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RESEARCH ARTICLE

Global topology of human connectome is insensitive to early life environments – A prospective longitudinal study of the general population

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Abstract

The widely acknowledged detrimental impact of early adversity on child development has driven efforts to understand the underlying mechanisms that may mediate these effects within the developing brain. Recent efforts have begun to move beyond associating adversity with the morphology of individual brain regions towards determining if and how adversity might shape their interconnectivity. However, whether adversity effects a global shift in the organisation of whole-brain networks remains unclear. In this study, we assessed this possibility using parental questionnaire and diffusion imaging data from The Avon Longitudinal Study of Parents and Children (ALSPAC, $N = 913$), a prospective longitudinal study spanning more than 20 years. We tested whether a wide range of adversities—including experiences of abuse, domestic violence, physical and emotional cruelty, poverty, neglect, and parental separation—measured by questionnaire within the first seven years of life were significantly associated with the tractography-derived connectome in young adulthood. We tested this across multiple measures of organisation and using a computational model that simulated the wiring economy of the brain. We found no significant relationships between early exposure to any form of adversity and the global organisation of the structural connectome in young adulthood. We did detect local differences in the medial prefrontal cortex, as well as an association between weaker brain wiring constraints and greater externalising behaviour in adolescence. Our results indicate that further efforts are necessary to delimit the magnitude and functional implications of adversity-related differences in connectomic organization.

KEYWORDS
ALSPAC, connectome, early adversity, generative network modelling, graph theory, structural connectivity

Research Highlights

- Diverse prospective measures of the early-life environment do not predict the organisation of the DTI tractography-derived connectome in young adulthood
- Wiring economy of the connectome is weakly associated with externalising in adolescence, but not internalising or cognitive ability
- Further work is needed to establish the scope and significance of global adversity-related differences in the structural connectome

1 | INTRODUCTION

Early adversity is a robust predictor of later cognitive and socioemotional difficulties (McGinnis et al., 2022; Mooney et al., 2022; Reiss et al., 2019). Some of these developmental outcomes appear to be partially mediated by changes in neural structure (Hanson et al., 2015; Kim et al., 2022; McLaughlin et al., 2014; Tottenham et al., 2010), which may come about through mechanisms of experience-dependent plasticity (Kolb & Gibb, 2014; Reha et al., 2020) or accelerated maturation of the brain (Callaghan & Tottenham, 2016; Tooley, et al., 2021). Enhanced insight into the mechanistic pathway connecting early experiences to later difficulties could inform efforts to mitigate the harms of adversity (Shonkoff, 2016).

Most neuroscience studies of early adversity have used magnetic resonance imaging (MRI) to identify focal associations with the morphology of individual brain regions, especially the surface area and volume of the prefrontal cortex, amygdala, and hippocampus, with mixed results (for a systematic review, see McLaughlin et al., 2019). However, patterns of connectivity *between* regions are increasingly recognized as a crucial determinant of the initial emergence of brain structure, as well as for its support of adaptive functioning across the lifespan (Collin & Van Den Heuvel, 2013; Medaglia et al., 2015). Indeed, analyses at the level of circuits and of the whole connectome have identified features of neurodevelopmental and mental health conditions in network topology (Bassett et al., 2018; Fornito & Bullmore, 2015; Taylor et al., 2023). Thus, while preliminary diffusion imaging studies of adversity have focussed on the 'integrity' of specific tracts (Bick et al., 2017; Choi et al., 2009, 2012; Corbo et al., 2016; Dennison et al., 2019; Hanson et al., 2013, 2015; McCarthy-Jones et al., 2018; Poletti et al., 2015; Tendolkar et al., 2018; Ursache and Noble, 2016), analysing the organization of whole-brain networks offers a complementary and valuable window into the impact of adversity (Ho et al., 2018).

The network neuroscience approach to early adversity is still in its infancy, with few studies scattered across multiple modalities. Individuals with a history of early adversity tend to have sparser and more heterogeneous connectomes when assessed with functional MRI (Goetschius et al., 2020); however see also, Korgaonkar et al. (2023), and diffusion tensor imaging (DTI) (Ohashi et al., 2017, 2019; Puetz et al., 2017), altered centrality of key regions in MRI-derived morphometric similarity networks (Teicher et al., 2014), and decreased global efficiency of the DTI-derived connectome (Kim et al., 2019). Recently, a rodent study using a computational model that compresses whole-brain networks into two parameters—which approximate the 'cost' and 'value' of connections—detected a difference in the DTI-derived connectomes of mice exposed to unpredictable postnatal stress versus unexposed mice: the former appear to have been subject to weaker constraints on the formation of structural connections (Carozza et al., 2023).

A current challenge in the network neuroscience approach to adversity is that most studies are cross-sectional case-control comparisons of participants who do and do not self-report a history of adversity. This approach bears a few critical limitations, including (1) the use of retrospective self-report, which is less reliable than prospective measures of adversity (Newbury et al., 2018), (2) a simplistic binarization of adversity that collapses variability in scope and severity (McLaughlin et al., 2021), (3) a narrow conceptualisation of what qualifies as adversity, often considering abuse or poverty alone, and (4) reliance on small samples recruited for elevated exposure or symptoms of psychopathology. In other areas, such as the study of the cognitive and grey-matter correlates of adversity, the field is moving beyond these limitations using multivariate approaches and cohort studies (Barch et al., 2022; Bignardi et al., 2022a; Carozza et al., 2022a; Rakesh et al., 2022). These methods have not yet been applied to the adversity-exposed structural connectome. As such, it is not clear which elements of the early environment reliably predict which global brain network differences across individuals, nor how widely these differences are observed. A pivotal question thus emerges: Are adversity-related differences in the structural connectome present in the wider population, beyond the potentially inflated effects we would see in extreme-group designs? If so, are some forms of adversity stronger predictors of whole-brain organisation than others?

In this project, we aim to answer these questions directly by leveraging a longitudinal cohort study with prospective measures of early-life experience across childhood, the Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al., 2013; Fraser et al., 2013). We reconstructed the structural connectome of each participant in young adulthood through diffusion imaging and probabilistic tractography. We first used a data-driven Partial Least Squares (PLS) regression to identify aspects of the childhood environment that predict whole-brain organisation. We then simulated the growth of these brain networks

using generative network modelling, a computational strategy that constructs complex networks based on the interplay between two wiring constraints: a cost on long-distance connections and a preference for topologically favourable ones (Akarca et al., 2021; Betzel et al., 2016; Vértes et al., 2012). As this method compresses significant topological complexity into a single trade-off, it may uncover differences unobservable in singular measures of global topology. For this reason, we then ran a second PLS regression predicting model parameters in young adulthood, before finally assessing the relationship between brain wiring parameters and cognitive and socioemotional functioning in adolescence.

We made three specific hypotheses. First, based on previous data-driven analyses of the developmental impact the early environment (Bignardi et al., 2022b; Carozza et al., 2022b), we expected forms of early-life deprivation to load most strongly on the PLS components predicting global topology and brain wiring parameters. Secondly, in line with results from a rodent model of postnatal stress (Carozza et al., 2023), we expected significant component(s) in the second PLS to predict a weaker penalty on long-distance connections and a weaker preference for connections between regions with shared neighbours. Finally, we predicted that weaker constraints on brain wiring would be correlated with lower IQ and higher internalising and externalising in adolescence.

2 | METHODS

2.1 | Participants

ALSPAC is a longitudinal population-based cohort study based in Avon, United Kingdom (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). ALSPAC initially recruited 14,541 pregnant women with expected delivery dates between April 1, 1991 and December 31, 1992. From this initial sample, 14,062 infants were alive at birth and 13,988 a year later. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, for variables collected after age seven, the total sample is 14,901 children and 14,833 unique mothers. ALSPAC continues to follow these children, their mothers, and their mothers' partners.

