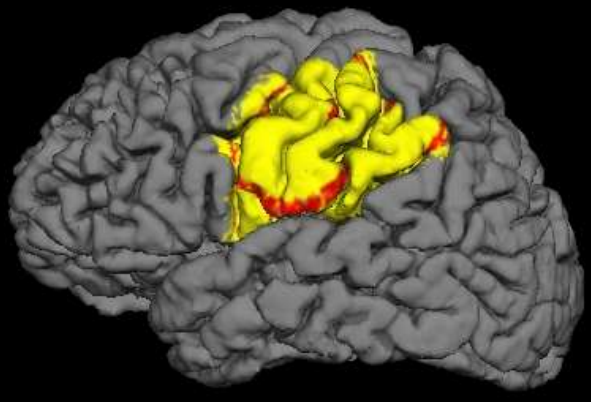
FreeSurfer Introduction

Outline

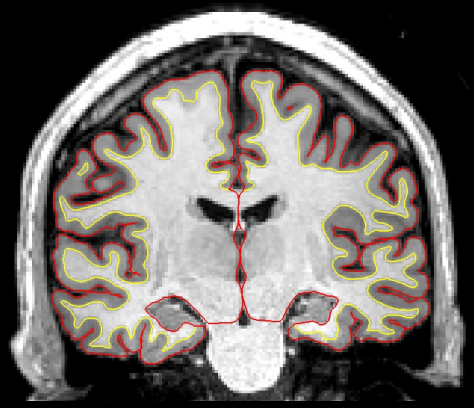
- Cortical surface model
- Surface-based analysis
- Surface-based Inter-subject Registration
- Multi-modal integration
- Volume too
- Course geared toward Data ->Publication

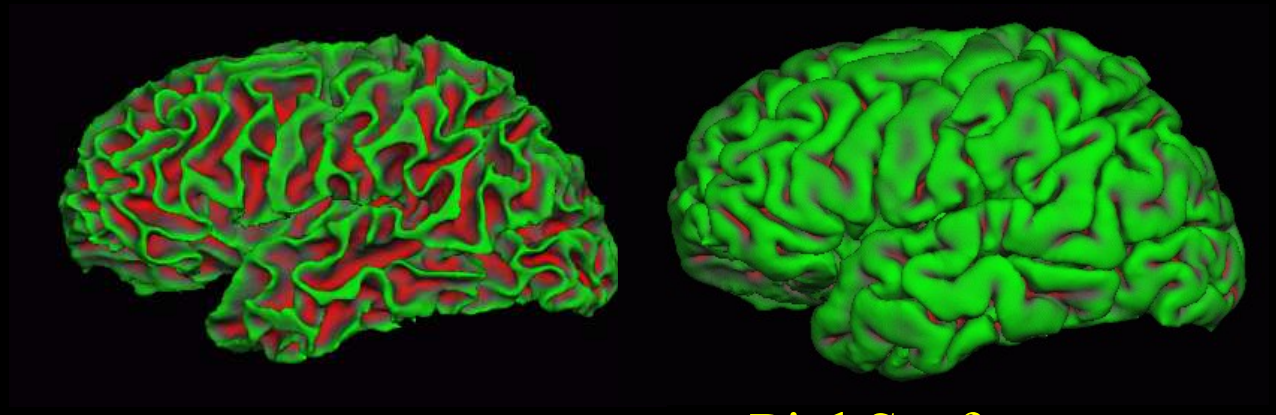
Use FreeSurfer



Cortex and Surface-based Analysis

Cortex is a 2D Surface Folded in 3D space



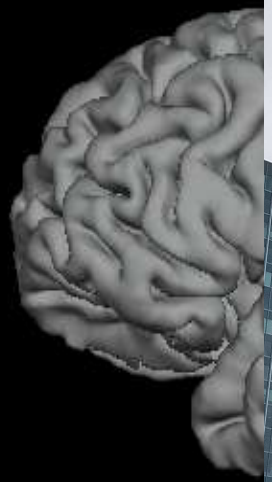


White Surface

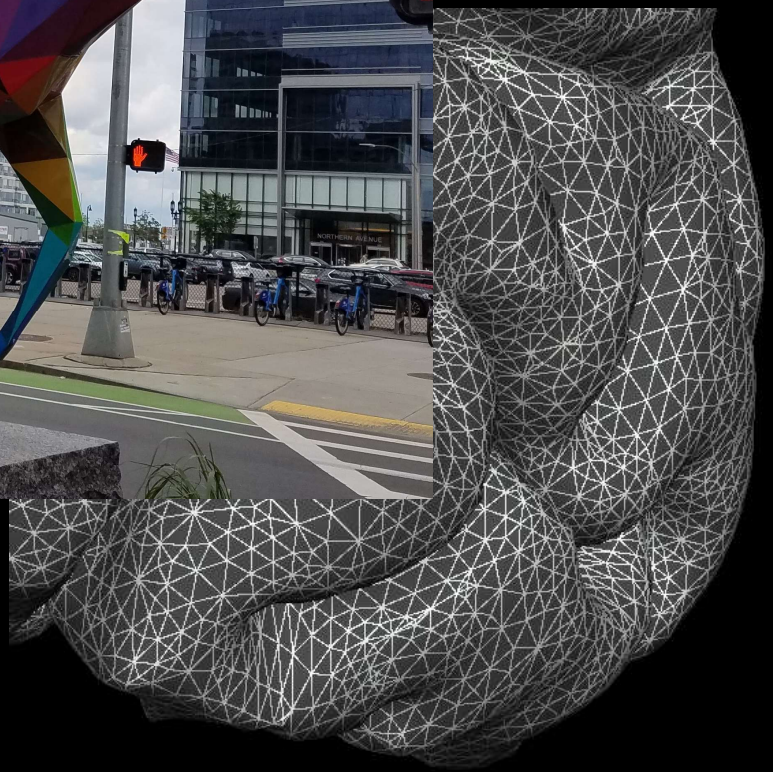
Pial Surface

FreeSurfer
https://surfer.nmr.mgh.harvard.edu

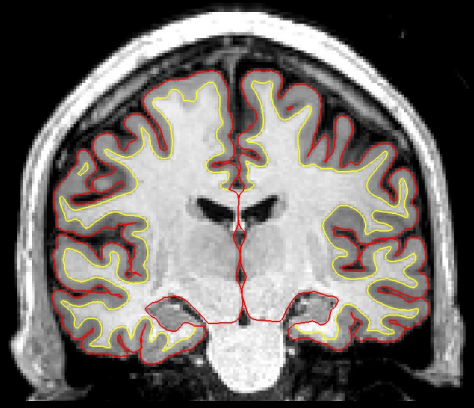
Triangular Mesh Surface Model

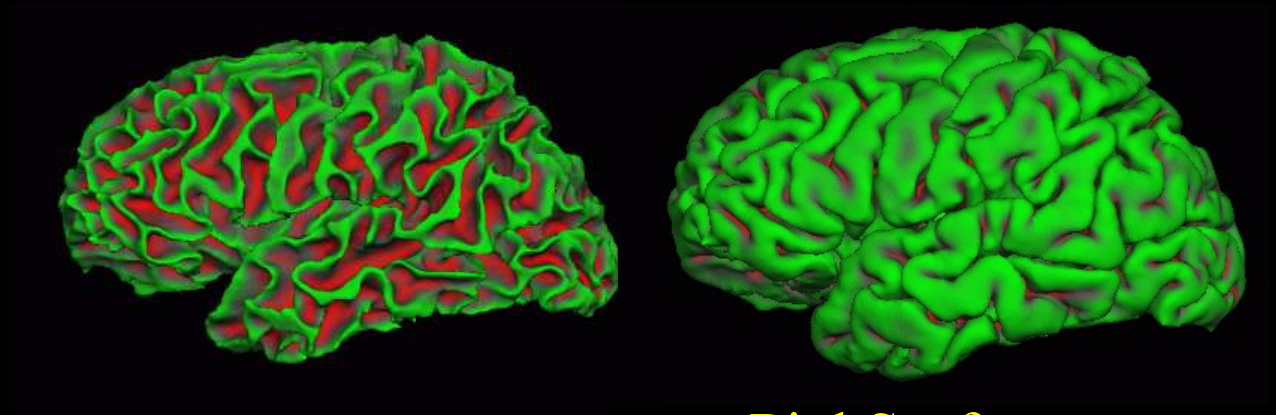


Okuda San Miguel



Cortex is a 2D Surface Folded in 3D space

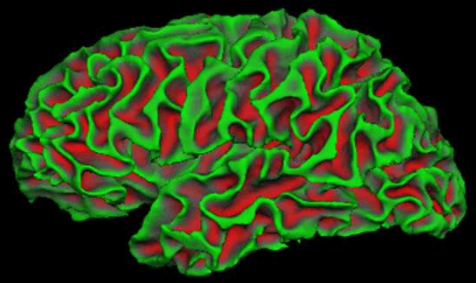




White Surface

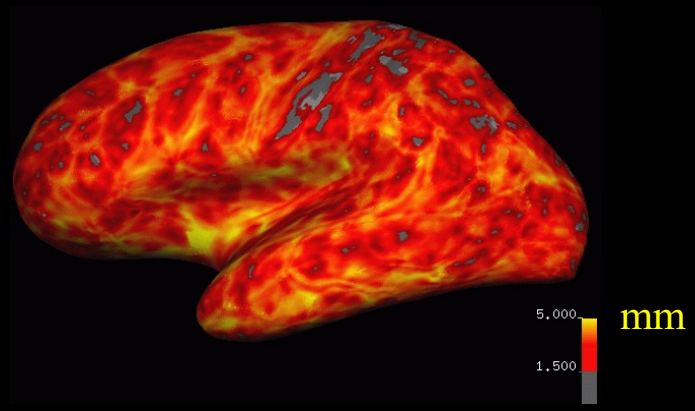
Pial Surface

FreeSurfer
https://surfer.nmr.mgh.harvard.edu



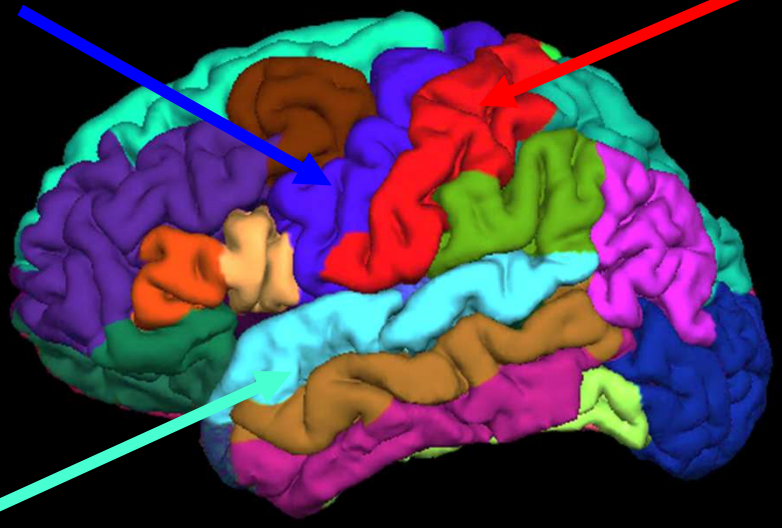
Cortical Thickness

- Distance between white and pial surfaces
- One value per vertex
- Surface-based more accurate than volume-based



"Overlay", "Heat map"

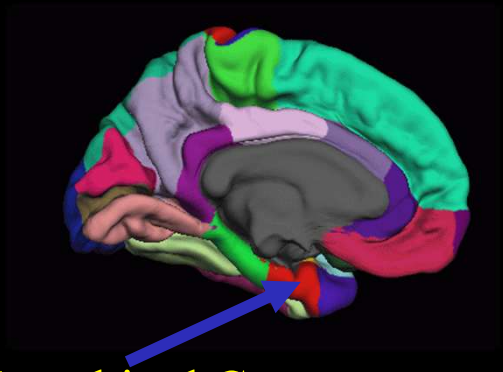
Automatic Surface Parcellation: Desikan/Killiany Atlas (35 ROI's)



subject → label → lh.aparc.annot

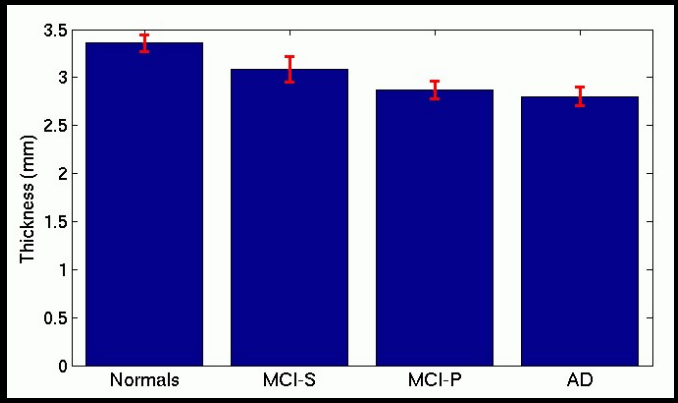
An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest, Desikan, R.S., F. Segonne, B. Fischl, B.T. Quinn, B.C. Dickerson, D. Blacker, R.L. Buckner, A.M. Dale, R.P. Maguire, B.T. Hyman, M.S. Albert, and R.J. Killiany, (2006). NeuroImage 31(3):968-80.

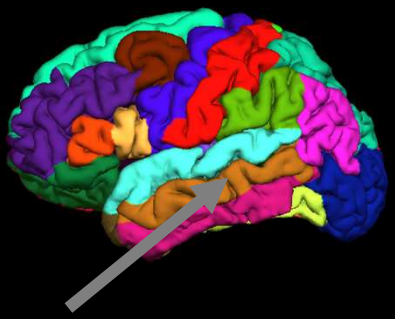
Thickness and Area ROI Studies



Entorhinal Cortex

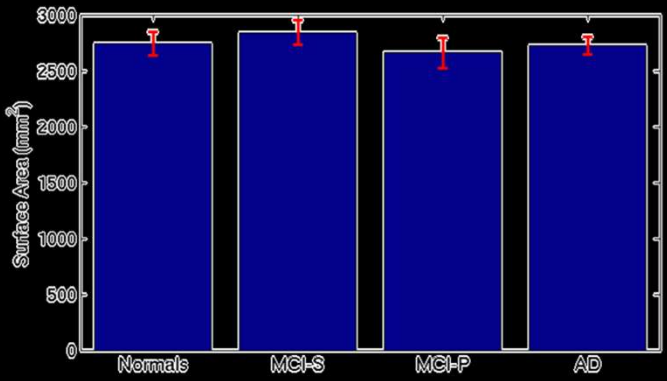
Thickness of Entorhinal Cortex





Middle Temporal Gyrus

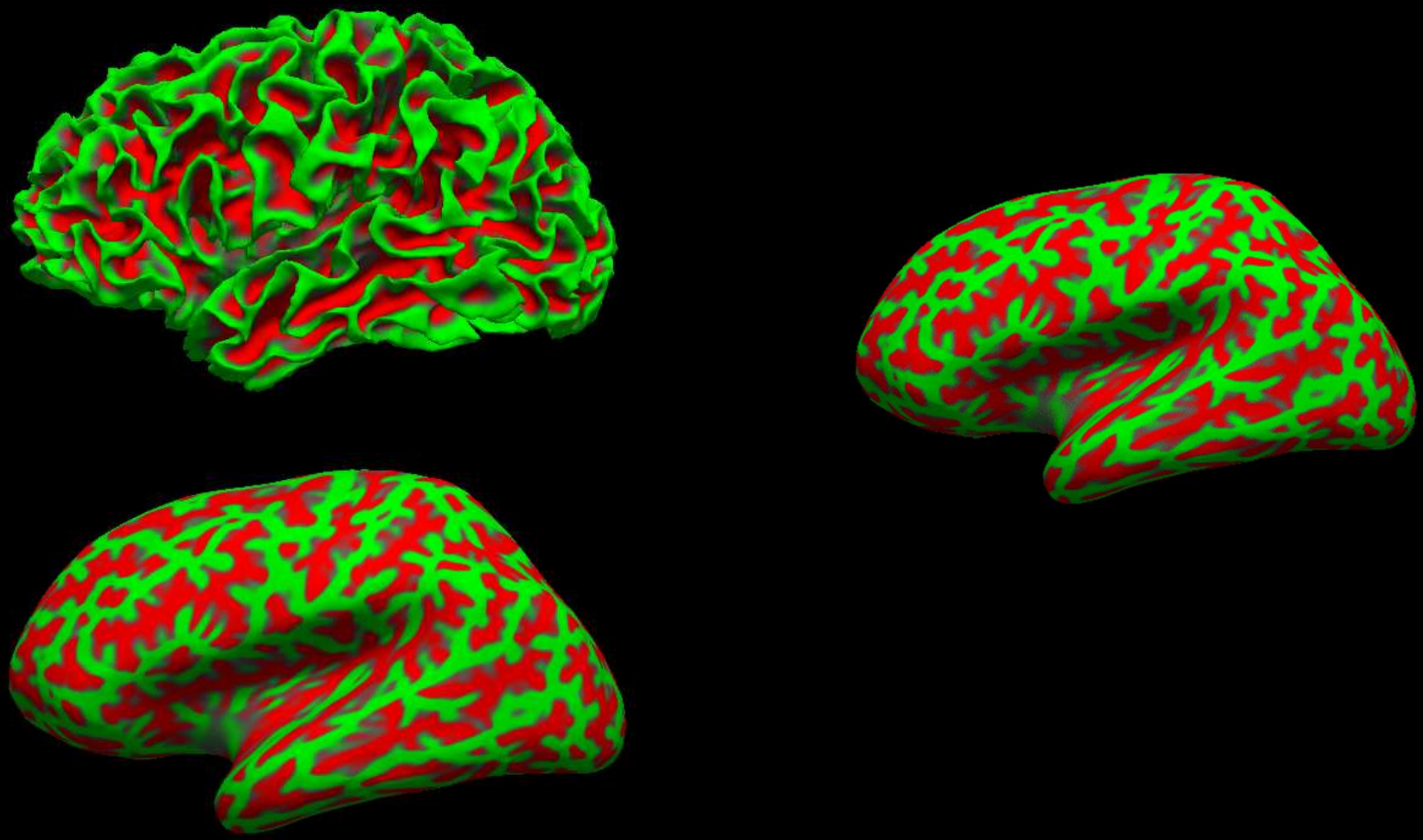
Surface Area of MTG



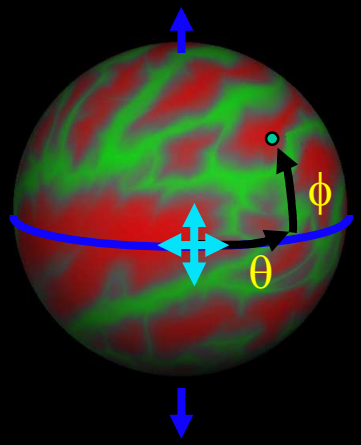
Gray matter volume also possible

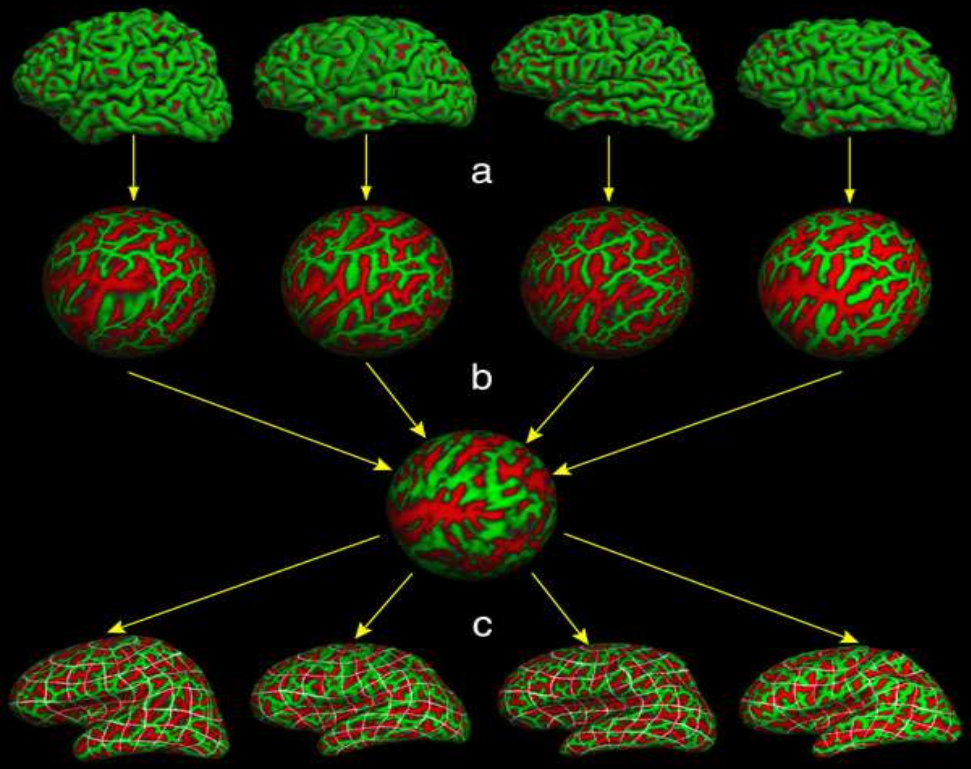
Surface-based Intersubject Registration And Group Analysis

Spherical Inflation



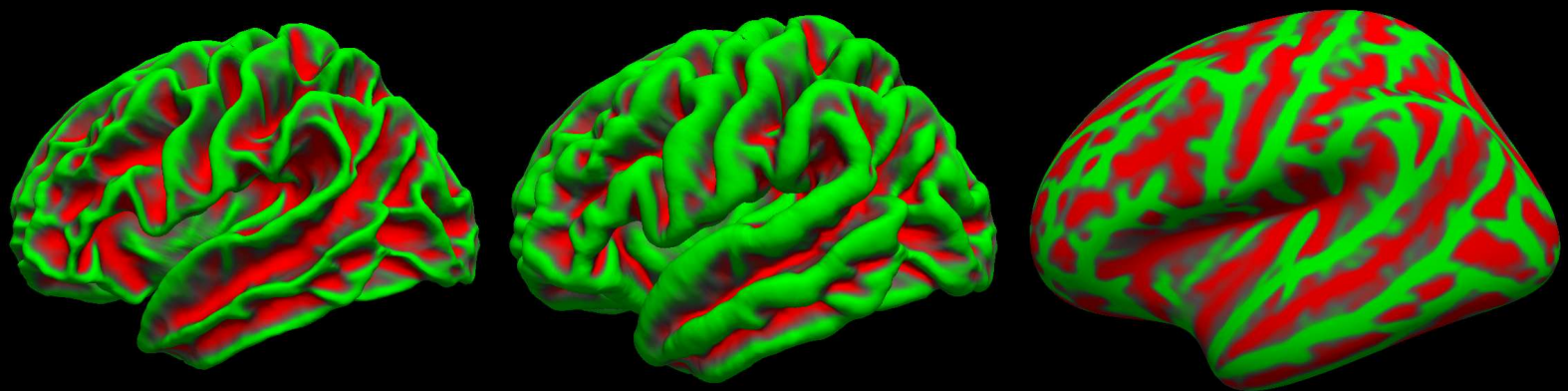
A Surface-Based Spherical Coordinate System

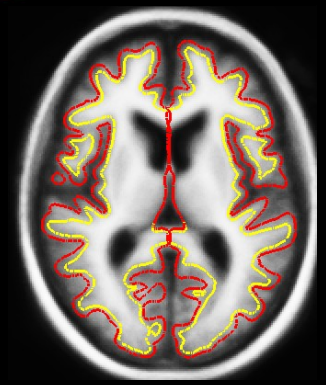




Common space for group analysis (like Talairach)

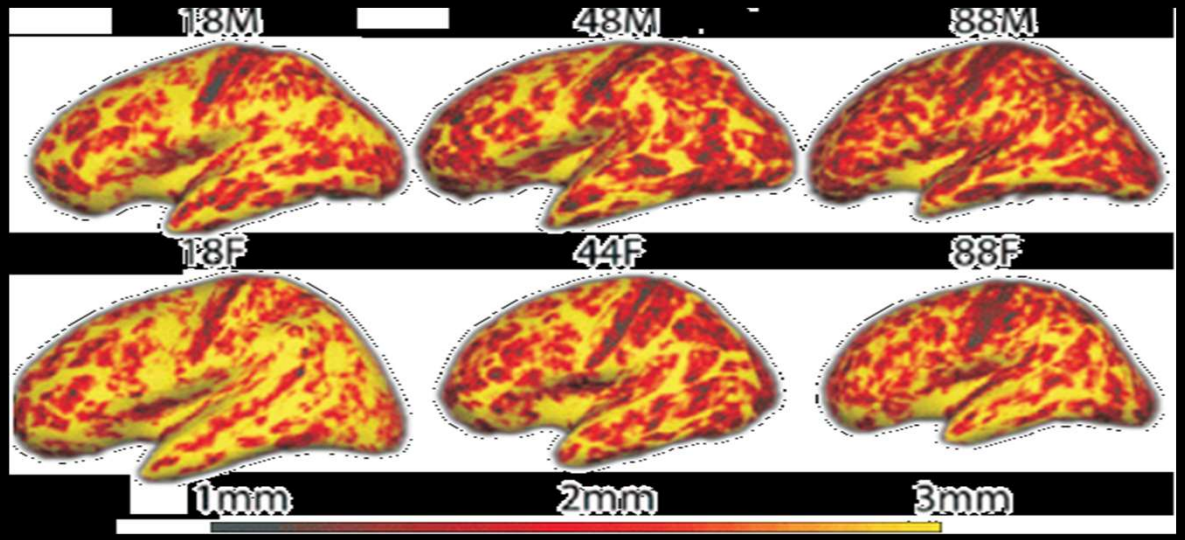
fsaverage Space





- Default registration space
- Like the MNI152 but for surfaces

Aging Exploratory Analysis

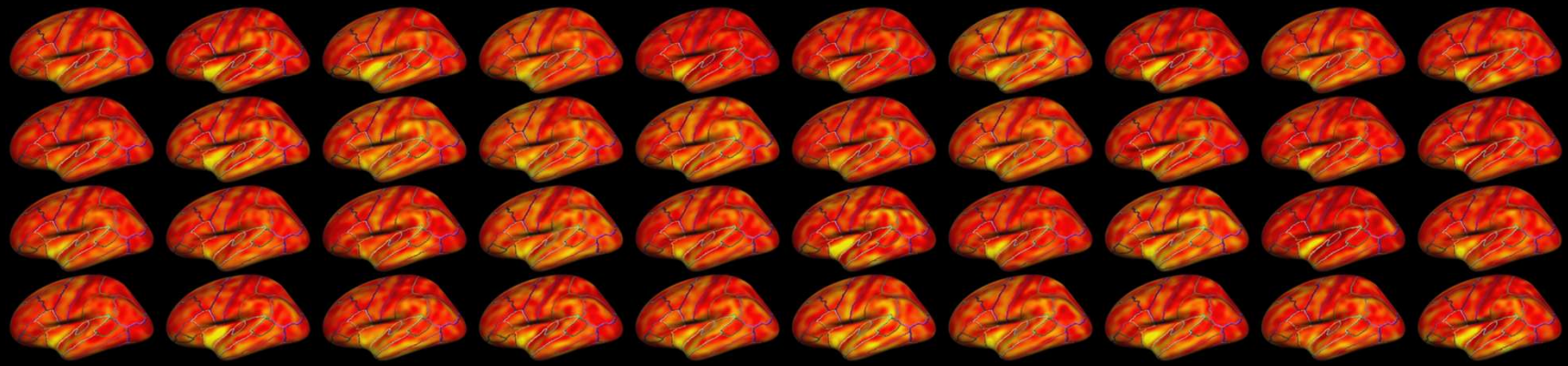


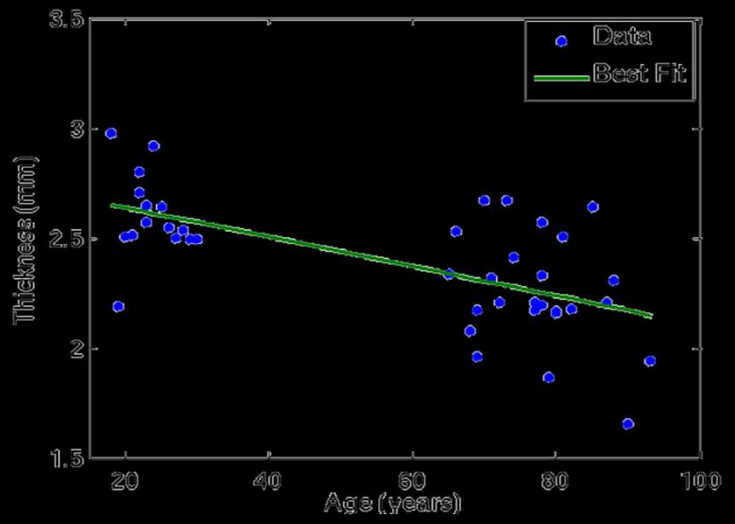
In which areas does thickness
Change with age?

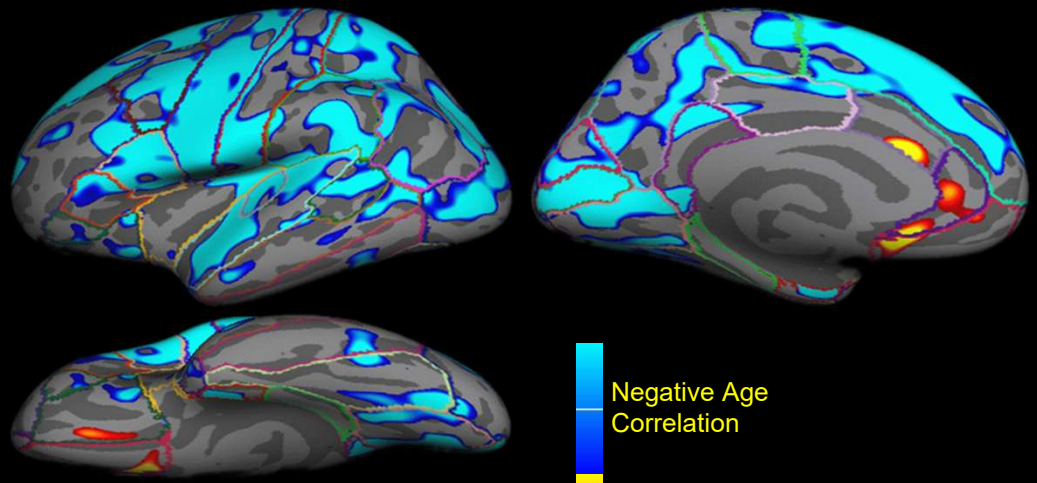
Cortical Thickness vs Aging
Salat et al, 2004, Cerebral Cortex

Aging Thickness Study

N=40 (all in fsaverage space)







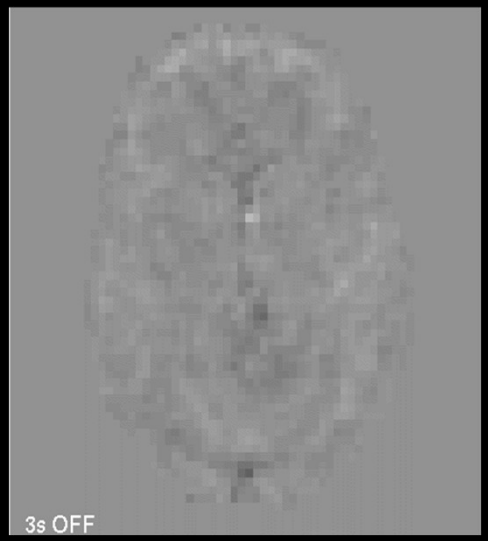
p<.01

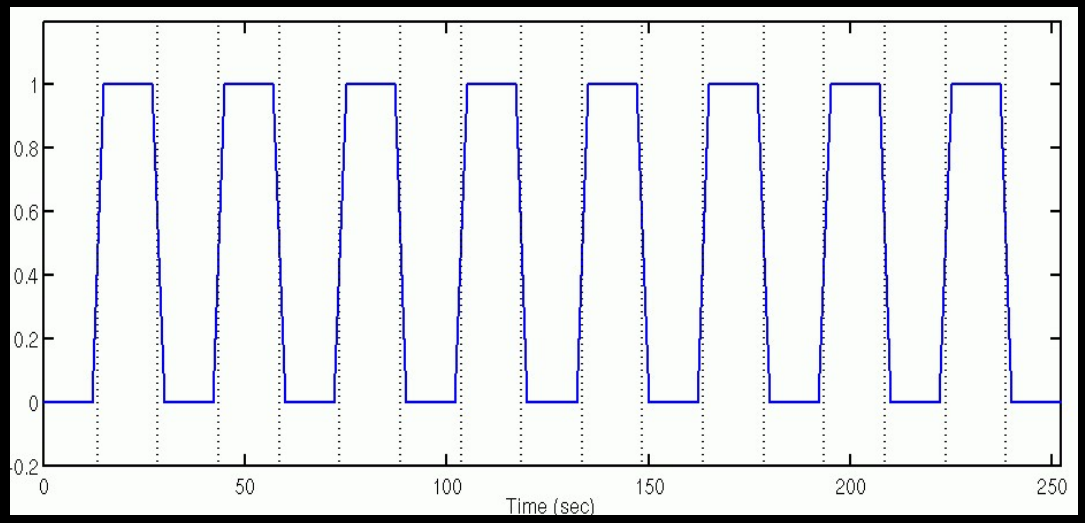
Negative Age Correlation

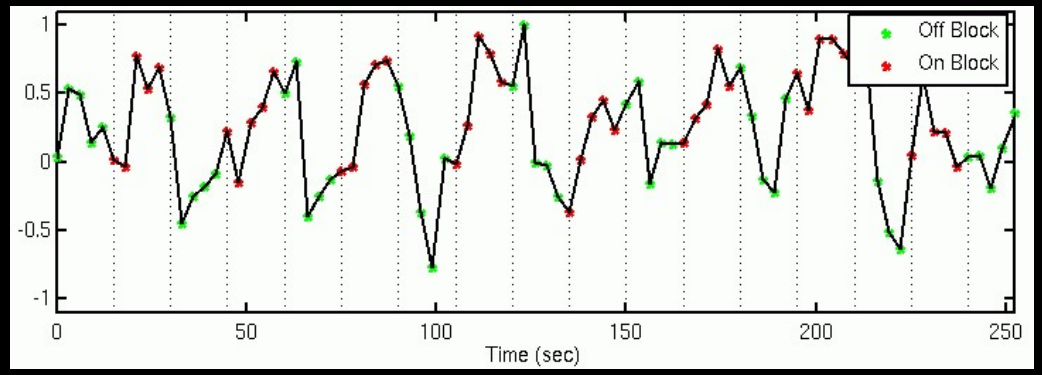
Positive Age Correlation

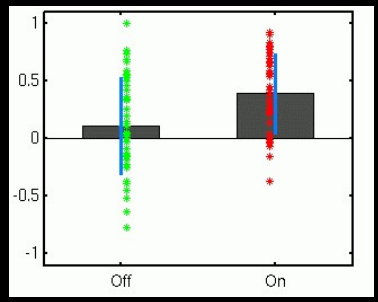
Surface-based Multimodal Integration

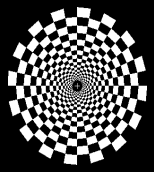
Visual/Auditory/Motor Activation Paradigm







