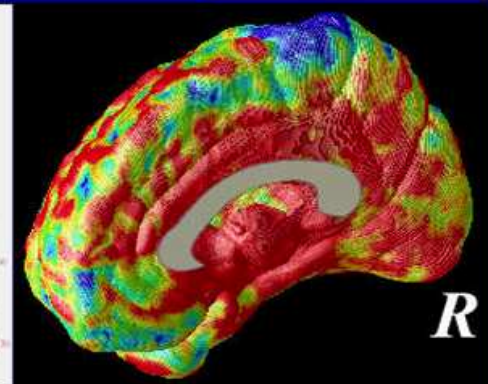
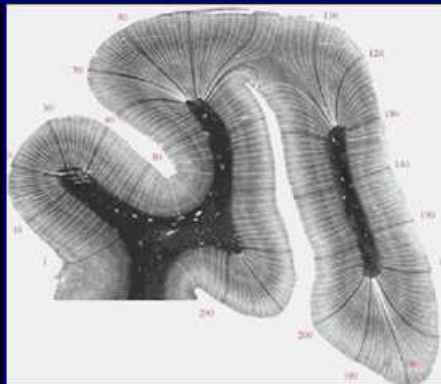
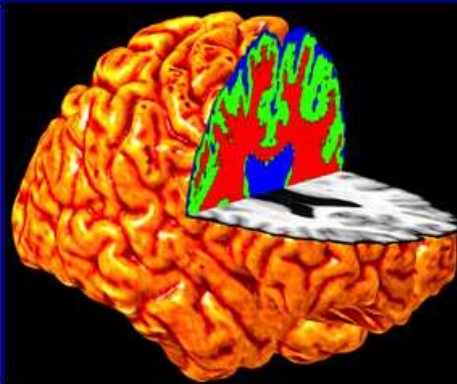
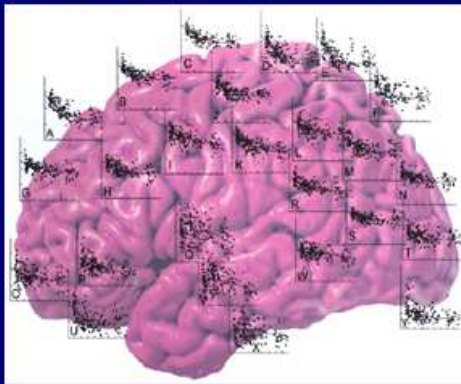
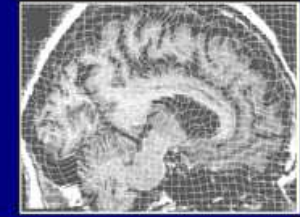
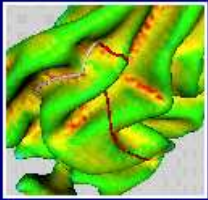
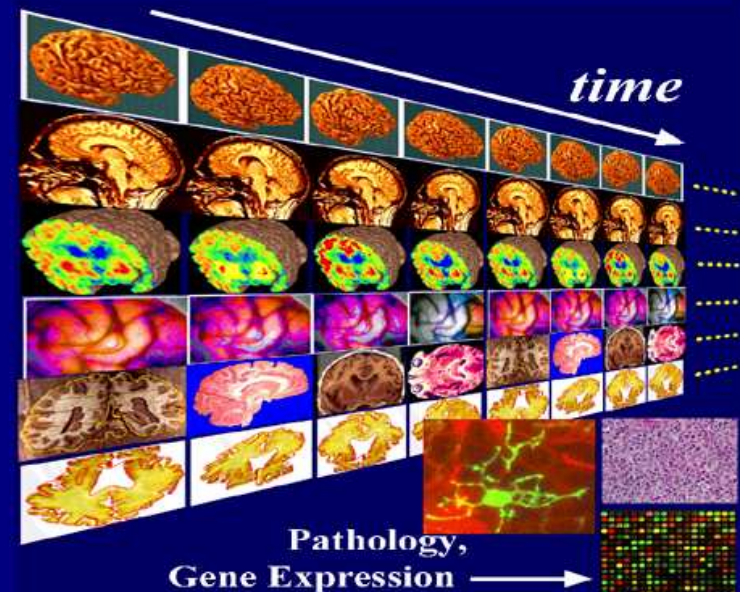


MAPPING BRAIN CHANGES IN AGING & ALZHEIMER'S DISEASE



Paul Thompson
Associate Prof. of Neurology
Laboratory of Neuro Imaging
UCLA School of Medicine
Los Angeles, CA
and many colleagues!



Can We Track Alzheimer's Disease Spreading in the Living Brain?

3D MRI,
CT scans

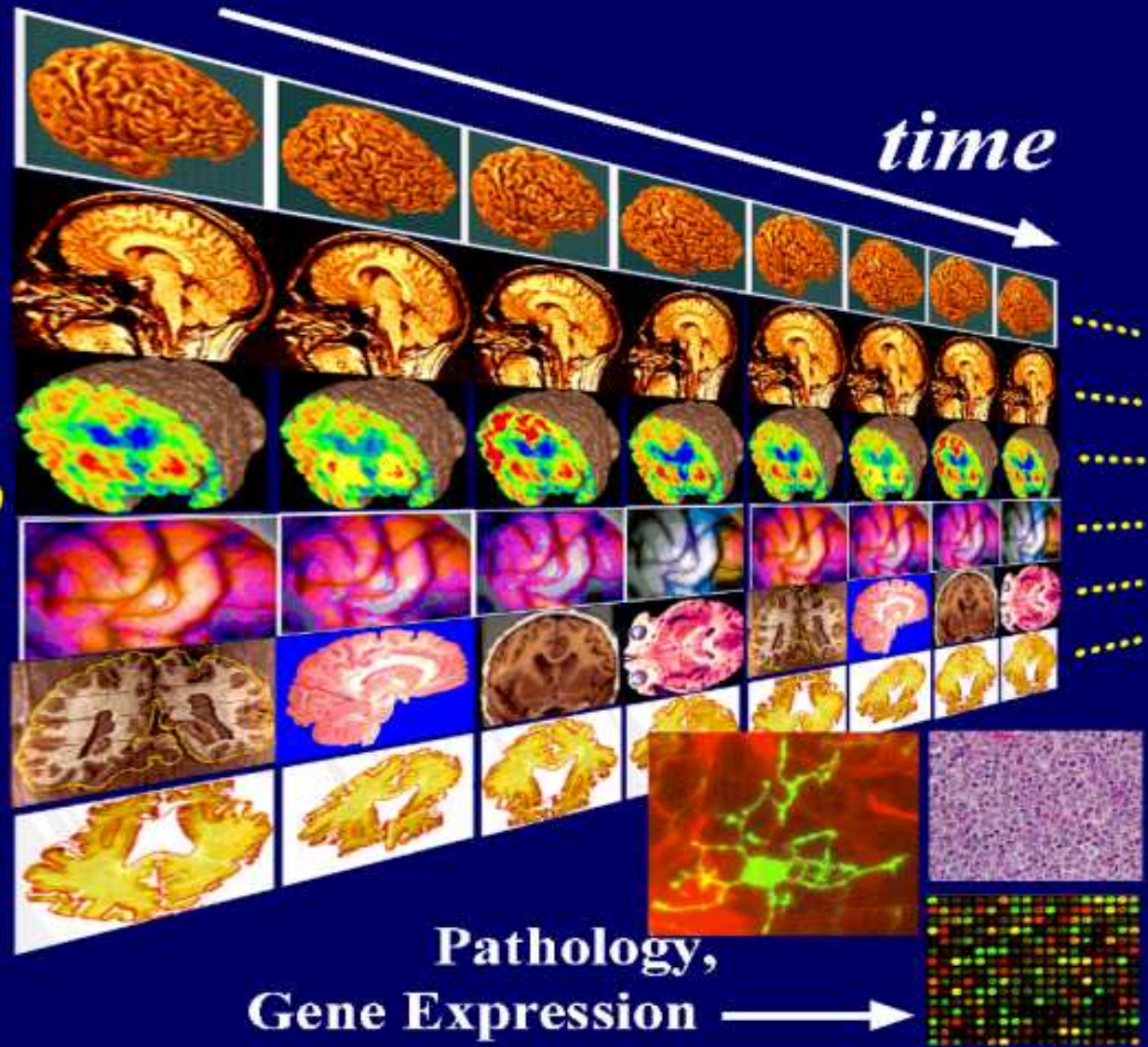
PET, SPECT,
fMRI, MRS
(CHO/CRE, NAA)

Direct
Mapping

Cryo

Histo

⋮



Why Do We Need to Map How Alzheimer's Disease Spreads?

**Not uniform: which brain areas change
earliest? Is there a sequence?**

Where are drugs slowing the spread?

By how much?

**How can we tell if a drug is
slowing tissue loss?**

**Where do brain changes most correlate with/
predict memory decline, cognitive changes?**

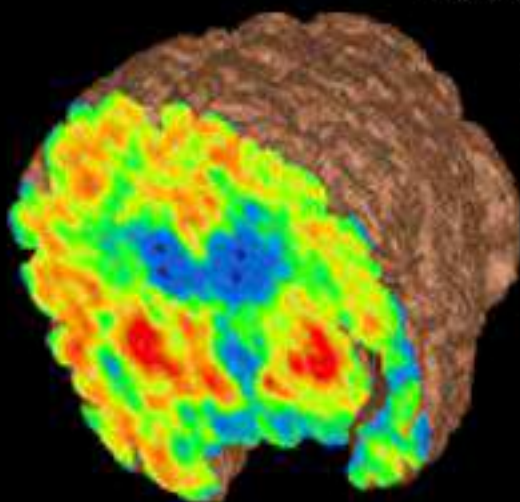
What about

FTD, VaD; MCI; those at genetic risk?

Mapping Brain Function and Structure

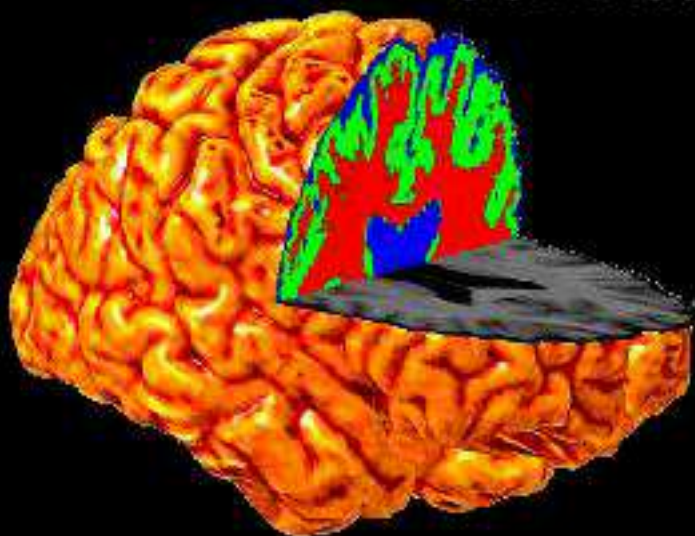
energy use, blood flow
radiotracer injection

PET



cortical thinning

MRI



*non-invasive;
can map change if
done repeatedly
normal volunteers
(vast database)*

Increasing Use of Longitudinal MRI & Brain Mapping Methods

New Brain Mapping methods

DEVEL



Giedd
NIMH

SCHIZ



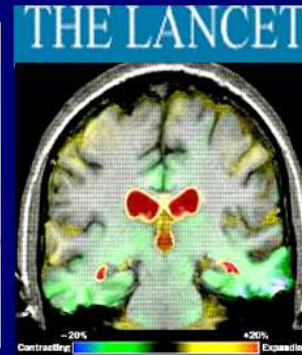
Rapoport
NIMH

DEVEL



Sowell
UCLA

ALZHEIMER'S ALZHEIMER'S



Fox
London



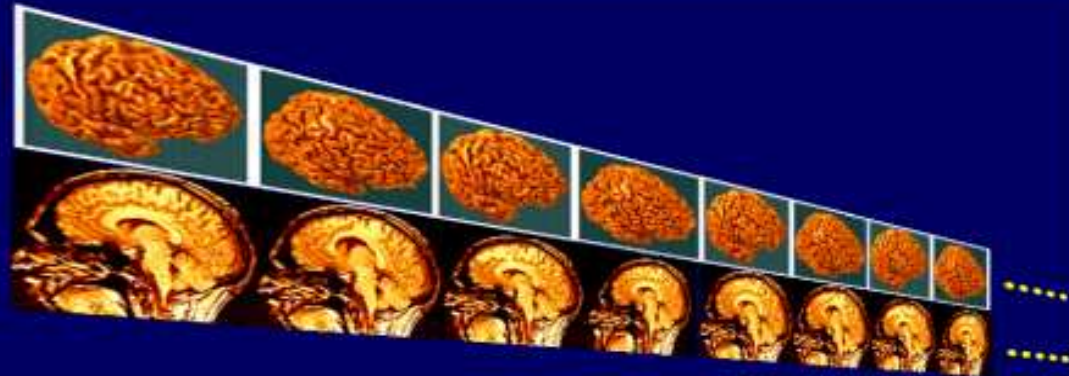
UCLA/CMR
Queensland



*Why is this New? Maps (localizing) vs. Volumes
Increased Detection Sensitivity to Change
New Statistical Maps to Detect Modulation
(drug, gene, etc.)*

Image Acquisition

Serial
3D MRI



*Scan 30 AD pts every 3 months
for 4 years as their disease progresses*

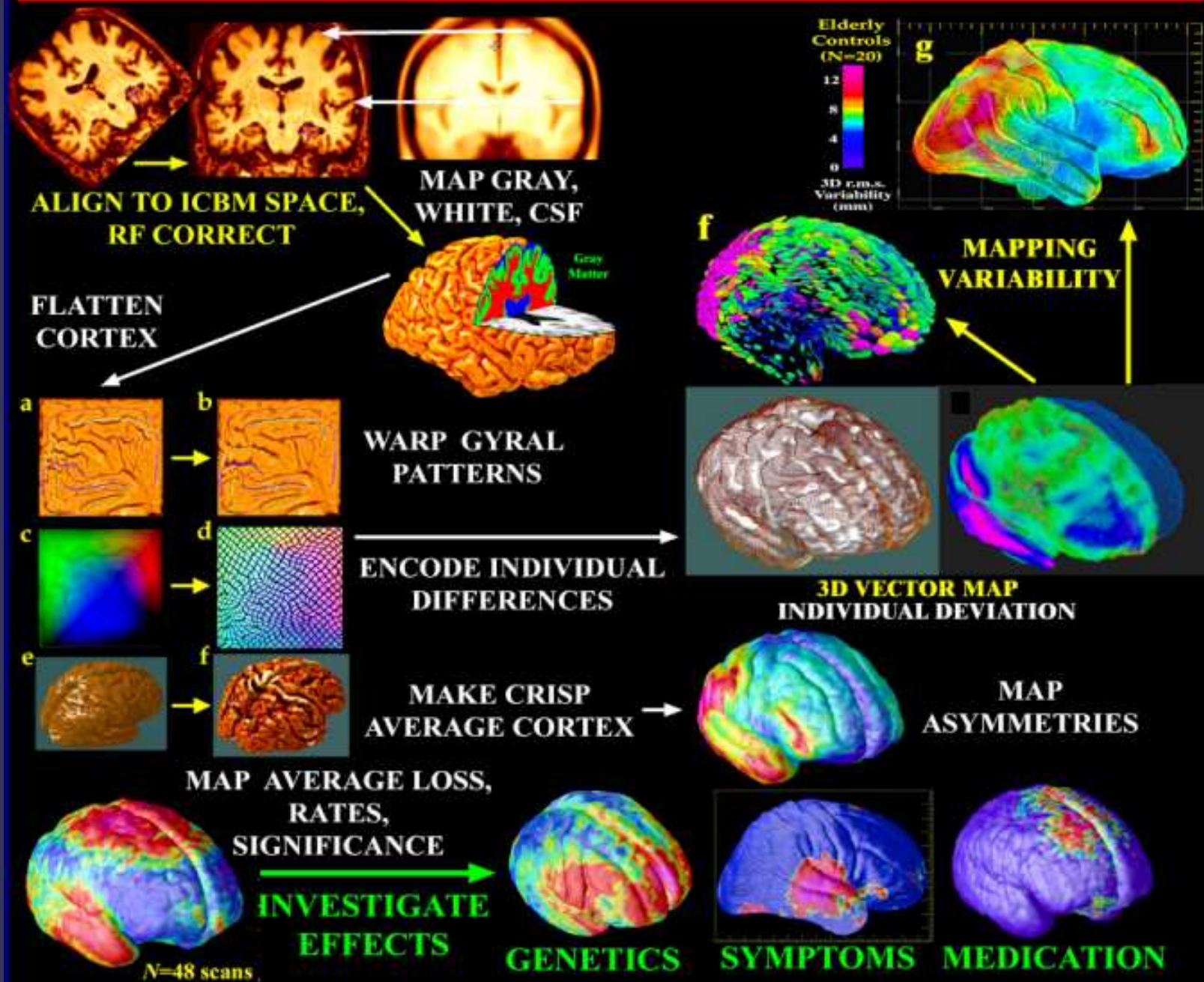
Scan 30 healthy controls

(age, gender, education matched)

