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Childhood poverty and the organization of structural brain connectome

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ABSTRACT

Socioeconomic disadvantage is associated with atypical development in specific brain regions, yet the relation between poverty and whole brain network organization (i.e., the *connectome*, a set of brain regions connected with neuronal pathways) has not been characterized. Developmental studies indicate that the connectome undergoes rapid change during childhood and is consequently likely to be highly sensitive to both salutary and detrimental influences. We investigated associations between the socioeconomic disparities measured by the income-to-needs ratio (INR) in childhood and structural brain network organization with 144 healthy children between 6 and 11 years of age (mean age = 8 years). INR of girls was positively and logarithmically associated with the extent to which brain networks were efficiently organized, suggesting that girls in more impoverished environments had less efficient brain network organization. Lower INR was associated with network inefficiency in multiple cortical regions including prefrontal cortex, cingulate, and insula, and in subcortical regions including the hippocampus and amygdala. These findings suggest that childhood poverty may result in wide-spread disruptions of the brain connectome among girls, particularly at the lowest INR levels, and are differentially expressed in females and males.

1. Introduction

In 2016, 18 percent or 13.2 million children in the US were living in poverty (Fund, 2017). Exposure to socioeconomic disadvantage exerts pervasive effects on the developing nervous system with implications for both mental and physical health that persist across the lifespan (Chen and Miller, 2013; Marmot, 2003; McEniry, 2013; Pickett and Wilkinson, 2015). The associations between socioeconomic status (SES) and mental and physical health are observable across the entire socioeconomic gradient (Marmot, 2003; Minkler et al., 2006). However, the most dramatic influence of poverty on children's health and well-being are primarily observed under the most impoverished circumstances (Reiss, 2013). Because poverty represents a clear threat to healthy growth and development, an emerging literature has focused on how poverty shapes the developing brain. Studies of brain structure and function indicate that beginning as early as infancy, adverse effects of poverty are detected in many brain regions (Hair et al., 2015; Hanson et al., 2013; Liberzon et al., 2015; Noble et al., 2006, 2015). It has been reported that certain brain

regions are particularly sensitive to socioeconomic disadvantage including the hippocampus (Barch et al., 2016; Hair et al., 2015; Hanson et al., 2011, 2015; Luby et al., 2013), amygdala (Hanson et al., 2015; Javanbakht et al., 2015; Kim et al., 2013; Luby et al., 2013; Merz et al., 2018; Muscatell et al., 2012; Suzuki et al., 2014; Taylor et al., 2006), and prefrontal lobe (Hair et al., 2015; Hanson et al., 2013; Holz et al., 2015; Johnson et al., 2016; Katsnelson, 2015; Noble et al., 2006, 2015).

Although most studies of neuroanatomic changes in human neurodevelopment have focused on regional changes in volume or morphology, the impact of poverty on the complex pattern of anatomical links among regions of the whole brain (i.e., global connectivity) has not been reported. Accumulating evidence suggests that the socioeconomic disadvantage impacts white matter (WM) tracts (Dufford and Kim, 2017; Gianaros et al., 2013; Gullick et al., 2016; Noble et al., 2013) and the resting-state functional connectivity of the default-mode network (Sripada et al., 2014). Moreover the network architecture and circuits as well as sensory systems of the brain are altered in childhood exposed to adversity (Teicher et al., 2016). These alterations in connections between

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brain regions revealed by neuroimaging techniques likely reflect a variety of cellular and epigenetic disturbances. For instance, rodent models of early life exposure to impoverished environments (denying the dam adequate access to nesting materials) restrict neurogenesis, decrease dendritic arborization, alter gene expression and reduce structural connectivity in the offspring (Bolton et al., 2018; Brunson et al., 2005; Moriceau et al., 2009; Naninck et al., 2015). Thus, it is plausible that early life impoverishment could affect the development of connectivity between brain regions in humans (Scheinost et al., 2017), and examining this possibility is a major innovation of the present work.

Gray matter regions of the human brain are highly interconnected through the WM tracts forming a brain network, called a “connectome” (Sporns et al., 2005). The connectome can be used to identify how the specific pattern of connections among brain regions either support or restrict emergent neurophysiological functions and behaviour, which allows an expanded theoretical and mathematical framework to interpret brain function more than conventional univariate metrics such as estimates of brain metabolism, blood oxygen–level, regional volume and cortical thickness (Bassett et al., 2018). Developmental studies have demonstrated that these brain networks are dynamic systems that are highly vulnerable to insults during sensitive periods, especially early life adversity (Cao et al., 2017). In humans, the connectome can be generated using fiber tractography that maps connections between brain regions (Sporns et al., 2005). Using graph theory both to globally and locally quantify network characteristics of the brain, it is possible to determine whether the structural connectome in children is shaped by early life events including exposure to impoverished environments. Only one study in adults has evaluated the link between SES and network structure, but used anatomical MRI to infer variations in cortical thickness rather than WM tracts. The inference from this study was that adults living in higher SES environments had a greater number of highly segregated and interconnected brain clusters (i.e., network modules) (Krishnadas et al., 2013). While this important finding suggests widespread alterations in white matter connectivity, fiber tractography techniques using diffusion tensor imaging (DTI) can now directly measure the role of WM tracts in local and global connectivity rather than depending on statistical inference (Ursache et al., 2016). Moreover, WM tract integrity itself is influenced by SES (Ursache et al., 2016).

