REPORT



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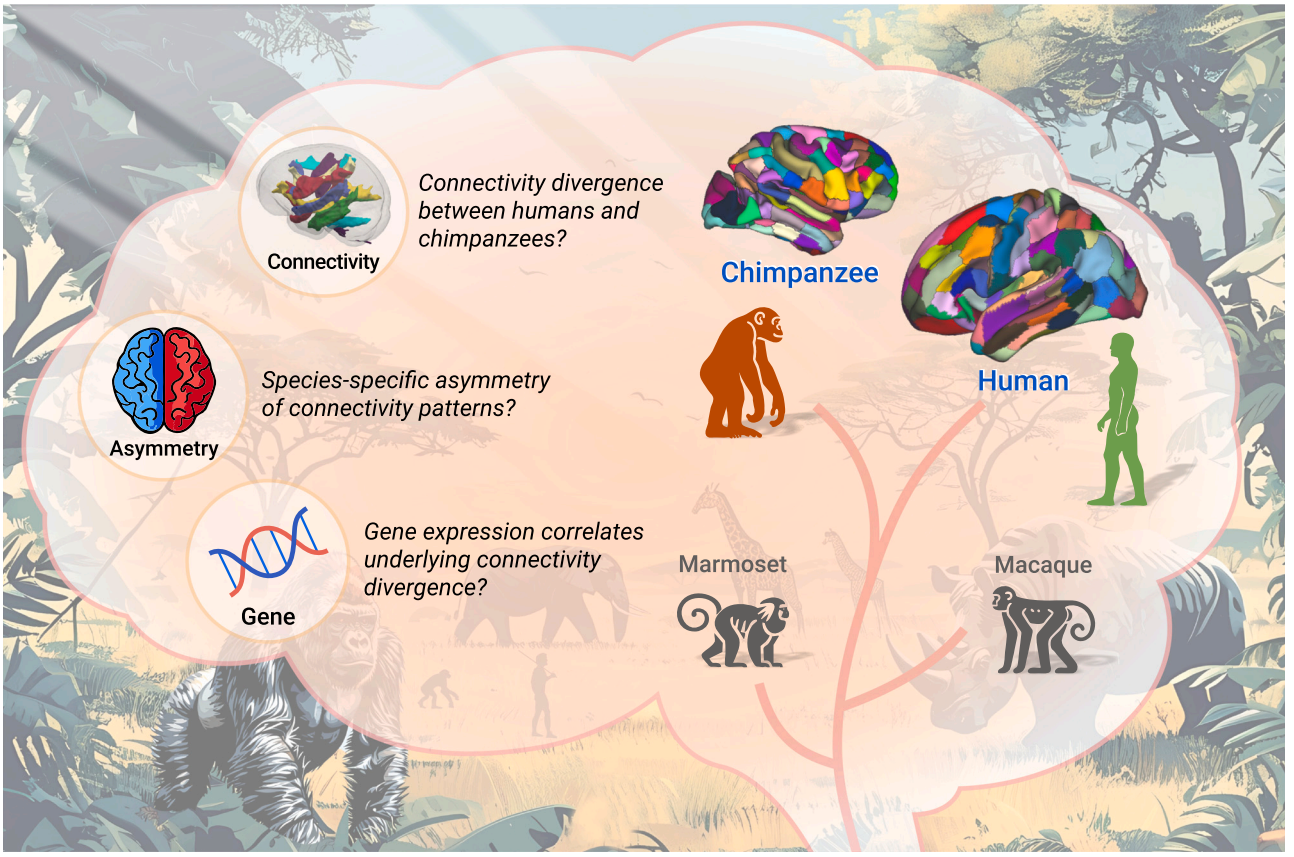
## GRAPHICAL ABSTRACT




## PUBLIC SUMMARY

- This study presents the most refined chimpanzee brain atlas to date, the Chimpanzee Brainnetome Atlas (ChimpBNA).
- Chimpanzee-human connectivity divergence deviates from the pattern of cortical expansion.
- Species-specific connectional asymmetric patterns were examined.
- Genes related to divergent connectivities suggested influences on neural circuit development and evolution.
- The standardized atlasing approach provides a meaningful method for cross-species comparisons.

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# The Chimpanzee Brainnetome Atlas reveals distinct connectivity and gene expression profiles relative to humans

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Chimpanzees (*Pan troglodytes*) are one of humans' closest living relatives, making them the most directly relevant comparison point for understanding human brain evolution. Zeroing in on the differences in brain connectivity between humans and chimpanzees can provide key insights into the specific evolutionary changes that might have occurred along the human lineage. However, such comparisons are hindered by the absence of cross-species brain atlases established within the same framework. To address this gap, we developed the Chimpanzee Brainnetome Atlas (ChimpBNA) using a connectivity-based parcellation framework. Leveraging this new resource, we found substantial divergence in connectivity patterns between the two species across most association cortices, notably in the lateral temporal and dorsolateral prefrontal cortex. These differences deviate sharply from the pattern of cortical expansion observed when comparing humans to chimpanzees, highlighting more complex and nuanced connectivity changes in brain evolution than previously recognized. Additionally, we identified regions displaying connectional asymmetries that differed between species, likely resulting from evolutionary divergence. Genes highly expressed in regions of divergent connectivities were enriched in cell types crucial for cortical projection circuits and synapse formation, whose pronounced differences in expression patterns hint at genetic influences on neural circuit development, function, and evolution. Our study provides a fine-scale chimpanzee brain atlas and highlights the chimpanzee-human connectivity divergence in a rigorous and comparative manner. In addition, these results suggest potential gene expression correlates for species-specific differences by linking neuroimaging and genetic data, offering insights into the evolution of human-unique cognitive capabilities.

