Sex- and Brain Size–Related Small-World Structural Cortical Networks in Young Adults: A DTI Tractography Study

Chaogan Yan[1], Gaolang Gong[2], Jinhui Wang[1], Deyi Wang[1], Dongqiang Liu[1], Chaozhe Zhu[1], Zhang J. Chen[2], Alan Evans[2], Yufeng Zang[1] and Yong He[1]

[1]State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China and [2]McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Quebec H3A2B4, Canada

Address correspondence to Dr Yong He, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing 100875, China. Email: yong.he@bnu.edu.cn.

The anatomical connectivity of the human cerebral cortex resembles a "small-world" architecture, which is characterized by the coexistence of structurally segregated and integrative connectivity patterns. However, organizational differences in networks among individuals remain largely unknown. Here, we utilize diffusion tensor imaging tractography and graph-theoretical approaches to investigate the effects of sex and brain size on the topological organization of human cortical anatomical network. Weighted cortical networks were constructed from 72 young healthy participants by measuring anatomical connection densities between 78 cortical regions. As expected, all participants showed a small-world topology (high local clustering and short paths between nodes), which suggests a highly efficient topological organization. Furthermore, we found that females had greater local efficiencies than males. Moreover, smaller brains showed higher local efficiency in females but not in males, suggesting an interaction between sex and brain size. Specifically, we show that several brain regions (e.g., the precuneus, precentral gyrus, and lingual gyrus) had significant associations between nodal centrality and sex or brain size. Our findings suggest that anatomical network organization in the human brain is associated with sex and brain size and provide insights into the understanding of the structural substrates that underlie individual differences in behavior and cognition.

Keywords: brain size, connectivity, DTI, gender, graph theory, small-world

Introduction

The human brain is a large complex interconnected system that is capable of generating and integrating information from multiple sources in real time (Sporns and Zwi 2004). The study of anatomical connectivity patterns of the human brain is thought to be crucial because it can 1) provide information about relatively invariant brain characteristics which constrain cortical dynamics and cognitive processes, 2) increase our understanding of how functional brain states emerge from underlying structural substrates, and 3) provide mechanistic insights into how the brain's function is affected by disruptions in its structural basis (Sporns et al. 2005).

Recent advances in modern neuroimaging techniques and graph theory–based network analyses have allowed us to map the anatomical connectivity patterns of the human brain in vivo. Using cortical thickness measurements derived from structural magnetic resonance imaging (MRI), He et al. (2007) constructed the structural network of the human brain at a macroscopic level by computing interregional thickness correlations. Furthermore, they demonstrated that the brain network follows a "small-world" topology, which is characterized by a high degree of local clustering and short path lengths linking individual network nodes (Watts and Strogatz 1998). Small-world network theory implies that the structural network of the human brain is optimally organized to support both modularized and distributed information processing (Sporns et al. 2004; Bullmore and Sporns 2009). Importantly, they also identified several network hubs (i.e., brain regions showing important influence over information flow between other nodes in the network) that were predominantly located in heteromodal association cortical regions, which have long-distance connections (He et al. 2007; Chen et al. 2008). Such a morphometry-based network analysis also has recently revealed abnormal topological patterns in brain diseases such as Alzheimer's disease (He et al. 2008), schizophrenia (Bassett et al. 2008), and multiple sclerosis (He, Dagher, et al. 2009). The development of diffusion tractography (fiber tracking) has facilitated noninvasive study of anatomical networks in the human brain. Deterministic "streamline" tractography based on diffusion tensor imaging (DTI) techniques allows us to infer the continuity of fiber bundles from voxel to voxel (Mori and van Zijl 2002). Several recent studies (Hagmann et al. 2007, 2008), including ours (Gong et al. 2009), utilized the deterministic tractography methods to construct anatomical networks of the human brain by exploring the density or existence of fiber connections between anatomically distinct brain regions. Using probabilistic diffusion tractography methods, Iturria-Medina et al. (2008) established weighted human brain anatomical networks by characterizing interregional anatomical connectivity probabilities. These anatomical networks consistently showed a small-world architecture and several embedded network hubs (e.g., the medial parietal cortex) (Hagmann et al. 2007, 2008; Iturria-Medina et al. 2008; Gong et al. 2009).

Sex and brain size are 2 key factors that shape neural systems and account for behavioral and cognitive variability between individuals. Males score higher on the mental rotation test, spatial navigation problems, the embedded figures test, and engineering and physics problems, whereas females perform better on emotion recognition, social sensitivity, and verbal fluency (Baron-Cohen et al. 2005). Sexual dimorphism has been repeatedly demonstrated in brain anatomy, morphology, metabolism, and neurochemistry (Gur et al. 1982, 1999; Nishizawa et al. 1997; Good et al. 2001; Allen et al. 2003; Dubb et al. 2003; Cosgrove et al. 2007). For example, females tend to have smaller brains than males (Willerman et al. 1991; Andreasen et al. 1993; Jancke et al. 1997; Cosgrove et al. 2007; Leonard et al. 2008); they also have higher percentages of

gray matter (GM), even after correcting for brain size (Gur et al. 1999; Good et al. 2001; Leonard et al. 2008). There is also evidence for constraints of brain size on cerebral structures. For instance, previous studies have demonstrated an effect of brain size on brain morphology (e.g., cortical thickness, GM volume, and cortical folding) and metabolism (Armstrong 1983; Luders et al. 2002; Rilling 2006; Im et al. 2008; Leonard et al. 2008; Toro et al. 2008). Humans with larger brains show greater numbers of neurons and glial cells (Samuelsen et al. 2003; Larsen et al. 2006) but lower percentages of GM (Luders et al. 2002; Im et al. 2008; Leonard et al. 2008). However, it remains largely unknown whether and how the organizational patterns of the connections and networks of brain structures are affected by sex and brain size.

Here, we hypothesized that there are sex- and brain size–related differences in the patterns of anatomical connectivity in the human brain. To test our hypothesis, we performed a DTI tractography study on a large cohort of healthy participants (72 young adults). After constructing interregional networks for each participant, we further calculated topological parameters using graph-theoretical approaches (e.g., small-world and nodal centrality theories) and investigated their associations with sex and brain size.

