

# Functional networks in the infant brain during sleep and wake states

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Functional brain networks are assessed differently earlier versus later in development: infants are almost universally scanned asleep, whereas adults are typically scanned awake. Observed differences between infant and adult functional networks may thus reflect differing states of consciousness rather than or in addition to developmental changes. We explore this question by comparing functional networks in functional magnetic resonance imaging (fMRI) scans of infants during natural sleep and awake movie-watching. As a reference, we also scanned adults during awake rest and movie-watching. Whole-brain functional connectivity was more similar within the same state (sleep and movie in infants; rest and movie in adults) compared with across states. Indeed, a classifier trained on patterns of functional connectivity robustly decoded infant state and even generalized to adults; interestingly, a classifier trained on adult state did not generalize as well to infants. Moreover, overall similarity between infant and adult functional connectivity was modulated by adult state (stronger for movie than rest) but not infant state (same for sleep and movie). Nevertheless, the connections that drove this similarity, particularly in the frontoparietal control network, were modulated by infant state. In sum, infant functional connectivity differs between sleep and movie states, highlighting the value of awake fMRI for studying functional networks over development.

**Key words:** early development; fMRI; functional connectivity; pattern similarity; consciousness.

## Introduction

The discovery of resting-state functional connectivity, or the synchronous fluctuation of brain regions during rest, transformed the way that neuroscientists think about brain function (Biswal et al. 1995, Biswal 2012). In the decades since its discovery, resting-state functional magnetic resonance imaging (fMRI) has been used to map different functional networks of the brain (e.g. default mode, control, and salience networks; Raichle et al. 2001, Corbetta and Shulman 2002, Dosenbach et al. 2006), describe brain network properties like modularity and flexibility (Bullmore and Sporns 2009, Bassett and Sporns 2017), predict cognitive abilities (Finn et al. 2015, Rosenberg et al. 2016), characterize reliable individual differences (Gordon et al. 2017, Gratton et al. 2020), and establish clinical biomarkers (Baker et al. 2019, Dhamala et al. 2023). Given this, resting-state fMRI has been increasingly used in developmental populations to track the emergence of functional networks relevant to cognition (Grayson and Fair 2017, Fair et al. 2021) and developmental disorders (Milham et al. 2012, Finn et al. 2014, Hull et al. 2017), including in dozens of published studies in infants (Gao et al. 2017, Zhang et al. 2019) and large-scale, longitudinal data collection efforts (e.g. HBN and ABCD in adolescents, BCP, dHCP, and HBCD in infants; Alexander et al. 2017, Casey et al. 2018, Howell et al. 2019, Fitzgibbon et al. 2020, Eyre et al. 2021, Volkow et al. 2021).

Resting-state functional connectivity is typically acquired while participants perform the simple task of staring at a fixation cross and letting their minds freely wander. Participants are actively discouraged from closing their eyes and falling asleep, as this impacts functional network measurements

(Tagliazucchi and Laufs 2014). More recently, however, naturalistic stimuli (such as movies) have become popular for collecting functional network measures (Sonkusare et al. 2019), particularly in developmental populations (Vanderwal et al. 2019), given that they help reduce head motion (Vanderwal et al. 2015, Frew et al. 2022). Functional brain networks differ between rest and movies in both adults (Betti et al. 2013, Lynch et al. 2018) and over development (Sanchez-Alonso et al. 2021). In fact, movies are increasingly being recognized as better than traditional fixation-rest tasks for test-retest reliability (Wang et al. 2017, Zhang et al. 2022), characterizing individuals (Vanderwal et al. 2017), and predicting behavior (Finn and Bandettini 2021, Gal et al. 2022), perhaps because movies (unlike rest) create a consistent brain state over time across participants. This has led some to argue for the need to examine the dynamics of cognitive states during typical resting-state (Gonzalez-Castillo et al. 2021) and to embrace more task-like paradigms (Finn 2021).

Yet, when it comes to infants, resting-state functional connectivity is measured differently: infant functional networks are almost exclusively assessed during natural sleep (Zhang et al. 2019). This is a reasonable approach, especially for young infants who spend lots of time sleeping (Poppe et al. 2021). Moreover, from a practical perspective, it is notoriously difficult to collect fMRI data in awake infants, who move at will, cannot understand or follow instructions, have short attention spans, and need frequent touch, feeding, and diaper changes. Nonetheless, studying the infant brain only in the sleep state may provide an incomplete picture, given sleep/wake differences in adults (Tagliazucchi and Laufs 2014, Song and Tagliazucchi 2020) and the sometimes

limited reliability of functional connectivity in sleeping infants (Dufford et al. 2021, Wang et al. 2021). Thus, apparent differences in functional brain networks between infants and older populations may not be attributable entirely to development *per se* and could be confounded by different states of consciousness. In line with this, the organization and properties of infant functional networks during sleep are more similar to adults in deep sleep than adults who are awake (Mitra et al. 2017).

Although qualitatively similar (Larson-Prior et al. 2009, Houldin et al. 2019), in adults, functional networks differ between sleep/wake states (Tagliazucchi and Laufs 2014) and across sleep stages (Haimovici et al. 2017, Stevner et al. 2019). Such state differences are pronounced in higher order associative networks, particularly the frontoparietal control and default mode networks (Horowitz et al. 2009, Spoormaker et al. 2012, Houldin et al. 2021). In general, sleep/wake differences in these networks come in the form of reduced functional connectivity during sleep. Similar results have also been found in other altered states, including under anesthesia (Boveroux et al. 2010, Qiu et al. 2017; cf. Chamberlain and Rosenberg 2022) and in disorders of consciousness (Li et al. 2023).

Currently, it is unknown whether scanning infants in an awake state may likewise yield differences in functional network measures. There are some reasons to believe that functional networks may not differ between sleep/wake states in infants. Indeed, infant sleep is different from adult sleep, with developmental changes in the interaction between the brainstem and cortex in rodents (Blumberg et al. 2014, Cirelli and Tononi 2015) and in sleep patterns and electroencephalography (EEG) microstructure in humans (Lokhandwala and Spencer 2022). Furthermore, infants spend more time in rapid eye movement (REM) sleep (Roffwarg et al. 1966, Knoop et al. 2021), which in adults tends to be more similar to wakefulness than non-REM sleep (Chow et al. 2013). Finally, the higher order associative networks that most distinguish sleep from wake in adults have a more protracted structural development than sensorimotor networks (Giedd and Rapoport 2010, Sydnor et al. 2021) and are observed inconsistently in sleeping infants (Hu et al. 2022a).

At the same time, there is also some suggestive evidence that functional networks may differ between sleep/wake states in infants. In fact, in the very first awake infant fMRI study, the prefrontal cortex was activated by forward versus backward speech but only during wake and not sleep states (Dehaene-Lambertz 2002). Indeed, there is growing evidence in awake studies that the prefrontal cortex contributes to cognitive function early in life (Raz and Saxe 2020, Ellis et al. 2021), despite its protracted development. As a result, higher order associative networks, including key nodes in the frontal lobe, may be more engaged and more inter-connected when infants are awake compared with asleep, when these networks may show reduced connectivity. Thus, infant functional networks may appear more adult-like when acquired in an awake state.

Recent advances have made it possible to scan infants with fMRI while they are awake and engaged in cognitive tasks (Ellis et al. 2020). This allowed us to examine infant functional networks during the wake state. Namely, we measured functional connectivity in infants scanned while they watched a movie awake and compared this with functional connectivity while they slept naturally. We further compared the infant data with awake adults scanned while watching the same movies or completing a canonical resting task with fixation. We used an adult atlas for parcellation and network labels (Schaefer et al. 2018) as in past studies (Sanchez-Alonso et al. 2021, Kardan et al. 2022), so as to have common regions for comparisons across age groups. We

first tested whether infants have a more similar pattern of whole-brain functional connectivity within (sleep–sleep, movie–movie) versus across (sleep–movie, movie–sleep) behavioral states. We next used pattern classification to decode behavioral state from functional connectivity patterns within and across age groups. We then tested whether having infants watch movies increases the similarity of their functional connectivity patterns to adults (who are typically scanned awake in functional connectivity studies). To interpret the resulting similarity, we quantified the contributions of individual network connections within and across functional networks. The results show that although both infant sleep and infant movie yield adult-like functional connectivity, the networks involved are modulated by state. This highlights the value of both sleep and awake infant fMRI for characterizing the nature and early development of functional brain networks.

## Materials and methods

### Participants

Sleep fMRI data were collected from 14 unique infants (7 female) who fell asleep naturally while we collected data for other awake fMRI experiments (not discussed here). In total, we obtained 20 usable sleeping runs from infants ranging from 3.9 to 24.9 mo of age ( $M = 11.2$ ,  $SD = 5.0$  mo). One participant contributed 2 sleep runs in the same session, separated by 8.5 min. Five participants had more than one session with usable sleep data ( $M = 1.4$  sessions, range: 1 to 3 sessions), with an average of 5.3 mo between sessions (range: 1.3 to 15.0 mo). One additional sleep run was excluded because the infant woke up after 1.5 min.