## INTRODUCTION

Chimpanzees (*Pan troglodytes*) are among humans' (*Homo sapiens*) closest living primate relatives, with a shared ancestor dating back approximately 6–8 million years ago.[1] Despite having brains about one-third the size of humans,[2,3] chimpanzees demonstrate many similarities in neuroanatomical[4,5] and cognitive functions,[6–9] including social behavior, working memory, and tool use. Their genetic and neurobiological proximity to humans makes them a critical comparative reference for understanding human evolution.[10] While neuroimaging has advanced quantitative comparisons of brain structure between chimpanzees and other primates,[11–17] changes in cortical morphology alone cannot fully explain evolutionary adaptations, particularly in association cortices.[18,19]

Evolutionary changes in wiring space, especially in the white matter tracts beneath the cortex, significantly influence anatomical and functional differences between species.[18,20,21] These anatomical connections characterize brain regions and support flexible cognitive functions.[22,23] Recent studies have mapped chimpanzee brain connections using diffusion MRI and revealed substantial interspecies differences with humans.[18,20,21,24–28] Moreover, understanding brain evolution requires a genetic perspective, as molecular mechanisms may drive interspecies differences in brain connections, providing insights into cognitive diversity and adaptation among primates.[29,30] However, comprehensive whole-brain connectional analyses of chimpanzee-human connectivity divergence, coupled with genetic investigations into species differences in brain connections, are still lacking. Additionally, understanding neuroanatomical and functional asymmetries—linked to advanced cognitive processes like language and tool use[31,32]—requires brain-wide studies beyond localized structural features.[33,34]

A major challenge in cross-species neuroscience is the lack of a standardized brain reference system with biologically meaningful subregions for direct comparisons among species.[35] Previous comparative analyses have defined homologous brain regions among species using cytoarchitecture, myeloarchitecture, macroanatomy, connectivity patterns, functional activation, or a combination of these features, leading to a variety of brain atlases for humans[36–39] and chimpanzees.[13,25,40,41] However, inconsistencies in the modalities and scales used to construct these atlases render cross-species comparisons challenging. Recent connectivity-based parcellation has successfully delineated distinct brain areas in humans, macaques, and marmosets using anatomical connections,[37,42,43] demonstrating the feasibility of parcellating the chimpanzee brain based on diffusion MRI. Such a standardized atlasing approach also enables meaningful cross-species comparisons.[33] Meanwhile, generating homologous white matter tracts across species within a connectivity blueprint framework has been used to predict homologous cortical areas, even when their relative locations have shifted. This approach also helps identify unique aspects of brain organization, offering new opportunities to investigate evolutionary changes in brain wiring.[44,45]

To address these gaps, we developed the Chimpanzee Brainnetome Atlas (ChimpBNA), the most refined atlas of the chimpanzee brain to date, using a connectivity-based parcellation framework (Figure 1A).[37] Leveraging this atlas, we reconstructed homologous white matter tracts and built connectivity blueprints for humans and chimpanzees. These blueprints enabled fine-grained analyses of connectivity divergence at the subregion level and the identification of associated white matter tracts (Figure 1B).[44,45] We further examined brain-wide lateralization of connectivity patterns in each species, aligning these to a common space to explore their relationship with interspecies connectivity divergence (Figure 1C).[18] Finally, we identified the genes and their expression patterns associated with connectivity divergence between species (Figure 1D). This comprehensive approach integrates fine-grained chimpanzee parcellation with cross-species connectivity and genetic analyses, offering novel insights into human brain evolution.

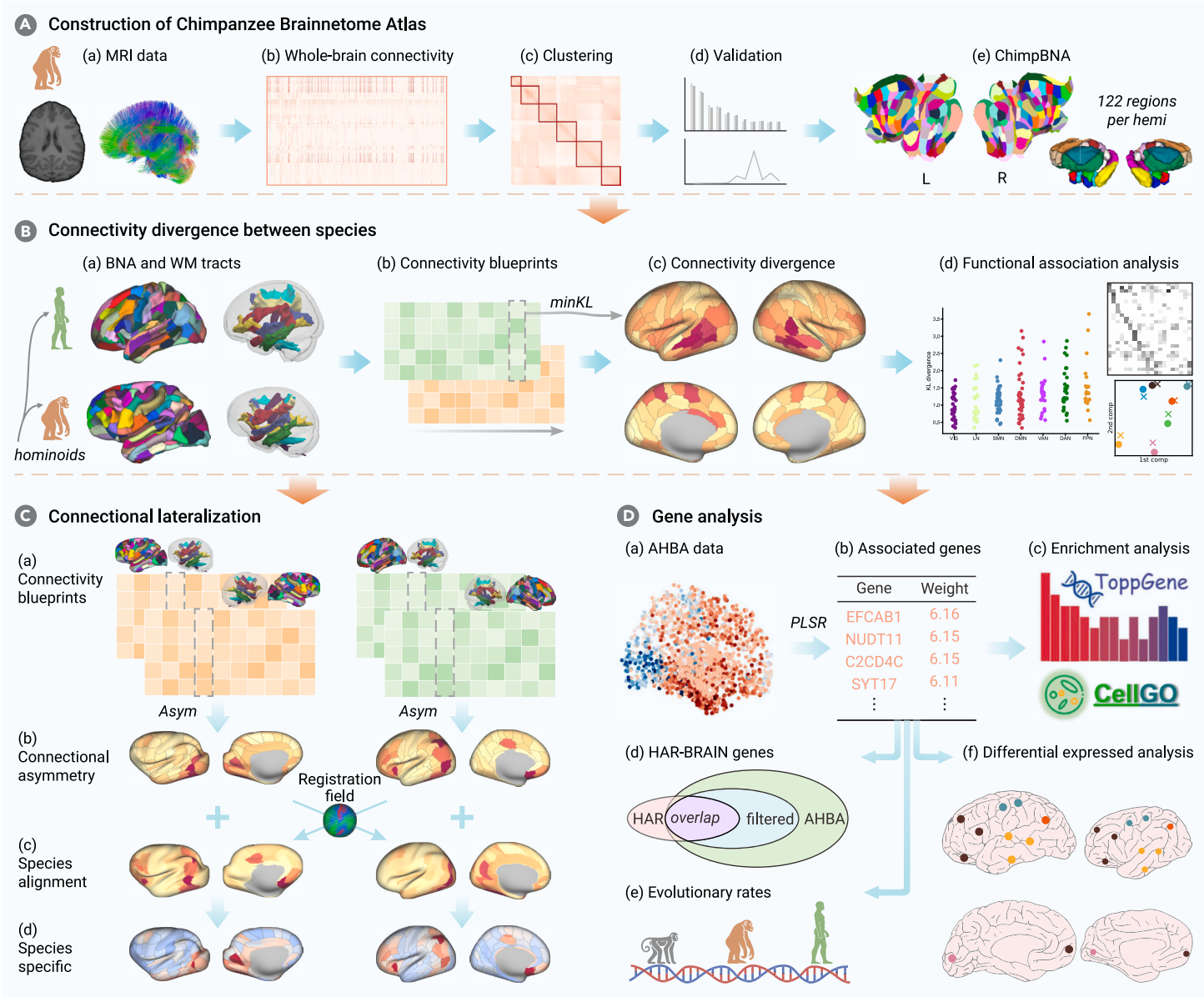


**Figure 1. Analysis pipeline** (A) Using a connectivity-based parcellation procedure, we used MRI data from chimpanzee brains (a) to construct the Chimpanzee Brainnetome Atlas. Tractography and similarity matrices were computed (b) to perform spectral clustering (c). The clustering results were validated using several indices (d), and the final whole-brain parcellation was obtained (e). (B) We utilized the Brainnetome Atlases of humans and chimpanzees along with homologous white matter tracts (a) to build regional connectivity blueprints for each species (b), which were used to explore connectivity divergence between two species (c), followed by a functional association analysis (d). (C) We used the connectivity blueprints from both hemispheres for each species (a) to investigate asymmetric connectivity patterns (b), which were aligned into a common space (c) to investigate the species-specific asymmetric connectivity patterns (d). (D) AHBA data (a) were used to identify genes associated with connectivity divergence using PLSR (b). The filtered genes were input to gene enrichment and cell type enrichment analyses (c), as well as evolutionary investigation, including overlap with HAR-BRAIN genes (d), assessment of evolutionary rates (e), and differentially expressed analysis between the two species (f).