Materials and Methods

Participants
Seventy-three young healthy volunteers (38 females: 20.9 ± 1.5 years old, range 18-24 and 35 males: 21.4 ± 2.1 years old, range 18–27) participated in this study. All are right-handed and had no history of neurological or psychiatric disorders and never previously participated in any MRI experiment. Written informed consent was obtained from each participant, and this study was approved by the Institutional Review Board of Beijing Normal University Imaging Center for Brain Research. Data of one male participant (19 years old) was excluded because the scans did not cover the whole brain; thus, the following analyses were based on data of the remaining 72 participants.

Image Acquisition
MRI data were acquired using a SIEMENS TRIO 3-T scanner in the Imaging Center for Brain Research, Beijing Normal University. Participants lay supine with their head snugly fixed by straps and foam pads to minimize head movement. T_1-weighted, sagittal 3D magnetization prepared rapid gradient echo (MP-RAGE) sequences were acquired and covered the entire brain (128 slices, repetition time [TR] = 2530 ms, echo time [TE] = 3.39 ms, slice thickness = 1.33 mm, flip angle = 7°, inversion time [TI] = 1100 ms, field of view [FOV] = 256 × 256 mm², in-plane resolution = 256 × 192). Diffusion tensor images were acquired by using a single-shot echo-planar imaging–based sequence (coverage of the whole brain, 2.5-mm slice thickness with no interslice gap, 49 axial slices, TR = 7200 ms, TE = 104 ms, 64 diffusion directions with b = 1000 s/mm², and an additional image without diffusion weighting [i.e., b = 0 s/mm²], acquisition matrix = 128 × 128, FOV = 230 × 230 mm²).

Network Construction

White and GM Segmentation
White and GM segmentation was implemented by SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). First, individual structural images (T_1-weighted MP-RAGE images) were coregistered to the b_0 images (in the DTI native space) using a linear transformation (Collignon et al. 1995). The transformed structural images were then segmented into GM, white matter (WM), and cerebrospinal fluid (CSF) by a unified segmentation algorithm (Ashburner and Friston 2005). Brain size for each participant was obtained by computing the total of GM, WM, and CSF volumes.

Network Node Definition
The procedure of node definition has been described previously (Gong et al. 2009). Briefly, a nonlinear transformation T from the DTI native space to the Montreal Neurological Institute (MNI) space was acquired in the previous unified segmentation step (Ashburner and Friston 2005). The inverse transformation T^{-1} was then used to warp the automated anatomical labeling (AAL) template from the MNI space to the DTI native space, a procedure in which discrete labeling values were preserved by a nearest-neighbor interpolation method with SPM5 package (Fig. 1). To avoid selecting connected fiber bundles erroneously in the follow-up procedure when an AAL mask contained too many WM voxels that were not truly adjacent to the cortex, WM voxels in the raw AAL cortical mask were removed if no cortical voxels existed within their 2-mm cubic neighborhood. Using this procedure, we obtained 78 cortical regions (39 for each hemisphere, see Supplementary Table 1), each representing a node of the cortical network.

WM Tractography
To reconstruct WM bundles in the whole cerebral cortex, we performed the following steps. First, the distortion of diffusion-weighted images was corrected for effects of eddy currents using an affine registration (Woods et al. 1998). The diffusion tensor matrix was then calculated on a voxel-by-voxel basis, and diagonalization was performed to yield 3 eigenvalues and eigenvectors (Basser and Pierpaoli 1996). DTI tractography was further implemented using a continuous streamline-tracking algorithm (Mori et al. 1999). Here, fiber bundles of the brain were reconstructed with DTI studio-2.4 (Johns Hopkins University, Baltimore, MD) by selecting all WM voxels as seed voxels for fiber tracking. For each voxel, the orientation of the largest component of the diagonalized diffusion tensor was assumed to represent the orientation of the dominant fiber bundles. Tracking was initiated from the center of the seed voxel and iterated along its diffusion orientation. When the track entered a new voxel, the iteration direction was reset to the new voxel's diffusion orientation. This tracking procedure traced a fiber f and continued until a voxel classified as non-WM was reached or until the turning angle between adjacent voxels was greater than 70°.

Network Edge Definition
Two nodes i and j were connected by an edge $e = (i, j)$ if there was at least one fiber f with end points in both region. For each edge e, we calculated the connection density between the end nodes as its weight $u(e)$ (Hagmann et al. 2008)

$$w(e) = \frac{2}{S_i + S_j} \sum_{f \in F_e} \frac{1}{l(f)},$$

where S_i and S_j denote the cortical surfaces of AAL regions i and j, respectively, F_e denotes the set of all fibers connecting regions i and j and hence contributing to the edge e, and $l(f)$ denotes the length of fiber f along its trajectory. As a result, we obtained a weighted anatomical network for each participant.