Therefore, to investigate the effects of poverty on brain development, we examined the association between income-to-needs ratio (INR) and topology of structural brain networks in children. INR compares household income to the federal poverty threshold, which is based on household income and family size and is a more accurate indicator of economic well-being than household income alone. Based on the behavioral and neuroimaging findings in humans and the neurobiological data in animals (Cao et al., 2017; Hackman et al., 2010; Nithianantharajah and Hannan, 2006), we hypothesized that the INR would be correlated with

brain network organization with degraded network features at lower INR values, reflected by the most commonly used network measures quantifying the network's global integration and segregation and the importance of each individual node (Rubinov and Sporns, 2010). Because of the growing acceptance that exposure to environmental adversity is reflected in sex-specific influences on the brain and behaviour of males and females (Miller and Halpern, 2014; Sandman et al., 2013), we additionally examined whether child sex moderated the impact of exposure to childhood poverty and brain network characteristics. Finally, we tested whether regions within the brain network differed in sensitivity to childhood poverty to determine if such associations were specific to well-known regions related to the poverty (e.g., hippocampus and amygdala) or more broadly distributed in the brain network.

2. Methods

Participants. Participants were recruited from a subset of children participating in longitudinal developmental studies who were born at one of two hospitals in the greater Los Angeles area (UC Irvine Medical Center or Long Beach Memorial Medical Center). One hundred and forty-four children were recruited for participation (Table 1). All children were between 6 and 11 years old (mean \pm SD: 8.09 \pm 1.35 years; 79 males and 65 females), singletons, and right-handed (defined by the modified version of the Edinburgh Handedness Inventory; Oldfield, 1971). For the purposes of this study, inclusion criteria were: stable neonatal course (median Apgar score = 9, range 7–10), no congenital, chromosomal, or genetic anomalies, and no evidence of intraventricular hemorrhage (determined by ultrasound), periventricular leukomalacia, and/or low-pressure ventriculomegaly in the newborn period. All children had normal neurological findings at the study entry, reviewed on MRI scans by a neuroradiologist. Children were typically developing in the appropriate grade for their age. After providing a complete description of the study to all participants, written and verbal informed consent was obtained from a parent and affirmed assent was obtained from the children. The research protocol was approved by the Institutional Review Board for protection of human subjects.

Income-to-needs ratio (INR). INR is determined by comparing household income to the federal poverty line for a given year and a given household size. Ratios below 1.00 indicate that the income for household is below the federal poverty line identified based on the number of individuals that the income supports, while a ratio of 1.00 or greater indicates income above the federal poverty level for a household of that size (Grieger et al., 2009). A ratio of 1.25, for example, indicates that income was 25 percent above the federal poverty threshold (U.S. Census Bureau., 2004). Family income in this study was assessed based on an INR at the time of MRI acquisition, calculated by dividing total family income by the poverty threshold, determined based on family size, at the

Table 1
Demographic characteristics of a sample of children.

	Female	Male	t, χ^2	P
<i>N</i>	65	79		
Age, mean(SD), years	8.12 (1.40)	8.06 (1.31)	0.27	0.79
Gestational length, mean(SD), weeks	37.63 (3.30)	37.32 (3.32)	0.55	0.58
Income-to-needs ratio (INR)	2.70 (1.63)	3.21 (1.56)	1.92	0.06
Race/ethnicity			4.91	0.30
Hispanic	21	29		
Non-Hispanic White	18	32		
African American	3	4		
Asian	3	2		
Multiethnic	20	12		
Maternal Characteristics				
Education (years)	14.5	15.4	1.90	0.06
Race/ethnicity			2.20	0.70
Hispanic	21	32		
Non-Hispanic White	27	34		
African American	4	3		
Asian	8	5		
Multiethnic	5	5		

time of assessment specified by the U.S. Census Bureau. The range of the INR was 0.11–6.29 (see Table 1), and 32.6% of the sample lived in poverty ($\text{INR} \leq 1$) or near poverty ($\text{INR} \leq 2$). INR was log-transformed for all analyses due to the positively skewed distribution (Noble et al., 2015).

