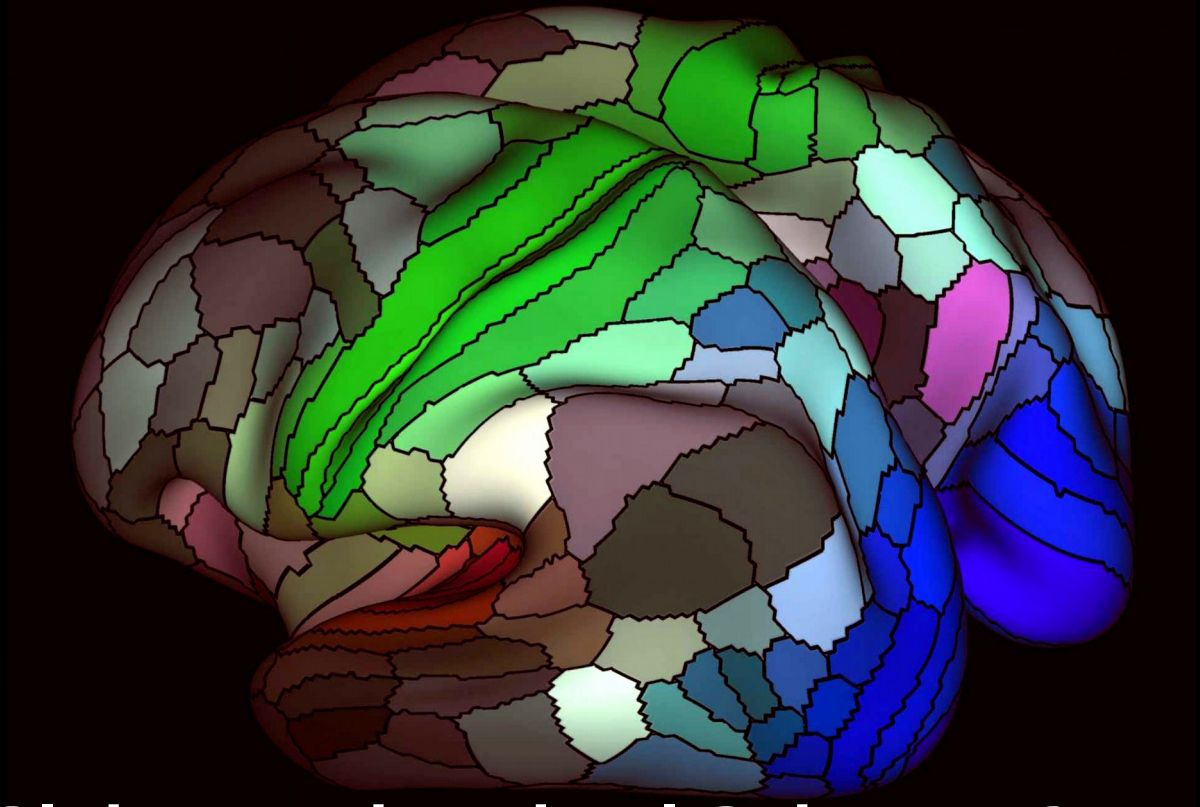
Gradient organization of the brain across species

