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RESEARCH ARTICLE | *Higher Neural Functions and Behavior*

The intrinsic neonatal hippocampal network: rsfMRI findings

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Howell AL, Osher DE, Li J, Saygin ZM. The intrinsic neonatal hippocampal network: rsfMRI findings. *J Neurophysiol* 124: 1458–1468, 2020. First published September 23, 2020; doi:10.1152/jn.00362.2020.—Many adults cannot voluntarily recall memories before the ages of 3–5, a phenomenon referred to as "infantile amnesia." The development of the hippocampal network likely plays a significant part in the emergence of the ability to form long-lasting memories. In adults, the hippocampus has specialized and privileged connections with certain cortical networks, which presumably facilitate its involvement in memory encoding, consolidation, and retrieval. Is the hippocampus already specialized in these cortical connections at birth? And are the topographical principles of connectivity (e.g., long-axis specialization) present at birth? We analyzed resting-state hippocampal connectivity in neonates scanned within 1 wk of birth (Developmental Human Connectome Project) and compared it with that of adults (Human Connectome Project). We explored the connections of the whole hippocampus and its long-axis specialization to seven canonical cortical networks. We found that the neonatal hippocampal networks show clear immaturity at birth: adults showed hippocampal connectivity that was unique for each cortical network, whereas neonates showed no differentiation in hippocampal connectivity across these networks. Furthermore, neonates lacked long-axis specialization (i.e., along the anterior-posterior axis) of the hippocampus in its differential connectivity patterns to the cortical networks. This immaturity in connectivity may contribute to immaturity in memory formation in the first years of life.

NEW & NOTEWORTHY Although both animal data and human data suggest that the hippocampus is immature at birth, to date, there are no direct assessments of human hippocampal functional connectivity (FC) very early in life. Our study explores the FC of the hippocampus to the cortex at birth, allowing insight into the development of human memory systems. In particular, we find that adults and neonates exhibit vastly different hippocampal connectivity profiles—a finding that likely has large developmental implications.

connectivity; development; hippocampus; infantile amnesia; rsfMRI

INTRODUCTION

Many adults cannot voluntarily recall memories before the ages of 3–5, a phenomenon referred to as "infantile amnesia" (Alberini and Travaglia 2017). One potential reason for this is that the hippocampus (the primary brain structure responsible for episodic memory formation in adults) and its connections with the rest of the brain may be particularly immature at birth and therefore may lack the infrastructure and capacity to form long-lasting memories. Indeed, the growth and development of the hippocampus appears to be especially protracted in both humans and other animals. In macaques, the hippocampus continues to mature after 1 year of age (roughly age 3–5 in humans) (Jabès et al. 2011). In humans, infants show robust hippocampal growth during the first year of life (Uematsu et al. 2012), but the growth rate is slower than other cortical and subcortical structures measured in the same period (Gilmore et al. 2012). Child data indicate that volumetric and structural changes in the hippocampus continue through childhood (DeMaster et al. 2014; Gilmore et al. 2012; Seress 2007), and some studies even suggest limited hippocampal growth continues until adulthood (Duerden et al. 2020; Giedd et al. 1996; Østby et al. 2009). Furthermore, episodic memory performance may be influenced by changes in the patterns of hippocampal connectivity from middle childhood to adulthood, including along the long axis of the hippocampus (Blankenship et al. 2017; DeMaster et al. 2014; Ghetti et al. 2010; Gogtay et al. 2006; Poppenk and Moscovitch 2011; Riggins et al. 2016). At younger ages, hippocampal gray matter volume has been linked to early language ability (Deniz Can et al. 2013), and one recent study showed potential hippocampal activation for learned items in 2-yr-old toddlers (Prabhakar et al. 2018). However, the functional connectivity of hippocampus very early in life is less well understood. Therefore, an understanding of the hippocampal network at birth and its development may lead to greater understanding of memory development.

Recently, Vos de Wael and colleagues (2018) showed the hippocampus has a clear intrinsic pattern of functional connectivity (FC) to a set of cortical networks in adults. Specifically, they showed higher (i.e., most positive) connectivity from the hippocampus to the default mode and limbic networks and lowest (i.e., least positive) connectivity to the frontoparietal and ventral attention networks (from Yeo et al. 2011). Furthermore, this connectivity pattern differed between the anterior and posterior portions of the hippocampus, with the anterior hippocampus showing larger differences in connectivity to the networks than the posterior hippocampus. This so-called long-axis specialization of the hippocampus is consistent with previous research showing that the anterior and posterior portions of the hippocampus display different patterns of structural and functional connectivity and may be uniquely activated in response to cognitive, memory, and spatial demands (for reviews, see Poppenk et al. 2013 and Strange et al. 2014). The development of the hippocampal network and the long-axis gradient likely plays a

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significant part in the emergence of the ability to form long-lasting memories. For instance, the work of Riggins et al. (2016) examined the relationship of anterior/posterior connectivity and episodic memory in 4- and 6-yr-old children and found developmental differences even between these two ages. Although this work in young children is notable, the fact remains that we know very little about the hippocampus, its connections, and its relationship to memory formation during the earliest stages of life.

To this end, we compared the resting-state hippocampal connectivity patterns to a set of cortical networks in neonates and adults. In adults, resting-state connectivity—determined by spontaneously correlated activity of disparate brain regions—is used as a reliable marker of intrinsic functional connectivity (FC) between those regions (Biswal et al. 1995; Raichle 2009; Smith et al. 2013; Sporns 2013). Furthermore, in adults, FC at rest is predictive of task-based activity (Cole et al. 2014; Osher et al. 2019; Smith et al. 2009; Tobyne et al. 2018).

More recently, researchers have begun using resting-state FC to probe the developing brain. Developmental studies using FC have shown the FC of some networks is mature (i.e., similar in character or pattern to adults) at birth, whereas others take months or longer to become adultlike (for reviews, see Gao et al. 2017 and Grayson and Fair 2017). In particular, multiple studies indicate the connectivity of visual and somatomotor networks is not only functional but also highly adultlike at birth (Gao et al. 2015b; Lin et al. 2008; Liu et al. 2008). Other areas such as the default mode network, dorsal attention network, frontoparietal network, and some perceptual regions show relatively immature functional and structural characteristics at birth and experience large modifications postnatally (Gao et al. 2015b; Natu et al. 2019), although the frontoparietal network may have important functional roles even within the first year of life (Linke et al. 2018).

Although we cannot assess memory functions in neonates, here we investigated the connectional maturity of the hippocampus, the structure known to support long-term memory later in life. To assess hippocampal maturity at birth, we analyzed FC between seven cortical networks and the hippocampus as a whole as well as along the hippocampal long axis in both neonates and adults. We also compared neonatal versus adult hippocampal connectivity to the cortex at a finer, voxelwise scale. Based on previous literature suggesting the immaturity of the hippocampus at birth, we hypothesized that neonates would differ from adults in their hippocampal connectivity to the cortex, particularly to the more immature networks (e.g., default mode and frontoparietal).

