Evolutionary expansion of connectivity between multimodal association areas in the human brain compared with chimpanzees

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The development of complex cognitive functions during human evolution coincides with pronounced encephalization and expansion of white matter, the brain's infrastructure for region-to-region communication. We investigated adaptations of the human macroscale brain network by comparing human brain wiring with that of the chimpanzee, one of our closest living primate relatives. White matter connectivity networks were reconstructed using diffusion-weighted MRI in humans ($n = 57$) and chimpanzees ($n = 20$) and then analyzed using network neuroscience tools. We demonstrate higher network centrality of connections linking multimodal association areas in humans compared with chimpanzees, together with a more pronounced modular topology of the human connectome. Furthermore, connections observed in humans but not in chimpanzees particularly link multimodal areas of the temporal, lateral parietal, and inferior frontal cortices, including tracts important for language processing. Network analysis demonstrates a particularly high contribution of these connections to global network integration in the human brain. Taken together, our comparative connectome findings suggest an evolutionary shift in the human brain toward investment of neural resources in multimodal connectivity facilitating neural integration, combined with an increase in language-related connectivity supporting functional specialization.

connectome | evolution | chimpanzee | multimodal | comparative connectomics

A key step toward understanding human behavior is to understand how the human brain supports advanced cognitive functions such as social cognition, language, and theory of mind—abilities that are highly developed in humans (1–3). Comparative studies have pointed to several brain adaptations that may have facilitated the emergence of complex cognition during human evolution. The modern human brain is approximately three times larger in volume than that of early hominins, vastly exceeding the predicted brain size for a primate species of the same body size (4–6). Cellular examinations have indicated more pronounced dendritic branching of pyramidal cells in the human brain compared with other primates, suggesting a greater potential for neural integration of information in humans (7–9). Indeed, the human brain allocates relatively more cortex to association areas than to primary sensory and motor areas (4, 10–12), along with proportionally more white matter compared with other primates (13–15). These observed differences suggest that the evolution of advanced cognitive features in humans was accompanied by widespread modifications to the complex architecture of the human brain and its connectivity. The topological organization of these brain connectivity adaptations and their potential role in the evolution of complex cognition remains an open question.

Here we investigated adaptations of human brain connectivity by means of comparative connectomics—the study of differences in the topological organization of connectomes (16). The macroscale connectome describes the comprehensive network of corticocortical white matter connections important for region-to-region communication and global information integration within the brain (17). We compared the human connectome with that of the chimpanzee (*Pan troglodytes*), one of our closest living primate relatives. Both humans and chimpanzees have evolved specialized features since the divergence from our last common ancestor roughly 7–8 Mya (18); however, the chimpanzee brain

Significance

Comparative connectomics provides a powerful framework for studying cross-species differences in brain network architecture, offering important insights into the origin of human brain function. The present study highlights key differences between the human and chimpanzee connectome that have arisen since the divergence from our last common ancestor. Comparative analysis suggests an evolutionary shift in the human connectome toward investment of neural resources in global integration of multimodal information and enhanced functional specialization, potentially supporting the enhancement of complex cognitive function during human evolution. Identification of human connectome adaptations has broad implications for our fundamental understanding of human brain function and may contribute to our knowledge of human-specific mental disorders that involve macroscale changes to the brain's wiring architecture.

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Data deposition: Connectivity matrices and analysis scripts are available at the USC Multimodal Connectivity Database (UMCD), http://umcd.humanconnectomeproject.org (IDs 3036 and 3037).

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has remained relatively similar in size to that of early hominins (5, 19), making comparisons between the human and chimpanzee connectomes particularly valuable for discovering connectome changes that may have accompanied encephalization in human evolution. In the simplest case, white matter volume may have increased equally across all connections of the network with human brain expansion. Alternatively, the human connectome may show specific adaptations in its topology, revealing subtle changes in the layout and strength of connections in support of larger brain size and possibly advanced cognitive traits.

