

Group-wise Parcellation of the Cortex through Multi-scale Spectral Clustering

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Abstract

The delineation of functionally and structurally distinct regions as well as their connectivity can provide key knowledge towards understanding the brain's behaviour and function. Cytoarchitecture has long been the gold standard for such parcellation tasks, but has poor scalability and cannot be mapped in vivo. Functional and diffusion magnetic resonance imaging allow in vivo mapping of brain's connectivity and the parcellation of the brain based on local connectivity information. Several methods have been developed for single subject connectivity driven parcellation, but very few have tackled the task of group-wise parcellation, which is essential for uncovering group specific behaviours. In this paper, we propose a group-wise connectivity-driven parcellation method based on spectral clustering that captures local connectivity information at multiple scales and directly enforces correspondences between subjects. The method is applied to diffusion Magnetic Resonance Imaging driven parcellation on two independent groups of 50 subjects from the Human Connectome Project. Promising quantitative and qualitative results in terms of information loss, modality comparisons, group consistency and inter-group similarities demonstrate the potential of the method.

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1. Introduction

The delineation and identification of structurally and functionally distinct brain regions has been an ongoing and prominent objective for understanding the brain's function and organisation for over a century (Zilles and Amunts, 2010). Traditional approaches have built parcellation maps from anatomical microstructure (cytoarchitecture, myeloarchitecture) from histological sections of the brain. While there is still no universally accepted parcellation of the cortex, Brodmann's cytoarchitectural map (Brodmann and Garey, 2007) is arguably the most commonly used reference map. Cytoarchitecture based parcellations are unfortunately poorly scalable and cannot be mapped in vivo.

In vivo macro-scale connectivity data provides complementary information to anatomical microstructure. Advances in medical imaging such as diffusion (dMRI) and functional Magnetic Resonance Imaging (fMRI) have provided means of identifying in vivo structural and functional connections within the brain. dMRI allows estimation of structural connections within the brain by measuring the anisotropy of the diffusion of water molecules in the brain, which is constrained by the white matter's fibres connecting different regions of the gray matter. In contrast to this, fMRI measures the increase of oxygenation due to brain activity over a specific time period. Functional connections can be established by evaluating the temporal correlation between the fMRI signals in different brain regions.

Cortical areas can be seen as regions in the brain that differ based on microarchitecture (cyto or myeloarchitecture), connectivity and function (Eickhoff et al., 2015). In particular, local microstructure and connectivity are believed to conjointly enable locally specific neurological computations (Passingham et al., 2002), *i.e.* determine the functionality of a region in the brain. As a result, microstructure and connectivity provide partially overlapping and complementary information, and are both necessary to study in order to increase our under-

standing of the brain’s organisation. Connectivity-driven parcellation, while
30 not providing actual cortical areas on their own, can therefore provide essential
information for mapping the functions of the brain.

Furthermore, it provides a sensible basis for the construction of brain connectivity networks or *connectome* at the macro-scale, which can provide key knowledge towards understanding neurological processes and diseases. Due to
35 the high dimensionality of connectomic data, building such connectivity networks requires the parcellation of the cortical surface into distinct regions, where each brain region constitutes a node in the network. The most commonly used parcellations are random parcellations or cortical folding based parcellations (Tzourio-Mazoyer et al., 2002; Destrieux et al., 2010) derived from anatomical
40 landmarks. However, those parcels do not necessarily reflect the underlying connectivity of the brain and can therefore introduce a bias and a loss of information in the constructed network (Sporns, 2011).

Connectome construction and functional or cortical mapping have both motivated the development of dMRI and fMRI driven parcellation methods, the
45 aim being to regroup regions of the cortical surface that have similar functional or structural connectivity profiles. The problem is typically cast as a clustering problem driven by the correlation between tractography connectivity profiles or fMRI time series. Several approaches have focused on a specific subregion of the brain (Anwander et al., 2007; Johansen-Berg et al., 2004; Jbabdi et al., 2009; Mars et al., 2011), which allows the application of common clustering meth-
50 ods such as k-means clustering. The problem becomes more complicated when a complete cortex parcellation is sought due to the increased dimensionality and noise. Several approaches have been considered for fMRI and dMRI-driven parcellation with different levels of success: anatomical parcellation refinement
55 (Clarkson et al., 2010), Markov Random Fields (Ryali et al., 2013; Honnorat et al., 2015), and edge detection (Cohen et al., 2008). However, clustering remains the most natural way of tackling the parcellation task, as we are seeking to regroup regions sharing similar connectivity patterns based on pairwise affinity. Gaussian Mixture Models (Yeo et al., 2011; Lashkari et al., 2010), Spectral

60 clustering (Craddock et al., 2012; Shen et al., 2013) and Hierarchical clustering
(Moreno-Dominguez et al., 2014; Blumensath et al., 2013) have attracted most
attention.

When performed independently, finding correspondences between single sub-
ject parcellations can be a challenge. Indeed, the parcels' boundaries can be very
65 different from one subject to the next, the differences being exacerbated by the
influence of noise. Group-wise parcellation can potentially handle better noisy
and locally unreliable individual data while at the same time providing an av-
erage parcellation representative of the similarities between subjects in a group.
In addition, building group averages are also essential in order to understand
70 group specific connectivity behaviours and disruptions.

Few approaches have tackled the task of finding group-wise parcellations.
We can distinguish two different kinds of approaches: the first one directly
estimates a group parcellation from averaging the connectivity data of all sub-
jects (Roca et al., 2010; Clarkson et al., 2010), the second approach estimates
75 single-subject parcellations where parcel correspondences between subjects are
established (Shen et al., 2013; Parisot et al., 2015; Arslan et al., 2015). The for-
mer is attractive due to its simplicity, but can lead to a loss of information and
does not yield individual parcellations. The method proposed by Arslan et al.
(2015) relies on a joint spectral decomposition of the surface mesh with connec-
80 tivity weighted edges. One drawback of this approach is the strong influence of
the mesh structure on the final parcellation.

Shen et al. (2013) proposed an iterative method for fMRI driven parcellation
that alternates between the estimation of a group parcellation and minimising
the differences between single subject parcellations and the group in the spectral
85 domain. The method requires an initialisation which influences the run time
as well as the obtained parcellations and implies spatial alignment between
subjects.

Group-wise parcellation tasks strongly depend on the alignment of connec-
tomic data between subjects. Unless they are specifically coupled to an actual
90 registration task, parcellation methods require an anatomical alignment of brain

surfaces (typically volumetric or cortical folding based alignment). While this provides a rough alignment of the connectomic data, it does not imply that it is registered locally. This fact must be taken into account when seeking correspondences between subjects and when evaluating the similarities between different
95 subjects' parcellations.

In this paper, we propose a group-wise parcellation method that is inspired by the concept of co-segmentation in computer vision (Kim et al., 2012). We simultaneously estimate coherent parcellations across resolutions and subjects through a spectral clustering formulation. For each subject, we capture con-
100 nectivity boundaries at different resolutions through the construction of a set of high resolution parcellations. Correspondences between the different resolutions and subjects are enforced through links between subjects and parcellations resolutions that are based on localisation and connectivity similarity. The common parcellation is then estimated through a joint decomposition of the global affinity matrix that encodes intra-subject affinities and inter-subjects connections.
105 The proposed method was introduced in Parisot et al. (2015). Here, we extend the method through a refined estimation of inter-subjects links that makes the method more robust to the quality of the registration of the connectomic data. We present an extended experimental evaluation of the parcellation method, notably through comparisons to cytoarchitectonic and fMRI data. We apply the
110 method on diffusion MR data from two groups of 50 subjects. Qualitative and quantitative experiments show a good reproducibility between the two groups as well as strong local similarities with Brodmann, myelin and task activation maps. The fundamental issues and implications associated with connectivity driven parcellation and tractography are then discussed on the basis of these
115 results.

2. Material and Methods

The proposed method is summarised in Fig.1. In this section, we first detail the dataset and preprocessing steps used, followed by the construction of a multi-

120 resolution base parcellation. Edges between the base parcellation resolutions
and subjects are then introduced. They are constructed based on overlap on
the original surface mesh and similarities in connectivity respectively. Finally,
we describe the quantitative measures used for evaluation.

2.1. Notations

125 We summarise here the notations used throughout the paper for increased
clarity. We refer to the cortical surface of a subject S_i as a mesh $\mathcal{M} = \{\mathcal{V}, \mathcal{E}\}$.
 N_v is the number of vertices and K is the number of sought parcels. Vertices
on the mesh are referred to as $\mathbf{v} \in \mathcal{V}$. The cortical surface is parcellated into
a set of L high resolution parcellations. A supervertex V_s at scale $s \in \llbracket 1, L \rrbracket$
130 refers to a whole parcel (an ensemble of vertices). The number of supervertices
or parcels at scale s is N_s .

χ^{S_i} is the structural connectivity matrix of subject S_i obtained from trac-
tography, of size $N_v \times N_v$. We call $\chi^{S_i}(\mathbf{v})$ the row of the connectivity matrix at
vertex \mathbf{v} . $W_s^{S_i}$ is the affinity matrix of subject S_i at scale s , of size $N_s \times N_s$. It is
135 computed by averaging the values of χ^{S_i} associated with vertices in the same
supervertex and by computing the correlation between the rows of this low res-
olution connectivity matrix. W^{S_i} is concatenation of the affinity matrices $W_s^{S_i}$
and is introduced in section 2.3. Its size is $(\sum_s N_s) \times (\sum_s N_s)$. Similarly to
 χ^{S_i} , we call $W^{S_i}(V_s)$ the row of the affinity matrix at supervertex V_s .