How Invasive Animal Studies Inform Noninvasive Mapmaking in Humans



Journal Club on Lab Animal Science, Oct 1st, 2019

Dr. Alessandro Crimi

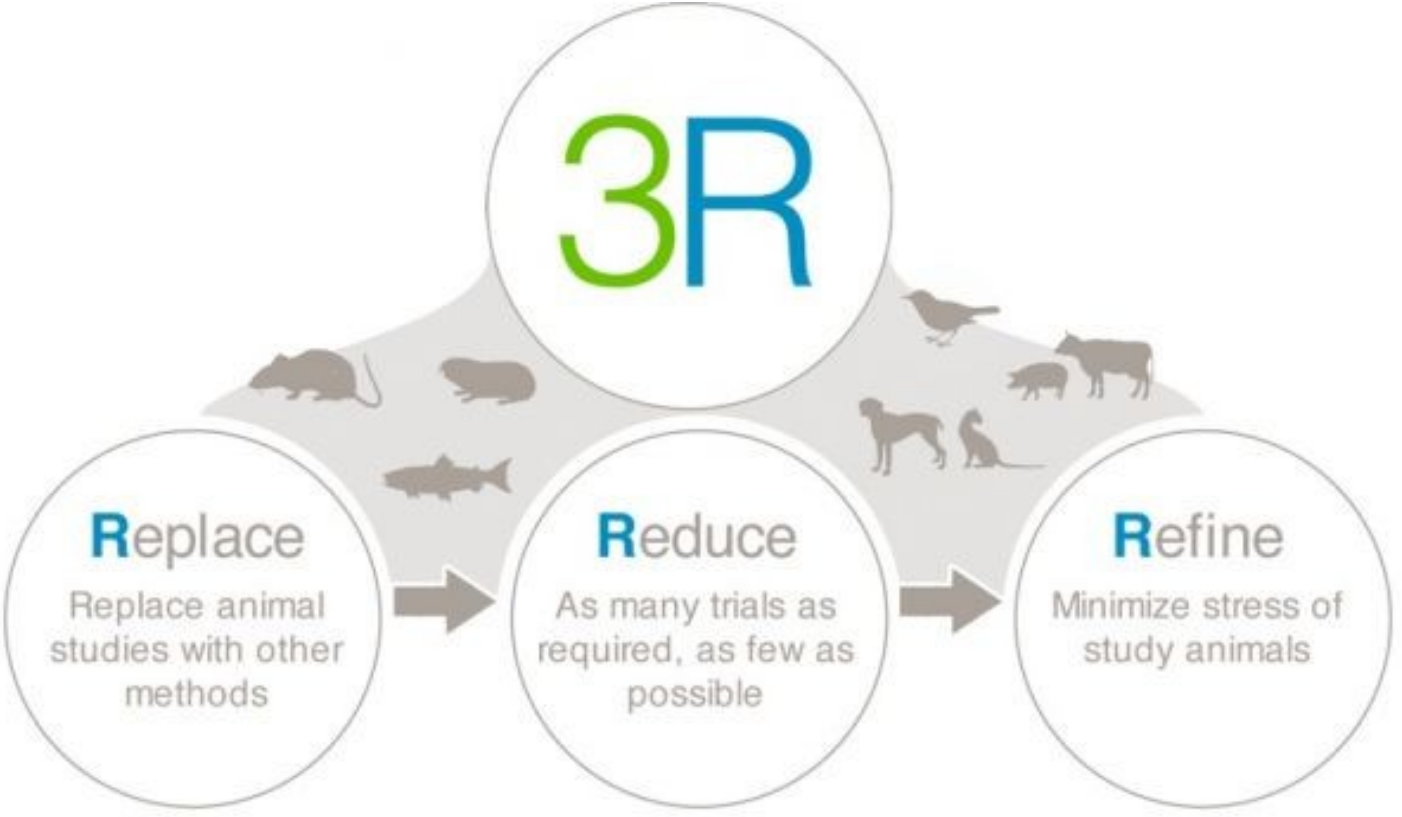
Agenda

- Review of recent animal/human studies about parcellation

- What are gradients?
- Multimodal gradients across mouse cortex

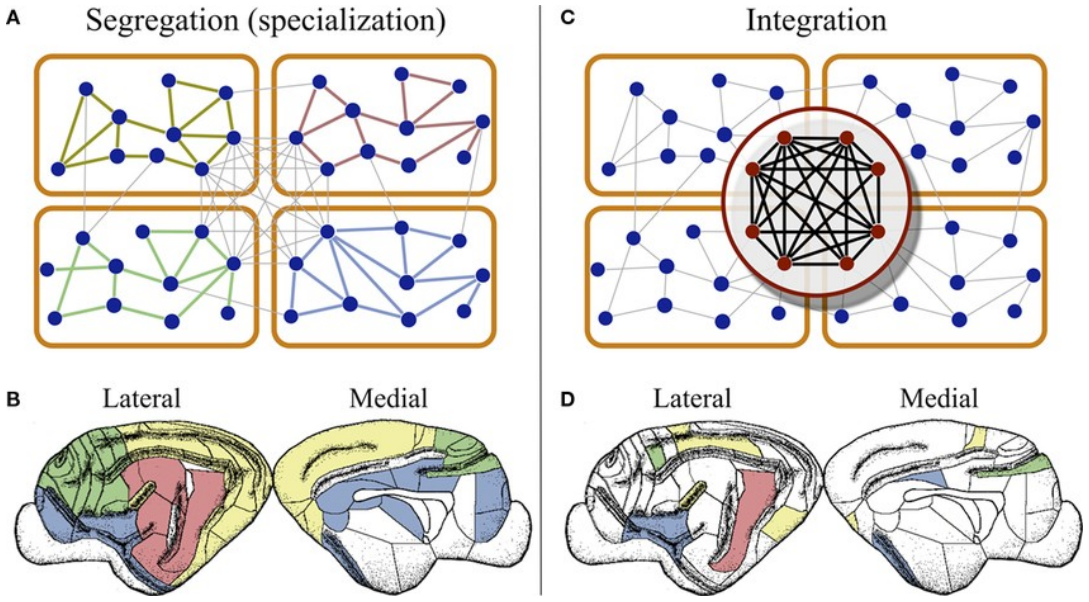
3 Rs principle

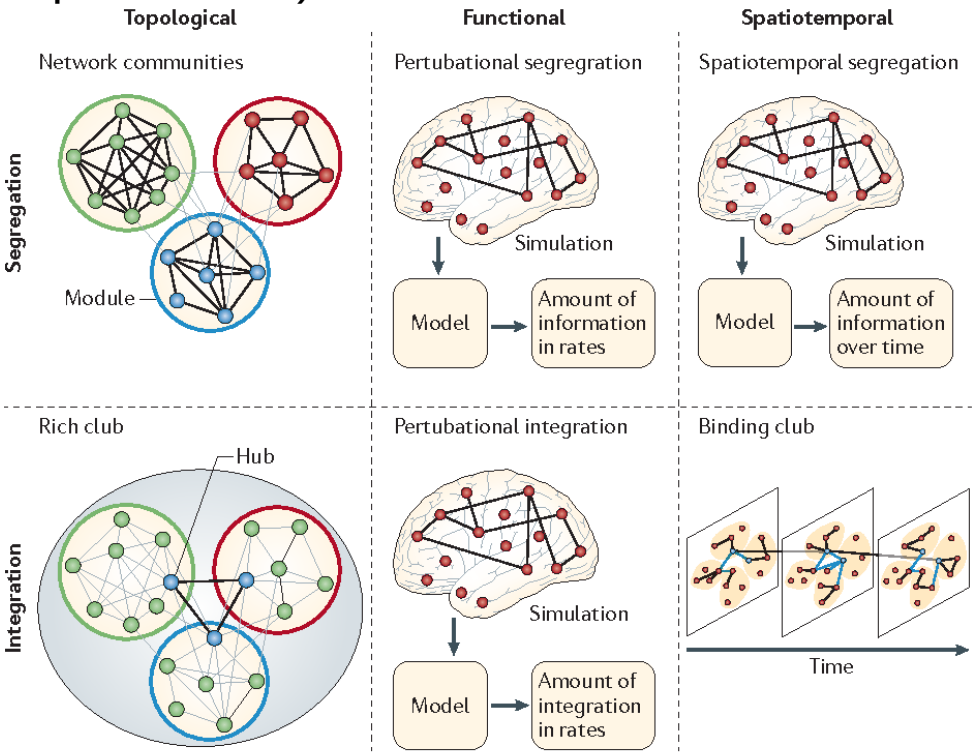
Replace, Reduce, Refine



Current perspectives

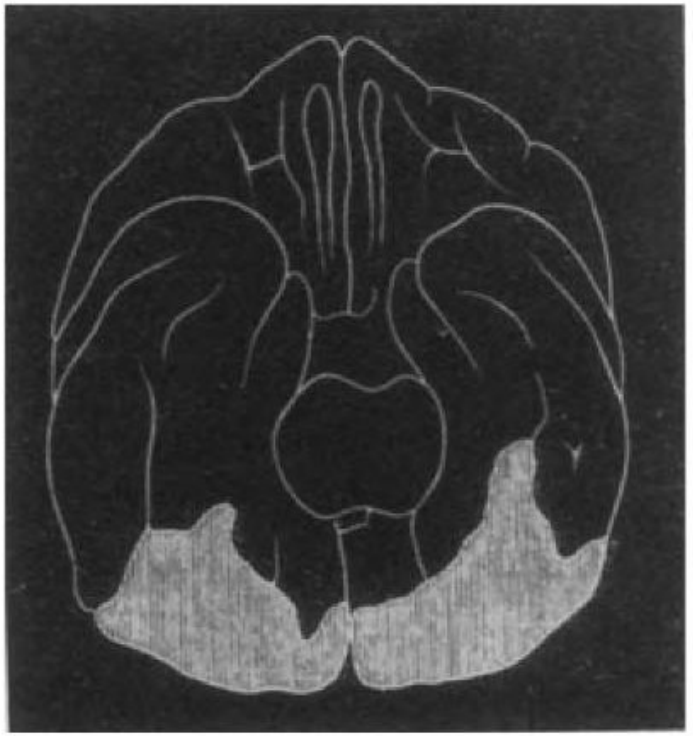
1. Segregation and Integration
2. Causality or temporal correlation
3. Everything is a gradient (connectivity, gene expressions...)



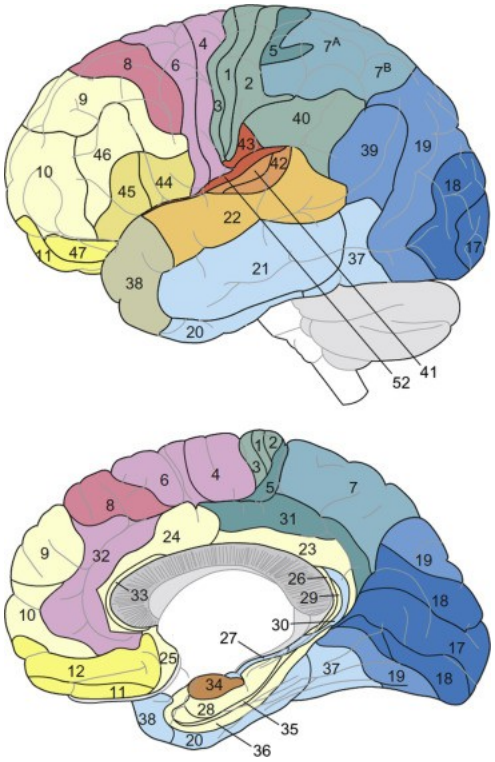


Deco et al. 2015, Nature Reviews

Parcellating the brain



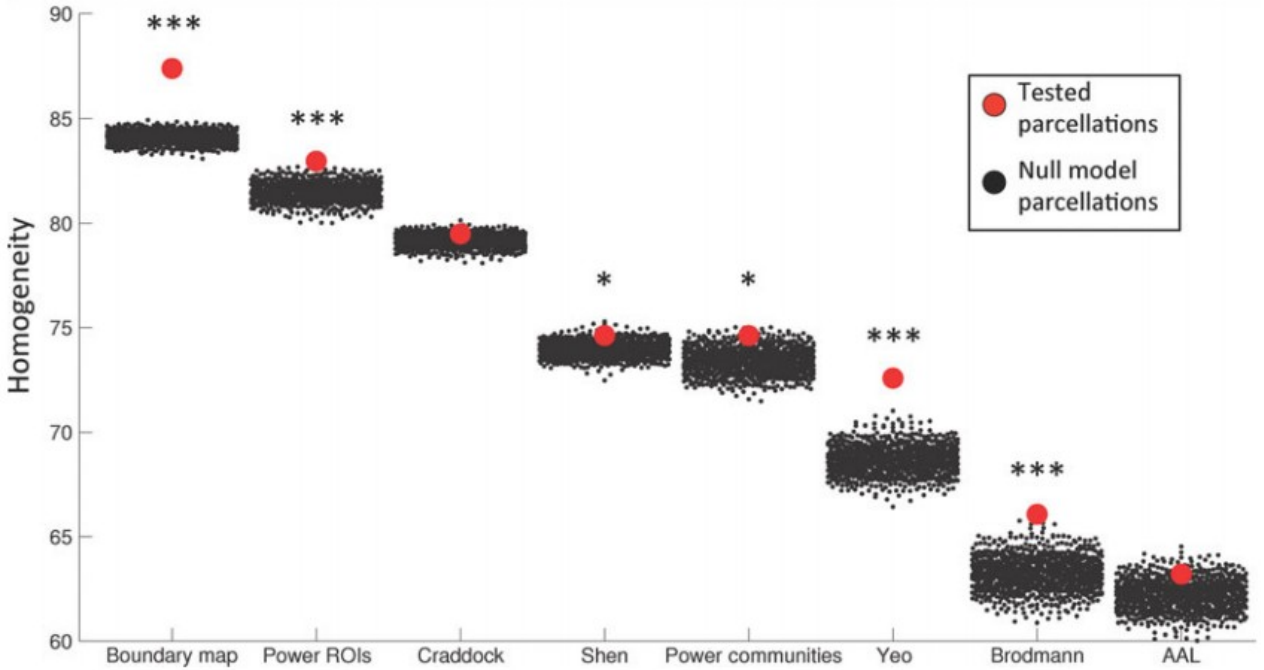
Brown & Schaffer 1888



Broadman 1909 (CerebralCortex 2006 representation)

Parcellating the brain

«...Parcellation should
1. each parcel be homogenous (similar functional connectivity pattern at all points within the parcel).
2. should contain parcels that overlap known human cortical areas that have been well described with cytoarchitectonics.
3. should have a large scale network structure that is consistent with the known network structure of the brain.
4. parcels that accurately represent cortical areas in group-average data should serve as reasonable a priori ROIs in individual subjects….»



Gordon et al. (Cerebral Cortex 2014)

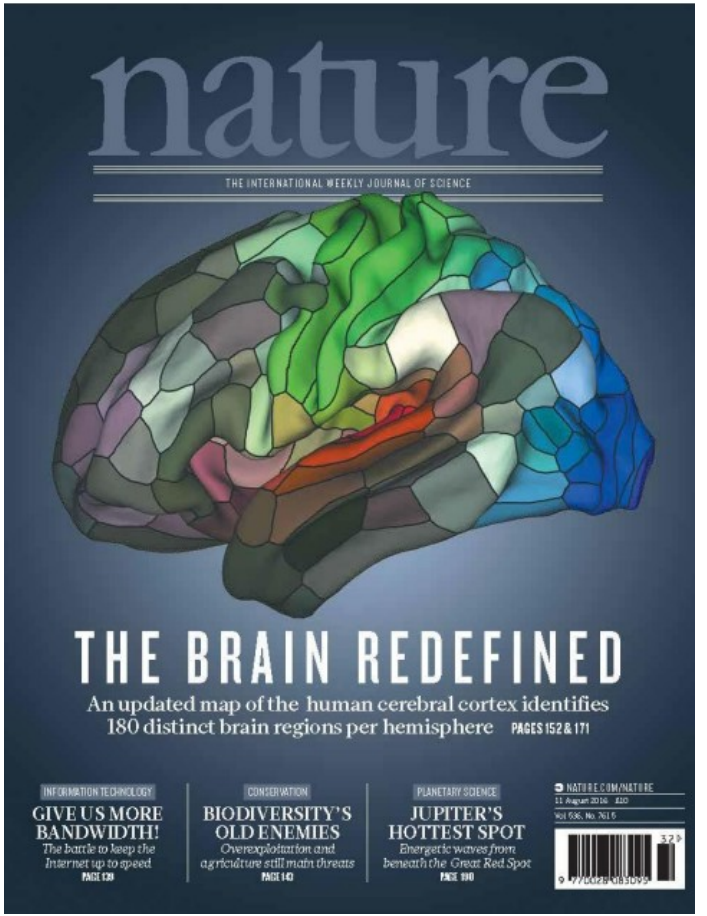
The truth: everybody criticizes but uses AAL for humans
Allen Atlas for mice