ALSPAC collected rich data on the early environment through maternal questionnaire across the first seven years of the child's life; these variables were used to estimate exposure to early-life adversity (see Section 2.2). Measures of IQ and internalizing and externalizing behaviour were collected during childhood and again in adolescence; the latter of the two timepoints was used to estimate cognitive and behavioural difficulties (see Section 2.3). Finally, a subset of ALSPAC subjects participated in three neuroimaging sub-studies when they reached young adulthood; these data were used to reconstruct the structural connectomes (see Section 2.5). For a timeline of data collection, please see Table S1. Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Bristol (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies. Further details are available in a fully searchable data dictionary on the study website (http://www.bristol.ac.uk/alspac/researchers/our-data/).

2.2 | Early adversity measures

Maternal self-report questionnaires were used to measure the child's exposure to early adversity. To assess this comprehensively, we chose a range of experiences falling under the theoretical dimensions of deprivation (i.e., the absence of a normative helpful experience) and threat (i.e., the presence of a harmful experience) (McLaughlin et al., 2014). ALSPAC administered the questionnaires five times across childhood, and relevant study questions are listed in Table S2. Eight exposures are coded as binary variables, including emotional domestic violence, physical domestic violence, parental physical cruelty, parental emotional cruelty, sexual abuse, physical abuse, a change in primary caregiver, and parental separation. Questionnaires also assessed three exposures as composite scores of multiple questions: financial difficulties, maternal caregiver neglect, and paternal caregiver neglect. The financial difficulties score is the sum of how difficult the mother found it to afford food, clothing, heating, rent or mortgage, and items for the child. The maternal and paternal caregiver neglect scores are the additive inverse of the sum of how frequently the mother and her partner engaged in a range of activities with the child, such as feeding or playing. The three composite scores demonstrated adequate internal consistency across time points, with Cronbach's alphas falling between 0.88–0.92 (financial difficulties), 0.55–0.76 (maternal caregiver neglect), 0.79–0.88 (paternal caregiver neglect). The Z-scores of the composite scores were used in all analyses.

2.3 | Cognitive and behavioural measures

Participants completed the Wechsler Abbreviated Scale of Intelligence (WASI) at age 15.5 (Wechsler, 1999). The age-adjusted standardized subscale scores were used to estimate a total IQ score as a measure of general intelligence. When participants were 16 years old, their mothers completed the short form of the parent Strengths and Difficulties Questionnaire (SDQ) (Muris et al., 2003), which consists of 25 items about the behaviour of the child over the preceding 6 months (Goodman, 1997). In line with previous work (Goodman et al., 2010), two of the five subscales (conduct and hyperactivity/inattention) were summed as a measure of externalising behaviour, while two other subscales (emotional and peer relationships problems) were summed as a measure of internalising behaviour.

2.4 | Imputation of missing data

Participants lacked an average of 11.9% of questionnaire, cognitive, and socioemotional data, while individual variables were missing in an

average of 13.5% of participants (Figure S1). To establish the plausibility that our data were missing at random, we checked for demographic predictors of missingness using Kolmogorov–Smirnoff and two-sided chi-square tests as implemented in the *finalfit* package in R (Harrison et al., 2020). After Bonferroni correction for multiple comparisons, participants who lacked cognitive and socioemotional data were more likely to be female and non-White and to come from families of a lower social class and weekly income.

Missing data for all retained participants was imputed using a random forest algorithm as implemented in the *missForest* package (Stekhoven & Bühlmann, 2011). The algorithm consists of an iterative process of training and prediction, which continues until the difference between the new imputation and the previous imputation begins to rise for both categorical and continuous variables. The algorithm demonstrates greater accuracy than other imputation methods, accommodates mixed data types, and does not require tuning (Tang & Ishwaran, 2017; Waljee et al., 2013). The method also produces unbiased estimates of the accuracy of the imputation (Breiman, 2001). Our estimates indicated good performance for both continuous (normalized root-mean-square error = 0.1545) and categorical variables (proportion of falsely classified entries = 0.0377). Before and after imputation, similar descriptive statistics were observed on both demographic (Table S3) and adversity (Table S4) variables.

2.5 | Acquisition of neuroimaging data

In young adulthood (ages 18–24), eligible participants were invited to complete a multimodal neuroimaging protocol as part of one of three Sub-Studies: (1) the ALSPAC Testosterone study of normatively developing males (N = 513, 18–19.5 years, 100% male), (2) the ALSPAC Psychotic Experiences study of subclinical psychosis (N = 252, 19–21.5 years, 35% male), and (3) the ALSPAC Schizophrenia Recall-by-Genotype study of genetic variants contributing to schizophrenia (N = 196, 21–24.5 years, 36% male) (Sharp et al., 2020). No brain imaging data were collected before this point. All MRI data were acquired at Cardiff University Brain Research Imaging Centre (CUBRIC) on the same 3T Tesla General Electric HDx (GE Medical Systems) using an 8-channel head coil.

T1-weighted (T1w) structural scans were obtained at 1 mm isotropic resolution using the following parameters: 3D fast spoiled gradient echo (FSPGR) with repetition time (TR) = 7.8–7.9 ms; echo time (TE) = 3.0 ms; inverse time (TI) = 450 ms; flip angle = 20°. High angular resolution diffusion weighted images (HARDI) were obtained using a spin-echo echo-planar imaging sequence. A total of 30 (Study 1) or 60 (Studies 2 and 3) gradient orientations and three (Studies 1 and 3) or six (Study 2) non-diffusion weighted (b = 0 s/mm^2) images were acquired using the following parameters: TR = cardiac gated, TE = 87 ms, b = 1200 s/mm^2; flip angle = 90°. Additional acquisition details are available elsewhere (Sharp et al., 2020).

2.6 | Pre-processing and connectome reconstruction

Pre-processing was performed using QSIPrep 0.14.2, which is based on Nipype 1.6.1. A description of steps can be found in Methods S1, and additional details at https://qsiprep.readthedocs.io/en/latest/workflows.html.

After excluding N = 37 participants with diffusion data missing and N = 11 scans with technical errors, N = 913 diffusion imaging scans were available for processing. In-scanner head motion was low across these scans (M = 0.429 mm, SD = 0.282 mm; Figure S2) and corrected in preprocessing, but as previous work indicates that participant movement can bias tractography-derived estimates of structural connectivity (Baum et al., 2019), we excluded N = 2 subjects with mean framewise displacement above 3 mm following previous work (Akarca et al., 2021). In the case of participants who participated in more than one study (N = 43), imaging data from the first scan was analysed, yielding a final N = 868 participants. Across the three sub-studies, the final sample had a mean age of 20.36 years (SD = 1.42) and 29% were female.

Fibre orientation distributions (FODs) were estimated via constrained spherical deconvolution (Tournier et al., 2004, 2008) using an unsupervised multi-tissue method (Dhollander et al., 2016, 2019). FODs were intensity-normalized using *mtnormalize* (Raffelt et al., 2017). The white matter FODs were then used for tractography, which was carried out using probabilistic streamline fibre tracking with second-order integration (Tournier et al., 2010) with whole-brain seeding. Ten million streamlines were generated with a maximum length of 250 mm, minimum length of 30 mm, and FOD power of 0.33. To improve the biological accuracy of the weight estimates, streamlines were filtered using SIFT2 (Smith et al., 2015).

A structural connectome was then built from each tractogram using the 100-parcellation 17-network Schaefer atlas (Schaefer et al., 2018). This cortical parcellation is derived from resting-state fMRI data using a gradient-weighted Markov Random Field model. The number of streamlines connecting each pair of regions were counted and turned into connectivity matrices, which were symmetrized. Self-connections were removed.

