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Groupwise Structural Parcellation of the Cortex: A Sound Approach Based on Logistic Models

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Abstract. Current theories hold that brain function is highly related with long-range physical connections through axonal bundles, namely *extrinsic connectivity*. However, obtaining a groupwise cortical parcellation based on extrinsic connectivity remains challenging. Current parcellation methods are computationally expensive; need tuning of several parameters or rely on ad-hoc constraints. Furthermore, none of these methods present a model for the cortical extrinsic connectivity. To tackle these problems, we propose a parsimonious model for the extrinsic connectivity and an efficient parcellation technique based on clustering of tractograms. Our technique allows the creation of single subject and groupwise parcellations of the whole cortex. The parcellations obtained with our technique are in agreement with anatomical and functional parcellations in the literature. In particular, the motor and sensory cortex are subdivided in agreement with the human homunculus of Penfield. We illustrate this by comparing our resulting parcels with an anatomical atlas and the motor strip mapping included in the Human Connectome Project data.

1 Introduction

The human brain is arranged in areas based on criteria such as cytoarchitecture or axonal connectivity. Current hypotheses attribute specialized functions to several of these areas. Hence, parcellating the cortex into such areas and characterizing their interaction is key to understanding brain function. Diffusion MRI (dMRI) enables the in vivo exploration of long-range physical connections through axonal bundles, namely *extrinsic connectivity*. Current theories hold that extrinsic connectivity is strongly related to brain function, e.g. this has been shown in macaques [15]. Hence, parcellating the cortex based on its extrinsic connectivity can help to understand the internal organization of the brain. However, obtaining a whole-cortex groupwise parcellation based on extrinsic connectivity remains challenging [9]. Current extrinsic connectivity parcellation methods are computationally expensive; need tuning of several parameters or rely on ad-hoc constraints. For example, Clarkson et al. [4] propose to iteratively refine an anatomical parcellation using information from dMRI. This technique’s main drawback is the strong dependence on the initial anatomical parcellation. Lefranc

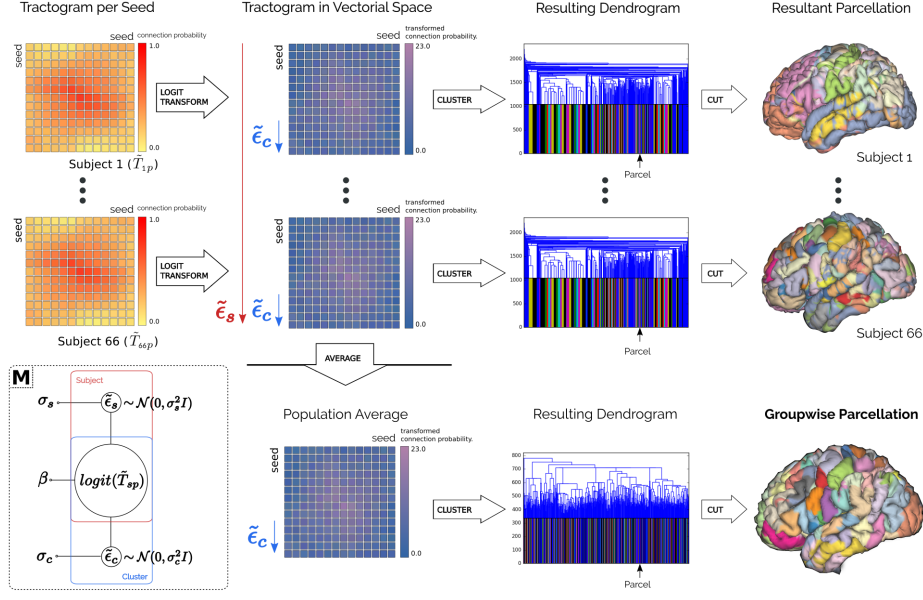


Fig. 1: Lower left corner: graphical model of the linear relationship between a tractogram ($\tilde{T}_{sp}$); the intra-cluster ($\tilde{\epsilon}_c$) and across-subject ($\tilde{\epsilon}_s$) variability. We transform the tractograms into a vectorial space while explicitly accounting for the variability, allowing us to propose a clustering technique in accordance.