Movie-watching fMRI data were collected from 22 unique infants (14 female) who watched 1 of 2 cartoon movies, described in detail in a previous publication (Yates et al. 2022). Six of these movie participants overlapped with the sleep participants. In total, we obtained 34 usable movie-watching runs from infants ranging from 3.6 to 32.6 mo of age ( $M = 12.8$ ,  $SD = 7.3$  mo). Two participants had 2 usable movie-watching runs in the same session, separated by several minutes (10.5 and 15.9 min). Six infants completed more than one session with usable movie-watching runs ( $M = 1.5$  sessions, range: 1 to 6 sessions), with an average of 3.5 mo between consecutive sessions (range: 1.4 to 6.3 mo). The 34 runs do not include data from infants who had excessive head motion (>3mm framewise displacement) for more than 4% of the time ( $N = 37$ ), who did not look at the screen during more than half of the movie ( $N = 6$ ), who did not complete the movie because of fussiness ( $N = 9$ ), or because of technical error ( $N = 1$ ). The strict threshold of 4% maximum motion timepoints (rather than 50%, which we typically use for task-based awake infant fMRI studies) was chosen to equate the average proportion of usable timepoints between infant sleep and infant movie groups.

For comparison, we collected awake resting (staring at fixation) and movie-watching runs from 12 adults (7 female) aged 18 to 32 yr ( $M = 21.4$ ,  $SD = 3.4$  yr). We supplemented these 12 new adult movie-watching runs with 66 additional movie-watching runs we previously collected for other studies from 48 unique adults (27 female, age:  $M = 21.8$ ,  $SD = 3.2$  yr). In total, we thus had 12 runs of awake fixation-rest and 78 runs of movie-watching from adults. This does not include movie runs in which adults fell asleep part-way ( $N = 2$ ) or runs with excessive head motion (>3mm framewise displacement;  $N = 1$ ).

Infants who participated at Yale University ( $N = 10$  sleep,  $N = 19$  movie) were recruited through the Yale Baby School, an outreach

initiative to families who give birth at the Yale New Haven Hospital. Infants who participated at Princeton University ( $N = 4$  sleep,  $N = 3$  movie) were recruited via word-of-mouth and flyers. We did not have permission to collect detailed demographic information on the families at either site. However, to provide an approximate sense of the sample composition, we did obtain IRB approval to collect education, race, and ethnicity data in our most recent participant pool for subsequent studies at Yale University ( $N = 51$  families): the education of the primary caregiver was 25% Doctoral degree, 29% Master's degree, 24% Bachelor's degree, 2% Associate's degree, 10% some college, 4% vocational/trade school, 4% high school diploma, and 2% some high school; the race of the infants was identified as 61% White, 24% Asian/Asian-American, 12% Black/African-American, 2% two or more races, and 2% unknown; and the ethnicity of the infants was identified as 80% Non-Hispanic/Latino, 18% Hispanic/Latino, and 2% unknown. Adults were recruited from the New Haven, Connecticut area. No demographic information was obtained from these participants, although many were affiliated with Yale University. The study was approved by the Human Subjects Committee (HSC) at Yale University. All adults provided informed consent, and parents provided informed consent on behalf of their infant.

## Materials

Infant sleep runs were collected during natural sleep with the display turned off, without visual stimulation. Sleep state was not assessed physiologically, but all infants were assumed to be asleep based on extended eye closure and stillness, as viewed online via an MR-safe camera. Infants stayed asleep for variable durations, between 1.76 and 5.97 min ( $M = 4.31$ ,  $SD = 1.34$  min). We often stopped a sleep scan after 5 min to transition to anatomical scans or to try waking the child up for additional awake functional runs. Otherwise, we kept collecting sleep data until the child naturally woke up.

Infant movie runs were collected while infants watched 1 of 2 silent cartoon movies, previously described in Yates et al. (2022). The first movie, "Aeronaut", is a 3-min long segment of a short film about a miniature pilot and a little girl (<https://vimeo.com/148198462>). For all participants, the movie spanned 45.5 visual degrees in width and 22.5 visual degrees in height. The second movie, "Mickey", is a 2.37-min long segment of popular cartoon show where characters celebrate a birthday party. This movie was displayed in a smaller size, spanning 22.75 visual degrees in width and 12.75 visual degrees in height. Movie runs were collected while infants watched Aeronaut once ( $N = 25$ ), Aeronaut twice in a row ( $N = 1$ ), Mickey once ( $N = 7$ ), or Mickey twice in a row ( $N = 1$ ). We collapsed across both movies in all analyses, to capture the general effect of movie-watching on functional connectivity. Infant movie runs were thus between 2.37 and 6.00 min long ( $M = 3.01$ ,  $SD = 0.66$  min).

Adult fixation-rest runs were collected during quiet rest while participants stared at a white fixation cross (2 visual degrees) on a black background. Participants were not instructed to think about anything in particular. These rest runs always lasted 5 min, and the order of rest and movie-watching runs was counterbalanced across the 12 participants who completed both. Adult movie-watching data consisted of participants who watched Aeronaut once ( $N = 52$ ), Mickey once ( $N = 11$ ), or Mickey twice in a row ( $N = 15$ ), often interleaved with other movie-watching or experimental runs not described here. Adult movie runs were between 2.37 and 4.73 min long ( $M = 3.24$ ,  $SD = 0.76$  min).

The code used to display the movies and fixation is available at [https://github.com/ntblab/experiment\\_menu/tree/Movies/](https://github.com/ntblab/experiment_menu/tree/Movies/). The

code used to perform the data analyses is available at [https://github.com/ntblab/infant\\_neuropipe/tree/RestingState/](https://github.com/ntblab/infant_neuropipe/tree/RestingState/). Raw and preprocessed functional data are available on DataDryad: <https://datadryad.org/stash/dataset/doi:10.5061/dryad.nvx0k6dzf>.

## Data acquisition

We used a previously validated procedure for collecting infant fMRI data (Ellis et al. 2020) and adult comparison data. All adult data and most infant data ( $N = 16$  infant sleep runs,  $N = 26$  infant movie runs) were collected at the Brain Imaging Center in the Faculty of Arts and Sciences at Yale University. Data were acquired using a Siemens Prisma (3T) MRI using the bottom half of the 20-channel head coil. We used a whole-brain T2\* gradient-echo EPI sequence (TR = 2s, TE = 30ms, flip angle = 71, matrix = 64x64, slices = 34, resolution = 3mm iso, interleaved slice acquisition) to acquire functional images for both adults and infants. For infants, we collected a T1 PETRA sequence (TR1 = 3.32ms, TR2 = 2250ms, TE = 0.07ms, flip angle = 6, matrix = 320x320, slices = 320, resolution = 0.94mm iso, radial slices = 30,000) as the anatomical image. For adults, we collected a T1 MPRAGE sequence (TR = 2300ms, TE = 2.96ms, TI = 900ms, flip angle = 9, iPAT = 2, slices = 176, matrix = 256x256, resolution = 1.0mm iso), which included the top half of the 20-channel head coil. The remaining infant movie and sleep runs were collected at the Scully Center at Princeton University ( $N = 4$  sleep,  $N = 5$  movie) using a Siemens Skyra (3T) MRI and at the Magnetic Resonance Research Center (MRRC) at Yale University ( $N = 3$  movie) using a Siemens Prisma (3T) MRI. All acquisition procedures were the same, with the exception that the functional EPI sequence had slightly different parameters at these latter 2 sites (TE = 28ms, slices = 36).

## Procedure

All procedures followed lab conventions that have been used in our prior publications (e.g. Ellis et al. 2021, Yates et al. 2022). Infants and their parents met with researchers prior to their first scanning session. For almost all participants, these visits were conducted in-person as a "mock scanning" session; however, some visits were conducted over zoom in accordance with COVID-19 policies. We then scheduled scans for times the families thought their infant would be most comfortable. We extensively screened parents and infants for metal before and on the day of the scan. Infants were then equipped with 3 layers of hearing protection: silicone inner ear putty, over-ear adhesive covers, and ear muffs. Parents were permitted to bring comfort items (e.g. metal-free blankets) for their infant, and infants were wrapped with a vacuum pillow to reduce movement. We projected stimuli directly on the ceiling surface of the scanner bore, and recorded participants' faces with a camera (MRC high-resolution camera) during the session. Adults similarly viewed stimuli on the scanner bore ceiling and were monitored with a camera, but only had 2 layers of hearing protection (earplugs and optoacoustics noise-canceling headphones), were not given comfort items or a vacuum pillow, and did not attend a mock scanning session. For both adults and infants, additional tasks were sometimes run during their scanning session.