In addition to the 100-node Schaefer atlas connectomes, which were used for the primary analysis, we also built connectomes from the 246-node Brainnetome parcellation (Fan et al., 2016) for the sake of a sensitivity analysis. This higher-resolution parcellation includes 36 sub-cortical regions; as such, it permitted the consideration of local differences in the hippocampus, amygdala, and basal ganglia (see Section 2.14, and Table S5 for a list of subregions).

2.7 | Connectome harmonization

The raw connectomes showed differences in density and topology (Figure S6) across sub-studies. As data were collected on a single scanner, these systematic differences were likely due to the difference

in the number of gradient directions and sample differences across sub-studies (see Section 2.5). To eliminate these differences while preserving relationships with adverse experiences, we batch harmonized the raw connectomes using ComBat (Johnson et al., 2007). This method, originally developed for use with genomics data, estimates parameters using an empirical Bayes regression with terms for study site and for relevant covariates. As such, it standardizes data across sites by eliminating variability due to unwanted factors without losing the variability due to meaningful differences in variables of interest. Previous work has shown it successfully controls for scanner variability in diffusion imaging data (Fortin et al., 2017), and that it preserves network topology when applied to tractography-derived connectivity matrices (Onicas et al., 2022). We applied batch harmonization to the connectomes, adjusting the edge weights of the connectivity matrices to eliminate the bias introduced by systematic scanner and site effects across studies. We preserved the covariates of age at scan, ethnicity, birthweight, month of birth, social class, family income, and exposure to each form of adversity. We did not preserve the covariate of sex, as the all-male design of Study 1 resulted in strong associations between sex and study ID.

After harmonization, following previous studies (Akarca et al., 2021; Betzel et al., 2016), we enforced an average connectome density of $\rho = 10\%$ across the sample to eliminate spurious connections and highlight topological variation across subjects (Zalesky et al., 2016). A mean of 499.86 and *SD* of 36.41 edges was achieved by retaining only connections of at least 1899 streamlines. Connectomes were then binarized.

2.8 | Global and local network topology

To assess the global topology of the empirical connectomes, we computed four measures: global efficiency, calculated as the average inverse shortest path length of the network (Bullmore & Sporns, 2009); mean clustering coefficient, defined as the fraction of triangles around a node (Watts & Strogatz, 1998); mean node betweenness centrality, corresponding to the fraction of all shortest paths in the network that contain a given node (Kintali, 2008); and small-worldness, defined as the ratio of clustering to shortest path length compared to its random network equivalent (Humphries et al., 2006). The measure of small-worldness was normalized using randomly rewired networks that preserved the same density and degree sequence as the empirical networks.

To evaluate the connectivity of the left and right medial prefrontal cortex (PFC) in the Schaefer connectomes, as well as the bilateral amygdala, hippocampus, and basal ganglia in the Brainnetome connectomes, we computed three local measures of topology as well: the degree or number of connections of both regions, their clustering coefficient (defined above), and their nodal efficiency, or the average inverse shortest path length in the neighbourhood of the node.

All measures were computed using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/Home) in MATLAB.

2.9 | Partial least-squares prediction of global topology

To characterise the relationship between exposures to adversity and brain organisation, we ran PLS regression using *plsregress* in MATLAB. This method decomposes a predictor matrix *X* and outcome matrix *Y* to obtain the set of latent components that best explains the covariance between *X* and *Y*, then predicts *Y* from the decomposition *of X* using a linear regression. Thus a PLS regression is an effective method when the predictor matrix includes many variables that exhibit multicollinearity (Höskuldsson, 1988).

To determine the number of predictor components that best explained the variation in our response variables (the measures of global topology outlined above) we used a permutation testing procedure. This consisted of randomizing rows of the response matrix, rerunning the PLS regression, and calculating the correlation between each predictor components and the first response component. A total of 10,000 permutations were run, generating a null distribution of correlations for each component. Only components with observed correlations greater than 95% of permuted correlations were retained as significant.

To test which predictor and outcome variables loaded significantly onto each component, we used a bootstrapping procedure. First, we generated 10,000 bootstrap samples by sampling with replacement from all participants. Then, we computed 95% confidence intervals for the variable loadings using *bootci* in MATLAB, which implements the bias corrected and accelerated percentile method (DiCiccio & Efron, 1996). Due to sign flipping, we implemented Procrustes variable rotation to ensure accurate estimates.

2.10 | Generative network modelling

We then simulated the connectomes using generative network modelling (Betzel et al., 2016; Vértes et al., 2012), which forms complex networks by adding a single connection at a time in a probabilistic manner.

First, a seed network was constructed by identifying the 50 edges with the highest average value across the sample, so that—following previous work (Akarca et al., 2021; Betzel et al., 2016; Carozza et al., 2023)—the seed would comprise of 10% of the final number of connections (see Figure S2). A single connection at a time was then added to this initial network by trading off the 'cost' it would incur against the topological 'value' it would bring to the network. This probability is computed using the following wiring equation (Vértes et al., 2012):

$$P_{i,j} \propto (D_{i,j})^{\eta}(K_{i,j})^{\gamma} \quad (1)$$

The first term of the equation, $D_{i,j}$, represents the biological cost of a connection between brain regions *i* and *j*. As this metabolic and material expense is proportional to the length of a tract, $D_{i,j}$ is approximated using the Euclidean distance between *i* and *j*. The magnitude of the

parameter η determines the strength of the penalty imposed on long-distance connections. The second term, $K_{i,j}$, represents the value of a connection. This is estimated using one of various measures of topological similarity between the two regions (known as 'generative rules'; see below). The magnitude of the parameter γ determines the strength of its contribution to wiring probability.

At each step of the simulation, the model multiples the cost and value terms to obtain the relative probabilities of all possible new structural connections. Then, a single connection is added to the network. As this connection changes the topology of the network, the model re-computes the $K_{i,j}$ term for all remaining potential connections, thereby updating $P_{i,j}$ as well. Thus, over time, the network gradually organizes through continually re-negotiating the relative probabilities of new structural connections. The simulation is finalised when the number of edges matches that of the target network.

Depending on the respective values of η and γ, the model negotiates the trade-off between cost and value differently, resulting in a unique network topology at the end of the simulation. Therefore, it is possible to systematically manipulate the terms of the probability equation to match the observed brain organisation of an individual. Identifying the parameters that best simulate the connectomes of individuals may shed light on the constraints and goals that account for the organisation of their brain structure (Akarca et al., 2021; Bassett & Betzel, 2017).

2.11 | Identification of optimal model

Due to the high computational demands incurred by generative network modelling and our large sample size, we first constructed a consensus network that summarised connectivity across all participants (Figure 2a, Figure S3). This was achieved by identifying the edges shared by 50% of participants ($N = 982$ edges, 9.82% network density). We then tested the ability of thirteen different generative models to simulate this consensus network, so as to efficiently identify the optimal generative rule.

In addition to a purely spatial model, which did not implement a topological preference term, the 13 models included: two homophily models (number of common neighbours and matching index); five clustering-based models (the average, minimum, maximum, difference in, and product of clustering coefficients); and five degree-based models (the average, minimum, maximum, difference in, and product of node degrees) (Betzel et al., 2016). Models were computed using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/Home) in MATLAB.

For each model, we tested 100,000 parameter combinations in the space defined by $-15 \leq \eta \leq 0$ and $0 \leq \gamma \leq 2$ using a grid search procedure. The fit of each simulation to the consensus network was assessed according to the following energy equation (Betzel et al., 2016):

$$E = \max\left(KS_k, KS_c, KS_b, KS_d\right) \quad (2)$$

The equation is composed of the Kolmogorov-Smirnov (KS) statistics comparing the simulations to the consensus network on the distributions of four key nodal features—node degree (k), clustering coefficient (c), betweenness centrality (b), and edge length (d)—that have previously been used for this purpose (Akarca et al., 2021; Betzel et al., 2016; Zhang et al., 2021). A lower energy indicates less discrepancy between the distributions, reflecting a better simulation of the consensus network.

