The Heritability of Subcortical Structures Using a Twin and Non-Twin Sibling Design

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Introduction

In many Imaging-genetics studies the heritability of the quantitative phenotype under study is often a prerequisite for its use in future analyses (such as GWAS). The current work extends previous work from our group examining the heritability of the hippocampus[1] and its subfields to examine the heritability of subcortical structures, specifically, the thalamus, pallidum and striatum.

Methods

Data Acquisition: The WU-Minn Human Connectome Project[2].

- S1200 Release of structural imaging data on 1086 healthy young adults (ages 22-34), including 149 pairs of genetically confirmed MZ twins and 94 pairs of genetically confirmed DZ twins (n = 1086);
- 3T T1w Structural MRI scans (TE/TR=2.14/2400 ms, TI=1000ms, a=8º, 0.7 mm^3 isotropic voxels).

Image Preprocessing.

- Minc-bpipe library (https://github.com/CobraLab/minc-bpipe-library): N4correction (bias field), Cutneck, Head and Brain masks using BeAST (Total Brain Volume Extraction) and registration to MNI space;
- Manual quality control for motion, intensity, MNI outline and brain mask.

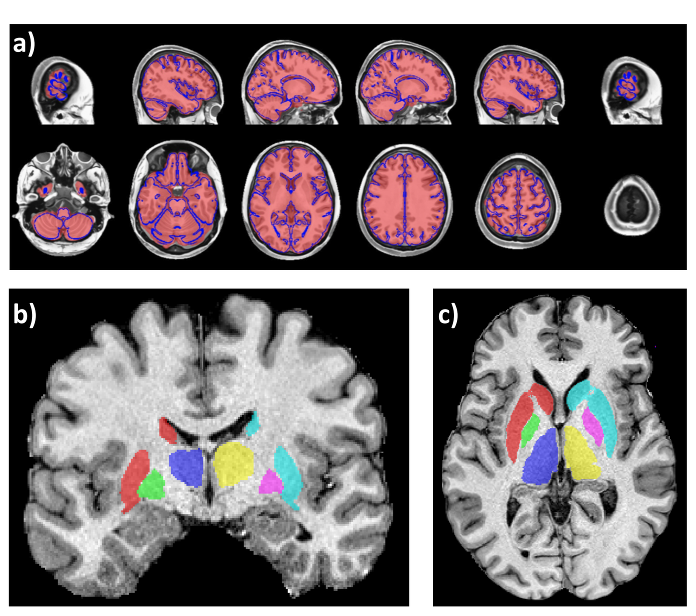


Figure 1. a) Minc-bpipe library: pink brain mask generated by BEAST, blue outline of the MNI Brain; b) MAGeT: coronal view of labelled subcortical structures; c) MAGeT: axial view of labelled subcortical structures.

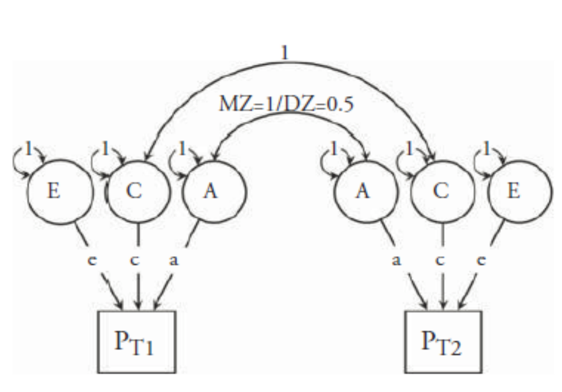
Image Processing.

- Subcortical labels and volumes were obtained using MAGeTbrain[3,4] and the CoBrA Lab subcortical atlases[5];
- Manual quality control for segmentation accuracy reduced sample size to 821, 866 and 950 subjects passing for the striatum, the thalamus and the pallidum, respectively.

Heritability Estimates.

- The OpenMx package (version 2.12.2) in R (version 3.5.1) was used to compute heritability estimates of subcortical volumes through structural equation modeling[1];
- All volumes were adjusted for sex and age;
- Univariate model: heritability estimates of total brain volume (TBV) and subcortical structure volumes (both unadjusted and adjusted for TBV) across all subjects[1];
- Univariate model: heritability estimates of vertex-wise surface area and displacement[6];
- Bivariate model: shared heritability estimates and genetic correlation between total brain volume and subcortical volumes across all subjects[1].