## RESULTS

### Connectivity-based parcellation of the chimpanzee brain

Using a modified connectivity-based parcellation framework (Figure S1)[37] to develop the ChimpBNA, we delineated 26 initial seed masks (19 cortical and 7 subcortical) on the chimpanzee brain template and registered them to individual brains. Each region was subdivided into clusters based on whole-brain connectivity following validation of reproducibility and inter-hemispheric consistency. Based on probabilistic tractography data from 46 chimpanzees, the brain was parcellated into 200 cortical (Figure 2A) and 44 subcortical regions (Figure S2). The atlas is interactively accessible via a web viewer (Figure S3; https://molicaca.github.io/atlas/chimp_atlas.html).

The definition and naming of initial regions of the chimpanzee brain adopted conventions from the Human Brainnetome Atlas (HumanBNA).[37] Here, we merged the posterior superior temporal sulcus (pSTS) into other temporal regions due to its uncertain definition in chimpanzees, thus obtaining 19 cortical seeds (Table S1). Boundaries between large gyri were manually edited at the sulcal midpoint. The subregions were named based on topological positions due to limited reference atlases, with detailed results and terminology provided (Figures S4–S29; Table S2).

We compared the ChimpBNA with previous chimpanzee cortical parcellations, such as Bailey and Bonin's parcellation (BB38)[40] and Davi130 parcellation,[13] measuring the spatial correspondence of region labels and boundaries.[46] Average global consistency between atlas pairs was 0.60 (SD: 0.19), ranging from 0.31 to 1 (Figure S30A). The vertex-wise consistency of region assignment across atlases showed the highest consistency in the visual and sensorimotor cortex and lower consistency in the prefrontal and posterior parietal cortex (Figure S30B). The vertex-wise consistency of region boundary placement was higher in the primary sensorimotor cortical areas but more variable in the lateral frontal cortex (Figure S30C).

We further registered the ChimpBNA to the human brain space and compared it with the HumanBNA using a myelin-based alignment technique (Figure S31A).[18,47] The Brainnetome atlases of the two species demonstrated an

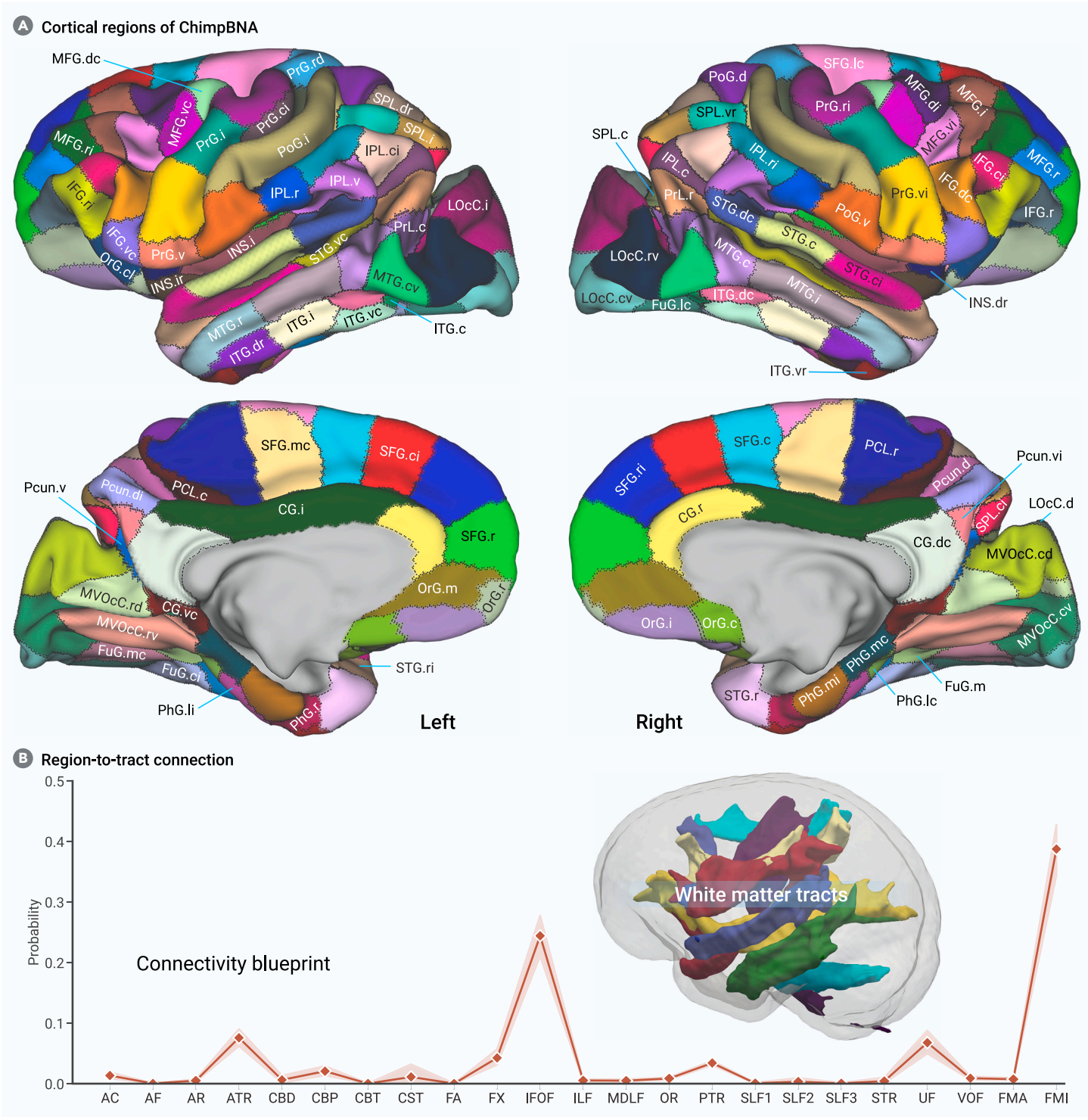


**Figure 2. The Chimpanzee Brainnetome Atlas and connections of the chimpanzee brain** (A) Cortical regions of the Chimpanzee Brainnetome Atlas. (B) Region-to-tract connections of the chimpanzee brain. The connectivity blueprint of an exemple region, superior frontal gyrus rostral part (SFG.r), is shown.

average global consistency of 0.58 (Figure S31B), with the highest consistency in the sensorimotor and visual cortices (Figure S31C).