et al. [10] calculate the average connectivity profile of regions using a watershed-driven dimension reduction, but they work parcellating predefined gyri. Parisot et al. [14] estimate a consistent parcellation across subjects using a spectral clustering approach, without averaging subject’s connectivity profiles. Nevertheless, the method needs tuning of several parameters, including the expected number of parcels specified a priori. Moreno-Dominguez et al. [12] present a parcelling method based on hierarchical clustering parcellation, in which it’s not necessary to set an a priori number of clusters. However, they use the cosine distance to compare tractograms and the centroid of tractograms to represent their union. This can lead to an erroneous parcellation since the centroid criterion doesn’t minimize the cosine distance between points. These examples show that an efficient groupwise parcelling technique alongside a sound model for the extrinsic connectivity is still needed.

In this work we present a parsimonious model for the cortical connectivity and an efficient parcelling technique based on it, both summarized in Fig. 1. Our model assumes that the cortex is divided in patches of homogeneous extrinsic connectivity. That is, nearby neurons in the cortex share approximately the same long-ranged physical connections, we call this the *local coherence criterion*. Our assumption is based on histological results in the macaque brain [19]. As

in clustered data models in statistics [16] we allow intra-patch variability and across-subject variability in the patches.

Nowadays, the most common tool to estimate the extrinsic connectivity of a point on the cortex in vivo is dMRI-based tractography [9]. To frame tractography within our cortical connectivity model, we use Logistic Random Effects Models [19]. This allows us to explicitly denote the relationship between tractography and the variability present in our model. Taking advantage of this, we propose an efficient clustering technique to create single subject and groupwise parcellations of the whole-cortex. Inspired by the method of Moreno-Dominguez et al. [12], our technique creates a dendrogram: a structure that comprises different levels of granularity for the same parcellation. We also create the dendrogram while imposing the local coherence criterion using only one parameter: the minimum size of each parcel. Then, by choosing cutting criteria, we can explore different parcellation granularities without recomputing the dendrogram.

We validate our technique by taking advantage of the information available in the Human Connectome Project (HCP). Using our technique, we create single-subject and groupwise parcellations for 66 subjects. Then, we compare our purely structural parcellations against an anatomical atlas [5] and responses to functional stimuli [2]. We show that our parcels subdivide some well-known anatomical structures in accordance with functional responses on the cortex.

2 Methods

2.1 Data and Preprocessing

In this work we used 66 male subjects aged 31-35 from the group S500 of the Human Connectome Project (HCP), all preprocessed with the HCP minimum pipeline [7]. The main advantages of using this public data base are: each subject possess a dense mesh representing their cortical surface, we use it to create seed-points for tractography; all the mesh’s vertices are coregistered across subjects, property that we use to create the groupwise parcellation; each subject possess the Desikan Atlas [5] parcellation already computed over their cortical mesh; for each cortical mesh there are also different z-score maps representing the response to different stimuli obtained with functional MRI (fMRI) [2]. Finally, the group S500 contains z-score maps representing the average functional response to stimuli for 100 unrelated subjects (U100). These studies are used to validate our technique’s results.

2.2 Cortical Connectivity Model and Tractography

Our model assumes that the cortex is divided in clusters of homogeneous extrinsic connectivity. That is, nearby neurons in the cortex share approximately the same long-ranged physical connections, we call this the *local coherence criterion*. Our assumption is based on histological results in the macaque brain [19]. As in

clustered data models in statistics [16] we allow intra-cluster and across-subject variability. We formalize this concept as:

$$K = \bigcup_{i=1}^k K_i, \forall 1 \leq i, j \leq k, i \neq j \rightarrow K_i \cap K_j = \emptyset \wedge \text{conn}(K_i) \neq \text{conn}(K_j) \quad (1)$$

where the set of points on the cortex K is the disjoint union of each cluster K_i and $\text{conn}(\cdot)$ is the extrinsic connectivity fingerprint of a cluster. We will make the notion of variability explicit in eq. 3. In this work, the connectivity fingerprint of a seed-point in the brain is a binary vector denoting to which other seed-points it is connected through axonal bundles. This is, the physical connections of a point $p \in K_i$ in the brain are represented by its connectivity fingerprint $\text{conn}(p) = \text{conn}(K_i)$.