## Gaze coding

During infant movie-watching runs, gaze was coded offline by 2–6 coders ( $M = 2.39$ ,  $SD = 0.98$ ). Coders determined whether the participant's eyes were on-screen, off-screen (i.e. closed, blinking, or looking off of the screen), or undetected (i.e. out of the camera's field of view). In one infant, technical issues prohibited us from collecting gaze data, but this infant was monitored live by a

researcher during data collection and determined to be attentive enough to warrant inclusion. Coders were highly reliable, reporting the same response code on an average of 93.58% ( $SD = 4.87\%$ ; range across participants = 76.62–99.62%) of frames. The modal response across coders from a moving window of 5 frames was used to determine the final response for the frame centered in that window. The response from the previous frame was used in the case of ties. Frames were pooled within fMRI timepoints, and the average proportion of timepoints included for eyes being on-screen was high ( $M = 92.72\%$ ,  $SD = 9.45\%$ ; range across participants = 63.38–100%). Gaze data were not collected during infant sleep or adult rest runs, and gaze data were not analyzed for adult movie runs.

## Preprocessing

Data were preprocessed using a custom awake infant fMRI pipeline (Ellis et al. 2020). All adult data came from distinct functional runs, while movie and sleep data from infants were sometimes cleaved into pseudo-runs when another task was performed in the same functional run ( $N = 14$  sleep runs,  $N = 20$  movie runs). We discarded 3 burn-in volumes from the beginning of each run/pseudo-run. Then we determined the centroid volume of each run/pseudorun by calculating the Euclidean distance between the brain mass in all volumes and choosing the volume that minimized the spatial distance to all other volumes, using this as the reference for motion correction. Volumes were realigned using slice-timing correction. During preprocessing, we excluded timepoints with greater than 3 mm of translational motion, temporally interpolating them so as not to bias linear detrending. In additional analyses, we examined the impact of a stricter motion threshold (0.2 mm).

We included participants who had more than 96% of timepoints without motion. Thus, almost all timepoints were included after motion exclusion in infant sleep runs ( $M = 99.74\%$ ,  $SD = 0.75\%$ ; range across participants = 96.72–100%), infant movie runs ( $M = 99.64\%$ ,  $SD = 0.76\%$ ; range across participants = 96.67–100%), adult rest runs (all 100% usable), and adult movie runs ( $M = 99.99\%$ ,  $SD = 0.12\%$ ; range across participants = 98.89–100%). Average framewise displacement was also low in general: infant sleep runs ( $M = 0.22$  mm,  $SD = 0.10$ ; range = 0.06–0.44), infant movie runs ( $M = 0.34$ ,  $SD = 0.22$ ; range = 0.09–0.76), adult rest runs ( $M = 0.08$ ,  $SD = 0.02$ ; range = 0.05–0.11), and adult movie runs ( $M = 0.10$ ,  $SD = 0.07$ ; range = 0.05–0.47). However, there was higher motion on average for infant movie runs compared with infant sleep runs ( $P < 0.001$ ), and for adult movie runs compared with adult rest runs ( $P = 0.026$ ). In subsequent analyses, we excluded motion confound timepoints, and for infant movie runs, we also excluded timepoints during which eyes were closed for a majority of movie frames in the volume (out of 48, given the 2-s TR and movie frame rate of 24 frames-per-second). We constructed the mask of brain versus non-brain voxels by thresholding based on the signal-to-fluctuating-noise ratio (Friedman and Glover 2006). Then, data were spatially smoothed with a Gaussian kernel (5mm FWHM) and linearly detrended in time. We used AFNI's (<https://afni.nimh.nih.gov>) despiking algorithm to attenuate aberrant timepoints within voxels. Finally, after removing excess burn-out TRs, functional data were z-scored within run/pseudorun.

The centroid functional volume was first registered to the anatomical image using FLIRT in FSL (Jenkinson et al. 2012), and adjusted manually as needed using MR-Align from mrTools (Gardner et al. 2018). Then, the anatomical image was aligned into standard space using ANTs (Avants et al. 2011), a nonlinear alignment algorithm. For infants, we used an initial linear

alignment with 12 DOF to align their anatomical data to an age-specific infant template in MNI space (Fonov et al. 2009), followed by nonlinear warping using diffeomorphic symmetric normalization. After this alignment, we used a predefined transformation (12 DOF) to linearly align between the infant template and adult MNI standard (MNI152). For adults, we used the same alignment procedure, except that participants were directly aligned to the adult MNI standard. For all analyses, we only considered voxels included in the intersection of all infant and adult brain masks.

## Whole-brain functional connectivity

Functional connectivity matrices were created using the Schaefer brain atlas parcellation (Schaefer et al. 2018). The Schaefer atlas consists of parcels discovered from resting-state functional connectivity data in adults and is available at multiple resolutions. To match the number of brain regions found in neonatal resting-state analyses (Scheinost et al. 2016), and to account for potential anatomical variability across participants, we used the 100-parcel version of the Schaefer atlas. These parcels were matched to 7 functional networks—visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal control, and default (Yeo et al. 2011). The number of parcels that made up each network ranged from 5 (limbic) to 24 (default), with an average of 14.29 parcels. Note that these network labels for parcels correspond to adult functional networks, and their applicability to infant functional networks has not been established. Nonetheless, we use these labels throughout the manuscript to give an idea of the localization of our effects with respect to adult data.

To construct individual functional connectivity matrices, we averaged BOLD activity over all voxels in each parcel and correlated this average timeseries with every other parcel using Pearson correlation, after excising motion timepoints. The resulting coefficients were transformed into z-scores by normalizing to the average and standard deviation of the correlations across parcels, to account for potential differences in absolute correlation values across groups. We created group-level connectivity matrices by averaging across runs within group. To measure similarity within group, we correlated the upper triangle of each individual run's functional connectivity matrix with the average functional connectivity matrix for all but that run. We refer to this correlation as "intersubject similarity," as it tells us how similar a given individual is to the group, with higher values meaning that there is a pattern of functional connectivity that is consistent across individuals. We used an analogous procedure for calculating similarity across groups, by correlating an individual's upper triangle with the other group's average of all runs. In our main analyses, we considered all runs from each group, including from different sessions of the same participants. In additional analyses, we report an alternative approach in which we first averaged runs from the same participant to ensure that only between-participant variance contributed to the results.

We used bootstrap resampling to evaluate the statistical reliability of these functional connectivity similarity scores (Efron and Tibshirani 1986). Specifically, we randomly sampled with replacement from the run-level similarity values (z-scored Pearson correlations) to form a new sample of the same size as the original group, computed the average similarity of the sampled values, and repeated this procedure 1,000 times to create a sampling distribution. This approach also allowed us to compute the reliability of differences between states and groups: on each resampling iteration, we subtracted the mean similarity within one state or group from the mean similarity with another state or group to create a sampling distribution of the difference. We calculated  $P$



values as the proportion of iterations with the opposite sign of the original effect, doubled for a 2-tailed test.

### Decoding state within and across age groups

We further investigated how states modulated functional connectivity using pattern classification. The input features for the classifier models were the correlation values for every parcel-to-parcel connection in the upper triangle of the functional connectivity matrix and the output was the state during which functional connectivity was measured. To assess how different networks contributed to decoding accuracy, we also trained and evaluated classifiers on the subset of features within and across specific networks.

For each age group, we divided runs into training and test sets (approximately 90% training and 10% test), while subsampling runs from the more populous state so that the classifier was trained and tested with 50% of the examples from each state. In the training set, we further split the data (again 90% training and 10% test) to tune the cost parameter of a linear support vector machine classifier. The best cost parameter from these inner loops was used to train the classifier on the whole training set that was then applied to the held-out test data. This procedure was iterated across 10 folds. We used a generalization approach to assess whether the same features were important for classifying state in adults and infants by applying the best classifier trained in one age group to the other age group.

To determine statistical significance for classification analyses, we used the same bootstrap resampling approach as before, resampling with replacement at the run level 1,000 times. The *P* value was calculated as the proportion of iterations where classification accuracy was lower than chance (50%), doubled for a 2-tailed test. For network analyses, we visualize all network connections that are significant at the 0.05 level, and additionally indicate which connections survive Holms–Bonferroni correction on the alpha value.

Our main classification analyses required subsampling runs from the more populous state, which in theory could lead to underpowered results. Thus, in additional analyses, we retained the original distribution of participants from each state (e.g. 63% of infant runs were awake movie-watching, so the training and test set each had 63% movie runs). This meant that chance accuracy would no longer be 50%, as a random model would tend to guess the more populous state. Thus, for calculating statistical significance, we compared the true accuracy with a permuted null distribution, creating an “empirical chance.” Specifically, we repeated the full classification pipeline 1,000 times after randomly shuffling the labels. We then transformed the true classification accuracy into a *z*-score by subtracting the mean of the null distribution and dividing by its standard deviation. The *P* value was calculated as the proportion of iterations in the null distribution with higher classification accuracy than the true effect, doubled for a 2-tailed test.