What is a cortical area

Glasser et al. 2016 Nature

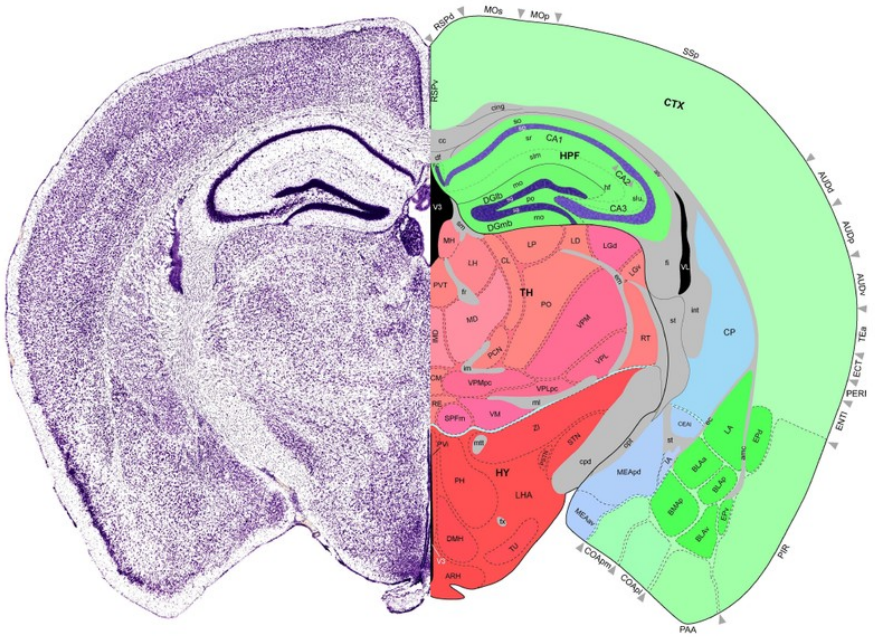
FACT definition

«...A cortical area is a distinctive region of cortex that differs reliably from neighboring areas in one or more neurobiological properties from four basic categories: **F**unction, **A**rchitecture, **C**onnectivity, and/or **T**opographic organization.…»



Allen Brain Atlas**es**

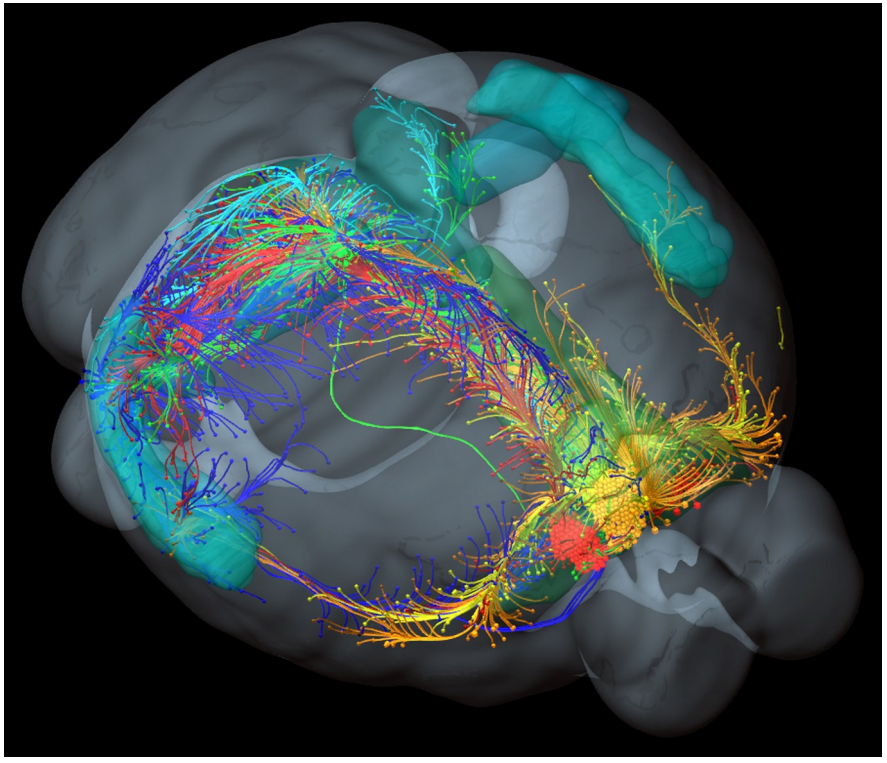
AMBA



Architecture

Sunkin et al. 2012

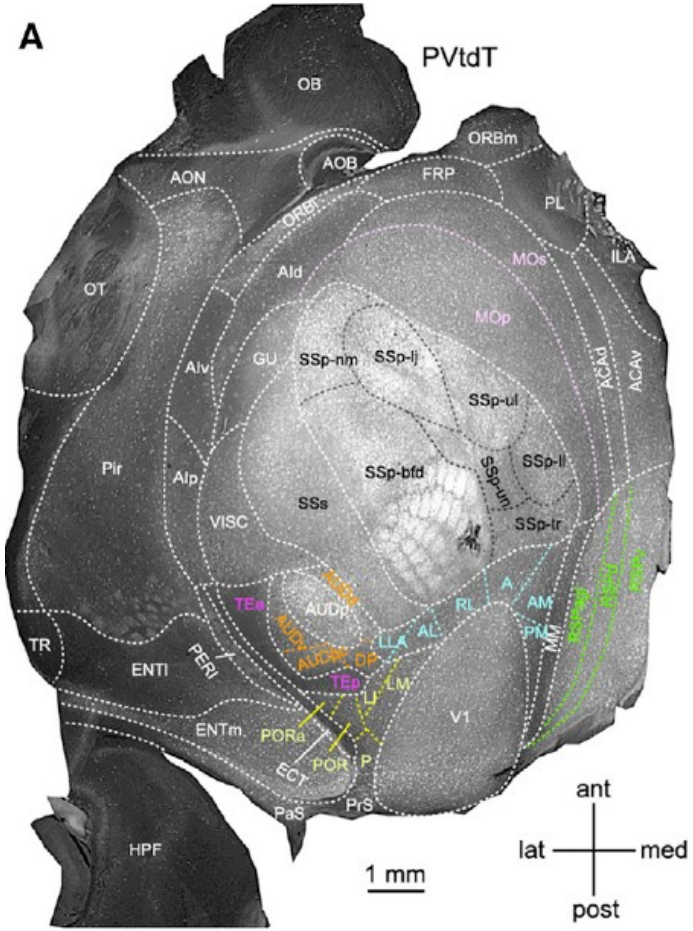
ACBA

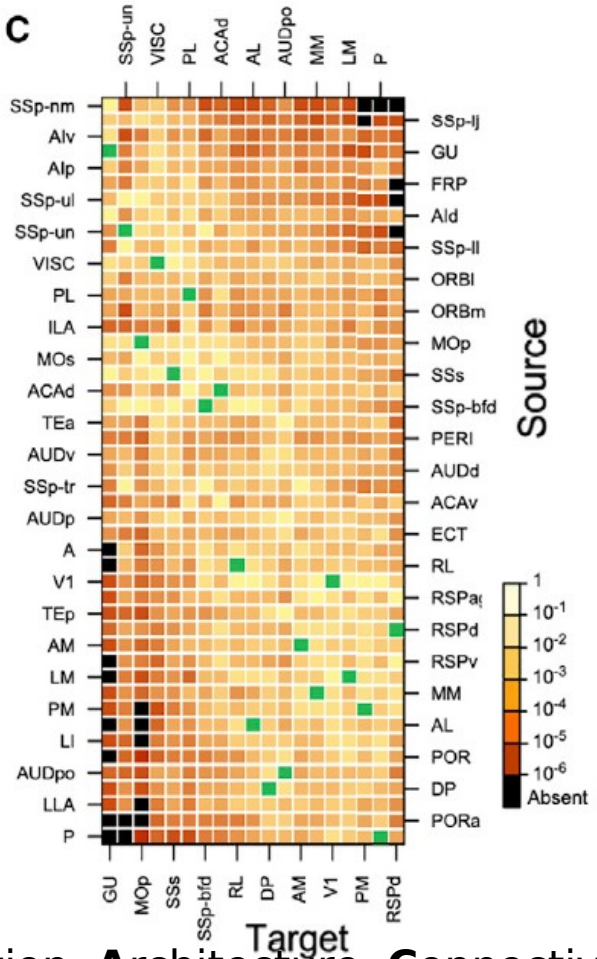


Connectivity

Oh et al. 2014

Parcellation and Connectivity of Mouse Cortex





- Wang&Burkhalter atlas (Gamanut et al 2018) (a competitor of the AllenConnectivity Atlas Oh et al. 2014):
- 41 areas of the neocortex
- Parvalbumin (PV)-positive inhibitory inteneurons.
- Post-hoc: minimized experimental variability by targeting injections of a retrograde tracer (Diamidino Yellow) in post hoc-identified areas rather than a fixed grid of anterograde injections.
- Receptive field mapping in mice.
- Table:The strengths of the projections

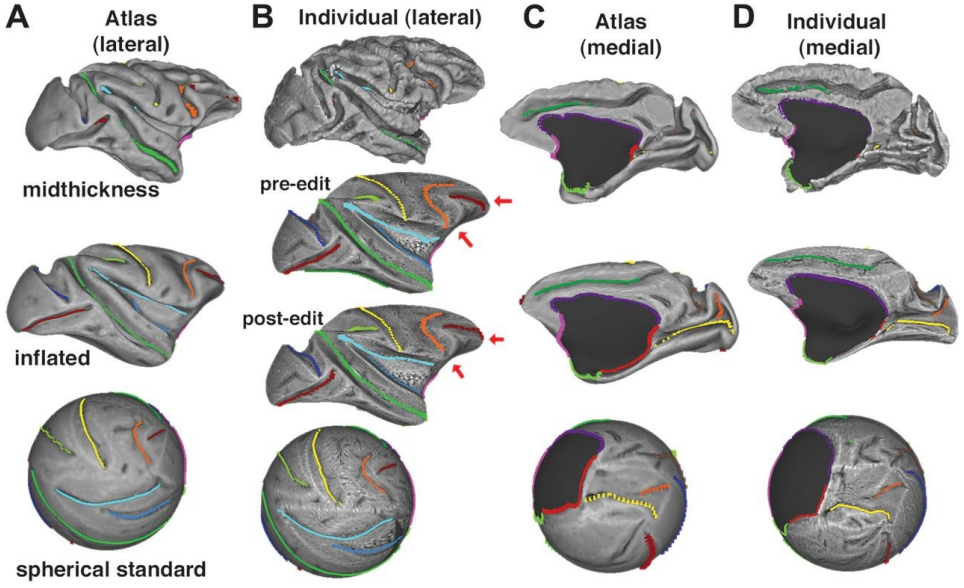
Function, **A**rchitecture, **C**onnectivity, and/or **T**opographic organization