Nowadays, the most common tool for estimating the extrinsic connectivity fingerprint of a point in vivo is probabilistic tractography [9]. Given a seed-point in the brain, probabilistic tractography creates a *tractogram*: an image where each voxel is valued with its probability of being connected to the seed through axonal bundles. One way of calculating these probabilities is with a Monte Carlo procedure, simulating the random walk of water particles through the white matter [3]. Each one of these paths is known as a streamline. If we think these streamlines as Bernoulli trials, were we get a value for the connection from our seed with other points (1 if they connected by the streamline, 0 if not) [3], then we can model the tractogram of the subject s in the seed-point p as:

$$T_{sp} = [P(\tilde{C}_{spi} = 1)]_{1 \leq i \leq n} = [\theta_{spi}]_{1 \leq i \leq n}, \quad \tilde{C}_{spi} \sim \text{Bernoulli}(\theta_{spi}) \quad , \quad (2)$$

where $\tilde{C}_{spi}$ is a Bernoulli random variable³ representing “the point p of the subject s is connected to the voxel i ”. Each Bernoulli’s parameter (θ_{spi}) represents the probability of being connected, and is estimated as the proportion of success in the Bernoulli trials of each seed.

To formulate the tractogram in accordance to our hypothesis of cortical connectivity, we model a tractogram as a vector of random variables. In our model, each element in a tractogram comes from a random variable depending of the point’s cluster alongside its intra-cluster and across-subject variability:

$$p \in K_c \rightarrow \tilde{T}_{sp} = [P(\tilde{C}_{spi} = 1 | \text{conn}(K_c), \tilde{\epsilon}_{ci}, \tilde{\epsilon}_{si})]_{1 \leq i \leq n} \quad , \quad (3)$$

in this case, the point p belongs to the cluster c ; $\tilde{\epsilon}_{ci}$ represents the intra-cluster variability and $\tilde{\epsilon}_{si}$ represents the across-subject variability for the connectivity to voxel i in the cluster c .

Since each $\tilde{C}_{spi}$ follows a Bernoulli distribution (Eq. 2) it’s difficult to find an explicit formulation for $P(\tilde{C}_{spi} = 1 | \text{conn}(K_c), \tilde{\epsilon}_{ci}, \tilde{\epsilon}_{si})$ accounting for the variabilities. For this, we use the generalized linear model (GLM) theory. In this theory, the data is assumed to follow a linear form after being transformed with an appropriate link function [11]. Using the following notation abuse:

$$\text{logit}(\tilde{T}_{sp}) \triangleq [\text{logit}(P(\tilde{C}_{spi} = 1 | \text{conn}(K_c), \tilde{\epsilon}_{ci}, \tilde{\epsilon}_{si}))]_{1 \leq i \leq n}, \quad (4)$$

³ For the sake of clarity we denote all random variables with a tilde, e.g. $\tilde{C}$.

we derive from GLM a logistic random-effects model [16] for each point p :

$$\text{logit}(\tilde{T}_{sp}) = \beta_c + \tilde{\epsilon}_c + \tilde{\epsilon}_s \in \mathbb{R}^n, \quad \tilde{\epsilon}_c \sim \mathcal{N}(\mathbf{0}, \sigma_c^2 Id), \quad \tilde{\epsilon}_s \sim \mathcal{N}(\mathbf{0}, \sigma_s^2 Id), \quad (5)$$

where ϵ_c and ϵ_s represent the intra-cluster and across-subject variability respectively. According to GLM theory $\beta_c \in \mathbb{R}^n$ is the extrinsic connectivity fingerprint of cluster K_c transformed:

$$\text{logit}^{-1}(\beta_c) = E(\tilde{T}_{sp}) = \text{conn}(K_c) . \quad (6)$$

The choice of logit as link function is based on the work of Pohl et al. [17]. There, they show that the logit function’s codomain is a Euclidean space, which allows us to transform and manipulate the tractograms in a well-known space.