Image Acquisition and Preprocessing. Children completed a neuroimaging battery that included high-resolution structural and diffusion tensor images (DTI) collected on a Philips 3T Achieva MRI scanner. All children used ear protection during MR scans, and children's head movement was minimized with restraining foam pads around the head. T1-weighted structural scans were acquired for the anatomical reference in the sagittal plane using an inversion-recovery spoiled gradient recalled acquisition (IR-SPGR) 3-dimensional sequence [repetition time (TR) = 11 ms; echo time (TE) = 3.35 ms; inversion time (IR) = 1.1 s; flip angle = 18°; imaging matrix = 240 × 240; 150 slices; voxel size = 1 × 1 × 1 mm³; turbo field echo (TFE) factor = 192 without SENSE (sensitivity encoding) acceleration; acquisition time = 421 s]. DTI scans were obtained using a spin-echo echo-planar imaging (SS-EPI) sequence [TR = 11.6 s; TE = 55 ms; 60 transverse slices; slice thickness = 2 mm; field-of-view = 224 × 224 mm²; imaging matrix = 128 × 128; in-plane voxel size = 2 × 2 mm²; 32 non-collinear directions; *b*-value of 800 s/mm²; one *b*₀ image; acquisition time = 485 s]. All scans were visually checked to ensure the acceptable image quality. MRI preprocessing was performed using Freesurfer (<http://freesurfer.net>), AFNI (<http://afni.nimh.nih.gov>), and FSL (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). DTI scans were corrected for the children's head movements and eddy current distortion during scanning (mean ± SD = 0.60 ± 0.17 mm; 0.20–0.98 mm; no association between mean head movements and INR; $r = -0.11$, $P = 0.19$). A diffusion tensor was computed with nonlinear iterative method to avoid negative eigenvalues, and the directional uncertainty of the principal diffusion direction was estimated using the 100-times jackknife resampling algorithm at each voxel (Taylor and Biswal, 2011).

Anatomical Parcellation. The whole brain with T1-weighted structural scan was parcellated into anatomically distinct 68 cortical and 14 subcortical regions using Desikan-Killiany atlas of Freesurfer. Subsequently, we generated multiple parcellation schemes to empirically address a possible effect of granularity of parcellation, as measured by number of regions, on brain network construction (de Reus and van den Heuvel, 2013; van Wijk et al., 2010) – the cortical regions were subdivided into sets of 114, 219, 448, and 1000 regions using Connectome Mapper (<http://www.connectomics.org/mapper>), which had approximately identical node size across both hemispheres (Hagmann et al., 2008). The five parcellation schemes (i.e., 64–1000 regions) were examined in further analyses (Fig. S1A).

Structural Network Characteristics. Probabilistic tractography, which allows multiple connections to achieve a minimal risk of type-2 error during the fiber extraction, was performed from the seeded WM regions using voxel-wise directional uncertainty [FA > 0.1; direction change < 60°; tract length > 1 cm; 30 seeds per voxel; 1000 Monte-Carlo iterations, generating 30,000 trials at each voxel] (Taylor and Saad, 2013). Consistent with previous investigations in children (Kim et al., 2014, 2016, 2017), structural connectivity (SC) was defined between any pair of nodes, if two regions were interconnected with at least 30 streamlines, as averaged FA values of interconnecting tracts reflecting the integrity of whiter-matter fascicles (Collin et al., 2014; van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013). For each parcellation scheme, the global network characteristics (Sporns, 2011) in terms of network segregation (clustering coefficient [γ] and modularity [Q]), integration (characteristic path length [λ] and global efficiency [GE]), and their optimal balance (small-worldness [$\sigma = \gamma/\lambda$]) were computed using Brain Connectivity Toolbox (<https://sites.google.com/site/bctnet>). Normalized measures (i.e., γ , λ , and σ) were used by comparison with distributions comprising 1000 constrained null (i.e., random) networks retaining the connection weights as well as the number of nodes (= brain regions), edges (= connections), and degree sequences (= the number of connections at each node) of individual networks (Maslov and Sneppen,

2002).

Characteristic path length was defined by the average of the shortest path length (i.e., the summation of connection distances along the shortest path in the SC network) between individual nodes and other nodes. Shorter characteristic path length computed in a network represents stronger potentials for the structural integration (Rubinov and Sporns, 2010). Global network efficiency, meanwhile, was computed as the average of the inverse of the shortest path lengths, which represents the network capacity to exchange information among network nodes (Latora and Marchiori, 2001). Clustering coefficient at each node was computed as the likelihood that the neighbors of a node are interconnected to each other. Then, the values were averaged across network nodes to yield a measure for global network clustering. Modularity was computed as the degree to which the network has an optimal partition with distinct subcommunities. The clustering coefficient and modularity measures represent the extent to which closely and densely coupled neighbors form local clusters or modules in the network, respectively. Last, small-worldness represents the extent to which a network has highly clustered nodes with shorter node-to-node distances. Mathematical details of the above-mentioned network variables are found in Rubinov and Sporns (2010).

