BIGBRAIN: LINEAR COMBINATION OF DISTANCE METRICS FOR AUTOMATED CORTICAL PARCELLATION

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Abstract: "BigBrain" a high-resolution 3D model of a human brain at nearly cellular resolution as been created from histological sections. We propose an automated parcellation of the BigBrain image and our parcellation framework is based on the linear combination of distance metrics. We performed a quantitative analysis of our results and ranked the metrics based on their similarity index compared to Brodmann atlas. We found that the Mahalanobis distance was the one that best maps the Brodmann parcellation scheme onto the BigBrain volume. The JuBrain atlas was used as target to optimize the linear combination of the metrics and results have been compared to four selected areas of the atlas in the inferior parietal lobule.

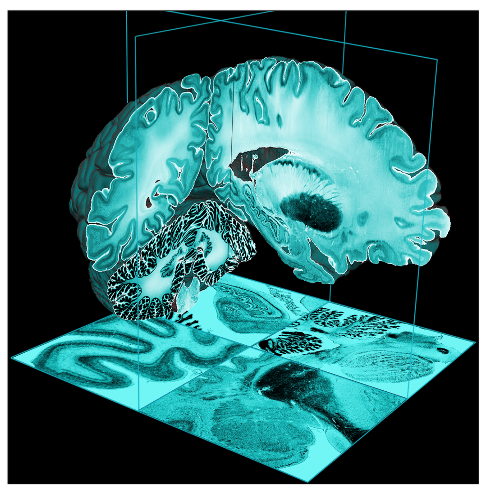
1. MATERIAL AND METHODS

1.1 Origin of the BigBrain dataset

BigBrain is a high-resolution 3D model of a human brain at nearly cellular resolution. It is a result of a collaboration between the Jülich Research Centre (Jülich, Germany) and the McGill Centre for Integrative Neuroscience (Montreal, Canada). The BigBrain dataset represents:

- **7,404 histological sections (20µm thick)**
- **Reconstructed 3D image at 20µm voxel**
- **Volume of nearly 1TB (Terabyte) in size**
- **125,000 times greater (in 3D) than MRI**

3D reconstruction:

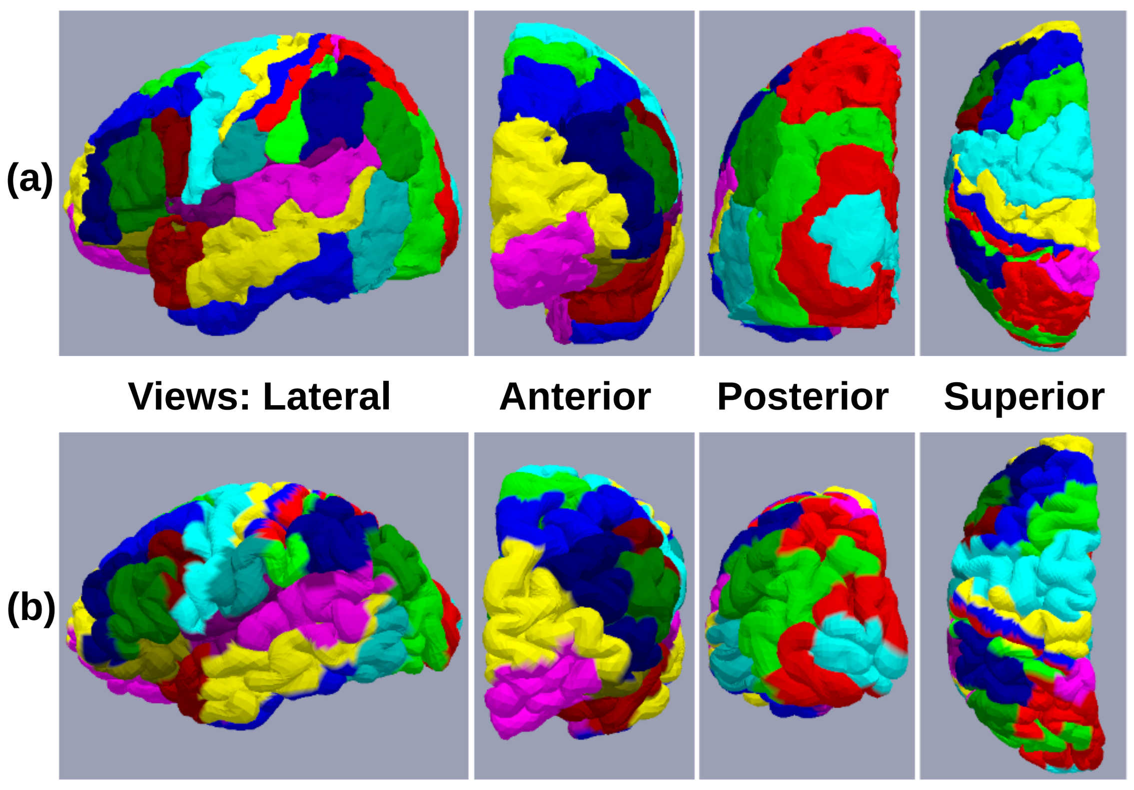


Microtome sectioning:

BigBrain data is available at: ***https://bigbrain.loris.ca/***

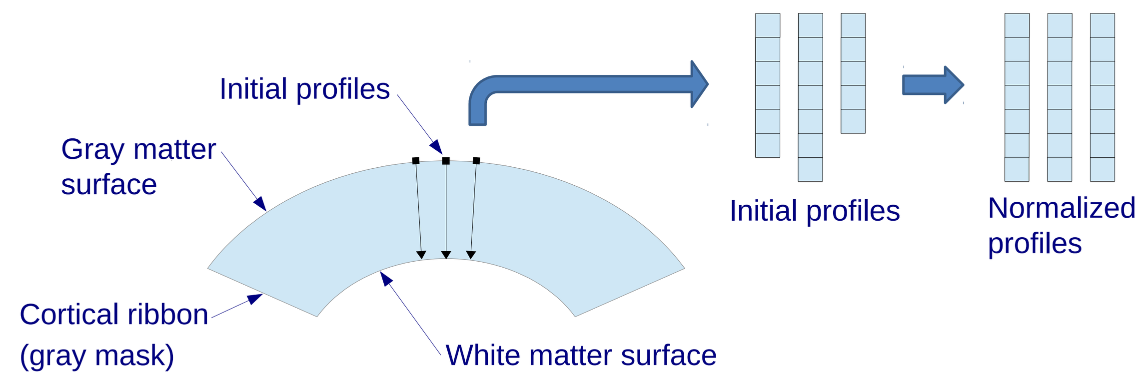
To create the 3D brain model, a large-scale microtome was used to cut coronally a complete paraffin-embedded brain. 7,404 sections at 20µm thickness were acquired and stained for cell bodies. Histological sections were digitized and the virtual brain image was reconstructed in 3D.

1.2 BigBrain image and Brodmann atlas



Brodmann atlas and its registration with BigBrain left hemisphere. (a) Brodmann atlas defined on the brain left hemisphere in 3D. (b) BigBrain left hemisphere registered with Brodmann atlas showing Brodmann areas onto the BigBrain with the same color code as for Brodmann atlas itself in (a).

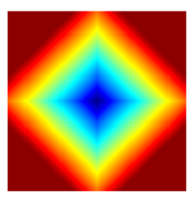
1.3 Profiles: 3D bars across cortical layers



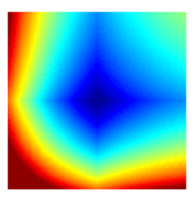
- **A profile is a 3D bar across the cortical layers which starts with a voxel on the gray matter surface and ends with a voxel on the white matter surface.**
- **A profile is composed of all neighbor voxels encountered on the path from the gray matter surface voxel down to the closest white matter surface voxel in the direction of the gray matter surface normal vector.**
- **Then all profiles are normalized in length and organized in straight vectors of same length with values corresponding to voxels intensities across cortical layers.**
- **Each voxel on the gray matter surface belongs to a distinctive profile. We use a three-dimensional 18-connected neighborhood for voxels along the path and no orphan voxel is left.**

