 2013). In contrast, it is also possible that central portions of the hippocampus (i.e., body) may be poorly intrinsically segregated, as has been suggested by proposals by Poppenk (2013) and Moser and Moser (1998), resulting in functional

gradations and overlapping connectivity driven by our methodological choice of anterior/posterior seeds. Future research would be needed to decipher between these possibilities.

4.2. Age-Dependent Analyses

Although widespread hippocampal connectivity appears to be present by age 4, the strength of some connections increased in older children. Because the results using a whole hippocampal seed mirrored the unique connectivity of anterior and posterior segments, for the sake of brevity, we will focus our discussion on the results of anterior and posterior seeds.

All regions demonstrating age-related increases in hippocampal connectivity have been previously linked to cognitive processes involving the hippocampus. For example, many temporal lobe regions have been identified as relay stations that project multimodal cortical inputs to the hippocampus for rich memory encoding (Lavenex & Amaral, 2000). Additionally, the strength of posterior hippocampal connectivity with the right middle temporal gyrus is associated with episodic memory performance during early childhood (4-6 years) (Riggins et al., 2016). Increasing hippocampal connectivity in more posterior regions, including the temporoparietal junction, may reflect ongoing age-related improvements in a number of cognitive processes that are supported by both of these regions, such as: autobiographical memory retrieval, prospection, navigation, and theory of mind (Maguire & Frith, 2003; Spreng, Mar, and Kim, 2009; Svoboda, McKinnon, and Levin, 2006). The piriform cortex and the peri-amygdaloid areas have known reciprocal connections with the ventral hippocampus in rodents (anterior hippocampus, in humans) (Eichenbaum, Schoenbaum, Young, and Bunsey, 1996) and have been implicated in the cognitive aspects of olfactory perception and odor memory (Bensafi, 2012). The emergence of olfactory memory is established very early in life, with the majority of adult odor-cued memories generated from the childhood years (<10 years) (for review, see

Larrson & Willander, 2009 and Mouly & Sullivan, 2010). Thus, the observed age-related

increases in hippocampal-piriform connectivity may be linked to the importance of olfactory

cues in autobiographical memory formation during childhood (Chu & Downes, 2000) versus

adulthood (see Supplementary Material). As a proposed site of long-term memory storage (Ross

& Eichenbaum, 2006), the observed increase in anterior cingulate-hippocampal connectivity may

play an important role in developmental improvements in long-term memory encoding,

consolidation, and storage (Poppenk & Moscovitch, 2011; Ross & Eichenbaum, 2006) and may

provide insight into the neural basis of well-documented changes in long-term memory

performance during middle childhood (Ghetti & Bunge, 2012).

Follow-up connectivity analyses revealed which large-scale brain networks the regions of

age-dependent connectivity belonged. Both anterior and posterior seeds were connected to the

default mode network, with only the region of anterior connectivity to the left superior temporal

gyrus being linked to the somatomotor network. Hippocampal involvement in the default mode

network is contentious, with some studies reporting inclusion (James, Tripathi, Ojemann, Gross,

& Drane, 2013; Kaplan et al., 2016) and others reporting only the surrounding parahippocampal

cortex as part of the network (Fair et al., 2008; Uddin, Kelly, Biswal, Castellanos, & Milham,

2009; Ward, Schultz, Huijbers, Van Dijk, Hedden, & Sperling, 2014). The present results

suggest that the hippocampus may be becoming increasingly connected to regions of the default

mode network during childhood. Interestingly, regions of increased posterior hippocampal

connectivity demonstrated more robust inclusion in the default mode network in comparison to

regions of increased anterior hippocampal connectivity, a trend which has been documented in

adults (Kim, 2015). It is possible that the posterior hippocampus becomes more functionally

integrated with the default mode network earlier than the anterior subregion. To the best of our

knowledge, this is the first evidence to suggest hippocampal connectivity with the somatomotor network; studies in adults suggest the hippocampus, and medial temporal lobe more generally, operate in isolation of this network (e.g., Kaplan, 2016; Hayes, 2012). The possibility of developmental changes in and relevance of hippocampal connectivity with these networks should be addressed by future research.

Due to a predominance of research investigating the memory functions of the hippocampus, less is known about how age-related increases in hippocampal connectivity may support the maturation of other known or suggested hippocampally-mediated behaviors (e.g., theory of mind; Spreng, Mar, & Kim, 2009) or the functionality of the default mode and somatomotor networks. Future investigations are necessary for systematic identification of the behavioral relevance of the ongoing functional integration of the hippocampus with these distributed regions and broader large-scale networks.

Interestingly, not all regions of age-dependent increase in connectivity were evident in the age-controlled analyses. Specifically, the anterior hippocampus did not demonstrate connectivity with the right piriform cortex or the left middle temporal gyrus in either age-controlled analysis, suggesting these functional connections may emerge during the studied age range. In contrast, all regions of posterior hippocampal connectivity were evident in at least one of the age-controlled analysis, suggesting these connections may exist early in life and increase in strength with age. Together, these differing patterns of results from age-controlled to age-dependent analyses reveal the possible emergence and refinement of both anterior and posterior functional connections during childhood.

4.3. Lack of Negative Associations

The current investigation found no evidence of significant negative hippocampal connectivity or decreasing connectivity with age. Previous studies that demonstrate age-constant or age-related decreases in connectivity have used a global signal regressor (Barber et al. 2013; Fair et al. 2009; Gabard-Durnam et al. 2014; Kelly et al. 2009) or had less stringent motion control (Fair et al. 2009; Gabard-Durnam et al. 2014; Power et al. 2015; Supekar et al. 2009). The global signal regressor is, however, a contentious tool in resting-state analyses, with clear benefits to controlling for noise (Power et al. 2015), but also widely acknowledged to induce difficult-to-interpret negative correlations (Murphy et al. 2009) and evidence that removal of the global signal eliminates meaningful functional connections (Schölvinck et al. 2010). Additionally, it is possible that there are no developmental decreases in connectivity during the narrow age-range in the current study (4-10 years) or decreases may be more variable and therefore not easily measured in terms of age-related differences.

4.4. Limitations and Future Directions

Despite strengths in examining hippocampal connectivity in a young, unexplored age range using whole and segmented hippocampal seeds, the present investigation had several limitations. First, the present investigation used a resting-state scan in which children passively viewed abstract shapes. This method was utilized as it was devoid of any overt task yet was engaging enough to minimize motion in the young sample (see Vanderwal et al., 2015 for similar approach). Previous studies have used a similar approach in order to obtain task-independent fMRI data in young children. For example, Emerson and Cantlon (2012) examined functional connectivity from scans during which children passively viewed an educational video on "letters, numbers, and other concepts". Critically, we report that a non-traditional low-level visual stimulation abstract shapes screen saver did not elicit significantly different hippocampal

network connectivity in comparison to a fixation in a sample of adults, providing preliminary

validation for this technique in collecting resting-state data from young children. Despite no

differences in the hippocampal connectivity between abstract versus fixation scans in adults, it is

possible that this methodological technique (as opposed to eyes open viewing fixation or eyes

closed) played a role in the present findings in children. For instance, increased attention during

video viewing may have elevated hippocampal network activity, resulting in the observed whole-

brain correlations or obscuring negative connectivity which may have been evident in a classic

resting-state paradigm (i.e., fixation). However, the abstract shapes are not enough to explain the

present results in light of the converging evidence of widespread connectivity found with the

amygdala using a standard fixation (Gabard-Durnam et al. 2014), overlap of our findings with

the existing rodent and adult neuroimaging literature on hippocampal networks, as well as, recent

and ongoing validation of non-traditional resting-state scans (e.g., Emerson & Cantlon, 2012;

Vanderwal et al., 2015).

Second, although the present investigation is the first of its kind to investigate

hippocampal network development in a large sample of young children (4-10 years), the final

sample includes many more children in younger age ranges (4-6 years, n=60) than older ages (7-

10 years, n=37). This is a consequence of data compilation across three studies, each designed to

examine unique research questions, but may obscure important age-related differences due to

low power in the older age groups. Future investigations with wider age ranges and longitudinal

designs would be beneficial to advance our current understanding of hippocampal networks.

Third, despite heeding methodological recommendations for ameliorating the effects of

motion in pediatric resting-state data (see Power et al. 2012, 2015; Power et al. 2014;

Satterthwaite et al. 2012; Van Dijk et al. 2012), it is possible motion contributed to the present

results. For instance, at standard statistical thresholds (i.e., voxelwise threshold $p<.005$, $p_{corrected}<.05$), age-controlled analyses revealed significant hippocampal connectivity with the whole brain, which may indicate inadequate control of nuisance signals induced by motion. At stricter thresholds, a hippocampal network reminiscent of that reported in adults (Vincent et al. 2006) emerged. The ability to test these effects was likely at least partially afforded by our large original sample ($N=187$) which enabled exclusion based on relatively conservative motion criteria while maintaining a large sample size ($n=97$). Ongoing consideration of the appropriate motion thresholds in pediatric neuroimaging is necessary.

Despite these limitations, the present study analyzed anterior, posterior, and whole hippocampal seeds which enabled the examination of regionally-specific developmental differences in hippocampal connectivity. Although the whole hippocampus seed was largely useful in tapping connectivity of its component parts, use of the whole hippocampal seed did obscure regions of unique age-related differences in connectivity. For instance, use of the whole hippocampal seed did not reveal age-related differences in connectivity with the left putamen, however age-related differences in connectivity with the left putamen were evident when using the anterior seed. Future investigations of hippocampal connectivity should keep the functional heterogeneity of the hippocampus in mind when determining whether whole or segmented regions are more appropriate for examining the process of interest.

Finally, and critically, it is necessary for future investigations to examine the cognitive, affective, and behavioral relevance of the observed maturation of hippocampal connections. Specifically, a developmental perspective may provide insight into on-going debates regarding the nature of the neural computations carried out by anterior and posterior hippocampi (for extended discussion, see Poppenk & Moscovitch, 2013).

4.5. Conclusion

In sum, the present study was the first to investigate functional hippocampal networks in a young pediatric population. Results revealed that even in childhood the hippocampus is a highly connected subcortical structure that demonstrates functional distinctions along the longitudinal axis. In addition, both stable and age-related differences in connectivity were apparent throughout early to late childhood. Demonstration of both age-dependent and age-controlled changes in hippocampal connectivity are relevant to ongoing investigations of hippocampally-mediated cognitions and behaviors in health and disease.

Acknowledgements

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Figure Legends

*Figure 1.* Age and gender distribution of final participant sample (*n*=97).

Figure 2. Motion parameters by age. Age (in years) plotted against mean FD, number of censored volumes, and maximum movement to illustrate correlations between age and motion were not a confound in the present analyses.

Figure 3. Correlations between whole bilateral hippocampal connectivity with nuisance signals (i.e., white matter, CSF, and global signal) as a function of age and mean framewise displacement.

Figure 4. Results of age-constant connectivity analyses. The first line of each panel depicts the results of the age-controlled analysis with the whole hippocampus. The second line of each panel depicts masks of unique and intersecting (green) regions of connectivity with anterior (blue) and posterior (yellow) hippocampal seeds thresholded at $p_{corrected}<10^{-15}$ (i.e., the results of the masking technique). The third row of each panel depicts the results of the quantitative anterior versus posterior analysis revealing regions of significantly greater anterior (blue) or posterior (yellow) connectivity thresholded at $p_{corrected}<.05$. Sagittal views are depicted from the left slicing towards the right; Coronal views are depicted with the left hemisphere on the left; Axial views provide an aerial view of the brain with left hemisphere depicted on the right.

