Supplementary Material for Predicting Brain Morphogenesis via Physics-Transfer Learning by Zhao et al.

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This **Supplementary Material** includes **Supplementary Notes S1-S3**, **Supplementary Figures S1-S9**, and **Figure Captions**.

Supplementary Note S1. Reduced-dimensional analysis

We extract the reduced-dimensional representations from morphological data by identifying key feature points (vertices) and connecting paths (ridges) across temporal frames. The raw morphological data is first filtered based on domain-specific criteria (e.g., intensity and thresholding). Density-based spatial clustering of applications with noise (DBSCAN) is implemented to remove noise and isolate ridge-relevant points, which represent the skeletal structure of the morphology [1]. A k-nearest neighbor graph is constructed over the cleaned ridge points. Nodes with a degree of 1 (endpoints) or 3 and above (junctions) are initially considered as vertex candidates. To account for spatial uncertainty, nearby candidate points are merged using a distance tolerance, resulting in a refined set of vertices representing biologically meaningful endpoints and bifurcations in the structure. Ridges are defined as spatially valid connections between vertices. For each time step, the final set of vertices and ridges forms a simplified graph representation of the morphology. The number of vertices and ridges is recorded to quantify the evolving complexity of the network over time.

To further assess the structure of neural network (NN)-based models, we incorporate tools from complex network theory [2]. These tools enable reduced-dimensional analysis of deep neural networks (DNNs), offering insight into their learned representations [2]. Resolving neuron activation patterns in the latent space provides a means to assess the model's uncertainty in generalizing to out-of-distribution (OOD) samples. For samples with high uncertainty, neurons in the latent space are expected to exhibit abnormally high node strengths, indicating a significant deviation from the activation patterns learned during training. PT models display consistent activation patterns between spherical and brain data compared to statistical learning (SL) models, indicating superior generalization and reduced uncertainty.

Supplementary Note S2. Information bottleneck (IB) analysis

To further disentangle the influence of configuration versus deformation curvature, we construct two datasets: one from morphogenetic processes on flat plates (lacking configuration curvature) and another from spherical geometries (with inherent configuration curvature). Monitoring information compression reveals greater compression on the spherical dataset ($\sim 34\%$) compared to the flat plate dataset ($\sim 31\%$) (Fig. S8d), suggesting that deformation curvature contributes more critically to the spatiotemporal complexity of morphogenesis by providing richer, more informative structural features for the model to learn.

Supplementary Note S3. Medical applications

Clinical experts diagnose brain malformations and diseases by integrating magnetic resonance imaging (MRI) data with clinical symptoms and patient history [3]. Structural MRI and accompanying metadata enable identification of a spectrum of conditions. White matter abnormalities underpin diagnoses of schizencephaly, gray matter heterotopia, and focal cortical dysplasia, cortical morphology reveals malformations such as polymicrogyria, cobblestone malformation, and lissencephaly, and overall brain volume anomalies diagnose megalencephaly and microcephaly [4]. Aggregated across the lifespan, MRI data inform reference brain charts that delineate normative and pathological developmental trajectories via neuroimaging biomarkers derived from structural and morphological metrics [5]. These biomarkers are critical for diagnosing neurodevelopmental and neurodegenerative disorders, including Alzheimer's disease, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder, anxiety disorders, bipolar disorder, major depressive disorder, and schizophrenia [5]. Generative AI models further hold promise for modeling longitudinal MRI changes and disease progression, advancing data-driven, personalized clinical decision-making [6].

Conventional approaches focus largely on anatomical geometry extracted from MRI data. Our physics-transfer (PT) framework, by contrast, integrates the physics of nonlinear elasticity governing brain morphogenesis into predictive models supported by a curated digital library (DL). The resulting curvature maps, robust morphological descriptors, serve as biomarkers of developmental brain disorders, reflecting the established links between aberrant curvature and pathology [7]. Within a digital twin paradigm, patient-specific brain morphology reconstructed from MRI can be input into the PT model to assess current structural states and forecast future development (Fig. S9a). Detection of a trajectory toward pathological morphological bifurcations may prompt timely clinical intervention, with ongoing MRI data facilitating iterative model refinement for real-time monitoring and prognostic evaluation.