The connectivity patterns of ChimpBNA subregions were analyzed via a region-to-region connectivity matrix derived from probabilistic tractography (Figure S32). For example, the left superior frontal gyrus rostral part (SFG.r) primarily connected with ipsilateral frontal subregions (e.g., superior frontal gyrus rostrointermediate part [SFG.ri], middle frontal gyrus rostral part [MFG.r]) and contralateral regions (e.g., superior parietal lobule caudal part [SPL.c], insular gyrus rostrodorsal part [INS.rd]) through the corpus callosum (Figure S32D).

Structural hemispheric asymmetry was assessed, revealing leftward gray matter volume dominance in regions such as the rostral inferior parietal lobule (IPL) and insula and rightward dominance in areas like the caudal IPL, anterior MFG, middle temporal gyrus (MTG), and part of lateral occipital gyrus (Figure S33A). Leftward surface area asymmetry was found in the rostral IPL, anterior temporal lobe, and medial occipital gyrus, while rightward asymmetries were found in the posterior IPL, anterior cingulate, and MTG (Figure S33B). The hemispheric asymmetry results showed consistent patterns with previous studies.[13,33,48]

We reconstructed 45 homologous white matter tracts of the chimpanzee brain following an *a priori* protocol[44] and performed probabilistic tractography from each vertex of the white/gray matter surface to the whole brain. Regional connectivity blueprints were derived by multiplying the unwrapped white matter tract matrix by the whole-brain connectivity matrix,[45] whose rows represented

the region-to-tract connectivity pattern of each subregion. Taking the left SFG.r as an example, the subregion was mainly connected with the forceps minor (FMI), left inferior fronto-occipital fascicle (IFOF), and anterior thalamic radiations (ATRs) (Figure 2B).

## Connectivity divergence between species

Leveraging connectivity blueprints for chimpanzees and humans, we explored the connectivity divergence between the two species by calculating the symmetric Kullback-Leibler (KL) divergence for each subregion of ChimpBNA and HumanBNA subregions.[45] The minimum divergence of each HumanBNA subregion was assigned to that region, resulting in a connectivity divergence map, where higher values indicated regions in humans with connectivity patterns more dissimilar to those in chimpanzees, i.e., may not be represented in this close phylogenetic relative (Figures 3A and S34).[45] The minimum divergence of each subregion of the ChimpBNA was also calculated (Figure S35). It should be noted that cladistic inferences about the direction of evolutionary change in trait values in this two-species pairwise contrast cannot be made with complete certainty because changes in brain connectivity may have occurred in both lineages since they last shared a common ancestor.

Regions with the greatest connectivity differences between species were located in the middle and posterior temporal lobe, especially in the anterior STS (aSTS) and both the rostral and caudal portions of the pSTS (rpSTS and cpSTS), caudal IPL (corresponding to rostroventral area 39 [A39rv] or PGa[49]), anterior precuneus (Pcun), insula, and inferior frontal gyrus (IFG) (Figure 3A). In contrast, the occipital and sensorimotor cortices showed lower divergence. Notably, the connectivity divergence map showed weak correlation with cortical expansion ($r$ = 0.057, $p_{spin}$ = 0.579; Figures 3C and S36),[14] indicating that the connectional changes reflect a unique aspect of brain reorganization.

Analyses at the functional network level revealed greater divergence in higher-order cognitive networks than the visual/somatomotor network (Mann-Whitney U test, $p$ = 0.0045), with the frontoparietal network having the greatest divergence (Figure S37).[50] Examining specific regions, greater connectivity divergence was observed in the anterior (A5m) and dorsal-middle (A7m) subregions in the Pcun compared to its ventral-middle (A31) and posterior (dmPOS) subregions (Figure 3Ba), which were driven by differences in connections of the superior longitudinal fasciculus I (SLF1), IFOF, and acoustic radiation (AR) (Figures S38A and S38B). Similarly, within the IPL, the anterior (A40rv) and posterior (A39rv) subregions showed greater divergence (Figures 3Bb, S38C, and S38D), while in the insula, anterior subregions diverged more than posterior ones (Figures 3Bc and S38E). These findings highlight heterogeneous connectivity differences across regions.

Using NeuroSynth data, we investigated the cognitive functions associated with the divergence maps. Highly divergent regions were characterized by higher-order functions such as "memories," "strategic," "shape," and "self,"[51–55] while less-divergent regions were related to more basic sensory and motor processing, including "arm," "somatosensory," and "foot" (Figure 3D).

We further compared chimpanzee and human atlases using connectivity blueprints as homologous features, visualized them in a low-dimensional space using t-distributed stochastic neighbor embedding (t-SNE) (Figure 3E). Regions with similar connectivity profiles clustered together in the resulting space, with cortical systems (frontal, sensorimotor, temporal, parietal, insular, cingulate, and occipital) assigned distinct colors. The sensorimotor, cingulate, and occipital regions tended to form a group, while other regions, especially the insular subregions, were scattered across different cortical systems (Figure 3E). The median coordinates of each cortical system showed that the primary cortex (sensorimotor and occipital) was more similar between species, while the frontal and parietal regions were farther apart, with the greatest dissimilarity in the temporal regions (Figure 3E, inset).

## Whole-brain-level connectional lateralization

To investigate the connectional lateralization of the chimpanzee brain, we split the connectivity blueprint into two hemispheres, $CB_L$ and $CB_R$, each containing unilateral and commissural tracts (21 unilateral and 2 commissural tracts). We calculated the KL divergence between homotopic subregions to assess inter-hemispheric connectivity differences. Regions with high asymmetry included the posterior temporal lobe, IPL, medial occipital cortex, and MFG (Figure 4A, top left). Similarly, inter-hemispheric differences in humans were calculated and showed patterns consistent with previous studies (Figure 4A, bottom right).[56]

Since the data for the two species were in different spaces, we used a myelin-based alignment to transform the asymmetric connectivity patterns between chimpanzees and humans.[18,47] This allowed us to identify species-shared and species-specific regions with asymmetric connectivity within a common space.