Network Analysis

Small-World Properties
The small-world model was originally proposed by Watts and Strogatz (1998). Small-world networks have highly local clustering (i.e., neighboring nodes are connected tightly) and short average paths (i.e., one node is only a few paths away from any other node in the network), thereby supporting the coexistence of segregation and integration. In this study, we investigated small-world properties of weighted brain networks. The weighted clustering coefficient C_w of a network is the average of the clustering coefficient over all nodes, where the clustering coefficient C_i of a node i is defined as the likelihood that the node's neighbors are connected with each other (Onnela et al. 2005) and is expressed as
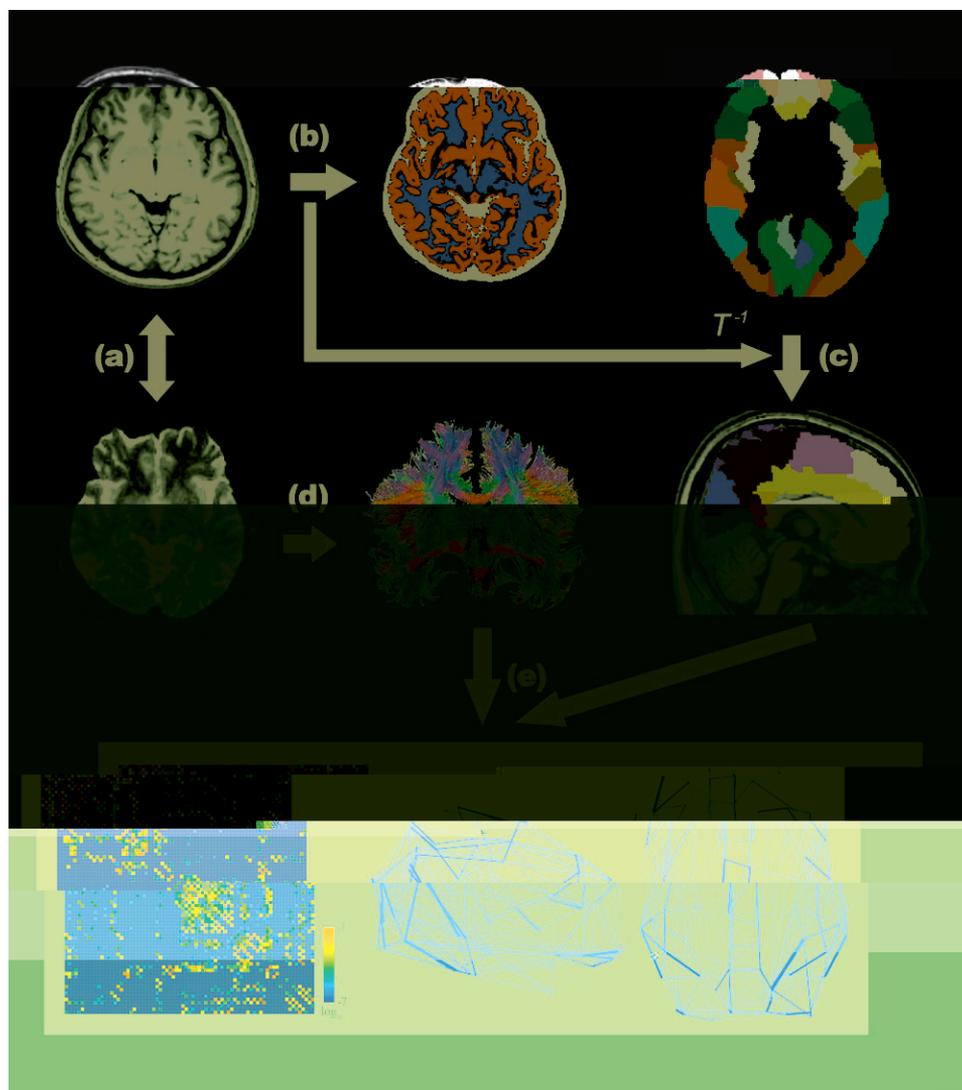
Figure 1. A flowchart for the construction of cortical anatomical network by DTI. (*a*) The structural T_1-weighted structural image was transformed to DTI native space by a linear transformation. (*b*) The transformed T_1 image was segmented into GM, WM, and CSF images in the DTI native space by a unified segmentation algorithm. A nonlinear transformation T from DTI native space to MNI space was created during the unified segmentation. (*c*) The inverse transformation T^{-1} was applied to the AAL template in the MNI space to create the participant-specific AAL mask in the DTI native space. All registrations were implemented in the SPM5 package. (*d*) All WM fibers were reconstructed in the whole brain by using DTI deterministic tractography. (*e*) The connection matrix was created by computing the fiber density between each pair of regions. In the left panel, all connections are symmetric and displayed with a logarithmic color map; in the middle (sagittal view) and right (axial view) panel, nodes are placed at their respective centers of mass, and edges are coded according to connection weight.

$$C_i = \frac{2}{k_i(k_i-1)} \sum_{j,k} \left(\tilde{w}_{ij} \tilde{w}_{jk} \tilde{w}_{ki} \right)^{1/3},$$

where k_i is the degree of node i, and $\tilde{w}_{ij}$ is the weight, which is scaled by the sum of all edges weights to control each participant's cost at the same level. For isolated nodes or nodes with just one connection, that is, $k_i = 0$ or $k_i = 1$, the clustering index is defined as $C_i = 0$. The weighted clustering coefficient C_w quantifies the extent of local cliquishness or local efficiency of information transfer of a network (Watts and Strogatz 1998; Latora and Marchiori 2001).

The path length between node i and node j is defined as the sum of the edge lengths along this path, where each edge's length was obtained by computing the reciprocal of the edge weight, $1/\tilde{w}_{ij}$. The shortest path length L_{ij} between node i and node j is the length of the path with the shortest length between the 2 nodes. The weighted characteristic shortest path length L_w of a network was measured here by using a "harmonic mean" length between pairs as proposed by Newman (2003), that is, the reciprocal of the average of the reciprocals:

$$L_w = \frac{1}{\frac{1}{N(N-1)} \sum_{i=1}^{N} \sum_{j \neq i}^{N} \frac{1}{L_{ij}}},$$

where N is the number of nodes. The weighted characteristic shortest path length L_w quantifies the ability of a network to propagate information in parallel or the global efficiency (in terms of $1/L_w$) of a network.

The normalized weighted clustering coefficient $\hat{C}_w = C_w^{real}/C_w^{rand}$ and the normalized weighted characteristic path length $\hat{L}_w = L_w^{real}/L_w^{rand}$ were also computed, where C_w^{rand} and L_w^{rand} are the mean weighted clustering coefficient and the mean weighted characteristic path length of 100 matched random networks that preserve the same number of nodes, edges, and degree distribution as the real networks (Maslov and Sneppen 2002), whereas the corresponding weights are redistributed. The normalized weighted clustering coefficient $\hat{C}_w$ and the normalized weighted characteristic path length $\hat{L}_w$ quantify the local efficiency and global efficiency $(1/\hat{L}_w)$, corrected for differences in the numbers of edges and degree distribution across participants since each network is relative to its own random counterpart. A real network is considered

small-world if it meets the following criteria: $\hat{C}_w = C_w^{real}/C_w^{rand} \gg 1$ and $\hat{L}_w = L_w^{real}/L_w^{rand} \approx 1$ (Watts and Strogatz 1998), which means it has much higher local efficiency than random networks but still approximately preserves the high global efficiency of the random networks.

Nodal Centrality

The betweenness centrality B_i of a node i is defined as the number of shortest paths between pairs of other nodes that pass through the node (Freeman 1977). In this study, we calculated the normalized betweenness as $b_i = B_i/\langle B_i \rangle$, where $\langle B \rangle$ is the average nodal betweenness of the network. The global centrality measure b_i captures the influence of a node over information flow between other nodes in the network, and we calculated it here with the MatlabBGL package (http://www.stanford.edu/~dgleich/programs/matlab_bgl/).

