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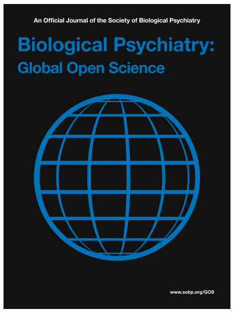

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Causal Effects of Enhanced Parenting on Resting-State Graph Properties of Adolescents at Risk for Maltreatment

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Supplement Description:
Supplement Methods, Results, Tables S1-S3

Abstract

Background: This study investigates the sustained causal effects of enhanced early caregiving quality on adolescent brain network properties, approximately 11 years after families received an attachment-based parenting intervention.

Methods: Participants included 60 adolescents whose parents were referred by Child Protective Services (CPS) because of risk for child maltreatment and 35 adolescents from families without a CPS history (total N=95). CPS-involved families were randomly assigned to either the target intervention (Attachment and Biobehavioral Catch-up, ABC; N=31) or a control intervention (Developmental Education for Families, DEF; N=29) before the infants turned 2. During adolescence (M_{age}=13.4 years, SD=0.37), participants underwent a 6-minute resting-state functional MRI scan.

Results: Graph theoretical analyses were completed with intervention status as the group-level predictor of interest. Adolescents who received ABC exhibited distinct global and local network properties compared to the DEF group. The ABC group demonstrated lower current-flow global efficiency and more hierarchical structure, indicating intervention-driven modulation of connectome-wide neurodevelopmental outcomes. Node-specific analyses also indicate intervention effects on clustering coefficients and communicability distances in frontal, limbic, and parietal cortices, suggesting nuanced effects of early interventions on local network properties. Exploratory moderation analyses revealed associations between brain network metrics and externalizing symptoms in the DEF group—indicative of neurobiological risk—that were absent in the ABC and low-risk groups.

Conclusions: The results suggest that the ABC intervention causally shapes the development of the resting-state connectome and associated regulatory health, offering insights into the neural pathways through which early enhanced care may get under the skin of at-risk adolescents.

Key words: randomized controlled trial; caregiving adversity; parenting; resting-state network properties; externalizing; graph theory

INTRODUCTION

High-quality, nurturing parental care during infancy supports the healthy development of the connectome (1-3) and the absence of such care (e.g., neglect, abuse) poses a serious threat to children's health and brain development (4). Thus, with parents at risk of providing insensitive care, it is critical to intervene early in development to prevent the downstream effects of problematic care (5). The present study leverages data from a longitudinal randomized clinical trial, conducted approximately 11 years after the intervention, to examine the causal effects of an early evidence-based parenting program on complex network properties in adolescents at risk for maltreatment.

A key level at which to identify the negative impact of adversity on children's health is the resting-state functional connectome (rs-fMRI), which reflects low-frequency temporal fluctuations of intrinsic neural activity and interactions between different brain regions (6). Caregiving adversity is associated with disruption in resting-state functional communication between the limbic system (e.g., amygdala, hippocampus, insula) and regions supporting top-down regulation (e.g., prefrontal cortex) (7), which supports optimal social and emotional health (8). Although informative, this research has mostly examined the connectivity between pairs of nodes, without considering the larger network, making it limited in scope as disruption in one connection may be compensated for or associated with further disruptions elsewhere in the network (9,10). Examining the organization of the network can elucidate emergent properties of the entire network and specific nodes as part of a local network (11) and inform us about the impact of insensitive care on brain-wide functional organization (12). Graph theory provides tools for assaying diverse emergent network properties by reducing the vast search space of brain networks in meaningful ways (11). For example, segregation captures how a network is clustered into subnetworks, which is necessary for specialized processing to occur. Integration reflects how efficiently information is distributed across the network. Resilience captures how a network can be vulnerable to disruption. Finally, hierarchy reflects the extent to which nodes are organized into hierarchical levels (10). Together, these metrics reflect specific instantiations of broader categories of network function.

The Development of Network Properties During Adolescence

The normative development of network properties during adolescence has been studied in resting-state functional networks. This work suggests that network segregation and integration increase with age, the strength of short-range links declines over time (13), whereas long-range connections and cortical-cortical communication exhibit a steady increase throughout development (13, 14). These changes that characterize adolescence reflect a functional specialization of distributed networks and an increasing reliance on higher-order cortical networks rather than subcortical or sensory circuits (13, 15-17).

Disruption in the specialization of these networks has been associated with significant regulatory difficulties in youth. For instance, recent work in the ABCD study has suggested that reduced modularity in resting-state and task networks may be a neurobiological marker of externalizing behavior (18). Others have also shown that a loss of segregation between the default mode and executive networks emerged as a correlate of both transdiagnostic internalizing and externalizing problems (19). Together, these findings suggest that alterations in resting-state network properties may underlie a broad spectrum of regulatory difficulties in youth.

A few studies have also examined how retrospective reports of early maltreatment and parenting quality relate to resting-state network properties. For example, the increase in resting-state network integration within the salience network during adolescence mediated the association between maltreatment severity and depressive symptoms and problematic substance-use behaviors (20). Non-social adversities and increase in social adversity severity have been predominantly associated with efficiency within large-scale resting-state networks (20-23), and increase in local and global clustering (24). Furthermore, higher network resilience was predictive of better psychosocial resilience in youth with higher cumulative adversity risk (25). A recent study has also identified positive parenting as a moderator between childhood history of abuse and resting-state functional connectivity (rs-fc) between and within canonical resting-state networks, such that increased rs-fc both within and between networks being associated with less positive parenting practices (26). These studies suggest that increases in within-network efficiency (20-23), local and global segregation (24), and lower network resilience (25) may link the experiences and risks of adversity with impaired self-regulation, with positive parenting being a key mediator (26).

The Effects of Enhanced Care on Quality of Parenting and Children's Brain Development

The Attachment and Biobehavioral Catch-up (ABC) (27) is one of the most researched early interventions that is designed to enhance the biobehavioral development of children at risk for maltreatment. The active ingredient of ABC is the frequent in-the-moment commenting during sessions (1 per minute) that supports parents in increasing responsive, nurturing, and sensitive care and reducing frightening behavior when interacting with the infant. ABC has been shown to enhance parental sensitivity, children's attachment security, emotion regulation (27), executive functioning (28), and functional brain development (29, 30). To investigate the effects of ABC on neuromaturation, we conducted a follow-up assessment in middle childhood. We observed intervention effects on amygdala–orbitofrontal cortex (OFC) resting-state functional connectivity 8 years post-intervention. Specifically, both the ABC and low-risk comparison groups showed age-typical near-zero connectivity, whereas the control intervention group who received the Developmental Education for Families (DEF) group exhibited a pattern of negative functional connectivity that is more commonly seen in older adolescents (6). Moreover, using tasks designed to identify brain responses associated with caregiver relationships and emotional processing, we have shown that ABC causally increases activation associated with the representations of maternal cues (30) and enhances top-down regulation of responses to fearful/neutral faces, as compared to the control intervention group (29). This body of work highlights ABC's potential to reduce the impact of insensitive and non-responsive care by intervening early during sensitive periods of development. However, it remains unclear whether and how these developmental benefits are sustained beyond middle childhood, when the prevalence of regulatory problems rapidly increases. By leveraging data from a longitudinal randomized clinical trial evaluating the efficacy of ABC during adolescence, we begin to address these critical questions.