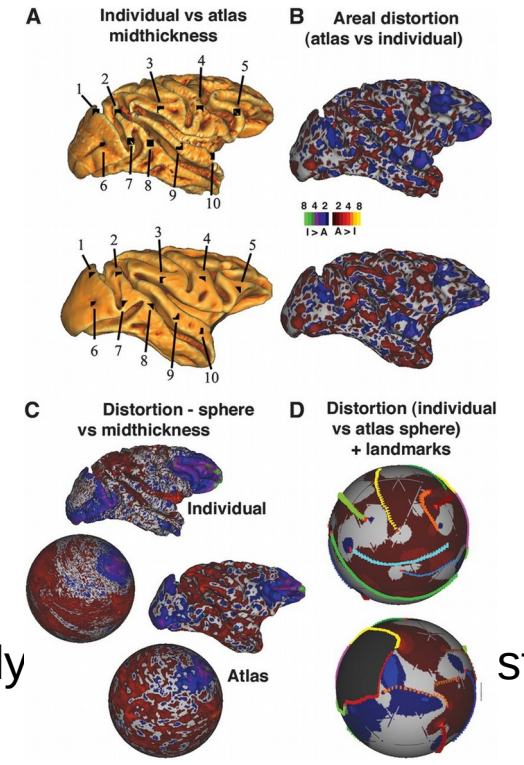
Marmoset 117 Paxinos atlas

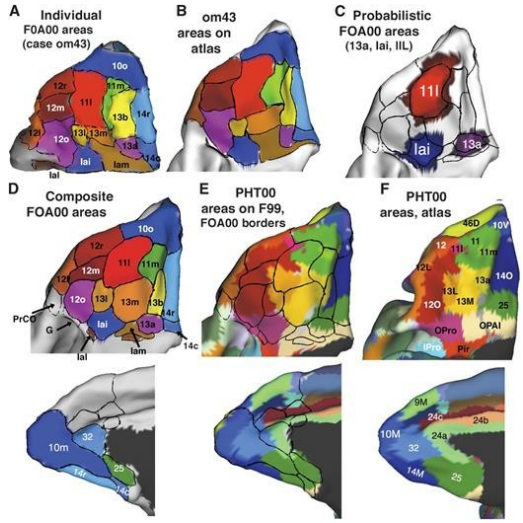
- Parcellation based on cytoarchitecture and cholinesterase histochemistry (Paxinos et al. 2011)
- Expanded with retrograde fluorescent tracers and Online map done in the 2016 http://analytics.marmosetbrain.org/

Cortical Parcellations of the Macaque Monkey Analyzed on Surface-Based Atlases

(van Essen et al., Cerebral Cortex 2012)







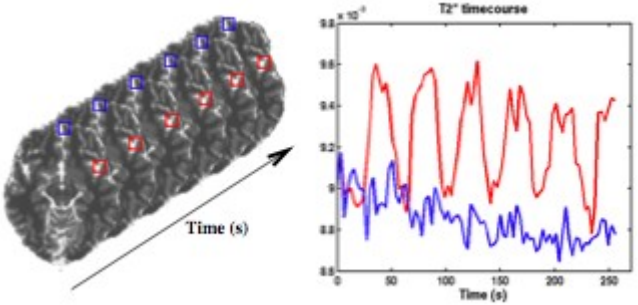
- The macaque monkey is the most intensively studied nonhuman primate.
- F99 is a one single-subject atlas with mapped cytoarchitectures and other data from literature (Paxinos and Franklin 2000; Saleem and Logothetis 2007).

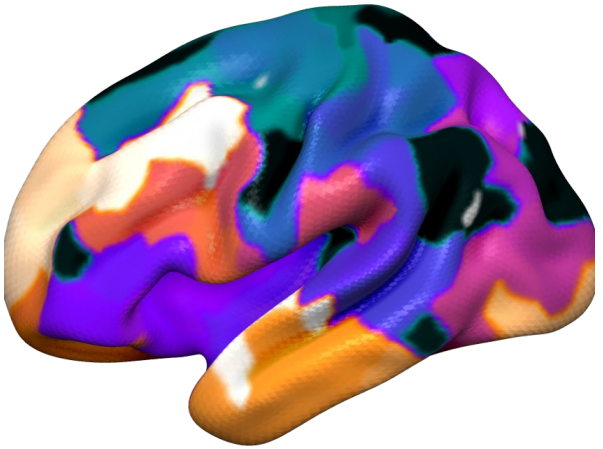
Human parcellation

- Conceptually grounded on animal studies,
- But based mostly on 1 aspect:
- Based on **A**rchitectural properties measured in vivo (AAL) or postmorten (Broadman).
- **F**unctional tasks localized distinct areas (Gordon Atlas, Power Atlas…)
- Topographic analyses of visuotopy of visual cortex, seomatotopy of somatosensory and motor cortex….
- Connectivity based (post-analysis of tractography)

Human Task based fMRI atlas

- Hemodynamic response: blood releases oxygen to firing neurons at a greater rate than to inactive neurons.
- This causes a change of the relative levels of oxyhemoglobin and deoxyhemoglobin (oxygenated or deoxygenated blood) that can be detected on the basis of their differential magnetic susceptibility.
- Atlases mostly constructed by clustering from responses in time of different subjects, after labled.
- Atlases generally include also at rest activitiy (DMN, Saliency...)





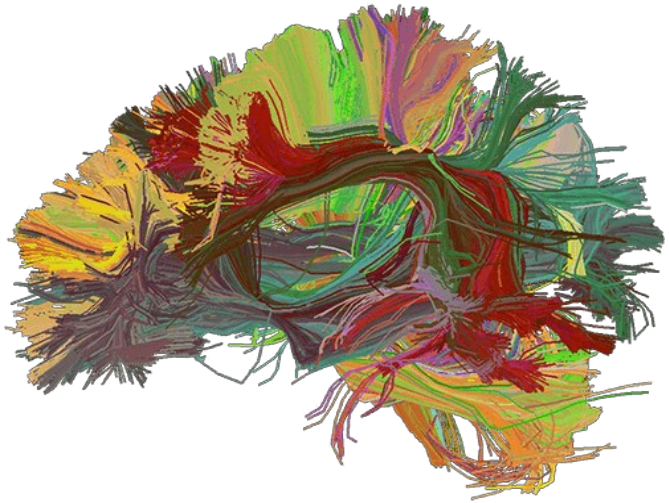
Gordon et al. (Cerebral Cortex 2014)

Human Connectivity based parcellation

- Lipophilic dyes have been used as anatoimical tracers in post mortem human brains (Burkhalter & Bernardo 1989).
- DTI-based parcellation relies on

  unsupervised clustering

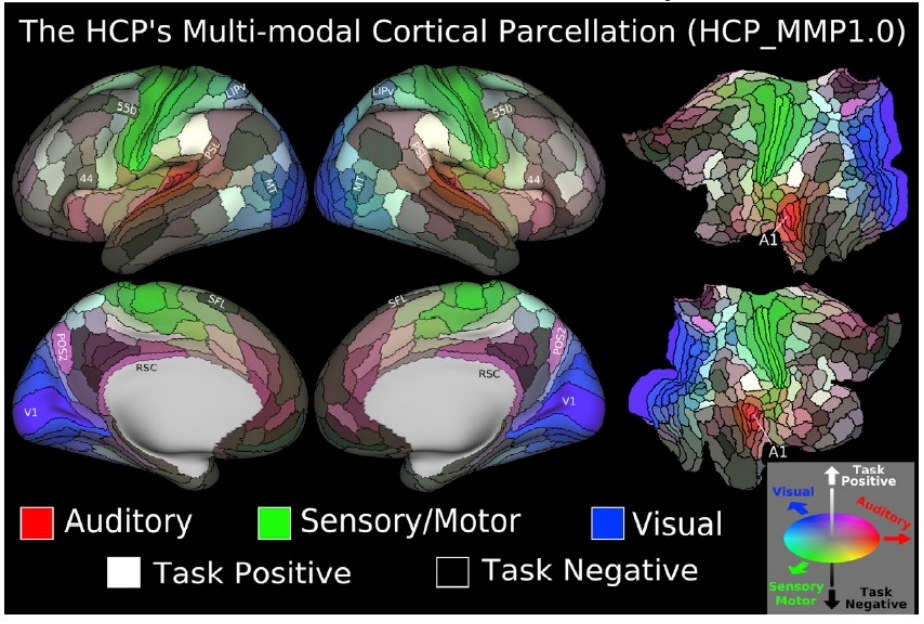
  (e.g. Wang et al. Neuroinformatics 2016)
- They confirmed AAL is imprecise.
- They are also criticized.