MATERIALS AND METHODS

Participants

Neonates. Neonatal data came from the initial release of the Developing Human Connectome Project (dHCP) (http://www.developingconnectome.org; Makropoulos et al. 2018). Neonates were recruited and imaged in London at the Evelina Neonatal Imaging Centre after gathering informed parental consent to image and release the data. The study was approved by the UK National Research Ethics Authority (14/LO/1169). All 40 neonates from the initial dHCP release were included in our analyses; no neonatal data were excluded (15 female, 36–44 wk old at scan).

Adults. Adult data came from the Human Connectome Project (HCP), WU-Minn HCP 1200 Subject Data Release (https://www.humanconnectome.org/study/hcp-young-adult; Van Essen et al. 2013). All participants gave written consent, and experimental procedures were approved by the Institutional Review Board (IRB # 201204036; Title: Mapping the Human Connectome: Structure, Function, and Heritability), and our data analysis adheres to The Ohio State University ethical guidelines for using public data. Participants were scanned at Washington University in St. Louis (WashU). We included 40 participants in our analyses (15 female; 20–35 yr old). These adult participants were motion-matched to the neonates. Specifically, we matched each neonatal participant with an adult from the HCP dataset with the same gender who showed the most similar motion parameter (i.e., framewise displacement, FD). Although the resulting group of adults were motion-matched to the neonates, we found that the groups were significantly different in the average gray-matter temporal signal-to-noise ratio (tSNR), with neonates exhibiting higher tSNR values [$t(78) = -6.8774$, $P = 1.3469 \times 10^{-9}$]. To ensure that any results were not driven by tSNR differences between groups, we identified an additional group of HCP adults ($n = 40$, 22 female) whose tSNR was matched to the tSNR of the neonates [$t(78) = -1.5237$, $P = 0.132$] and replicated our results (see Supplemental Fig. S1-1; all Supplemental material is available at https://doi.org/10.5281/zenodo.3973370).

MRI Acquisition

Neonates. All acquisition information comes from the dHCP data release documentation. Imaging was carried out on a 3T Philips Achieva (running modified R3.2.2 software) using an imaging system specifically designed for neonates with a 32-channel phased array head coil (Hughes et al. 2017). Neonates were scanned during natural sleep; resting-state FC patterns have been shown to stay largely consistent while awake, asleep, or under anesthesia (Liu et al. 2015; Larson-Prior et al. 2009).

RESTING-STATE FMRI. High-temporal-resolution functional magnetic resonance imaging (fMRI) developed specifically for neonates was collected using multiband (MB) 9× accelerated echo = planar imaging [echo time (TE)/repetition time (TR) = 38/392 ms, voxel size = $2.15 \times 2.15 \times 2.15$ mm^3]. The resting-state scan lasted ~15 min and consisted of 2,300 volumes for each run. No in-plane acceleration or partial Fourier transform was used. Single-band reference scans with bandwidth matched readout and additional spin-echo acquisitions were also acquired with both anterior-to-posterior/posterior-to-anterior fold-over encoded directions.

ANATOMICAL MRI. High-resolution T2-weighted and inversion recovery T1-weighted multislice fast spin-echo images were acquired with in-plane resolution 0.8×0.8 mm^2 and 1.6 mm slices overlapped by 0.8 mm (T2-weighted: TE/TR = 156/12,000 ms; T1-weighted: TE/TR/TI = 8.7/4,795/1,740 ms).

Adults. All acquisition information comes from the HCP data release documentation. Scanning for the 1,200 WU-Minn HCP subject was carried out on a customized 3T Connectome Scanner adapted from a Siemens Skyra (Siemens AG, Erlanger, Germany), equipped with a 32-channel Siemens receiver head coil and a "body" transmission coil specifically designed by Siemens to accommodate the smaller space (due to special gradients) of the WU-Minn and MGH-UCLA Connectome scanners.

RESTING-STATE FMRI. Participants were scanned using the gradient-echo echo-planar imaging sequence (TE/TR = 33.1/720 ms, flip angle = 52°, 72 slices, and voxel size = $2 \times 2 \times 2$ mm^3). Scanning lasted ~15 min and consisted of 1,200 volumes for each run. Each participant finished two resting-state fMRI sessions. For each session, two phases were encoded: one right-to-left (RL) and the other left-to-right (LR). For our analyses, we used the LR phase encoding from the first session. Participants were instructed to relax and keep their eyes open and fixated on a bright, projected cross-hair against a dark background.

ANATOMICAL MRI. High-resolution T2-weighted and T1-weighted images were acquired with an isotropic voxel resolution of 0.7 mm^3 (T2-weighted 3D T2-SPACE scan: TE/TR = 565/3,200 ms; T1-weighted 3D MPRAGE: TE/TR/TI = 2.14/2,400/1,000 ms).

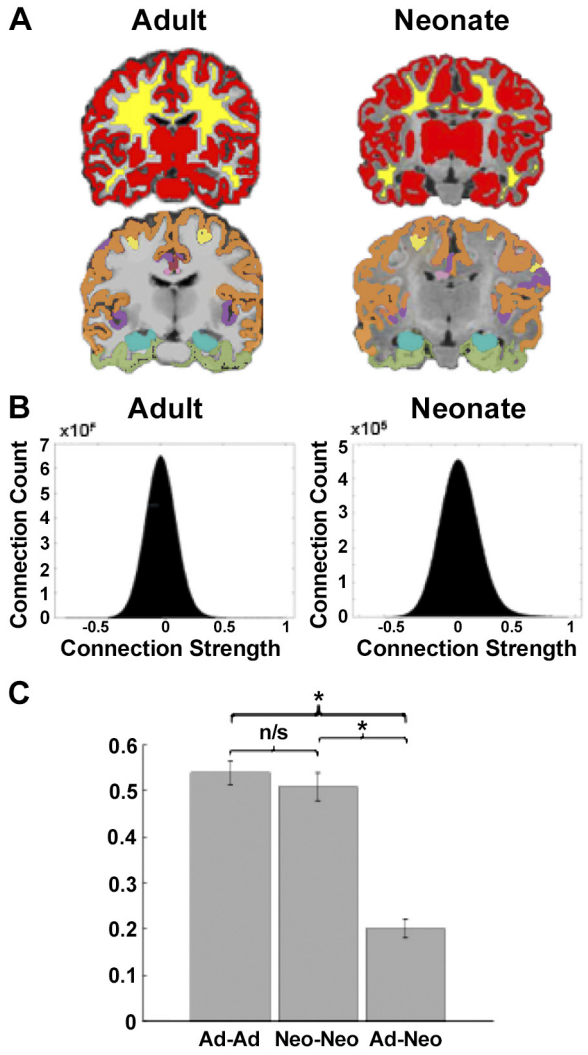

Fig. 1. Preliminary data checks. *A*: gray matter (red), white matter (yellow), and network registrations on the anatomical images of a representative adult and neonate subject; registration image: aqua, hippocampus; orange, SM; yellow, DA; purple, VA; green, Lim; pink, FP; red, DM. Visual network is not shown in these slices. *B*: voxelwise correlations distributions of a representative adult and neonate. *C*: between-subjects and between-groups correlations (using *t* tests) demonstrate high within-group reliability of connectivity, but low between-groups reliability between adults and neonates. $^*P < 0.05$; DA, dorsal attention; DM, default mode; FP, frontoparietal; Lim, Limbic; ns, nonsignificance; SM, somatomotor; VA, ventral attention; Vis, visual. Adults, $n = 40$, 15 female; neonates, $n = 40$, 15 female.