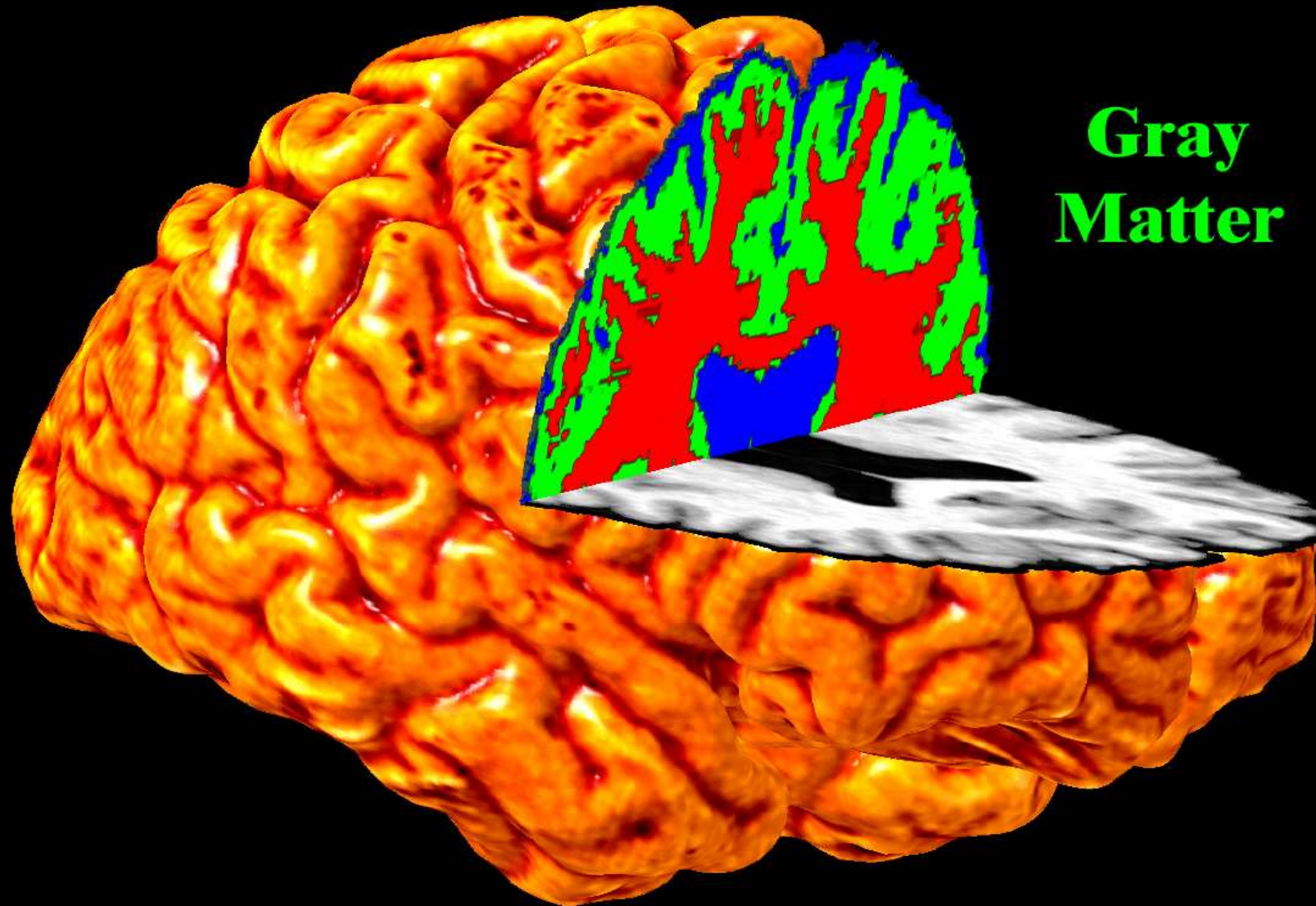
**Where is the cortex (gray matter)
getting thinner?**

**Can we track the spread of the
disease? (time-lapse film)**

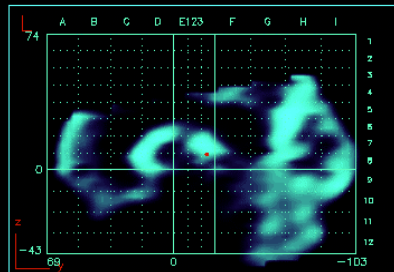
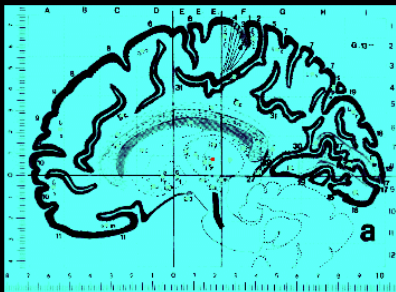
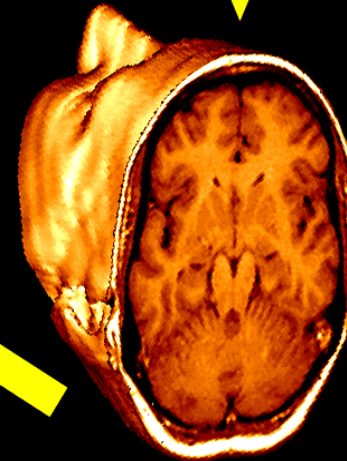
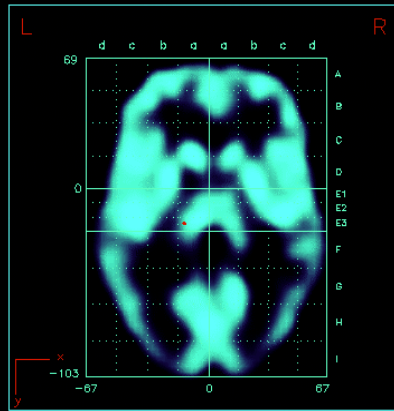
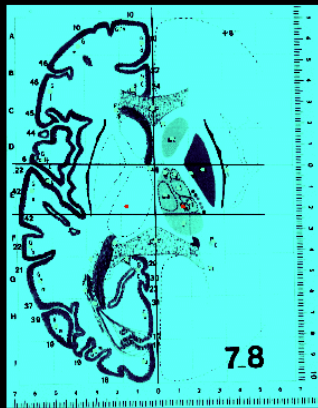
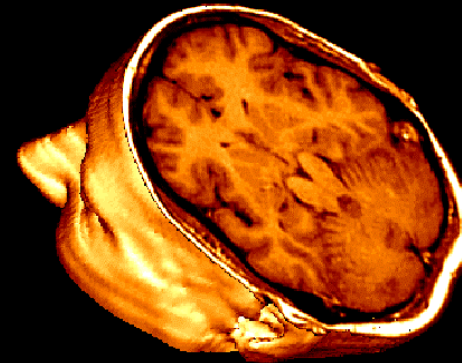
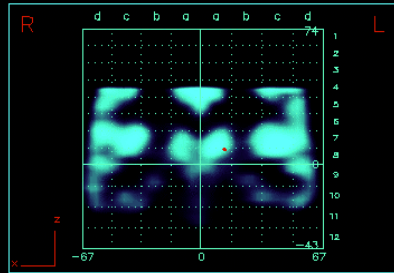
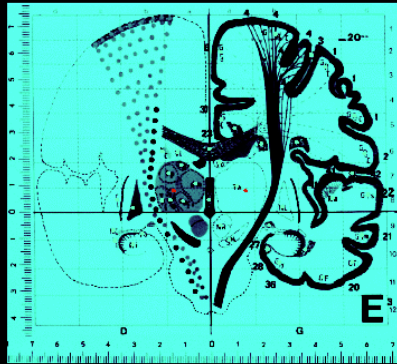
Analysis Pipeline (Thompson et al., 2004)



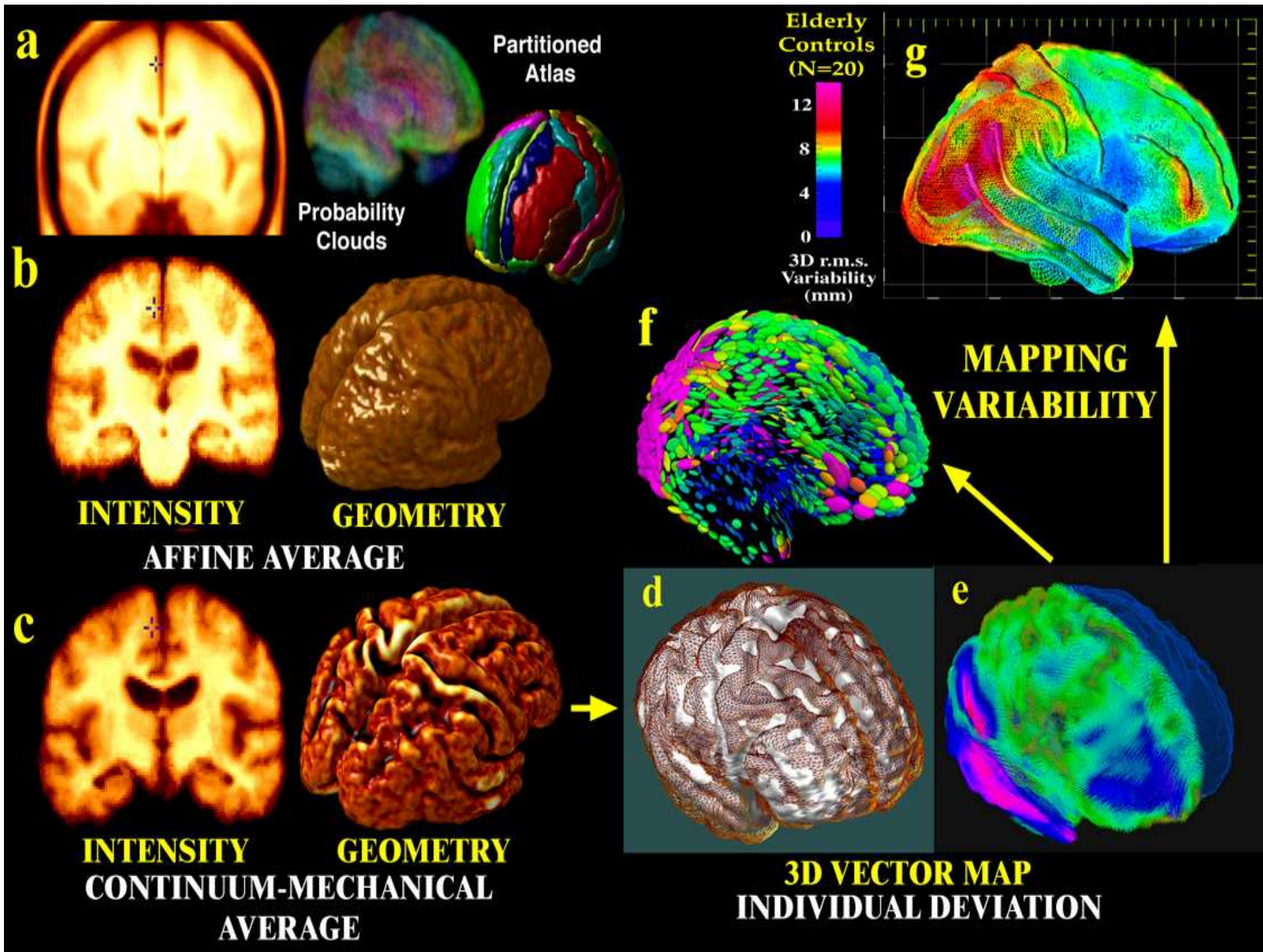
What Happens to Our Gray Matter?



Brain Mapping (Talairach, 1967)

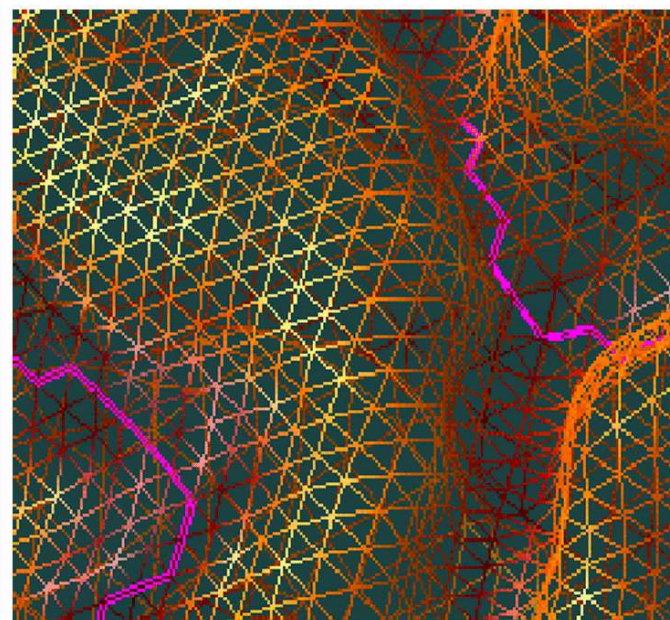
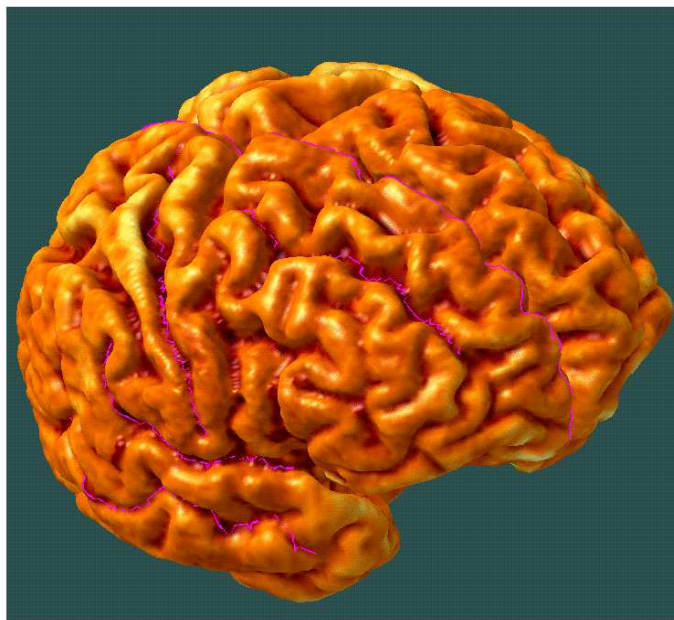
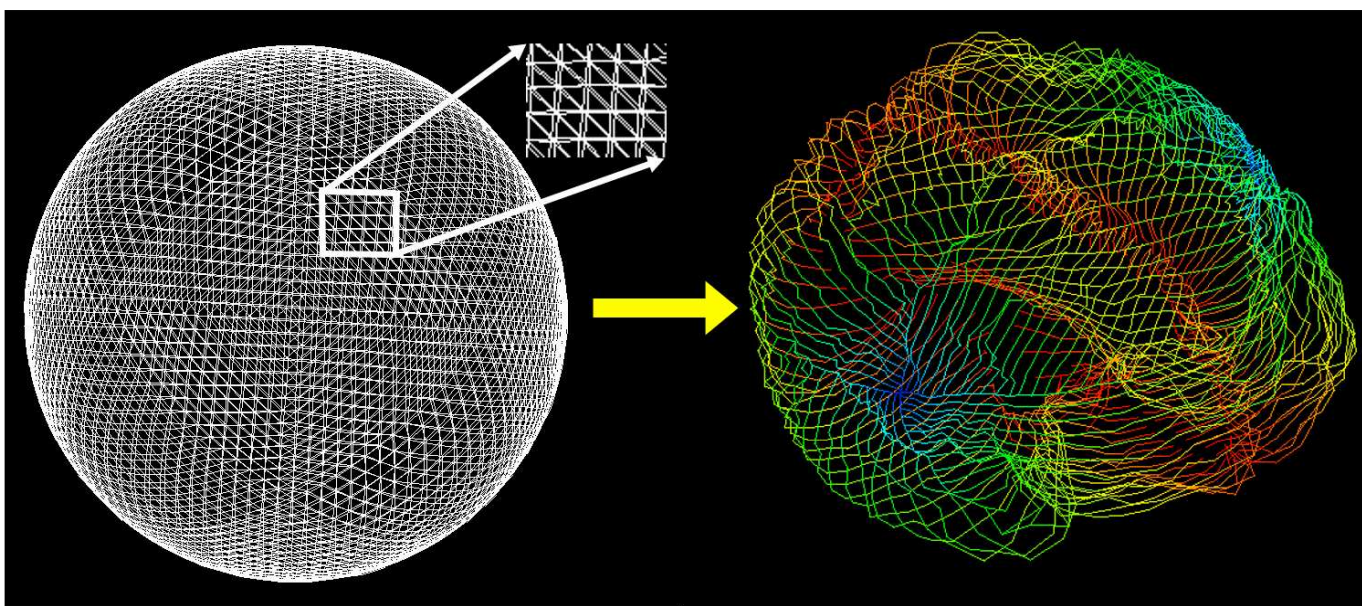