Unlike standardized data domains such as computer vision (CV) or natural language processing (NLP), brain MRI data exhibit significant heterogeneity due to varying imaging protocols, scanner types, and population diversity. Moreover, privacy and ethical constraints limit data sharing and integration, posing unique challenges. Progress in AI-driven modeling of brain development and predictive diagnostics thus depends on establishing open, well-curated, interoperable databases coupled with comprehensive digital libraries dedicated to brain morphology (Fig. S9b).

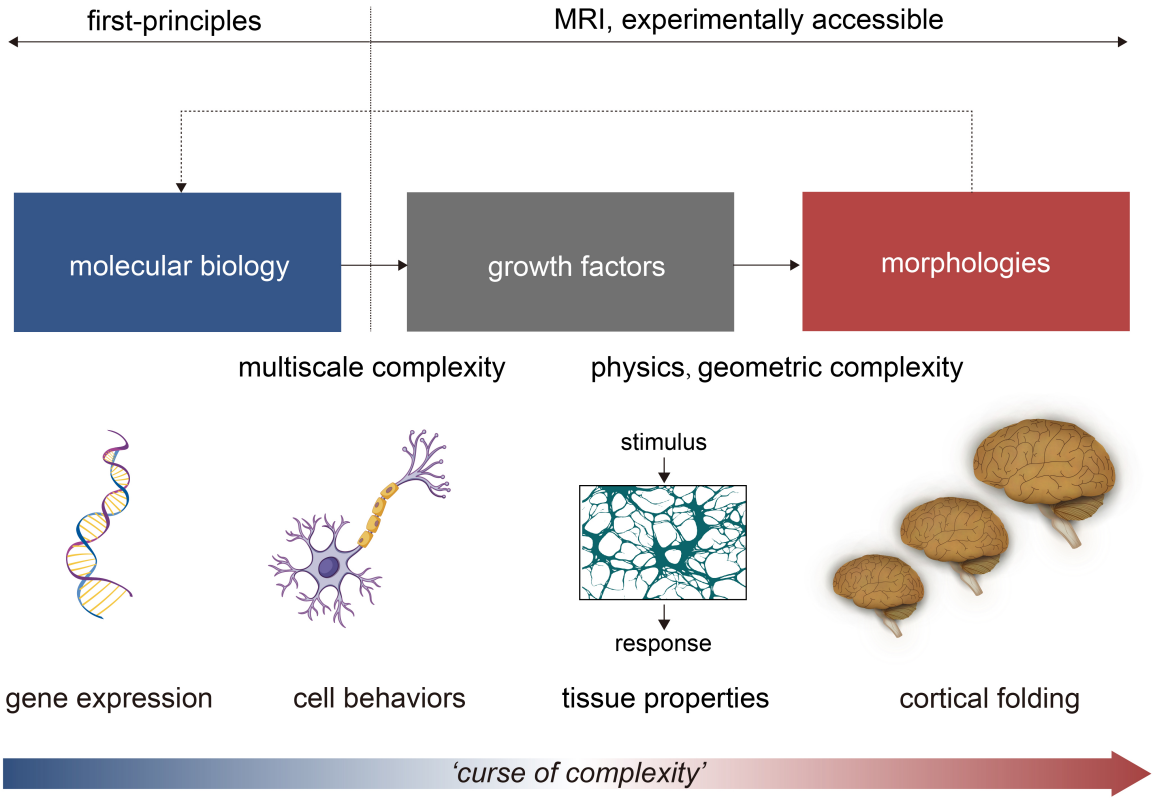

Figure S1. Accuracy-performance dilemma in multiscale modeling of brain morphological development. MRI: magnetic resonance imaging.

