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<https://doi.org/10.1523/JNEUROSCI.0439-26.2026>

Received: 11 March 2026

Revised: 11 June 2026

Accepted: 8 July 2026

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This Early Release article has been peer reviewed and accepted, but has not been through the composition and copyediting processes. The final version may differ slightly in style or formatting and will contain links to any extended data.

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Title Page

Evolutionary Reorganization of the Self-Processing Network Across Primates

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Abstract

Understanding the evolutionary origins of the structural substrates underlying self-processing is central to elucidating the neural basis of human cognition. Although self-related behaviors differ markedly across primates, the extent to which the underlying neural architecture is conserved or reorganized remains unclear. Here, we investigated shared and species-specific characteristics of the self-processing network (SPN) across humans ($n = 46$, 19 males), chimpanzees ($n = 46$, 18 males), and macaques ($n = 43$, 22 males) using a comparative connectomic framework. We mapped a meta-analysis-derived human SPN onto nonhuman primates within a shared homologous connectivity space defined by conserved white-matter tracts. We compared local microstructural properties and gene expression signatures between humans and macaques, and further included chimpanzees as an intermediate evolutionary reference for large-scale structural connectivity. SPN regions exhibited highly similar myelin-sensitive contrast profiles in humans and macaques, accompanied by shared expression patterns of related genes, which were also enriched for human-accelerated brain genes. Large-scale connectivity revealed pronounced species differences, with chimpanzees occupying an intermediate position between humans and macaques. Importantly, evolutionary modifications of the SPN were domain-specific: Interoceptive-processing subnetworks showed greater similarity between macaques and chimpanzees; Exteroceptive-processing subnetworks showed closer correspondence between chimpanzees and humans; and Mental-self-processing subnetworks exhibited greater interspecies differentiation. Moreover, these changes were accompanied by a progressive reorganization of network hubs from insular regions in macaques to cingulate regions in humans. Together, these findings reveal a scale-dependent evolutionary organization of SPN structural substrates and provide a framework for understanding the conservation and reorganization of self-processing architectures across primates.

Keywords: self-processing; cross-species comparison; connectomics

Significance Statement

Self is a central construct in cognition, yet its neural evolution remains poorly understood. By comparing local biological features between humans and macaques and using chimpanzees as an intermediate reference for structural connectivity, this study reveals a scale-dependent dissociation in the reorganization of self-processing network (SPN) structural substrates across primates. Local microstructural and transcriptional features of the SPN are highly conserved between humans and macaques, whereas large-scale network architecture is selectively and nonuniformly reorganized. This reorganization follows domain-specific patterns that diverge from whole-brain evolutionary trends and is accompanied by systematic shifts in network hub organization. These findings provide a framework for understanding how neural architectures associated with human self-processing may have emerged from conserved primate brain systems.

Introduction

The self is central to cognition, enabling organisms to integrate internal bodily states, external sensory information, and social signals into a coherent representation of the individual (Qin & Northoff, 2011; Davey et al., 2019; Wolff et al., 2019; Qin et al., 2020; Keskin et al., 2025). Self-processing comprises hierarchically organized functions: interoceptive processing relates to internal bodily states; exteroceptive processing supports multisensory integration between the body and environment; and mental-self processing underlies abstract, reflective representations of the self (Qin et al., 2020). Although disruptions of self-processing are implicated in neurological and psychiatric disorders (Damiani et al., 2019; Northoff et al., 2021; Scalabrini et al., 2024), its evolutionary neural substrates remain unclear. Addressing this question is important for understanding human cognition and establishing non-human primate (NHP) models, particularly macaques, for mechanistic investigation of self-processing and its pathological changes (Fang et al., 2019; Miyamoto, 2024; Lei, 2023).

NHP studies have examined self-processing mainly through self-awareness-related behaviors. Chimpanzees exhibit self-agency (Kaneko & Tomonaga, 2011), pass the mirror self-recognition (MSR) test (Gallup, 1970), and recognize themselves in distorted mirrors (Kitchen et al., 1996), whereas macaques generally do not show spontaneous mirror self-recognition (Anderson & Gallup, 2015; Gallup, 1977; Suddendorf & Collier-Baker, 2009), although trained individuals can pass the MSR test after associating visual and somatosensory feedback (Chang et al., 2015, 2017). Yet chimpanzee studies are ethically constrained, and macaque self-related capacities remain debated despite their experimental tractability. These limitations highlight the need for neurobiological features supporting cross-species comparison in their self-processing capacities, independent of overt behavioral performance.

Local biological properties provide one comparative route. Cortical myelination has been widely used to assess microstructural similarity and infer putative homologies between cortical regions across primate species (Gao et al., 2020; Glasser & Essen, 2011), while regional gene expression profiles capture shared developmental and transcriptional constraints (Morgan et al., 2019; Wang et al., 2025; Xia et al., 2022). These features tend to show conserved cross-species correspondences (Li et al., 2025; Wu et al., 2025), but may miss species-specific reorganization in higher-order association cortices. Connectomic architecture is more sensitive to species-specific variation in large-scale organization and is therefore essential for characterizing evolutionary trajectories of self-processing-related brain regions (Passingham et al., 2002; Thiebaut de Schotten & Forkel, 2022).

Structural connectivity is suited to this aim because anatomical wiring constrains information flow, shapes functional specialization, and supports integration across distributed regions (Ayer & Amunts, 2022; Thiebaut de Schotten & Forkel, 2022), while also supporting homologous mapping. Forty-two homologous white-matter tracts have been established in humans, chimpanzees, and macaques, and each cortical region's connectivity "fingerprint" with these tracts allows the detection of homologous areas across species (Bryant et al., 2020; Warrington et al., 2020), as validated for well-established homologous regions, such as MT (Mars et al., 2018). Thus, structural connectivity fingerprints provide a behavior-independent method for mapping self-related regions in NHPs (Mars et al., 2018). Because evolutionary modifications of the connectome architecture have been central to the emergence of human cognition (Changeux et al., 2021), structural connectivity provides a critical entry point for studying the reorganization of the self-processing network (SPN) and its potential relevance to self-related behavioral capacities.

In the present study, we adopted a meta-analysis-derived human framework that categorizes self-processing into Interoceptive-processing, Exteroceptive-processing, and Mental-self-processing domains and associated brain regions (Qin et al., 2020). We constructed a shared homologous connectivity space based on conserved white-matter tracts and mapped self-processing regions from humans onto macaques (Mars et al., 2018). Then, we compared local microstructural and transcriptional features in humans and macaques, with chimpanzees included as an intermediate reference for network-level properties. Based on prior evidence that microstructural and transcriptional features are relatively conserved across primate species (Charvet et al., 2022), whereas large-scale connectivity is more sensitive to evolutionary reorganization, we expected greater cross-species similarity at the local level but more pronounced dissimilarity in large-scale network organization, particularly within the Mental-self-processing subnetwork.

Materials and Methods

Data Acquisition and Preprocessing

Human Data

We randomly selected 46 participants (age $\pm$ SD: 30.07 $\pm$ 3.72 years; 19 males) (to match the sample size of chimpanzees data; see below) from the Human Connectome Project (HCP) S1200 release. Detailed acquisition parameters have been reported previously (Van Essen et al., 2013). Briefly, structural images were acquired on a Siemens 3T Skyra scanner with a 32-channel head coil. T1-weighted images were obtained using a 3D magnetization-prepared rapid gradient echo (MPRAGE) sequence (repetition time [TR] = 2400 ms, echo time [TE] = 2.14 ms, flip angle [FA] = 8°, isotropic resolution = 0.7 mm). T2-weighted images were collected using a 3D T2-weighted Sampling Perfection with Application-optimized Contrasts using different flip-angle Evolutions (SPACE) sequence with identical geometry (TR = 3200 ms, TE = 565 ms, variable FA, isotropic resolution = 0.7 mm). Diffusion-weighted images (DWI) were acquired using single-shot, multiband spin-echo echo-planar (SE-EPI) imaging (TR = 5520 ms, TE = 89.5 ms, isotropic resolution = 1.25 mm, b = 1000, 2000, and 3000 s/mm², 96 directions). To correct susceptibility-induced distortions, additional DWI scans were acquired with reversed phase-encoding directions.

Chimpanzee Data

Imaging data from 46 adult chimpanzees (Pan troglodytes, 18 males) were obtained from the National Chimpanzee Brain Resource. Data acquisition was conducted at the Emory National Primate Research Center using a 3T MRI scanner, following previously published protocols. Animals were anesthetized with propofol (10 mg/kg/h) during scanning (Chen et al., 2013). All procedures were approved by the Emory University Institutional Animal Care and Use Committee. All scans were collected before 2012, prior to the implementation of U.S. regulations restricting chimpanzee research, and no new data were acquired for this study.

T1-weighted images were acquired using a 3D MPRAGE sequence (TR = 2600 ms, TE = 3.06 ms, FA = 8°, resolution = 0.7 × 0.7 × 1.0 mm³). DWI scans were collected using a single-shot SE-EPI imaging sequence with 60 diffusion directions (TR = 5900 ms, TE = 86 ms, isotropic resolution = 1.8 mm, b = 1000s/mm², 60 directions). Additional DWI scans were acquired with reversed phase-encoding directions.

Macaque Data

A total of 43 rhesus macaques (*Macaca mulatta*, 22 males) were included. All experimental procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Care and Use Committees of the Kunming Institute of Zoology (KIZ) and the Institute of Biophysics (IBP), Chinese Academy of Sciences.

Animals were premedicated with atropine (0.05 mg/kg, intramuscular) and ketamine (10 mg/kg, intramuscular). Anesthesia was maintained with continuous intravenous propofol (15 mg/kg/h). End-tidal CO₂ and respiratory rate were continuously monitored using MRI-compatible equipment.

Thirty macaques were scanned at KIZ using a United Imaging uMR 790 3T scanner with a 12-channel head coil. High-resolution T1-weighted images were acquired twice and averaged (fast spoiled gradient echo [FSPGR] sequence; TR = 13.01 ms, TE = 5.6 ms, FA = 8°, isotropic resolution = 0.5 mm). T2-weighted images were obtained using a fast spin-echo sequence (TR = 3400 ms, TE = 396.48 ms, FA = 59°, isotropic resolution = 0.5 mm). Diffusion-weighted images were acquired twice (TR = 7740 ms, TE = 90 ms, isotropic resolution = 1.0 mm, b = 1000 and 2000 s/mm², 64 directions), along with reversed phase-encoding scans for distortion correction.

The remaining 13 macaques were scanned at IBP using a Siemens 3T Prisma scanner with a custom four-element surface coil. T1-weighted images were acquired using an MPRAGE sequence (TR = 2200 ms, TE = 2.84 ms, FA = 8°; isotropic resolution = 0.5 mm), and T2-weighted images using a SPACE sequence (TR = 3200 ms, TE = 392 ms, FA = 120°, isotropic resolution = 1.0 mm). Diffusion-weighted images were acquired (TR = 6720 ms, TE = 81 ms, isotropic resolution = 1.2 mm, b = 1000 and 2000 s/mm², 64 directions). To correct susceptibility-induced distortions, additional DWI scans were acquired with reversed phase-encoding directions.