The Present Study

This study examined how early parenting interventions following maltreatment risk influence the adolescent resting-state connectome. We collected rs-fMRI data from 13-year-olds whose parents had been randomly assigned to receive ABC (target) or DEF (control) intervention in infancy, following CPS-involvement. A non-CPS-involved comparison group was also recruited. Using graph theoretical analyses, we examined global and local resting-state network properties across the three groups (see Table 1 for graph property formulas, definitions, and hypotheses). To contextualize our findings, we conducted exploratory analyses examining the association between network properties and externalizing symptoms, followed by an examination of the moderating role of intervention groups on brain-behavior associations.

Methods

Participants

Families were referred to the ABC intervention by Child Protective Services (CPS) as part of a foster care diversion program due to risk for maltreatment, including homelessness, neglect, drug use, and possible physical or sexual abuse. Eligible families had infants under 2 years old with no known neurodevelopmental disorders (e.g., Rett syndrome, Down syndrome). Consenting families were randomly assigned to either Attachment and Biobehavioral Catch-up (ABC; target) or Developmental Education for Families (DEF; control). Randomization was performed using a random-number table in a parallel design with a 50:50 allocation ratio. Randomization was successful, with no significant pre-intervention differences in demographics or stress hormone regulation (31).

A low-risk comparison group was recruited at age 8 through school and community advertisements. “Low risk” refers to children not referred by CPS and therefore less likely to have experienced neurodevelopmental disruption from early insensitive care at rates above the general population. While some may have faced adversity, their exposure was presumed lower than that of the CPS-involved group. The low-risk comparison group served as a community baseline for evaluating the ABC and DEF groups—not to infer equivalency between the low-risk and the CPS-involved groups when no group differences emerge. Rather, the comparison allows us to examine the extent to which sensitive caregiving mitigates risk pathways and to assess which group (ABC or DEF) more closely resembles the community sample.

All CPS-referred participants who completed the intervention were eligible for follow-up. Of 137 adolescents assessed at age 13, 95 completed a resting-state MRI; 42 were excluded due to refusal, braces, motion, or technical issues (see Supplementary Section 1). No demographic differences emerged between those with and without scans. The sample was racially and ethnically diverse, with most identifying as Black or biracial (see Table 2).

Procedures

The MRI scans were completed at the (blinded) using a 64-channel head coil in a 3-Tesla Sigma MAGNETOM Prisma Scanner (Siemens, Erlangen, Germany). Families received financial incentives to complete the scans (adolescent: $15; parent: $100). All visits followed a structured timeline, and there were no group differences in the start time of resting-state data acquisition (see Supplementary Section 2). Diffusion-weighted images were acquired prior to the resting-state scan. During the resting-state scan, participants viewed a fixation cross, were instructed to stay still, keep their eyes open, avoid falling asleep, and let their minds wander. All participants were treated ethically. The study procedures were approved by the (blinded).

Interventions

Both interventions were manualized, 10 sessions long, and delivered in the families' homes by trained coaches before the infants turned 2 years old.

Target intervention: ABC was designed to enhance the biological and behavioral regulation of young children at risk for receiving insensitive care by encouraging parents to (i) nurture the infant when the infant is distressed; (ii) follow the infant's lead by interacting responsively when the infant is not distressed; (iii) and reduce threatening behaviors. Parent coaches frequently commented about the quality of the parent-infant interactions, thus encouraging nurturing and sensitive responses to the child's cues for engagement (27).

Control intervention: DEF was developed to enhance children's motor, language, and intellectual development (32). Sessions focused on psychoeducation about children's early developmental milestones and activities that parents can engage in to enhance their children's intellectual development. Unlike the original program, DEF did not target responsive care.

Measures

Demographics

We assessed age, sex, race, ethnicity, family income, and caregiver education via self-report. Income data were missing for 29 families (N_{ABC}=12; N_{DEF}=11; $N_{low\text{-}risk}$=6) hence, the averages in Table 2 reflect only those who provided income information.

Externalizing symptoms

The Child Behavior Checklist (CBCL) externalizing problems subscale assesses parent-reported behavioral symptoms related to aggression and rule-breaking in children and adolescents aged 6 to 18 years (33). This subscale is composed of 35 items. In the present study, the CBCL showed excellent internal consistency (Cronbach's α=.942). T-scores were used in all analyses. One participant did not have CBCL data (see Table 2).

Network properties

The list of examined global network properties, their definition, and interpretation is available in Table 1.

Table 1. Examined network properties and their formulas, interpretations, and hypotheses.

Metric	Level	Property	Formula	Interpretation	Hypotheses
Segregation	Local	Clustering Coefficient	$C_i = \frac{1}{n}\sum_{i \in N} \frac{2t_i}{k_i(k_i - 1)}$	Clustering coefficient is the extent to which the neighbors of a node are also connected to each other, thus forming a more interconnected network around that node. Given that the presence of multiple densely interconnected subnetworks within a larger network is needed for the computation of different types of information simultaneously, higher clustering indicates that the node is more likely to be part of such a subnetwork.	In youth with trauma exposure, Suo and colleagues (24) found a positive association between clustering in the left superior frontal gyrus and trauma symptoms. Thus, we hypothesized that adolescents in the DEF group would exhibit higher clustering coefficients in this region compared to ABC.
	Global	Transitivity	$T = \frac{\sum_{i \in N} 2t_i}{\sum_{i \in N} k_i\,(k_i - 1)}$	Transitivity reflects the proportion of all possible subnetworks (i.e., triads) that are actually present in the network. Higher transitivity suggests that more densely interconnected subnetworks are present. Given that such subnetworks are needed for the computation of multiple types of specialized processing, higher transitivity suggests that a network has a greater capacity to compute multiple types of information simultaneously.	Suo and colleagues (24) studied trauma-exposed pediatric patients and found greater global clustering (i.e., higher transitivity) in those who developed PTSD. Thus, we hypothesized that the less sensitive early care in the DEF group would be evidenced by higher transitivity, relative to ABC.
Integration	Local	Communicability Distance	$\xi_i = \sum_j G_{ii} + G_{jj} - 2G_{ij}$	Communicability distance reflects the extent to which a node (i) conveys information clearly and (ii) with as little waste as possible. Clarity is reflected in the number of possible paths between nodes (i.e., with more paths, the noise from each path will be cancelled out) and waste is reflected in the extent to which the information emitted by a node is returned to itself instead of the target nodes.	DEF control treatment has been linked to reduced top-down regulation of threat cues (29), which could be mediated by more efficient transmission of threat-related information. Given that lower levels of communicability distance indicates that a node is a less wasteful and more efficient communicator, we expected that nodes key to threat-processing would show lower communicability distance in the DEF than in the ABC group.
	Global	Current-Flow Global Efficiency	$E = \frac{1}{nm}\sum_{i=1}^{N}\sum_{j=1, j \neq i}^{N} \frac{1}{R_{ij}}$	Current-flow global efficiency reflects the extent to which a network is able to distribute information as efficiently (i.e., more quickly/strongly) as possible. Higher global efficiency indicates that a network is able to integrate the processing that occurs within subnetworks.	Prior empirical work has shown positive associations between maltreatment severity and resting-state global efficiency (20-23). Thus, we hypothesized that the protective effects of ABC would be evidenced by lower global efficiency in ABC, compared to the DEF group.
Centrality	Local	Eigenvector centrality	$\epsilon_i = \varkappa_{\lambda_{max}, i}$	Eigenvector centrality captures the extent to which a node is connected to higher influence nodes (i.e., those with high eigenvector centrality). Influence is a relative quantity and it is possible to compute because all values are obtained simultaneously via singular value decomposition. Higher values suggest that a node has greater influence over	Although no work has examined eigenvector centrality in youth at risk for maltreatment, we do have evidence that compared to the ABC group, DEF is linked to reduced top-down regulation of threat cues (29), and thus we expected that nodes key to threat processing (e.g, amygdala, hippocampus, insula) would have an increased