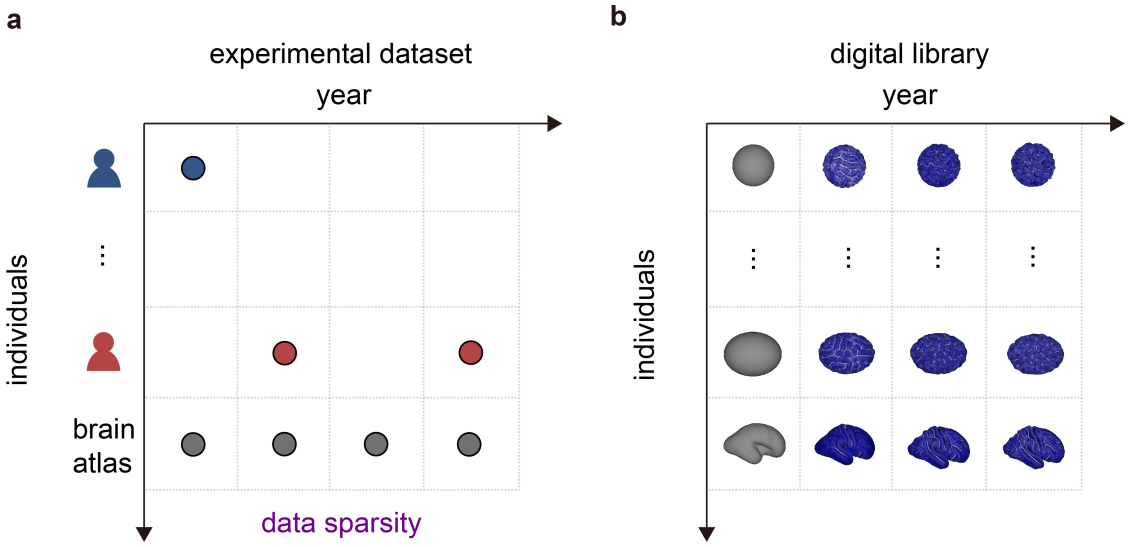

Figure S2. Experimental magnetic resonance imaging (MRI) datasets and finite element analysis (FEA) digital library (DL) of brain morphological development. (a) Experimental datasets collected from the literature [8]. **(b)** DL constructed from our FEA.

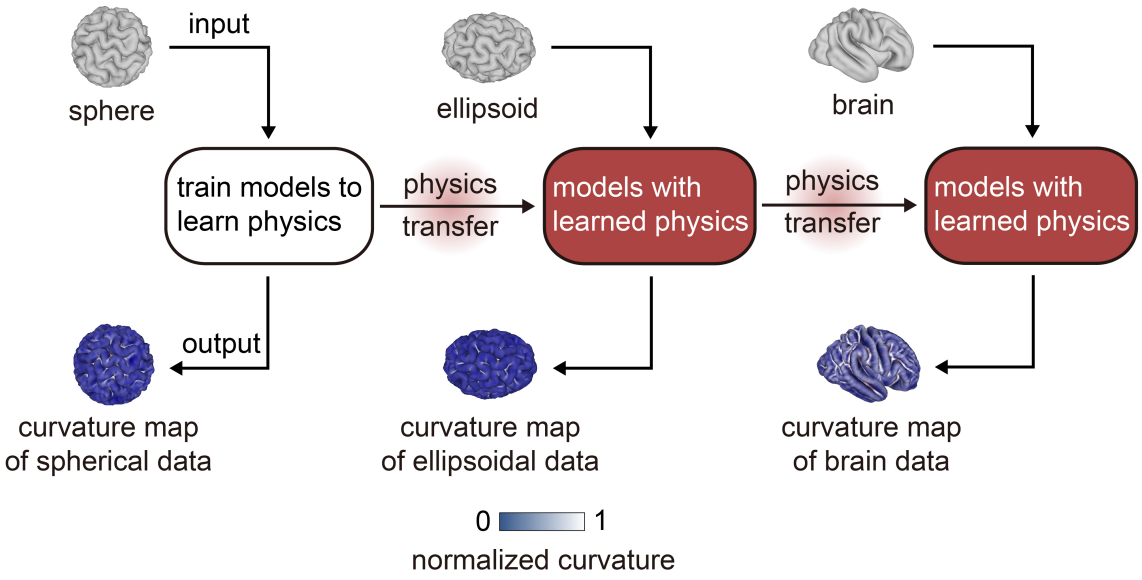

Figure S3. Physics-transfer (PT) framework that learns the physics of developmental nonlinear deformation across models of varying geometric complexities.

