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STRUCTURAL-CONNECTIVITY-BASED INDIVIDUAL PARCELLATIONS IMPROVE REGIONAL CORTICAL THICKNESS HERITABILITY STUDY

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ABSTRACT

In this study, we subdivided a widely used cortical surface atlas into a group parcellation based on the structural connectivity obtained from white matter tractography. This group parcellation was further adapted to the specificity of each individual’s white matter. The interest of this strategy was validated in a study of the heritability of cortical thickness, via comparison with random subdivisions of the initial atlas. Firstly, this validation shows that in certain morphological regions, the individual data-driven subdivisions of the atlas capture homogeneous architectural entities in terms of cortical thickness. Subsequently, in such regions, it is shown that one parcel obtained through the data-driven strategy retains the high thickness heritability of the initial atlas region. This property probably means that the spatial adaptation of the group parcellation to individual subjects enables the method to track the architectural entity that generates this heritability.

Index Terms— parcellations, heritability, structural connectivity, cortical thickness, inter-subjects variability

1. INTRODUCTION

Because a better understanding of the genetic origin of cortical architecture is of paramount interest, pioneering works have examined the genetic influences of structural phenotypes [1, 2, 3], sulcal features [4, 5], connectomes [6] or diffusion MRI-derived measurements [7, 8]. However, fine cortical architecture presents unique spatial specificities in each individual, making the inter-subject variability within a population especially difficult to assess. Current studies often consider surface phenotypes defined from regions of an atlas - usually projected onto individuals via spatial normalisation driven by cortical folding measurements. This strategy is sub-optimal given that the architectural entities making up the cortical surface are subject to inter-individual variations in terms of spatial organization - such as particular region topography [9] or rare folding architecture [10].

One classical surface phenotype is the regional thickness, where the vertex-based thickness is averaged for each region of an atlas. The inter-subject variability of this region-averaged phenotype is expected to truly reflect the differences

in thickness between these subjects, but may also stem from the slight misalignment of the atlas mentioned above.

In line with a recent proposal to perform individual spatial adaptations of an atlas using machine learning [9], we first propose to refine the spatial resolution of a widely used coarse atlas [11] using structural connectivity - a measure derived from diffusion MRI of white matter fibers. We then propose to adapt the finer group parcellation obtained to the specificity of each individual subject using connectivity-based signatures. The individual parcellations obtained through this process are supposed to reflect the specificity of each subject’s white matter, which act as a proxy of the underlying architecture, especially in highly connected regions. We therefore hypothesize that this parcellation scheme should improve the inter-subject stability of the cortical thickness estimation compared with random subdivisions of the coarse atlas regions. To substantiate this hypothesis, we will compare the regional thickness estimated from the data-driven parcellations with the regional thickness estimated from randomized splits of the coarse atlas (fixed from one subject to the other). We will then examine the potential improvement obtained with the data-driven parcellation scheme when attempting to track high thickness heritability from large morphological regions to finer areas reflecting unique architectural entities.

2. METHODS

2.1. MRI data acquisition and pre-processing

Imaging data are issued from the Human Connectome Project [12] (HCP) S1200 release dataset.

3T MRI were acquired at 0.7 mm isotropic voxels resolution and pre-processed with the HCP minimal pre-processing pipeline [13]. Freesurfer [14] recon-all pipeline was applied on each pre-processed individual MRI to obtain a cortical segmentation and a mesh extraction of the white matter-grey matter interface. These meshes were then re-sampled to the lateralized Freesurfer fs_LR referential (32492 vertices by hemisphere) using an embedded Brainvisa [15] toolbox.

Diffusion MRI were acquired at 1.25 mm isotropic voxels resolution and processed using probtrackx2 matrix1 mode of FSL software [16] with a brain mask sampled in the fs_LR referential. This probabilistic streamline reconstruction algo-

rithm led to whole-brain tractograms for 1004 individuals of the dataset.

Group	Relatives	MZ	Females	Males
200S	58	12	111	89
1004S	889	266	544	460

Table 1. Groups repartition

2.2. Individual parcellations generation

We used a group-based clustering algorithm [17] (*Constellation*) to create a subdivision of the Desikan-Killiany [11] atlas. To build this group parcellation, we selected the 200 first subjects of the dataset (200S, see Table 1 for characteristics) whose tractograms were regionally filtered and reduced to produce structural connectivity profiles for each vertex of the fs_LR referential. These connectivity fingerprints were then clustered using a k-medoids algorithm to propose candidate subdivisions with different number of parcels, for each of the 72 regions of the Desikan atlas. The final subdivision of each region was selected by computing the best clustering silhouette score: this yielded a whole-brain parcellation of 193 regions (*Constellation atlas*).