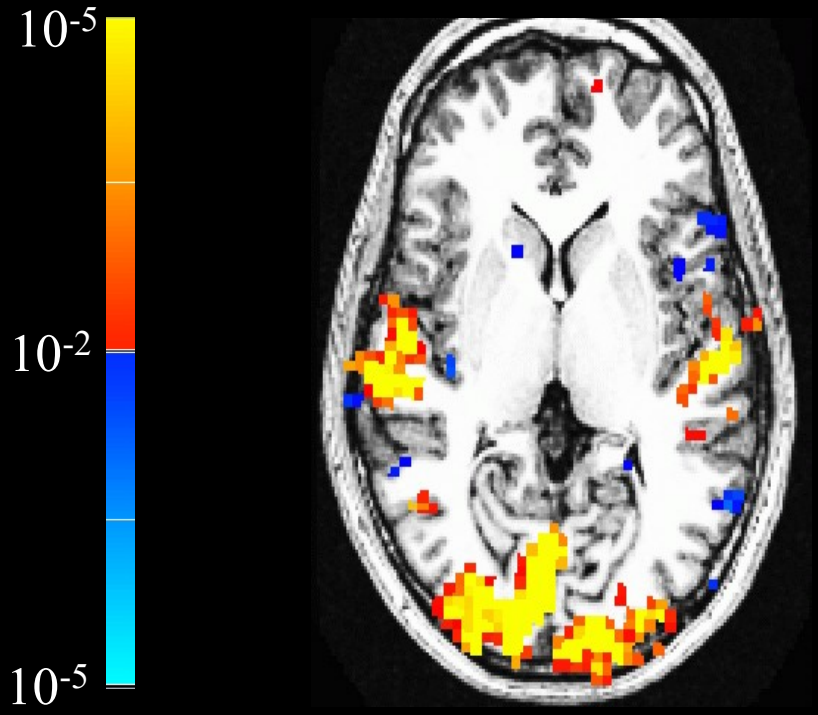




15 sec 'ON', 15 sec 'OFF'

- **Flickering Checkerboard**
- **Auditory Tone**
- **Finger Tapping**

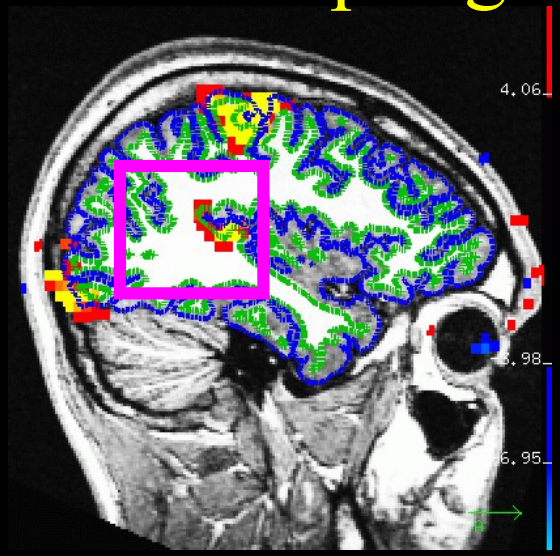
On-vs-Off

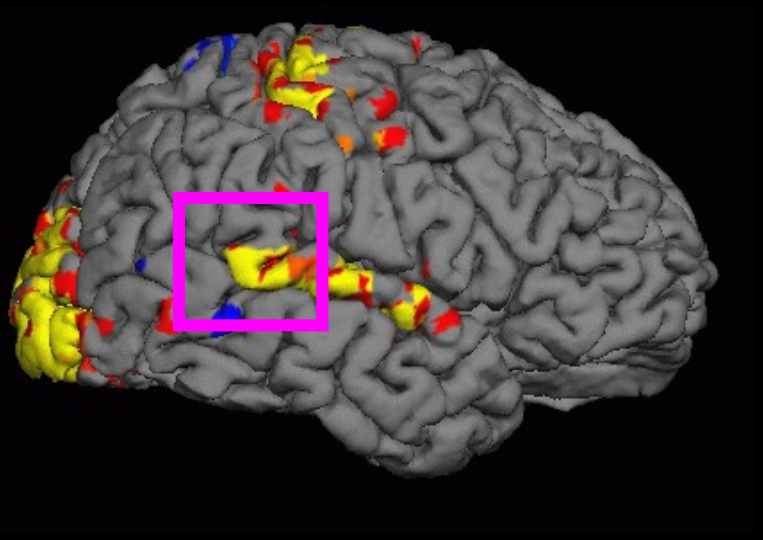


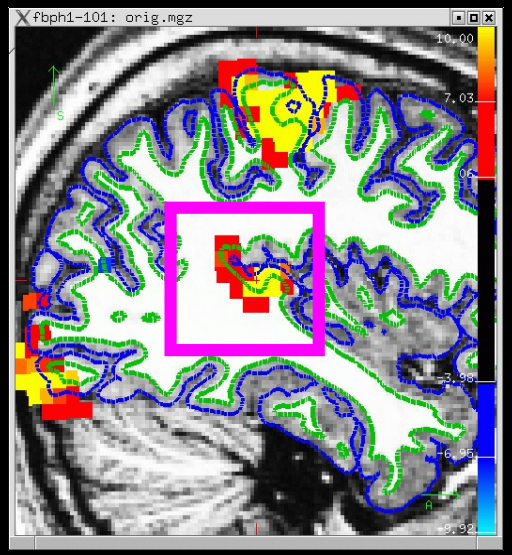
Significance Map
(Thresholded p<.01)

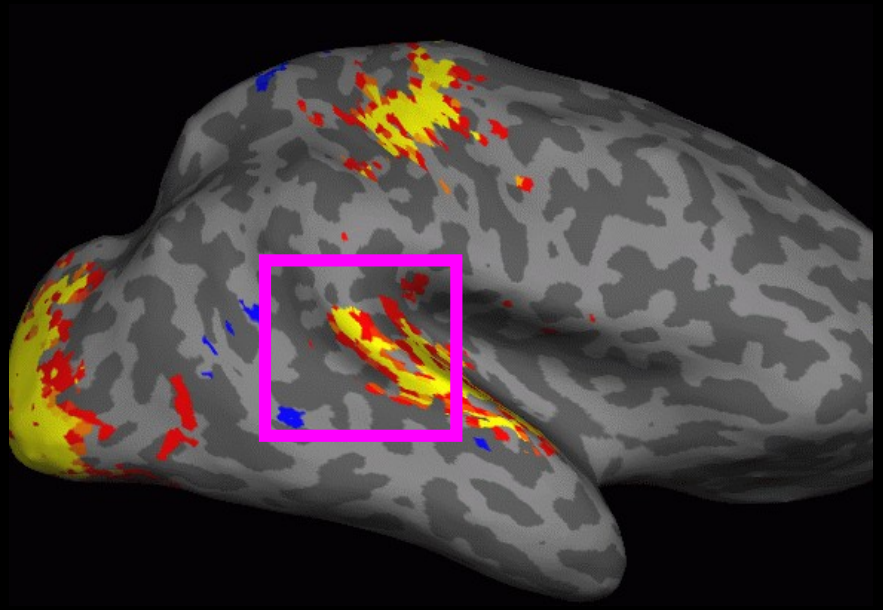
15 sec ‘ON’, 15 sec ‘OFF’
- Flickering Checkerboard
- Auditory Tone
- Finger Tapping

Sampling on the Surface



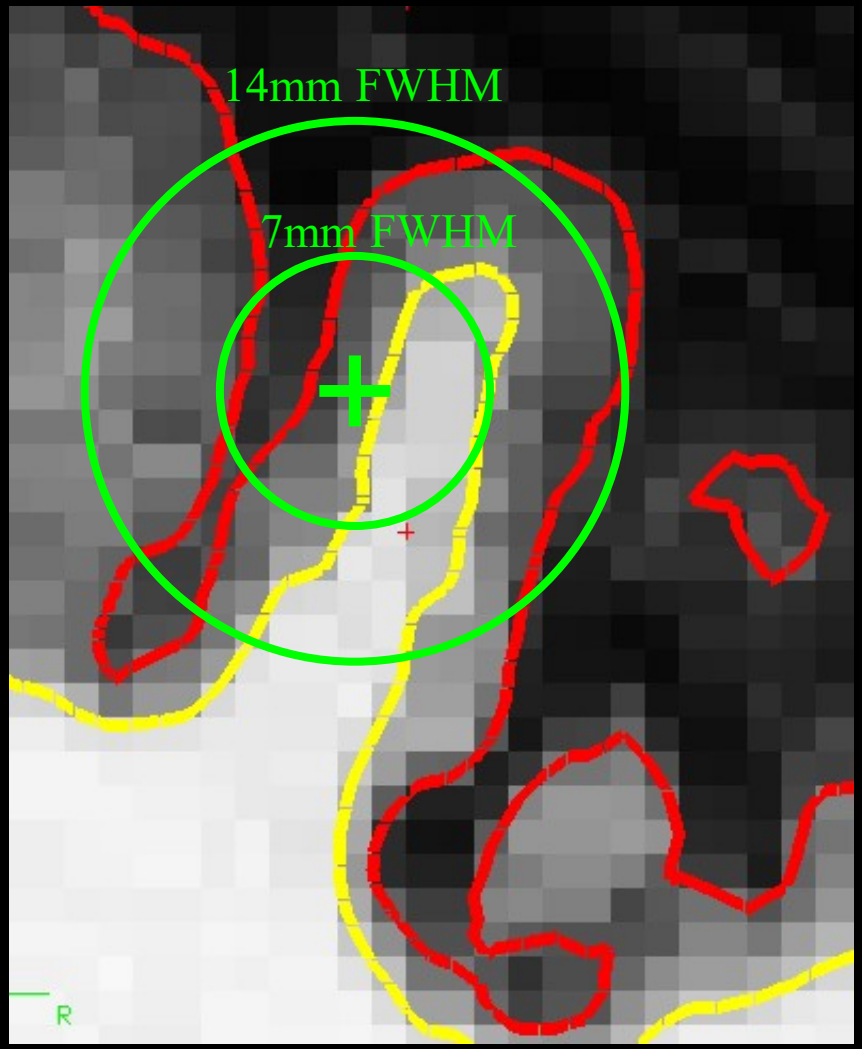






Surface-based Spatial Smoothing

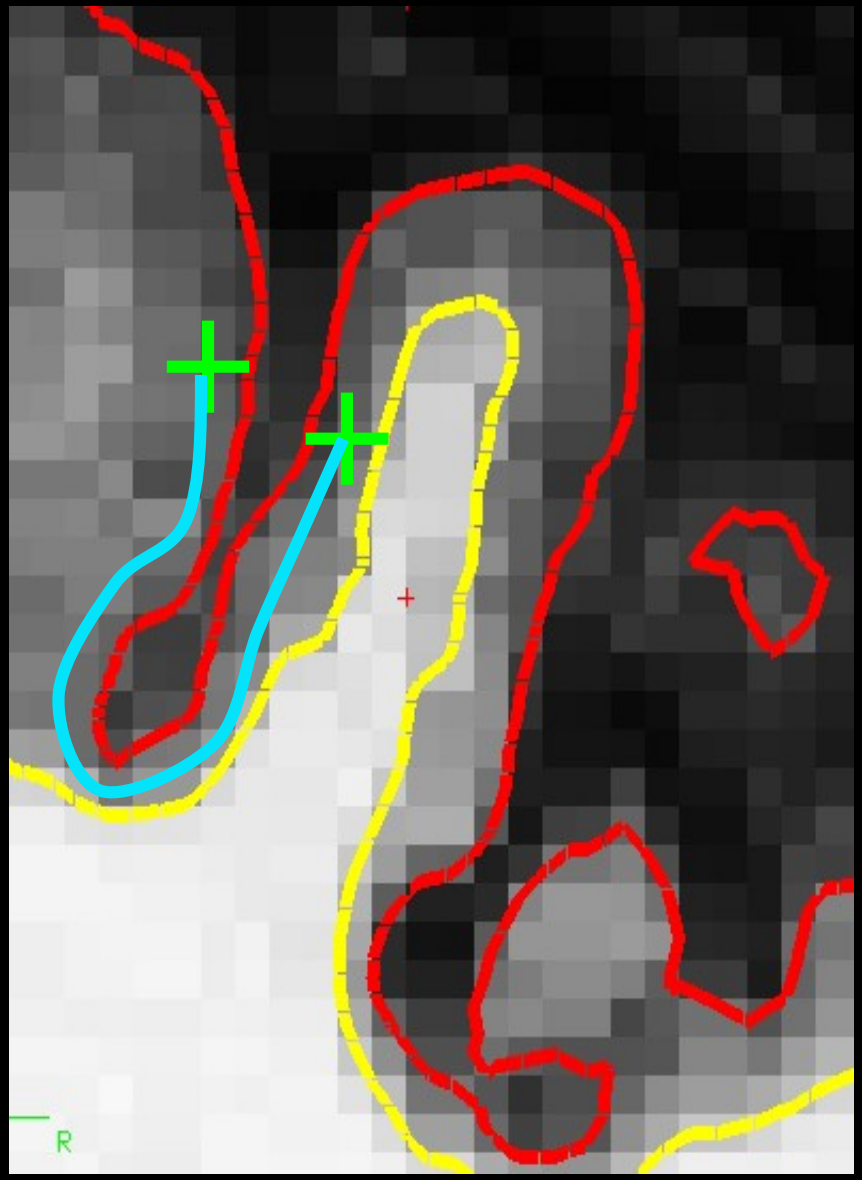
Volume-based Smoothing



- Smoothing is averaging of "nearby" voxels
- Mixing of tissue types
- Jumping across sulci

*

Surface-based Smoothing

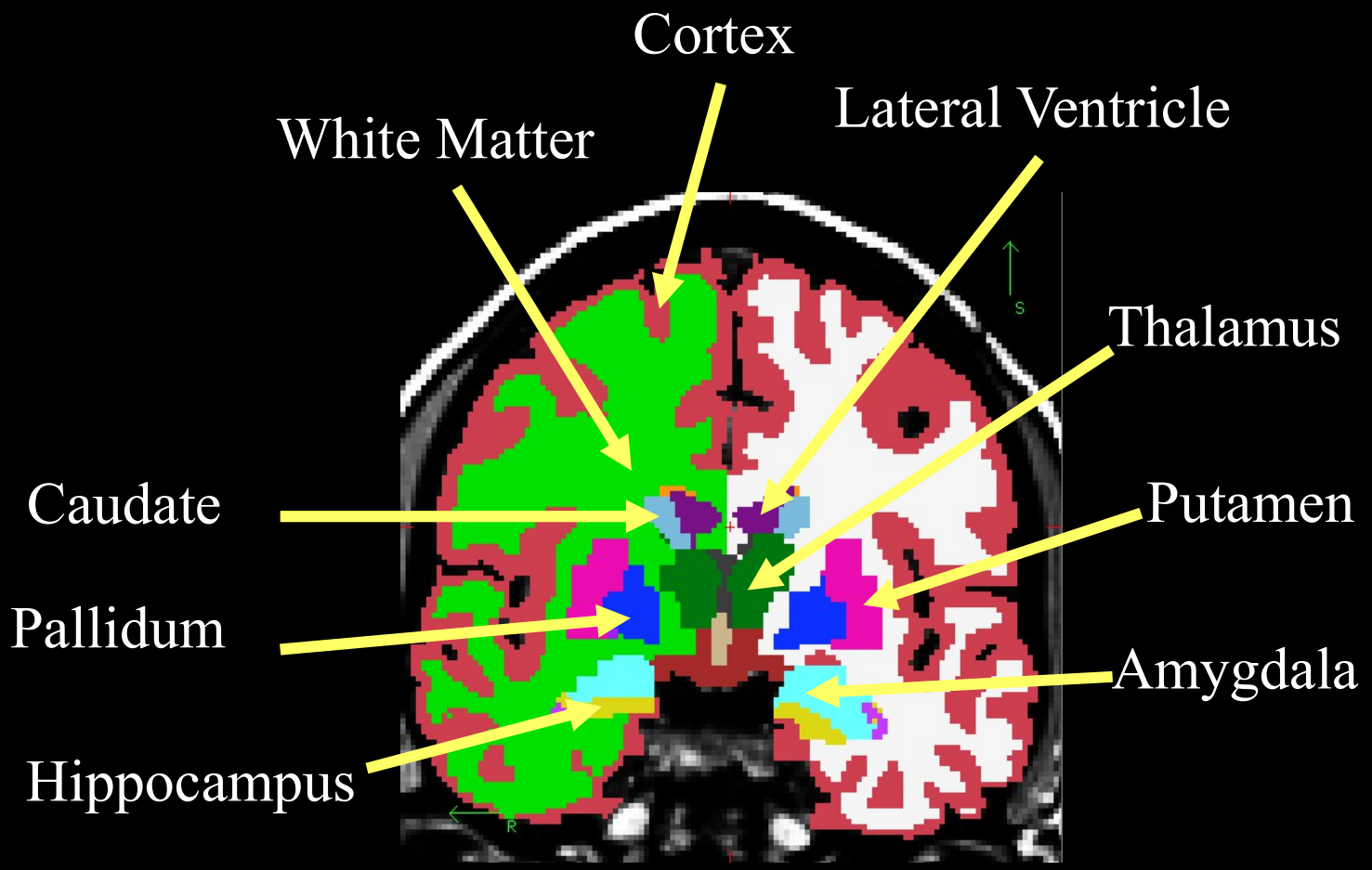


- Smooth along the surface but not normal to it.

Volume Analysis: Automatic Individualized Segmentation

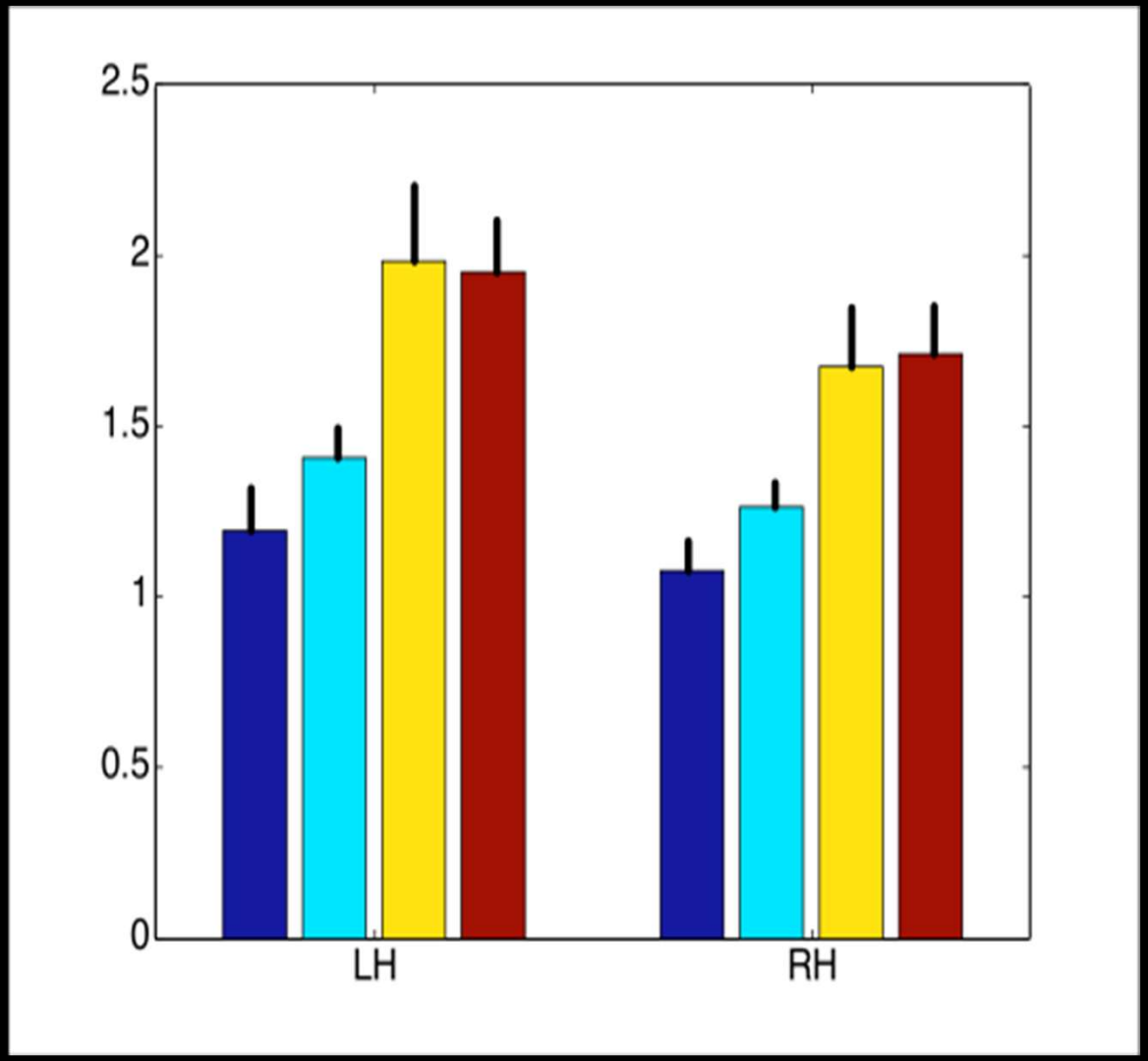
Surface-based coordinate system/registration appropriate for cortex but not for thalamus, ventricular system, basal ganglia, etc…

Volumetric Segmentation (aseg)



Not Shown: Nucleus Accumbens

Volume Differences Predictive of AD



Lateral Ventricular Volume (Percent of Brain)

Healthy
Did NOT convert
Did convert
Probable AD

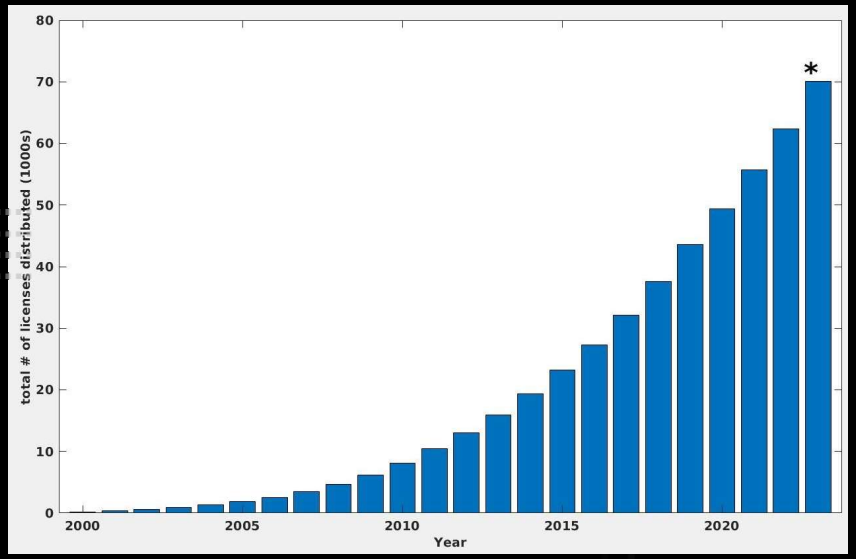
Data courtesy of Drs Marilyn Albert and Ron Killiany

Other Stuff

- Longitudinal Analysis
- fMRI Analysis (FS-FAST)
- PET Analysis (PETsurfer)
- Diffusion Analysis (TRACULA)
- Non-linear volume registration (SynthMorph)
- Skull Stripping (SynthStrip)
- Segmentations
    - Hippocampal and Amygdalar subfields (segmentHA_T1.sh)
    - Thalamic Nuclei (segmentThalamicNuclei.sh)
    - Subcortical limbic (mri_ sclimbic_seg)
    - Pineal and Pituitary (mri_pglands_seg)
    - Claustrum (mri_claustrum_seg)
    - Arousal Nuclei (AANsegment)
    - Brainstem (segmentBS.sh)
- 3rd Party: MNE for EEG and MEG analysis

FreeSurfer Usage

Licenses (free): 90,000 total



- Total # licenses distributed as of June 9, 2023

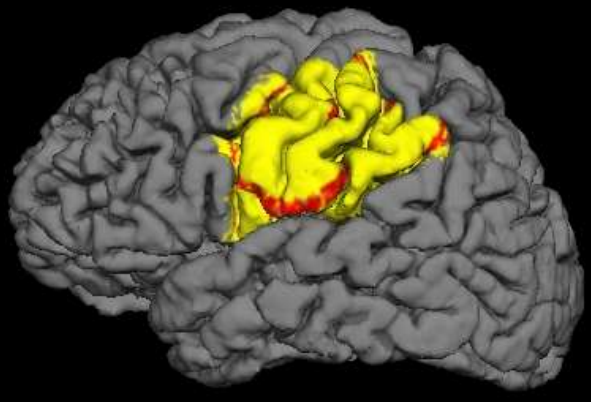
Citations: ~50,000

Table 1: Metrics of FreeSurfer Impact and Significance (Oct 2024) and Change Since 2020		Change
Core FreeSurfer Publications	Total = 51,251 citations	
Cortical Reconstruction I [4]	11668 citations	+65%
Cortical Reconstruction II [5]	6975 citations	+45%
Surface-based Registration [6]	3505 citations	+40%
Cortical Thickness [7]	6498 citations	+54%
Automatic Volume Segmentation [8]	9429 citations	+70%
Automatic Surface Segmentation [9]	4710 citations	+57%
"FreeSurfer" Paper Fischl 2012	8466 citations	+230%
Major Brain Imaging Projects that use FreeSurfer		
Alzheimer's Disease Neuroimaging Initiative (ADNI)	>5000 cases	
Framingham Heart Study (FHS)	>10,000 cases	
Human Connectome Project – Young Adult (HCP-YA)	1200 cases	
Human Connectome Project -- Aging (HCP-A)	>1500 cases	
Human Connectome Project – Children (HCP-C)	>1350 cases	
Superstruct Project (Dr. Randy Buckner)	1570 cases	
Open Access Series of Imaging Studies (OASIS)	416 cases	
Enhanced NeuroImaging Genetics Meta Analysis (ENIGMA)	>50,000 cases	
UK Bio Bank (United Kingdom)	~100,000 cases	
Rotterdam Study (PI: Dr. Arfan Ikram)	12,000 cases	
Adolescent Brain and Cognitive Development (ABCD)	10,000 cases	
FreeSurfer Usage Statistics		
Total number of licenses distributed since 2000	76,191	+55%
Average number of licenses per year since 2011	4757	
Posts to FreeSurfer mailing list	~1500/year	
Some Disorders/Diseases studied with FreeSurfer	Citations (Approx)	
Alzheimer's Disease (AD) [10-14]	3785	+71%
Parkinson's Disease [15-18]	1334	+95%
Huntington's Disease [19-22]	769	+39%
Schizophrenia [23-27]	3170	+62%
Major Depressive Disorder (MDD) [28-31]	2232	+78%
Multiple Sclerosis (MS) [32-35]	1892	+63%

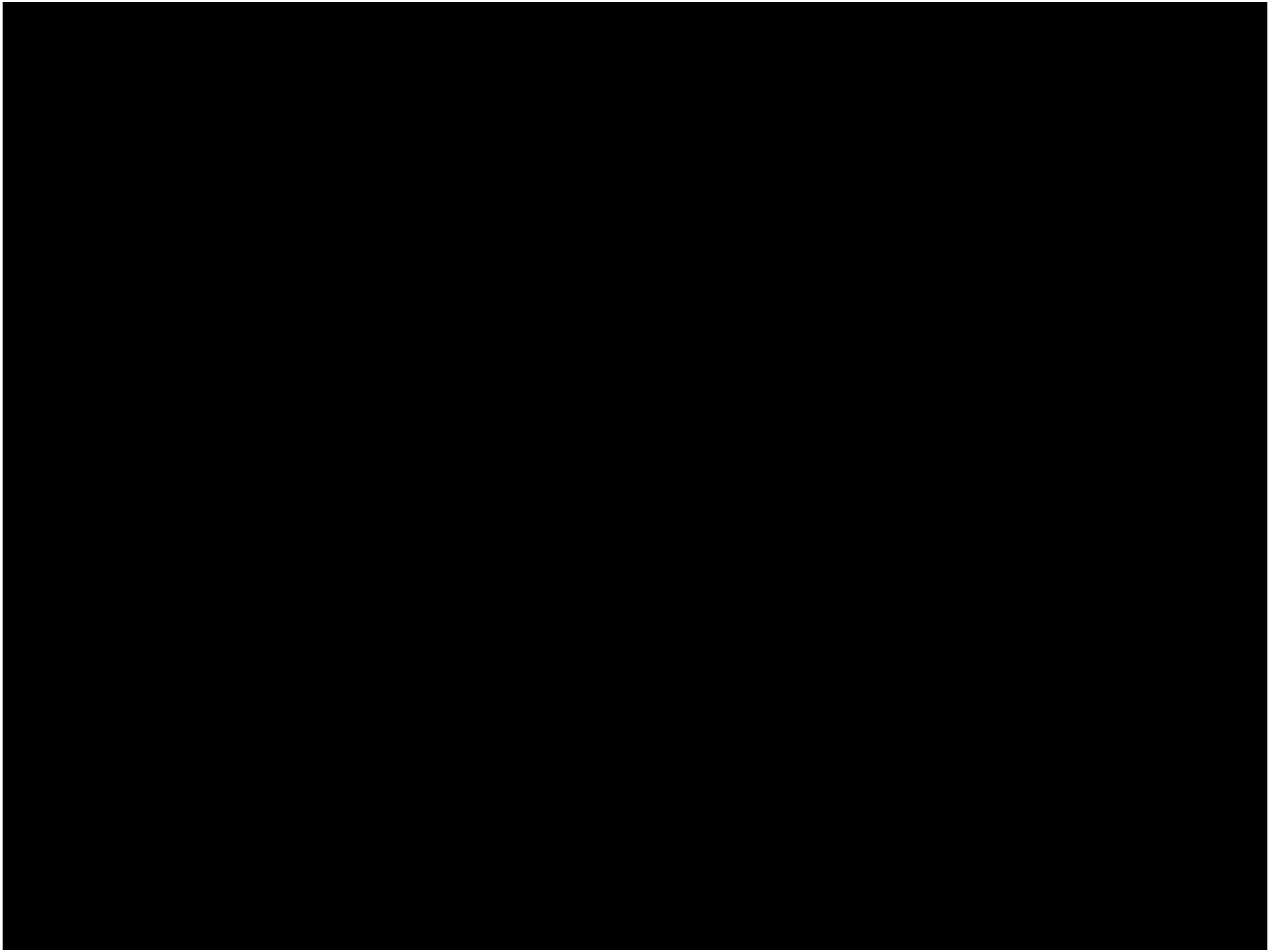
Summary

- Cortical extraction and labeling
- Subcortical Segmentation
- Surface-based Inter-subject Registration
- Fully automated
- Multi-modal integration

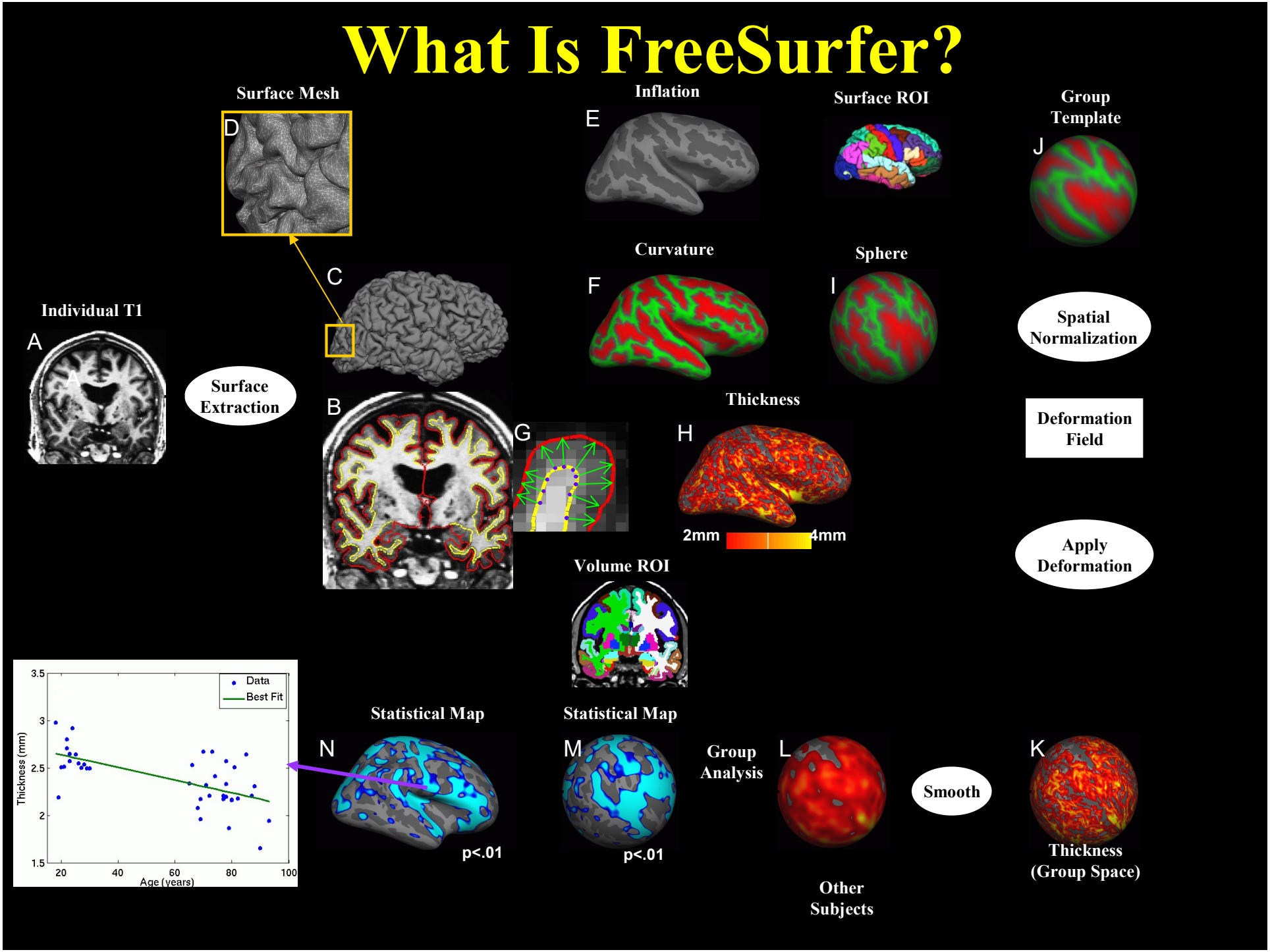
Use FreeSurfer



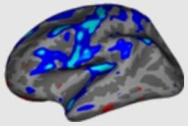
Be Happy



What Is FreeSurfer?



Search for Answers



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Virtual FreeSurfer Course

The virtual FreeSurfer course is scheduled for **April 29th, 30th & May 1st, 2024**. **The course will take place between 9am and 5pm Eastern Daylight Time (EDT) on these days.** This is a two day course that offers a basic introduction to FreeSurfer. A FreeSurfer Virtual Machine (VM) will be provided to course participants so that they can easily work with FreeSurfer and practice data during the course. Before registering, review the tentative schedule (listed below) to make sure it will work for you and review the technical requirements to be sure your computer can run the course software. You will be required to verify your computer can properly host the course software by **April 3rd** in order to stay enrolled in the course. If your computer cannot run the course materials, your course registration will be cancelled and a full refund issued to you.

Registration is now FULL for the April/May 2024 Virtual FreeSurfer Course!

Computer verification deadline: **April 3rd, 2024**

If you have a specific question about the FreeSurfer courses that was not answered by this website and our FAQ or would like to host a course in your area, you can email one of the course organizers (fscourse AT mgb.org).

Course Details

Click on any of the topics below for more information:

- **Overview**
- **Technical Requirements**
- **Schedule**
- **Payment**
- **FAQ**
- **Topics Covered During the Course**

Overview

The two day course consists of talks and tutorials that run throughout the day. Attendees are expected to attend all talks and tutorials.