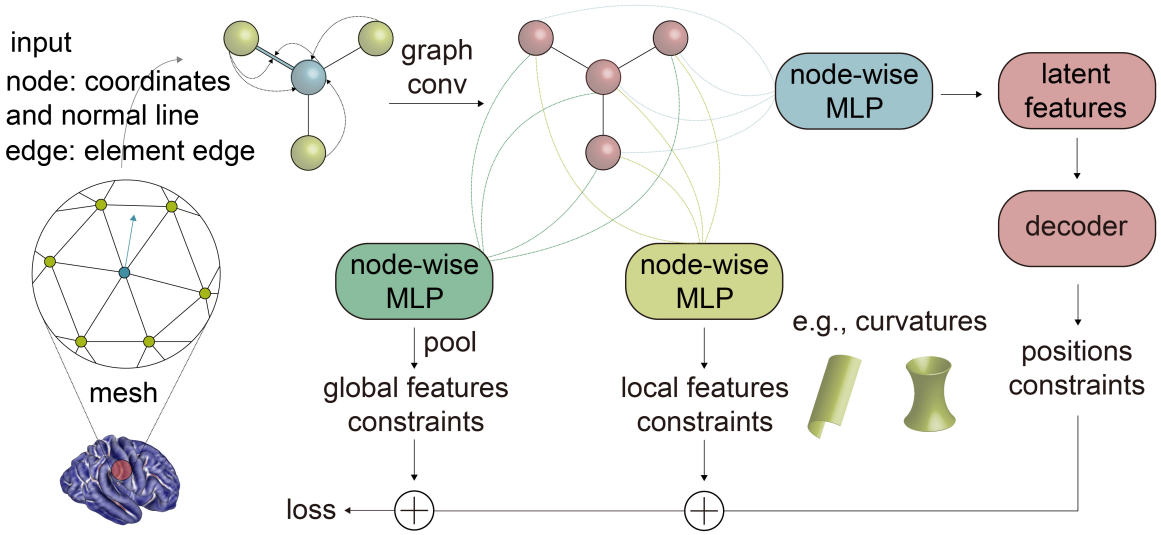

Figure S4. The neural network (NN) architecture. An encoder-decoder architecture is employed to capture the complexity of morphological development. The model takes as input a graph representation of the morphology, where node features include coordinates and normal directions. The output is local curvatures. Additionally, the 3D coordinates of the morphologies and global features, such as the gyrification index, are incorporated into the loss function to constrain the model. MLP: multilayer perceptron.

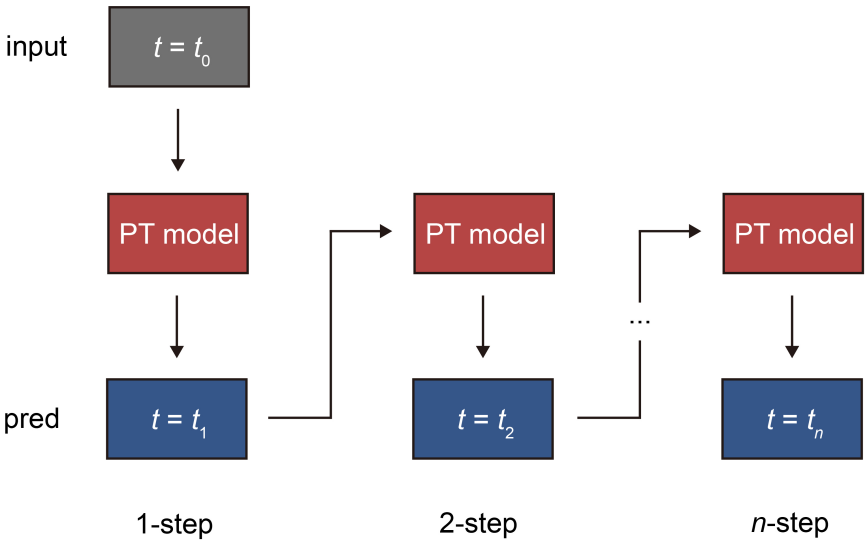

Figure S5. Schematic diagram of multi-step autoregressive prediction.