1.4 Distance metrics definitions

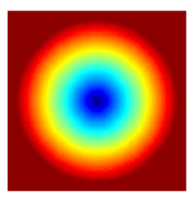
City block: $d(x,y)=\sum_{i=1}^{n}|x_i-y_i|$



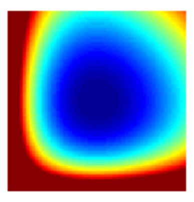
Canberra: $d(x,y)=\sum_{i=1}^{n}\frac{|x_i-y_i|}{|x_i+y_i|}$



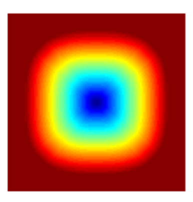
Euclidean: $d(x,y)=\sqrt{\sum_{i=1}^{n}(x_i-y_i)^2}$



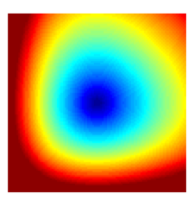
Squared chord: $d(x,y)=\sum_{i=1}^{n}\left(\sqrt{x_i}-\sqrt{y_i}\right)^2$



Minkowski: $d(x,y)=\left(\sum_{i=1}^{n}|x_i-y_i|^p\right)^{1/p}$ $(p=3)$:



Squared Chi: $d(x,y)=\sqrt{\sum_{i=1}^{n}\frac{(x_i-y_i)^2}{|x_i+y_i|}}$



- **We also tested the Mahalanobis distance defined by:**

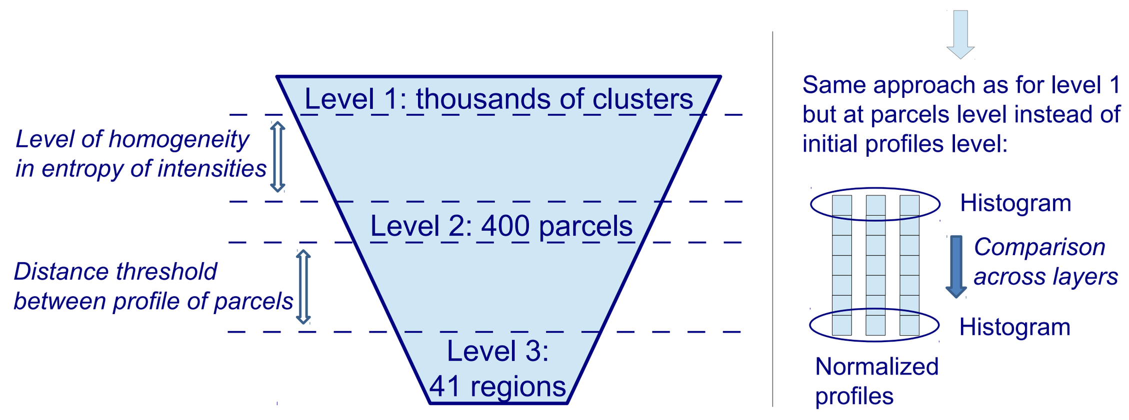
$$d(x,y)=\sqrt{(x-y)^T S^{-1}(x-y)} \quad where: \; S=\text{covariance matrix}$$

- **We used entropy measurement to construct the histogram of clusters:**

$$E(p(x))=\sum_{x\in X} p(x)\log(p(x)) \quad where: \; p(x)=histogram\ of\ x$$

1.5 Multilevel parcellation algorithm

First level: Initial profiles merging with distance metrics (Thousands of clusters) → **Second level: Entropy measurement on 3D clusters** (Close to 400 parcels) → **Third level: Distance metrics on the profile of parcels** (Close to 41 regions)



- **At the first level of parcellation distances between starting profiles and their neighboring profiles are computed. Neighboring profiles with similar distances are labeled and regrouped to form 3D clusters.**
- **The second level of parcellation is achieved using entropy of 3D clusters in a global process of similar neighbors merging.**
- **The third level of parcellation uses the same distance metric of level 1. Histograms of the intensities across cortical layers are constructed and distances of neighbor parcels are based on their distribution.**

