Subcortical structure areal expansion in the human compared to the chimpanzee and heritability

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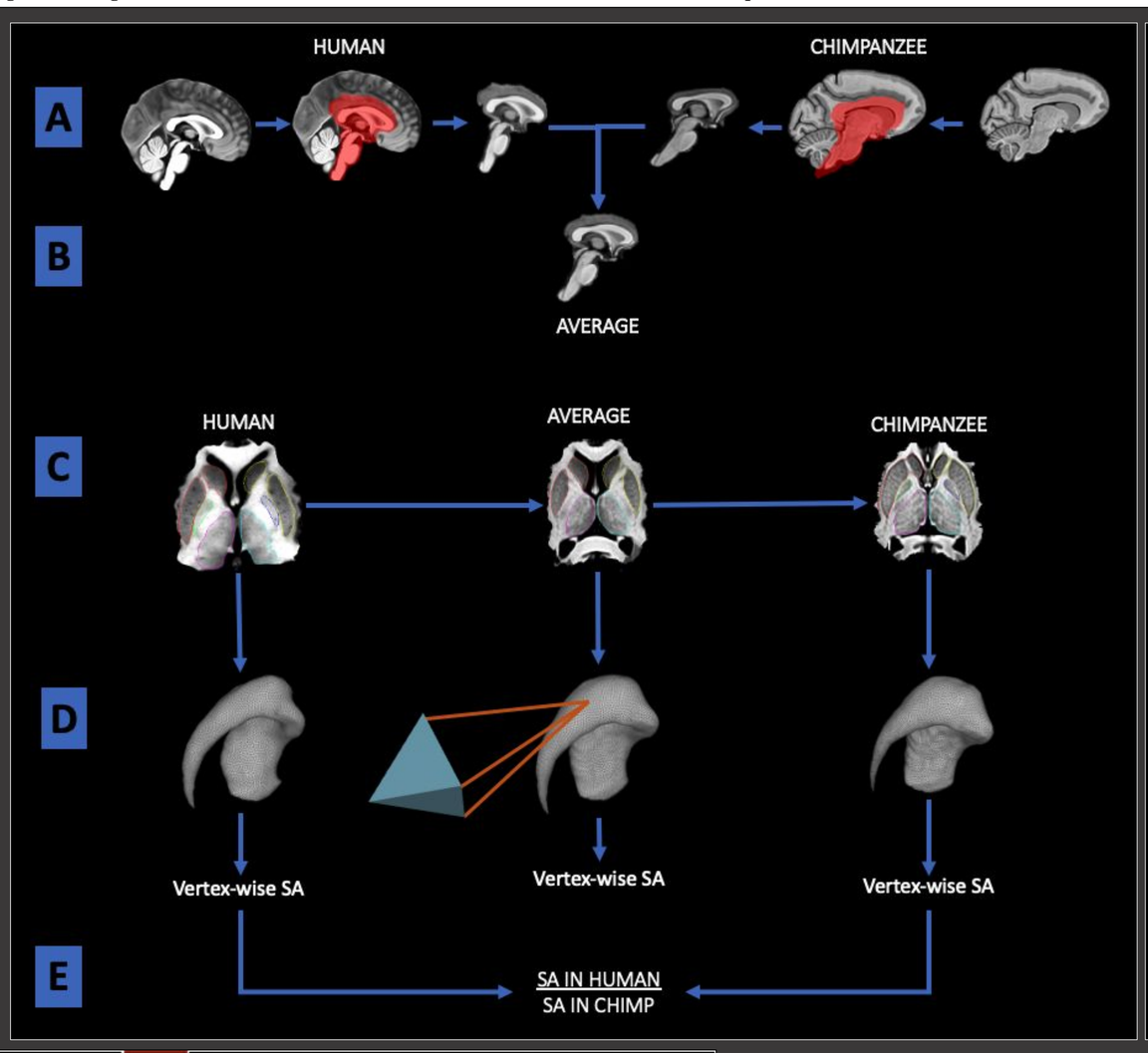
INTRODUCTION.

Animal models are critical for studying the influence of genes and environment on the brain. Previous work has shown that cortical areas that are most preserved across species (i.e. proportionally less variable in size) tend to be more heritable [4, 7]. However, this relationship is unknown in subcortical structures (striatum, thalamus, globus pallidus), despite their critical role in human behaviour and as connection hubs [5]. We address this aim by mapping human-chimp differences in subcortical shape, and comparing these difference maps with subcortical shape heritability in humans. A better understanding of homologies and differences in humans and in animals could lead to clearer interpretations of how the results of animal studies translate directly to humans.

