

Evaluating Brain Anatomical Correlations via Canonical Correlation Analysis of Sulcal Lines

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Abstract. Modeling and understanding the degree of correlations between brain structures is a fundamental problem in neuroscience. Correlated anatomic measures may arise from common genetic and trophic influences across brain regions, and may be overlooked if structures are modeled independently. Here, we propose a new method to analyze structural brain correlations based on a large set of cortical sulcal landmarks (72 per brain) delineated in 98 healthy subjects (age: 51.8 +/-6.2 years). First, we evaluate the correlation between any pair of sulcal positions via the total covariance matrix, a 6×6 symmetric positive-definite matrix. Second, we perform canonical correlation analysis to measure the degree of correlations between any two positions, and derive from it a p-value map for significance testing. We present maps of both local and long-range correlations, including maps of covariation between corresponding structures in opposite hemispheres, which show different degrees of hemispheric specialization.

1 Introduction

Understanding structural correlations between brain structures is a challenging problem in neuroscience. Most computational anatomic studies of development and disease study deficits or changes by modeling individual brain structures independently, or create voxel-based maps of group anatomical differences. This reveals factors (e.g., age or disease) that influence each brain structure individually, but may miss important supra-regional correlations, such as brain regions that develop or fail to develop together, or correlations between structures in opposite brain hemispheres. Mechelli et al. [1] discovered (1) spatial correlations between corresponding regions in opposite brain hemispheres, except in the visual cortex, and (2) some negative correlations between functionally distinct regions in the same hemisphere. Neuroscientists are interested in identifying the reasons of such long-range brain correlations, and what causes them at a genetic and environmental level. Despite many hypotheses, few tools allow such long-range correlations to be measured, and thus studied empirically.

An efficient, parsimonious model of the complex patterns of brain correlations should help to identify factors that influence them. Inter-hemispheric correlations

(i.e., correlations between point in anatomically homologous structures in both hemispheres) are of interest as they shed light on how their functions become specialized or depend on each other. Furthermore, information on statistical correlations could reduce the difficulty of automated segmentation and labeling of brain structures. Accessing anatomical correlations also opens up a broad range of studies and comparing groups (e.g., disease versus normal) and a new path to generate hypotheses regarding patterns of brain growth.

First-order models (mean anatomical templates), and second-order models (variability models) [2] of the brain have previously been built to capture the 3D variations of each anatomical point independently around a mean anatomy, after registration of multi-subject anatomical images to a common reference space. These variations are often represented by covariance matrices, or variability tensors, as variations may not be the same in all directions. Here, we go one step further and model the joint variability of all pairs of anatomical points, to see how the displacement of any point in a specific subject w.r.t. a reference anatomy covaries with the displacement of neighboring or distant point.

In Section 2, we introduce the main tool of our analysis: the total covariance matrix (TCM) between two vector variates, and we recall how to extract from it some matrix and scalar measures to test if these two variables are correlated. In Section 3, we experiment this framework on TCMs defined from anatomical landmarks (sulcal curves). We start by studying the TCMs of 6 sulcal positions to the rest of the brain, which eventually lead us to analyze the TCMs of all sulcal positions of one hemisphere with their homologous positions in the opposite hemisphere.

2 The Total Covariance Matrix

2.1 Definition

Let $X = \{X_i\}_{i=1..N}$ and $Y = \{Y_i\}_{i=1..N}$ be the sets of N measures of two random vectors whose dimensionality is d . Computing the correlation between X and Y requires to know not only the variability of each vector (i.e., its covariance matrix), but also their cross-covariance. We therefore define the TCM of X and Y that contains this information as $\Lambda(X, Y)$:

$$\Lambda(X, Y) = \frac{1}{N-1} \sum_{i=1}^N \begin{pmatrix} X_i - \bar{X} \\ Y_i - \bar{Y} \end{pmatrix} \begin{pmatrix} X_i - \bar{X} \\ Y_i - \bar{Y} \end{pmatrix}^\top, \quad (1)$$