1.6 Linear combination of metrics

Metrics: 7 distances parcellations (Individual metrics)

Areas: JuBrain (4 areas) Inferior Parietal Lobe (Selected target)

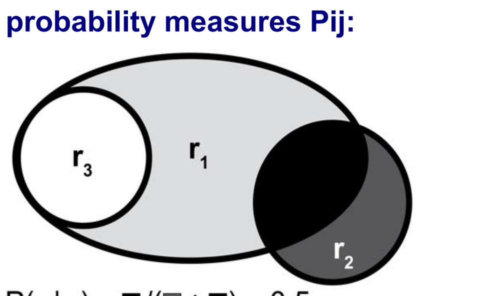
→ **Distance matrix: Inner product normalization** (Empirical kernel) → **Optimization: kernel target alignment** (Distance learning)

- **The individual parcellation results for each of the seven distance metrics are linearly combined to obtain an improved parcellation.**
- **This framework is based on a distance learning approach with a kernel target alignment using areas of the JuBrain atlas as target.**
- **The principle is illustrated by selecting four areas of the JuBrain atlas in the Inferior Parietal Lobule (areas PF, PFm, PGa, and PGp).**
- **The JuBrain atlas was registered to the BigBrain and for comparison, the selected areas were mapped onto the MNI-Colin27 brain template.**

2. RESULTS

2.1 Similarity index measurements

Formulation of conditional probability measures Pij:



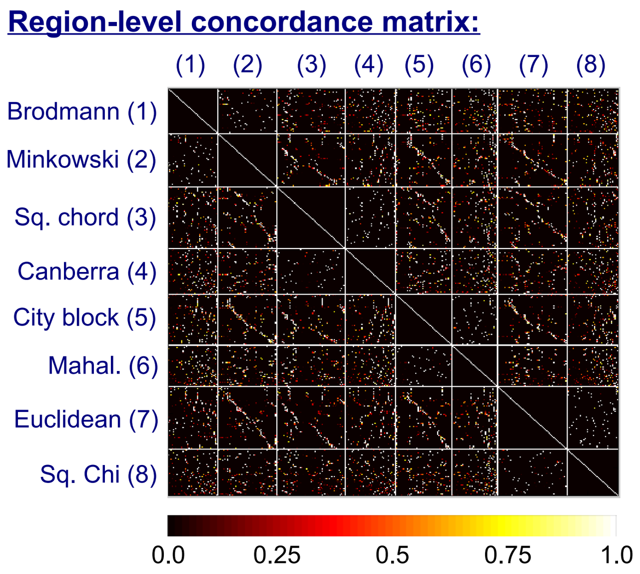
P(r1|r2) = ■/(■ + ■) ≈ 0.5

P(r2|r1) = ■/(□ + ■ + □) << 0.5

P(r3|r1) = □/(□ + ■ + □) << 1

P(r1|r3) = □/□ = 1.0

Region-level concordance matrix:



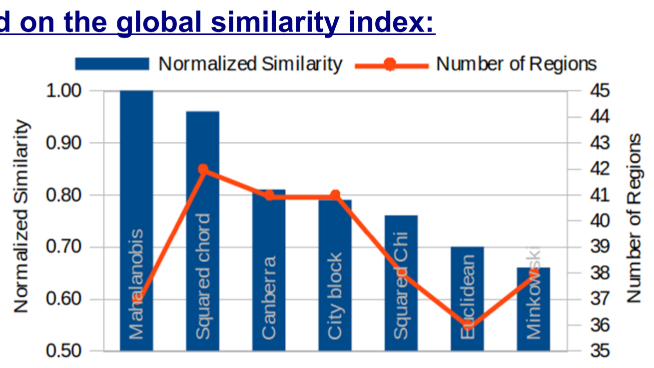
Global similarity index:

To address the global similarity or concordance of two parcellations we compute the fraction of all possible pairs of voxels that are either in the same region or in different regions in both parcellations:

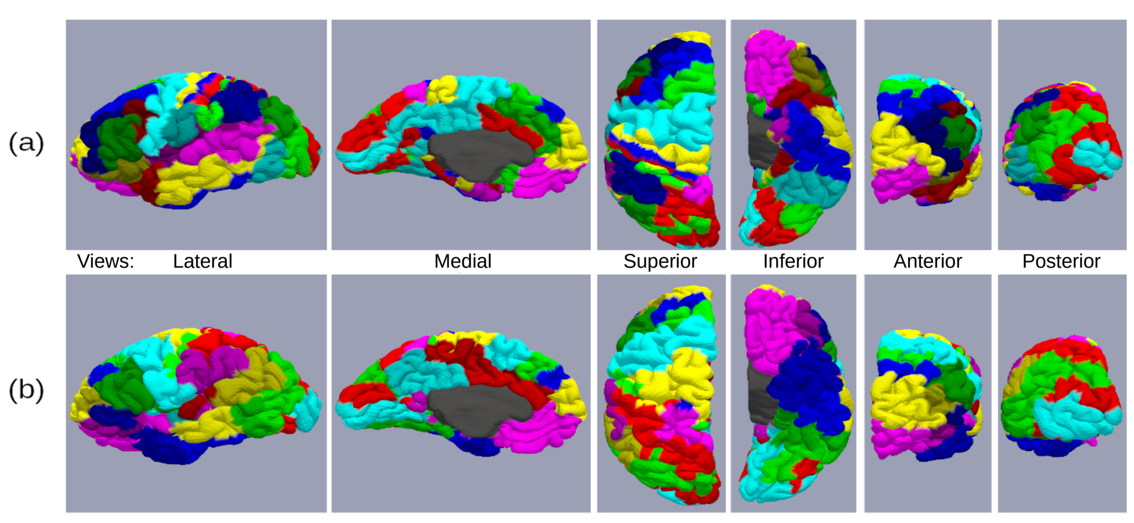
$$\frac{\sum_{ij}\binom{|r_i\cap r_j|}{2}-\left(\sum_i\binom{|r_i|}{2}\sum_j\binom{|r_j|}{2}\right)\Big/\binom{M}{2}}{\frac{1}{2}\left(\sum_i\binom{|r_i|}{2}+\sum_j\binom{|r_j|}{2}\right)-\left(\sum_i\binom{|r_i|}{2}\sum_j\binom{|r_j|}{2}\right)\Big/\binom{M}{2}}$$

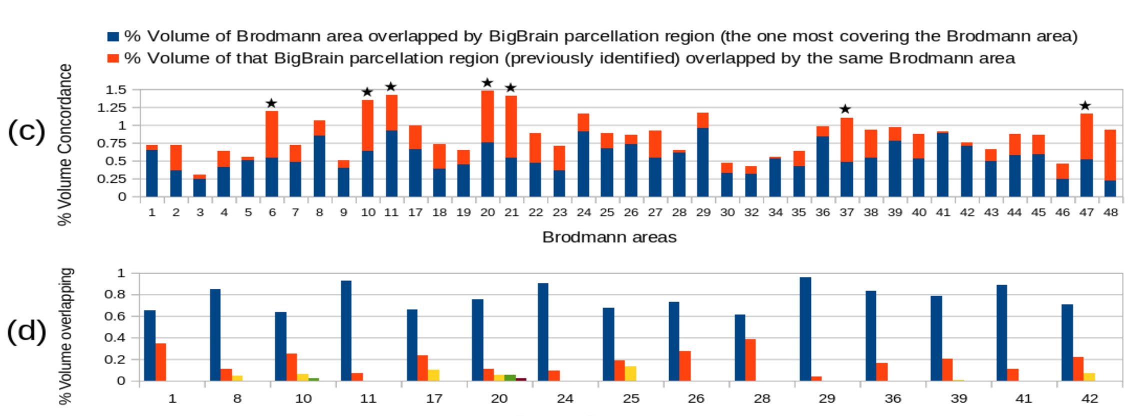
Ranking of distance metrics based on the global similarity index:

Distance Metrics	Normalized Similarity	Number of Regions
Mahalanobis	1.00	37
Squared chord	0.96	42
Canberra	0.81	41
City block	0.79	41
Squared Chi	0.76	38
Euclidean	0.70	36
Minkowski	0.66	38