Outline

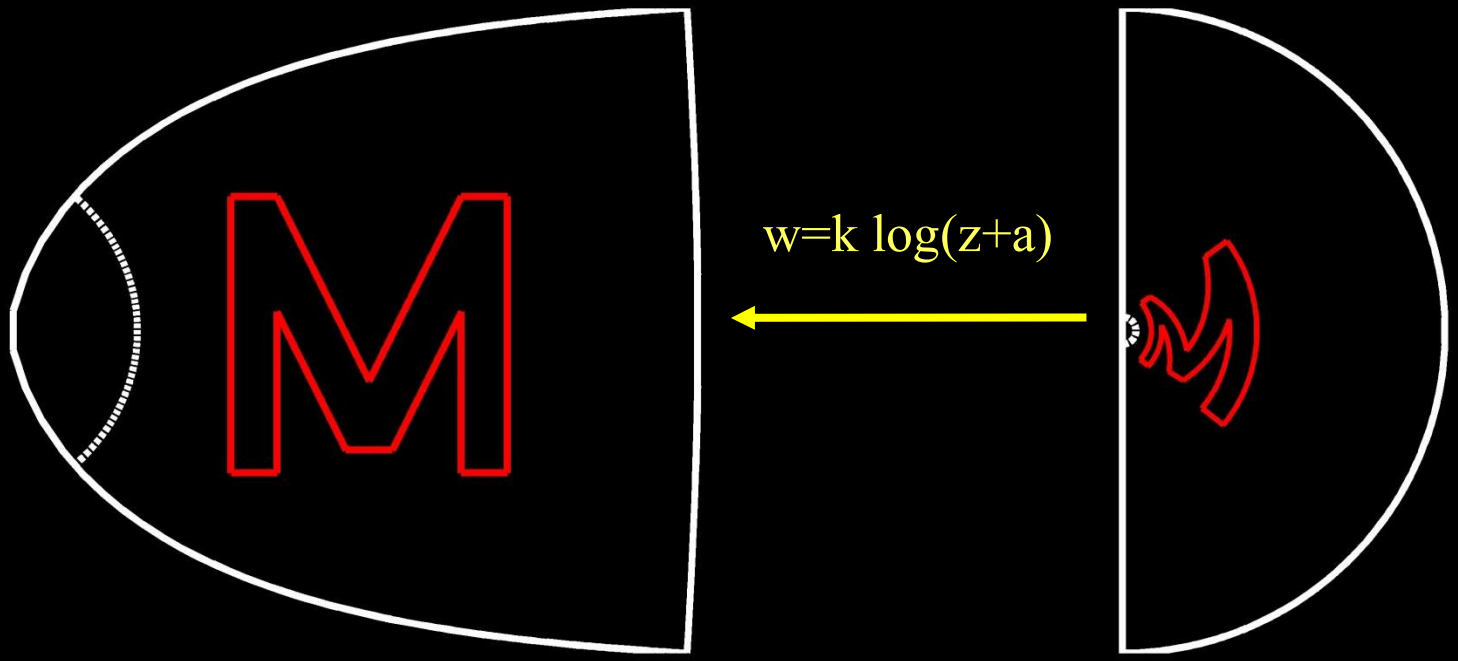
- A Brief History of FreeSurfer
- What are Surfaces Good For Anyway?
- Inferring Microstructural Features
- Longitudinal Analysis
- DWI/Tractography
- fMRI

What Can One Do With A Surface Model?

goal: use model to imposed desired activity pattern on V1

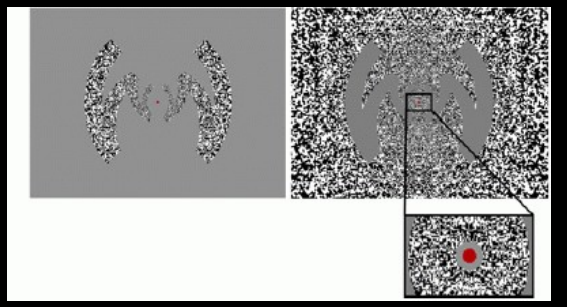
desired shape of activity pattern

required shape of stimulus



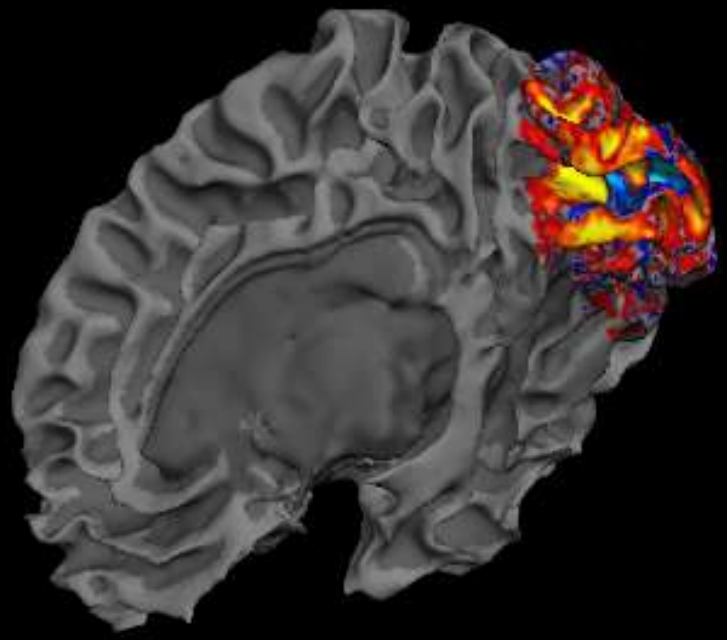
left primary visual cortex

right visual hemifield



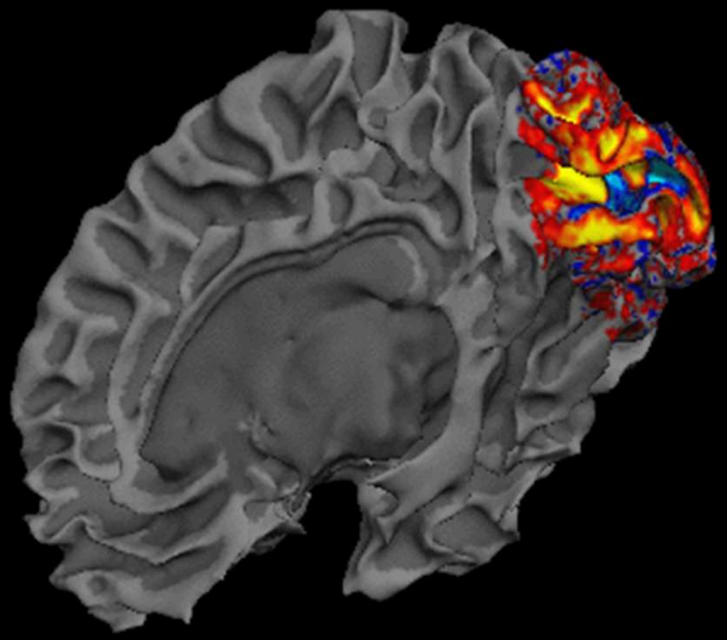
Collaboration with **Jon Polimeni** and Larry Wald.

Tangential Resolution Measured with Surface-based Analysis



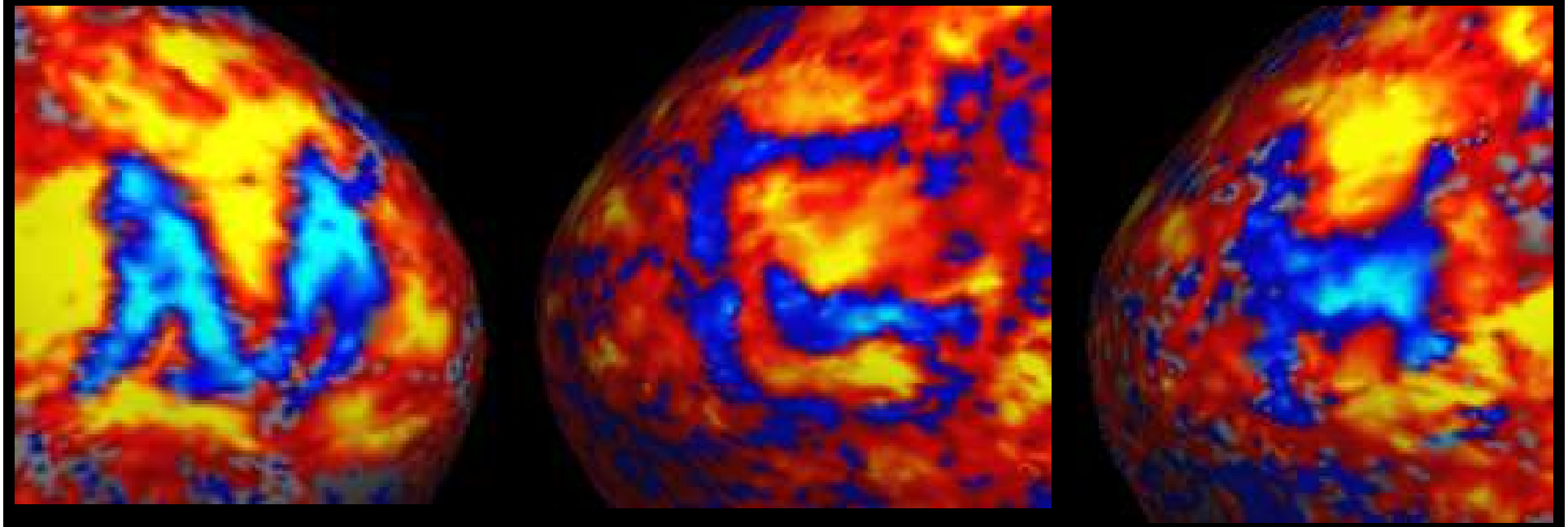
Collaboration with Jon Polimeni and Larry Wald. Polimeni, et al, 2010, NI.

Tangential Resolution Measured with Surface-based Analysis



Collaboration with Jon Polimeni and Larry Wald. Polimeni, et al, 2010, NI.

NeuroMarketing!



Aim 1 of our NCRR Center Grant, spelling:

"MGH Center for Functional Neuroimaging Technologies; and NCRR Center for Research Resources."

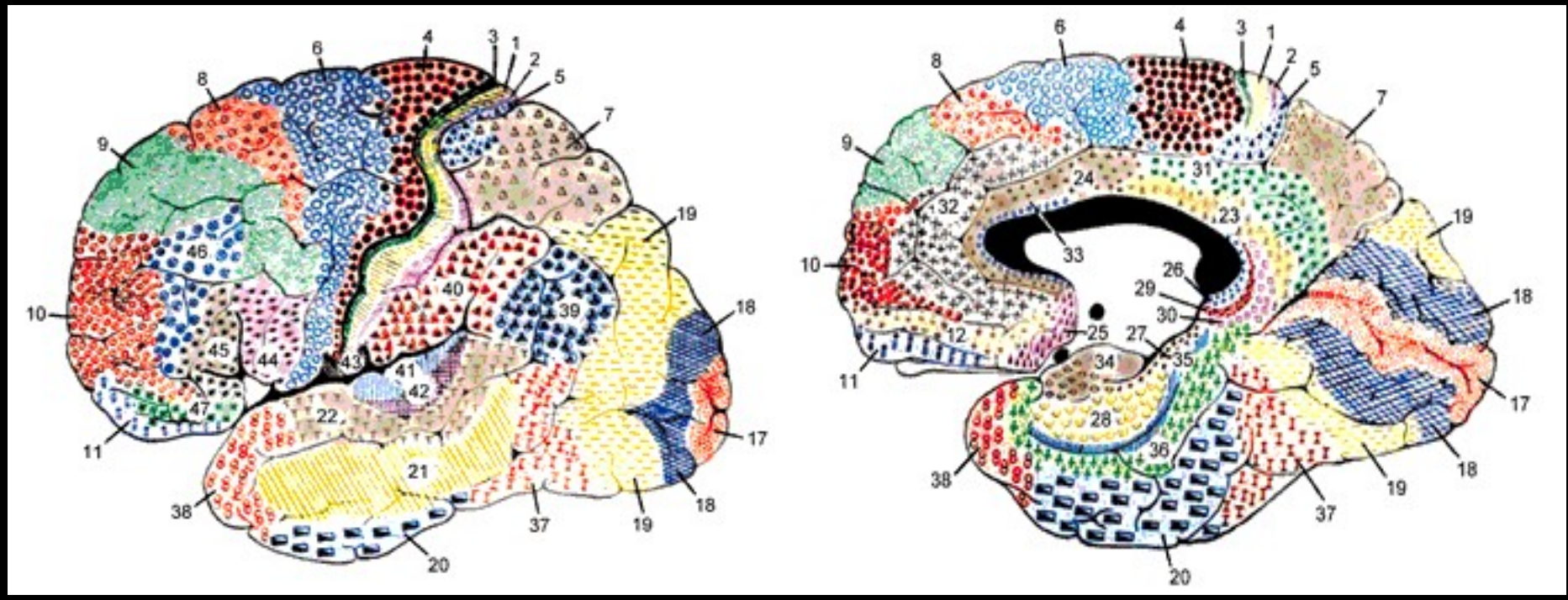
(just kidding)

Thanks to Larry Wald for this slide.

Outline

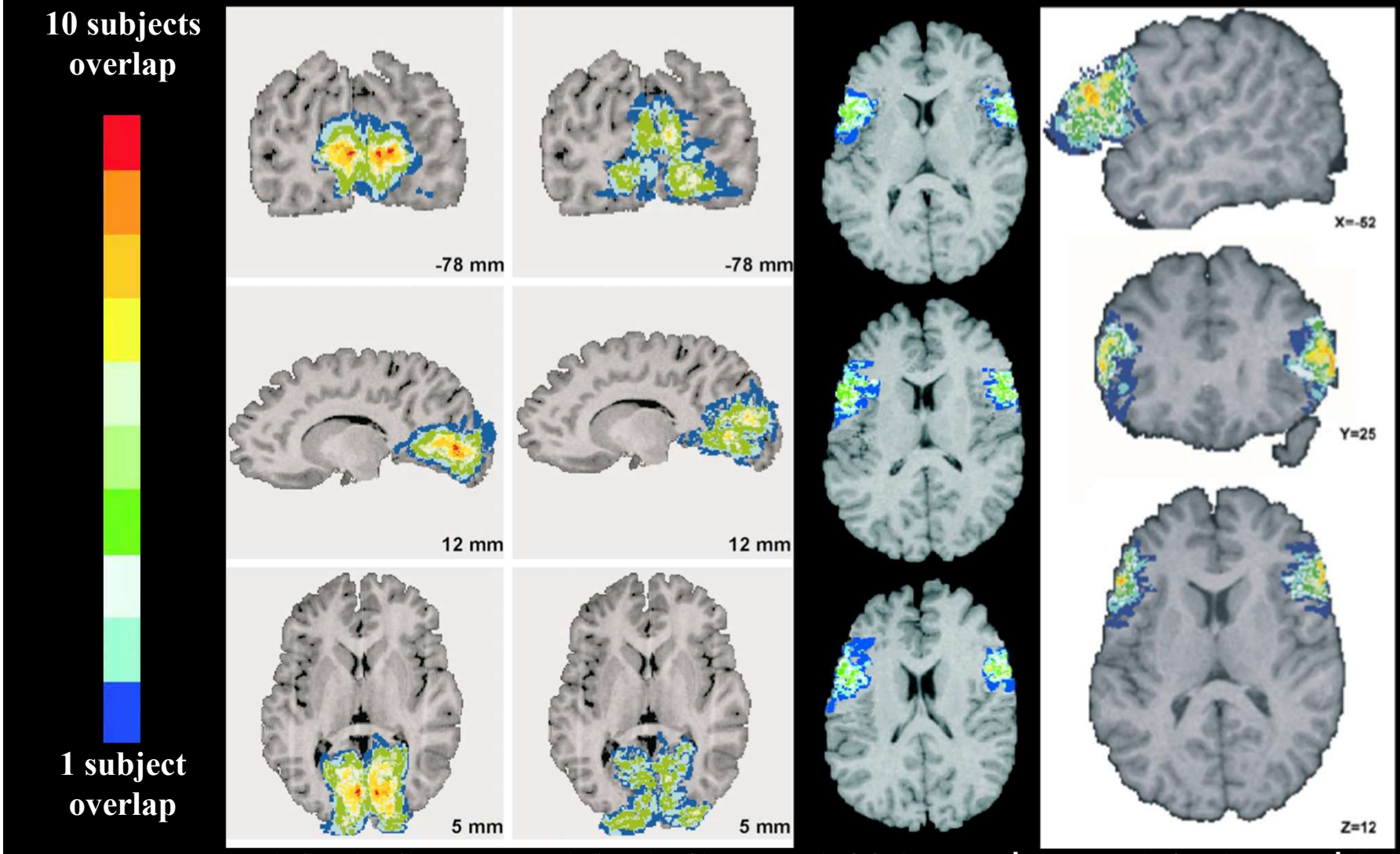
- A Brief History of FreeSurfer
- What are Surfaces Good For Anyway?
- Inferring Microstructural Locations
- Longitudinal Analysis
- DWI/Tractography
- fMRI

Surface-based Registration Performance



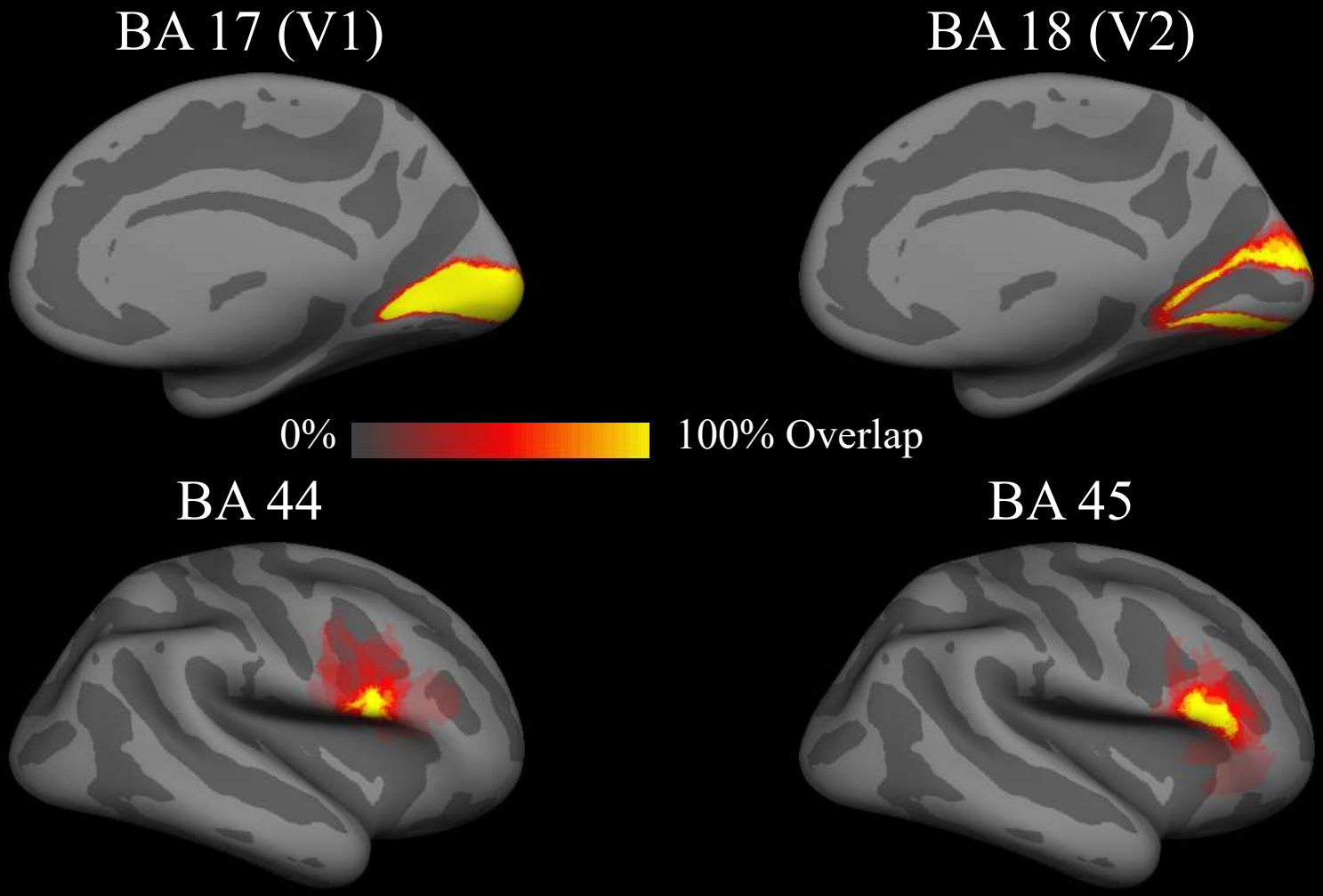
Brodmann, 1909

Predicting Brodmann Areas: Talairach Coordinates



(Amunts et al, 2000, 2004)

Predicting Brodmann Areas from Folding Patterns

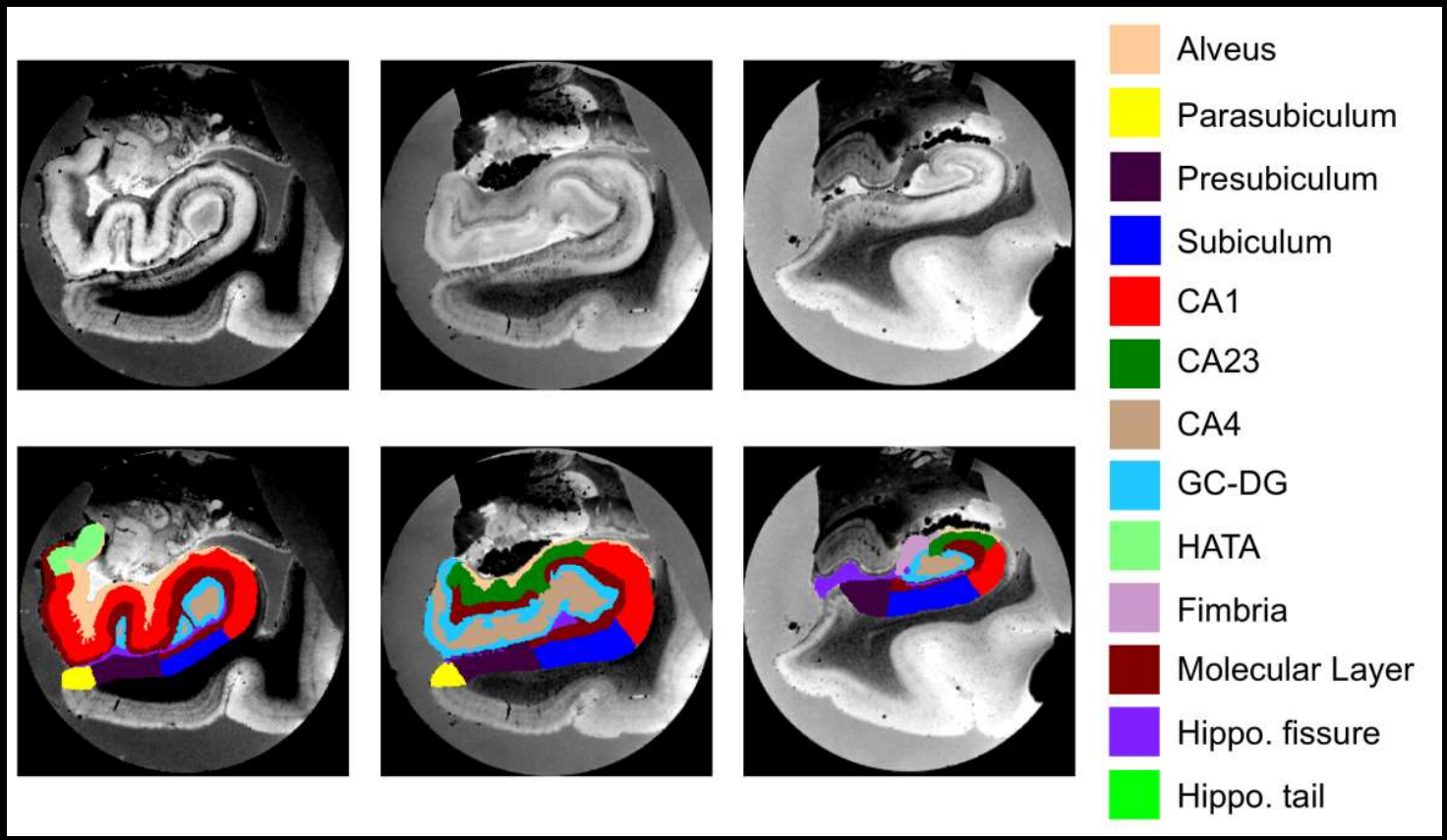


Fischl, et al, 2007. Thanks to Katrin Amunts, Karl Zilles and Hartmut Mohlberg for the data, and to Niranjini Rajendran and Evelina Busa for the analysis.

Ex vivo MRI of hippocampal subfields

Resolution as high as 0.1 mm isotropic

- Allows precise manual tracing of hippocampal subfields.
- The delineation only relies on geometry for subdividing the CA.



Joint work with J. Eugenio Iglesias, Koen van Leemput and Jean Augustinack

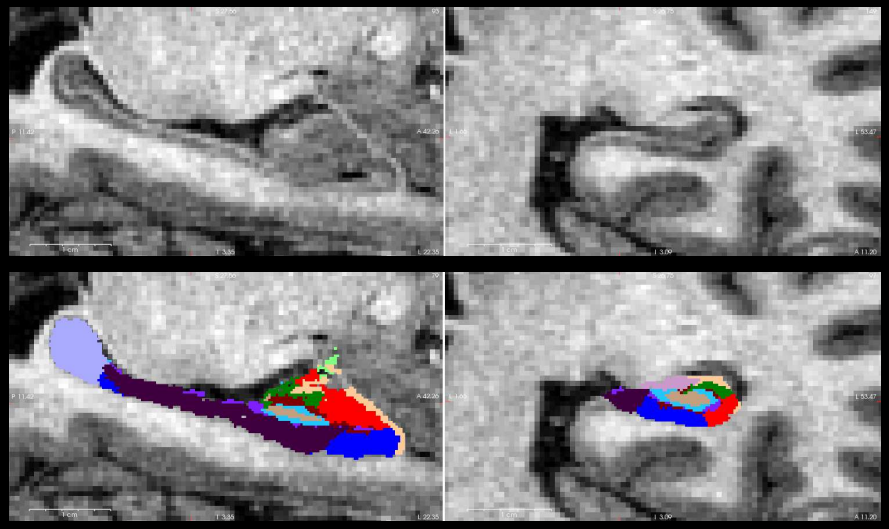
Automated Segmentation

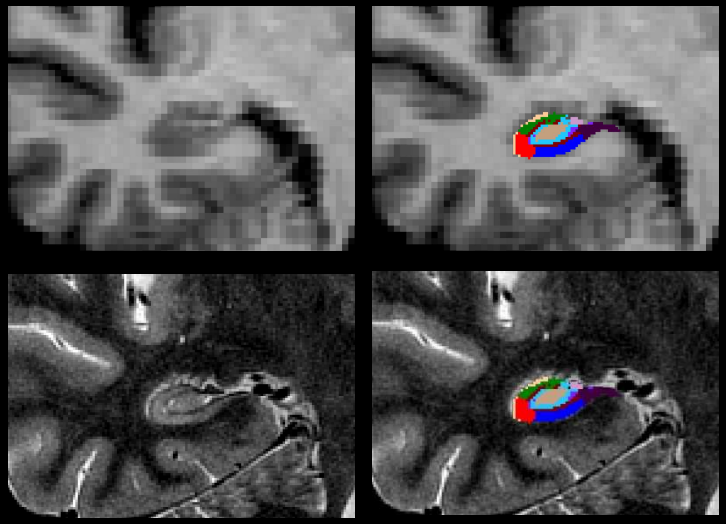
We use the atlas as a prior, and connect it to the image through a Gaussian likelihood term for each label.

- This makes the segmentation sequence-independent.

0.6 mm isotropic T1 (Winterburn et al.)

1 mm T1 + 0.4x0.4x2 mm T2 (ADNI)





Joint work with J. Eugenio Iglesias, Koen van Leemput and Jean Augustinack

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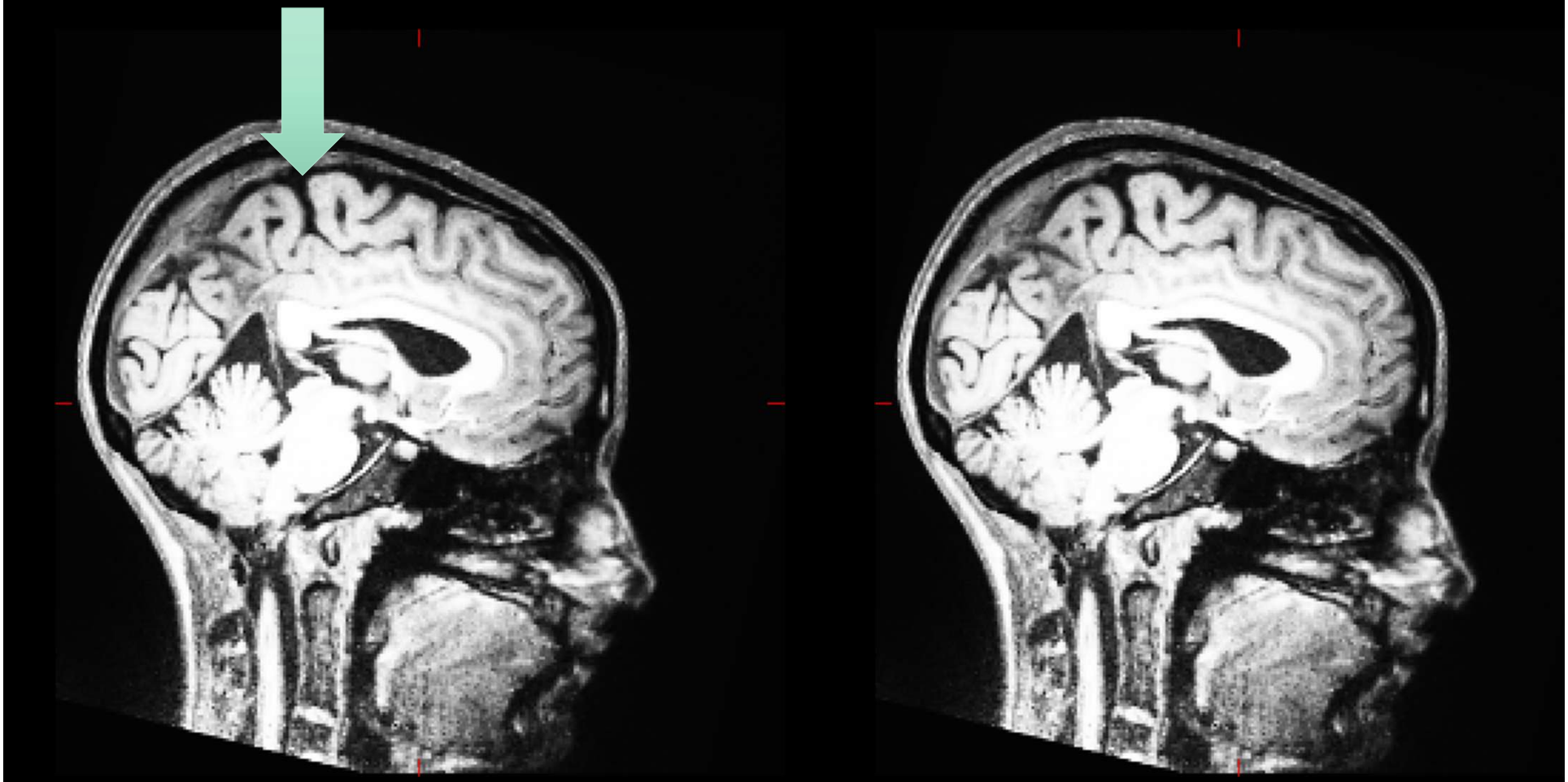
Robust Registration

