An overview of Human Connectome Project (HCP) database

HCP Course Attendees: WELCOME!

August 28 – September 1, 2016
Joseph B. Martin Conference Center
Boston, MA

HUMAN
Connectome
PROJECT

Mapping structural and functional connections in the human brain

The “WU-Minn” HCP consortium

10 institutions:

Washington University
University of Minnesota
Oxford University

Saint Louis University
University of Oxford, University d’Annunzio
Indiana University, Warwick University
Ernst Strungmann Institute (Frankfurt)
Radboud University (Nijmegen), Duke University
Advanced MRI Technologies (Sebastopol CA)

>>100 HCP consortium members

HCP is grateful to the NIH Blueprint

Outline

Course logistics

Cortical cartography

- Maps, parcellations
- Connectivity – ground truth principles
- Variability, atlases, and alignment

Human Connectome Project

- History & overview
- Methodological highlights and teasers
- The HCP-style paradigm

Human Brain Numbers

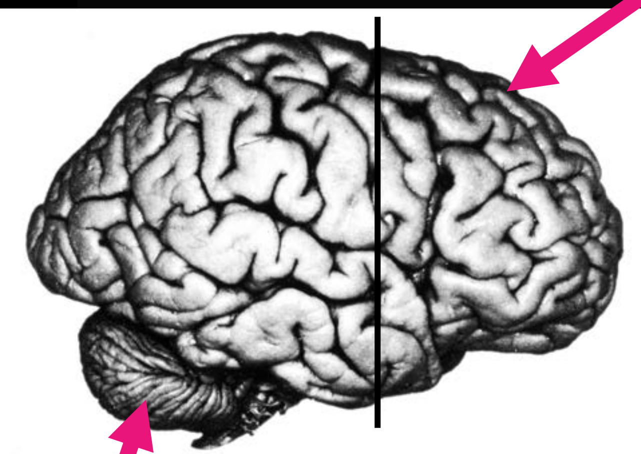
Whole brain: 1500g; 86 billion neurons[1]

Cerebral cortex:

~80% of brain mass (GM + WM); a wide range of functions
16 billion neurons (~20%)
150 trillion synapses (~10,000/neuron)
160,000 km myelinated WM axons (~1 cm/neuron)

Cerebral cortex

White matter



Cerebellum:

- 10% of brain mass
- 69 billion neurons (80%)
- coordinates movements, thoughts

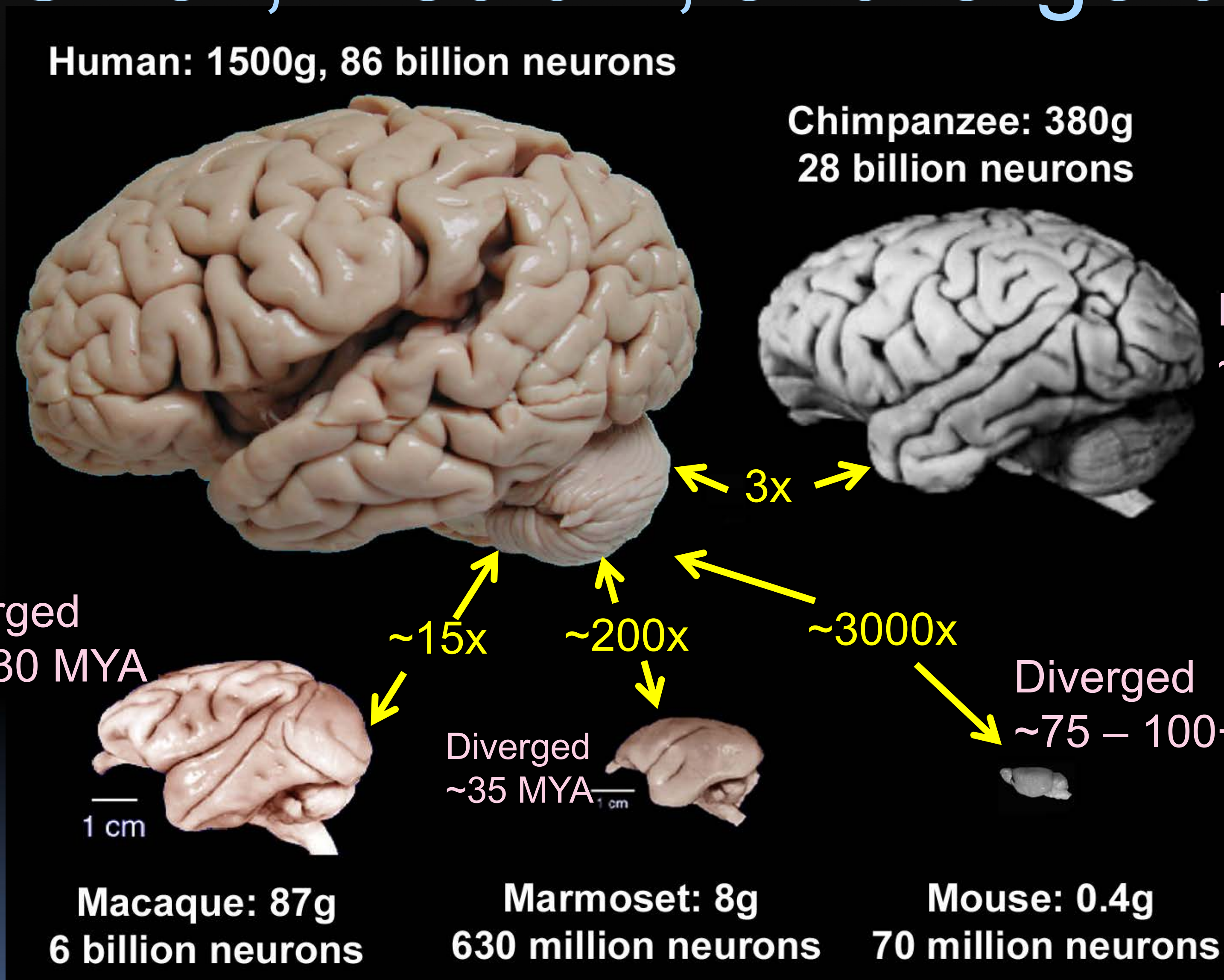
Rest of brain:

- 8% of brain mass
- 0.7 billion neurons (0.8%)
- vital 'housekeeping' functions

Subcortical "nucleus"

Azevedo et al. (J. Comp. Neurol., 2009)
Pakkenberg et al. (Exp. Gerontol., 2003)

Small, medium, and large brains

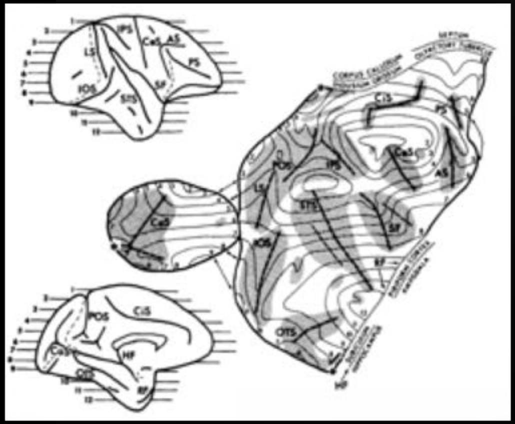


Herculano-Houzel (Front. Hum. Neurosci., 2014)

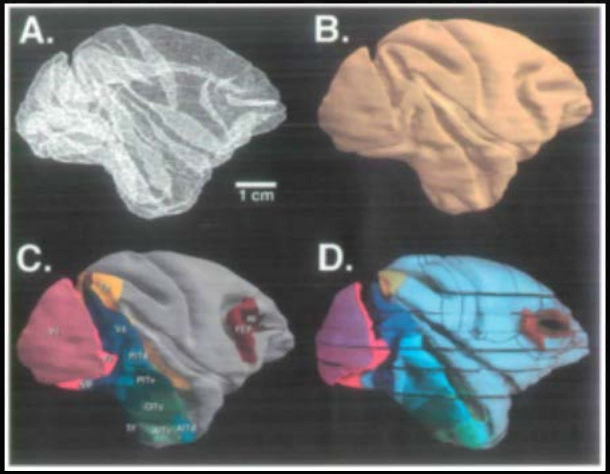
- Dramatic expansion of human brain in last 2 million years
- Cortical convolutions vary enormously. Enter “cortical cartography”

Cortical cartography– humble beginnings (pre-MRI)

Pencil-and-paper flat map
(Van Essen & Maunsell, 1980)

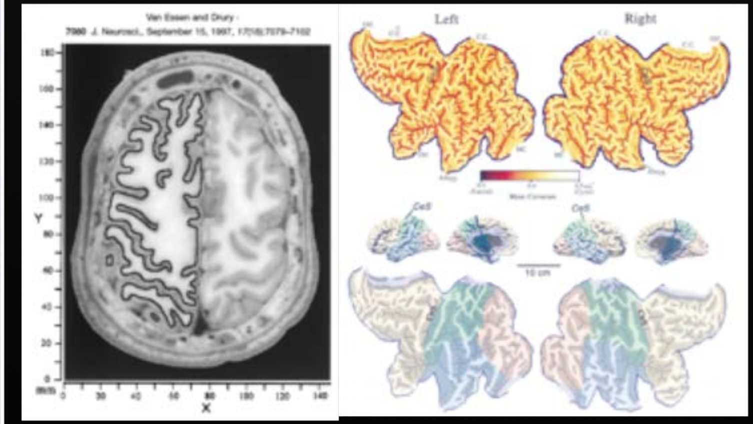


Computerized surface reconstruction



Carman et al., 1995

The Visible Man



Van Essen & Drury, 1997

Earth maps can display

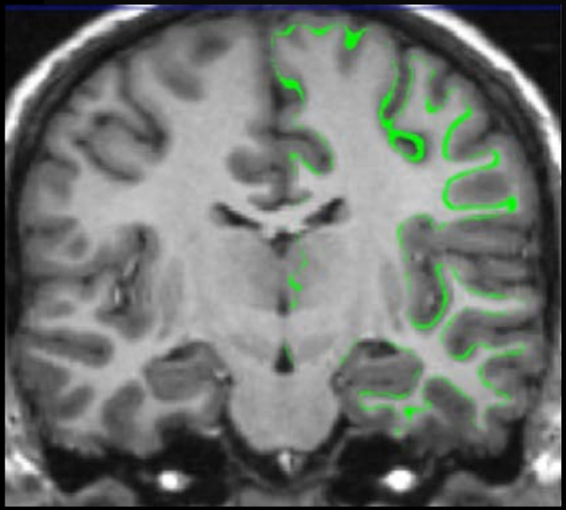
- Geography
- Political subdivisions
- Lots of other information

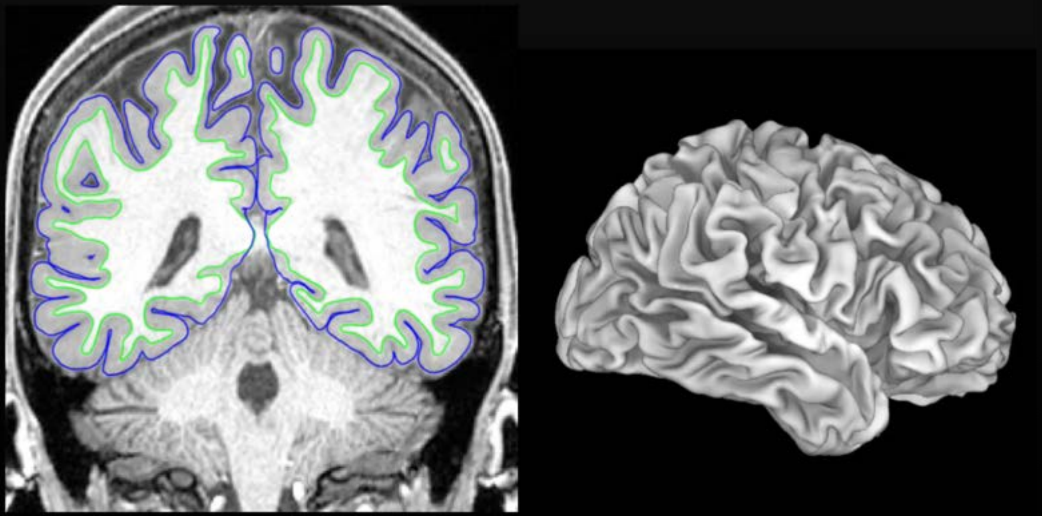
And then, the MRI revolution began!

- Structural MRI (T1w, T2w)
- Segmentation algorithms
- Functional MRI
- Diffusion MRI

Bruce Fischl

Capturing cortical convolutions





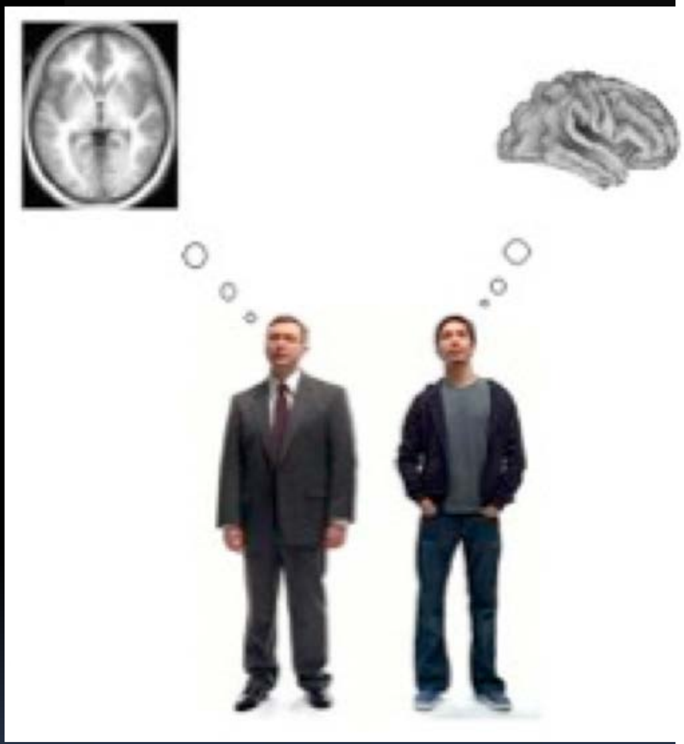
- Conventional T1w: 1mm isotropic voxels
- Standard FreeSurfer: good but imperfect

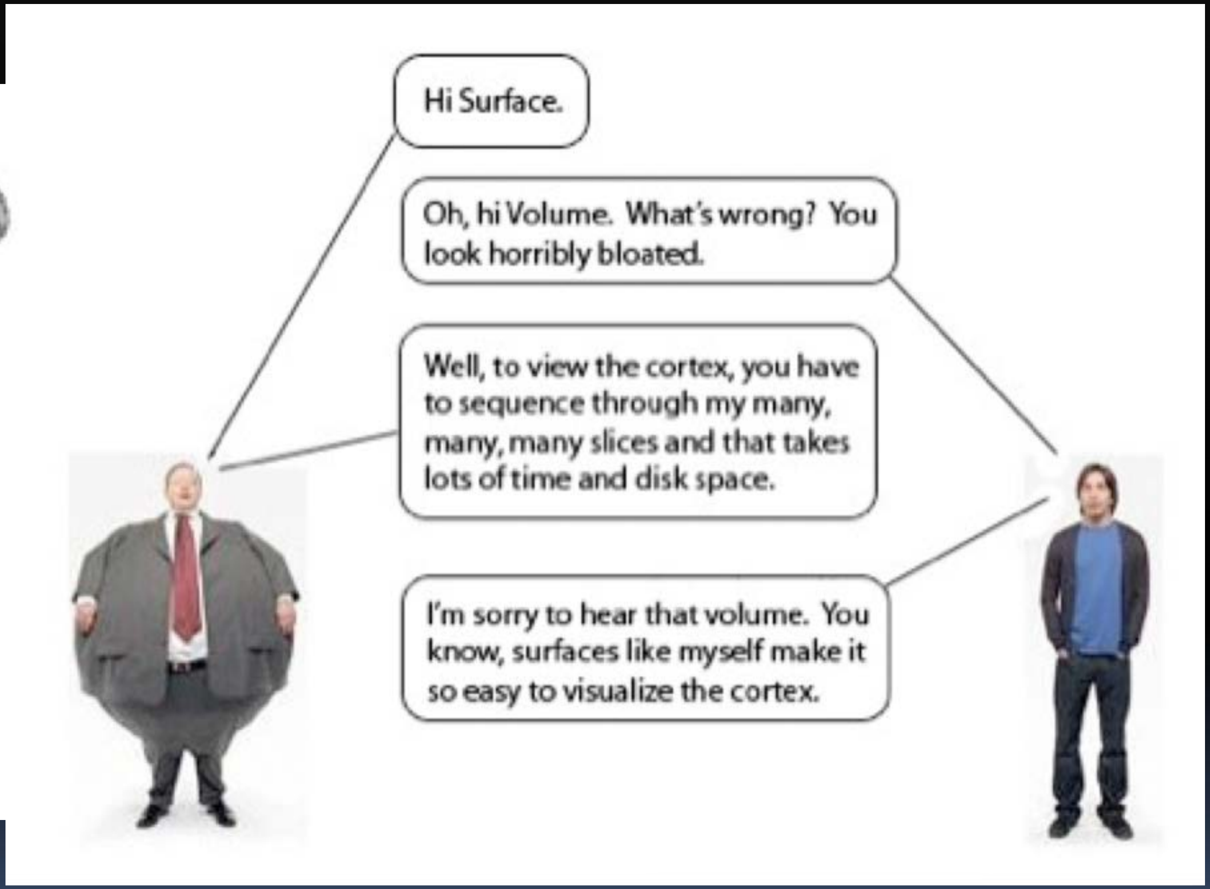
HCP structural MRI:

- High-quality structural MRI: 0.7 mm voxels
- Customized FreeSurfer segmentation (uses T1w + T2w; now part of FreeSurfer 6.0)

Glasser et al. (Neuroimage, 2013) HCP ‘Pipelines Paper’

A surface-centric perspective





Courtesy John Harwell (and Apple Computer)

Many options for segmentation, surface inflation/flattening:

- Brain Voyager
- MNI CIVET
- Standard FreeSurfer (e.g., v6.0)
- HCP Structural Pipeline (uses FreeSurfer with T1w + T2w)
- Many others….

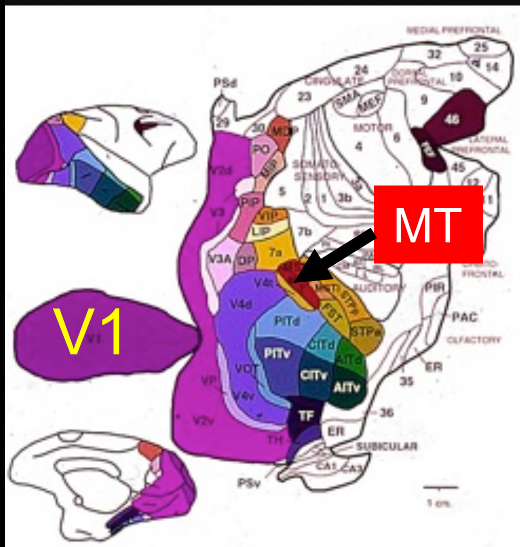
They aren't equivalent in quality and fidelity.