Courtesy of D.
Rottenberg,
Minneapolis VA



Building Brain Models

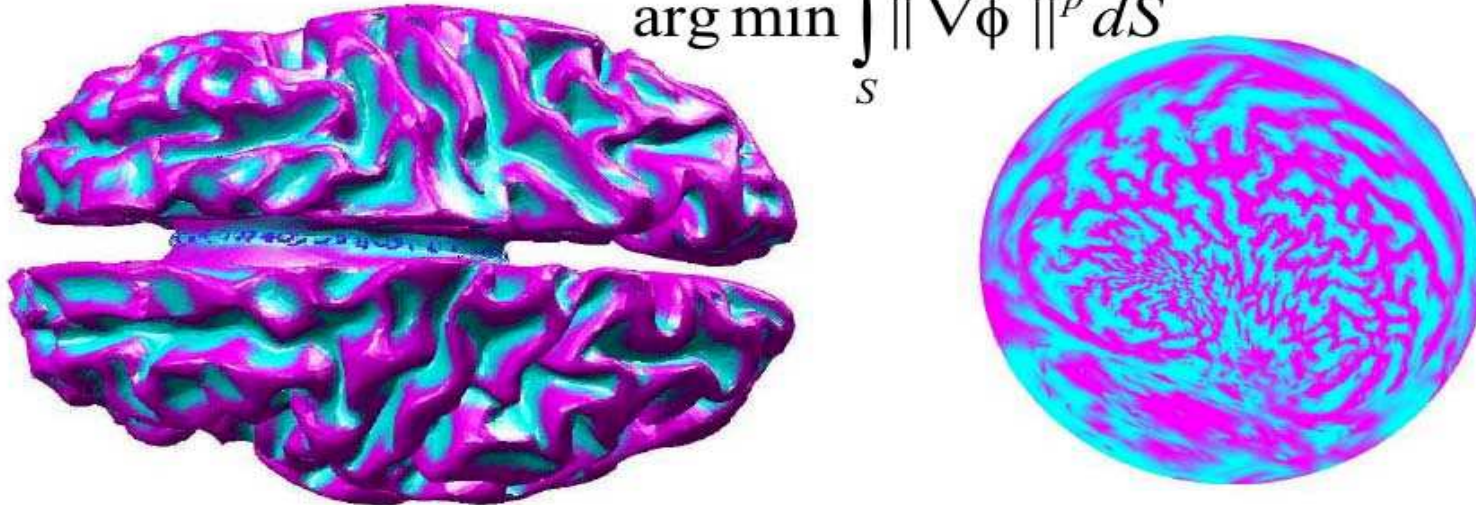
(1000 adults, ICBM; 1000+ children and teens, NIMH)



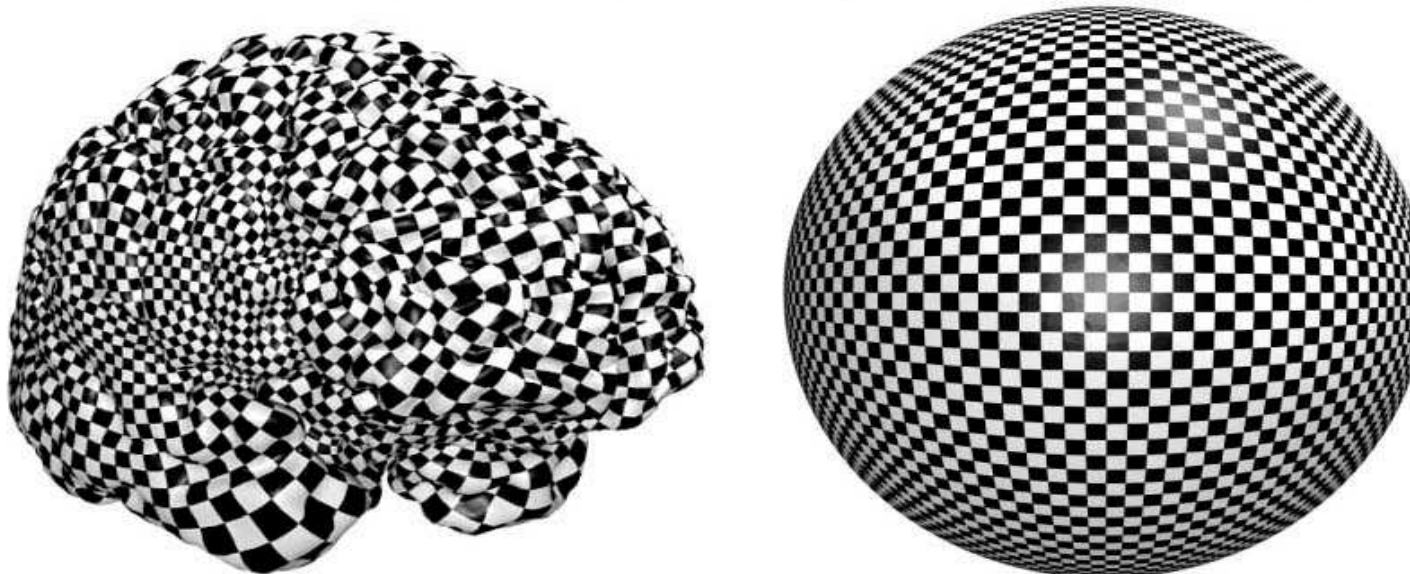
CONFORMAL SURFACE MAPPING

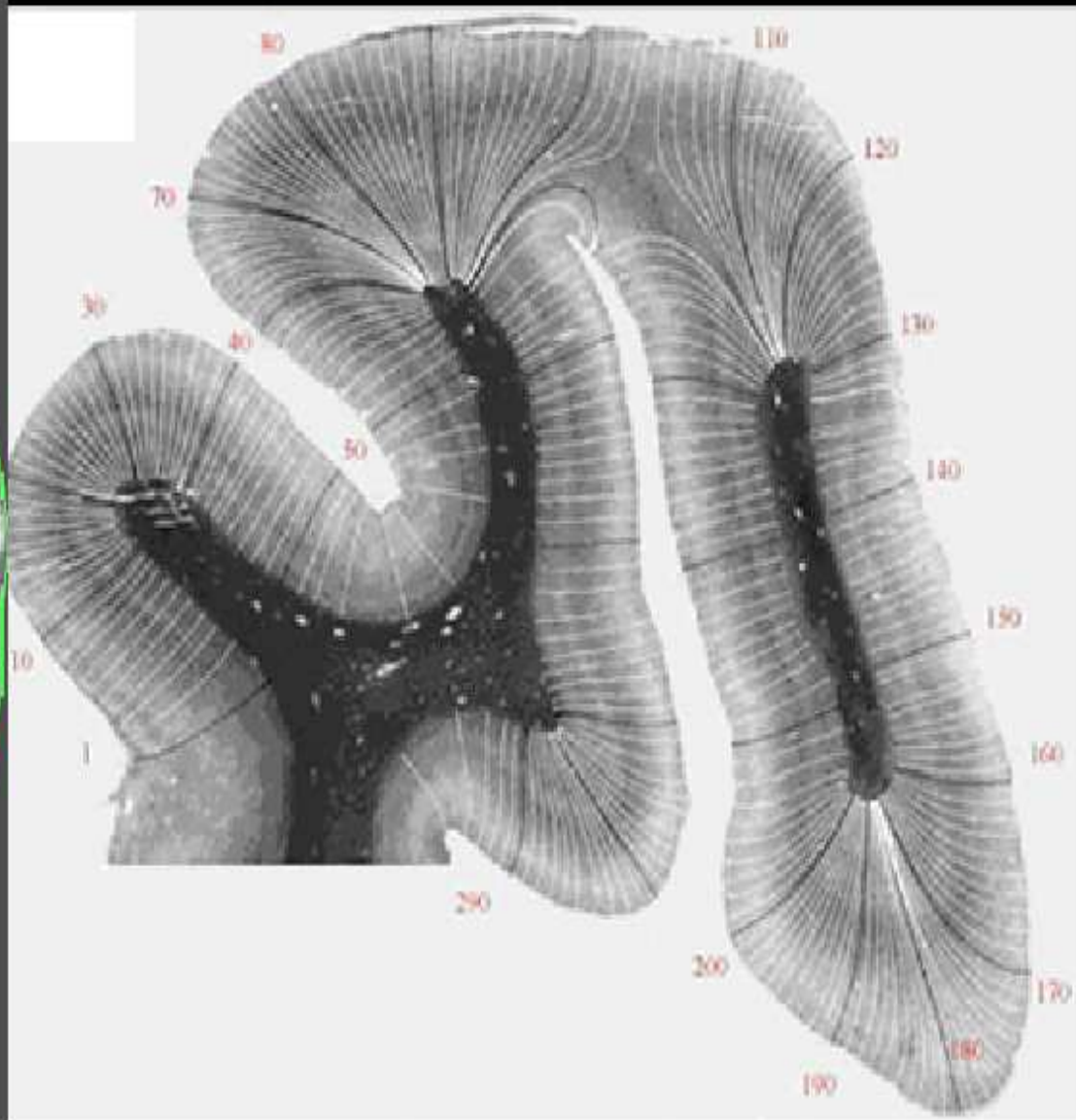
P-harmonic (A. Joshi et al., ISBI04)

$$\arg \min_S \int_S \|\nabla \phi\|^p dS$$

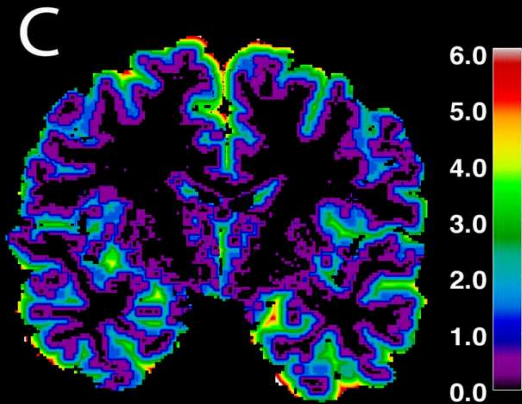
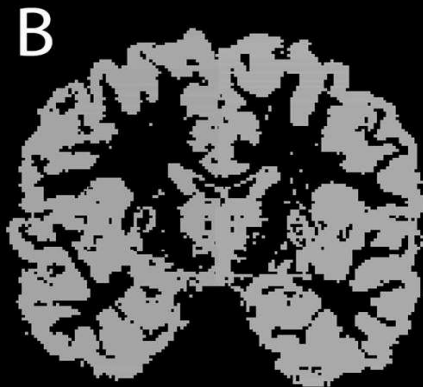
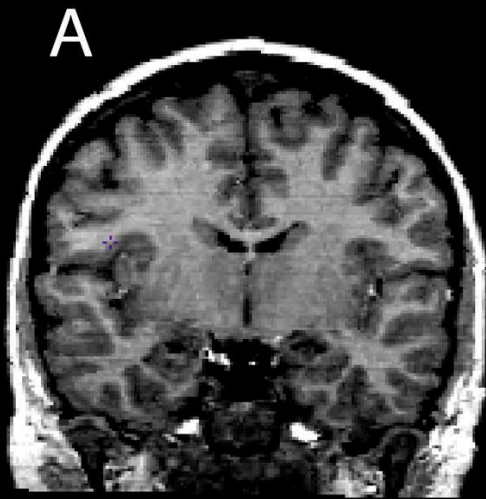


Harmonic map to S^2 (Y. Wang et al., ISBI04)

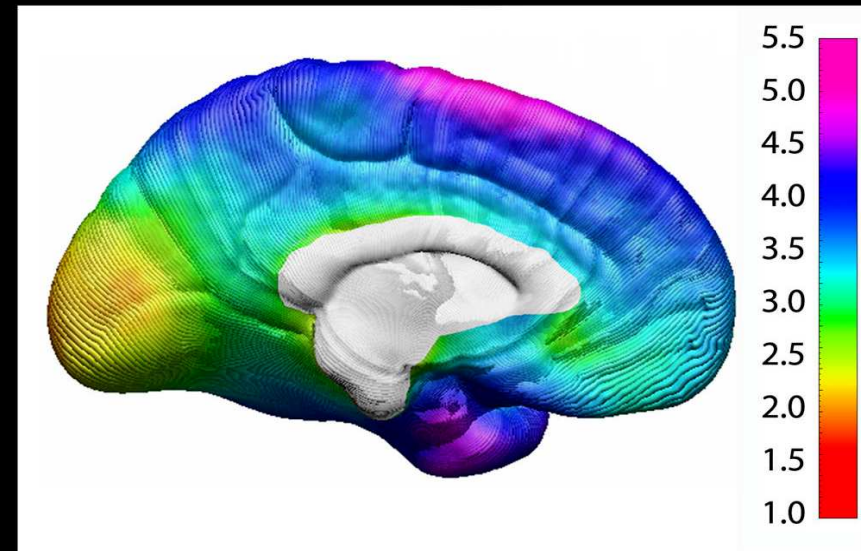




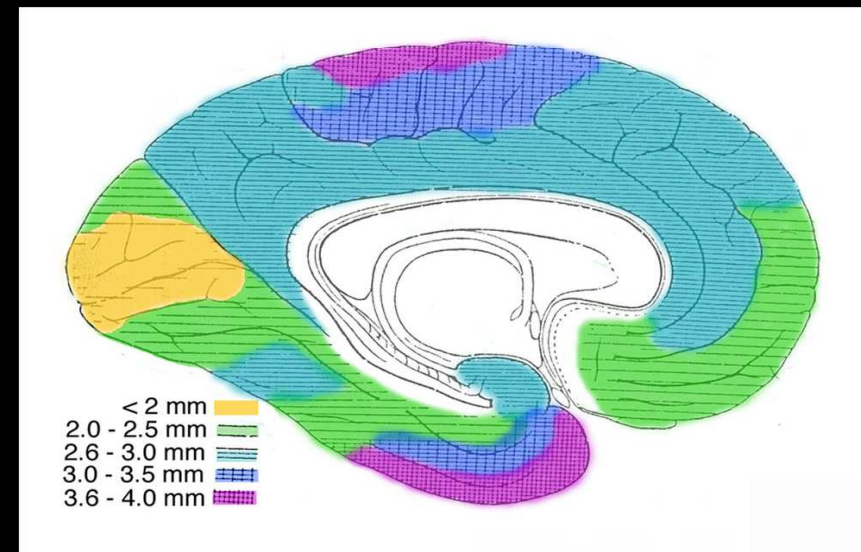
Meihe Xu, Alain Pitiot, Paul Thompson, et al.



D Thompson, Sowell 2003 (N=45)

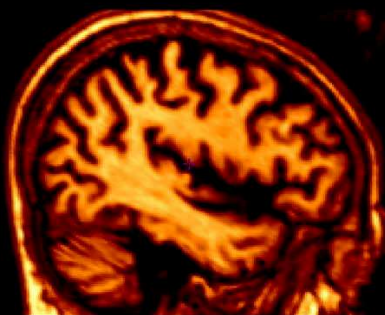


E Von Economo 1929

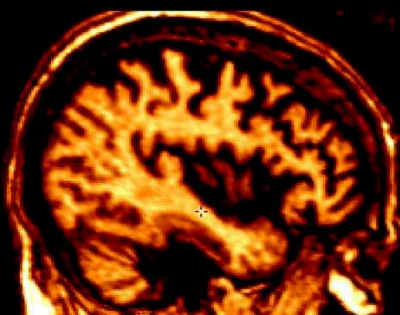


PATIENT

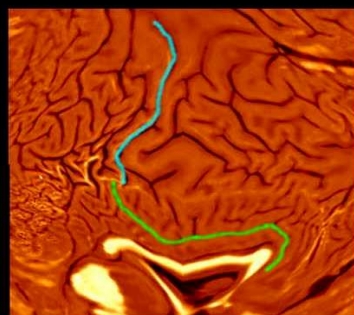
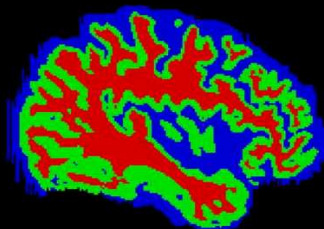
CONTROL



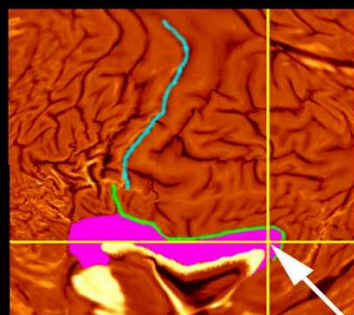
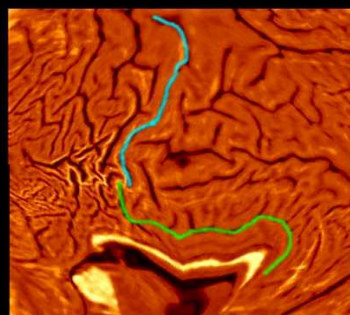
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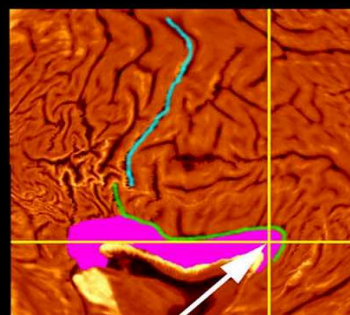
2