MRI Preprocessing

Data processing and analysis were done using resources from the Ohio Supercomputer Center (https://www.osc.edu/) and the Center for Cognitive and Behavioral Brain Imaging (https://ccbbi.osu.edu/).

Neonates. The dHCP data were preprocessed using the dHCP minimal preprocessing pipelines (Makropoulos et al. 2018). Anatomical MRI preprocessing included bias correction, brain extraction using the Brain Extraction Tool (BET) from the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL) (Jenkinson et al. 2012), and segmentation of the T2w volume using their DRAW-EM algorithm (Makropoulos et al. 2014). The gray and white matter segmentations that resulted were used as anatomical masks in further analyses; these masks were manually checked for accuracy.

Minimal preprocessing for the resting-state fMRI included (Fitzgibbon et al. 2020) distortion correction, motion correction, two-stage registration of the MB-EPI functional image to the T2 structural image, temporal high-pass filtering (150 s high-pass cut-off), and individual component analysis (ICA)-based denoising using FSL's ICA-based X-noiseifier (FIX) (Salimi-Khorshidi et al. 2014). In addition to this minimal preprocessing, we smoothed the data [Gaussian filter, full-width half-maximum (FWHM) = 3 mm] across the gray matter and applied a band-pass filter at 0.009–0.08 Hz. To further denoise the data, we used aCompCor (Behzadi et al. 2007) to regress out physiological noise (heartbeat, respiration, etc.) from the white matter and cerebrospinal fluid (CSF).

Adults. HCP data were preprocessed using the HCP minimal preprocessing pipelines (Glasser et al. 2013). For the anatomical data, a PreFreeSurfer pipeline was applied to correct gradient distortion, produce an undistorted "native" structural volume space for each adult participant by anterior commissure-posterior commissure registration (hereafter referred to as "acpc space"), extract the brain, perform a bias field correction, and register the T2-weighted image to the T1-weighted image. In addition, each participant's brain was aligned to a common MNI152 template brain (with 0.7 mm isotropic resolution). Then, the FreeSurfer pipeline (based on FreeSurfer 5.3.0-HCP) was performed with a number of enhancements specifically designed to capitalize on HCP data (Glasser et al. 2013). The goal of this pipeline was to segment the volume into predefined structures, to reconstruct the white and pial cortical surfaces, and to perform FreeSurfer's standard folding-based surface registration to their surface atlas (fsaverage).

For the resting-state fMRI data, minimal functional analysis pipelines included the following: removing spatial distortions, correcting the motion, registering the fMRI data to structural and MNI152 templates, reducing the bias field, normalizing the four-dimensional image to a global mean, and masking the data with the final brain mask. After completing these steps, the data were further denoised using the ICA-FIX method (Salimi-Khorshidi et al. 2014). To mirror the adult and neonatal preprocessing pipelines, we unwarped the data from MNI152 to acpc space, allowing both groups to be analyzed in "native" space. We then applied spatial smoothing (Gaussian filter, FWHM = 3 mm) within the gray matter, band-pass filtered at 0.009–0.08 Hz, and implemented aCompCor to regress out physiological noise, just as we did with the neonates.

All subsequent analyses in neonates and adults were performed in each subject's native space, except for the whole brain voxelwise analysis.

Connectivity Analyses

We used the 7-network cortical parcellation identified by Yeo et al. (2011). For the whole hippocampus and long-axis analyses, the hippocampal label was binarized from FreeSurfer's (surfer.nmr.mgh.harvard.edu) aparc+aseg parcellation and visually inspected for accuracy in each subject. For the first long-axis gradient analysis, this label was further sectioned into anterior and posterior portions via manual segmentation using FreeSurfer, with the uncal apex as the dividing marker (Poppenk and Moscovitch. 2011). All labels (cortical networks, hippocampal labels) were originally in combined volumetric and surface-based registration (CVS) average-35 MNI152 space and then registered to each individual subject's anatomical data using ANTs (Advanced Normalization Tool) 3dWarpMultiTransform (ANTs version 2.1.0; https://doi.org/10.5281/zenodo.3973370; Avants et al. 2011). ANTs is routinely used for developmental dataset registrations (Alexander et al. 2019; Dean et al. 2018). The resulting registrations were checked for accuracy. Similarly, for the long-axis gradient analysis, the hippocampal label in CVS was split into nine equally spaced "slices" along the anterior-posterior axis. Using the same ANTs registration technique for all regions of interest provided an extra measure of consistency between groups and between analyses; however, as an added quality check, we ran our whole hippocampus to network analysis using the binarized hippocampal label provided by the dHCP and HCP for each individual. These second results are nearly identical (see Supplemental