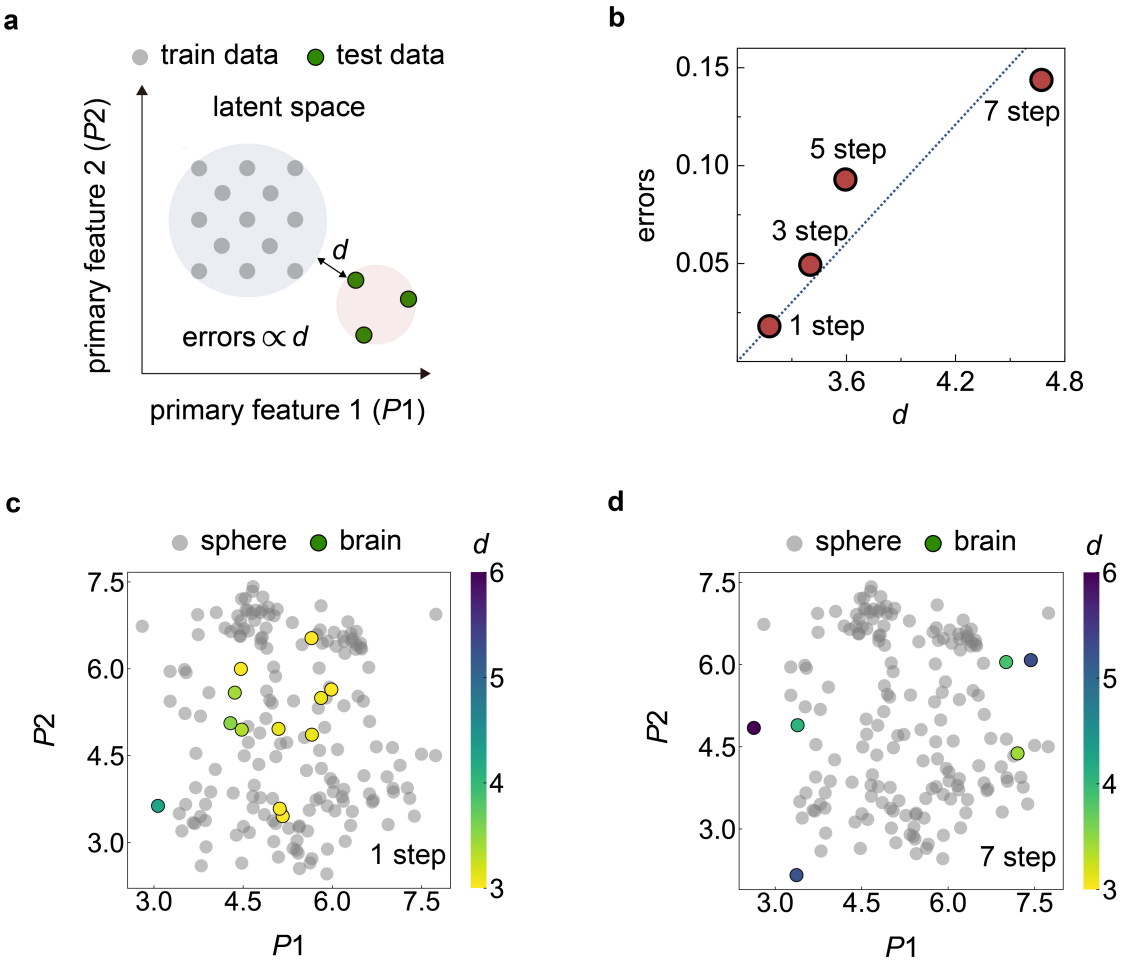

Figure S6. Distribution differences of latent features for assessing model generalization. **(a)** Quantifying the relationship between latent space features and generalizability for prior estimation of model performance. **(b)** Prediction error increases with the distance between training spherical data and testing brain data, indicating reduced generalizability with greater dissimilarity. **(c,d)** In the latent space, the 1-step brain input is closest to the sphere dataset and yields the lowest prediction error **(c)**, whereas the 7-step input is farthest and has the highest error, illustrating reduced generalization with increasing input complexity **(d)**.