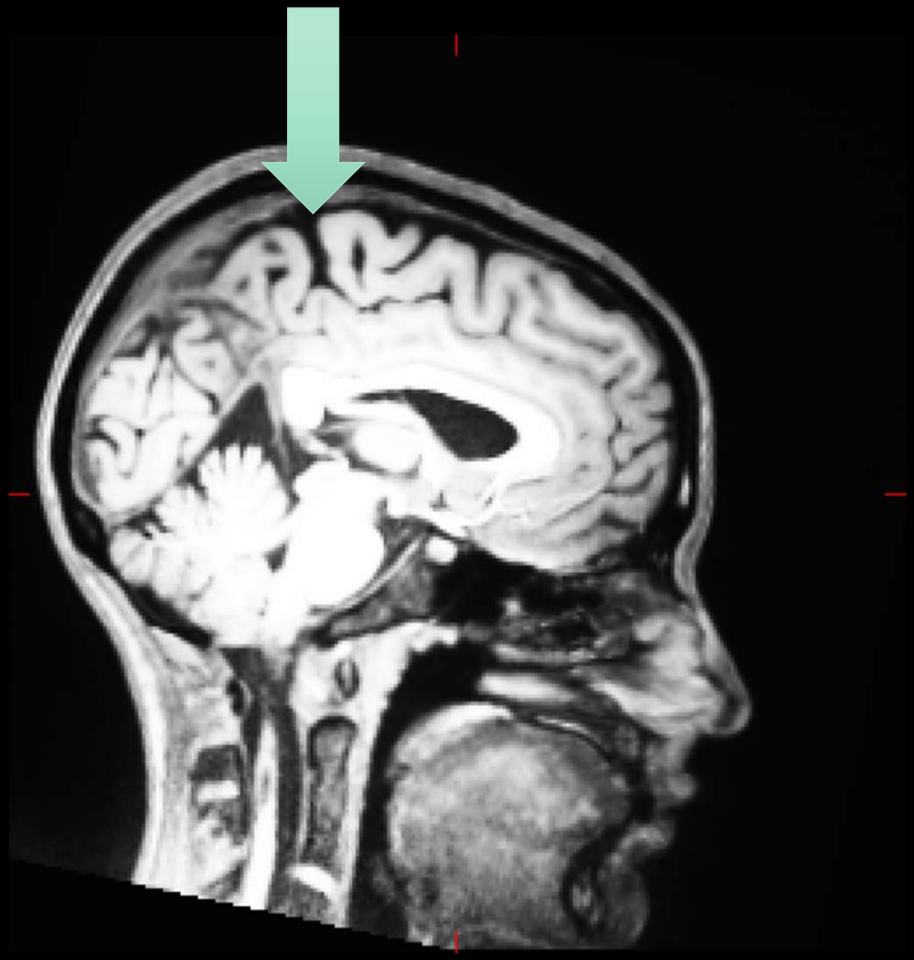


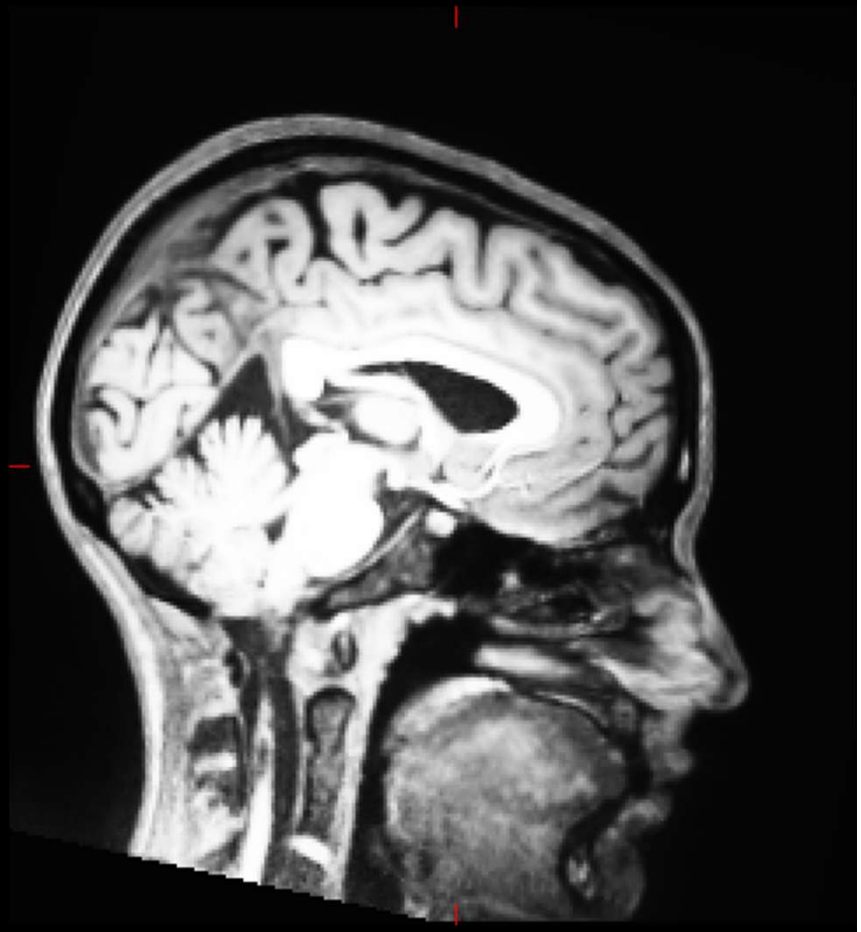
Target

Target

Reuter et al, 2010 NeuroImage

Robust Registration



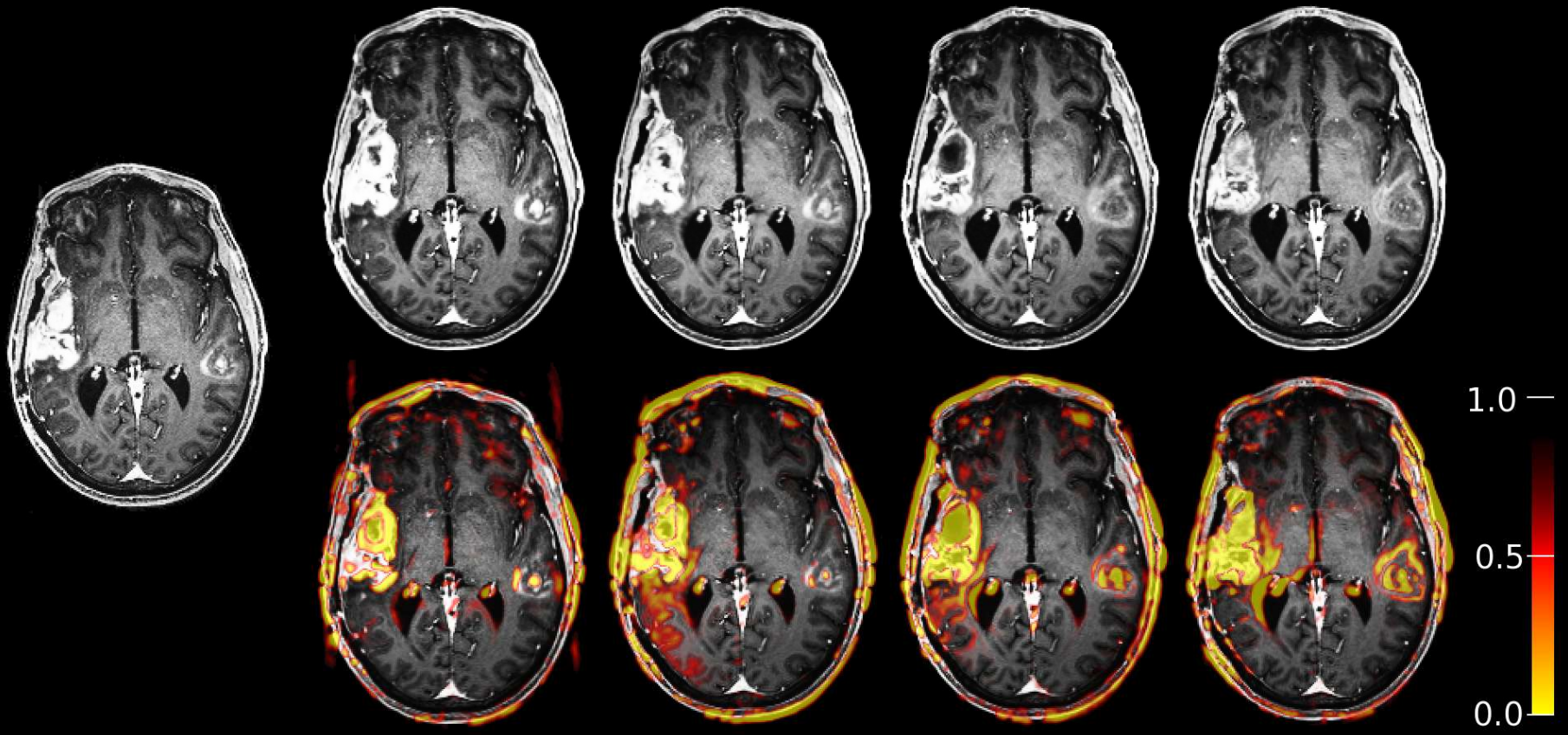


Registered Src correlation ratio

Registered Src Robust

Reuter et al, 2010 NeuroImage

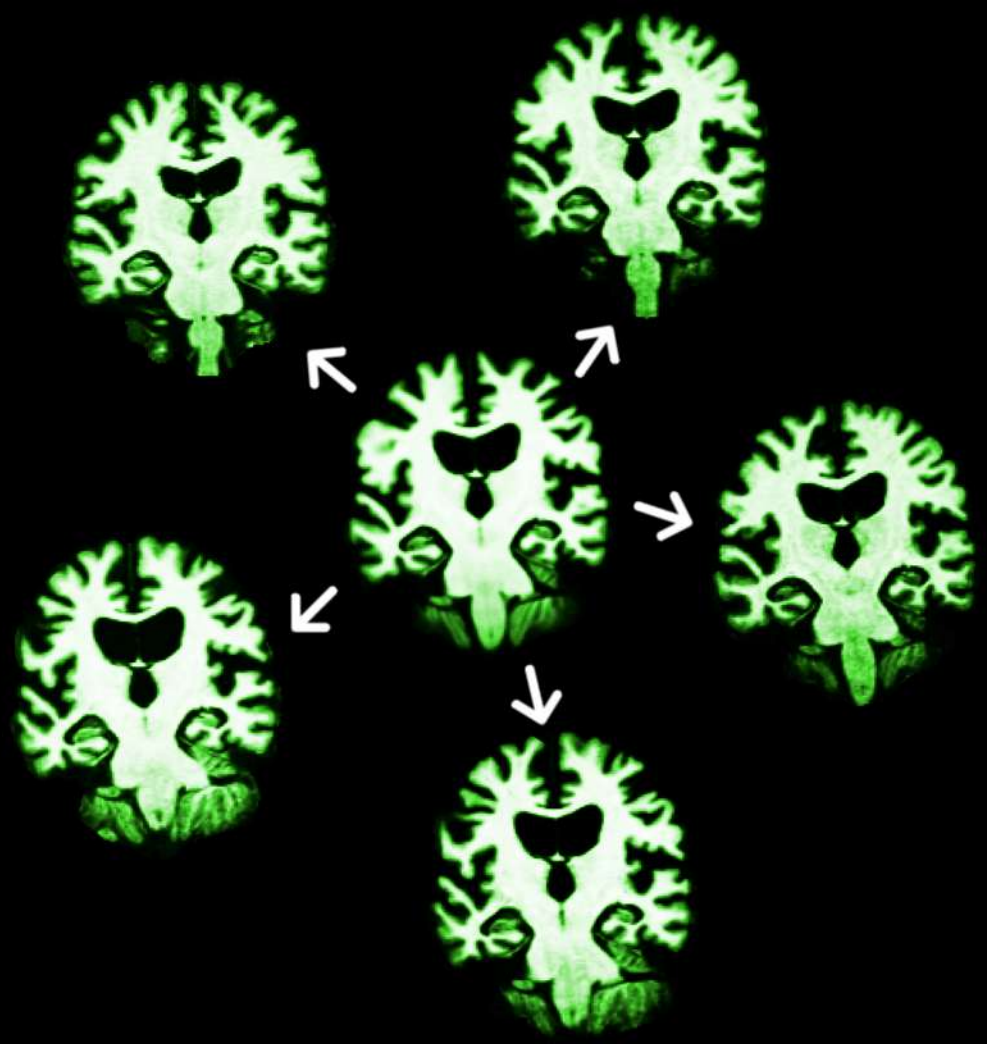
Robust Registration



Tumor data with significant intensity differences in the brain, registered to first time point (left).

Reuter et al, 2010 NeuroImage

Longitudinal Processing



1. Create unbiased subject template (iterative registration to median)
2. Process template
3. Initialize time points
4. Let it evolve there

- Avoid Bias: All time points are treated the same
- Increases sensitivity and reliability!

Reuter et al. OHBM 2010, NeuroImage 2011 & 2012

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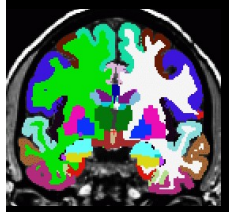
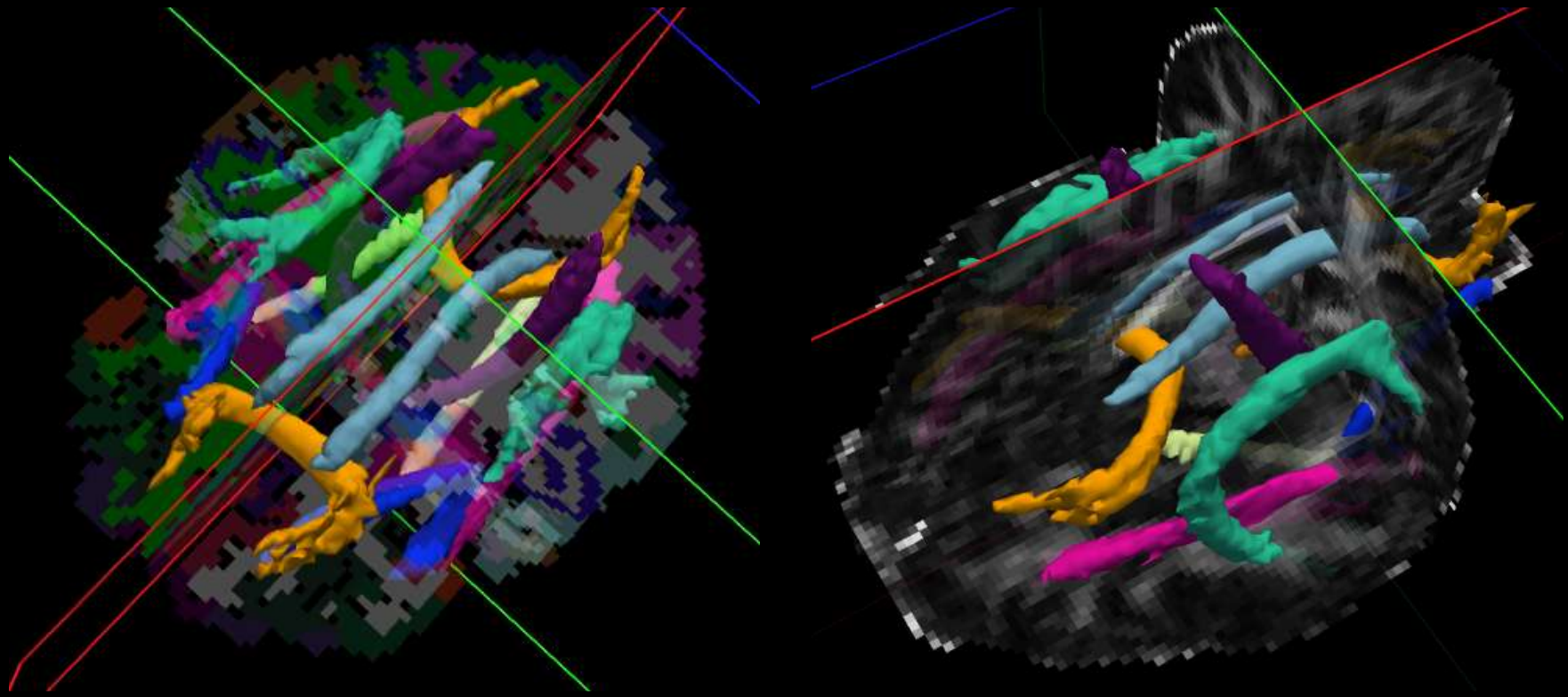


Tractography with TRACULA

(TRActs Constrained by the Underlying Anatomy)



- Completely automated modeling of 18 major fascicles
- Uses prior probabilistic information on the anatomical structures that each fascicle goes through or next to

Collaboration with Anastasia Yendiki, Lilla Zöllei, Saad Jbabdi, Tim Behrens and Jean Augustinack

Outline

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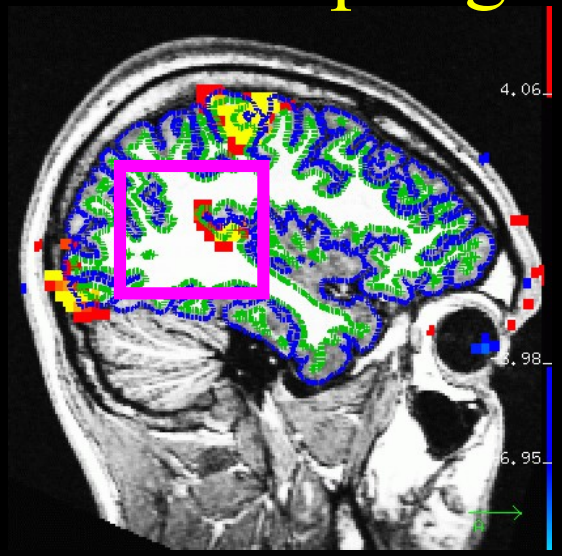
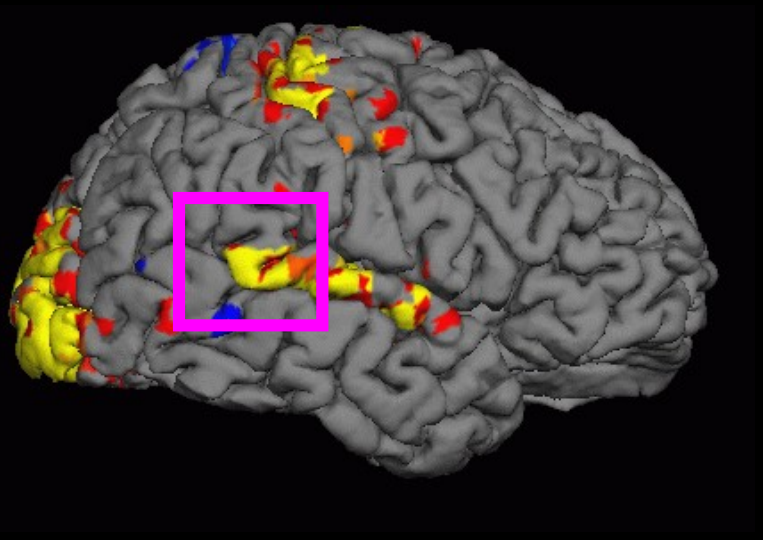
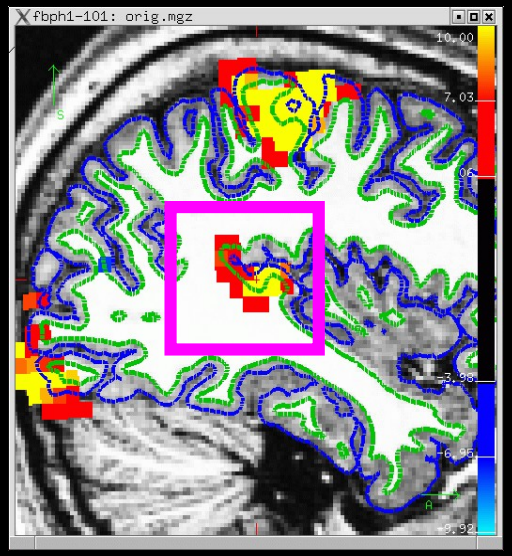
Sampling on the Surface

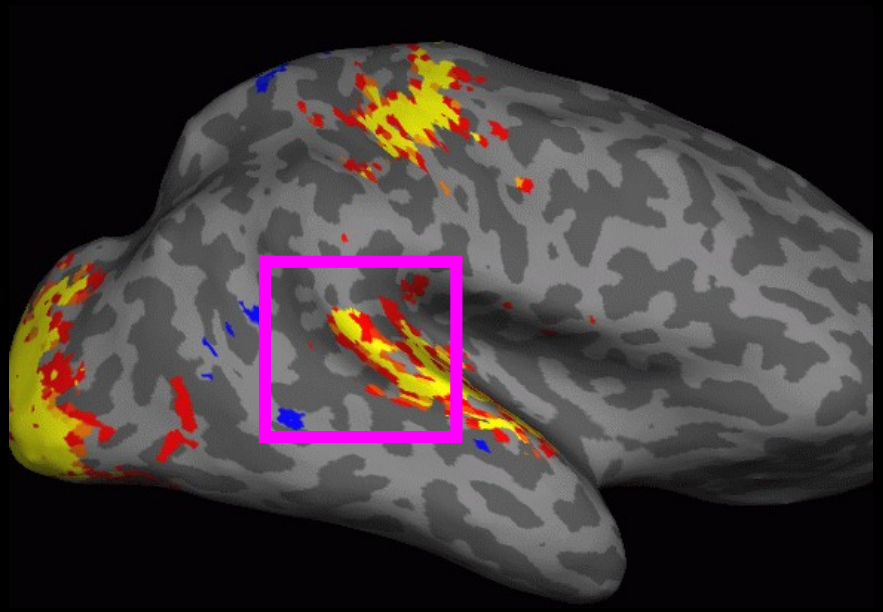




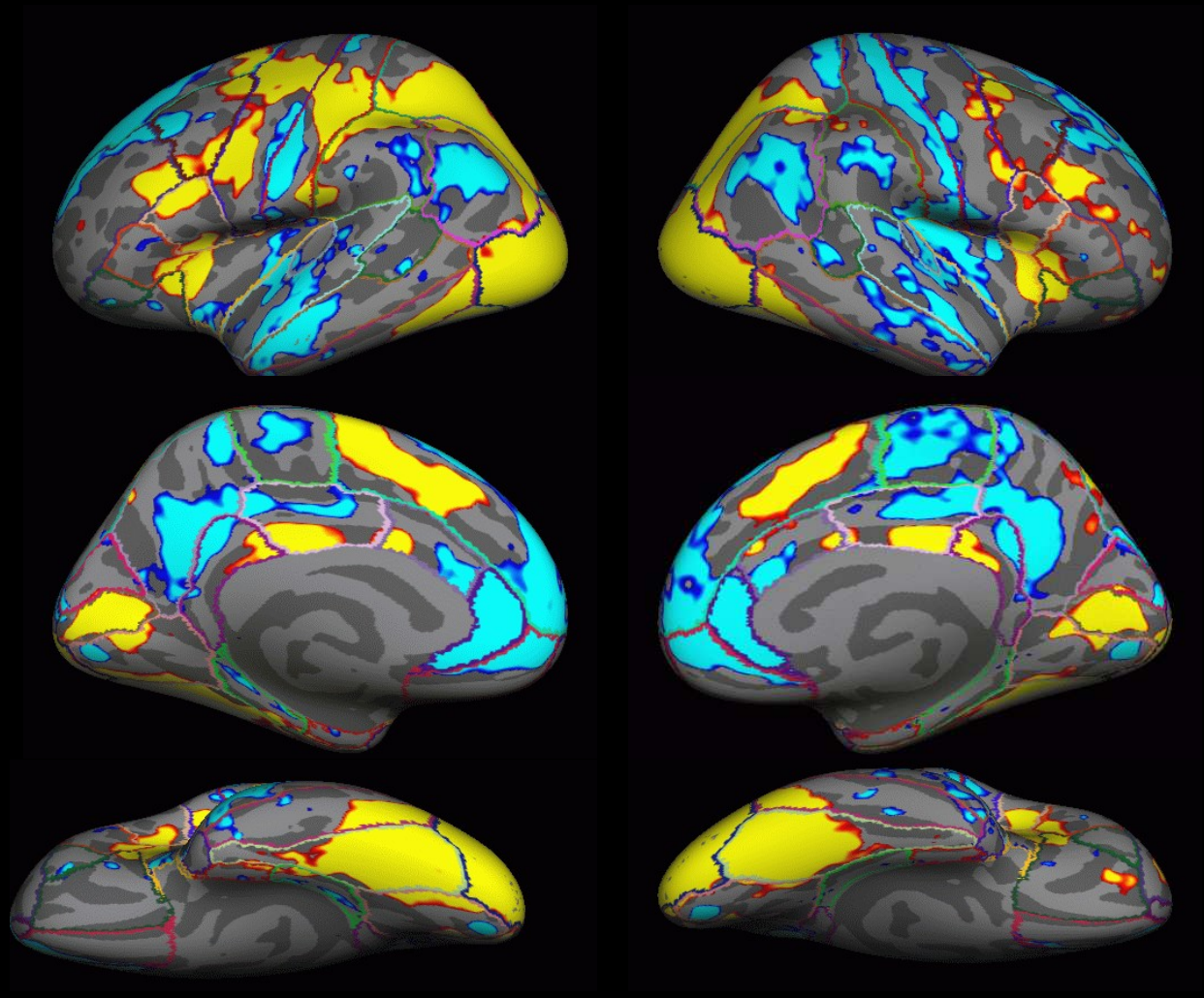
15 sec ‘ON’, 15 sec ‘OFF’

- Flickering Checkerboard
- Auditory Tone
- Finger Tapping



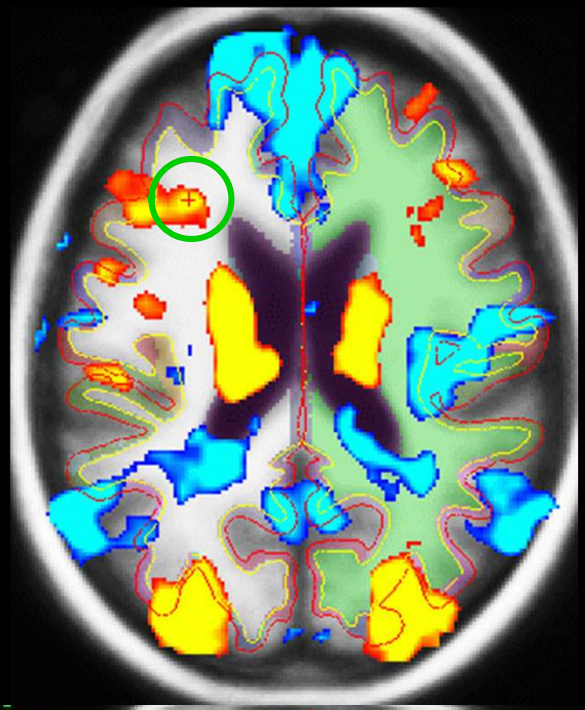


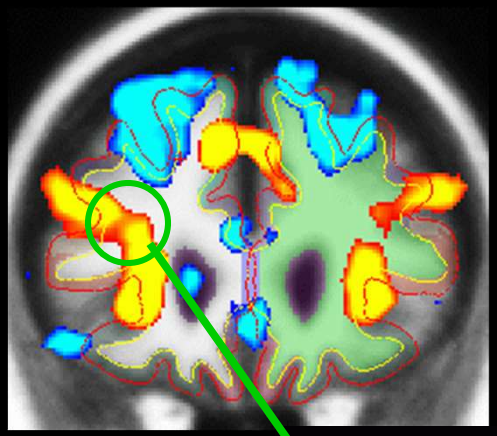
fMRI Working Memory Paradigm Group Analysis



Probe-vs-Fixation. Data Functional Biomedical Informatics Research Network (fBIRN)

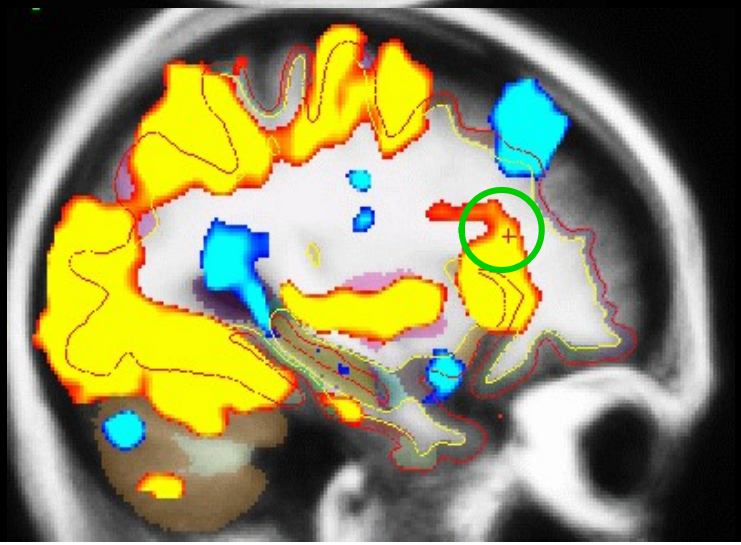
Group fMRI Analysis: Volume vs Surface

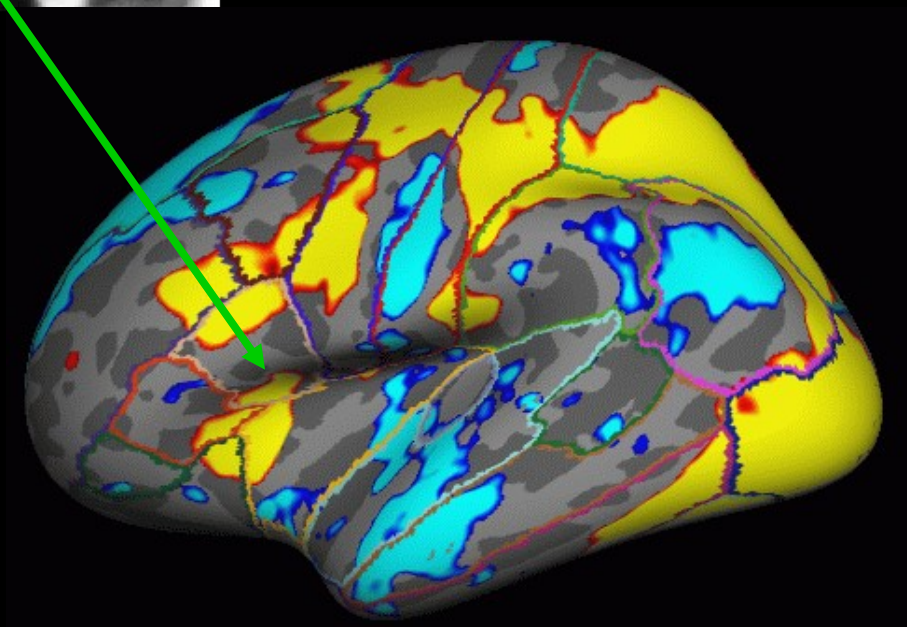




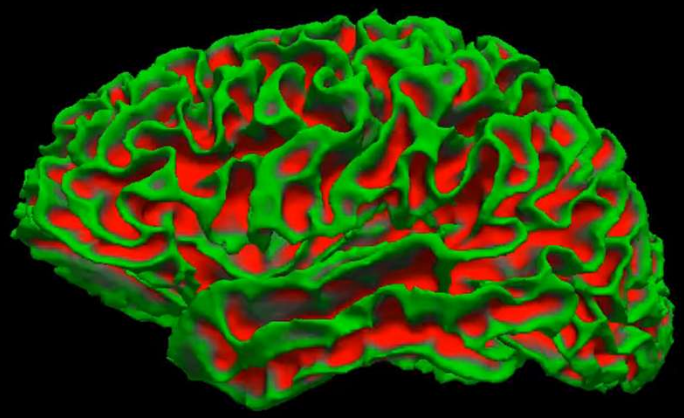
Affine registration to MNI305

5mm volume smoothing vs.
10mm surface smoothing

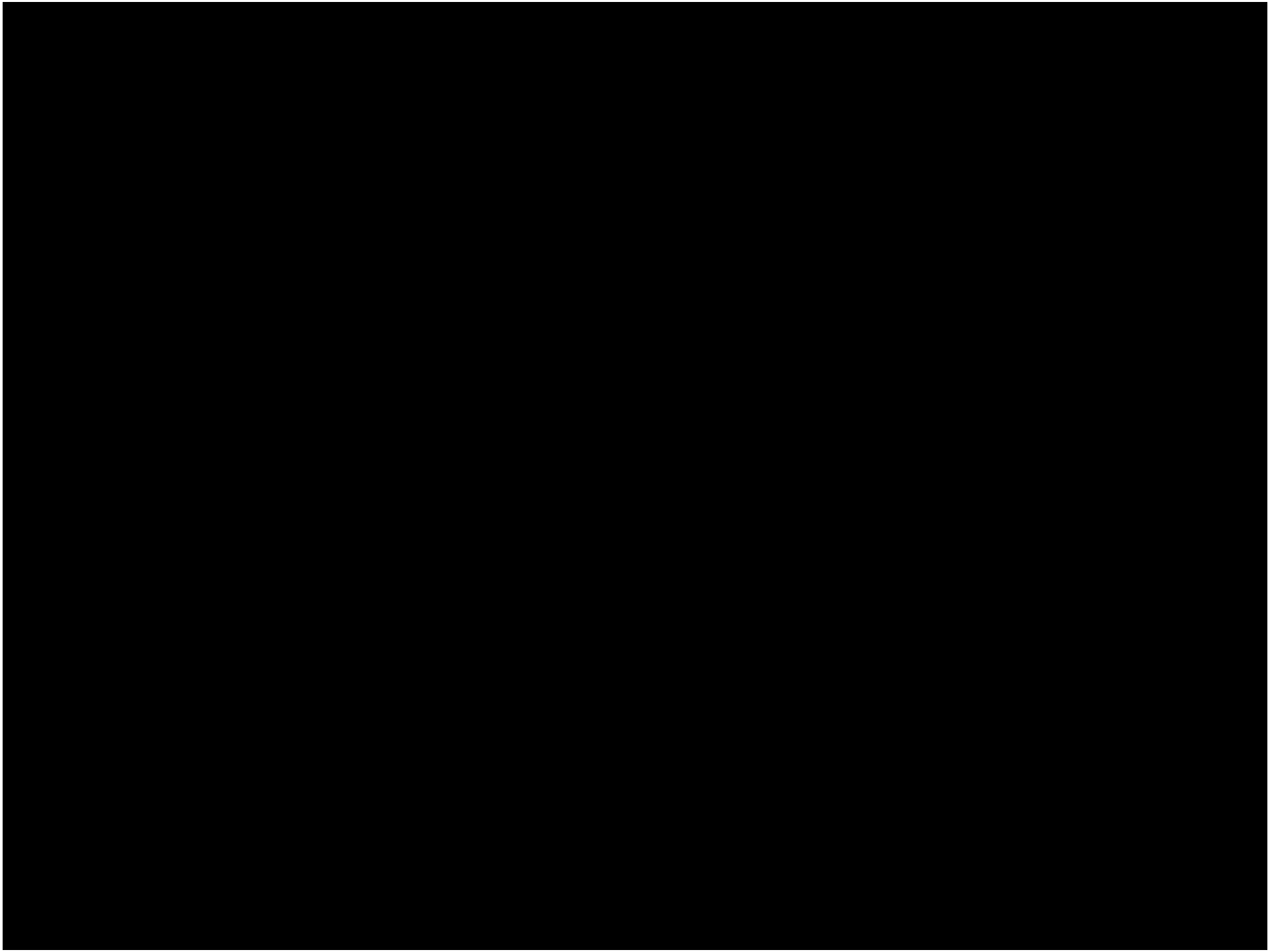




Why Should I Use FreeSurfer?



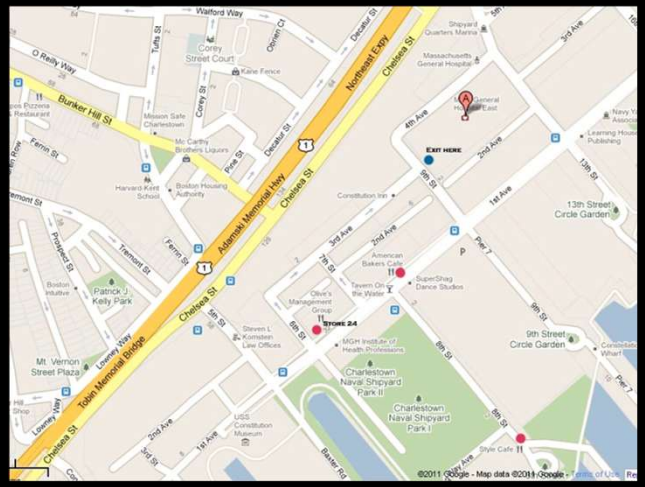
Please do not try this yourself without expert supervision – it can be extremely dangerous!



Food and such

12:20	Registration		
12:20 - 1:20	**Lunch** (Suggestions for where to eat)	--	--
12:25	Optional Lunch Talk - A Non-physicist's Intro to MR		

Cafeteria in main building (Building 149)



Morning coffee and "breakfast" – muffins, bagels, fruit
Afternoon coffee and some snacks

Tuesday evening socializing at Boston Beer Works

To Caffeinate or not to Caffeinate?

Please don’t spill coffee (or anything else!) on the laptops.
If you do, please be prepared to fund a replacement!