Image Preprocessing

Diffusion data were processed using parallel preprocessing and tractography workflows, and all subsequent cross-species comparisons used the same connectivity construction and statistical procedures.

Human structural and diffusion data were processed using the HCP minimal preprocessing pipelines (<https://github.com/Washington-University/HCPpipelines>). Structural

preprocessing included bias-field correction, tissue segmentation, cortical surface reconstruction with FreeSurfer (version 5.3-HCP), registration to Montreal Neurological Institute (MNI) space. Diffusion preprocessing included denoising, correction for susceptibility distortions and eddy currents, and alignment to structural images (Glasser et al., 2013).

Chimpanzee and macaque data were processed using the HCP-NHP pipelines (<https://github.com/Washington-University/NHPPipelines>), which closely parallel the human workflow. Chimpanzee data were registered to the Yerkes29 chimpanzee template (Donahue et al., 2018), and macaque data to the Yerkes19 macaque template (Donahue et al., 2018; Van Essen et al., 2012). Diffusion data preprocessing followed procedures analogous to those used for human data.

We derived the T1w/T2w ratio as a myelin-sensitive MRI contrast following established procedures (Glasser & Essen, 2011; Sui et al., 2022). The T1w/T2w ratio was treated as a proxy for cortical myeloarchitecture, rather than a direct quantitative measure of intracortical myelin content. Because the T1w/T2w-derived contrast can be affected by transmit-field (B1+) inhomogeneity and residual intensity biases in the underlying T1w and T2w images, structural images were processed with bias-field correction within the HCP/HCP-NHP preprocessing pipelines. In the PreFreeSurfer stage, a bias-field estimate was derived from the square root of the product of the T1w and T2w images ($\sqrt{T1w \times T2w}$), which reduces tissue contrast while preserving spatially smooth intensity variations that can be used for bias-field estimation. In the PostFreeSurfer stage, residual bias correction was further applied to the T1w/T2w-derived myelin-sensitive contrast maps by estimating low-spatial-frequency deviations relative to a group-average reference and reducing remaining large-scale intensity variations, including potential transmit-field-related effects. These procedures were used to improve the stability of regional myelin-sensitive contrast profiles, although residual bias cannot be fully excluded. Chimpanzees were excluded from the myelin-sensitive contrast analysis due to the lack of available T2-weighted images.

Generation of Anatomical Connectivity Blueprints

Diffusion tensors were fitted using FMRIB's Diffusion Toolbox (FDT) in FSL. Voxel-wise fiber orientation modeling was performed with BedpostX, allowing up to three fiber orientations per voxel (Behrens et al., 2007). Individual cortical surface models (~32,000 vertices per hemisphere) generated by the HCP pipeline based on FreeSurfer's surface reconstruction were used for all analyses.

Using established tractography protocols (Bryant et al., 2020; Warrington et al., 2020), we applied XTRACT to identify 42 homologous white-matter tracts across humans, chimpanzees, and macaques. Probabilistic tractography was performed with probtrackx2, and species-specific connectivity blueprints were then generated using xtract_blueprint (Fig. 1A). These blueprints were represented as vertex-by-tract matrices, in which each entry quantified the probability that a given cortical vertex connected to a specific tract (Behrens et al., 2007; Mars et al., 2018).

Definition of the Self-Processing Network

Human

Coordinates defining the three-level human self-processing network (Interoceptive-processing, Exteroceptive-processing, and Mental-self-processing) were obtained from prior studies (Qin et al., 2020) and projected onto the cortical surface. For each coordinate, the nearest surface vertex was identified and expanded into a ROI using a 12-mm surface dilation.

Because subsequent analyses focused on cortical surfaces, subcortical regions (i.e., thalamic areas identified in both the Interoceptive-processing and Mental-self-processing subnetworks) reported in the original studies were excluded. A midline cingulate region without specified laterality was represented bilaterally. The three subnetworks were then merged (Table S1), and overlapping ROIs were combined, yielding a total of 31 cortical ROIs. Each ROI was labeled according to its location in the HCP multimodal parcellation (HCP-MMP) atlas (Glasser et al., 2016).

Chimpanzees and Macaques

To identify homologous self-processing regions in chimpanzees and macaques, we quantified interspecies dissimilarity using symmetric Kullback-Leibler (KL) divergence between connectivity blueprints (Mars et al., 2018). Let H denote the human connectivity blueprint and C denote the NHP connectivity blueprint. Here, H_{ik} represents the probability that the cortical vertex i_{th} in the human brain is connected to tract k , and C_{jk} represents the probability that the cortical vertex j_{th} in the NHP brain is connected to the tract k . The dissimilarity (D_{ij}) between human vertex i_{th} and NHP vertex j_{th} is then defined as:

$$D_{ij} = \sum_k H_{ik} \log_2 \frac{H_{ik}}{C_{jk}} + \sum_k C_{jk} \log_2 \frac{C_{jk}}{H_{ik}}$$

For each of the 31 ROIs in the human SPN, we computed an average connectivity fingerprint by averaging the connectivity blueprints of all vertices within that ROI (i). This regional fingerprint was then compared with the connectivity fingerprint of every vertex j on the cortical surface of the NHP (J). The vertex exhibiting the minimal KL divergence was selected as the best-matched homologous location (j^*):

$$j^* = \arg \min_{j \in J} D_{ij}$$

The selected vertex (j^*) served as the center of the corresponding ROI in the NHP brain and was expanded using surface-based dilation. To account for interspecies differences in cortical surface area, dilation distances were set to 6 mm for chimpanzees and 4 mm for macaques. This procedure yielded species-specific SPNs for both chimpanzees and macaques, each comprising 31 cortical ROIs corresponding to those defined in humans (Fig. 1B).

We assessed the reliability of our method following previous studies (Mars et al., 2018). Specifically, the dissimilarity matrix derived from KL divergence values was used to transfer a cortical map from one species to another via distance-weighted interpolation. Using this approach, a predicted macaque myelin-sensitive contrast map was generated based on the human myelin-sensitive contrast map. Method reliability was assessed by computing Spearman's rank correlation between the predicted and empirically measured macaque myelin-sensitive contrast maps. To ensure that the observed correlation was not driven by spatial autocorrelation, 10,000 surrogate maps were generated using BrainSMASH, and the empirical correlation was evaluated against this null distribution (Burt et al., 2020).

Myelin-Sensitive Contrast Analysis

Based on the T1w/T2w-derived contrast maps and the predefined SPN ROIs in humans and macaques, we extracted mean myelin-sensitive contrast values for each SPN region in each participant or animal. Group-averaged myelin-sensitive contrast maps and regional profiles were generated by averaging data across 46 human participants and 43 macaques, respectively. Cross-species spatial correspondence of SPN myelin-sensitive contrast profiles was assessed using Spearman's rank correlation across the 31 corresponding SPN regions. To compare myelin-sensitive contrast between SPN and non-SPN cortex, we computed mean contrast values within SPN and non-SPN cortical regions for each participant or animal.

To determine whether the cross-species correspondence observed in SPN myelin-sensitive contrast profiles reflected a network-specific property rather than a general feature

of homologous primate cortex, we performed an additional specificity analysis. An independently defined baseline set of 27 homologous cortical regions, compiled from previous studies, was used as a reference set (Ruan et al., 2025). For both the SPN and the homologous baseline set, we computed the group-averaged macaque myelin-sensitive contrast profile and correlated it with the corresponding profile of each human participant using Spearman's rank correlation. This procedure yielded subject-level distributions of human-macaque correlation coefficients for the SPN and baseline sets.

Gene Expression Analyses

Human Gene Expression Data

Regional gene expression data were obtained from six postmortem brains (1 female, ages 24.0-57.0, 42.50 ± 13.38) in the AHBA (<https://human.brain-map.org>) (Hawrylycz et al., 2012). Data were processed using the abagen toolbox (version 0.1.3; <https://github.com/rmarkello/abagen>) and mapped to the 31 self-processing ROIs in MNI space (Arnatkevičiūtė et al., 2019; Markello et al., 2021). Probes were reannotated, filtered for signal quality, and collapsed to gene-level expression values, yielding a $31 \times 15,633$ region-by-gene matrix.

Identification of Relevant Genes

We applied PLSR to examine the relationship between regional gene expression and cortical microstructure (T1w/T2w-derived myelin-sensitive contrast) within the SPN in humans. Specifically, PLSR was used to identify latent components that maximally covary with the SPN myelin-sensitive contrast map, thereby capturing optimally weighted linear combinations of gene expression patterns associated with regional variation in myelin-sensitive contrast (Fig. 3A). The statistical significance of PLS components was assessed using permutation testing with 10,000 permutations. The first PLS component (PLS1) was further evaluated using 10,000 bootstrap resamples to estimate the standard error of each gene's weight. For each gene, a Z score was calculated as the ratio of its PLS weight to its bootstrap-derived standard error. Genes with Z scores greater than 3 or less than -3 were retained for subsequent analyses. To further validate the biological relevance of the selected genes, we tested whether they were significantly enriched for human-accelerated brain-related genes (HAR-BRAIN genes) using a hypergeometric test (Wei et al., 2019).

To further assess the robustness of PLS-derived gene weights, we performed a split-half validation analysis. In each iteration, the 31 SPN regions were randomly divided into two subsets, and PLSR was fitted independently in each subset using the same regional myelin-

sensitive contrast values and gene expression matrix. Spearman correlations were then computed between the gene-weight vectors derived from the two halves across all genes included in the PLSR model. To assess consistency with the full model, we also correlated the gene-weight vector from each half with that obtained from the full dataset. This procedure was repeated 10,000 times, and the resulting correlation distributions were summarized.

Macaque Gene Expression Data

Macaque gene expression data were obtained from large-scale single-nucleus RNA sequencing and spatial transcriptomic analyses across 143 cortical regions defined on the D99 cortical atlas (Chen et al., 2023). Thus, the resulting dataset consists of a $143 \times 15,929$ region-by-gene expression matrix. Since the ROIs of the macaque SPN do not directly align with the D99 parcellation, an additional mapping procedure was performed to extract gene expression data relevant to self-processing, following the approach used in humans (Markello et al., 2021). Specifically, for each ROI, we identified all overlapping regions in the D99 atlas. We then assigned weights to the overlapping D99 regions based on the number of shared surface vertices, which served as an approximation of their relative areal contribution to the ROI. Gene expression profiles from the overlapping D99 regions were combined using these weights to compute a weighted average expression vector for each self-processing ROI. This procedure resulted in a gene expression matrix of 31 self-processing ROIs by 15,929 genes.