To project this group parcellation onto each of the 1004 subjects of the dataset (1004S, see Table 1 for characteristics), the first part of the previous process was repeated to obtain vertex-based structural connectivity profiles. Each vertex was then labeled according to the closest connectivity profile - in terms of euclidean distance - in the group parcellation, resulting in 1004 individual parcellations [18].

2.3. Statistical analysis of the regional thickness estimated from individual parcellations

To assess the relevance of these individual parcellations for the study of the cortical thickness phenotype, we performed a large scale statistical analysis based on randomly generated subdivisions of Desikan-Killiany regions. To this end, we computed 1000 Voronoi diagrams: first, we randomly sampled each region of the Desikan-Killiany atlas with as many seeds as the number of parcels selected for the Constellation atlas. To build a whole-brain parcellation, a Voronoi-based algorithm was applied regionally using seed growth geodesic to the cortical surface, producing random subdivisions of Desikan regions. This process was repeated 1000 times to generate 1000 different high resolution atlases.

For each parcellation scheme (the data-driven Constellation one and the 1000 fixed Voronoi diagrams) and for each of the 1004 subjects, we computed the mean and standard deviation of each parcel thickness using Freesurfer software outputs. Note that the Voronoi diagrams granularity is exactly

the same as the Constellation granularity in each region of the Desikan atlas. The key difference is that Voronoi parcels are fixed across subjects in the Freesurfer referential while Constellation parcels are spatially adapted to each subject using the individual tractograms. Consequently, Constellation parcels vary in terms of location, shape and topography.

In order to select the relevant regions of interest for further study, we evaluated the pertinence of each regional data-driven subdivision for the study of the regional cortical thickness phenotype: for each Desikan region, we separately aggregated the thickness standard deviations of Voronoi-based parcels and Constellation-based parcels, resulting in two distributions. We then performed a Student T-test on these distributions, under the null hypothesis $H_0 : \{Given a Desikan region, the thickness standard deviations estimated from Constellation parcels are smaller than the ones estimated from Voronoi parcels\}$. As a result, we selected regions that remained significant after a Bonferroni correction for the number of Desikan regions (72). We argue that the data-driven parcels of these regions provide a better estimate of the regional thickness phenotype than random splits of similar granularity.

To better understand why these regions perform better with the Constellation method, we studied how the regional thickness of the Constellation parcels relates to that of Voronoi parcellations. As regions cannot be matched between template parcellations (Voronoi and Constellation), we constructed a matching for each vertex of the mesh: a given vertex is part of a specific parcel for each of the Voronoi parcellations and for the Constellation atlas, allowing us to match the corresponding regional thicknesses of all parcellations at this vertex. Using this matching at each vertex, we were able to calculate a standard score (Z-score) of the Constellation regional thickness in the distribution composed of the regional thickness estimates from all parcellations. The resulting contrast maps represent how the mean over 1004 subjects of the regional thickness differs for the Constellation method compared to randomly generated subdivisions. We interpret the Z-score on these maps as a statistic indicating whether we can reject the null hypothesis: "the regional thickness estimates issued from Constellation-based individual parcellations do not differ from the ones issued from a random parcellation"

2.4. Heritability of the regional thickness estimated from individual parcellations

We then conducted a twin-based heritability study of the regional thickness phenotype. Heritability is defined as the additive variance that can be explained by genetic influences, and can be estimated using a twin-based design by assuming that monozygotic (MZ) twins share all of their genetic heritage whereas dizygotic (DZ) and relatives in the same household share half of their genetic heritage, on average. To this

end, we used the *SOLAR* algorithm [19] on the regional thickness phenotype. As covariates, we took into account influences of *age*, age^2 , *sex* and $age \times sex$. We obtained regional heritability scores for the Desikan-Killiany atlas and the Constellation atlas. We kept scores that remained significant after a Bonferroni correction for the number of regions considered in each parcellation, i.e. p-values of: $p < 0,05/72$ for the Desikan atlas and $p < 0,05/192$ for the Constellation atlas - we excluded the region containing unassigned vertices as it was not relevant for our study.

3. RESULTS

3.1. Analysis of the regional thickness phenotype

Desikan region	P-value
lh.caudalanteriorcingulate	$3.05e - 22$
lh.entorhinal	$5.97e - 103$
lh.frontalpole	$1.88e - 05$
lh.inferiorparietal	$1.01e - 45$
lh.isthmuscingulate	$1.37e - 66$
lh.middletemporal	$8.56e - 31$
lh.paracentral	$3.71e - 97$
lh.parsorbitalis	$5.12e - 12$
lh.parsstriangularis	$4.15e - 29$
lh.postcentral	$3.30e - 06$
lh.posteriorcingulate	$1.31e - 06$
lh.precuneus	$2.13e - 20$
lh.supramarginal	$1.43e - 34$
rh.frontalpole	$1.50e - 05$
rh.isthmuscingulate	$1.32e - 67$
rh.middletemporal	$6.03e - 27$
rh.paracentral	$1.59e - 04$
rh.parsorbitalis	$4.62e - 72$
rh.supramarginal	$2.33e - 40$