Cognitive Assessments of Children. Children's general intelligence was assessed using the Perceptual Reasoning Index (PRI) of the Wechsler Intelligence Scale for Children (WISC-IV) with subscales of Matrix Reasoning, Block Design, and Picture Concepts. The PRI is relatively language free and culturally independent (Baron, 2004) and two of the subscales (Matrix Reasoning and Block Design) have been shown to be excellent indicators of general intelligence (Baron, 2004; Wechsler, 2002). Expressive language was evaluated using the Expressive Vocabulary Test (2nd Edition, EVT-2) (Williams, 2007a). The EVT-2 uses both labeling and synonym items to assess expressive vocabulary in children and adults ages 2.5 to 90 + without relying on reading or writing. The EVT-2 has been shown to have good validity, internal reliability ($\alpha = 0.94$ through $\alpha = 0.97$ for children ages 6–10 years), and excellent stability ($r = 0.95$) (Williams, 2007b).

Statistical Analysis. Multiple linear regression analyses were performed to examine the associations between INR and network characteristics, which collects representative measures for network integration [characteristic path length (λ) and global efficiency (GE)], segregation [clustering coefficient (γ) and modularity (Q)] and small-worldness (σ). Models were designed to control age, sex, gestational length, child race/ethnicity, maternal race/ethnicity, and maternal education length as factors previously shown to be associated with INR (Noble et al., 2015) and network characteristics (Kim et al., 2014, 2017). To control false positives, the number of computed global network measures was corrected after the regression analyses – i.e., false-discovery-rate (FDR) corrected $P < 0.05$. Subsequent analyses investigated if the best fit model was linear, logarithmic, or quadratic for the nuisance variables. Next, to examine whether there was a sex difference, the INR for each sex was set as the predictor of interest, controlling for age, gestational length and maternal education length with logarithmic or quadratic terms if appropriate. To investigate whether the association between INR and network measure was specific to a certain brain region, node-wise multiple linear regression analyses were conducted on the efficiency measure computed at each parcellated region (i.e., local network efficiency; c.f., Fig. S1B). Node maps were set for a threshold of $P < 0.05$ (FDR correction for each parcellation).

3. Results

INR and global efficiency of the brain network. Initial multiple regression analyses were performed with linear terms adjusting for age, sex, gestational length, child race/ethnicity, maternal race/ethnicity, and maternal education length for 5 different brain parcellations (Table S1-5). Low INR was associated significantly with decreased global network efficiency independent of the nuisance variables (Table S1). The

association was significant ($P < 0.05$) for all nuisance variables and for all parcellation schemes, but was best fitted for the parcellation scheme with 462 brain regions controlling for age, sex, gestational length, and race/ethnicity ($\beta = 0.238$, $P = 0.009$, $F(6,137) = 3.91$, adjusted $R^2 = 0.109$, $P = 0.001$, Table S1; FDR-corrected for 5 global network measures – See the Statistical Analysis). Therefore, further analyses were conducted using this 462 parcellation scheme. However, the findings of this study with respect to the association between INR and global network efficiency (including the sex difference and regional specificity) did not change with the generated parcellation schemes (c.f., Table S1-6), suggesting overall consistency regardless of the adopted brain network construction. Only the sex \times income interaction was significant ($\beta = 0.211$, $P < 0.05$) when it was included in the model using the entire sample, indicating stronger associations of low INR among girls (see the sex difference section below). There were no age \times income or gestational length \times income interactions when they were included in the model, suggesting invariant associations across child age and gestational length. Results remained significant when the models included quadratic and logarithmic terms. No other network measures (i.e., characteristic path length, clustering coefficient, modularity, and small-worldness) showed significant associations with INR values.

Sex differences in the association between INR and brain network. We next investigated associations between INR and global efficiency by sex. Initial analyses revealed that regression models were best fit using age, gestational length, and race/ethnicity (Table S6). Lower INR was significantly associated with decreased global efficiency

in girls ($\beta = 0.446$, $P = 0.001$, $F(5,59) = 4.47$, $R^2_{\text{adjusted}} = 0.213$, $P = 0.002$; Fig. 1A, Table 2), but not in boys ($\beta = 0.060$, $P = 0.627$, $F(5,73) = 3.07$, $R^2_{\text{adjusted}} = 0.117$, $P = 0.014$). Quadratic term for age was

Table 2

Associations between family INR and global network efficiency. Family INR was significantly associated with global network efficiency in girls, independent of age, gestational length, and race/ethnicity ($\beta = 0.446$, $P = 0.001$, $F(5,59) = 4.47$, $R^2_{\text{adjusted}} = 0.213$, $P = 0.002$), but not in boys ($\beta = 0.060$, $P = 0.627$, $F(5,73) = 3.07$, $R^2_{\text{adjusted}} = 0.117$, $P = 0.014$).