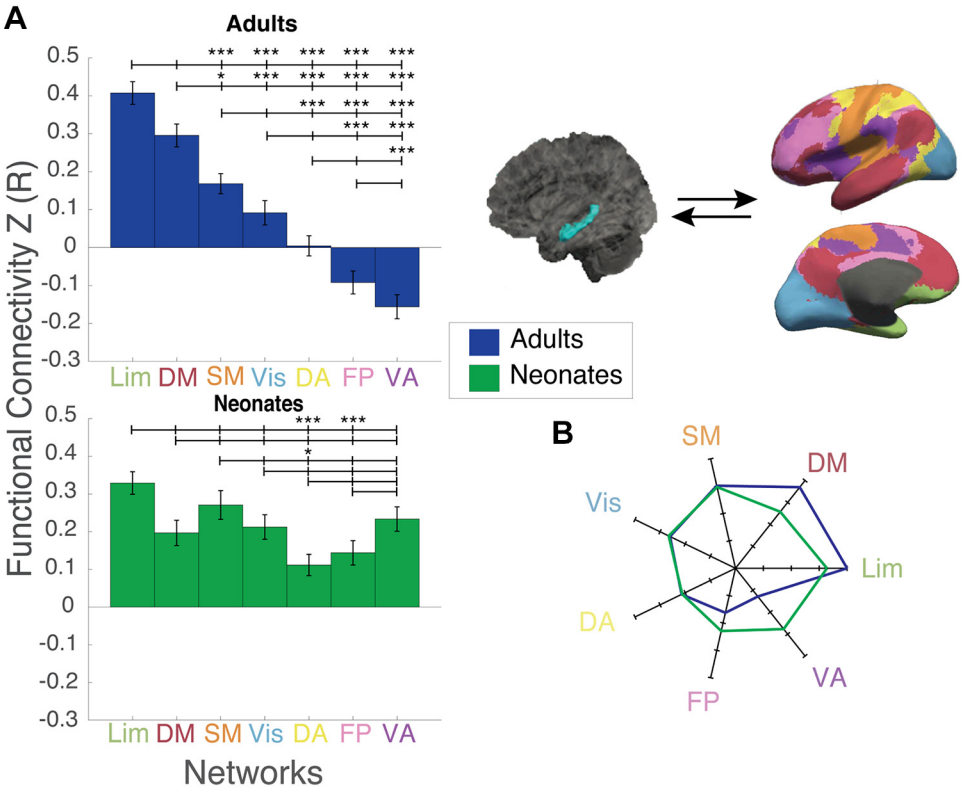

Fig. 2. Hippocampal connectivity to cortical networks. *A*: comparison (through ANOVA and subsequent *t* tests) of hippocampal connectivity to the seven cortical networks in adults (*top*) showed a hierarchy of hippocampal connectivity, whereby the highest FC was with Lim, followed by DM, SM, and Vis, almost no FC with DA, and negative FC with FP and VA. In contrast, neonates (*bottom*) show the same level of FC to almost all of the seven networks. *B*: rose plot to the right shows adult connectivity compared with neonates to highlight the differences between groups in the pattern of hippocampal FC to these networks. Brain images on the *top right* depict connectivity between the hippocampus (*left*) and the seven cortical networks (*right*). $^{*}p_{HB} < 0.05$; $^{***}p_{HB} < 0.005$. Adults, n = 40, 15 female; neonates, n = 40, 15 female. DA, dorsal attention; DM, default mode; FC, functional connectivity; FP, frontoparietal; Lim, limbic; SM, somatomotor; VA, ventral attention; Vis, visual.

Fig. S2-1) to the first (Fig. 2), thus increasing confidence that our results are not due to registration error.

After registration to the anatomical data, we registered the labels onto the functional data in neonates using an inverse warp of the func2anat matrix provided by the dHCP. In adults, the labels in acpc space after ANTs registration were then resampled to 2 mm cubic voxels to align with the functional data. We manually checked individuals from each sample to ensure the accuracy and fit of the labels to the individual functional data. We extracted the BOLD activation in each label over the time course, averaged within each label, and correlated the hippocampal activity—first whole hippocampus, then along the long axis (for both anterior-posterior and gradient slices)—with activity in each of the seven networks to create a Fisher's *z*-scored correlation matrix using Matlab r2018b (The MathWorks, Inc., Natick, MA).

We also explored differences in the hippocampal connectivity to the whole cortex at a voxelwise scale between adults and neonates to determine whether specific regions within the networks were driving adult-neonate differences. Hippocampal connectivity to the cortex was calculated by correlating the average hippocampal signal and the signal of each voxel within the cortical gray matter mask during the time course for each individual in functional space. To compare the connectivity between adults and neonates, images from both groups were registered to the template space (i.e., CVS average-35 MNI152) before running a between-groups analysis. Although this is the only template-space analysis we performed, template-space analyses have been routinely performed to compare infants with adults using similar registration methods (Gao et al. 2009; Gao et al. 2015a).

Experimental Design and Statistical Analyses

Although *t* tests were performed between regions, we corrected for multiple comparisons using the Holm–Bonferroni correction (Holm 1979); all connectivity values were Fisher's *z*-transformed (Fisher 1915) to normalize the data.

Before doing any of the planned analyses, we first performed data quality checks. To make sure there was no significant motion difference between groups, we calculated the framewise displacement (FD) (Power et al. 2012) based on the six motion parameters estimated from a rigid-body transformation provided by dHCP and HCP. We manually checked if the registration of the gray and white matter masks, as well as the network and hippocampal labels, in the adults and neonates was accurate. Because we are performing comparisons of correlations between groups, we next wanted to ensure that the correlation distributions were similar and were normally distributed in both neonates and adults; we did this by assessing the correlation of each voxel to every other voxel in the brain and by plotting the distribution of those correlations. We also performed between-subjects reliability of correlation matrices within and across the adult and neonate groups. We calculated the connectivity of each region (i.e., each of the seven networks and the hippocampus) to every other region for each subject. This connectivity matrix was then correlated with every other subject's value either between or within groups to assess intersubject reliability; in other words, we correlated the connectivity of every adult to every other adult (within group) and every neonate to every other neonate, as well as compared every adult with every neonate (between groups).

Our first analysis examined the relationship of the whole hippocampus to the seven cortical networks. After running a one-way ANOVA with network as the independent variable and connectivity as the dependent variable for both groups, we computed pairwise comparisons between each unique combination of connectivity values to the networks [e.g., hippocampal limbic (Hipp-Lim) vs. hippocampal ventral attention (Hipp-VA)] to determine networks with significantly different FC to the hippocampus (Snedecor and Cochran 1989). To ensure these network differences were not being driven by outside factors, we also ran a repeated-measures analysis of covariance (ANCOVA) including age and sex as covariates. Rose plots comparing the connectivity pattern of adults and neonates were created by subtracting the mean connectivity across all networks from each individual network (for adults

and neonates separately) and plotting the resulting magnitude to show the relative connectivity patterns of the hippocampus to the networks for each group and to compare these patterns between groups.

For our hippocampal-cortical voxelwise analysis, we used FSL's randomize function to compare between groups and perform permutation testing (to correct for multiple comparisons) to determine areas of greater connectivity in adults versus neonates and vice versa. After mapping the individual correlation matrices from subject (native) space into a common template space (Freesurfer's CVS atlas in MNI152), we used randomize with default 5,000 permutations and clustered the results using FSL's threshold-free cluster enhancement (TFCE), which corrects for familywise error (FWE). This produced a list of potential clusters with each cluster's associated P value; the P values were then thresholded at a $P < 0.0005$, and only those clusters that remained significant after that point are reported in this article.

For the first long-axis hippocampus analysis, we first computed a two-way ANOVA in each group (separately) using location (i.e., anterior or posterior hippocampus) and network as independent variables and FC as the dependent variable. Pairwise comparisons were then made between the anterior and posterior FC values to each network for each group (e.g., adult antHipp-Lim vs. adult postHipp-Lim). For the second long-axis analysis, we conducted a two-way ANOVA at each slice using group and network as independent variables and connectivity as the dependent variable. We also computed a one-way ANOVA at each slice for each group with network as the independent variable. As in the whole hippocampal analysis, rose plots were created by subtracting out the mean connectivity to all networks (e.g., mean connectivity of adult anterior hippocampus to all networks) from each network and group in the anterior and posterior labels individually to demonstrate comparative connectivity differences between the anterior and posterior regions in each group.