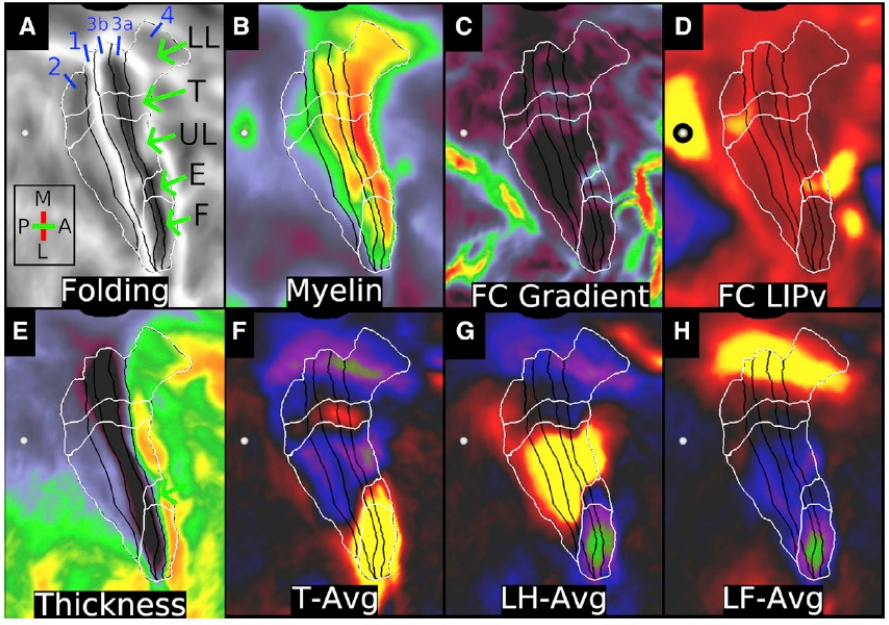


Multimodal Parcellation (Glasser atlas)

- The HCP_MMP1.0 Multimodal Cortical Parcellation
- 180 Areas from different modalities from 210 subjects.
- Unsupervised clustering combining different modalities.
- The multimodal boundaries identified were meticulously compared with the prior neuroanatomical literature to identify 83 previously described cortical areas in literature, and topographic known subdivisions.

(Glasser et al. Nature 2016)





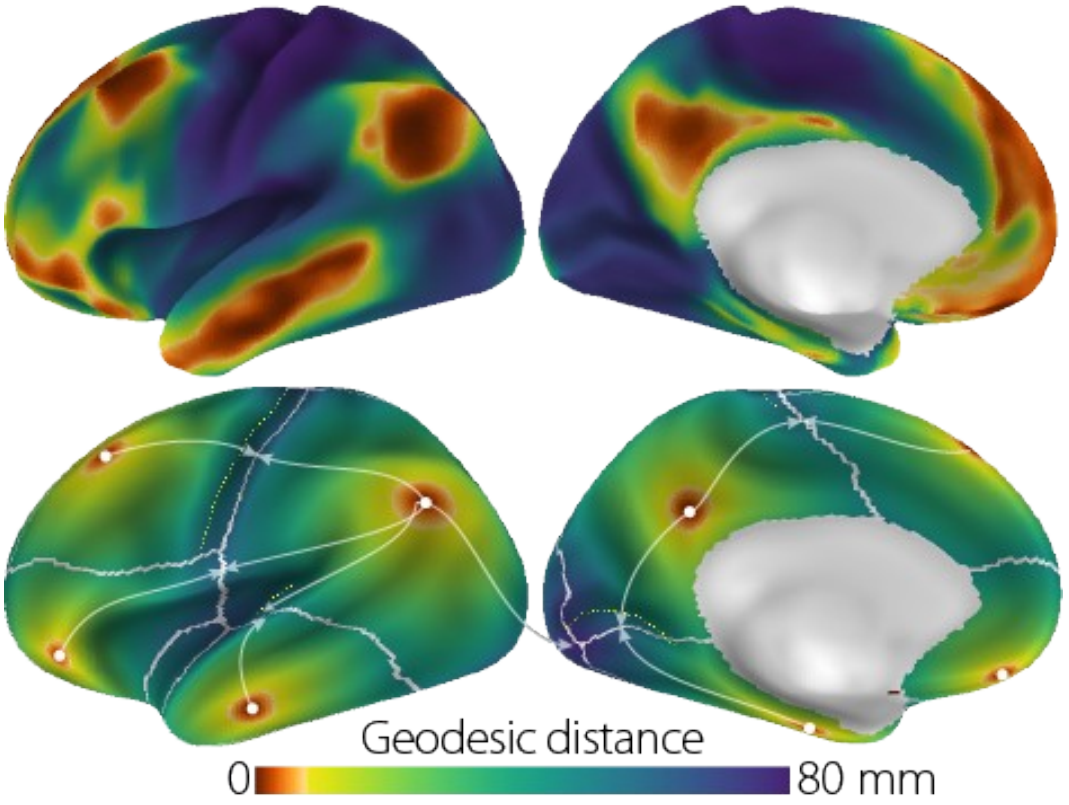
Summary

- The most convincing atlas are those based

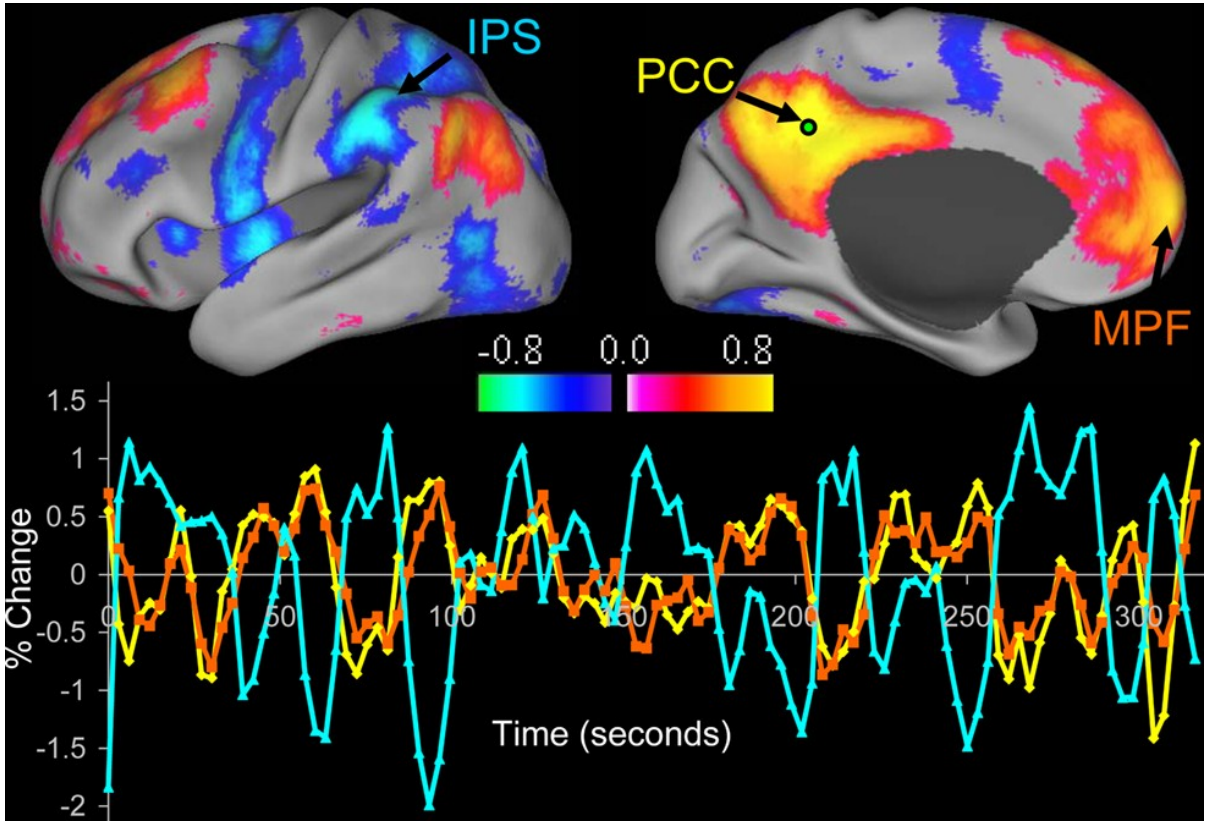
  on the convergence of multimodal information or comprising somehow **FACT** features:
- Glasser atlas for humans, Wang&Burkhalter atlas for mice.
- Although unimodal and highly criticized atlas

  remain the most used (AAL for humans, Allen for mice)