We hypothesize that human connectome adaptations may promote a modular topology but with specific costly investments in connections serving global integration and advanced cognitive functions. Long-range connectivity is considered to be disproportionally costly compared with local connectivity in expanding primate brains, favoring modular network architectures that limit long-range connections (14, 20, 21). However, to maintain—and putatively enhance—integrative communication required for complex brain function, the human brain may have also invested costly neural resources in connectivity between expanding higher-order areas (16, 22). Investments in costly integrative connectivity will be adaptive if the associated changes in brain function result in a cognitive or behavioral advantage that enhances Darwinian fitness (23–26). Thus, connectome modifications that maximize the adaptive value of an expanding brain while minimizing the associated increases in wiring cost may confer a selective advantage during evolution.

Comparing the human and chimpanzee connectome, we show evidence of human connectome adaptations for strengthening the connectivity between multimodal association areas in support of efficient network integration and for increasing modular network topology, indicating cost-effective functional specialization. Our findings identify enhanced global neural integration of highly processed information as an important factor in human brain evolution.

Results

Network Features of Human-Chimpanzee Shared Brain Connectivity. We started by comparing connectome features shared between humans ($n = 57$) and chimpanzees ($n = 20$). Individual connectomes were reconstructed for both species, with network nodes based on regions of cytoarchitectural homology between humans and chimpanzees (*Methods*) and connections based on normalized fiber streamline counts derived from in vivo diffusion-weighted MRI. The human and chimpanzee group-averaged connectomes displayed a large overlap in their topological organization, with both connectomes showing evidence of characteristic small-world, modular, and rich-club organization (16) (*SI Appendix*, *Results*). Furthermore, the overall strength of connections was strongly correlated between the two species (Pearson's $r = 0.69$, $P = 6.77 \times 10^{-50}$; *SI Appendix*, *Results*).

We labeled connections consistently observed (≥60% of subjects) in both species as human-chimpanzee shared connections (Fig. 1*A*). Shared connections were categorized into three classes (Fig. 1*B* and *SI Appendix*, Table S1) according to the classical division of the cortex into primary, unimodal association, and multimodal association areas (27). These three connection classes were then compared in terms of their weighted edge betweenness centrality, a graph theoretical measure of the importance of a connection within the network (28). This metric was chosen because it incorporates both the strength of a connection and the connection's topological position in the network (Fig. 1*C*). Shared connections linking bilateral multimodal association areas were found to be more central in humans compared with the same set of connections in chimpanzees {median, 0.0203 [interquartile range (IQR), 0.0189–0.0213] vs. 0.0174 [IQR, 0.0160–0.0178]; Wilcoxon rank-sum $Z = 5.75$; effect size, $r = 0.655$; $P = 9.11 \times 10^{-9}$} (Fig. 2 *A* and *B*, *Left*). In contrast, the network centrality of shared connections linking bilateral primary areas was lower in humans compared with chimpanzees [median, 0.0276 (IQR, 0.0233–0.0307) vs. 0.0480 (IQR, 0.0414–0.0516); Wilcoxon rank-sum $Z = -6.18$; $r = -0.704$; $P = 6.45 \times 10^{-10}$] (Fig. 2*B*, *Right*). The centrality of shared connections