2.3 Single Subject and Groupwise Parcelling Methodologies

In the previous section we hypothesised that the cortex is divided in clusters with homogeneous extrinsic connectivity, alongside intra-cluster and across-subject variability. In using the previous hypothesis, it is important to remark that we don’t have a priori knowledge of the cluster’s location or their variability. But, thanks to the proposed logistic random effects model, we formulated the problem of finding these clusters as a well-known clustering problem. This is because, after transforming the tractograms with the logit function as in eq. 4 they will be in a Euclidean space [17]. Even more, eq. 5 states that the transformed tractograms come from a mixture of Gaussian distributions. This is known as a Gaussian mixture model.

To solve the Gaussian mixture model and find the clusters, we use a modified Agglomerative Hierarchical Clustering (AHC) algorithm. This was inspired by the method of Moreno-Dominguez et al. [12]. To enforce the local coherence criterion we also modify the algorithm to accept one parameter: the minimum size of the resulting clusters. Clusters smaller than this size are merged with neighbors, i.e. physically close clusters in the cortex. As we are working in a Euclidean space, we use the Euclidean distance and the centroid as similarity and linkage functions, improving performance. Our technique’s time complexity is $O(n^2 \log(n))$, with n the number of tractograms to cluster [13]. AHC creates a dendrogram: a structure that comprises different levels of granularity for the same parcellation. This allows us to explore different parcellation granularities by choosing cutting criteria, without the need of recomputing each time.

The main advantage of the model we proposed in the previous section is that it allows us to create a groupwise parcellation using linear operations. Assuming direct seed correspondence across subjects, as in the HCP data set, our model lets us remove the subject variability of each seed’s tractogram by calculating the expected value across subjects:

$$E_s(g(\tilde{T}_{sp})) = E_s(\beta_c + \tilde{\epsilon}_c + \tilde{\epsilon}_s) = \beta_c + \tilde{\epsilon}_c + E_s(\tilde{\epsilon}_s) = \beta_c + \tilde{\epsilon}_c. \quad (7)$$

where the last equality is due to $E_s(\tilde{\epsilon}_s) = 0$ (Eq. 5). This allows us to create population-representative tractograms for each seed free of across-subject variability, which then can be clustered to create a groupwise parcellation.

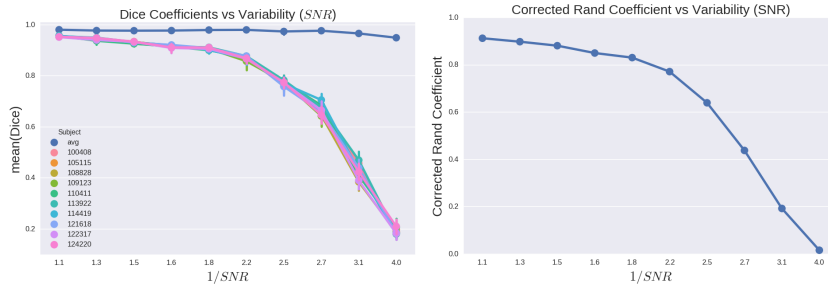


Fig. 2: Clustering performance for different levels of variability. SNR comprises both intra-cluster and across-subject variability, at smaller SNR more variability is present. Left, best overlap between synthetic regions and clusters in the dendrogram. Right, best corrected rand coefficient for horizontal cutting. The coefficients close to 1, specially in the average case (dark blue line), show the compatibility between our parcellation technique and the proposed model.