Cross-Species Gene Expression Similarity

From the subset of genes overlapping with HARs identified in the preceding PLSR analysis, we further restricted the gene set to human-macaque orthologs using Ensembl BioMart (<https://useast.ensembl.org/info/data/biomart/index.html>) (Durinck et al., 2005). Based on the sign of their PLS-derived Z scores ($Z > 3$ or $Z < -3$), genes were divided into positively weighted and negatively weighted groups, corresponding to positive and negative associations with SPN myelin-sensitive contrast, respectively. These two gene sets were analyzed separately in subsequent analyses. For each species, we first computed the mean expression level of each gene set across the self-processing ROIs. We then assessed cross-species similarity by performing Spearman's rank correlation analyses between human and macaque average expression values across the 31 corresponding brain regions. This approach specifically evaluates the similarity of spatial expression profiles across SPN regions between the two species.

Structural Connectome Construction

To characterize the SPN from a high-dimensional structural connectivity perspective and enable cross-species comparisons, probabilistic fiber tractography was performed on preprocessed diffusion-weighted imaging data from humans, chimpanzees, and macaques using MRtrix3 (version 3.0.3) (<https://www.mrtrix.org/>). Tractography combined a probabilistic streamline algorithm (Behrens et al., 2003; Parker & Alexander, 2005) with constrained spherical deconvolution (CSD) (Tournier et al., 2007) to model multiple fiber orientations within each voxel. Whole-brain tractography was achieved by random seeding throughout the brain.

Tracking parameters were identical across species and included a default step size equal to 0.5 times the voxel size, a maximum angular deviation of 45° between successive steps, and exclusion of streamlines shorter than twice the voxel size. For each human subject, 20 million streamlines were generated, whereas 10 million streamlines were generated for each chimpanzee and macaque subject (Ruan et al., 2025). Tractograms were reconstructed for all individuals across species. To reduce tractography-related biases and improve quantitative interpretability, SIFT2 (Smith et al., 2015) was applied, assigning a biologically meaningful cross-sectional area multiplier to each streamline across all three species. Crucially, although the total number of generated streamlines differed across species and was selected to provide adequate sampling relative to brain size, SIFT2 reduced the dependence of connection weights on raw streamline counts by optimizing streamline-specific weights to better match the underlying Apparent Fibre Density (AFD) (R. E. Smith et al., 2022). In addition, voxel-volume scaling within the SIFT2 framework helps account for differences in spatial resolution and improves the quantitative comparability of tractography-derived connection weights across datasets (Smith et al., 2022).

After constructing self-processing ROIs on the cortical surface, the `wb_command` label-to-volume-mapping tool was used to convert the surface-based ROIs into volumetric representations. These volumetric self-processing ROIs were then combined with whole-brain tractograms to construct ROI-ROI structural connectomes using the `tck2connectome` tool. This procedure yielded 31×31 weighted connectivity matrices, with each element representing the structural connection strength between a pair of self-processing ROIs (Fig. 4A). To mitigate the influence of spurious connections inherent to dense probabilistic tractography-derived networks, we applied a consistency-based thresholding procedure. In the main analysis, connections were retained if they were present in at least 75% of subjects within each species (Tooley et al., 2025). To assess sensitivity to this choice, we repeated the main ROI-ROI analyses across consistency thresholds ranging from 50% to 90% in 5% increments. At each threshold, the same consistency criterion was applied across species,

and the resulting ROI-ROI connectomes were entered into the statistical analyses as in the main analysis.

In addition to ROI-ROI connectomes, we also generated ROI-tract connectomes by averaging vertex-wise connectivity blueprint values within each ROI from the previously derived vertex-to-tract connectivity data (Fig. 4A). The ROI-ROI connectome captures structural connectivity exclusively among regions belonging to the SPN, thereby characterizing the internal organization of the SPN. In contrast, the ROI-tract connectome quantifies the relationships between SPN regions and major whole-brain fiber tracts, providing insight into how this network interfaces with broader brain regions.

Cross-Species Comparison of Structural Connectome

To examine similarities and differences in SPN connectivity patterns across species, connectivity matrices from all individuals were first vectorized, and pairwise dissimilarities between individuals were computed to construct an RDM (Fig. 4B&C). For symmetric ROI-ROI connectomes, only the lower triangular elements excluding the diagonal were included, whereas for ROI-tract connectomes, all matrix elements were vectorized. Dissimilarity between any two connectivity patterns was quantified using correlation distance, as $1 - r$, where r denotes Spearman's rank correlation coefficient. As a complementary analysis conducted directly in the original dissimilarity space, we performed PERMANOVA on the RDMs with species as the grouping factor using 10,000 permutations (Anderson, 2001). This analysis tested whether between-species dissimilarities exceeded within-species dissimilarities without relying on low-dimensional MDS projections.

Based on the resulting RDM, MDS was applied to embed individual SPN connectivity patterns into a two-dimensional space, enabling intuitive visualization of their relative relationships across species. The quality of the MDS embedding was evaluated using Kruskal's Stress-1. To assess whether the observed geometric relationships depended on the dimensionality of the embedding, we additionally repeated the MDS analysis using three-dimensional solutions and compared the resulting species organization with the two-dimensional results. Distances between species were then computed in the MDS space to characterize overall differences in SPN connectivity patterns among humans, chimpanzees, and macaques.

For statistical inference, individual-to-centroid distances were calculated in the MDS space. For each species pair, the centroid of the evolutionarily less derived species was used as a reference, and the Euclidean distance between this centroid and each individual from the

evolutionarily more derived species was computed. For example, in the human-chimpanzee comparison, distances were calculated between each human individual and the chimpanzee centroid. Analogous procedures were applied to the human-macaque and chimpanzee-macaque comparisons.

The same analytical framework was also applied to each of the three self-processing subnetworks, with analyses restricted to the regions within each subnetwork.

Graph-Theoretical Analysis

For each subject, weighted small-worldness properties of the SPN were computed from ROI-ROI connectomes using the Python implementation of the Brain Connectivity Toolbox (bctpy, <https://github.com/aestrivex/bctpy>) (Rubinov & Sporns, 2010). To control for the potential influence of network density on graph-theoretical metrics, we additionally performed a proportional thresholding analysis. For each subject, the weighted SPN connectome was thresholded across a range of network densities from 40% to 65% in 5% increments, retaining the strongest connections at each density level. This procedure generated density-matched networks in which human, chimpanzee, and macaque connectomes had the same number of edges at each threshold. The density range was determined based on the topological constraints of the SPNs. The lower bound of 40% was selected to avoid substantial network fragmentation and disconnected nodes, which can compromise the estimation of characteristic path length and small-worldness. The upper bound of 65% was set below the minimum empirical density observed across all unthresholded subject networks (66.9%), ensuring that density matching could be applied without introducing absent connections. Small-worldness was then recalculated at each density threshold and compared across species using the same statistical framework as in the main analysis.

Degree centrality and eigenvector centrality were computed for each region using the NetworkX package (<https://networkx.org/>). Nodal degree reflects a node's capacity for information communication within the network, while eigenvector centrality captures a node's influence by accounting not only for the number of its connections but also for the importance of the nodes to which it is connected (Lohmann et al., 2010; Onias et al., 2014). Both measures were normalized to the range [0, 1] and averaged to obtain a composite centrality measure C for each region. Cross-species similarity in regional importance was assessed by computing Spearman's rank correlations of C values across corresponding regions.

Unified Correlation-based Comparison of Local and Network Features

To test whether local and network-level comparisons were affected by differences in analytical representation, we conducted an additional subject-level analysis using a consistent correlation-based framework. Taking T1w/T2w as an example, we computed the Spearman correlation between the group-averaged macaque SPN microstructural profile (31 regions) and the corresponding profile of each individual human subject. Using the same procedure, we derived analogous distributions of human-macaque correlations for SPN connectivity patterns and for graph-theoretical centrality measures. Correlation coefficients were Fisher z-transformed and compared across measures using paired t-tests.

Statistical Analysis

All statistical analyses were conducted using R (version 4.4.1) and SPSS (version 26). Correlation coefficients were Fisher r-to-z transformed and then compared. Statistical tests were selected according to data distribution, with parametric tests (paired-sample t tests and analysis of variance [ANOVA]) applied when normality assumptions were met and nonparametric tests (Mann-Whitney U tests and Aligned Rank Transform ANOVA [ART-ANOVA]) applied otherwise. Results from parametric tests are presented using bar plots, whereas results from nonparametric tests are visualized using violin plots. Bonferroni correction was applied for multiple comparisons when appropriate. All correlation analyses were performed using Spearman's rank correlation. Benjamini-Hochberg FDR correction was applied to families of related correlation analyses and subnetwork-level tests where appropriate. A comprehensive summary table was provided (Table S2), specifying the statistical test, corresponding effect size metric, and multiple-comparison correction applied for each major analysis.

Results

Shared Myelin-sensitive Contrast Profiles in the SPN Across Humans and Macaques

To enable a valid cross-species comparison of the SPN, we first mapped the human SPN onto NHPs using a previously established comparative connectomics framework based on connectivity blueprints (Mars et al., 2018). In this framework, cortical regions are characterized by their connection profiles to a set of 42 homologous white-matter tracts across species, thereby providing a common anatomical reference space for cross-species cortical alignment (Fig. 1; see *Materials and Methods* for details). Using established macaque cortical atlases as anatomical references, we quantified the spatial overlap between the identified SPN regions and atlas-defined parcellations (the Cortical Hierarchy Atlas of the Rhesus Macaque [CHARM], level 5) (Jung et al., 2021). Note that the identified SPN regions showed spatial overlap with similarly labeled atlas regions (Table S1). Prior studies also provide external validation for the functional relevance of these mapped regions. For example, area 6 and area 9 have been implicated in metacognitive processing (Miyamoto, 2024), while the medial prefrontal and posterior cingulate regions are key default mode network (DMN) nodes involved in internally oriented and self-referential processes (Jenkins, 2019; Yeshurun et al., 2021) and have also been identified in both macaques and chimpanzees (Garin et al., 2022).

Furthermore, we used cortical T1w/T2w-derived myelin-sensitive contrast as an external benchmark to independently validate the reliability of this connectivity blueprint-based mapping. This contrast, estimated using the T1w/T2w ratio, is widely used in neuroimaging studies as a proxy for cortical myeloarchitecture (Glasser & Essen, 2011). Utilizing the connectivity blueprint as the reference space, we projected the group-averaged human whole-brain myelin-sensitive contrast map onto the macaque cortex based on blueprint similarity, yielding a predicted macaque myelin-sensitive contrast map (Fig. S1A, right panel). A significant correlation was observed between the predicted and empirical macaque myelin-sensitive contrast patterns ($\rho = 0.693$, $p < 0.001$; Fig. S1B), and remained significant after controlling for spatial autocorrelation using 10,000 BrainSMASH surrogates ($p < 0.001$), supporting the validity of the cross-species mapping.