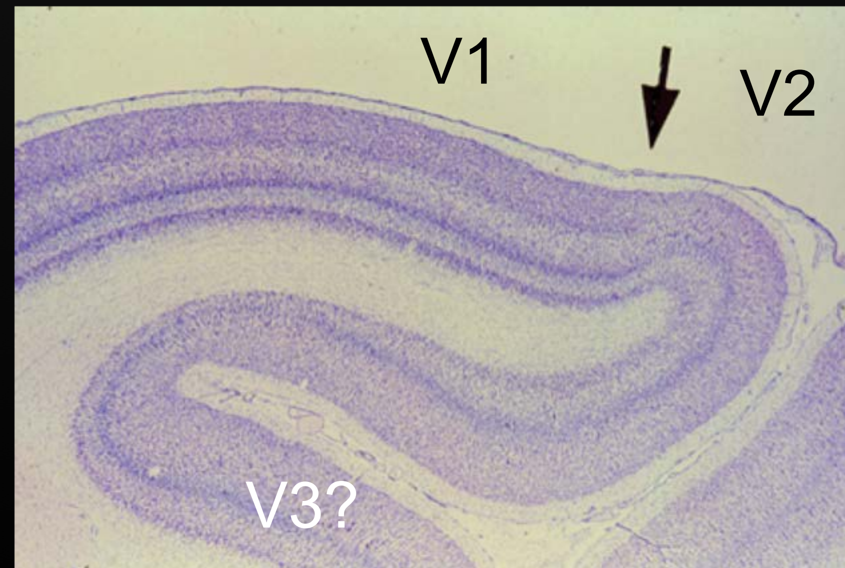
Cortical surface area: 100,000 mm^2/hemisphere

Thickness: 1.5 – 4mm

- ~150K mesh is desirable (<1mm between vertices)
- HCP registers to "164k" standard mesh
- HCP also downsamples to "32k" mesh, best for fMRI, connectivity analyses

Macaque cortical parcellation – the early days





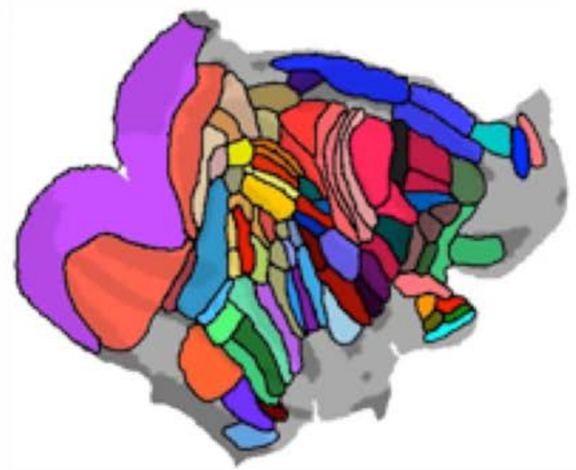
Parcellation based on "FACTs":
- Function
- Architecture
- Connectivity
- Topography

Many methods
(invasive and noninvasive)

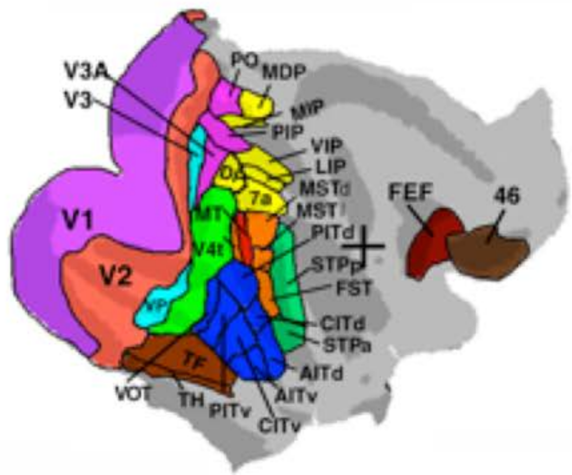
Poster children: areas V1, MT
But - most other areas are fuzzy, debatable
- Subtle boundaries
- Noise and bias in the data
- Discordant results from different approaches
- Cortical parcellation is really hard!!

2000 - 2012: Improved atlases, parcellations

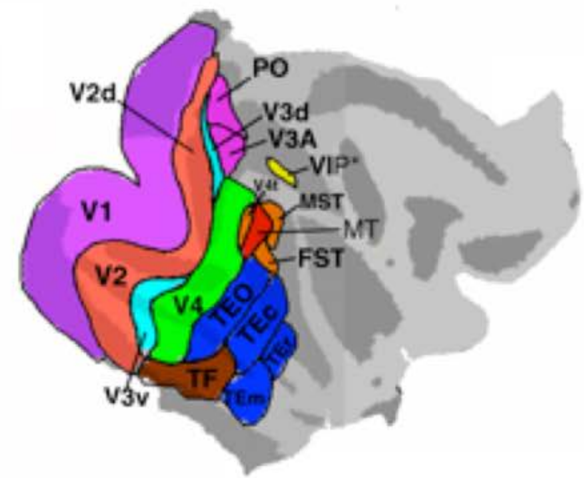
Many macaque parcellations registered to F99 atlas (Van Essen, 2004)



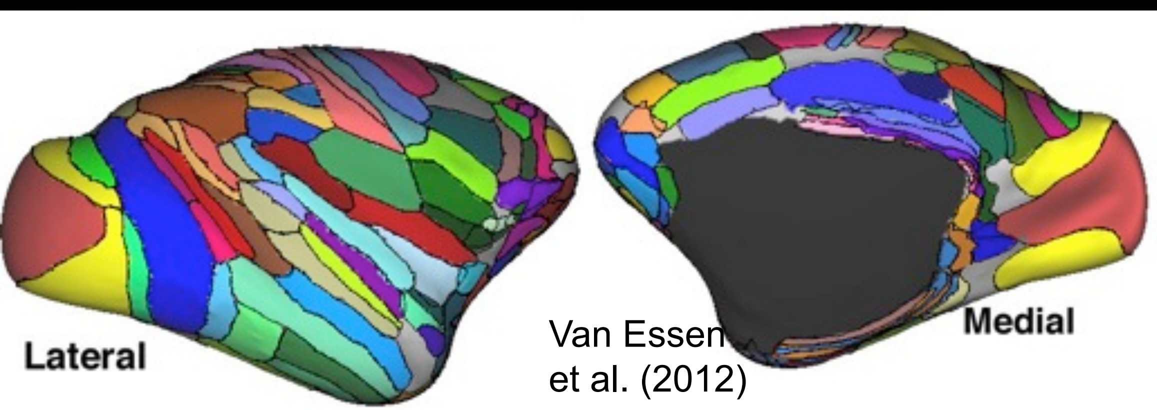
Lewis & VE (2000)



Felleman & VE (1991)



Ungerleider & Desimone (1986)



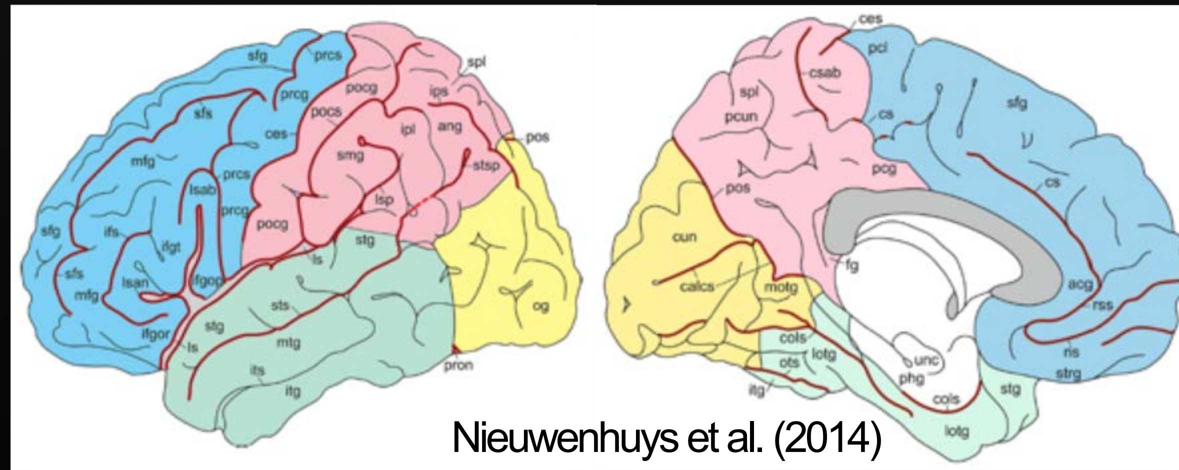
Van Essen et al. (2012)

A composite parcellation:

- 130 - 140 areas total
- 100-fold range in area size
- Good, but still far from ‘ground truth’

Human cortical geography

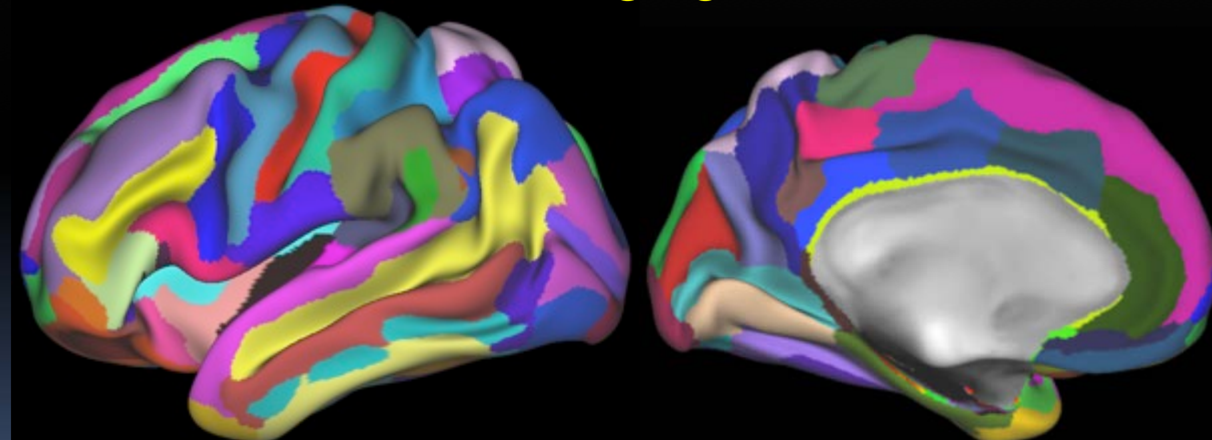
Lobes, gyri and sulci
But highly variable!



Nieuwenhuys et al. (2014)

Human geographic atlases used in neuroimaging:

FreeSurfer
aparc.a2009s

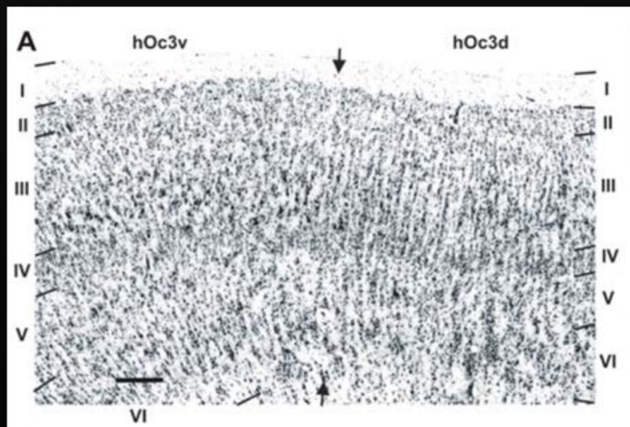


AAL, other atlases also available.
But parcels are not well correlated with functionally distinct cortical areas

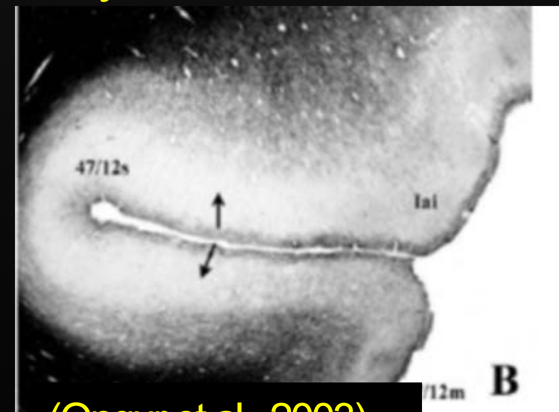
Human cortical architectonics

Cytoarchitecture

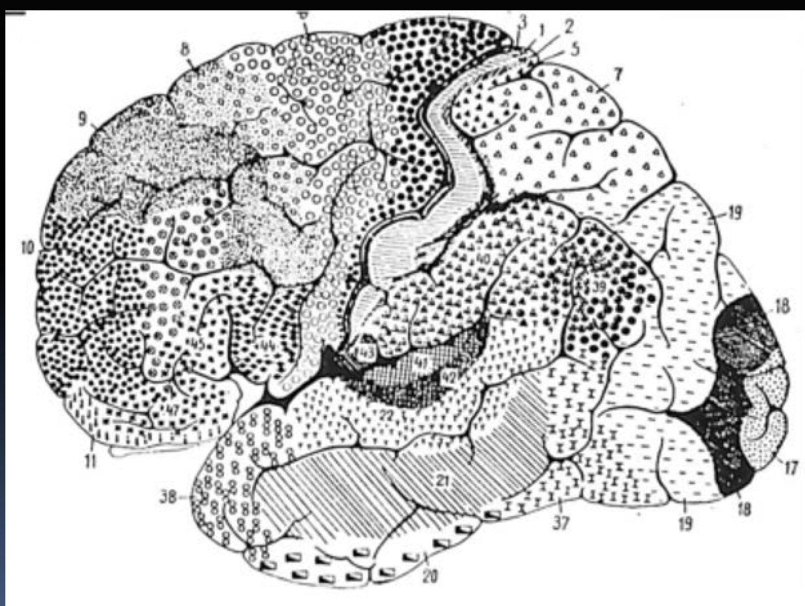
Kujovic et al., 2012



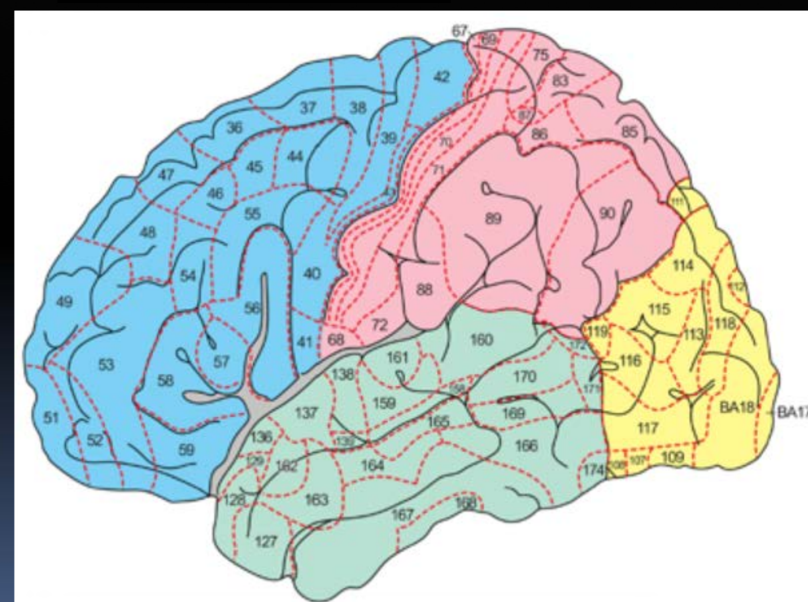
Myeloarchitecture



(Ongur et al., 2003)



Brodmann (1909)

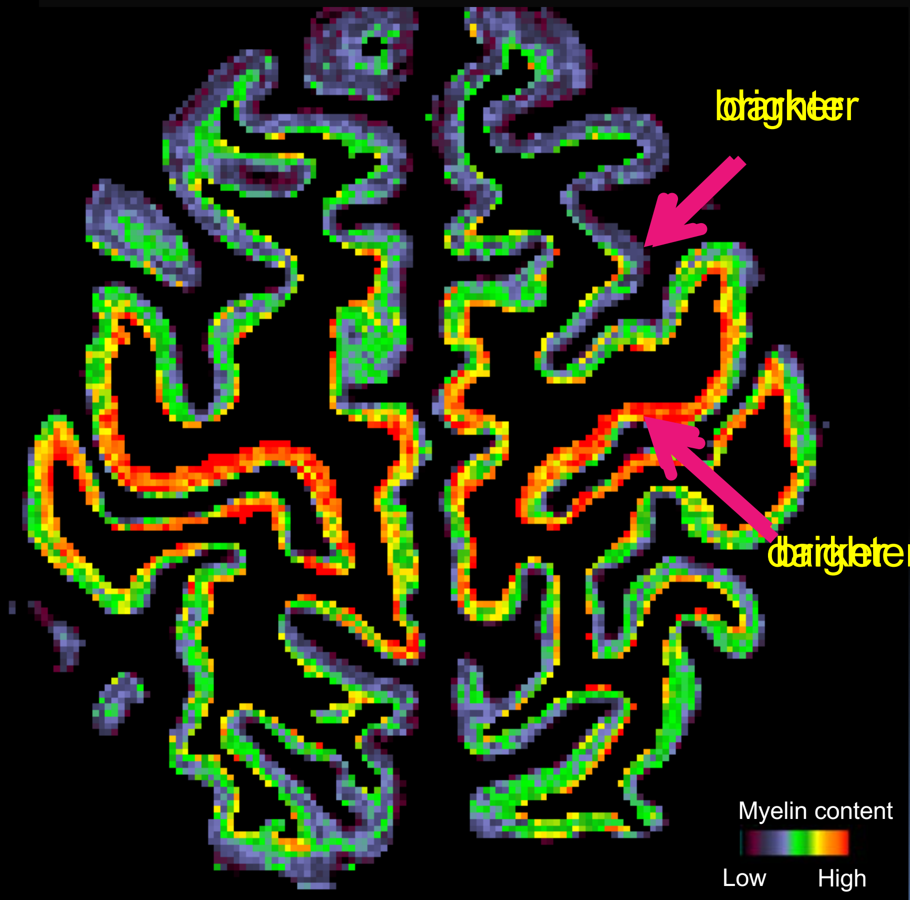


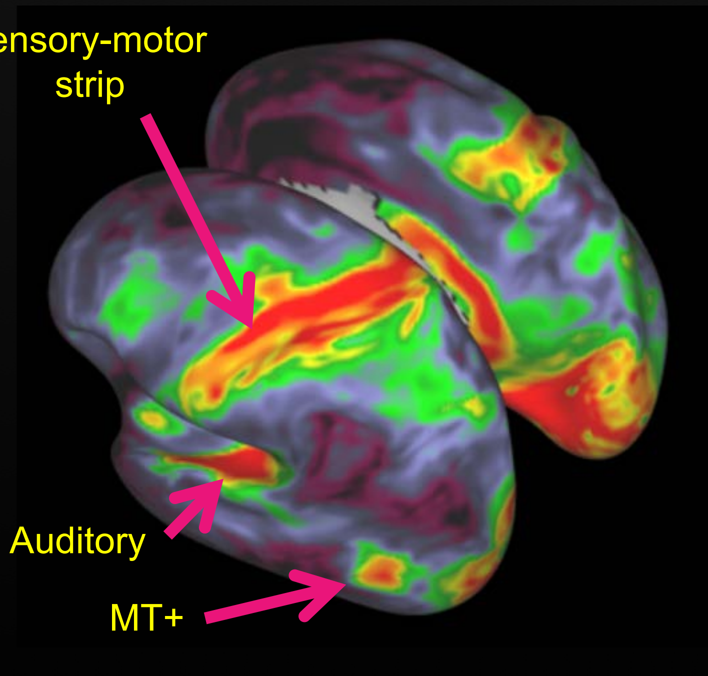
Nieuwenhuys et al. (2014);
Vogt (1903); O. and C. Vogt (1919)