3 Experiments and Results

3.1 Reliability of the Clustering Algorithm for the Model

In the previous sections we presented a model for the cortical extrinsic connectivity and a clustering technique to parcellate the brain. Our technique allows us to create single subject and groupwise parcellations, encoded with different levels of granularity in a dendrogram. However, is not immediate that the chosen clustering algorithm (AHC) solves a Gaussian mixture model (eq. 5) since it was not designed for this particular case [13]. That is, it's not immediate that the algorithm finds the clusters if they are stated as in the model (eq. 5). Now we show that the modified version of the algorithm (sec. 2.3) to enforce the local coherence criterion (sec. 2.2), solves the model for reasonable levels of variability. Moreover, it retrieves the right clusters using one of the simplest criterion to cut the dendrogram: the horizontal cut, i.e. cutting the dendrogram just by choosing the cut's height.

To test the technique, we started by creating synthetic data from the model (eq. 5). We randomly took 10 subjects from our chosen set alongside their extant Desikan parcellations. Then, we created synthetic connectivity fingerprints representing the connections between their Desikan areas. Next, for each vertex in their cortical surface we: replicated those fingerprints; transformed them with the logit function and added cluster-specific variability and across-subject variability as in our model. Finally, we grouped the vertex based on their connectivity using our clustering technique.

If our parcelling technique is able to solve the model, then the Desikan Areas should be encoded in the resulting dendrogram. To show that the Desikan areas were encoded in the resulting dendrogram, we calculated the best obtainable overlap between each Desikan area and the clusters in the dendrogram using

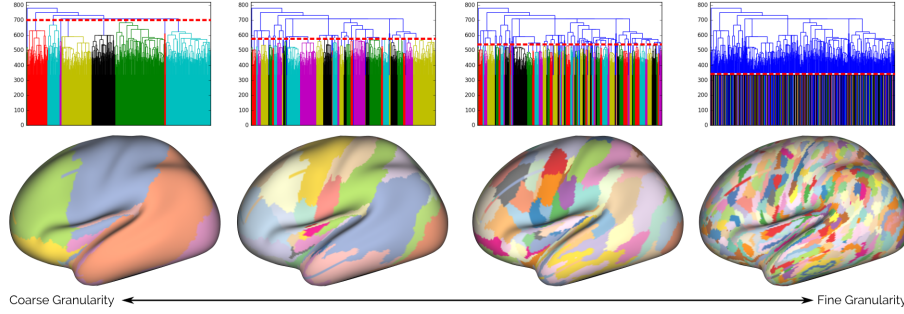


Fig. 3: Groupwise dendrogram created by our technique. We can retrieve different granularities of the same parcellation by choosing cutting height, shown as a red dotted line. Motor and Sensory cortex appear at coarse levels of granularity.

the Dice coefficient. To evince the accuracy of the horizontal cut criterion, we compared every obtainable parcellation through cutting our dendrogram in the average subject case against the Desikan atlas using the corrected Rand index [8]. A Rand index of 1 means that the two parcellations were equal.

Fig. 2-left shows the best dice coefficients obtained for every Desikan region under different levels of variability. The Signal-to-Noise-Ratio (SNR) in the figure represents the amount of variability added respect to the original variability of the synthetic connectivity fingerprint. The result in fig. 2-left shows that parcels were retrieved and well-encoded inside the dendrogram for reasonable levels of variability, specially in the average case (dark blue line) where we get rid of the across-subject variability by averaging. Fig. 2-right shows the best obtainable rand index using horizontal cut on the dendrogram under different levels of variability. The high Rand indices obtained show that we can solve our model by simply using the horizontal cut criterion.