Next, we extracted myelin-sensitive contrast values from SPN regions of interest (ROIs) in both humans and macaques and observed a strong correspondence in regional myelin-sensitive contrast profiles across the 31 SPN regions between the two species ($\rho = 0.773$, $p < 0.001$; Fig. 2A-C). To assess whether this correspondence exceeded a general homologous cortical baseline, we further compared it with an independently defined set of 27 homologous

cortical regions compiled from previous studies (Ruan et al., 2025). The SPN showed significantly stronger human-macaque similarity than this baseline set (baseline: $\rho = 0.628$; paired t-test: $p < 0.001$, Cohen's $d = 3.325$; Fig. S1C), suggesting that the observed SPN pattern is not fully explained by general cross-species similarity among homologous cortical regions. Consistent with previous findings in humans (Keskin et al., 2025), SPN regions in the human brain data exhibited significantly lower myelin-sensitive contrast values than non-SPN regions (Fig. 2D; paired-sample t-test, $p < 0.001$, Cohen's $d = 17.435$). Importantly, the same pattern of lower myelin-sensitive contrast values in SPN regions was also observed in macaques (Fig. 2E; Mann-Whitney U test, $p < 0.001$, Rank-biserial correlation = 1.0). Together, these results indicate that the SPN in macaques may share structural features (i.e., myelin-sensitive contrast) with that in humans.

Transcriptional Correlates of Myelin-sensitive Organization in the SPN

We next examined whether the observed similarity in myelin-sensitive contrast profiles was accompanied by shared cross-species transcriptional signatures. We analyzed gene expression associated with regional myelin-sensitive contrast within the SPN in humans using data from the Allen Human Brain Atlas (AHBA). Following established approaches (He et al., 2025; Morgan et al., 2019; Wang et al., 2025), we first applied partial least squares regression (PLSR) to relate regional myelin-sensitive contrast values to whole-brain gene expression profiles (Fig. 3A). The first PLS component (PLS1) accounted for 48.28% of the variance in myelin-sensitive contrast (Fig. 3B), a proportion significantly greater than expected by chance ($p = 0.021$), as confirmed by permutation testing ($n = 10,000$). Consistent with this, regional myelin-sensitive contrast values showed a strong negative correlation with PLS1 scores ($\rho = -0.775$, $p < 0.001$; Fig. 3C). These findings indicate that PLS1 captures key gene expression patterns that are closely linked to regional myelin-sensitive contrast within the human SPN, providing a foundation for subsequent cross-species comparisons. To assess the robustness of the PLS-derived gene weights, we performed a split-half validation across 10,000 random partitions of the 31 SPN regions. Gene-weight vectors derived from the two halves showed consistent correlations across all genes included in the PLSR model (mean $\rho = 0.633$; Fig. S1D), and both half-sample estimates were strongly correlated with the full-data gene weights (first half vs. full dataset: mean $\rho = 0.885$; second half vs. full dataset: mean $\rho = 0.898$; Fig. S1E). These results support the stability of the myelin-sensitive contrast-associated transcriptional pattern identified by PLSR.

Next, we identified 4,627 genes with extreme loadings on PLS1 ($|Z| > 3$) using bootstrap analyses ($n = 10,000$). To further assess the evolutionary relevance of this myelin-sensitive contrast-associated transcriptional profile, we examined whether genes with extreme PLS1

loadings were enriched for human-accelerated brain-related genes (HAR-BRAIN). Among these genes, 141 overlapped with HAR-BRAIN genes. A hypergeometric test, which evaluates whether the observed overlap exceeds what would be expected by chance, confirmed that this enrichment was statistically significant ($p = 0.028$; Fig. 3D). This enrichment suggests that the transcriptional profile associated with variation in myelin-sensitive contrast within the SPN partially reflects genes implicated in human brain evolution.

Of these 141 genes, 130 human-macaque orthologs were identified using BioMart. Notably, the majority exhibited positive loadings ($Z > 3$; $n = 95$), indicating preferential expression in SPN regions with lower myelin-sensitive contrast, while a smaller subset of genes with negative loadings ($Z < -3$; $n = 35$) was more highly expressed in SPN regions with higher myelin-sensitive contrast. To assess cross-species conservation, we calculated the mean expression of positively or negatively loaded genes in each SPN ROI and assessed Spearman correlations between human and macaque values. We found a significant correlation between humans and macaques in the expression patterns for genes with positive loadings ($p = 0.567$, $p < 0.001$; Fig. 3E), whereas no such association was observed for genes with negative loadings ($p = 0.019$, $p = 0.919$).

These results suggest that the myelin-sensitive transcriptional profile within the SPN, particularly genes preferentially expressed in regions with lower myelin-sensitive contrast, shows partial human-macaque conservation and may provide a molecular context for the conserved local microstructural organization of the SPN.

Cross-Species Differences in SPN Connectivity

While local microstructural profiles and associated transcriptional signatures within the SPN exhibited broadly similar patterns in humans and macaques, the two species differ substantially in self-related behaviors. This discrepancy suggests that mechanisms beyond local microstructural properties and gene expression may contribute to the evolutionary reorganization of the SPN. Given evidence that large-scale structural connectivity constitutes a fundamental substrate of neural function (Axer & Amunts, 2022; Lee et al., 2022; Leergaard & Bjaalie, 2022; Thiebaut de Schotten & Forkel, 2022), we next examined cross-species differences in the structural connectivity of the SPN. To further clarify the evolutionary reorganization of the SPN, we additionally included chimpanzees as an intermediate species, enabling a more detailed characterization of species-related transitions from macaques through chimpanzees to humans.

Cross-species differences in SPN connectivity were assessed using representational dissimilarity matrices (RDMs) at two connectome levels: region-to-region (ROI-ROI) and region-to-tract (ROI-tract) (Fig. 4A; see *Materials and Methods* for details). The ROI-ROI connectome characterizes structural connectivity among SPN regions, capturing the network's internal organization, while the ROI-tract connectome quantifies connections from SPN regions to major whole-brain fiber tracts, reflecting the network's integration with the global brain architecture. These two connectivity levels were therefore used to distinguish reorganization of the SPN's internal architecture from changes in its embedding within the broader white-matter scaffold. To compare SPN connectivity patterns across species, we computed pairwise dissimilarities between individuals, defined as 1 minus Spearman's rank correlation coefficient (r), to create an RDM (Fig. 4B&C).

Based on these RDMs, multidimensional scaling (MDS) projected individual SPN connectivity patterns into a two-dimensional space, allowing for intuitive visualization of their relative similarities across species (Fig. 4D&E). In this framework, the RDMs characterize the high-dimensional geometry of inter-individual connectome dissimilarities, whereas MDS provides a low-dimensional visualization of this structure. To test whether the observed species separation was present in the original dissimilarity space, we performed PERMANOVA directly on the RDMs. Species had a significant effect at both connectivity levels (ROI-ROI: pseudo- $F = 403.298$, $p < 0.001$; ROI-tract: pseudo- $F = 184.752$, $p < 0.001$), indicating that between-species dissimilarities exceeded within-species variability. The two-dimensional MDS solutions showed reasonable stress values (ROI-ROI: Kruskal's Stress-1 = 0.115; ROI-tract: Kruskal's Stress-1 = 0.168), and the same species organization was observed in three-dimensional embeddings with lower Kruskal's stress-1 values (0.0836 and 0.121, respectively).

We then conducted a two-way analysis of variance (ANOVA) on the distances between species within this MDS space, with Connectome Level (ROI-ROI vs. ROI-tract) as the within-subject factor and Species Pair (human-chimpanzee [H-C], human-macaque [H-M], chimpanzee-macaque [C-M]) as the between-subject factor (Fig. 4D&E). The analysis revealed a significant main effect of Species Pair ($F_{(2,270)} = 106.30$, $p < 0.001$, partial $\eta^2 = 0.441$), but no main effect of Connectome Level ($F_{(1,270)} = 0.89$, $p = 0.346$, partial $\eta^2 = 0.003$). Importantly, a significant interaction between Connectome Level and Species Pair was observed ($F_{(2,270)} = 28.82$, $p < 0.001$, partial $\eta^2 = 0.176$).

Post hoc analyses showed that at the ROI-ROI level, human-macaque distances were significantly greater than both H-C and C-M distances (all $p < 0.001$, vs. H-C: Cohen's $d = 3.014$; vs. C-M: Cohen's $d = 2.768$), whereas the latter two did not differ ($p = 0.708$, Cohen's

d = 0.265). At the ROI-tract level, all species pairs differed significantly. Although the H-M distance remained the largest (vs. H-C: $p < 0.001$, Cohen's $d = 1.232$; vs. C-M: $p = 0.028$, Cohen's $d = 0.569$), it was smaller than that observed at the ROI-ROI level ($p < 0.001$). Moreover, unlike the ROI-ROI pattern, H-C distances were greater than C-M distances ($p = 0.007$, Cohen's $d = 0.569$). Together, these findings indicate that evolutionary modifications of the SPN across humans and NHPs are network-specific rather than uniform across the brain. Similar interspecies distance patterns were observed across consistency thresholds ranging from 50% to 90% (Fig. S2A; Table S3), indicating that the ROI-ROI findings were not dependent on the primary 75% threshold.

Subnetwork-Specific Changes in Relative Interspecies Distances within the SPN

Previous studies have shown that the SPN can be divided into three closely connected levels of self-processing: Interoceptive-processing, Exteroceptive-processing, and Mental-self-processing (Qin et al., 2020). These levels form a hierarchical transition, allowing body-environment information to be integrated and propagated from interoceptive processing to exteroceptive processing, and then to mental-self processing. To further explore differences in SPN connectivity, we examined the connections within each subnetwork. RDM and MDS analyses were performed separately for each subnetwork. Then, we conducted a three-way ANOVA, with Connectome Level and Subnetwork (Interoceptive-processing, Exteroceptive-processing, Mental-self-processing) as within-subject factors and Species Pair as a between-subject factor (Fig. 5). Significant main effects were found for all three factors, along with significant two-way and three-way interactions (Table S3). To clarify these interactions, we conducted simple-effect analyses. At the ROI-ROI connectome level (Fig. 5A), the relative distances between species, particularly between C-M and H-C, shifted across subnetworks.

Interoceptive-processing network: Within the Interoceptive-processing subnetwork, the C-M distance was the shortest (vs. H-C: $p = 0.001$, Cohen's $d = 2.597$; vs. H-M: $p < 0.001$, Cohen's $d = 2.040$), while the H-C distance was significantly shorter than H-M ($p < 0.001$, Cohen's $d = 1.296$). This result indicates that macaques and chimpanzees may be more similar to each other in their interoceptive processing than they are to humans. That is, both NHPs exhibit similar structural organization in regions associated with cardiorespiratory, gastrointestinal, and urogenital signals.