				the network via its access to other influential nodes.	influence on the network in the DEF group, as evidenced by greater eigenvector centrality.
		Communicability Betweenness Centrality	$cb_i = \frac{1}{(n-1)^2 - (n-1)} \sum_j \sum_k \frac{(e^Z)_{jk} - \left(e^{Z+E(i)}\right)_{jk}}{(e^Z)_{jk}}$	Communicability betweenness centrality is the extent to which communication between other nodes flows through the node of interest. Nodes with high communicability betweenness act as intermediaries that facilitate the exchange of information between regions.	In trauma-exposed youth, Suo and colleagues' (24) found increased betweenness centrality in superior frontal, prefrontal and temporal cortices, and reduced betweenness centrality in parietal regions in those who developed PTSD. Thus, we hypothesized that the less sensitive early care in the DEF group would be evidenced by greater betweenness centrality in superior frontal, prefrontal and temporal cortices, and reduced betweenness centrality in parietal regions in the DEF group as compared to the ABC group.
Resilience	Global	Assortativity	$r = \frac{l^{-1}\sum_{(i,j)\in L} W_{ij} k_i k_j - \left[l^{-1}\sum_{(i,j)\in L} \frac{1}{2} W_{ij}\left(k_i + k_j\right)\right]^2}{l^{-1}\sum_{(i,j)\in L} \frac{1}{2} W_{ij}\left({k_i}^2 + {k_j}^2\right) - \left[l^{-1}\sum_{(i,j)\in L} \frac{1}{2} W_{ij}\left(k_i + k_j\right)\right]^2}$	Assortativity is the extent to which the nodes in network tend to connect with other nodes that have similar strength (i.e., sum of the weights linked to a node). Higher assortativity indicates that highly connected nodes (hubs) tend to be linked to one another, creating redundancy in the network's functional architecture. This redundancy makes the network resilient, as information can still flow efficiently even if a node/hub is disrupted. Lower assortativity suggests that nodes/hubs are more isolated, making the network more vulnerable to targeted damage.	Based on Bezek and colleague's (25) work showing that higher assortativity is associated with psychosocial resilience among youth at high cumulative risk for adversities, we hypothesized that ABC would support similar resilience, as evidenced by higher assortativity, relative to DEF.
Hierarchy	Global	Hierarchical Structure	$\beta = -\log(C \sim k)$	Hierarchical structure reflects the extent which nodes with higher strength have lower clustering (coefficient). Such networks will be organized into distinct, tightly clustered subgraphs, connected by fewer, selectively connected hub nodes. This layered structure supports hierarchical information flow, while lower hierarchy suggests a more parallel, distributed mode of processing. Importantly, low hierarchy does not mean disorganization but indicates reliance on parallel integration rather than hierarchical influence.	Given the dearth of research in this area examining hierarchical brain structure, we constructed a hypothesis via the lens of the accelerated neuromaturation hypothesis (1). This theory suggests that early adversity, without a sensitive and responsive caregiver to co-regulate the child, promotes earlier maturation of brain networks, allowing children to cope in a more adult style at an earlier age. However, this more rapid trajectory is thought to come with a cost - early maturing systems remain less nuanced and adaptive, as compared to those with additional time to experience the world in a protected context allowing for greater refinement based on such interactions. Given evidence that brain modularity increases from childhood to adolescence (41), we expected the DEF group, which lacks that parental buffering, to evidence a more mature appearing pattern than ABC, namely increased levels of hierarchy. It is important to note that our measure only reflects the extent to which the network is structured hierarchically and does not reflect the level of adaptivity, and efficiency engendered by a given structure.

Where Y~X indicates the regression Y on X, N = set of all nodes, L = set of all links, n = # of nodes, m = # of links, A = n x n adjacency matrix wherein each entry = 1 if the corresponding row/column nodes are connected and 0 if not, W= n x n weight matrix wherein each entry is the link weight attached for the corresponding row/column node, $t_i = \sum_{j,h \in N} \left(W_{ij} W_{ih} W_{jh}\right)^{1/3}$, the node strength $k_i = \sum_{j \in N} W_{ij}$, the matrix with node strengths along the diagonal $D = diag(k_i)$, the weight-adjusted adjacency matrix $Z = D^{-1/2} A D^{-1/2}$, the total network strength $l = \sum_{i,j \in N} W_{ij}$, $E(i)$ = n x n matrix with entries = 0 except in row and column i and -1 and = -1 in row/column i wherever a link is present in A, the pseudo-inverse of Laplacian matrix $L^{+} = \left(pinv(D - Z)\right)$, the resistance distance matrix $R_{ij} = L_{ii}^{+} + L_{jj}^{+} - 2L_{ij}^{+}$, the communicability matrix $G = e^{Z}$, $\varkappa_{\lambda_{max}}$= the eigenvector associated with the largest eigenvalue associated with the singular value decompensation of Z.

Resting-State Data Processing

MRI data preprocessing

See Supplementary Section 3 for MRI acquisition parameters. Using the FMRIB Software Library (FSLv6.0.4) (34) the initial preprocessing steps were motion correction, (ii) spatial smoothing (5mm FWHM), and fieldmap correction using topup (fieldmap parameters: EPI, 2x2x2mm, echo spacing=.59 ms; TE=40ms). To identify motion artifacts, ICA-AROMA was applied (35). However, removal of these artifacts was applied to a second set of preprocessed data that were identical except that spatial smoothing was not applied. This was done to improve the separation of signal from adjacent ROIs, as such smoothing would blur signal across ROI boundaries. To ensure that ICA-AROMA successfully removed all visible motion related variance, we computed DVARS on the timeseries *after* motion components had been removed and flagged any runs in which more than 10% of volumes had a DVARS value that deviated by $\geq .5$. Flagged runs were visually inspected for remaining motion-related variance and, if evident, we examined the ICA components not identified by ICA-AROMA. Components that appeared motion-related were added to ICA-AROMA's original list and component removal was redone, after which the DVARS process described above was redone to determine if sufficient motion-related variance was removed. This procedure was performed on 10 participants.

All additional processing steps were completed using the Graph Theory GLM toolbox (GTG; https://www.nitrc.org/projects/metalab_gtg) v.0.5. Preprocessing steps included 2nd order polynomial detrending, bandpass filtering (.01-.1Hz), and partialing of nuisance signals, including the mean white matter, ventricular, and global signal. The squared versions of each of these parameters were also included, along with the temporal derivatives of all signals, resulting in a total of 9 nuisance parameters.