The energies of the $N = 100$ top-performing simulations were compared across models to identify the optimal generative rule. This rule was used to simulate the connectomes of individuals.

2.12 | Identification of optimal parameters

To obtain precise estimates of the parameters that best replicated the connectomes of each participant, a second grid search of 160,000 parameter combinations was run in the parameter space defined by $-13 \leq \eta \leq -3.5$ and $0.25 \leq \gamma \leq 1$. To account for the probabilistic nature of the simulations, results of all subsequent analyses were averaged across the top $N = 10$ lowest-energy simulations.

The realism of the final simulations was assessed by exploring the spatial layout of six features of the networks (Akarca et al., 2021): node degree, betweenness centrality, clustering coefficient, edge length, local efficiency, and matching index. The value of each nodal statistic was averaged across the top $N = 10$ simulations of all participants, resulting in a 3-by-100-by-6 matrix. The same procedure was performed on the empirical connectomes. Linear correlations between the nodal statistics of the simulations and the nodal statistics of the connectomes were then calculated.

At each node, the spatial error (or discrepancy) of each measure was calculated by subtracting its average value in the top $N = 10$ simulations from its average value in the empirical connectomes (Akarca et al., 2021). Thus, a lower spatial error indicates more similarity between a brain region's local topology in the simulations and in the empirical connectomes. To summarize the success of spatial layout across the brain, a measure of absolute error was calculated by summing the Z-scores of each spatial error.

2.13 | Partial least-squares prediction of brain wiring

To characterise the relationship between exposures to adversity and brain organisation, we repeated the PLS protocol outlined above, retaining the same predictor matrix X but substituting the brain wiring parameters η and γ for measures of global topology in the outcome matrix Y.

2.14 | Sensitivity analyses

Finally, we conducted exploratory analyses to test whether our results varied at more extreme values of early adversity. First, we constructed

a composite measure of SES by subtracting the Z-score of total financial difficulties across childhood from the Z-score of average monthly family income across childhood. Next, we constructed a composite measure of explore to violence by taking the sum of instances of abuse, domestic violence, emotional cruelty, and physical cruelty across childhood. We used these measures to construct three subgroups: a group of the 50 participants with lowest SES scores ('deprivation'), a group of the 50 participants with highest violence scores ('threat'), and a group of the 50 participants with highest SES scores ('control'). We then compared these three groups on global measures of topology, brain wiring parameters, and the local topology of the medial PFC, hippocampus, amygdala, and basal ganglia.

3 | RESULTS

3.1 | Demographic and adversity measures

After quality control and eliminating repeated scans (see Section 2), $N = 868$ young adults were included in the study ($M = 244.27$ months, $SD = 17.06$ months). The sample had a moderate history of adversity: 21% of participants were exposed to domestic violence and 13% had suffered physical or sexual abuse before age 8, while 12% were raised in households with annual incomes below £10,400 (which, accounting for inflation from 2000 to 2023, is currently equivalent to £22,400). For comparison, the estimated incidence of physical and sexual abuse in the UK is 14.8% and 6.3%, respectively (Bellis et al., 2014), while the current threshold for poverty for a couple with two children is £26,400 per year (Department for Work and Pensions, 2023). Additional demographic data can be found in Table S3, and descriptive statistics of internalising and externalising behaviours, IQ, and adversity measures in Table S4.

Generally, forms of early deprivation were negatively correlated with IQ and positively correlated with externalising and internalising behaviours, and forms of early threat exposure were positively correlated with externalising and internalising behaviours (Figure 1; see Figure S4 for confidence intervals). Correlations between variables were comparable before and after the imputation of missing data (Figure S5).

3.2 | Connectome reconstruction

We utilised diffusion imaging and probabilistic fibre tracking to reconstruct the structural connectomes of each participant. To control for sample and acquisition differences, we harmonized the raw connectomes across studies using ComBat, a Bayesian approach that eliminates site effects whilst preserving other important covariates (Johnson et al., 2007), which in this case included demographic and early life experience measures (see Section 2). Harmonization largely eliminated differences in global topological measures across studies (see Figure S6 and accompanying statistics).

3.3 | Prediction of later global topology

We first sought to identify forms of early-life adversity that predict measures of global topology in young adulthood. Because measures of the early environment and experiences are highly correlated amongst themselves, including in our sample (Figure 1), we chose to implement a PLS regression – a procedure that deals well with multicollinearity (Höskuldsson, 1988). This method decomposes both the matrix of predictors and the matrix of outcomes, then finds a linear regression model that maximally explains covariance between the two matrices.

Upon performing a permutation testing procedure, no predictor component of the PLS attained significance. We therefore did not assess the optimal number of components or the loadings of early-life environment measures. The first predictor component exhibited a correlation with the first response component of only $r = 0.015$ ($p_{permuted} = 0.677$) after controlling for participant age at scan and explained only 0.034% of variance in global topology. Thus, in our sample, early-life experience does not appear to co-vary with singular measures of global brain organisation in young adulthood.

3.4 | Identification of optimal generative network model

Because commonly employed metrics of global topology offer a limited view into the complex topology of the human brain (Fornito et al., 2016), we then compressed the overall organisation of the connectomes using generative network modelling (Vértes et al., 2012). This affords the opportunity of distilling differences across individuals and between groups that may otherwise be unobservable using singular features of network organisation (Carozza et al., 2023).

Due to the computational demands of generative network modelling, we first constructed a consensus network that summarizes connectivity across the sample (Figure S3). We used this consensus network to identify the model that best replicates the organisation of the biological connectomes (see Section 2, Figure 2b). Following previous work (Akarca et al., 2021; Betzel et al., 2016; Vértes et al., 2012), we tested thirteen generative models from three categories: (i) homophily models, which favour connections between regions with similar connectivity neighbourhoods; (ii) clustering-based models, which compute the value of a potential connection based on the clustering coefficients of the two regions; and (ii) degree-based models, which consider the nodal degrees of the regions.

Model energy was evaluated using Equation (2). We compared the 100 lowest-energy simulations of the consensus network from each rule (Figure 2c). An ANOVA and post-hoc Tukey test confirmed that the homophily category of models achieved lower energy than both clustering- ($diff = -0.0932$, $p < 1.0 \times 10^{-14}$) and degree-based models ($diff = 0.0373$, $p < 1.0 \times 10^{-14}$), in addition to the purely spatial model ($diff = -0.0878$, $p < 1.0 \times 10^{-14}$). Within the homophily category, the matching model outperformed the neighbour model ($diff = -0.0114$, $p = 2.2 \times 10^{-14}$). In other words, a generative model that trades off