where $\bar{X} = (\sum_1^N X_i)/N$ and $\bar{Y} = (\sum_1^N Y_i)/N$. We denote by Σ_{XX} (resp. Σ_{YY}) the covariance matrix of X (resp. Y): $\Sigma_{XX} = E[(X - \bar{X})(X - \bar{X})^\top]$. The cross-covariance of X and Y is given by: $\Sigma_{XY} = E[(X - \bar{X})(Y - \bar{Y})^\top]$. By further developing Eq. 1, one can write $\Lambda(X, Y)$ in a simpler way:

$$\Lambda(X, Y) = \begin{pmatrix} \Sigma_{XX} & \Sigma_{XY} \\ \Sigma_{YX} & \Sigma_{YY} \end{pmatrix}. \quad (2)$$

Λ is a $2d \times 2d$ matrix. It has the same properties as a classical covariance matrix: it is symmetric and positive definite. Then, we may also call Λ a tensor. In the 3D case, Λ is a 6×6 tensor.

2.2 Analysis of Total Covariance Matrices

In its current form, it is difficult to appreciate the meaning of the TCM and it cannot be easily represented (it is an ellipsoid in 6D). However, several matrix, vector and scalar measures may be derived from it. Here, we will focus on quantifying the correlation of X and Y through the Canonical Correlation Analysis.

Canonical Correlation Analysis (CCA): CCA [3] refers to the method of finding vector bases that maximize the correlation between two vector variates, and is the generalization of the correlation coefficient to multivariate data. In the scalar case, we define the correlation coefficient between x and y as: $\rho = \sigma_{xy} / \sqrt{\sigma_{xx} \cdot \sigma_{yy}}$, where σ_{xx} (resp. σ_{yy}) is the variance of x (resp. y), and σ_{xy} is the cross-variance of x and y . Similarly, the correlation matrix Γ in the multivariate case is defined as:

$$\Gamma(X, Y) = \Sigma_{XX}^{-1/2} \Sigma_{XY} \Sigma_{YY}^{-1/2}. \quad (3)$$

We have the property that $\Gamma(Y, X) = \Gamma(X, Y)^\top$. Taking the mean trace of the Γ gives us an average correlation coefficient $\bar{\rho}$. The range of $\bar{\rho}$ lies between -1 (anti-correlation) and 1 (correlation). 0 means absence of correlation (e.g. if X and Y are independent). However, sometimes an average correlation coefficient in multivariate statistics may not reveal a potential correlation. This is the case, for instance, when only one component of X is correlated with one component of Y . Taking the average correlation coefficient may discard this relationship. To distinguish between correlations along potentially different axes, one needs to run a canonical correlation analysis, which is nothing else than decomposing Γ in singular values: $\Gamma = U.S.V^\top$, where U and V are orthogonal matrices of correlation vectors, and S is a diagonal matrix of correlation coefficients ρ_i .

Significance Testing: To test the statistical significance of correlations, [4] proposed to test the dimensionality of the correlation matrix. If its rank is zero, then there is no correlation ($\rho_i = 0, \forall i$). If we reject this hypothesis, then the rank is at least one, which means that at least two directions in space are correlated. We use the Bartlett-Lawley test [4] with the null hypothesis: $H_0 : \text{rank}(\Gamma) = 0$: $L(\Gamma) = -(N - d + \frac{1}{2}) \sum_{j=1}^d \log(1 - \rho_j^2)$. L 's distribution is chi-squared under the Gaussian assumption on X and Y with d^2 degrees of freedom. We can consequently derive a p-value for testing the significance of correlations.

3 Experiments

We used a dataset of sulcal landmark curves manually delineated in 98 subjects by expert anatomists, according to a precise protocol with established reliability

within and across raters [2]. The dataset consists of 47 men and 53 women (age: 51.8 +/- 6.2 years), all normal controls. The lines are traced in 3D on the cortical surface. We included the maximal subset of all curves that consistently appear in all normal subjects, 72 in total (36 per hemisphere). MR images used for delineations were first linearly aligned to the ICBM stereotactic space [5].