Figure 2. Univariate Model Path Diagram. Image taken from Blokland, G.A.M., et al. The Oxford Handbook of Quantitative Methods in Psychology. Chapter 10



Heritability Estimates of Subcortical Structure Volumes

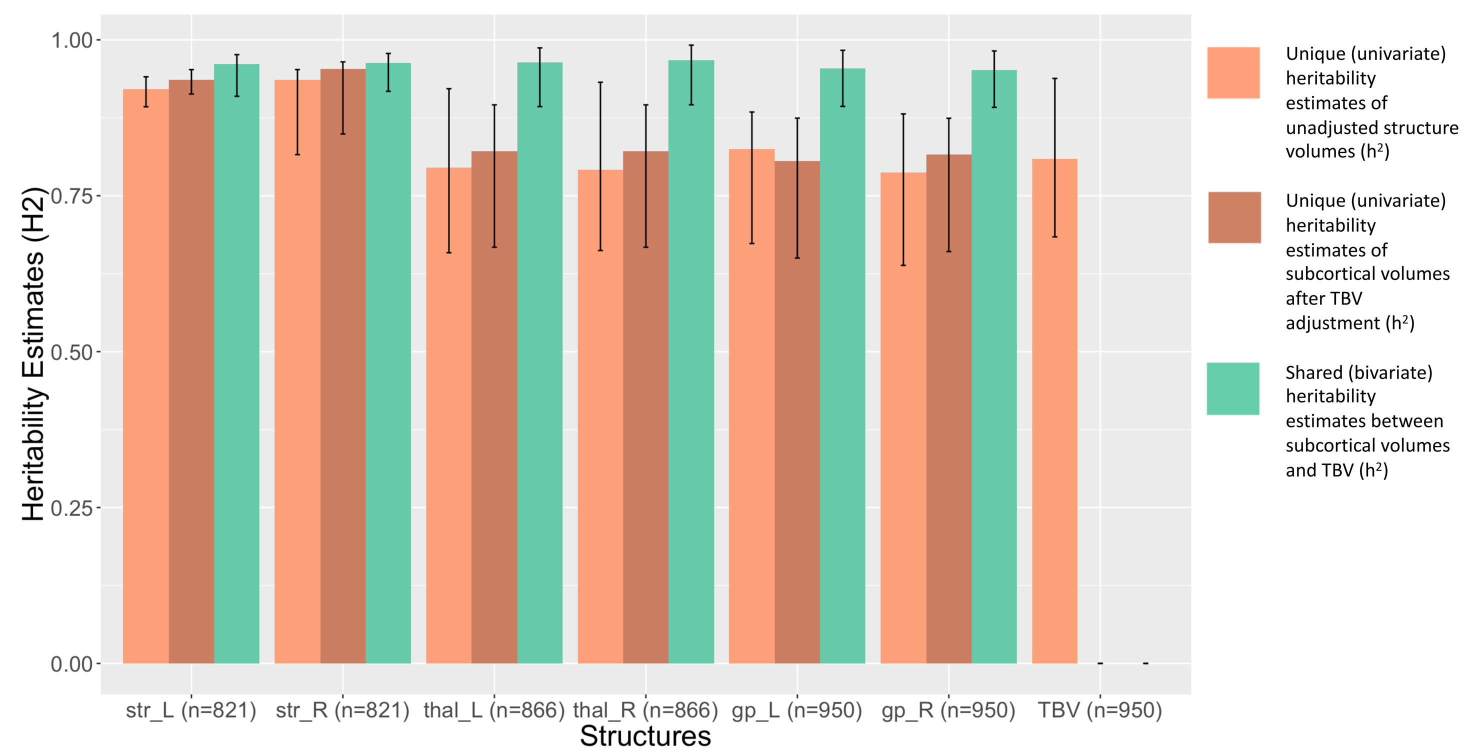


Figure 3. Heritability estimates (h^2) for left (L) and right (R) subcortical structure volumes and TBV with 95% confidence intervals.