140 X^{S_i} is the parcellation matrix of a subject S_i , introduced in section 2.4 and
of size $(\sum_s N_s) \times K$. $C_{s,s+1}^{S_i}$ is the constraint matrix of subject S_i between
the supervertex parcellation scales s and $s + 1$ introduced in section 2.4. Its
size is $N_{s+1} \times N_s$. C^{S_i} is the concatenation of the resolution wise constraint
matrices. Finally, W , C and X are the concatenations of the affinity, constraint
145 and parcellation matrices for all subjects in the group. D is the degree matrix
of W , *i.e.* the diagonal matrix which contains the sum of each row of W at the
corresponding row.

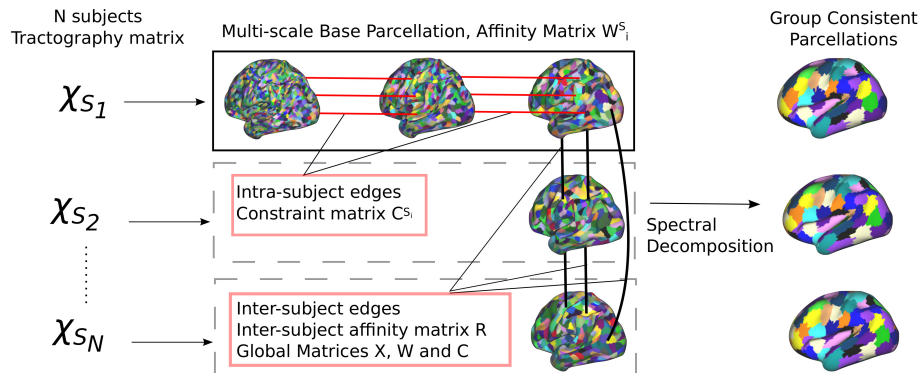


Figure 1: Overview of the group-wise parcellation method. Each subject S_i is associated with a connectivity matrix χ_{S_i} that drives the construction of a multi-scale base parcellation. Intra-subject edges (between base parcellation resolutions) and inter-subject edges (between all pairs of subjects at the coarsest parcellation resolution) are built to allow a common spectral decomposition of the affinity matrix (Pearson’s correlation between the tractography connectivity profiles).

2.2. Dataset and Preprocessing

We perform our experiments on 100 subjects randomly selected from the 500
 150 subjects release (November 2014) of the Human Connectome Project¹ (HCP)
 database. We randomly separate the database in two distinct groups of 50
 subjects each and test the method independently on the two groups.

The structural and diffusion data have been preprocessed following the HCP’s
 minimal preprocessing pipelines (Glasser et al., 2013). The cortical surface is
 155 represented as a triangular mesh made of 32k nodes $\mathcal{M} = \{\mathcal{V}, \mathcal{E}\}$, where the
 nodes have a 2mm spacing. \mathcal{V} represents the set of $N_v = 32k$ nodes, while \mathcal{E}
 describes the connections or edges between neighbouring nodes. An essential
 preprocessing stage to our approach is the registration of all cortices to a com-
 mon reference space. We are using here the HCP’s provided registration, which
 160 registers the sulcal depth information of all surfaces following an MRF based
 method (Robinson et al., 2014). This yields matching mesh nodes across all

¹Human Connectome Project Database, <https://db.humanconnectome.org/>

subjects.

The diffusion MR images have been acquired using a multi-shell approach, with three shells at b-values 1000, 2000, and 3000 s/mm^2 and 90 gradient directions per shell. The tractography matrix is obtained from the preprocessed
165 dMRI data using FSL’s bedpostX and probtrackX methods (Behrens et al., 2007; Jbabdi et al., 2012). The former estimates the orientation of the fibres passing through each voxel of the brain volume while the second performs probabilistic tractography based on the estimated fibre orientations. The proba-
170 bilistic tracking is done on the native mesh (before registration) representing the gray/white matter interface. 5000 streamlines are seeded from each of the surface vertices and the obtained tractography matrix records the number of streamlines that reached the rest of the mesh.

One issue associated with tractography, especially with probabilistic trac-
175 tography, is the bias towards short range connections. Indeed, long range connections are weakened or even missed due to the accumulation of uncertainty along the tract. As a result, there can be a strong discrepancy between the short and long range connectivity strengths even though the actual connections have the same strength. This can have a strong impact on the obtained parcellation.
180 This issue is often accounted for by thresholding the shortest fibres (Roca et al., 2009). However, the value of this threshold is typically decided heuristically and it is very difficult to estimate what threshold value yields an appropriate representation of the connectivity between vertices of the mesh. Another approach, which we adopt here, is to compute the element-wise log transform of the trac-
185 tography matrix (Jbabdi et al., 2009; Moreno-Dominguez et al., 2014). The log transform reduces the dynamic range of fibre counts and therefore reduces the strong discrepancy between short range connections fibre counts and the long range ones. This parameter free option greatly reduces the bias towards short connections while not losing any information from a thresholding process.
190 This approach remains a suboptimal way of handling tractography’s bias with respect to the lengths of the connections. Investigating a more principled approach approach that is integrated in the tractography process (Girard et al.,

2014) would yield more accurate results. It is however, a difficult challenge for tractography that is beyond the scope of this paper.

195 In the remainder of this paper, we call χ^{S_i} the log-transformed tractography matrix of a subject S_i and $\chi^{S_i}(\mathbf{v})$ the row of this matrix corresponding to the mesh node \mathbf{v} (*i.e.* the vertex’s connectivity profile).

2.3. Supervertex Parcellation

The first step of our multi-scale approach is the construction of a set of
200 high resolution parcellations where all vertices in the same parcel are highly correlated. The objective of this step is two-fold: first, the aim is to reduce the noise and high dimensionality of the data at the vertex level. Second, through the construction of this multi-scale parcellation, we aim to capture local connectivity information at different resolutions. This objective relates
205 to the work of Mota et al. (2014), where the authors aim to derive statistics that are coherent across a set of random parcellations. Our aim is slightly different here though, as we aim to identify consistent parcel boundaries rather than parcel-wise information. Due to the similarity of this parcellation concept with the superpixel approach (Achanta et al., 2012), we refer to those highly
210 correlated parcels as *supervertices* in the remainder of this paper.

In order to construct each supervertex level - or resolution -, we are inspired by the work of Peyré and Cohen (2004) who employ the Fast Marching algorithm to evaluate feature weighted geodesic distances on surface meshes. In our case, minimising a correlation weighted geodesic distance with respect to a super-
215 vertex centre allows the construction of spatially contiguous parcels that agree with the correlation information. While the most straightforward option would be to follow the SLIC superpixel methodology (Achanta et al., 2012), the Fast Marching approach allows the construction of spatially contiguous supervertices without having to tune a parameter that relatively weights contiguity and con-
220 nectivity. Indeed, the Fast marching method allows integration of connectivity information in the computation of the geodesic distance.

Considering a *seed* vertex \mathbf{v}_0 (which will be the centre of the supervertex),

we seek to compute the geodesic distance $d(\mathbf{v}_0, \mathbf{v}) = U(\mathbf{v})$ from that vertex to the all remaining nodes $\mathbf{v} \in \mathcal{V}$. This problem can be cast as a front propagation
 225 problem, where U follows the Eikonal equation $\|\nabla U\|^F = 1$. Here, F is the so-called speed function that characterises the front propagation and allows to control the evolution of the front with a specific feature. We design the speed function so that the front propagates faster towards regions that have highly correlated connectivity profiles:

$$F(\mathbf{v}) = \exp(\mu \rho(\chi^{S_i}(\mathbf{v}_0), \chi^{S_i}(\mathbf{v}))). \quad (1)$$

230 Where $\rho(.,.)$ is the Pearson’s correlation coefficient and μ is a weighting parameter.

The correlation weighted geodesic distance can be computed for each seed by solving the aforementioned Eikonal equation using the Fast Marching algorithm (Sethian, 1996).

235 Next, we build our supervertex map through an iterative process. Given a set of N_s seeds uniformly sampled on the cortical surface, we first assign all the remaining nodes to a supervertex by minimising their geodesic distance to all seeds. The supervertex centre is then recomputed as the node that has the highest average correlation with the rest of the nodes in the supervertex. This
 240 process is then repeated until convergence. We construct three supervertex parcellations at three different resolutions for $N_s = \{3000, 2000, 1000\}$. The supervertex parcellation scheme is illustrated in Fig.2, while an example base parcellation is shown in Fig.3.

Each supervertex parcellation level is associated with a $N_s \times N_s$ merged
 245 connectivity matrix that is computed by averaging the fibre counts in the tractography matrix of the vertices within the same supervertex. The correlation between the rows of this merged tractography matrix yields the affinity matrix W^{S_i} that will drive our spectral clustering based parcellation approach. Spatial contiguity of the parcellations is later enforced by removing edges (i.e. entries
 250 in W^{S_i}) between supervertices that are not immediate neighbours.

