Regional Study of the Genetic Influence on the Sulcal Pits

Yann Le Guen[a], Guillaume Auzias[b,c], Ghislaine Dehaene-Lambertz[d], François Leroy[d], Jean-François Mangin[a], Edouard Duchesnay[a], Olivier Coulon[b,c], Vincent Frouin[a]

[a]UNATI, Neurospin, I2BM, CEA, Université Paris-Saclay, Gif-sur-Yvette, France,
[b]Institut de Neurosciences de la Timone, UMR 7289, Aix Marseille Université, CNRS, Marseille, France
[c]Laboratoire des Sciences de l'Information et des Systèmes, UMR 7296, Aix Marseille Université, CNRS, Marseille, France
[d]Cognitive Neuroimaging Unit, U992, INSERM, Neurospin, I2BM, CEA, Université Paris-Saclay, Gif-sur-Yvette, France

ABSTRACT

The influence of genes on cortical structures has been assessed through various phenotypes already. However, the heritability of the sulcal pits, which are the deepest points of the sulci, has not yet been estimated. These pits are assumed to be under tight genetic control and to have close relationship with underlying functional organization. We estimated the heritability of these pits depth using the HCP pedigree data. Our results confirm previous hypothesis, with significant heritability estimates found for the pits of central and superior temporal sulci, and underline the pit as biomarkers of interest for future genome wide association studies.

Index Terms— imaging-genetic, heritability, sulcal depth, sulcal pits

1. INTRODUCTION

The human cerebral cortex is highly convoluted and this process of gyrification starts in utero. Several biological and physical mechanisms have been proposed to explain the formation of the first gyri, which is assumed to be related to the protomap as described in [1]. The central sulcus materializes such relationship between sulci and function by defining a boundary between the primary sensory and motor areas. In order to represent the first cortical folding locations, the notion of sulcal pits (or roots) was proposed by [2]–[4]. They correspond to indivisible units whose locations and relative spatial organization are supposed to be stable across individuals, as opposed to sulci that form later and show a large geometrical and topological intersubject variability. In order to extract these putative first cortical folding locations, algorithms have been defined over the past few years to extract the deepest points lying at the bottom of sulcal basins [3], [5]. These points located at the maximum depth in a basin show less intersubject variability than more superficial ones [4], [5]. Previous studies have shown that the spatial pattern of the sulcal pits is more consistent in monozygotic twins than unrelated individuals [6], [7], leading to the hypothesis of the pits being under strong genetic control and having close relationship to functional areas [4]. Furthermore a longitudinal study, has demonstrated that the spatial distribution of the pits located in deep sulci already exists at term birth and becomes more pronounced during the first two years of life along with the rapid brain volume increase [8]. This result suggests a genetic plan implemented before birth. This genetic control can be characterized by a heritability study, which consists in estimating the phenotypic variance explained by the genes additive effects.

To the best of our knowledge, the heritability of the sulcal pits depth has not been estimated yet. In a recent study [9], the depth profile of the central sulcus has been extracted in a pedigree study and the highest heritability estimates were found at the two peaks, in sulcal depth position profile. These two peaks, close to the hand and mouth cortical regions, actually correspond to the definition of the sulcal pits and reinforced the idea of a tighter genetic control at these points than other parts along the sulcus. Still little is known about the genetic heritability of sulcal pits in the rest of the cortex and the underlying associated genetic variants. Moreover, the potential genetic influence on the asymmetrical distribution of some of the pits is unknown.

Several studies have already emphasized the feasibility of using the sulcal pits as biomarkers to distinguish healthy subjects from diseased ones. Examples of such applications range from quantitatively describing the abnormal sulcal pattern in polymicrogyria [10] to characterizing the atypical sulcal pattern in children with developmental dyslexia [11] by using sulcal graph matching. Understanding the genetic underpinnings would provide insight into neuro-developmental disorders.