Statistical Analysis

To determine the relationships between the network parameters (weighted clustering coefficient C_w, weighted characteristic path length L_w, normalized weighted clustering coefficient $\hat{C}_w$, normalized weighted characteristic path length $\hat{L}_w$, and nodal centrality b_i) and sex and brain size, a multiple regression analysis was performed. The network parameters were dependent variables, and the independent variables were sex (1 for men and −1 for women), brain size, and their interaction. For significant interactions, Pearson's correlation coefficient analysis was further performed between the network parameter and brain size in each gender group to analyze the simple effect. A significance level of $P < 0.05$ was set for all statistical tests. Uncorrected P values for nodal centrality are reported as exploratory results in nature.

Results

Sex Effect on Brain Size

We found that women's brains were significantly smaller than those of men ($t = 2.30$, $P = 0.02$), which is a result consistent with previous postmortem and MRI studies (Dekaban 1978; Willerman et al. 1991; Andreasen et al. 1993; Jancke et al. 1997; Cosgrove et al. 2007; Leonard et al. 2008). One possible explanation is that females have smaller statures than males (Peters et al. 1998). However, the difference in brain size between males and females remains after correcting for height (Dekaban 1978; Skullerud 1985). Another possible reason for smaller brain size in females is that females have fewer total neurons (Pakkenberg and Gundersen 1997; Rabinowicz et al. 1999, 2002), larger neuronal densities (Haug 1987; Witelson et al. 1995), and higher cortical metabolic rates (expressed per unit volume) (Hatazawa et al. 1987).

Small-World Cortical Anatomical Networks

We calculated the weighted clustering coefficient (C_w) and the weighted characteristic path length (L_w) for both the anatomical networks and 100 corresponding random networks with the same numbers of nodes, edges, and degree distributions for each participant. The clustering coefficients of brain networks are approximately 4 times larger than those of comparable random networks ($\hat{C}_w = 3.7 \pm 0.2$), whereas the path lengths are approximately equivalent to random networks ($\hat{L}_w = 1.3 \pm 0.04$) (Table 1). High values of $\hat{C}_w$ and equivalent $\hat{L}_w$ are the 2 main characteristics of small-world networks, indicating that the anatomical networks of the human brain have greater local interconnectivity or cliquishness and shorter mean distances between regions. This result is consistent with previous anatomical network studies of the human brain

using diffusion tractography (Hagmann et al. 2007, 2008; Iturria-Medina et al. 2008; Gong et al. 2009).

Relationship between Small-World Parameters and Sex/Brain Size

Weighted Clustering Coefficient C_w

The multiple regression analysis showed a significant gender difference in C_w ($t = -2.48$, $P = 0.02$) (Fig. 2a) and a significant negative correlation between C_w and brain size ($t = -2.94$, $P = 0.004$) (Fig. 3a), with a significant interaction between the 2 factors ($t = 2.22$, $P = 0.03$). Furthermore, simple-effect analysis demonstrated a significant correlation between C_w and brain size in females ($r = -0.53$, $P = 0.0007$) but not in males ($r = -0.09$, $P = 0.61$) (Fig. 4a). Thus, sex differences persist in local efficiency after controlling for brain size differences. Interestingly, we noted that the brain size effect on local efficiency was not significant in males.

Weighted Characteristic Path Length L_w

There were no significant gender difference in L_w ($t = -1.08$, $P = 0.28$) (Fig. 2b) and there was no significant correlation between L_w and brain size ($t = -0.67$, $P = 0.50$) (Fig. 3b), with no significant interaction between the 2 factors ($t = 1.15$, $P = 0.25$). These results suggest that the global efficiency of structural networks of the brain is not affected by sex or brain size.

Table 1
Small-world human cortical anatomical networks

| Small-world properties	Mean	Standard deviation
Weighted clustering coefficient, C_w	4.0×10^{-4}	0.4×10^{-4}
Weighted characteristic path length, L_w	732.1	29.9
Weighted clustering coefficient of random network, C_w^{rand}	1.1×10^{-4}	0.1×10^{-4}
Weighted characteristic path length of random network, L_w^{rand}	555.6	13.7
Normalized weighted clustering coefficient, $\hat{C}_w$	3.7	0.2
Normalized weighted characteristic path length, $\hat{L}_w$	1.3	0.04
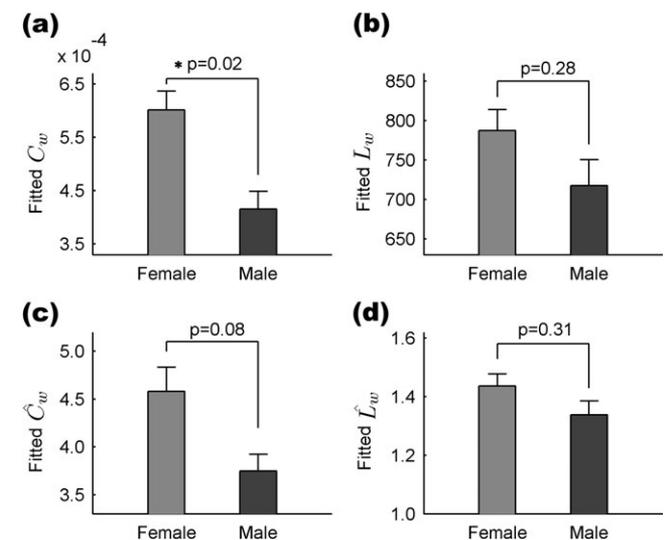
Figure 2. Sex effect on small-world properties. Females had greater C_w (a) and $\hat{C}_w$ (c) in the cortical anatomical networks as compared with males, suggesting a denser local clustering or cliquishness of connections. There were no significant sex differences in L_w (b) and $\hat{L}_w$ (d).

Normalized Weighted Clustering Coefficient $\hat{C}_w$

Analysis showed a trend in gender differences of $\hat{C}_w$ ($t = -1.77$, $P = 0.08$) (Fig. 2c) and a significant negative correlation between $\hat{C}_w$ and brain size ($t = -2.15$, $P = 0.04$) (Fig. 3c), along with a trend in interaction between the 2 factors ($t = 1.87$, $P = 0.06$). Furthermore, simple-effect analysis showed that there is a significant correlation between $\hat{C}_w$ and brain size in females ($r = -0.39$, $P = 0.01$) but not in males ($r = -0.04$, $P = 0.81$) (Fig. 4b). These results imply that females with smaller brains would have higher local network efficiency, whereas that effect of brain size was not observed in males.