Matt Glasser

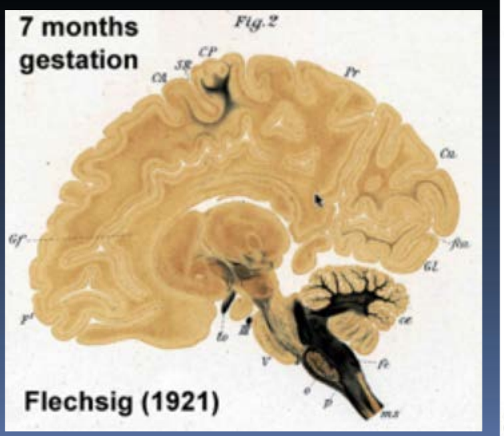
Myelin maps in cerebral cortex

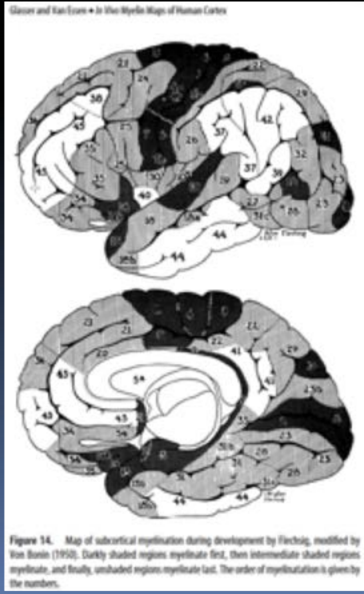
Divide and conquer: T1w/T2w ratio





Early myelination:
Heavy adult myelination





Glasser & Van Essen (2011); Glasser et al. (2013)

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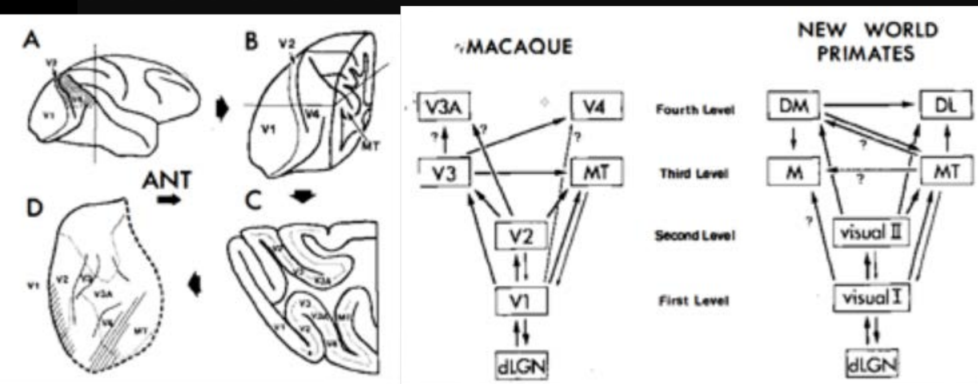
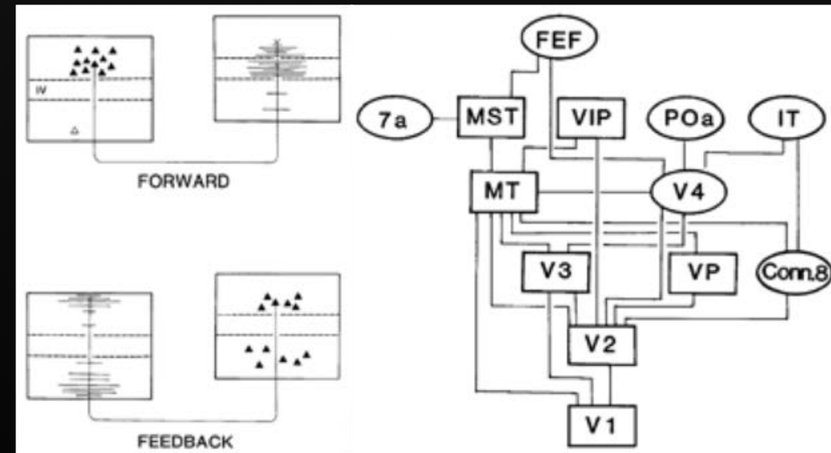
- Methodological highlights and teasers

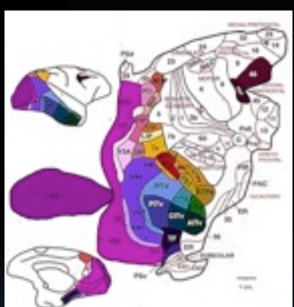
Macaque cortical connectivity (1979 - 2000)



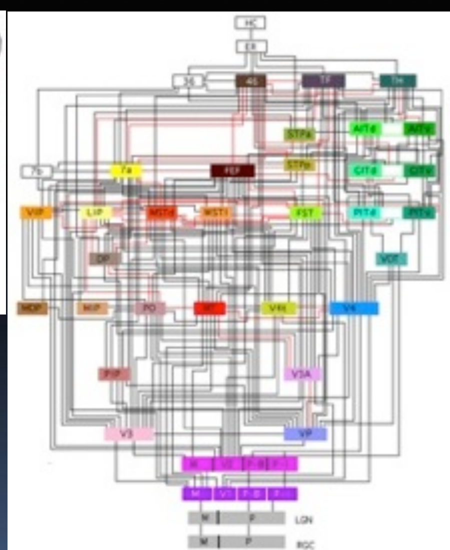
Van Essen (1979)

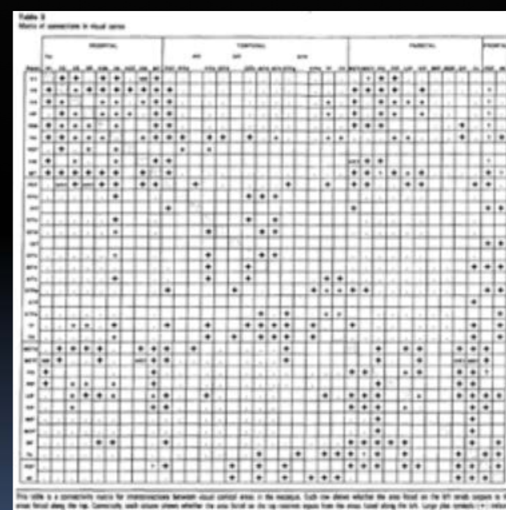


Maunsell & Van Essen (1983)

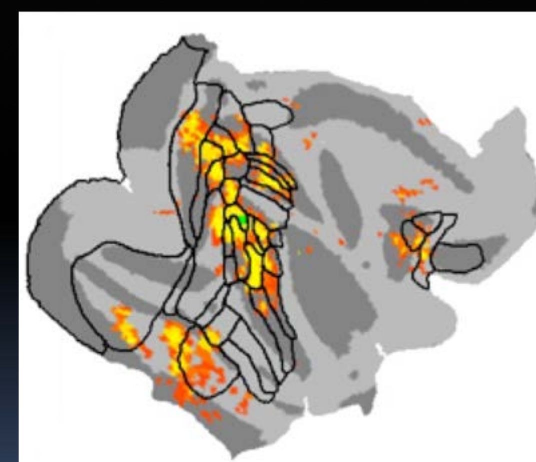


Felleman &
Van Essen (1991)





A binary connectivity matrix
"parcellated connectome"



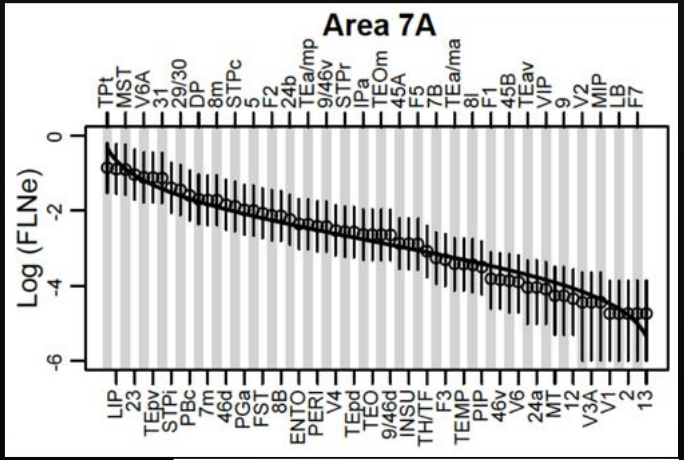
Connectivity density
(MSTd injection)
Lewis & Van Essen (2000)
Wide range of conection strengths!

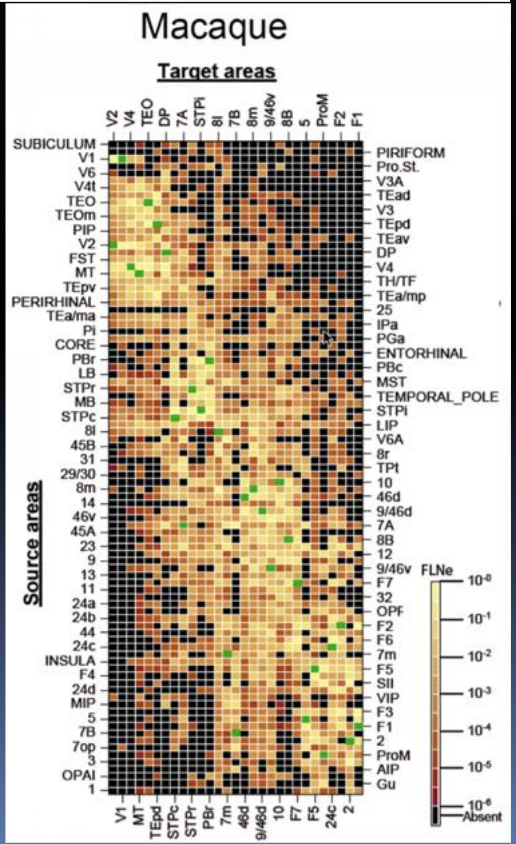
1991: Little quantitative connectivity data available

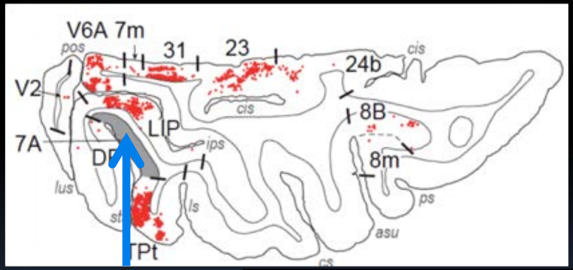
Cortical Connectivity: ‘ground truth’ in macaque

Macaque anatomical tracers (Markov et al., 2012, 2014)

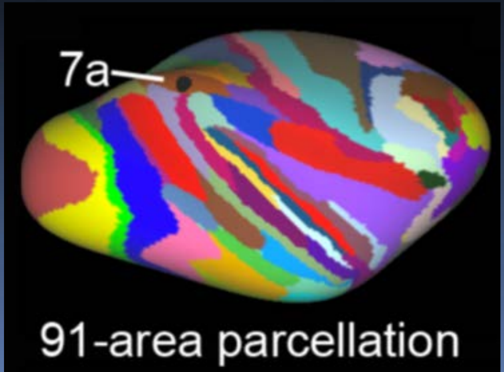
- Average of 55 inputs to each cortical area!
- Connection strengths: > 5 log units(!); lognormal distribution!
- 29x91 matrix; 1,615 identified pathways!
- Total = ~10^4 pathways (cortical + subcortical)

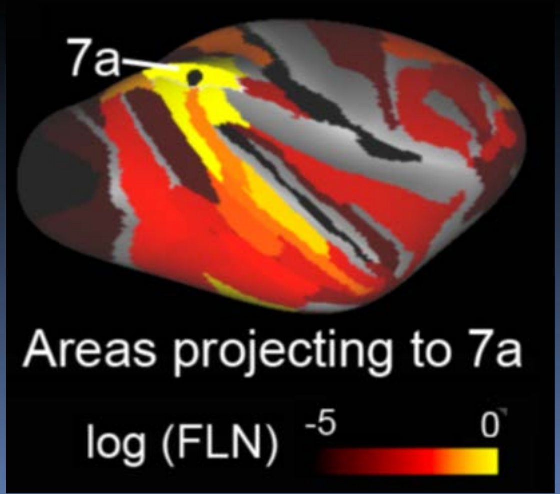






Tracer in Area 7A



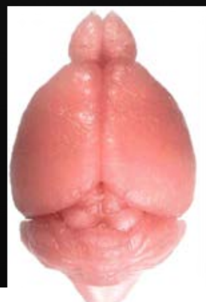


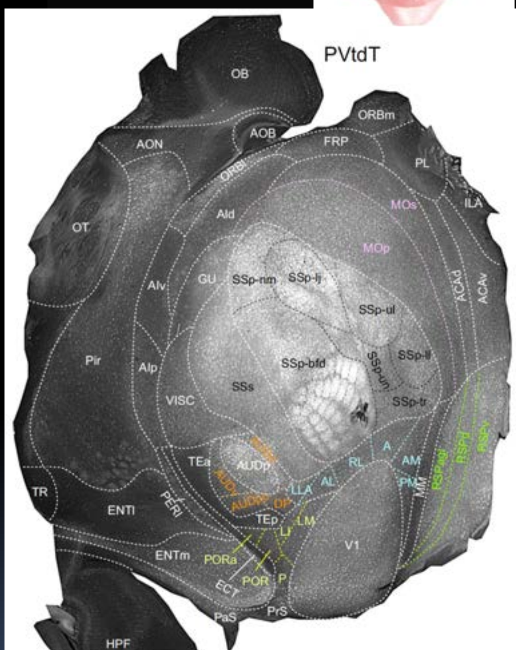
Mouse: Parcellations and Connectivity

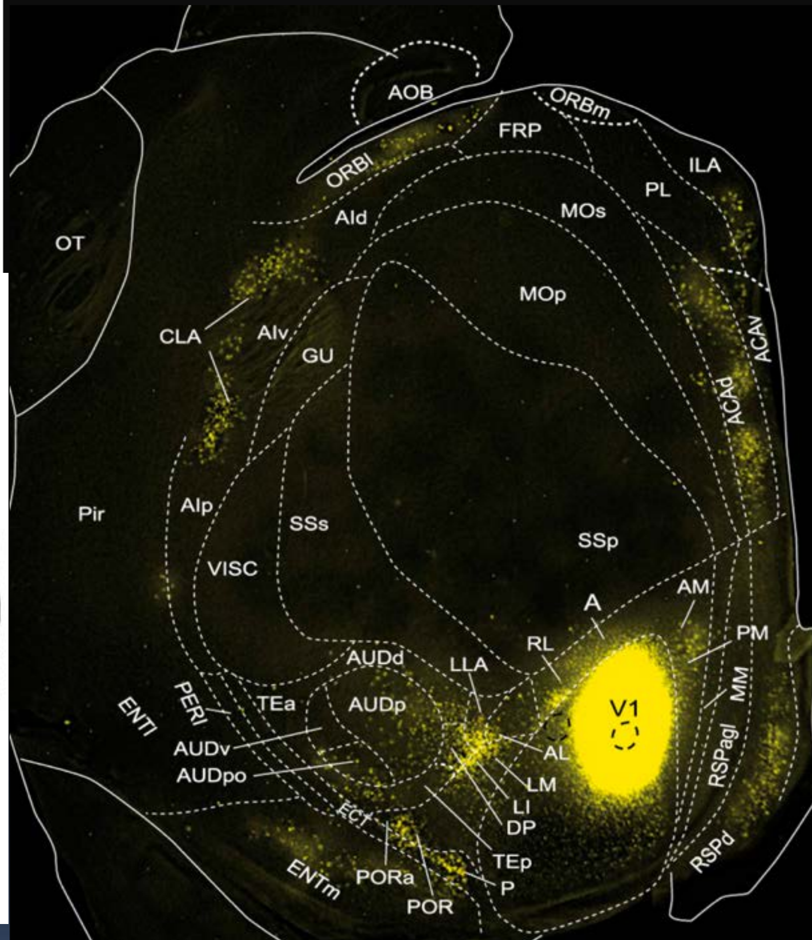
MOUSE: 41 areas

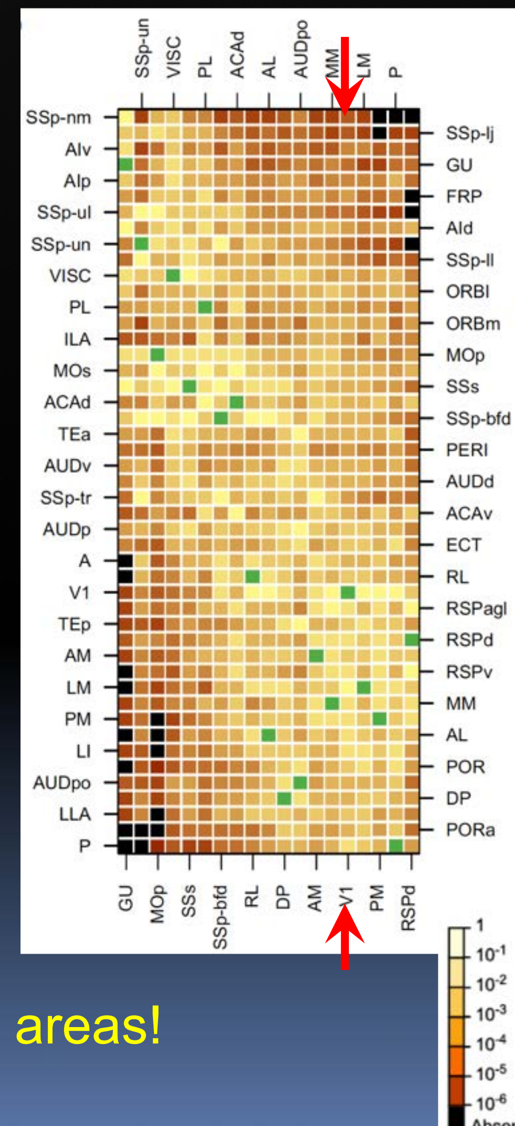
19 x 41 connectivity matrix
“parcellated connectome”