	β	SE	t	P
Girls ($N = 65$, $R^2_{\text{adjusted}} = 0.213$)				
Age	0.005	0.083	0.063	0.950
Gestational length	0.001	0.035	0.034	0.973
Hispanic	0.032	0.277	0.117	0.907
Other	0.705	0.295	2.389	0.020
Income-to-needs ratio	0.446	0.123	3.636	0.001
Boys ($N = 79$, $R^2_{\text{adjusted}} = 0.117$)				
Age	-0.096	0.086	-1.125	0.264
Gestational length	0.091	0.034	2.691	0.009
Hispanic	-0.405	0.307	-1.321	0.191
Other	-0.205	0.263	-0.780	0.438
Income-to-needs ratio	0.060	0.122	0.489	0.627

Note. Values are computed for the 462 parcellation scheme. Income-to-needs ratio represents the logarithm to the base 10 of family Income-to-needs ratio. Ethnicity was dummy coded as Hispanic [0 (No) or 1 (Yes)] and Other [African American, Asian or Multiethnic; 0 (No) or 1 (Yes)], using Non-Hispanic White as the reference category.

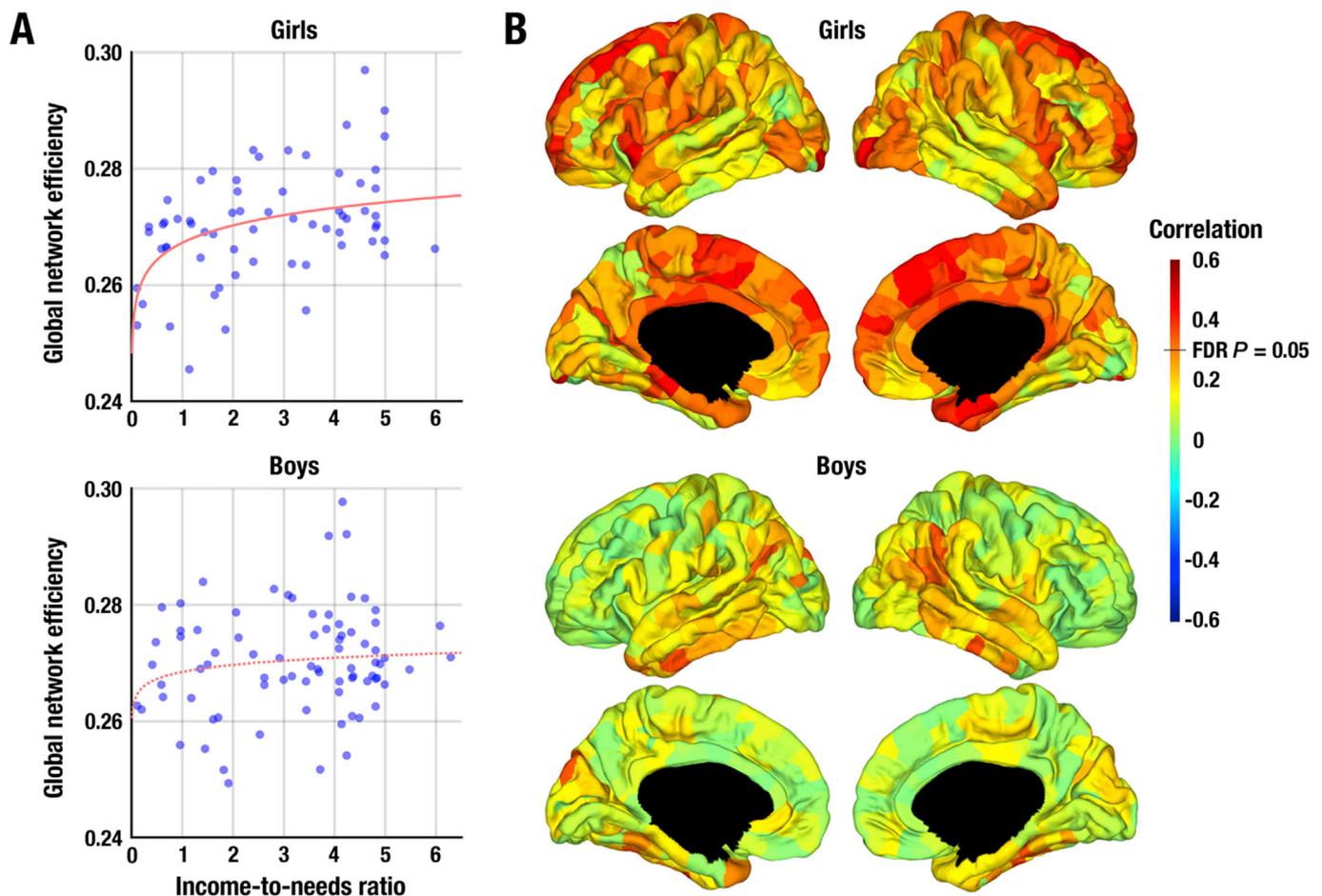


Fig. 1. Family INR is logarithmically related to the global network efficiency in girls ($N = 65$). (A) Multiple regression analysis showed that, when adjusting for age, gestational length, and race/ethnicity, family INR was significantly associated with global brain network efficiency in girls ($\beta = 0.446$, $P = 0.001$; solid line), not in boys ($\beta = 0.060$, $P = 0.627$; dashed line). (B) Girls' family INR was significantly associated with local efficiency in widespread cortical areas of lateral and medial prefrontal, cingulate and insula regions. Maps are thresholded at $P < 0.05$ (FDR corrected).

not used in the model, since it did not account for additional unique variance, which was not consistent with a recent study (Noble et al., 2015). However, results still remained significant when a quadratic term for age included in the model (cf. quadratic models in Table S7).

Regional specificity in girls. We then visualized the significant regions to assess the specificity of associations between INR and local network efficiency in girls (Fig. 1B). When adjusting for age, gestational length, and child race/ethnicity, INR accounted for the most significant variation of the local efficiency – lower INR (= poverty) was associated with decreased global efficiency in widespread brain regions of girls ($P < 0.05$, FDR corrected). These encompassed the subcortical regions including the bilateral hippocampus and amygdala (Table S8), and the cortical regions including the bilateral superior and inferior frontal, rostral middle frontal, superior and inferior parietal, anterior and posterior cingulate, lateral occipital, precuneus, precentral, postcentral, supramarginal, lingual, cuneus, fusiform, entorhinal, and insula cortex. Compared to the frontal and subcortical regions, relatively fewer areas in the temporal cortex showed a significant association between INR and local efficiency (see Fig. 1B). Notably, the relation of local network efficiency to INR was most evident at the lowest levels of INR (i.e., among the children with the lowest household incomes), consistent with the global efficiency findings described above. No significant associations were found in boys (Fig. 1B).