Correlations Between Subcortical Structure Volumes and TBV

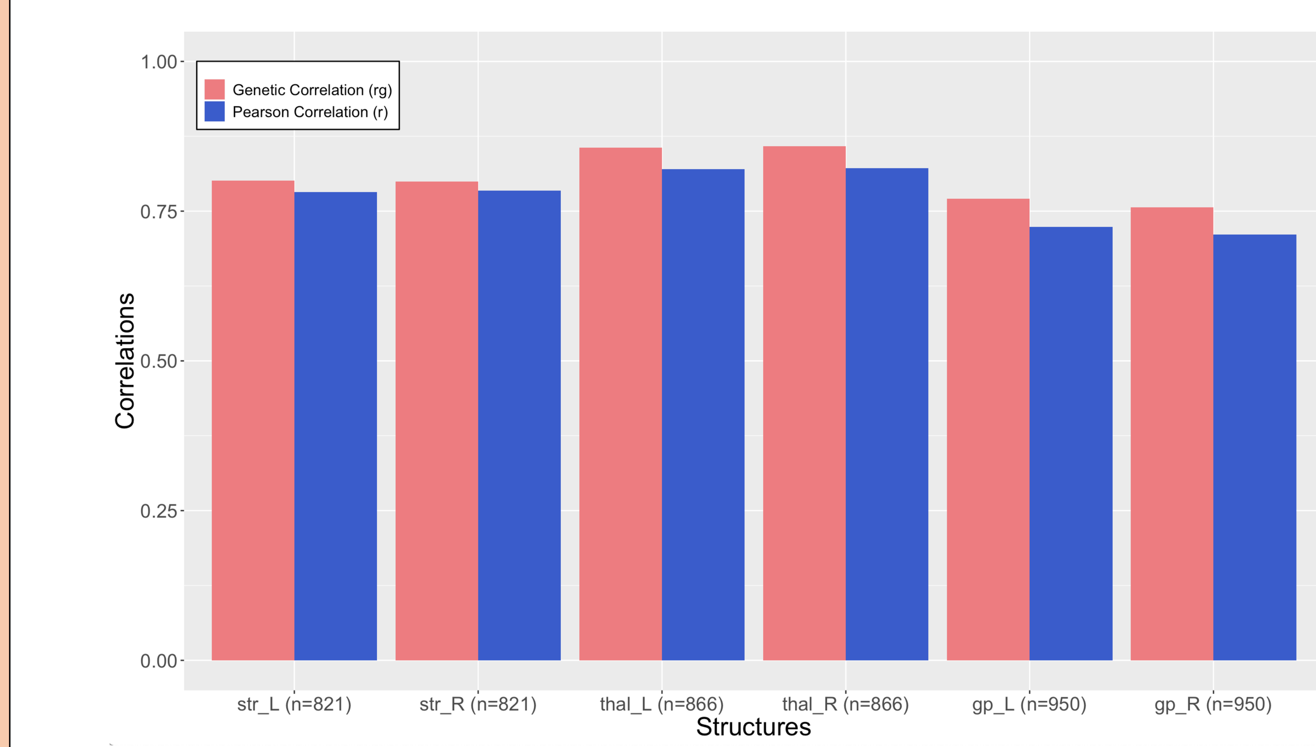


Figure 4. Pink bars indicate genetic correlation (r_g) between subcortical volumes and TBV; blue bars indicate Pearson correlation (r) between subcortical volumes and TBV.

