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Heritability of the language network using resting state fMRI data

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Abstract

Language is a singularity of the human species. Part of the genes that are associated with brain capabilities are expected to underlie the human language faculty. Estimation of the part of variance attributable to genetic variation across subjects in functional brain imaging within the regions of the language, provide us a quantification of the genetic influence, called heritability. UK Biobank (UKB) with 19,336 subjects as well as Human Connectome Project (HCP) with 1113 subjects are used for that purpose. The present work consists in estimating the heritability of the language network (LN), by using resting state fMRI connectivity computed with regions of interest (ROI) extracted from task based fMRI. Significant heritabilities were observed (UKB: $h^2=10\%$ - 14% HCP: $h^2=22\%$ - 43%). The heritability h^2 obtained from different population studies are highly variable. The substantial differences between the two cohorts are studied and discussed here. Despite these differences, it seems that the brain organization supporting language in human is under genetic influence.

Introduction

- Functional MR imaging (fMRI) is recognized to produce valuable phenotypes to study the genetic roots of the human brain organization underlying language. Two specific settings are classically used to acquire such phenotypes:
 - Language specific task-based fMRI produces individual activations in language ROIs that are considered as phenotypes, but
 - Resting state fMRI (rsfMRI) can be a valid alternative to produce functional connectivity which assess how signal co-vary between language ROIs [1].
- In this work, the heritability studies utilize the co-activation of specific ROIs using resting state fMRI data as language phenotype.
- Two different kind of cohorts were used:
 - HCP composed of related subjects (twins and siblings).
 - UKB composed of non related subjects.
- A gap of heritability estimation between differently designed cohorts has been reported in [2].
- This study aims to:
 - Estimate the heritability of a specific language network.
 - Bring some clarification to the origin of the observed h^2 gap by studying the different design parameters:
 - The length of the time series.
 - Pedigrees vs genotyped SNPs.
 - The subjects relatedness: Model the shared environment between subjects using the household information (HHID)

Materials and Methods

UK Biobank (UKB)

- 19,336 participants underwent a rsfMRI experiment.
- Duration = 6 min, TR = 0.735s → 490 time points.
- QC on genetic data, excluding thus, subjects with unusual heterozygosity, high missingness, sex mismatches. Only subject identified as belonging to the British ancestry were kept.
- Age range: 40-70 years old, N = 18,851, F: 8,918, M: 9,933.

Human Connectome Project (HCP)

- 1,113 participants underwent a rsfMRI experiment. 143 monozygotic, 85 dizygotic verified twins and family members.
- Two sessions of 2 runs each. Duration = 14:33 min, TR = 720 ms → 1,200 time points per run.
- QC on genetic data, updating thus, the zygosity measures self reported by twins. Only subject whom performed the 4 runs & identified as Caucasian were kept.
- Age range: 22-37 years old, N = 739, F: 606, M: 507.

Phenotypes

- Seven ROIs identified by [3] from task fMRI experiments were used. See Fig 2a.
- Average signal was extracted from the ROI at each time frame.
- Functional connectivity was computed between each pair using partial correlation → 21 edges strength. See Fig 2b.

Heritability

- Depending on the genetic data available, two ways are considered to estimate the kinship matrix using:
 - GCTA (Genome wide complex trait analysis) [4] on genotyped SNPs → HCP and UKB.
 - SOLAR (Sequential Oligogenic Linkage Analysis Routines) [5] on pedigrees → HCP.
- Covariates (UKB): sex, genotype array type, age, age^2 , sex*age, sex* age^2 and the 10 first genetic principal components for population structure.
- Covariates (HCP): sex, age, age^2 , sex*age, sex* age^2 and ethnicity.
- Multiple test corrected with Bonferroni correction.

Discussion

- Higher heritability estimations in HCP compared to UKB. See Fig 4 & 6c.
- Length of the time series: the h^2 obtained after cutting the time series length (See Fig 3) reduce the gap. See Fig 5, 6d, 6e, 6f.
- In HCP, h^2 computed on genotyped SNPs are slightly higher than those obtained with pedigrees. See Fig 6a.
- Taking into account the household effect does not substantially impact the heritability estimates. See Fig 6b.
- It is noteworthy that:
 - Heritabilities have different estimates on both left and right hemispheres but behave similarly when varying the values of the studied parameters.
 - The pattern of heritability across the phenotypes remains consistent between the two cohorts.
 - Results are consistent with those obtained by [6] using surface area and cortical thickness as phenotypes.