Figure 5. Results of age-dependent connectivity analyses (A) compared with similar views from the age-controlled analysis (B). The first row of Panel A depicts regions of age-related

differences in connectivity with a whole bilateral hippocampal seed. The second row of Panel A

depicts masks of unique and intersecting regions of age-related connectivity with anterior and

posterior hippocampal seeds. Note: All thresholded at $p_{corrected}$<.05; Sagittal views are depicted

from the left slicing towards the right; Axial views are presented from an aerial perspective with

left hemisphere depicted on the right.
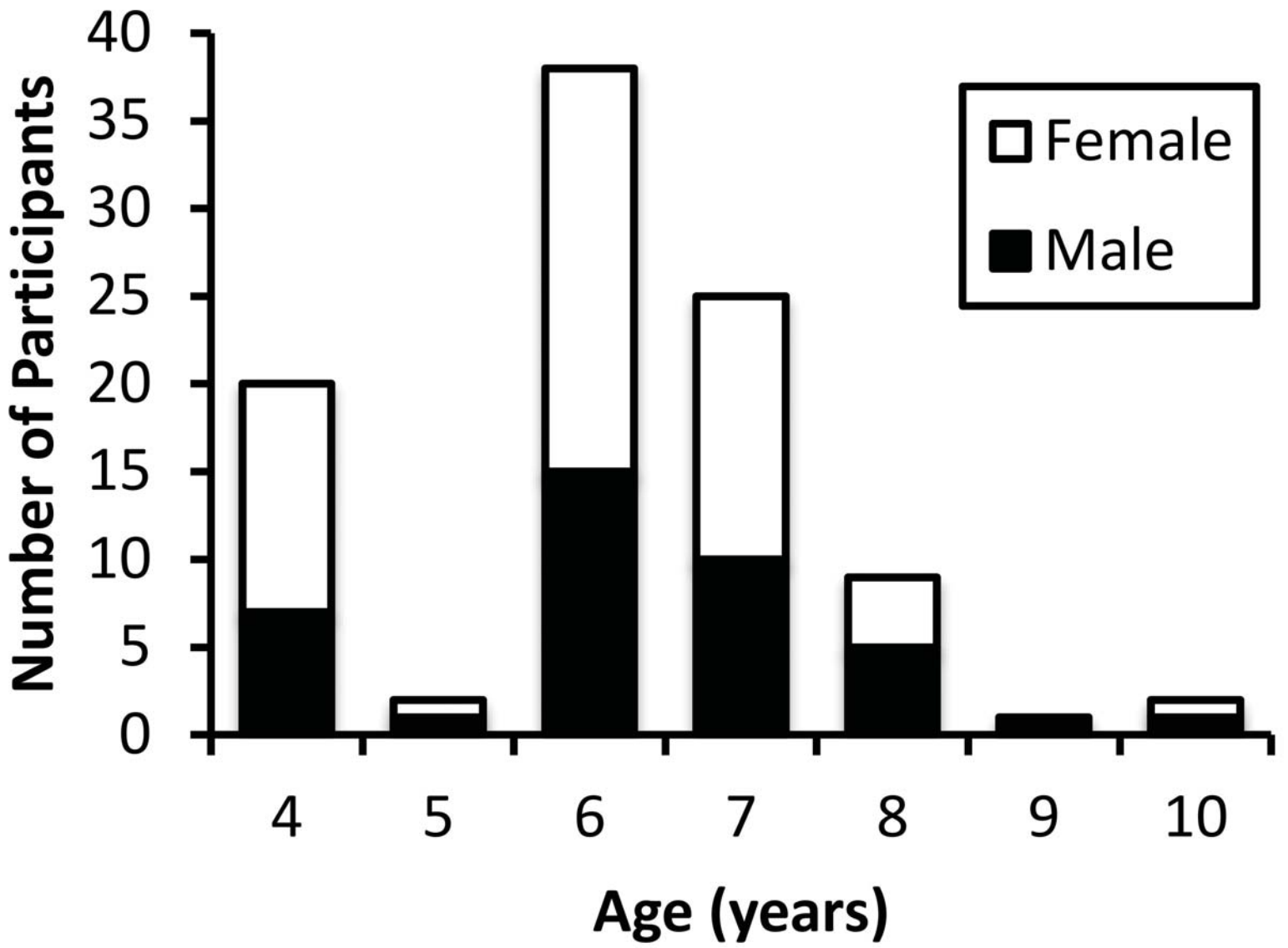
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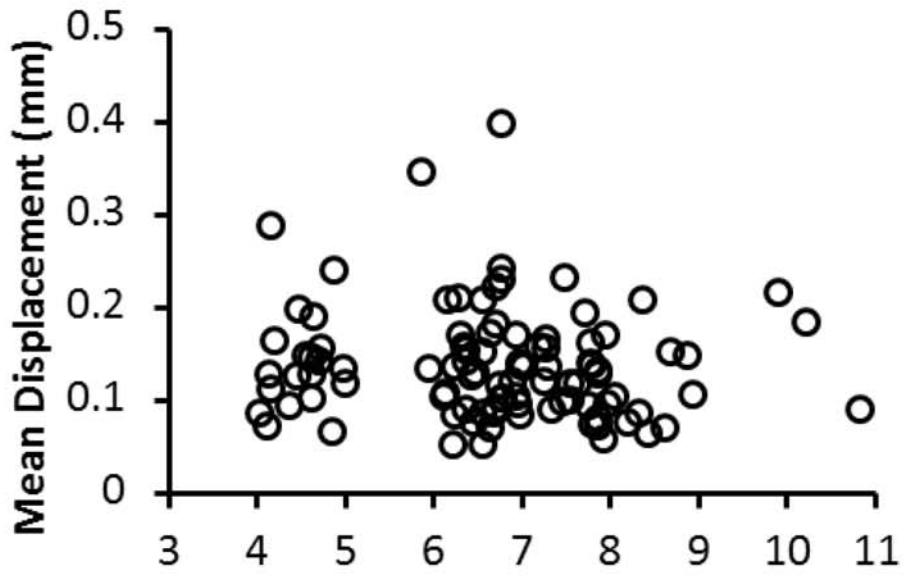