Normalized Weighted Characteristic Path Length $\hat{L}_w$

There were no significant gender differences in $\hat{L}_w$ ($t = -1.03$, $P = 0.31$) (Fig. 2d) and no significant correlation between $\hat{L}_w$ and brain size ($t = -1.51$, $P = 0.14$) (Fig. 3d) with no significant interaction between the 2 factors ($t = 1.08$, $P = 0.29$). This implies that the normalized weighted characteristic path length of the brain structural networks was not affected by sex or brain size.

Nodal Characteristics and Hub Regions

To identify hub regions in the anatomical network of the human brain, we examined the normalized nodal betweenness centrality, b_i of the cortical region for each participant and then av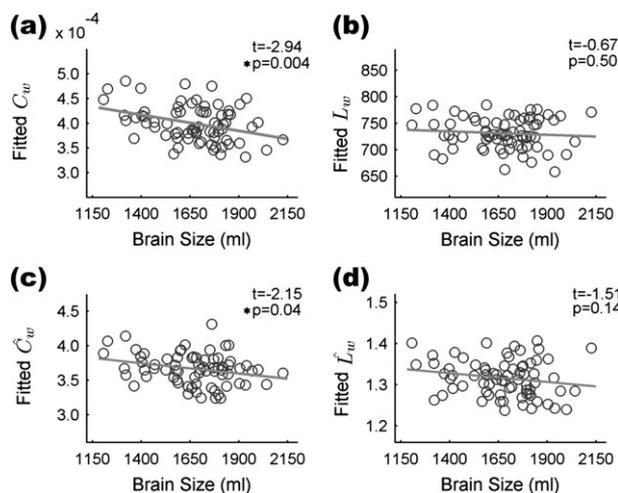eraged across all participants. Nineteen regions were identified as hubs because of their large values in b_i values ($b_i > 1.5$, i.e., the betweenness value of a node is 1.5 times greater than the average betweenness of the network) (Fig. 5 and Table 2). These hubs included 12 regions of the heteromodal or unimodal association cortex (bilateral precuneus [PCUN], bilateral dorsolateral superior frontal gyrus [SFGdor], bilateral superior parietal gyrus [SPG], bilateral inferior temporal gyrus [ITG], left middle occipital gyrus [MOG], right lingual gyrus [LING], left medial superior frontal gyrus [SFGmed], and right middle temporal gyrus [MTG]), 5 regions of the primary motor and sensorimotor cortex (bilateral precentral gyrus [PreCG], bilateral postcentral gyrus [PoCG], and left calcarine fissure and surrounding cortex [CAL]), and 2 regions of the paralimbic cortex (bilateral orbital part of the inferior frontal gyrus [ORBinf]).

Relationships between Nodal Betweenness and Sex or Brain Size

Compared with males, females showed significant greater betweenness centrality in 2 association cortical regions (right PCUN and right superior occipital gyrus [SOG]) and 1 primary cortical regions (left PreCG) and significant smaller betweenness centrality in 1 paralimbic region (right median cingulate and paracingulate gyri [DCG]) (Fig. 6a and Table 3).

Figure 3. Brain-size effect on small-world properties. Brain size showed significant negative correlations with C_w (a) and $\hat{C}_w$ (c). There were no significant correlations between the brain size and L_w (b) or $\hat{L}_w$ (d).
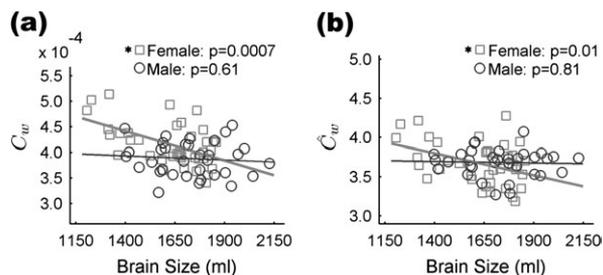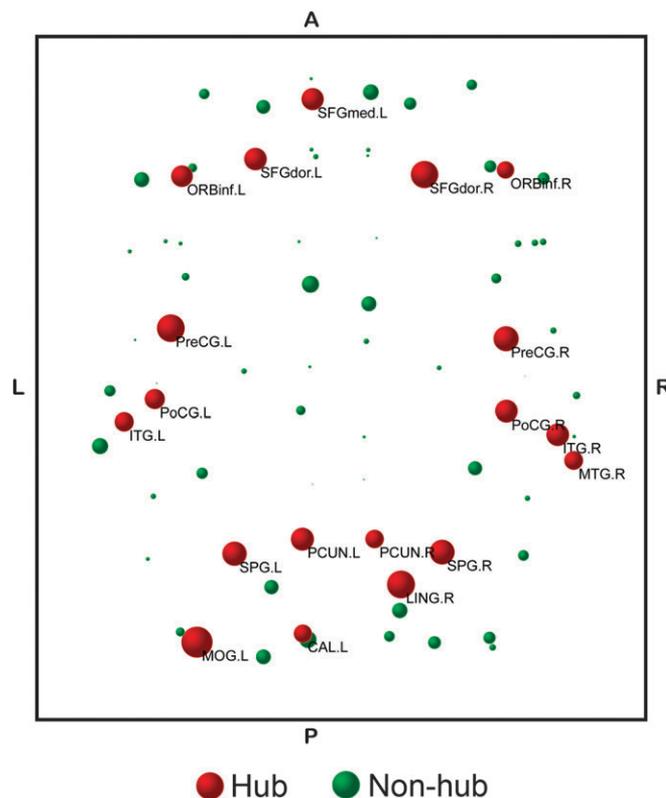

Figure 4. The relationships between small-world network parameters and brain size within female and male groups. The correlation between brain size and C_w (a) or $\hat{C}_w$ (b) was significant in females but not in males.

Figure 5. Hub regions in the human cortical anatomical networks. Nineteen hub regions were identified in the cortical network, including 12 regions of the heteromodal or unimodal association cortex (bilateral PCUN, bilateral SFGdor, bilateral SPG, bilateral ITG, left MOG, right LING, left SFGmed, and right MTG), 5 regions of the primary motor and sensorimotor cortex (bilateral PreCG, bilateral PoCG, and left CAL), and 2 regions of the paralimbic cortex (bilateral ORBinf). Nodes represent cortical regions and the size of the nodes (i.e., diameter) represents the magnitude of normalized nodal betweenness centrality (Table 2). A, anterior; P, posterior; L, left; R, right.