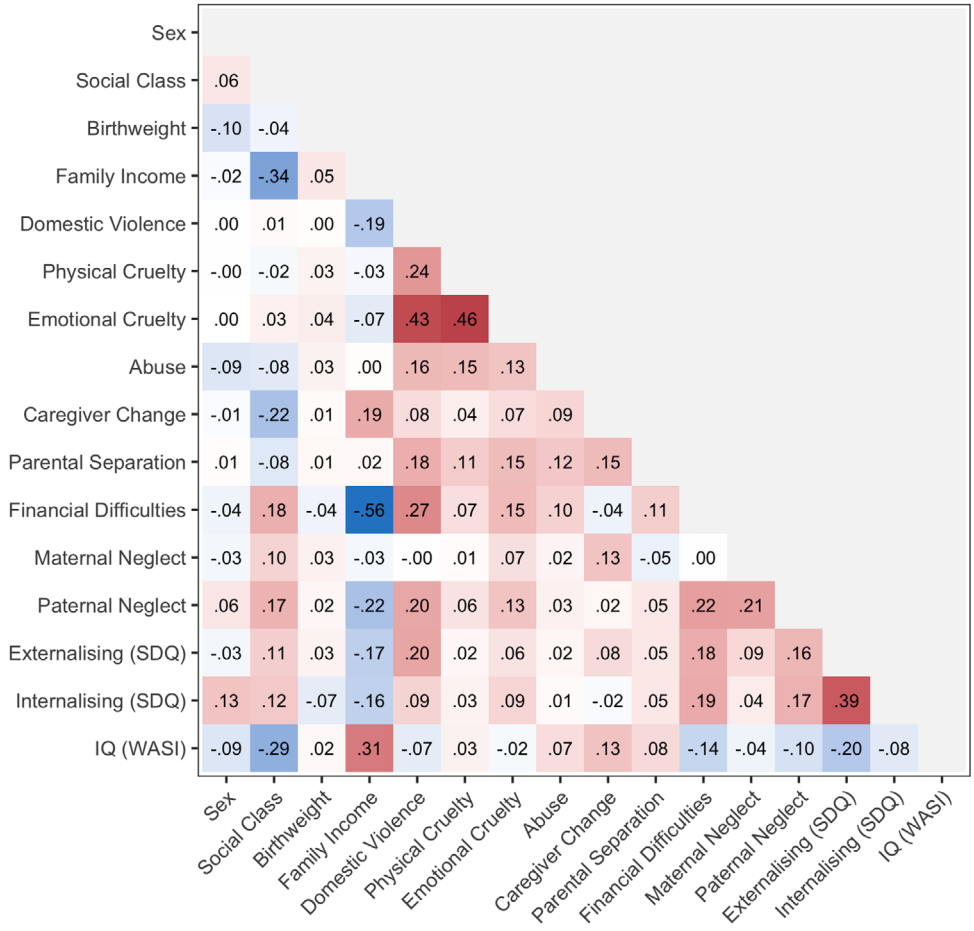


FIGURE 1 Spearman correlations between demographic variables, exposures to early adversity, and cognitive and socioemotional measures. White indicates no correlation across the sample ($N = 868$); red indicates positive associations and blue negative. SDQ, Strengths and Difficulties Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence.

the cost of a structural connection with the value of similar neighbourhoods produced networks that most closely resembled the distribution of topological features of the consensus network.

The homophily-based rules also achieved low energy within a narrow range of parameter combinations (parameter distributions for all rules can be found in Figure S7), and overall model energy for these rules tended to be limited by the degree term of the energy equation (Figure S8). Comparable differences in energy across rules were observed when models were re-run using a more stringent threshold for the consensus network and/or a more moderate seed network (Table S6), indicating that the homophily model was robustly superior to the others.

3.5 | Assessment of individual model fit

We then used the homophily model to simulate the connectomes of each individual. To obtain precise parameter estimates, we performed a second grid search of 160,000 parameter combinations in the space defined by $-13 \leq \eta \leq -3.5$ and $0.25 \leq \gamma \leq 1.0$. To account for the stochastic nature of the generative network model, we averaged results across the top ten lowest-energy networks for each individual for all subsequent analyses.

The parameters producing the lowest-energy networks for each participant are shown in Figure 2d. As η and γ showed a strong negative correlation ($r = -0.86$, $p < 2.2 \times 10^{-16}$), a stronger penalty on connections between distant regions generally accompanied a stronger preference for connections between regions with similar neighbours. Each of the terms comprising the energy equation follows a similar pattern across the parameter landscape (Figure S9), indicating that covarying η and γ replicated differences across individuals in all four of the nodal statistics.

The low energy that the matching model achieved across the sample ($M = 0.0846$, $SD = 0.0070$) indicates that it successfully replicated distributions of key nodal features of the connectomes. However, the energy equation does not test whether the simulations mimic the spatial layout of connectomes derived from tractography. Following previous work (Akarca et al., 2021; Arnatkeviciute et al., 2021; Betzel et al., 2016), we therefore calculated the correlation between simulated and empirical connectomes on six nodal characteristics. As shown

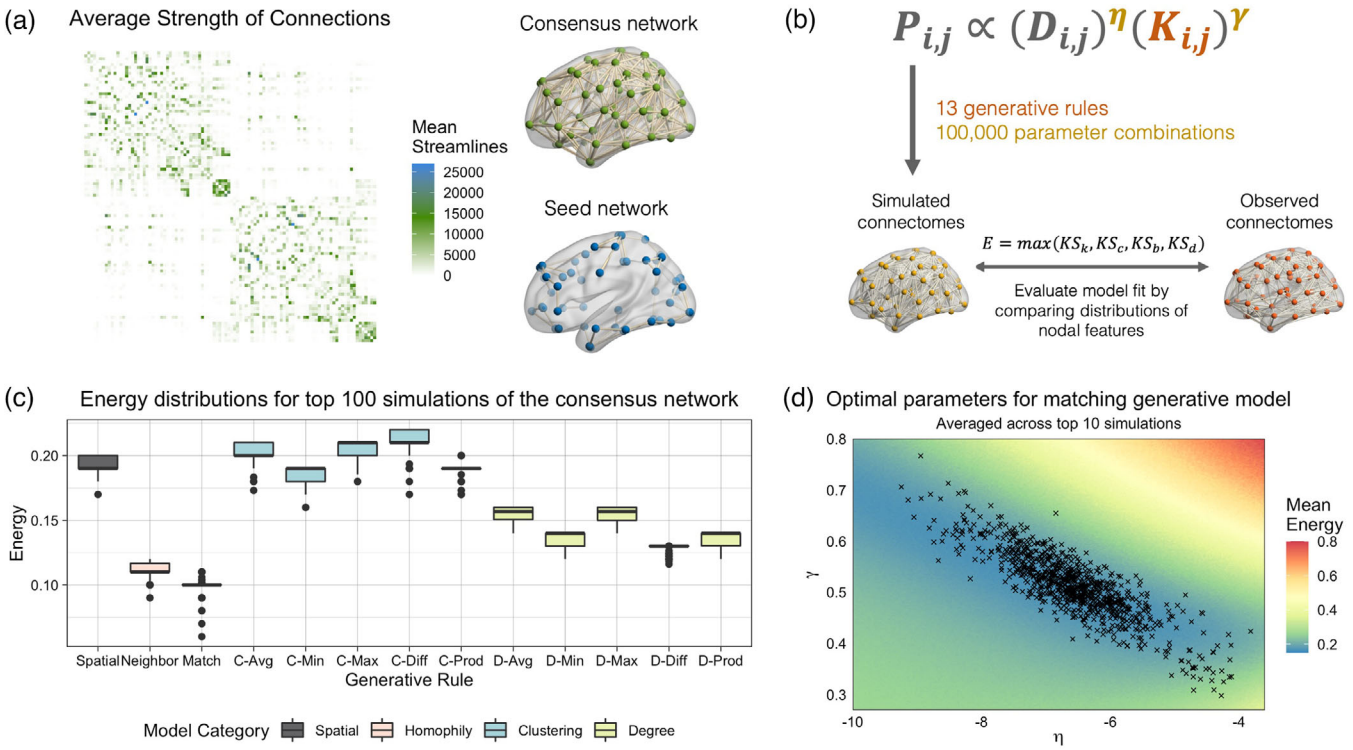


FIGURE 2 Identification of optimal generative model and parameters. (a) The average strength of connections across the sample ($N = 868$) was used to construct a seed network of the 50 strongest edges. The consensus network was composed of connections shared by at least 50% of subjects. (b) Using a grid search of the parameter space, 100,000 simulations were generated for each of the 13 generative rules: a purely spatial model, which considers only the distance between two regions; two homophily models, which also consider a measure of the similarity of the neighbourhoods of the respective regions; five clustering-based models, which compare the clustering coefficients of the regions; and five degree-based models, which compare their node degree. Model fit was evaluated using the energy equation shown. (c) The energy of the top 100 best-performing synthetic networks for each subject across all generative rules. (d) The optimal values of η and γ, averaged across the top 10 lowest-energy simulations using the matching rule. Values were obtained by testing an additional 160,000 parameter combinations in a narrow low-energy window of the initial grid search. Each point in the scatterplot represents a single participant.