2. MATERIAL AND METHODS

2.1. Subjects, MRI Acquisition

In this work, we used the data released in December 2015 by the Human Connectome Project (HCP), details are available in the HCP reference manual S900. The number of participants included in our analysis is 882 (387/495 M/F), consisting of 170 twin pairs (85 monozygotic (MZ) and 85 dizygotic (DZ)), 456 siblings (including 83 with MZ pairs, 75 with DZ pairs) and 86 unpaired individuals, aged

between 22 and 37 years old ($\mu \pm \sigma = 28.8 \pm 3.7$ years). The unpaired individuals did not contribute to the genetic parameters estimation, but allowed a more accurate estimation of mean and variance effects. The 15 missing subjects compare to the S900 release are the ones from MEG2 release, which were not available in house at the time of writing. MR images were acquired by using a Siemens 3T scanner housed at Washington University in St Louis, using MPRAGE and SPACE sequences for respectively T1 and T2 weighted images which both have a 0.7 mm isotropic resolution.

2.2. Image processing and sulcal pits extraction

We used the T1w and T2w volumes, preprocessed by HCP, from each individual subject's MR data as inputs of the HCP Freesurfer pipeline, which is based on Freesurfer 5.3.0 with a number of enhancements specifically designed to capitalize on HCP data.

The cortical surface toolbox from BrainVISA (brainvisa.info 4.5.0) was used to extract the sulcal pits from the white meshes of both hemispheres in the native space for each individual [5]. The procedure first estimates the depth of each point on the surface using the depth potential function (DPF) [12], which integrates information from both convexity and curvature. On this depth map a filtered watershed algorithm was applied to localize the deepest point in each basin.

After the extraction of the pits at the individual level, we computed the symmetric group-level cluster regions as proposed in [5]. Briefly, the correspondences between cortical meshes from the left and right hemispheres were obtained through spherical interhemispheric registration based on the Freesurfer symmetric template *fsaverage_sym* [13]. The individual sulcal pits were iteratively smoothed corresponding to a Gaussian with 5 mm FWHM, maintaining a peak value of 1.

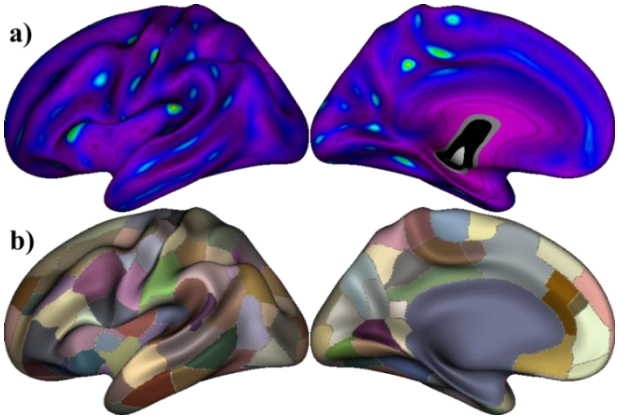

Figure 1. (a) Density map corresponding to the sum of the smoothed pits map across subjects. **(b)** Group-level sulcal basins obtained after performing the watershed on the density map.

The smoothed maps from both hemispheres were projected onto the left side of *fsaverage_sym*, and summed across subjects to obtain the group density map (**Fig. 1 (a)**). From this density map, group-level clusters of pits -denoted in the following as areals- were obtained by applying a watershed algorithm as detailed in [5] (**Fig. 1 (b)**). Note that using a symmetric template is crucial for quantifying the asymmetry: information from both hemispheres was taken into account when computing sulcal pit clusters so that cortical areals of the same size and shape were compared across hemispheres.