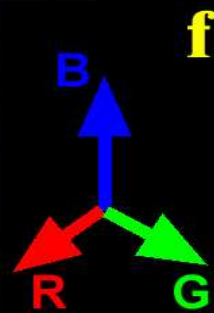
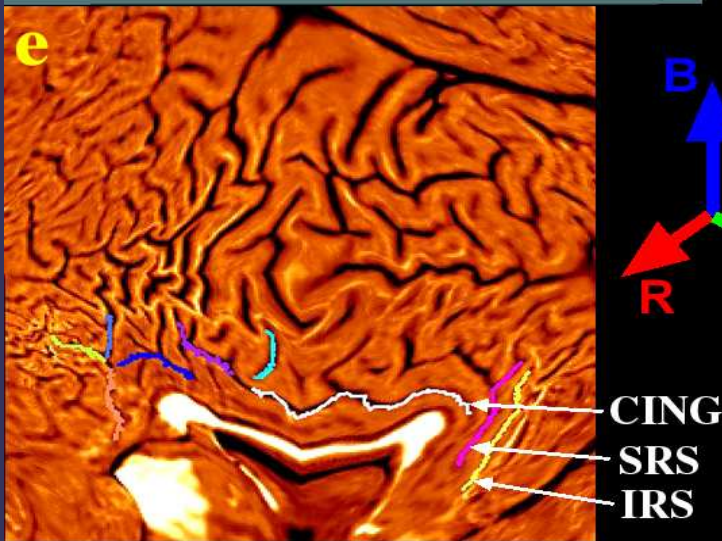
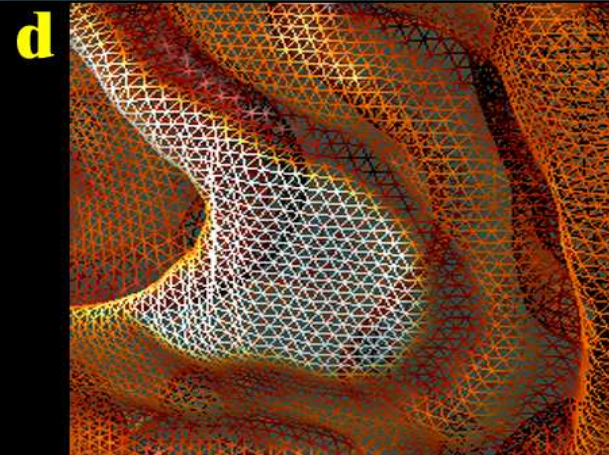
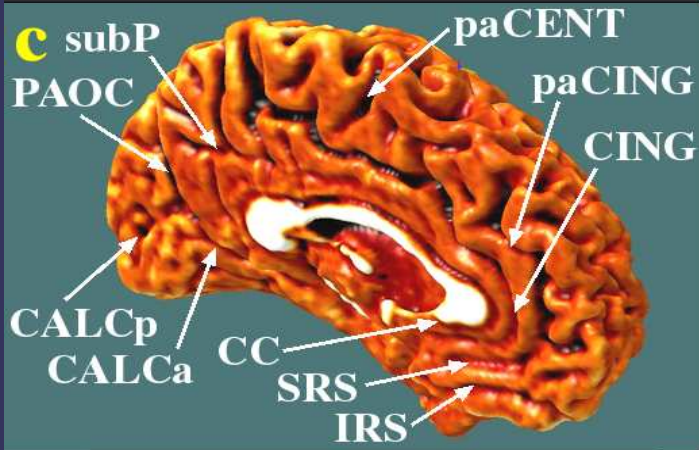
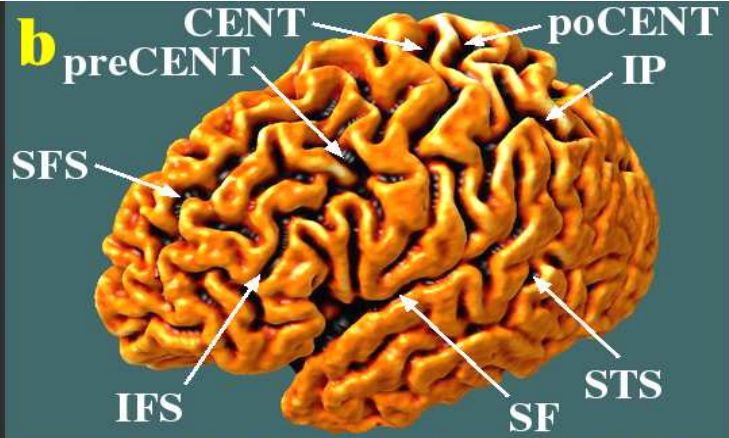
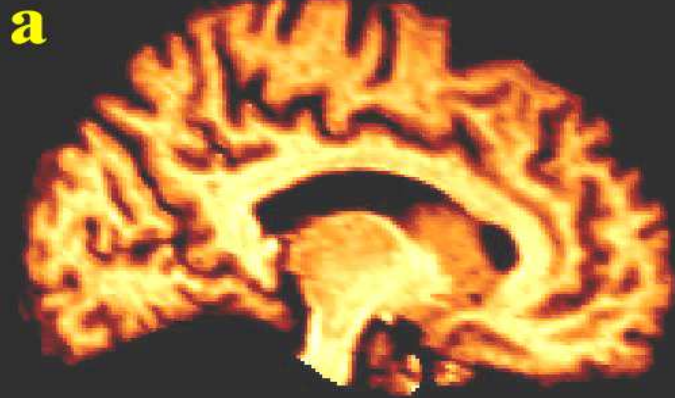
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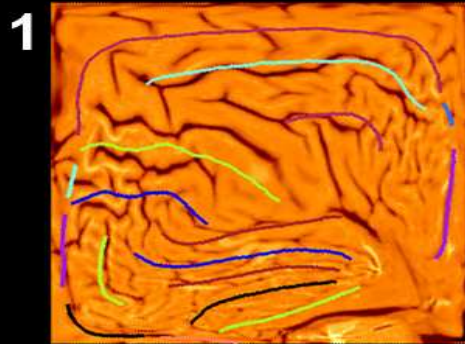
4



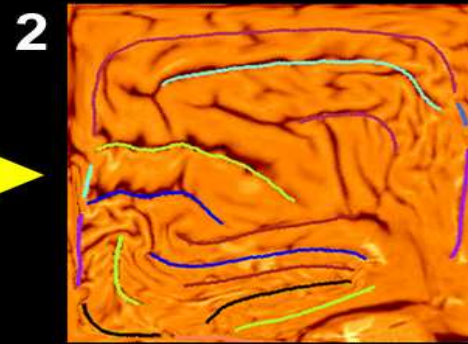
COMPARE



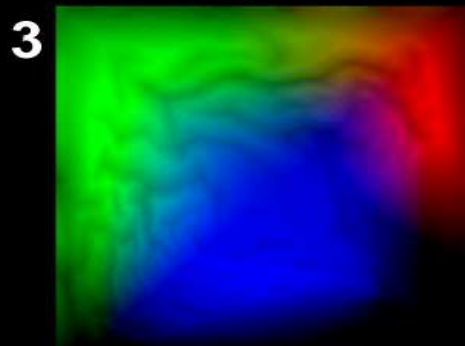
Individual Flat Map



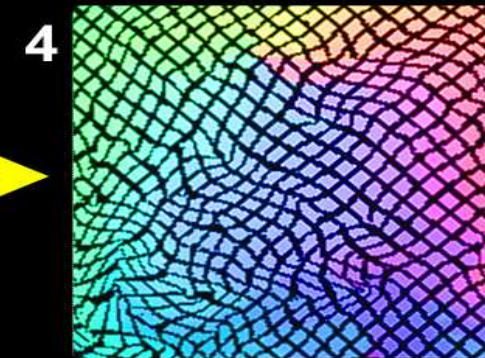
Warped to Average Curve Template



3D Cortical Point Locations (Color-Coded)



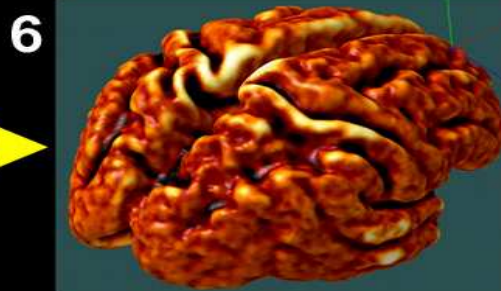
Warped 3D Locations



Cortical Average Before Sulcal Matching



Average after Sulcal Matching

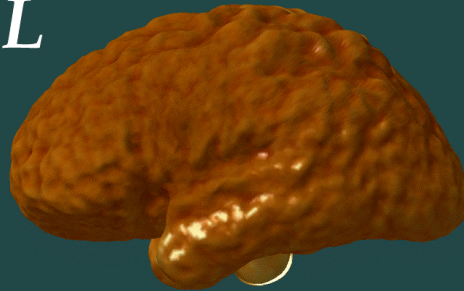


**Sulcal
Pattern
Matching**

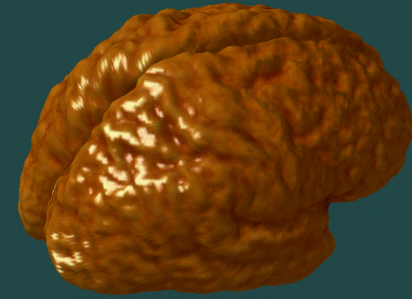
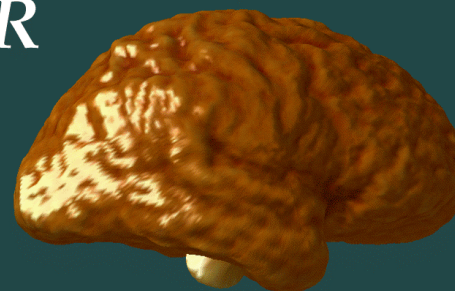
3D Average Anatomy

Before

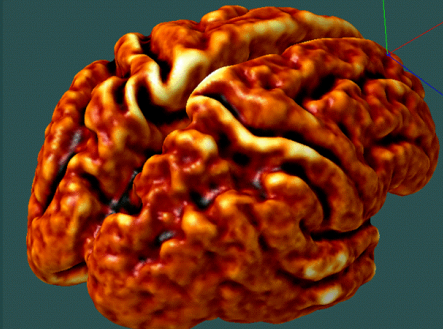
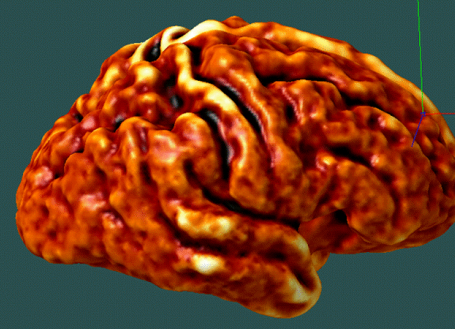
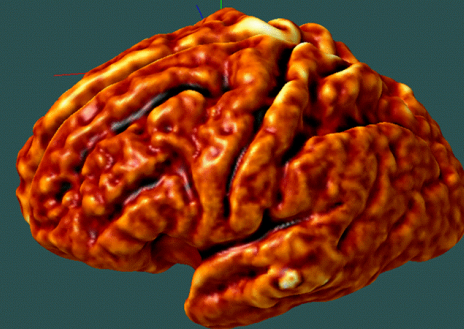
L



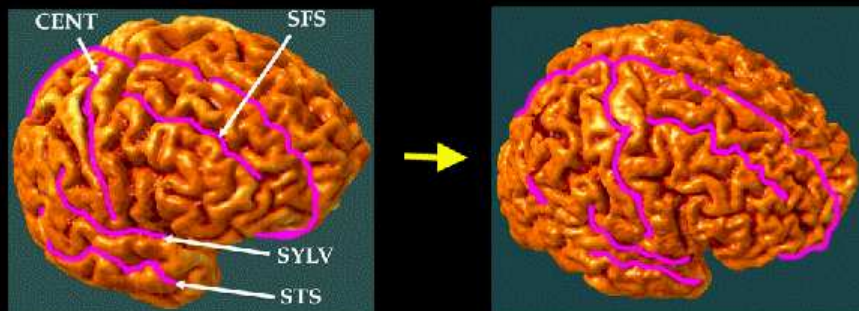
R



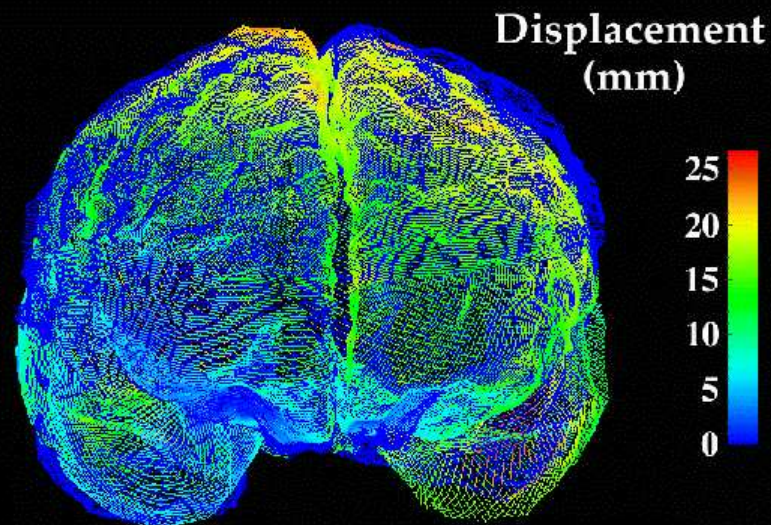
After



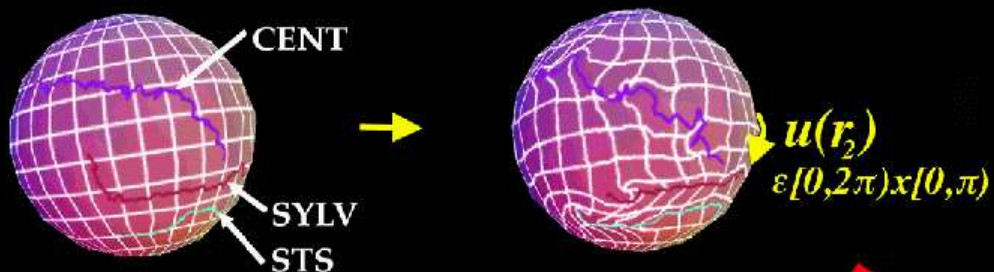
3D Models



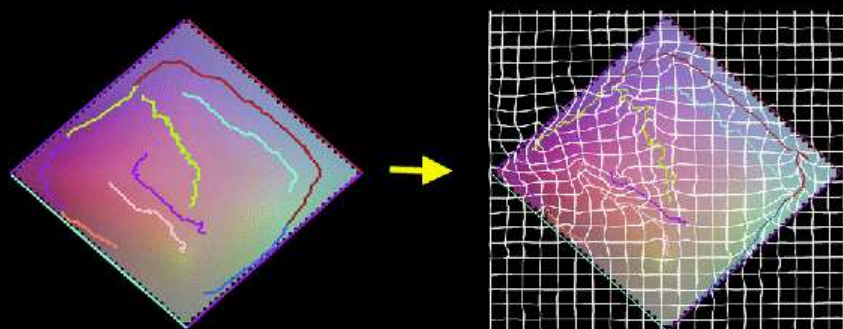
3D Matching Field



Spherical Tensor Maps

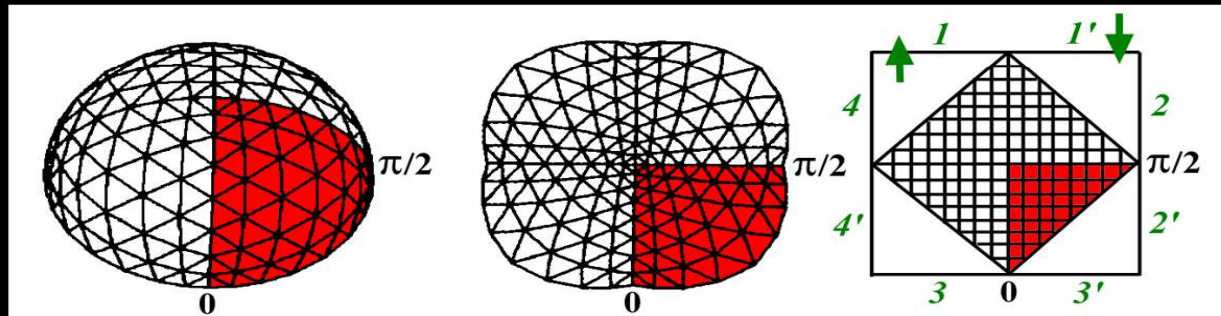
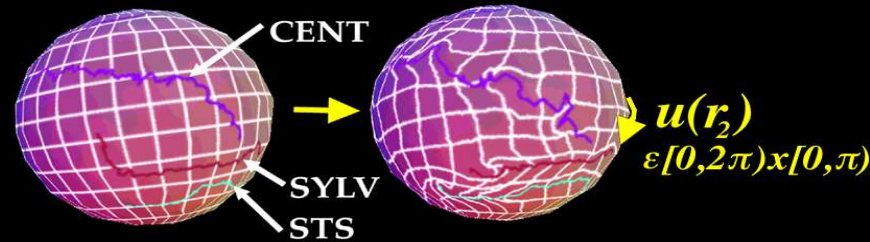


Flat Tensor Maps



$$\begin{aligned}
 & [(\lambda+\mu) \nabla(\nabla \bullet) + \mu \nabla^2]^* u(r_2) \\
 & + F(r_2 - u(r_2)) = 0; \quad u(r_2) = u_0(r_2) \text{ if } r_2 \in S_2 \\
 & u_{,i}^j = \partial u^j / \partial r_2^i + \Gamma_{ik}^j u^k \\
 & \Gamma_{jk}^i = \frac{1}{2} g^{il} (\partial g_{lj} / \partial r_2^k + \partial g_{lk} / \partial r_2^j + \partial g_{jk} / \partial r_2^l) \\
 & [(\lambda+\mu) \nabla(\nabla \bullet) + \mu \nabla^2]^* u(r_1) \\
 & + F(r_1 - u(r_1)) = 0; \quad u(r_1) = 0 \text{ if } r_1 \in S_1
 \end{aligned}$$