### Similarity of functional connectivity between infants and adults

We next tested for differences in the similarity of functional connectivity across groups (e.g. infant sleep to adult movie vs. infant movie to adult movie). First, we tested for the main effect of infant state on overall similarity to adults: (infant sleep to adult movie + infant sleep to adult rest) - (infant movie to adult movie + infant movie to adult rest). Then, we tested for the main effect of adult state on overall similarity to infants: (infant sleep to adult rest + infant movie to adult rest) - (infant sleep to adult movie +

infant movie to adult movie). Finally, we tested for an infant state by adult state interaction: (infant sleep to adult movie - infant movie to adult movie) - (infant sleep to adult rest - infant movie to adult rest). For each test, we performed bootstrap resampling on the contrast values across participants to determine significance.

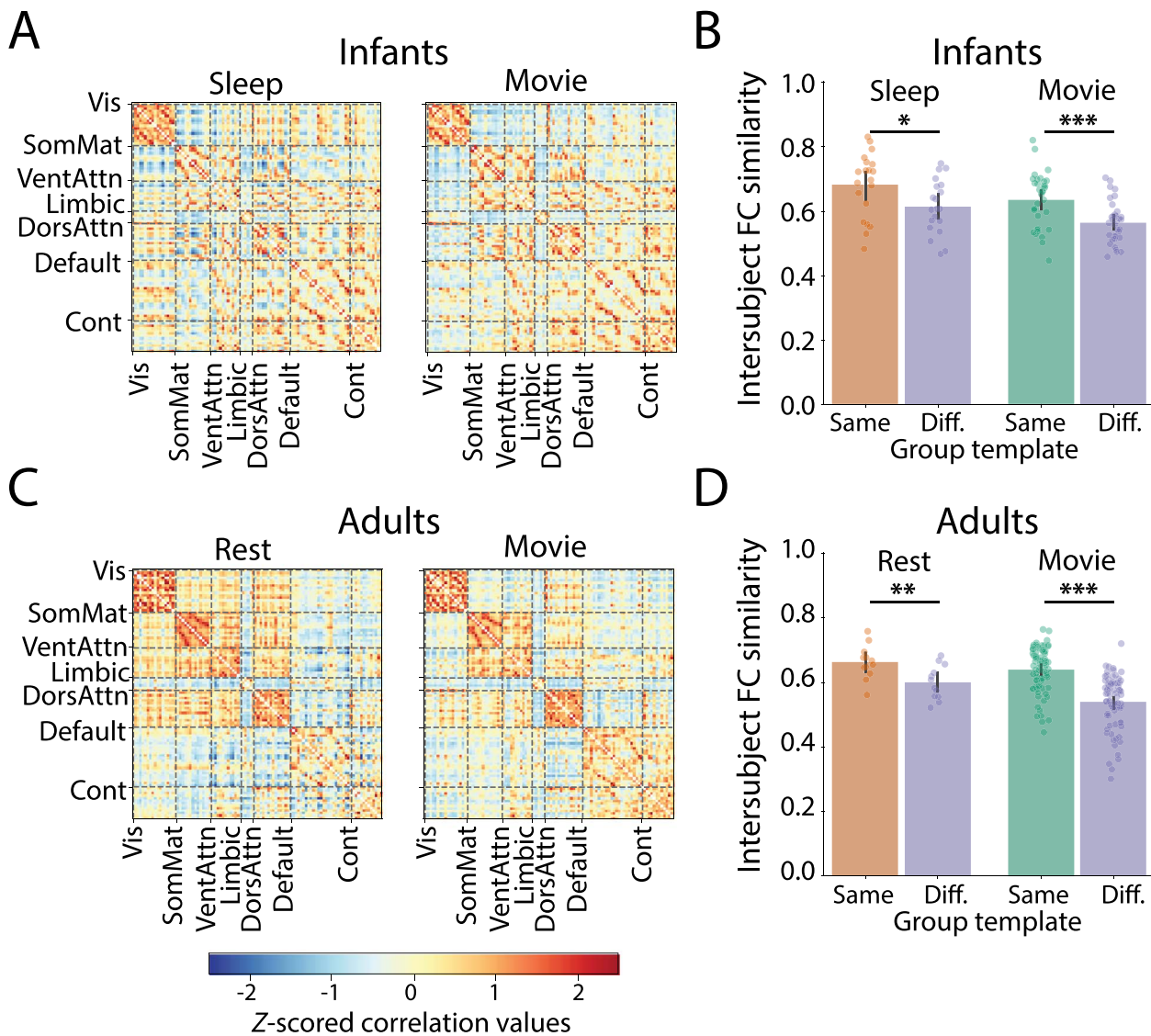
Finally, we evaluated the relationship between functional connectivity similarity and participant age with bootstrap resampling. Namely, we randomly sampled bivariate similarity-age pairs with replacement and re-calculated the Pearson correlation between similarity and age over the sampled pairs on each of 1,000 iterations. Again, the *P* value was calculated as the proportion of resampled coefficients with the opposite sign as the original effect, doubled for a 2-tailed test.

### Contribution of individual connections to overall network similarity

To understand which parcels drove overall similarity between 2 functional connectivity matrices, we used the fact that the Pearson correlation between 2 variables (in this case, vectorized matrices) is the sum of their pointwise products, after normalizing each variable by mean-centering and dividing by the root sum of squares (Turk-Browne 2013). Thus, for each run, the normalized pointwise product for a given cell in the matrix quantifies how much the functional connectivity between that pair of parcels contributed to the overall network similarity between that run and the average of other runs. We tested where in the brain these normalized pointwise product values differed between group and state comparisons. For example, we asked whether the same or different connections made sleeping versus movie infants similar to adults.

First, for each comparison of functional connectivity between an individual run and the average of a different group (e.g. a single infant sleep run to all adult rest runs), we created a normalized pointwise product matrix, where summing the values of the upper triangle of this matrix would equal the Pearson correlation between the upper triangles of the individual participant and group functional connectivity matrices. All values of pointwise product matrix were then converted to relative or proportional scores by dividing them by the overall correlation. We visualize the magnitude of these parcel-by-parcel contributions to the overall similarity between 2 groups by averaging across participants and plotting the top 1% of contributing connections on a Circos plot.

Next, we tested for differences in the contributions of connections between one group comparison (e.g. infant sleep and adult rest) and another group comparison (e.g. infant movie and adult rest). We visualize the top 1% of connections that contributed more to the similarity of one comparison over the other by subtracting the mean normalized pointwise product values from one another. We then ran our statistics at the network level. Specifically, we averaged the normalized pointwise product values for each group comparison per network (e.g. all parcel connections within the visual network, all parcel connections between the visual and somatomotor networks, etc.). Then, as before, we used bootstrap resampling to calculate the statistical reliability of differences. On each iteration, we subtracted the mean normalized pointwise product of one group comparison from the mean normalized pointwise product value of the other group comparison. In additional analyses, we also used a connection lesioning approach, where we assessed how removing one connection at a time changed the resulting correlation between groups. As with the decoding analysis, we visualize all network connections that are significant at the 0.05 level, and additionally



**Fig. 1.** Functional connectivity (FC) in infants and adults in different behavioral states. (A, C) Visualization of the average z-scored FC matrix in infants and adults, respectively. (B, D) Intersubject similarity values comparing the upper triangle of the FC matrix for an individual run with the average FC matrix of all other runs within the infant and adult age groups, respectively, for the same state (orange and green) or different states (purple). For example, “Sleep-Same” refers to the average correlation between the sleep FC matrix from one infant and the average sleep FC matrix from all other infants, while “Sleep-Diff.” refers to the average of the same individual sleep FC matrices correlated with the average movie FC matrix. The dots represent individual run data and error bars represent 95% bootstrap confidence intervals. \*\*\*  $P < 0.001$ , \*\*  $P < 0.01$ , \*  $P < 0.05$ . Network labels: visual (Vis), somatomotor (SomMat), ventral attention (VentAttn), limbic, dorsal attention (DorsAttn), default, and frontoparietal control (Cont).

indicate which connections survive Holms–Bonferroni correction on the alpha value.

## Results

### Functional network similarity within and across behavioral states

We first assessed the similarity of infant functional networks during natural sleep and awake movie-watching (Fig. 1A) by correlating the functional connectivity matrix of a single infant run with the average of all other infant runs. We found that infant functional networks were highly similar across participants within sleep ( $M = 0.681$ ) and movie ( $M = 0.633$ ) states, with slightly lower similarity across these 2 states (individual sleep to average movie:  $M = 0.614$ ; individual movie to average sleep:  $M = 0.564$ ). Average similarity did not significantly differ between sleep and movie (difference  $M = 0.048$ ,  $P = 0.066$ ; Fig. 1B).

