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Authors

Kim, Dae-Jin
Davis, Elysia Poggi
Sandman, Curt A
et al.

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ORIGINAL ARTICLE

Prenatal Maternal Cortisol Has Sex-Specific Associations with Child Brain Network Properties

Dae-Jin Kim[1], Elysia Poggi Davis[2,3], Curt A. Sandman[3], Olaf Sporns[1,4], Brian F. O'Donnell[1], Claudia Buss[5,6], and William P. Hetrick[1]

[1]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405, USA, [2]Department of Psychology, University of Denver, Denver, CO 80208, USA, [3]Department of Psychiatry and Human Behavior, University of California Irvine, Orange, CA 92866, USA, [4]Indiana University Network Science Institute, Indiana University, Bloomington, IN 47405, USA, [5]Institut für Medizinische Psychologie, Charité Centrum für Human-und Gesundheitswissenschaften, Charité Universitätsmedizin, Berlin 10117, Germany, and [6]Department of Pediatrics, University of California Irvine, Irvine, CA 92697, USA

Address correspondence to William P. Hetrick, Department of Psychological and Brain Sciences, Indiana University, 1101 East 10th Street, Bloomington, IN 47405, USA. Email: whetrick@indiana.edu

Abstract

Elevated maternal cortisol concentrations have the potential to alter fetal development in a sex-specific manner. Female brains are known to show adaptive behavioral and anatomical flexibility in response to early-life exposure to cortisol, but it is not known how these sex-specific effects manifest at the whole-brain structural networks. A prospective longitudinal study of 49 mother child dyads was conducted with serial assessments of maternal cortisol levels from 15 to 37 gestational weeks. We modeled the structural network of typically developing children (aged 6–9 years) and examined its global connectome properties, rich-club organization, and modular architecture. Network segregation was susceptible only for girls to variations in exposure to maternal cortisol during pregnancy. Girls generated more connections than boys to maintain topologically capable and efficient neural circuits, and this increase in neural cost was associated with higher levels of internalizing problems. Maternal cortisol concentrations at 31 gestational weeks gestation were most strongly associated with altered neural connectivity in girls, suggesting a sensitive period for the maternal cortisol–offspring brain associations. Our data suggest that girls exhibit an adaptive response by increasing the neural network connectivity necessary for maintaining homeostasis and efficient brain function across the lifespan.

Key words: connectome, fetal programming, maternal cortisol, pregnancy, sex differences

Introduction

Through the intimate relationship with the maternal host, the human fetus participates in a dynamic exchange of environmental (intrauterine) information over the course of gestation. Among the most important exchanges between the mother and her fetus is information contained in patterns of biological signals that originate from the maternal stress system. The developing fetus is exposed to massive changes in the maternal endocrine stress system over the course of gestation. One of the major maternal stress signals, glucocorticoids (GCs, cortisol in humans) from the adrenal gland increases 2- to 5-fold over the course of gestation (Sandman and Davis 2012). Although the fetus is partially protected early in gestation from maternal cortisol by a placental enzyme (11B-HSD2), as gestation progresses maternal cortisol crosses the placenta and plays a critical role in fetal maturation. This hormone affects all tissues (Chrousos and Kino 2007) and regulates physiological functions that maintain basal and stress-related homeostasis that are involved in cellular, molecular, and physiological networks serving growth, reproduction, immune, and central nervous

system activities (Nicolaides et al. 2010). While the effects of maternal GCs on the central nervous system have been extensively characterized in nonhuman animals, the consequences for human fetal exposures to elevated maternal cortisol on brain network organization are unknown.

Because the fetal period in the human life cycle is unmatched by any other in growth and development, it is the stage in the lifespan that is most vulnerable to both organizing and disorganizing influences. Disruption in the timing or sequence of neurological development results in tissue remodeling producing altered brain networks and brain morphology (McMullen et al. 2012). Remodeled tissue modifies the function and physiological capacity of an organ throughout the lifespan and is a fundamental assumption of how fetal exposures influence health and disease. In fact, many complex neuropsychiatric and neurodevelopmental alterations that contribute to the global burden of mental illness are characterized both by early-life exposures to intrauterine and neonatal insults (Mwaniki et al. 2012) and by altered brain anatomy (Geuze et al. 2005; Woon and Hedges 2008; Bellani et al. 2011) and connectivity (Ryman et al. 2014).

Fetal exposure to elevated maternal cortisol during sensitive periods of cellular proliferation, differentiation, and maturation can produce structural and functional changes in the brain (Buss et al. 2012). Moreover, prenatal exposure to stress signals, such as maternal cortisol, exerts distinct influences on male and female development (Sandman et al. 2013). Because male fetuses heavily invest their resources in growth, they are left with a relative poverty of resources to respond to maternal signals of stress and adversity. This may explain why under adverse or hostile conditions, males have poorer neonatal and infant health outcomes (Torday et al. 1981; Peacock et al. 2012; Walker et al. 2012; Aiken and Ozanne 2013; Gabory et al. 2013), including widespread differences throughout the brain (Amat et al. 2005; Murmu et al. 2006; Buss et al. 2007; Behan et al. 2011; Buss et al. 2012). High morbidity and mortality in male neonate and infants exposed to prenatal stress eliminates the weak and results in a relatively homogenous cohort of the fittest and strongest. In contrast, the female fetus does not invest as heavily in growth as the male but conserves resources and adjusts to maternal signals including changes in maternal GC concentration (Clifton 2010; Saif et al. 2016). Because the female fetus adapts to subtle maternal signals, they escape morbidity and mortality penalties and are more likely to survive adversity during early development and unlike males, express a highly variable biological and behavioral repertoire. Survival and the resulting high variability increase the probability that persisting effects of prenatal maternal stress hormones are more likely to be observed among girls (Sandman et al. 2013; Kim et al. 2014). Sex differences have been reported in the association between prenatal exposures to cortisol and amygdala volume (Buss et al. 2012) and child anxiety (Sandman and Davis 2012) that persist into preadolescence (Sandman et al. 2013) in girls but not in boys. Synthetic GCs alter variants (isoforms) of glucocorticoid receptor (GR) expression differently between males and females across development (Saif et al. 2016). There is strong suggestive evidence that males and females express GR variants during sex-specific gestational intervals. Because of the sexually dimorphic GR profile differences, males are more responsive to some isoforms at term and females are more responsive to other isoforms at midgestation (Saif et al. 2016). Accordingly, it is reasonable to expect that human fetal exposure to maternal signals of biological stress will be associated with unique patterns of the efficient brain network in males and females and that these patterns will be reflected by fetal exposure to elevated maternal cortisol concentrations at specific gestational intervals.