2.4. Heritability computation

In each areal on the symmetric template, we selected, separately on each hemisphere, all subjects having a deep sulcal pit and considered the DPF value associated to the deepest pit as our phenotype. The variance components method, as implemented in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) [14], was used for the heritability estimations of the local-DPF of the pit in each areal. The covariance matrix Ω for a pedigree of individuals is given by: $\Omega = 2 \cdot \Phi \cdot \sigma_g^2 + I \cdot \sigma_e^2$, where σ_g^2 is the genetic variance due to the additive genetic factors, Φ is the kinship matrix representing the pair-wise kinship coefficients among all individuals, σ_e^2 is the variance due to individual-specific environmental effects, and I is the identity matrix, assuming all environmental effects are uncorrelated among family members. Narrow sense heritability is defined as the fraction of the phenotype variance σ_p^2 attributable to additive genetic factors: $h^2 = \sigma_g^2 / \sigma_p^2$. Significance of the heritability is tested by comparing the likelihood of the model in which σ_g^2 is constrained to zero with the one of a model in which σ_g^2 is estimated. Before testing for the significance of heritability, phenotypes values for each individual within the HCP cohort were adjusted for the following covariates: sex, age, age², age·sex interaction, age²·sex interaction and estimated total intracranial volume by Freesurfer (eTIV). Inverse Gaussian transformation was also applied to ensure normality of the measurements. To correct multiple comparisons, our significance threshold for a strict Bonferroni correction is $p < 0.05 / (45 \times 2) \approx 5.6 \cdot 10^{-4}$.

3. RESULTS AND DISCUSSION

We successfully extracted the sulcal pits from the cortical surfaces of all the 882 individuals white meshes, thus demonstrating the reproducibility and reliability of the methods introduced in [5]. In the following text and table, the names given to areals lying at the bottom of sulci correspond to the ones found in Figure 6 of [3]. For the circular insular areals located in the vicinity of the Sylvian fissure our names follow the ones in Table S1 of [8].

We define the frequency of pits as the number of selected subjects having at least one deep sulcal pits divided by the total number of individuals.