3.2 Parcelling Subjects From the Human Connectome Project

We next applied our parcellation technique to the HCP data. First, we performed Constrained Spherical Deconvolution (CSD) based tractography [20] from a dense set of points in the cortex. Then, we used our technique to parcellate the cortex by clustering the tractograms. Specifically, since each subject has a surface representing their gray-matter/white-matter interface, we used their vertices as seeds to create tractograms. To avoid superficial cortico-cortical fibers [18], we shrank each of the 66 surfaces $3mm$ into the white matter. For each subject, we fitted a CSD model [20] to their diffusion data using Dipy (version 0.11) [6] and created 15000 streamlines per seed-voxel using the implementation of probabilistic tractography in Dipy. Later, we created a tractogram as in (Eq. 2) by calculating the fraction of particles that visited each white-matter voxel. Then, we transformed each tractogram with the logit function [17] as in eq. 4. We clustered the tractograms of each subject using the modified AHC algorithm while imposing a minimum cluster size of $3mm^2$ in the finest granularity.

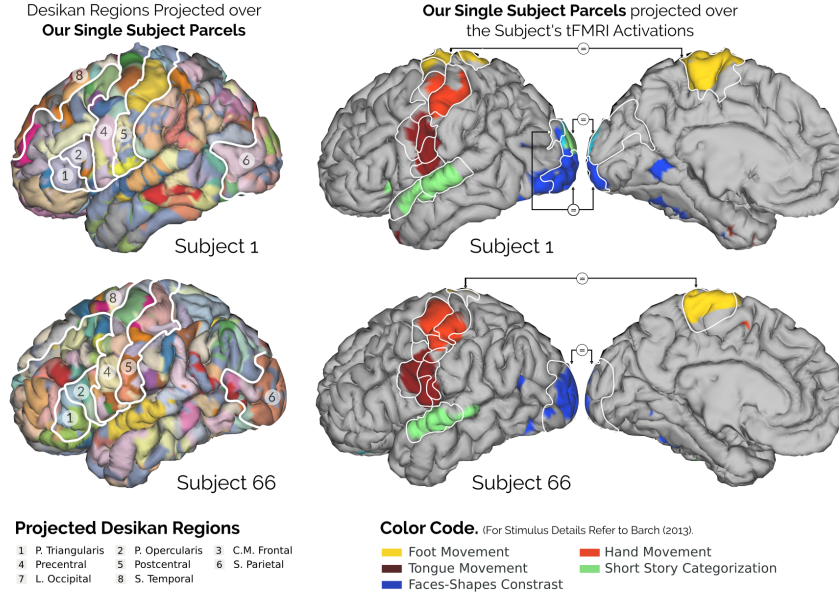


Fig. 4: Single subject parcellations created with our technique, alongside both anatomical (left) and functional (right) comparisons from sec. 3.3. Motor and Sensory Cortex (regions 4 and 5) appear to be found and their subdivision is consistent with the motor strip mapping in HCP.

To create the groupwise parcellation, we took advantage of the vertex correspondence across subjects in the HCP data set. Since we are in a vectorial space we calculated the average tractogram of each seed. Then, we created the groupwise parcellation by clustering the average tractograms with our proposed technique (sec. 2.3). The resulting dendrogram for the groupwise case, alongside some of the obtainable parcellations, are in fig. 3.

3.3 Functional and Anatomical Comparison

Here we present a proof of concept that our resulting dendrograms encode parcellations with both anatomical and functional meaning by comparing our results against an anatomical atlas and a functional study. To make the comparisons we extracted a parcellation from each subject's dendrogram using the horizontal cut criterion since it showed good accuracy in sec. 3.1. We manually searched for parcellations with a minimum of 36 parcels and a maximum of 150. This was made to get parcellations with coarse granularity while having at least the amount of parcels in the anatomical atlas of Desikan [5].