One of the most consistent consequences of fetal exposure to maternal biological stress signals is the increased child internalizing problem (de Weerth et al. 2003; Davis et al. 2007; Bergman et al. 2010; Davis and Sandman 2012). Prenatal exposure to high levels of maternal cortisol is associated with more fearful behavior during infancy and greater anxiety during childhood. Further, these associations are more pronounced among females (Sandman et al. 2013; Davis and Pfaff 2014). Thus, we assessed whether the neural consequences of fetal exposure to maternal cortisol might underlie individual variability in child internalizing problems.

In this study, we investigate for the first time the sex-specific effects of human fetal exposure to a ubiquitous maternal signal of stress (cortisol) on the topology of structural brain networks (human connectome) and the associated risk for internalizing problems of preadolescent boys and girls. We anticipated that there would be global stability of small-world network organization in both boys and girls (Gong et al. 2009; Lim et al. 2015); however, we predicted that there is a sensitive period during pregnancy in which the sexually dimorphic brain (Bale and Epperson 2015) is more susceptible to varying levels of maternal cortisol concentrations (Buss et al. 2009, 2012; Davis and Sandman 2012; Sandman et al. 2015). We examined network properties and internalizing behavior problems in preadolescent boys and girls who were exposed to varying levels of maternal cortisol at discrete gestational intervals.

Materials and Methods

Participants

Forty-nine typically developing children (27 boys and 22 girls; all right-handed; age 6.2–9.4 years) were recruited for this study (Supplementary Table 1). English-speaking, healthy adult pregnant women with singleton pregnancies were recruited by 15 gestational weeks. Exclusion criteria were 1) tobacco, alcohol, or other drug use in pregnancy, 2) uterine or cervical abnormalities, and 3) presence of conditions associated with neuroendocrine dysfunction. In this psychologically low-risk sample, neither maternal anxiety nor depressive symptoms were significantly associated with maternal cortisol. After the detailed description of the study, 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.

Prenatal Maternal Plasma Cortisol

Maternal blood samples were collected during the course of gestation at 15, 19, 25, 31, and 37 gestational weeks (Supplementary Fig. 1A). All maternal blood samples were collected at least 1 h after the participant had eaten (mean time of day = 13:34 ± 1:33). A 20-mL blood sample was drawn using antecubital venipuncture into EDTA vacutainers. All samples were centrifuged at 2000 × g for 15 min; plasma was then extracted and stored in polypropylene tubes at −70 °C until assayed. Plasma cortisol levels were determined with a competitive binding, solid-phase, enzyme-linked immunosorbent assay (IBL America). Plasma samples (20 μL) and enzyme conjugate (200 μL) were added to the antibody-coated microtiter wells, thoroughly mixed, and incubated for 60 min at room temperature. Each well was washed 3 times with wash solution

(400 μL per well) and struck to remove residual droplets. Substrate solution (100 μL) was added to each well and incubated for 15 min at room temperature. The absorbance units were measured at 450 nm within 10 min after the stop solution (100 μL) had been added. The assay has <9% cross-reactivity with progesterone and <2% cross-reactivity with 5 other naturally occurring steroids. The interassay and intraassay coefficients of variance are reported as <8%, and the minimum detectable level of the assay was 0.25 μg/dL. All statistical analyses were performed with cortisol concentrations standardized and residualized for time of day at sample collection and gestational week at assessment. Maternal anxiety and depressive symptoms were evaluated at 15, 19, 25, 31, and 37 gestational weeks using the State Anxiety Inventory (STAI: Spielberger 1983) and the Center for Epidemiologic Studies Depression Sale (CES-D: Radloff 1977)—CES-D: mean ± standard deviation (SD) = 5.9 ± 3.5 (range of scale: 1–27) and STAI: mean ± SD = 18 ± 5.1 (range of scale: 10–40). Prenatal maternal anxiety (r = −0.10–0.24, P's > 0.10) or depressive symptoms (r = −0.06–0.21, P's > 0.10) were not significantly associated with either average prenatal maternal cortisol concentrations or maternal cortisol concentrations at the 5 time points.

Child Behavioral Problems

Child internalizing problems were measured using the Achenbach System of Empirically Based Assessment (Achenbach and Rescorla 2001), which offers a comprehensive approach to assess adaptive and maladaptive functioning. It is a reliable and valid measure that is widely used in research and clinical practice with children. The parent report form, the Child Behavior Checklist (CBCL), was administered to mothers by a trained interviewer who was directly supervised by a clinical psychologist. The CBCL contains 113 items representing a broad scope of behaviors. It has high test–retest stability and good internal consistency. Responses were made on a 3-point Likert scale ranging from 0 (not true) to 2 (very true). The Internalizing behavioral problems score was calculated using standard scoring. Raw sum scores were transferred to T scores based on the sex-specific reference tables.

Magnetic Resonance Imaging Acquisition

Magnetic resonance imaging (MRI) acquisition was performed on a 3-Tesla Philips Achieva scanner. Single-shot echo-planar diffusion tensor images (DTI) (repetition time [TR] = 11.6 s; echo time [TE] = 55 ms; 60 transverse slices; slice thickness 2 mm; field of view = 224 × 224 × 120 mm; imaging matrix = 128 × 128; in-plane voxel size = 2 × 2 mm^2; 32 noncollinear directions; b-value of 800 s/mm^2; a single b_0 image) and T1-weighted images for anatomical reference (inversion-recovery spoiled gradient recalled acquisition (IR-SPGR) sequence; TR = 11 ms; TE = 3.35 ms; inversion time = 1.1 s; flip angle 18°; imaging matrix = 240 × 240; 150 sagittal slices; voxel size = 1 × 1 × 1 mm^3) were acquired. All scans were visually checked to ensure the acceptable MR quality.

Data Processing

Preprocessing was performed using AFNI (http://afni.nimh.nih.gov), FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki), and Freesurfer (http://freesurfer.net). DTI images were corrected for eddy current distortion and subject motion, where no significant difference was found in children's head movements during scanning (mean ± SD in mm; girls: 0.59 ± 0.136; boys: 0.60 ± 0.161; P = 0.81). A diffusion tensor was estimated using nonlinear iterative method to avoid negative eigenvalues, and the principal diffusion direction and its directional uncertainty were computed using the 100-times jackknife resampling algorithm at each voxel (Taylor and Biswal 2011). The gray-matter cortex was parcellated into 68 anatomically distinct regions of interest (ROIs) using Desikan-Killiany atlas of Freesurfer, and subdivided into a set of 1015 smaller regions (mean ± SD = 0.68 ± 0.3 cm^3; Supplementary Fig. 1B and C) (Hagmann et al. 2008). White-matter pathways were reconstructed with probabilistic tractography using voxel-wise directional uncertainty (with fractional anisotropy [FA] >0.1; direction change <60°; tract length >1 cm; 30 seeds per voxel; 1000 Monte-Carlo iterations per seed) (Taylor and Saad 2013).