Brain Gradients across species



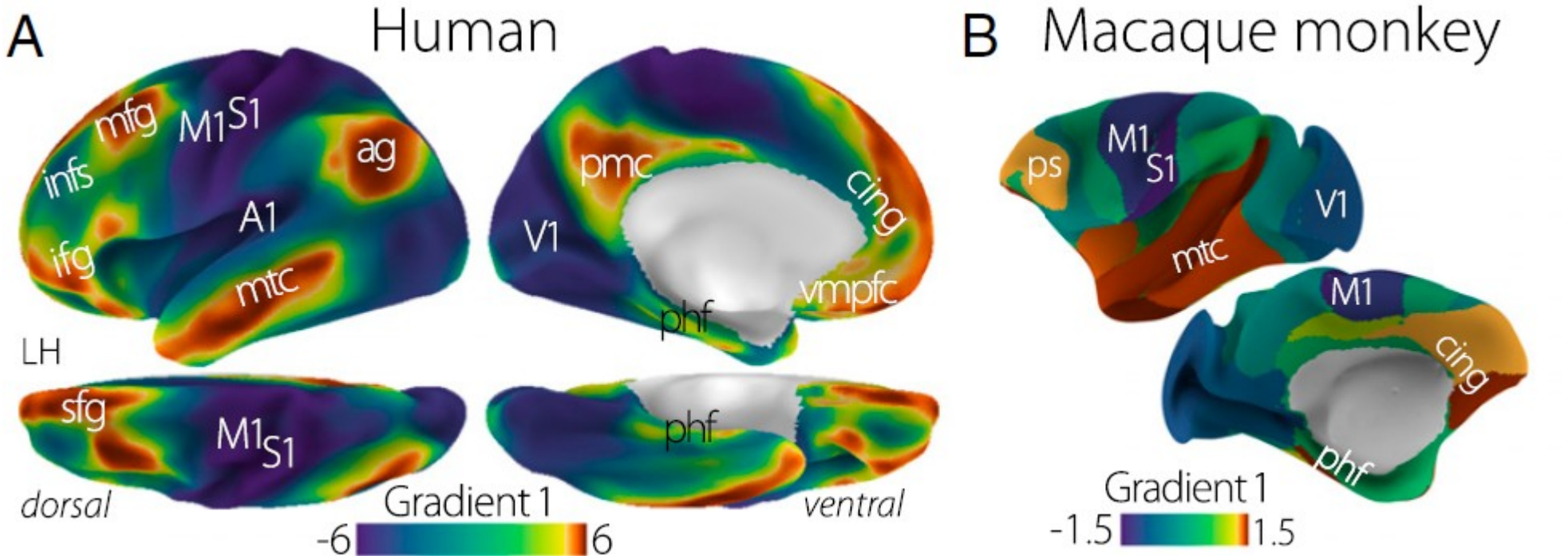
Brush up on Functional Connectivity



Fox & Greicius 2010

Functional Gradient of cortical organization

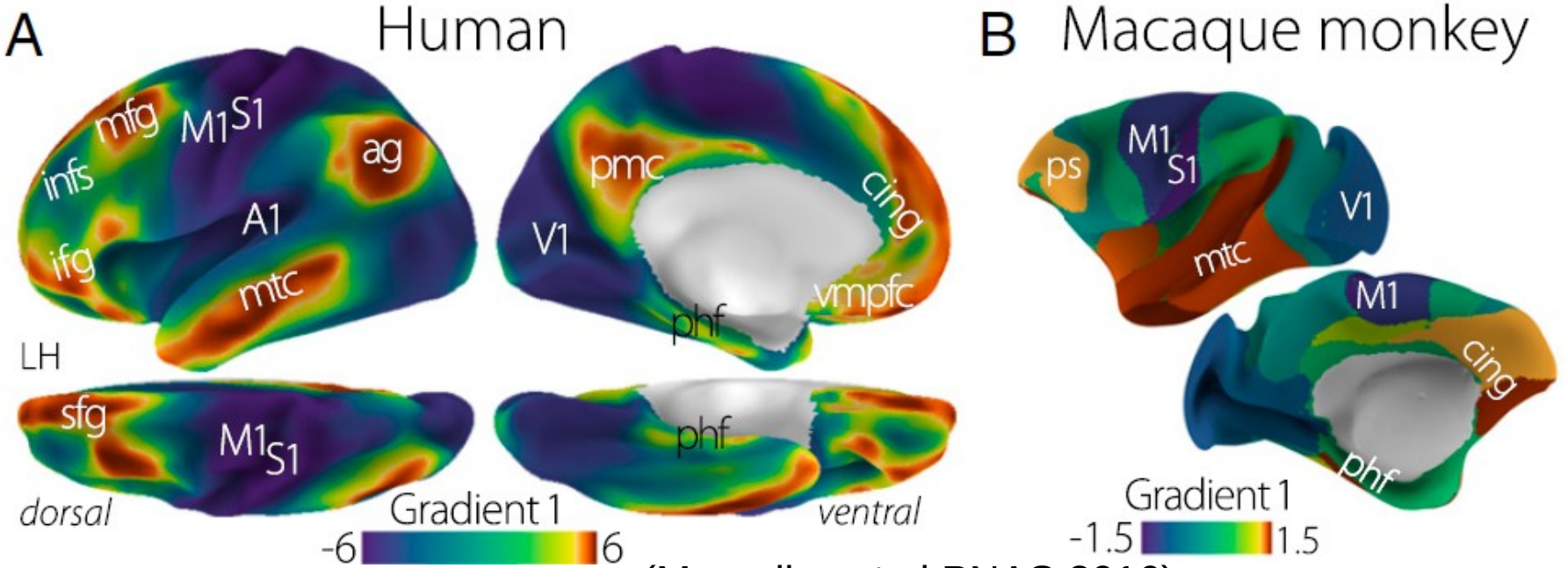
- Functional gradient extending from perceptial to motor region.
- DMN are in (a nonlinear space) equidistant.



(Margulies et al PNAS 2016)

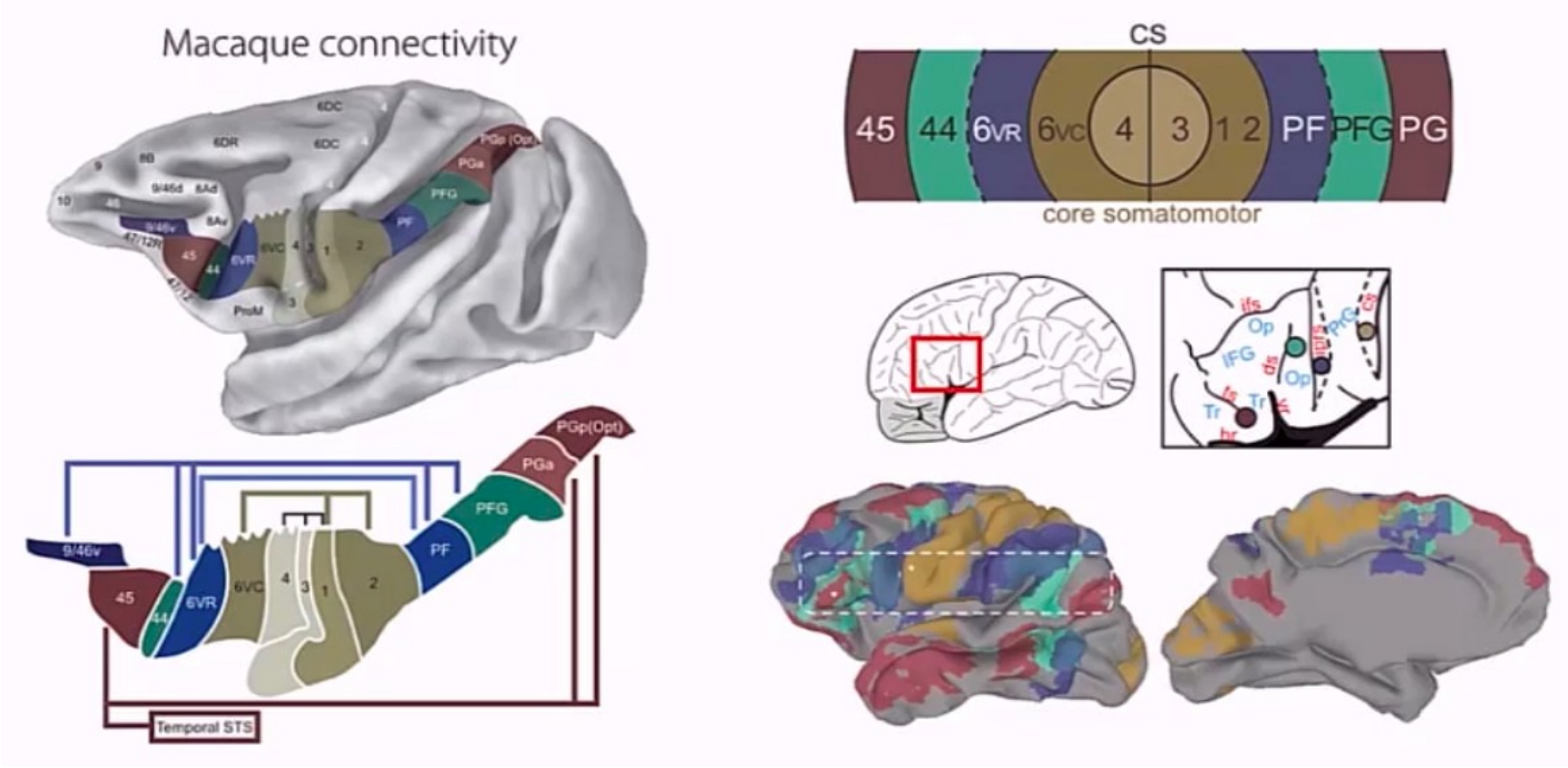
Functional Gradient of cortical organization

- 1 hour resting state fMRI (Anesthesia for the Macaques)
- 820 Humans and 8 monkeys
- No atlas, but 91,282 voxels



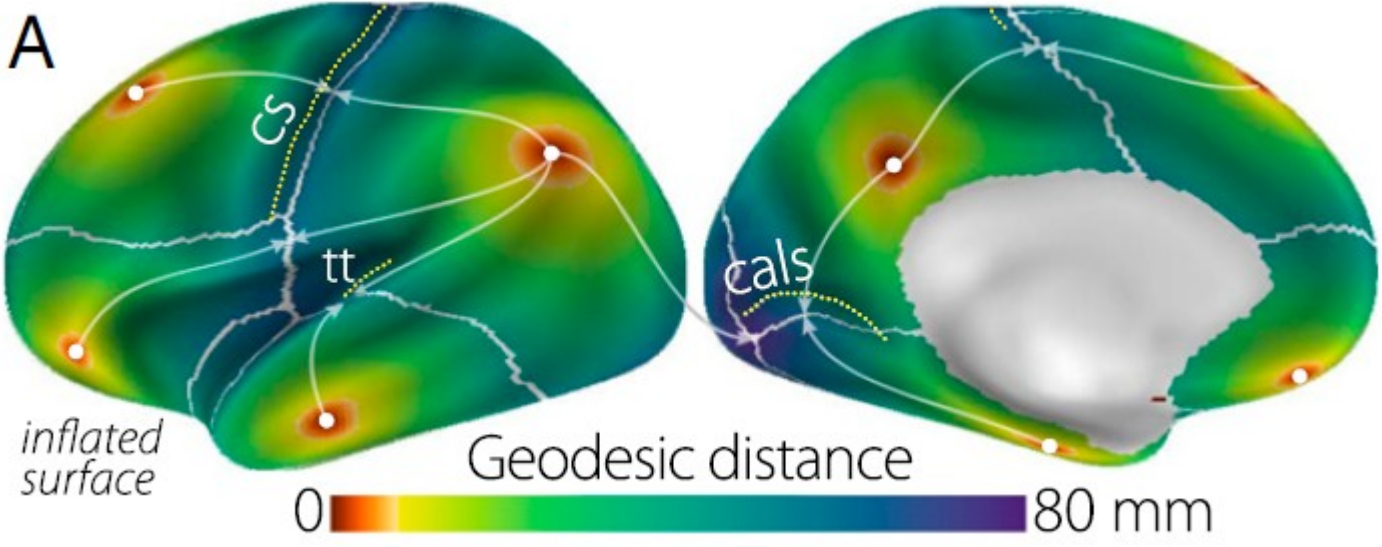
(Margulies et al PNAS 2016)

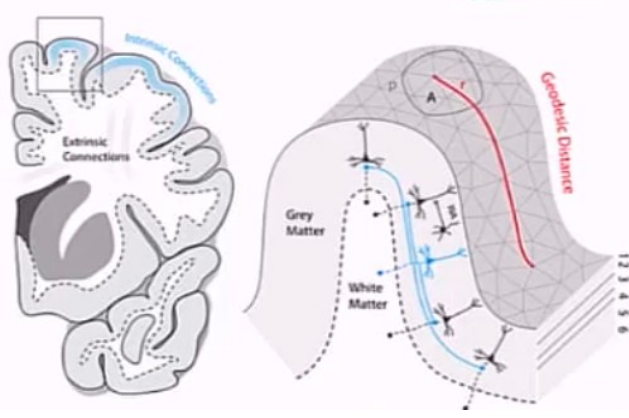
Macaque details



Functional Gradient of cortical organization

- A non linear dimensionality reduction method was used to map distances.