Covariant Matching



$$[(\lambda+\mu) \nabla(\nabla\bullet)+\mu\nabla^2]^* u(r_2) + F(r_2-u(r_2))=0; u(r_2)=u_0(r_2) \text{ if } r_2 \in S_2$$

$$u_{,k}^i = \partial u^j / \partial r_2^k + \Gamma_{ik}^j u^i$$

$$\Gamma_{jk}^i = \frac{1}{2} g^{il} (\partial g_{lj} / \partial r_2^k + \partial g_{lk} / \partial r_2^j + \partial g_{jk} / \partial r_2^l)$$

$$[(\lambda+\mu) \nabla(\nabla\bullet)+\mu\nabla^2]^* u(r_1) + F(r_1-u(r_1))=0; u(r_1)=0 \text{ if } r_1 \in S_1$$

Alternatively: represent surfaces as level sets (Memoli, Sapiro, Thompson, 2004)

Find map u from \mathbf{M} to \mathbf{N} minimizing:

$$E[\vec{u}] \triangleq \int_{\mathcal{M}} e[\vec{u}] d_{\mathcal{M}}v \quad e[\vec{u}] \triangleq \frac{1}{2} \|\mathbf{J}_{\vec{u}}\|_{\mathcal{F}}^2$$

Use $\|\cdot\|_{\mathcal{F}}^2 = \sum_{ij} (\cdot)_{ij}^2$

$$\vec{u} : \mathcal{M} \rightarrow \{\psi = 0\}.$$

$$\Pi_{\{\psi=0\}}(\vec{\alpha}) = \vec{\alpha} - \psi(\vec{\alpha}) \nabla \psi(\vec{\alpha}).$$

Harmonic Case:

$$e[\vec{u}](x) \triangleq \frac{1}{2} g^{pq}(x) h_{ij}(\vec{u}(x)) \frac{\partial u^i}{\partial x_p} \frac{\partial u^j}{\partial x_q}.$$

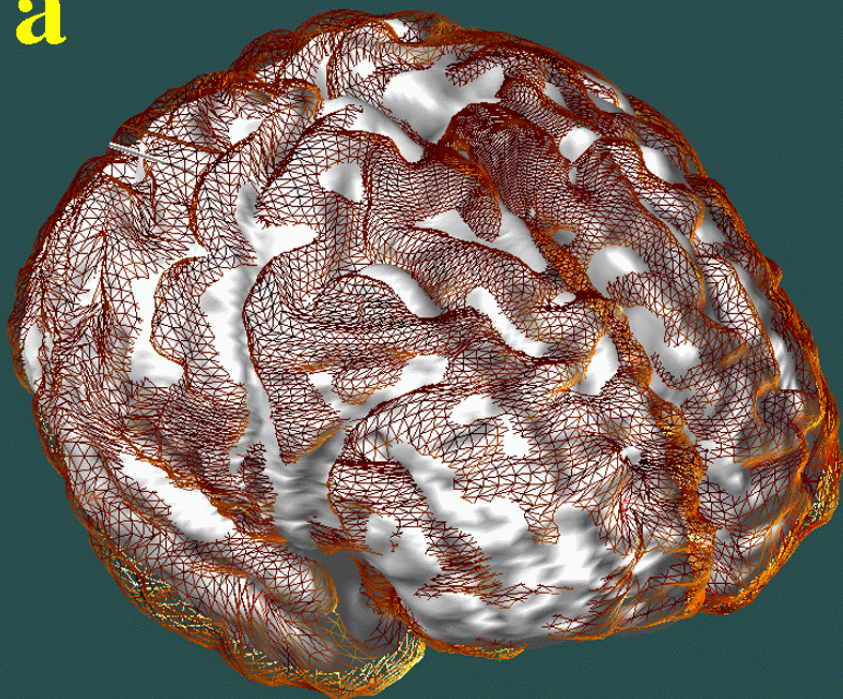
E-L:

$$\Delta_{\mathcal{M}} u^l + \Gamma_{ij}^l(\vec{u}) g^{\alpha\beta} \frac{\partial u^i}{\partial x^\alpha} \frac{\partial u^j}{\partial x^\beta} = 0$$

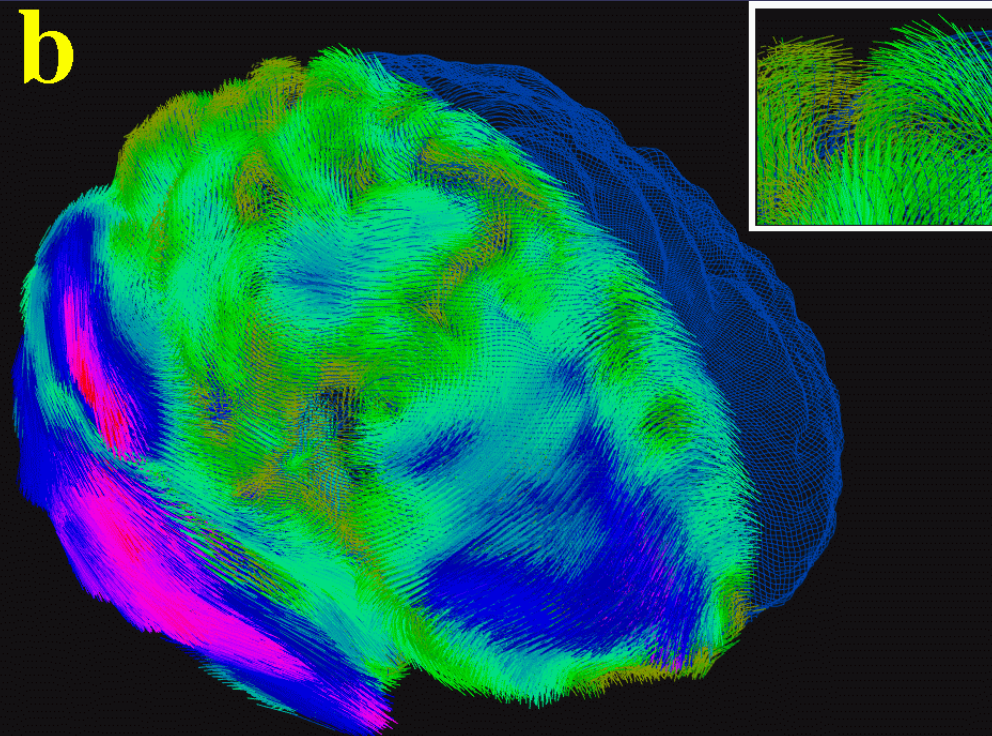
Gradient Descent, Onto Level Set:

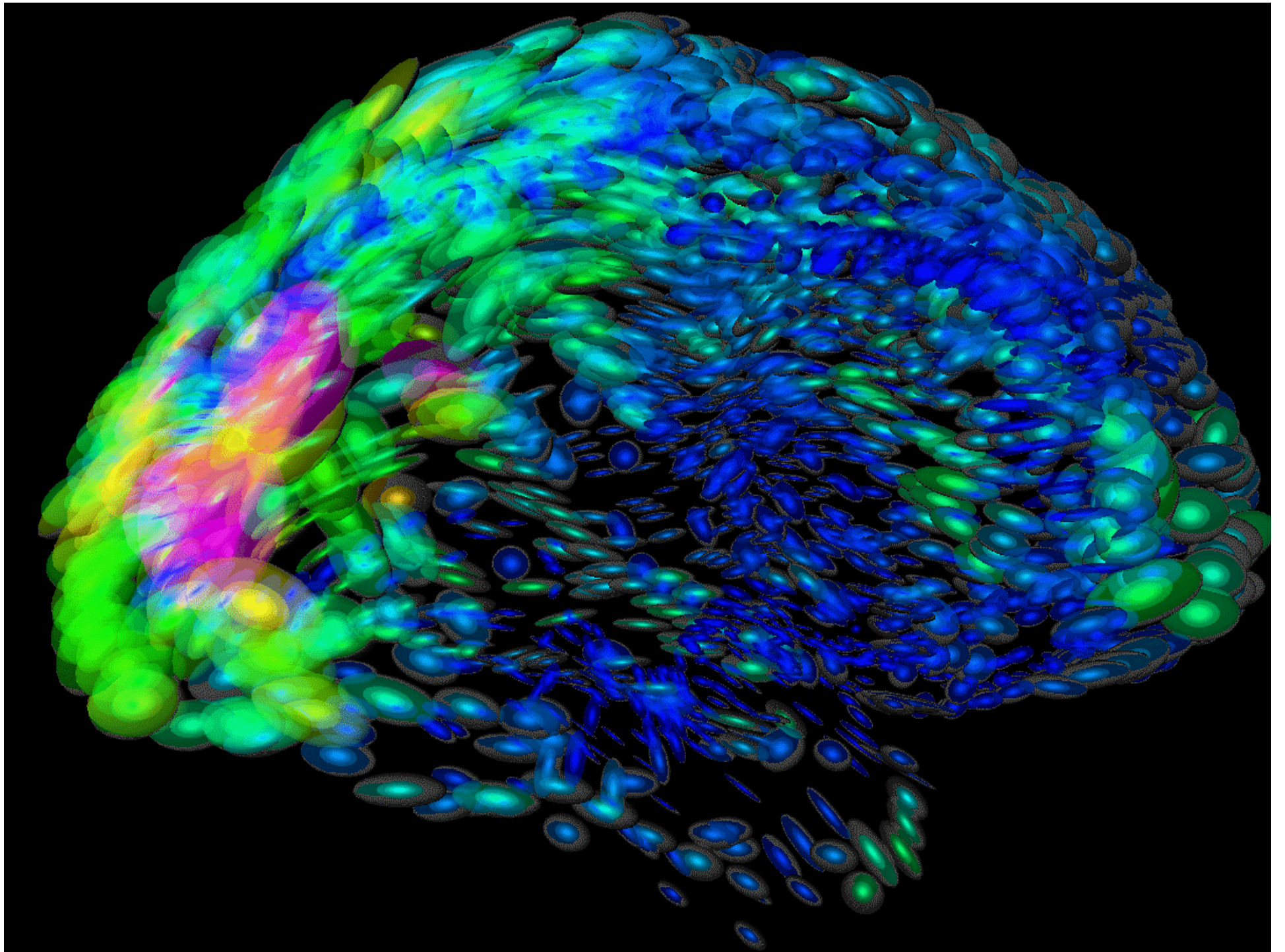
$$\frac{\partial u^i}{\partial t} = \Delta u^i + \sum_{k=1}^d \mathbf{H}_{\psi}(\vec{u}) \left[\frac{\partial \vec{u}}{\partial x_k}, \frac{\partial \vec{u}}{\partial x_k} \right] \frac{\partial \psi}{\partial u^i}(\vec{u})$$

a



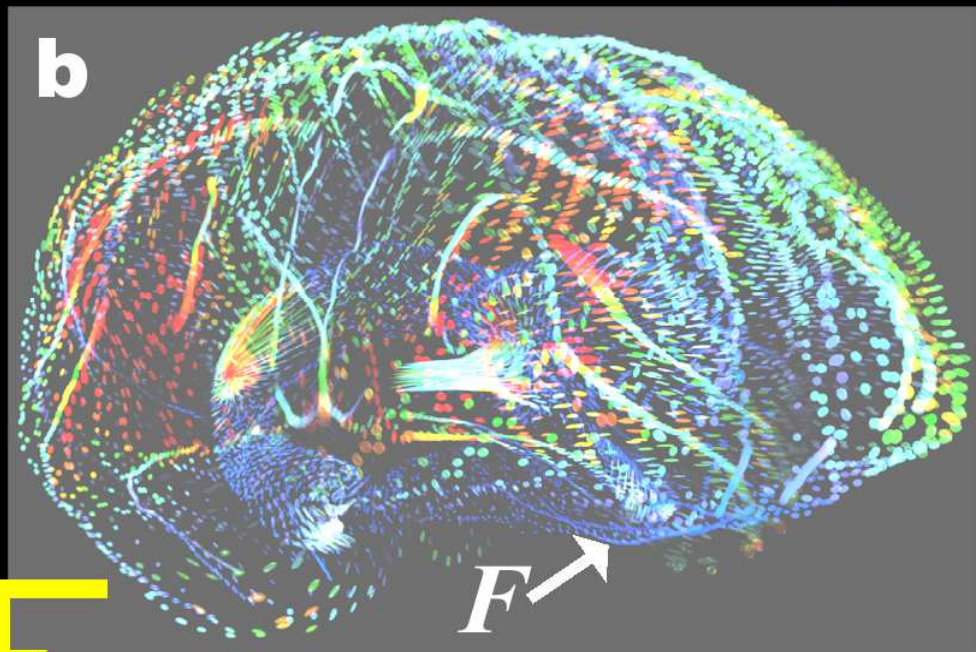
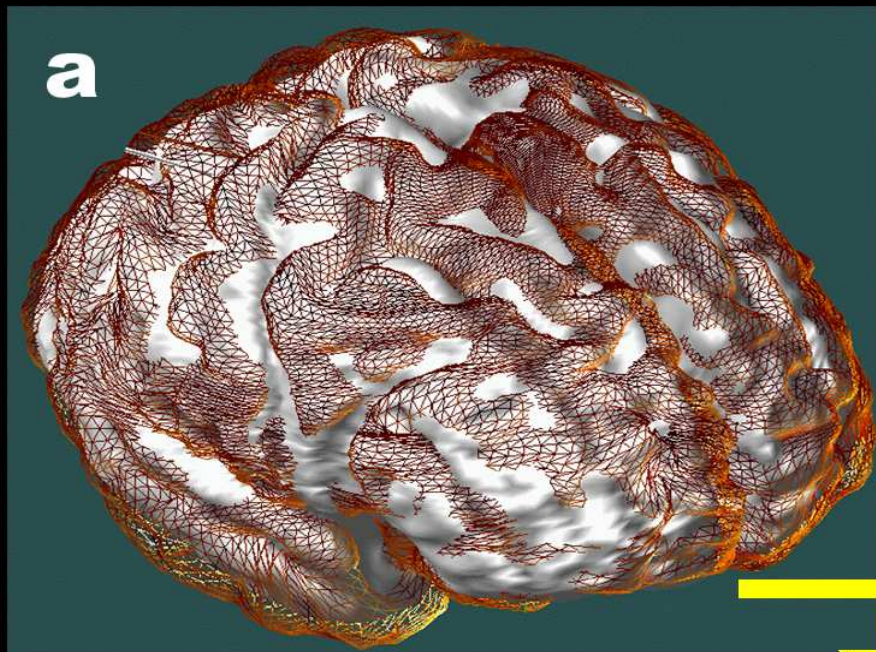
b



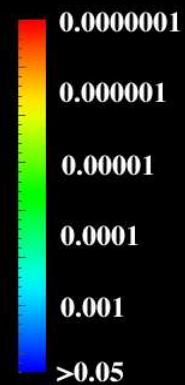
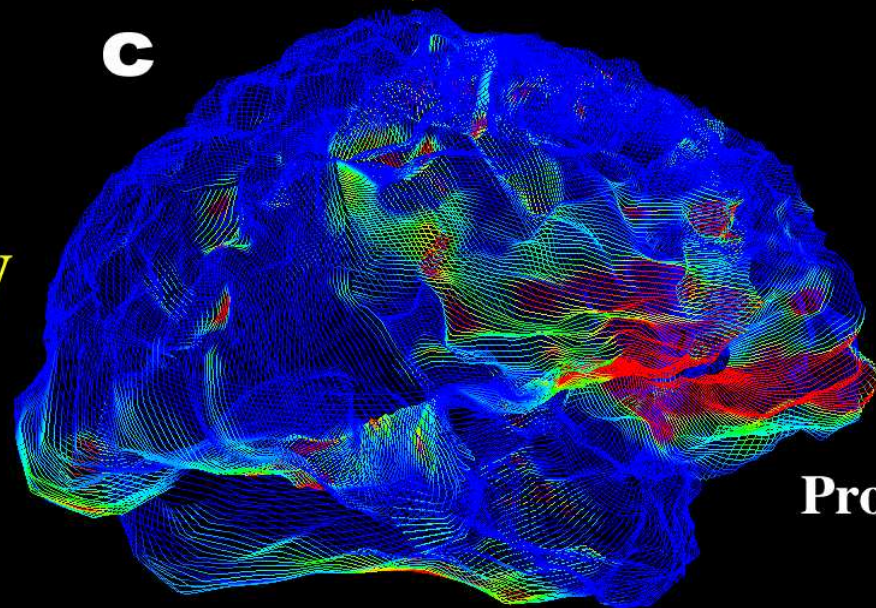