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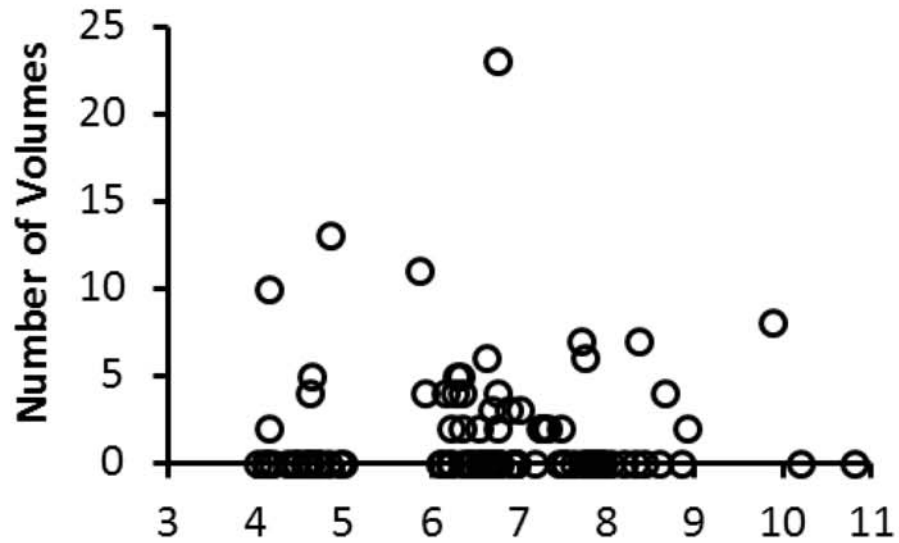
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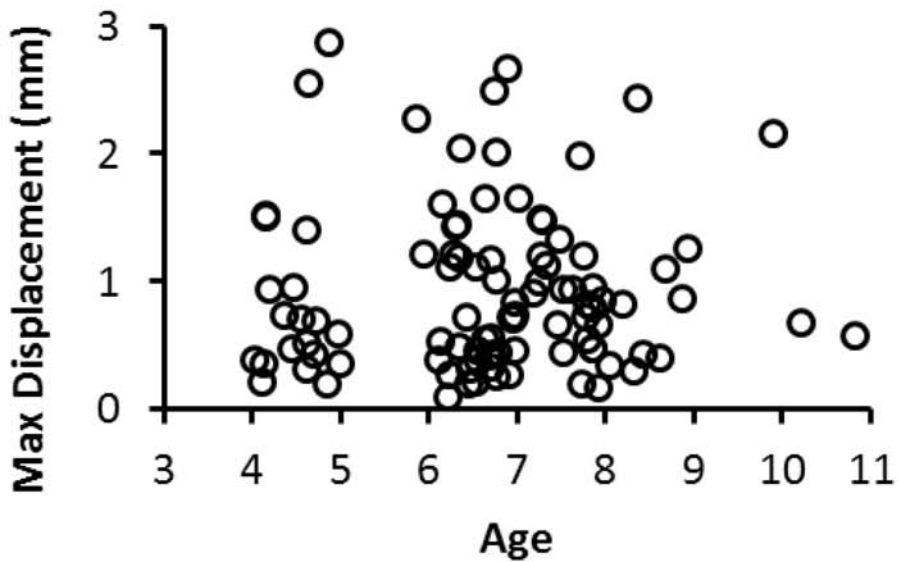
Whole Bilateral Hippocampal Connectivity x Age
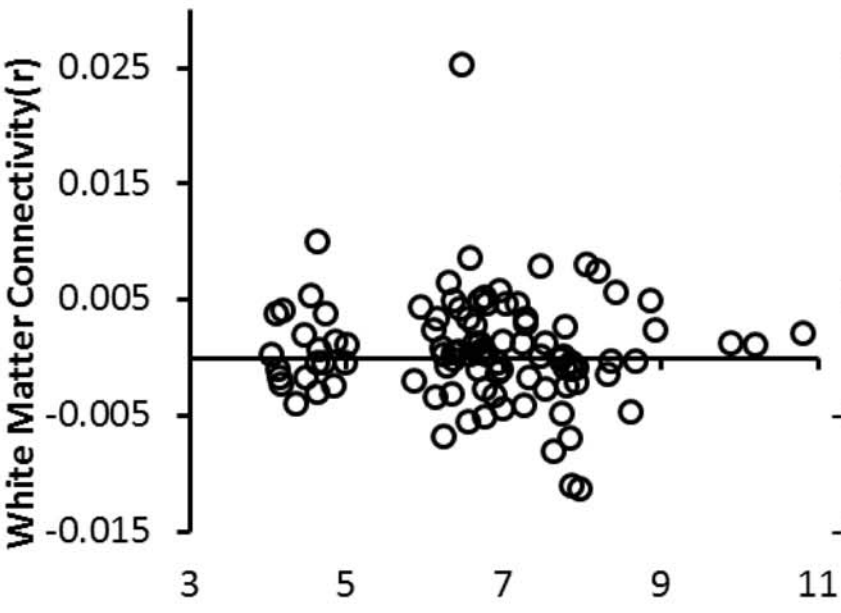
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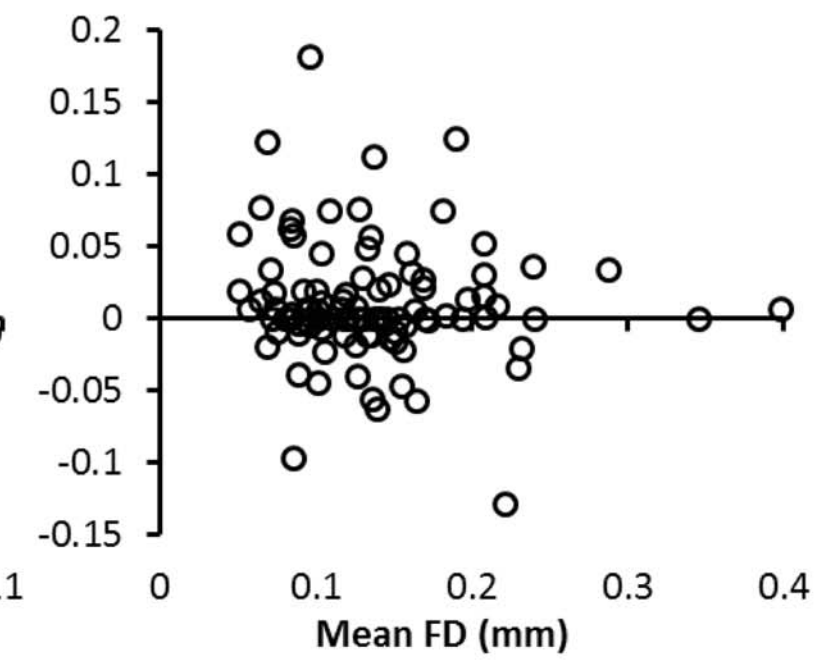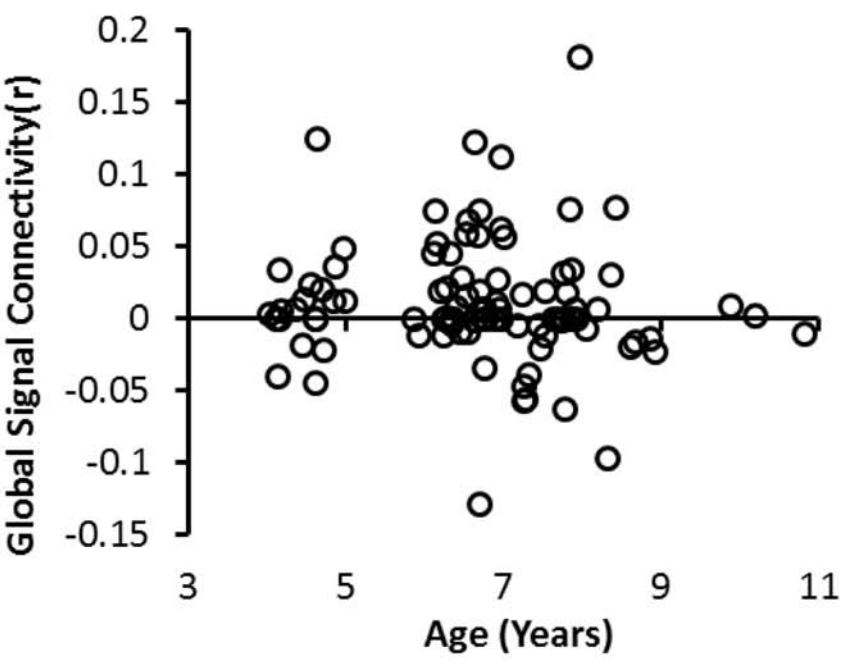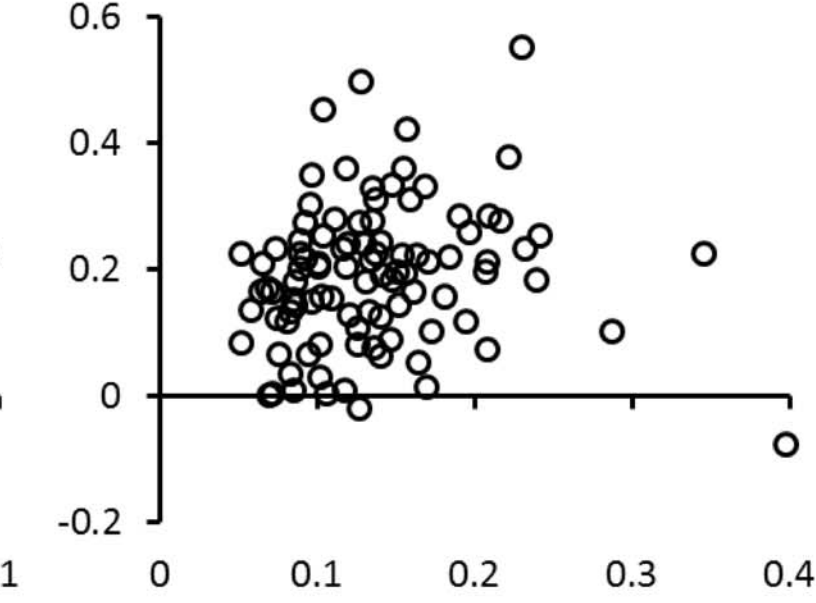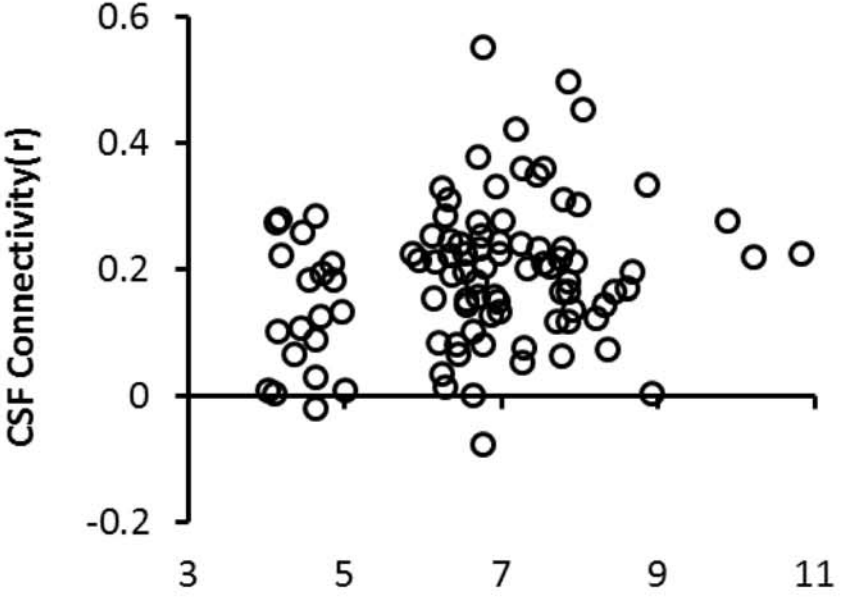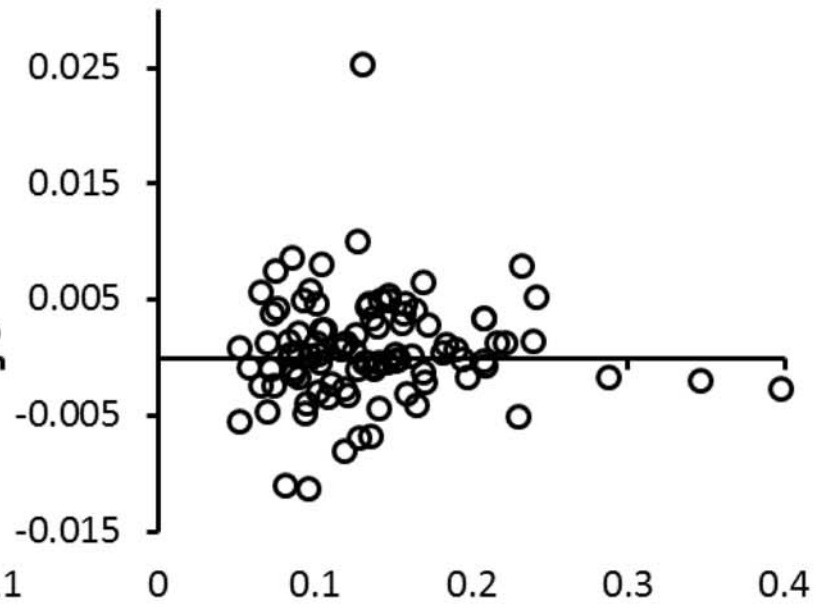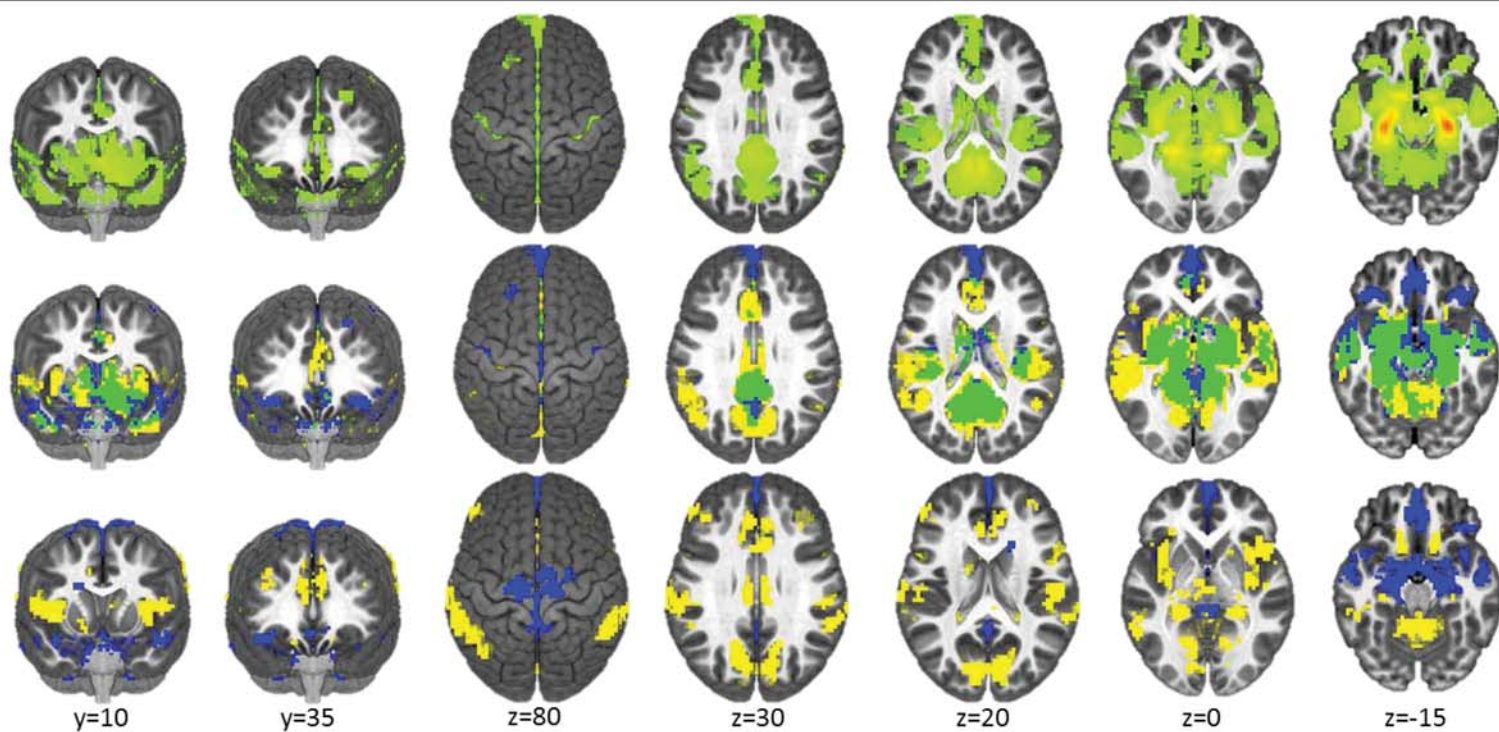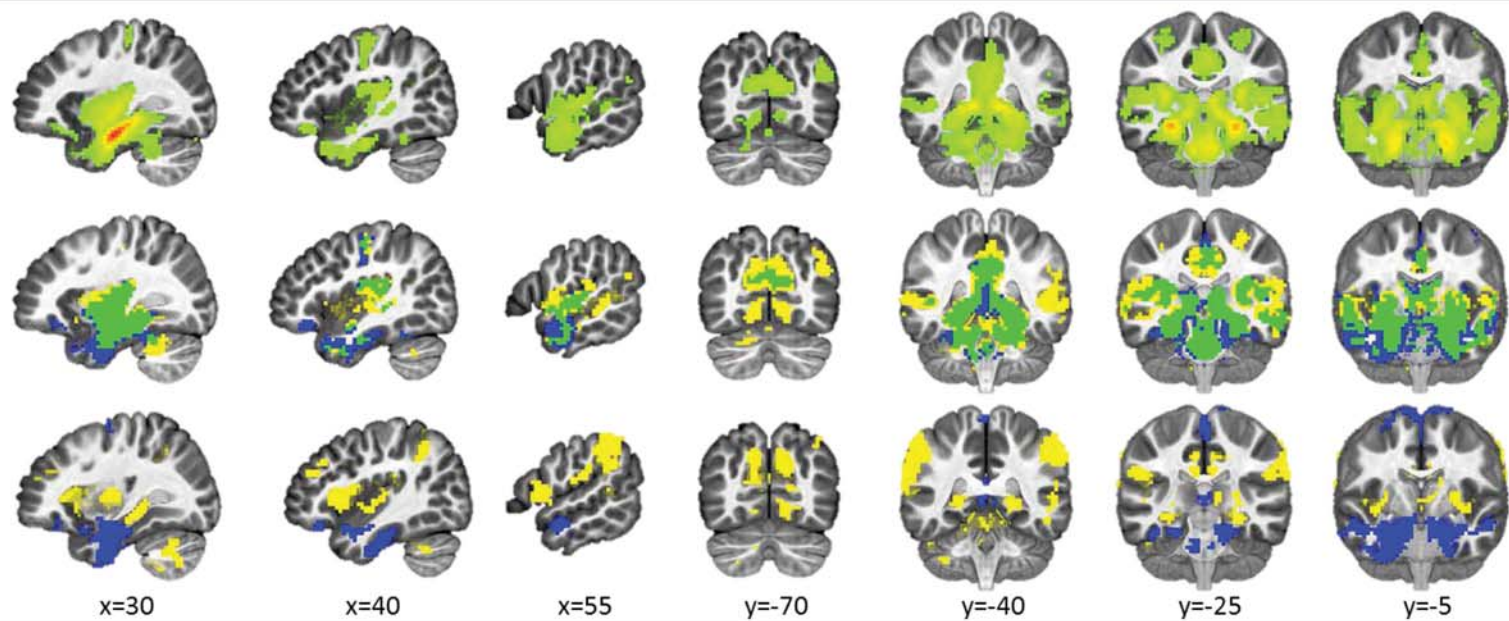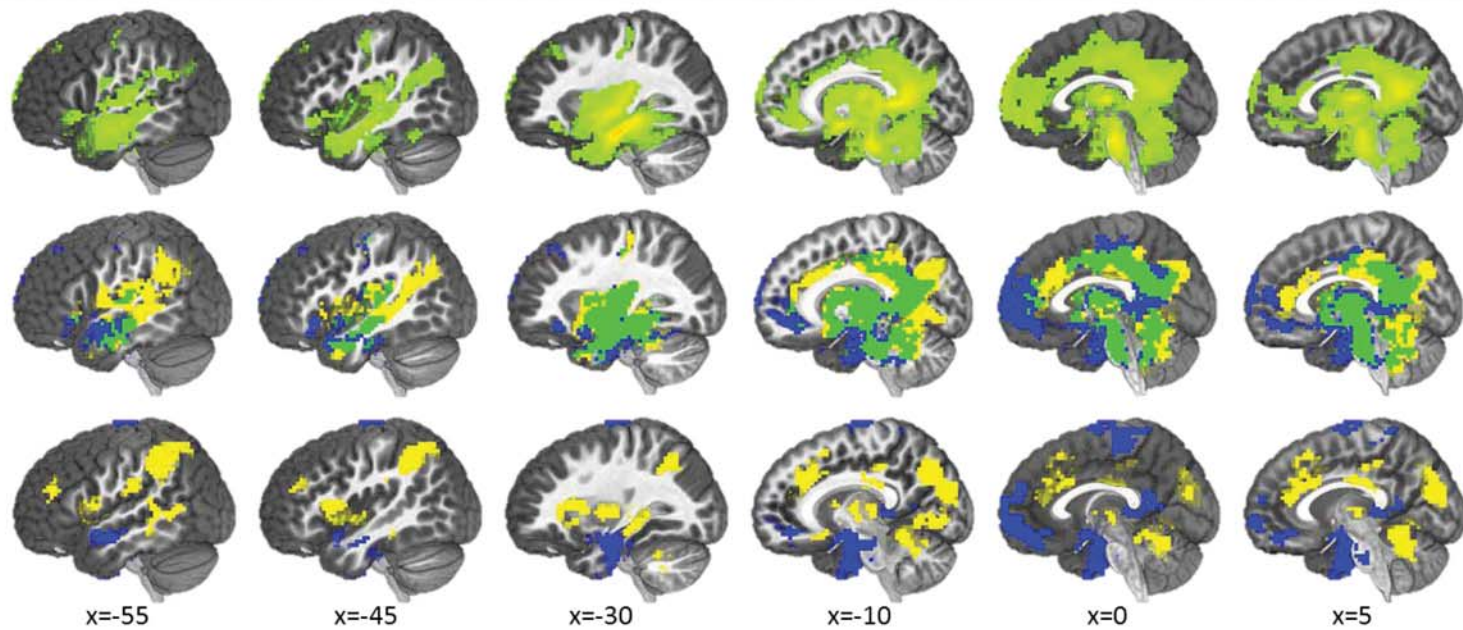
x=-55　　x=-45　　x=-30　　x=-10　　x=0　　x=5