Brain size was significantly and negatively correlated with betweenness centrality in 1 association cortical region (left LING), 1 primary cortical region (right CAL), and 1 paralimbic region (right ORBinf). Brain size was also significantly and positively correlated with betweenness centrality in 2 paralimbic regions (left orbital part of the superior frontal gyrus [ORBsup] and left medial orbital part of the superior frontal gyrus [ORBsupmed]) (Fig. 6b and Table 3).

Table 2

Hub regions in the human cortical anatomical networks

Hub regions	Class	Normalized betweenness, b_i
MOG.L	Association	2.75
LING.R	Association	2.46
PreCG.L	Primary	2.44
SFGdor.R	Association	2.41
PreCG.R	Primary	2.21
SPG.R	Association	2.19
SPG.L	Association	2.14
PCUN.L	Association	2.02
ITG.R	Association	1.99
SFGdor.L	Association	1.98
PoCG.R	Primary	1.98
SFGmed.L	Association	1.95
ORBinf.L	Paralimbic	1.91
PoCG.L	Primary	1.77
ITG.L	Association	1.68
MTG.R	Association	1.65
PCUN.R	Association	1.62
CAL.L	Primary	1.59
ORBinf.R	Paralimbic	1.53

Note: The hub regions ($b_i > 1.5$) in the human anatomical network were listed in a descending order of their normalized betweenness centrality, b_i. The regions were classified as primary association and paralimbic as described by Mesulam (1998). L, left; R, right.

Several brain regions showed significant interactions in nodal centrality between sex and brain size. Compared with males, females showed smaller correlations between the brain size and betweenness centrality in 2 association cortical regions (right PCUN and right SOG) and 1 primary cortical region (left PreCG) and greater correlations in 1 paralimbic region (right DCG) (Fig. 6c and Table 3).

Discussion

In this study, we utilized DTI on a large sample of young healthy participants to investigate the relationships between topological organization of human cortical anatomical networks and sex and brain size. The anatomical networks of brains had prominent small-world properties and included several hub regions, which were predominantly located in association cortex. Furthermore, we found that females have higher local efficiency in their cortical anatomical networks than males. Also, the participants with smaller brains had higher local efficiency than those with larger brains and that correlation was found only in females. In addition, we also noticed that several specific brain regions (e.g., PCUN, PreCG, LING, and CAL) showed significant associations with sex and/or brain size in nodal centrality (Table 3). In sum, we demonstrate for the first time that the anatomical connectivity patterns of the human cerebral cortex are associated with sex and brain size, which might provide new insights into our understanding of the underlying structural substrate of behavioral and cognitive differences among individuals.
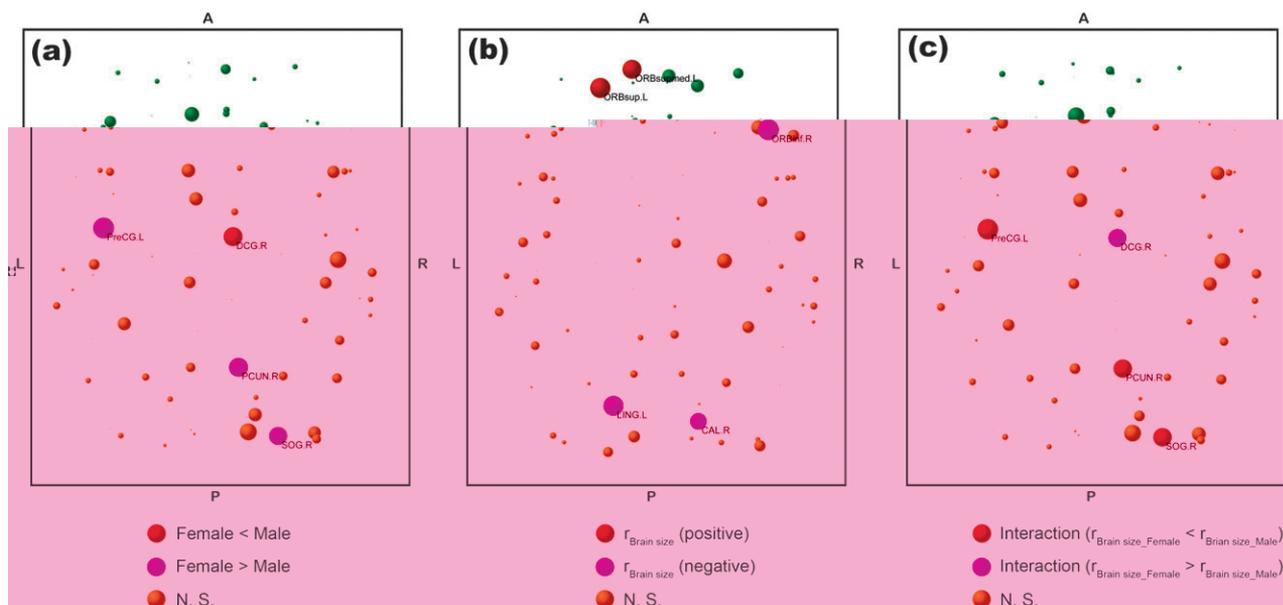

Figure 6. Sex and brain size effects on nodal characteristics. (a) Compared with males, females showed significant greater betweenness centrality in 2 association cortical regions (right PCUN and right SOG) and 1 primary cortical region (left PreCG) and significant smaller betweenness centrality in 1 paralimbic region (right DCG). (b) Brain size showed significantly negative correlation with betweenness centrality in one association cortical region (left LING), 1 primary cortical region (right CAL) and 1 paralimbic region (right ORBinf), and showed significantly positive correlation with betweenness centrality in 2 paralimbic regions (left ORBsup and left ORBsupmed). (c) Compared with males, females showed smaller correlations between brain size and betweenness centrality in 2 association cortical regions (right PCUN and right SOG) and 1 primary cortical regions (left PreCG) and greater correlation in one paralimbic region (right DCG). Nodes represent cortical regions and the size of the nodes (i.e., diameter) represents the significance of sex and brain size effects (Table 3). A, anterior; L, left; P, posterior; R, right; $r_{Brain\ size}$, the relationships between nodal betweenness centrality and brain size; $r_{Brain\ size\_Female}$, the relationships between nodal betweenness centrality and brain size in the female group; and $r_{Brain\ size\_Male}$, the relationships between nodal betweenness centrality and brain size in the male group.