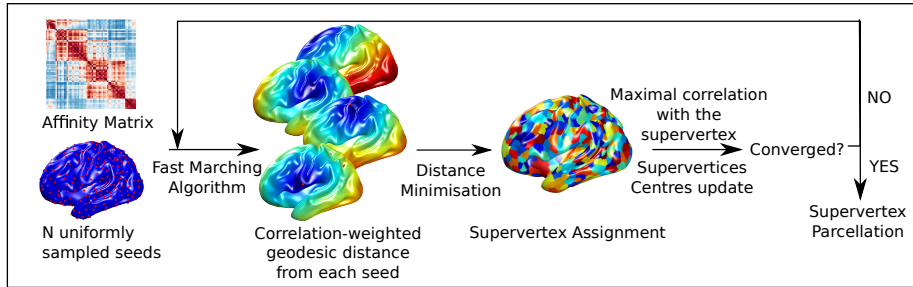


Figure 2: Overview of the supervertex parcellation method. After initialisation with a uniformly sampled set of seeds, we alternate until convergence between minimising the geodesic distance of all nodes to the seeds to obtain the parcellation, and reevaluating the seeds.

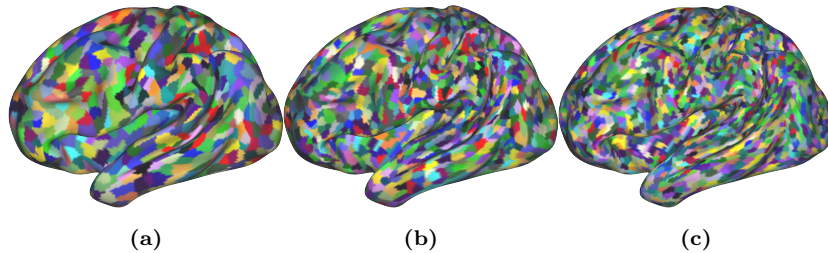


Figure 3: Visual example of the three resolutions of the supervertex parcellation.

2.4. Single-subject Parcellation

The multi-scale supervertex parcellation captures connectivity information at different resolutions. We seek to exploit this knowledge in order to recover a coherent parcellation for a given subject S_i across all resolutions. This can
 255 be done by constructing inter-resolution edges between supervertices that are embedded in a constraint matrix. In the spectral clustering framework, this forces connected supervertices to be assigned to the same cluster.

A supervertex \mathbf{V}_s at a given scale s is connected to the supervertex \mathbf{V}_{s+1} at the coarser scale $s + 1$ that shares the largest amount of vertices on the
 260 original mesh. The strength of the edge is set as the amount of overlap between both supervertices so that the strongest correspondences in terms of parcel assignments are enforced to supervertices in the most similar locations. The

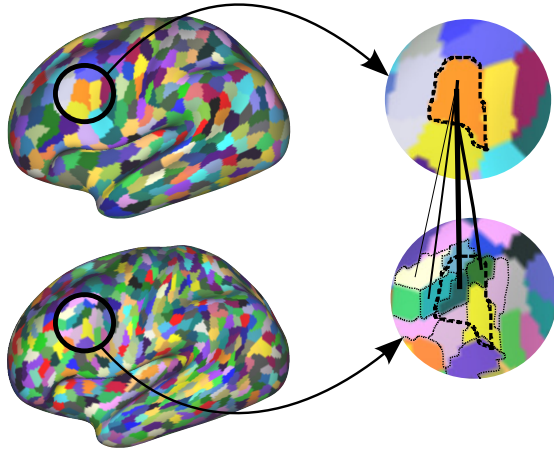


Figure 4: *Illustration of the inter-resolutions links. Connections links are constructed between two supervertices at the different resolutions if they share vertices on the original mesh. The strength of the edge is established by the number of shared vertices.*

inter-resolution edges are therefore written as follows:

$$C_{s,s+1}^{S_i} = \frac{|\mathbf{V}_s \cap \mathbf{V}_{s+1}|}{|\mathbf{V}_s|} \quad (2)$$

Where $|\mathbf{V}_s|$ is the number of vertices in the supervertex \mathbf{V}_s . The construction
 265 of inter-resolutions links is illustrated in Fig.4.

These links allow simultaneous clustering of the three base parcellation levels
 into a coherent K clusters parcellation represented at different levels of precision
 (based on the size of the supervertices). This is done following the multi-scale
 normalised cut method (Yu and Shi, 2003). In this setting, we seek to recover for
 270 each scale s a $N \times K$ parcellation matrix that describes the cluster assignments
 of the supervertices:

$$X_s^{S_i}(\mathbf{V}_s, j) = \begin{cases} 1 & \text{if } \mathbf{V}_s \in \text{parcel } j \\ 0 & \text{otherwise} \end{cases} \quad (3)$$

All resolutions can then be parcellated simultaneously by concatenating all
 parcellation and affinity matrices into global multi-scale parcellation and affinity

275 matrices:

$$X^{S_i} = \begin{pmatrix} X_1^{S_i} \\ \vdots \\ X_L^{S_i} \end{pmatrix}, \quad W^{S_i} = \begin{pmatrix} W_1^{S_i} & & 0 \\ & \ddots & \\ 0 & & W_L^{S_i} \end{pmatrix} \quad (4)$$

Here W_i is the merged affinity matrix associated with the resolution level i . Coherence of the parcellations between the different resolutions is enforced by the inter-resolution links that are encoded in the following constraint matrix:

$$C^{S_i} = \begin{pmatrix} C_{1,2}^{S_i} & -I_{N_2} & & 0 \\ & \ddots & \ddots & \\ 0 & & C_{L-1,L}^{S_i} & -I_{N_L} \end{pmatrix} \quad (5)$$

Here I_N is the $N \times N$ identity matrix.

280 This matrix controls the obtained parcellation over all scales through an imposed constraint on the parcellation matrix:

$$C^{S_i} X^{S_i} = 0 \quad (6)$$

Spectral decomposition of the multi-scale affinity matrix W^{S_i} subject to equation 6 yields a parcellation that captures variations in connectivity profiles at different scales. At each resolution, the supervertices are assigned to a particular
 285 parcel. This results in parcellations at different degrees of precisions in terms of boundaries, depending on the supervertex resolution.

A limitation of the proposed multi-scale parcellation is the absence of correspondences between subjects, which is essential if one is aiming to identify group specific connectivity features. Parcel boundaries can substantially vary across
 290 subjects, due to noise and anatomical differences. Group-wise parcellation can provide parcellations that are more robust with respect to locally unreliable data on the subject level, while at the same time ensuring that correspondences are enforced across subjects.

2.5. Group-wise Parcellation

295 It is straightforward to rewrite the N models (one per subject) into a joint optimisation problem. This can be done very easily by concatenating all the

subjects’ affinity and inter-scale constraint matrices, which results in the estimation of a joint parcellation matrix defined as follows:

$$X = \begin{pmatrix} X^{S_1} \\ \vdots \\ X^{S_N} \end{pmatrix} \quad (7)$$

while the joint affinity and constraint matrix can be defined as:

$$C = \begin{pmatrix} C^{S_1} & & 0 \\ & \ddots & \\ 0 & & C^{S_N} \end{pmatrix}, \quad W = \begin{pmatrix} W^{S_1} & & 0 \\ & \ddots & \\ 0 & & W^{S_N} \end{pmatrix} \quad (8)$$

300 In this setting however, all the subjects’ parcellations are estimated independently and no correspondences are enforced. Obtaining a meaningful matching parcellation across subjects requires the definition of inter-subject connections that describe which regions should be assigned to the same label.

For this task, we cannot solely rely on the cortical surface registration for
 305 two reasons. First, anatomical/sulcal alignment does not imply that structural connections are registered as well, *i.e.* connectivity patterns can differ locally across subjects. The same parcellation should not be imposed on subjects who have different local connectivity profiles. Second, the registration itself is likely imperfect, and local errors could affect the structural correspondences between
 310 subjects. For those reasons, direct vertex to vertex comparisons across subjects are not reliable enough to obtain meaningful matches. Carrying comparisons on the supervertex scale (Parisot et al., 2015) can decrease the impact of a poor alignment. However, the connections remain subpar and biased with anatomical information since our data is only aligned in terms of cortical folding. These
 315 possible errors and biases are likely to get stronger if we increase the resolution of our supervertex parcellations as we get closer to a vertex to vertex comparison set up.

We are tackling these issues with a two-fold approach. When seeking to match a supervertex $\mathbf{V}_L^{S_i}$ in subject S_i (supervertex belonging to the coarsest

320 resolution) with a supervertex in another subject S_j , we first follow the approach
in Parisot et al. (2015) and find the supervertex $\mathbf{V}_L^{S_j}$ that has the highest overlap
(in terms of number of original mesh vertices) with $\mathbf{V}_L^{S_i}$. We then consider all
the supervertices that are immediate neighbours of $\mathbf{V}_L^{S_j}$ and seek the one with
the most similar connectivity pattern with the rest of the brain. As connectivity
325 profiles can differ from one brain to the next, we do not directly compare the
connections across the brain, but the correlation of connectivity profiles of one
supervertex with all the others. In other words, we compare if two supervertices
are similar in terms of connectivity to the same cortical regions, even though
the actual connectivity profiles of these supervertices can differ.

330 Inter-subject edges are created between the matched supervertices $\mathbf{V}_L^{S_i}$ and
 \mathbf{V}_L^{opt, S_j} and weighted as the correlation between the low dimensional merged
connectivity profiles associated with each supervertex:

$$R_{i,j}(\mathbf{V}_L^{S_i}, \mathbf{V}_L^{opt, S_j}) = \alpha \rho \left(W^{S_i}(\mathbf{V}_L^{S_i}), W^{S_j}(\mathbf{V}_L^{opt, S_j}) \right) \quad (9)$$

Here α is a weighting parameter that controls the influence of the inter-subjects
weights and $\rho(\cdot)$ is the Pearson’s correlation coefficient. Weighting the edges
335 with the correlation between the matched supervertices allows control of how
similar two parcellations are expected to be locally, based on the similarity of
the two subjects’ underlying data.