RESULTS

Preliminary Data Checks

Comparison of the framewise displacement in adults and neonates showed no significant difference of FD between adults and neonates [$t(78) = -0.48$, $P = 0.63$]. Visual inspection of the gray and white matter masks (which are critical for resting-state preprocessing) in Fig. 1*A* shows they are accurately delineating gray/white matter in both neonates and adults; the cortical networks [limbic (Lim), default mode (DM), somatomotor (SM), visual (Vis), dorsal attention (DA), frontoparietal (FP), ventral attention (VA)] and hippocampal labels also appear to be correctly localized, suggesting that the regions are accurately identified in both neonates and adults (Fig. 1*A*). Figure 1*B* demonstrates that both neonates and adults have normally distributed correlation values that are centered around 0. Between-subjects reliability of correlation matrices within and across the adult and neonate groups (Fig. 1*C*) showed the connectivity matrices (i.e., region-to-region connectivity of each of the seven networks and the hippocampus to each other) of each adult subject to each other adult subject were highly correlated (Fig. 1*C*, *left* bar), as were the matrices of each neonate subject to each other neonate subject (Fig. 1*C*, *middle* bar), and a pairwise comparison of subject variability within groups (e.g., adult-adult correlations compared with neonate-neonate correlations) was not significant [$t(78) = 0.76$, $P = 0.45$]. But subject-to-subject (i.e., each adult to each neonate) correlations across the two groups were significantly lower than the within-group correlations (Fig. 1*C*, *right* bar) [adult-adult vs. adult-neonate, $t(78) = 14.09$, $P = 3.87 \times 10^{-23}$; neonate-neonate vs. adult-neonate, $t(78) = 11.95$, $P = 2.63 \times 10^{-19}$], suggesting that although the connectivity data are reliable, neonates have different connectivity patterns than adults.

Whole Hippocampus

Adults. We first explored the connectivity of the whole hippocampus to the cortical networks. In adults, there was a main effect of network, suggesting that some networks are more strongly connected with the hippocampus than others [Fig. 2*A* (*top*); one-way ANOVA, $F(6,273) = 47.11$, $P = 1.84 \times 10^{-39}$]. Subsequent pairwise comparisons (Supplemental Table S2-I) showed a clear hierarchy of connectivity, such that hippocampal connectivity was highest to the Lim network versus (i.e., significantly higher than) hippocampal connectivity to VA, FP, DA, Vis, and SM networks. Hippocampal connectivity to DM was higher than hippocampal connectivity to VA, FP, DA, Vis, and SM. Hippocampal-SM connectivity was third highest and higher than hippocampal connectivity to VA, FP, and DA. Hippocampal-Vis connectivity was the next highest (vs. VA and FP), and connectivity with DA was higher than with VA. In summary, hippocampal connectivity was the highest to Lim, followed by DM, then SM, Vis, and DA; hippocampal connectivity was the lowest (negatively correlated) with the FP and VA network. After controlling for age and sex, a robust main effect of network remained [repeated-measures ANCOVA, $F(6,32) = 32.935$, $P = 2.34 \times 10^{-12}$].

In previous literature, the hippocampus is occasionally included as a part of the DM network; our finding of high hippocampal-DM correlation and anticorrelation between the hippocampus and attention (i.e., FP and VA) networks falls in line with earlier work on the connectivity of the DM network (Buckner et al. 2008) and is a good sign of the reliability of our results.

Neonates. In contrast to the adult pattern, although neonates did show a main effect of network [$F(6,273) = 5.12$, $P = 2.27 \times 10^{-5}$], pairwise comparisons [Fig. 2*A* (*bottom*) and Supplemental Table S2-II] indicated that only connectivity to the Lim and SM networks significantly differs from the rest, with significantly greater connectivity from the hippocampus to Lim versus DA [$t(78) = 5.31$, $p_{HB} = 2.15 \times 10^{-5}$] and Lim versus FP [$t(78) = 4.22$, $p_{HB} = 1.33 \times 10^{-3}$] and significantly greater connectivity to SM versus DA ($t(78) = 3.35$, $p_{HB} = 0.023$). The main effect of network remained after controlling for age (both at birth and at scan) and sex [repeated-measures ANCOVA, $F(6,31) = 15.110$, $P = 5.23 \times 10^{-8}$].

Adults versus neonates. Pairwise comparisons between adults and neonates showed significant differences between the groups, with significantly less connectivity in adults to Vis [$t(78) = -2.64$, $p_{HB} = 0.040$], DA [$t(78) = -2.77$, $p_{HB} = 0.035$], FP [$t(78) = -5.33$, $p_{HB} = 5.49 \times 10^{-6}$], and VA [$t(78) = -8.62$, $p_{HB} = 5.86 \times 10^{-13}$] networks compared with in neonates.

Hippocampus to Cortex Voxelwise Analysis: Adults versus Neonates

We next explored the connectivity of the hippocampus to the entire cortex at a voxelwise scale; because our previous analysis only focused on seven canonical networks, we may have missed differences between neonates and adults at a finer grain than that seen on a network level. Thresholding the unpaired t test results of the whole brain clusters at $P < 0.0005$ produced 26

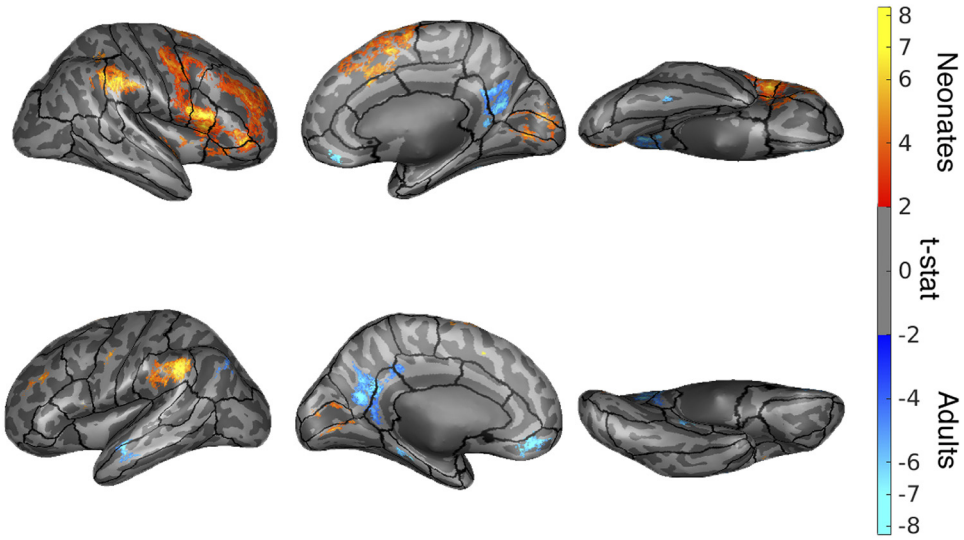

Fig. 3. Hippocampal connectivity to cortex. Comparison of adult and neonate hippocampal connectivity to the cortex at a voxelwise grain. FWE-corrected t test results for the contrast of neonate > adult connectivity are shown in warm colors and for the contrast of adult > neonate are shown in cool colors. Adult, $n = 40$, 15 female; neonate, $n = 40$, 15 female. FWE, familywise error.