Structural Connectome

A structural brain network for each child was constructed with 1000 cortical regions (=network nodes) excluding subcortical areas (Supplementary Fig. 1D). The structural connection (=network edge) was defined, if at least 30 streamlines exist between 2 regions, as averaged FA values of interconnecting tracts reflecting the integrity of whiter-matter fascicles (Kim et al. 2014, 2015). Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) was used to compute the global network characteristics in terms of network segregation (clustering coefficient [γ] and modularity [Q]), integration (characteristic path length [λ] and global efficiency [E]), and their optimal balance (small-worldness [σ = γ/λ]) (Sporns 2011). 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, edges, and degree sequences of individual networks (Maslov and Sneppen 2002). Permutation tests (=1000 permutes for P < 0.05) were used to compare the global network properties between boys and girls.

Briefly, a description of the above-mentioned network variables is as follows—c.f., Rubinov and Sporns (2010). A "network" is a set of nodes and their interconnections mathematically represented as a "graph". A node of a brain network often refers to a single neuron, a set of neurons, or anatomically/functionally distinct brain regions. The interconnection, called an edge, can be defined by structural or functional connectivity between 2 nodes of the brain, which might be either directed or undirected, and either binary or weighted. "Connectome" refers to a comprehensive structural network map of the brain organized in terms of nodes and edges. Sometimes, the network of functional interactions in the brain is also called a connectome. "Path length" is the number of steps (for a binary network) or the summation of connection distances (for a weighted network) along the shortest path from one node to another. A shorter path length between brain regions can represent a stronger potential for structural integration. "Characteristic path length" refers to the average shortest path length across all nodes in the network. "Network efficiency" is the average of the "inverse" of connection distances across all nodes in the network. Contrary to the path length, efficiency is less influenced by isolated nodes (i.e., if the path length → ∞, then the efficiency = 0). The efficiency of a network roughly represents the capacity to exchange information (Latora and Marchiori 2001, 2003). "Clustering coefficient" describes a probability that neighborhood (=connected) nodes for a node are also connected to each other. The clustering coefficient of a network is defined by the average of clustering coefficients from all nodes. "Modularity" is a statistical measure to estimate the degree to

which the network is subdivided into clearly delineated modules. "Module" is a set of highly interconnected nodes forming a subnetwork in the network. The optimal modular network would have a large number of connections within each module and a small number of connections among modules. The term "community" can also be used as an equivalent. "Network integration" captures the degree to which information in the network is transferred among different and/or distant nodes for the higher node-, community-, or network-wide interaction. "Network segregation" is the presence of highly connected nodes to form a cluster or module in the network. It is assumed that network segregation in the brain is highly related to clusters or modules. "Small-world network organization" indicates that, compared with the randomly connected network, the clustering coefficient of the network is larger (i.e., more highly clustered) while the characteristic path length is equal to that of random network (i.e., short path length). Mathematically, it is computed as the ratio of clustering coefficient and characteristic path length, which are normalized relative to the random networks.

Rich-Club Organization

Rich-club nodes of a network have been defined as the nodes that are not only much more connected but also highly linked to themselves (van den Heuvel and Sporns 2011). Given the sorted connection weights, w_l^{ranked}, the weighted rich-club coefficient, ϕ, was defined as a function of node degree, k, by $\phi(k) = W_{>k}/\sum_{l=1}^{E_{>k}} w_l^{ranked}$, where $W_{>k}$ and $E_{>k}$ represent the sum of weights and the number of connections for nodes with >k, respectively (Opsahl et al. 2008). Because $\phi(k)$ of the random networks has a similar curve with a small-world network, $\phi(k)$ is typically normalized relative to a set of null random networks (=1000 in this study) with the same size and degree distribution, resulting in a normalized rich-club coefficient, $\phi_n(k)$ (Colizza et al. 2006). For comparison across individuals with varying degree distribution (Fig. 1A), all nodes were sorted by degree, k, and the nodes with lowest degree were incrementally removed (i.e., 10 nodes at a time = 1%) allowing the comparison of equal-sized core networks for boys and girls (Ball et al. 2014).

Community Detection

Consensus clustering was applied to obtain consistent modular partitions (Sporns and Betzel 2016). For the individual network and 1000 random networks preserving the degree distribution, Louvain modularity (Q) algorithm (Blondel et al. 2008) was applied to compute maximized differences of Q for the varying resolution parameter g—i.e, $\text{argmax}_{g\in[0.5,2.0]}(Q^h - Q^h_{\text{random}})$ with 0.05 increments, where g tunes the number and size of detected communities and Q^h is the highest modularity from 1000-times repetitions (Supplementary Fig. 2). Then, the agreement matrix (whose elements represent the probability that 2 nodes are assigned to the same module) was constructed using the optimal g from 1000 repetitions, and the consensus communities (Lancichinetti and Fortunato 2012; Bassett et al. 2013) were computed by means of comparisons with random networks to obtain a single consistent partition.

Results

We present results based on the connectome-wide analysis, utilizing 1000 × 1000 weighted network matrices constructed with probabilistic tractography and DTI. Details on the network measures in this study can be found in previous articles (Rubinov and Sporns 2010; van den Heuvel and Sporns 2011).

No Sex Differences in Global Network Measures

For both boys and girls, the averaged node degree (=the number of connections in a network) showed a slowly decaying heavy-tailed distribution (Fig. 1A), called an exponentially truncated power-law degree distribution following $p(k) = k^{a-1}e^{k/kc}$, suggesting a modular small-world architecture of the given network (Amaral et al. 2000) and the existence of highly connected hub nodes (Achard et al. 2006). Qualitative characteristics of the structural connectome did not differ in terms of the number of extracted connections ($T = 1.27$, $P = 0.21$; Supplementary Fig. 3A) and the averaged structural connectivity ($T = 1.47$, $P = 0.15$; Supplementary Fig. 3B). Overall network topology (Fig. 1B) exhibited small-world network architecture for both boys and girls (i.e., highly clustered [$\gamma > 1$] with relatively short paths [$\lambda \sim 1$] resulting in $\sigma > 1$), but each global network measure showed no significant difference (all $P > 0.05$), indicating that global measures of network topology did not differ between boys and girls.