In the common human space, exclusive *OR* maps were calculated to identify human-specific asymmetric connectivity (Figure 4B).[57] Humans displayed unique asymmetric connectivity in the dorsal IPL, anterior insular cortex, middle cingulate cortex (MCC), posterior orbitofrontal cortex (OFC), and most of the lateral prefrontal cortex (PFC) (Figure 4B, bottom left). Correlating these human-specific asymmetry patterns with the connectivity divergence map highlighted regions with marked differences, including the posterior IPL, temporal lobe, posterior OFC, and dorsolateral PFC (Figure 4B, bottom right).

Chimpanzees exhibited unique connectional asymmetries in the posterior temporal regions and medial occipital cortex (Figure 4B, top left), with marked connectional changes in the caudoventral temporal lobe (Figure 4B, top right), highlighting chimpanzee-unique connectivity features distinct from humans.

We further investigated tract contributions to these asymmetric patterns in specific subregions. In humans, the rostrodorsal A39 (A39rd) showed human-specific asymmetric connectivity driven by the IFOF, middle longitudinal fasciculus (MdLF), and SLF2 (Figure 4C, left). For inferior parietal lobule ventral part (IPL.v) in chimpanzees, inter-hemispheric differences were primarily driven by SLF2 (Figure 4C, middle), consistent with previous findings that the C2 subregion of the chimpanzee IPL showed significant rightward SLF2 asymmetry.[33] The SLF2 also contributed to the asymmetry in the MFG (Figure S39A). In the highly asymmetric middle temporal gyrus caudoventral part (MTG.cv) of chimpanzees, lateralized connections were associated with the inferior longitudinal fascicle (ILF) and vertical occipital fascicle (VOF) (Figure 4C, right). Additionally, connectional asymmetries in medioventral occipital cortex rostrodorsal part (MVOcC.rd) and medioventral occipital cortex caudoventral part (MVOcC.cv) were influenced by asymmetric optic radiation connections (Figure S39B).

## Gene expression associations with connectivity divergence between species

We investigated the association between the connectivity divergence map and gene expression using the Allen Human Brain Atlas (AHBA).[58] Partial least-squares regression (PLSR) revealed a significant correlation between the first component (PLS1 score) and the divergence map ($r$ = 0.39, $p_{spin} < 0.011$; Figure 5A). 1,939 genes with a $Z$ score greater than 3 were filtered using 10,000 times bootstrapping, including key genes such as *EFCAB1*, *NUDT11*, *C2CD4C*, and *SYT17* (Table S3). These genes were enriched in excitatory neurons, particularly L6 and L2-3 intratelencephalic excitatory neurons (Figure 5B), and associated with neuronal formation, projections, and synapses (Figure 5C).

Additionally, 71 of these genes overlapped significantly with human-accelerated genes related to brain processes (HAR-BRAIN genes,[14] $p < 0.005$; Figure 5D; Table S4) but were not enriched in selective sweep regions[59] or Neanderthal-introgressed SNPs,[60] indicating that these differences are rooted deeply in the timing of evolutionary divergence between humans and chimpanzees rather than emerging more recently as various *Homo* species evolved. Evolutionary rate analysis ($dN/dS$) indicated positive selection ($dN/dS > 1$) for 56 genes in the chimpanzee-human clade compared to only 14 in the macaque data (Welch's t test, $p < 0.0001$; Figure 5E; Table S5).[61]

Using PsychENCODE data,[29] we examined differential gene expression between humans and chimpanzees across 16 homologous brain regions. Of the 1,939 genes, 1,473 overlapped with PsychENCODE data (Table S6) and were analyzed in three regions of interest: the superior temporal cortex (STC), dorsolateral frontal cortex (DFC), and primary visual cortex (V1C). Paired t tests revealed significant differences in the STC ($t$ = 16.26, $p < 0.001$, Bonferroni corrected) and DFC ($t$ = 8.16, $p < 0.001$, Bonferroni corrected) but not the V1C ($t$ = −1.88, $p$ = 0.0599). Effect sizes were greatest in the STC (Cohen's d = 0.42) and DFC (Cohen's d = 0.21), with minimal effects in the V1C (Cohen's d = 0.05). Differentially expressed genes were identified at false discovery rate (FDR) = 0.01 (122 in the STC, 92 in the DFC, and 118 in the V1C; Figure S40), with differences unrelated to major cell type ratios (Figure S41). These findings suggest a potential association between gene expression differences and connectivity divergence between species.