Hippocampus, amygdala, and other subcortical regions in girls. Both the bilateral hippocampus and amygdala, in which the volumes are known to be associated with poverty indicators (Hanson et al., 2015; Luby et al., 2013), showed significant associations between lower INR and decreased local network efficiency ($P < 0.05$, FDR corrected with cortical and subcortical regions; Table 3) – the lower INR was significantly associated with decreased network efficiency in these regions. This finding is consistent with prior research that focused on these regions (Katsnelson, 2015). However, this association was not specific to the hippocampus and amygdala because all other subcortical regions evaluated had significant or trend-level positive associations with INR and local efficiency (Table S8). No significant associations were found in boys.

Relation to cognitive outcomes. In the total sample, higher INR was associated with higher Perceptual Reasoning Index (PRI) scores ($r = 0.33$, $P < 0.001$) on the Wechsler Intelligence Scale for Children (WISC-IV). Examination of the subscales revealed significant associations between INR and Block Design (BD; $r = 0.36$, $P < 0.001$) and Matrix Reasoning ($r = 0.30$, $P < 0.001$), but not Picture Concepts ($r = 0.13$, $P = 0.11$). Higher INR additionally was associated with better performance on the Expressive Vocabulary Test (EVT; $r = 0.37$, $P < 0.001$). Sex, however, did not moderate the relation between INR and WISC or EVT (P 's > 0.60). Further, no significant mediation of cognitive outcomes (i.e.,

WISC and EVT) for the association between INR and network characteristics were found. Global efficiency was positively associated with BD score of PRI ($r = 0.18$, $P = 0.027$), which was consistent with our previous report (Kim et al., 2016), but no other associations were found between the cognitive outcomes and network measures.

4. Discussion

This study investigated whether the socioeconomic disparities in childhood were associated with alterations in the linkages among brain regions assessed with the structural connectome. We found that exposure to poverty, described by INR during early childhood, predicted the efficiency of brain network architecture. Lower INR measured in childhood was associated with a reduction in the normative pattern of efficient connectedness within the brain network. Importantly, the association of INR on the brain network in these children was significant only among girls. Girls from low-income families had reduced network efficiency in many areas of the brain, including the prefrontal cortex, cingulate cortex, and insula as well as the hippocampus and amygdala. Occipital and temporal lobe regions were relatively less affected by exposure to poverty. These tractography-based structural connectome findings compliment findings from conventional voxel- or region-specific (i.e., ROI) approaches and indicate more wide-spread global consequences of poverty on the whole brain network structure than has been previously observed (e.g., Dufford and Kim, 2017; Gianaros et al., 2013).