significant FWE-corrected (Smith and Nichols 2009) clusters in the neonates > adults comparison (i.e., 26 clusters where neonatal hippocampal FC significantly exceeds adult hippocampal FC) and 14 significant clusters in the adults > neonates comparison (Fig. 3). Specifically, neonates show greater hippocampal FC to the frontal and parietal areas, bilateral lingual and pericalcarine cortex, and cuneus when compared with adults; frontoparietal differences were particularly prevalent within the right hemisphere. Adults, on the other hand, displayed greater hippocampal FC than the neonates primarily to the bilateral isthmus cingulate and precuneus. Cluster sizes and indices for clusters greater than 200 voxels along with peak voxel location and associated brain regions are reported in Supplemental Tables S3-I and S3-II and largely follow the results from the seven-network analysis—the neonatal hippocampus shows greater FC to the frontoparietal and attention-relevant areas, whereas the adult hippocampus shows greater FC with regions associated with the default mode and limbic networks.

Anterior-Posterior Hippocampus

Adults. We next explored the anterior versus posterior hippocampal connectivity patterns in neonates and adults; previous literature in both humans and other animals suggests functional differentiation of the anterior and posterior hippocampal segments, and thus, we may expect these segments to have differences in FC to the seven cortical networks. In adults, a two-way ANOVA indicated a main effect of network [$F(6,546) = 60.04$, $P = 5.04 \times 10^{-57}$] and an interaction between network and anterior/poster hippocampus [$F(6,546) = 14.31$, $P = 3.54 \times 10^{-15}$] (Fig. 4*A*, *top*).

Pairwise comparisons between the anterior and posterior portions of the hippocampus in adults show greater anterior versus posterior connectivity to the Lim [$t(78) = 3.53$, $p_{HB} = 0.0035$], DMN [$t(78) = 2.38$, $p_{HB} = 0.03$], and SM [$t(78) = 3.19$, $p_{HB} = 0.0082$] networks, and decreased anterior versus posterior connectivity to the DA [$t(78) = -3.07$, $p_{HB} = 0.0087$], frontoparietal [$t(78) = -5.79$, $p_{HB} = 9.99 \times 10^{-7}$], and VA [$t(78) = -3.92$, $p_{HB} = 0.0011$] networks. These results suggest the anterior hippocampus was primarily driving the negative correlations with VA and FP seen at the level of the whole hippocampus in adults.

Neonates. In neonates, the two-way ANOVA showed only a significant main effect for network [$F(6,546) = 7.67$, $P = 6.30 \times 10^{-8}$] (Fig. 4*A*, *bottom*). Neonates show no significant differences between the anterior and posterior portions of the hippocampus to any of the networks, suggesting no differentiation/specialization of the hippocampal segments in their connections to the rest of the brain.

Long-Axis Gradient

Finally, we investigated the long-axis gradient, which has been demonstrated to map onto a differential functional gradient of the hippocampus. We broke up the hippocampus in each subject into nine different segments along the anterior-posterior axis and compared the seven-network connectivity to these segments in neonates and adults (Fig. 5).

Adults. Adults showed clear differentiation of network connectivity along the long axis, whereas neonates showed no clear differentiation (Fig. 5, *top*). The Lim and DM in adults appeared to have an initial rise and fall of FC along the anterior-posterior gradient of the hippocampus that differentiated them from the Vis, SM, and DA, and the FP and VA showed a similar rise and fall of negative FC along the gradient. One-way ANOVAs for adults at each slice indicated a main effect of network in adults in all but the most posterior slice: *slice 1*, $F(6,273) = 23.61$, $P = 1.89 \times 10^{-22}$; *slice 2*, $F(6,273) = 40.45$, $P = 4.19 \times 10^{-35}$; *slice 3*, $F(6,273) = 50.09$, $P = 2.61 \times 10^{-41}$; *slice 4*, $F(6,273) = 49.56$, $P = 5.48 \times 10^{-41}$; *slice 5*, $F(6,273) = 49.07$, $P = 1.11 \times 10^{-40}$; *slice 6*, $F(6,273) = 25.10$, $P = 1.12 \times 10^{-23}$; *slice 7*, $F(6,273) = 13.40$, $P = 2.57 \times 10^{-13}$; *slice 8*, $F(6,273) = 5.51$, $P = 2.12 \times 10^{-5}$.

Neonates. In the neonates, one-way ANOVAs show no main effect of network in any of the slices (at $P < 0.001$) (Fig. 5, *bottom*).

Adults versus neonates. To compare between the two groups, we performed two-way ANOVAs (with network and group as independent variables and FC value as the dependent variable) for each of the nine slices. There was a significant interaction between network and group for the anterior seven slices—*slice 1*, $F(6,546) = 7.30$, $P = 1.64 \times 10^{-7}$; *slice 2*, $F(6,546) = 16.25$, $P = 2.95 \times 10^{-17}$; *slice 3*, $F(6,546) = 18.98$, $P = 3.99 \times 10^{-20}$;

