

## Correction

### NEUROSCIENCE

Correction for “Evolutionary expansion of connectivity between multimodal association areas in the human brain compared with chimpanzees,” by Dirk Jan Ardesch, Lianne H. Scholtens, Longchuan Li, Todd M. Preuss, James K. Rilling, and Martijn P. van den Heuvel, which was first published March 18, 2019; 10.1073/pnas.1818512116 (*Proc Natl Acad Sci USA* 116:7101–7106).

The authors wish to note the following: “No new MRI data were acquired for this study. All chimpanzee MRIs were obtained from a data archive of scans obtained prior to the 2015 implementation of US Fish and Wildlife Service and National Institutes of Health regulations governing research with chimpanzees. All the scans reported in this publication were completed by the end of 2012. All chimpanzee MRI scans are part of the National Chimpanzee Brain Resource (<http://www.chimpanzeebrain.org>).”

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# 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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The authors declare no conflict of interest.

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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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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 fronto-temporal 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 adaptations 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,  $31.9 \pm 11.3$  y) and 58 adult human females (*Homo sapiens*; age 21–76 y; mean age,  $48.3 \pm 14.3$  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.

- Devaine M, Hollard G, Daunizeau J (2014) Theory of mind: Did evolution fool us? *PLoS ONE* 9:e87619.
- Berwick RC, Friederici AD, Chomsky N, Bolhuis JJ (2013) Evolution, brain, and the nature of language. *Trends Cogn Sci* 17:89–98.
- Seyfarth RM, Cheney DL (2014) The evolution of language from social cognition. *Curr Opin Neurobiol* 28:5–9.
- Rilling JK (2014) Comparative primate neuroimaging: Insights into human brain evolution. *Trends Cogn Sci* 18:46–55.
- Holloway RL, Sherwood CC, Hof PR, Rilling JK (2009) Evolution of the brain in humans—Paleoneurology. *Encyclopedia of Neuroscience*, eds Binder MD, Hirokawa N, Windhorst U (Springer, Berlin).
- Rilling JK (2006) Human and nonhuman primate brains: Are they allometrically scaled versions of the same design? *Evol Anthropol* 15:65–77.
- Elston GN, Benavides-Piccione R, Elston A, Manger PR, Defelipe J (2011) Pyramidal cells in prefrontal cortex of primates: Marked differences in neuronal structure among species. *Front Neuroanat* 5:2.
- Elston GN, Benavides-Piccione R, DeFelipe J (2001) The pyramidal cell in cognition: A comparative study in human and monkey. *J Neurosci* 21:RC163.
- Bianchi S, et al. (2013) Dendritic morphology of pyramidal neurons in the chimpanzee neocortex: Regional specializations and comparison to humans. *Cereb Cortex* 23:2429–2436.
- Avants BB, Schoenemann PT, Gee JC (2006) Lagrangian frame diffeomorphic image registration: Morphometric comparison of human and chimpanzee cortex. *Med Image Anal* 10:397–412.
- Donahue CJ, Glasser MF, Preuss TM, Rilling JK, Van Essen DC (2018) Quantitative assessment of prefrontal cortex in humans relative to nonhuman primates. *Proc Natl Acad Sci USA* 115:E5183–E5192.
- Bruner E, Preuss TM, Chen X, Rilling JK (2017) Evidence for expansion of the pre-cuneus in human evolution. *Brain Struct Funct* 222:1053–1060.
- Rilling JK, Insel TR (1999) Differential expansion of neural projection systems in primate brain evolution. *Neuroreport* 10:1453–1459.
- Hopkins WD, Rilling JK (2000) A comparative MRI study of the relationship between neuroanatomical asymmetry and interhemispheric connectivity in primates: Implication for the evolution of functional asymmetries. *Behav Neurosci* 114:739–748.
- Rilling JK, Insel TR (1999) The primate neocortex in comparative perspective using magnetic resonance imaging. *J Hum Evol* 37:191–223.
- van den Heuvel MP, Bullmore ET, Sporns O (2016) Comparative connectomics. *Trends Cogn Sci* 20:345–361.
- Sporns O, Tononi G, Kötter R (2005) The human connectome: A structural description of the human brain. *PLoS Comput Biol* 1:e42.
- Langergraber KE, et al. (2012) Generation times in wild chimpanzees and gorillas suggest earlier divergence times in great ape and human evolution. *Proc Natl Acad Sci USA* 109:15716–15721.
- Schoenemann PT (2013) Hominid brain evolution. *A Companion to Paleoanthropology*, eds Bailey DH, Geary DC (Blackwell Publishing, Oxford, UK), pp 136–164.
- Barrett HC (2012) A hierarchical model of the evolution of human brain specializations. *Proc Natl Acad Sci USA* 109:10733–10740.
- Gollo LL, et al. (2018) Fragility and volatility of structural hubs in the human connectome. *Nat Neurosci* 21:1107–1116.
- Hofman MA (2014) Evolution of the human brain: When bigger is better. *Front Neuroanat* 8:15.