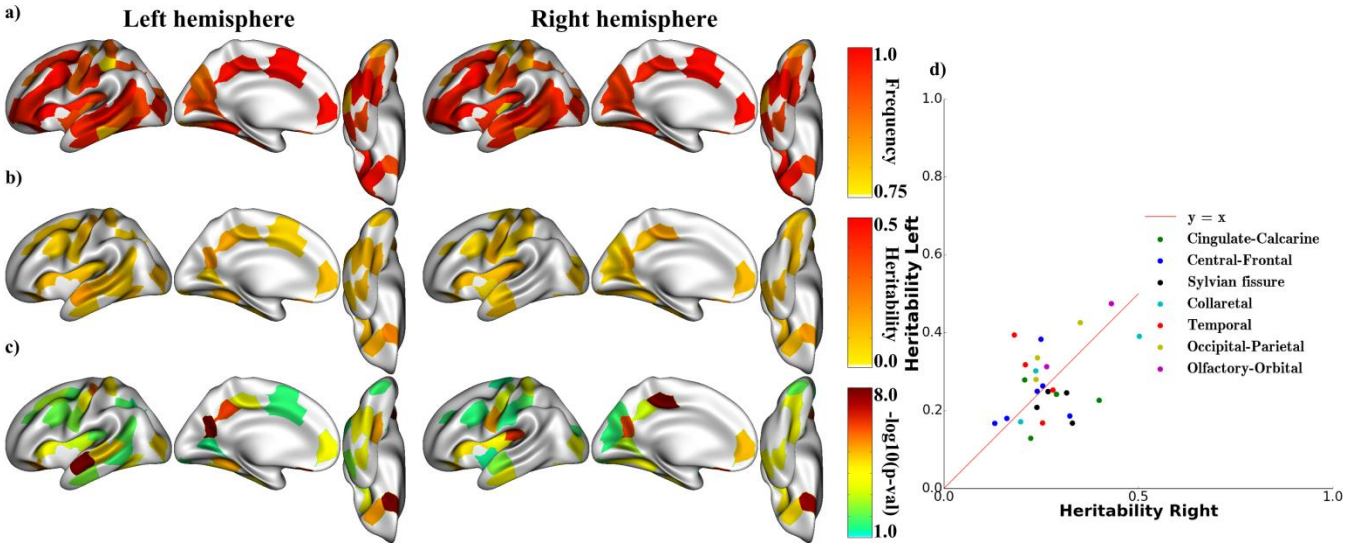

Figure 2. **(a)** Deep pits frequency in each areal. **(b)** Heritability and **(c)** associated –log10(p-values) for all the areals being significant without correction ($p < 0.05$). The areals which are significant after strict Bonferroni are shown with a color above yellow. **(d)** Correlation between left and right hemispheres heritability for areals having an associated $p < 0.05$. Significant Pearson correlation 0.413 ($p = 0.036$). In the legend, we have group significant areals according to their location. Frontal-Central includes: central a, b, c; postcentral a, junction precentral and frontal, sup frontal c; Temporal: sup temporal b, inf temporal a, b; Occipital-Parietal: occipito-temporal a, lateral-occipital, parieto-occipital a, subparietal; Olfactory-Orbital: olfactory, orbital; Collateral: collateral a, c, e; Sylvian fissure: circular insular b, c, d, e; Cingulate-Calcarine: cingulate a, e; calcarine a, c.

Table 1. Heritability estimates for significant clusters after strict Bonferroni correction ($p < 0.05 / (45\times2) \approx 5.6\cdot10^{-4}$)

Left hemisphere		**Right hemisphere**	
Trait	***h²±SE (p)***	***Trait***	***h²±SE (p)***
central a	0.38±0.08 ($1.5\cdot10^{-6}$)	**central c**	0.32±0.07 ($6.5\cdot10^{-6}$)
central b	0.25±0.07 ($1.2\cdot10^{-4}$)	**cingulate a**	0.29±0.07 ($1.2\cdot10^{-5}$)
cingulate a	0.24±0.07 ($1.4\cdot10^{-4}$)	**cingulate e**	0.4±0.06 ($1.9\cdot10^{-10}$)
cingulate e	0.23±0.07 ($2.5\cdot10^{-4}$)	**circular insular b**	0.27±0.07 ($3.6\cdot10^{-5}$)
circular insular b	0.25±0.07 ($1.8\cdot10^{-4}$)	**circular insular c**	0.24±0.07 ($1.4\cdot10^{-4}$)
collateral a	0.39±0.1 ($3.3\cdot10^{-5}$)	**circular insular d**	0.33±0.07 ($3.0\cdot10^{-7}$)
collateral c	0.3±0.07 ($6.5\cdot10^{-6}$)	**circular insular e**	0.32±0.09 ($1.5\cdot10^{-4}$)
inf temporal a	0.32±0.09 ($1.5\cdot10^{-4}$)	**collateral a**	0.5±0.07 ($1.3\cdot10^{-9}$)
lateral occipital	0.28±0.07 ($2.2\cdot10^{-5}$)	**collateral c**	0.24±0.07 ($1.3\cdot10^{-4}$)
occip temporal a	0.25±0.07 ($9.4\cdot10^{-5}$)	**collateral d**	0.26±0.08 ($2.4\cdot10^{-4}$)
occip temporal c	0.26±0.07 ($9.7\cdot10^{-5}$)	**inf temporal b**	0.25±0.07 ($9.0\cdot10^{-5}$)
olfactory	0.47±0.07 ($4.3\cdot10^{-10}$)	**lateral occipital**	0.24±0.07 ($2.2\cdot10^{-4}$)
orbital	0.31±0.07 ($5.1\cdot10^{-6}$)	**occip temporal a**	0.28±0.08 ($1.5\cdot10^{-4}$)
parieto occip a	0.43±0.07 ($8.7\cdot10^{-9}$)	**olfactory**	0.43±0.08 ($3.0\cdot10^{-8}$)
postcentral a	0.26±0.07 ($3.7\cdot10^{-5}$)	**orbital**	0.26±0.07 ($2.9\cdot10^{-5}$)
subparietal	0.34±0.07 ($5.0\cdot10^{-7}$)	**parieto occip a**	0.35±0.07 ($6.0\cdot10^{-7}$)
sup temporal b	0.39±0.06 ($8.7\cdot10^{-10}$)	**postcentral a**	0.25±0.08 ($4.0\cdot10^{-4}$)
sup temporal c	0.25±0.06 ($2.6\cdot10^{-5}$)		