Within-state similarity was higher than across-state similarity for sleep (difference in sleep–sleep and sleep–movie:  $M = 0.067$ ,  $P = 0.018$ ), and for movie (difference in movie–movie and movie–sleep:  $M = 0.069$ ,  $P < 0.001$ ). We used a somewhat liberal motion exclusion threshold as in prior studies (Ellis et al. 2020, 2021, Yates et al. 2022), but similar results were obtained with a stricter threshold (Fig. S1). These analyses contained more than one session or run from a subset of participants (mixing within- and between-participant variance), but the results were again similar if we first averaged runs within each unique participant to isolate between-participant variance (Fig. S2). Finally, given the importance of data quantity in functional connectivity analyses (Sylvester et al. 2023), we reran our analyses retaining only participants who had more than 2.9 min of usable data across runs within session. This amount of data can yield 95–100% accuracy in predicting infant functional connectomes (Wang et al. 2021). We replicated the pattern of results from our main analyses of infants and

adults in this restricted sample (Fig. S3). The one exception is that by restricting our analyses to those infants with the most usable data, we saw greater intersubject similarity within the sleep state compared with within the movie state (see also Fig. S1). However, this effect disappeared when all data were fixed to the same duration (Fig. S4). Thus, infant functional networks show comparable similarity across participants within sleep and movie states. Nonetheless, the network configurations seem to differ between states, as evidenced by decreased similarity across sleep and movie states compared to within states.

We next performed parallel analyses in adults as a point of comparison for the infant data (Fig. 1C). Adult functional networks were highly similar across runs in rest ( $M = 0.663$ ) and movie ( $M = 0.640$ ) states, with slightly lower similarity across these 2 states (individual rest to average movie:  $M = 0.599$ ; individual movie to average rest:  $M = 0.539$ ). Average similarity did not significantly differ between rest and movie (difference  $M = 0.023$ ,  $P = 0.172$ ; Fig. 1D). Within-state similarity was higher than across-state similarity for both rest (difference in rest–rest and rest–movie:  $M = 0.063$ ,  $P = 0.006$ ) and movie (difference in movie–movie and movie–rest:  $M = 0.101$ ,  $P < 0.001$ ). Importantly, the range and pattern of intersubject similarity values for adults was almost identical to that of the infants, confirming the quality of the infant data and the reliability of functional networks early in development.

### Classification and generalization of behavioral state

Given the within versus across state differences observed above, we hypothesized that it should be possible to decode infant behavioral state from patterns of functional connectivity using multivariate classification (Lewis-Peacock and Norman 2014). We first attempted to decode behavioral state within group based on whole-brain patterns of functional connectivity (Fig. 2A). Indeed, we could robustly decode infant state (sleep vs. movie:  $M = 91.33\%$  vs. 50%,  $P < 0.001$ ) and adult state (rest vs. movie:  $M = 93.33\%$ ,  $P < 0.001$ ; Fig. S5). There was no significant difference between infant state decoding accuracy and adult state decoding accuracy ( $P = 0.718$ ). To unpack these whole-brain results, we next attempted to decode behavioral state in each group at the level of networks (Fig. 2B). For both infants and adults, behavioral state was encoded throughout the brain, with functional connectivity varying by state within and across most pairs of networks. These results persisted if rather than subsampling participants to balance training examples we instead used a stratification approach that retained the original distribution of participants (Fig. S6).

This evidence that behavioral state can be decoded within both infants and adults, and in similar networks, leaves open a question about whether the same connectivity features encode state information in each group. If so, the parcel–parcel connection weights learned by the state classifier in one group should enable decoding of state in the other group (Fig. 2C). We first trained a classifier to distinguish rest versus movie in adults and tested whether it could generalize to distinguish sleep versus movie in infants (where rest and sleep were coded as the same class). This adult classifier was able to decode infant state reasonably well ( $M = 63.00\%$  vs. 50%,  $P < 0.001$ ). Surprisingly, however, generalization worked even better in the opposite direction: A classifier trained to distinguish sleep versus movie in infants robustly decoded rest versus movie in adults ( $M = 74.56\%$ ,  $P < 0.001$ ). This difference between the 2 classifiers in terms of generalization was statistically significant ( $P < 0.001$ ). We again performed a network-level analysis to gain a better understanding of where

this generalization occurs in the brain (Fig. 2D). Although adult-to-infant generalization occurred in many network connections, infant-to-adult generalization was much stronger, particularly in visual-ventral attention connections and ventral attention within network connections.

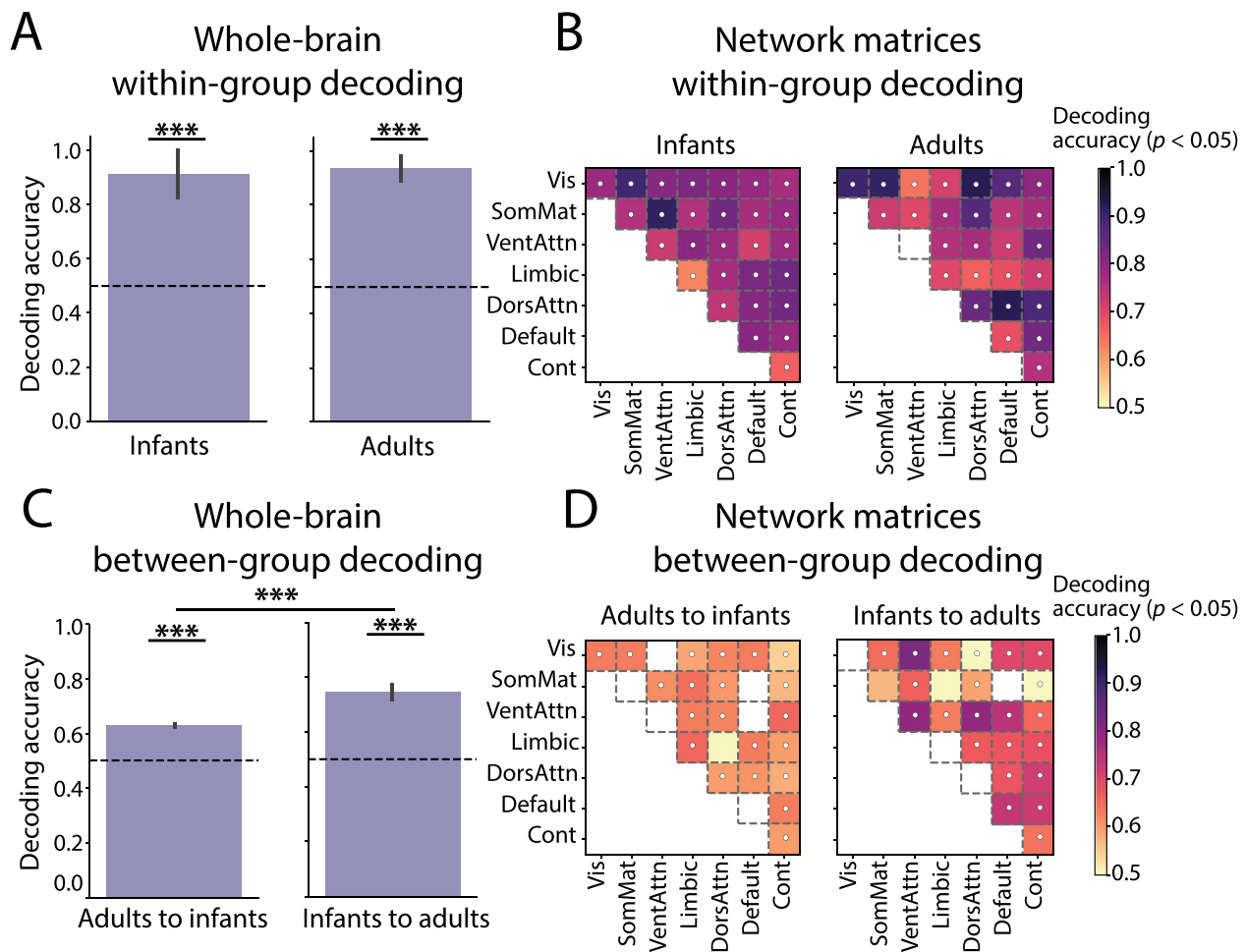
One interpretation of this asymmetry is that the connectivity features most useful for decoding infant state are represented in the adult brain, but that they are not the most useful features for adult decoding and thus are not weighted heavily enough in the adult classifier to allow their detection when tested on infant data. This bias toward adult features could have resulted from our use of an adult atlas for parcellation. However, when the analyses were repeated using an atlas based on neonatal functional connectivity (Scheinost et al. 2016), both within-age group decoding in infants and generalization from adults to infants remained unchanged (Fig. S7). Interestingly, within-age group decoding in adults and generalization from infants to adults decreased significantly when using an infant atlas compared to the adult atlas. This suggests that the asymmetry in decoding generalization does not result from the use of an adult atlas *per se*, but rather reflects a difference in the features of connectivity that are most useful for decoding within adults and infants.

### Functional network similarity between infants and adults

Infants and adults showed a comparable range of functional network similarity values within and across states in their own age group. Furthermore, some state-related features of functional connectivity were shared between infants and adults in the classifier generalization analyses. Here we test the similarity of infant and adult functional networks in more detail. We conducted a similar analysis to Fig. 1, except that this time we compared functional connectivity similarity across age groups. In particular, we correlated the functional connectivity matrix of an infant in either the sleep or movie state with the average of all adult runs in either the rest or movie state.