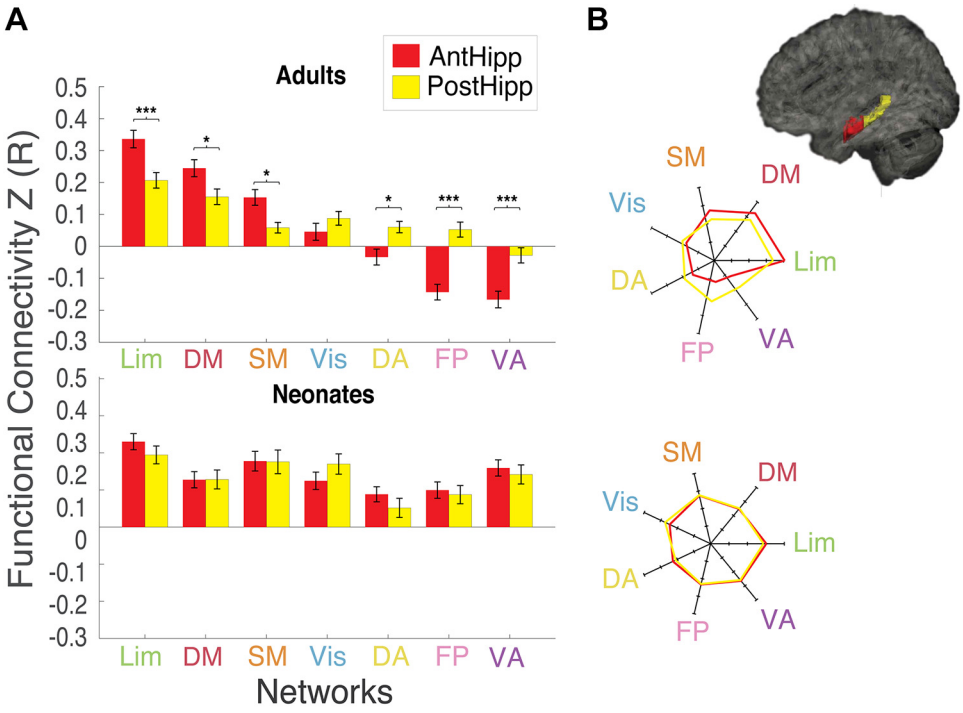

Fig. 4. Anterior/posterior hippocampal connectivity to networks. *A*: anterior versus posterior hippocampal-network connectivity in adults (*top*) and neonates (*bottom*). *B*: rose plot comparing anterior versus posterior hippocampal-network connectivity pattern in adults (*top*) and neonates (*bottom*). *t* tests used for all statistics. Brain image to the right shows the anterior (red) and posterior (yellow) hippocampal labels *$p_{HB} < 0.05$; ***$p_{HB} < 0.005$. Adult, $n = 40$, 15 female; neonate, $n = 40$, 15 female.

slice 4, $F(6,546) = 17.22$, $P = 2.83 \times 10^{-18}$; *slice 5*, $F(6,546) = 17.93$, $P = 5.05 \times 10^{-19}$; *slice 6*, $F(6,546) = 5.79$, $P = 7.26 \times 10^{-6}$; *slice 7*, $F(6,546) = 4.87$, $P = 7.27 \times 10^{-5}$; and *slice 8*, $F(6,546) = 3.89$, $P = 8.26 \times 10^{-4}$—but no group differences for the most posterior slice. These results show that the biggest differentiation of hippocampal connectivity to the seven networks occurs in the anterior two-thirds of the hippocampus in adults, but neonates do not show this differentiation.

DISCUSSION

Our results show that the functional connectivity of the hippocampal network is vastly immature at birth. Previous functional

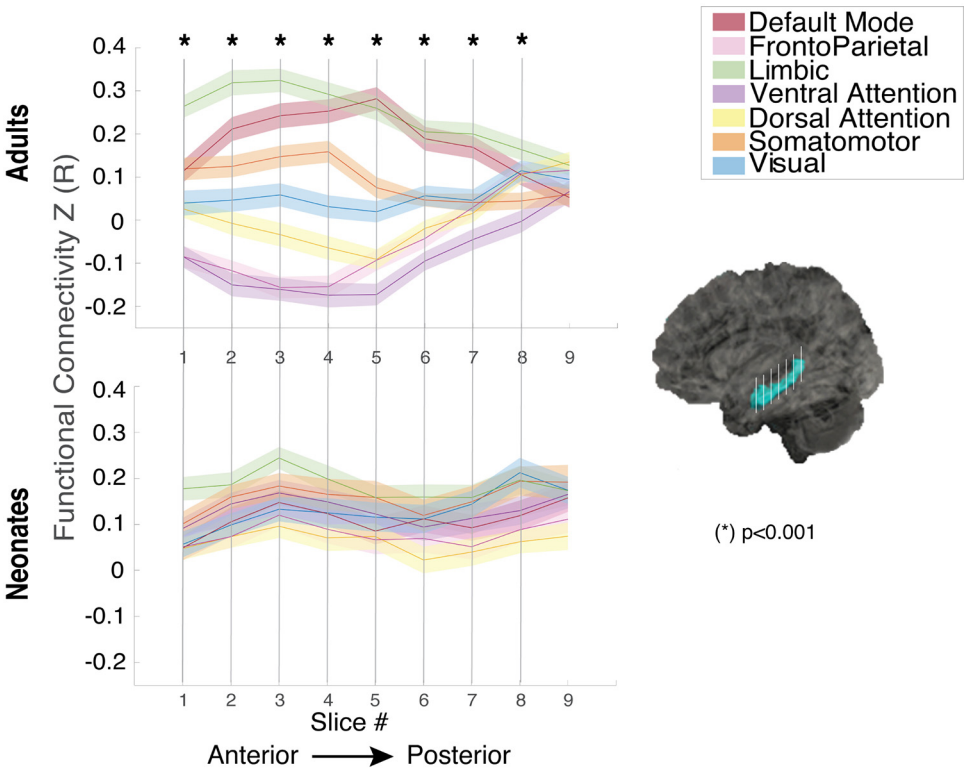

Fig. 5. Connectivity along the long-axis gradient to networks. Comparison of the connectivity of the long-axis gradient of the hippocampus to the seven networks in adults (*top*) and neonates (*bottom*). The slices are arranged anterior-to-posterior. Lighter coloring surrounding each line represents the standard error. Brain image on the right demonstrates the hippocampus (aqua) segmented into slices (white lines). *$P < 0.001$ represents the slices where the ANOVA shows an interaction between network and group. Adult, $n = 40$, 15 female; neonate, $n = 40$, 15 female.

and volumetric evidence in both nonhuman primates and humans suggests that the hippocampus continues to structurally develop beyond 1 yr of age, even into middle childhood (Blankenship et al. 2017; Jabès et al. 2011; Keresztes et al. 2018; Lavenex and Banta Lavenex 2013; Riggins et al. 2016). Although there is some evidence to suggest that the hippocampus is playing a key role in memory formation even early on in rodents (Alberini and Travaglia 2017; Travaglia et al. 2018), it has been suggested that the long-lasting memories of very young children may be created in a fundamentally different way from adult long-term memories and may rely on cortical mechanisms rather than the traditional hippocampal method (Ellis and Turk-Browne 2018; Gómez and Edgin 2016). Interestingly, multiple studies comparing preterm with term infants show no differences in gray matter volume in the hippocampus (when measured at 2 yr of age) with decreased gestational age, implying that substantial hippocampal growth occurs before birth (Alexander et al. 2019; Ge et al. 2015; Thompson et al. 2008); our work suggests that although the hippocampus may exist to some extent at birth, adultlike hippocampal-cortical connectivity does not. Specifically, the hippocampus does not have clear preferential connectivity to any particular network at birth and lacks any long-axis gradient of connectivity, suggesting that the hippocampus, the cortical networks it interacts with, and/or some combination of both are immature at birth and may therefore be unable to form long-term memories using adultlike mechanisms. Indeed, the cortex itself is still maturing early on (Gao et al. 2015b; Ofen et al. 2007; Salzwedel et al. 2019), and it is likely that this cortical immaturity, in addition to hippocampal immaturity, is contributing to the differences in memory formation between adults and neonates.