Computing Functional Connectivity Matrices and Graph Properties

T1-weighted images were processed with FreeSurfer, incorporating T2-weighted images to improve pial surface reconstruction. We then mapped the Human Connectome Project (HCP-MMP1) atlas (36) to each participant's cortical mantle, converted the atlas surface into 3D structural space, and merged to create a 370 ROI atlas. Note that the MMPI hippocampus ROIs were merged with the segmented hippocampus to create one hippocampus ROI per hemisphere. Boundary-based registration was used to transform this atlas from anatomical to functional space.

Following this, the timeseries for each ROI was extracted by the largest principal component for each ROI and robust correlations were used to create functional connectivity matrices via GTG. Networks were thresholded at 0 to retain only positive links and the remaining weights were retained in the computation of the graph properties. No sparsity threshold was used, as such thresholds are arbitrary and not needed for weighted networks. Specifically, because of the bias induced by there being no natural weight threshold, past best practice was to compute properties across a range of thresholds and create some representative combination (e.g., AUC). However, with weighted matrices, the most representative value is that corresponding to the original non-sparsified matrices. Specifically, small weights will be removed early in the range of thresholds, and thus have a correspondingly small influence over property computation, whereas the values obtained by combining across a range of thresholds will be dominated by larger weights, as they are retained across more matrices. Thus, in the limit, the influence of each link on the amalgamated property value must approach its influence on the property value obtained from the un-thresholded matrix (ignoring the 0 threshold). Finally, 4 global graph properties and 4 nodal properties were computed for each participant's matrix. Of the 370 ROIs, the nodal properties were calculated for 234 that we hypothesized would be meaningfully relevant for the questions of interest (see Supplementary Section 4 for the list of included ROIs).

Analytic plan

Permutation-based (5000 permutations) general linear models were completed using GTG. The main analyses included only the CPS-involved participants, intervention assignment (ABC vs. DEF) was entered as the main predictor of interest. Because participants were randomly assigned to intervention groups, covariates were excluded from primary analyses, as randomization protects against confounding by balancing variables across groups. Given that variance in higher-level properties can be driven by fundamental aspects of the network, we controlled for the global network's density and total strength for all analyses. For analyses of node-specific properties, we also controlled for that node's node strength and degree. False Discovery Rate (FDR) correction was applied across the 234 ROIs included in our network analyses, as well as over the global network metrics tested. FDR correction is widely used and suitable for large connectivity matrices. Secondary analyses of significant findings examined whether the mean property value for the ABC and DEF groups differed from the low-risk comparison group, to determine which group was more similar to the low-risk sample of adolescents without a history of CPS-involvement.

To contextualize the intervention effects, we conducted exploratory regressions in R (4.4.2) examining the associations between self-report CBCL externalizing T-scores and the local and global graph properties that showed intervention effects. Specifically, with CBCL externalizing T-scores as the dependent variable in all models and a graph property as the predictor of interest, with global network density, total strength, and intervention group included as covariates in all analyses and the relevant node degree/strength for node-specific properties. Two regressions were computed for each graph property, with the first testing the main effect of the graph metric and the second testing the interaction between intervention groups (ABC vs. DEF) and the metric. To determine the uniqueness of significant findings, regressions were recomputed with the addition of the other properties (and associated covariates as appropriate) in the model. To aid in the interpretation of interactions, simple slopes were computed (via the *simple_slopes* function in the *reghelper* R package).

All neuroimaging data are made publicly available on NIMH's Data Archive. The data analytic code will be made available upon reasonable request from the corresponding author. Information on power analysis is available in Supplementary Section 5.

Results

Demographics

See Table 2 for detailed demographics and group statistics. Groups did not differ significantly in age, sex, ethnicity, race, or framewise displacement. Parental education was higher in the low-risk group than in ABC and DEF, and family income differed between the low-risk and DEF groups but not between low-risk and ABC.

Network properties

Significant intervention effects were found in two global and two local graph properties. Table 3 summarizes the results and includes the low-risk group. Findings held when controlling for parental education (Supplementary Section 6) and excluding outliers (Supplementary Section 7).

Global network properties

Current Flow Global Efficiency

ABC had significantly lower current-flow global efficiency than DEF (*b*=5.96, 95% CI [1.82, 10.09], R^2=.702, *p*=.005). Follow-up analyses indicated that the low-risk group also had lower current-flow global efficiency than DEF (*b*=4.51, 95% CI [0.47, 8.55], R^2=.67, *p*=.029), but the low-risk and ABC groups did not differ from each other (*b*=-1.54, [-5.60, 2.53], R^2=.67, *p*=.455) (see Figure 1A).

Hierarchical Structure

DEF networks had significantly lower hierarchical structure than ABC (*b*=-.06, 95% CI [-0.11, -0.02], R^2=.641, *p*=.008). Follow-up analyses indicated that DEF was also lower than the low-risk group (*b*=-.05 [-0.10, -0.01], R^2=.566, *p*=.025), but the low-risk and ABC groups did not differ from each other (*b*=0.01, CI 95% [-0.04, 0.06], R^2=.566, *p*=.652) (see Figure 1B).

Figure 1. Intervention effects on global graph properties

[FIGURE 1]

Note: * = p<.05; ** = p<.01; ABC = Attachment and Biobehavioral Catch-up (active treatment); DEF = Developmental Education for Families (control treatment); Low-risk = control group without a history of CPS-involvement; SE = standard error; ns = non-significant.

Local Network Properties

Clustering Coefficient

DEF had significantly higher left superior frontal gyrus (s6-8) clustering than ABC (*b*=.05, CI 95% [0.02, 0.08], R^2=.938, *p*<.001). Follow-up analyses indicated that DEF was also higher than the low-risk group (*b*=0.03, CI 95% [0.01, 0.05], R^2=.937, *p*=.012), but the ABC and low-risk groups did not differ from each other (*b*=-0.02, CI 95% [-0.04, 0.01], R^2=.937, *p*=.129). ABC had significantly lower right piriform clustering than the DEF (*b*=0.04, CI 95% [0.02, 0.06], R^2=.959, *p*< .001). Follow-up analyses indicated that ABC was also lower than the low-risk group (*b*=-0.03, CI 95% [-0.05, -0.01], R^2=.952, *p*=.011), but the DEF and low-risk groups did not differ from each other (*b*=0.01, CI 95% [-0.01, 0.03], R^2=.952, *p*=.177) (see Figure 2A and B).

Communicability Distance

ABC had significantly higher communicability distance in the PFm subregion of the left angular gyrus than DEF (b=-0.05, CI 95% [-0.07, -0.02], R^2=.926, p<.001). Follow-up analyses indicated that DEF also had lower values than the low-risk comparison group (b=-0.03*, CI 95% [-0.05, -0.00], R^2=.926, p=.018), but the ABC and low-risk groups did not differ from each other (b=0.02, CI 95% [-0.01, 0.04], R^2=.926, p=.157) (see Figure 2C).

Table 2. Sociodemographic characteristics of the participants.