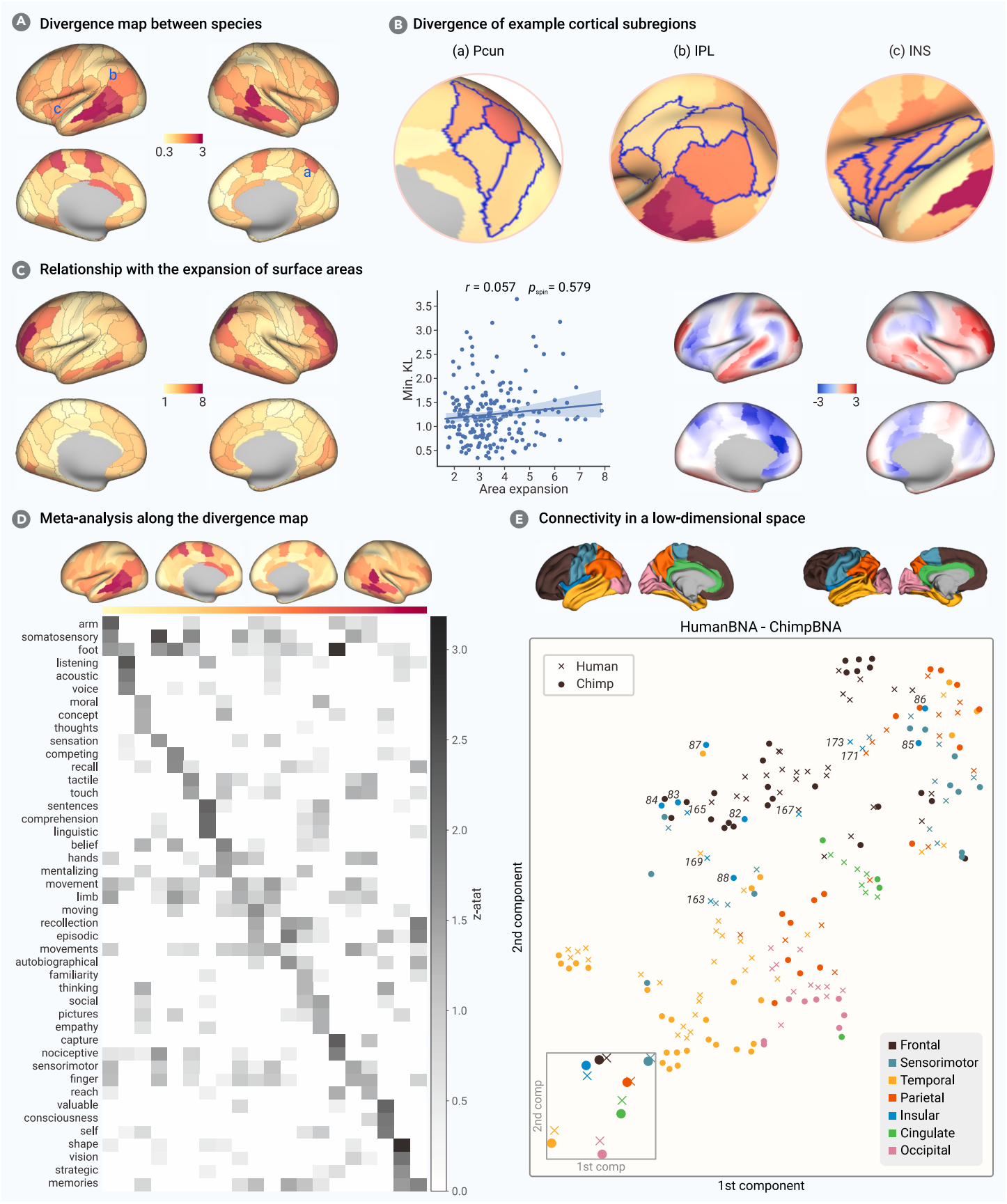


**Figure 3. Connectivity divergence between species** (A) Connectivity blueprints were used to calculate the KL divergence between species to quantify the dissimilarity of their connectivity profiles. (B) Connectivity divergence of several example regions of interest (ROIs). (C) The connectivity divergence map showed weak correlation with the cortical expansion map between chimpanzees and humans ($r = 0.057$, $p_{spin} = 0.579$). (D) The divergence map was used for functional decoding. (E) Subregions of chimpanzees and humans were projected into a low-dimensional space based on their connectivity profile.

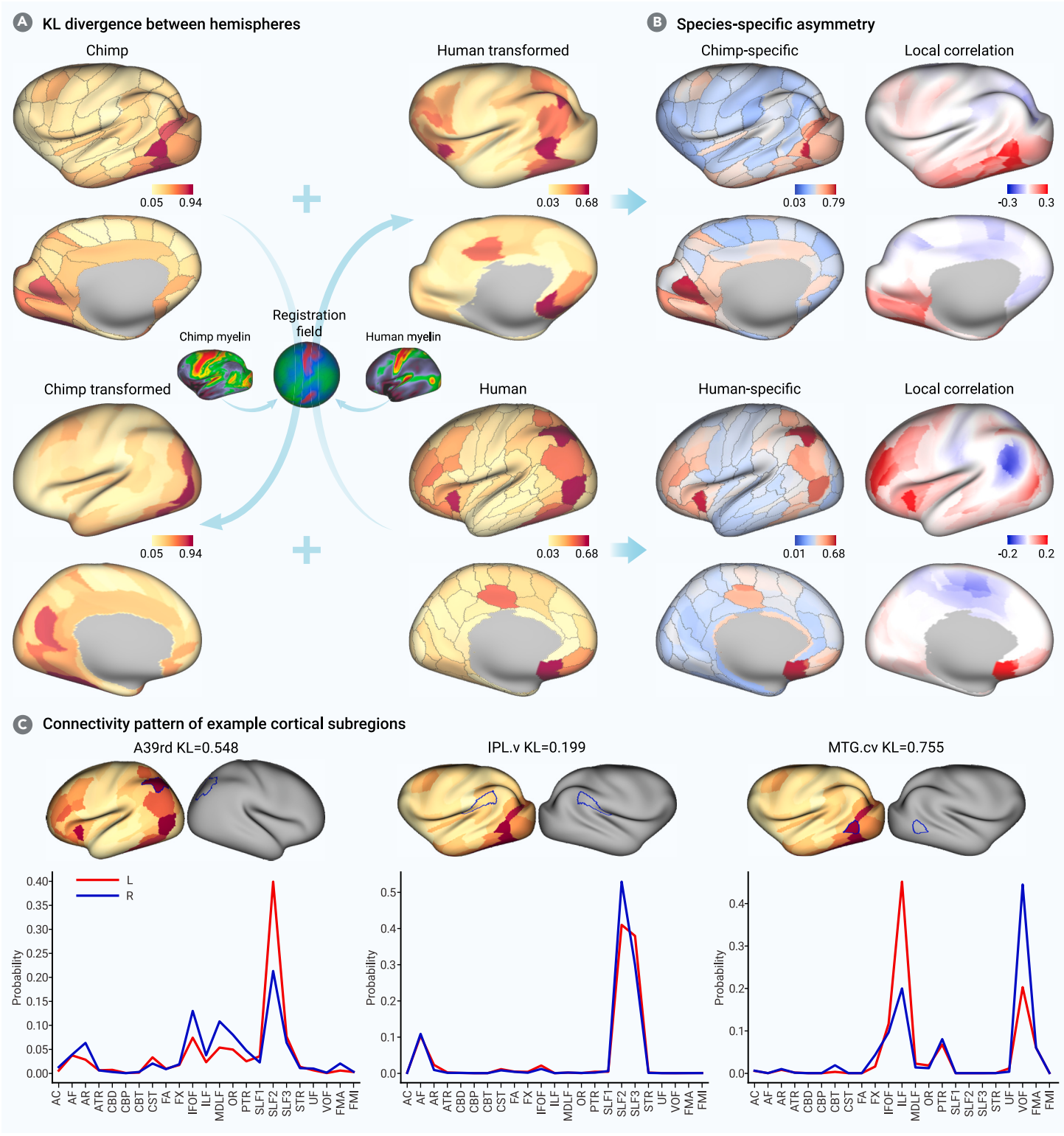


**Figure 4. Species-specific whole-brain level connectional lateralization** (A) Connectivity blueprints were used to calculate the KL divergence between homotopic subregions across hemispheres. The divergence maps of connectional lateralization of chimpanzees and humans were aligned and compared. (B) Species-specific asymmetric connectivity patterns and the weighted local correlation with the connectivity divergence map. (C) Connection probability of tracts for several example ROIs.