x=30　　x=40　　x=55　　y=-70　　y=-40　　y=-25　　y=-5

y=10　　y=35　　z=80　　z=30　　z=20　　z=0　　z=-15

| Anterior | Posterior | Intersection | 10 ▮ 0 |

t

A

B

x=-60   x=-11   x=29   x=61   z=5   z=-25

Anterior   Posterior   Intersection   10 ▮▮▮▮▮ 0
                                                                   t

Table I

Peak coordinates (MNI) of regions demonstrating age-independent connectivity with bilateral whole hippocampus; thresholded to voxelwise threshold of $p<10^{-15}$, cluster-extant of 16.

Region	k	x	y	z	t
Right Hippocampus	14563	26	-14	-21	12.61
Bilateral Superior Medial Gyrus					
Bilateral Amygdala					
Bilateral Anterior Cingular Cortex					
Bilateral Caudate					
Bilateral Cerebellum					
Bilateral Fusiform Gyrus					
Bilateral Inferior Frontal Gyrus					
Bilateral Lingual Gyrus					
Bilateral Medial Frontal Gyrus					
Bilateral Middle Cingulate Cortex					
Bilateral Middle Temporal Gyrus					
Bilateral Parahippocampal Gyrus					
Bilateral Posterior Cingulate Cortex					
Bilateral Putamen					
Bilateral Rolandic Operculum					
Bilateral Superior Orbital Gyrus					
Bilateral Superior Temporal Gyrus					
Bilateral Temporal Pole					
Bilateral Thalamus					
Left Angular Gyrus					
Pons					
Left Precentral Gyrus	136	-43	-17	60	10.6
Right Precentral Gyrus	134	41	-14	54	10.44
Left Middle Frontal Gyrus	56	-25	28	45	10.52
Right Middle Temporal Gyrus	32	50	-56	21	10.36
Left Precentral Gyrus	26	-58	1	21	10.23

Table II

Peak coordinates (MNI) of regions demonstrating age-independent connectivity with bilateral anterior hippocampus; thresholded to voxelwise threshold of $p<10^{-15}$, cluster-extant of 21.

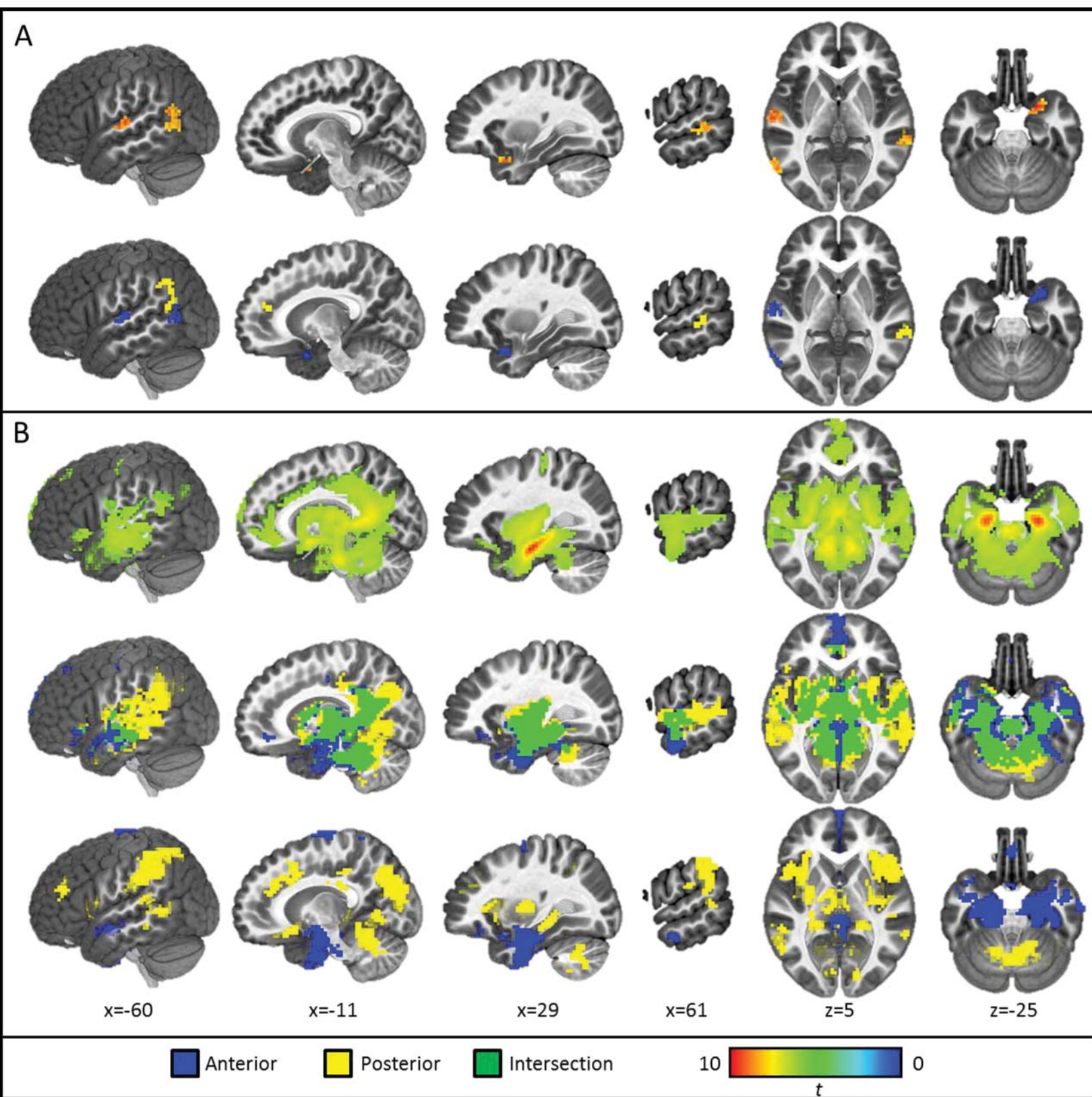| Region	k	x	y	z	t
Right Hippocampus	9553	26	-14	-21	12.63
Bilateral Posterior Cingulate					
Bilateral Caudate					
Bilateral Cerebellum					
Bilateral Fusiform Gyrus					
Bilateral Lingual Gyrus					
Bilateral Midbrain					
Bilateral Middle Temporal Gyrus					
Bilateral Parahippocampal Gyrus					
Bilateral Putamen					
Bilateral Superior Temporal Gyrus					
Bilateral Thalamus					
Left Inferior Frontal Gyrus (p. Orbitalis)					
Pons					
Left Mid Orbital Gyrus	651	-10	37	-12	10.76
Right Mid Orbital Gyrus					
Bilateral Anterior Cingulate Cortex					
Bilateral Superior Medial Gyrus					
Right Inferior Frontal Gyrus (p. Orbitalis)	67	38	34	-15	10.9
Left Precentral Gyrus	66	-43	-17	60	10.52
Right Precentral Gyrus	45	41	-14	54	10.22
Left Middle Frontal Gyrus	30	-25	28	45	10.27
Right Middle Temporal Gyrus	23	44	-41	3	10.43