Infants in both states had moderately similar functional connectivity to adults (Fig. 3A), with no main effect of infant state (mean difference in infant sleep vs. infant movie:  $M = 0.046$ ,  $CI = [-0.027, 0.067]$ ,  $P = 0.404$ ). However, there was a main effect of adult state on similarity to infants (mean difference in adult rest vs. adult movie:  $M = -0.241$ ,  $CI = [-0.280, -0.186]$ ,  $P < 0.001$ ). Follow-up tests revealed that, regardless of infant state, infants were more similar to adults watching a movie than adults resting (infant sleep to adult rest vs. infant sleep to adult movie:  $M = -0.106$ ,  $P < 0.001$ ; infant movie to adult rest vs. infant movie to adult movie:  $M = -0.127$ ,  $P < 0.001$ ; infant sleep to adult rest vs. infant movie to adult movie:  $M = -0.107$ ,  $P < 0.001$ ; infant movie to adult rest vs. infant sleep to adult movie:  $M = -0.127$ ,  $P < 0.001$ ). In other words, infant functional networks during sleep or movie better resemble adults performing a naturalistic viewing task than adults fixating a cross while resting. We did not find a significant interaction between infant state and adult state ( $M = -0.028$ ,  $CI = [-0.071, 0.027]$ ,  $P = 0.424$ ). There was no difference between infant sleep ( $M = 0.351$ ) and infant movie ( $M = 0.330$ ) in similarity to adult rest (difference  $M = 0.021$ ,  $P = 0.258$ ), nor a difference between infant sleep ( $M = 0.457$ ) and infant movie ( $M = 0.458$ ) in similarity to adult movie (difference  $M = -0.000$ ,  $P = 0.938$ ). Importantly, although motion was higher for infants watching a movie compared with sleeping, average framewise displacement did not relate to similarity to adults for any comparison (Fig. S8).

The analyses above aggregated across all infants we tested. However, these infants ranged from 3 to 33 mo old, spanning



**Fig. 2.** Classification and generalization of behavioral state based on FC. (A) Significant decoding of states across the whole brain within age groups compared to chance (0.5). Error bars represent variability across 10 folds. (B) This was reflected in significant state decoding within and across pairs of networks ( $P < 0.05$ , uncorrected), with darker cells indicating larger effects, and white dots denoting cells that survived Holms–Bonferroni correction. (C) Although infant state could be decoded with the adult classifier, adult state was decoded much more robustly with the infant classifier. (D) Repeating this analysis for networks revealed some generalization from adults to infants, but more robust and widespread generalization from infants to adults. \*\*\*  $P < 0.001$ .

substantial developmental changes. We therefore performed an exploratory analysis of how similarity to adults changed with infant age (Fig. 3B). When compared with adult rest, the correlation between infant age and infant–adult similarity of functional connectivity did not reach significance for infant sleep ( $r = -0.441$ ,  $CI = [-0.732, 0.236]$ ,  $P = 0.184$ ) or infant movie ( $r = 0.237$ ,  $CI = [-0.004, 0.504]$ ,  $P = 0.052$ ). When compared with adult movie, there was again no significant correlation with age for infant sleep ( $r = -0.377$ ,  $CI = [-0.707, 0.458]$ ,  $P = 0.280$ ) or infant movie ( $r = 0.051$ ,  $CI = [-0.224, 0.338]$ ,  $P = 0.716$ ). Thus, there was no clear evidence of infant age-related differences in similarity to adults, though this question would be better addressed with a larger sample size and more uniform coverage of the age range.

### Network connections responsible for infant similarity to adult movie-watching

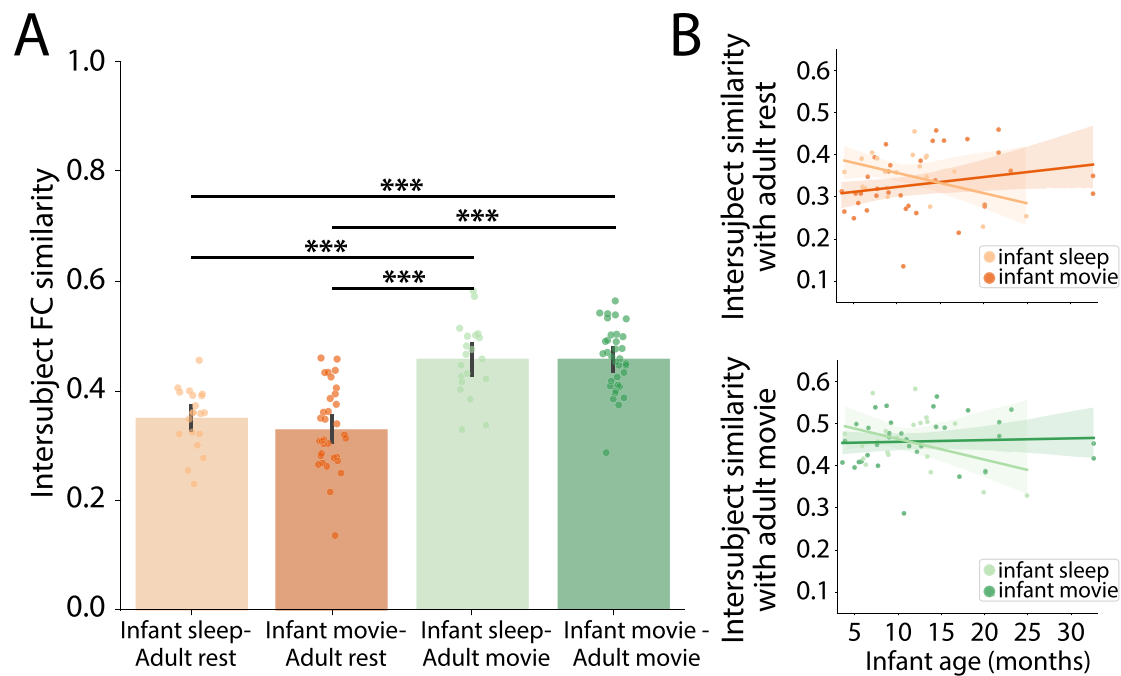
Our prior analysis showed a large main effect of adult state on similarity between infants and adults, with both sleeping and movie infants showing more similar functional connectivity to adults watching movies versus resting. To interpret this effect, we used a pointwise product approach to assess which parcel connections made a relatively larger contribution to this similarity. Averaging across infant sleep and movie states, the top

connections responsible for similarity to adults were largely the same connections for adult rest and adult movie states. These connections were mainly between parcels labeled with the same network, particularly in the visual network and default-mode network (Fig. 4A). To determine which connections contributed more to average infant similarity with adult movie compared with adult rest, we subtracted the average normalized pointwise product values of these 2 comparisons and visualized the top 1% of connections that contributed more to one comparison over another. We then calculated the significance of these differences at the network level with bootstrap resampling (Fig. 4B). Whereas similarity between infants and adult rest was driven more by within-network connections, similarity between infants and adult movie was driven more by connections between the visual network and other networks. This suggests that showing a movie revealed visual system interactions across the adult brain that are also present in the infant brain.

### Modulation of network connections driving adult similarity by infant state

The results so far show comparable overall levels of similarity between infant and adult functional connectivity for both sleep and movie infant states. However, which network connections





**Fig. 3.** FC similarity between infants and adults. (A) Intersubject similarity values from correlating the upper triangle of an individual infant FC matrix with the upper triangle of the average adult FC matrix for different combinations of infant and adult states. The dots represent individual run data and error bars reflect 95% bootstrap confidence intervals. (B) Relationship between infant age and similarity to adults across the different comparisons. The shaded region signifies the 95% confidence interval for the line of best fit. \*\*\*  $P < 0.001$ .