Figure 1: Methods. **(A)** 3D surface representations of the subcortical structures were compared between magnetic resonance imaging (MRI) templates of the human (0.3 mm resolution 3T T1w brain template from the MAGeTbrain pipeline, group-wise average from 5 subjects at high-resolution) [4, 11] and the chimpanzee (0.4 mm resolution brain template developed in our group, Devenyi et al., in prep, generated by averaging T1w MRI data from 216 chimpanzees (139 at 3T; 77 at 1.5T) from the National Chimpanzee Brain Resource (NCBR; https://www.chimpanzeebrain.org)). A subcortical brain mask was manually generated for each template and the subcortical structures were brought into correspondence using ANTs (https://github.com/ANTsX/ANTs, [3]) to create a mean subcortical human-chimpanzee hybrid template. **(B)** The MAGeT subcortical surfaces were transformed from the human to the chimpanzee, using the vector warp fields generated through the human-chimpanzee hybrid. **(C)** The MAGeTbrain surface meshes were transformed from the human subcortical brain to the average and chimpanzee subcortical brains. **(D)** Vertex-wise surface area (SA) maps were extracted with the CIVET 2.0 [2] depth_potential function, and **(E)** the expansion map between two brains was created by examining the ratio between template-specific vertex-wise surface area, after accounting for linear differences.



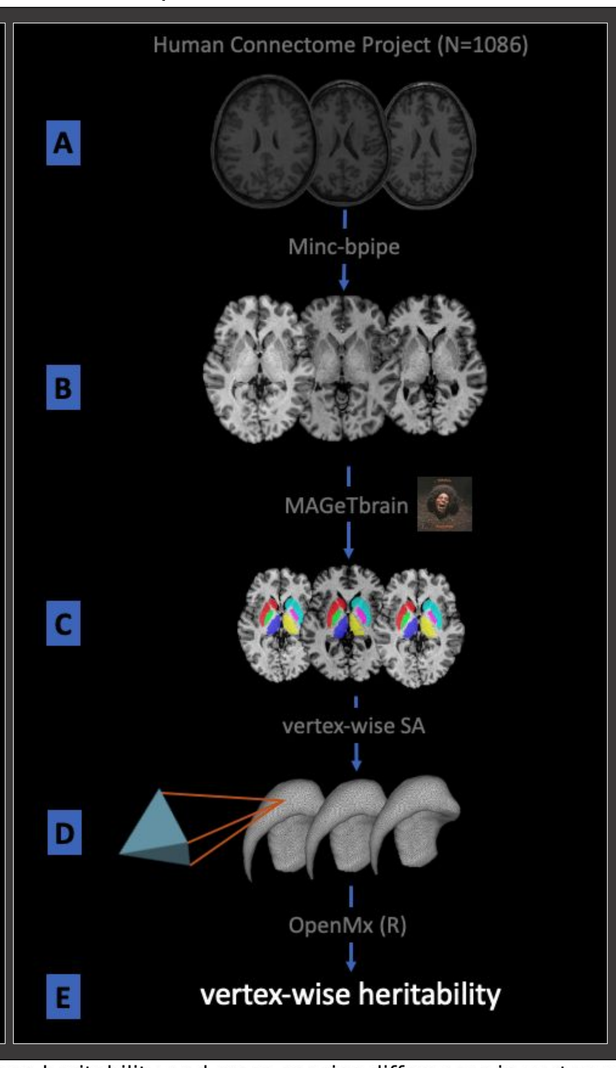
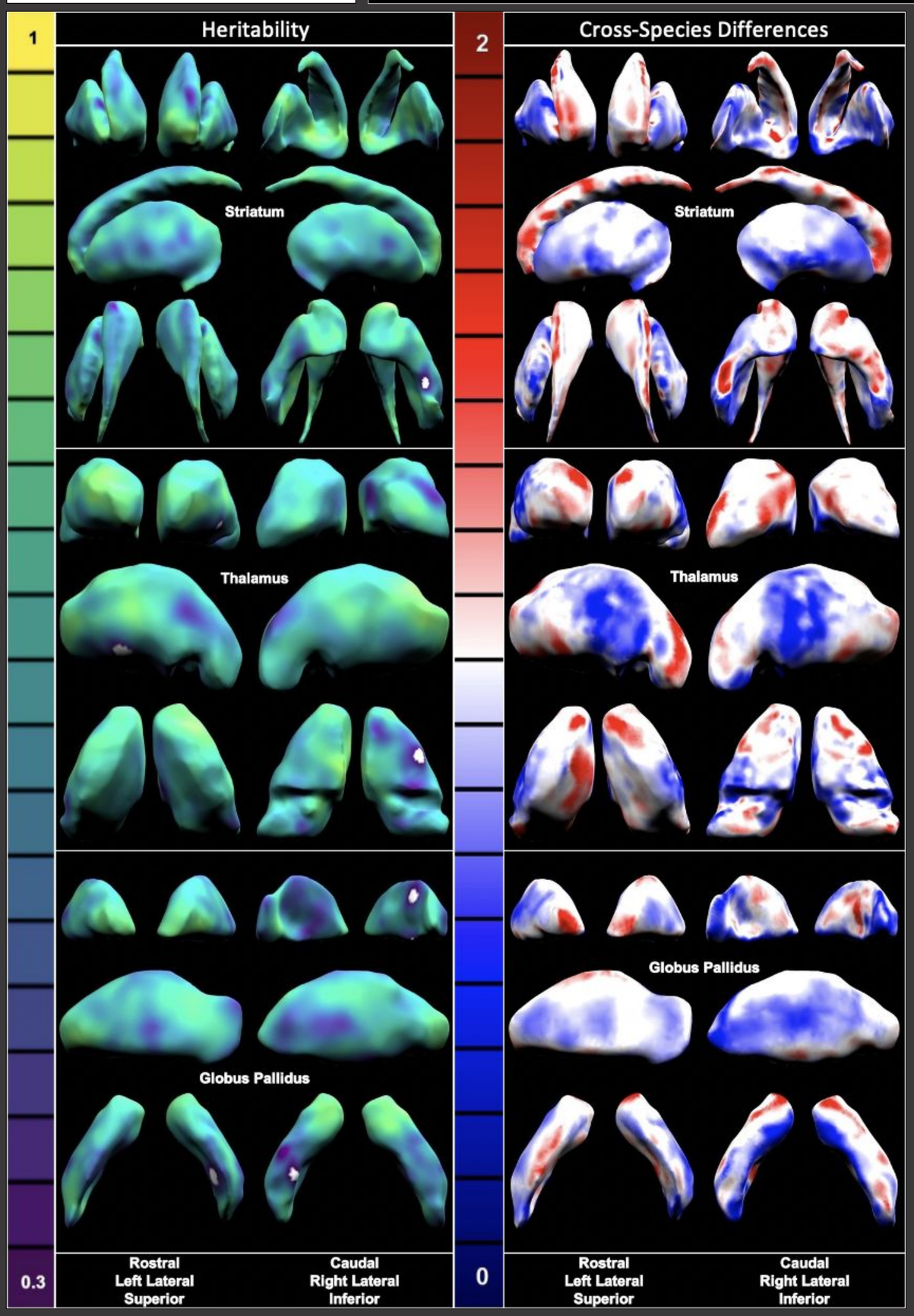