Table 3
Sex and brain size effects on regional characteristics

	Regions	Class	*t* value	*P* value
Main effect of sex				
Female > male	PreCG.L	Primary	−2.34	0.02
	PCUN.R	Association	−2.14	0.04
	SOG.R	Association	−2.02	0.05
Female < male	DCG.R	Paralimbic	2.16	0.03
Main effect of brain size				
Negatively correlated with brain size	ORBinf.R	Paralimbic	−2.64	0.01
	LING.L	Association	−2.54	0.01
	CAL.R	Primary	−2.11	0.04
Positively correlated with brain size	ORBsup.L	Paralimbic	2.59	0.01
	ORBsupmed.L	Paralimbic	2.44	0.02
Interaction of sex and brain size				
$r_{\text{Brain size\_Female}} > r_{\text{Brain size\_Male}}$	DCG.R	Paralimbic	−2.02	0.05
$r_{\text{Brain size\_Female}} < r_{\text{Brain size\_Male}}$	PreCG.L	Primary	2.35	0.02
	SOG.R	Association	2.12	0.04
	PCUN.R	Association	2.10	0.04

Note: $r_{\text{Brain size\_Female}}$, the relationship between nodal betweenness centrality and brain size in the female group; $r_{\text{Brain size\_Male}}$, the relationship between nodal betweenness centrality and brain size in the male group; L, left; R, right.

Small-World Anatomical Networks in Humans

Recent studies have demonstrated small-world topologies in large-scale structural networks in human brain (Hagmann et al. 2007, 2008; He et al. 2007, 2008; Bassett et al. 2008; Iturria-Medina et al. 2008; Gong et al. 2009). Consistent with these studies, we also found the cortical anatomical networks in our study demonstrated small-world architectures (Watts and Strogatz 1998) as they had an almost identical path length ($\hat{L}_{W} \approx 1$) but were more locally clustered ($\hat{C}_{W} \gg 1$) in comparison with matched random networks. Together with the previous findings, our finding suggests that the small-world topology is a fundamental principle for the structural organization of complex brain networks. Using computational modeling simulation approaches, Sporns et al. (2000) have demonstrated the emergence of a small-world topology when networks are evolved for the high complexity of dynamic behavior defined as an optimal balance between local specialization and global integration. Our findings thus provide additional support for the hypothesis that the human brain has evolved into a complex but efficient neural architecture for maximizing the power of information processing (Sporns et al. 2004; Kaiser and Hilgetag 2006).

Sex and Brain Size Effects on Small-World Cortical Anatomical Networks

We showed that females have greater local clustering in cortical anatomical networks as compared with males, which suggests a denser local clustering or higher local network efficiency (Fig. 2). Although recent studies have showed that the human brain networks are structurally and functionally organized in a small-world fashion (for reviews, see Bullmore and Sporns 2009; He, Chen, et al. 2009), little is known about the sex effect on such a network topology. Sex-related differences in cortical structures of the human brain have been well documented. For example, Gur et al. (1999) found that women have a higher percentage of GM and a lower percentage of WM than men. They also showed, by choosing brain size–matched participants, that the higher proportions of GM in females were independent of brain size. This result was also found by several other groups (Good et al. 2001; Leonard et al. 2008). Cerebral GM contains neuronal cell bodies,

dendrites, and short protrusions that are important for regional information processing (Gur et al. 1999; Zhang and Sejnowski 2000). Thus, a higher percentage of GM in females increases the proportion of tissue available for computational processes, which provides further support for our finding of high local network efficiency in females.

We also found that brain size is significantly and negatively correlated with local clustering (Fig. 3), suggesting that smaller human brains are more efficient in local information transfer. Previous studies have demonstrated that brain size is associated with cortical anatomical characteristics, such as cortical volume, surface area, and cortical thickness. For instance, Luders et al. (2002) reported that participants with smaller brains had relatively larger proportions of GM, even after correcting for the sex effect, which was further confirmed by Leonard et al. (2008) and Im et al. (2008). As mentioned above, a higher percentage of GM corresponds to larger proportion of tissue available for regional information processing. Thus, our result of higher local network efficiency in smaller brains is compatible with the previous studies. However, it is worthy to note that several theoretical studies have predicted that as brain size increases, there must be a drop in interhemispheric connections due to the increasing time constraints of the transcallosal conduction delay, and consequently, a greater local clustering of interneuronal connections is required (Ringo et al. 1994; Anderson 1999). Those studies are inconsistent with our experimental results. The relationship between brain size and topological organization of brain networks needs to be further studied.

Interestingly, we found that there were significant interactions between sex and brain size on local network efficiency, and further simple-effect tests revealed that the brain size effect on local efficiency is significant in females but not in males. Previous studies have suggested different effects of brain size on the morphologies of anatomical structures between males and females. For example, Sullivan et al. (2001) and Leonard et al. (2008) reported that females with smaller brains have a bigger corpus callosum, but this effect was not significant in males. Planum temporal lobe sizes (Leonard et al. 2008) and CSF volumes (Gur et al. 1999) also depend on brain size in women, whereas in men, they do not. Leonard et al. (2008) reported both females and males with smaller brains have higher proportions of GM, but the relationship is stronger in females than males. This finding was also confirmed in the current study: The proportion of GM was significantly correlated with brain size in both the female group ($r = -0.88$, $P = 3 \times 10^{-13}$) and the male group ($r = -0.74$, $P = 6 \times 10^{-7}$). These results are compatible with our findings of significant correlations between network efficiency and brain size in females. The insignificant correlations in males could be attributable to their larger brain sizes and fewer constraints in brain network shaping. Nonetheless, it is worthy to note that there is also evidence for closer association between brain size and brain structures in males than in females. For instance, Gur et al. (1999) reported that there were more significant correlations between brain size and the whole WM volume in men than in women. Leonard et al. (2008) found that the relative size of left Heschl's gyrus depends on brain size only in men. These controversial findings suggest that the role that sex-related differences in brain size play in shaping brain structures is complicated and needs further investigation.