The FreeSurfer Team

Bruce

Doug

fMRI/PET

Martin

Longitudinal

Anastasia

Tractography

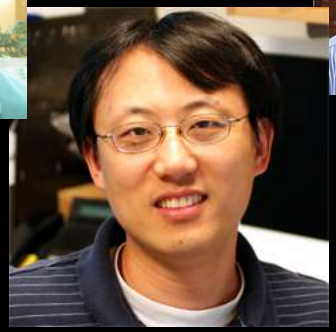
Lilla

Registration/ Pediatric

Zeke

Software Engineers

Nick



Ruopeng

Andre

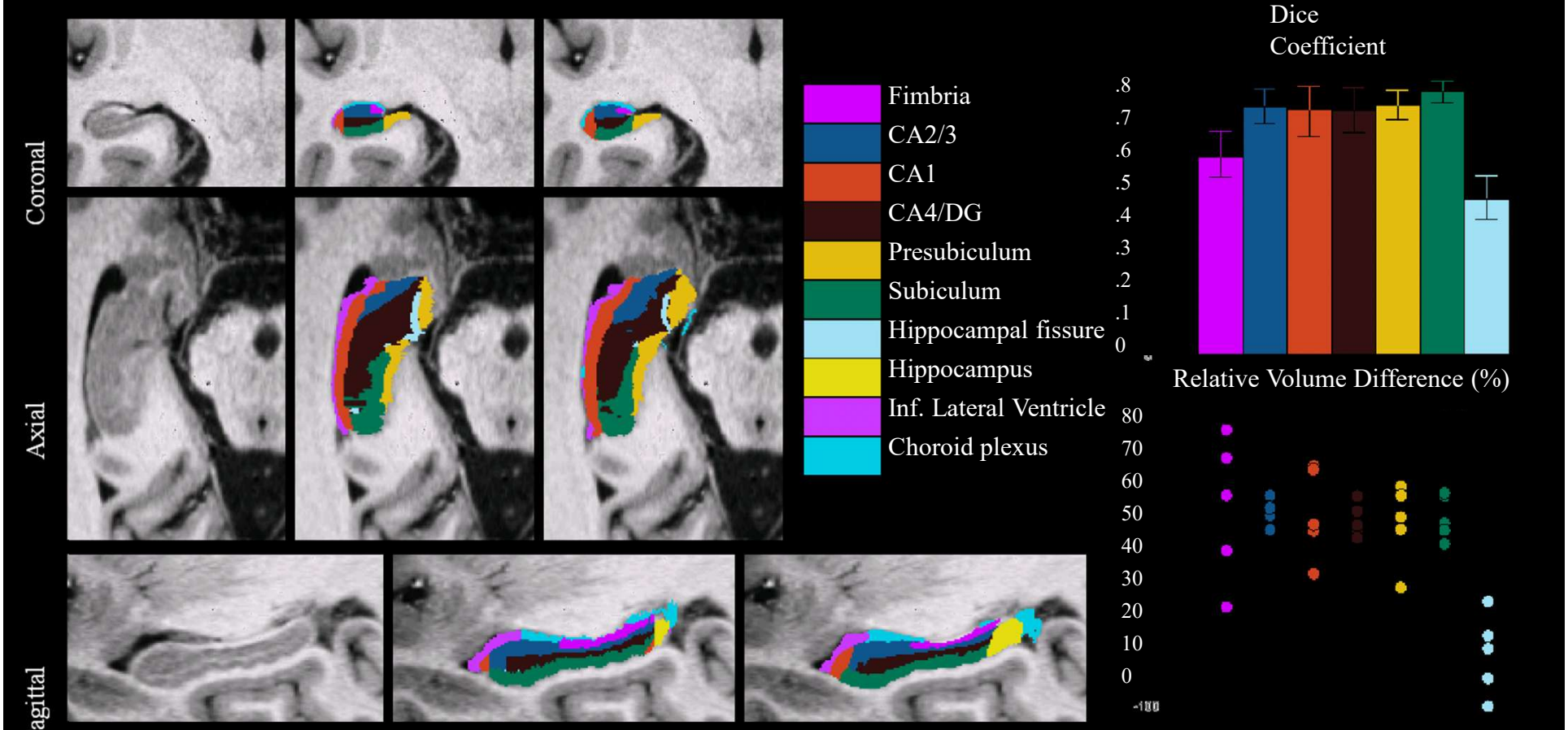
MR Sequences

Allison

Recon Editing & Exvivo Data

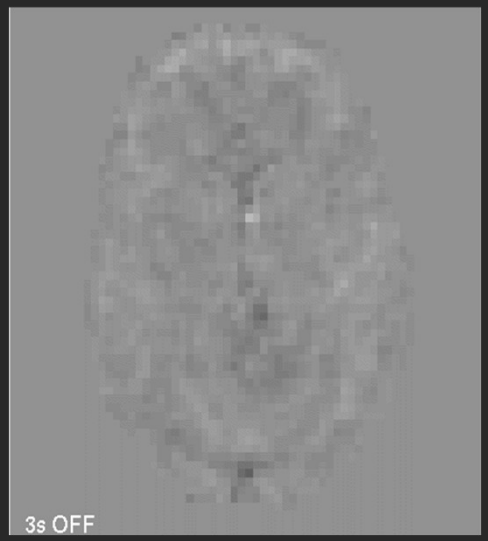
Automated Subfield Segmentation

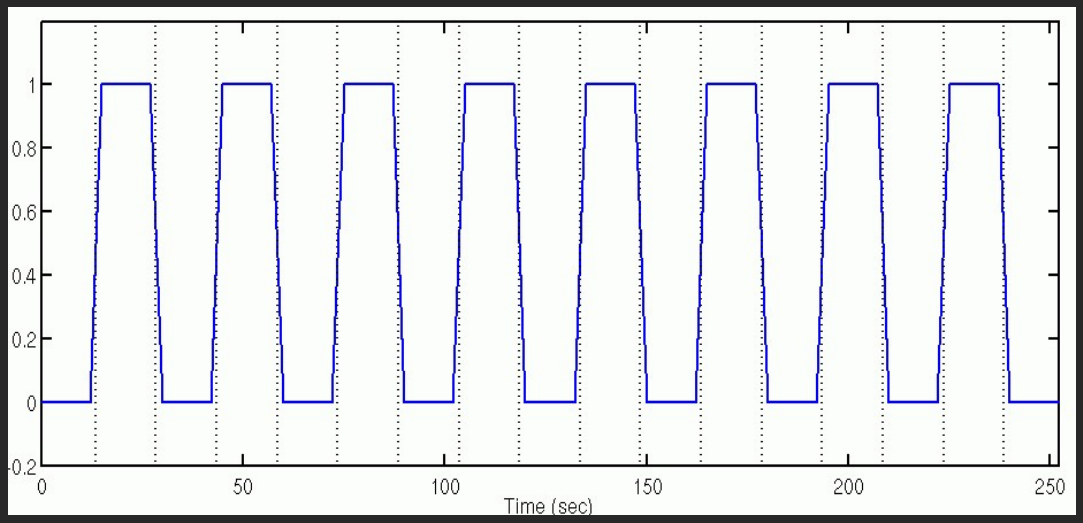
- Leave-one-out cross-validation with 5 subjects

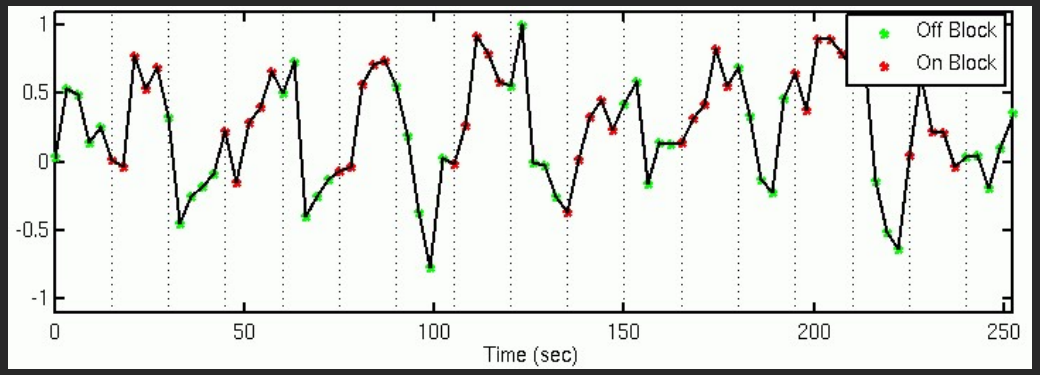


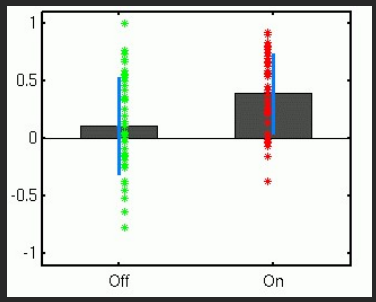
Collaboration with Koen van Leemput, J. Eugenio Iglesias and Jean Augustinack

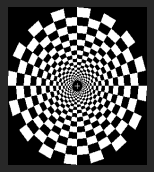
Visual/Auditory/Motor Activation Paradigm







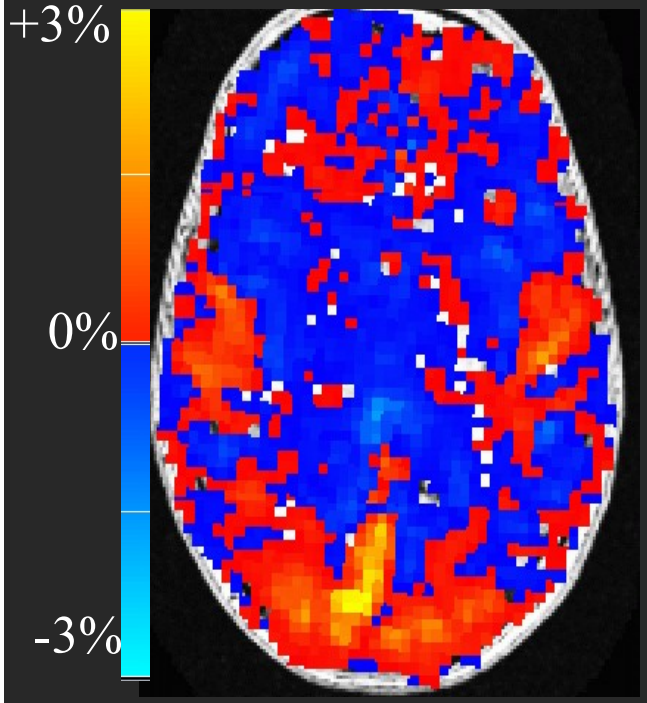




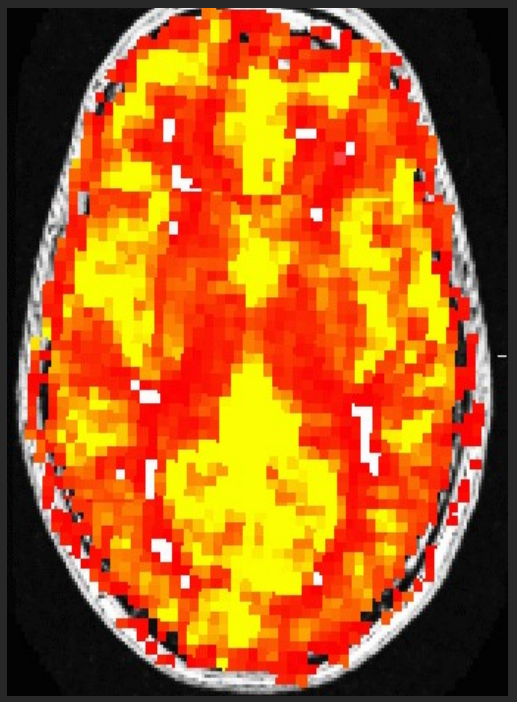
15 sec 'ON', 15 sec 'OFF'

- **Flickering Checkerboard**
- **Auditory Tone**
- **Finger Tapping**

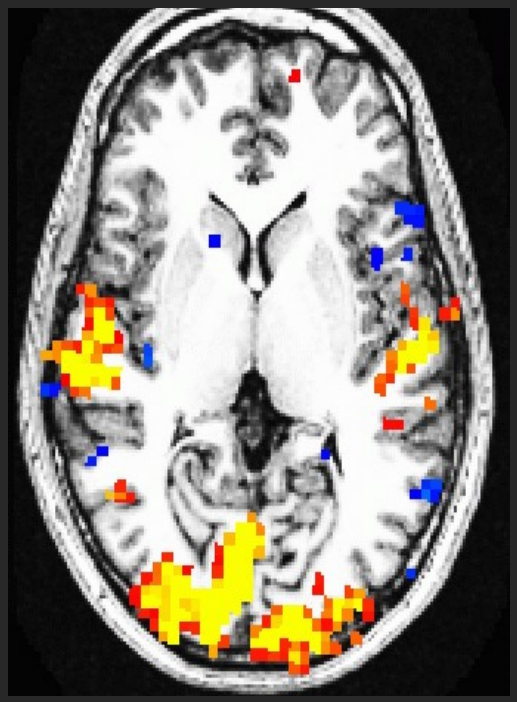
On-vs-Off SPMs



Contrast Amplitude
CON, COPE, CES



Contrast Amplitude
Variance
(Error Bars)
VARCOPE, CESVAR

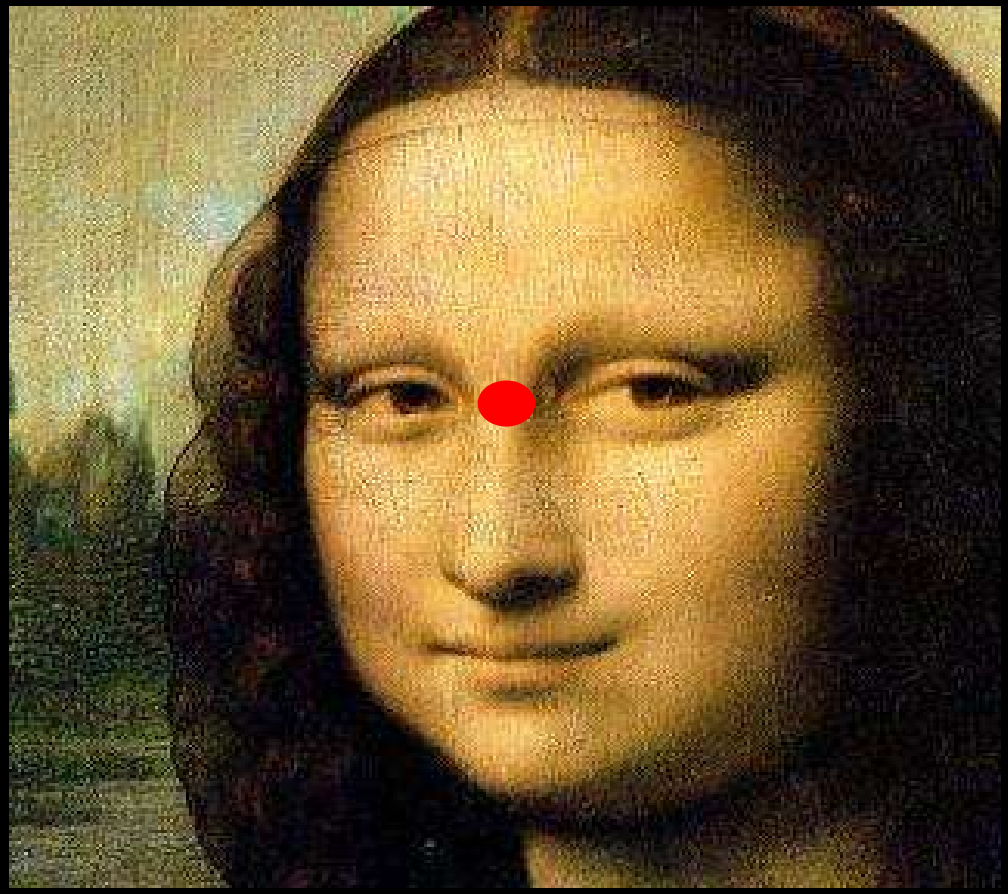


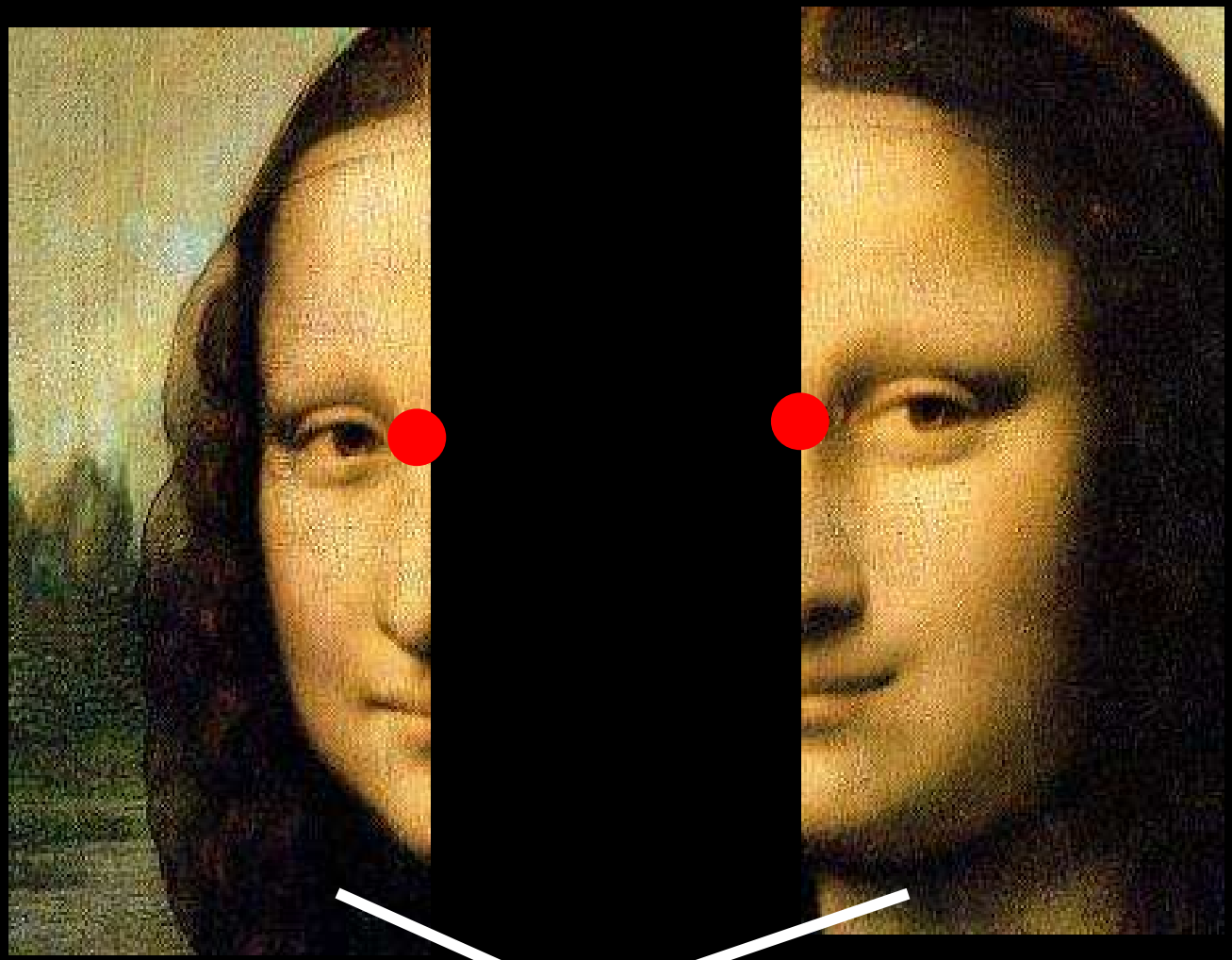
Significance
t-Map (p,z,F)
(Thresholded p<.01)

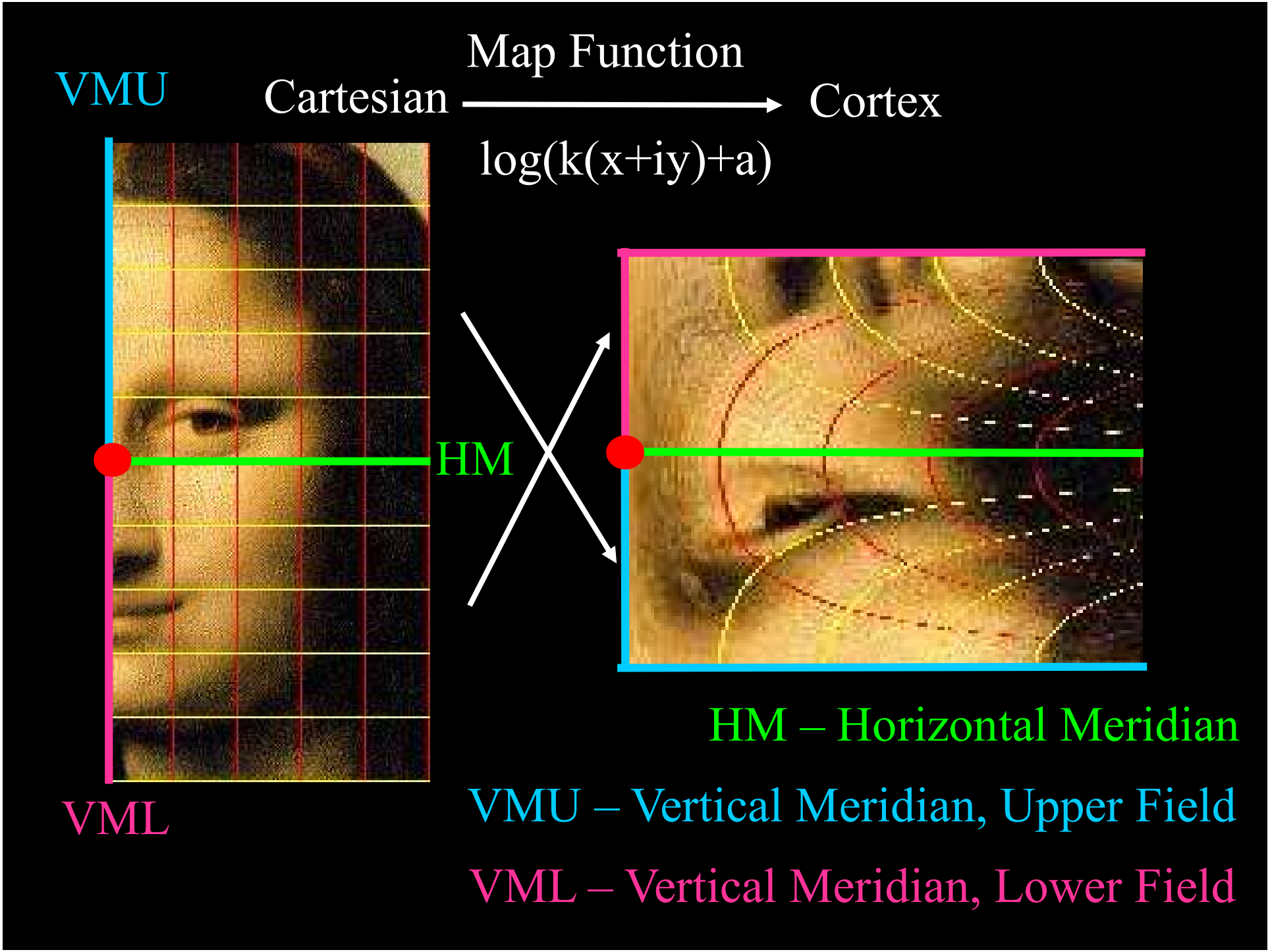
Outline

- Anatomical Analysis
- Surface-based (Cortex)
- Volume-based
- Multi-modal integration
- DWI/Tractography
- fMRI – retinotopy

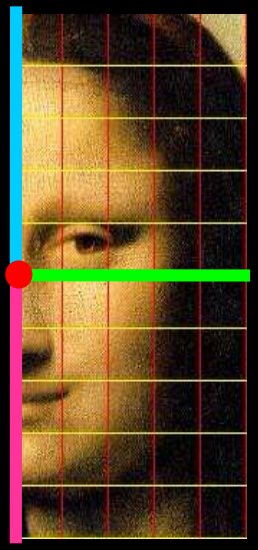
What does your brain do to Mona?

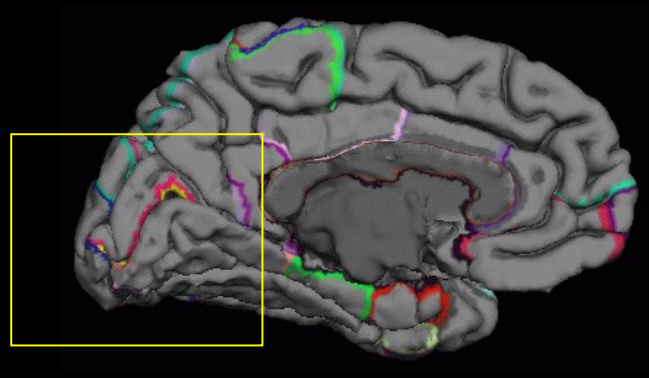


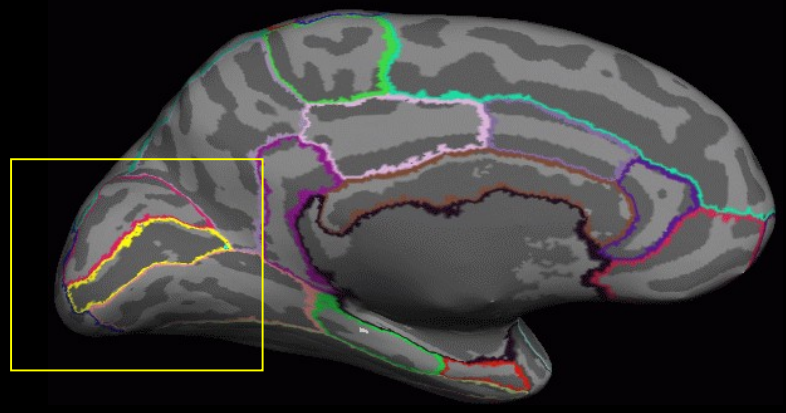

Left Cortical Hemisphere
Right Cortical Hemisphere

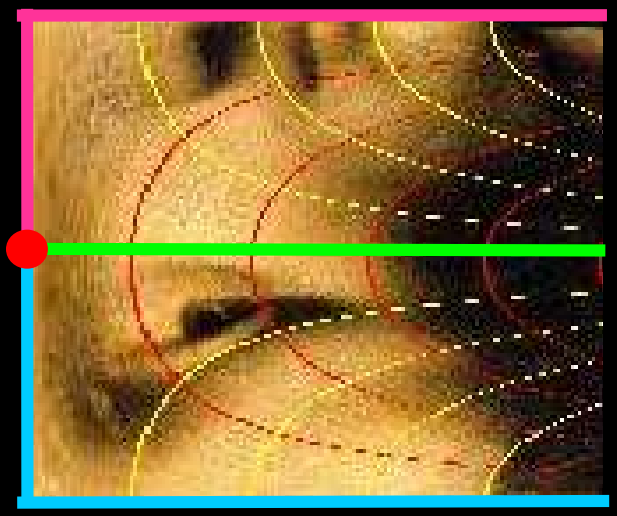

VMU
Cartesian
Map Function
Cortex
log(k(x+iy)+a)
HM
VML
HM – Horizontal Meridian
VMU – Vertical Meridian, Upper Field
VML – Vertical Meridian, Lower Field

V1 – Primary Visual Cortex





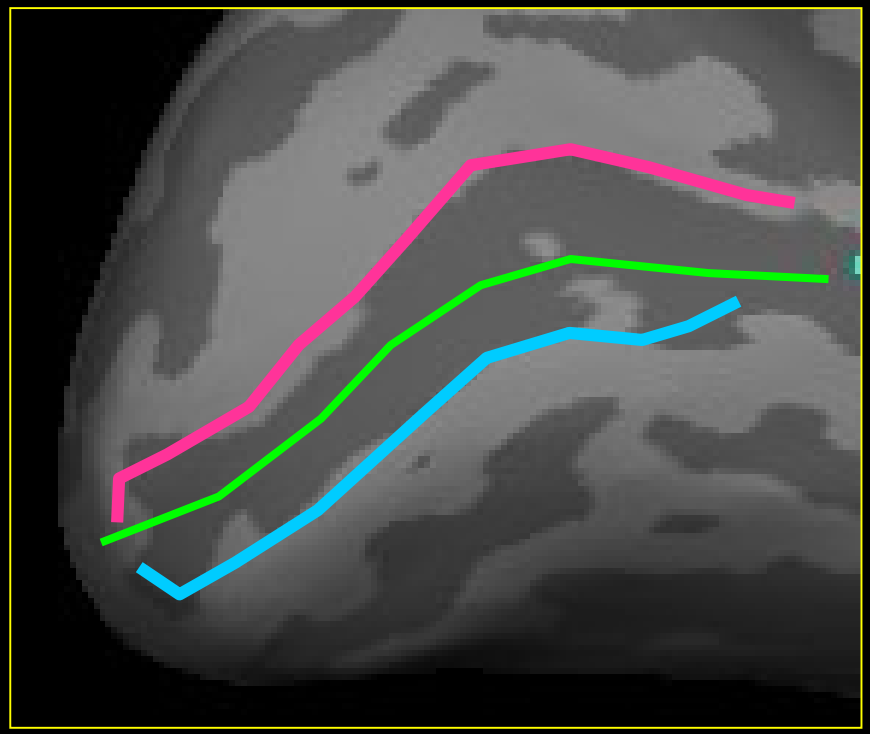




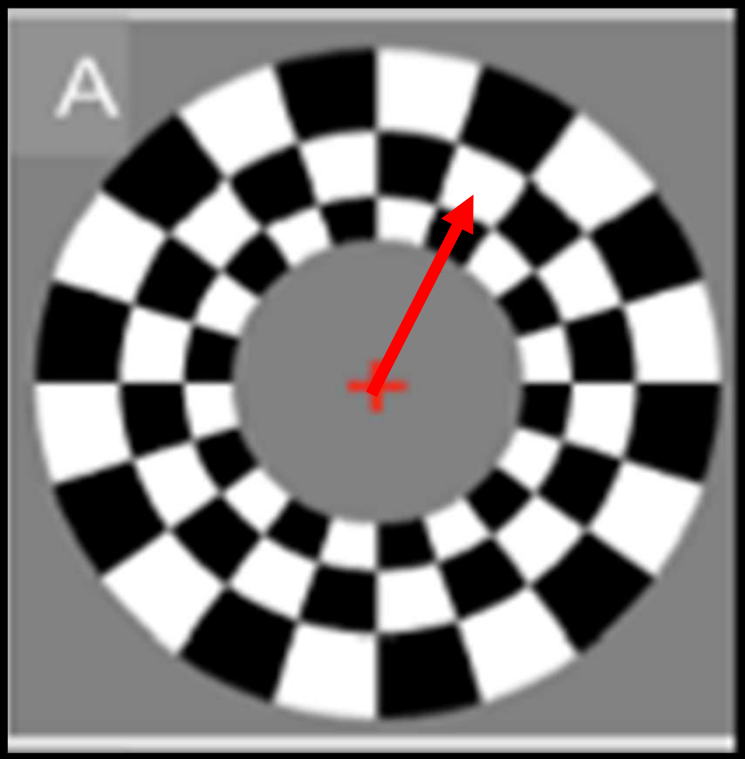
VML

HM

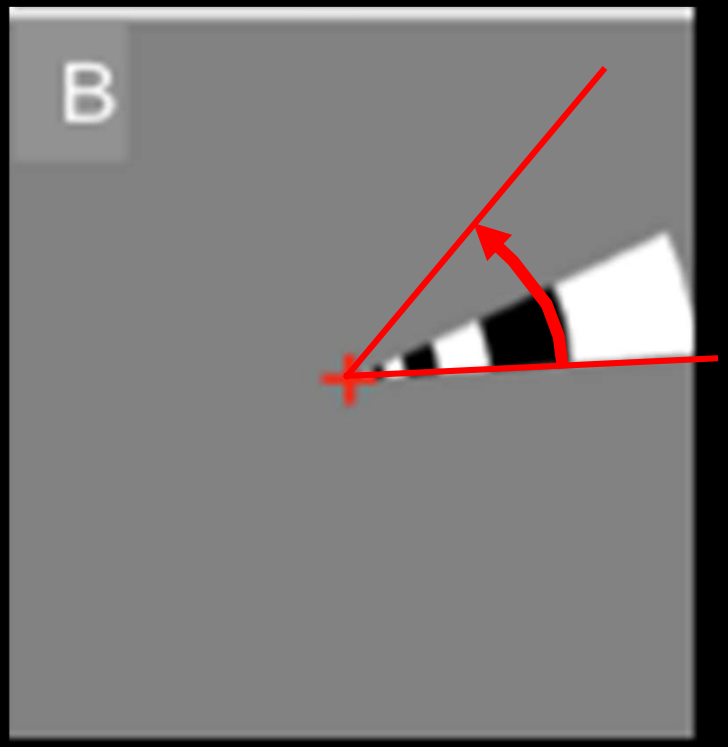
VMU



Retinotopic fMRI



Ring (Exp/Con)
(Eccentricity)



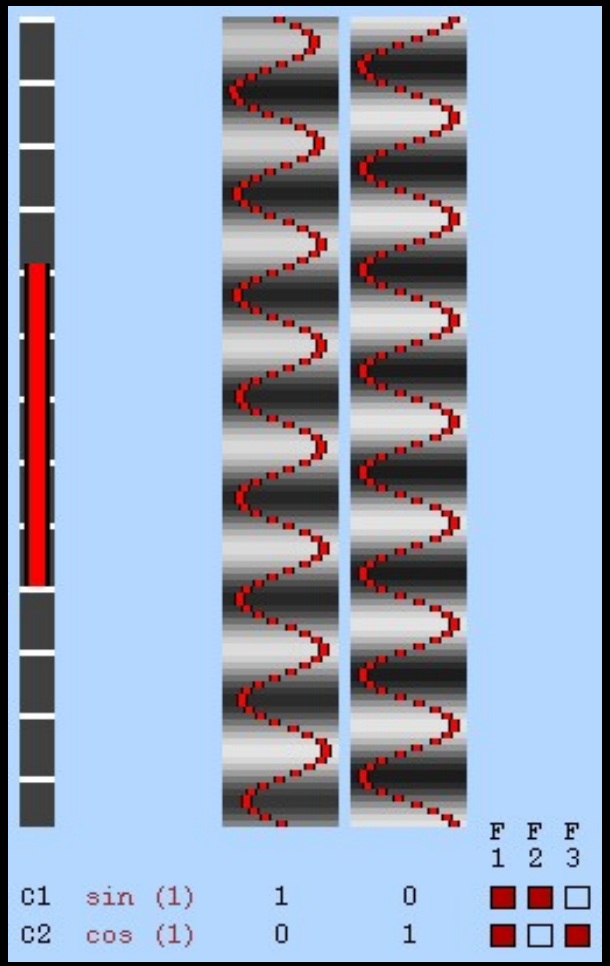
Wedge (Rot)
(Azimuth)

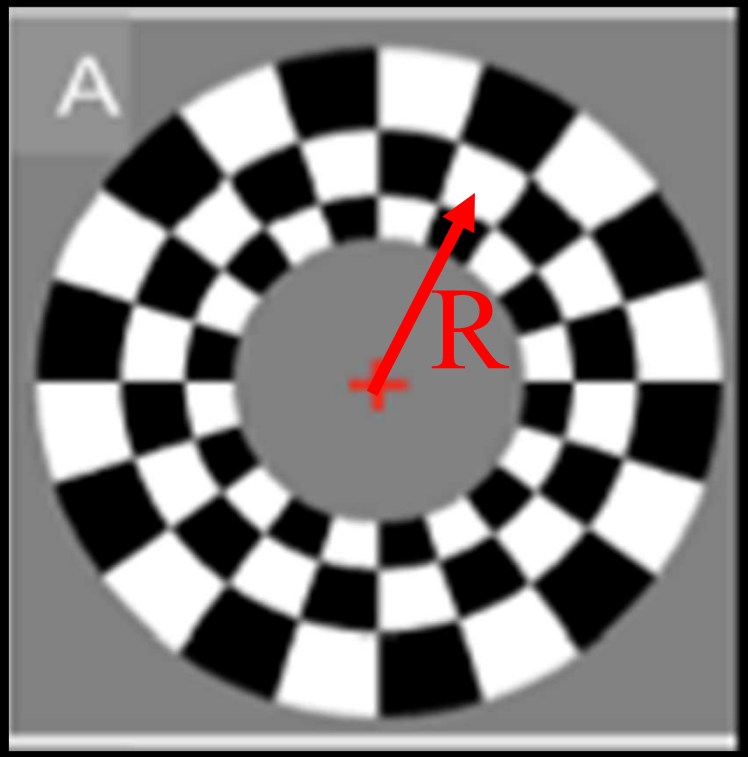
Retinotopic fMRI Analysis

®1=Asin(R)®2=Acos(R)