Exteroceptive-processing network: In the Exteroceptive-processing subnetwork, the pattern shifted: H-C distance became the shortest (both $p < 0.001$; vs. H-M: Cohen's $d = 2.532$; vs. C-M: Cohen's $d = 1.772$), while C-M remained significantly shorter than H-M ($p = 0.001$, Cohen's $d = 0.760$). This finding suggests that chimpanzees and humans may be more similar

to each other than chimpanzees and macaques in integrating external sensory information with interoceptive signals to link bodily and environmental cues.

Mental-self-processing network: In the Mental-self-processing subnetwork, which extends self-processing to external stimuli not directly related to the body (such as one's own name or personal belongings), all interspecies distances were greater than in the other two self-subnetworks. Additionally, H-M remained the longest distance (both $p < 0.001$; vs. H-C: Cohen's $d = 1.772$; vs. C-M: Cohen's $d = 1.802$), but H-C and C-M did not differ significantly ($p = 1.000$, Cohen's $d = 0.0298$).

Together, across the transitions from Interoceptive-processing to Exteroceptive-processing to Mental-self-processing, the relative distances between species shift systematically: $C-M < H-C$ in Interoceptive-processing, $C-M > H-C$ in Exteroceptive-processing, and $C-M \approx H-C$ in Mental-self-processing. This result suggests a domain-dependent transition in the structural organization of SPN subnetworks, from regions associated with body-centered processing to those associated with more abstract self-related processing. Similar subnetwork-specific patterns were also observed across consistency thresholds ranging from 50% to 90% (Fig. S2B, Table S3).

At the ROI-tract connectome level (Fig. 5B), a different pattern emerged. Although the absolute distances among species increased progressively from the Interoceptive-processing to the Exteroceptive-processing then to the Mental-self-processing subnetwork, their relative relationships remained consistent, with $H-C < C-M < H-M$ across all subnetworks (Table S4). These findings suggest that the internal organization of the SPN follows a unique, domain-specific evolutionary trajectory that is not reducible to its broader white-matter embedding.

Small-Worldness Organization and Hub Shifts of the SPN across Species

To further investigate the topological organization of the SPN across species, we conducted graph-theoretical analyses.

First, we compared the small-worldness (σ) of the SPN, a measure reflecting the network's balance between local specialization and global integration (Rubinov & Sporns, 2010; Latora & Marchiori, 2001, 2003) (Fig. 6A). An aligned rank transform ANOVA (ART-ANOVA) revealed a significant main effect of species on σ ($F_{(2,132)} = 108.39$, $p < 0.001$, $\eta^2 = 0.622$). Post-hoc analyses showed that humans exhibited significantly higher σ values than both chimpanzees and macaques (both $p < 0.001$), and chimpanzees had higher σ values than macaques ($p < 0.001$). These results indicate a species-dependent gradient in SPN small-worldness across humans and NHPs, with the human SPN achieving the greatest

balance and efficiency between local processing and global information integration. Because small-worldness can be influenced by network density, we further repeated this analysis using density-matched SPN connectomes generated by proportional thresholding across densities from 40% to 65% in 5% increments. The species effect on small-worldness remained significant across all density thresholds (all $p < 0.001$; Fig. S3A), and the direction of group differences was consistent with the original analysis. These results indicate that the observed species differences in SPN small-worldness were not driven solely by differences in edge density.

Next, we examined interspecific differences in the topological role of individual nodes within the SPN. We computed two commonly used graph-theoretical centrality measures: degree centrality, which quantifies the number of direct connections a node has, and eigenvector centrality, which reflects a node's influence based on the importance of its neighbors (Lohmann et al., 2010; Onias et al., 2014). These measures were combined into a composite metric termed "composite centrality" (see *Materials and Methods* for details) (Fig. 6B). Cross-species similarity analysis of node composite centrality distributions revealed that humans and chimpanzees shared the most similar SPN patterns ($p = 0.700$, $p < 0.001$), whereas the similarities between humans and macaques ($p = 0.232$, $p = 0.210$) and between chimpanzees and macaques ($p = 0.310$, $p = 0.090$) were not statistically significant (Fig. 6C). Similar cross-species patterns were observed when examining degree and eigenvector centrality separately (Figs. S3C, D, F&G). These findings of graph-based similarities in network centrality suggest that SPN nodes may occupy comparable functional roles in humans and chimpanzees but not in macaques.

Beyond cross-species similarities in node centrality, we observed notable topographic shifts in hub organization. Fig. 6D shows the spatial distribution of nodes on the brain surface, with node color representing composite centrality. In macaques, the nodes with higher composite centrality were primarily located in the insular cortex, indicating that the insula may be the central hub of the SPN in macaques. In chimpanzees, insular regions remained important, while cingulate regions also emerged as prominent nodes. In humans, the SPN's hub shifted predominantly to the cingulate cortex. To assess the consistency of the observed hub-reorganization pattern across centrality definitions, we further examined degree and eigenvector centrality separately. Across both metrics, the spatial distributions of high-centrality nodes were broadly consistent with the composite centrality results (Figs. S3B&E). This consistency was further quantified by the spatial agreement among centrality measures within each species: correlations among degree, eigenvector, and composite centrality maps were strongly positive in all species (all $p > 0.827$, all $p < 0.001$). Together, these results

indicate that the observed hub reorganization was not specific to the composite centrality metric, but was supported by convergent patterns across complementary measures of node centrality.

Together, this cross-species pattern reveals a clear reorganization in the composite centrality topography from macaques to chimpanzees and humans: from the insula in macaques, to a combination of insula and cingulate regions in chimpanzees, and finally to predominantly cingulate regions in humans, consistent with a structural transition from body-centered sensory integration networks toward regions associated with higher-order self-related processing.

Finally, we tested whether the apparent dissociation between local microstructural conservation and network-level reorganization depended on the use of different analytical representations. Under a unified correlation-based framework, human-macaque similarity remained significantly higher for myelin-sensitive contrast profiles than for either SPN connectivity patterns or graph-theoretical centrality profiles (paired t-tests on Fisher z-transformed correlations, both $p < 0.001$). Thus, the stronger conservation of local microstructural profiles relative to network-level organization was preserved when all measures were evaluated using the same correlation-based approach.

Discussion

In this study, we compared the SPN across humans and NHPs, spanning local microstructural and transcriptional signatures to large-scale network organizational properties, using a comparative connectomic framework. We found that self-processing regions exhibited similar local microstructural properties and transcriptional signatures between humans and macaques, whereas large-scale connectivity patterns of the SPN followed a primate evolutionary gradient from macaques to chimpanzees, and then to humans, with topographic reorganization across species. The three subnetworks (i.e., Interoceptive-processing, Exteroceptive-processing, and Mental-self-processing) displayed a distinct hierarchical transition. Notably, these species-specific modifications of the SPN differed from ROI-tract patterns. Together, these findings provide a cohesive picture of both evolutionary conservation and species-specific differences in the SPN across humans and NHPs (Fig. 7).

Similar Local Microstructural and Transcriptional Signatures of Self-processing Regions

At the local microstructural level, we focused on T1w/T2w-derived myelin-sensitive contrast, a feature often used to infer homology across species (Miller et al., 2012). We found that regional myelin-sensitive contrast profiles were highly similar between humans and macaques. Importantly, this cross-species correspondence was stronger than that observed in an independently defined homologous cortical reference set, indicating that the SPN pattern was not fully explained by general cortical similarity across homologous regions. Consistent with previous findings (Keskin et al., 2025), human SPN regions in our data exhibited significantly lower myelin-sensitive contrast than non-SPN ones. Importantly, this pattern was recapitulated in macaques, further supporting a conserved local microstructural profile of the SPN across species. These local structural findings may carry functional implications, though variation in myelin-sensitive contrast should not be interpreted as a direct readout of self-processing ability. Lightly myelinated association cortices have been associated with more complex intracortical circuitry (Glasser et al., 2014) and longer intrinsic timescales (Ito et al., 2020), which may support temporal integration relevant to the continuity of self-awareness and self-experience (Smith et al., 2022; Wolff et al., 2022).

By integrating variation in myelin-sensitive contrast with gene expression data, we identified transcriptional components that closely tracked the myelin-sensitive contrast profile of the human SPN. These genes significantly overlapped with HAR-BRAIN genes enriched for human-specific adaptations related to brain development and connectivity (Wei et al., 2019), and their spatial expression pattern was partially conserved between humans and

macaques. Together, the conserved local microstructural organization of the SPN appears to be associated with a partially preserved transcriptional architecture that may include molecular components implicated in human brain evolution.

Species-Specific Modifications in the SPN in Relation to Whole-Brain Connectivity across Species

While local microstructural and transcriptional features of the SPN showed substantial similarities across humans and macaques, the SPN is inherently high-dimensional, and its organization cannot be fully captured by local microstructural and transcriptional measures alone (Thiebaut de Schotten & Forkel, 2022; Passingham et al., 2002). Large-scale connectivity analyses, incorporating chimpanzees as an intermediate evolutionary reference, revealed pronounced species-related reorganization of SPN architecture. Importantly, this local-network dissociation was preserved under a unified correlation-based framework, indicating that it was not attributable to differences in analytical representation.

Representational similarity analyses revealed that SPN connectivity was most dissimilar between humans and macaques, with chimpanzees occupying an intermediate position. Graph-theoretical analyses further demonstrated a monotonic increase in small-worldness from macaques to chimpanzees to humans, reflecting enhanced efficiency in balancing local specialization with global integration (Rubinov & Sporns, 2010). Notably, this trajectory did not fully mirror ROI-tract connectome results, indicating that SPN reorganization may be network-specific rather than reflecting uniform, brain-wide changes.

Distinct Hierarchical Transitions of Self-Processing Subnetworks

All three primate species examined here exhibit self-related interoceptive processing (Craig, 2002; Charbonneau et al., 2022; Candia-Rivera et al., 2024), whereas humans and chimpanzees can pass the MSR test (Anderson & Gallup, 2015; Gallup, 1970) and macaques succeed only after training (Chang et al., 2015, 2017). Previous studies have shown that interconnections among regions constrain information flow and cognition (Thiebaut de Schotten & Forkel, 2022). By decomposing the SPN into three subnetworks (Qin et al., 2020), we found that the structural organization of the SPN differed across these functional domains in a species-dependent manner.