Gamanut et al.
(Neuron, 2018;
Kennedy,
Burkhalter, & Van
Essen labs)









- Mouse: 41 cortical areas; view on physical flatmap
- Retrograde tracer in V1 reveals inputs from all cortical areas!
- Connection “weights” vary by ~100,000-fold

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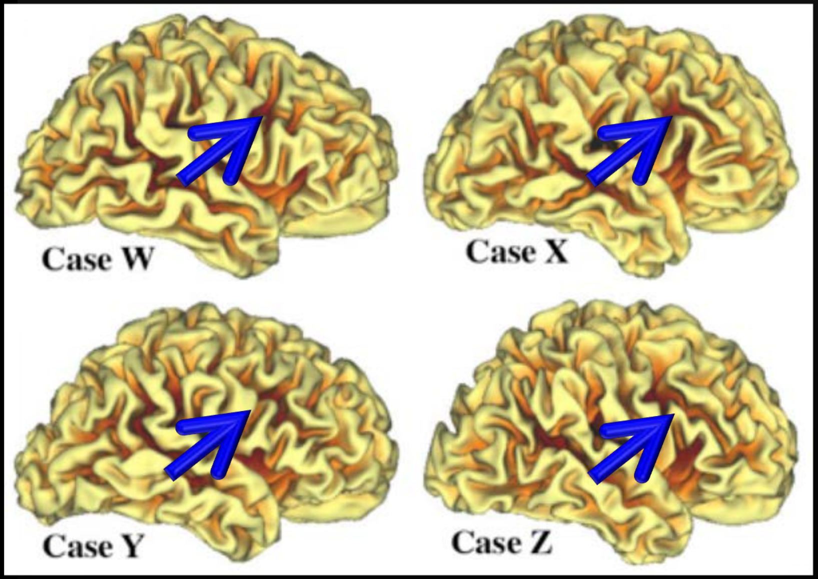
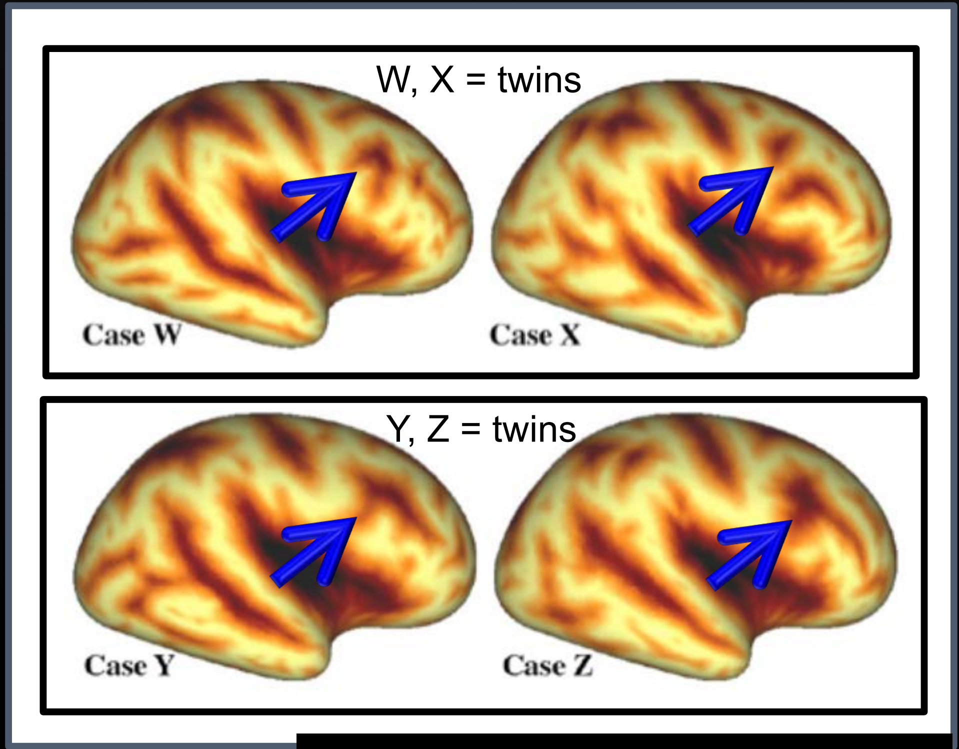
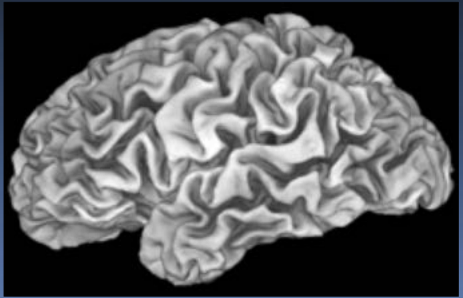
Human Cortical Convolutions

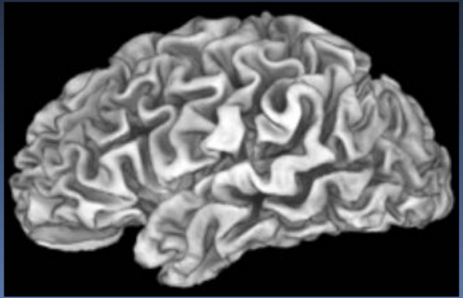




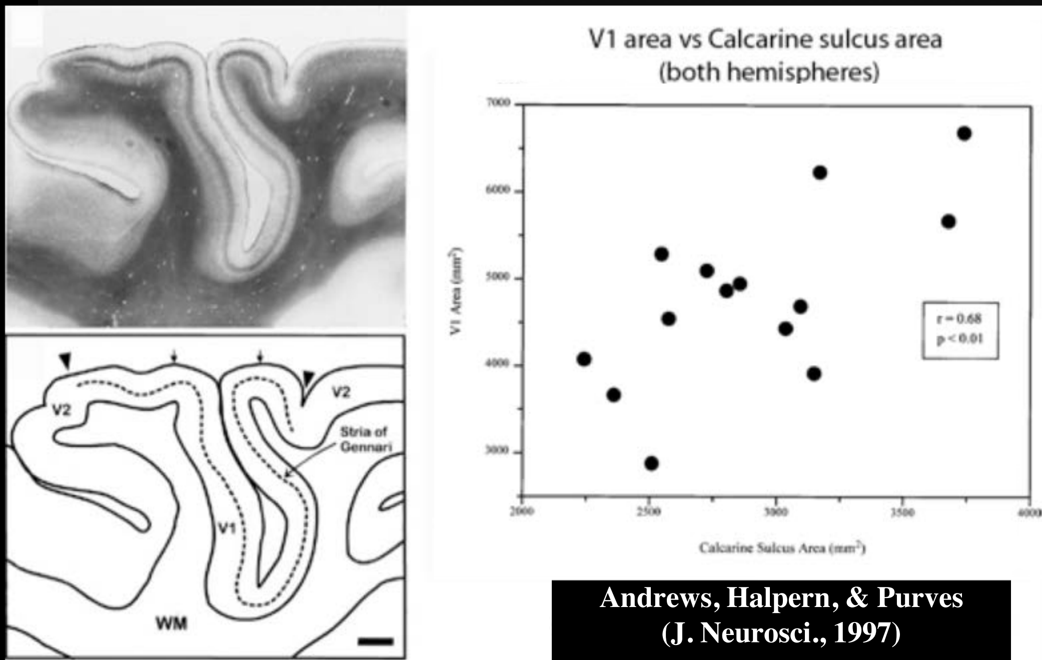
Botteron, Dierker, Todd et al. (OHBM 2008)

- Convolutions are complex!
- Highly variable across individuals
- More variable in ‘higher cognitive’ regions
- Variable even in identical twins, but some heritability
- HCP: MZ, DZ twins & siblings

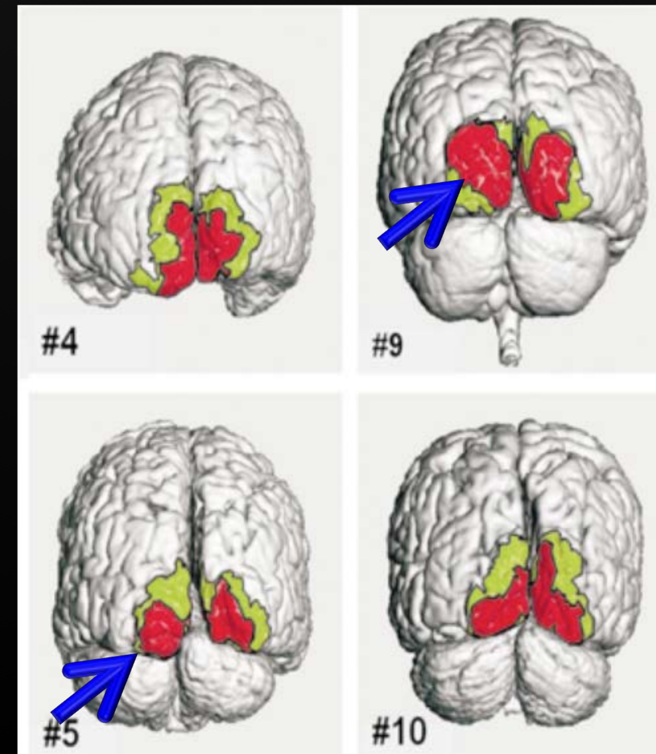




Variability in Human Cortical Areas



Andrews, Halpern, & Purves
(J. Neurosci., 1997)



Areas 17, 18 in 4 individuals
(Amunts et al., 2000)

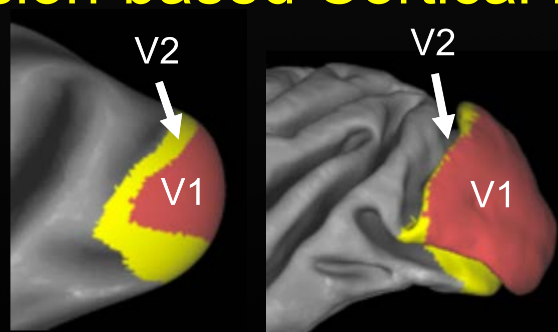
- Cortical areas vary in size (> 2x) across individuals
- Does size correlate with behavior, cognitive capabilities?
- Can be addressed using HCP data
- Cortical areas vary in relation to folds
- But what makes the cortex fold?!

Cortical folding: mainly prenatal, as connections are established

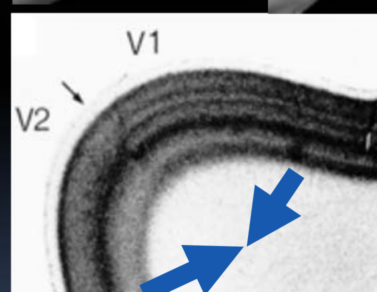
Hill et al. (2010)

Tension-based Cortical Folding? (Van Essen - Nature,1997)

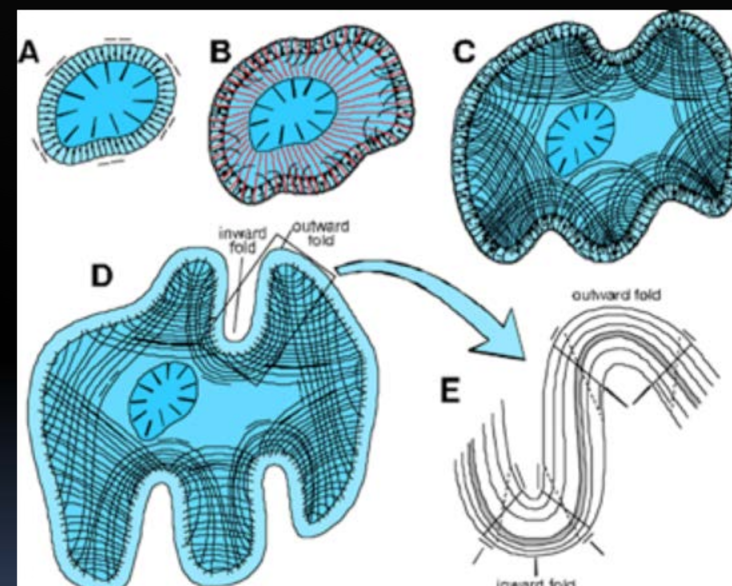
Macaque V1, V2 differentiate while cortex is smooth; gyrus in between forms later



Gyrus forms as major, topographic V1-V2 pathway is established (~E108)



Coogan & Van Essen (1996)



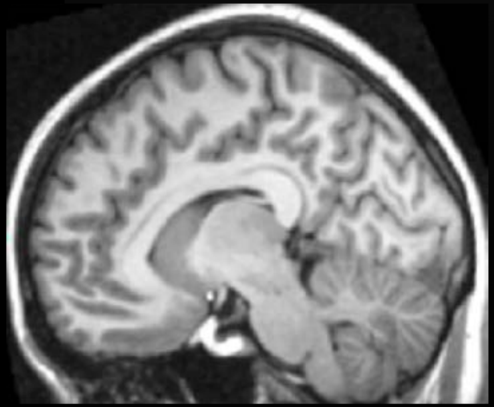
An aha moment!

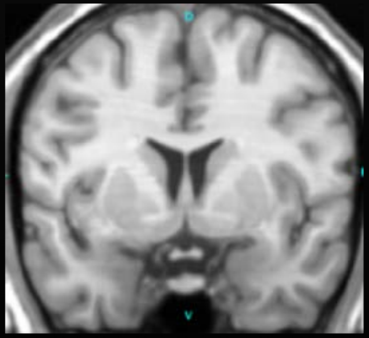
- Consistent folding in regions dominated by major pathways
- Variable folding in ‘balkanized’ regions (small areas, variable connectivity)
- One of multiple mechanisms? (also ‘buckling’, differential proliferation?)

Volume-based registration to an atlas

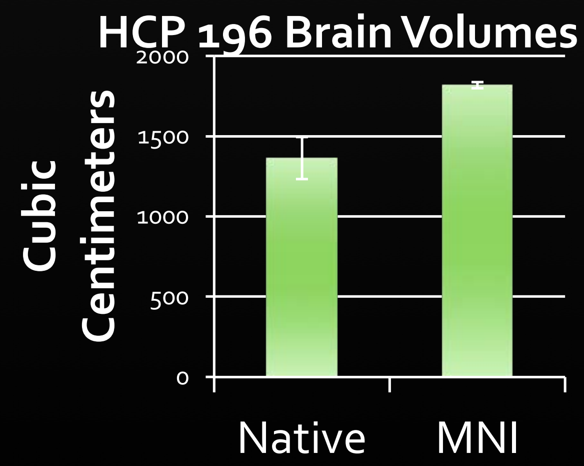
Multiple target options (e.g.,Talairach vs group average MRI)

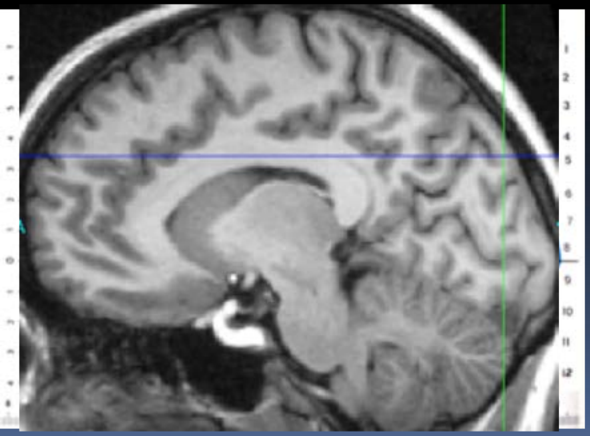
- Even nonlinear registration doesn't align all gyri, sulci
- Beware of 'drift': MNI152 = 137% average individual volume
- Smoothing in volume blurs across cortical ribbon boundaries



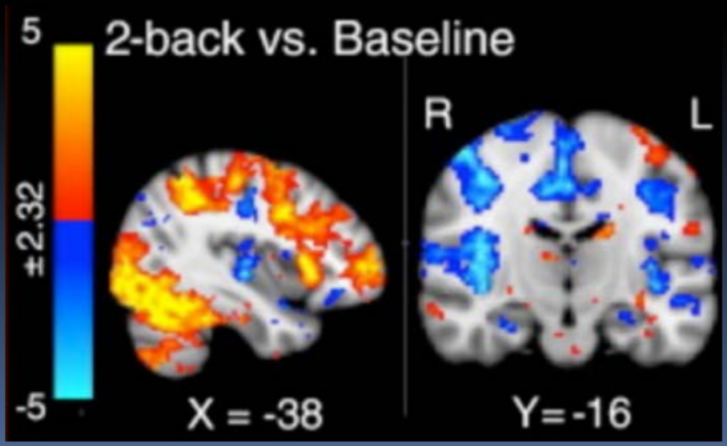


Individual





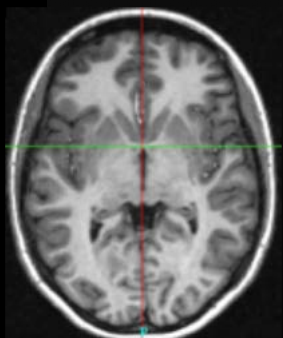
FSL FNIRT (nonlinear)



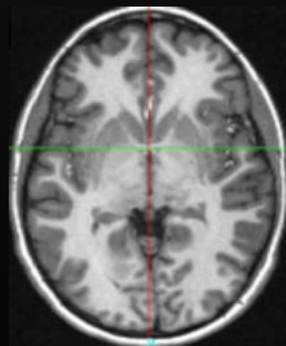
A typical task-fMRI contrast

Surface-based registration for accurate cortical alignment

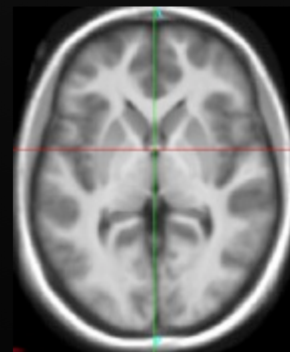
Case 1

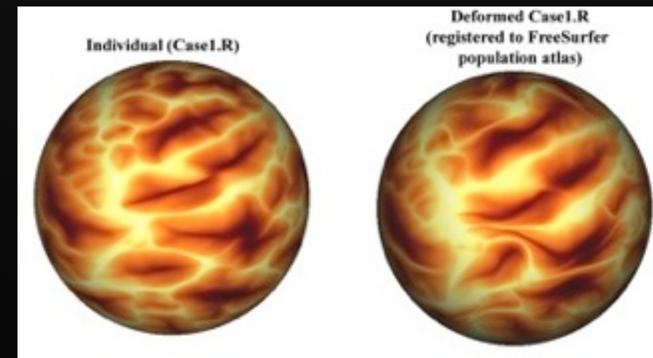


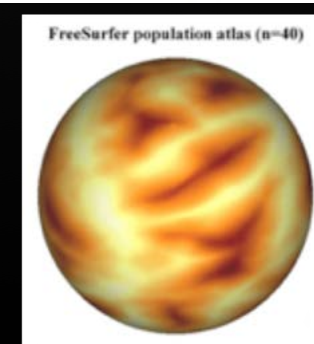
Case 2

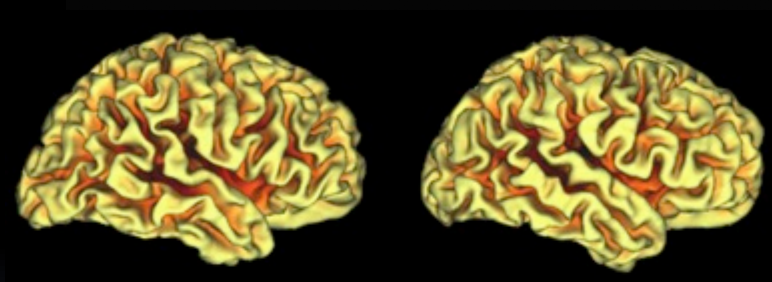


volume registration
FSL's 'FNIRT'
atlas









Surface-based registration
'fsaverage' atlas

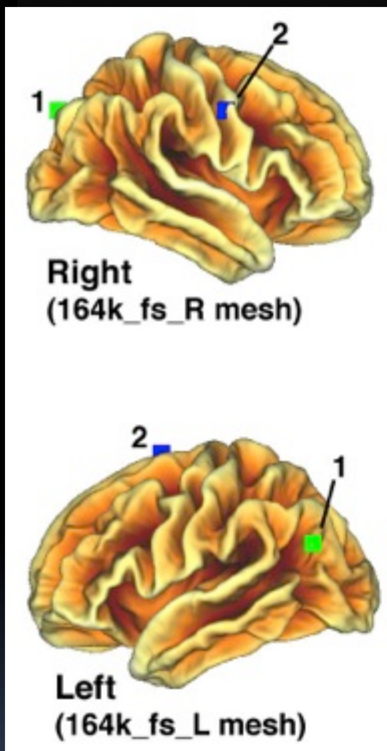
FreeSurfer shape-based spherical registration