Elevated Prenatal Maternal Cortisol and More Network Cost in Girls

To investigate general effects of prenatal maternal cortisol on children's brain network, associations between averaged prenatal maternal cortisol concentrations during pregnancy (adjusted for time of day and gestational week) and global network characteristics were examined in boys and girls, respectively. For girls, measures of network segregation (i.e., clustering coefficient [γ] and modularity [Q]), including small-worldness (σ), were significantly associated with average prenatal maternal cortisol concentrations (γ: $r = -0.52$, $P = 0.019$; Q: $r = -0.52$, $P = 0.019$; σ: $r = -0.50$, $P = 0.026$; False Discovery Rate (FDR) corrected; Fig. 1C), suggesting that a higher maternal cortisol concentrations during pregnancy are associated with less segregated network organization in girls, whereas no such associations were observed in boys and total samples (all $P > 0.5$). Exploring the effect of cortisol levels over the course of pregnancy, significant associations were only found at 31 weeks of gestation (i.e., third trimester) in girls (γ: $r = -0.61$, $P = 0.007$; Q: $r = -0.59$, $P = 0.010$; σ: $r = -0.59$, $P = 0.009$; FDR corrected; Fig. 1D and Table 1), but not at 15, 19, 25, and 37 weeks gestation. Collectively, the effect size of associations between the cortisol and network variables was uniformly largest in magnitude at 31 weeks (Supplementary Fig. 4), suggesting the existence of a sensitive period for the effects of maternal cortisol on girls' brains. Importantly, the network cost, defined by the number of connections in the brain (i.e., the more connections, the higher wiring cost to construct a brain connectome) (Achard and Bullmore 2007), was positively associated with mean prenatal maternal cortisol concentrations only in girls ($r = 0.64$, $P = 0.002$; Fig. 1E). Further, the associations for γ, Q, and σ were significantly different between girls and boys (all $P < 0.05$; one-tailed Fisher's z-test; Supplementary Fig. 5).

Intact Rich-Club Organization of Boys and Girls

As network organization with the highly connected nodes was anticipated in Figure 1A, the normalized rich-club coefficient, ϕ_n, had a peak for most children if the top 10% of nodes by degree and above were remained as core networks ($\phi_{n,\text{peak}}$: girls = 1.094 at top 91%; boys = 1.095 at top 93%) (Fig. 2A). We

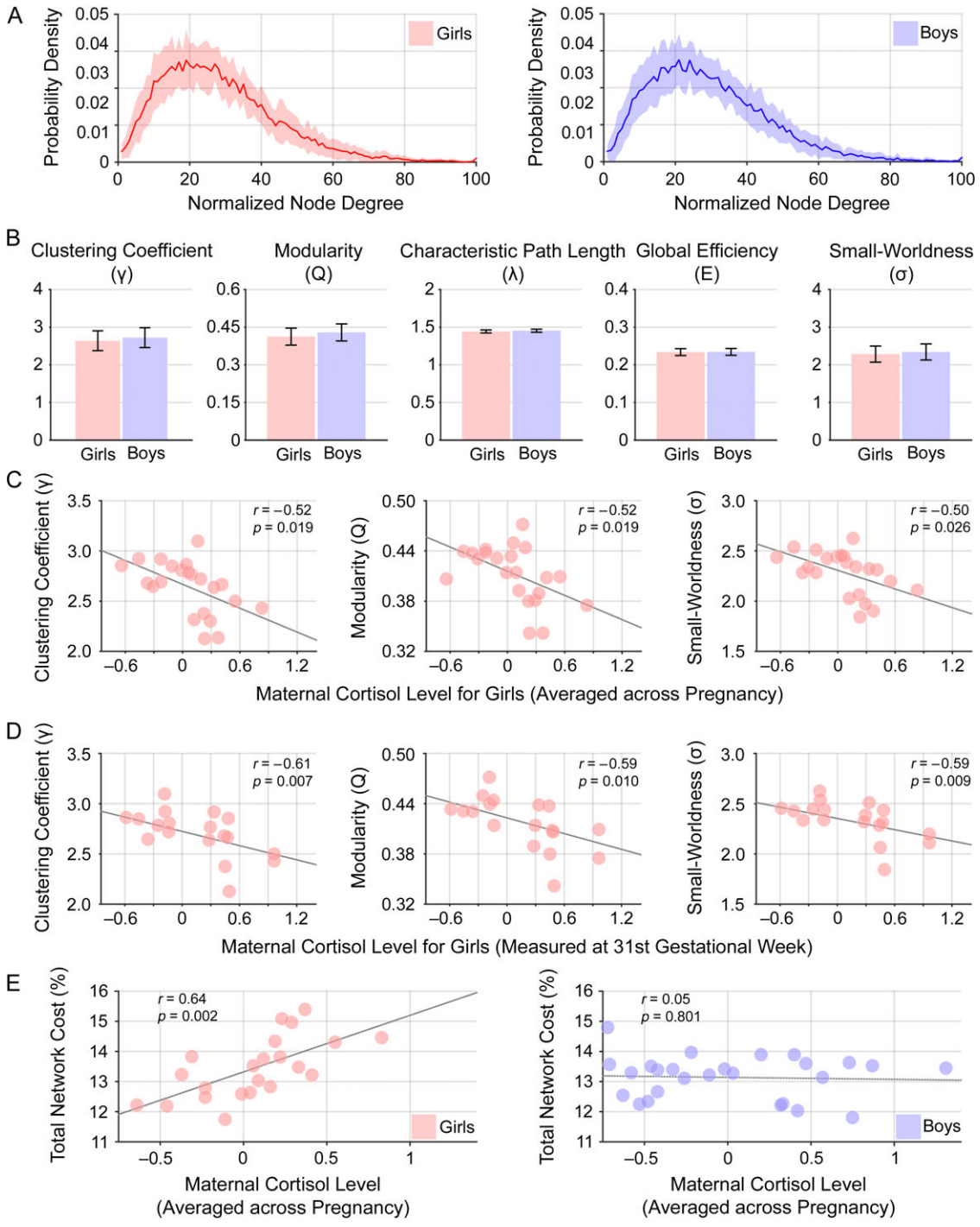

Figure 1. Structural connectome organization of the typically developing children. (*A*) Mean degree distribution, normalized by the number of total nodes (=1000), for girls ($n = 22$; red line) and boys ($n = 27$; blue line) with shaded regions for the SD. (*B*) Comparisons of global network measures for girls and boys in terms of network segregation (clustering coefficient [γ] and modularity [Q]), integration (characteristic path length [λ] and global efficiency [*E*]), and their optimal balance (small-worldness [σ]). (*C*, *D*) Significant associations of maternal cortisol and global network characteristics for girls. Measures of network segregation (clustering coefficient [γ] and modularity [Q]) and small-worldness (σ) were negatively associated with the cortisol level: (*C*) mean cortisol level during pregnancy and (*D*) at 31 weeks in the third trimester (children's age controlled; FDR $P < 0.05$). (*E*) For girls, the total network cost, defined by the number of connections within a network, was positively associated with the elevated maternal cortisol level.