	ABC group N = 31		DEF group N = 29		Low-risk group N = 35		Group difference	
Variables	**%**	**n**	**%**	**n**	**%**	**n**	**Statistic**	**p-value**
Sex, Female	41.9	13	48.3	14	42.9	15	$\chi^2_{(2, N=95)} = .285$	$p = .867$
Race								
African-American	67.7	21	65.5	19	37.1	13	$\chi^2_{(8, N=95)} = 13.63$	$p = .092$
White-American	3.23	1	10.3	3	17.1	6		
Biracial	16.1	5	10.3	3	34.3	12		
Asian-American	3.23	1	0	0	0	0		
Other	9.68	3	13.8	4	11.4	4		
Hispanic ethnicity	9.68	3	20.7	6	22.9	8	$\chi^2_{(2, N=95)} = 2.166$	$p = .339$
Parental education								
No High School	25.8	8	10.3	3	2.86	1	All 3 groups:	
GED	12.9	4	17.2	5	2.86	1	$\chi^2_{(10, N=95)} = 28.945$	$p = .001$**
High school diploma	32.3	10	48.3	14	25.7	9	Post-hoc comparisons:	
Some college	29	9	20.7	6	40	14	ABC vs. DEF: $\chi^2_{(4, N=60)} = 4.589$	$p = .332$
4-year college	0	0	3.45	1	20	7	ABC vs. Low-risk: $\chi^2_{(5, N=66)} = 18.21$	$p = .003$**
Postgraduate	0	0	0	0	8.57	3	DEF vs. Low-risk: $\chi^2_{(5, N=64)} = 15.023$	$p = .01$*
	Min - Max	**Mean (SD)**	**Min - Max**	**Mean (SD)**	**Min - Max**	**Mean (SD)**		
Age (years)	13.019 - 14.362	13.515 (.425)	13.025 - 14.211	13.405 (.355)	12.959 - 14.096	13.319 (.324)	F(2,92) = 2.391	$p = .097$
Income (USD)	$6,000 - 130,000	$44,042.11 (31,318.97)	$794 - 50,000	$27,377.44 (14,044.45)	$12,000 - 280,000	$63,577.93 (66,4544.98)	All 3 groups: $F_{(2,63)} = 3.43$ Post-hoc comparisons: ABC vs. DEF: $B = –16,665$, $SE = 15,375$, $t = –1.08$ ABC vs. Low-risk: $B = 19,536$, $SE = 13,797$, $t = 1.42$ DEF vs. Low-risk: $B = 36,200$, $SE = 14,026$, $t = 2.581$	 $p = .039$* $p = .283$ $p = .162$ $p = .012$*
Framewise Displacement (mm)	0.027 - 3.604	0.238 (.207)	0.028 - 4.669	.237 (.2)	0.03 - 5.392	0.267 (.222)	F(2,92) = 0.045	$p = .956$

CBCL-Externalizing T-Score	53.03 (10.29)	49.29 (11.14)	46.74 (6.85)	All 3 groups: $F_{(2,91)} = 3.662$ Post-hoc comparisons: ABC vs. DEF: *B* = -3.747, *SE* = 2.463, *t* = -1.521 ABC vs. Low-risk: *B* = -6.289, *SE* =2.33, *t* = -2.699 DEF vs. Low-risk: *B* = 2.543, *SE* = 2.395, *t* = 1.062	 *p* = .03* *p* = .131 *p* = .008** *p* = .291

Note. * = *p* < .05; ** = *p* < .01; ABC = Attachment and Biobehavioral Catch-up (active intervention); DEF = Developmental Education for Families (control intervention); GED - General Education Development Test; CBCL - Child Behavior Checklist.

Figure 2. Intervention effects on local graph properties.

[FIGURE 2]

Note. Cortical areas where intervention effects remained statistically significant after false discovery rate (FDR) correction for multiple comparisons across all examined nodes are shown on the average inflated brain surface. Corresponding group differences for these areas are displayed in the barplots. Clustering Coef. = clustering coefficient; Comm. Distance = communicability distance; Left s6-8 = left superior portion of the transition area between Brodmann areas 6 and 8 located in superior frontal gyrus; Right Pir. Area = right piriform cortex; Left PFm = left parietal area F, part m, located in angular gyrus; * = $p < .05$; *** = $p < .001$; ABC = Attachment and Biobehavioral Catch-up (active treatment group); DEF = Developmental Education for Families (control treatment group); Low-risk = control group without a history of CPS-involvement; SE = standard error; ns = non-significant.

Table 3. Intervention effects on local and global graph properties

	Global Graph Properties[1]		**Local Graph Properties**[2]		
Property Name	**Current-Flow Global Efficiency**	**Hierarchical Structure**	**Clustering Coefficient**		**Communicability Distance**
	n/a	**n/a**	**Left s6-8**	**Right Pir. Area**	**Left PFm**
Primary Analyses: *ABC (reference group) vs. DEF*	ABC < DEF: 5.96** [1.82, 10.09]	ABC > DEF: -0.06** [-0.11, -0.02]	ABC < DEF: 0.05*** [0.02, 0.08]	ABC < DEF: 0.04*** [0.02, 0.06]	ABC > DEF: -0.05*** [-0.07, -0.02]
Follow-up analyses: *Low-risk (reference group) vs. ABC*	n.s. -1.54 [-5.60, 2.53]	n.s. 0.01 [-0.04, 0.06]	n.s. -0.02 [-0.04, 0.01]	ABC < Low-risk: -0.03* [-0.05, -0.01]	n.s. 0.02 [-0.01, 0.04]
Low-risk (reference group) vs. DEF	Low-risk < DEF: 4.51* [0.47, 8.55]	Low-risk > DEF: -0.05* [-0.1, -0.01]	Low-risk < DEF: 0.03* [0.01, 0.05]	n.s. 0.01 [-0.01, 0.03]	Low-risk > DEF: -0.03* [-0.05, -0.00]

Note. Cell entries are unstandardized β-values and their associated 95% confidence intervals. * = p < .05; ** = p < .01; *** = p < .001; n.s. – non-significant; n/a - not applicable; s6-8 = superior portion of the transition area between Brodmann areas 6 and 8 located in superior frontal gyrus; Pir. Area = piriform cortex; PFm = parietal area F, part m, located in angular gyrus; ABC = Attachment and Biobehavioral Catch-up (active treatment group); DEF = Developmental Education for Families (control treatment group); Low-risk = control group without a history of CPS-involvement.
[1]A total of four global properties were examined (current flow global efficiency, hierarchical structures, assortativity, and transitivity), and two remained statistically significant after correction for multiple comparisons, resulting in a 50% significance rate.
[2]A total of four local network properties (clustering coefficient, communicability betweenness centrality, eigenvector centrality, and communicability distance) were examined across 234 cortical and subcortical regions. After correction for multiple comparisons, two regions remained significant for clustering coefficient and one for communicability distance, corresponding to significance rates of 0.0085% (2/234) and 0.0043% (1/234), respectively, and 0% significance percentage for the remaining two local network properties that did not yield significant results.

Exploratory Analyses

Associations with CBCL externalizing symptoms

No main effects were significant. Intervention group significantly moderated the effect of all properties examined. Current-flow global efficiency, hierarchical structure, right Piriform and left s6-8 clustering showed a more negative association with externalizing symptoms in the ABC group compared to the DEF group, with the opposite relationship observed for left PFm communicability distance, which is expected given that this property is keyed in the opposite direction. Figure 3 shows effects across all three groups; the low-risk group is included for illustration and had an intermediate profile. See Table 4 for partial correlations, Table 5 for interactions and slopes, and Supplementary Section 8 for the same with the low-risk group included.