The inter-subject anatomical and connectivity variability is further accounted
for by limiting the connection between subjects to the coarsest supervertex par-
340 cellation resolution. This allows more differences between parcellations at the
higher resolution (*i.e.* parcellations that are more faithful to the subject’s con-
nectivity information) while at the same time ensuring correspondences between
the parcellations.

The inter-subject edges are incorporated in the framework by updating the

345 group-wise affinity matrix (Eq. 8) as follows:

$$W = \begin{pmatrix} W^{S_1} & R_{1,2} & \cdots & R_{1,N} \\ R_{2,1} & W^{S_2} & \cdots & R_{2,N} \\ \vdots & \vdots & \ddots & \vdots \\ R_{N,1} & R_{N,2} & \cdots & W^{S_N} \end{pmatrix} \quad (10)$$

2.6. Optimisation

The next step is the joint spectral decomposition of this affinity matrix subject to the inter-layer constraints to recover the group's parcellation matrix. The group-wise parcellation can be recovered by optimising the following multi-scale normalised cut objective criterion:

$$\text{maximise} \quad E(X) = \frac{1}{K} \sum_{l=1}^K \frac{X_l^T W X_l}{X_l^T D X_l} \quad (11)$$

$$\text{subject to} \quad X \in \{0, 1\}^{N \times K}, \quad (12)$$

$$X 1_k = 1_N, \quad (13)$$

$$C X = 0 \quad (14)$$

This problem is unfortunately NP-complete, but a near global-optimal solution can be estimated in a two-step approach (Cour et al., 2005). The first step
 350 is to solve the relaxed continuous problem Z^* derived from problem 11. This is done using the Rayleigh-Ritz theorem (Yu and Shi, 2004) by computation and normalisation of the K largest eigenvector of a matrix QPQ , defined as:

$$\begin{aligned} P &= D^{-\frac{1}{2}} W D^{-\frac{1}{2}} \\ Q &= I - D^{-\frac{1}{2}} C^T (C D^{-1} C^T)^{-1} C D^{-\frac{1}{2}} \end{aligned} \quad (15)$$

Matrix P is the normalised affinity matrix obtained by multiplication with the degree matrix D of W . Q is the so-called *projector* matrix, that ensures we are
 355 seeking a solution that respects constraint 14.

The second optimisation step consists of discretising the global solution of Z^* (Yu and Shi, 2003) so as to find the closest solution to the relaxed problem that satisfies the discrete problem.

The group average parcellation can then be obtained from the individual
360 subjects parcellation through majority voting. Our objective using the simple
majority voting approach is to identify which brain regions are in agreement
between subjects, i.e. to find the regions that best summarise the similarities
between subjects.

2.7. Evaluation: Quantitative Measures

365 The evaluation of brain parcellation tasks is a challenge in itself since there
is no ground truth to compare to. In order to provide a quantitative evaluation
of our approach, we compute measures that intuitively should be characteristic
of a good parcellation.

2.7.1. Information Loss

370 Our first objective is to obtain parcellations that represent the data as well
as possible. A parcel’s average connectivity profile should be as close as possible
to all the connectivity profiles of the vertices within the parcel. We evaluate the
faithfulness of our parcellations to the data by evaluating the information that
is lost by approximating the vertices’ connectivity profiles with the parcels’
375 averages. This is done by creating a $N_v \times N_v$ matrix χ_{av} from the merged
connectivity matrix, by assigning the same merged profile to all vertices in the
same parcel (see Fig.5). We then compute the Kullback-Leibler Divergence
(KLD) between this matrix and the original tractography matrix χ that are
normalised to be probability mass functions. The KLD measures how much
380 information is lost by approximating the tractography matrix χ with χ_{av} . A
low KLD therefore corresponds to a faithful parcellation.

2.7.2. Silhouette Index

We further evaluate the quality of our clustering using the Silhouette index
(Rousseeuw, 1987), which is a commonly used cluster validity measure. It has
385 notably been used several times for evaluation of brain parcellations (Craddock
et al., 2012; Eickhoff et al., 2014). The Silhouette index computes for each

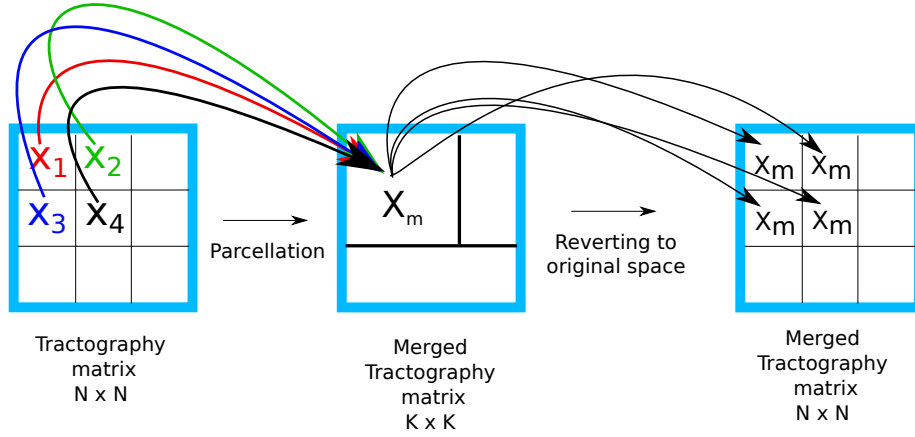


Figure 5: Illustration of the merging process in order to build a merged connectivity matrix and the $N_v \times N_v$ matrix.

vertex a score of confidence with respect to its cluster assignment.

$$s(\mathbf{v}) = \frac{b(\mathbf{v}) - a(\mathbf{v})}{\max(a(\mathbf{v}), b(\mathbf{v}))} \quad (16)$$

Here $a(\mathbf{v})$ is the average dissimilarity between \mathbf{v} and all vertices within the same parcel. $b(\mathbf{v})$ is the average dissimilarity between \mathbf{v} and all elements in the cluster that has the highest similarity. The Silhouette index takes values between -1 and 1, where -1 suggests that the vertex has been misclassified. A value close to zero suggest that the vertex is equally similar to two different clusters. Here, we define the dissimilarity between vertices as the opposite of the correlation matrix.

2.7.3. Group Consistency

We evaluate the quality of our group-wise constraint through a group consistency measure that is inspired by the Minimum Description Length principle (Rissanen, 1978). After a group parcellation, we compute an average connectivity matrix by averaging all subjects' merged connectivity matrices. The group average is then compared to each individual subject's connectivity matrix, the idea being that the distance should be minimal if the average is representative of all subjects. The measure we compute is the Sum of Absolute Differences

(SAD) between the normalised connectivity matrices. Normalisation allows fair comparisons across varying numbers of parcels. In addition, this measure has
405 the potential to identify outliers within a group that will strongly differ from the group average.

2.7.4. *Overlap Between Parcellations*

Parcels are quantitatively compared and matched using the measure of spatial overlap proposed in Bohland et al. (2009). This measure is non symmetric,
410 and evaluates the proportion of one region i that is contained in another region j . We refer to r_i and r_j as the ensembles describing the vertices that belong to regions i and j respectively. The similarity measure P_{ij} is then defined as:

$$P_{ij} = \frac{|r_i \cap r_j|}{|r_j|} \quad (17)$$

where $|r|$ is the number of voxels in ensemble r . When applied on different subjects, this measure relies on the vertex correspondences obtained from the
415 sulcal registration. A symmetric measure is also defined as $O = \sqrt{P_{ij}P_{ji}}$.

We match two parcellations by selecting the parcels that have the highest similarity scores. It should be noted that several parcels can be matched to the same one and therefore merged into a larger parcel. We use the symmetric measure O as a measure of overlap for quantitative evaluation. This is more
420 flexible than the commonly used Dice Similarity Coefficient as it does not search for perfect overlap but also for inclusion of a parcel in another. Furthermore, this approach allows to compare parcellations with a very different number of parcels, which can be very useful when comparing to other methods and modalities.

425 2.7.5. *Bayesian Information Criterion*

The proposed measurements used to evaluate single subject parcellations cannot be used for comparing group parcellations since our group-wise parcellation is not directly derived from a joint connectivity matrix. We compute instead the Bayesian Information Criterion (BIC) as described in Thirion et al.
430 (2014) for evaluating group-wise parcellations.

We evaluate how well the parcellations agree with the underlying brain structure by comparing to task fMRI activation maps. Each vertex is associated with the concatenated task activation maps of all subjects within the group considered. The signal \mathbf{y} (concatenated activation maps) within each parcel is modelled using a probabilistic model as:

$$\mathbf{y} \approx \mathcal{N}(\mu \mathbf{1}, \sigma_1 I_{N_s} + \sigma_2 \mathbf{X} \mathbf{X}^T) \quad (18)$$

Here, μ is the average signal within a parcel, \mathbf{X} is a known matrix that identifies which subject the vertex value corresponds to. The estimation of the parameters $(\mu, \sigma_1, \sigma_2)$ is carried out in each parcel using the Expectation Maximisation algorithm. Parameters σ_1 and σ_2 respectively express the variance within and between subjects. The BIC criterion then evaluates the goodness of fit by penalising the negative log likelihood by the complexity of the model (number of parcels).