We confirmed results from the method described in [5] with a high reliability of pit extraction across individuals (pit frequencies above 90%) in the following areals: superior temporal (*b*, *c*, *d*), cingulate (*a*, *c*, *e*), calcarine (*a*, *b*), inferior temporal (*b*, *d*, *e*), intraparietal (*a*, *b*, *c*), postcentral (*c*), circular insular (*a*, *b*, *c*, *d*), subparietal, superior frontal (*a*, *d*), inferior frontal (*a*, *c*), lateral occipital, occipito temporal (*a*, *c*), olfactory, orbital, parieto-occiptal (*a*), junction between superior frontal and precentral, junction between precentral and inferior frontal. **Fig. 2 (a)** shows the areals with frequency above 75% on both sides. These areals were selected for our heritability study. We estimated the heritability of the pit depth in areals with a frequency above 75% and thus focused on the ones lying in deep sulci.

Heritability estimates, for the depth of pits by areal, with an associated uncorrected p-value below 0.05 are summarized on **Fig. 2 (b)**. The opposite of the logarithm (base 10) of the p-values are displayed on **Fig. 2 (c)**, the significant areals after Bonferroni correction have a color above yellow, values above $3.26 \approx -\log10(0.05/ (45\times2))$. Their heritability values, standard error, and uncorrected p-values are outlined in **Tab. 1**. Among these results, we underline the heritability values found in the central regions (*a*, *b*, *c*) on both sides, even if they are not all significant after strict Bonferroni correction. These findings are in line with the three peaks of heritability found in [9], in which the authors study the heritability by segment of the depth profile of the central sulcus. The pits in the central sulcus might co-localized with the functional area boundaries of the finder tapping and oral movement tasks as suggested by results in [9]. We also found two significant heritability values for areals in the cingulate *a*, *e* located respectively in the motor area and the anterior cingulate playing a role in a variety of autonomic functions as well as higher-level cognitive functions. Interestingly, we did not obtain significant (after correction) heritability for areals in the right superior temporal sulcus, whereas we noticed two significant ones in the left hemisphere. The superior temporal sulcus has been

widely shown as one of the most asymmetrical areas in the human brain, together with areas such as the planum temporale and the Hesch's gyrus [13]. In particular, it was shown that the asymmetry of the superior temporal sulcus depth profile is human-specific [15]. Because this asymmetry is weakly observed in the chimpanzee [15], it has been proposed that these human specific asymmetries might be related to language left lateralization [13]. Our results suggest that their might be a strong specific underlying genetic plan to build the necessary structures to give birth to the language mechanisms.

However, despite the noticeable exceptions listed above, most of our results indicate symmetric heritability values across hemisphere, notably in the following significant areals: circular insular *b*, collateral *a*, *c*, lateral occipital, occipito-temporal *a*, olfactory, orbital parieto occipital *a*. **Fig. 2 (d)** presents the heritability in the left hemisphere versus the ones in the right hemisphere, for all clusters which have an heritability with an associated p-value below 0.05. Only considering these clusters, we found a significant Pearson correlation between the heritability in the left and right hemispheres. This might be in line with the "symmetry rule" postulated in [9], suggesting a symmetric genetic influence in most areas of the human brain.

4. CONCLUSION

For the first time, the hypothesized strong control of genetics on the sulcal pits has been evaluated. The regional distribution of heritability values suggests a variable genetic control over specific areas, such as in the superior temporal sulcus *b* areal. In addition, this work demonstrated that the sulcal pits can be extracted robustly and efficiently to produce a phenotype of interest for association studies or case/control comparison across a large number of individuals.

5. ACKNOWLEDGMENTS

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