chose the top 10% nodes (vertical dashed line in Fig. 2*A*) as rich-club nodes for boys and girls. This nominal threshold was highly consistent with a previous rich-club analysis with newborn infants (Ball et al. 2014). Rich-club nodes for each child were averaged to create a node-wise probability map. The highest probabilities for rich-club nodes (Fig. 2*B*) were found in the insula, superior parietal cortex, superior frontal cortex, and precuneus, consistent with the rich-club members for adults (van den Heuvel and Sporns 2011) and newborns (Ball et al. 2014). Additionally, the cingulate (isthmus and caudal anterior),

Table 1 Cortisol associations with network measures during pregnancy

Weeks		15	19	25	31	37
N	Girls	15	21	21	20	20
	Boys	19	27	26	26	24
γ	Girls	−0.29	−0.10	−0.20	−0.61*	−0.24
	Boys	−0.29	0.33	−0.27	0.02	0.00
Q	Girls	−0.40	0.06	−0.14	−0.62*	−0.37
	Boys	−0.32	0.36	−0.30	−0.08	−0.15
σ	Girls	−0.27	−0.11	−0.19	−0.59*	−0.22
	Boys	−0.34	0.31	−0.25	0.03	0.00

Note: Values for γ, Q, and σ represent Pearson's correlation coefficients (r) with children's age controlled (*FDR $P < 0.05$). *N*, the number of children in each group.

frontal (rostral middle and inferior [orbitalis and triangularis]), temporal (superior, middle, and pole), inferior parietal, and entorhinal cortex were identified as top 10% common rich-club nodes for boys and girls. Highly overlapped rich-club organization indicates similar levels of connectivity in both sexes among these significantly linked nodes of the brain.

Elevated Prenatal Maternal Cortisol and Altered Rich-Club Network Cost in Girls

All network nodes can be classified into 3 categories (van den Heuvel and Sporns 2011): 1) rich-club connections (RC), interconnecting only rich-club nodes, 2) local connections (LO), linking only nonrich-club nodes, and 3) feeder connections (FD), linking rich-club nodes and nonrich-club nodes (Fig. 2*C*). The network cost of each category also showed positive correlations with mean prenatal maternal cortisol concentrations for LO ($r = 0.64$, $P = 0.002$) and FD ($r = 0.58$, $P = 0.006$), while RC connections had a marginal association ($r = 0.43$, $P = 0.051$) in Figure 2*D*. Positive associations between prenatal maternal cortisol concentrations and network cost were prominent only at 31 gestational weeks for RC ($r = 0.59$, $P = 0.008$) and FD ($r = 0.61$, $P = 0.006$) connections of girls (Fig. 2*E*, left), but not other weeks of gestation. The relative proportion of RC, FD, and LO in each child was grossly preserved (RC:FD:LO in %; girls, 4.57:31.95:63.49; boys, 4.42:31.78:63.79), comparable to the previous rich-club analysis in adults (van den Heuvel et al. 2012). However, maternal cortisol concentrations only at 31 gestational weeks were associated with increased ratios of RC and FD connections and with less proportion of LO connections among girls (RC: $r = 0.49$, $P = 0.03$; FD: $r = 0.49$, $P = 0.03$; LO: $r = -0.51$, $P = 0.03$; Fig. 2*E*, right), whereas no significant associations were found with prenatal maternal cortisol concentrations among boys (all $P > 0.4$).

Elevated Prenatal Maternal Cortisol and Girls' Modular Network Cost

We used consensus clustering (Sporns and Betzel 2016) to further investigate the community structure of children's brain networks. While the number of network communities varied from 3 to 7 due to inter-subject variability (Fig. 3*A*), 4 modules were consistently found across children as expected from Figures 1 and 2; 1) the bilateral medial prefrontal cortex extending toward the precuneus and posterior cingulate, 2) the bilateral medial occipital cortex centered in the cuneus and pericalcarine cortex, and 3) and 4) the frontal and temporoparietal cortex for the left and right hemisphere (Fig. 3*B*). Each module also had its own rich-club nodes as central places—module 1: the superior frontal and isthmus cingulate cortex; module 2: the superior parietal gyrus, precuneus, and inferior parietal cortex; modules 3–4: the insula, superior parietal, superior temporal, temporal pole, and rostral middle frontal cortex (c.f., Fig. 2*B*). Mean prenatal maternal cortisol concentrations were positively associated with the between-module cost only in girls ($r = 0.62$, $P = 0.003$; FDR corrected; Fig. 3*C*). Further, the increased between-module cost was positively associated with prenatal maternal cortisol at 15 and 31 gestational weeks (week 15: $r = 0.68$, $P = 0.007$; week 31: $r = 0.55$, $P = 0.015$; FDR corrected; Fig. 3*D*), but not other weeks (all $P > 0.05$).

Modular Network Costs and Internalizing Problems in Girls

Higher average prenatal maternal cortisol predicted girls' internalizing problems ($\beta = 0.50$, $t = 2.6$, $P < 0.05$). Further, between-module network costs (i.e., increased number of connections) were associated with higher levels of internalizing problems ($\beta = 0.44$, $t = 2.2$, $P < 0.05$). Because fetal exposure to maternal cortisol was associated both with girls' internalizing problems and between-module network cost, we evaluated whether network cost mediated the association between prenatal maternal cortisol and internalizing behavioral problems. Figure 3*E* illustrates that network cost mediates the relation between prenatal maternal cortisol and child behavioral problems. When network cost was included in the model, the relation between prenatal maternal cortisol and child behavior no longer was significant ($\beta = 0.37$, $t = 0.14$, $P = 0.16$). This final model accounts for 28% of girls internalizing problems and supports the argument that the association between prenatal maternal cortisol and child internalizing problems is partially explained by the effects of fetal exposure on elevated maternal cortisol altering developing brain networks. Externalizing behavioral problems were not significantly associated with prenatal maternal cortisol ($\beta = 0.08$, $t = 0.35$, $P = 0.73$).