## DISCUSSION

Atlases are essential for investigating brain structure and function, providing standardized maps to facilitate comparisons across studies.[62] Developing uniform brain atlases across species enhances comparative research and provides crucial insights into human brain evolution.[63,64] However, mapping nonhuman primate brains remains incomplete, with existing atlases constructed using inconsistent modalities and scales, hindering the translation of results across species.[35] Existing chimpanzee brain atlases, such as Bailey's early histology-based atlas from the 1950s[25,40,41] and the more recent macroanatomical Davi130,[13] lack fine-grained parcellation and connectivity information. To address this gap, we developed the ChimpBNA based on anatomical connectivity profiles. ChimpBNA provides robust and biologically plausible subregions, confirming known cytoarchitectural boundaries and identifying novel subdivisions,[37,65] refining our understanding of chimpanzee brain organization and enabling comparative neuroanatomy.

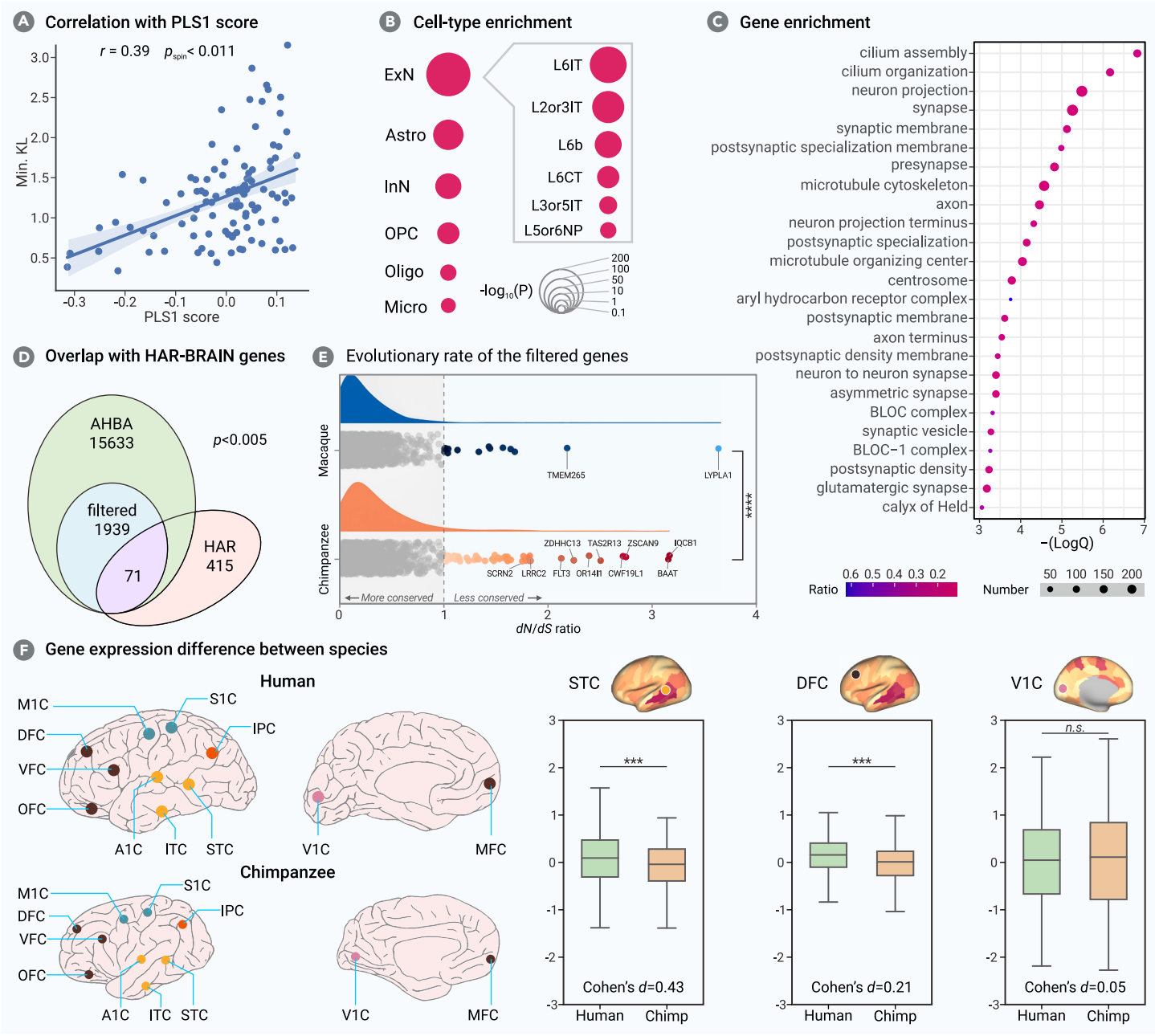


**Figure 5. Gene association with connectivity divergence between species** (A) The divergence map shows a significant correlation with the PLS1 score of genes from the AHBA dataset ($r = 0.39$, $p_{spin} < 0.011$). (B) Cell type enrichment analysis of genes with weights ($|Z| > 3$) in PLSR. (C) These genes were enriched in neuronal projection and synapse formation. (D) 71 genes overlapped with HAR-BRAIN genes ($p < 0.005$). (E) 56 genes had a $dN/dS$ ratio >1, compared to only 14 genes in macaques (Welch's t test $p < 0.0001$). (F) Differential analysis of gene expressions using the PsychENCODE database (STC: $t = 16.26$, $p < 0.001$; DFC: $t = 8.16$, $p < 0.001$; V1C: $t = -1.88$, $p = 0.599$). ***$p < 0.001$.

Understanding how brains evolve requires detailed comparisons of anatomical and functional characteristics across species.[66] While previous work has focused on cortical expansion and reorganization,[14] examining connectivity patterns—especially differences in wiring between homologous white matter tracts rather than species-specific tracts—quantitatively identifies both common principles and unique specializations throughout evolution.[45]

This study presented a connectivity divergence map highlighting cortical regions with significant connectivity differences between humans and chimpanzees, which were associated with higher-order functions in humans. However, these conclusions are limited by the lack of chimpanzee-specific cognitive data and other anatomical and physiological features that were not captured by our analysis. These limitations aside, the overall results point to divergences in neuroanatomy that may underlie species-specific cognitive and motor specializations.[67] For instance, in the Pcun—a heterogeneous region involved in complex cognition—the anterior (A5m) and middle (A7m) subregions, associated with sensorimotor and cognitive processes, showed greater divergence than the posterior subregion (dmPOS), which supports visual processing.[68] These differences might reflect humans' advanced cognitive abilities compared to chimpanzees' superior motor adaptability.[69] Similarly, regions associated with tool use, such as the IFG and rostroventral IPL (A40rv),[51,70] exhibited marked divergence. Although nonhuman primates share many tool-using capabilities, humans uniquely exhibit greater manual dexterity and conceptual knowledge of tools.[51] The temporal lobe also revealed significant divergence in connectivity patterns, even though its cortical expansion is less pronounced than the frontal lobe.[24,71–74] The arcuate fasciculus, a tract central to language processing, extends further anteriorly and inferiorly in the human temporal lobe, supporting advanced linguistic functions like speech and comprehension.[18,44]