3. Results

3.1. Parameter Selection

The parameter μ for the construction of the supervertices is set heuristically to 3. The parameter α that controls the strength of the connections between the subjects has a more important impact on the obtained parcellation. α should be high enough to impose consistency between subjects but also allow local differences between them to remain faithful to the underlying data. Furthermore, isolated supervertices tend to appear when α is too high.

We make use of the KLD and SAD measures to optimise the parameters as they provide complementary information. We compute the KLD to make sure the parcellation remains faithful to the data, while the SAD evaluates if group consistency is imposed. We optimise α on one group of 50 subjects for both hemispheres. We compute the KLD and SAD for 20 to 250 parcels and α ranging from 0.01 to 3.5.

The first observation is that the measures follow what is expected intuitively with respect to the number of parcels: the KLD decreases with the number of

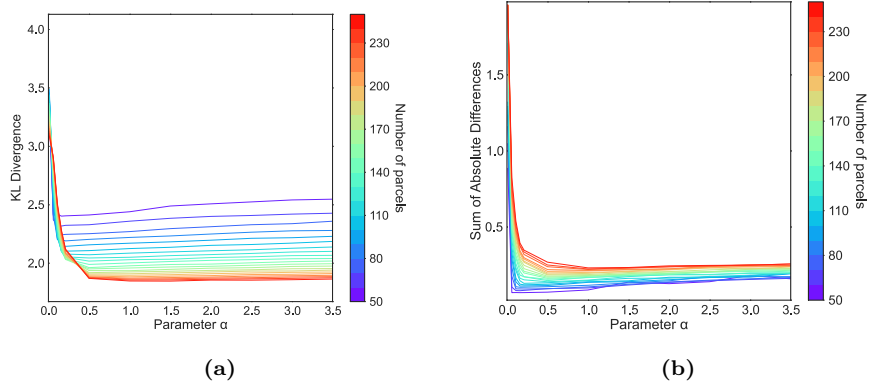


Figure 6: Evolution of the KLD (a) and SAD (b) value of α for the right hemisphere.

parcels. This is expected since a high resolution reduces the amount of averaging
 460 necessary during the construction of the merged matrix. In contrast, the SAD
 progressively increases with the number of parcels. This is due to the fact that
 more anatomical differences are conserved when the resolution increases.

As shown in Fig. 6, both measures follow similar trends, sharply decreasing
 when increasing α , then stabilising or slowly increasing. The strong improve-
 465 ment of the measures at low α values can be explained by the fact that par-
 cellations are not imposed to be similar if the connections are too weak, as a
 result, the number of parcels selected is spread across all subjects, resulting in
 very low parcellation resolutions for all subjects. This increases the value of the
 KLD (low resolution) and the value of the SAD (no agreement imposed between
 470 subjects).

The SAD measure has a tendency to increase after reaching a minimum. Iso-
 lated supervertices tend to appear when the correspondences between subjects
 are set too high, which decreases the quality of the parcellation. We essentially
 seek parcellations that are faithful to the underlying connectivity data while
 475 preventing the appearance of isolated supervertices. Therefore, we select for
 each parcellation resolution the optimal value of α as the closest value that
 both stabilises the KL divergence and minimises the SAD. We observe for both

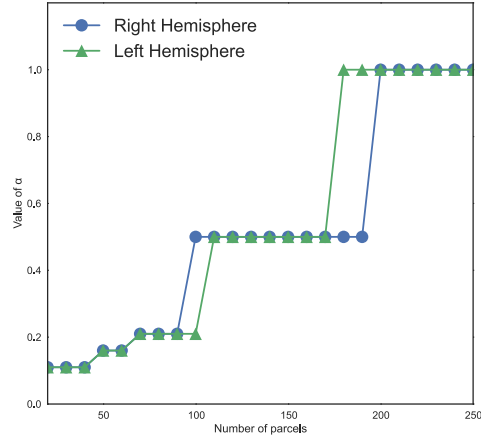


Figure 7: Evolution of the optimal value of α for both hemispheres.

hemispheres that the value of α has to be increased regularly with the number of parcels (Fig.7).

480 All our remaining experiments are carried out on our second group of 50 subjects that have not used for parameter optimisation with the optimal value of α .

3.2. Methods comparison

After parameter optimisation, we perform the group-wise parcellation scheme
 485 on our second group. The first observation, as shown in Fig. 8, is that we obtain parcellations that have direct correspondences yet remain subject specific (*i.e.* the shape and location of parcels can differ from one subject to the next). Isolated supervertices may appear, which can be due to links that are too strong or too numerous.

490 The proposed group-wise method was then quantitatively compared to gyral (Destrieux et al., 2010) and random (Poisson disk sampling) parcellations, as well as connectivity driven parcellations from **k-means**, hierarchical and spectral clustering (Sec. 2.4 and **normalised cuts** (Craddock et al., 2012)). Hierarchical clustering is performed using the spatially constrained linkage method as de-

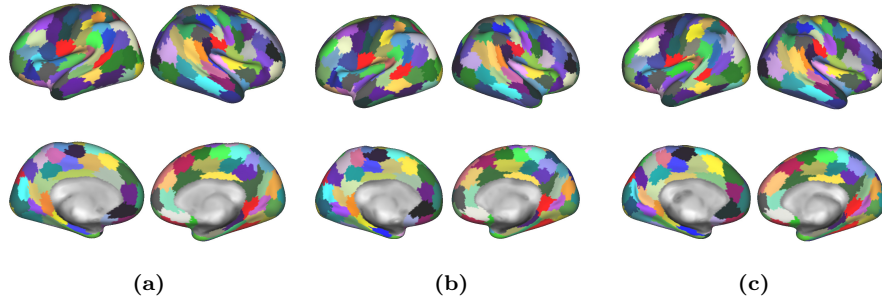


Figure 8: Visual example of single subject parcellations obtained from the group-wise scheme (100 parcels). Identical colours between different subjects indicate corresponding parcels (there is no inter-hemispheric matching).

495 scribed in Moreno-Dominguez et al. (2014). We are using the average linkage method as we have observed that it yields the best quantitative results. This has also been observed by Moreno-Dominguez et al. (2014) for dMRI driven parcellation. All clustering methods are initialised from the finest supervertex resolution so as to reduce the impact of noise. Hierarchical and spectral
500 clustering methods are spatially constrained (we only preserve neighbouring connections) to obtain contiguous parcels. The spatial contiguity of k-means clusterings is artificially enforced by only keeping the connections with the 10 closest neighbours. This yielded compact parcels of similar sizes. Poisson Disk Sampling generates regions of approximately equal size by ensuring that two
505 region centres are not closer than a given threshold which controls the number of obtained parcels. For single subject parcellations, correspondences between the different parcellations have to be established to compute the SAD. The matching is suboptimal since boundaries can be very different across subjects. This biases the values of the SAD but also highlights the main issue associated
510 with single-subject parcellations which is the difficulty to find correspondences between subjects.

We compute the KLD, SAD and Silhouette index for all methods. Figure 9 shows boxplots of the measures for all methods and subjects in the group. We observe that spectral methods tend to show better performance for all mea-

515 **surements** and that the group-wise approach yields very similar KL values as the single subject approach. In other words, the obtained parcellations remain as faithful to the data despite the group constraint while achieving the best results in terms of group consistency. **The same behaviour can be observed for Silhouette index computations.**

520 **Interestingly, k-means clustering yields the best performance for KLD measurements, but the lowest score amongst connectivity driven methods for both Silhouette index and SAD. On the one hand, the different spatial constraint (keeping the 10 closest neighbours rather than the nearest neighbour) could allow to construct parcellations that follow connectivity patterns more precisely.**
525 **On the other hand, this limited constraint yields irregular clusters that are sensitive to noise, which reduces the quality of the parcellation and its reproducibility. This assumption is supported by the low performances obtained for the Silhouette index and SAD (quality of clustering and group consistency). Furthermore, we also observe an increase in performance for all measurements**
530 **using our multi-scale approach compared to Normalised cuts. This highlights the added value of using multiple scales for the parcellation task. The gap in performance is particularly striking for Silhouette index computations.**

Since the surfaces have been registered based on sulcal information, we expect strong similarities between subjects regarding the gyral parcellation. This
535 is confirmed by the low values of the SAD, which are on par with the ones obtained from the group-wise parcellation. The performance in terms of information loss and cluster validity indices is on the other hand the worst across all methods.