Anatomical Comparison. To assess if some anatomical structures were present in the dendrogram and if our resulting parcels were subdividing them, we compared the extracted parcellation with the Desikan atlas [5]. It's important to

Anatomical Comparison: Desikan Regions Projected over **Our Groupwise Parcels**

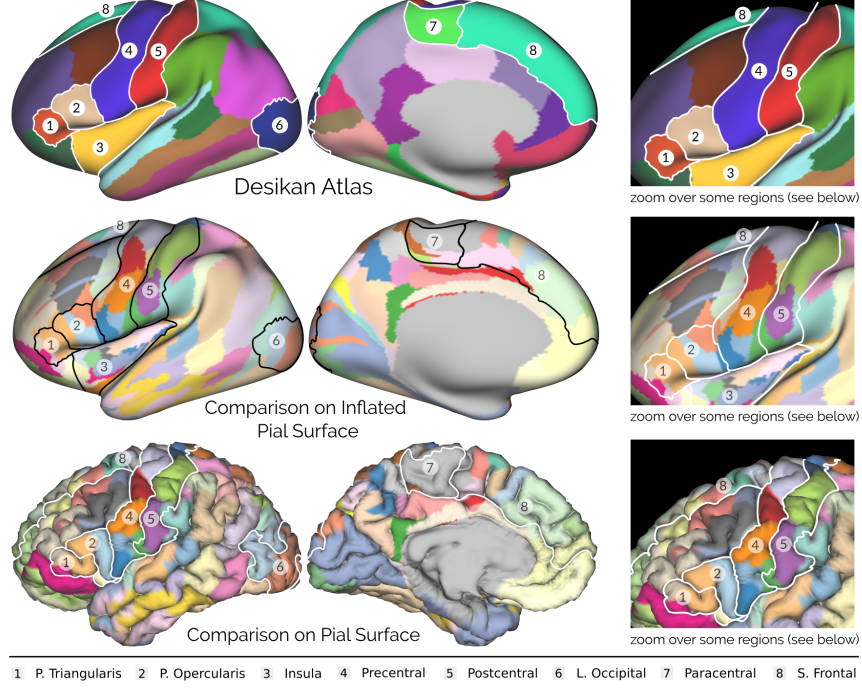


Fig. 5: Relation between our pure extrinsic parcellation and the anatomical atlas of Desikan [5]. Some regions from Desikan projected over a parcellation with less than 150 parcels. Motor and Sensitive cortex appears to be found.

remark that each subject in the HCP already has this atlas computed. We projected the Desikan regions over our parcels and then calculated: how many of our parcels were inside each projection and how many of them had more than 90% of its area inside the projection. Comparisons with 8 regions of the Desikan atlas for the single-subject and the groupwise case are in the fig. 4-left and the fig. 5 respectively. The table 1 shows the fraction of parcels inside of each projections that were well contained. Our division of the inferior frontal cortex differs from the Desikan's [5] (regions 1 and 2 in fig. 5). However, it's similar to that of Anwender et al. [1]. In particular, our orange and cyan parcels inside regions 1 and 2 correspond with their blue and green parcels in Fig. 4, panels I, II, IV and V [1]. The Insula; Motor and Sensory cortex (regions 3, 4 and 5 in fig. 5) were well subdivided for both single subject and groupwise parcellations.

Functional Comparison. We studied if our parcels were related to brain function. To do so we calculated their overlap with thresholded maps representing responses to functional stimuli [2]. These maps are also available for each subject in the HCP. The fig. 4-right shows the functional comparison for two single

Functional Comparison

Our Groupwise Parcels

Parcellation created using less than 150 parcels

projected over

tFMRI Activations

Average activations for 100 subjects from the group U100 in the Human Connectome Project. Each z-score map was thresholded ($z > 5$)

Color Code

(For Stimulus Details Refer to Barch (2013).)