We used the methodology outlined in [2] to determine the mean curve for each sulcal line by modeling samples as deformations of a single average curve. Mean curve computation involves filtering each sample by B-spline parameterization, minimization of total variance, and sulcal matching by dynamic programming.

In the following, we investigate the potential correlations between locations on different sulci. First, we study the correlation between particular sulcal lines and other cortical points not belonging to the same structure: we call this study *sulcal correlation*. Second, we assess *inter-hemispheric correlations* between corresponding anatomical points in the two hemispheres.

3.1 Sulcal Correlation for 6 Specific Positions

Methodology: Obviously, this study is a combinatorial challenge. We sampled the 72 mean sulci with approximately 1000 points (average of 14 points per sulcus), which gives a total of 499500 pairs of points to process. To limit the number of pairs investigated, we focused on two major sulcal lines: the Central Sulcus (CS) and the Inferior Temporal Sulcus (ITS). These sulci lie in different lobes, develop at different times during gyrogenesis (CS developing earlier) and are distant in terms of fiber and functional connectivity, so they are good candidates for assessing inter-structure correlation, as little correlation is expected *a priori*. For each of these lines, three reference positions are picked: the beginning, middle, and end point. First, for each of the three reference positions, we extract the set of corresponding sulcal positions in each of the 98 subjects. Second, we compute the TCM of Eq. 2 with each of the remaining 999 average sulcal positions. We end up with a sparse field of TCMs. However, we would be more comfortable with a dense field of TCMs, as we could map those onto an average cortex to facilitate the visual interpretation of the results. We use Log-Euclidean (LE) metrics [6] and the methodology exposed in [2] (combination of a radial basis function interpolation with an harmonic partial differential equation) for extrapolating TCMs on a mean cortical surface. This type of interpolation was shown to preserve all the features of a covariance matrix, and has desirable properties like absence of swelling effect, and a smooth interpolation of the eigenvectors. Moreover, leave-one-out tests showed that this type of interpolation is able to predict missing data in regions locally correlated. This interpolation is consequently well adapted for TCMs. The correlation matrix and the p-value derived from the CCA can be computed at any point of this mean cortex. Notice that even if we only focused only on the p-value defined in Sec. 2.2, other measures are potentially interesting, such as the principal vectors of correlation which are currently under investigation. This is why we need to extrapolate the full TCMs and not just the p-value.

The main problem for the curve matching procedure proposed in [2] is the *aperture problem*: correspondences in the direction tangent to the curve are almost impossible to retrieve without additional expert knowledge. To keep our results independent from this, we need to cancel the contribution in this tangential direction. The method proposed in this paper is the following. We define at each position of the mean sulci the Frenet frame, which gives us the plane orthogonal to the curve. Then, we project the sulcal positions onto this plane, which zeroes out the tangential component. Note that we lose one degree of freedom in the dimensionality of the data: vectors no longer have three degrees of freedom but two. This must be accounted for in the statistical tests of Sec. 2.2.

Results: p-value derived from the CCA are shown in Fig. 1 (the significance level was set to 0.0001 to correct for multiple comparisons). A large area around the reference points shows high p-values: as expected, points that are anatomically close to the reference do have a correlated distribution among individuals. More interestingly, regions with high p-values most often include the structures' opposite hemisphere counterparts, but not always: the first (upper) and middle CS positions are highly correlated (Fig. 1 top panel, 1st and 2nd row), while the most inferior position is not, most likely because its variability across subjects is extremely low (Fig. 1 top panel, 3rd row). In right-handed subjects, we know that some measures of motor skill correlate with gray matter volume positively in the left CS, but negatively in the right CS [7]. Logically, such functional specializations may promote correlations between the two hemispheres in these regions of the CS. The posterior part of the ITS shows lowest correlation with its opposite hemisphere counterpart. Unlike the bottom of the CS, the posterior tip of the ITS is highly variable and asymmetric in structure and function - it is specialized for understanding the semantics of language in the left hemisphere, but for understanding prosodic aspects of language in the right hemisphere. This may suggest partially independent developmental programs for these functionally specialized structures. The long-range correlation between the back of the ITS and the left and right intra-parietal sulci is of interest, as the planum temporale and planum parietale are the two distinct areas most widely studied in neuroscience for their very high hemispheric asymmetry. Nevertheless, it is intriguing that 5 of the 6 sulcal positions studied reflect a correlation with their symmetric counterpart in the opposite hemisphere. In the following, we test if this observation can be generalized to all sulcal positions.