Within the Interoceptive-processing subnetwork, chimpanzees were more similar to macaques than to humans, suggesting relative conservation of structural architecture associated with basic interoceptive processing across NHPs. This pattern may relate to locomotor differences between quadrupedal NHPs and bipedal humans, which likely influence

the sensory and bodily signals processed by this subnetwork (Yates et al., 2014). The thalamo-insular pathway, crucial for homeostatic regulation such as thermoreception and nociception, is highly conserved in macaques and chimpanzees but expanded and integrated with prefrontal regions in humans to support higher-order cognitive functions ((Bud) Craig, 2003). Furthermore, the distribution of von Economo neurons (VENs), which are closely associated with interoceptive processing, provides convergent support for this evolutionary pattern: VENs are concentrated in the human anterior insula, a key Interoceptive-processing node, whereas NHPs retain a more primitive granular cortical structure with fewer VENs (Nimchinsky et al., 1999; Allman et al., 2010; Evrard et al., 2012; Cauda et al., 2014; Evrard, 2019).

In contrast, the Exteroceptive-processing subnetwork showed greater chimpanzee-human than chimpanzee-macaque similarity, suggesting a more human-like structural architecture in regions linking bodily signals with external sensory information. This pattern aligns with behavioral findings from the MSR task (Gallup, 1970, 1977) and with self-agency studies (Couchman, 2012; Kaneko & Tomonaga, 2011). For example, macaques can detect directional discrepancies, whereas chimpanzees show a more human-like capacity to monitor intentionality and distinguish their own actions even from identical recordings of past self-generated behavior. This suggests a more advanced form of self-agency in chimpanzees than in macaques (Couchman, 2012; Kaneko & Tomonaga, 2011).

In the Mental-self-processing subnetwork, interspecies distances were greater than in the other subnetworks, and chimpanzee-human and chimpanzee-macaque distances became comparable. This suggests greater differentiation of network substrates associated with abstract self-related representations, such as personal belongings. This pattern parallels human-specific expansions in regions critical for mentalizing and abstract self-referential cognition, such as the temporoparietal junction, temporal pole, and anterior cingulate cortex (Amano et al., 2025). Moreover, VENs have been linked to complex social behaviors, and their higher abundance in humans relative to chimpanzees and macaques provides additional anatomical context for our findings.

Together, these findings reveal subnetwork-specific SPN modifications, reflecting a trajectory from bodily self-processing to externally oriented self-processing, and ultimately to abstract mental-self processing (Qin et al., 2020).

Evolutionary Reorganization of Hubs within the SPN

To further characterize the evolutionary transformation of the SPN, we examined species-dependent reorganization of network hubs using regional composite centrality metrics (Farahani et al., 2019; Van Den Heuvel et al., 2010).

In macaques, network hubs were primarily confined to the insula, consistent with an SPN organization dominated by interoceptive and affective processing (Critchley & Seth, 2012; Evrard, 2019). In contrast, humans exhibited a pronounced hub shift toward cortical midline structures (CMS), core regions of DMN implicated in higher-order self-referential processing, autobiographical memory, and mentalizing (Northoff et al., 2006; Seeley et al., 2012). This topological reorganization aligns with evidence linking high CMS resting-state activity to continuous self-referential processing and the integration of internal bodily signals into the self (Qin & Northoff, 2011; Yeshurun et al., 2021). This redistribution of network centrality, together with the expansion and increased density of VENs in the human CMS and anterior insula, may provide a structural substrate for efficient communication across distributed networks (Allman et al., 2010; Cauda et al., 2014). Chimpanzees showed an intermediate hub organization, suggesting a mixed topology that retains an interoceptive foundation while incorporating broader self-related integration (Allman et al., 2010). Together, these findings suggest a graded reorganization of SPN hub architecture across primates, from an insula-centered configuration linked to bodily and interoceptive processing toward a more cingulate-centered configuration linked to higher-order self-related processing.

Limitations and Future Directions

Cross-species diffusion MRI involves differences in acquisition protocols, tractography sampling, and scanning conditions, including anesthesia in nonhuman primates. These factors may affect tractography quality and connectivity estimates. Although we used parallel preprocessing and tractography workflows, SIFT2 weighting, and complementary robustness analyses, residual acquisition- or state-related effects cannot be fully excluded. Future studies with more harmonized acquisition protocols or independent validation data will further strengthen cross-species connectomic comparisons.

T1w/T2w-derived myelin-sensitive MRI contrast is not a direct or quantitative measure of intracortical myelin and may be affected by transmit-field (B_1^+) inhomogeneity, residual intensity bias, and other non-myelin-related factors. Therefore, our analyses focused on relative spatial topographies rather than absolute T1w/T2w magnitude, and gene-expression associations should be interpreted as spatial covariation with an MRI-derived microstructural

index. Future work using quantitative myelin imaging or histological validation will help clarify the biological specificity of these findings.

Conclusion

In summary, this study provides a comprehensive, multi-level characterization of the SPN across primate evolution. By integrating local microstructural, transcriptional, and large-scale network analyses, we demonstrate that the SPN is supported by conserved local biological substrates while undergoing progressive topological reorganization. Our findings characterize the evolutionary reorganization of SPN structural substrates across humans and NHPs, reveal subnetwork-specific patterns of architectural differentiation, and provide a structural framework for interpreting species differences in self-related processing (Fig. 7).

Data, Materials, and Software Availability

The macaque imaging data reported in this study are available from the lead contact upon reasonable request. This study also analyzes previously published, publicly available human and chimpanzee imaging datasets, which can be accessed through the Human Connectome Project (<https://www.humanconnectome.org>) and the National Chimpanzee Brain Resource (NCBR) (<https://www.chimpanzeebrain.org/>), respectively. No original code was generated for this study. Any additional information required to reanalyze the data is available from the lead contact upon request.

Acknowledgments

We thank the Core Technology Facility at the Kunming Institute of Zoology, Chinese Academy of Sciences, for providing MRI services. This study was supported by STI2030-Major Projects (2021ZD0200200, 2021ZD0204200, 2022ZD0205100, and 2021ZD0203900). Chimpanzee data were provided in part by the National Chimpanzee Brain Resource (supported by NIH NS092988, NIH HG011641, NIH AG067419, NSF EF-2021785, and NSF DRL-2219759).

Author Contributions

J.R., P.K., J.W., L.F., G.N., and N.L. designed the research. J.R., Y.Q., C.M., X.D., M.Q., and N.L. performed the investigation. J.R., Y.Q., and C.M. conducted the formal analysis and validation. J.R. prepared the visualizations. J.R. and N.L. wrote the original draft. J.R., P.K., J.W., L.F., G.N., and N.L. edited the manuscript.

Competing Interest Statement

The authors declare no competing interests.

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Fig. 1. Overview of the analytical framework for cross-species mapping of the self-processing network (SPN)

(A) Generation of vertex-to-tract connectivity blueprints from preprocessed diffusion MRI (dMRI) data using the XTRACT toolbox. (B) Definition of a three-level human SPN and cross-species mapping to macaques using symmetric Kullback-Leibler (KL) divergence.

Fig. 2. Myelin-sensitive contrast profiles of the SPN in humans and macaques

(A-B) Myelin-sensitive contrast values for all regions of the SPN in humans (A) and macaques (B). In each panel, the left subpanel shows the cortical surface distribution of SPN ROIs, with distinct ROIs indicated by different colors, while the right subpanel displays the SPN ROIs ranked by myelin-sensitive contrast values from highest to lowest. Colors correspond across the two subpanels. (C) Cross-species correlation of myelin-sensitive contrast values across homologous SPN regions between humans and macaques. (D-E) Comparison of myelin-sensitive contrast values between regions within the SPN and regions outside the network (non-self regions) in humans (D) and macaques (E). ***, $p < 0.001$.

Fig. 3. Cross-species comparison of myelin-sensitive contrast-associated transcriptional signatures in the SPN

(A) Identification of myelin-sensitive contrast-associated genes in the SPN using partial least squares regression (PLSR). Human gene expression data from the Allen Human Brain Atlas (AHBA) were processed to yield a regional expression matrix (31 ROIs $\times$ 15,633 genes). Genes were ranked according to their PLS-derived Z scores, defined as the ratio of each gene's PLS weight to its bootstrap-estimated standard error, and genes with Z scores > 3 or < -3 were retained based on their association with SPN myelin-sensitive contrast. (B) Variance explained by the leading PLS components. (C) Correlation between regional myelin-sensitive contrast values and regional PLS1 scores. (D) Intersection between retained genes and human-accelerated brain-related (HAR) genes. (E) Cross-species similarity of expression patterns for the intersecting genes identified in (D) with Z scores > 3 between humans and macaques. *, $p < 0.05$; ***, $p < 0.001$.

Fig. 4. Cross-species distances of SPN connectivity patterns

(A) ROI-ROI connectomes were generated using MRtrix3-based probabilistic tractography, while ROI-tract connectomes were derived by averaging vertex-level connectivity blueprint values within each ROI. (B-C) Representational dissimilarity matrices (RDMs) of individual-level connectivity patterns at the ROI-ROI (B) and ROI-tract (C) connectome levels. (D-E) Interspecies distances derived from multidimensional scaling (MDS) embeddings, quantified as individual-to-heterospecies centroid distances at the ROI-ROI (D) and ROI-tract (E) levels. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Fig. 5. Cross-species distances of self-subnetwork connectivity patterns

(A-B) Interspecies distances derived from MDS embeddings, quantified as individual-to-heterospecies centroid distances within each self-subnetwork. Distances are shown for the interoceptive (left), exteroceptive (middle), and mental-self (right) subnetworks at the ROI-ROI (A) and ROI-tract (B) levels. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Fig. 6. Graph-theoretical properties of the SPN.

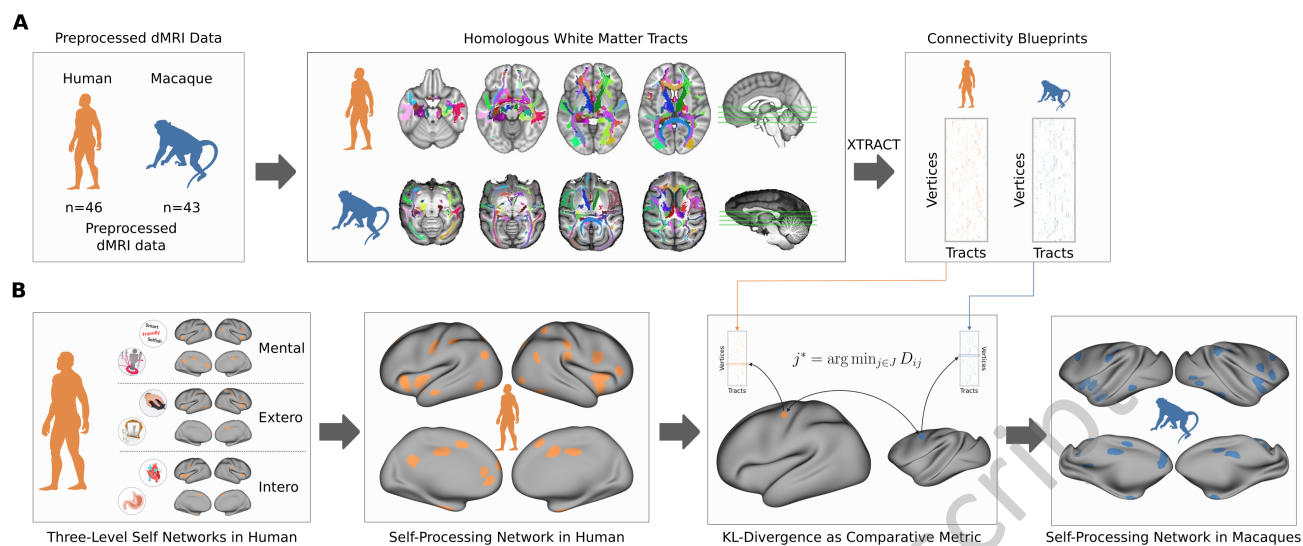
(A) Small-worldness properties of the SPN across humans, chimpanzees, and macaques. (B) Composite centrality values of SPN regions. (C) Similarity of composite centrality values of SPN regions across species. (D) Cortical surface representation of SPN ROI composite centrality, with higher (more red) values indicating regions that are more central within the network and therefore more likely to act as hubs. ***, $p < 0.001$.