Table III

Peak coordinates (MNI) of regions demonstrating age-independent connectivity with bilateral posterior hippocampus; thresholded to voxelwise threshold of $p<10^{-15}$, cluster-extant of 21.

Region	k	x	y	z	t
	1266				
Right Hippocampus	1	29	-26	-12	12.06
Bilateral Anterior Cingulate Cotex					
Bilateral Amygala					
Bilateral Angular Gyrus					
Bilateral Caudate					
Bilateral Cuneus					
Bilateral Fusiform Gyrus					
Bilateral Inferior Temporal Gyrus					
Bilateral Insular Cortex					
Bilateral Lingual Gyrus					
Bilateral Middle Cingulate Cortex					
Bilateral Middle Temporal Gyrus					
Bilateral Olfactory Cortex					
Bilateral Parahippocampal Gyrus					
Bilateral Posterior Cingulate Cortex					
Bilateral Precuneus					
Bilateral Putamen					
Bilateral Superior Temporal Gyrus					
Bilateral SupraMarginal Gyrus					
Bilateral Thalamus					
Cerebellum					
Midbrain					
Pons					
Left Precentral Gyrus	69	-34	-20	48	10.32
Right Precentral Gyrus	52	35	-20	48	10.16
Right Angular Gyrus	31	53	-62	24	10.31
Left Inferior Frontal Gyrus	28	-49	19	-6	10.27

Table IV

Peak coordinates (MNI) of regions demonstrating statistically different anterior versus posterior age-independent connectivity; thresholded to voxelwise threshold of p<.001, cluster-extant of 21.

Region	k	x	y	z	t
Anterior > Posterior					
Right Anterior Hippocampus	1602	23	-14	-21	5.62
Left Anterior Hippocampus					
Bilateral Amygdala					
Bilateral Parahippocampal Gyrus					
Bilateral Middle Temporal Gyrus					
Bilateral Olfactory Cortex					
Bilateral Fusiform Gyrus					
Left Mid Orbital Gyrus	291	-1	58	-12	4.21
Right Mid Orbital Gyrus					
Bilateral Rectal Gyrus					
Right Posterior Cingulate Cortex	113	5	-35	3	3.99
Left Posterior Cingulate Cortex					
Left Paracentral Lobule	111	-1	-29	60	4.01
Right Precentral Gyrus	85	14	-17	78	4.17
Left Paracentral Lobule	58	-10	-14	78	4.43
Right Inferior Frontal Gyrus (pars Orbitalis)	38	44	34	-18	4.19
White Matter	23	20	10	24	3.99
Posterior > Anterior					
Right Cuneus	1631	14	-64	39	-4.21
Left Cuneus					
Bilateral Lingual Gyrus					
Bilateral Cerebellum					
Bilateral Precuneus					
Left Inferior Parietal Lobule	736	-55	-44	48	-4.5
Left SupraMarginal Gyrus					
Left Angular Gyrus					
Right Inferior Frontal Gyrus	635	47	10	6	-4.2
Right Insula					
Right Putamen					
Left Posterior Hippocampus	627	-25	-35	-3	-4.5
Left Putamen					
Bilateral Thalamus					
Left Insula					
Left Inferior Frontal Gyrus					
Right SupraMarginal Gyrus	453	59	-41	42	-4.2

Right Inferior Parietal Lobule					
Right Superior Temporal Gyrus					
Right Anterior Cingulate Cortex	184	5	34	15	-3.89
Left Middle Temporal Gyrus	139	-58	-53	3	-3.83
Left Superior Medial Cortex	137	-7	34	30	-3.88
Left Anterior Cingulate Cortex					
Right Posterior Hippocampus	108	29	-32	-9	-6.25
Left Middle Cingulate Cortex	93	-7	-17	27	-4.16
Right Middle Cingulate Cortex	80	8	-32	42	-4.17
Right Straight Gyrus	54	14	19	-15	-4.2
Right Inferior Frontal Gyrus	51	38	34	27	-3.72
Left Straight Gyrus	39	-16	25	-15	-4.44
Left Middle Frontal Gyrus	36	-52	40	21	-3.81
Left Caudate Nucleus	23	-13	1	15	-3.83

Table V

Center of mass coordinates (MNI) of regions demonstrating non-overlapping anterior or posterior connectivity derived from individual anterior or posterior connectivity analyses thresholded to voxelwise threshold of $p<10^{-15}$, cluster-extant k=21.

Region	k	x	y	z
Anterior				
Pons	1458	6	-13	-21
Bilateral Temporal Pole				
Bilateral Fusiform Gyrus				
Bilateral parahippocampal gyrus				
Bilateral Amygdala				
Bilateral Thalamus				
Left Superior Medial Gyrus	571	-1	54	2
Bilateral Rectal Gyrus				
Right Superior Medial Gyrus				
Bilateral Mid Orbital Gyrus				
Bilateral Olfactory Cortex				
Left Supplementary Motor Area	95	1	-18	51
Right Supplementary Motor Area				
Left Inferior Frontal Gyrus (pars Orbitalis)	84	-40	30	-13
Right Inferior Frontal Gyrus (pars Orbitalis)	67	41	32	-14
Left Precuneus	42	-1	-58	32
Right Precentral Gyrus	21	40	-15	42
Posterior				
Right Lingual Gyrus	2864	15	-46	4
Bilateral Posterior Cingulate Cortex				
Bilateral Cuneus				
Left Lingual Gyrus				
Bilateral Cerebellum				
Right Middle Temporal Gyrus				
Bilateral Fusiform Gyrus				
Bilateral Rolandic Operculum				
Left Superior Temporal Gyrus	1424	-48	-29	10
Left Angular Gyrus				
Left SupraMarginal Gyrus				
Left Rolandic Operculum				
Let Middle Temporal Gyrus				
Left Inferior Temporal Gyrus				
Left Insula				
Left Putamen				

Right Anterior Cingultae Cortex	275	-2	28	23
Right Putamen	58	17	13	-11
Left Inferior Temporal Gyrus	45	-41	7	-37
Right Postcentral Gyrus	33	40	-20	49
Right Caudate Nucleus	30	17	-3	16
Left Postcentral Gyrus	30	-32	-25	53
Left Thalamus	22	0	-14	-1

Table VI

Peak coordinates (MNI) of regions demonstrating age-related increases in connectivity with bilateral whole hippocampus; voxelwise threshold p<.001, cluster-extant of 16.

Region	k	x	y	z	t
Left Middle Temporal Gyrus	56	-64	-59	18	3.84
Right Middle Temporal Gyrus	33	68	-35	6	3.8
Left Superior Temporal Gyrus	31	-64	-20	9	3.84
Right Piriform Cortex	26	23	10	-24	3.97
Right Periamygdaloid Cortex					

Table VII

Peak coordinates (MNI) of regions demonstrating age-related increases in connectivity with bilateral anterior hippocampus; voxelwise threshold p<.001, cluster-extant of 16.

Region	k	x	y	z	*t*
Right Piriform Cortex	29	23	10	-24	3.96
Right Periamygdaloid Cortex					
Left Superior Temporal Gyrus	29	-64	-17	9	3.95
Left Middle Temporal Gyrus	21	-58	-65	9	3.76

Table VIII

Peak coordinates (MNI) of regions demonstrating age-related increases in connectivity with bilateral posterior hippocampus; voxelwise threshold p<.001, cluster-extant of 16.

Region	k	x	y	z	*t*
Left Angular Gyrus	47	-61	-59	42	3.79
Left Inferior Parietal Lobe					
Left Middle Temporal Gyrus					
Right Middle Temporal Gyrus	34	68	-35	6	3.84
Left Anterior Cingulate Gyrus	25	2	40	24	3.61

Supplementary Material

S.1. Adult Resting State

The present study used a non-traditional resting-state scan to investigate the development

of hippocampal networks in a young pediatric population (4-10 years). A non-traditional resting-

state scan was selected to maximize data retention due to movement by engaging children with

minimal visual stimulation. This low-level visual stimulation was hypothesized to engage similar

hippocampal networks as the more traditional (i.e., fixation) resting-state scan (Greicius,

Krasnow, Reiss, & Menon, 2003). This hypothesis was tested in a sample of **22** adults who

completed a canonical resting-state scan (i.e., passive fixation viewing) as well as the abstract

shapes scan completed by the children in the current study. **Adults included in final analysis**

were restricted to the same motion and sleep criteria as children (see Methods), resulting in

a final sample of 18 (8 female, *M*=21.40, *SD*=3.10, range = 18.37-32.82 years).

Adult data were processed in the same manner as described in the Methods; with the

exception of normalization to an adult MNI template (Fonov, Evans, McKinstry, Almli, &

Collins, 2009).

S.1.1. Fixation Versus Abstract Shapes.

First, paired samples *t*-test were run to compare z-scores of whole-brain whole,

anterior, and posterior hippocampal connectivity between the traditional fixation scan and

the abstract shape scan to confirm the abstract shapes did not elicit significant differences

in hippocampal connectivity in comparison to a canonical resting-state scan (i.e., a

fixation). Results were cluster-corrected using $p_{uncorrected} < .00$**1**, cluster extant >**21** for $p_{corrected} <$

.05. Results revealed no significant differences in **whole, anterior, or posterior** hippocampal

connectivity between fixation and abstract scans, indicating that the non-traditional abstract

resting-state scan does not significantly alter hippocampal connectivity in adults. Consistent with other reports (**Vanderwal et al., 2015; Riggins et al., 2016**), this provides preliminary support for use of non-traditional resting-state scans in capturing hippocampal functional networks.