In our fully adjusted sensitivity analyses, the interaction term remained consistently significant, indicating a robust moderation and highlighting the unique influence of each property on network organization and behavioral outcomes.

Table 4. Partial correlations between residualized network properties showing intervention effects.

		Global Graph Properties		Local Graph Properties		
		Cur.-Flow Gl. Efficiency	Hier. Structure	Cl. Coef. - Right Pir. Area	Cl. Coef. – Left s6-8	Comm. Dist. - Left PFm
Global Graph Properties	Cur.-Flow Gl. Efficiency	1				
	Hier. Structure	-.32*	1			
Local Graph Properties	Cl. Coef. - Right Pir. Area	.49***	-.26*	1		
	Cl. Coef. - Left s6-8	.42***	-.15	.38**	1	
	Comm. Dist. - Left PFm	-.52***	.37**	-.49***	-.31*	1

Note. Covariates included global network density and total strength for all analyses. For analyses of node-specific properties, we also controlled for that node's node strength and degree. * = p<.05; ** = p<.01; *** = p<.001; Cur.-Flow Gl. Efficiency = Current-Flow Global Efficiency; Hier. Structure = Hierarchical Structure; Cl. Coef. = clustering coefficient; Comm. Dist. = communicability distance; Right Pir. Area = right piriform cortex; Left s6-8 = left superior portion of the transition area between Brodmann areas 6 and 8 located in superior frontal gyrus; Left PFm = left parietal area F, part m, located in angular gyrus.

Table 5. Statistical Summary of Intervention Group by Network Property Interactions Predicting CBCL Externalizing T-Scores.

Property	Effect	Terms	Estimate	SE	t-value	p-value
Hierarchical Structure		Intercept	-7.51	75.06	-0.10	.923
	Interaction	ABC vs. DEF	58.68	19.74	2.972	<.001***
	Simple slopes	ABC	-8.25	17.28	-0.48	.635
		DEF	50.43	19.04	2.65	.01 *
Current-Flow Global Efficiency		Intercept	-1.17	73.79	-0.016	.987
	Interaction	ABC vs. DEF	0.47	.204	2.279	.027*
	Simple slopes	ABC	-0.26	0.22	-1.21	.23
		DEF	0.20	0.20	1.03	.31
Cl. Coef. - Right Pir. Area		Intercept	-26.81	79.05	-.339	.736
	Interaction	ABC vs. DEF	35.06	16.90	2.075	.043*
	Simple slopes	ABC	16.55	39.31	-.42	.68
		DEF	18.52	38.07	.49	.63
Cl. Coef. - Left s6-8		Intercept	-54.37	80.28	-0.677	.501
	Interaction	ABC vs. DEF	42.37	14.48	2.927	.005**
	Simple slopes	ABC	-34.59	29.10	-1.19	.24
		DEF	7.78	28.63	0.27	.79
Comm. Dist. - Left PFm		Intercept	1069.49	16547	.065	.949
	Interaction	ABC vs. DEF	-64.59	19.55	-3.304	.002**
	Simple slopes	ABC	-2.00	31.61	-0.06	.95
		DEF	-66.59	33.21	-2.00	.05*

Note. ABC served as the reference group in all models. Covariates included global network density and total strength for all analyses. For analyses of node-specific properties, we also controlled for that node's node strength and degree.
* = p < .05; ** = p < .01; ABC = Attachment and Biobehavioral Catch-up (active treatment group); DEF = Developmental Education for Families (control treatment group); Cl. Coef. = clustering coefficient; Comm. Dist. = communicability distance; SE = standard error; Left s6-8 = left superior portion of the transition area between Brodmann areas 6 and 8 located in superior frontal gyrus; Right Pir = right Piriform cortex; Left PFm = left parietal area F, part m, located in angular gyrus.

Figure 3. Significant Interactions Between Group and Network Properties Predicting CBCL Externalizing Subscale T-Scores.

[FIGURE 3]

Note. Clustering Coef. = clustering coefficient; Comm. Distance = communicability distance; s6-8 = superior portion of the transition area between Brodmann areas 6 and 8 located in superior frontal gyrus; Pir. Area = piriform cortex; PFm = parietal area F, part m, located in angular gyrus; ABC = Attachment and Biobehavioral Catch-up (active treatment group); DEF = Developmental Education for Families (control treatment group); Low-risk = control group without a history of CPS-involvement.

Discussion

The present study used data from a longitudinal RCT to examine the effects of enhanced early care on adolescents' brain network properties approximately 11 years after families received the attachment-based ABC intervention. Our analyses provide preliminary evidence of causal effects on network properties during adolescence, with implications for externalizing problems. Adolescents in the ABC group exhibited less efficient information transmission and a more hierarchical structure compared to the DEF group. Node-specific measures showed lower integration around the piriform cortex and superior frontal gyrus, and more efficient left angular gyrus communication in ABC than in DEF. Importantly, the low-risk comparison group showed an intermediate slope, which was more similar to that of ABC, suggesting that enhanced care in children at risk for caregiving adversities mitigates the negative impact of maltreatment on brain network organization during adolescence.

Global network topology assesses overall brain organization by capturing emergent characteristics from interactions among all nodes (11). In our study, ABC and the low-risk groups showed lower current-flow global efficiency than DEF. Global efficiency reflects the ease with which information is integrated and transferred across the network (37). Research suggests that global efficiency increases over time (38) and may be further accelerated by adversity exposure (20, 21). Therefore, higher DEF global efficiency may reflect accelerated neurodevelopment following insensitive early care. ABC may slow this neuromaturation down through enhancements in caregiving quality. Although greater efficiency of information communication across the network might at first appear to be advantageous, leaving the DEF group with the better outcome, there are ample reasons to believe that this is not the case. Specifically, less efficient communication across the network may reflect an extended period of synapse pruning and network specialization (1), which in turn allows adolescents more time to learn from their environment and develop more nuanced network organization.

Our analyses also revealed intervention effects on global network hierarchy, with ABC and low-risk groups having greater hierarchy than DEF. Stronger hierarchy supports cognitive growth and information integration (39-41). Lower hierarchy in DEF suggests that early insensitive care shapes the connectome toward distributed organization. Importantly, low hierarchical structure does not indicate a lack of organization, but rather a structure wherein information processing and integration may rely more on distributed and parallel processing than a hierarchical cascade of influence (42). Hence, these results suggest that early insensitive care may fundamentally shape how the connectome is organized, with adverse early experiences leading to increased reliance on a more distributed organization, as indicated by lower levels of hierarchical structure in the DEF group, whereas enhanced care following maltreatment, as seen in the ABC group, may allow for the development of hierarchical network structure.