Table 2. P-values of left hemisphere and bilaterally significant regions where Constellation method better estimate regional thickness than chance

Among the 23 regions with significant improvement of the stability of the thickness phenotype, we present in Table 2 those of the left hemisphere, and those bilaterally present. All these regions remained highly significant after Bonferroni correction: maximal p-value of $p = 1.6e - 4$. The results appear fairly symmetrical as among these regions 6 appeared bilaterally: *paracentral*, *supramarginal*, *middletemporal*, *parsorbitalis*, *isthmuscingulate* et *frontalpole*. Interestingly, regions seem slightly more significant in the left hemisphere (13) than in the right hemisphere (10).

The comparison of the Constellation average (across subjects) regional thickness with Voronoi parcellations are shown

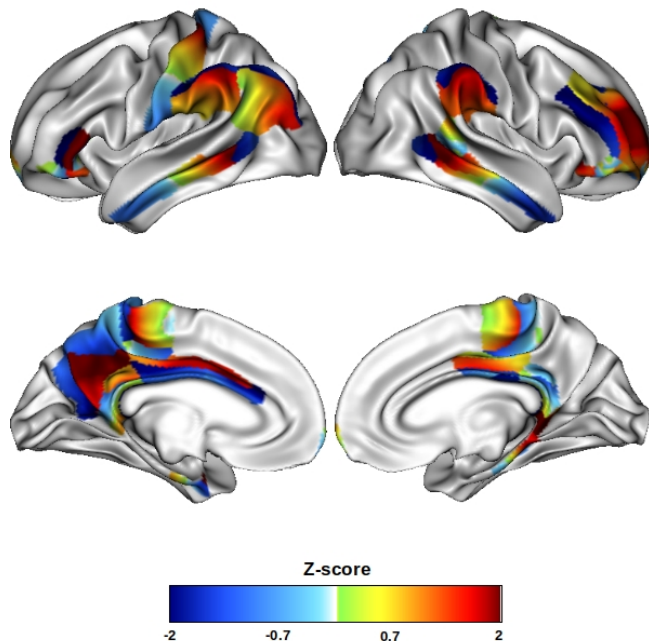


Fig. 1. Standard score of the average (across subjects) Constellation regional thickness by comparison with the ones of Voronoi parcellations, printed for regions where Constellation better aggregates regional thickness. Left hemisphere (*resp.* right) on the left (*resp.* right).

in Figure 1. We focused these maps on the regions where Constellation method better aggregates regional thickness, and used a contrast colormap: lower Z-scores (*resp.* higher) mean that the regional thickness is, on average, smaller (*resp.* larger) than chance when defined with Constellation method. Overall, we can observe a high contrast inside each Desikan region, meaning that Constellation subdivisions have extreme regional thicknesses compared with random subdivisions. Consequently, this result hints that the Constellation method performs a better separation of underlying structural entities with respect to cortical thickness. For example, the *left supramarginal* region yield Z-scores between -2.5 and 1.8.

3.2. Heritability of the regional thickness phenotype

We show the results of the regional thickness heritability study in Figure 2. Overall, Constellation regions present fairly high heritability scores: mean 0.54, min 0.25, max 0.75. Among the significant heritability scores of the selected Constellation regions (see Table 3 for details), some present a relatively high contrast. For instance, the Desikan *left paracentral* has a heritability score of 0.6, but using the Constellation method one subdivision has a score of 0.65

Desikan region	Desikan h2r	Constellation h2r
lh.caud. ant. cing.	0.44	[0.32, <i>ns</i>]
lh.frontalpole	0.49	[0.45, 0.32]
lh.inferiorparietal	0.66	[0.59, 0.51, 0.45]
lh.isthmuscingulate	0.44	[0.44, 0.31, <i>ns</i>]
lh.middletemporal	0.58	[0.50, 0.39]
lh.paracentral	0.60	[0.65, 0.38, <i>ns</i>]
lh.parsorbitalis	<i>ns</i>	[0.26, <i>ns</i>]
lh.parsstriangularis	0.57	[0.30, 0.28, 0.27]
lh.postcentral	0.59	[0.59, 0.58]
lh.posteriorcingulate	0.49	[0.48, <i>ns</i>]
lh.precuneus	0.72	[0.60, 0.56, 0.48]
lh.supramarginal	0.70	[0.65, 0.56]
rh.bankssts	0.54	[0.36, <i>ns</i> , <i>ns</i>]
rh.isthmuscingulate	<i>ns</i>	[0.36, 0.36, 0.33]
rh.middletemporal	0.58	[0.50, 0.39]
rh.paracentral	0.64	[0.38, <i>ns</i> , <i>ns</i>]
rh.parahippocampal	0.57	[0.58, 0.40]
rh.posteriorcingulate	<i>ns</i>	[0.34, <i>ns</i> , <i>ns</i> , <i>ns</i>]
rh.rostral. mid. front.	0.64	[0.66, <i>ns</i>]
rh.supramarginal	0.71	[0.65, 0.55]