- Foot movement
- Hand Movement
- Tongue Movement
- Short Story Categorization
- Shapes-Faces Contrast
- Faces-Shapes Contrast

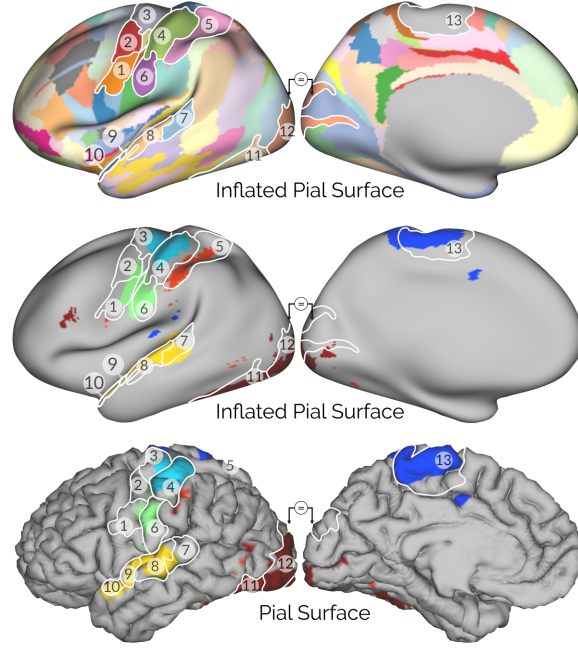


Fig. 6: Relation between our pure extrinsic parcellation and a functional study [2]. Some of our groupwise parcels projected over responses to task-related functional activations. Our division of the Motor and Sensitive cortex appears to be consistent with the motor strip mapping.

subject parcellations. The fig. 6 shows a projection from our groupwise parcels over averaged tFMRI activations. Each color encodes the response to a different stimulus thresholded with a z -score > 5 . The comparison for the average-subject case was done against the average functional responses in the Unrelated100 population from the HCP. Table 2 shows the highest dice coefficient achieved by one of our regions for each task. Here it is important to remark that, in general, each stimulus will generate a functional response in both motor and sensory cortex. Our hypothesis is that this happens because, for example, while a subject is moving the hand he's also feeling it. Therefore, an overlapping of 0.5 suggests that at least one of our parcels in the motor or sensory cortex is having a good overlapping with the functional response, as confirmed visually. Table 2 shows high dice coefficients for each subject, but shows even higher coefficients for the average subject. We hypothesize that averaging tractograms in the Euclidean space is removing the across-subject variability.

4 Discussion and Conclusion

In this work we presented a parsimonious model for the long-range structural connectivity. Our model assumes that the cortex is divided in patches of homo-

Table 1. Area Proportion Contained (see fig. 4-left)									Variability
	1	2	3	4	5	6	7	8	
Single Subj.	0.4	0.6	0.8	0.8	0.8	0.7	0.2	0.6	$\pm 0.1, min : 0.07, max : 0.16$
Average Subj.	0.0	0.3	0.9	0.8	0.8	0.3	0.2	0.6	N/A

Table 2. Best Dice Coefficient for Task (see fig. 4-right)					
	Foot	Hand	Tongue	Story	Shape/Face
Single Subj.	0.54 ± 0.10	0.46 ± 0.09	0.50 ± 0.1	0.43 ± 0.09	0.56 ± 0.19
Average Subj.	0.62	0.60	0.58	0.65,	0.54

Table 1: Area proportion contained for parcels inside Desikan projections. Table 2: Best dice coefficient obtained for each functional task. Our parcels are mostly contained inside one anatomical region and overlap well with the activations.

geneous extrinsic connectivity, with intra-patch and across-subject variability. Then, using Logistic Random Effects Models we formulate tractography in accordance to our model. This allowed us to transformed the tractograms into a Euclidean space. Working within this sound framework enabled us to easily manipulate and compare tractograms. Taking advantage of this we presented an efficient technique to parcellate the whole cortex in single subject and groupwise cases. The groupwise case assumes seed correspondence across-subject, we expect our model to account errors in seeds coregistration as across-subject variability. Our technique creates a dendrogram using only one comprehensive parameter: the minimum size of each cluster. Then, different parcellation granularities can be obtained just by choosing at which height to cut the dendrogram. Also, as a preliminary validation of our results we showed that our pure structural parcellation had good agreement with anatomical and functional parcellations.

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