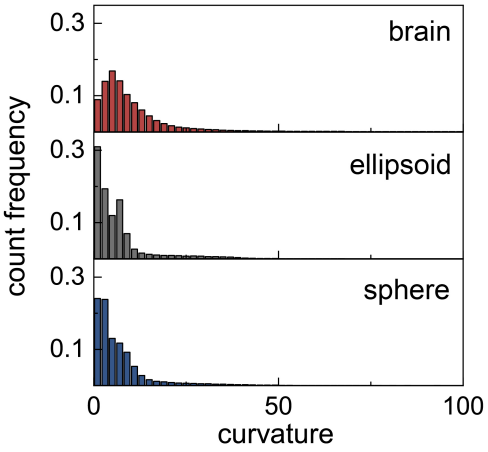

Figure S7. Distribution of local curvature across domains.

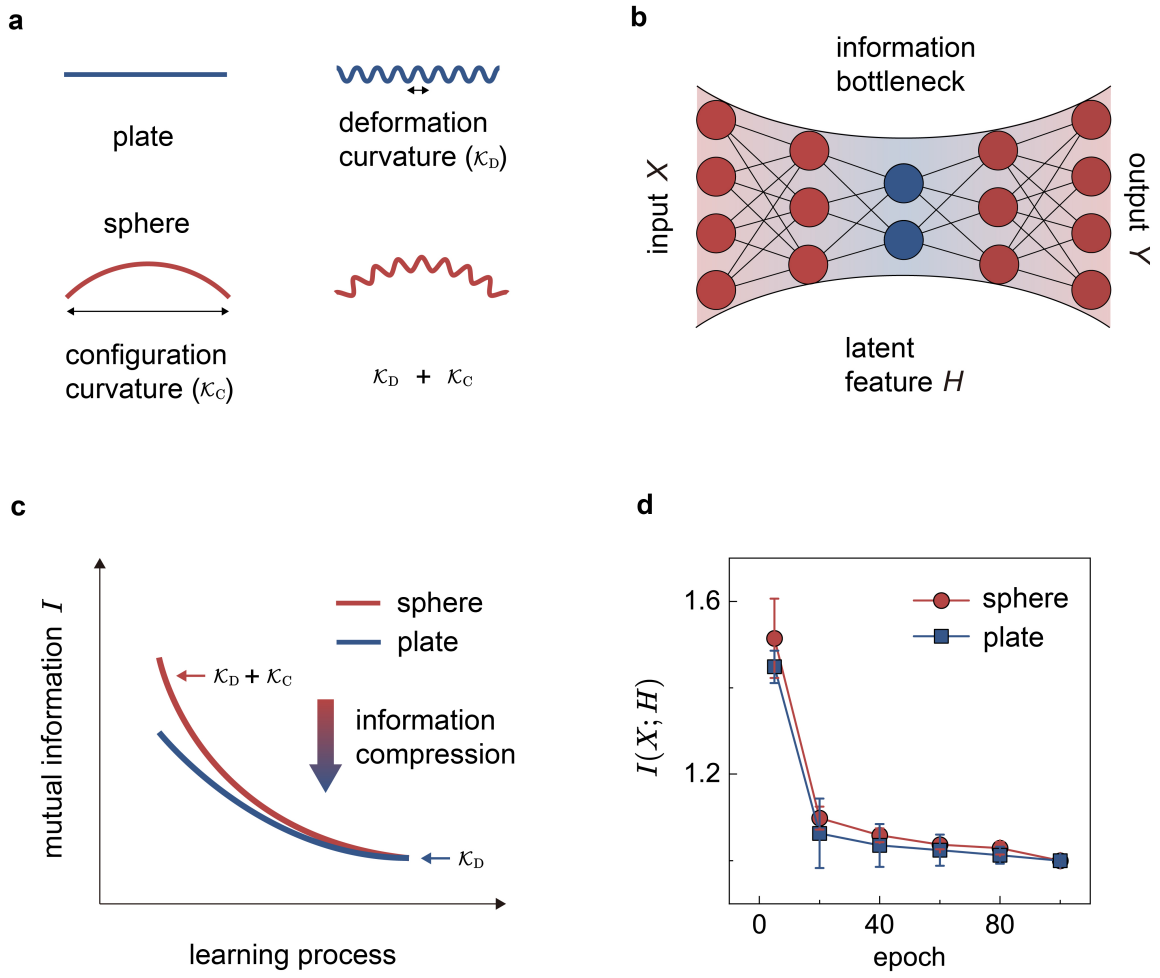

Figure S8. The information bottleneck theory and physics-transfer model distinguish the effects of curvature at different scales. **(a)** Curvatures at different scales during morphogenesis. **(b)** Deep neural network (DNN) and information bottleneck framework. **(c)** Convergence of mutual information during training reflects the extraction of latent features that capture morphogenetic