The logarithmic association between INR and global efficiency reflects the fact that the lower end of the family income distribution has a disproportionately greater effect on children's neural network efficiency. This indicates that children exposed to the greatest poverty are more likely to show the neurological fingerprint of deprivation, in that the children with lower INR tend to have the less efficient transfer of local information among all regions in their brain network (Sporns, 2011). This may indicate a deficit of topological shortcuts supporting long-distance interactions from one brain region to another (Betzel and Bassett, 2018), which has been associated with network-level abnormalities in development (Cao et al., 2017), aging (Zuo et al., 2017), and psychosis (Rubinov and Bullmore, 2013). This extends a recent large-sample study showing wide-spread reductions in surface area related to childhood poverty that also were more apparent at the lowest end of the SES continuum (Noble et al., 2015) and a report of decreased gray matter volume in lower INR female infants (Betancourt et al., 2016). Specifically, the present results suggest that local structural impairments [i.e., decreased cortical thickness and reduced gray matter volume reported by Noble et al. (2015) and Betancourt et al. (2016), respectively] are likely to be associated with impaired WM connections, which is reflected by inefficient brain network organization. Socioeconomic

Table 3
Associations between family INR and local network efficiency at the hippocampus and amygdala in girls ($N = 65$).

Regions	Right hemisphere					Left hemisphere				
	R^2_{adjusted}	β	SE	t	P	R^2_{adjusted}	β	SE	t	P
Hippocampus	0.103					0.185				
Age		0.145	0.088	1.649	0.104		0.196	0.084	2.330	0.023
Gestational length		-0.019	0.037	-0.509	0.613		-0.028	0.035	-0.794	0.430
Hispanic		0.072	0.296	0.243	0.809		0.227	0.282	0.806	0.423
Other		0.334	0.315	1.058	0.294		0.775	0.300	2.578	0.012
Income-to-needs ratio		0.375	0.131	2.865	0.006		0.376	0.125	3.011	0.004
Amygdala	0.153					0.106				
Age		0.112	0.086	1.303	0.198		0.130	0.089	1.469	0.147
Gestational length		-0.047	0.036	-1.306	0.197		-0.046	0.037	-1.221	0.227
Hispanic		0.021	0.287	0.074	0.942		-0.145	0.297	-0.487	0.628
Other		0.202	0.306	0.659	0.513		0.197	0.316	0.622	0.537
Income-to-needs ratio		0.431	0.127	3.391	0.001		0.359	0.148	2.423	0.008

Note. Bold values represent significant associations with FDR corrected $P < 0.05$ for the 462 parcellation scheme. Income-to-needs ratio represents the logarithm to the base 10 of family income-to-needs ratio. No associations were found in boys. Ethnicity was dummy coded as Hispanic [0 (No) or 1 (Yes)] and Other [African American, Asian or Multiethnic; 0 (No) or 1 (Yes)], using Non-Hispanic White as the reference category.

disparities in brain development, represented by INR in a family, may therefore be most critical among children with very low family-income, consistent with earlier behavioral studies (Dearing et al., 2001). These findings also suggest that network efficiency, the extent to which each network node interacts more directly and strongly in a network promoting the higher structural integration (Sporns, 2011), might be an important metric for evaluating the effects of interventions designed to mitigate the neurological consequences of poverty on children and improve their caregiving and educational environment (Hackman et al., 2010; Neville et al., 2013).

Alterations in network efficiency associated with INR were found globally across both subcortical regions (Table S6) including the hippocampus and amygdala (Table 3) and cortical regions including the bilateral superior frontal, paracentral, precentral, anterior and posterior cingulate, supramarginal, inferior frontal, caudal middle frontal, temporal pole, and insula cortex (Fig. 1B). The extensive associations between childhood INR in the local network efficiency suggest global disruptions of the brain connectome resulted from the childhood poverty, consistent with a recent volumetric study showing widespread reductions in regional volumes related to childhood poverty (Luby et al., 2013). However, significant associations appeared to be more dominant in the bilateral superior and inferior frontal, insula, and cingulate cortex than in the occipital, temporal, and parietal cortex. These regions are related to language, emotional, and executive functions, which appear to be particularly sensitive to the effects of socioeconomic disparities (Hackman and Farah, 2009; Kim et al., 2013; Liberzon et al., 2015; Noble et al., 2015).