Deviation from Atlas

Normal Variability



Abnormality Map

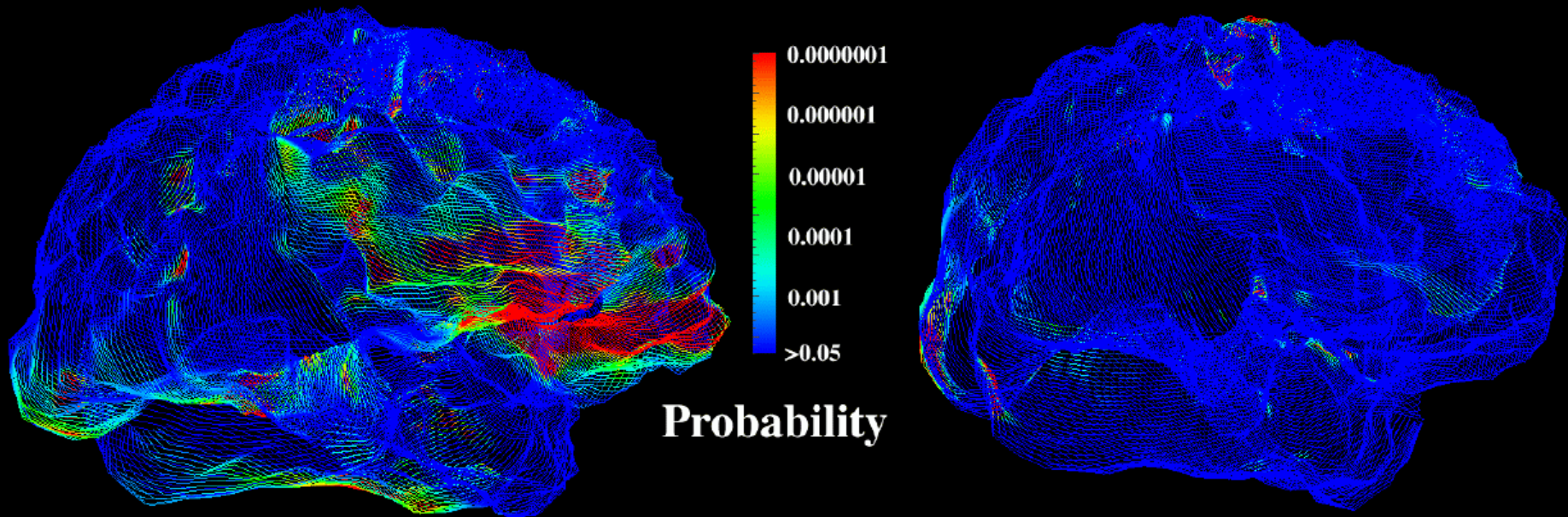


Probability

Pathology Detection

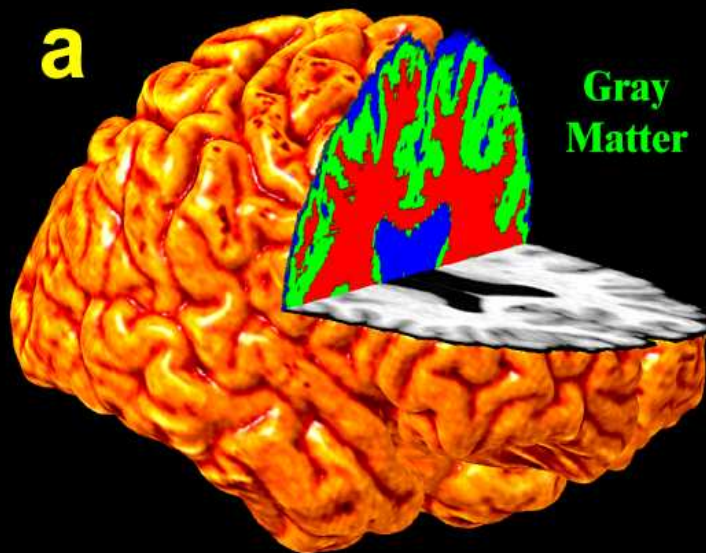
Dementia Patient

Elderly Normal Subject

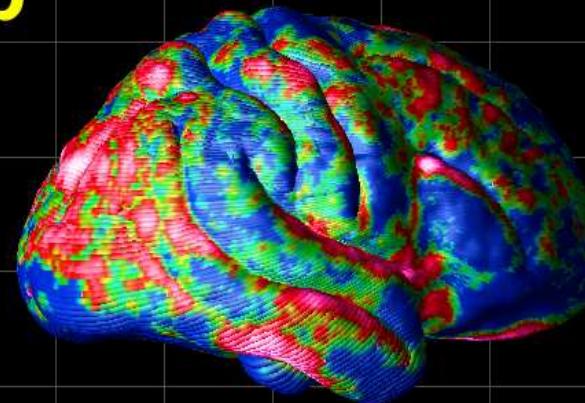


Application 1 - Alzheimer's Disease (MCI, ApoE)

Average Gray
Matter Loss
($N=46$)

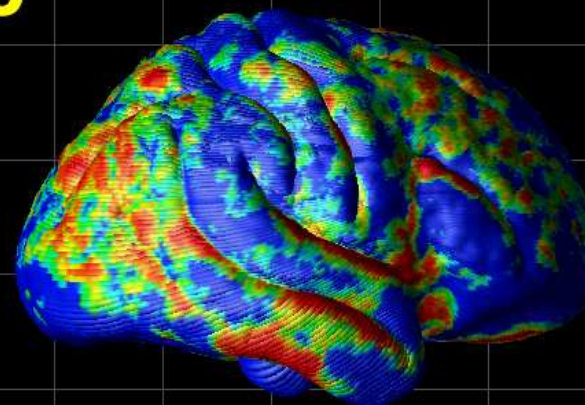


b

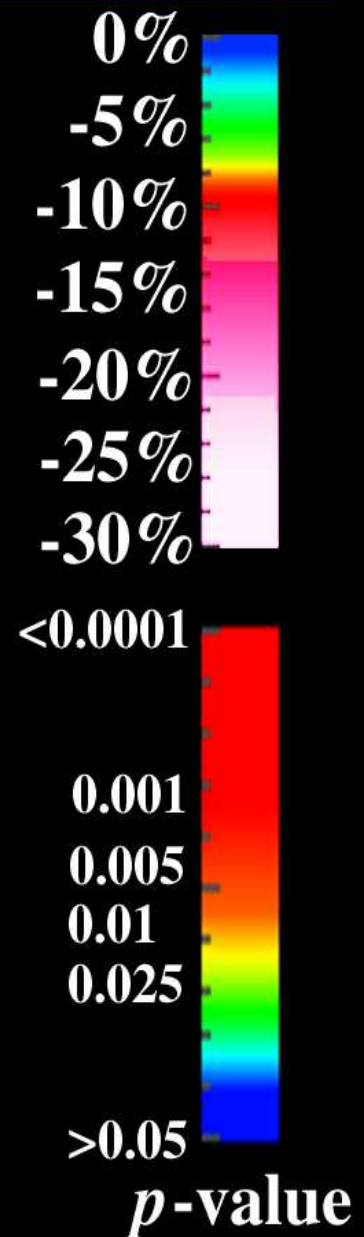


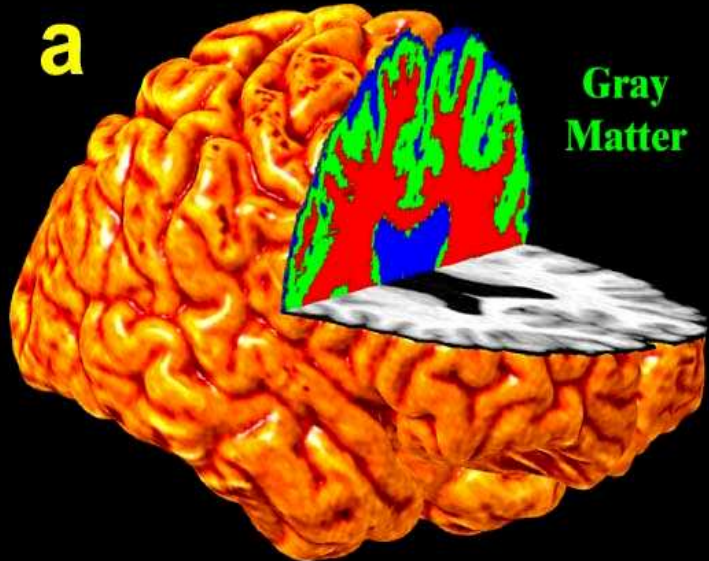
MAGNITUDE

c

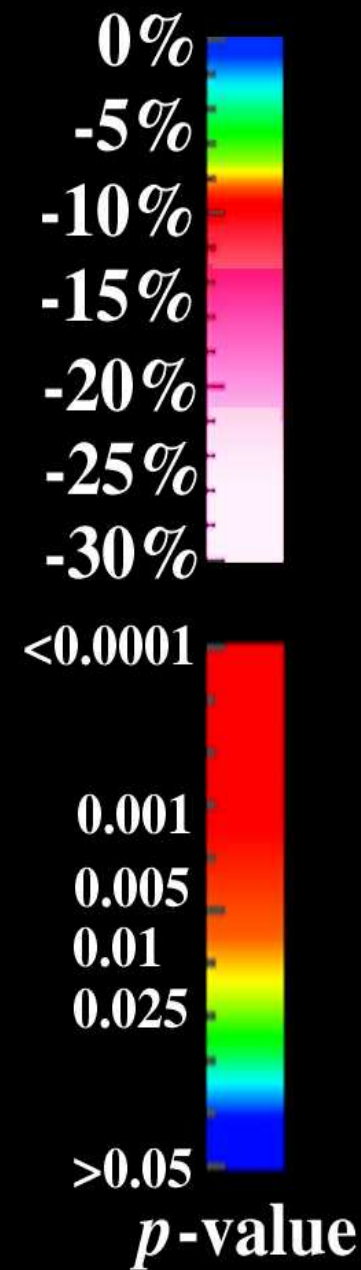
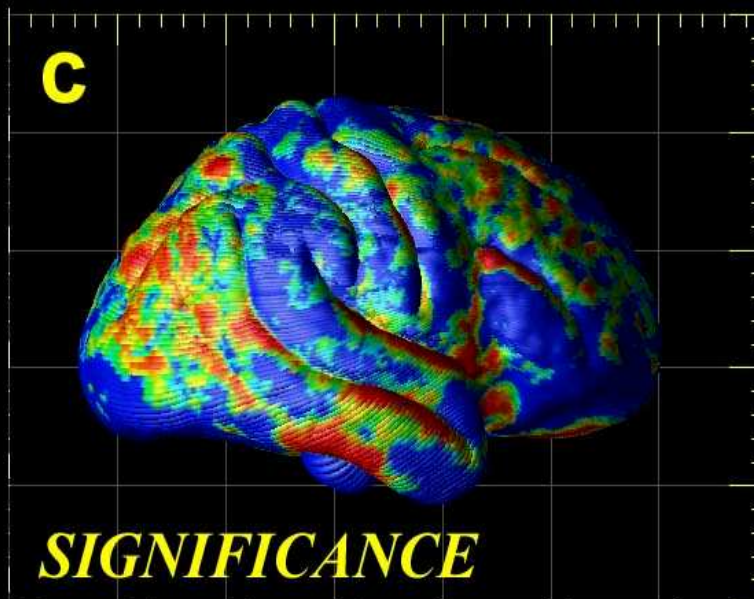
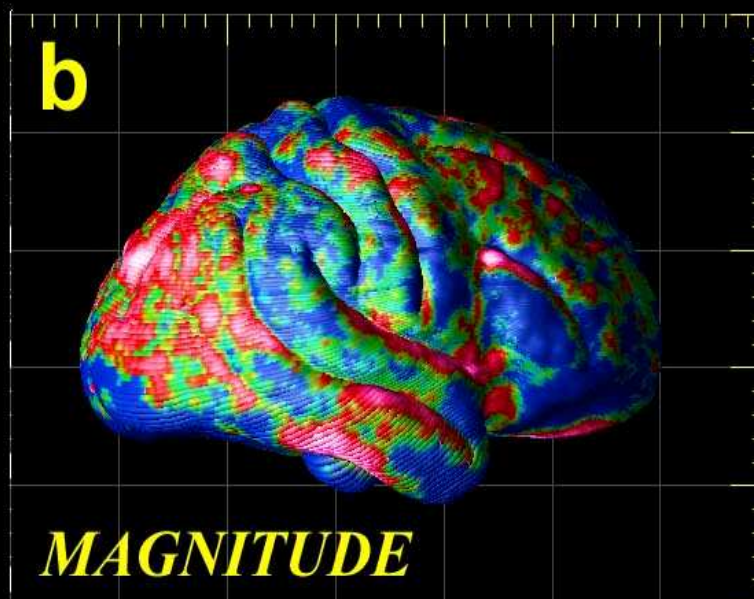
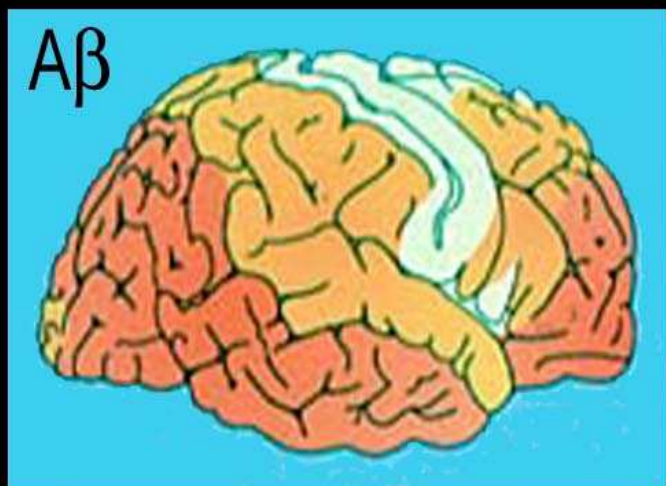


SIGNIFICANCE



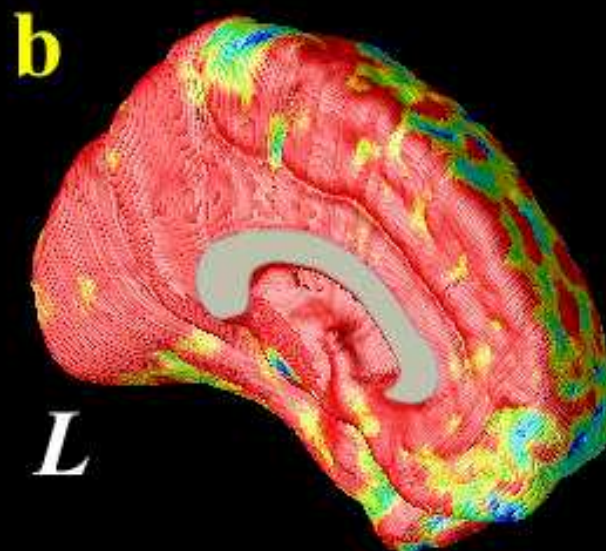
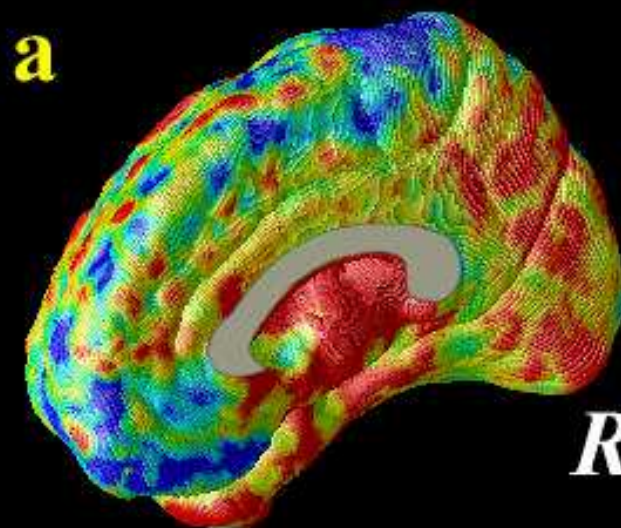


Braak Stage B

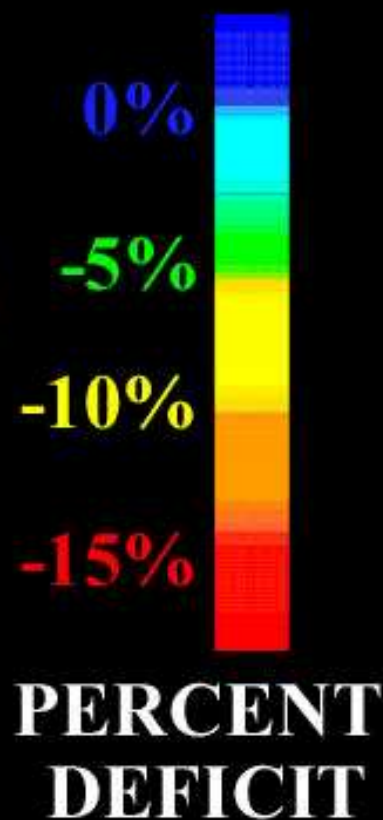
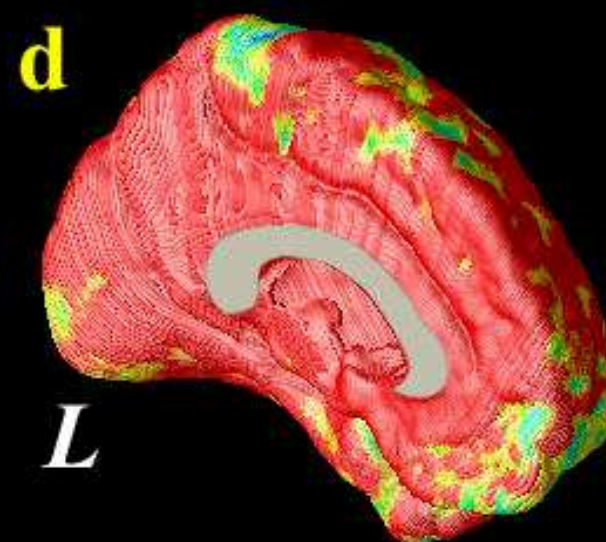
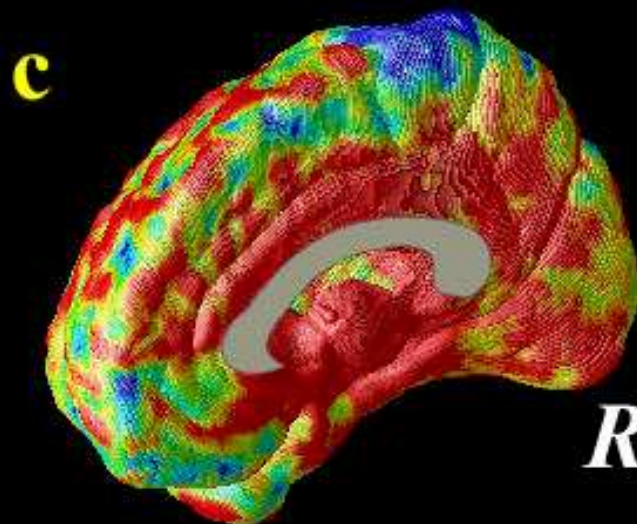