S.1.2. Age-Independent Connectivity in Adults

Age-independent hippocampal connectivity was tested in the adults to provide a brief, though underpowered, qualitative comparison between the hippocampal networks revealed in the children's analysis and the hippocampal networks in a more developed adult sample using the same abstract shape resting-state scan. It should be noted, however, that evidence suggests that some regions of the brain may not fully "mature" until nearly the third decade of life (Sowell et al., 2003). Given that our adult sample is heavily weighted towards individuals in their early twenties, we advise caution in regarding the following results as a fully mature hippocampal network. Rather, readers are encouraged to consider the adult results as a more developed, but potentially still developing, hippocampal network.

Consistent with the main text, separate analyses were run for whole, anterior, and posterior hippocampus. Similar to the analysis in children, thresholding the whole hippocampal results to a voxelwise *p*<.001 revealed a single cluster spanning most gray matter regions of cortex (k=28,970). Similar to the approach with the child group, the threshold was increased to a point at which clusters emerged (*p*<.00001). Full results for analysis of whole, anterior, and posterior hippocampus can be found in Supplementary Tables 1-3, respectively. Direct statistical comparisons of the adult and child networks was methodologically infeasible given that each group was normalized to separate age-

appropriate templates. Results are discussed below as they relate to similarities or differences in the child results.

Adult age-independent results revealed a hippocampal network of regions consistent with what was found in children, including: medial prefrontal cortex, posterior cingulate cortex, bilateral angular gyrus, precuneus, bilateral precentral gyrus, pons, middle temporal gyrus, orbital cortex, straight gyrus, lingual gyrus, piriform cortex, and cerebellum. Notable differences from the child data include: (1) adults demonstrate more localized connectivity than the children, specifically as it applies to the absence of connectivity along the middle temporal gyrus and with midline subcortical structure (e.g., thalamus, putamen, caudate), (2) adults had connectivity with bilateral dorsolateral prefrontal cortex which was absent in the right hemisphere in children, (3) adults show connectivity with the left paracentral lobule, a region lacking connectivity in all child analyses, and (4) the widespread mid-cingulate connectivity evident in children was not found in adults.

Analyses in the main text revealed six regions that demonstrated age-related increases in hippocampal connectivity during childhood: left superior temporal gyrus, left temporoparietal junction, right piriform cortex, anterior cingulate cortex, and bilateral middle temporal gyrus. These regions were compared with the adult connectivity maps to determine whether these connections are present in a more mature adult network or if additional network changes occur before reaching an adult state. Although adults demonstrated connectivity with the left superior temporal gyrus, the masking technique revealed that this connectivity was with posterior hippocampus,whereas the children demonstrated age-related increases in anterior connectivity with this region. In contrast,

hippocampal connectivity with right piriform cortex, anterior cingulate cortex, left temporoparietal junction, and right middle temporal gyrus were absent in the adult analysis.

The results in this adult sample confirm the primary findings and interpretations included in the main text by highlighting that the major components of the adult hippocampal network are evident in children, but many regions may still be undergoing developmental change. In particular, regions of anterior and middle cingulate, lateral temporal cortex extending into the temporoparietal junction, right dorsolateral prefrontal cortex, and many midline subcortical structures may still undergo significant developmental change beyond the studied range of 4-10 years. Notably, there were few regions evident in the adult hippocampal network that were absent in children.

As seen in the child analyses, use of a whole hippocampal seed seems to capture regions of both anterior and posterior hippocampal connectivity, with whole connectivity maps appearing to be an additive map of both anterior and posterior connectivity analyses. However, unlike what was found in children, the anterior and posterior seeds appeared significantly less functionally independent in adults. In fact, the current pattern of results suggests the posterior hippocampus is highly synchronized with the activity of the anterior hippocampus: in the adult masking approach, nearly every region which survived cluster-correction was connected with the anterior hippocampus or was overlapping with few regions of unique posterior hippocampal connectivity. Consistent with this observation, in statistical tests of anterior versus posterior connectivity ($p_{uncorrected}<.001$), the only regions of significantly different connectivity were located in bilateral anterior hippocampus and ventromedial prefrontal cortex (Supplementary Table 4, Supplementary Figure 1C). That

is to say that the anterior hippocampus is more highly connected with the anterior hippocampus (as would be expected), but the posterior hippocampus is not significantly more connected with the posterior portions than anterior portions. This is a surprising finding in light of the extant adult literature which suggests functional distinctions along the longitudinal axis in adults (e.g., Poppenk et al., 2013; Poppenk & Moscovitch, 2011; Strange et al., 2014). This apparent contradiction with the extant literature does not appear to be driven by inaccurate mask placement, and may suggest increased functional integration of hippocampal subregions with age or may simply be a consequence of an under-powered adult sample.

Finally, many methodological considerations should be taken into account when comparing and interpreting similarities and differences between the adult and child samples. Of greatest concern are the differences in sample size and thresholding as these parameters will dictate the statistical power available to detect an effect as well as how large the effect size and cluster extent must be in order to be reported. Due to widespread hippocampal connectivity, different voxelwise thresholds were selected for presentation of child and adult analyses. This necessarily implies that one analytic technique may be more conservative than another. Therefore, the absence of adult connectivity to regions indicated as undergoing age-related increases in connectivity during childhood may not necessarily imply that region is no longer connected in adults or that this finding in children is a false positive. At varying thresholds these networks may be more or less consistent. However, with these caveats mentioned, it is possible that failure to identify regions of hippocampal connectivity in the adult hippocampal network map may signal

possible targets of age-related decreases in hippocampal connectivity that occur in late childhood or adolescence.
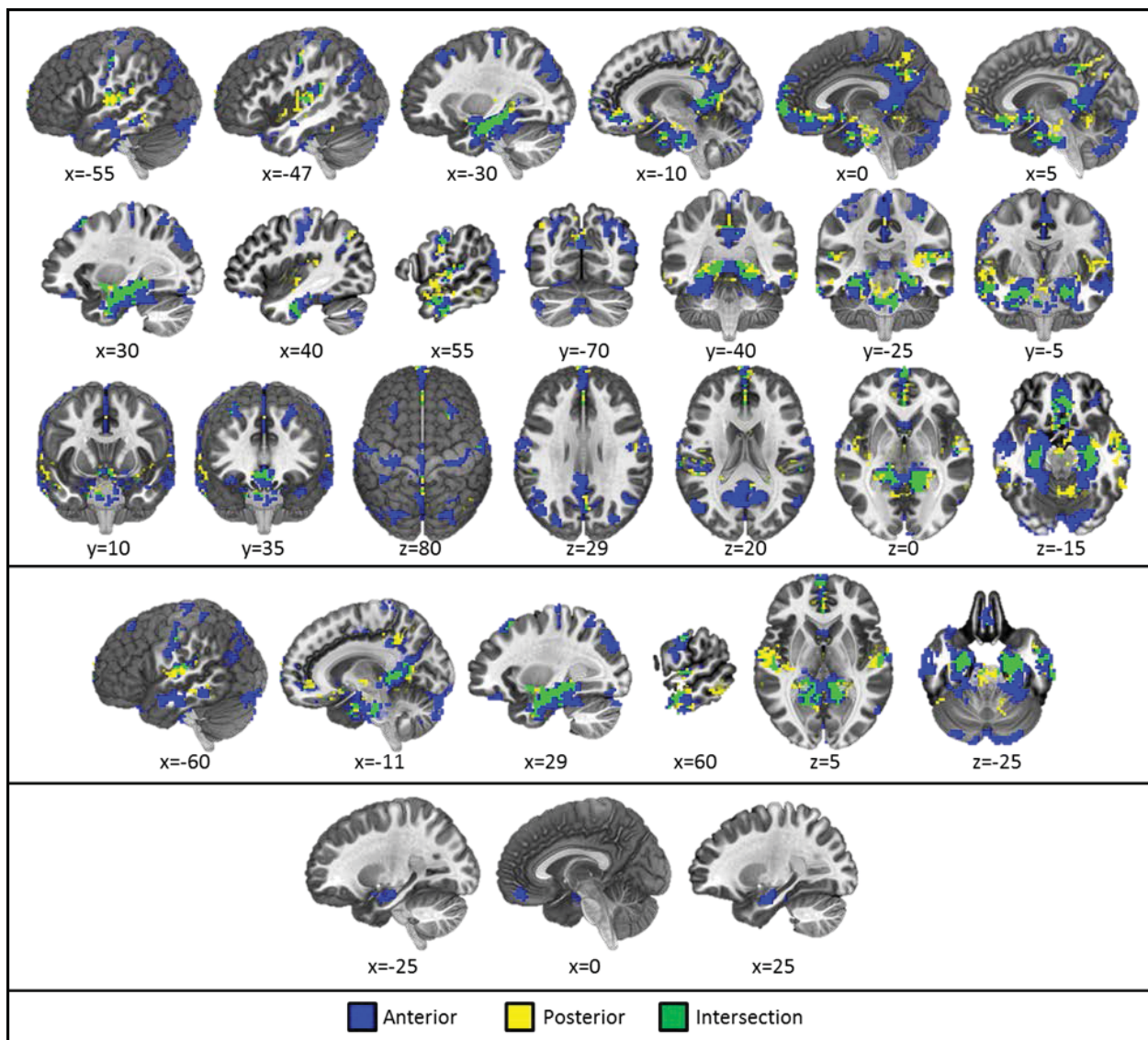
Supplementary Figure 1. **Results of adult age-independent connectivity analyses. (A) Masks of unique and intersecting regions of connectivity with anterior and posterior hippocampal seeds for comparison to Figure 4 in the main text. (B) Masks of unique and intersecting regions of connectivity with anterior and posterior hippocampal seeds for comparison with child age-dependent results (Figure 5). (C) Regions of statistically greater anterior versus posterior connectivity.**

Supplementary Table I

Peak coordinates (MNI) of regions demonstrating age-independent connectivity with bilateral whole hippocampus; thresholded to voxelwise threshold of p<.00001, cluster-extant of 21.

Region	K	x	y	Z
Right Anterior Hippocampus	4062	24	-18	-18
Left Anterior Hippocampus				
Pons				
Bilateral Fusiform Gyrus				
Medial Prefrontal Cortex				
Posterior Cingulate Gyrus				
Right Inferior Temporal Gyrus				
Bilateral Amygdala				
Bilateral Parahippocampal Gyrus				
Left Superior Temporal Gyrus	351	-48	-24	9
Left Posterior Insula				
Left Precentral Gyrus				
Left Angular Gyrus	344	-39	-75	42
Left Superior Parietal Lobule				
Left Superior Occipital Gyrus				
Left Middle Temporal Gyrus				
Left Middle Temporal Gyrus	293	-66	-9	-21
Left Inferior Temporal Gyrus				
Right Lingual Gyrus	247	12	-102	-12
Right Cerebellum				
Right Precentral Gyrus	247	45	-15	54
Left Middle Frontal Gyrus	119	-30	33	51
Left Superior Frontal Gyrus				
Left Precentral Gyrus	115	-33	-27	54
Right Superior Temporal Gyrus	109	57	-15	6
Right Angular Gyrus	102	48	-66	27
Left Paracentral Lobule	85	-3	-33	72
Right Superior Frontal Gyrus	71	30	30	54
Right Middle Frontal Gyrus				
Right Cerebellum	58	42	-72	-45
Left Inferior Frontal Gyrus	49	-48	21	33
Right Superior Parietal Lobule	49	24	-78	51
Left Supplementary Motor Area	37	0	-9	51
Left Precuneus	31	-6	-57	69
Right Inferior Frontal Gyrus	29	33	36	-18
Right Inferior Temporal Gyrus	26	66	-48	-9

| Left Inferior Occipital Gyrus | 23 | -39 | -90 | -15 |

Supplementary Table II

Peak coordinates (MNI) of regions demonstrating age-independent connectivity with bilateral anterior hippocampus; thresholded to voxelwise threshold of p<.00001, cluster-extant of 21.