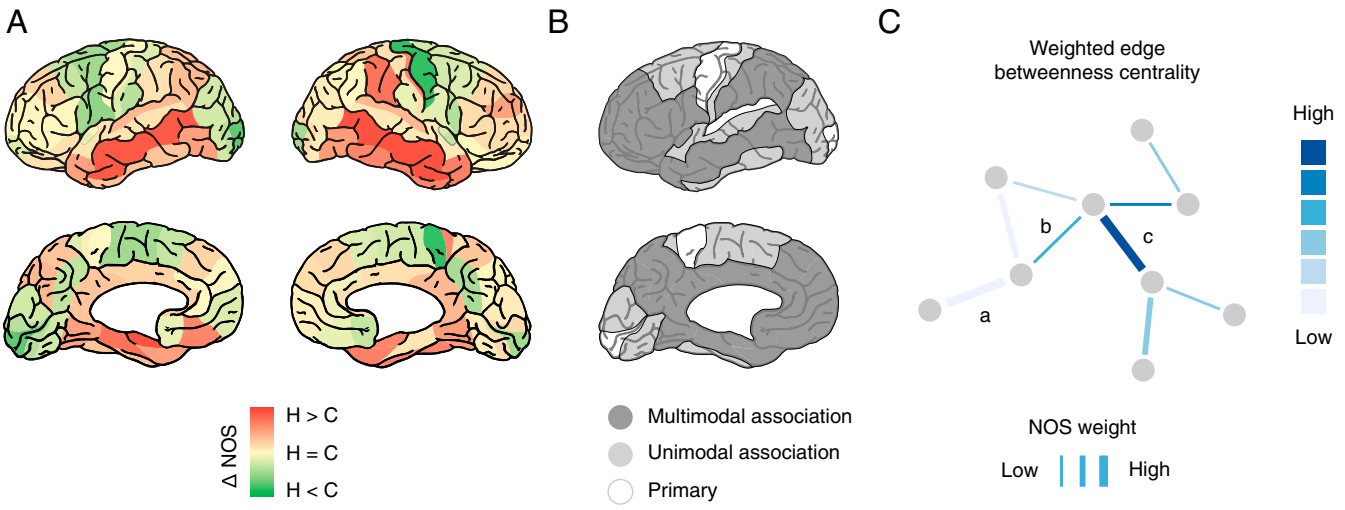

Fig. 1. Analysis of human-chimpanzee shared connections. The normalized strength of shared connections was obtained in both humans and chimpanzees; the data are shown here as the between-species strength difference averaged per cortical region (*A*). The cortex was then divided into multimodal association areas, unimodal association areas, and primary areas (*B*), followed by calculation of weighted edge betweenness centrality of connections linking areas in each of the three categories (*C*). Weighted edge betweenness centrality captures the proportion of weighted shortest paths between all node pairs (*i*, *j*) that pass through a given edge. It incorporates information on both topology and weight (represented here as thickness of the edges) of the connections in the network. In the toy example shown here, edge *a* has high weight, but its weighted edge betweenness centrality is relatively low owing to its peripheral location in the network. Edge *b* has lower edge weight than *a*, but a higher proportion of shortest paths pass through it, resulting in a higher edge betweenness centrality. Finally, edge *c* has both high weight and a central position in the network with a high proportion of shortest paths passing through it, resulting in high edge betweenness centrality. C, chimpanzee; H, human; NOS, normalized number of streamlines.