Although lower INR in our study was associated with lower global network efficiency when the entire sample of boys and girls was examined, detailed analysis indicated that this association was apparent in girls, but not boys. These findings are consistent with previous reports of sex differences in the association between early adversity and alterations both in the core anatomical regions and in the distributed functional networks. For instance, we found that fetal exposure to biological markers of early-life adversity was associated with cortical thinning, particularly, in the frontal and temporal regions primarily in girls [age = 7.3 ± 0.9 years] (Sandman et al., 2018). The susceptibility to exposure to childhood adversity has also been reported to be sex-specific in targeted brain regions (e.g., salience and emotion regulation networks spanning the amygdala, anterior cingulate and anterior insula cortex) in adult males and females [mean age > 28 years] (Gupta et al., 2017). Furthermore, childhood adversity also was reported to alter the sexually dimorphic functional neurodevelopment of inhibitory behavioral control, suggesting the early life adversity may confer risk for drug use in susceptible individuals and resilience in others with marked differences between the sexes (Elton et al., 2014). Our finding is consistent with a growing understanding that there are unequal consequences for males and females exposed to a variety of stressors. Sex-specific associations between INR and network efficiency in our study suggest that, girls from more impoverished environments are less likely to develop complex network connections. The implicated regions in girls that were most apparent included the lateral and medial frontal cortex. These results suggest that these regions and the associated networks may be especially sensitive to conditions of poverty, in particular, at the lower ends. This study therefore confirmed and expanded the previous findings by showing that exposure to poverty in early childhood has immediate and disruptive effects on anatomical links among vast regions of the brain which is most evident in preadolescent girls.

In our sample, INR exerted the expected effects on behavioral outcomes. Children from impoverished environments performed significantly more poorly than children from advantage on sub-scales from a standardized test of intelligence and on measures of expressive language. These findings applied equally to boys and girls. It is surprising that the decrease in global neural efficiency associated with exposure to poverty did not mediate the cognitive measures assessed in these children. Accordingly, it is possible that INR influences neural systems in ways that

are not detected by the current behavioral tasks. Otherwise, INR-related effect observed at the neural level might be compensatory/adaptive towards their disadvantaged environment as well as indicative of negative environment. Perhaps a more global assessment of child intellectual abilities would be a more sensitive reflection of the behavioral consequences of the reduction in neuroanatomical connections resulting from exposure to poverty, as in previous studies of IQ association with network metrics in children (Kim et al., 2016) and healthy adult subjects (Li et al., 2009; Zalesky et al., 2011).

This study has several limitations. The INR measure is a global indicator of socioeconomic disadvantage and does not reveal specific aspects of early deprivation that are responsible for the significant associations found in this study. Although different indicators (e.g., aspects of deprivation) are related to distinct childhood outcomes (Duncan et al., 2017) and childhood poverty is related to the spectrum of different types of threats and deprivations (Sheridan and McLaughlin, 2014), INR is a well-accepted metric of a general index of family's economic well-being (Grieger et al., 2009). In this study, only girls living in the most impoverished environments had less efficient brain network organization; however, the INR values of girls were marginally lower than INR values of boys ($P = 0.06$, Table 1). Therefore, it is difficult to rule out the possibility that boys exposed to more extreme poverty levels (similar to the levels experienced by girls in this sample) also have reduced neuronal network efficiency. In addition, the INR associations in this study were the result of correlational findings in a cross-sectional sample. Future research should investigate potential longitudinal relationship between the socioeconomic disparity and brain network characteristics as well as the specific aspects of poverty that affect these relations. Finally, while multiple b_0 -images are preferred in current DTI analyses to increase the sensitivity of diffusion measures (e.g., diffusion tensor), one b_0 -image was acquired during DTI scanning in this study, which might lead to erroneous tensor estimation due to the artifacts in b_0 -images.

In summary, the study provides novel findings suggesting that children exposed to poverty exhibit inefficient brain network organization across multiple regions, and that these associations are more apparent in girls compared to boys. These findings confirm and extend previous conclusions that childhood socioeconomic disparities lead to a notably altered trajectory of brain development. Specifically, girl's SES may lead to diverse developmental trajectories, that are not restricted to a unique influence on a specific brain region. If this true, it suggests that white matter connections are more sensitive than gray matter to the impact of poverty. Extending the previous connectome-based observations to sex differences, we suggest that there are distinctive sensitivities in, and consequences for, boys and girls exposed to early adversity. Further, applications of novel connectome approaches to the analysis of socioeconomic brain will substantially increase our understanding of the atypical brain development and sexually dimorphic progress of mental illnesses resulted from early life adversities. Because the organization of the brain connectome is susceptible to external forces, such as poverty in this case, it may be a sensitive metric for investigating neurological impairments associated with high vulnerability and risk factors related to childhood developmental disorders.

5. Author contributions

D.-J.K. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: E.P.D., L.M.G., C.A.S., W.P.H. Acquisition of data: E.P.D., L.M.G., C.A.S. Analysis and interpretation of data: D.-J.K., E.P.D., L.M.G., C.A.S., O.S., B.F.O., W.P.H. Drafting of the manuscript: D.-J.K. Critical revision of the manuscript for important intellectual content: E.P.D., C.A.S., L.M.G., O.S., B.F.O., W.P.H. Statistical analysis: D.-J.K. Obtained funding: E.P.D., C.A.S., W.P.H. Administrative, technical, or material support: W.P.H. Study supervision: E.P.D., C.A.S., W.P.H.

Competing financial interests statement

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2018.09.041>.

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