The study also sheds light on hemispheric asymmetries in brain connectivity, a feature shared by humans and nonhuman primates.[33,48] Chimpanzees exhibited asymmetry in regions associated with auditory perception, action observation, and language-related processing, such as the IPL, MFG, and temporal cortex, often involving the SLF2.[33,75,76] In humans, these asymmetries were more

pronounced in regions supporting empathy, planning, and abstract reasoning.[77–79] Although chimpanzees have been reported to exhibit each of these abilities, the available evidence suggests that their aptitudes in these domains of function are more limited compared to humans.[80] Moreover, caution should be exercised when inferring the direction of evolutionary changes in these species-specific patterns due to limited information about the brain connectivity of the last common ancestor.

Gene expression association analysis revealed that genes linked to connectivity divergence play critical roles in neuronal projection, synaptic function, and axonal processes, highlighting their contributions to macroscale brain connections.[30,81] Many of these genes show signatures of positive selection in the chimpanzee-human clade and overlap with HAR-BRAIN genes, which are enriched in human-specific adaptations related to brain development and connectivity.[14,82] This could be explained by a more recent common ancestor between chimpanzees with humans and shared genetic adaptations and positive selection events, especially those related to hominoid traits,[83,84] which was further confirmed by our finding that there was no enrichment with human-evolved elements in more recent evolutionary diversification across *Homo* species.

Technical and methodological limitations pertinent to interpretation of our results must be acknowledged. The first concern is the false positives produced by tractography.[85] Despite this, diffusion MRI tractography remains irreplaceable for *in vivo* and non-invasive investigations of brain organization in humans and nonhuman primates.[86] Together with *ex vivo* neuroanatomical data, joint analysis may mitigate these technical issues and offer even deeper insights.[28,87] Second, differences in brain size between species could lead to more acute tract curvatures in smaller brains, and the relatively low resolution of chimpanzee diffusion images limits the ability to map smaller subcortical nuclei and the cerebellum. These regions deserve greater attention in future studies.[88,89] Finally, parcellation reliability also poses challenges, as macroanatomical boundaries may not fully align with cortical differentiation defined by connectivity profiles.[37] Future work should quantitatively compare ChimpBNA with microstructural parcellations to improve the robustness of these boundaries.

## CONCLUSION

ChimpBNA represents a significant advance in comparative neuroscience, providing a detailed map of chimpanzee brain organization and enabling more precise comparisons with humans. Future work should focus on establishing even more accurate homology mapping across species, further enhancing the utility of cross-species atlases in understanding brain evolution.

## MATERIALS AND METHODS

The schematic of the experimental design is depicted in Figure 1. We first developed the atlas of the chimpanzee brain using a connectivity-based parcellation framework, i.e., the ChimpBNA (Figure 1A).[37] We then reconstructed homologous white matter tracts and built connectivity blueprints for humans and chimpanzees and investigated cross-species connectivity divergence at the subregion level (Figure 1B).[44,45] Next, we examined species-specific asymmetry of connectivity patterns in each species (Figure 1C).[18] Finally, we identified the genes and their expression patterns associated with connectivity divergence between species (Figure 1D). Further details regarding the methods employed in this study can be found in the supplemental information.

Human participants recruitment procedures and informed consent forms were approved by the Washington University institutional review board. Chimpanzee recruitment procedures followed protocols approved by ENPRC and the Emory University Institutional Animal Care and Use Committee (IACUC, approval no. YER-2001206). All data were obtained before the 2015 implementation of U.S. Fish and Wildlife Service and National Institutes of Health regulations governing research with chimpanzees. All chimpanzee scans were completed by the end of 2012; no new data were acquired for this study.

## DATA AND CODE AVAILABILITY

The surface and volumetric representation files of the ChimpBNA and source data supporting all figures are available at the GitHub repo (https://github.com/FANLabCASIA/ChimpBNA). The ChimpBNA is also accessible via a web viewer (https://molicaca.github.io/atlas/chimp_atlas.html). The chimpanzee data are available from the National Chimpanzee Brain Resource (http://www.chimpanzeebrain.org/). The human data are available from the Human Connectome Project (https://db.humanconnectome.org/). The human gene expression data are available from the Allen Brain Atlas (https://human.brain-map.org/static/download). The single-nucleus RNA sequencing data from the human adults are available at https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE207334. The gene expression data for humans and chimpanzees are available at BioMart (https://www.ensembl.org/info/data/biomart/index.html) and PsychENCODE dataset (https://evolution.psyencode.org/). The cell type data are available at http://www.brainrnaseq.org/.

The HCP-Pipeline is available at https://github.com/Washington-University/HCPpipelines, and the NHP-HCP-Pipeline is available at https://github.com/Washington-University/NHPPipelines. The preprocessing was conducted by FreeSurfer v.6.0 (http://surfer.nmr.mgh.harvard.edu/) and FSL v.6.0.5 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki). The gene processing pipeline is available (abagen, https://github.com/rmarkello/abagen), and gene enrichment analysis was conducted at https://toppgene.cchmc.org/. The cell type enrichment analysis was conducted at http://www.cellgo.world. The brain maps were presented using Workbench v.1.5.0 (https://www.humanconnectome.org/software/connectome-workbench). The tracts were visualized using ITK-SNAP 4.0.1 (http://www.itksnap.org/) and Paraview 5.11.0 (https://www.paraview.org/).

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## AUTHOR CONTRIBUTIONS

Yufan Wang, L.C., C.C., and L.F. conceived and designed the research; Yufan Wang, L.C., and D.L. performed the experiments; C.W. designed the web viewer; Y.L., Yaping Wang, C.G., H.W., C.T.E., W.V., W.D.H., C.C.S., T.J., C.C., and L.F. contributed to the interpretation of the results; Yufan Wang wrote the paper; and Yufan Wang, L.C., W.V., W.D.H., C.C.S., C.C., and L.F. edited and reviewed the paper. All authors contributed to and approved the manuscript.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## SUPPLEMENTAL INFORMATION

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