Percent Loss in AD: Medial Cortex

INITIAL DEFICIT

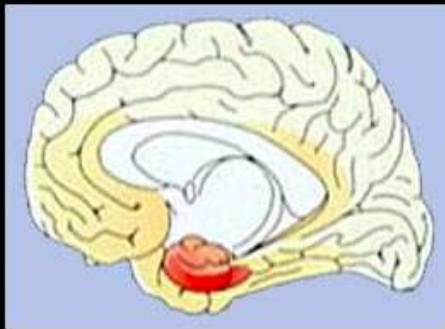
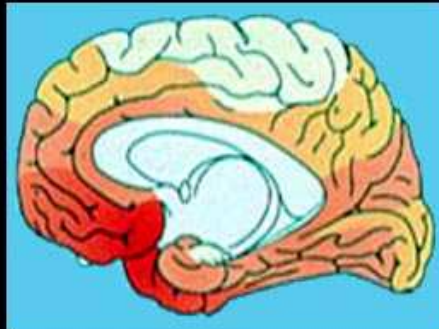


1.5 YEARS LATER



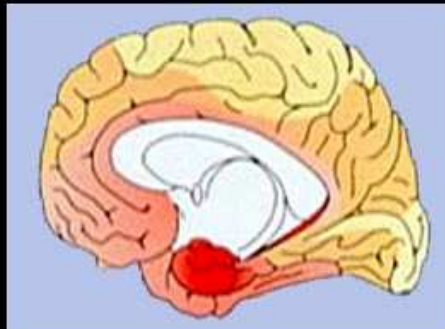
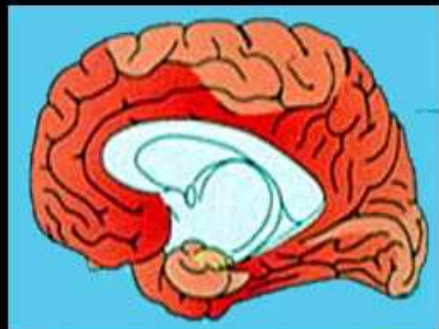
$A\beta$

NFT



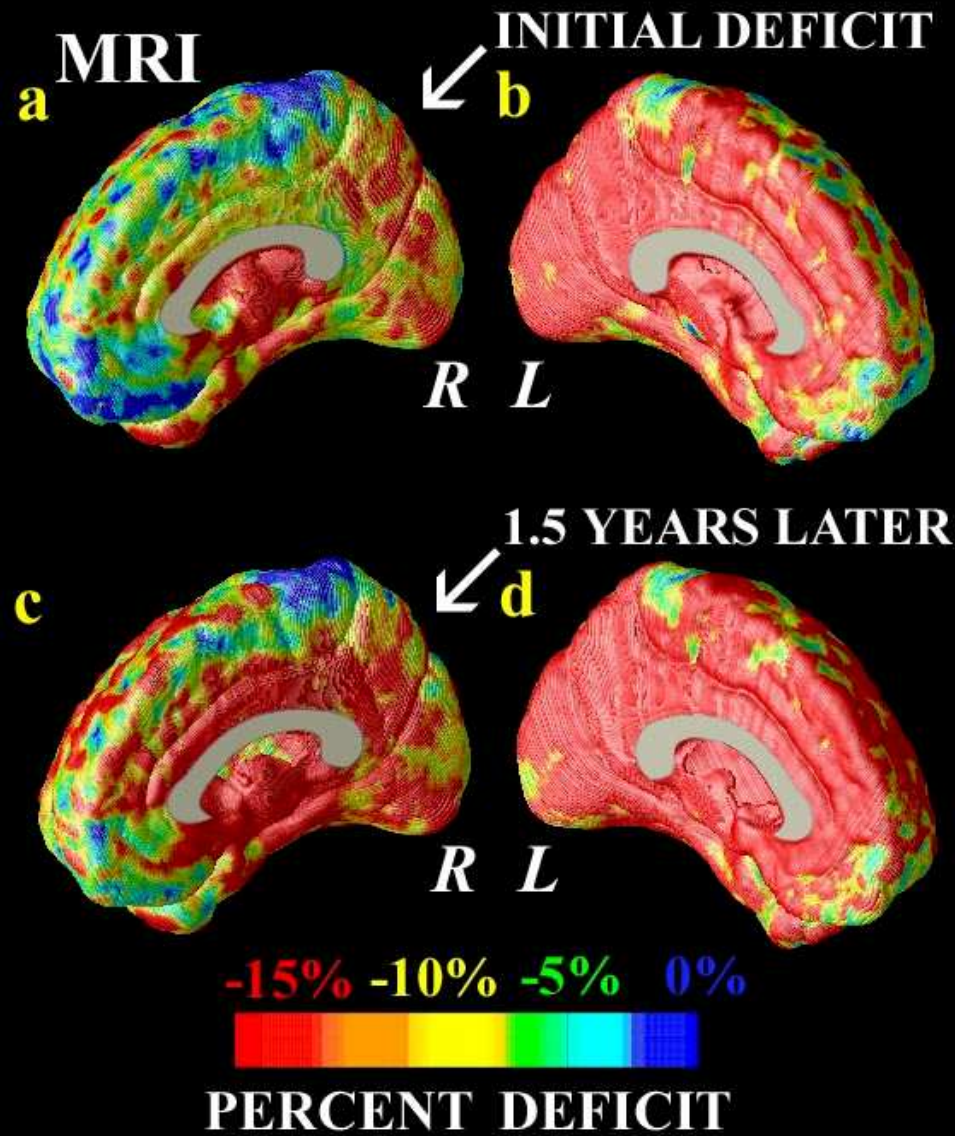
Braak Stage B

Stage III, IV



Braak Stage C

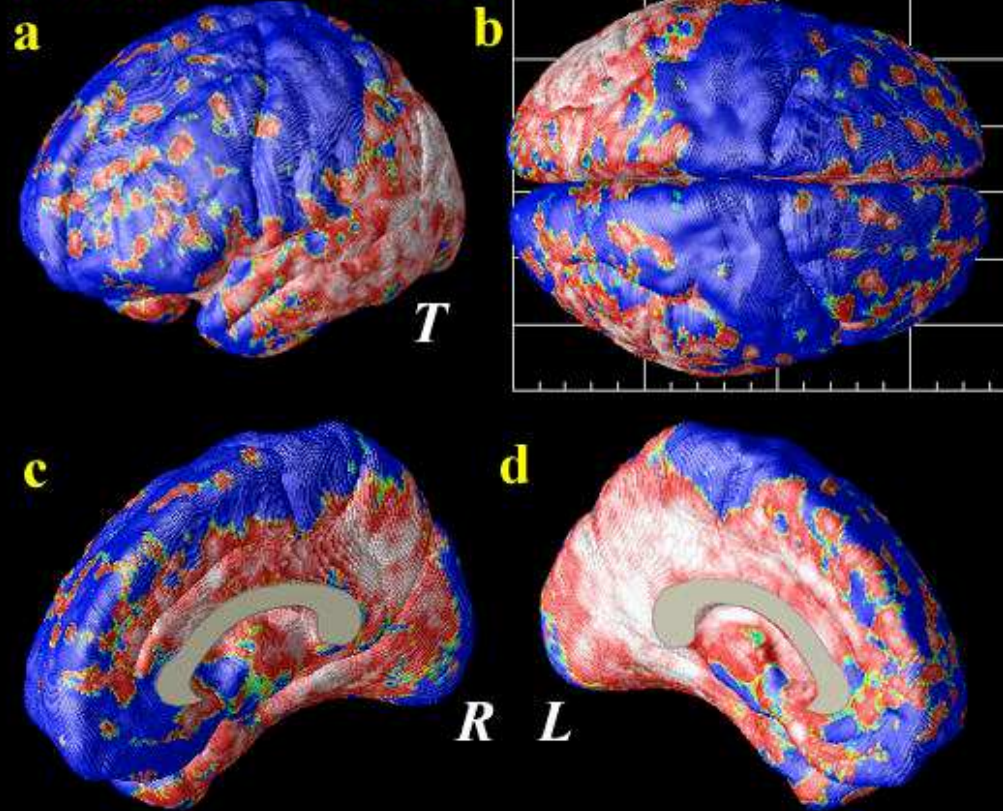
Stage V, VI



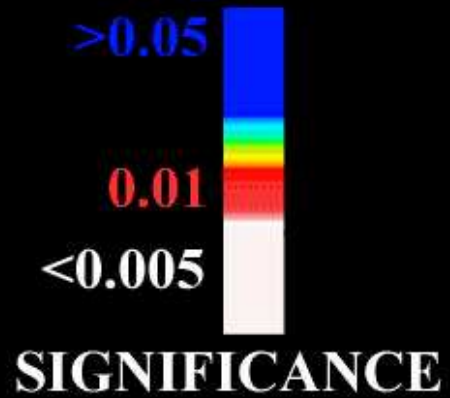
Correlation with MMSE Score

INITIAL DEFICIT

S/M

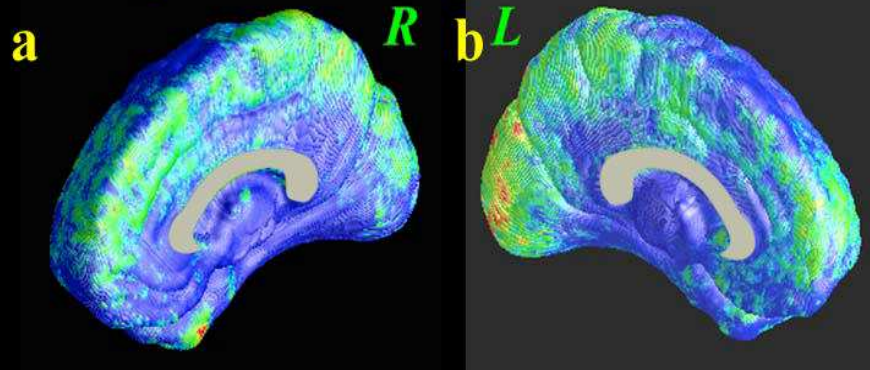


1.5 YEARS LATER

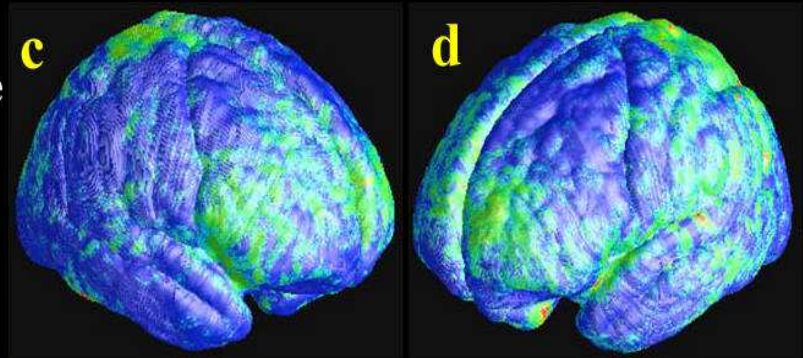


Rate of Gray Matter Loss

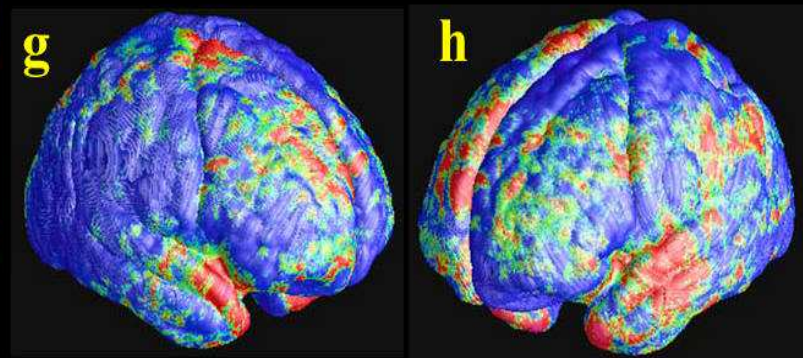
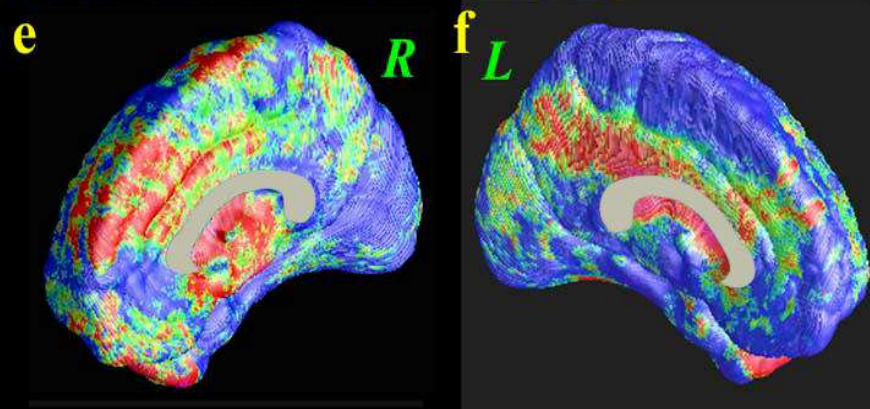
Elderly Normal Subjects



Average Annual Loss

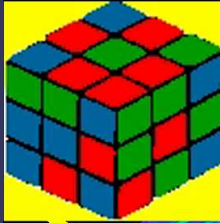


Alzheimer's Disease Patients



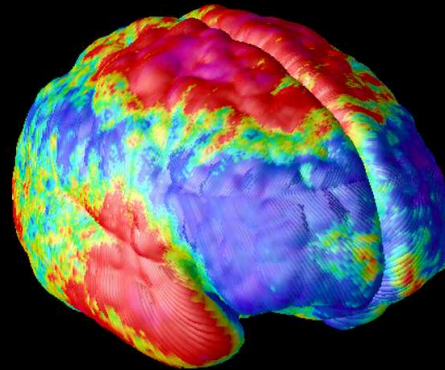
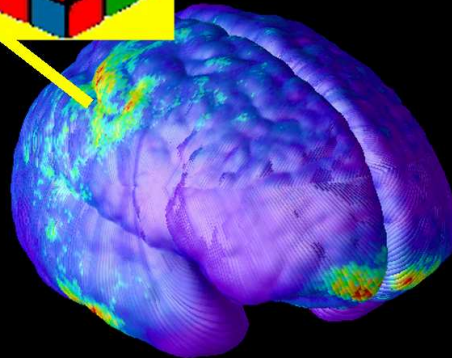
Teens lose Gray Matter (Sculpting)

Michelangelo/Disused Highways

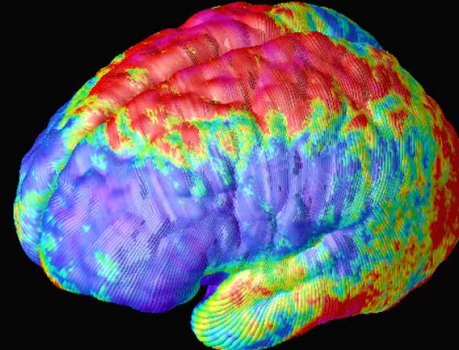
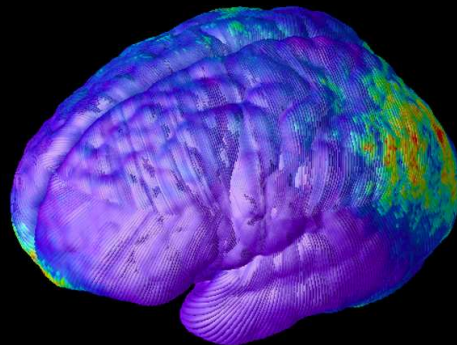
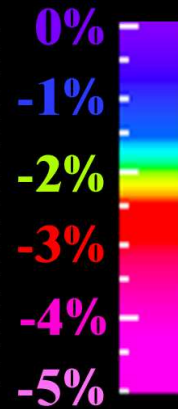
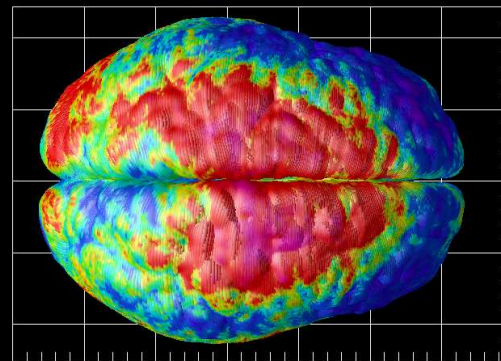
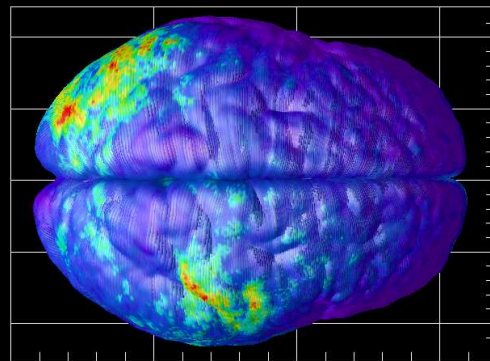