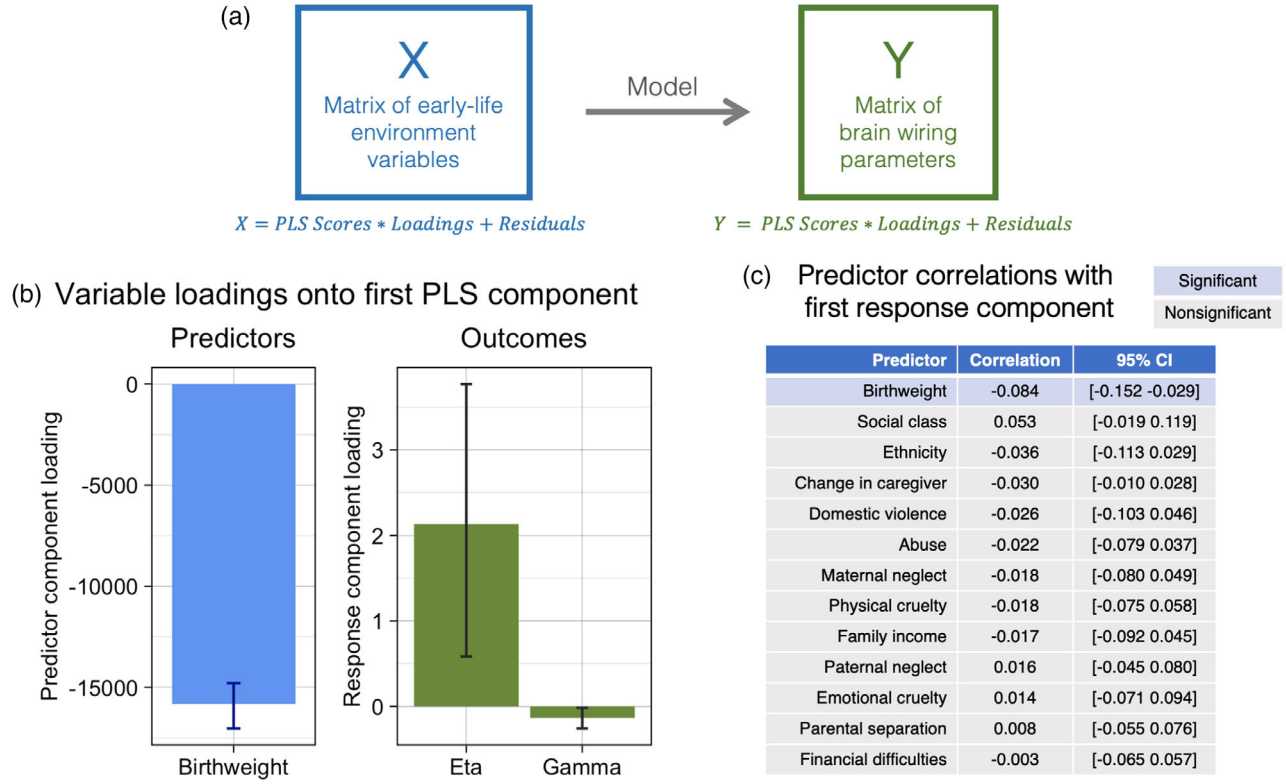
in Figure S10, two out of the six measures used in the energy equation exhibited similar anatomical localisation (edge length: $r = 0.63$, $p < 1 \times 10^{-4}$; mean matching index: $r = 0.23$, $p = 0.02$). This indicates that while the simulations successfully replicated the distributions of key nodal features, the layout of some of these features was arranged differently in space.

3.6 | Prediction of later brain wiring

Having established the parameters that best simulate the connectomes of each individual in young adulthood, we then sought to identify forms of early-life adversity that predict these brain wiring parameters using a second PLS regression (Figure 3a). Upon performing a permutation testing procedure, we found that the first predictor component of the PLS attained significance ($r = 0.0815$, $p_{permuted} = 0.0155$) whilst controlling for participant age at scan. In other words, one latent factor was sufficient to explain the covariance between early-life experience and brain wiring in young adulthood. As shown in Figure S11, this component explains 0.71% of variance in η and γ.

To determine which measures of early-life environment loaded significantly onto this first predictor component, we ran a bootstrap and resampling procedure. As shown in Figure 3b, only a lower birthweight (loading = −15823, CI = [−14794, −17025]) loaded onto the component (all other loadings can be found in Table S7). In terms of outcomes, η loaded positively onto the response component while γ loaded negatively (η loading = 2.13, CI = [0.58, 3.77], γ loading = −0.13, CI = [−0.26, −0.02]). Thus, while a lower weight at birth predicts a more moderate penalty on long-range connections and a weaker preference for connections between brain regions with shared neighbours, this explained little variability in brain organisation, and no predictive contribution of early adversity was detected.

Given differences in variable scoring and scales, a comparison of the predictor variable loadings themselves is not meaningful. As such, to assess their relative relationship with brain wiring parameters, we also computed correlations between each predictor variable and the first response component of the PLS. As Figure 3c shows, the small correlation between birthweight and the first response component was much larger than that exhibited by any form of early adversity. A bootstrapping procedure showed that 95% confidence intervals for all other variables included zero.



Predictor	Correlation	95% CI
Birthweight	-0.084	[-0.152 -0.029]
Social class	0.053	[-0.019 0.119]
Ethnicity	-0.036	[-0.113 0.029]
Change in caregiver	-0.030	[-0.010 0.028]
Domestic violence	-0.026	[-0.103 0.046]
Abuse	-0.022	[-0.079 0.037]
Maternal neglect	-0.018	[-0.080 0.049]
Physical cruelty	-0.018	[-0.075 0.058]
Family income	-0.017	[-0.092 0.045]
Paternal neglect	0.016	[-0.045 0.080]
Emotional cruelty	0.014	[-0.071 0.094]
Parental separation	0.008	[-0.055 0.076]
Financial difficulties	-0.003	[-0.065 0.057]

FIGURE 3 Birthweight alone predicts brain wiring in young adulthood. (a) The relationship between early-life environment variables and brain wiring parameters was assessed using a Partial Least Squares regression, a method robust to multicollinearity. (b) Permutation testing determined one significant component, and bootstrapping was used to generate 95% confidence intervals for variable loadings. Birthweight significantly loaded onto the predictor component, such that lower birthweight entailed a higher PLS score. Both brain wiring parameters (η and γ) significantly loaded onto the response component, such that a higher PLS score predicted a more moderate penalty on long-distance connections and a weaker preference for connections between regions with shared neighbours. (c) Correlations between each early-life environment variable and the first PLS response component, ranked by absolute value. Blue shading indicates that the bootstrapped 95% confidence interval for the correlation did not include zero, whilst grey shading indicates that it did.

3.7 | Sensitivity analyses

One possible confound is that participant head motion in the scanner may have influenced parameter estimates and thus confounded the relationship with early adversity. However, mean frame-wise head displacement was not correlated with η ($r = 0.027$, $p = 0.413$) or γ ($r = -0.008$, $p = 0.806$).

A second possibility is that the incidence of psychotic experiences in half of participants in Sub-Study 2 and/or the high genetic risk of schizophrenia in half of participants in Sub-Study 3 obscured the impact of early-life experiences. To test this possibility, we re-ran the brain wiring PLS on the normatively developing participants of Sub-Study 1 alone. However, this once again produced a single significant predictor component ($p = 0.042$) on which only birthweight loaded significantly (−13091 [−11607, −10667]). Similarly, a PLS predicting global topology from early-life adversity within this study uncovered no significant components.