Conclusion

- Different parameters have a substantial impact on heritability estimates; the method used, the length of the time series analysed and the environmental effect.
- The household information does not capture well the environmental impact.
- The results suggest some genetic influence on the phenotypes we chosen which indicates that the human language brain organization is under relatively strong genetic control.

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Methodology

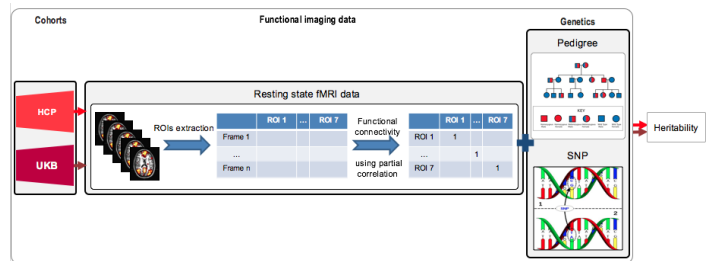


Figure 1: The heritability estimation process using both HCP and UKB cohorts

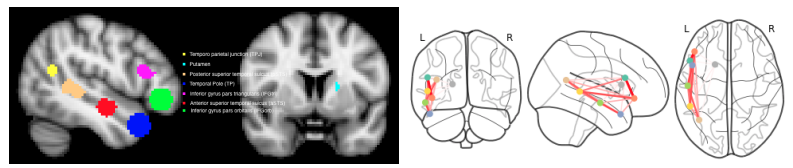


Figure 2: (a) Seven ROIs implicated in language computed from task fMRI [3]. (b) Mean functional connectivity calculated using partial correlation metric over all UKB rs fMRI subjects

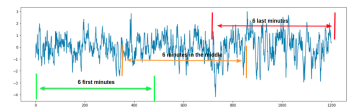


Figure 3: Different cut of the time serie (6 minutes)

Results

HCP/UKB heritability -resting state data-

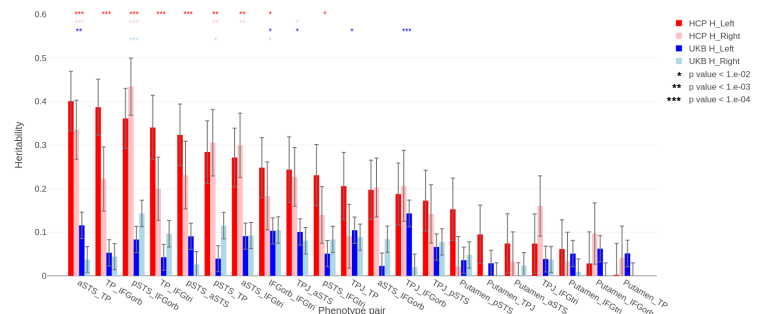


Figure 4: Heritability of the 21 edges of functional connectivity from rs fMRI

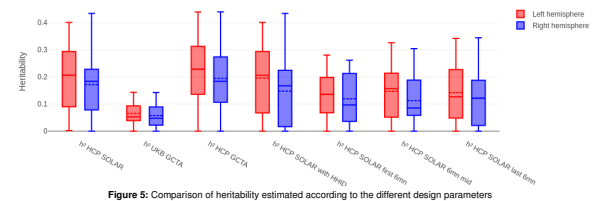


Figure 5: Comparison of heritability estimated according to the different design parameters

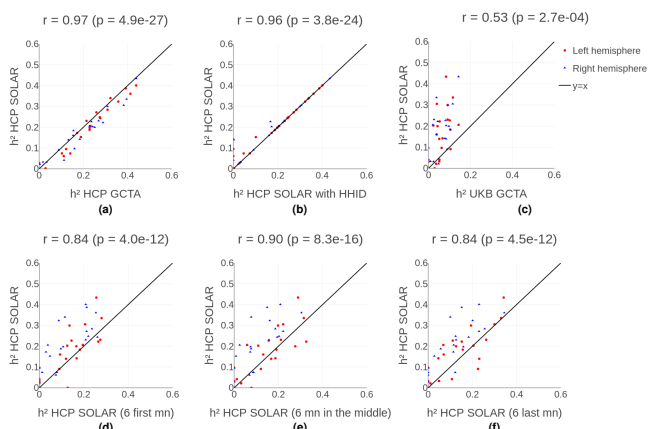


Figure 6: Comparison between heritability obtained with SOLAR on HCP (concatenation of the 4 runs) and the ones obtained with: (a) GCTA on UKB, (b) SOLAR on HCP taking into account the shared environment, (c) GCTA on UKB, (d) SOLAR on HCP (6 first minutes of the signal), (e) SOLAR on HCP (6 minutes in the middle of the signal), (f) SOLAR on HCP (6 last minutes of the signal)