3.3. Inter-modality Comparisons

540 We then compared the boundaries of our parcellations with myelin maps, Brodmann’s areas and fMRI task activation maps. All modalities are obtained from the HCP dataset (myelin, Brodmann) Glasser et al. (2013) or using the HCP processing scripts (task fMRI). Myelin maps are calculated as the ratio of T1-weighted and T2-weighted MRI (Glasser and Van Essen, 2011). The Brod-

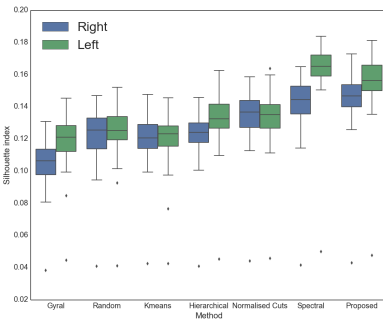
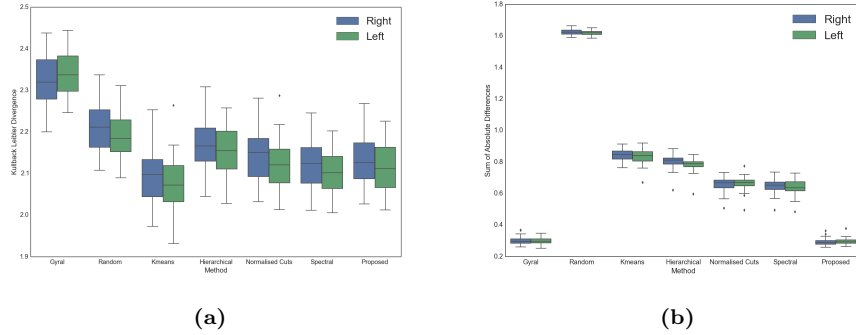


Figure 9: Boxplots of the values of the KLD (a), SAD (b) and Silhouette index (c) for all parcellation methods.

545 mann parcellation was mapped onto the Conte69 brain surface atlas (Van Essen et al., 2012). It was then mapped onto each subject’s surface using the cortical folding driven registration’s deformation field.

The task fMRI data is preprocessed following the HCP preprocessing pipelines (gradient unwarping, motion and distortion correction, registration to the MNI 550 space and projection to the cortical surface). Task activation maps are then obtained using standard FSL tools (FEAT) that use general linear modelling to construct activation maps (Barch et al., 2013). The analysis is carried out across sessions (single subject activation maps) and then across subjects (group-wise activation map).

555 Observations are made on the group average level, as well as the individual
subject level. Our aim is to show that we obtain sensible average maps as well
as faithful individual maps. All modalities provide complementary information,
and therefore a complete match cannot be expected in any of the cases. How-
ever, we can expect local correlation between our parcel boundaries and other
560 modalities.

For all resolutions, we observe strong correspondences between our parcels’
boundaries and strong variations of myelination, specifically in the motor areas,
both on the average map and the single subject level. This is illustrated in
Fig.11 for randomly selected subjects and the average maps.

565 Furthermore, single subject parcellations appear to have similar boundaries
with Brodmann’s cytoarchitectonic motor areas (BA 1, 2, 3a-b, 4a-b and 6).
Quantitative comparisons are proposed on the basis of the atlas concordance
measure of Bohland et al. (2009). For all parcellation resolutions, we compute
the overlap O between all Brodmann areas and our parcels. Due to the small
570 size of these regions, areas BA 1, 3 and 4 are merged into a single parcel. We
compare the quantitative results obtained with the other considered parcellation
methods (spectral, hierarchical and random). In particular, random parcella-
tions show how our results relate to chance. Figure 10 shows boxplots of the
average overlap scores over all subjects for all resolutions, Fig. 11 shows visual
575 examples of the overlap for different subjects, while Fig. 12 shows a spatial
comparison to random parcellations overlap scores. On average over all parcel-
lation resolutions, we obtain very good overlap measurements with the motor
areas (BA 1-6), and outperform other methods. Interestingly, we observe that
good overlap scores are only obtained around the motor area for all connectivity
580 driven methods. The fact that results can be significantly lower than the overlap
with random parcellations for all subjects and methods in some areas could sug-
gest that either the structural connectivity differs with cytoarchitecture, or that
the Brodmann map and structural connectivity data are not properly registered.

Our average parcellation is also compared to the composite parcellation pro-
585 posed in Van Essen et al. (2012) where each region is derived from reliable

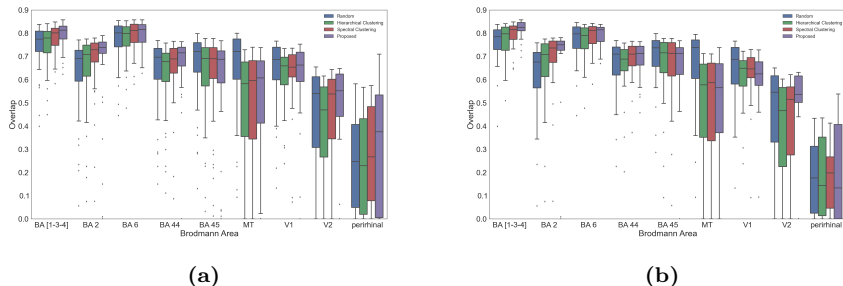


Figure 10: *Boxplots of the average overlap over all subjects between our parcels and Brodmann areas for all computed resolutions. (a) left hemisphere, (b) right hemisphere.*

local parcellations. Parcels are derived from different modalities such as cytoarchitecture and retinotopy. Given the size of most regions, we compare the parcellation to a high resolution connectivity driven parcellation (200 regions). Visual comparisons are shown in Fig. 11c and comparisons with the performance of random parcellations are shown in Fig. 12b. Here again, we compute overlap scores between our group average and the composite parcellation and compare it to the performance of random parcellations. We again obtain good performance around the motor area, and worse results in other regions, notably around the visual cortex. In addition to data quality and disagreement of dMRI with other modalities, these results could be linked to the size of the groups used to build the composite and group parcellations, which could be too small to fully correspond. Another explanation could be that some regions have too much inter-subject variability and cannot be summarised properly without a dMRI driven registration step.

Task activations are only compared on the group level due to the fact that individual task activation maps can be very noisy. We are therefore only comparing our average parcellation to average activation maps. Visual comparisons are proposed in Fig. 13 between the boundary of our average parcellations and activation maps for different tasks.

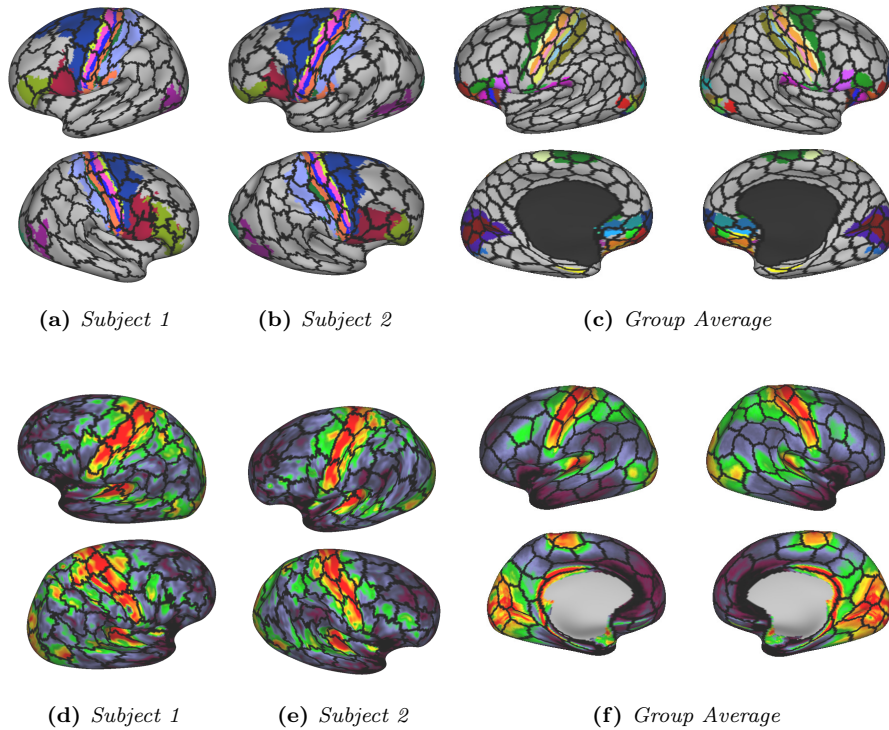


Figure 11: Visual examples of the overlap between our parcels' boundaries (black lines) and Brodmann areas (a,b), myelin maps (d-f), the composite parcellation Van Essen et al. (2012) (c) for two randomly selected subjects and the group average map.

605 **3.4. Group-wise Parcellation Evaluation**

While a set of 50 subjects remains limited, group parcellations at this level should start showing consistency across different groups and are less sensitive to inter-subject variability. We evaluate the reproducibility between two different groups by comparing our average parcellations obtained from our two groups of
 610 50 subjects. The average parcellations are computed through majority voting from all 50 individual parcellations, while the average connectivity map is simply the average of all subjects' merged connectivity maps.

We computed the overlap between our different parcels after matching them, as well as the SAD in order to compare the built connectivity networks. Those

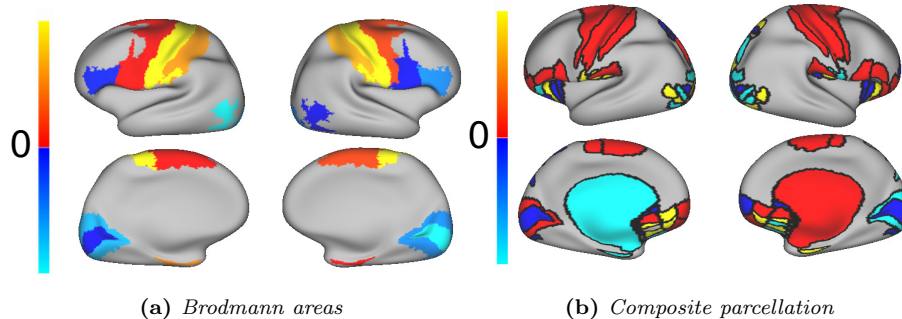


Figure 12: Comparison of the performance of the group-wise parcellation w.r.t random parcellations for (a) the Brodmann map and (b) the composite parcellation Van Essen et al. (2012). Values higher than zero (red to yellow) have a higher overlap than random parcellations, worse overlaps are shown in blue. (a) For each parcel, we count the number of times a parcel overlaps better (+1) or worse (-1) for all subjects and parcellation resolutions. (b) Overlaps are compared for 200 parcels, and averaged over the 50 random parcellations. Yellow and cyan parcels have an overlap difference of more than 20 % between both parcellations, other cases are shown in red and blue.