R=Eccentricity Radius

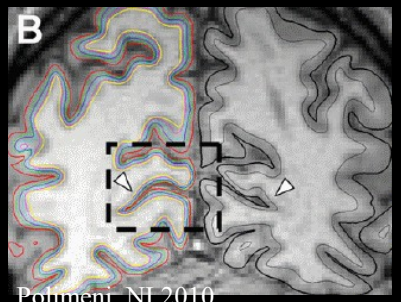
$$R = \tan^{-1}(®1/®2)$$



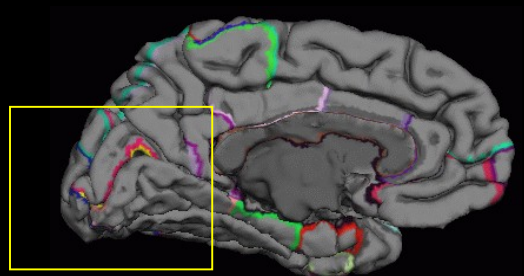


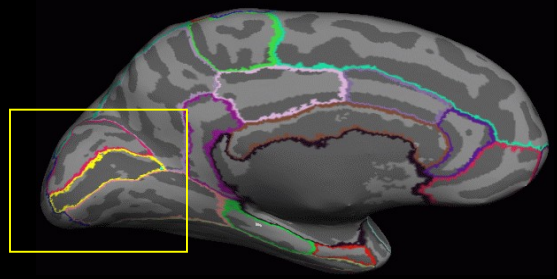
Eccentricity

Retinotopy Results

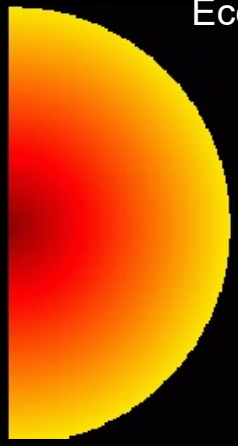


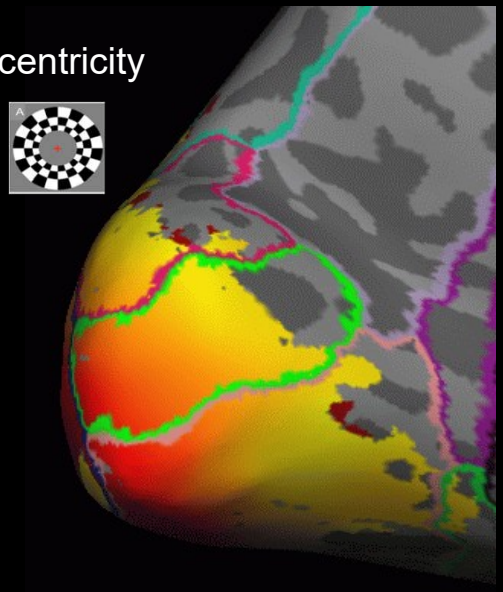
Polimeni, NI 2010

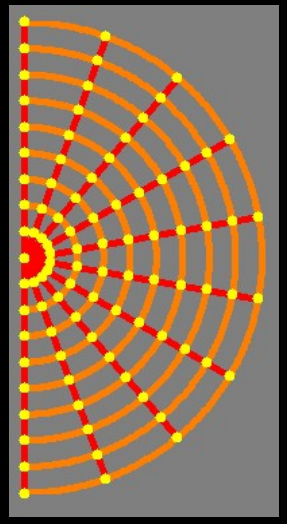




Eccentricity



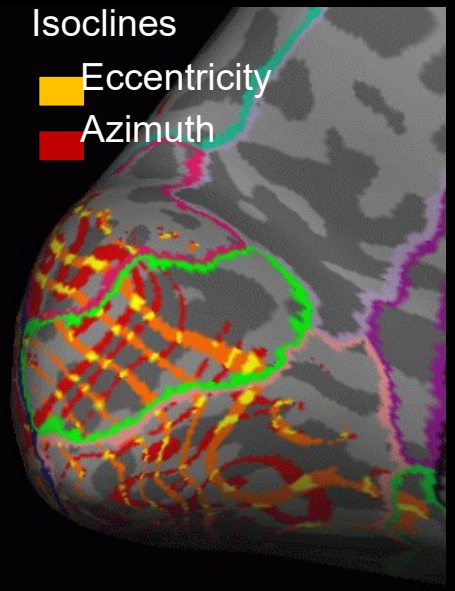




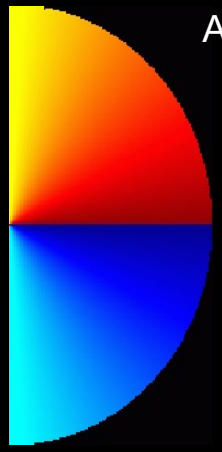
Isoclines

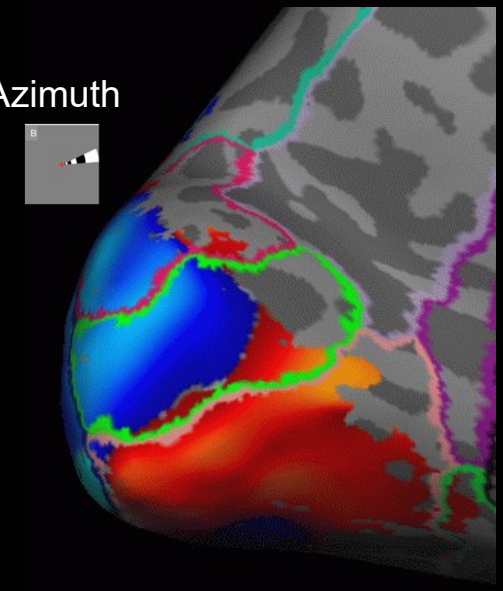
Eccentricity

Azimuth

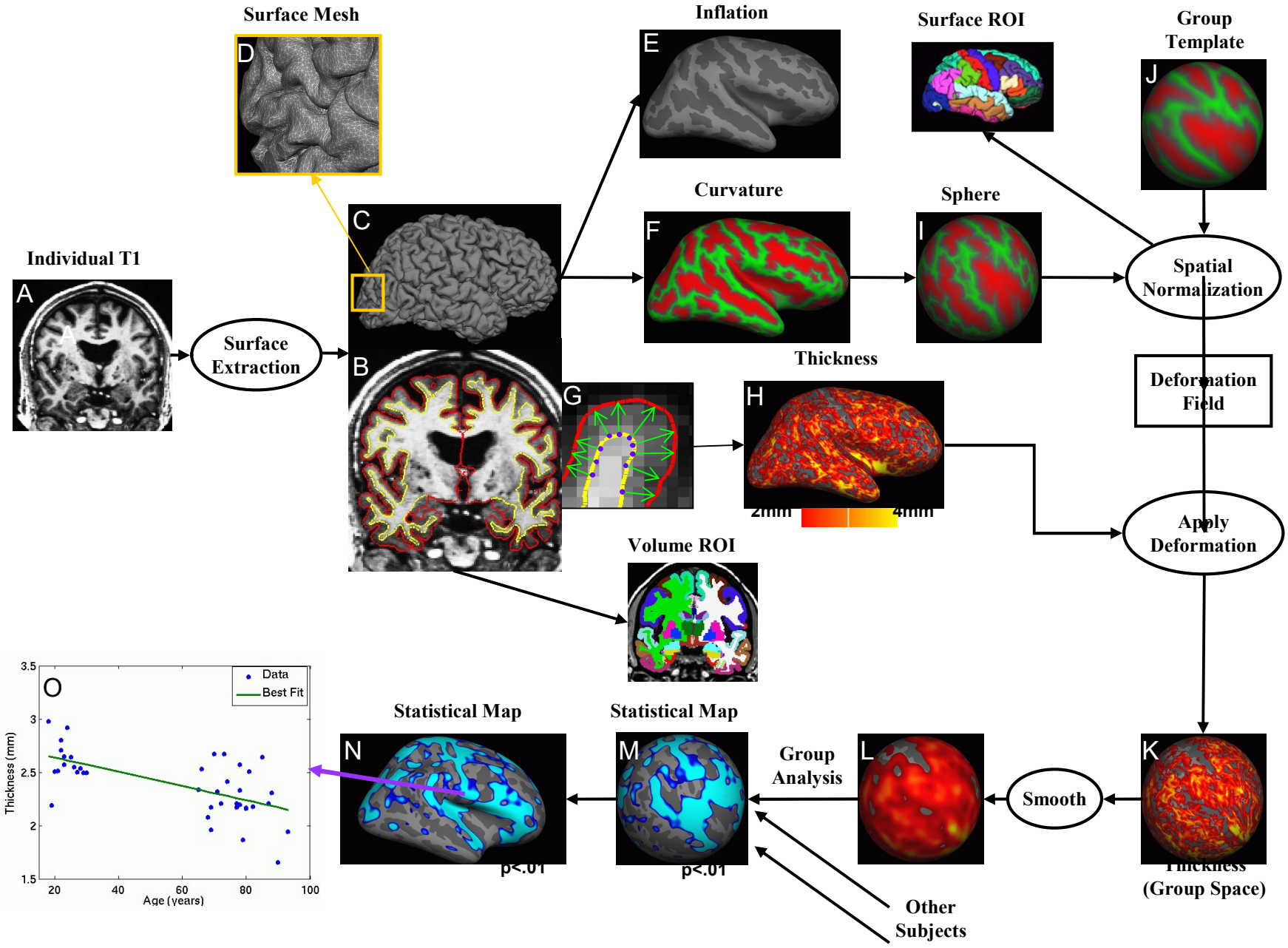


Azimuth

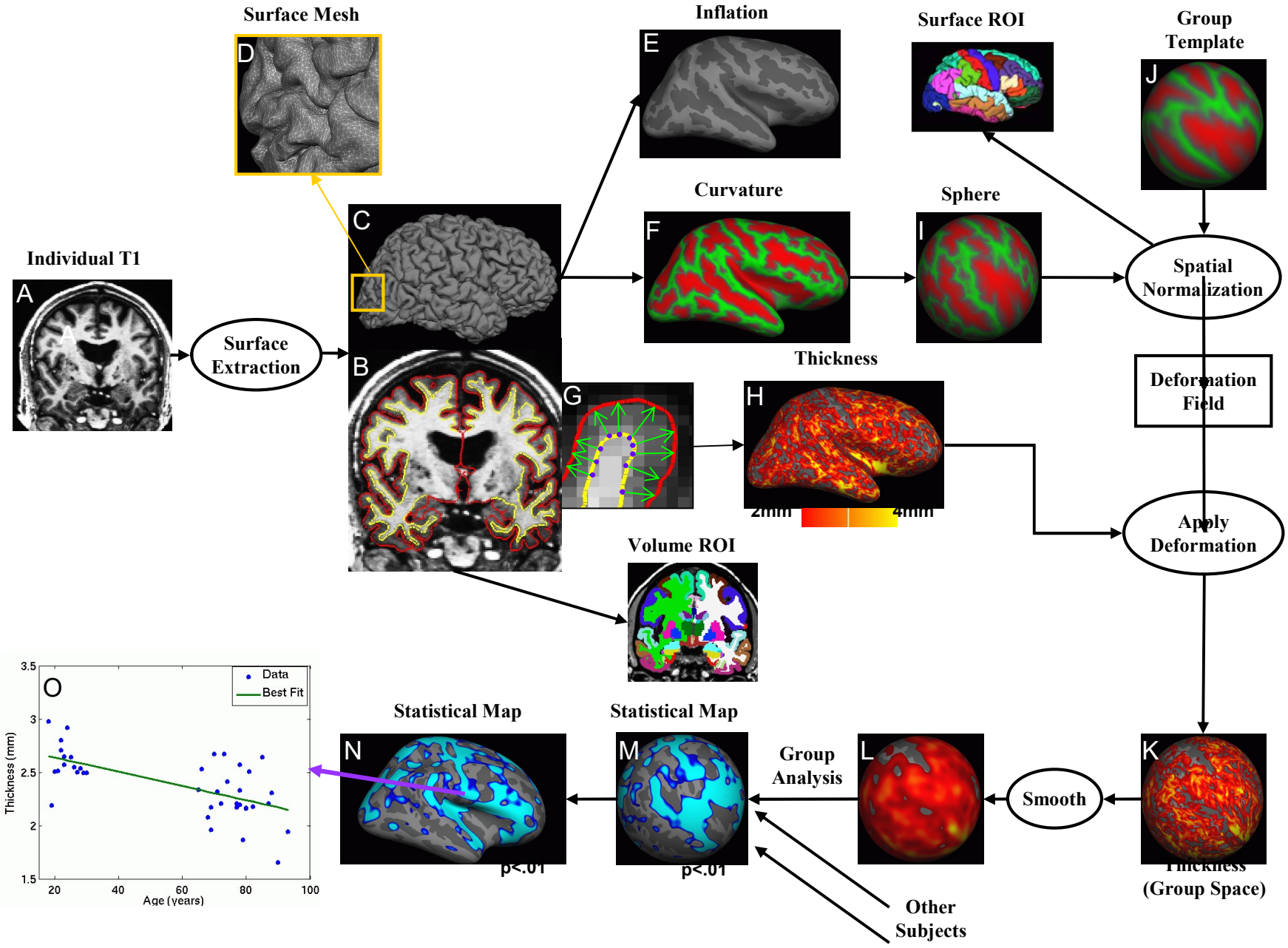




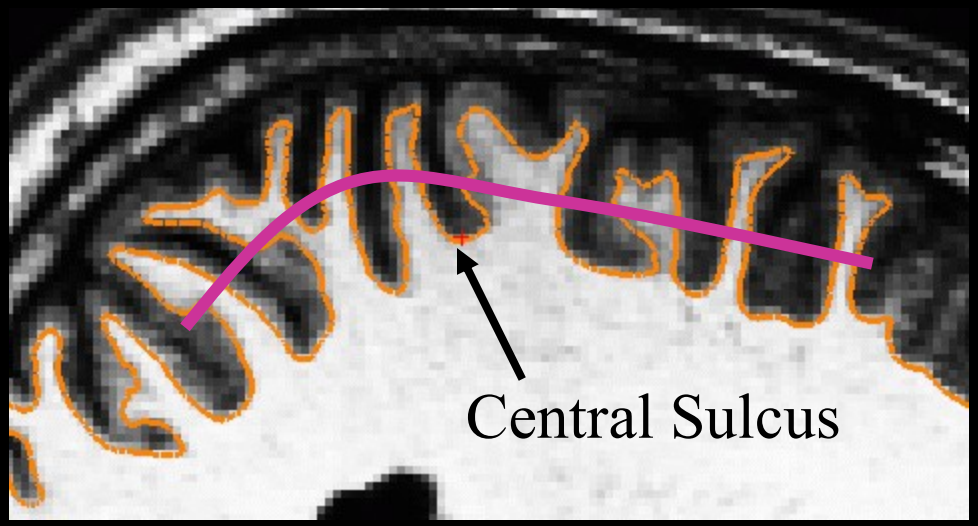
FreeSurfer Analysis Pipeline Overview



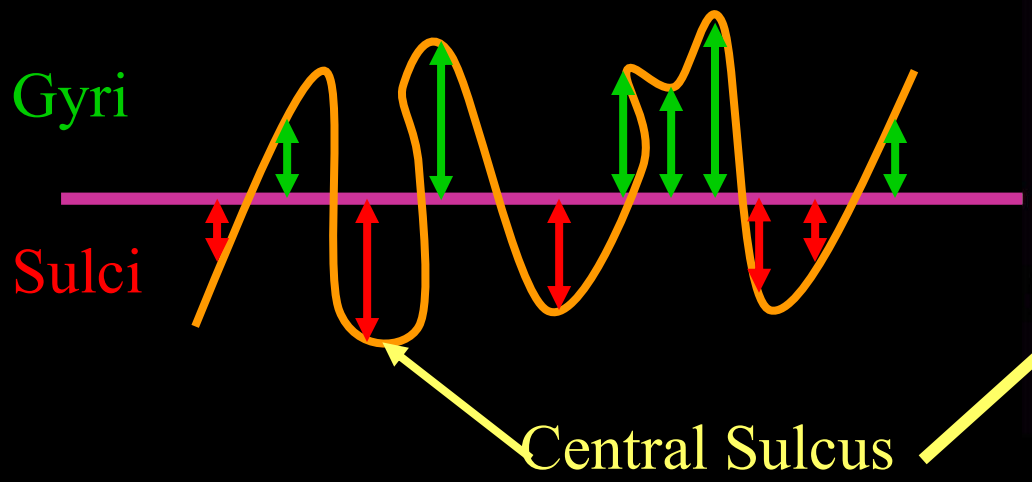
FreeSurfer Analysis Pipeline Overview

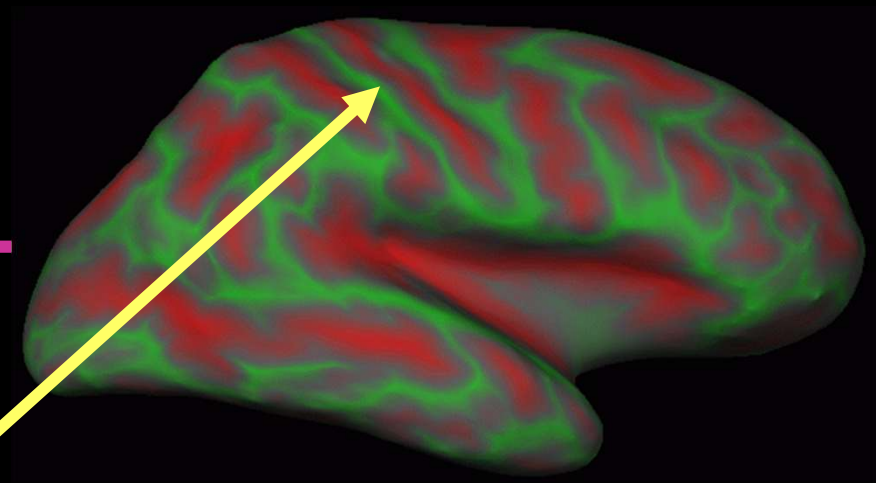


Quantifying Folding Patterns



- Height or Depth Encodes Folding Pattern
- Every vertex has a value





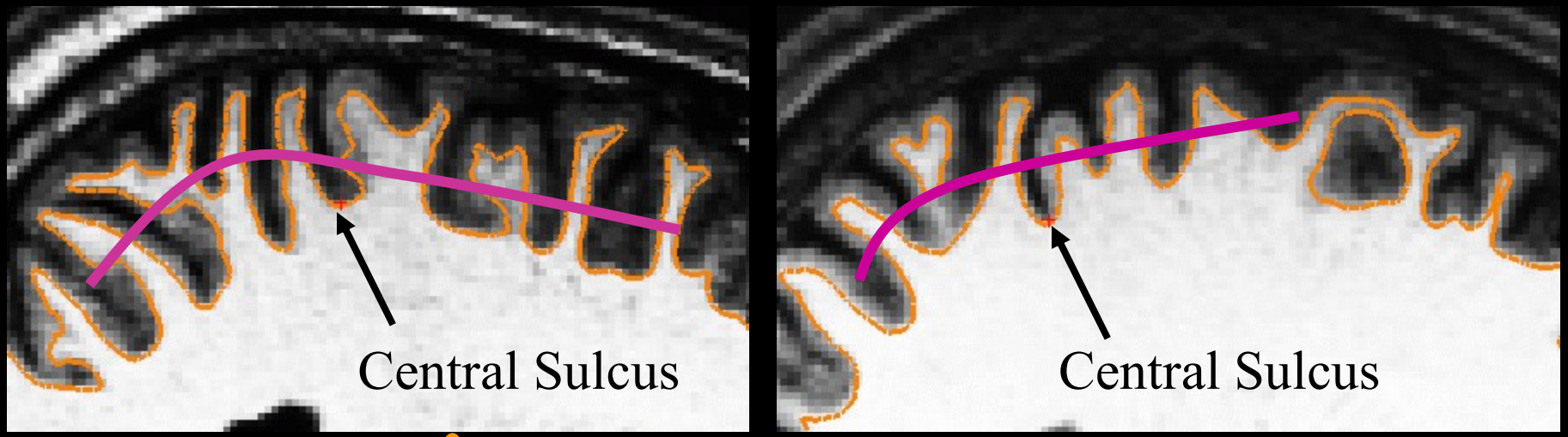
Motivation

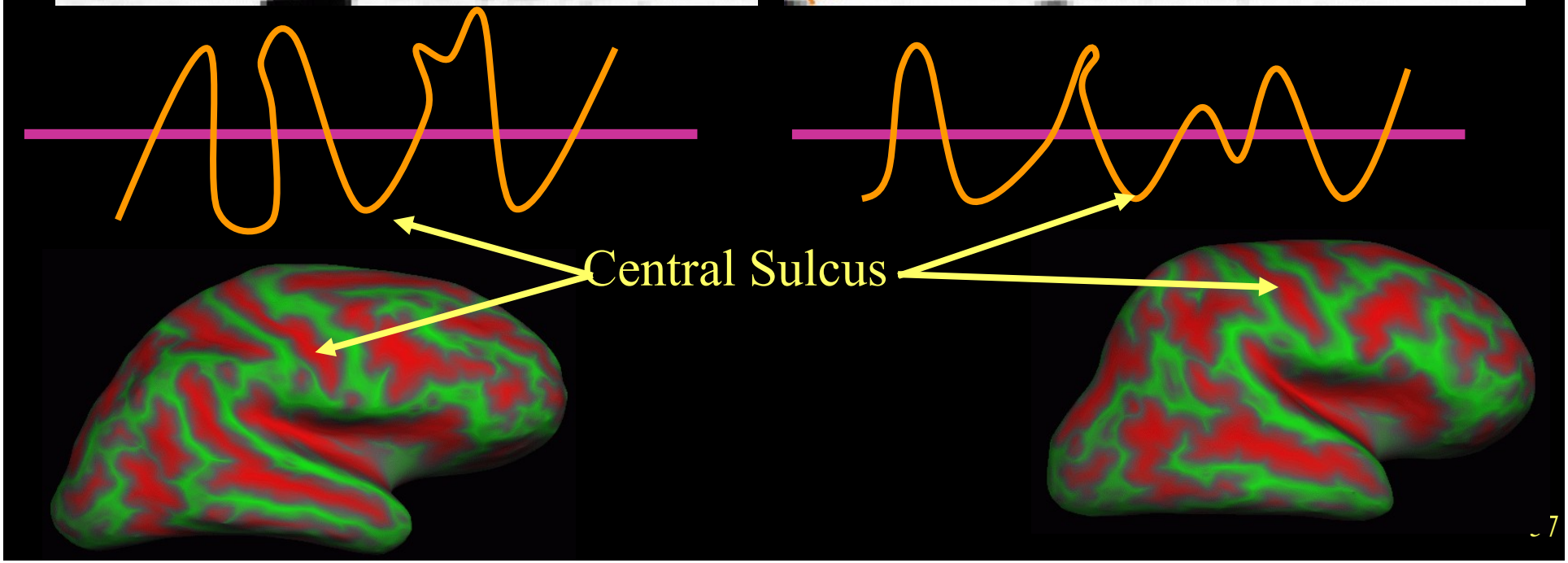
To a large degree, function follows the folding patterns. So if you align the folding patterns between two subjects you will align the function.

Intersubject Registration

Subject 1

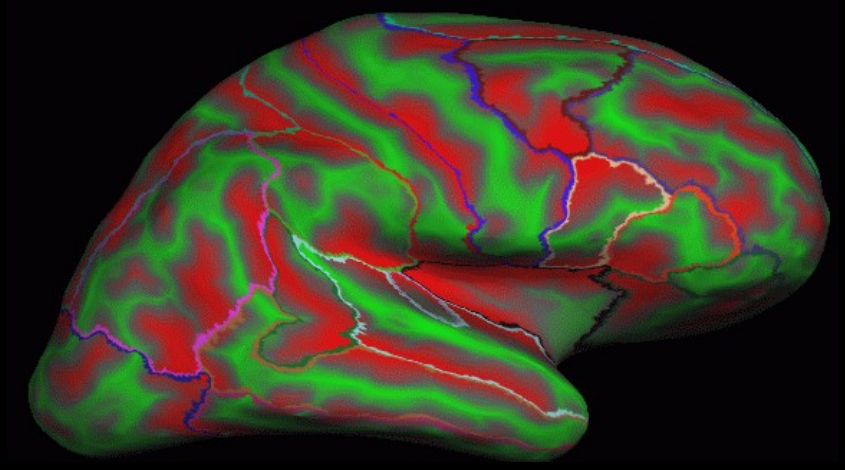
Subject 2



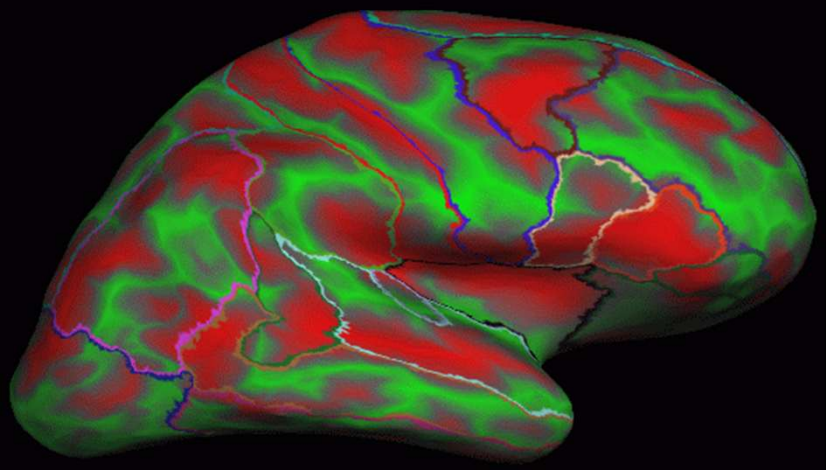


Surface Registration

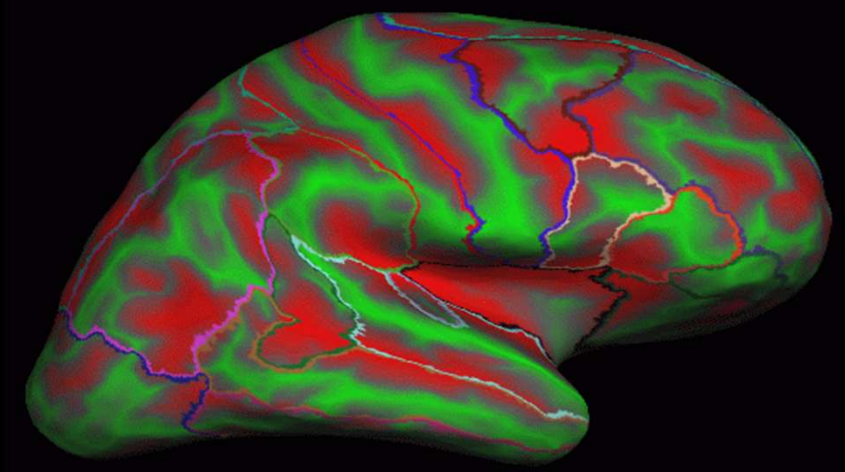
Subject 1



Subject 2 (Before)



Subject 2 (After)



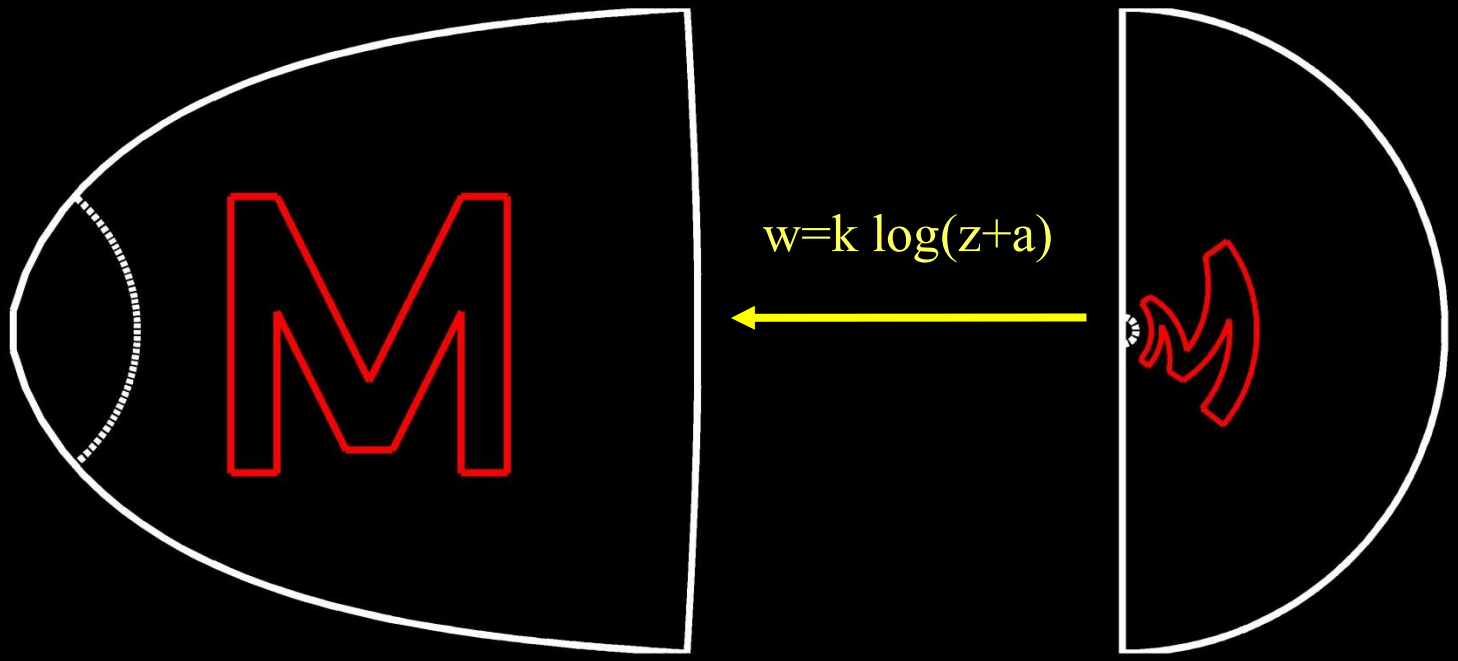
- Shift, Rotate, Stretch
- High dimensional (~500k)

What Can One Do With A Surface Model?

goal: use model to imposed desired activity pattern on V1

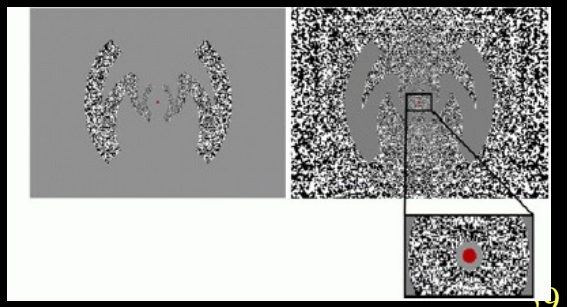
desired shape of activity pattern

required shape of stimulus



left primary visual cortex

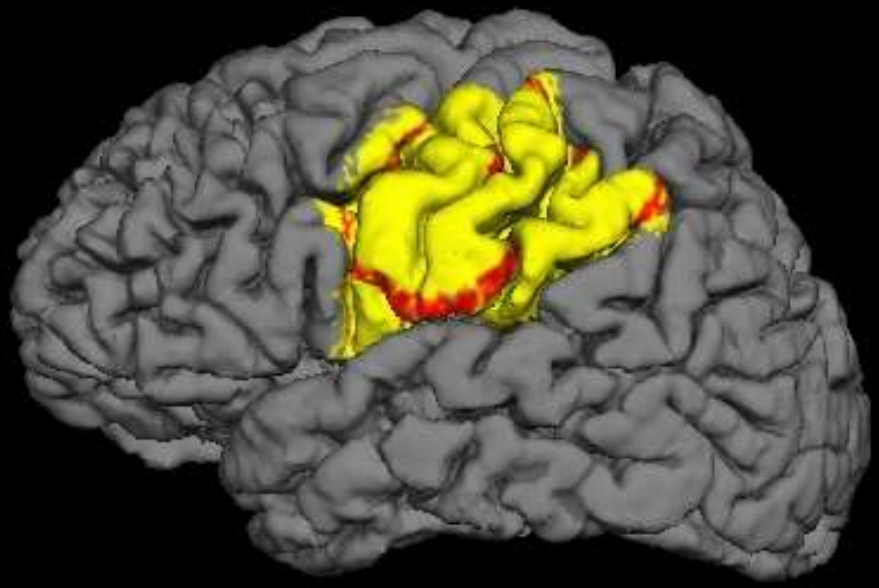
right visual hemifield



Collaboration with **Jon Polimeni** and Larry Wald.

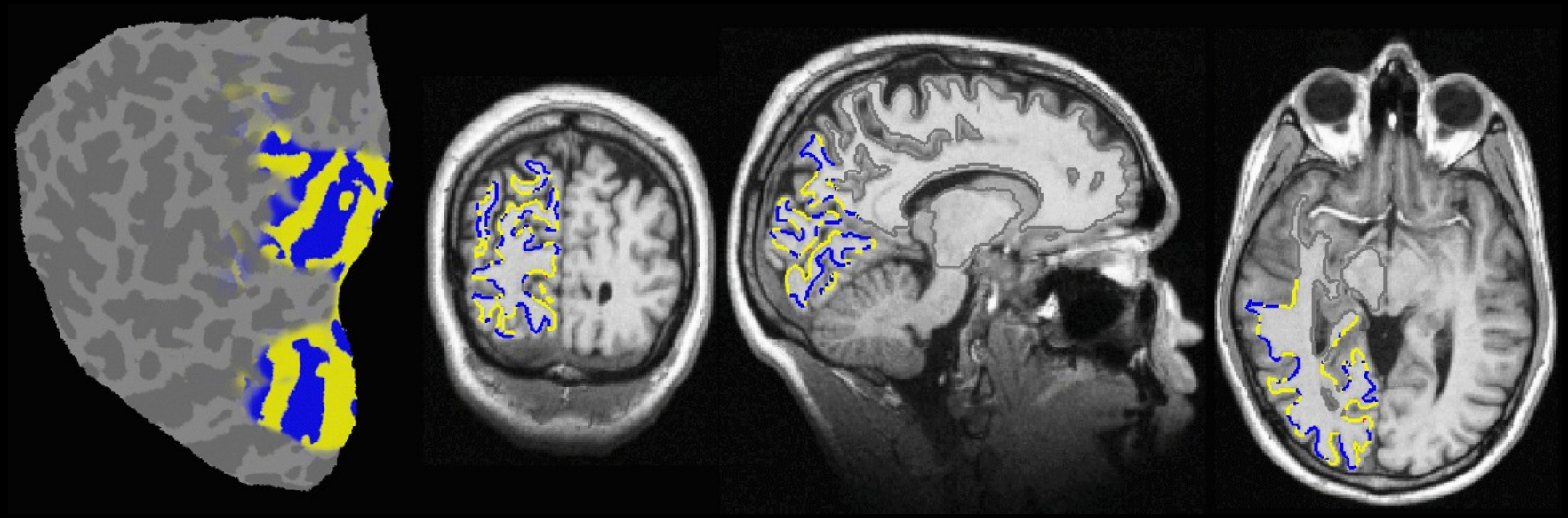
Thanks!

Use FreeSurfer



Be Happy

Retinotopy Field Sign Maps



- Changes in orientation between V1, V2, etc

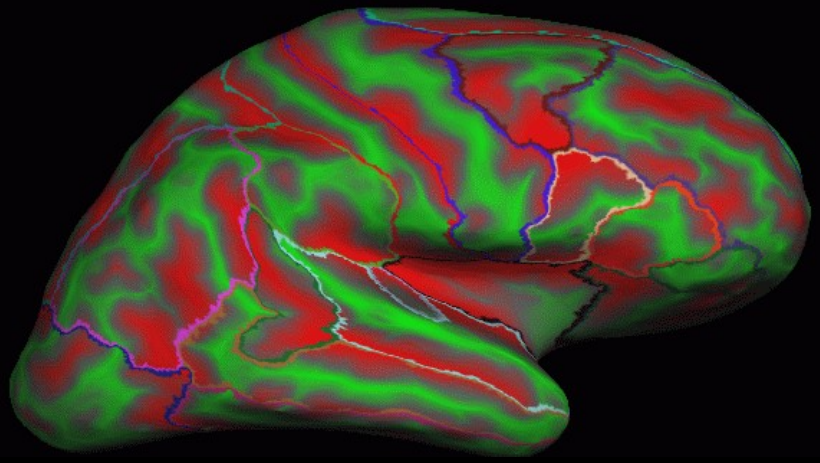
From (Sereno et al, 1995, Science).