Adults showed a clear hierarchy of FC to the seven networks [consistent with Vos de Wael et al. (2018)], whereas neonates lacked this hierarchy. Furthermore, the comparison between adults and neonates shows significant differences between groups to all networks except the SM network, and only marginally significant differences between groups in the Vis and DA networks. The similarity between adults and neonates in connectivity to the SM and Vis networks may be due to the relative maturity of these areas at birth (Arcaro and Livingstone 2017; Dall'Orso et al. 2018; Deen et al. 2017; Gao et al. 2017; van den Hurk et al. 2017).

To more specifically determine which regions in the networks were responsible for the differences seen between adults and neonates, we conducted a voxelwise cortical analysis. Our results indicate that neonates have higher connectivity to much of the cortex as compared with adults with the exception of areas of bilateral medial orbitofrontal, isthmus cingulate, and precuneus. This is consistent with Riggins et al.'s (2016) conclusion that 4-yr-old children rely more on regions "outside" the canonical hippocampal network to complete episodic memory tasks, and other research suggesting the infant cortex is more broadly tuned than in adults (Ellis &Turk-Browne 2018). The few regions where adults display higher FC than neonates reside mainly within the DM network and highlight the immaturity of this network: adults show significantly greater DM-hippocampal connectivity than neonates, consistent with Gao et al.'s (2015a) finding that this network is one of the last to develop in the first year of life.

Our anterior-posterior analysis and long-axis gradient analyses again suggest that the FC differentiation of the hippocampus is lacking at birth. Consistent with previous literature, adults display changes along the long-axis such that the anterior hippocampus shows greater connectivity to the Lim network than the posterior hippocampus but greater posterior versus anterior FC to the attention (i.e., FP and VA) networks; in fact, the anterior hippocampus is especially anticorrelated with these networks, as is consistent with previous literature (Buckner et al. 2009; Vos de Wael et al. 2018). The greatest differentiation in FC to the networks in adults occurred within the anterior two-thirds of the hippocampus. In contrast, neonates showed no specificity to any of the networks along the long-axis or the anterior-posterior analysis. Blankenship et al. (2017), Langnes et al. (2019), and Riggins et al. (2016) show evidence of specialization along the longitudinal axis in 4- and 6-yr-old children, but no such evidence is seen in our results, suggesting that maturational changes within the hippocampus may occur before age 4 to produce the preferential connectivity seen in children and adults. Future studies of infants and toddlers can better elucidate when after birth this change in specialization of the long axis occurs.

Several limitations warrant discussion. A major problem in imaging children is motion artifact. We used the motion-corrected data that were released by the dHCP, took steps in preprocessing to ensure that physiological artifacts were removed from the data in both neonates and adults (Power et al. 2014; Yan et al. 2013), and further motion-matched the neonatal and adult groups. Given that motion-related artifacts are a major confound in FC analyses (Power et al. 2012; Satterthwaite et al. 2013), our approach should minimize the risk of spurious correlations. Other steps we took to minimize potential confounds included visual inspection of spatial registration results [and using established registration procedures that have been previously performed on infants (Alexander et al. 2019; Dean et al. 2018; Gao et al. 2009; Gao et al. 2015a)], performing the analyses in the native space of each individual, and checking the reliability of the correlation values across participants in each group to ensure they were not particularly noisy in the neonatal group. A result of particular note is that neonates showed primarily positive FC from the hippocampus to the networks, whereas adults showed slightly negative FC for some networks. Blankenship et al. (2017) similarly fail to show any negative hippocampal FC in their sample of 4- and 6-yr-old children [but this may be due to their preprocessing steps, see Murphy and Fox (2017) for discussion]. Here, we used the same preprocessing steps in both neonates and adults and used aCompCor and other preprocessing steps that should not necessarily remove negative correlations if they were there. Indeed, we found a normal distribution of correlation values in both neonates and adults (Fig. 1*A*), suggesting that negative correlations do exist in neonates, but not between the hippocampus and the cortex. Furthermore, regardless of the negative versus positive correlation differences, we observe a difference in the pattern of FC in adults (demonstrated in the rose plots) primarily in the anterior portion of the hippocampus; this is missing in neonates.

Differences in arousal states between the groups present another challenge. Mitra et al. (2017) showed differences in resting-state connectivity between sleeping infants and waking adults. However, observation of Mitra et al.'s data suggests that although the magnitude of connectivity may differ between arousal states, the overall pattern of connectivity remains similar (i.e., the same clusters of connectivity are observed in sleep and in rest, and their relative comparison with other clusters remains

similar across sleep states and age groups). Furthermore, although notable differences are seen between the 24-mo sleeping infants and waking adults in the study by Mitra et al., this difference is far less pronounced in the younger 6-mo infants. Based on previous EEG studies (Roffwarg et al. 1966), it is possible that younger infants experience less slow-wave sleep and more REM sleep, and thus, younger infants (versus older infants) during sleep would be expected to look more like awake adults due to the high similarity of REM and wakefulness activity patterns in EEG, particularly in infants. Because we would expect more awake-like REM sleep and less slow-wave sleep in young infants, we believe that the neonates in the current study are unlikely to show major wake/sleep confounds in their connectivity patterns. Finally, analysis of the same dataset but specifically of visual network connectivity showed striking *similarities* in connectivity patterns between neonates and adults (https://www.biorxiv.org/content/10.1101/712455v1), therefore suggesting that any differences in data acquisition and/or sleep states between adults and neonates are unlikely to systematically lead to the differences in network connectivity that we find here.

Finally, we found the motion- and gender-matched HCP adults considered for the present study tended to have lower tSNR than their respective dHCP counterparts. To ascertain this discrepancy was not the cause of observed group differences, we identified a separate group of 40 HCP adults whose tSNR matched that of the 40 neonates used here and performed our whole hippocampus to network analysis on this group. The resulting pattern matches the pattern observed from the previous analyses (i.e., using the original 40 HCP adults), reiterating that identified differences in connectivity patterns between adults and neonates are likely not spurious by-products of discrepant data quality (Supplemental Fig. S1-1).

In conclusion, our results suggest that the resting-state FC patterns of the human hippocampus are immature at birth. This immaturity may play a key role in infantile amnesia, and the vast differences between adults and neonates shown here suggest a fundamentally different memory and learning system from that of adults may be present at this point in development.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.L.H. and Z.M.S. conceived and designed research; A.L.H. performed experiments; A.L.H., D.E.O., and J.L. analyzed data; A.L.H. and Z.M.S. interpreted results of experiments; A.L.H. prepared figures; A.L.H. drafted manuscript; A.L.H., D.E.O., J.L., and Z.M.S. edited and revised manuscript; A.L.H., D.E.O., J.L., and Z.M.S. approved final version of manuscript.

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