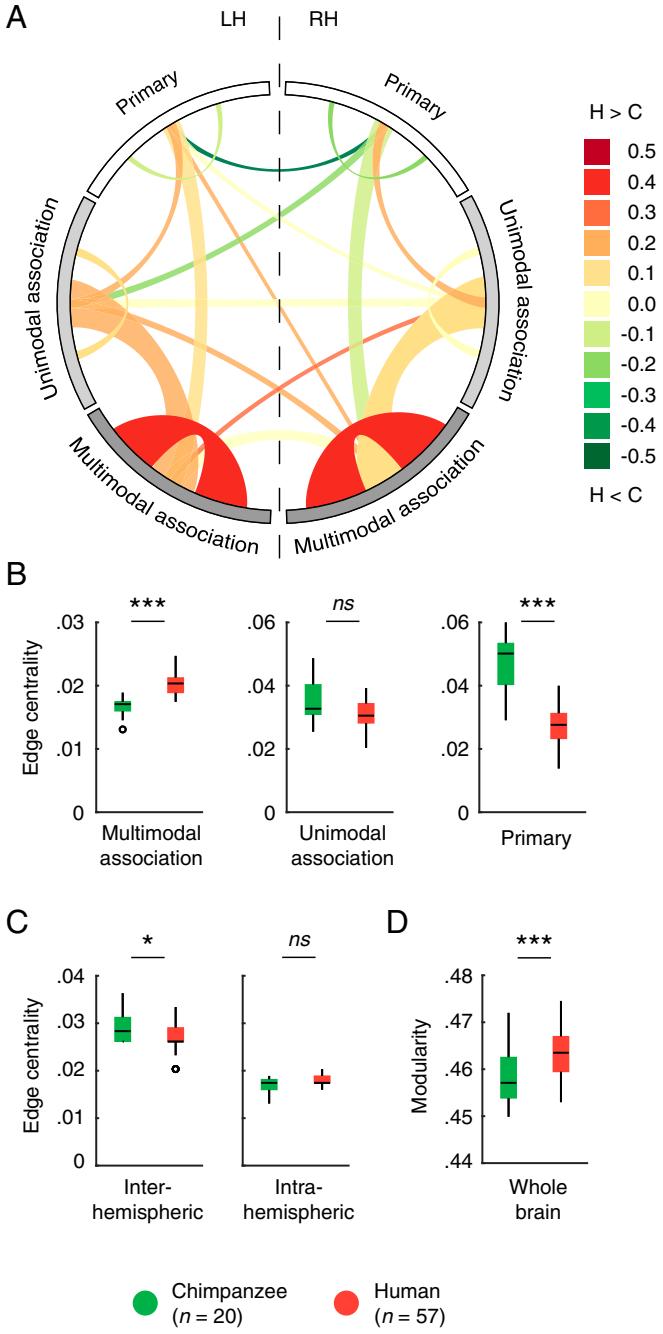

Fig. 2. Human-chimpanzee shared connectivity within and between hemispheres. (*A*) Circos connectogram (56) depicting human-chimpanzee shared connections, bundled per cortical category (outer circle). The bundle color indicates weighted edge betweenness centrality in humans relative to chimpanzees. The bundle width is proportional to the number of connections contained in each bundle. (*B*) Weighted edge betweenness centrality of shared connections between multimodal association areas (*Left*), between unimodal association areas (*Middle*), and between primary areas (*Right*) in humans (red) compared with chimpanzees (green). Connections across two cortical categories are shown in *SI Appendix*, Fig. S1. (*C*) Weighted edge betweenness centrality of interhemispheric and intrahemispheric shared connections in humans and chimpanzees. (*D*) Weighted network modularity of shared connectivity in humans and chimpanzees. ***$P < 0.001$; *$P < 0.05$; *ns*, not significant ($P > 0.05$), C, chimpanzee; H, human; LH, left hemisphere; RH, right hemisphere.

linking bilateral unimodal association areas was not statistically different between the two species ($P = 0.072$; Fig. 2*B*, *Middle*), consistent with their position in the middle of the cortical hierarchy from primary to multimodal association areas. These results support the hypothesis of a selective increase in connectivity between higher-order areas in the human brain compared with chimpanzees.

We further assessed how proportional reductions in interhemispheric white matter volume in humans relative to chimpanzees (13, 14) are reflected in the network structure of the underlying connectivity. It has been hypothesized that human brain expansion should favor a shift toward a more modular network structure and enhanced hemispheric specialization through decreasing interhemispheric connectivity (13, 14, 16, 20). Our comparative connectome analysis indicated that weighted edge betweenness centrality of interhemispheric connections was indeed lower in humans compared with chimpanzees [median, 0.0262 (IQR, 0.0262–0.0291) vs. 0.0276 (IQR, 0.0262–0.0320); Wilcoxon rank-sum $Z = -2.07$; $r = -0.236$; $P = 0.0381$] (Fig. 2*C*, *Left*). This effect was particularly driven by the reduced centrality of interhemispheric connections between primary areas in humans compared with chimpanzees (Fig. 2*A* and *SI Appendix*, Fig. S2).

We next examined network modularity, a global network measure indicating the extent to which a network can be subdivided into modules with high within-module connectivity but low between-module connectivity (29, 30). We observed higher weighted network modularity in humans compared with chimpanzees [median, 0.463 (IQR, 0.458–0.467) vs. 0.457 (IQR, 0.453–0.463); Wilcoxon rank-sum $Z = 3.01$; $r = 0.344$; $P = 2.60 \times 10^{-3}$] (Fig. 2*D*). Intrahemispheric connectivity did not show a clear overall difference in network centrality between the two species ($P = 0.34$), but subdivision into the three connection classes revealed a lower centrality of intrahemispheric connections between primary areas but a higher centrality of intrahemispheric connections between multimodal association areas in humans compared with chimpanzees (Fig. 2 and *SI Appendix*, Fig. S2).