Figure 2: methods. Heritability measures were computed via a twin and non-twin sibling design, using MRI data of healthy adult twin (monozygotic and dizygotic) and non-twin siblings from **(A)** the Human Connectome Project (HCP; n=1086 participants; 3T; T1w; 0.7 mm isotropic voxels) [10]. **(B)** Images were preprocessed using the minc-bpipe-library (https://github.com/CobraLab/minc-bpipe-library/), and **(C)** subcortical structures were segmented using MAGeT [11] and the CoBrA Lab subcortical atlases [9]; 1008, 1007 and 1009 subjects passed quality control for the globus pallidus, thalamus and striatum, respectively. (D) The morpho setting of MAGeTbrain output vertex-wise SA measures. (E) OpenMx (version 2.12.2) was used to compute heritability estimates using structural equation modeling [8] with a 5% FDR threshold.



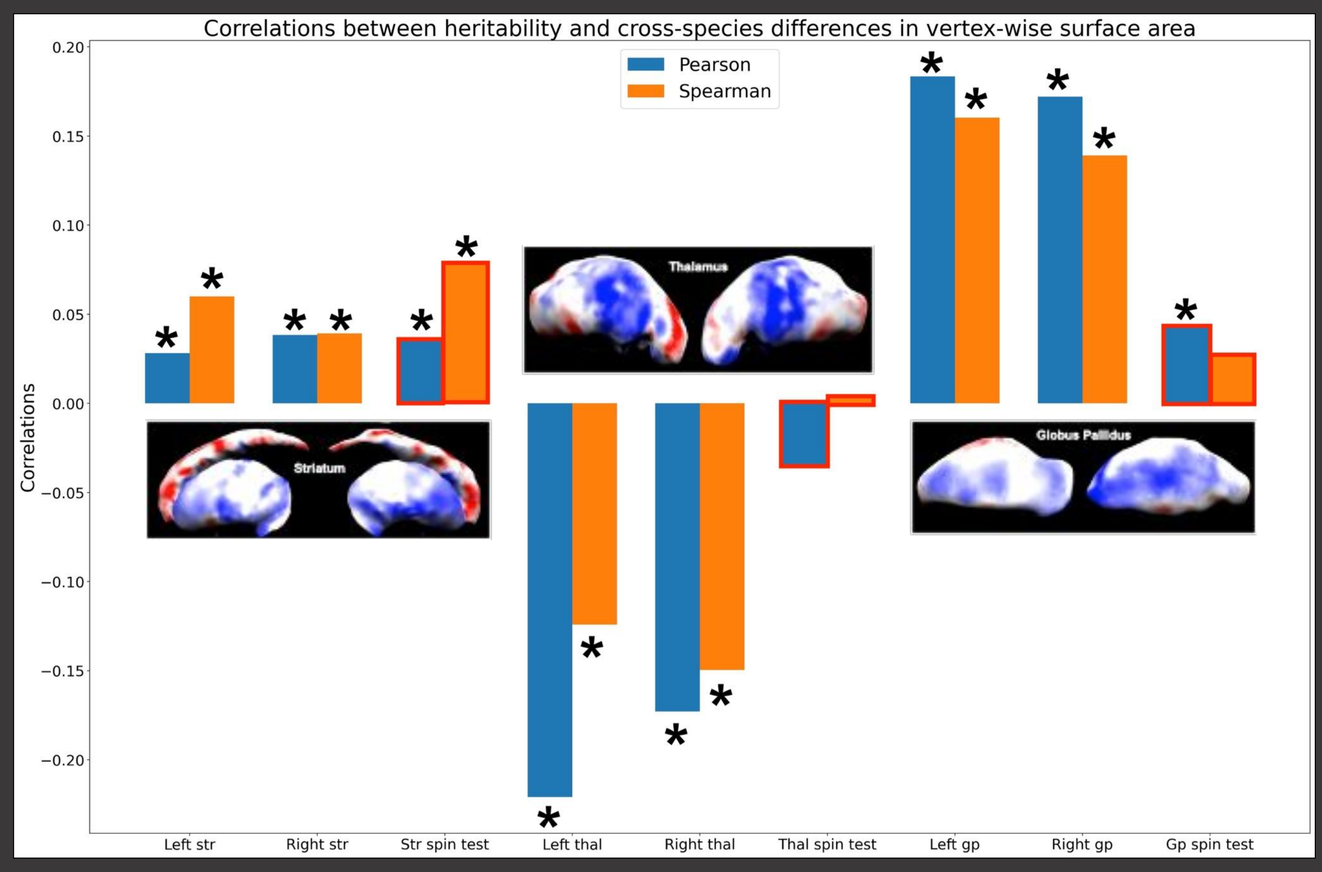


Figure 3 (above). We computed the Pearson (blue) and Spearman (orange) correlations between vertex-wise heritability and comparative human-specific expansion using Scipy-Stats in Python 3.8.3 and applied a 5% Bonferroni correction across the 12 regressions, by structure. We then compared the heritability maps to the cross-species differences maps by adapting the canonical bilateral cortical spin-test to subcortical surface objects [2]. Stars indicate correlations that had a significance value below 5%.

Figure 4 (left). Left-hand side: univariate heritability estimates (h^2) for vertex-wise surface area; areas in gray failed to pass an FDR correction threshold of 5%. Right-hand side: human-specific contracted (value below 1) and expanded (value above 1) areas relative to the chimpanzee, computed via the ratio of the vertex-wise surface area in the human to the vertex-wise surface area in the chimpanzee, displayed on the human subcortical surfaces.

RESULTS.

- Portions of the lateral putamen, thalamus and globus pallidus are contracted in the human compared to the chimpanzee, whereas the caudate and left medial thalamus and rostral globus pallidus were observed to have undergone preferential expansion (see Figure 4).
- There are to be higher heritability values in the surface area of the caudal portions of the striatum, the rostral thalamus and the caudo-inferior globus pallidus (see Figure 4).
- Simple correlation tests that do not account for the spatial information between the values of two brain maps inflate the significance of the correlations between maps (see Figure 3). For vertex-wise surface area, the bilateral subcortical spin-test yielded significant Pearson and Spearman correlations for the striatum and a significant Pearson correlation for the globus pallidus.

CONCLUSIONS.

Our study shows how spatially-distributed heritability patterns are significantly positively correlated with human-specific aerial expansion in the striatum and globus pallidus. Given the complexity of gene-brain-environment interactions, future work will examine if there exists a relationship between comparative differential regional expansion and neurodevelopment, as observed in the cortex [4].

REFERENCES.

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