Discussion

Our findings, in a normative sample of mother child dyads, suggest that fetal exposure to maternal cortisol is associated with sexually dimorphic patterns of brain networks in childhood. Small-world network architecture, rich-club organization, and distinct modular structure were evident for both sexes in typically developing children. However, higher levels of prenatal maternal cortisol were associated only in girls with a reduction in the extent of network segregation, revealed by the higher network cost (denser connectivity) within the rich-club and among modules of the network. In addition, higher network costs in girls were associated with higher levels of internalizing behavior problems, and network cost appeared to mediate the relationship between prenatal maternal cortisol concentrations and girls internalizing problems. Findings also suggested that the third trimester during pregnancy constitutes a sensitive period contributing to sex differences in network responses to maternal cortisol.

Examining global aspects of network organization in preadolescent children, our findings indicated that small-world topology, that is, a highly segregated network with relatively shorter connections, is present in both sexes (Fig. 1*A*,*B*). Further, as previously suggested in newborns (at term-equivalent age of 40 weeks post conception; Ball et al. 2014) and adults (mean

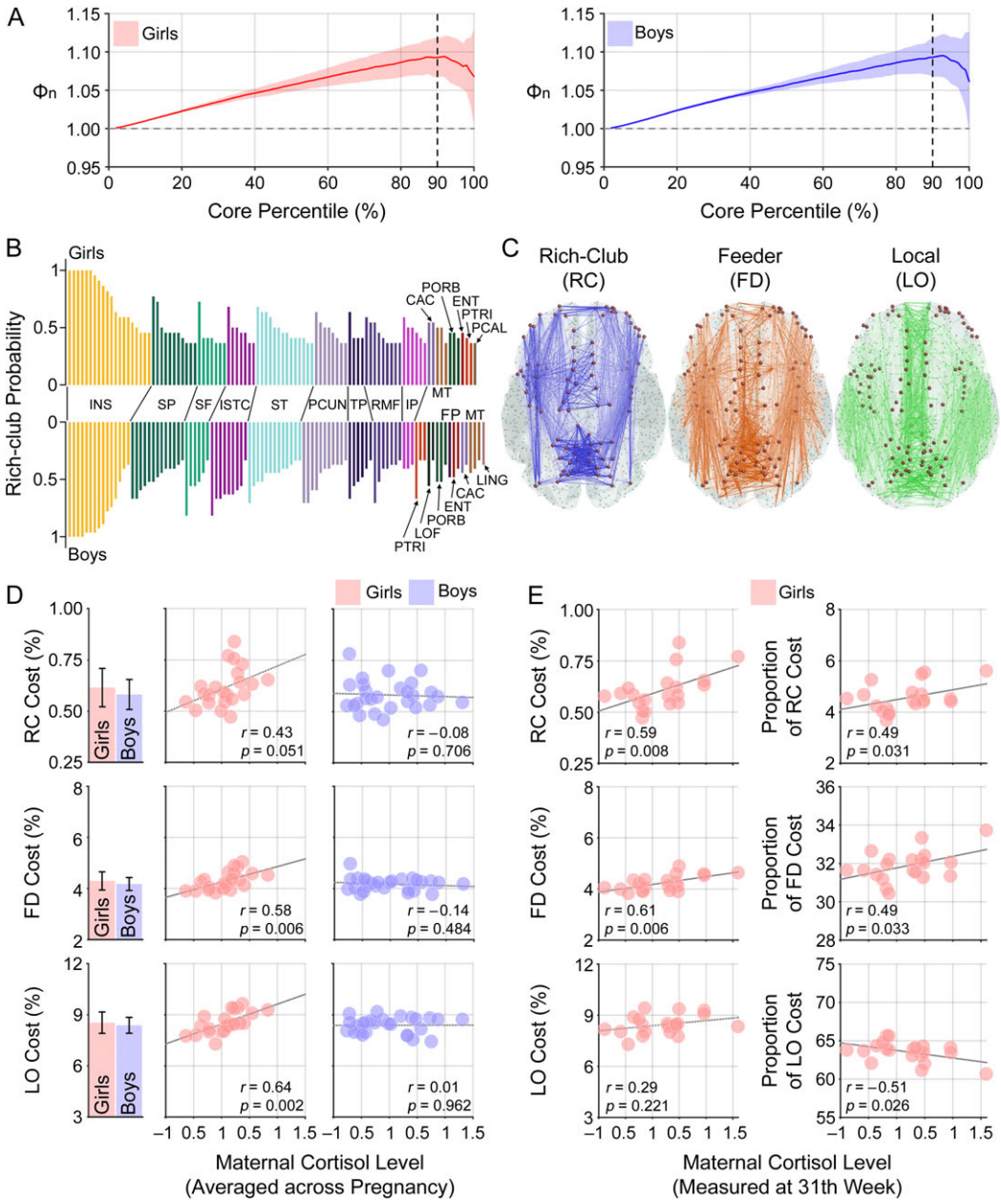

Figure 2. Rich-club organization and network cost. (*A*) Mean rich-club curve (ϕ_n) for girls (red line) and boys (blue line), overlaid on the shaded regions for SD, where rich-club members were defined as the top 10% of core nodes (vertical dashed line). (*B*) Rich-club probability at each node was computed by the proportion belonging to the rich-club nodes across children. Top 10% of rich-club memberships (≈100 nodes), highly overlapped for girls (top) and boys (bottom) including the major rich-club regions—that is, insula (INS), superior parietal (SP), superior frontal (SF), and precuneus (PCUN). (*C*) Connectivity representation of RC (blue line), FD (orange line), and LO (green line) connections. Red and gray dots indicate the defined rich-club and nonrich-club nodes, respectively. FD and LO connections were downsampled 10 times for visualization. (*D*) Associations between the mean cortisol level and network cost for RC, FD, and LO connections (children's age controlled; FDR $P < 0.05$). (*E*) Cortisol level measured at 31 weeks of gestation for girls ($n = 20$) showed significant associations with the network cost (left) and the relative proportion (right) for RC, FD, and LO connections (children's age controlled; FDR $P < 0.05$).

age = 30 years; van den Heuvel and Sporns 2011), our findings confirmed the presence of "rich-club" organization, centered on a set of high-degree regions that are also highly interconnected among each other, comprising the frontal, parietal, and temporal cortex, precuneus, cingulate, and insula of the children regardless of the sex (Fig. 2*A*–*C*). In addition, the modular profiles of brain networks were preserved for boys and girls, also suggesting comparable community structure for both sexes (Fig. 3*A*, *B*), concordant with a recent modular analysis of brain development (Lim et al. 2015). Sexual dimorphism has been well documented in terms of the brain anatomy (Giedd et al. 2012), possibly contributing to sex differences in human cognitive abilities (Halpern 2000); however, sex differences in the connectome have not been consistently found. In adults, there has been some evidence for sex differences in the connectome. For example, higher small-worldness (σ) with lower global efficiency (> 21 years; Sun et al. 2015) and lower network cost with higher global/local efficiency (>19 years; Gong et al. 2009) were reported