Sex and Brain Size Effects on Nodal Characteristics of Cortical Anatomical Networks

Nodal betweenness centrality is a network measurement that captures the influence of a node on information flow between other nodes in the network. Nodes with high betweenness may serve as way stations for network traffic or as centers of information integration (Hagmann et al. 2008). Nineteen hub regions were identified in the cortical anatomical network (Fig. 5 and Table 2). They were predominately located in regions of heteromodal and unimodal association cortices (PCUN, SFGdor, SPG, ITG, MOG, LING, SFGmed, and MTG) receiving convergent inputs from multiple other cortical regions (Mesulam 1998), which suggests that they play pivotal roles in human structural cortical networks. The findings are in accordance with several previous studies in which these association cortical regions have been identified as critical nodes in both structural and functional brain networks in humans (Achard et al. 2006; He et al. 2007; Hagmann et al. 2008; Iturria-Medina et al. 2008; Gong et al. 2009) and nonhuman primates (Sporns and Zwi 2004; Honey et al. 2007).

In this study, we found that there were significant gender differences on the nodal betweenness centrality of cortical anatomical networks. Females showed greater nodal centrality in 2 association cortical regions (PCUN and SOG) and 1 primary cortical region (PreCG) than those of males, suggesting that these regions play more important roles in information transfer within the brain network in females (Fig. 6a and Table 3). Previous functional brain imaging studies have suggested that females have higher cerebral glucose metabolism in the PCUN and PreCG than males (Willis et al. 2002). Structural imaging studies have found that females showed larger GM volume in the SOG and PreCG than males (Goldstein et al. 2001; Good et al. 2001; Luders et al. 2005). The higher glucose metabolism and larger GM volume in females may indicate more neuronal processes in these regions, which could explain our finding of a more significant role in information transfer within the brain networks constructed from 78 brain regions. In this study, we also showed that DCG had lower nodal centrality in females. In a previous structural MRI study, Paus et al. (1996) found that females had smaller GM volume in the paracingulate sulcus than males; thus, we could speculate that it might be associated with the reduced network role of DCG in females demonstrated in our finding.

Brain size also had significant effect on the nodal centrality of cortical anatomical networks. We found that smaller brains showed higher nodal centrality in LING, CAL, and ORBinf (Fig. 6b and Table 3). Recently, Rilling (2006) showed that the occipital cortex is much smaller than allometric predictions of human brain size. Thus, our findings in the occipital lobe (LING and CAL) are compatible with the previous study. Furthermore, we showed that smaller brains had lower nodal centrality in 2 prefrontal regions (ORBsup and ORBsupmed) (Fig. 6b and Table 3), which was consistent with the study of Toro et al. (2008) showing larger brains associated with more cortical folding in the prefrontal cortex. We also found significant interactions between sex and brain size on nodal centrality. Compared with males, females showed smaller correlations between brain size and nodal centrality in PCUN, SOG, and PreCG and greater correlations in DCG (Fig. 6c and Table 3). Of note, these regions had a large overlap with those showing sex-related differences in nodal centrality. It is imperative that the biological mechanisms underlying sexual dimorphisms are further investigated in the future.

Further Considerations

Many previous studies using neurophysiological and neuroimaging data have demonstrated alterations of small-world and nodal characteristics in development (Fair et al. 2009; Micheloyannis et al. 2009), in normal aging (Achard and Bullmore 2007), and for brain disorders (Bassett et al. 2008; He et al. 2008; Liu et al. 2008; Wang et al. 2009). Recently, Li et al. (2009) reported that the topological parameters of brain anatomical networks are associated with intelligence. However, these studies did not take into account the effects of sex and brain size. Thus, our results have important implications for future studies on the topological organization of structural and functional brain networks.

There are also several issues that need to be further addressed. First, in the current study, we calculated brain size as the total volume of GM, WM, and CSF. This processing has been used in many previous studies (Gur et al. 1999; Luders et al. 2002; Im et al. 2008). However, several other studies computed brain size without CSF (Courchesne et al. 2000; Allen et al. 2002). In this study, we also reanalyzed the effects of sex and brain size on the small-world parameters of brain structural networks, using brain size taken as the total of GM and WM volumes. The results remain similar (Supplementary Table 2). Second, in this study, we showed effects of sex and brain size on the connectivity patterns of brain structural networks. Several recent studies have demonstrated that the structural connectivity of the human brain is highly correlated with functional brain connectivity using resting-state *functional magnetic resonance imaging* (Honey et al. 2009). Thus, we speculate that the connectivity patterns of functional brain networks could also be affected by sex and brain size, which needs to be studied in the future. Third, we found sex and brain size effects on network parameters in healthy young adults. Given that topological characteristics of brain networks have been found to change with normal development and aging (Achard and Bullmore 2007; Fair et al. 2009; Micheloyannis et al. 2009), it would be interesting to determine whether sex dimorphisms and brain size effects exist in other age groups and whether sex and brain size effects on cortical network parameters interact with age. Finally, we utilized a DTI deterministic tractography method to reconstruct human cortical anatomical networks. Despite being widely used, this method has a limited capacity for resolving crossed fiber bundles (Mori and van Zijl 2002). Thus, further work could be conducted on brain anatomical networks reconstructed by probabilistic diffusion tractography methods, which have the advantages of overcoming fiber crossings and robustness to the image noise (Behrens et al. 2003; Parker and Alexander 2005).

Conclusions

Using DTI tractography and graph-theoretical approaches, we investigated the relationships between anatomical connectivity patterns of human cortical networks and sex/brain size. We found that females had significantly greater local network efficiencies than males. Moreover, smaller brains showed higher local efficiency in females but not in males, which implies an interaction between sex and brain size. We also showed that several brain regions (e.g., the PCUN, PreCG, and

LING) had significant associations between nodal centrality and sex/brain size. Different from previous studies, the present study provides a network perspective into the understanding of how human cortical neuroanatomy is associated with sex and brain size. Our results also have implications for the understanding of the structural basis underlying the behavioral and cognitive differences that are related to sex and brain size. Further work could be conducted to examine how the topological organization of human cortical anatomical networks is altered during normal development and aging as well as in specific brain disorders, taking the effects of sex and brain size into account.

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Supplementary Material

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

Notes

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