3.2 Inter-Hemispheric Correlation Analysis

In this study, we specifically target the correlation between all points of one hemisphere and their homologous region in the other hemisphere. To do so, we first map all sulci of the right hemisphere onto the left. Then, we define a global mean, i.e. an average sulcal curve computed from the 98 left and right samples. Global means provide a common reference curve to compare left and right positions. Correspondences between global means and left and right average curves are computed using the same framework as for the samples. For any given position on the global mean, we obtain corresponding points on left and right

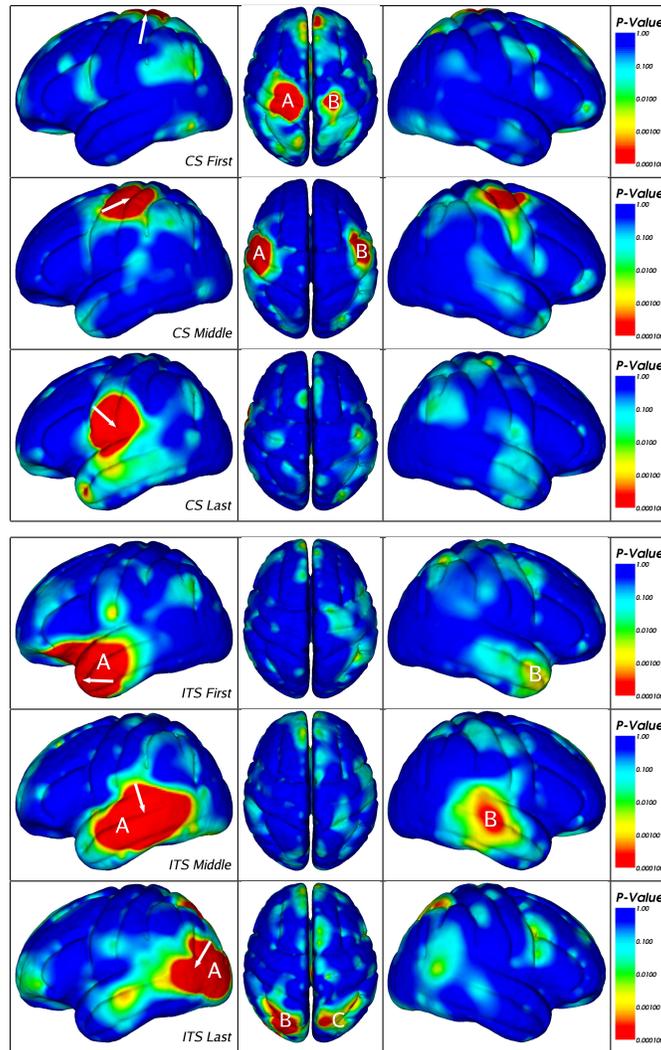


Fig. 1. Correlation Maps between Specific Reference Points and Other Brain Regions. **Top panel: the Central Sulcus.** A white arrow in each row indicates a reference landmark; correlations with the reference landmark are plotted. Correlations for 3 reference landmarks on the CS are shown: the first (top row), the middle (second row), and the last, i.e. most inferior, position (third row) on the sulcal trace. Corresponding regions in the opposite hemisphere are highly correlated for the top and middle points (marked A and B). The lower end of the sulcus, however, exhibits low correlation with its symmetric contralateral counterpart. **Bottom panel: The Inferior Temporal Sulcus.** The same 3 positions as for the CS are analyzed. The first (top row) and middle (second row) positions are symmetrically correlated (marks A and B). The last position (third row) correlates less with its opposite hemisphere counterpart, than with the intra-parietal sulci (marked B and C).