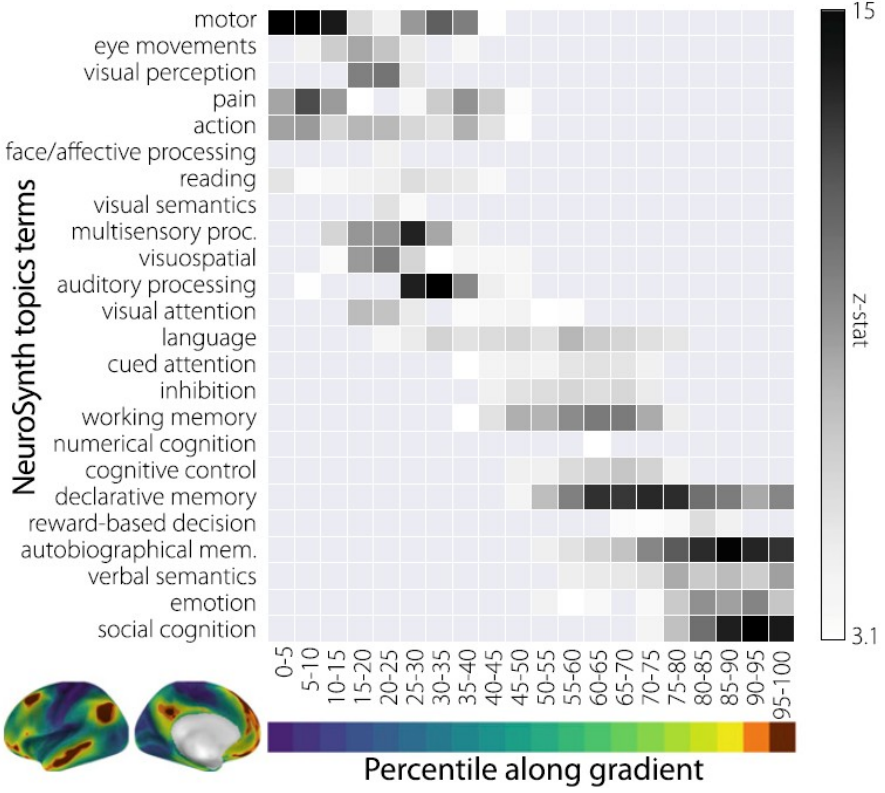




(Margulies et al PNAS 2016)

Functional Gradient of cortical organization

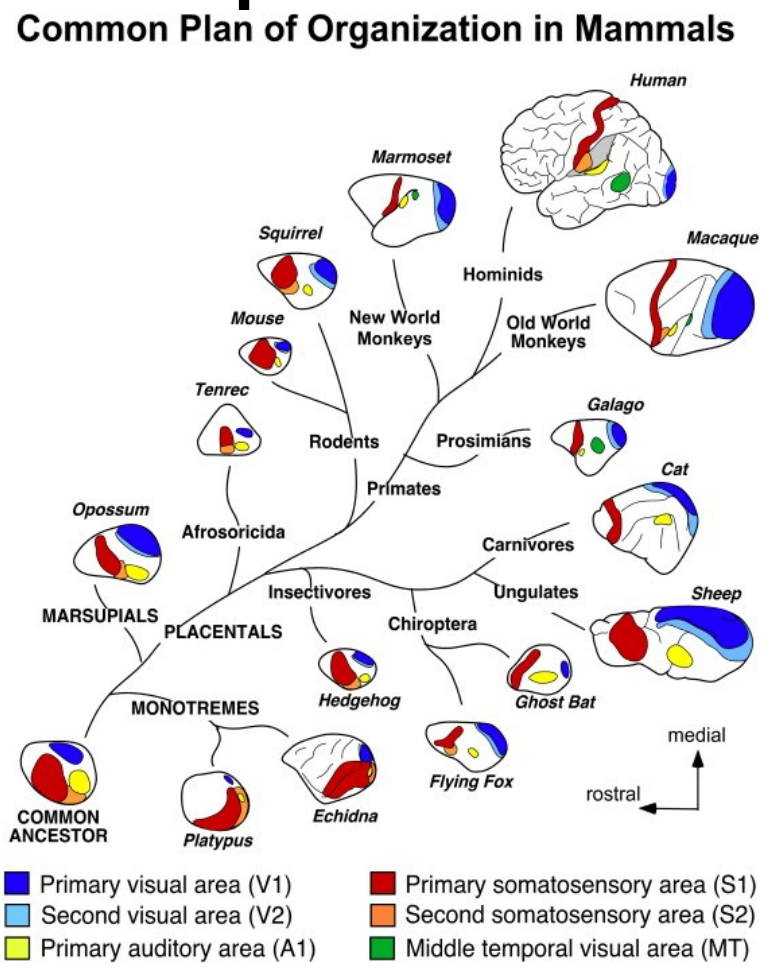
Metaanalysis of regions of interest along the gradient shows a gradient from motor to social cognition known areas



Gradients across species

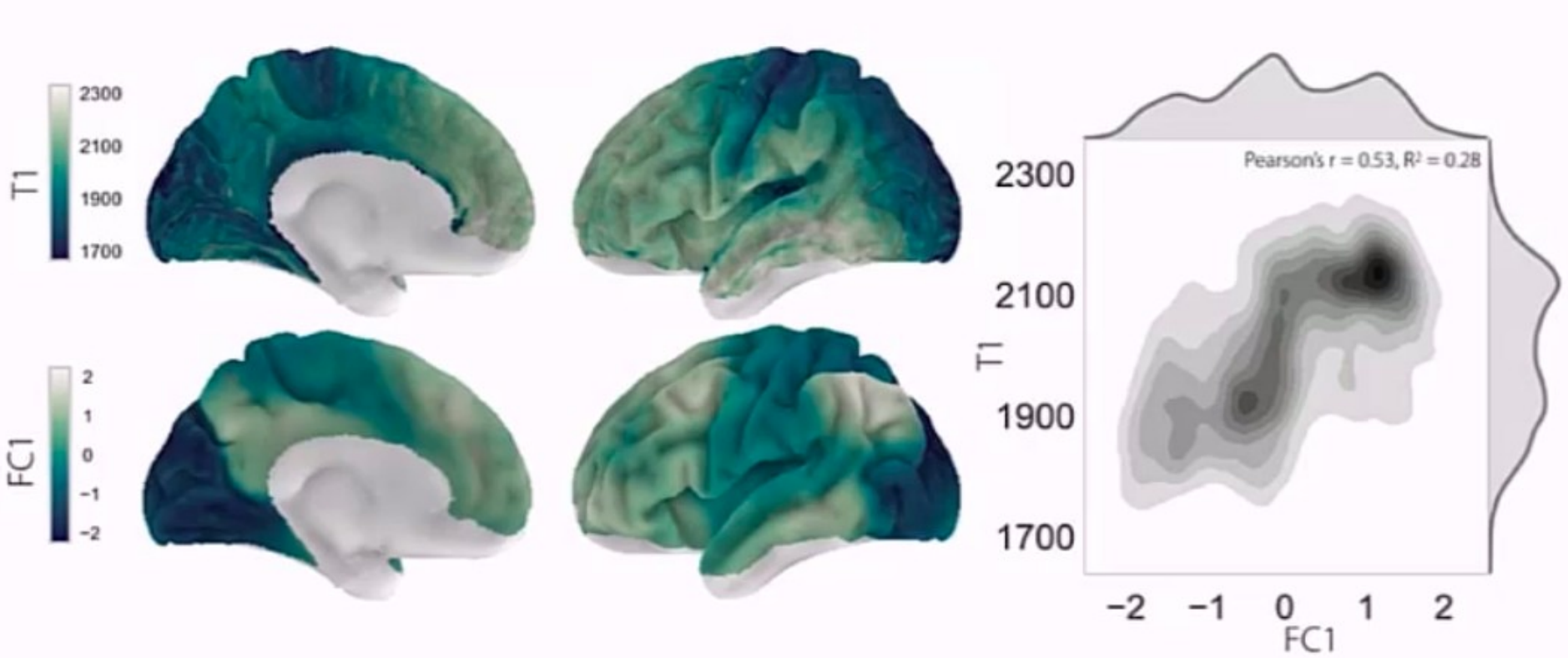
- «Gradients fit common plan of organization in Mammals»

  Krubitzer
  Neuron 2019



(Krubitzer Neuron 2007)