Local network properties focused on the intervention's impact on specific regions within the network. Significant effects emerged for clustering coefficient (10) and communicability distance (43). Greater clustering in the DEF group, compared to the ABC and low-risk groups, suggest higher embedding of the node within subnetworks, possibly reflecting early maturation that may limit refinement based on environmental input. The superior frontal gyrus (SFG) involvement in higher-level control may support enhanced behavior adjustment in complex environments under early maturation but may increase risk for regulatory difficulties. The advantage of increased clustering around piriform is less clear, given its olfactory function (44). However, its subnetwork, including amygdala, hippocampus, and orbitofrontal cortex (45, 46), is crucial for affect-based memory formation and learning (47). Tighter clustering may facilitate better affect-based learning but could limit adaptation and increase externalizing symptom risk due to accelerated maturation during infancy and reduced plasticity to environmental input by adolescence.

Lower angular gyrus communicability distance in the DEF group implies more efficient communication compared to ABC and low-risk groups–that is, higher quality information is transmitted from that node with less waste. Given its role in attentional processing (48), this may indicate that angular gyrus is driving the focus of attention to a greater extent in the DEF than in the ABC or comparison groups, potentially compensating for weaknesses elsewhere in the network or reflecting early maturation.

Consistent with evidence that adversity and parenting quality often serve as moderators of brain-behavior health (6, 49–53), we conducted exploratory moderation analyses to anchor our neuroimaging findings in self-reported externalizing outcomes. Positive associations emerged between most network properties and externalizing symptoms in the DEF group, but not in the ABC or low-risk groups (except for communicability distance, which is keyed in the opposite direction), suggesting that without the benefit of ABC, these network properties, except hierarchical structure, may increase risk for externalizing problems in adolescents exposed to maltreatment. The non-significant associations in the ABC group suggest that these network properties do not yet function as regulatory pathways. Adolescents in ABC may instead rely on other neurobiological mechanisms or benefit more from social buffering by parents or peers than the DEF group.

The findings related to global network hierarchy are particularly interesting. On average, adolescents in the DEF group exhibited lower network hierarchy than those in the ABC group. Within the DEF group, hierarchical structure was positively associated with externalizing symptoms, suggesting that reduced hierarchy plays a protective or compensatory role in high-risk environments. This pattern also offers a different perspective on prior work, which has generally found reduced modularity (18) and loss of segregation between canonical resting-state networks (19) and externalizing symptoms. Given the positive association between hierarchy and externalizing symptoms in maltreated youth without the benefits of ABC, our results raise the possibility that a less hierarchically organized network is a protective rather than a risk factor. In other words, a less hierarchically organized network may facilitate more flexible information processing and behavioral regulation, mitigating externalizing outcomes. Future longitudinal research is encouraged to explore the moderating role of parental quality in brain-behavior associations, and whether lower modularity and network hierarchy precede reductions in externalizing symptoms (i.e., are protective) versus being downstream of risk exposure or symptom expression.

Importantly, our exploratory results align with prior work (26), showing that parenting quality is an important moderator of resting-state network connectivity in maltreated youth. Although these are cross-sectional associations and we are limited in our ability to infer developmental trajectories, the results suggest that the ABC intervention may promote resilience against externalizing problems by buffering against the emergence of neurobiological risk pathways.

Several strengths and limitations should be noted. Key strengths include the study's prospective, decade-long design and strong ecological validity. ABC was delivered to children with experiences of neglect, abuse, and homelessness, enhancing generalizability to populations most vulnerable to caregiving-related disruptions. Rigorous data quality procedures (e.g., ICA-AROMA) also improved data retention. Although a larger sample size would be beneficial, this remains one of the largest longitudinal RCT samples in the field (54). The low-risk comparison group was recruited at age 8 rather than in infancy; thus, recruitment timing should be considered when interpreting results involving the low-risk group. Finally, resting-state scan duration was relatively short, though comparable to scans commonly used in the literature.

Despite these limitations, we show that enhanced care following early risk for maltreatment has sustained effects on adolescents' local and global resting-state network properties ~11 years after a brief parenting intervention. Given the randomized design, these effects reflect the benefits of ABC, a manualized 10-session program designed to enhance parental sensitivity. The results suggest that early insensitive care leads to more efficient connectome-wide communication during adolescence. Enhanced sensitive care in the ABC group supports the development of a hierarchical network structure, whereas insensitive care in the DEF group produced connectivity patterns more evenly distributed across the connectome. Overall, ABC may alter the developmental trajectory of the adolescent connectome, providing a potential neural pathway through which early sensitive care enhances behavioral regulation in youth at risk for caregiving adversities.

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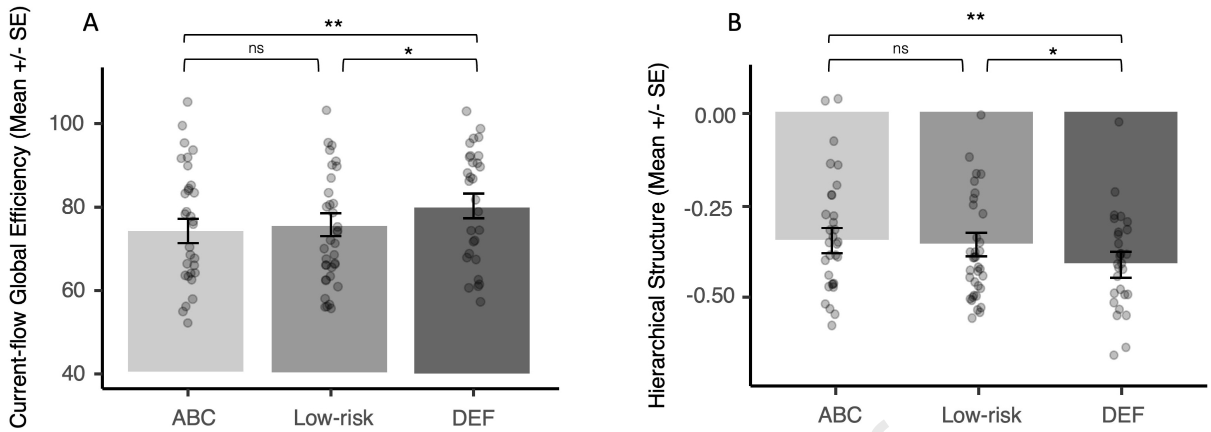
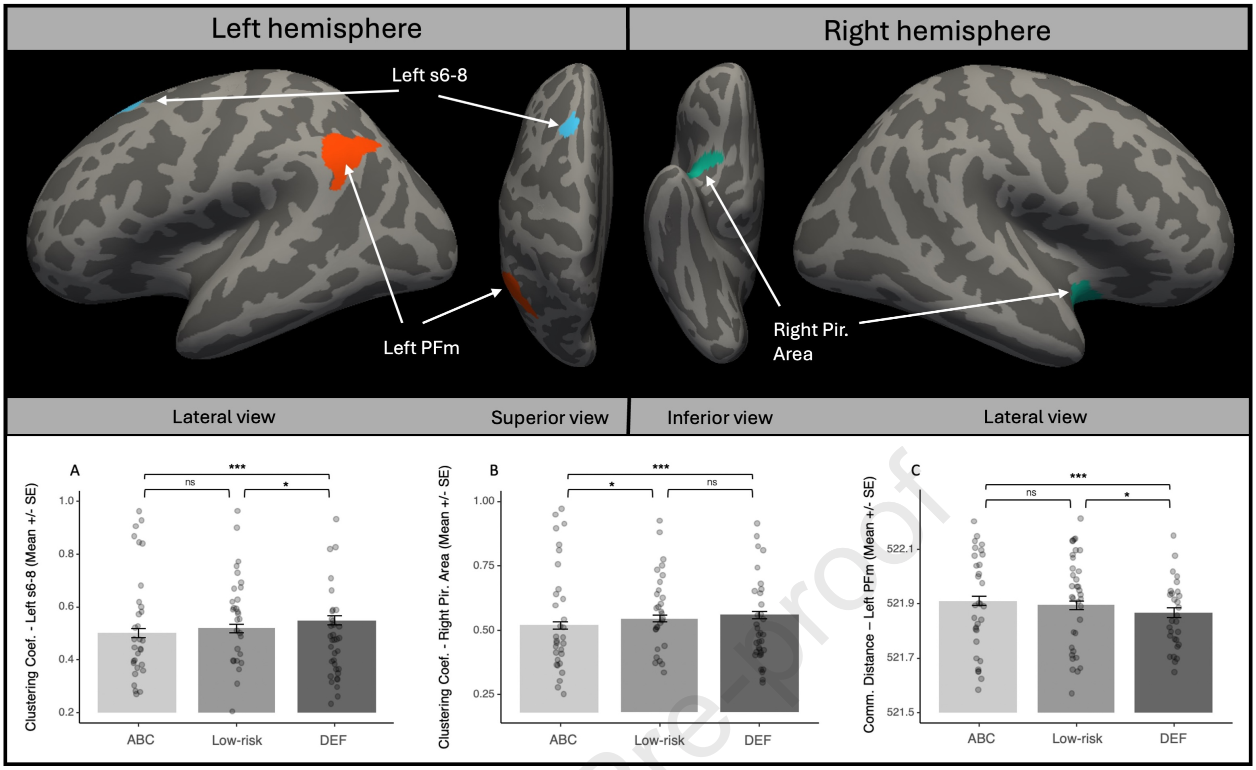