Language Network Connectivity. We further examined the shared connectivity between areas involved in language processing, a cognitive feature highly developed in humans (2, 31). We found two frontal language-related areas, FCBm and FBA (approximating the classical Broca's area) (32) that exhibited a lower relative connection strength in humans, particularly in the left hemisphere (Fig. 1*A*). We examined whether the observed net decrease could be explained by a change in the network fingerprint of these regions, with decreases in some of the regions' connections masking increases in others. We considered regions involved in human language processing (33–35), including the inferior frontal gyrus (FCBm, FBA), supramarginal gyrus (PF), angular gyrus (PG), superior temporal gyrus (TA, TB), middle temporal gyrus (TE1), and inferior temporal gyrus (TE2) (Fig. 3*A*). The connection strength between the frontal areas FCBm and FBA and the other language-related areas was higher in humans compared with chimpanzees [median, 0.80 (IQR, 0.73–0.84) vs. 0.71 (IQR, 0.61–0.80); Wilcoxon rank-sum $Z = 2.68$; $r = 0.305$; $P = 7.4 \times 10^{-3}$] (Fig. 3*B*, *Left*). In contrast, the strength of connections between the two frontal regions and the rest of the brain was significantly lower in humans compared with chimpanzees [median, 1.01 (IQR, 0.99–1.03) vs. 1.13 (IQR, 1.11–1.17); Wilcoxon rank-sum $Z = -6.46$; $r = -0.737$; $P = 1.01 \times 10^{-10}$] (Fig. 3*B*, *Right*). This divergence between lower overall strength but higher strength within the language network suggests a shift from a broader participation in the overall network toward a more specific connectivity of language areas FCBm and FBA in humans, supporting enhanced specialization of brain function.

Human-Specific Connectivity. We next examined the network role of connections that were consistently observed in the human sample (≥60% of subjects) but were not observed in the chimpanzee

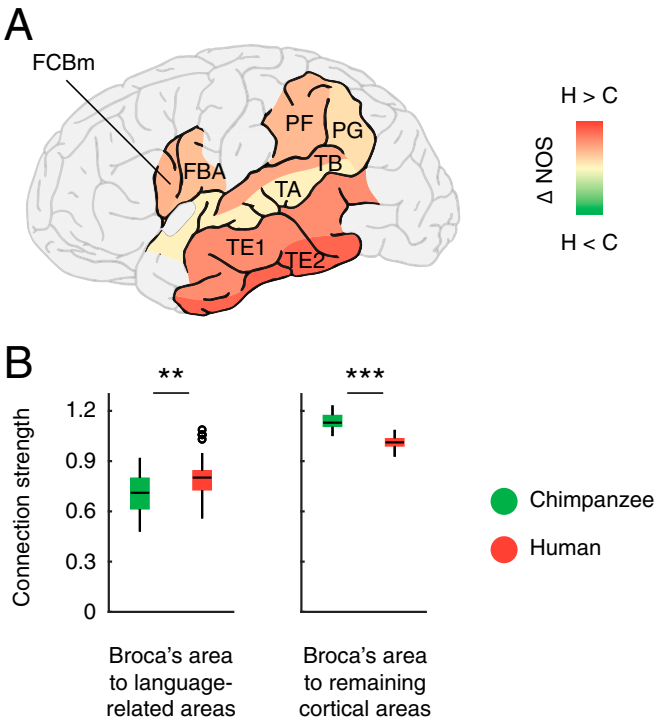

Fig. 3. Cross-species connectivity differences in tracts related to human language processing. (*A*) Normalized strength of connections between areas of the language network, averaged per cortical region. Averages are based on connections between language-related areas. (*B*) Strength of connections between FBA/FCBm and other language-related areas (*Left*) and strength of connections between FBA/FCBm and the remaining cortical areas (*Right*). Areas connected to FBA and FCBm not directly involved in language included FA, FB, FC, FDp, IA, IB, PB, PC, and PFD (area descriptions provided in *SI Appendix*, Table S1). The normalized number of streamlines is shown as connection strength. C, chimpanzee; H, human. ***$P < 0.001$; **$P < 0.01$.