Vertex-Wise Heritability Estimates

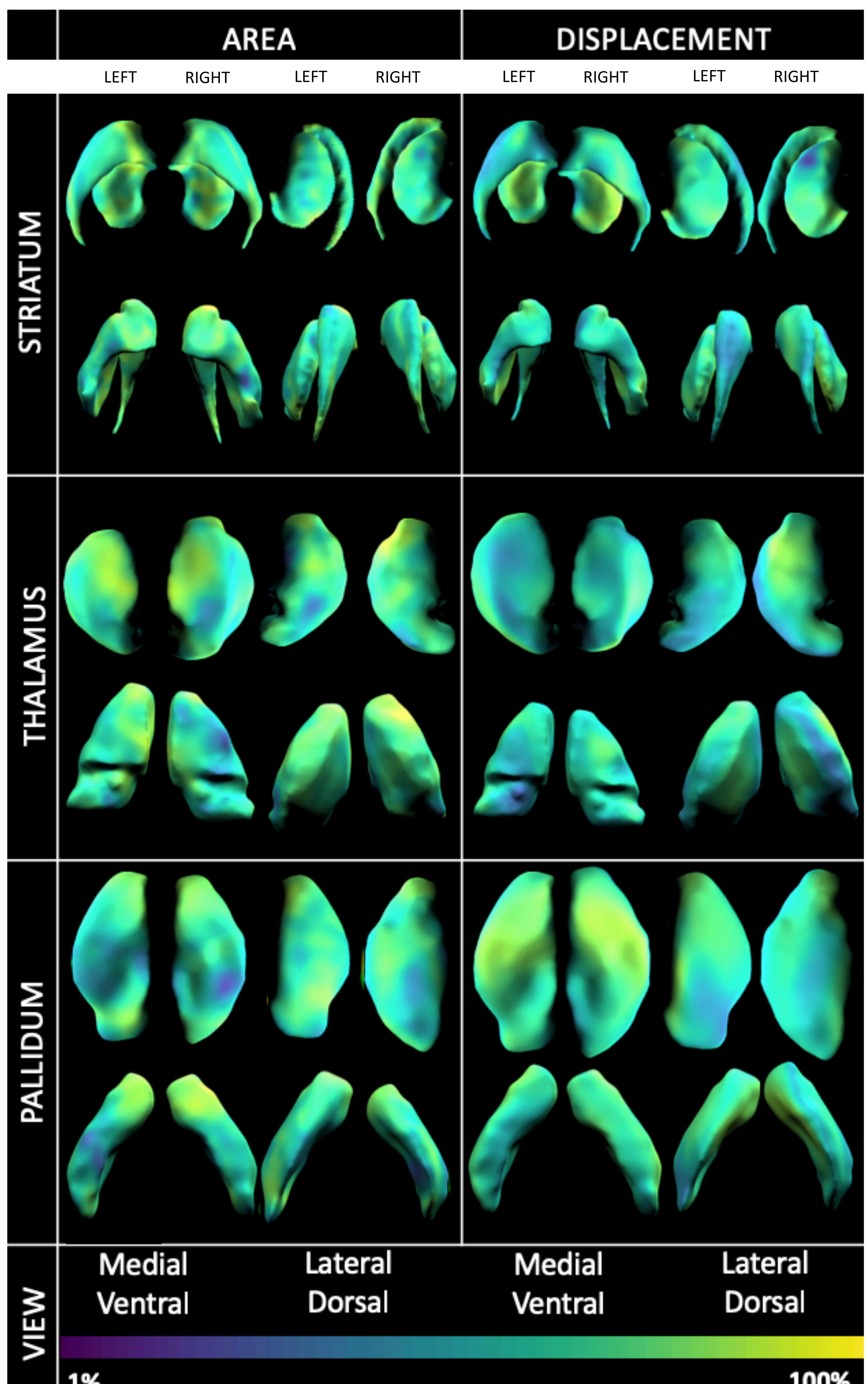


Figure 5. Vertex-wise heritability estimates (h^2) of subcortical structure surface area and displacement for left and right subcortical structures, ranging from 1% (purple) to 100% (yellow).

	Left Striatum	Right Striatum	Left Thalamus	Right Thalamus	Left Pallidum	Right Pallidum
Vertex-Wise Surface Area (%)	67	61	64	59	63	66
Vertex-Wise Displacement (%)	68	63	67	55	63	63

Figure 6. Mean heritability estimates (h^2) for vertex-wise surface area and displacement.

Results

- Univariate model showed significant genetic effects ($p < 0.001$) and yielded heritability estimates (h^2) ranging from 79% (right pallidum) to 94% (right striatum) before TBV adjustment and 81% (left pallidum) to 95% (right striatum) after TBV adjustment;
- Bivariate model showed significant genetic effects ($p < 0.001$) and yielded heritability estimates (h^2) ranging from 95% (left and right pallidum) to 97% (right thalamus);
- The genetic correlation (r_g) between TBV and subcortical volumes ranged from 76% (right pallidum) to 86% (left and right thalamus);
- Pearson correlation (r) between TBV and subcortical volumes ranged from 71% (right pallidum) to 82% (left and right thalamus);
- Highest heritability estimates of subcortical shape were bilaterally located at the caudate tail, medial putamen, rostral thalamus and rostral pallidum for vertex-wise surface area and at the medial putamen and rostro-medial pallidum for vertex-wise displacement.

Summary

- Adjusting subcortical volumes for TBV yields a slight increase in heritability estimates;
- Shared heritability between subcortical volumes and TBV is higher than unique heritability for subcortical volumes;
- Phenotypic (r) and genetic correlations (r_g) between subcortical volumes and TBV are very similar;
- Heritability estimates for vertex-wise displacement and surface area are independent of each other and have a heterogeneous distribution;
- Variance of subcortical structure volumes and overall subcortical shape largely due to genetic effects;
- Such findings can lead to a better understanding of the significance of genetic risk factors in subcortical diseases.

References

1. Patel et al (2017) *Human Brain Mapping* 38 (9): 4337–52. **2. Van Essen et al** (2013) *NeuroImage* 80: 62–79. **3. Chakravarty et al** (2013) *Human Brain Mapping 34 (10):* 2635–2654. **4. Pipitone et al** (2014) *NeuroImage* 101: 494–512. **5. Tullo et al** (2018) *Scientific Data* 5: 180107. **6. Patel et al** (2018) *NeuroImage* 178: 78–91.