Fig. 7. Schematic of the evolutionary trajectory of SPN across primates.

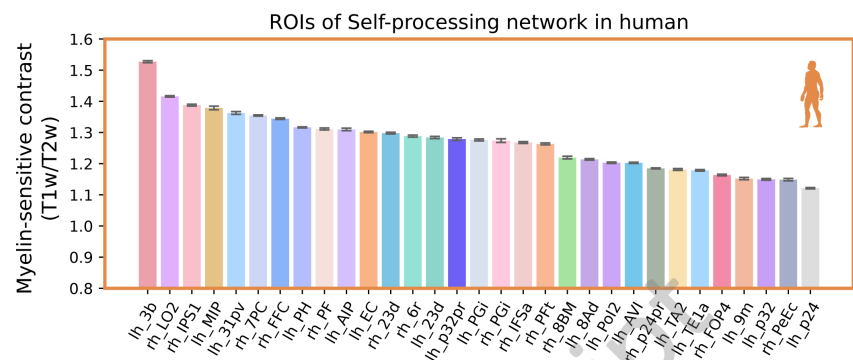
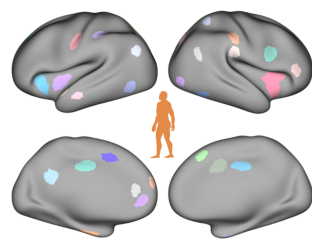
The schematic summarizes the domain-specific evolutionary trajectory and selective reorganization of the self-processing network (SPN). Decomposition of the SPN into interoceptive-processing, exteroceptive-processing, and mental-self-processing subnetworks reveals systematic shifts in interspecies similarity: macaques and chimpanzees show the greatest similarity in the interoceptive-processing subnetwork; chimpanzees and humans exhibit higher correspondence in the exteroceptive-processing subnetwork; whereas all species display the strongest species-specific differentiation in the mental-self-processing subnetwork. In parallel, the relative prominence of network hubs shows a hierarchical reorganization, shifting from predominantly insular hubs in macaques, to combined insular-cingulate hubs in chimpanzees, and to primarily cingulate hubs in humans. This coordinated reorganization reflects a structural shift in the SPN from architectures associated with body-

1280 centered integration toward those linked to increasingly abstract, mental forms of self-
1281 processing across primates.

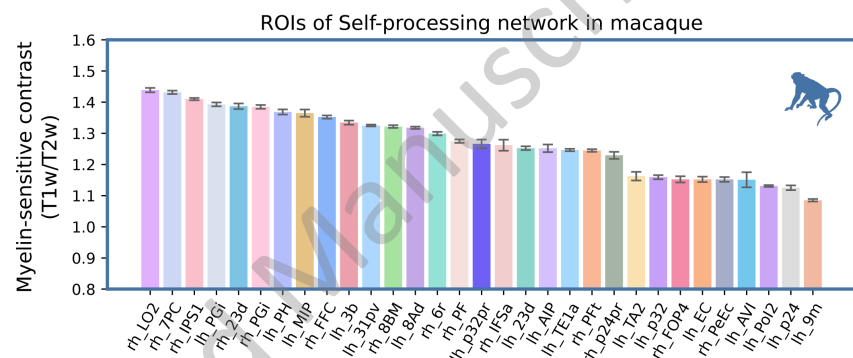
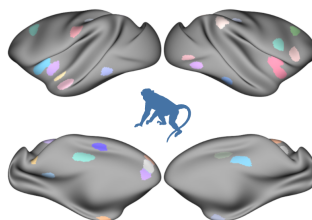
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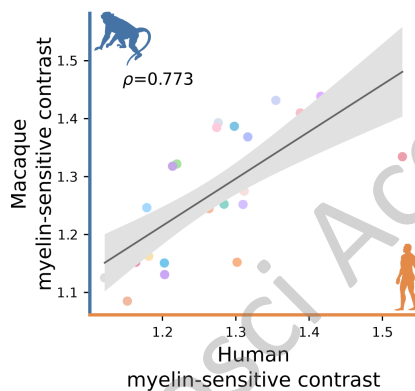
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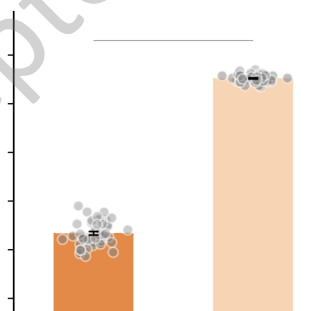
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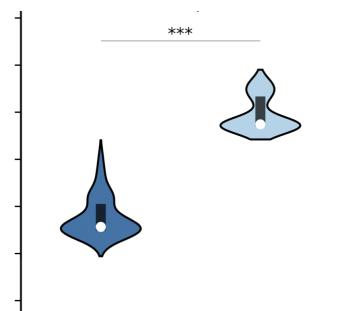
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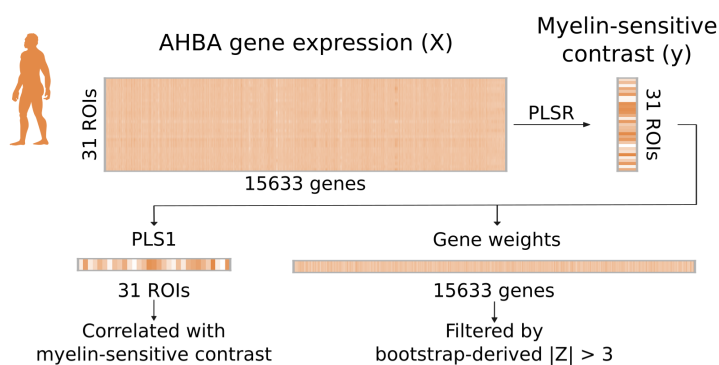
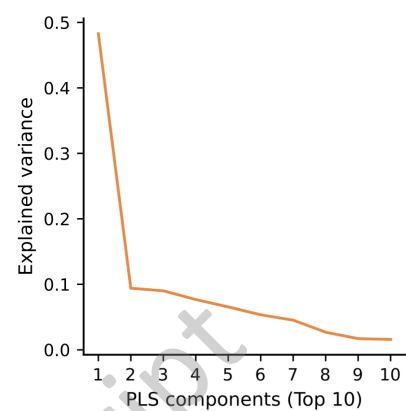
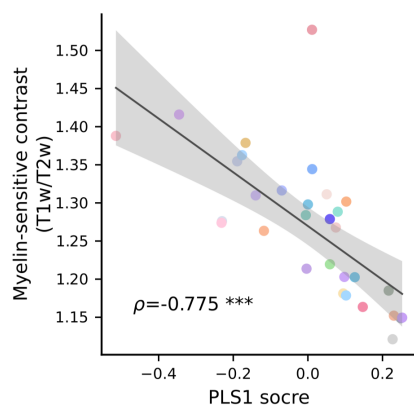
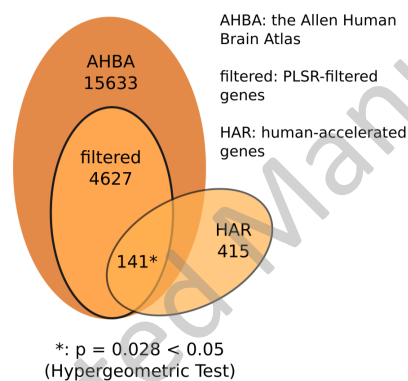
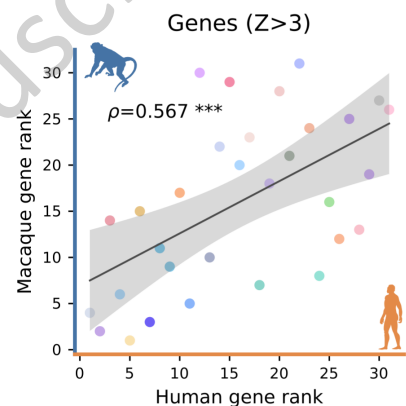