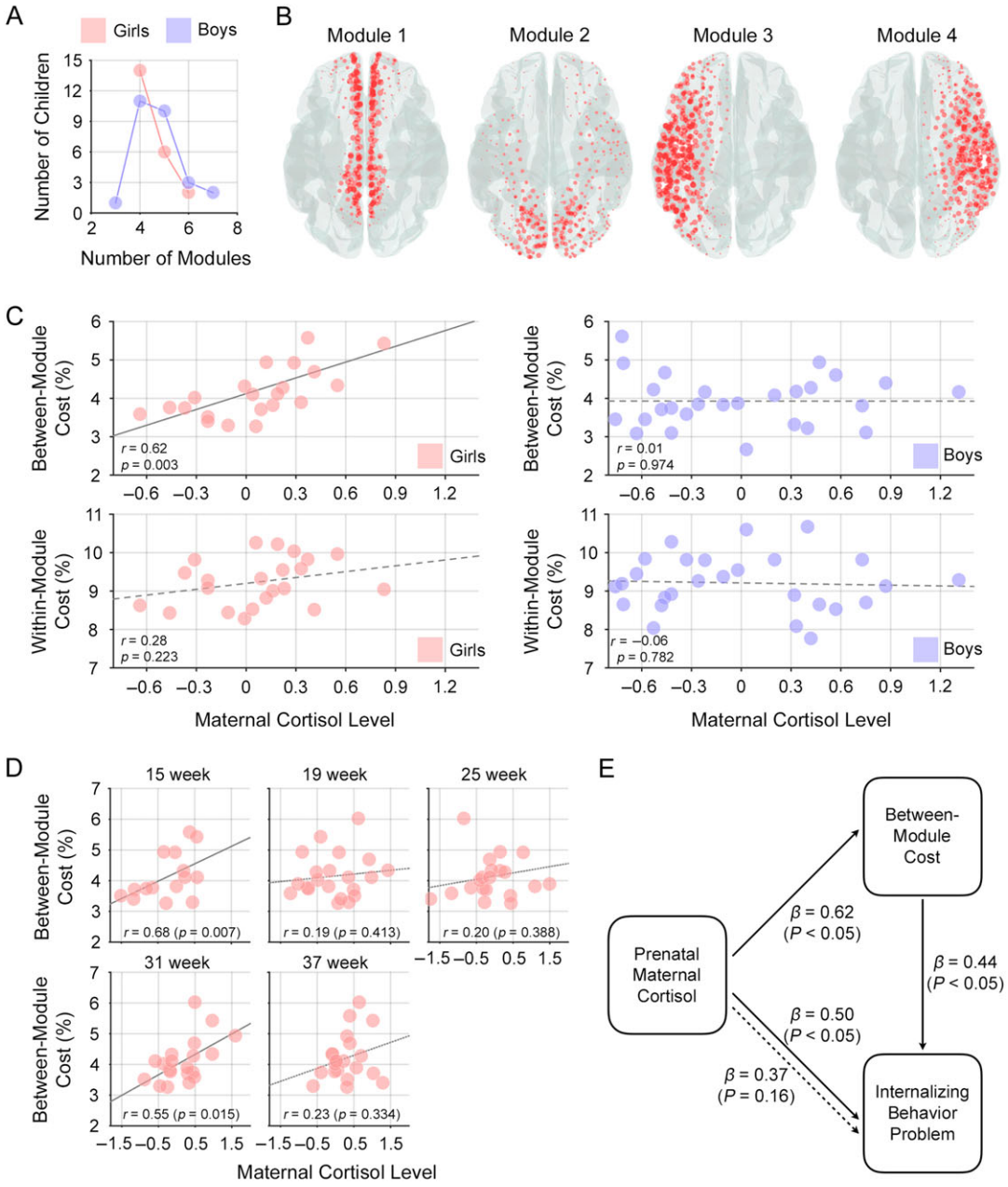

Figure 3. Network community and cortisol association. (*A*) Four major modules were mostly found for 14 girls (~64%) and 11 boys (~41%). (*B*) Module 1—bilateral medial prefrontal cortex including precuneus and posterior cingulate. Module 2—bilateral medial occipital cortex centered in the cuneus and pericalcarine cortex. Modules 3 and 4—frontal and temporo-parietal cortex for a single hemisphere. Larger red circle represents the higher probability of being in the module across the children. (*C* and *D*) Girls showed a positive association between the mean cortisol level and network cost for between modules, which was predominant at 15 and 31 weeks of gestation (children's age controlled with FDR $P < 0.05$). (*E*) Mediation of prenatal maternal cortisol on the internalizing behavior by between-module cost in girls. The mediational hypothesis was tested because 1) prenatal maternal cortisol was associated significantly (solid arrows) with between-module cost ($\beta = 0.62$, $P < 0.05$) and with internalizing behavior of girls ($\beta = 0.50$, $P < 0.05$), 2) the between-module cost of girls was associated with the internalizing behavior ($\beta = 0.44$, $P < 0.05$), and 3) the association between prenatal maternal cortisol and girls' internalizing behavior was not significant (dotted arrow; $\beta = 0.37$, $P = 0.16$) after controlling for the between-module cost.

for adult females. However, several recent studies showed no sex differences in modularity Q in 8- to 13-year-old children with a large number of samples ($n = 314$; Ingalhalikar et al. 2014) nor global-wide network metrics (e.g., clustering coefficient and efficiency; Ryman et al. 2014). In our typically developing sample (Supplementary Table 1), the results support previous findings that the brain connectome organization does not differ in male and female children at the global level.