sample (0% of subjects), which we here refer to as "human-specific connections." We note that with this term, we are not implying that these connections are unique to humans, although this is a possibility (*Discussion*). Human-specific connections constituted 5.9% of the human group connectome ($n = 33$ connections; Fig. 4*A* and *SI Appendix*, Fig. S3). These connections included predominantly intrahemispheric pathways ($n = 31/33$) and also could be characterized as connections linking multimodal association areas ($n = 13/33$) and connections linking unimodal and multimodal association areas ($n = 11/33$) (Fig. 4*B*). Furthermore, a subset of human-specific connections ($n = 9/33$) linked regions related to language processing (33–35) in the inferior frontal gyrus, supramarginal/angular gyrus, and temporal lobe, in line with previous comparative diffusion tensor imaging findings on primate arcuate fasciculus connectivity (36). In contrast, we observed only three chimpanzee-specific connections, all interhemispheric (*SI Appendix*).

We next compared the classes of human-specific connections and shared connections in terms of their ability to integrate information within the human brain network by means of graph theory analysis. Using edge statistics (37), we computed the contributions of both human-specific and shared connections to global network efficiency of the full set of connections of the human group connectome, controlling for network density and connection length (*Methods*). We observed a pronounced difference in integrative capacity between the two connection types, with a 1.5-fold greater contribution to network efficiency of human-specific connections compared with shared connections [median, 3.91×10^{-4} (IQR, 2.61×10^{-4}–6.52×10^{-4}) vs. 2.61×10^{-4} (IQR, 1.96×10^{-4}–3.26×10^{-4}); Wilcoxon rank-sum $Z = 3.76$; $r = 0.463$; $P = 1.67 \times 10^{-4}$] (Fig. 4*C*). The contribution to global efficiency of both connection types showed a twofold difference when short communication paths were computed specifically on the network of shared connections (*SI Appendix*).

We further examined the physical length of human-specific connections and shared connections by measuring the distance spanned by both types of connections in the human brain. Human-specific connections were found to be costlier in terms of their average physical length compared with connections shared between the two species [median, 74.1 mm (IQR, 39.1–91.5 mm) vs. 35.7 mm (IQR, 16.2–89.5 mm); Wilcoxon rank-sum $Z = 2.53$; $r = 0.130$; $P = 0.011$] (Fig. 4*D*).

Discussion

Our comparative connectome analysis suggests an evolutionary shift in the human brain network to invest costly neural resources