Surface Review

- Cortex is a 2D sheet folded into 3D
- Function is organized along the sheet
- Visualization
- Better to smooth in 2D instead of 3D
- Register across subjects by aligning anatomy (folding patterns) in 2D
- Common surface space (like Talairach) for group studies

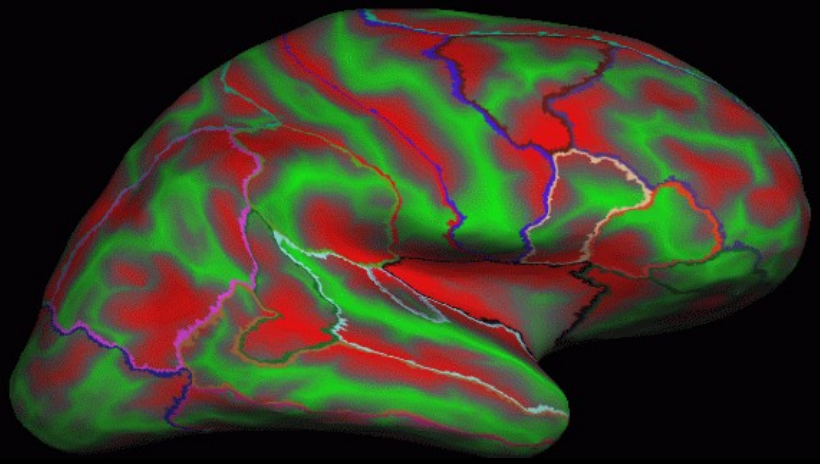
Surface Registration

Subject 1

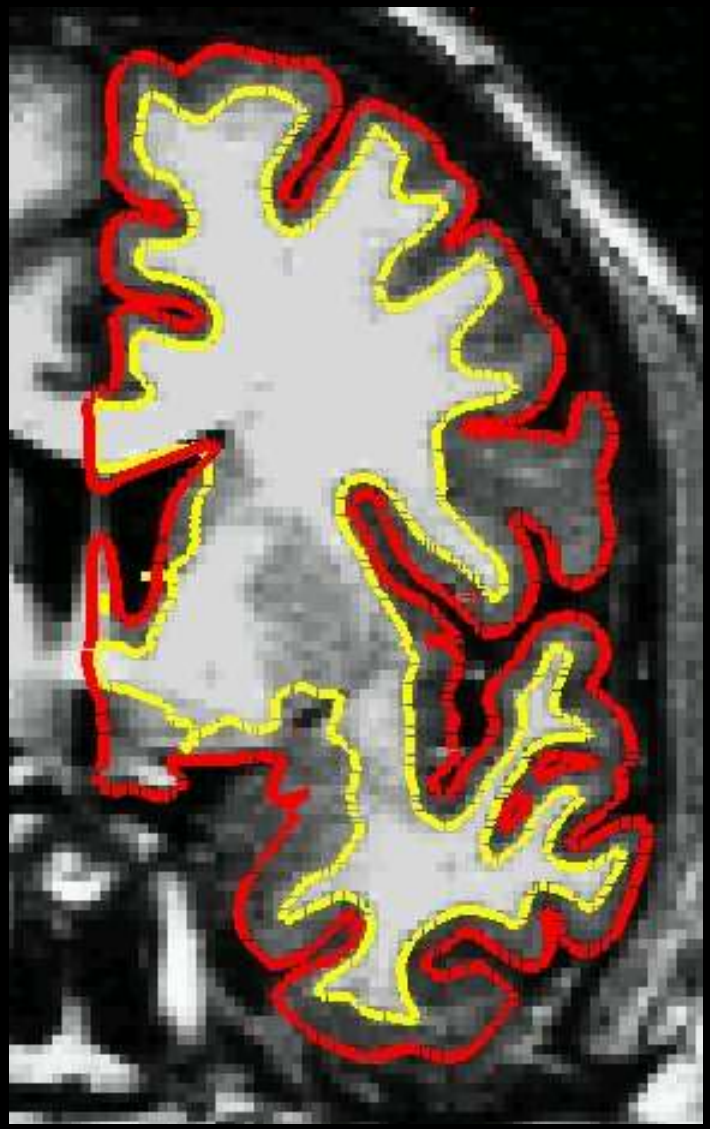


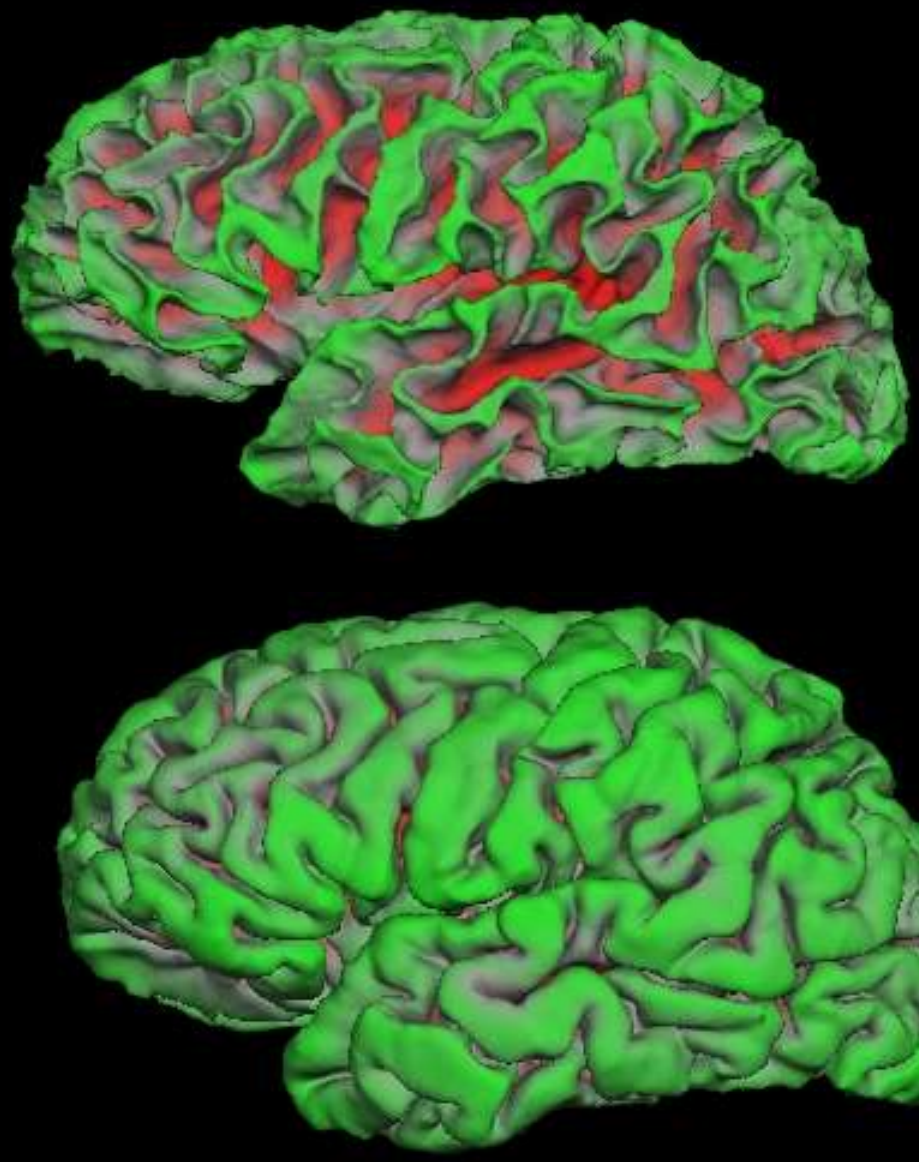
Subject 2 (Before)

Subject 2 (After)

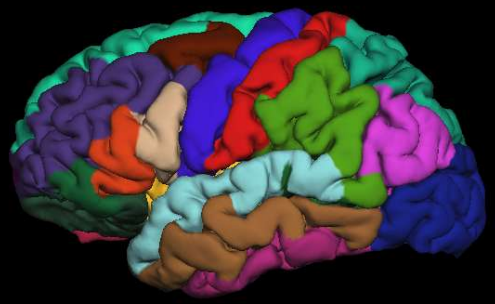


Surfaces: White and Pial

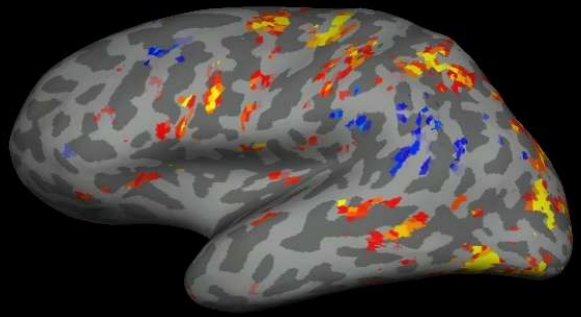




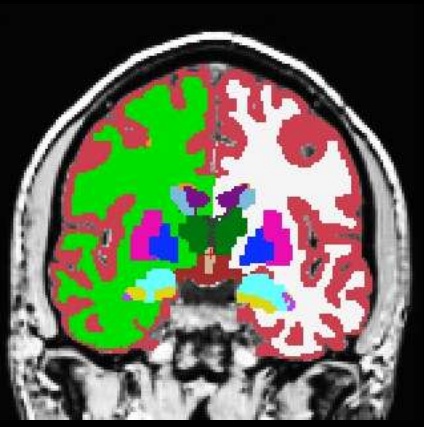
Surface and Volume Analysis



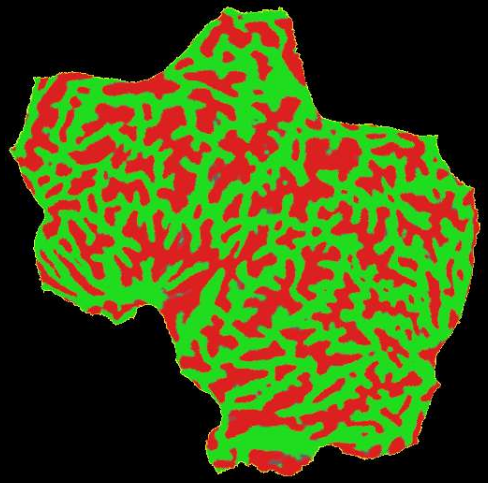
Cortical Reconstruction and Automatic Labeling



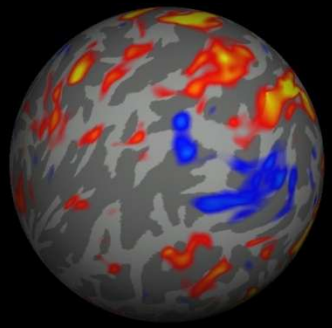
Inflation and Functional Mapping



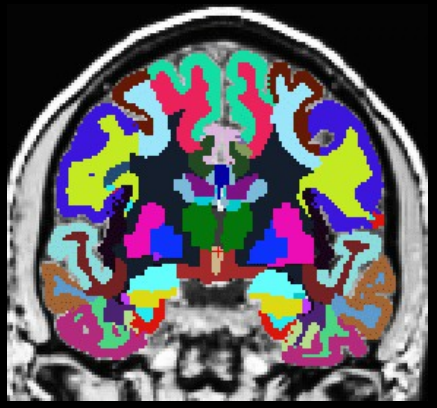
Automatic Subcortical Gray Matter Labeling



Surface Flattening

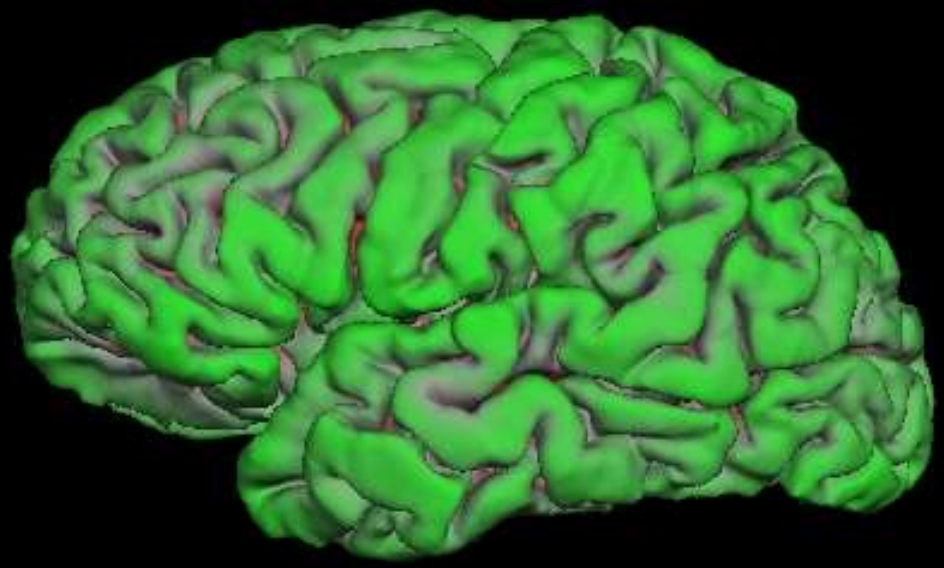


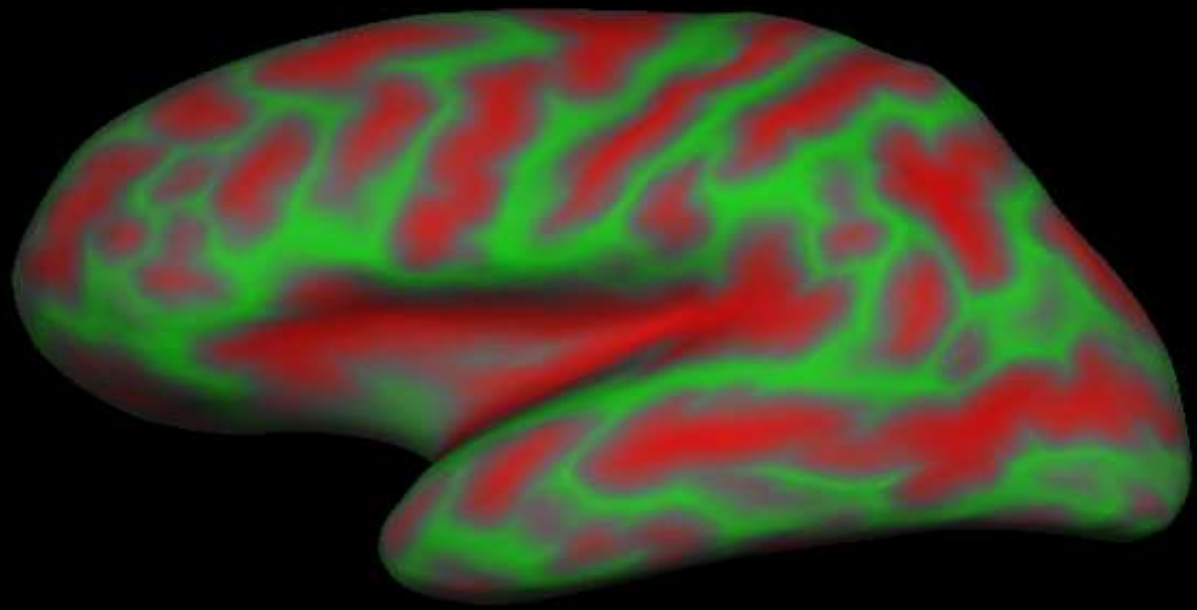
Surface-based Intersubject Alignment and Statistics



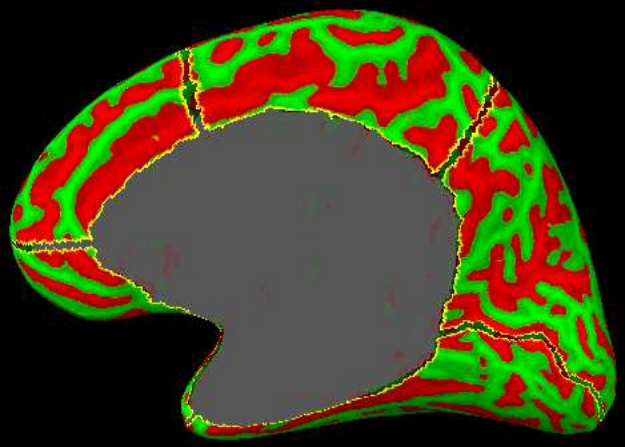
Automatic Gyral White Matter Labeling

Inflation

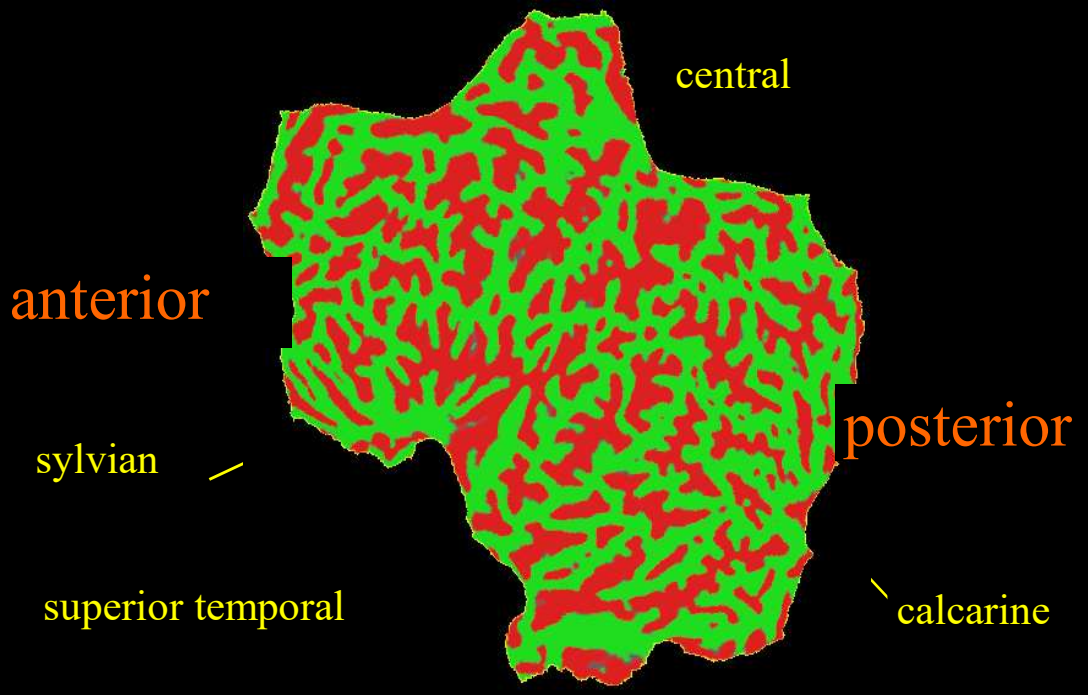




Surface Flattening – Whole Hemisphere

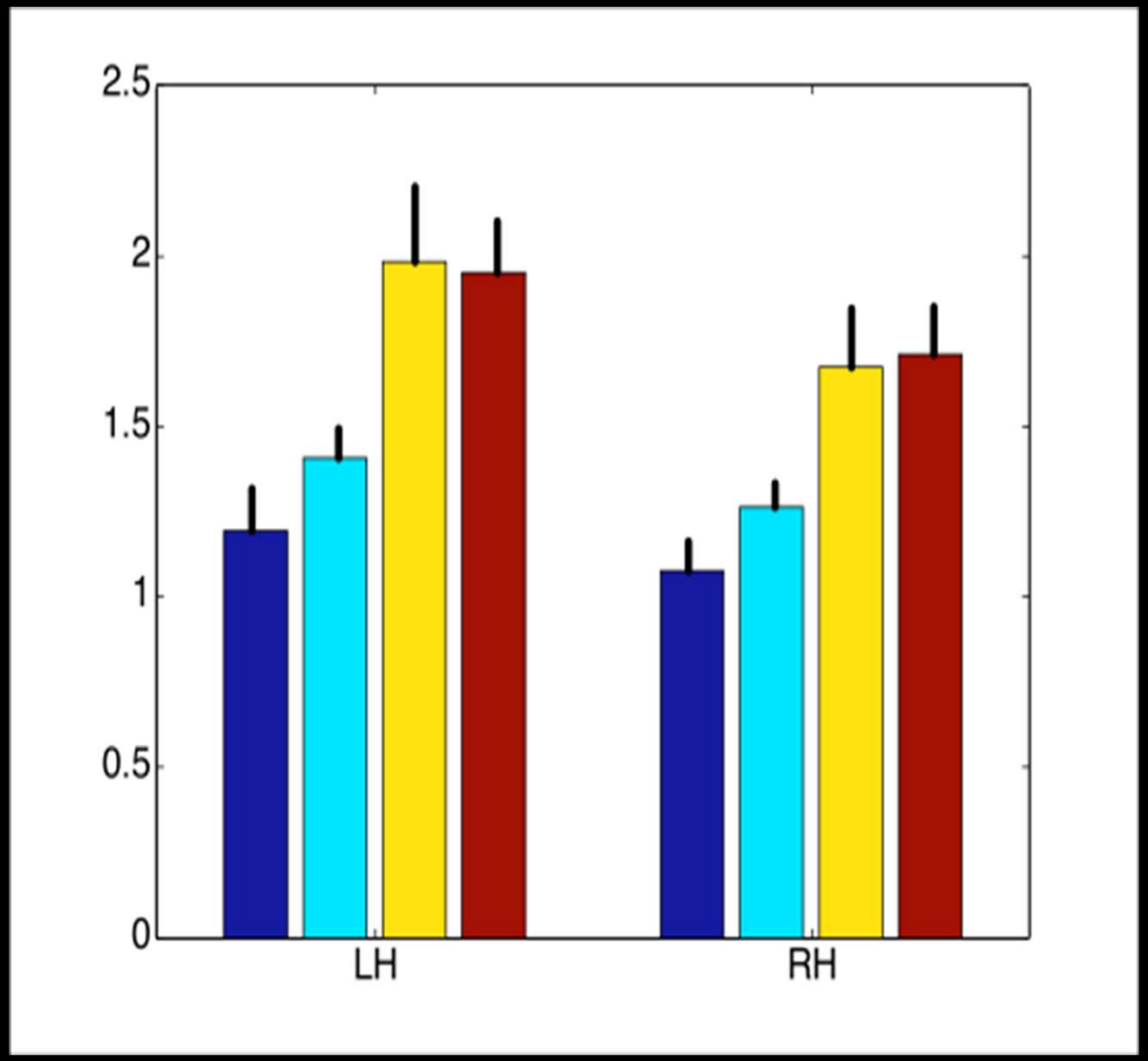


Inflated surface with cuts



Metrically optimal flat map

Volume Differences Predictive of AD



Data courtesy of Drs Marilyn Albert and Ron Killiany

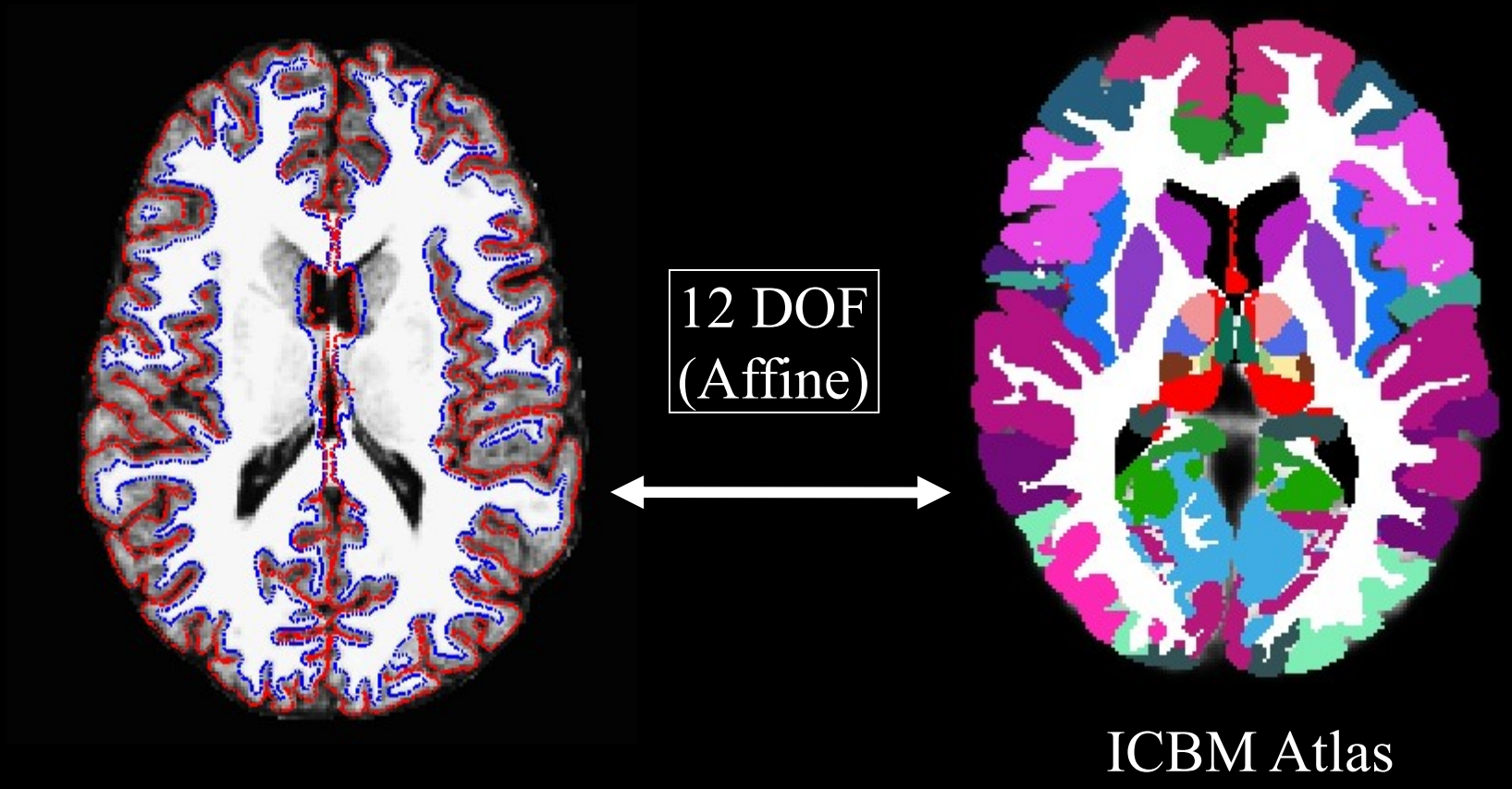
Why FreeSurfer?

1. Anatomical analysis is not like functional analysis – it is completely stereotyped.

2. Registration to a template (e.g. MNI/Talairach) doesn't account for individual anatomy.

3. Even if you don't care about the anatomy, anatomical models allow functional analysis not otherwise possible.

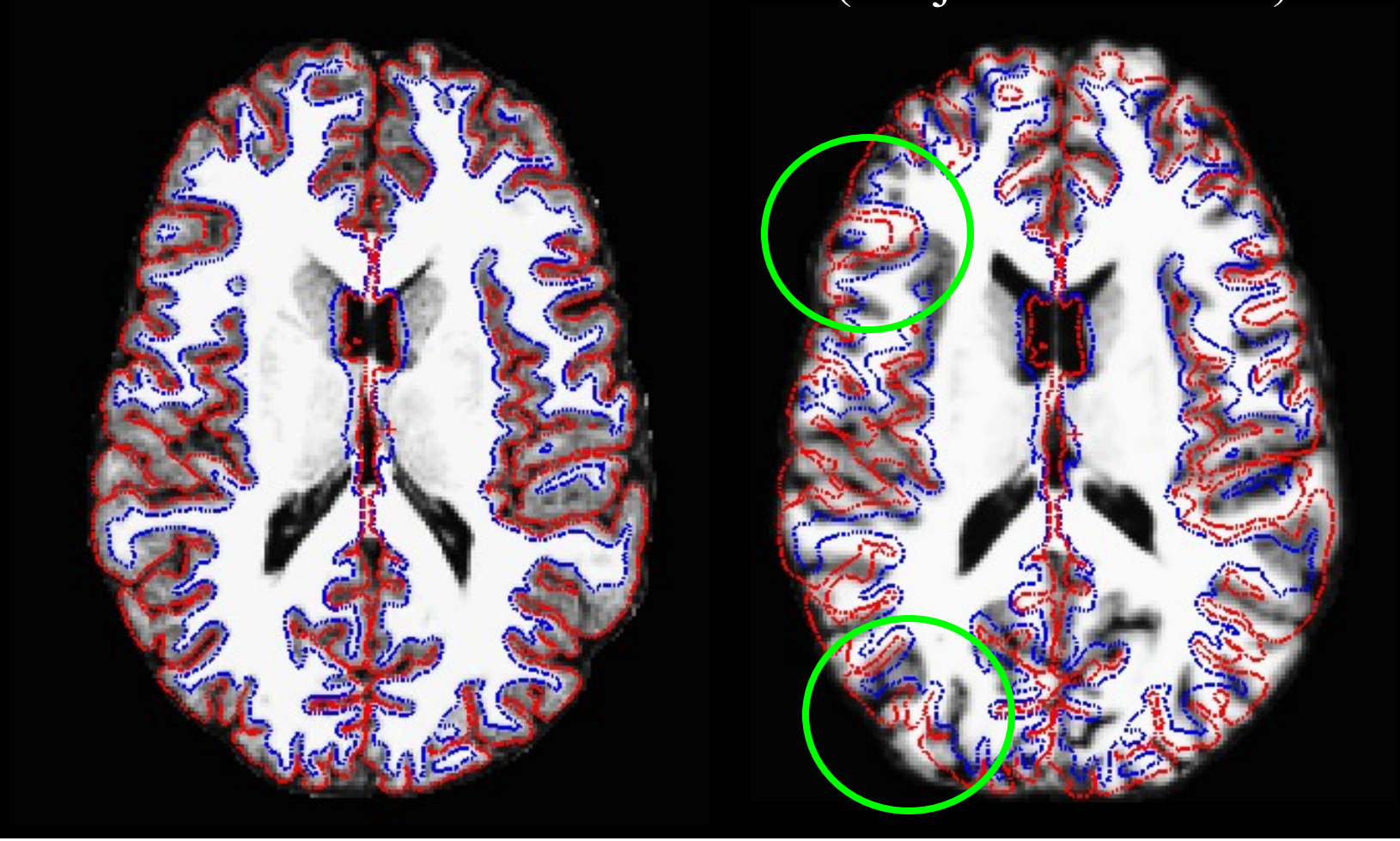
Why not just register to an ROI Atlas?



Problems with Affine (12 DOF) Registration

Subject 1

Subject 2 aligned with Subject 1
(Subject 1's Surface)



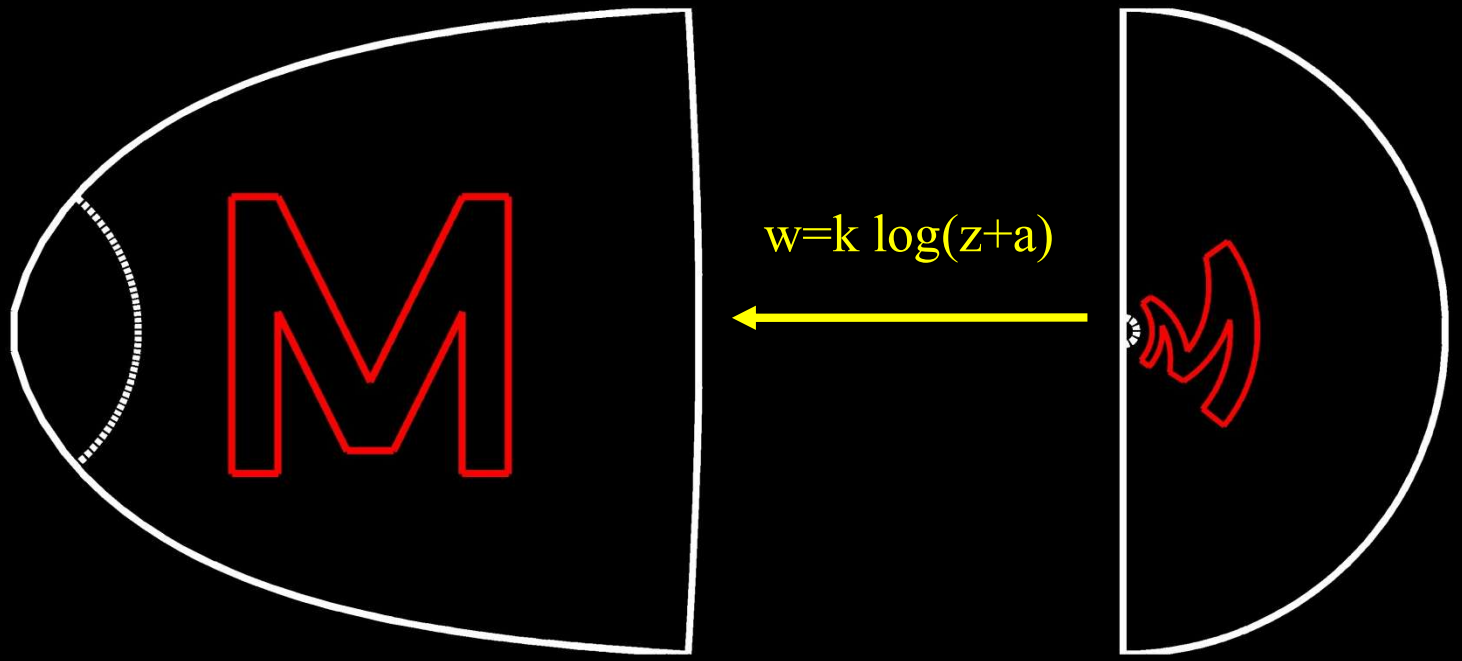
Talk Outline

1. Cortical (surface-based) Analysis.
2. Volume Analysis.
3. New Features in 5.1.

What Can One Do With A Surface Model?

goal: use model to imposed desired activity pattern on V1

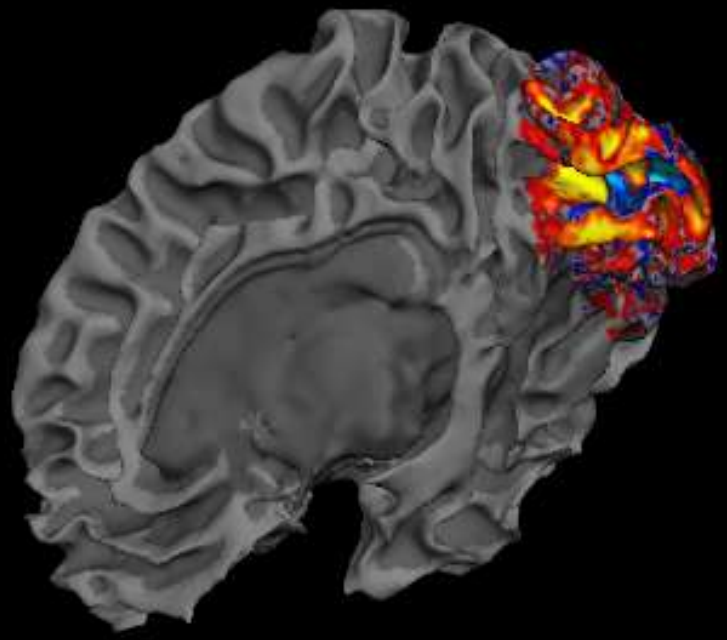
desired shape of activity pattern *required* shape of stimulus



left primary visual cortex right visual hemifield

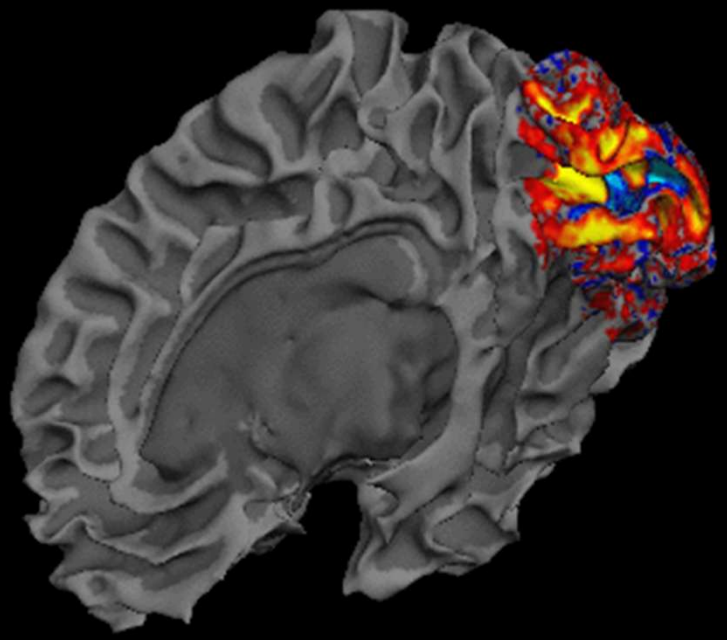
Collaboration with **Jon Polimeni** and Larry Wald.