Although the global network architecture is identical for both sexes, the responses of the fetal brain to elevated maternal cortisol concentrations differed between males and females. First, measures of global network segregation such as the clustering coefficient γ and the modularity Q were negatively associated with mean cortisol concentrations during pregnancy only in girls (Fig. 1C). The clustering coefficient captures the propensity of connected neighbors to form triangles,

and modularity describes how well the overall network can be decomposed into distinct (densely connected) network communities (Rubinov and Sporns 2010). Accordingly, our finding could be interpreted as a tendency for higher levels of maternal cortisol before term, when GR expression in girls is high, to result in less well-separated modules or "building blocks" within girls' brain networks. Interestingly, when the mothers had higher cortisol concentrations during pregnancy, more total network connections (=cost) were observed only in girls (Fig. 1*E*) with greater density of connections between specific modules (Fig. 3*C*). Since both sexes did not differ with regard to their developmental trajectory and intellectual performance as well as global network properties, these findings could suggest that the greater susceptibility to prenatal cortisol in girls required more neural resources (i.e., denser connections) in order to compensate and to retain fully functional global characteristics. Our findings are consistent with evidence that girls adapt their developmental trajectories to even subtle maternal signals and thus may be more greatly influenced by normative variations in prenatal maternal cortisol. These data are consistent with evidence that maternal cortisol is more strongly associated with risk for internalizing problems among girls (Sandman et al. 2013) and is associated with amygdala volume only among girls (Buss et al. 2012). Greater female susceptibility to early-life maternal signals may contribute to greater risk for affective disorders in women (Kim et al. 2014; Bale and Epperson 2015). Although because males are less likely to adjust their developmental course to more subtle maternal signals, they appear to have a greater vulnerability to more severe maternal stress (Mueller and Bale 2008) resulting in neurodevelopmental impairments, our network findings are in line with previous notions of a viability–vulnerability tradeoff for sex differences (Sandman et al. 2013). Male children in the present study were not susceptible to the consequences of normative variations in prenatal maternal cortisol (i.e., viability), but female children showed an adaptive strategy constructing their brain network in responses to relatively subtle variations in maternal signals (i.e., vulnerability).

The consequences of the timing of exposure to elevated maternal cortisol concentrations during gestation were also sex dependent and consistent with sex-specific differences in GR expression (Fig. 1*D*). For girls, the maternal cortisol levels measured at 31 gestation weeks revealed the following: 1) the number of connections of rich-club nodes (i.e., rich-club and feeder connections) was increased with elevated maternal cortisol, while the relative proportion of LO was decreased (Fig. 2*E*) and 2) the between-module connections were positively associated with cortisol (Fig. 3*D*). Previous studies reported that nerve fibers and synapses start to form a neural network in the second and third trimester (Kostovic and Jovanov-Milosevic 2006) and the number of cortico-cortical connections particularly increases around the rich-club regions during the third trimester of gestation (Ball et al. 2014). Thus, our finding at the 31st week of gestation supports and extends the sex-specific vulnerability of connections among distinct modules centered on the rich-club regions in this sensitive period (Ball et al. 2014).

According to the "cost-efficiency" theory of neural network architecture (Laughlin and Sejnowski 2003), more connections within a brain connectome make the information transfer among distributed regions more efficient at the expense of neural resources (Achard and Bullmore 2007; Bullmore and Sporns 2012) as has been argued in the case of cellular components (Chklovskii et al. 2002), physical length of axons (van den Heuvel et al. 2012), and functional synchrony reflecting more energy consumption (Bassett et al. 2009). Our study extends the idea of a cost-efficiency tradeoff of neural network formation. Girls' brains expended more cost with prenatal exposure to higher levels of maternal cortisol, without affecting the extent to which their brains were integrated and segregated given the identical global network architectures observed. This suggested an adaptive response to prenatal stress hormones, which resulted in the preserved architectural integrity of neural circuitry of girls at a global level. However, the increased neural cost observed in girls who had been exposed to higher cortisol levels may have behavioral consequences, as indicated by a correlation between network cost and internalizing problems. Mediational analysis suggested that the relation between prenatal maternal cortisol levels and subsequent internalizing problems in girls was mediated by network cost.

This study has several limitations. It was unclear whether the increased network cost in girls resulted from the whole brain or from specific subregions. Our subsequent analysis showed that no specific module had a dominant effect on increased neural cost in girls, possibly suggesting a whole brain-wide association between maternal gestational cortisol concentrations and network architecture. Further studies examining the prenatal cortisol–neural network cost association will be important. It was not possible in this study to measure directly the concentrations of fetal cortisol; however, there is evidence of a significant association between maternal and fetal levels (Gitau et al. 1998). Moreover, even though the placental barrier to maternal cortisol is protective to exposure early in gestation, elevated levels can reach the fetus at any time during gestation (Giannopoulos et al. 1982; Murphy et al. 2006). Further, we did not assess whether alterations to the child's hypothalamic–pituitary–adrenal (HPA) axis are a mechanism by which prenatal maternal cortisol influences child neurodevelopment. However, we (Davis et al. 2006, 2011; Edelmann et al. 2016) and others (Ter Wolbeek et al. 2015) have reported that prenatal exposure to elevated maternal cortisol is associated with persisting effects on HPA axis regulation. These findings suggest that the prenatal exposure to cortisol does have programming influences on the HPA axis and is one possible mechanism to account for the subsequent association with network architecture. Although one strength of the study is that mother–child pairs were assessed using a prospective and serial longitudinal design beginning during the fetal period and thus provides new evidence for persisting influences of fetal experiences on child neurodevelopment, the sample size of the groups of boys and girls was relatively small, which may have reduced power to detect effects. For instance, while the effect size of correlations at 31 weeks is consistently higher than other weeks (Supplementary Fig. 4), significant correlations of the 31 weeks were not statistically different from other weeks (*Ps* > 0.05, Steiger's *z*-test) due to the relatively small sample sizes in the present data set. Subsequent analysis with larger mother–child pairs could reveal the distinct effects of prenatal maternal cortisol on the children's brain network. Because this study used naturally occurring variations in maternal cortisol instead of experimental manipulations, it was not possible to separate prenatal maternal cortisol effects from the consequences of other factors that may have contributed to this association (e.g., genetic factors or postnatal experiences). Further studies of children who are not genetically related to their mothers (e.g., conceived by in vitro fertilization), monozygotic twins who differ as to whether they share a placenta or not, and/or studies of synthetic GC administration would be of fundamental importance to understand the

contributions of fetal environment to subsequent child development beyond effects of genetics (Melnick et al. 1978; Jacobs et al. 2001; Lewis et al. 2011; Davis et al. 2013).

Taken together, the current findings revealed fundamental sex differences in child brain network architecture in response to maternal cortisol concentrations during pregnancy. The brain networks of girls were susceptible to prenatal elevated exposure to this maternal stress hormone, but adapted by increasing network connectivity as indicated by the measure of neural cost. In girls, increased network cost was associated with higher levels of internalizing problems, suggesting that a behavioral cost may have been incurred by this alteration in network organization. Our findings support the hypothesis of a sex–dependent viability–vulnerability tradeoff between the sexes (Sandman et al. 2013), which has neural substrates that could be affected by consequences of early-life exposure to cortisol experienced during fetal development.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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Notes

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