615 values are compared to the ones obtained between two independent single subject parcellations and the overlap between two subjects parcellated within the same group. The evolution of the overlap with respect to the number of clusters is shown in Fig. 14.

After matching the parcels, we also computed the SAD between the two average maps. As expected, the value tends to increase with the number of parcels and are lower than the intra group SAD scores. However, we consistently obtain better values than the one obtained between spectral individual parcellations (where the matching process is identical) and, as illustrated in Fig. 15, very similar connectivity maps at low resolutions. Figure 16 shows how reproducible two regions are within the same group on average over all resolutions. We observe a similarity between reproducible regions between the two hemispheres.

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625

Our group-wise parcellations from the second group (not used for parameter optimisation) are also quantitatively compared the group-wise parcellations obtained using common clustering methods (k-means, hierarchical (using

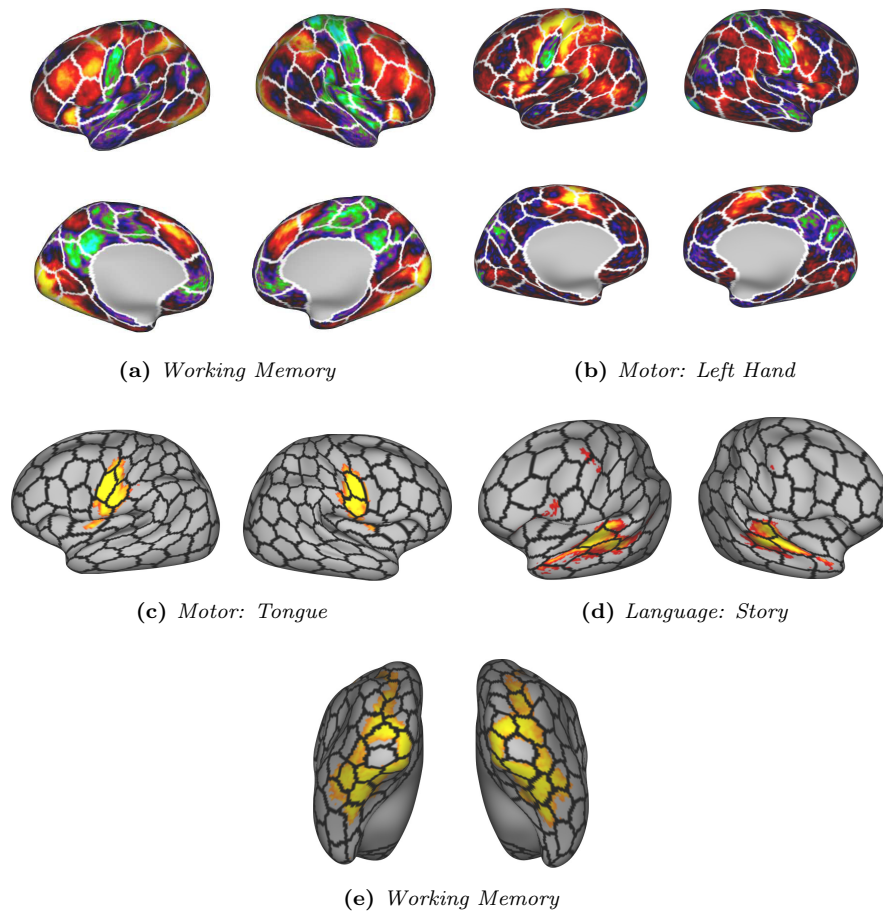


Figure 13: *Visual examples of the correspondences between average task activation maps and our average parcels' boundaries for a group of 50 subjects.*

630 the average linkage method) and spectral clustering (normalised cuts and our
multi-scale approach)) on the average connectivity matrix. For all clustering
tasks, the affinity matrix driving the clustering is the Pearson’s correlation co-
efficient between the average connectivity profiles over all 50 subjects in the
group. We do not compare to other group averages from single-subject meth-
635 ods here since the differences between single-subject parcellations are too high
to construct a meaningful average map. Methods are compared quantitatively
using the BIC criterion (sec. 2.7.5). The same task fMRI contrasts as the ones
proposed in Thirion et al. (2014) are considered here: the faces-shape contrast
of the emotional protocol, the punish-reward contrast of the gambling protocol,
640 the math-story contrast of the language protocol, the left foot-average and left
hand-average contrasts of the motor protocol, the match-relation contrast of the
relational protocol, the theory of mind-random contrast of the social protocol
and the two back-zero back contrast of the working memory protocol.

Results are shown in Fig. 17 for both hemispheres and all resolutions con-
645 sidered (20 to 250 parcels). We can see that the spectral methods yield the
best results (lower values are better) for both hemispheres and most resolu-
tions. Our group-wise approach tends to yield better results at the highest
resolutions, which could be linked to the fact that the lack of registration be-
tween dMRI connectivity networks (which will impact the average connectivity
650 matrix) has a stronger impact when more precision is required.

We also visualise the average intra and inter-subjects variance parameters
of the model (σ_1 and σ_2 respectively) in Fig. 18. All methods have similar
behaviour: the intra-subject variance monotonously decreases with the number
of parcels, while the inter-subject variance follows the opposite trend. A similar
655 behaviour was observed in Thirion et al. (2014). All methods appear to have
similar variances, with hierarchical and k-means clustering having the largest
inter-subject variance and intra-subject variance respectively.

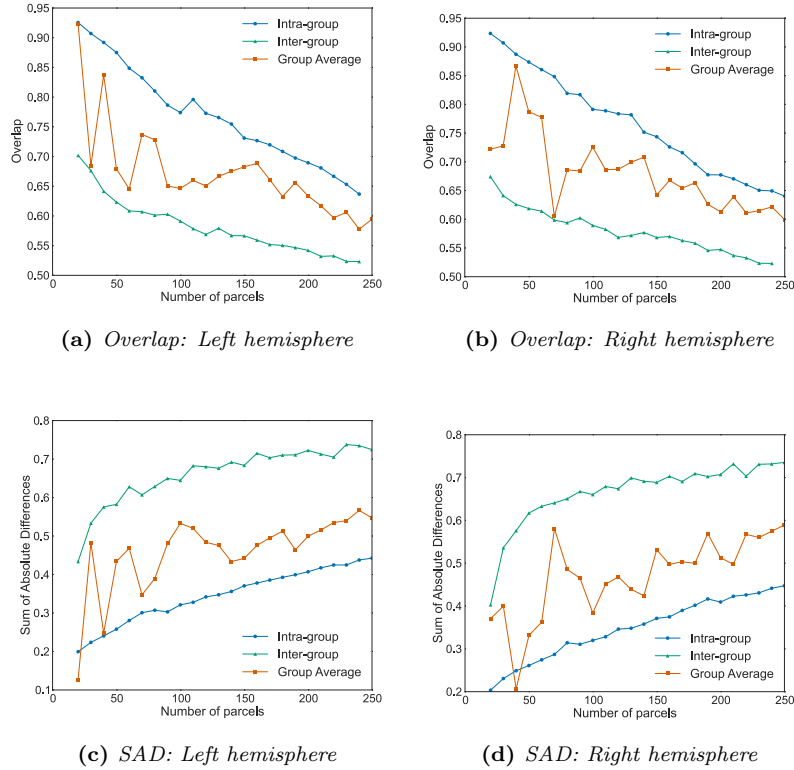


Figure 14: *Quantitative evaluation of the group consistency, compared to the intra-group consistency (obtained from a group-wise parcellation) and the inter-group consistency (obtained from single subject parcellations).*

4. Discussion

In this paper, we proposed a connectivity-driven parcellation method inspired from the concept of cosegmentation. The proposed method simultaneously estimates subject specific parcellations that have direct correspondences across subjects. Quantitative and qualitative experiments show that group consistency does not reduce the quality of the parcellation on the subject level. Furthermore, the comparison between two independent groups shows that we can obtain a good reproducibility despite a relatively small sample size.