Region	K	x	y	Z
Right Anterior Hippocampus	3194	24	-15	-18
Left Anterior Hippocampus				
Pons				
Bilateral Fusiform Gyrus				
Posterior Cingulate Gyrus				
Right Inferior Temporal Gyrus				
Bilateral Amygdala				
Medial Prefrontal Cortex	514	0	-48	-15
Right Lingual Gyrus	372	12	-102	-12
Right Inferior Occipital Gyrus				
Left Inferior Occipital Gyrus				
Left Cerebellum				
Right Precentral Gyrus	267	33	-27	72
Left Superior Temporal Gyrus	262	-48	-24	9
Left Precentral Gyrus				
Left Posterior Insula				
Left Angular Gyrus	246	-39	-75	42
Left Inferior Parietal Lobule				
Left Middle Temporal Gyrus	198	-66	-18	-24
Left Inferior Temporal Gyrus				
Left Precentral Gyrus	118	-27	-24	54
Left Paracentral Lobule	111	-6	-33	75
Right Superior Parietal Lobule	93	24	-78	51
Right Angular Gyrus	80	48	-66	27
Left Middle Frontal Gyrus	57	-30	33	51
Left Superior Frontal Gyrus				
Right Superior Temporal Gyrus	50	57	-15	6
Right Superior Fonrtal Gyrus	43	30	27	54
Right Middle Frontal Gyrus				
Left Inferior Temporal Gyrus	39	-66	-45	-15
Right Cerebellum	36	42	-72	-48
Right Inferior Frontal Gyrus	28	36	33	-18
Left Supplementary Motor Area	27	0	-9	51
Right Superior Parietal Lobule	26	33	-63	57
Left Precuneus	26	-6	-57	69
Left Angular Gyrus	21	-42	-63	30

Supplementary Table III

Peak coordinates (MNI) of regions demonstrating age-independent connectivity with bilateral posterior hippocampus; thresholded to voxelwise threshold of p<.00001, cluster-extant of 21.

| Region	K	x	y	Z
Right Anterior Hippocampus	918	27	-18	-18
Right Posterior Hippocampus				
Right Cerebellum				
Right Middle Temporal Gyrus				
Right Superior Temporal Gyrus				
Bilateral Medial Prefrontal Cortex	423	9	36	-12
Pons				
Bilateral Straight Gyrus				
Left Posterior Hippocampus	390	-27	-24	-15
Left Anterior Hippocampus				
Left Superior Temporal Gyrus	204	-48	-21	9
Right Posterior Cingulate Gyrus	138	6	-42	33
Right Precuneus				
Left Middle Temporal Gyrus	57	-69	-39	-6
Right Postcentral Gyrus	44	57	-15	42
Left Postcentral Gyrus	39	-39	-18	48
Right Inferior Temporal Gyrus	34	66	-48	-9
Right Angular Gyrus	33	42	-69	42
Right Superior Frontal Gyrus	23	27	24	54
Left Superior Temporal Gyrus	22	-42	-33	15

Supplementary Table IV

Peak coordinates (MNI) of regions demonstrating significantly different anterior versus posterior age-independent connectivity; thresholded to voxelwise threshold of p<.001, cluster-extant of 21.
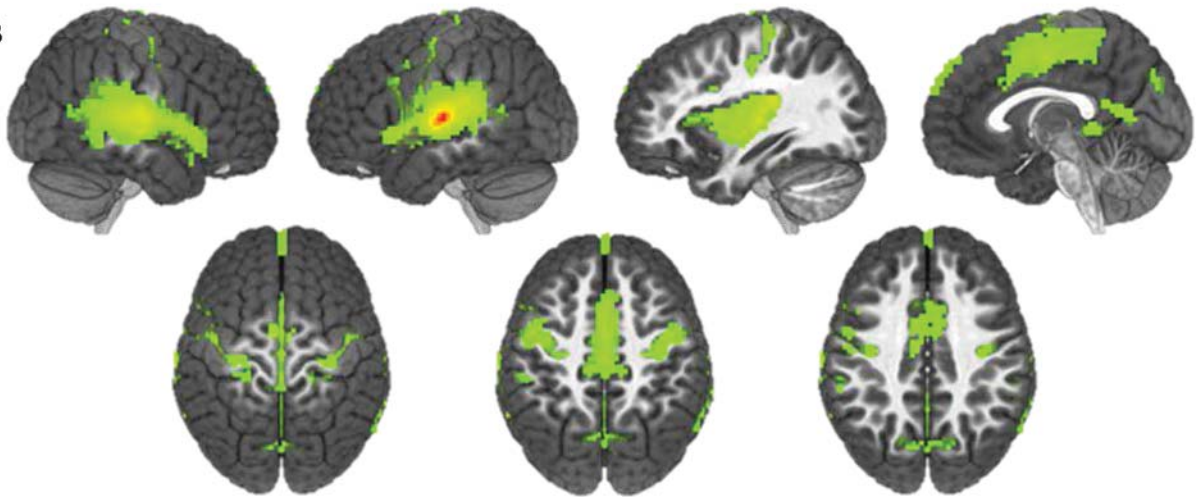
Region	k	x	y	Z
Right Anterior Hippocampus	96	24	-18	-14
Left Anterior Hippocampus	68	-24	-18	-18
Left Amygdala				
Right Medial Prefrontal Cortex	34	6	48	-15

A

x=65   x=-65   x=35   x=0

z=70   z=50   z=40
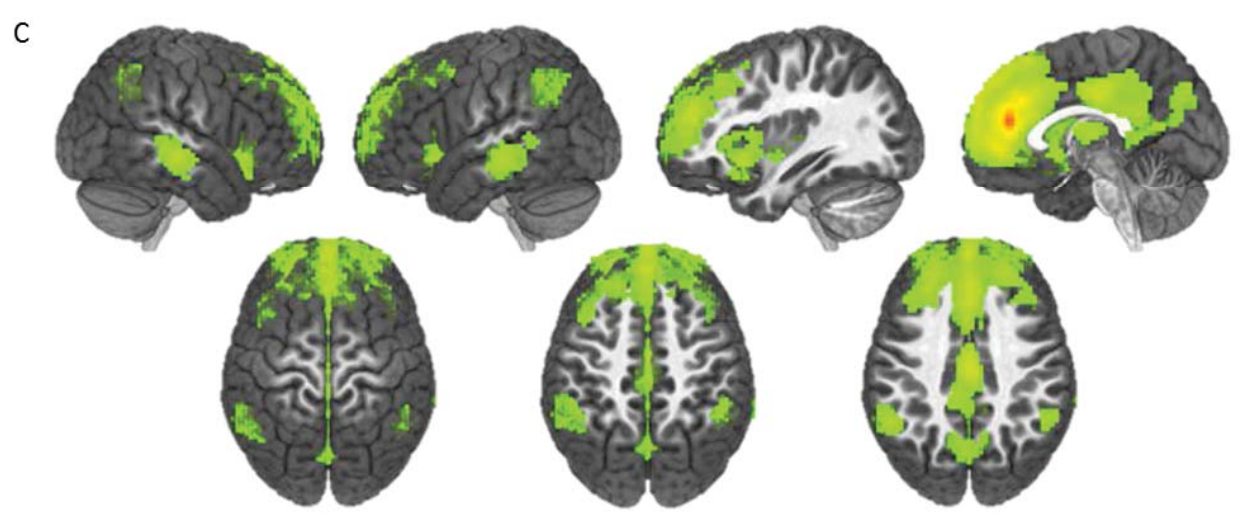
B

C

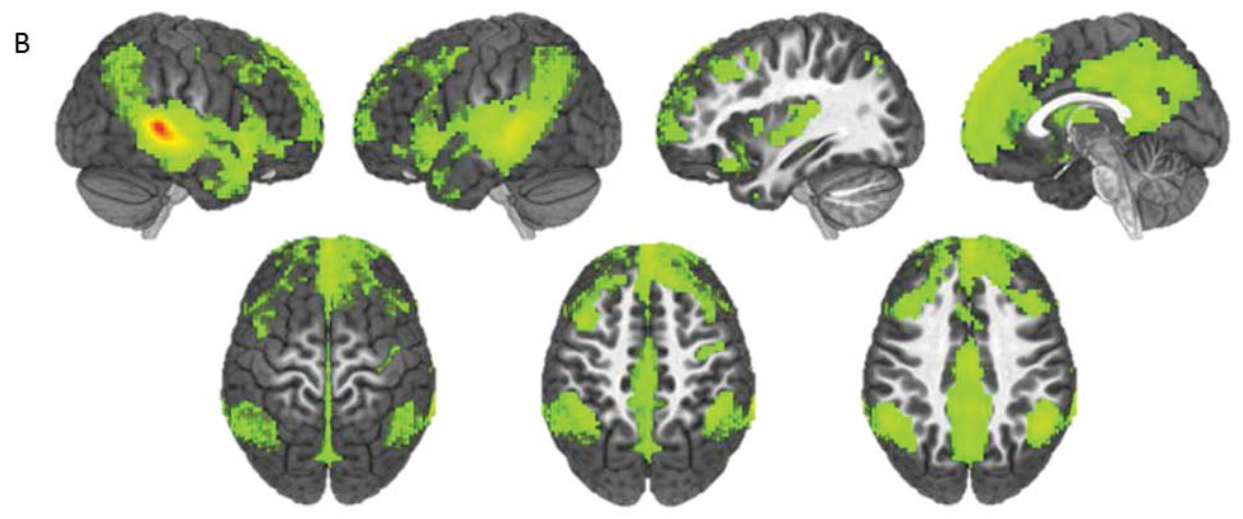10   0
                        t
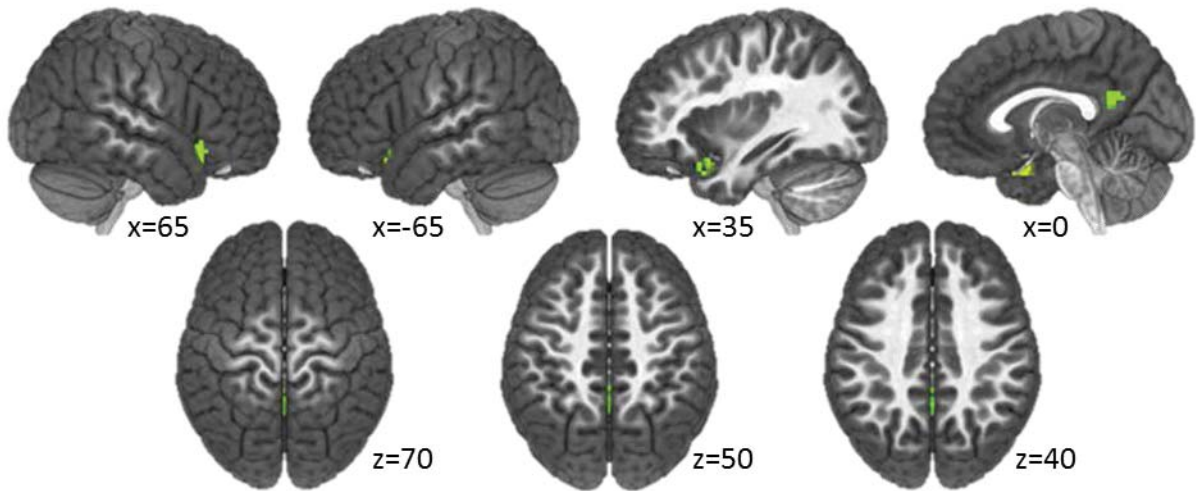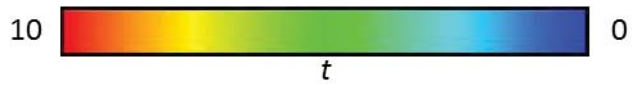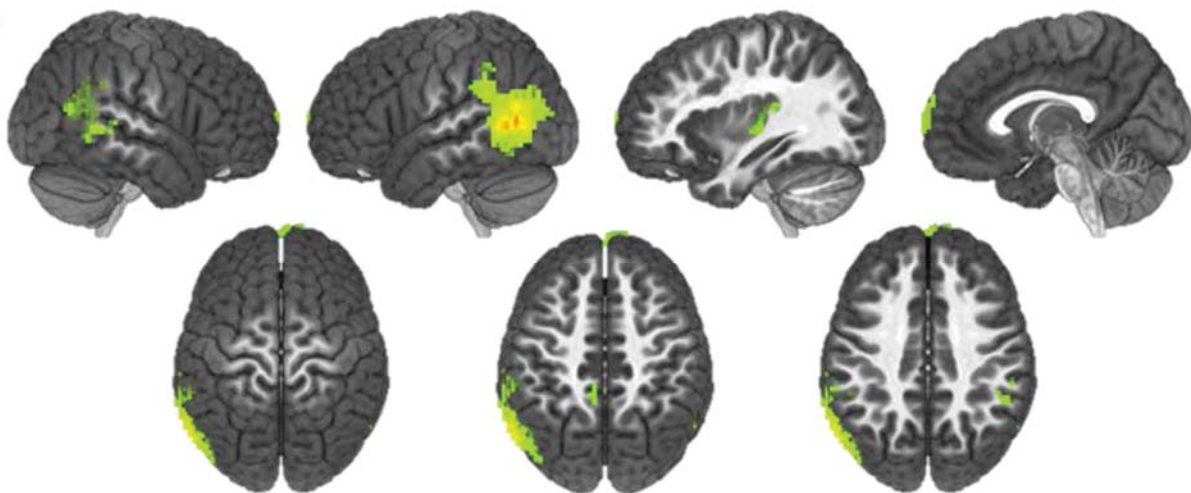
Supplementary Figure 2. **Whole-brain connectivity of regions demonstrating age-dependent anterior hippocampal connectivity during childhood. (A) Whole-brain connectivity of right piriform cortex. (B) Whole-brain connectivity of left superior temporal gyrus. (C) Whole-brain connectivity of left medial temporal gyrus. Thresholded at a voxelwise threshold of $p < 10^{-15}$, cluster-extent k>21.**