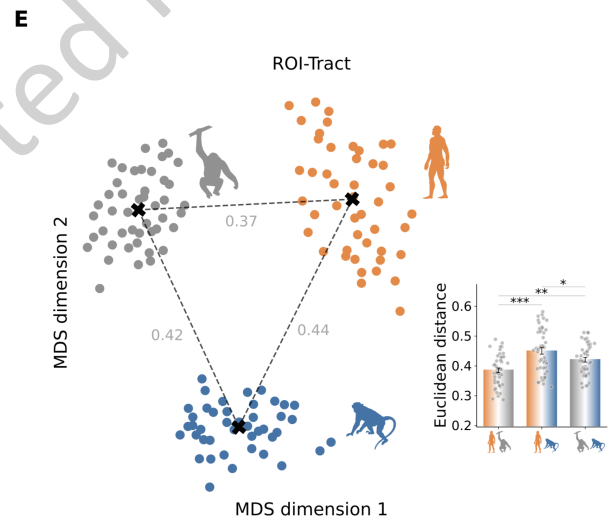
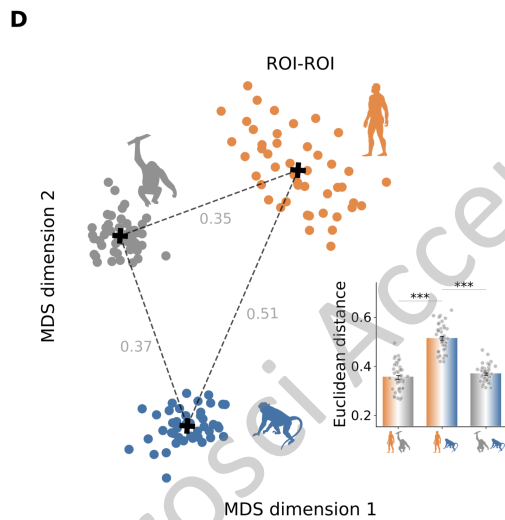
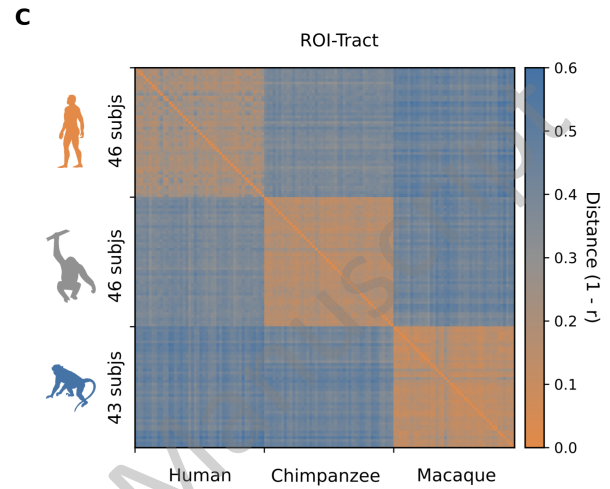
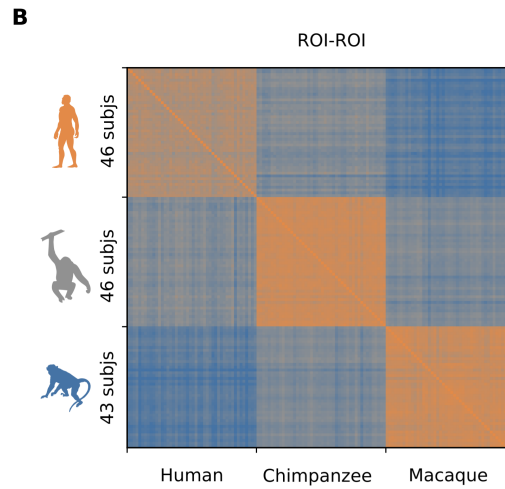
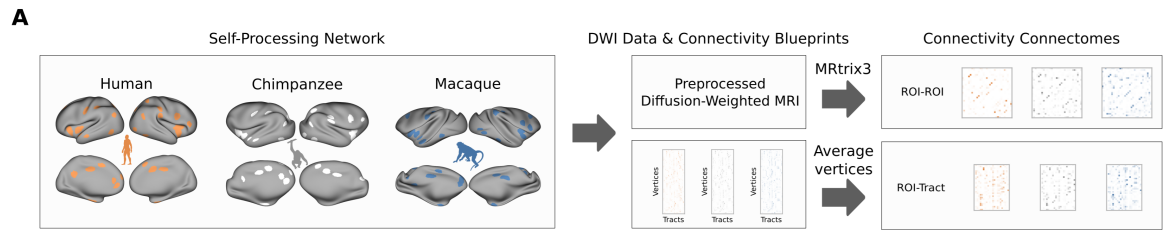
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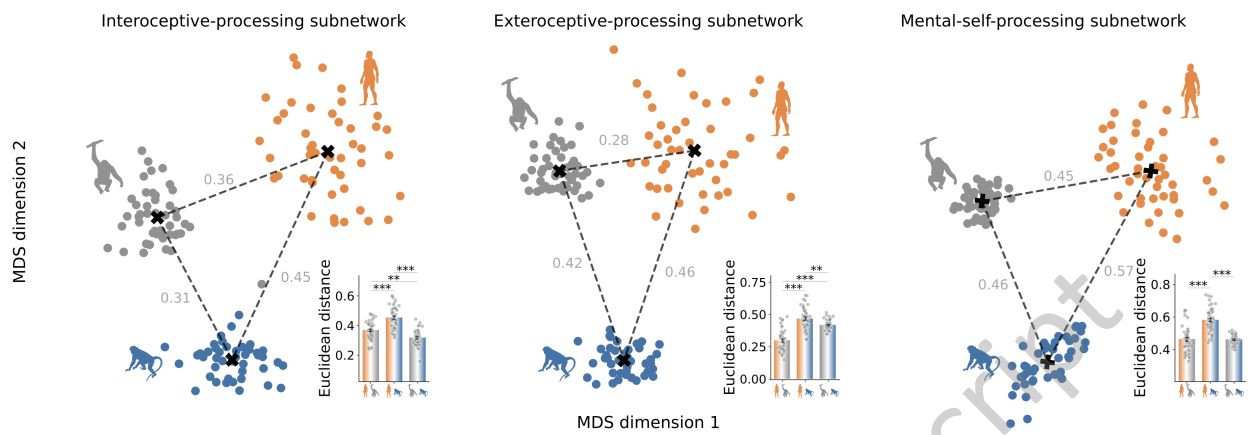
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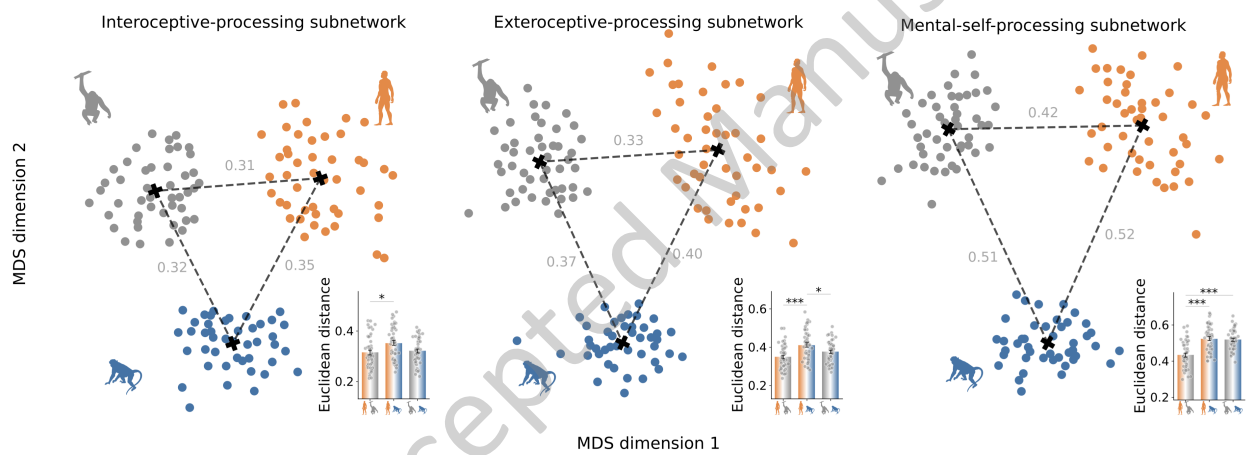
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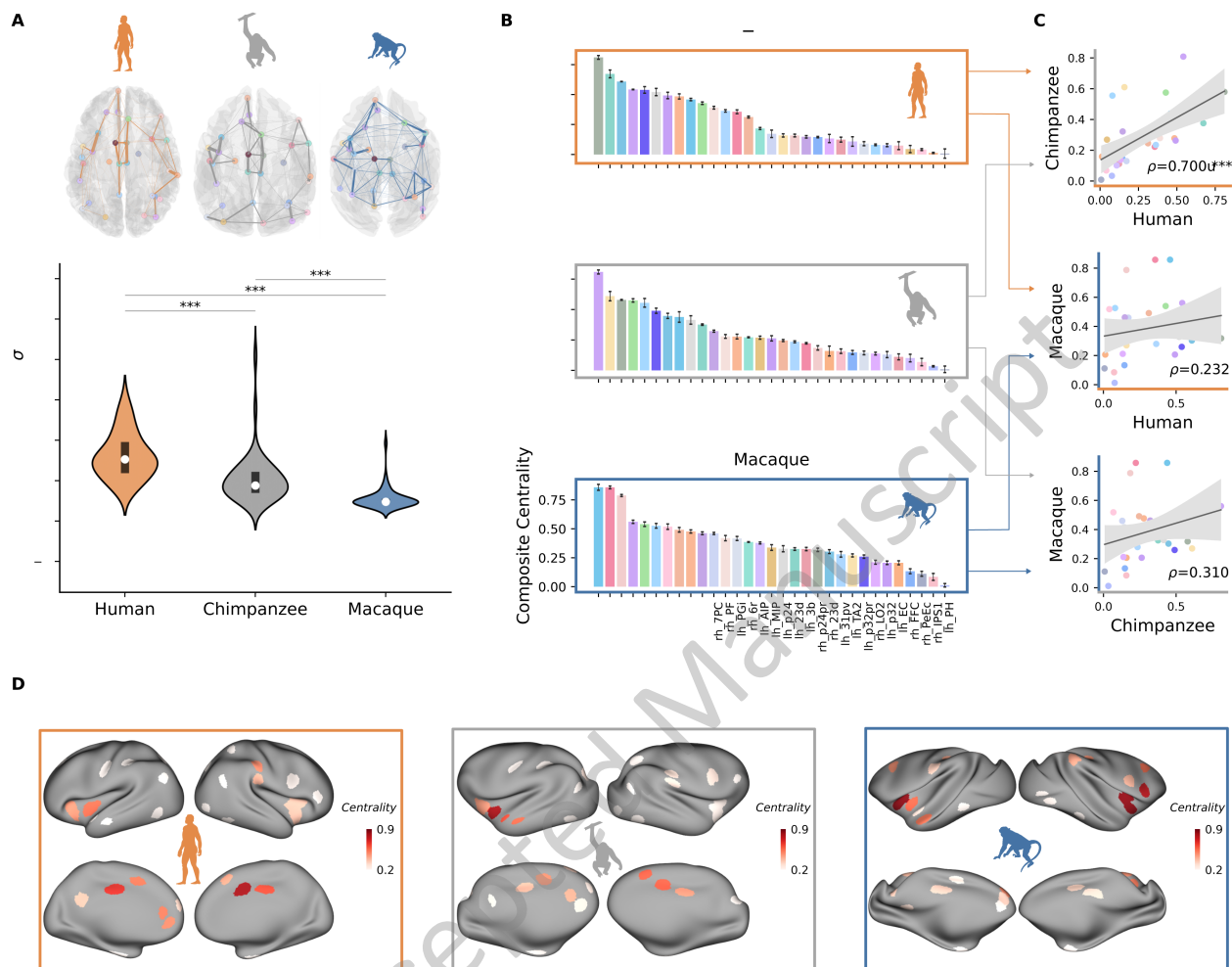


A. ROI-ROI

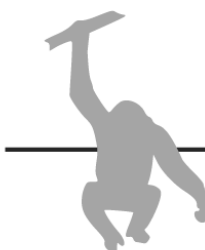


B. ROI-Track





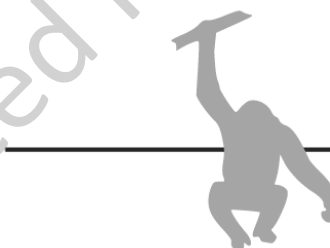
Intero



Extero



Mental



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