Multiple spherical registration methods

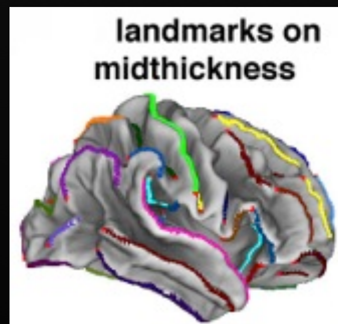
- FreeSurfer algorithm is good but not perfect
  - Large 'non-biological' distortions
  - Residual misalignment of functional areas
- Recent improvements: left-right correspondence; multimodal surface matching

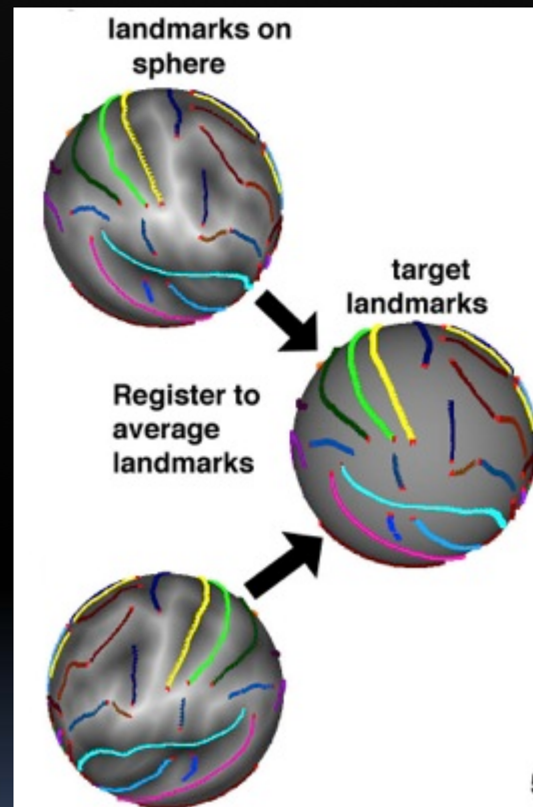
The "fs_LR" mesh aligns FreeSurfer left & right hemispheres

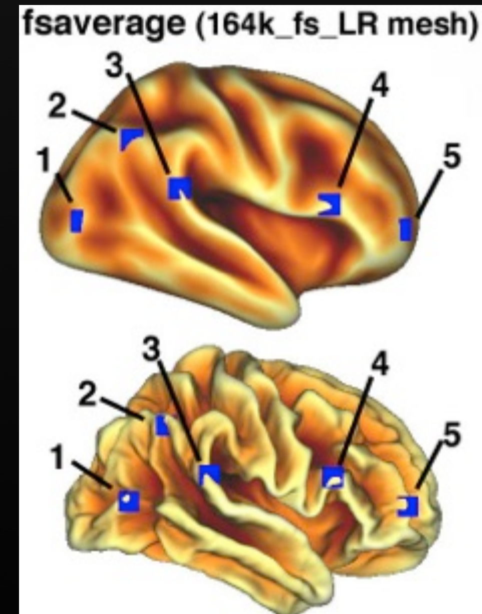
fsaverage hemispheres NOT in register

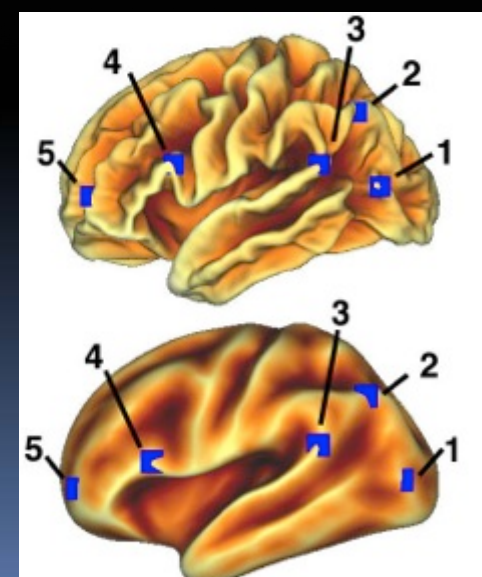


Van Essen et al. (2012b)



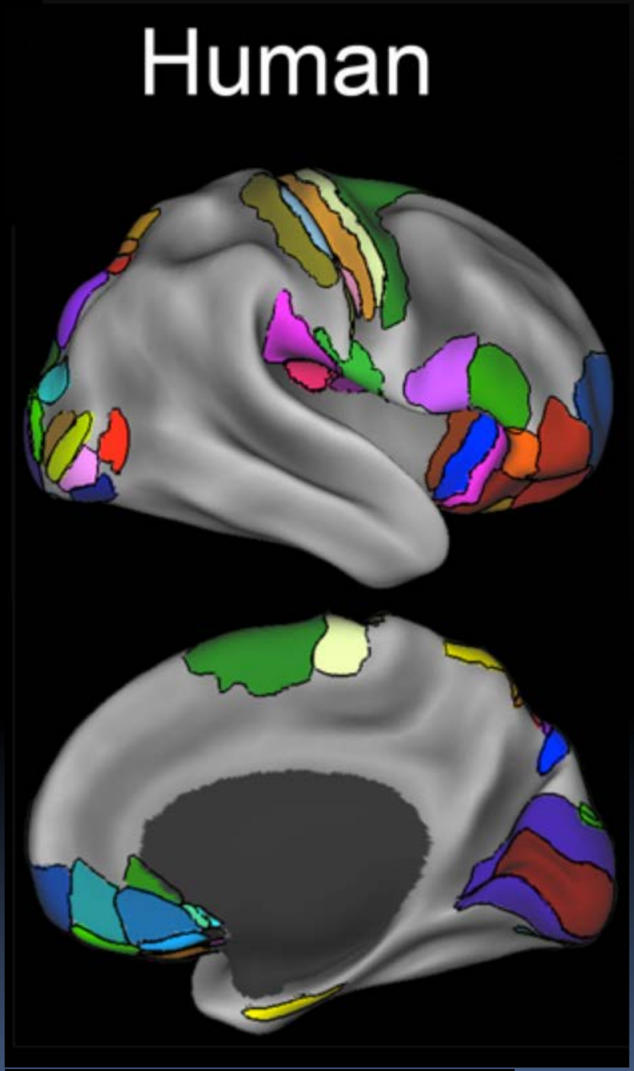






Accurate interhemispheric alignment: essential for evaluating hemispheric symmetries, asymmetries

A composite surface-based human cortical parcellation



Van Essen et al. (2012b)

'Entry requirements':

- Well-defined cortical areas
- Accurately mapped to individual surfaces
- Accurately registered to a surface-based atlas

Available in 2012:

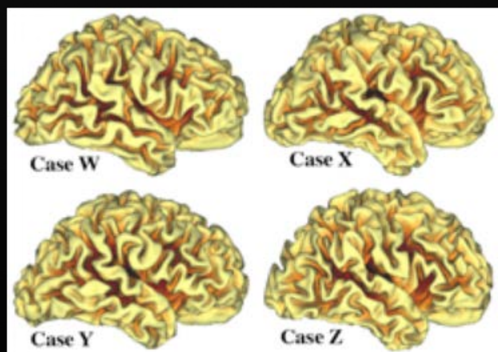
- Observer-independent architectonic (Fischl et al., 2008)
- Orbito-frontal multi-modal architectonic (Ongur et al. 2003)
- Retinotopic fMRI (Swisher et al., 2010; Kolster et al., 2010; Brewer et al., 2005)

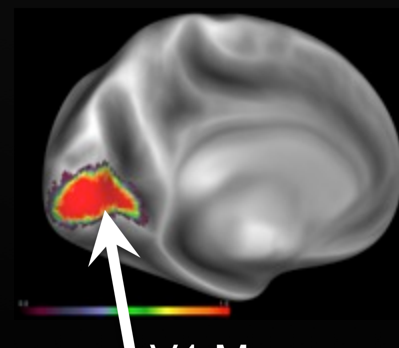
52 surface-mapped areas, 1/3 of hemisphere
Total: ~150 – 200 areas?
How to fill in the gaps? Stay tuned for this afternoon!

Improving Intersubject Alignment

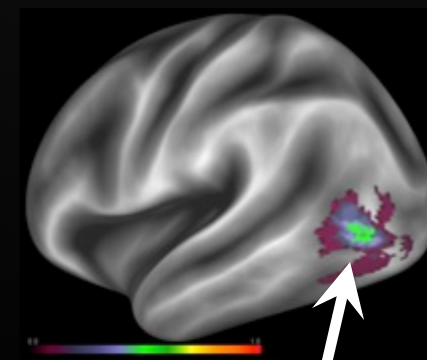
Shape-based alignment (FreeSurfer):

- performs well where folding is consistent
- poorly where folding is variable and area-folding correspondence is weak

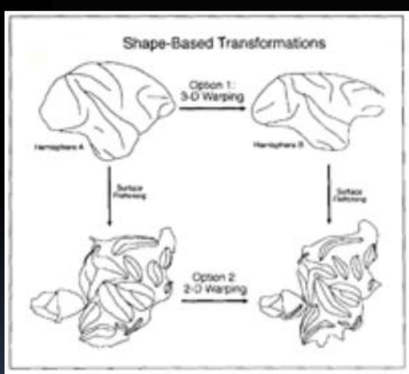




V1 Max
Overlap 100%



MT+ (hOc5) Max
Overlap 50%



A vision:

“In the future, it will be desirable to incorporate reliable <u>functionally based landmarks</u> along with geographic information in driving the transformations. “ (Drury et al., 1996)

Multimodal Surface Matching (MSM) can do this!

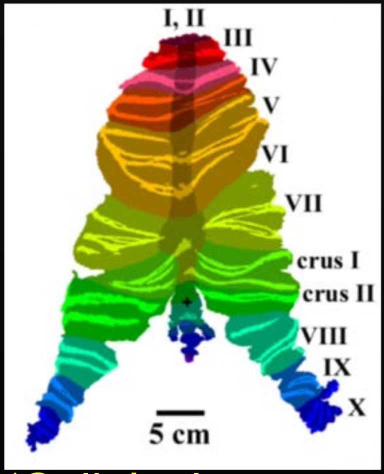
Emma Robinson, Mark Jenkinson et al. (2013, 2014, 2018)

- Stay tuned!

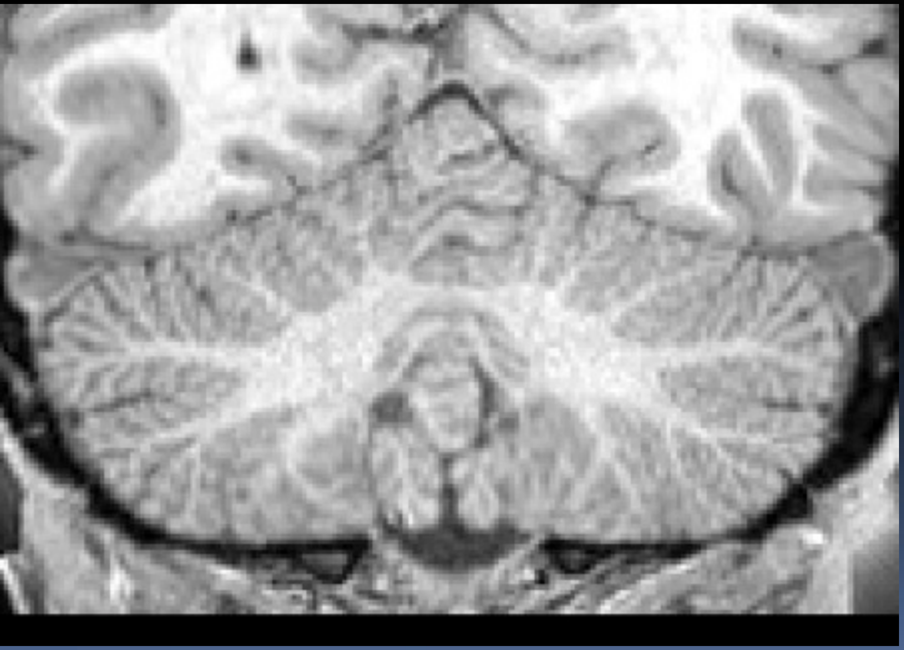
Cerebellar cortex is special!

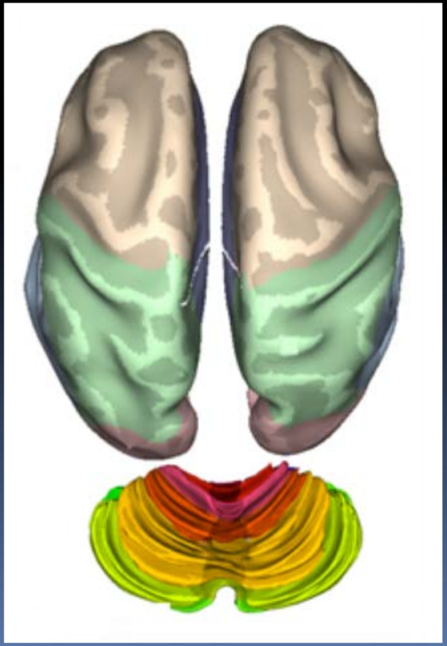
Compared to cerebral cortex:

- Convolutions are more regular (lobules, lamellae, folia)
- Cortex is thinner (<1mm vs 2.6mm average)
- Much less white matter (NO cortico-cortical connections!)
- Large surface area (>1,000 cm^2) despite small volume
- Hemispheres joined at midline - one sheet, not two!
- Automated segmentation not feasible (even on HCP MRIs)
- Can map data to 'colin' atlas cerebellar surface



'Colin' atlas
(Van Essen, 2004)





Coronal HCP subject 100307 Sagittal

Outline

Course logistics

Cortical cartography

- Maps, parcellations
- Connectivity – ground truth principles
- Variability, atlases, and alignment

Human Connectome Project

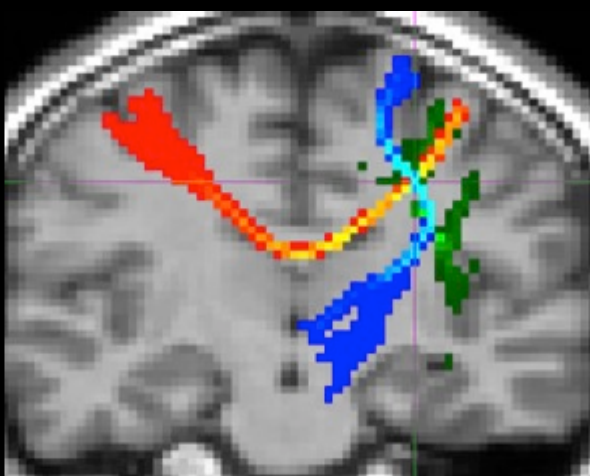
- History & overview
- Methodological highlights and teasers

Triple connectomes!

What's a connectome?

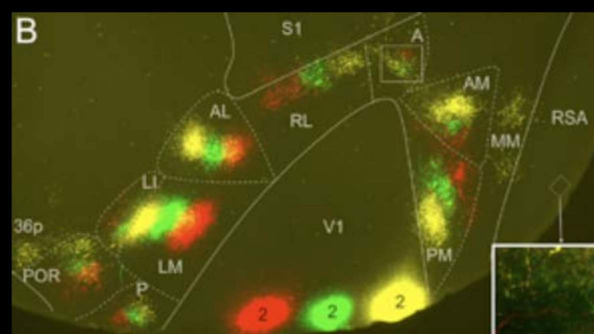
- A "comprehensive" map of neuronal connections

Macro-connectome
whole-brain, long-distance



Voxels: 1 – 2 mm

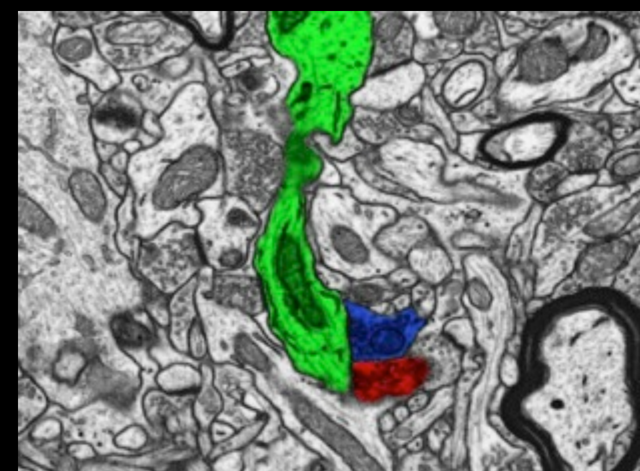
Meso-connectome
Cellular + long-distance



Mouse area V1 connections
(Wang & Burkhalter, 2008)

Many injections, many brains

Micro-connectome
(synapses, neurons)



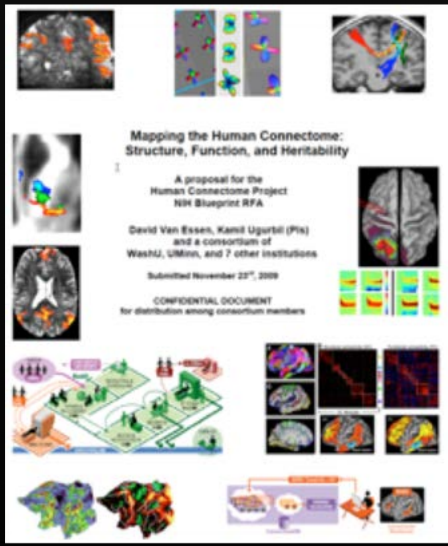
Volume reconstructed: <1 mm

- For the human brain, focus on the macro-connectome

Human Connectome Project: a brief history

- May, 2009: Request for Applications from NIH “Blueprint”
- September, 2010: NIH awards to two HCP consortia
  - $30M to “WU-Minn” consortium
    - Two+ years of methods development + piloting
    - Data acquisition:
      WashU (3T, 100 mT/m), UMinn (7T), SLU (MEG)
    - Target: 1200 subjects (twins + siblings)
    - Analysis: Oxford (fMRI, dMRI); MEG (Chieti, Frankfurt, Nijmegen)

  - “MGH/UCLA” consortium (MGH scanner with 300 mT/m gradients)
- 2013: “Lifespan Pilot” supplements to WU-Minn, MGH consortia



1) Acquire data on brain structure, function, and connectivity in healthy adults (twins and non-twin siblings).