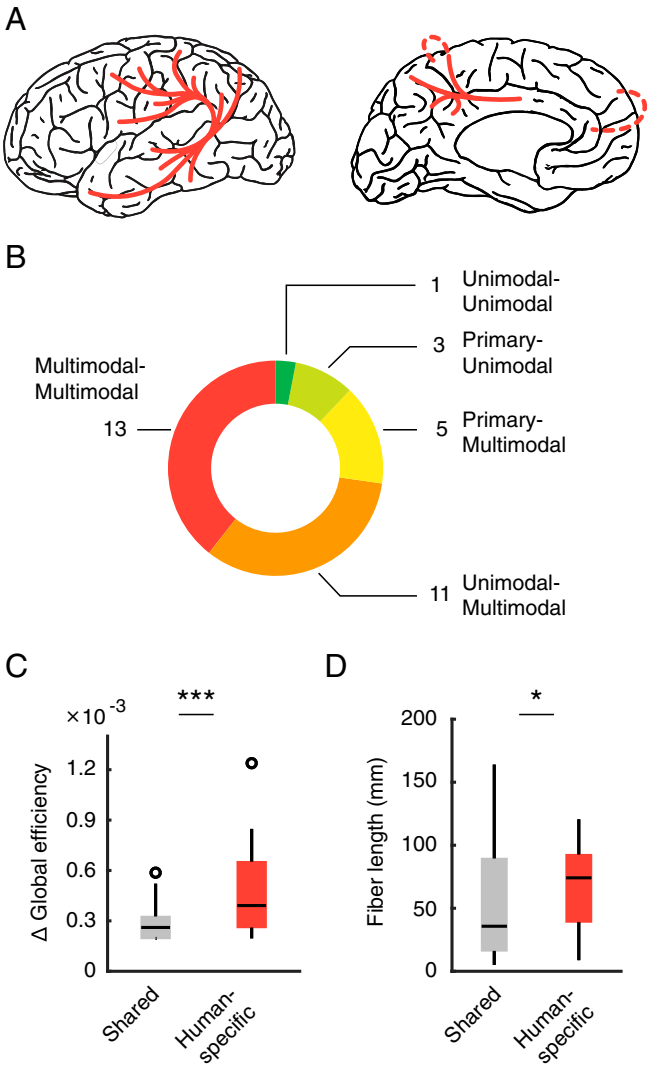

Fig. 4. Network properties of human-specific connections. (*A*) Schematic representation of left hemisphere connections observed in the human brain but not in the chimpanzee brain (dotted lines indicate interhemispheric connections). A connectogram is shown in *SI Appendix*, Fig. S3. (*B*) Division of human-specific connections based on the type of connected cortical areas. (*C*) Difference in global network efficiency of the human group connectome associated with human-specific connections ($n = 33$) and fiber length-matched human-chimpanzee shared connections ($n = 33$). ***$P < 0.001$; *$P < 0.05$. (*D*) Fiber lengths of shared connections ($n = 344$) and human-specific connections ($n = 33$).

in infrastructure for multimodal information integration, laying the connectome foundations for enhanced cognitive function. The higher connectivity between multimodal association areas in humans compared with chimpanzees indicates a focus on associative neural processing in humans, with relatively fewer neural resources spent on connections between primary areas. Furthermore, long-range human-specific connections are found to boost global network integration to a greater extent than connections shared between humans and chimpanzees, suggesting that the human connectome has made costly adaptations to the advantage of enhanced network integration.

The findings of lower interhemispheric connectivity and higher network modularity in the human brain compared with chimpanzees indicate a link between reduced interhemispheric coupling and enhanced network modularity over the course of human brain evolution. The higher network modularity and lower interhemispheric connectivity in the human connectome further support previous observations of smaller corpus callosum size with respect to the neocortex in humans compared with nonhuman primates (13, 14). Our findings suggest that connections supporting advanced cognition likely offset their high costs in the human connectome, while long-range connections involved in lower-level processing are weakened, leading to increased overall network modularity. Enhanced modularity has been purported to facilitate functional specialization and hemispheric lateralization of the brain (20, 29), which has been suggested to have accelerated human brain evolution in response to environmental changes (38).

The adaptations observed in language-related connectivity in humans extend previous comparative reports of stronger frontotemporal connectivity in humans compared with other primates, including chimpanzees (36, 39). Our present findings suggest an evolutionary specialization of areas FBA and FCBm (corresponding to Brodmann areas 44 and 45, respectively, and traditionally referred to as Broca's area) within the language network, with connectivity of these areas adapting from a more global to a more specialized connectivity fingerprint. The specific function of Broca's area in human speech production (31, 40) is supported by the observation of putative human-specific connections between Broca's area and middle and inferior temporal gyri in the left hemisphere, areas involved in semantic and lexical processing in humans (41–43). The enhancement and specialization of connectivity between language-related areas may have contributed to the evolution of complex language in the human lineage.

Some methodological and technical limitations need to be considered when interpreting our present results. First, the shared connectome represents a group-averaged subset of connections observed in the human and chimpanzee samples. It is possible that the reported differences in centrality and modularity are modified by connections that are not shared between the species. The majority of connections found in humans but not in chimpanzees were intrahemispheric (94%) and linked association areas (73%), suggesting that these connections are more likely to enhance rather than diminish multimodal centrality and modularity in the human brain network. Second, resampling of connection weights in our comparative connectome analysis allowed for direct cross-species comparisons of connectivity strength relative to the rest of the network, but at the expense of the inability to resolve differences in absolute strength between the species. Since interpretation of absolute strength differences across species is more prone to between-species biases due to differences in brain size and imaging parameters, we opted for the current resampling approach. (*SI Appendix, Results* provides results based on other connection weights.)

Third, diffusion-weighted MRI has limited accuracy in the reconstruction of complex fiber orientations, particularly of long- or very short-range fibers. It is possible that some existing connections in humans and chimpanzees might not have been identified or were underestimated in our study. In addition, our comparative connectome analysis is limited by the lack of an outgroup, such as another less closely related primate species. Further investigation of additional primate species is needed to examine whether the observed connectome adaptations may be potentially specific to humans. It remains to be determined how many of the connections that we labeled as human-specific connections reflect adaptations of the human brain or, alternatively, reflect connections that were lost in chimpanzee evolution.