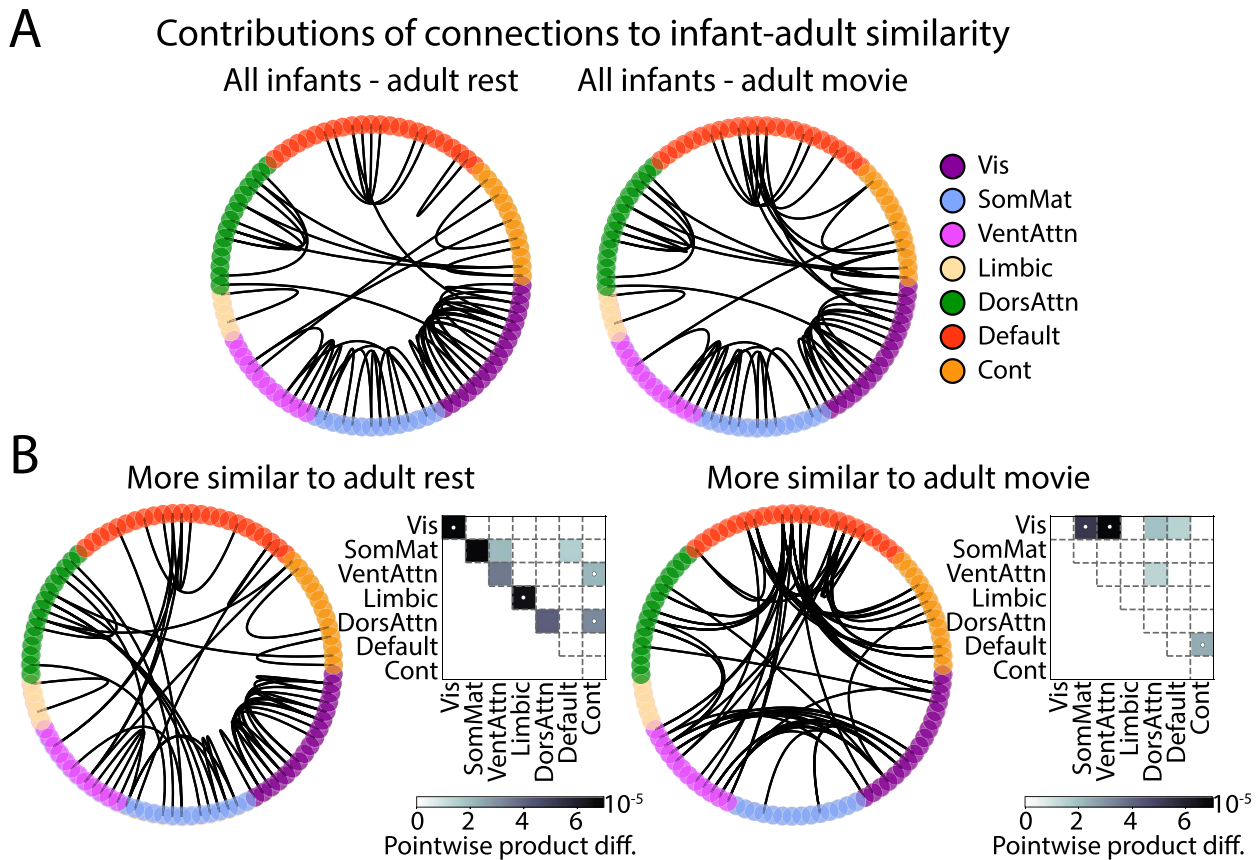
are responsible for this overall adult similarity could differ by infant state. We again performed a normalized pointwise product analysis to test for differences in contributions to adult similarity between infant sleep and infant movie states. Compared with adult rest (Fig. 5A), infant sleep similarity was driven by visual connections with other networks, whereas infant movie similarity was driven by ventral attention, dorsal attention, and control within-network connections; dorsal attention connections with other networks (ventral attention and somatomotor); and control connections with other networks (dorsal attention and visual). This infant state-dependent reorganization of network structure similarity to adult rest persisted in the comparison with adult movie (Fig. 5B). Similarity between infant sleep and adult movie was driven by visual-dorsal attention network connections, default-ventral attention connections, and control-somatomotor connections, whereas similarity between infant movie and adult movie was driven by control within-network connections and control connections to other networks (dorsal attention and visual). These results were replicated when we used a “lesioning” approach, removing network connections one at a time and assessing their impact on connectivity measures (Fig. S9). Thus, while infant state does not impact overall functional connectivity similarity to adults, it meaningfully changes which networks are more adult-like.

## Discussion

Motivated by the fact that almost all infant fMRI research to date has been conducted during sleep, this study fills a gap in the literature by examining functional brain networks in awake infants. As in adults, we found that whole-brain functional connectivity in infants differed between sleep and movie states. These states could be reliably decoded in held-out data within and across

groups. A surprising asymmetry in across-group generalization suggests that infant state differences in functional connectivity are preserved in adults, but that the strongest indicators of adult state are not as relevant in infancy. Overall similarity with adult functional connectivity was comparable in both infant states (and stronger when adults watched movies vs. rested), but different networks contributed more or less to the overall level of similarity depending on state. These results show that infant sleep/movie states modulate functional brain networks, highlighting the importance of considering infant behavioral state when assessing functional brain development relative to adults.

Differences in functional networks between rest and task are well-documented in adults and older children (Lynch et al. 2018, Finn and Bandettini 2021, Sanchez-Alonso et al. 2021), but much less is known about how functional networks differ between infants who are asleep (as is most common in the literature; Zhang et al. 2019) versus awake and engaging in a task (Nielsen et al. 2023). In fact, one might predict that functional networks would not differ between infant sleep/wake states, given that infants have different sleep patterns and stages than adults (Roffwarg et al. 1966, Knoop et al. 2021, Lokhandwala and Spencer 2022) and the networks involved in adult sleep emerge over development (Giedd and Rapoport 2010, Blumberg et al. 2014, Cirelli and Tononi 2015, Sydnor et al. 2021, Hu et al. 2022a). However, recent work has shown that functional networks as measured with EEG differ between quiet and active sleep in neonates (Tokariev et al. 2019) and are more strongly coupled and less clustered during sleep than wake in 6-mo-old infants (Smith et al. 2021). Here, we show that infants have more similar patterns of functional connectivity within the sleep state and within the movie state than across these states, and that these patterns can be decoded robustly by a classifier. Our results expand on previous



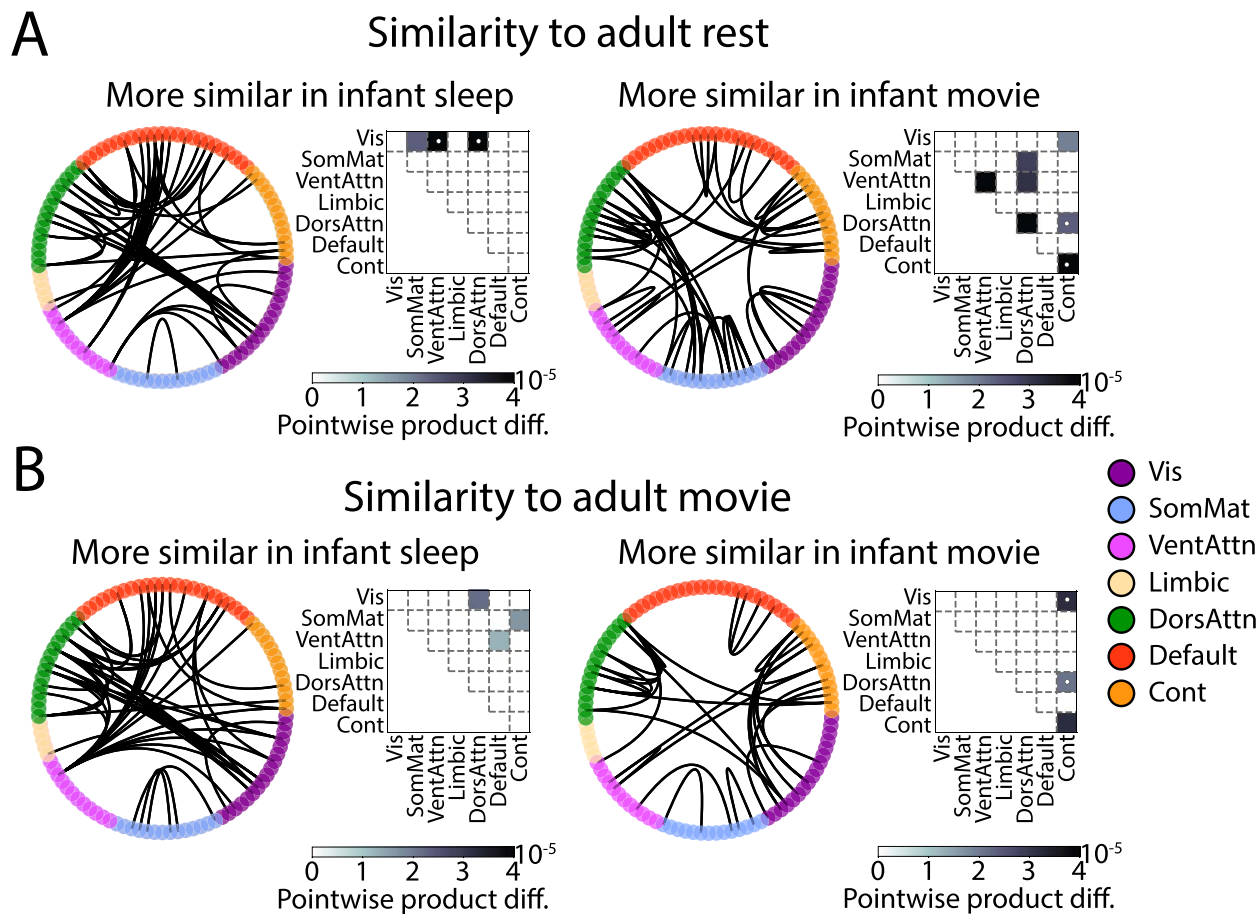
**Fig. 4.** Contributions of individual network connections to infant-adult similarity, as assessed by normalized pointwise products. (A) Circos plots showing the top 1% of connections that contributed to the similarity between all infants and adult rest, and between all infants and adult movie. (B) Differences in the contribution of network connections to infant similarity with adult rest versus adult movie. Circos plots show the top 1% of differences. Matrices indicate which network connections contributed significantly more to infant similarity with adult rest and adult movie at  $P < 0.05$ , uncorrected, with darker cells indicating larger effects. The white dots indicate which network connections survived Holms-Bonferroni correction.

findings in 2 ways: by (1) using fMRI, the dominant method to identify networks across the whole brain including away from the cortical surface; and (2) using movies in the awake state, because it will be necessary for future awake infant fMRI studies to employ engaging stimuli to reduce head motion and ensure compliance for more than a few seconds.