- Improved scanners, pulse sequences
- Multimodal imaging (~4 hours total scan – 4 x 1h sessions)
- Data quality: exceptionally high!
- 1200 subjects studied, ~1100 with MRI (completed September, 2015)
- 184 subjects scanned at 7T (completed November, 2015)
- Behavioral data (478 ‘subject measures’)
- Magnetoencephalography (95 subjects): Task-MEG, resting-state MEG
- Blood for genotyping (to dbGAP in fall, 2016)

2) Analyze the data

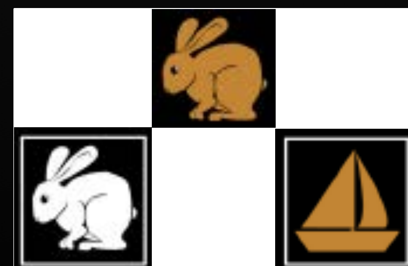
- Improved HCP preprocessing pipelines
- Better visualization (Connectome Workbench)
- Advanced analyses

Deanna Barch

HCP Behavioral tests

- NIH Toolbox; Penn Neuropsychological Battery
- Diverse phenotypes
  - Cognition
  - Emotional health
  - Motor skills
  - Sensory
  - Personality
  - Fluid intelligence
  - Family environmental factors
- Demographic, physical data
- Psychiatric status, substance use
- Some data are Restricted Access (separate Data Use Terms)

Cognitive: Match the shape



Sensory: Which feels different?

Personality – NEO-FFI (neuroticism)

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1	2	3	4	5

____ I am seldom sad or depressed.

____ Sometimes I feel completely worthless.

____ I rarely feel lonely or blue.

3) Share the HCP data

- ConnectomeDB database – a robust infrastructure
- 900-subject data release (June, 2015)
- 7T subjects (73 subjects, Part 1 – June, 2016)
- MEG data release (95 subjects, November, 2015)
- 1100-subject release - fall, 2016
- >6,000 investigators accepted HCP Data Use Terms (~600 Restr. Access)
- >10 petabytes (10,000 TB) of HCP data shared (7 PB downloaded, 3 PB in hard drives shipped)
- Release of extensively analyzed data

  ConnectmeDB: ‘Network matrices’; ‘MegaTrawl; dense connectome)

  BALSA database: Glasser et al., 2016 (Nature; Nature Neuroscience)
- >140 publications using HCP data
- HCP website: www.humanconnectome.org

The HCP-style Neuroimaging Paradigm

Seven core tenets (Glasser et al. Nature Neuroscience, 2016)

1) Collect lots of multimodal imaging data.
2) Maximize resolution, data quality (e.g., multiband fMRI, dMRI)
3) Minimize distortion and blurring of each subject's data
4) Respect geometry of brain structures ('CIFTI grayordinates').
5) Align data precisely across individuals and across studies.
6) Analyze results using an accurate brain parcellation.
7) Freely share the data (including publication-related data).

nature neuroscience

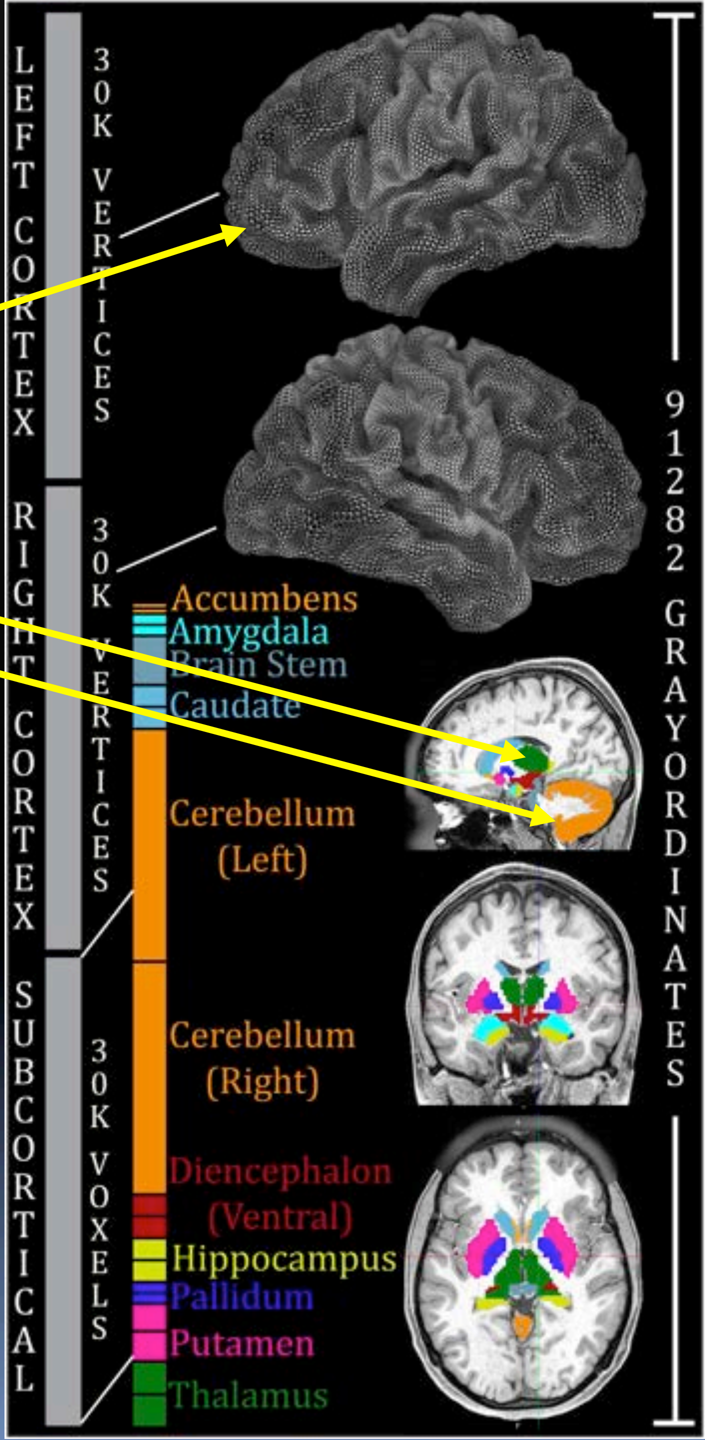
The Human Connectome Project's neuroimaging approach

Matthew F Glasser[1], Stephen M Smith[2], Daniel S Marcus[3], Jesper L R Andersson[2], Edward J Auerbach[4], Timothy E J Behrens[2], Timothy S Coalson[1], Michael P Harms[5], Mark Jenkinson[2], Steen Moeller[4], Emma C Robinson[6], Stamatios N Sotiropoulos[2], Junqian Xu[7], Essa Yacoub[4], Kamil Ugurbil[4] & David C Van Essen[1]

CIFTI "Grayordinates"

For gray-matter analyses (e.g., fMRI):

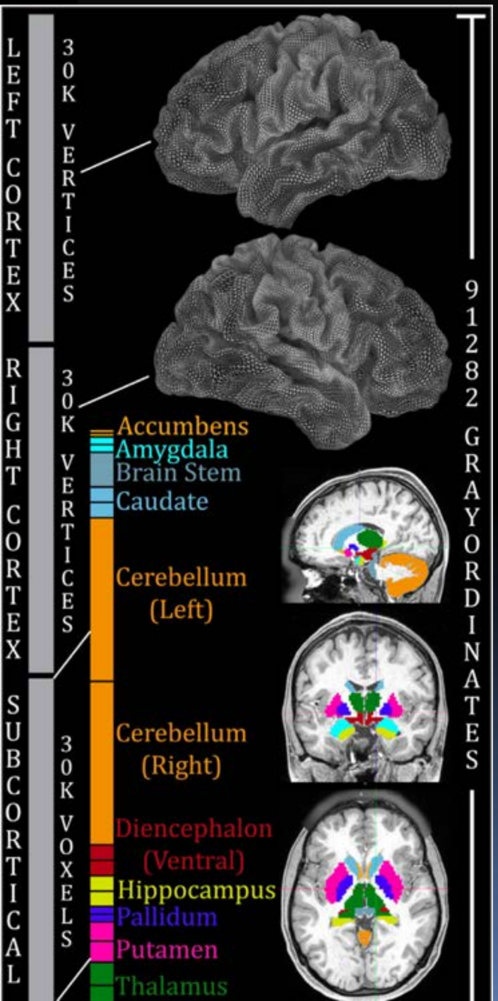
- Cortex plus subcortical gray matter only
- Appropriate geometric models
  - Cerebral cortex: surfaces, vertices
  - Subcortical: volumes, voxels
  - Cerebellar cortex: voxels (for now)
- Intersubject alignment:
  - Cortex: surface registration
  - Subcortical: nonlinear volume-based
- Spatial smoothing in grayordinates space (avoid blurring outside cortical ribbon)

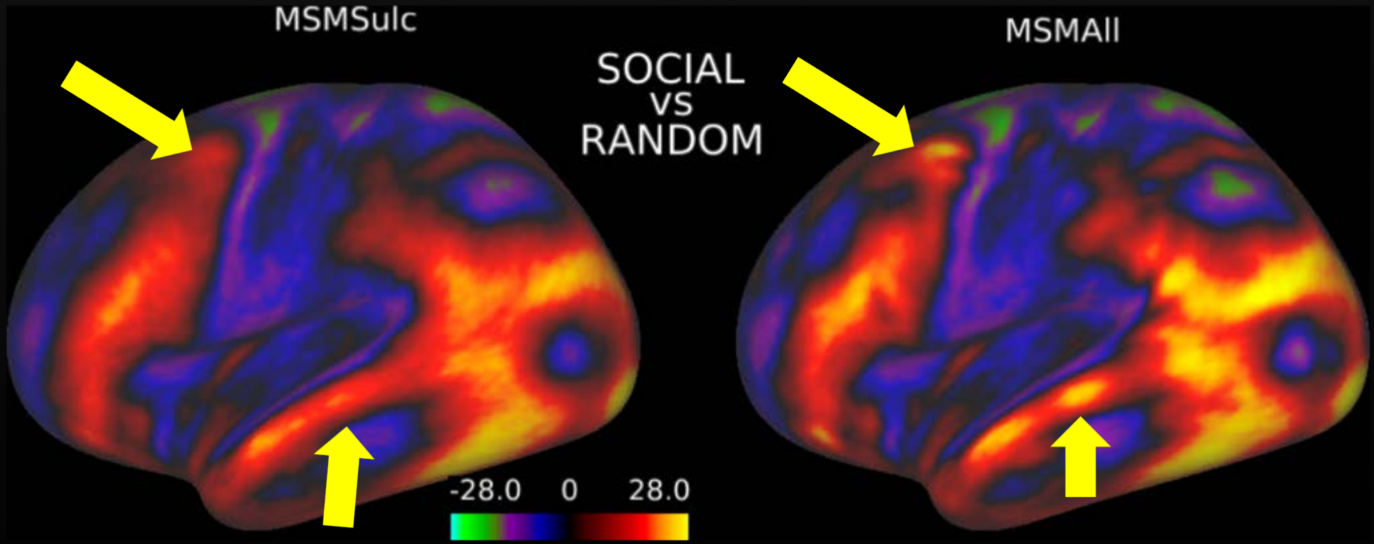


Glasser et al (2013) Neuroimage "HCP Pipelines Paper"

HCP Advances: Representation and Alignment

“CIFTI” format:
grayordinates
(vertices + voxels)





The HCP atlas approach

- A “CIFTI-based” composite coordinate system:
  - Grayordinates = cerebral cortex surface vertices + subcortical gray-matter voxels
  - Whiteordinates = white matter voxels (for tractography)

- Surface alignment (individuals to atlas)
  - Folding-based (MSMSulc) – ok but blurry task-fMRI assay
  - Much sharper for areal feature-based alignment (MSMAll)
- Enabled a new multimodal cortical parcellation

HCP Task-evoked functional MRI

- Seven tasks (1 hr scan time)
- Extensive brain coverage
- Diverse functional systems

