Genetic Association of Blood Pressure With Cortical Microstructure and Functional Connectivity

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Background and Aim

- High blood pressure (BP) is the leading modifiable and heritable risk factor for cardiovascular disease worldwide.
- Subclinical brain alterations, including reductions in regional white matter and gray matter volumes are common among people with high BP (Maillard et al., 2013). However, their microstructural properties and relation to brain function are unclear.
- **Our study sought to elucidate if shared genetic factors contribute to BP variations and their association with local cortical microstructure and intrinsic functional connectome organization.**

Methods

- Data were obtained from **Human Connectome Project** (S1200 release; Glasser et al. 2013; Van Essen et al., 2013). The sample was composed of monozygotic and dizygotic twins, siblings and unrelated individuals (N=1078; mean age=29 y; 597 women).
- Preprocessing and quality control by **HCP minimal preprocessing pipeline** (Glasser et al. 2013; Van Essen et al., 2013)
- Blood pressure: **Systolic and diastolic BP** measured in seated position, in the left arm using a semi-automatic blood pressure monitor after resting for at least five minutes.
- Brain measures at 3T (**Figure 1**):
  - Segmentation of T1w and T2w images and surface reconstruction using FreeSurfer version 5.3-HCP (Glasser et al. 2013)
  - Microstructure (T1w/T2w): **Microstructural intensity profiles** were created by sampling T1w/T2w values along 12 equidistant layers between the gray matter/white matter and gray matter/pial surfaces (Paquola et al., 2019)
  - **Functional connectivity**: Functional connectomes were constructed by cross-correlating resting-state time series of nodes
- Parcellation scheme: All brain measures were extracted within the **Schaefer-7-networks-400 parcels** solution in conte69 template space (Schaefer et al., 2018)
- To study macroscale functional connectome organization, we first used diffusion embedding, a nonlinear dimensionality reduction technique that resolves the principal axes of intrinsic functional differentiation (Vos De Wael et al., 2020; Coifman & Lafon, 2006). Next, we computed the Euclidean distance between the main axes' centre and all cortical nodes in 3D space (Park et al., 2021), which explained over 45% of variance in the affinity matrix (i.e. **functional manifold eccentricity**, **fME**).
- SOLAR 8.4.1.b (http://solar-eclipse-genetics.org) was used for **heritability** and **genetic correlation** analyses using the twin structure of HCP.

Results

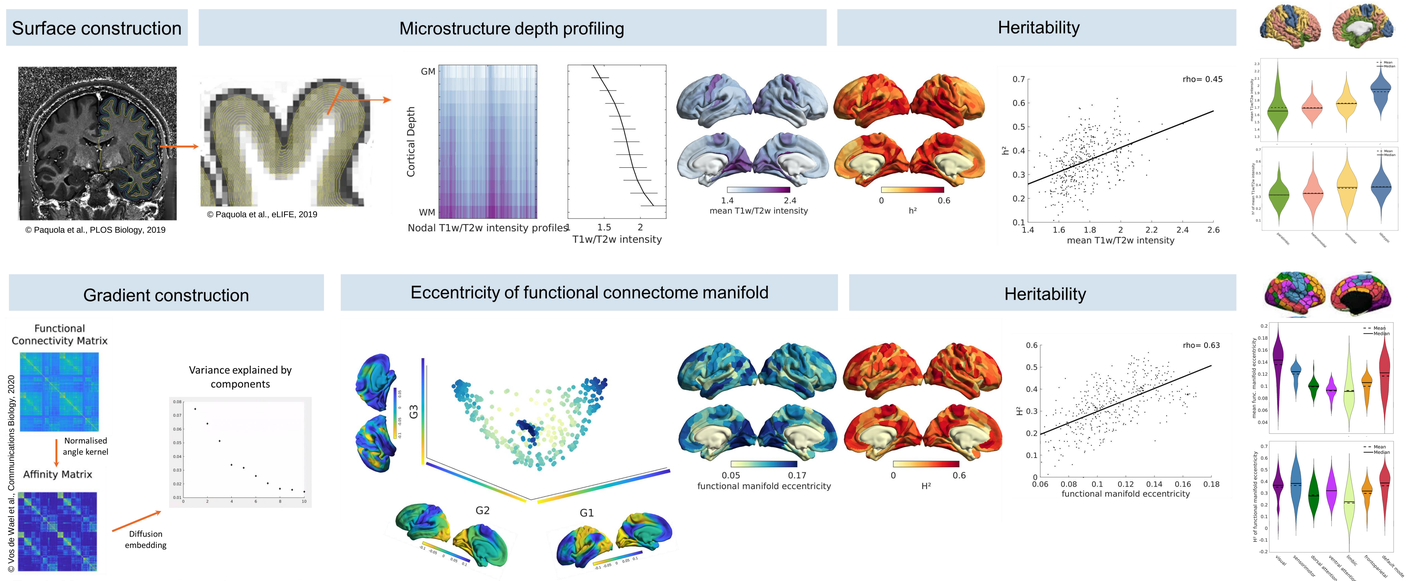

Fig 1. Microstructural and functional brain organization and heritability

top: Cortex-wide intensity profiles were calculated by systematic intensity sampling across intracortical surfaces (rows) and nodes (columns). Mean microstructural intensity and its heritability at each node (group-averages displayed on the cortex) were correlated. Violin plots show microstructural intensity (top) and its heritability vary within levels of laminar differentiation from paralimbic (lowest) to idiotypic (Mesulam, 1998; Paquola et al., 2019). This indicates a genetic basis of cortical myelination along distinct levels of laminar differentiation. *bottom*: Flowchart of constructing the principal functional connectome components (gradients). Scatterplot of first three components (explaining over 45% of variance) spreading out the functional manifold space. Colour coding indicates eccentricity from manifold center (fME). fME and its heritability at each node (group-averages displayed on the cortex) were strongly correlated. Violin plots show fME and its heritability vary within functional communities (Schaefer et al., 2018). Overall, regions with greater fME, indicating greater segregated network organization, were also more heritable. Heritability of fME was highest in default mode, somatomotor and visual networks.