- Rubin M, Ypma RJF, Watson C, Bullmore ET (2015) Wiring cost and topological participation of the mouse brain connectome. *Proc Natl Acad Sci USA* 112:10032–10037.
- Kaiser M, Hilgetag CC (2006) Nonoptimal component placement, but short processing paths, due to long-distance projections in neural systems. *PLoS Comput Biol* 2:e95.
- Bullmore E, Sporns O (2012) The economy of brain network organization. *Nat Rev Neurosci* 13:336–349.
- Betzel RF, Bassett DS (2018) Specificity and robustness of long-distance connections in weighted, interareal connectomes. *Proc Natl Acad Sci USA* 115:E4880–E4889.
- Mesulam M-M (1998) From sensation to cognition. *Brain* 121:1013–1052.
- Girvan M, Newman MEJ (2002) Community structure in social and biological networks. *Proc Natl Acad Sci USA* 99:7821–7826.
- Sporns O, Betzel RF (2016) Modular brain networks. *Annu Rev Psychol* 67:613–640.
- Rubin M, Sporns O (2010) Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage* 52:1059–1069.
- Rilling JK (2014) Comparative primate neurobiology and the evolution of brain language systems. *Curr Opin Neurobiol* 28:10–14.
- von Economo CF, Koskinas GN (1925) *Die Cytoarchitektur der Hirnrinde des erwachsenen Menschen* (Springer, Vienna).
- Dick AS, Tremblay P (2012) Beyond the arcuate fasciculus: Consensus and controversy in the connectonal anatomy of language. *Brain* 135:3529–3550.
- Glasser MF, Rilling JK (2008) DTI tractography of the human brain's language pathways. *Cereb Cortex* 18:2471–2482.
- Burks JD, et al. (2017) White matter connections of the inferior parietal lobule: A study of surgical anatomy. *Brain Behav* 7:e00640.
- Rilling JK, et al. (2008) The evolution of the arcuate fasciculus revealed with comparative DTI. *Nat Neurosci* 11:426–428.
- de Reus MA, Saenger VM, Kahn RS, van den Heuvel MP (2014) An edge-centric perspective on the human connectome: Link communities in the brain. *Philos Trans R Soc Lond B Biol Sci* 369:20130527.
- Gómez-Robles A, Hopkins WD, Sherwood CC (2014) Modular structure facilitates mosaic evolution of the brain in chimpanzees and humans. *Nat Commun* 5:4469.
- Eichert N, et al. (2018) What is special about the human arcuate fasciculus? Lateralization, projections, and expansion. *Cortex* S0010-9452(18)30151-5.
- Flinker A, et al. (2015) Redefining the role of Broca's area in speech. *Proc Natl Acad Sci USA* 112:2871–2875.
- Wei T, et al. (2012) Predicting conceptual processing capacity from spontaneous neuronal activity of the left middle temporal gyrus. *J Neurosci* 32:481–489.
- Visser M, Jefferies E, Embleton KV, Lambon Ralph MA (2012) Both the middle temporal gyrus and the ventral anterior temporal area are crucial for multimodal semantic processing: Distortion-corrected fMRI evidence for a double gradient of information convergence in the temporal lobes. *J Cogn Neurosci* 24:1766–1778.
- Dien J, Brian ES, Molfese DL, Gold BT (2013) Combined ERP/fMRI evidence for early word recognition effects in the posterior inferior temporal gyrus. *Cortex* 49:2307–2321.
- Dunbar RIM, Shultz S (2007) Evolution in the social brain. *Science* 317:1344–1347.
- Whiten A, Erdal D (2012) The human socio-cognitive niche and its evolutionary origins. *Philos Trans R Soc Lond B Biol Sci* 367:2119–2129.
- Barton RA, Venditti C (2013) Human frontal lobes are not relatively large. *Proc Natl Acad Sci USA* 110:9001–9006.
- Semendeferi K, Lu A, Schenker N, Damasio H (2002) Humans and great apes share a large frontal cortex. *Nat Neurosci* 5:272–276.
- Wang J, et al. (2013) Disrupted functional brain connectome in individuals at risk for Alzheimer's disease. *Biol Psychiatry* 73:472–481.
- van den Heuvel MP, Fornito A (2014) Brain networks in schizophrenia. *Neuropsychol Rev* 24:32–48.
- Li L, et al. (2013) Mapping putative hubs in human, chimpanzee and rhesus macaque connectomes via diffusion tractography. *Neuroimage* 80:462–474.
- de Reus MA, van den Heuvel MP (2013) The parcellation-based connectome: Limitations and extensions. *Neuroimage* 80:397–404.
- Fornito A, Zalesky A, Bullmore ET (2010) Network scaling effects in graph analytic studies of human resting-state fMRI data. *Front Syst Neurosci* 4:22.
- Bailey P, von Bonin G, McCulloch WS (1950) *The Isocortex of the Chimpanzee* (Univ of Illinois Press, Urbana, IL).
- Hagmann P, et al. (2008) Mapping the structural core of human cerebral cortex. *PLoS Biol* 6:e159.
- Honey CJ, et al. (2009) Predicting human resting-state functional connectivity from structural connectivity. *Proc Natl Acad Sci USA* 106:2035–2040.
- Krzywinski M, et al. (2009) Circo: An information aesthetic for comparative genomics. *Genome Res* 19:1639–1645.
- Brown JA, Rudie JD, Bandrowski A, Van Horn JD, Bookheimer SY (2012) Data from "The UCLA multimodal connectivity database: A web-based platform for brain connectivity matrix sharing and analysis." UMCD. Deposited March 8, 2019.

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

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