We did not find evidence for higher similarity between infants and adults in the awake state. Instead, infant functional networks were equally similar to adult functional networks regardless of sleep/movie state. This suggests that infant consciousness might not impact overall measures of functional network maturity, which validates previous studies that compared functional networks between sleeping infants and awake adults and bodes well for large-scale data collection efforts relying on sleeping fMRI data until early childhood (Fitzgibbon et al. 2020, Eyre et al. 2021, Volkow et al. 2021). Nevertheless, network-level analyses revealed modulation by infant state of which networks are most similar to adults, with connections between visual and dorsal attention networks among the strongest in infant sleep and connections within frontoparietal control network among the strongest in infant movie. These results are important because they mean that the functional maturity of certain networks may be underestimated in infant sleep data alone—particularly the frontoparietal control network, which is often characterized as one of the slowest developing networks in infancy (Gao et al. 2017, Zhang et al. 2019, Hu et al. 2022b). Whether this is true in general or an artifact of sleep data will

now require further investigation and data collection in awake infants.

Interestingly, infant functional networks were more similar to adults watching movies than to adults in a resting state, even when the infants were asleep. We do not think that this can be attributed to differences in noise between adult rest and adult movie, as functional networks were equally similar across participants in these states. As shown in Fig. 1, functional connectivity during adult rest consisted of stronger between-network connections than during adult movie, reflecting high integration (Bassett and Sporns 2017). Although previous work has shown greater between-network connections during tasks compared with rest, this is not always the case for movies (Gonzalez-Castillo and Bandettini 2018). Resembling adult movie, infants in both sleep and movie states showed weaker between-network connections, reflecting functional segregation. This observation may help explain the lower generalization from adults to infants in our multivariate decoding results: A classifier trained to distinguish adult rest and movie that then encounters infant data may choose the label “movie” more often if relying on features of network segregation. Thus, although some features relevant to state decoding may be preserved across development, those most heavily weighted in adults may not be applicable to infants. This result, which indicates that there are shared neural features between infants and adults despite a different neural pattern overall, fits with our prior work showing that infant neural event patterns during movie-watching are reflected in the



**Fig. 5.** Contributions of individual network connections to infant–adult similarity dependent on infant state, as assessed by normalized pointwise product values. Circos plots show the top 1% of connections that contributed more to the labeled comparison. Matrices indicate which network connections contributed significantly more in that comparison ( $P < 0.05$ , uncorrected), with darker cells indicating larger effects. The white dots indicate which network connections survived Holms–Bonferroni correction. (A) Contributions of network connections to similarity with adult rest for infant sleep and infant movie. (B) Contributions of network connections to similarity with adult movie for infant sleep and infant movie.

adult brain, despite differences in optimal neural event timescales (Yates et al. 2022).

We used movies as a comparison with sleep for this study because they are rich, activate multiple networks across the brain, and are highly engaging to infants. Nonetheless, infant–adult network similarity may differ in awake rest or other tasks, such as those that tax attention or have an auditory component. Indeed, this is a key motivation of this research: the nature and kind of the functional networks identified in infants will likely depend on the state of the infant during data collection. In future work, it will be important to investigate the reorganization of functional networks within (Yin et al. 2020) and across tasks in infants. These investigations will inform whether different states (such as movie-watching and rest) operate along a continuum in a common state space, or are instead qualitatively different and should be considered separately. We also did not find evidence of age-related changes in the similarity of functional networks between infants and adults in the current study. fMRI activity synchronizes across infants (and adults) watching the same movie (Yates et al. 2022), so this may not be the optimal task for characterizing individual differences. At the same time, infant functional connectivity during sleep yields identification rates (i.e. the ability to correctly match an individual’s functional connectivity pattern to themselves) that are moderate within-session (Wang et al. 2021) and poor across sessions (Dufford et al. 2021; though see

King et al. 2023 for discussion of methodological confounds in infant connectome fingerprinting). Thus, as the field of awake infant fMRI grows, it will be important to converge on the best task(s) for constructing reliable, yet individually identifiable functional networks.

As with all awake infant fMRI, this study has several limitations. First, the sample size was small, limiting the generalizability of our findings and our ability to estimate effect sizes. Moreover, because of the small sample size, we were unable to consider the impacts of other factors on functional connectivity, such as scanner site or movie content. Our hope is that this study nevertheless highlights some of the ways in which infant state may impact functional connectivity. This could help guide future studies with larger samples, perhaps in combination with the data we have shared from this study. Second, the amount of data used for calculating functional connectivity per participant was also small (around 4 min), especially when compared with current recommendations (Birn et al. 2013, Noble et al. 2019). Given the difficulty of collecting fMRI data from infants, especially in the awake state, this amount of data is near the limits of what is practical. However, the small amount of data likely influenced power and reliability. Indeed, longer functional acquisitions in infants can reveal more adult-like functional connectivity (Sylvester et al. 2023). Nonetheless, a recent study found that the ability to identify infants based on their functional connectivity plateaus between 2.5 and 3.5 min

of data (Wang et al. 2021), and we found similar results to our main analysis when analyzing only runs with at least 2.9 min of usable data (Figs. S3 and S4). Additionally, although we used rigorous inclusion criteria, our motion threshold was liberal relative to prior sleeping studies. Importantly, infants and adults did not differ in the number of usable datapoints, average framewise displacement in infants did not predict similarity in functional connectivity to adults, and our main results held when we used a stricter motion threshold even on the awake data. Nonetheless, the exclusion rate was much higher for infant movie runs (34/87 runs included) than for infant sleep runs (20/21 included), also reflected in significantly greater motion during awake movie-watching than during sleep on average. Given that motion hurts measurement of functional connectivity (Power et al. 2012, Satterthwaite et al. 2012, Van Dijk et al. 2012), our results may underestimate the impact of infants being awake (vs. asleep) on functional networks.

Another limitation is that we treated adult rest and infant sleep as equivalent, despite known differences between rest and sleep in adults (Tagliazucchi and Laufs 2014). Comparisons between infant movie and adult movie are better matched. In future work, it will be important to compare awake and sleeping infants with sleeping adults to fully understand sleep/wake differences across age groups. Characterizing sleep stages through simultaneous fMRI-EEG (Poppe et al. 2021) would also allow for a more fine-grained analysis of infant functional networks across different states. Finally, our main analyses relied on an adult functional parcellation atlas (Schaefer et al. 2018) which may or may not be appropriate for the infant brain. Data-driven approaches for defining regions and networks (e.g. independent components analysis, graph theory; Fair et al. 2021) have been instrumental in the field of developmental neuroimaging but would require more within-participant data than we had available. Infant atlases have also been created (Scheinost et al. 2016, Oishi et al. 2019, Wang et al. 2023), although their use may complicate comparisons with adults, for which they are inappropriate. Indeed, although state decoding in infants was similar using either an adult or infant atlas, state decoding in adults was lower when using an infant atlas (Fig. S7). This infant atlas had a similar number of parcels as the adult atlas, and thus it remains to be explored how the granularity of parcellation into more (e.g. Shen et al. 2013, Glasser et al. 2016, Gordon et al. 2016) or fewer (e.g. Harvard-Oxford; Desikan et al. 2006) regions and connections impacts the similarity of functional connectivity between infants and adults. A related issue is the suitability of adult network labels in the infant brain. In fact, the reduced clustering along the diagonal of the connectivity matrices depicted in Fig. 1A suggests that adult network labels may not fully capture the structure of infant functional connectivity. Even if the network structure was more similar, caution would still be warranted when using adult network labels in infants. For example, infant regions in the anatomical vicinity of the adult frontoparietal control network contributed more to adult similarity when infants were awake, but we do not yet know the functions of these regions in infants and whether they match the functions in adults (e.g. executive control; Dosenbach et al. 2006). In fact, we previously showed that attention engages frontal cortex in infancy, but not as much parietal cortex (Ellis et al. 2021).

In conclusion, infants show distinctive functional network profiles during movie and sleep states that result in comparable overall similarity to adults driven by different networks. This highlights the added value of awake fMRI, in complement to

more ubiquitous sleeping fMRI, for understanding early brain development.

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## Author contributions

Tristan Yates (Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing), Cameron Ellis (Conceptualization, Writing - original draft, Writing - review & editing), Nicholas Turk-Browne (Conceptualization, Supervision, Writing - original draft, Writing - review & editing)

## Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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*Conflict of interest statement:* The authors declare no conflicts of interest.

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