A

x=65   x=-65   x=35   x=0

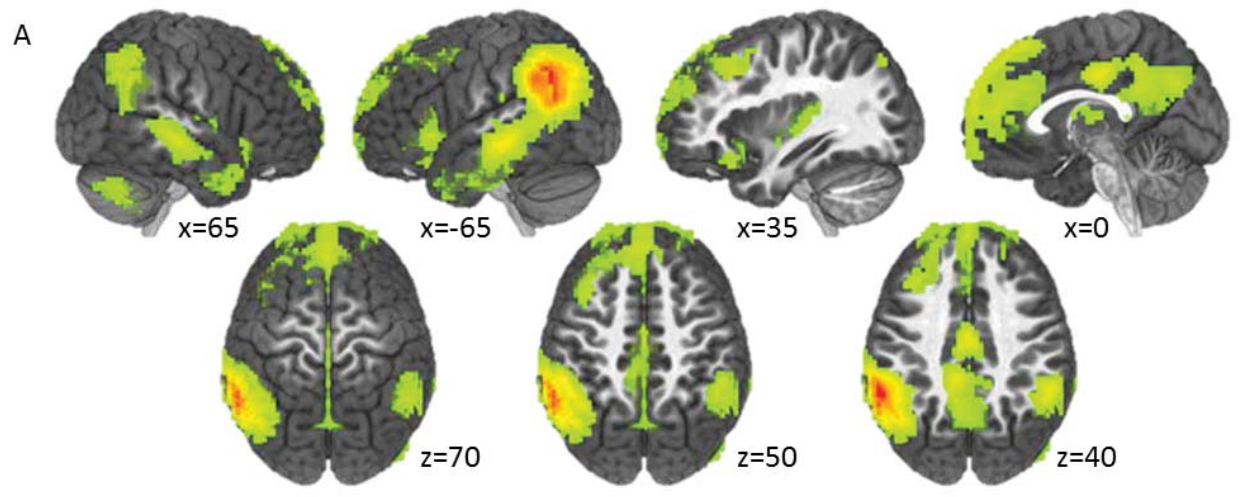z=70   z=50   z=40

B

C

10   t   0
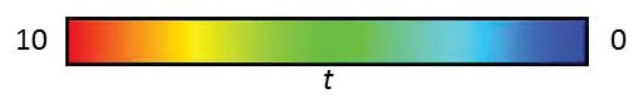
Supplementary Figure 3. **Whole-brain connectivity of regions demonstrating age-dependent posterior hippocampal connectivity during childhood. (A) Whole-brain connectivity of left angular gyrus at the temporoparietal junction. (B) Whole-brain connectivity of the right middle temporal gyrus. (C) Whole-brain connectivity of anterior cingulate cortex. Thresholded at a voxelwise threshold of $p<10^{-15}$, cluster-extent k>21.**
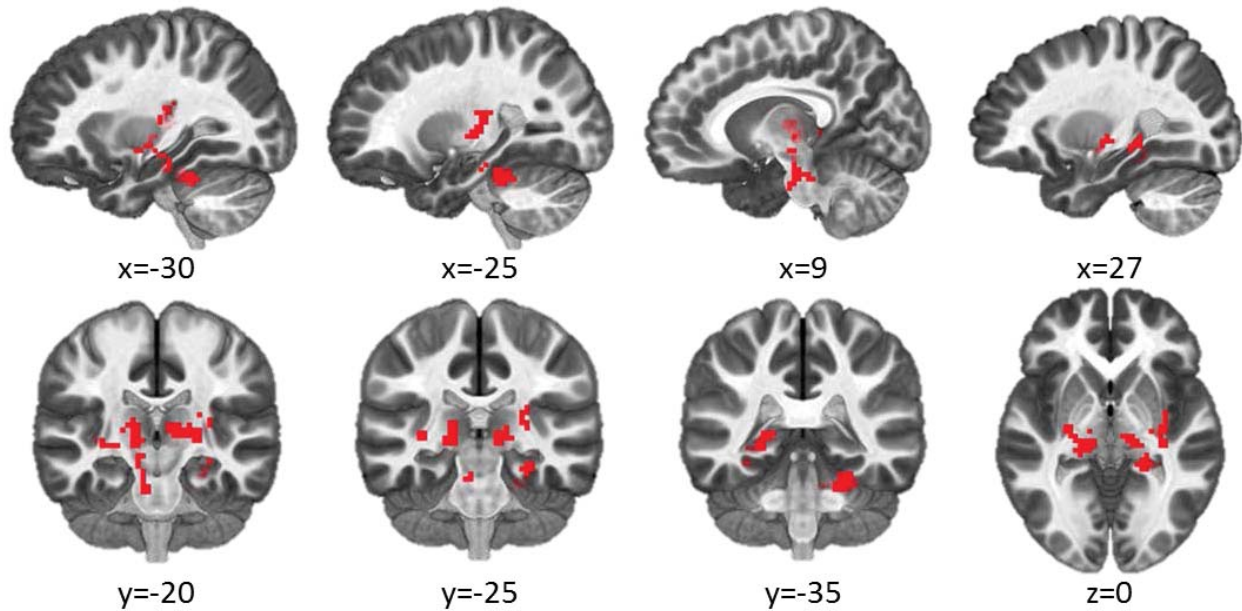
Supplementary Figure 4. **Regions of different posterior hippocampal connectivity between children in high versus low motion groups that overlapped with results in the posterior age-controlled analysis. Note: Thresholded at a voxelwise threshold of $p<.001$, cluster extent of 21; Sagittal views are depicted from the left slicing towards the right; Coronal views are depicted with the left hemisphere on the left; Axial views provide an aerial view of the brain with left hemisphere depicted on the right.**

Supplementary Table V
Peak coordinates (MNI) of regions demonstrating significantly different whole hippocampal connectivity between median-split high- and low-moving groups; thresholded to voxelwise threshold of p<.001, cluster-extant of 21. Note: None of these regions fell within the age-dependent or age-controlled whole hippocampal connectivity maps.

Region	k	x	y	Z
Left Inferior Occipital Gyrus	186	-40	-68	-9
Left Fusiform Gyrus				
Left Middle Temporal Gyrus				
Left Inferior Temporal Gyrus				
Right Fusiform Gyrus	161	44	-50	-18
Right Inferior Occipital Gyrus				
Right Middle Temporal Gyrus				
Right Inferior Temporal Gyrus				
Right Postcentral Gyrus	54	62	-17	33
Left Middle Occipital Gyrus	40	-31	-77	30
Right Superior Temporal Gyrus	31	56	-17	0
Right Precentral Gyrus	29	47	7	36
Right Postcentral Gyrus	28	50	-35	60
Pons	23	5	-17	-27
Left Subcortical White Matter	21	20	10	12

Supplementary Table VI
Peak coordinates (MNI) of regions demonstrating significantly different anterior hippocampal connectivity between median-split high- and low-moving groups; thresholded to voxelwise threshold of p<.001, cluster-extant of 21. Note: None of these regions fell within the age-dependent or age-controlled anterior hippocampal connectivity maps.

Region	k	x	y	Z
Left Middle Occipital Gyrus	98	-49	-77	3
Right Superior Temporal Gyrus	45	50	-17	-3
Right Postcentral Gyrus	40	62	-17	33
Right Caudate Nucleus	30	14	13	9
Right Middle Temporal Gyrus	27	44	-56	6
Right Precentral Gyrus	21	47	7	39

Supplementary Table VII
Peak coordinates (MNI) of regions demonstrating significantly different posterior hippocampal connectivity between median-split high- and low-moving groups; thresholded to voxelwise threshold of p<.001, cluster-extant of 21. Note: *Regions that fell within the age-controlled posterior hippocampal connectivity map.

Region	k	x	y	Z
Left Thalamus*	119	-10	-23	6
Left Putamen*				
Left Subcortical White Matter*				
Right Subcortical White Matter*	94	32	-23	-3
Right Putamen*				
Left Cerebellum*	55	-28	-38	-27
Left Thalamus*	53	14	-23	3
Left Postcentral Gyrus	41	-52	-17	33
Right Medial Posterior Hippocampus*	40	23	-32	-6
Right Midbrain*	36	11	-20	-12
Pons*				
Left Fusiform Gyrus	28	-40	-56	-15
Left Inferior Temporal Gyrus				
Right Postcentral Gyrus	28	50	-32	57
Right Middle Temporal Gyrus	27	53	-62	3
Left Lingual Gyrus	26	-19	-62	0
Right Inferior Temporal Gyrus	22	44	-53	-12
Right Fusiform Gyrus				
Right Superior Temporal Gyrus	22	47	-20	3
Left Insula	22	-37	-8	18
Right Rolandic Operculum	21	38	-26	21