Our comparisons with myelin maps, task fMRI and cytoarchitecture show

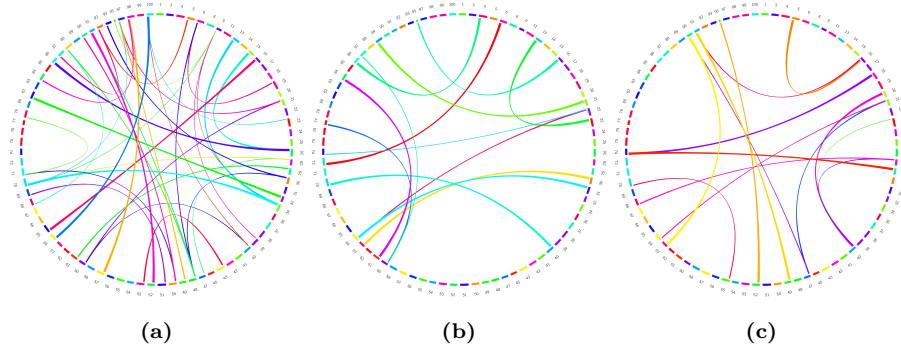


Figure 15: *Visualisation of the absolute difference between connectivity networks: (a, b) difference between the networks obtained for two subjects using single subject parcellation (a), and group-wise parcellation (b); (c) difference between the average networks for the two different groups tested. The circle represents the parcels on the cortical surface, connections are the edges connecting the parcels. The edges and their thickness correspond to the difference in connectivity strength (probtrackX fibre count) between the compared networks. The different colours are used here for visualisation purposes to differentiate the edges.*

that we obtain parcel boundaries that reflect other modalities, especially in the motor area where we observe strong similarities. Inter modality comparisons should however be considered carefully. First, all different modalities are obtained after a series of processing steps where several errors could be introduced
670 (cortical folding based registration, volume to surface projection, segmentation...). Furthermore, it is still unclear how much these modalities interact and how similar they are expected to be. Therefore, complete agreement is not to be expected. In particular, we have observed that all dMRI driven parcellations we
675 considered are generally performing worse than random parcellations in terms of overlap with Brodmann areas that are not in the motor area. There are several facts that can explain this phenomenon. The Brodmann maps are obtained from a single subject, then projected onto an atlas, which is then registered to the single subjects based on cortical folding. The registration process is based
680 on sulcal depth, which focuses strongly on the motor area where the folding patterns are more consistent between subjects. The observation that dMRI driven

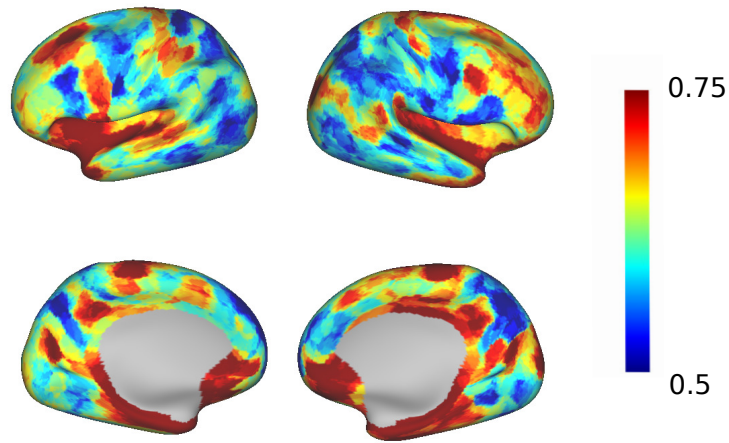
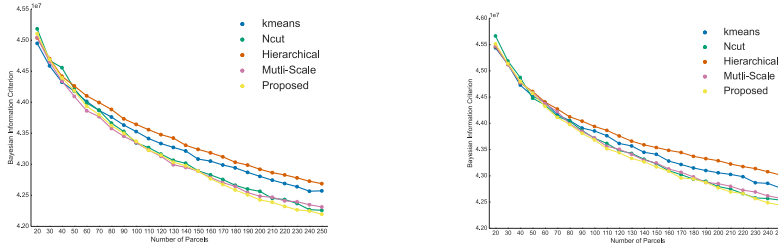


Figure 16: *Local overlap between the two group averages, averaged over all resolutions.*

parcellations are performing worse than chance suggests that Brodmann areas' boundaries are not properly aligned with the dMRI data. This is very likely to be the case for subjects that have very different folding patterns with respect to the reference surface. The fact that our comparisons are favourable in the motor area supports this theory. Other possible explanations could be that dMRI locally disagrees with cytoarchitectural boundaries, or that the dMRI processing steps and noise have introduced some errors that do not allow to recover these boundaries.

More generally, several facts associated with dMRI driven parcellations should be kept in mind when looking at the interpretability of parcellations or aiming at comparing them with different modalities (rs-fMRI parcellations for instance). dMRI and tractography represent the current best way of representing the physical connections in the brain in vivo. Parcels can therefore naturally be biologically interpreted as regions that are directly connected to the brain in a similar way. Because of this, dMRI is expected to be more robust and interpretable for longitudinal (ageing or development) connectome analysis than resting-state fMRI for instance, whose biological interpretation is not as natural (Eickhoff et al., 2015).



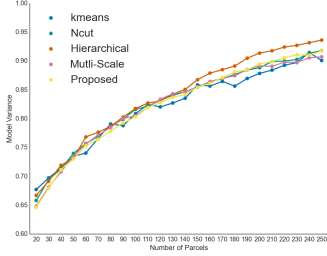
(a) *Left hemisphere*

(b) *Right hemisphere*

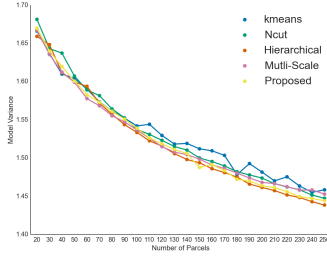
Figure 17: Comparison of group-wise parcellation methods using Bayesian Information Criterion scores for both hemispheres. Lower values correspond to better scores.

700 Nevertheless, the connections inferred from dMRI processing and tractography have to be considered carefully and put in perspective. The connections are obtained from the indirect measurement of the diffusion of water molecules in the brain. Processing the data and inferring the tracts is a tremendous problem in itself, and many aspects remain problematic. Large fibre bundles are often
705 predominant, while crossing and kissing fibres are often difficult to differentiate. Long range connection can also often be missed, due to a growing uncertainty along the tract. This makes tractography data prone to false negatives (interestingly, rs-fMRI is on the contrary prone to false positives). Another difficulty is to precisely determine the origin of the tracts, tractography having been observed to have a bias with ending tracts in gyri (Van Essen et al., 2013; Ng et al.,
710 2013), this could notably affect the location of parcel boundaries and should be remembered when comparing parcellations to other modalities for instance. Despite these encountered difficulties, dMRI remains the best way of evaluating the physical tracts in vivo. While the obtained tracts could not be completely
715 accurate, the evaluated similarity between connectivity profiles could still be correct (Knösche and Tittgemeyer, 2011), leading to accurate parcellations.

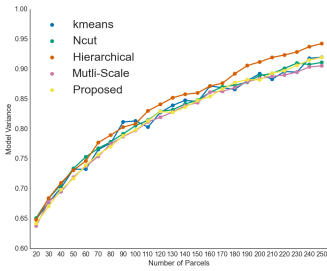
One drawback of spectral clustering approaches is the tendency to create similarly sized parcels. This size bias could explain why the quality of the



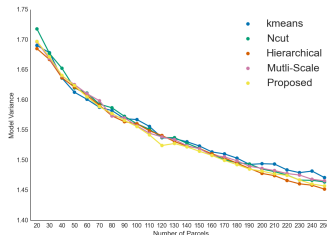
(a) *Left hemisphere - inter subjects*



(b) *Left hemisphere - intra subject*



(c) *Right hemisphere - inter subjects*



(d) *Right hemisphere - intra subject*

Figure 18: *Comparison of the intra and inter-subject model variance between group-wise parcellation methods both hemispheres.*

correspondences with cytoarchitectonic regions and task activation maps varies
 720 from one resolution to the next. Indeed, it is possible that some transitions
 in connectivity can only be captured at specific resolutions or degrees of pre-
 cision. This phenomenon could prevent from determining an optimal number
 of parcels as specific boundaries could be identified at specific resolutions. For
 this reason, the main objective of our evaluation was not to find an optimal
 725 number of parcels but rather to compare our approach at a given resolution
 with others. A possible way of exploiting this hierarchy of parcellations would
 be to combine the parcellations obtained at different resolutions, or identifying
 the most reliable boundaries over all resolutions. **Another issue associated with**

the hierarchical and spectral clustering method considered here is the imposed
730 spatial constraint to obtain spatially contiguous parcels. Only connections be-
tween neighbouring vertices are kept, which can lose critical information. On
the other hand, parcel can be subject to noise and irregular, as observed with
k-means clustering results.

One of the main advantages of using a group-wise parcellation method is the
735 possibility to perform direct comparisons between subjects as well as groups
(gender, age or diseased base groups). At the single subject level, this allows to
estimate which brain regions are the most consistent (inter-subject variability),
while the group level enables to evaluate the fundamental differences in connec-
tivity and function between two different groups. This could provide information
740 about the impact of a disease on the brain for instance. One big challenge would
be to identify whether the differences are due to noise and processing errors or
actual biological differences. Comparing one subject to the group could be a
way of identifying if a region in a specific subject is governed by noise. Our
method reduces the influence of noise and registration errors by finding local
745 correspondences at a coarse supervertex parcellation level and carrying a neigh-
bourhood search. This setting is better suited for identification of similarities
between subjects when working at the subject level. Group differences can then
be considered as noise should be strongly reduced at the group level.

A natural extension of the method would be to run it on much larger groups
750 in order to evaluate the reproducibility and obtain parcellations that are truly in-
dependent from inter-subject variability. Consequently we could estimate more
reliably the global differences between different kinds of groups. A further ex-
ploration of the parameter space on a larger group would also allow a better
design of the inter-subject edges. Finally, inter-modality comparisons could be
755 performed by applying the method to resting state fMRI. Comparing or combin-
ing dMRI and rs-fMRI driven parcellations could enable to identify functionally
specialised regions more accurately than by using a single modality.

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