average curves, giving in turn correspondences between left and right sulcal positions in the 98 subjects (the choice of the left hemisphere is arbitrary, and we obtained the same results when using the right hemisphere instead). Finally, we compute the TCM of Eq. 2 between left and right positions. As for the sulcal correlation study, we extrapolate this sparse field of TCMs to an average left hemisphere surface, and cancel the tangential component which is uncertain. Then, we extract p-values with the CCA and map those on the surface (Fig. 2).

As observed previously on a few specific sulcal positions, most points are correlated with their symmetric counterparts. Regions with lowest correlations include Broca’s and Wernicke’s areas, which were already shown to exhibit the greatest asymmetries in variability [2]. These cortical regions are specialized for language production and comprehension respectively, but most right-handers show a greater reliance on the left hemisphere for language processing, and the volumes of these regions are highly asymmetric between hemispheres.

4 Conclusions and Perspectives

In this paper, we represent the cross-covariance between one point and any other point of the brain by a total covariance matrix describing not only the variability of the two points, but also their cross-covariance. Canonical correlation analysis allows us to test for the significance of these correlations. Moreover, as TCMs have the same properties as classical covariance matrices (symmetric and positive-definite), we apply Log-Euclidean extrapolation to obtain a dense representation of initially sparsely-defined measures.

We apply this method to study sulcal and hemispheric correlations. We showed that the central sulcus was highly correlated with its symmetric, except in its inferior part which is not highly variable. For the central sulcus, where motor skill is correlated with volume and is also lateralized, a strong hand preference for motor skills is likely to promote negative correlations between hemispheres

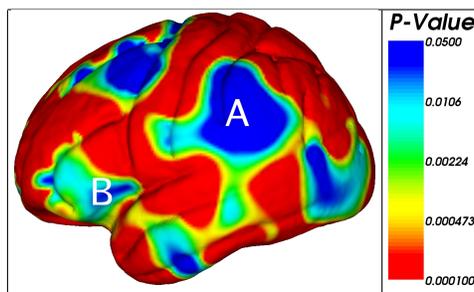


Fig. 2. Hemispheric correlations. Hot colors (red) correspond to $p\text{-value} \leq 0.0001$. Most of the cortex shows anatomical variations that are correlated with their counterparts in the opposite hemisphere. Un-correlated regions include Wernicke’s (marked A) and Broca’s areas (marked B), which, in most subjects, are known to be more heavily specialized for language processing in the left hemisphere.

for volumes in opposite regions. The Inferior Temporal Sulcus shows similar intriguing correlations, and its low correlation with its opposite counterpart may reflect their different developmental programs and functions.

Corresponding brain regions in each hemisphere are highly correlated, except for regions including Wernicke's and Broca's areas, which are known to be functionally specialized in one hemisphere. Any longer-range correlation - such as that found between the intra-parietal sulci and inferior temporal sulci - is in itself an interesting neuroscience finding. The planum parietale and temporale are distinct highly asymmetric systems in each of these regions, and the long-range correlations may reflect common factors driving programmed asymmetries for both regions.

Future work includes a concrete modeling of these correlations. We could store, for each point of the brain, a minimal set of correlated positions, such as the local neighborhood and the set of distant most correlated points. This information could be used as a prior to guide inter-subject non-linear registration algorithms. Furthermore, a detailed study of all possible correlations between cortical landmarks could help understand the effects of genes on brain maturation. Validations of long-range correlations could be made using other sources of information, such as functional MRI: Are jointly activated regions, or causal models, for a given task related to anatomical correlations as well as connectivity (fiber bundle)? All this information, if it converges to the same outcome, could contribute to understanding the functional organization of the brain. Finally, these results should be compared with those of other methods, such as surface-based versus volumetric registration algorithms; this comparison is currently underway for generating second-order models of brain variability [8].

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