Table 3. Heritabilities of Desikan and Constellation subdivisions for significant Constellation regions. *ns* stands for non significant.

whereas another has a score of 0.38, suggesting that our method focused the heritability on one subdivision. Additionally, in the *left precuneus*, the heritability score is 0.72 for the base Desikan region, but 0.6 for one subdivision and 0.48 for another, indicating that heritability scores of sub-regions may present a lower maxima but with a better separation. The *supramarginal* gyrus, highly heritable with a score of around 0.7 as a whole, bilaterally presents a fair contrast inside its subdivisions yielding scores of 0.65 and 0.56 on the left hemisphere and 0.65 and 0.55 on the right hemisphere. The *left inferiorparietal* region, a complex structure of the brain, also presents contrast with scores of 0.59, 0.51 and 0.45. Other regions present a lower yet significant heritability score for all of their subdivisions such as *left isthmuscingulate* and *left parstriangularis*, suggesting that genetic influences may not be as important as featured when using the Desikan atlas. Finally, some Desikan regions such as *left posteriorcingulate* and *left isthmuscingulate* are not significantly heritable whereas they have one heritable subdivision, suggesting that Constellation method successfully captured some structural entities.

4. DISCUSSION

The results presented in this study have several interesting implications. First of all, the finer the parcellation, the more difficult it is to obtain high heritability scores, and their sta-

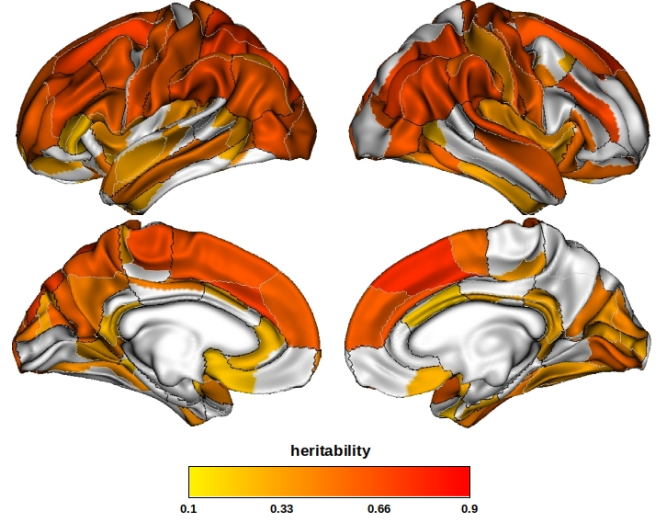


Fig. 2. Heritability of the regional thickness phenotype of Constellation parcellations. Desikan borders are represented in black and Constellation borders in white. Left hemisphere (*resp.* right) on the left (*resp.* right).

tistical significance, on regional phenotypes. Indeed, a coarse parcellation yield less variability between subjects by mixing structural entities that are inconsistent with each others: by construction of the heritability score it is easier to explain the phenotypic variance with the genetic variance thus resulting in high heritability scores. However, such high scores with relatively low anatomical significance, would have low significance in terms of genetic influences, potentially compromising further genetic studies. The granularity of the subdivisions we proposed was greater than that of the original atlas (193 vs 72), but the heritability of regional thickness decreased only slightly overall. Even more interestingly, some regions became significantly heritable, such as in *right isthmuscingulate* and *right posteriorcingulate*, and others became more heritable, such as in *left paracentral*. Furthermore, our data-driven framework for selecting regions of interest is based on the anatomical relevance of the phenotype definition and is therefore free from any selection bias, unlike conventional methods. Some Constellation subdivisions may not be relevant for the study of cortical thickness - for example regions with very long afferent fibers may not be correctly subdivided - but the regions highlighted in this study are of great importance for the regional thickness phenotype. Last but not least, our individual parcellations were not defined on the basis of cortical thickness data, but were built using structural connectivity as a proxy for the underlying white matter configuration. To conclude, the results presented here are in line with recent work proposing that highly connected regions are more heritable [6], and may help further association and transcriptomic studies to better understand the influence of genes expression on anatomical regions of the brain.

5. COMPLIANCE WITH ETHICAL STANDARDS

This research study was conducted retrospectively using human subject data made available in open access by the Human Connectome Project. Ethical approval was not required as confirmed by the license attached with the open access data.

6. ACKNOWLEDGMENTS

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