A
B
**
ns
*
Current-flow Global Efficiency (Mean +/- SE)
100
80
60
40
ABC
Low-risk
DEF
Hierarchical Structure (Mean +/- SE)
0.00
-0.25
-0.50


Left hemisphere
Right hemisphere
Left s6-8
Left PFm
Right Pir.
Area
Lateral view
Superior view
Inferior view
Lateral view
A
B
C
Clustering Coef. - Left s6-8 (Mean +/- SE)
Clustering Coef. - Right Pir. Area (Mean +/- SE)
Comm. Distance – Left PFm (Mean +/- SE)
ABC
Low-risk
DEF
ns
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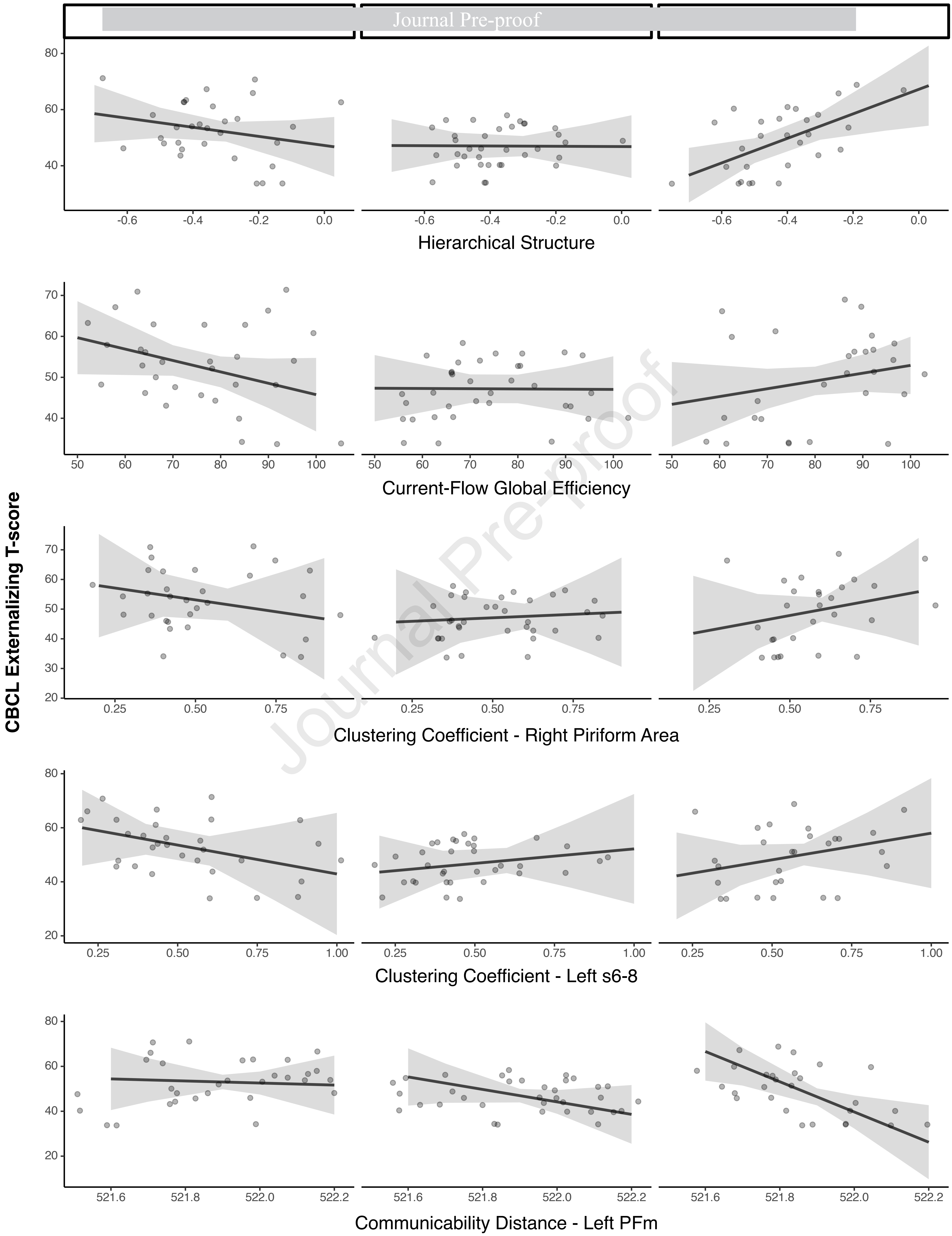
CBCL Externalizing T-score
Hierarchical Structure
Current-Flow Global Efficiency
Clustering Coefficient - Right Piriform Area
Clustering Coefficient - Left s6-8
Communicability Distance - Left PFm
-0.6
-0.4
-0.2
0.0
50
60
70
80
90
100
0.25
0.50
0.75
1.00
521.6
521.8
522.0
522.2
20
30
40
50
60
70
80

Early insensitive care, such as abuse and neglect, disrupts development of the resting-state connectome, making early intervention critical. This study tested whether the Attachment and Biobehavioral Catch-Up (ABC) parenting intervention in infancy leads to lasting causal effects on brain development in adolescents. Youth whose parents received ABC showed more hierarchically organized brain networks and greater network efficiency than those in a control intervention. In the control intervention—but not the ABC—group, brain network metrics were linked to behavioral problems, suggesting ABC promotes functional brain organization that protects against behavioral problems.