Myelin density

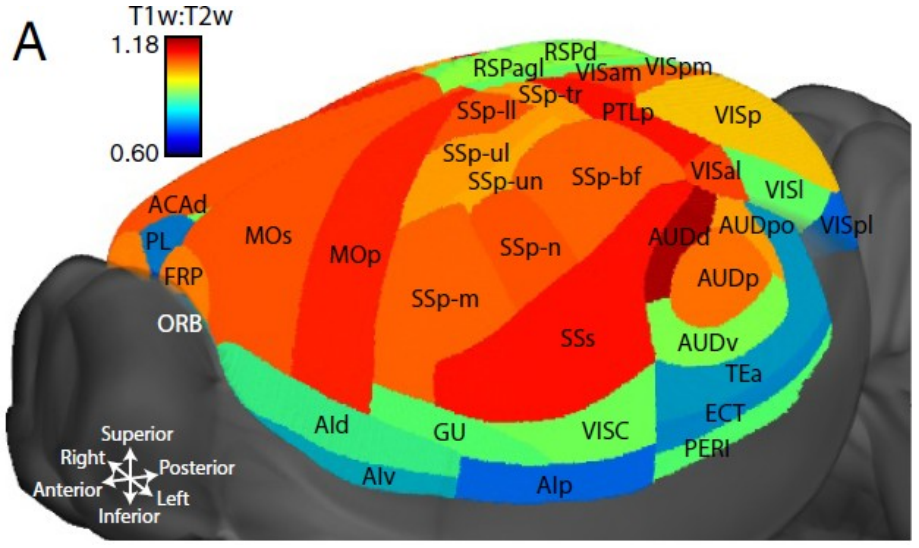


Siemens 7T, 8 subjects
MP2RAGE: 0.5 mm³

Openly available data from:
Gorgolewski et al, *Sci Data*, 2015

Multimodal gradients across mouse cortex

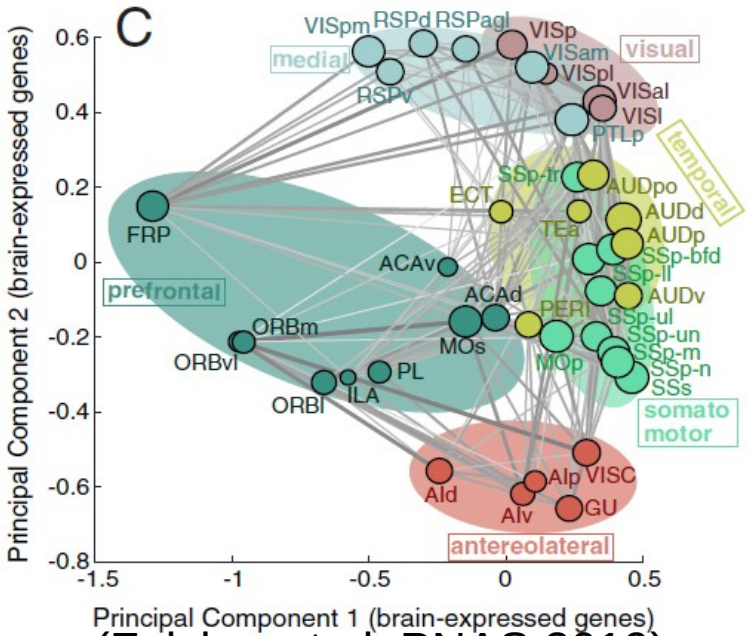
Gradients shown by functional connectivity (Margullies et al. 2016), microachitectures (Goulas et al. 2018) are also reflected in mouse cortex including *gene expression.*



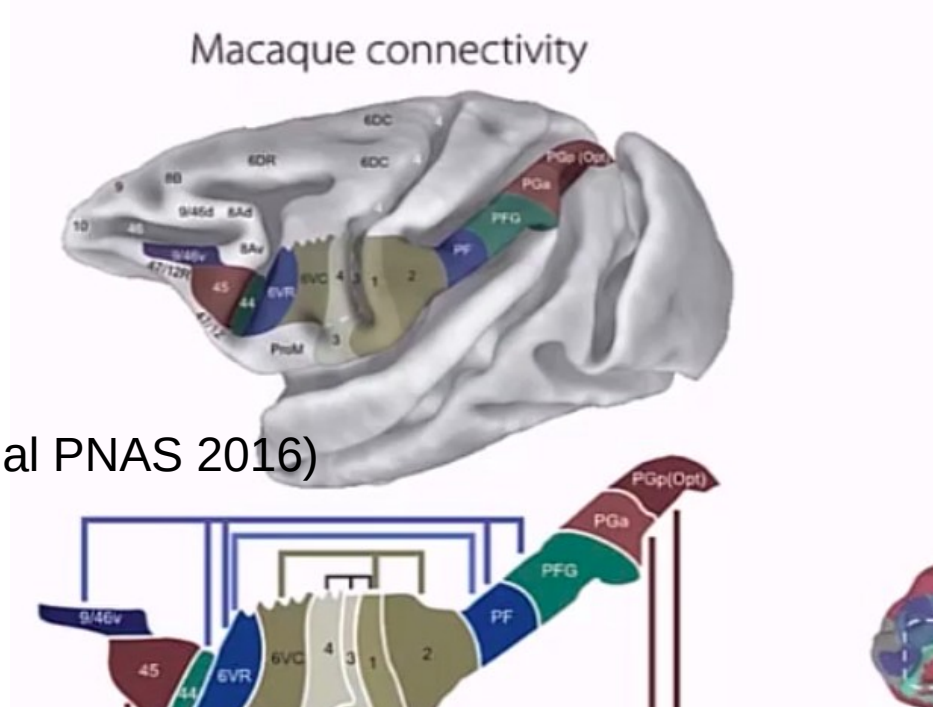
(Fulcher et al. PNAS 2019)

Gradient of expression in mice

- 4,181 genes from the ISH-Allen atlas, selected set of 86 receptor subunit and cell-type marker genes (including glutamate receptor subunits (Grin3a, Grin2d, Grik1, Grik2, Grik4, Grm2, Grm5); serotonin receptor subunits (Htr1a, Htr2c, and Htr5b); interneuron cell-type markers (Pvalb and Calb2); the myelin marker, Mobp; and a range of other receptor subunit genes, Trhr, Mc4r, Chrm5, Galr2, Hcrtr2, Hcrtr1,P2ry12, P2ry14, Cnr1, Oxtr, and P2ry2)
- PCA of the Allen brain atlas regions using the gene expressions as features

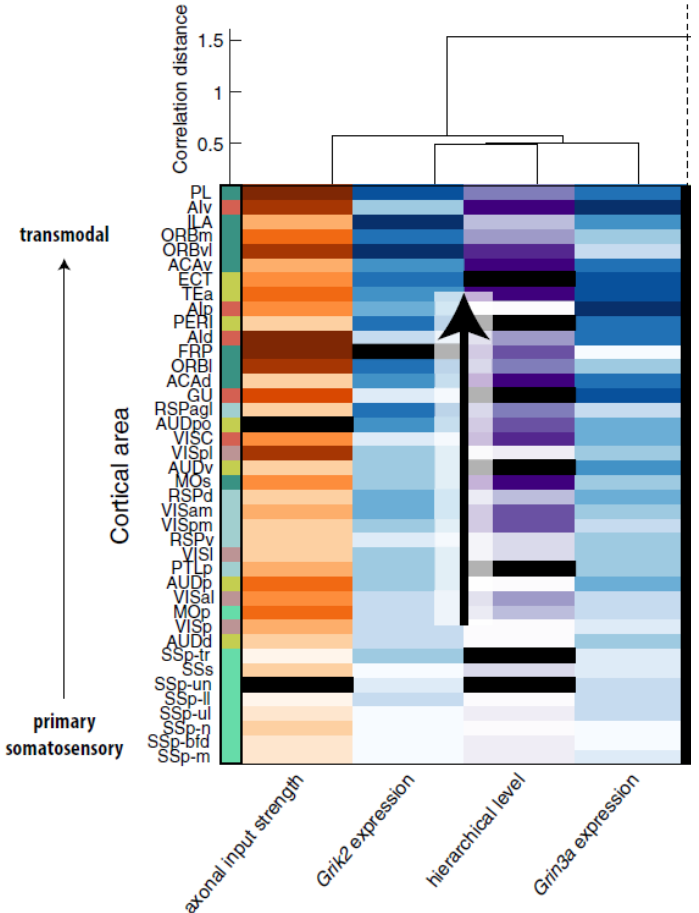


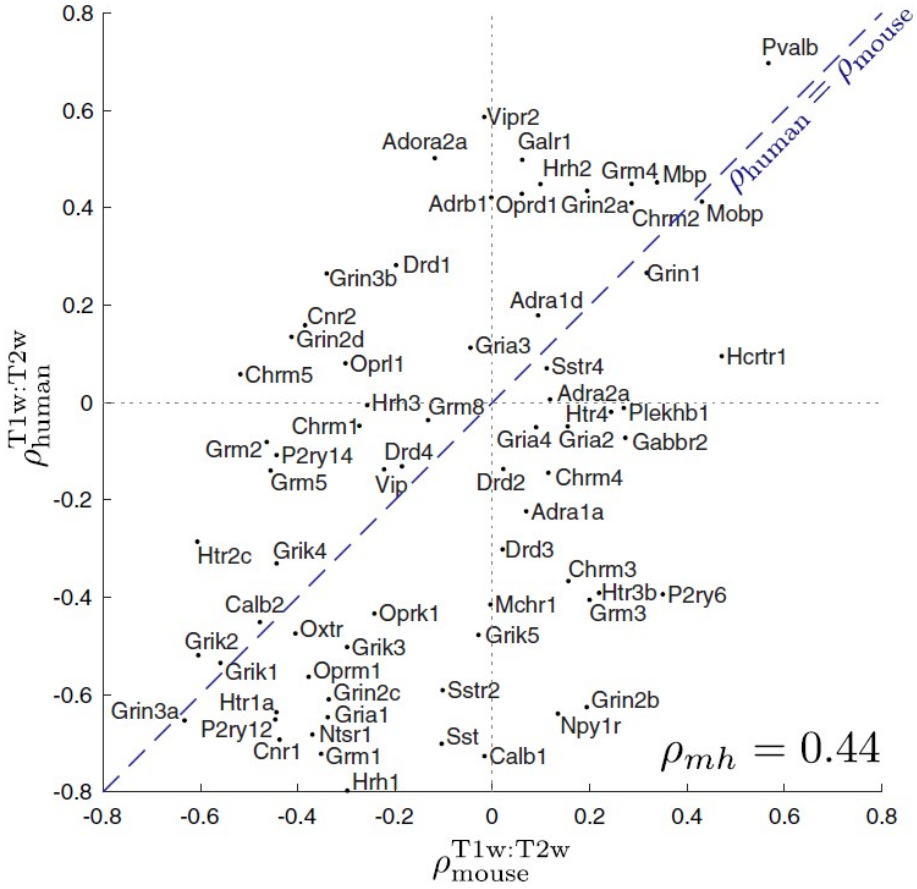
(Fulcher et al. PNAS 2019)



(Margulies et al PNAS 2016)

Further example with glutamate receptor subunits and humans





Summary

- Gradient organization is promising approach to explain common plan of organization.
- Gradient gene expression mouse/human were matching with some exceptions as the NMDA receptors Grind2b, Grind3b (other studies suggested Grin3a and Calb2 as diffentiating genes for humans).
- By the end of the day we need discretization though.