Tangential Resolution Measured with Surface-based Analysis



Collaboration with Jon Polimeni and Larry Wald.

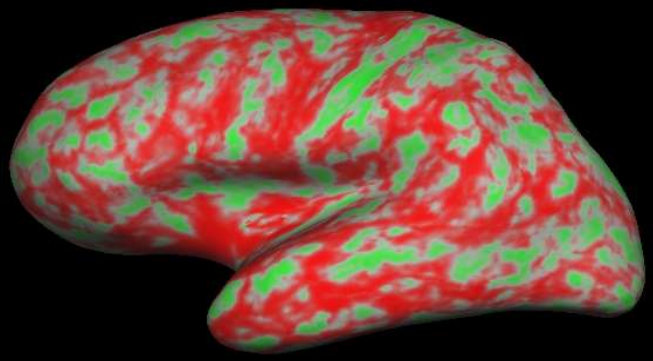
Tangential Resolution Measured with Surface-based Analysis



Collaboration with Jon Polimeni and Larry Wald.

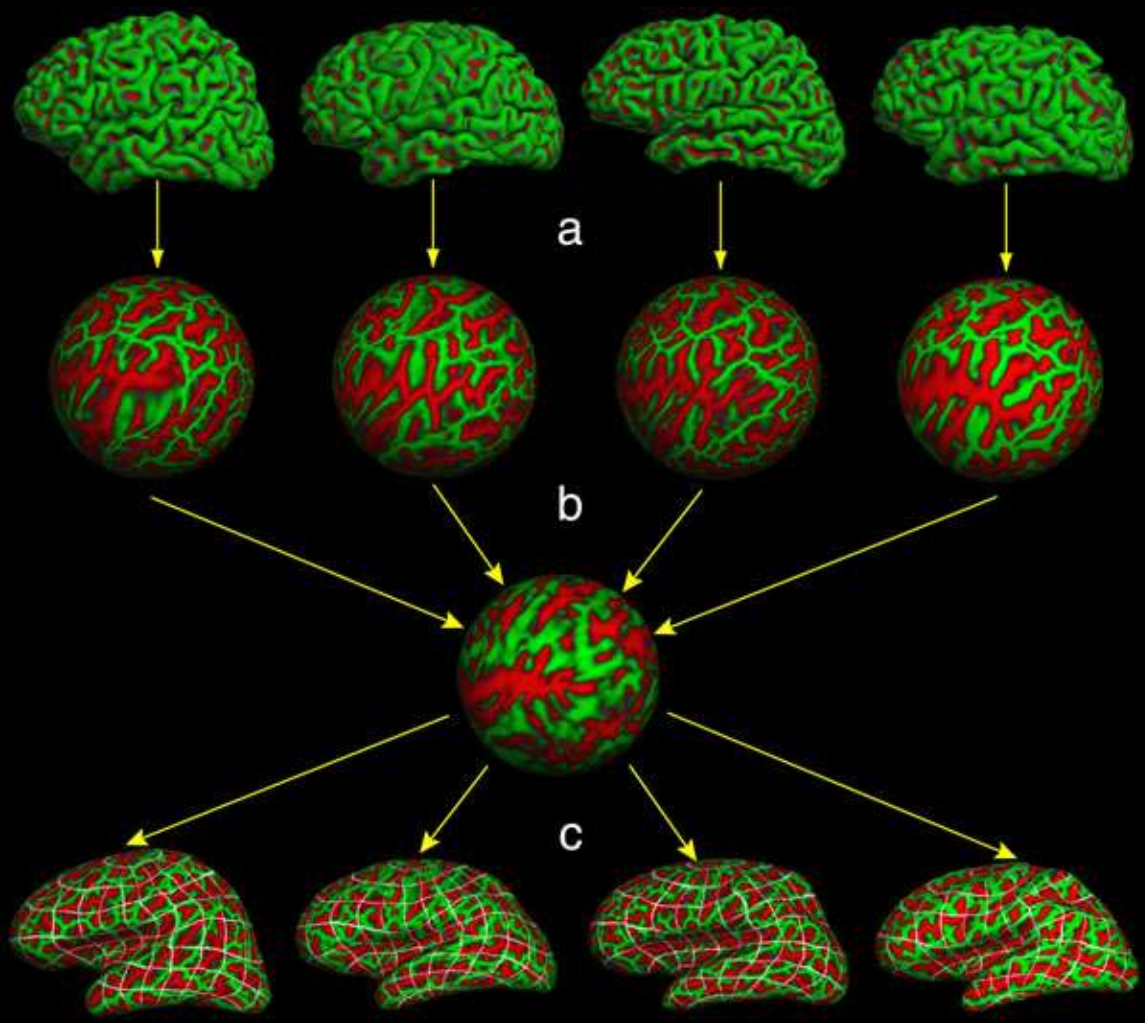
Cortical Thickness

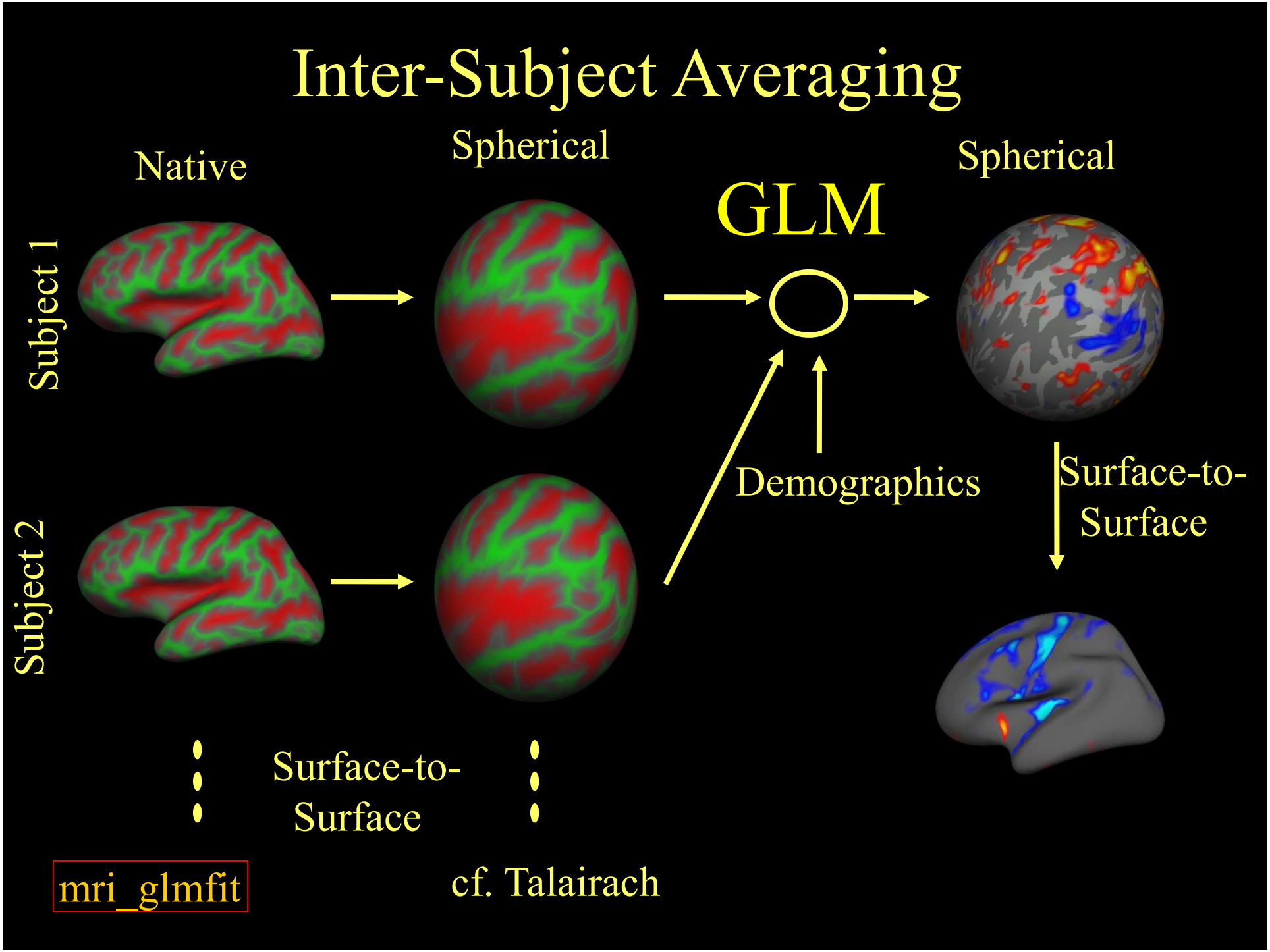
- Distance between white and pial surfaces
- One value per vertex



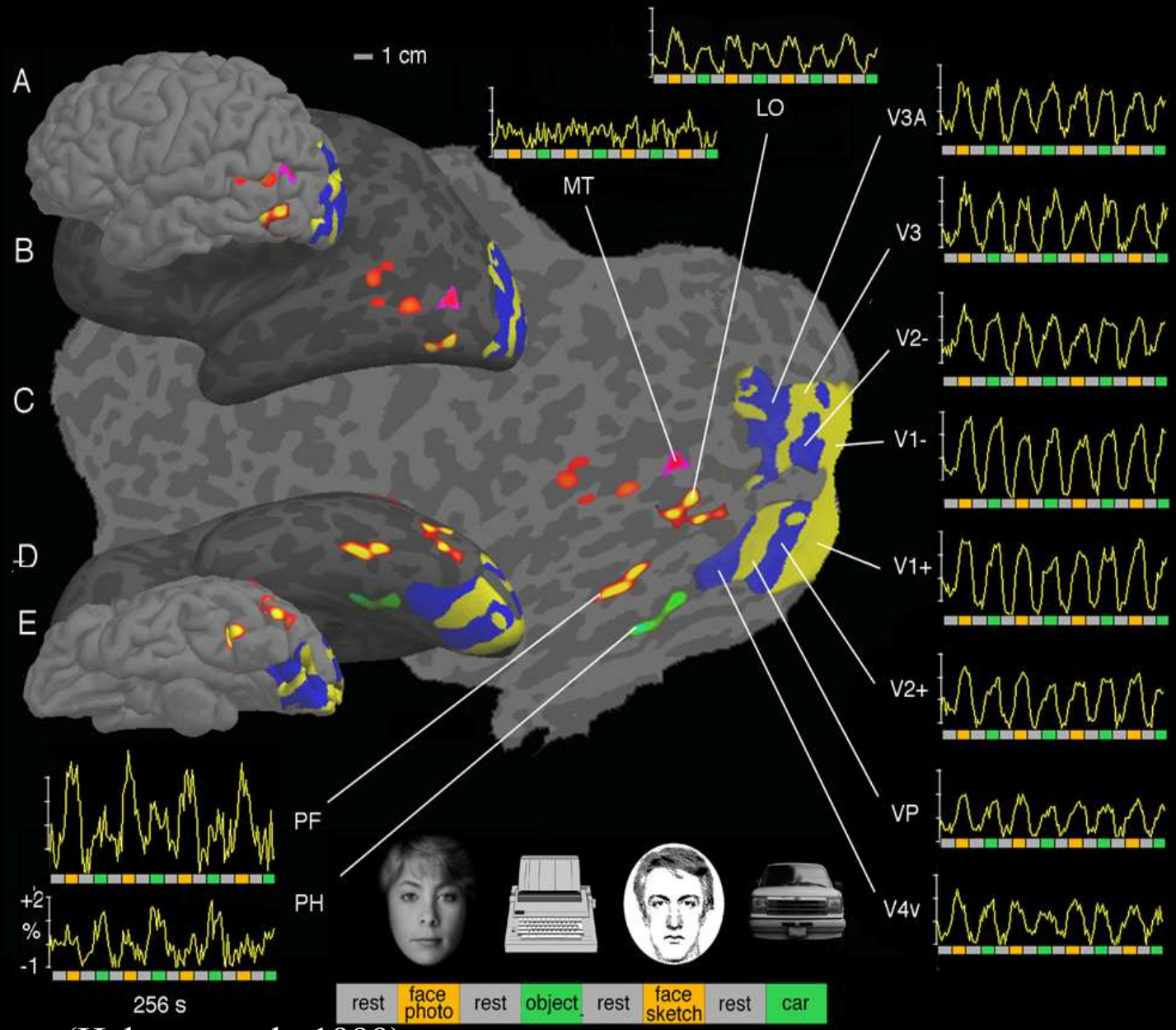
lh.thickness, rh.thickness

A Surface-Based Coordinate System




Inter-Subject Averaging
Native
Spherical
GLM
Spherical
Subject 1
Subject 2
Demographics
Surface-to-
Surface
Surface-to-
Surface
mri_glmfit
cf. Talairach

Visualization

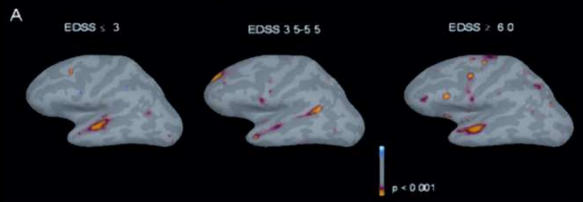


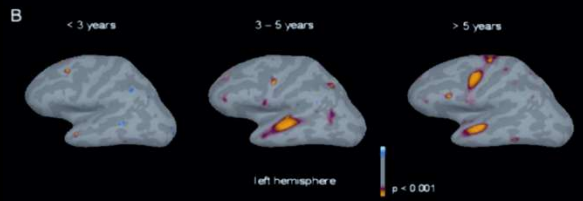
Borrowed from (Halgren et al., 1999)

Huntington's Disease

Rosas et al., 2002

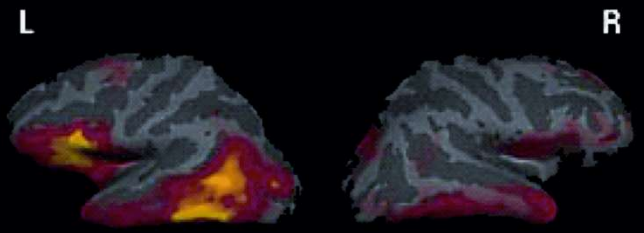
Multiple Sclerosis



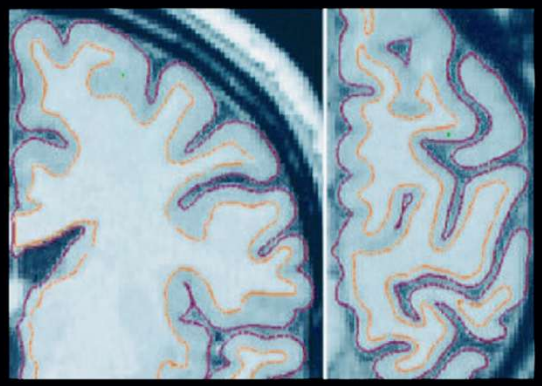


Sailer et al., 2003

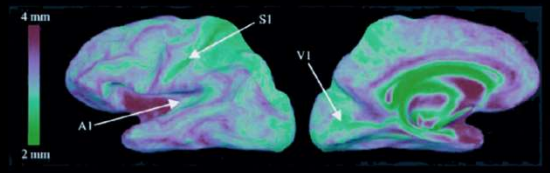
Schizophrenia



Kuperberg et al., 2003

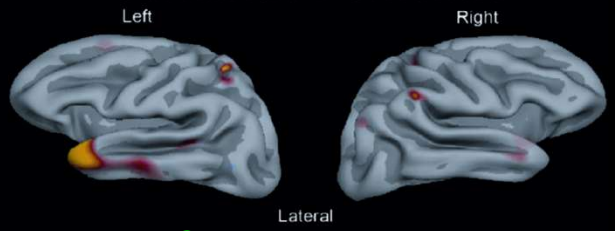


Normal Variation



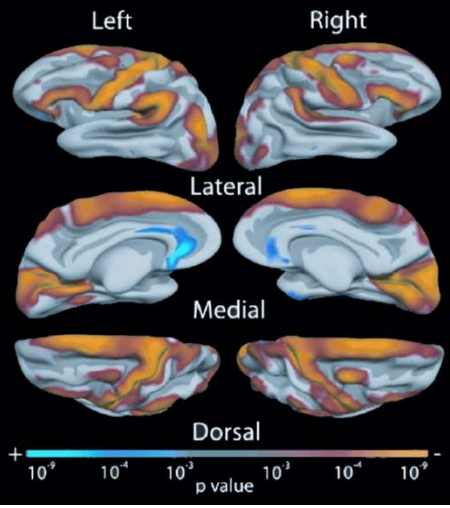
Fischl et al., 2000

Semantic Dementia



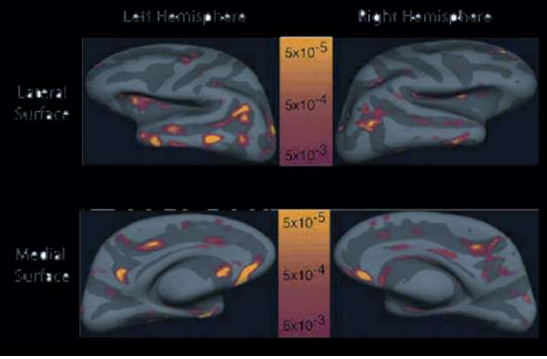
Gold et al., 2005

Aging



Salat et al., 2004

Animal Phobia



Rauch et al., 2004

Talk Outline

1. Cortical (surface-based) Analysis.
2. Volume Analysis.
3. New Features in 5.1.

Volume Analysis: Automatic Individualized Segmentation

Surface-based coordinate system/registration appropriate for cortex but not for thalamus, ventricular system, basal ganglia, etc…

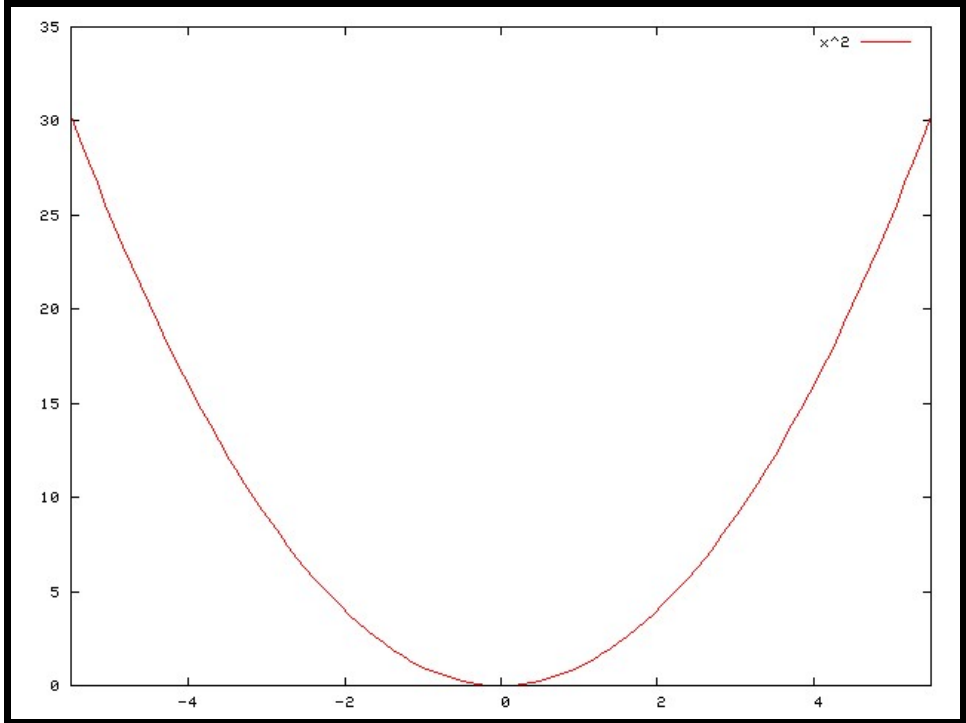
Anatomy is extremely variable – measuring the variance and accounting for it is critical (more in the individual subject talk)!

FreeSurfer Version 5.1: New Features

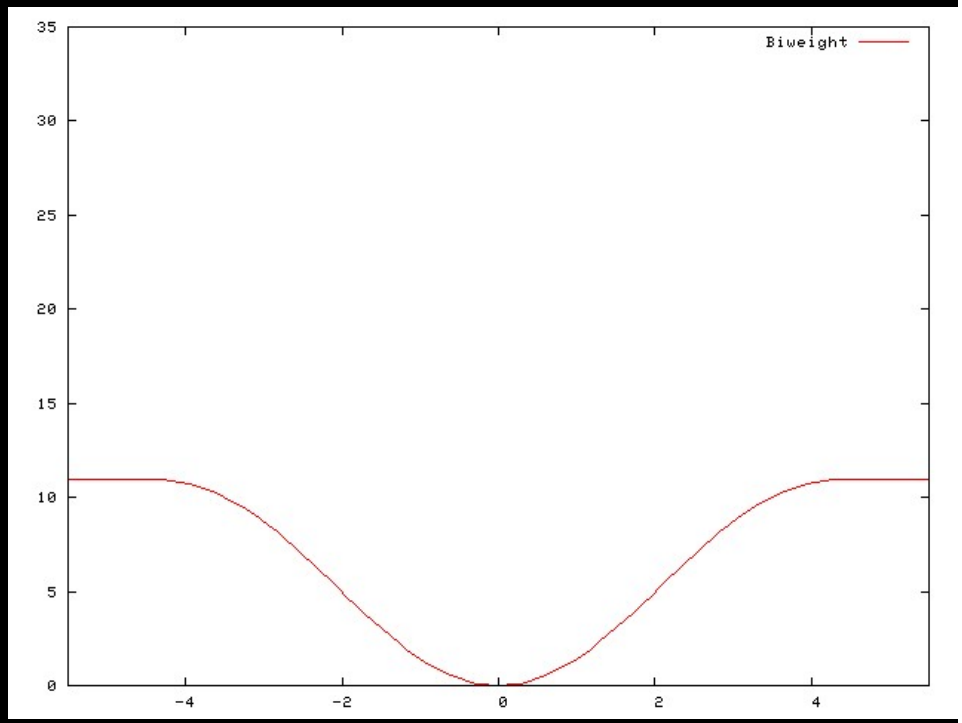
1. Longitudinal Analysis (Martin Reuter).
2. Automated tractography with Tracula (Anastasia Yendiki).
3. Automated Hippocampal Subfield segmentation (Koen van Leemput).
4. New Architectonic Areas (entorhinal cortex, Jean Augustinack).
5. Open Source! (modified BSD/MIT license)

Unbiased Robust Registration*

- The contribution of error is limited for outliers:



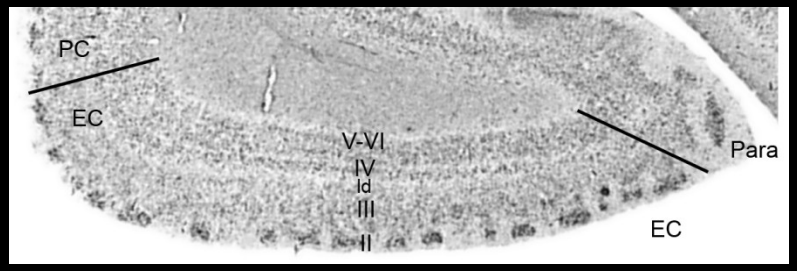
Squared Error

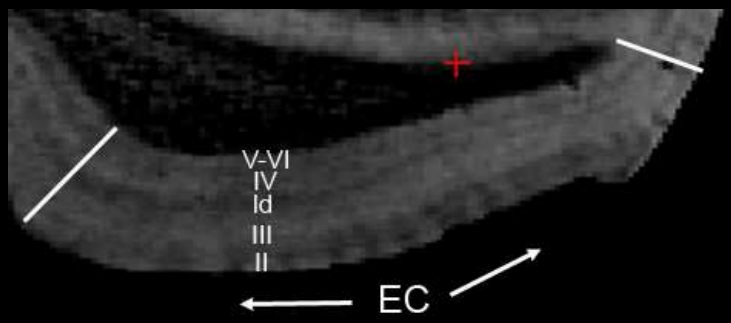


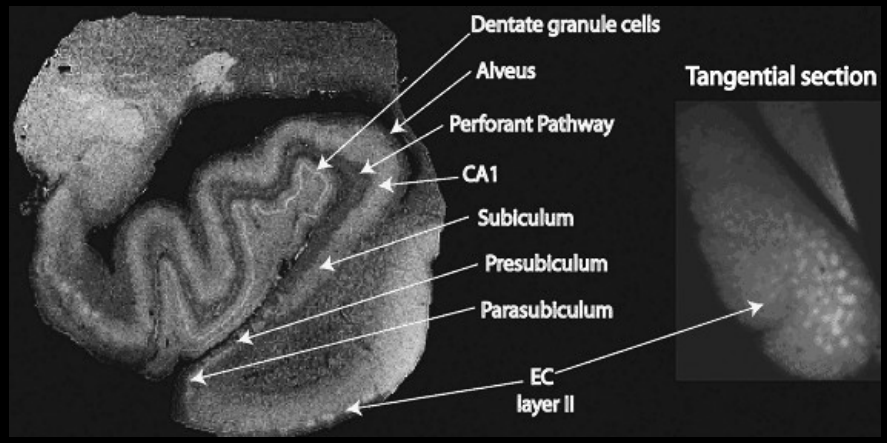
Tukey's Biweight

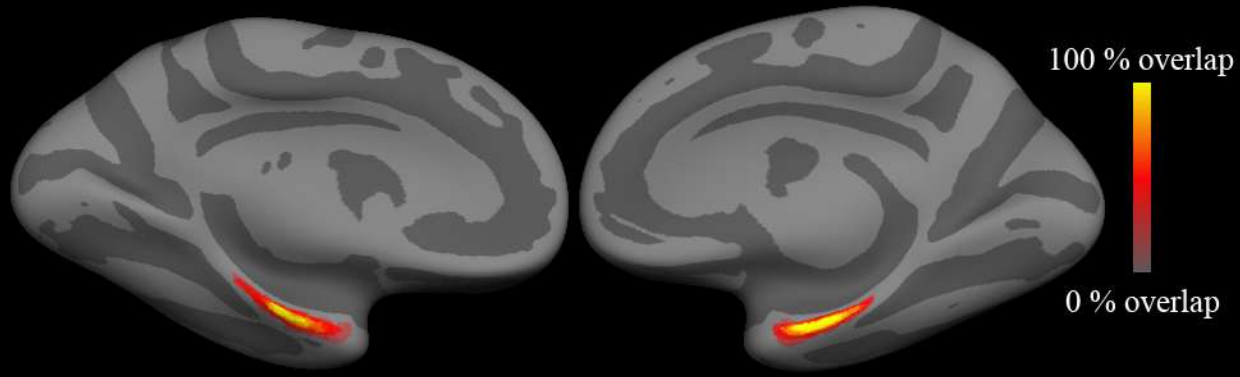
*Reuter, Rosas and Fischl, 2010, NeuroImage

New Areas: Entorhinal Cortex



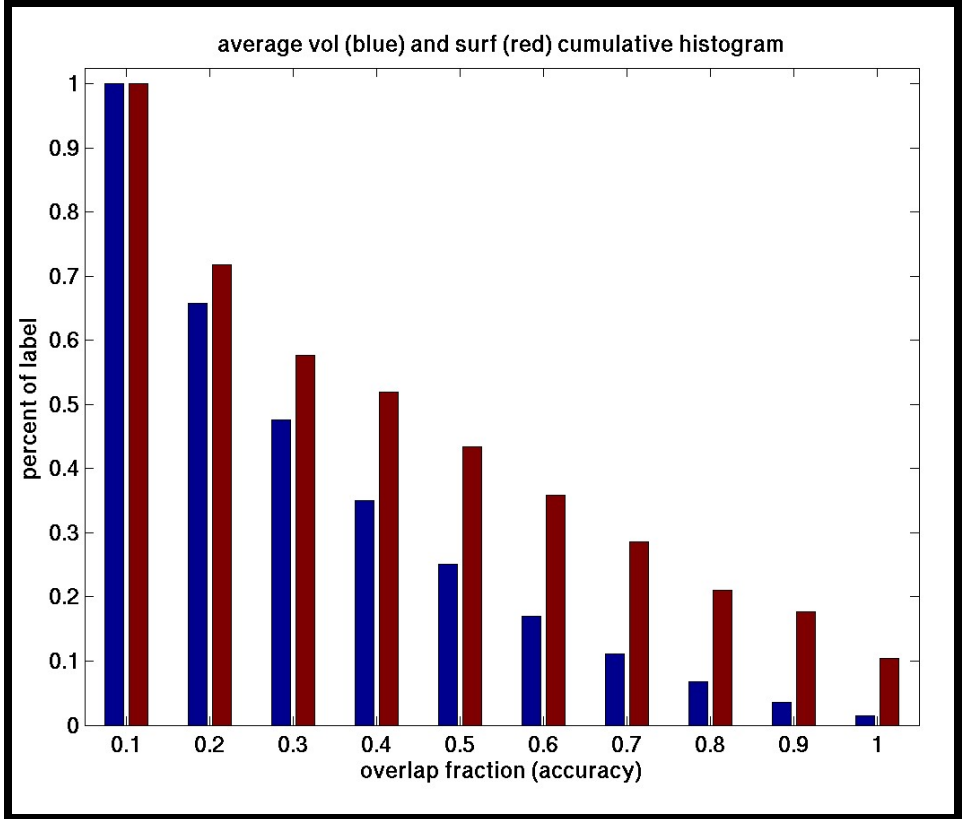




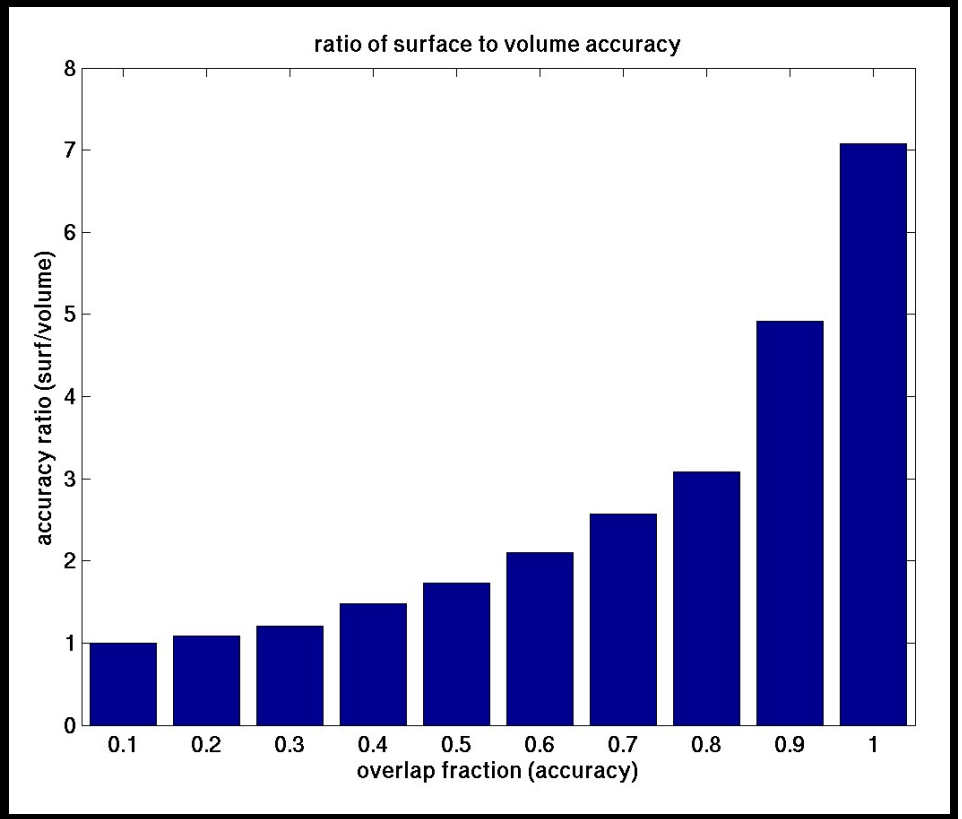


Fischl et al., 2009, NeuroImage

Comparing Coordinate Systems and Brodmann Areas

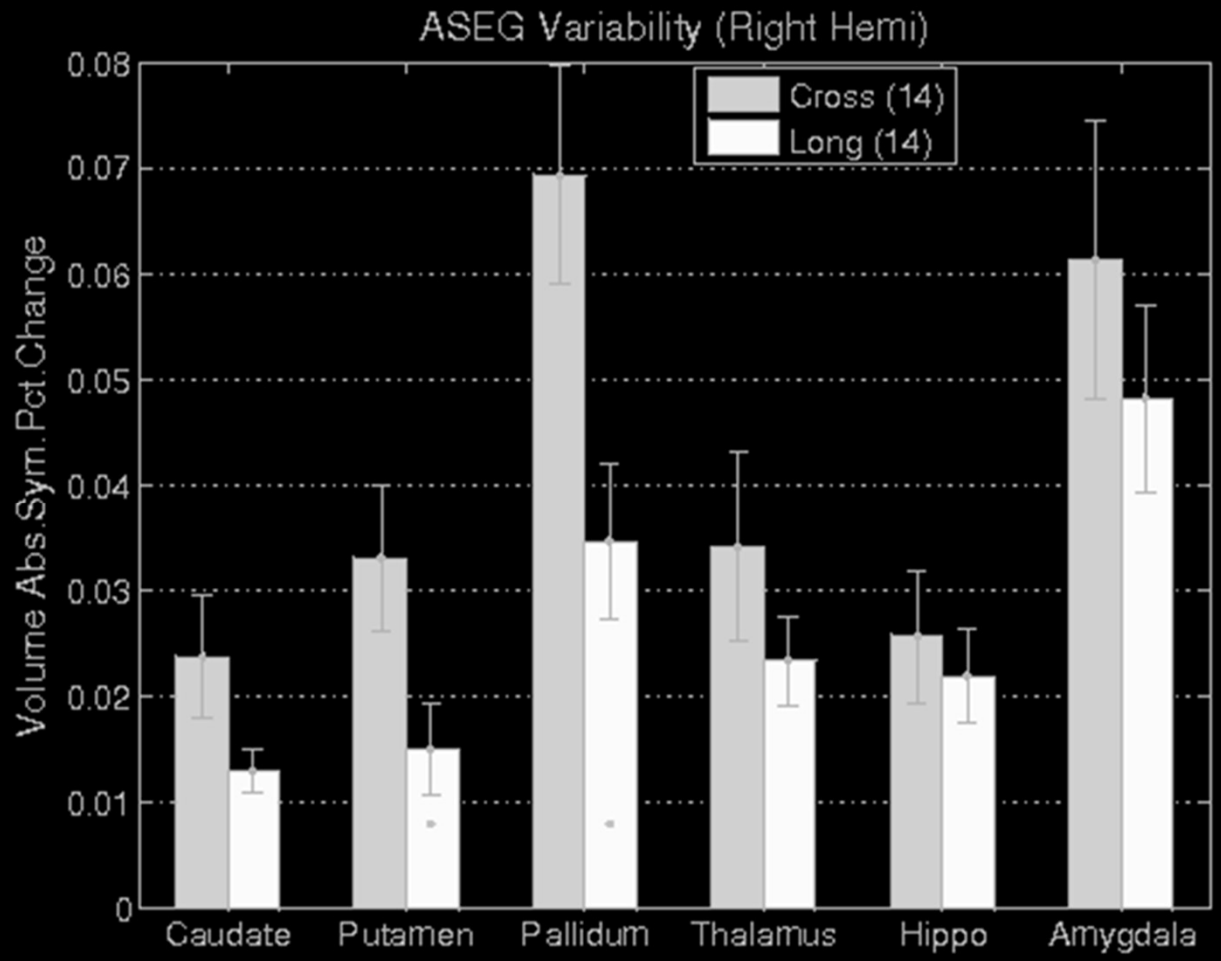


Cumulative histogram (red=surface, blue=nonlinear Talairach)



Ratio of surface accuracy to volume accuracy

Longitudinal Analysis: Increased Reliability



14 subjects scanned twice, two weeks apart.

Collaboration with Martin Reuter