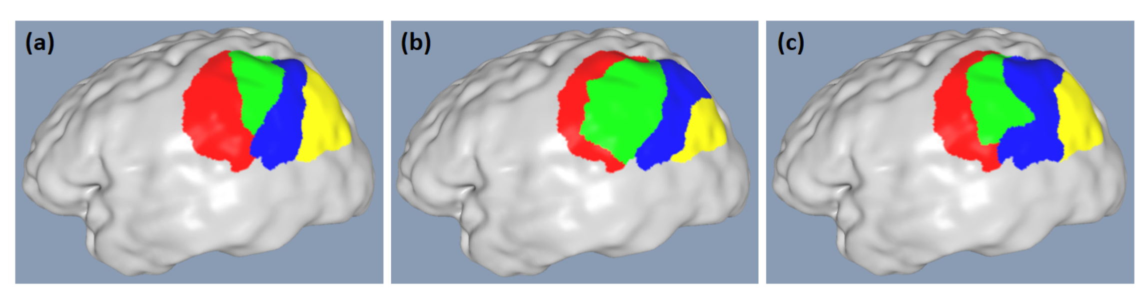
2.2 Mahalanobis and Brodmann comparison



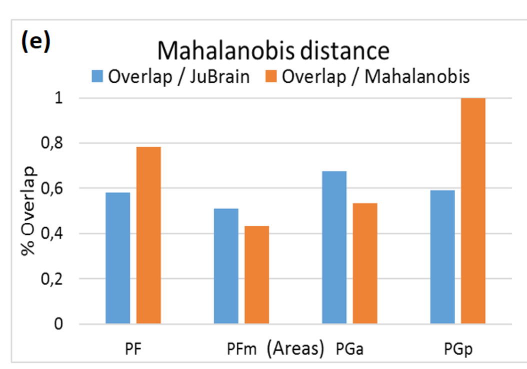


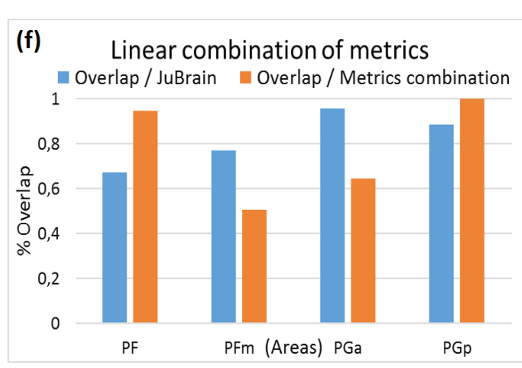
Comparison of BigBrain parcellation with Brodmann atlas using Mahalanobis distance. (a) BigBrain left hemisphere with mapped Brodmann areas. (b) BigBrain parcellation results using a color coding similar to Brodmann areas in (a) to highlight concordance. (c) Chart of concordance between Brodmann areas and BigBrain parcellation regions. (d) Chart of distribution of BigBrain parcellation regions overlapping Brodmann areas.

2.3 Linear metrics and JuBrain comparison



(d) Inferior Parietal Lobule (Lateral view): Area PF; Area PFm; Area PGa; Area PGp.





Mahalanobis distance and linear combination of metrics parcellations of BigBrain compared to JuBrain areas in Inferior Parietal Lobe. (a) JuBrain areas in the Inferior Parietal Lobe mapped onto MNI-Colin27 average brain template. (b) Mahalanobis distance metric parcellation of BigBrain constrained in the Inferior Parietal Lobe defined in (a). (c) Parcellation of BigBrain using a linear combination of the metrics with the result also constrained in the Inferior Parietal Lobe defined in (a). (d) Colormap legend of results for the selected areas in the Inferior Parietal Lobe. (e) and (f) Charts showing the quantitative similarities between (e) Mahalanobis distance and (f) Linear combination of the metrics compared to JuBrain areas in the Inferior Parietal Lobe. Bars represent the overlapping proportion between parcellations and the JuBrain reference.