principles. **(d)** Information compression during training for the spherical dataset and the flat plate dataset.

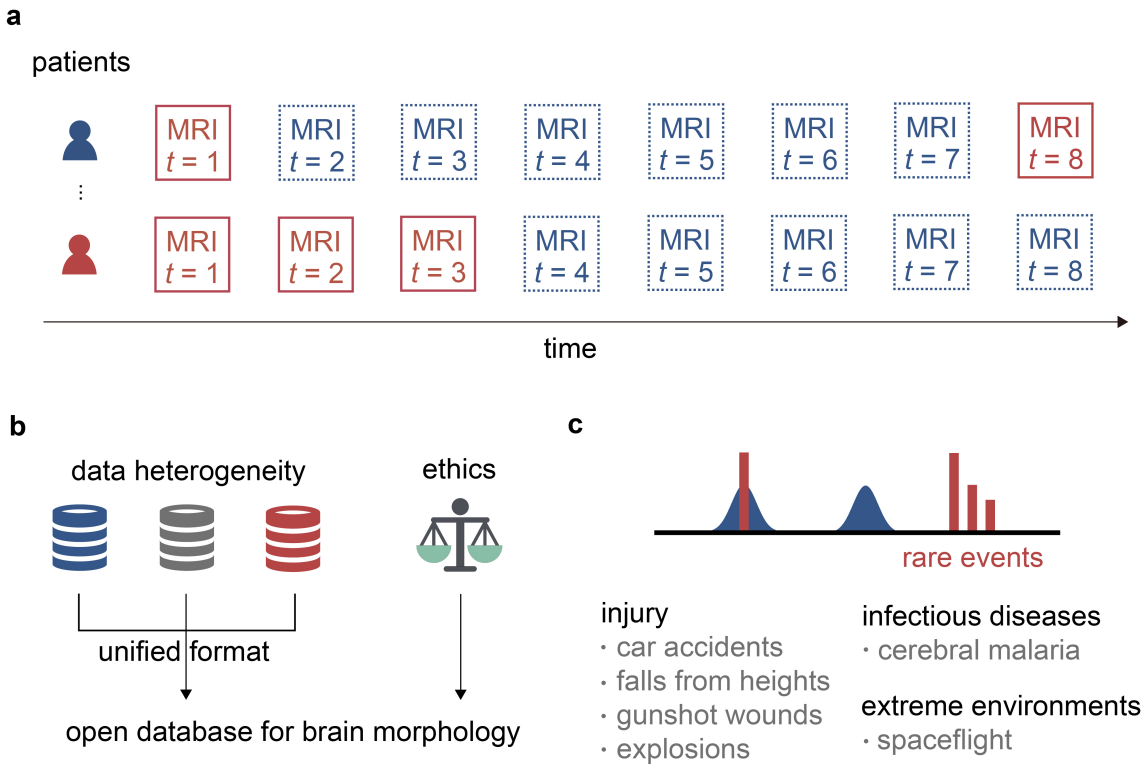

Figure S9. Medical applications and perspectives. **(a)** Longitudinal MRI data enable personalized prediction of brain morphological development using PT models. **(b)** Challenges in building an integrated open database for brain development. **(c)** Effects of rare events on brain morphogenesis and disease.

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