Third, it could be that a 10% threshold is too stringent and eliminates meaningful variation across participants. To investigate this, we re-thresholded the connectomes at 15% and 20% density and once again used PLS to predict global topology from measures of early-life adversity. However, as with the 10% threshold, no predictor component attained significance.

Another possible explanation for the lack of an observed relationship between early adversity and brain wiring is that the ALSPAC sample exhibits lower rates of poverty and exposure to violence than are reported in more diverse cohorts (Giano et al., 2020). This may be exacerbated by attrition, as participants with neuroimaging data showed higher income than baseline ALSPAC participants ($X^2 = 95.90$, $p < 2.2 \times 10^{-16}$) – albeit comparable rates of domestic violence exposure ($X^2 = 12.00$, $p = 0.68$). Given that PLS regressions estimate linear relationships between predictors and outcomes, the analysis could be failing to detect a non-linear relationship due to lack of variability in adversity scores.

We assessed this possibility by extracting comparison groups from extreme ends of the adversity spectrum. First, we created a measure of SES from family income and financial difficulties, and a measure of violence exposure by summing experiences of abuse, domestic violence, and cruelty (see Section 2). We then selected the 50 participants with lowest SES as a *deprivation* group, the 50 participants with highest violence exposure as a *threat* group, and the 50 participants with highest SES as an *unexposed* group.

Participants in the three subsamples necessarily came from highly different early-life environments. For instance, an ANOVA and post-hoc Tukey test showed that the deprivation group had greater subjective financial difficulties ($M = 40.56$, $SD = 10.20$) than the threat ($M = 19.64$, $SD = 15.03$; $p < 1.0 \times 10^{-14}$) or unexposed groups ($M = 0.00$, $SD = 0.00$; $p < 1.0 \times 10^{-14}$). Similarly, while all participants in the unexposed group had weekly family incomes above 400 GBP, 6% and 36% of the threat and deprivation groups respectively had weekly family incomes below 100 GBP. The threat group showed elevated rates of violence-based adversities: the sum of reports of domestic violence, for instance, was substantially higher in the threat group ($M = 4.54$, $SD = 1.98$) than in deprivation ($M = 1.30$, $SD = 1.82$; $p = 3.0 \times 10^{-14}$) and unexposed groups ($M = 0.16$, $SD = 0.55$, $p = 3.0 \times 10^{-15}$). Additional demographic information for each group can be found in Table S8.

We then ran ANCOVAs comparing the groups on brain wiring parameters and measures of global topology (see Section 2) while covarying birthweight. Notwithstanding the careful subsampling, there was no impact of group membership on η ($F_{2,144} = 0.52$, $p = 0.5928$) or γ ($F_{2,144} = 0.26$, $p = 0.7721$). Nor did group membership predict global efficiency ($F_{2,144} = 0.46$, $p = 0.630$), mean clustering ($F_{2,144} = 0.16$, $p = 0.849$), mean betweenness centrality ($F_{2,144} = 1.05$, $p = 0.354$), or small-worldness ($F_{2,144} = 0.38$, $p = 0.686$) (see Table S9 for descriptive statistics). Thus, in this sample, features of the early-life environment predicted neither brain wiring parameters nor global topology in young adulthood. Higher birthweight, on the other hand, predicted greater global efficiency ($F_{1,144} = 6.65$, $p = 0.011$), lower mean betweenness centrality ($F_{1,144} = 8.28$, $p = 0.005$), and lower small-worldness ($F_{1,144} = 7.7$, $p = 0.006$).

It is important to note that a lack of adversity-related variation in *global* topology does not entail the absence of adversity-related differences in *local* connectivity. To verify this possibility, we compared the degree, clustering coefficient, and nodal efficiency of the left and right medial prefrontal cortices (PFC) of the three subgroups – as numerous studies implementing different metrics have uncovered adversity-related differences in the structure of this region (McLaughlin et al., 2019).

In the right hemisphere, the medial PFC showed a lower clustering coefficient in unexposed group ($M = 3542.5$, $SD = 705.0$) compared to the deprivation group ($M = 3837.2$, $SD = 633.2$) and threat group ($M = 3850.3$ $SD = 699.3$), as demonstrated by an ANCOVA ($F_{2,144} = 3.49$, $p = 0.033$). Similarly, the unexposed group showed lower efficiency ($M = 6024.3$, $SD = 1016.5$) compared to the deprivation ($M = 6424.4$, $SD = 706.4$) and threat groups ($M = 6335.9$, $SD = 730.5$) in the right medial PFC ($F_{2,144} = 3.28$, $p = 0.041$). No difference was observed in degree ($F_{2,144} = 0.28$, $p = 0.755$). For the left hemisphere, an ANCOVA found that the medial PFC showed lower clustering coefficient in the unexposed group ($M = 3633.3$, $SD = 648.0$) compared to the deprivation ($M = 3891.5$, $SD = 706.3$) and threat ($M = 4019.5$ $SD = 670.5$) groups ($F_{2,144} = 4.19$, $p = 0.016$). No difference was observed in degree ($F_{2,144} = 1.121$, $p = 0.302$) or efficiency ($F_{2,144} = 2.72$, $p = 0.069$).

A further possibility is that differences in network topology are manifest subcortically, rather cortically. As the Schaefer parcellation does not include subcortical regions, we reconstructed the connectomes using the Brainnetome atlas (Fan et al., 2016). We assessed the local connectivity of 20 limbic regions, including subregions of the amygdala, hippocampus, and basal ganglia, and compared the three groups on their degree, clustering coefficient, and nodal efficiency. After correction for multiple comparisons, no significant differences were found.

3.8 | Relationship between brain wiring and cognitive and socioemotional functioning

Finally, we tested our last hypothesis, that weaker constraints on brain wiring would be related to lower IQ and higher internalising and externalising behaviours in adolescence. As these measures were collected before neuroimaging data, inference of a causal contribution of brain organisation is not possible, and we therefore chose to calculate a simple correlation. Given the strong association between η and γ, and following previous work (Carozza et al., 2023), we considered the wiring parameters together by multiplying their values. After controlling for sex, study ID, and birthweight, stronger wiring parameters showed a small negative correlation with externalising behaviour ($r = -0.079$, $p = 0.021$) which did not survive Bonferroni correction for multiple comparisons, and no relationship with either internalising behaviour ($r = -0.053$, $p = 0.117$) or IQ ($r = -0.021$, $p = 0.530$). As such, we find no evidence for a robust relationship between the wiring economy of the brain and cognitive and socioemotional functioning.

4 | DISCUSSION

We explored the relationship between the early-life environment and whole-brain networks in young adulthood. Using data from a large longitudinal sample, we first evaluated whether early adversity predicts later differences in global network topology. We then used generative network modelling to test whether adversity alters the economic trade-off that best replicates the organisation of the structural connectome. Contrary to our hypotheses, neither measures of global topology nor model parameters varied by exposure to violence, experiences of deprivation, or basic demographic characteristics apart from birthweight. This invariance held across subsamples taken from the extremes of the spectrum of adversity exposure. Thus, we found no evidence that adverse environments in childhood alter the organisation of whole-brain networks in young adulthood.

4.1 | Early adversity does not predict later brain organisation

Our first hypothesis was that forms of early-life deprivation would most strongly predict the later organisation of the DTI-derived structural connectome. Our analysis was well positioned to detect such a relationship, should it exist, given our use of the large ALSPAC

cohort—which prospectively collected rich measures of early-life experience (Boyd et al., 2013; Fraser et al., 2013)—and our choice of a data-driven PLS regression. However, across thresholds, there was no significant covariance between the early environment and the global efficiency, clustering, betweenness centrality, or small-worldness of the connectome in young adulthood. Upon predicting brain wiring parameters, one significant component did emerge, in line with previous work demonstrating that this compression strategy captures more variability than singular measures of topology (Carozza et al., 2023). However, following a bootstrapping procedure, only birthweight loaded significantly onto this component.