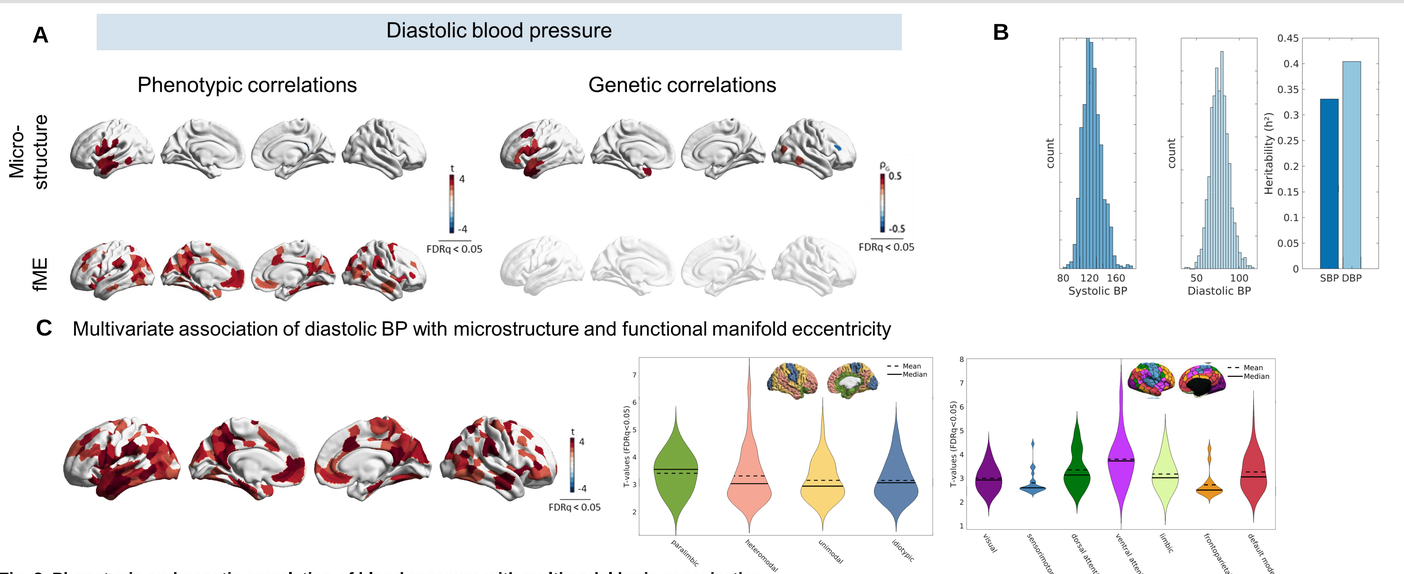

Fig. 2. Phenotypic and genetic correlation of blood pressure with multimodal brain organization

A) *left*: Phenotypic correlations of DBP with mean microstructural intensity and fME, respectively. DBP was associated with microstructure in left inferior sensorimotor regions, left inferior lateral parietal lobe and left lateral temporal regions, as well as with fME, particularly in ventral attention and default mode regions. *right*: Genetic correlations were only significant for microstructure, revealing a strong genetic effect in largely overlapping clusters in phenotypic correlations. **B**) Distributions of SBP and DBP in HCP S1200. BP was significantly heritable, but DBP more so than SBP. **C**) Multivariate phenotypic association of DBP with both microstructure and fME. Violin plots show distribution of FDR-corrected t-values within levels of laminar differentiation (Mesulam, 1998; Paquola et al., 2019) and functional communities (Schaefer et al., 2018). Strongest effects (i.e., highest mean t-values) were observed in paralimbic cortex and the ventral attention network, which are commonly associated with saliency processing, plasticity and cognitive flexibility.

Discussion

- We observed a relationship between BP and cortical microstructure which was strongly associated with genetic effects.
- The topography of results mirrored patterns reported in brain maturation and aging (Grydeland et al, 2019; Paquola, Bethlehem et al., 2019).
- Complementary functional analyses yielded that higher BP also related to greater eccentricity of macroscale functional organization, particularly in the salience network. Greater eccentricity has been related to a more segregated network organization (Park et al., 2021).
- In contrast, supplementary analyses showed that higher heart rate variability (a marker of health and adaptability) was related to reduced fME in the same regions (not shown).
- While fME was heritable, we did not observe genetic correlations with BP. This highlights differences between structure and function in genetic effects on BP-brain associations, which could relate to stability-plasticity network properties.
- Multivariate analyses of microstructure and fME revealed a susceptibility of paralimbic cortices and the ventral attention network to effects of BP.
- Together, our study provides converging evidence that cardiovascular variations modulate cortical microstructure and functional brain organization, which is partly based on shared genetic effects. We observe that regions known for their plasticity throughout the lifespan are least heritable and highly vulnerable to effects of elevated BP.

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