Language

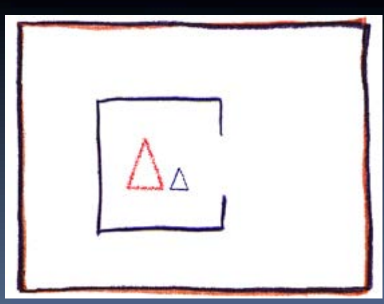
Story

Listen to short stories; Answer questions about the story

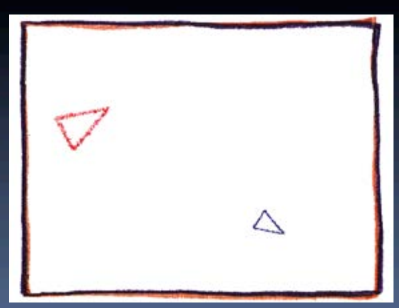
Math

Do arithmetic problems

Social Cognition

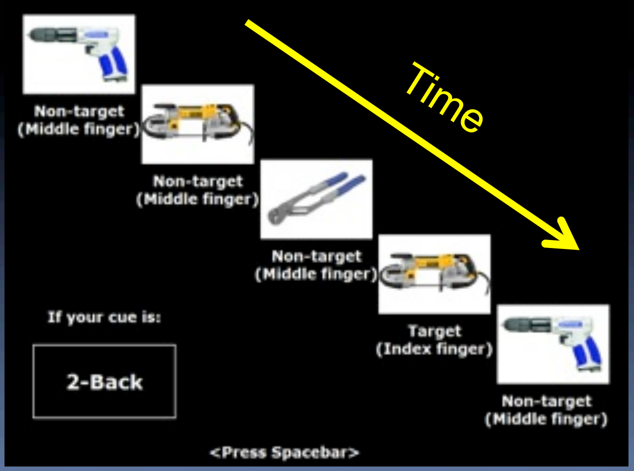


Social



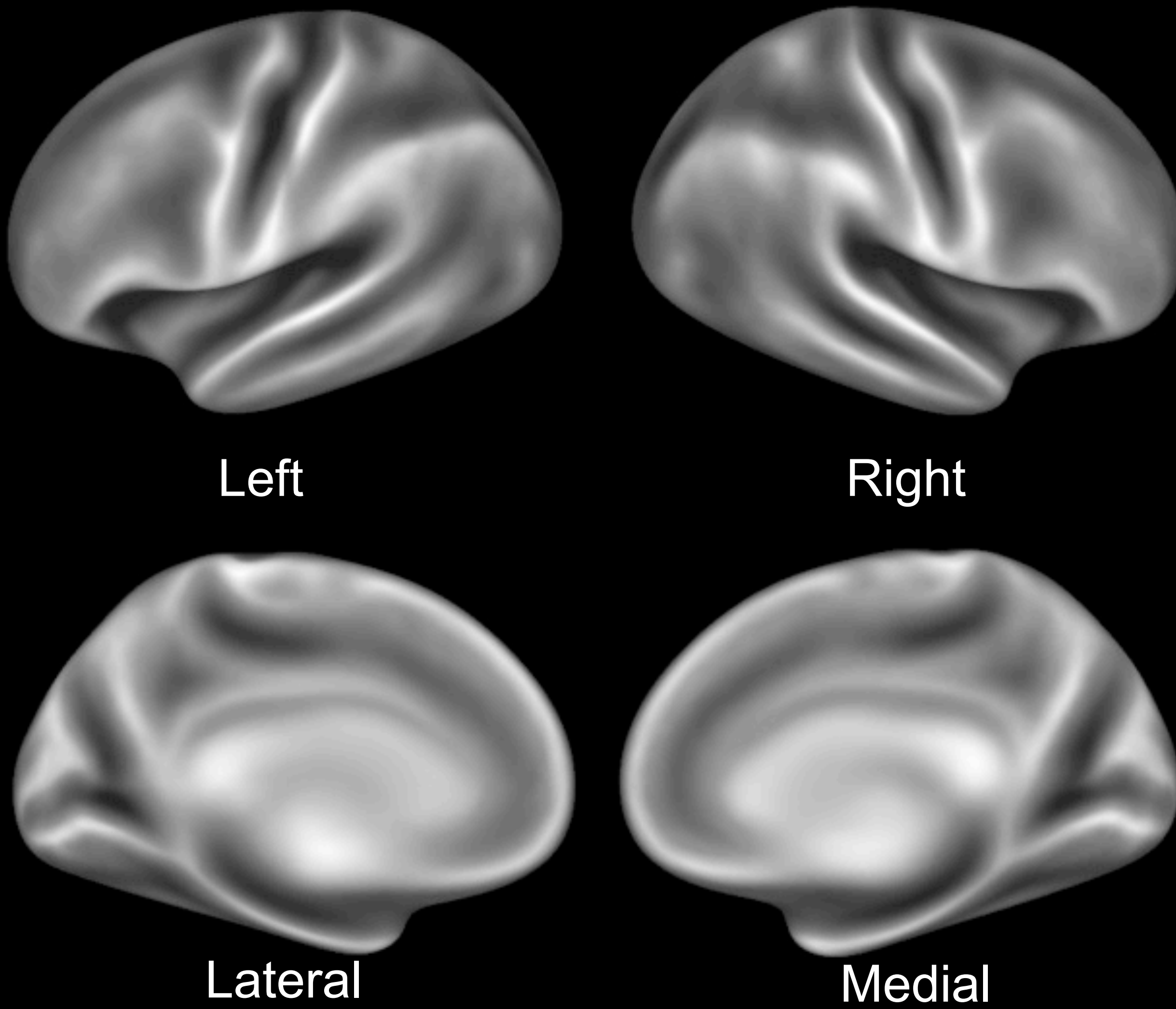
Random

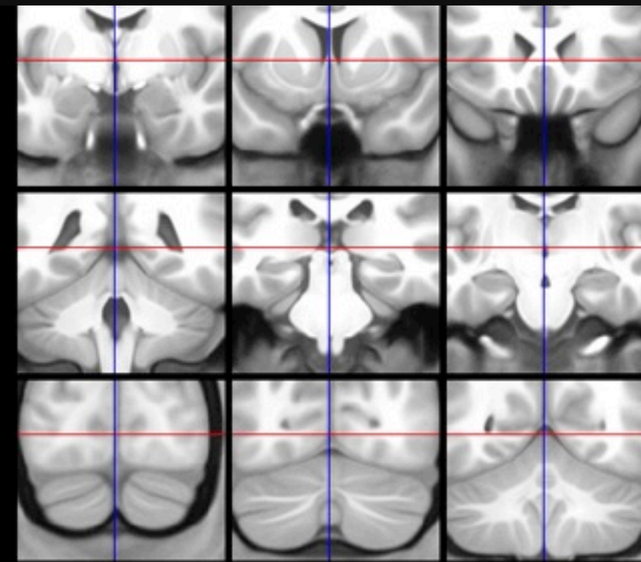
Working Memory

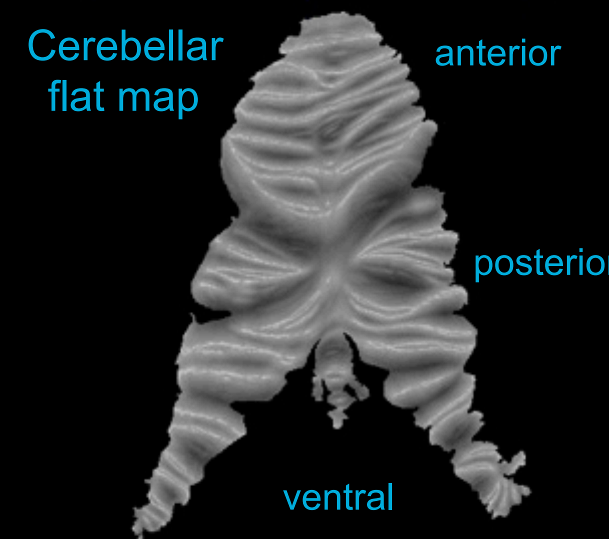


Faces, Places, Bodies, Tools

Whole-brain visualization

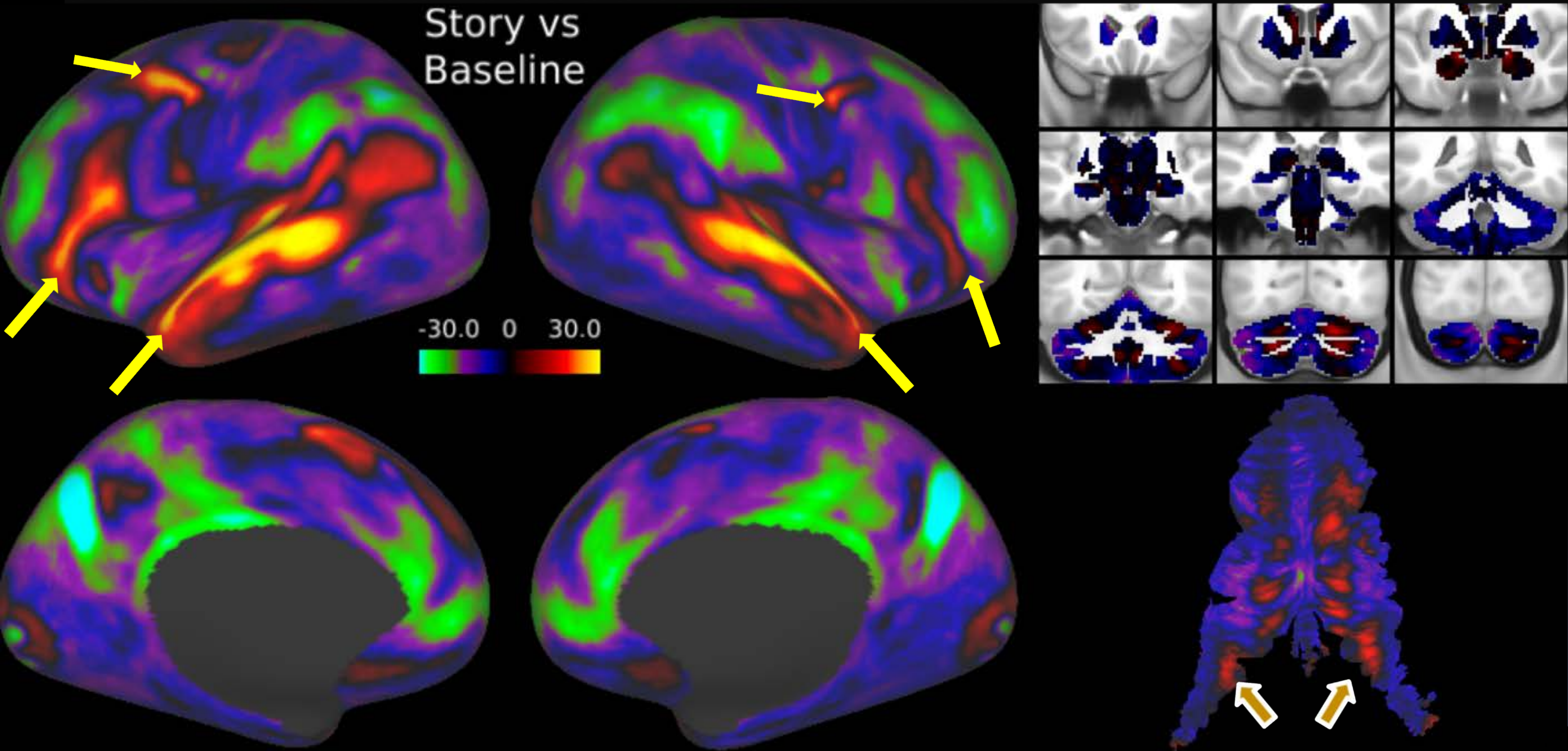






‘Colin’ cerebellum

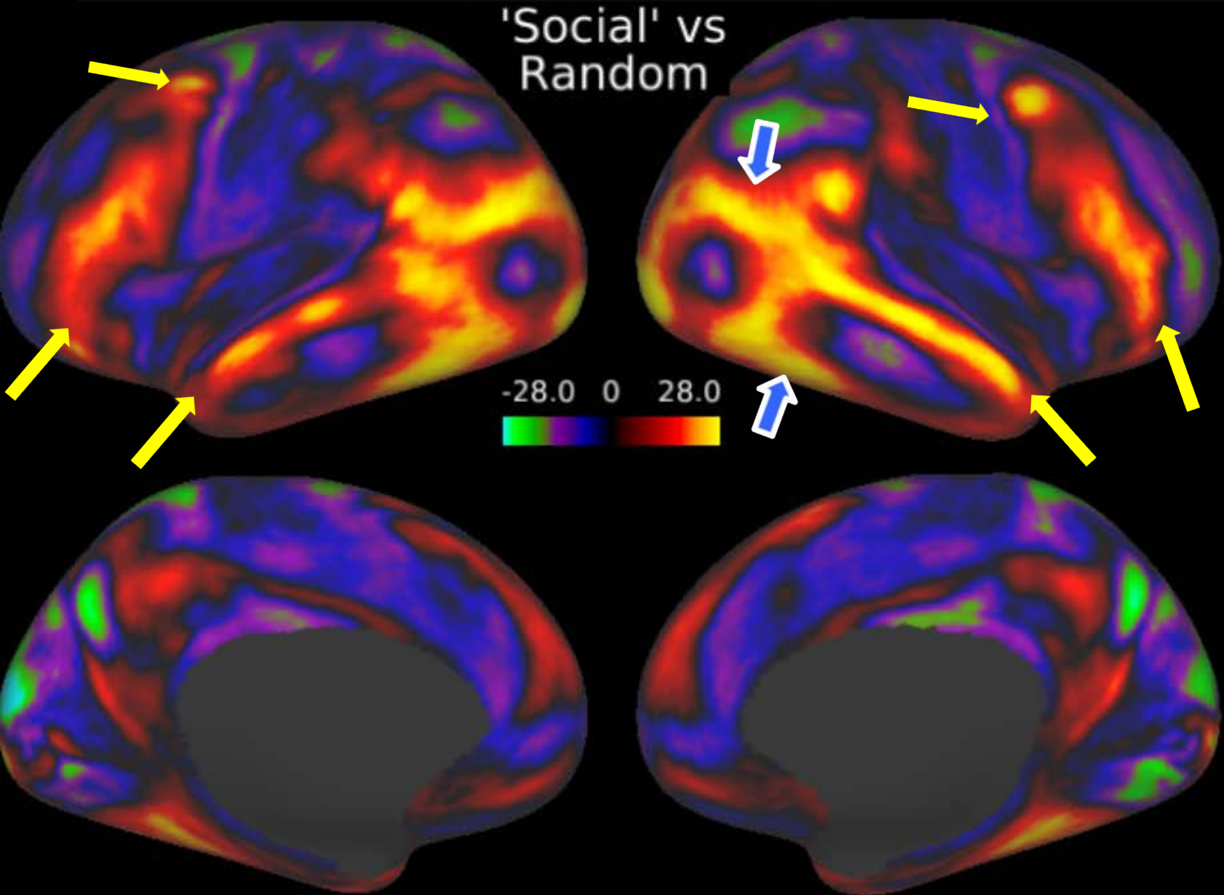
HCP Task-fMRI activations

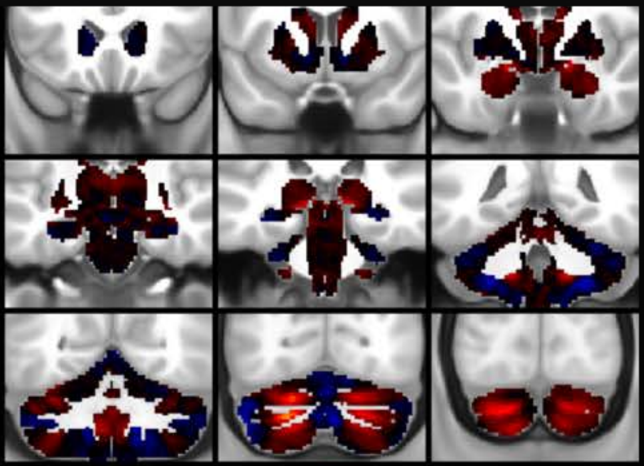


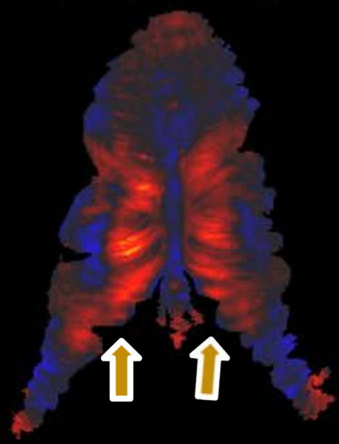
- ‘Story’ task language activations: bilateral but L > R
- Patchy cerebellar activations, R > L

HCP Task-fMRI activations

deactivation activation

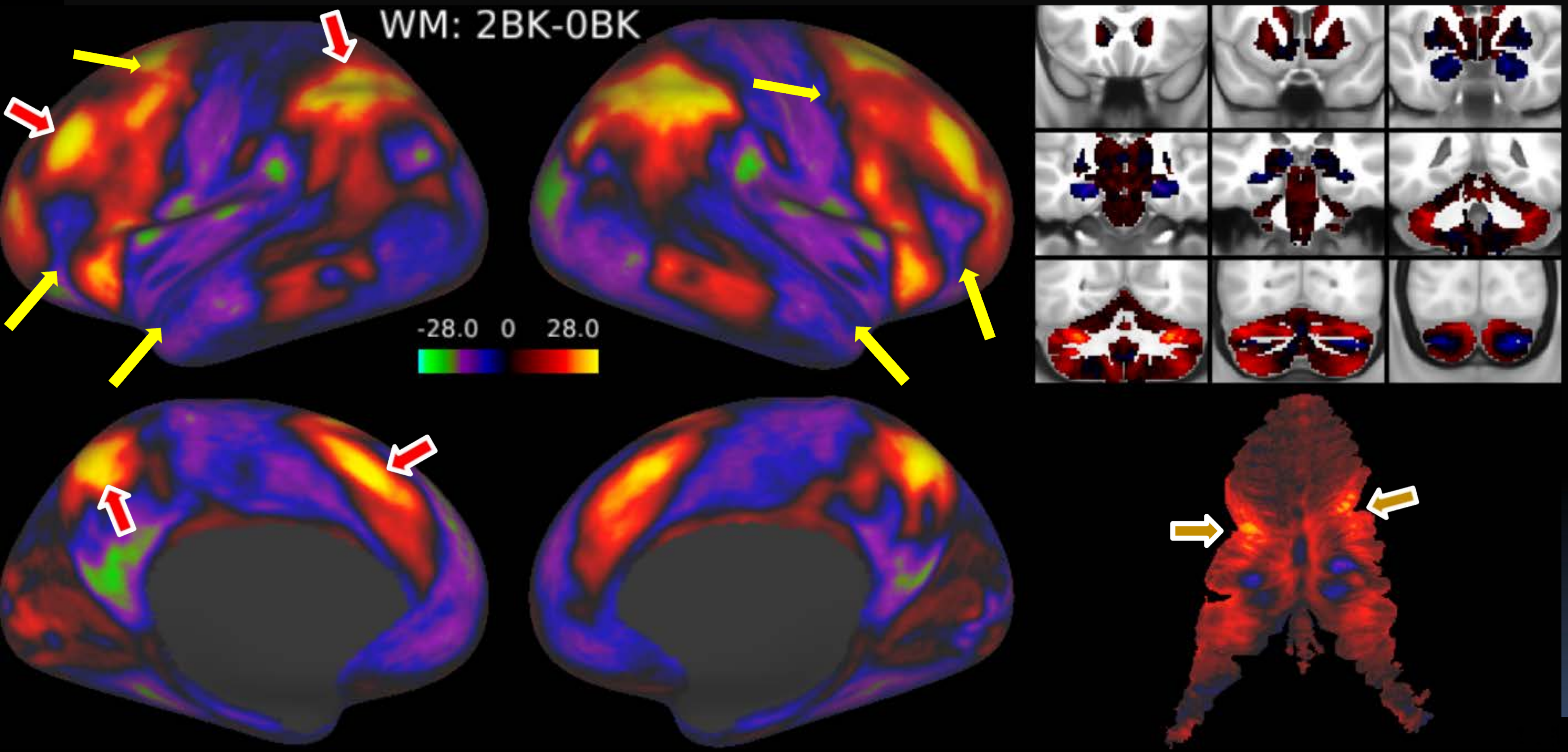






‘Social interaction’ vs. random: overlap (prefrontal) + distinct occipito-temporal

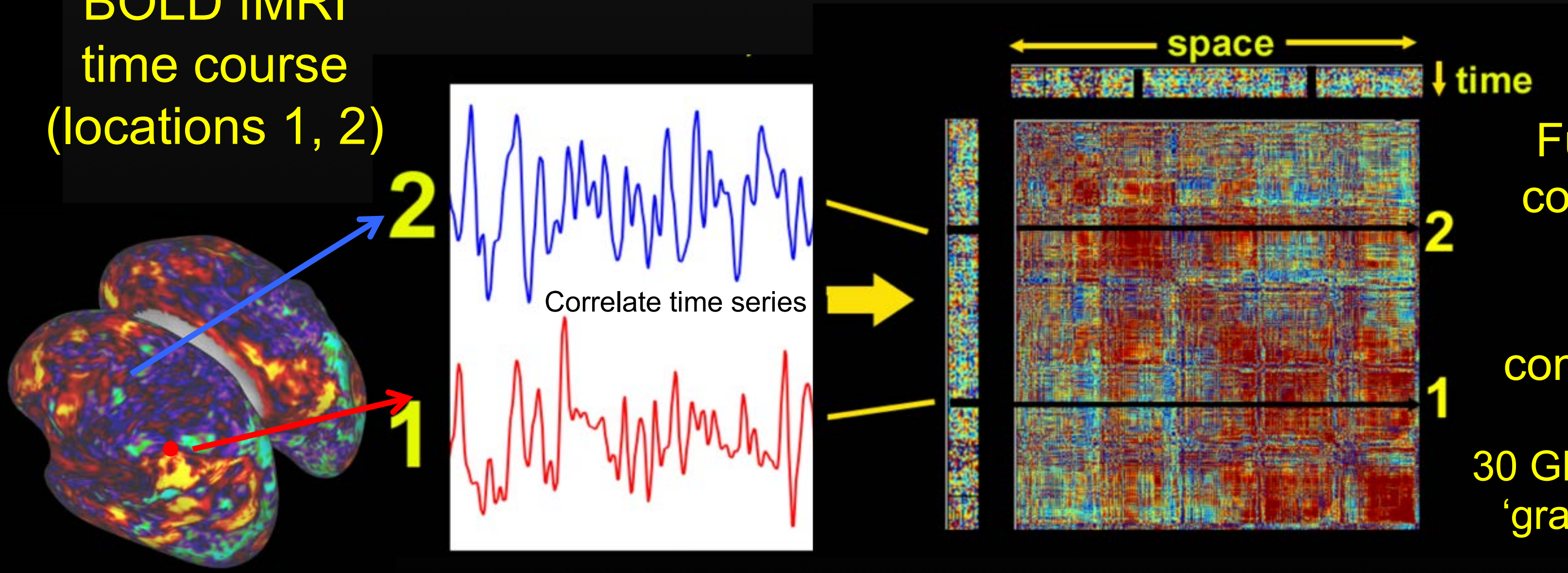
HCP Task-fMRI activations



- Working memory (2-back vs 0-back): prefrontal, cingulate, & cerebellar
- Different tasks engage complex, partially overlapping networks

Functional connectivity from R-fMRI correlations

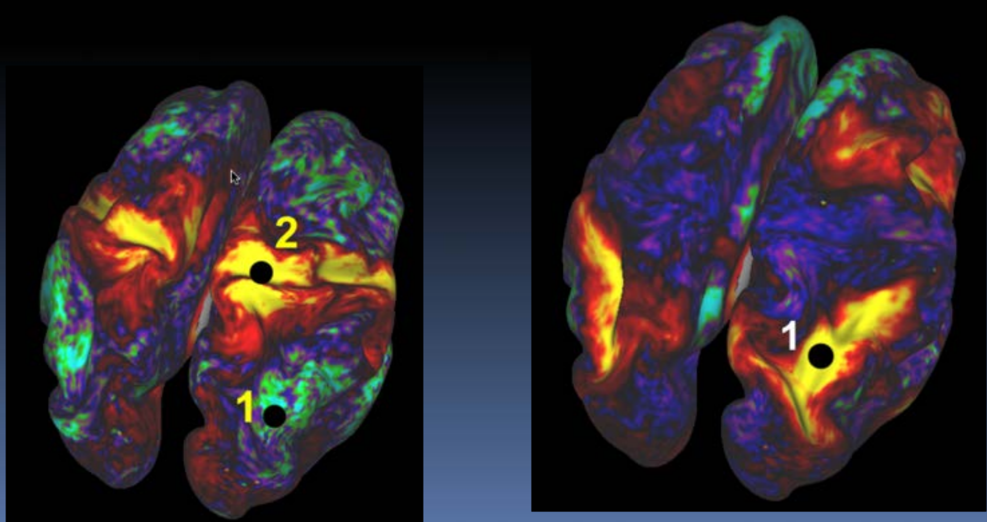
BOLD fMRI
time course
(locations 1, 2)