An outstanding question is whether brain expansion is the primary factor driving these connectome adaptions or whether additional environmental pressures have contributed to the evolution of the human connectome (44, 45). Furthermore, it remains a topic of ongoing investigation whether the expansion of frontal and parietal multimodal association areas in humans exceeds patterns of allometric scaling (6, 11, 12, 46, 47), and similarly, it remains to be established whether expansion of the underlying white matter connectivity exceeds allometry or follows a general blueprint of primate brain size scaling. Future studies including additional primate species will be crucial to our understanding of general vs. human-specific brain network adaptations and their role in the evolution of advanced cognitive capabilities in large-brained primates. Such comparative connectome efforts may also provide new insight into the etiology of human-specific mental illnesses (48, 49).

Methods

Chimpanzee and Human Subjects. MRI data were acquired from 22 adult female chimpanzees (*P. troglodytes*; age 18–54 y; mean age, 31.9 ± 11.3 y) and 58 adult human females (*Homo sapiens*; age 21–76 y; mean age, 48.3 ± 14.3 y) (*SI Appendix*, Figs. S4 and S5; details of MRI acquisition provided in *SI Appendix, Methods*) (50), of which 20 chimpanzee and 57 human datasets met quality control standards. The chimpanzees were housed at the Yerkes National Primate Research Center, Atlanta, GA. All animal procedures were approved by the Yerkes National Primate Research Center and Emory University's Institutional Animal Care and Use Committee (YER-2001206). Healthy human subjects without known neurologic conditions were recruited and underwent MRI at Emory University. All human procedures were approved by Emory University's Institutional Review Board (IRB00000028), and all human participants provided voluntary informed consent.

Cortical Parcellation. MRI-based brain surface reconstructions were parcellated into 72 distinct cortical areas (*SI Appendix*, Fig. S6). With network analyses known to be sensitive to differences in mapping of cortical areas (51, 52), we used the von Bonin-Bailey (BB38) cortical brain atlas (32, 53), describing 76 cortical regions (38 per hemisphere) based on cytoarchitectural homologies between the human and chimpanzee cortex (*SI Appendix, Methods*). We note that this cytoarchitectural atlas focuses on describing anatomically homologous regions between chimpanzees and humans, which does not necessarily denote functional homology. Tissue segmentation and cortical mapping were manually checked. Areas FH and LE of the BB38 atlas were merged with their neighboring areas FG and LC2, respectively, owing to the small size of these areas. The final atlas consisted of 72 cortical areas (36 per hemisphere).

Connectome Reconstruction. Cortical parcellation was combined with white matter streamlines reconstructed from diffusion tractography (*SI Appendix, Methods*) to obtain a corticocortical connectivity matrix for each subject. The entries in this matrix represent the normalized number of streamlines connecting each pair of cortical regions (i, j) (54, 55). We inspected connection densities in both samples and identified two outliers in the chimpanzee sample and one outlier in the human sample (connection density >1.5 times the interquartile range below the corresponding sample medians), which were excluded from further analysis. The final dataset included connectivity data of 20 chimpanzee and 57 human subjects. Binary group connectomes and individual weighted networks based on the normalized strength of shared connections were constructed for each species. More details are provided in *SI Appendix, Methods*.

Graph Theoretical Analyses. Human and chimpanzee brain networks were analyzed using graph theoretical tools (30). Graph analysis included the computation of binary and weighted network global efficiency, weighted

modularity, and weighted edge betweenness centrality as a metric of the participation of a connection in overall network efficiency. Edge statistics (37) was used to assess the effect on network efficiency of connections observed in humans but not in chimpanzees. From the human group connectome, a shared connection was selected, and network efficiency was computed with and without this connection. Next, a human-specific connection was swapped for the selected shared connection, and network efficiency was recomputed. The difference in global network efficiency after insertion of the human-specific connection was compared against the difference in global network efficiency after insertion of the shared connection (matched on fiber length). This procedure was repeated for all human-specific connections.

Data Sharing. Connectivity matrices and analysis scripts are available at the UMCD database, IDs 3036/3037 (57).

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