The lack of a contribution from experiences of adversity does not seem attributable to low variance in the project sample, as subsamples of participants who grew up in poverty or with elevated exposure to violence exhibited comparable values on all metrics of brain organisation to a subsample of unexposed individuals. Notably, these groups did differ in the connectivity of the medial prefrontal cortex (PFC), a region that has shown adversity-related differences across numerous studies and modalities (McLaughlin et al., 2019; Noble et al., 2015). Specifically, we found that the unexposed group has lower clustering and efficiency in the right medial PFC, as well as lower clustering in the left medial PFC, when compared to the deprivation and threat groups. These differences appear to indicate that adversity increases the density of connections in the PFC; without following the participants over time, it is unclear if this reflects a shift in the timing of maturation of the PFC or a diverging developmental trajectory (DiMartino et al., 2014).

Our observation of a lack of global differences contrasts previous studies that have shown a drop in the global efficiency of brain networks of female (but not male) children in poverty (Kim et al., 2019) and maltreatment-related increases in the sparsity and heterogeneity of the structural connectome (Ohashi et al., 2017, 2019; Puetz et al., 2017). This discrepancy may reflect our choice to use (1) a longitudinal sample, which avoids the spurious correlations induced by cross-sectional analyses (Spector & Brannick, 2011); (2) prospective measures of adversity, as retrospective measures can underestimate genuine exposure and inflate relationships with current well-being (Pinto & Maia, 2013; Susser & Widom, 2012); and (3) a large sample, which improves the robustness and generalisability of findings (Button et al., 2013; Falk et al., 2013). Thus, our analysis draws attention to the importance of rigorous analytical designs and broad sampling in accurately characterising the relationship between early adversity and later neural phenotypes.

Another plausible reason for differing results may be unmeasured confounds in previous work. In this study, higher birthweight predicted both generative modelling parameters and global measures of topology. Given that higher birthweight is associated with greater volume of grey and white matter into late adulthood (Wheater et al., 2021), brain size may have influenced the results of probabilistic fibre tracking. While studies typically deploy diffusion tensor measures in their native form (i.e. without normalizing for brain size), previous work has observed a relationship between intracortical volume and FA and MD, and suggested that it may be due to partial volume effects or intrinsic white matter differences (Takao et al., 2011; Eikenes et al., 2023). However, to our knowledge, only one study of adversity-related differences in whole-brain organisation reports controlling for head size or birthweight (Puetz et al., 2017). This critique extends to each diffusion imaging study of the FA or MD of particular tracts cited above (with the exception of Bick et al. (2015)). Given that birthweight and later head size can show negative correlations with low SES and maltreatment (Finch, 2003; Oliván, 2003; Weinberg et al., 1974), inadequate controls may be inflating observations of a relationship between early adversity and the strength or organisation of white matter connectivity.

Notably, our findings also contrast a previous generative modelling study which found that early postnatal stress attenuates wiring constraints in mice—although, as with the present study, groups did not differ on measures of global topology (Carozza et al., 2023). The randomization to an experimental paradigm, and thus the intensity and homogeneity of within-group experiences, may have resulted in a stronger effect on brain wiring in the rodents. It is also possible that fundamental differences at the neural and social levels (Feldman, 2017) account for the discrepancy.

Finally, it is possible that adversity-related differences in connectomic organisation were present in our participants earlier in life. In the ALSPAC cohort, neuroimaging data were collected up to around 20 years after data about experiences of adversity. Given that Puetz et al. (2017) and Kim et al. (2019) both analysed children, the differences they observed may fade over time through compensatory mechanisms or later experiences. Indeed, the human brain is characterised by distinctive experience-dependent plasticity and a long trajectory of maturation (Semple et al., 2013), which has been theorized to allow later experiences and relationships to exert top-down reparation of early neurobiological harm (Feldman, 2017). As discussed further below, this calls attention to the possibility that positive resiliency factors attenuate or moderate the impact of early-life adversity on whole-brain networks. Relatedly, it is possible that differences in birthweight across this sample are reflective of in-utero effects that, compared to postnatal experiences, could have had a more enduring and global impact on the connectome. In fact, premature birth has been shown to predict global topology of the brain in adolescence (Fischi-Gomez et al., 2016).

4.2 | Successful simulations co-vary brain wiring constraints

We found that, across thirteen generative rules, the matching index best replicated the organisation of the empirical connectomes. This adds to a growing body of studies showing that homophily outperforms other categories of generative models (Akarca et al., 2021; Betzel et al., 2016; Vértes et al., 2012; Zhang et al., 2021). It has been suggested that favouring connections between regions with similar connectivity patterns replicates the effects of macroscopic dynamics of Hebbian learning (Vértes et al., 2014). Relatedly, homophily may be the most biologically plausible strategy for network generation because it relies

on self-similarity, which is a form of information available locally rather than globally (Akarca et al., 2022).

In our second hypothesis, we expected the environmental PLS component to predict a weaker penalty on long-distance connections and a weaker preference for connections between regions with shared neighbours. While the predictor was constituted only by birthweight, η and γ did load onto the response component in opposite directions, likely due to their strong negative relationship—which echoes most previous findings (Akarca et al., 2021; Carozza et al., 2023; Zhang et al., 2021).

4.3 | Brain wiring is weakly related to externalizing behaviour

Finally, in our third hypothesis we predicted that weaker wiring constraints would be negatively correlated with IQ and positively correlated with internalising and externalising behaviours in adolescence. We found limited evidence in support of this hypothesis in the form of a weak negative correlation between the product of η and γ and externalising behaviour. This is consistent with previous findings that global network topology is associated with externalising symptoms in adversity-exposed individuals (Gilchrist et al., 2022; Puetz et al., 2017), but not with cognition across the socioeconomic gradient (Kim et al., 2019). However, other work has found a moderate correlation between η and γ and cognitive performance in children (Akarca et al., 2021). Our finding may therefore be due to the temporal ordering of the data collection in ALSPAC, in which cognition was assessed in adolescence and neuroimaging in adulthood; this same ordering proscribes a causal interpretation of the relationship between brain wiring and externalising behaviour.

4.4 | Limitations and future directions

Several limitations of our analysis point to promising follow-up investigations. First, replication in a more diverse cohort such as the Adolescent Brain Cognitive Development (ABCD) Study (Volkow et al., 2018) would confirm the generalisability of these results. Secondly, we used a broad range of experiences of deprivation and threat during childhood as our predictors, as previous theoretical and empirical work demonstrates their impact on brain development (McLaughlin et al., 2021; Lawson et al., 2017). However, future work should explore whether negative and positive experiences outside this time-frame – such as in adolescence or young adulthood, which were not available in this dataset – explain more variation in global network topology. Relatedly, analysing the connectomes of children at repeated intervals across development could test whether there are earlier differences in network organisation or brain wiring parameters that disappear over time, and if so, whether these earlier differences explain later variance in cognition or mental health. Finally, given conflicting reports of adversity-related differences in the strength or organisation of white matter tracts, the field would benefit from a systematic exploration of the sensitivity of previous findings to pre-processing and reconstruction decisions.

In summary, we found no evidence of a relationship between variations in the early-life environment and the organisation of the structural connectome in young adulthood. Future investigations should work to demarcate the extent and magnitude of the impact of early adversity on structural connectivity.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interests related to this publication.

DATA AVAILABILITY STATEMENT

Analyses were carried out in MATLAB and RStudio for R using code that is available on the Open Science Framework (https://osf.io/mtypg/?view_only=24a95ac712a84b37b71d6ffa6625bec8). Data are available by application to ALSPAC (www.bristol.ac.uk/alspac/researchers/access/). For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) licence to any Author Accepted Manuscript version arising from this submission.

ETHICS STATEMENT

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The ALSPAC Executive Committee approved this study, which consists of secondary analysis of fully anonymised ALSPAC data.

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SUPPORTING INFORMATION

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