Functional
connectivity
matrix
('dense
connectome')

30 GB = 90k x 90k
'grayordinates')

Functional
connectivity map
(location 2)



Functional
connectivity map
(location 1)

Correlation

Low High

HCP resting-state networks (RSNs)

Dimensionality reduction is vital: 90k grayordinates -> ~10^2 - 10^3 parcels

Objective: maximize within-parcel consistency

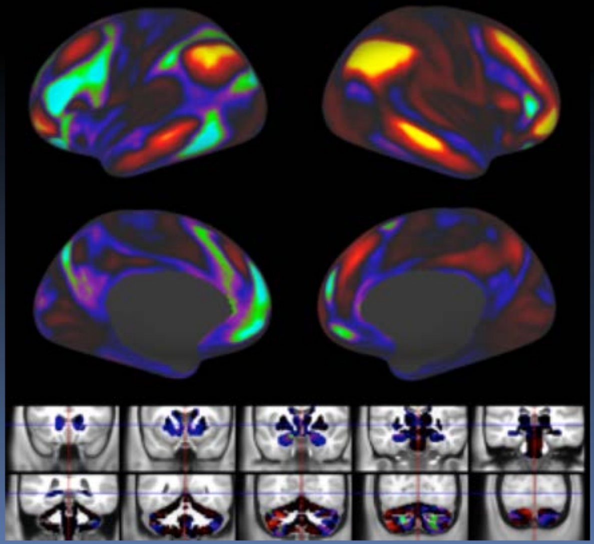
Johansen-Berg et al. (2004); Cohen et al., (2008)

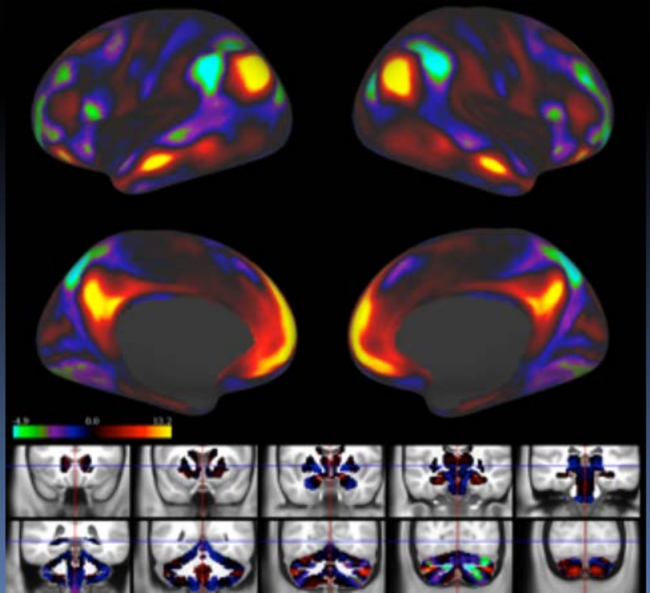
Independent Components Analysis (ICA) [Smith, Beckmann et al.]

- Spatial ICA maps (group average)
  - 'soft' (fuzzy) parcellation ('nodes')
  - Non-contiguous parcels (networks & sub-networks)

Steve Smith

Node #5
Fronto-Parietal





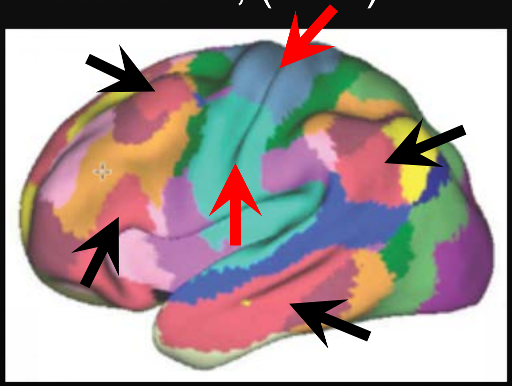
Node #2
Task-negative

Non-HCP advances in parcellation, network analyses

"Hard" RSN parcellations

- ICA or other clustering methods
- Topologically discontinous nodes
- Splitting of somato-motor strip
  upper vs lower body
  consistent with connectivity in macaque
  But not separate areas by architectonic and topography criteria

Yeo et al., (2011)



Parcellations having topological contiguity:

- Watershed by flooding from local minima
- Issues – incomplete coverage
- Many asymmetries; are they real and robust?
- Many other methods, parcellations

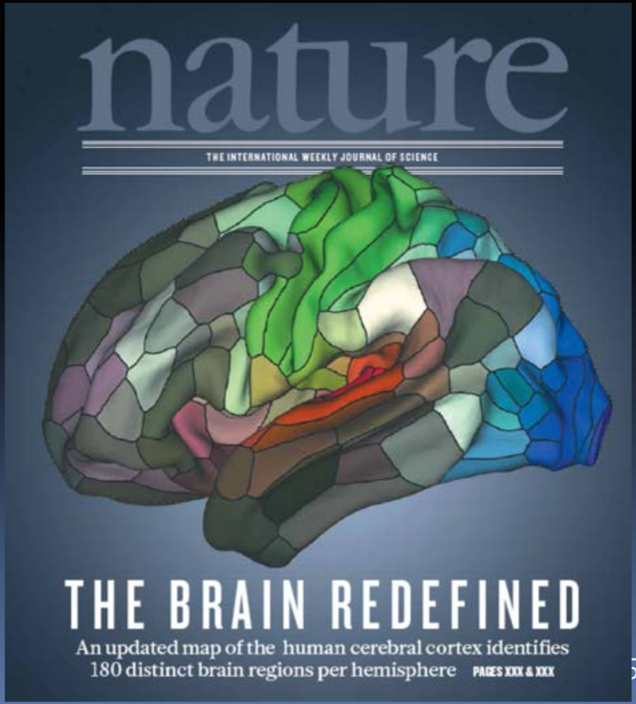
Gordon et al. (2014)

HCP advances in parcellation

Needed: Even better parcellations

- Requires a multimodal approach
- Reflect architectonics, topography, connectivity, function
- Parcellate individuals as well as group averages
- Stay tuned for the HCP_MMP1.0 parcellation!

Glasser, Coalson, Robinson, Hacker, Harwell, Yacoub, Ugurbil, Andersson, Beckmann, Jenkinson, Smith, and Van Essen (2016) A multi-modal parcellation of human cerebral cortex (Nature, doi: 10.1038/nature18933)

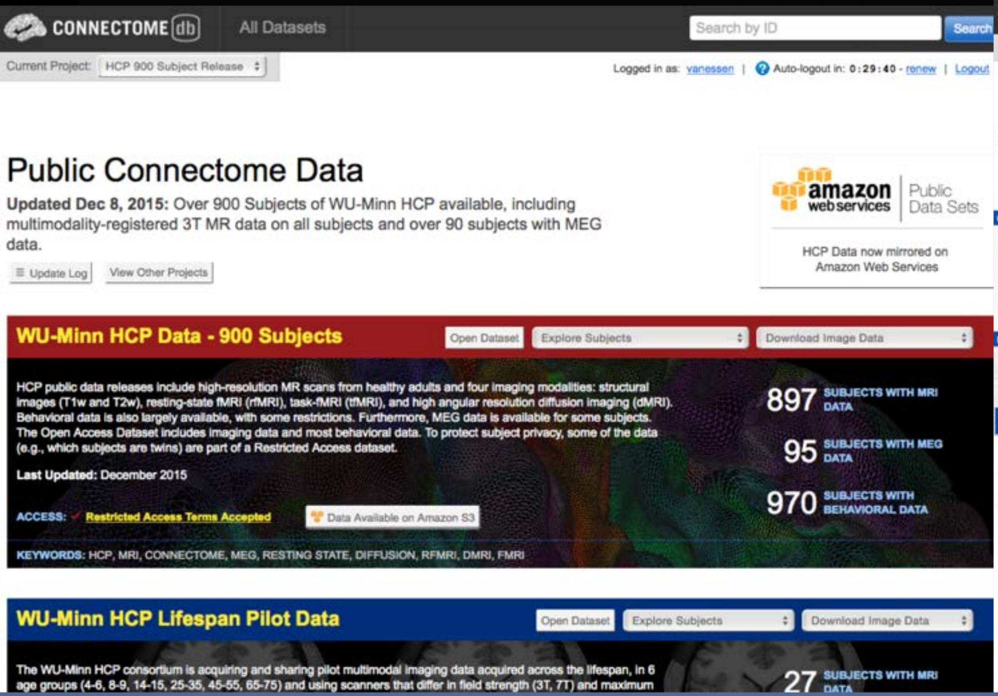


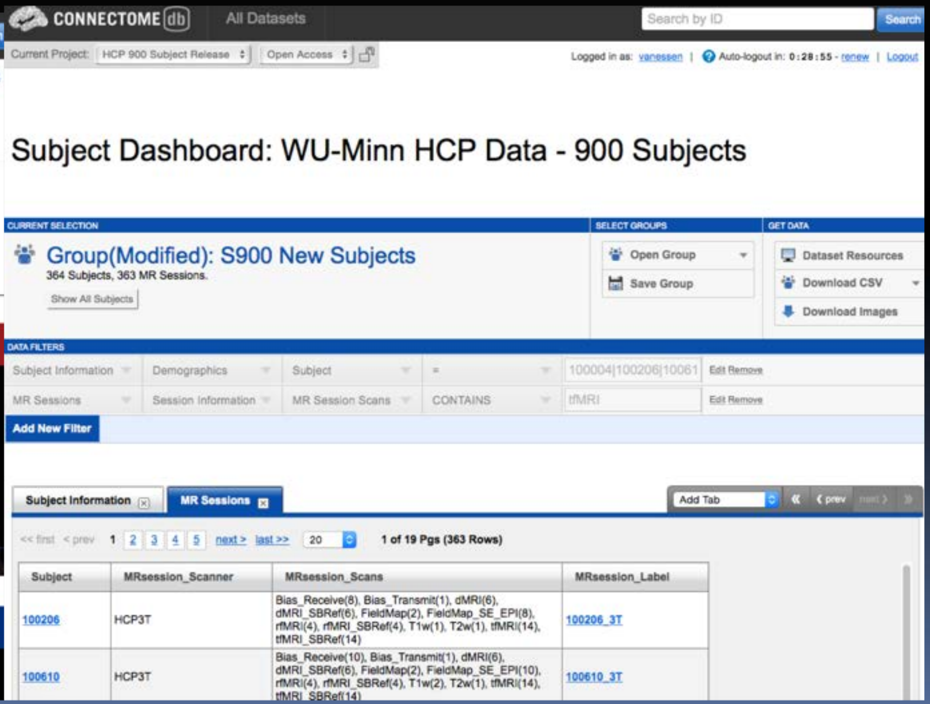
HCP-style Data Sharing - I

Dan Marcus

ConnectomeDB database

- Unprocessed data
- Minimally preprocessed data (+FIX denoised rfMRI data)
- User-friendly search capabilities
- Some group average data, but study-specific data needs a different home

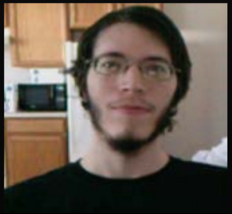




HCP-style Data Sharing - II

- “Scene files” in Connectome Workbench preserve what’s needed to replicate published figures – including “annotations”!
  - e.g., 42 figures (scenes) in Glasser et al. (Nature, 2016 + supplements)
- Upload scene files + associated data into BALSA (https://balsa.wustl.edu)
- URLs in figure legend links to scene in BALSA (e.g., https://balsa.wustl.edu/Qv4P)
- Freely downloadable for visualization and analysis


John Harwell


Tim Coalson


John Smith

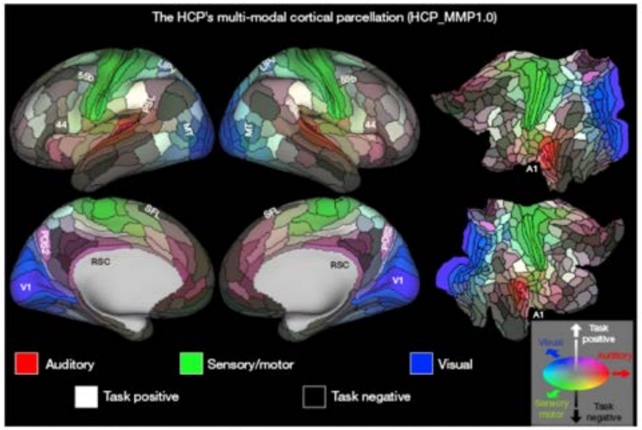
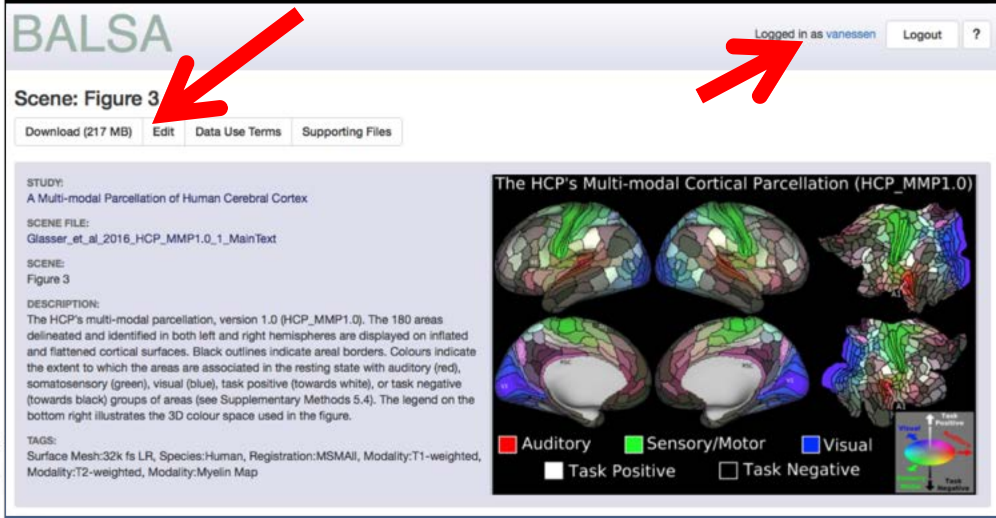


Figure 3 | The HCP's multi-modal parcellation, version 1.0 (HCP_MMP1.0). The 180 areas delineated and identified in both left and right hemispheres are displayed on inflated and flattened cortical surfaces. Black outlines indicate areal borders. Colours indicate the extent to which the areas are associated in the resting state with auditory (red), somatosensory (green), visual (blue), task positive (towards white), or task negative (towards black) groups of areas (see Supplementary Methods 5.4). The legend on the bottom right illustrates the 3D colour space used in the figure. Data at http://balsa.wustl.edu/WN56.



Lifespan Connectome Projects

- Young Adult HCP (2010 – 2016)
  - 1200 healthy adults (ages 22 – 35) - WashU, UMinn, Oxford
- Lifespan HCP Aging Project (2016 – 2020)
  - 1200 older adults (ages 36 – 100+) - WashU, UMinn, UCLA, MGH
- Lifespan HCP Development Project (2016 – 2020)
  - 1300 children (ages 5 – 21) - WashU, UMinn, UCLA, Harvard
- 14 “Disease Connectome” projects
- “Baby Connectome Project” (ages 0 – 5)
- Developing Human Connectome Project (prenatal – neonatal; UK)
- Data sharing via the Connectome Coordination Facility (CCF) & NIMH Data Archive (NDA)
- What will we learn from these projects? An immense amount!!

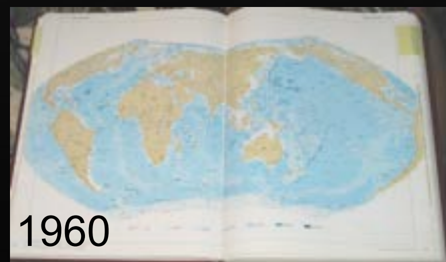
Revolutions in Cartography

EARTH

Classical maps

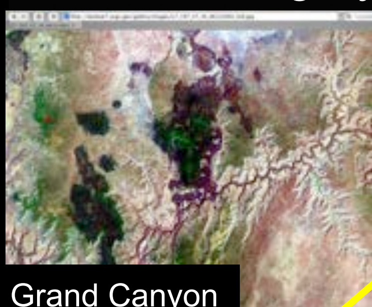
1630

Book atlases



1960

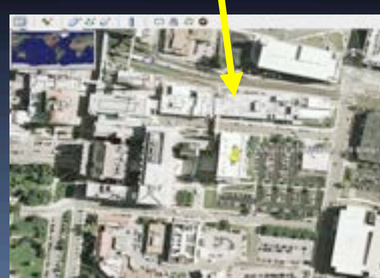
Satellite imagery



Grand Canyon

Google Earth

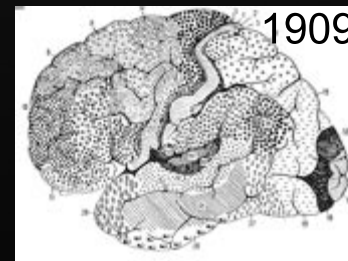
University of Minnesota



Washington University

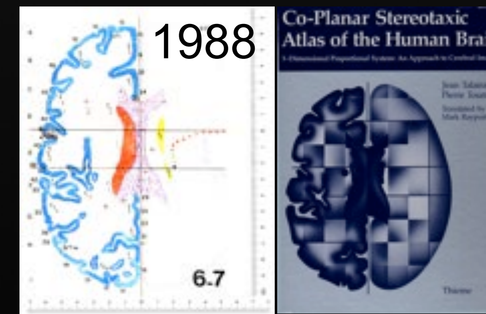
BRAIN

Classical maps



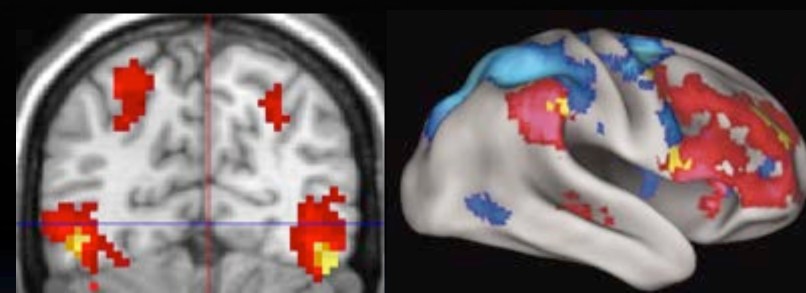
1909

Talairach atlas



1988

~2005: MRI; volumes + surfaces



2016 and beyond: Connectomics