**Normal
Adolescents**

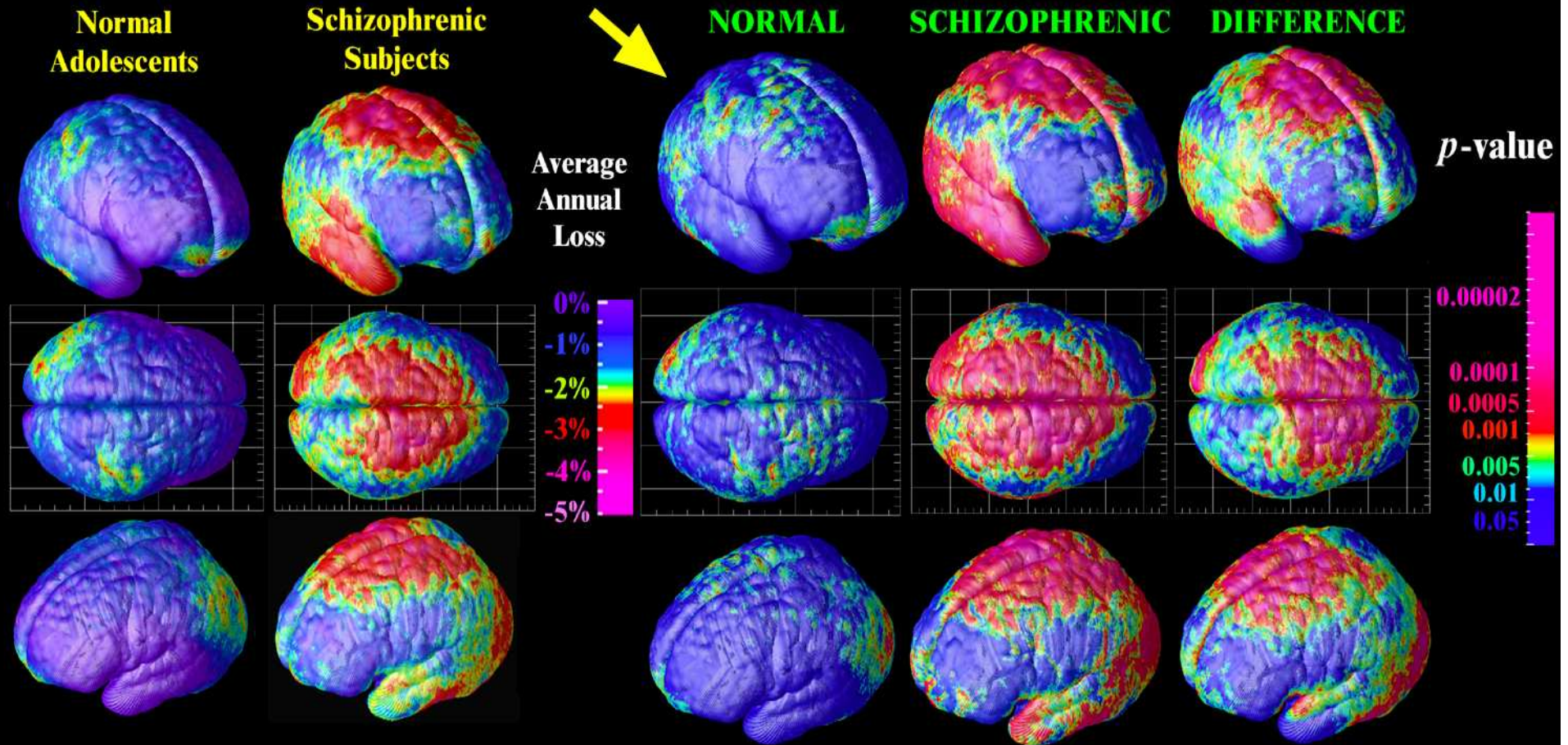
**Schizophrenic
Subjects**



**Average
Annual
Loss**



Application 2 - Schizophrenia; Map Adolescent Brain Change - Improve Signal Detection



Signal Detection/Processing on Cortex

Improve detection of subtle/diffuse effects
Scale space: filtering/Laplace-Beltrami flow

$$I(\mathbf{x}, t_{n+1}) = I(\mathbf{x}, t_n) + \Delta t \cdot \nabla^2_{\text{LB}} I(\mathbf{x}, t_{n+1})$$

Statistical Flattening: empower feature detection on a Surface

Roughness $\Lambda_{ij} = \text{Cov}[\partial X/\partial x_i, \partial X/\partial x_j]$

Smoothness $S_{ij} = [\Lambda^{-1}]_{ij}$

$$|\Lambda|^{-1/2} = (4 \ln 2)^{-D/2} \cdot \prod_{i=1}^D FWHM_i$$

Make a Smoothness Grid

$$g^{ij} (\partial^2 \mathbf{u} / \partial r^i \partial r^j) + \partial / \partial u^j (S^{ij}) \mathbf{u}_{r,i} = 0$$

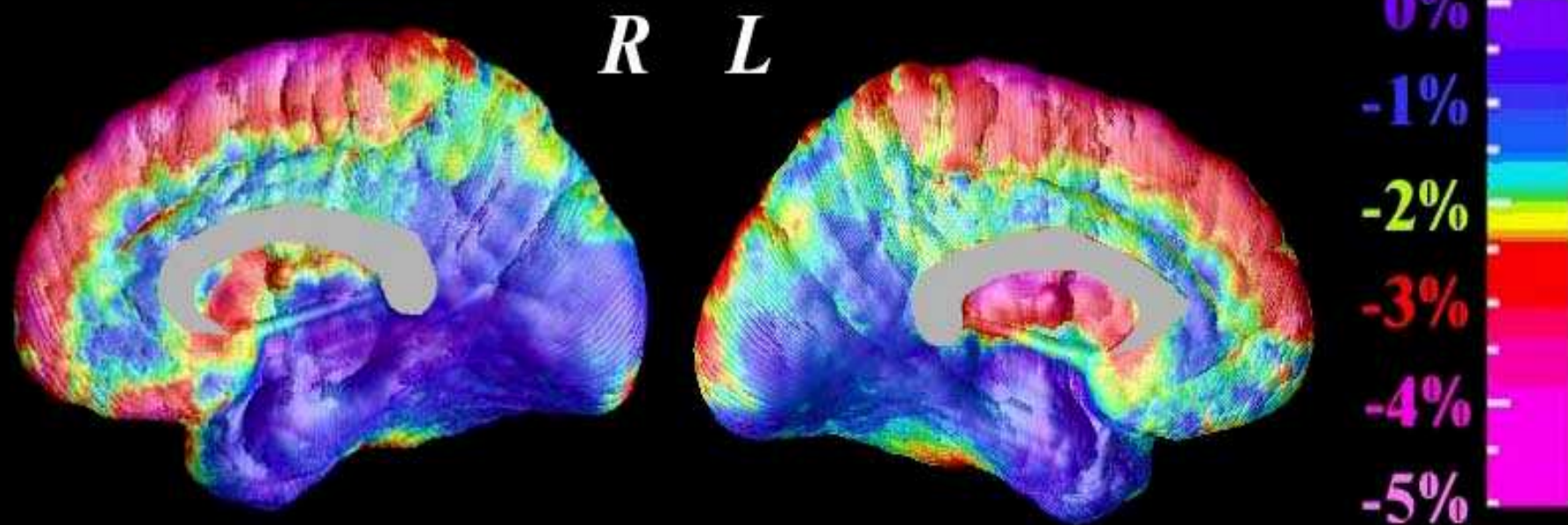
$$\rightarrow \nabla \mathbf{u}(\mathbf{x}) = S^{ij}$$

CELL SIZE SMOOTHNESS

Validate by permutation

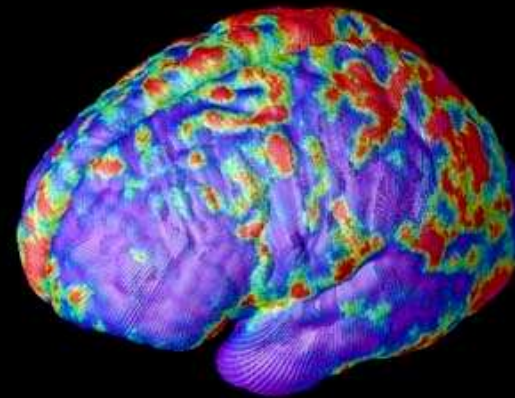
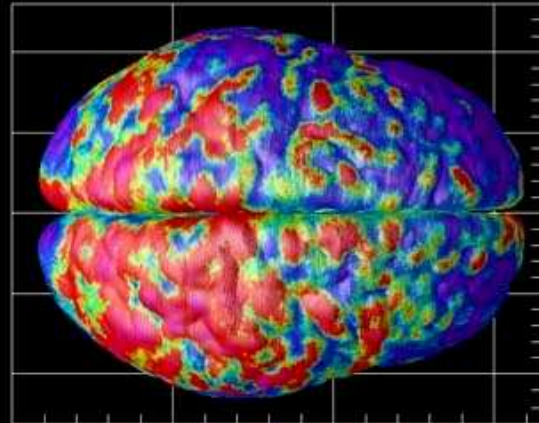
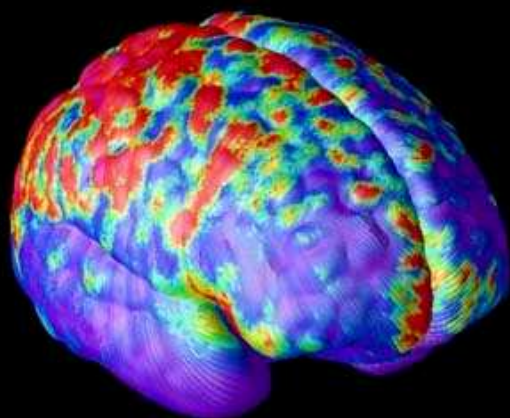
Loss Rate: *Medial Surface*
(Vidal et al., 2002)

**Average
Annual
Loss**

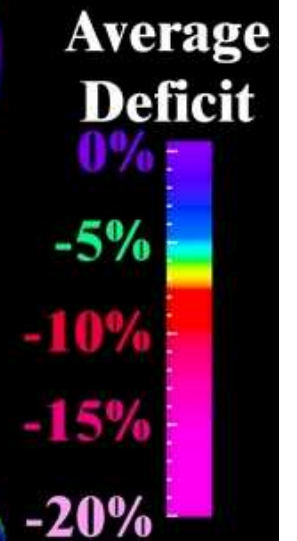
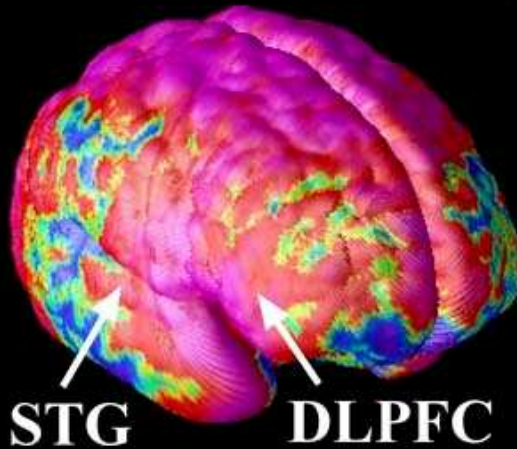


Early and Late Gray Matter Deficits in Schizophrenia

EARLIEST DEFICIT



5 YEARS LATER (SAME SUBJECTS)



STG

DLPFC

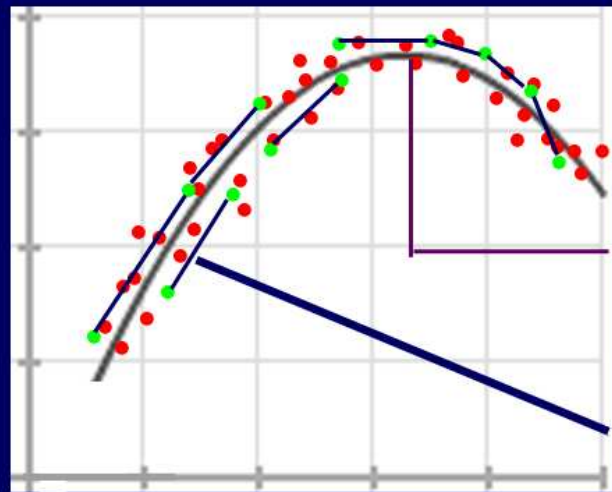
Thompson
et al., 2001

More Advanced Modeling of Change

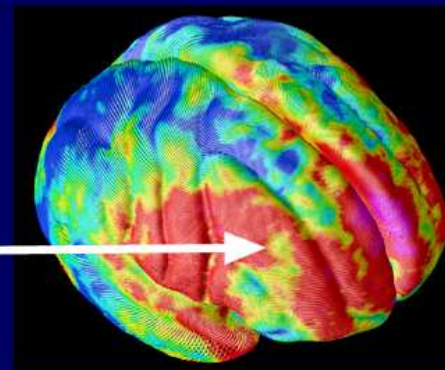
Nonlinear Models: map where is change slowing down/speeding up (meds., devel)

Mixed Models: combine longit./ cross-sec. data (devel., AD, tumor, SZ);
random effects term:

$$Y_{ij} = \alpha_i + f_{nonlin}(\text{Age}_{ij}, \underline{\beta}) + \varepsilon_{ij}$$



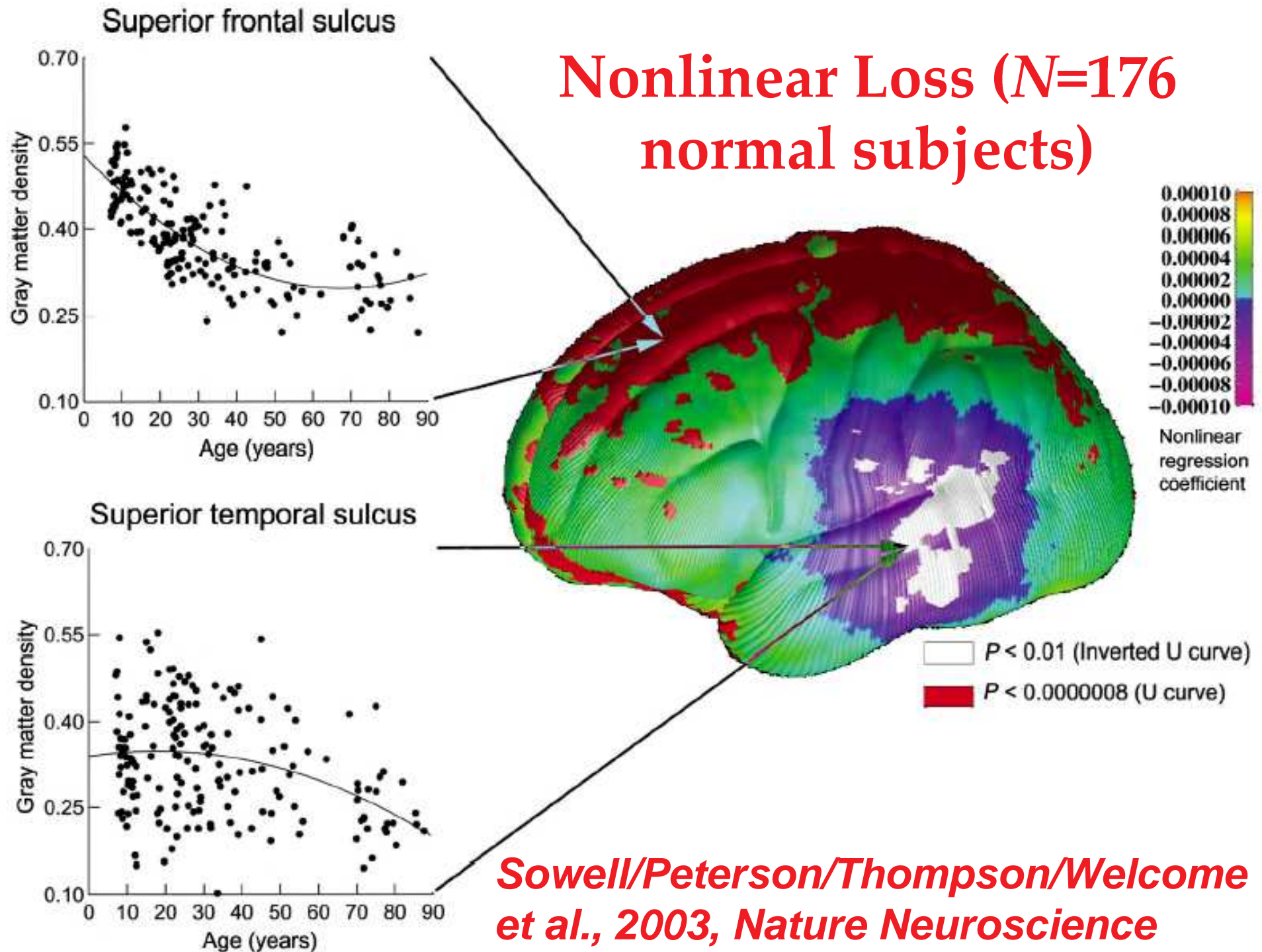
age



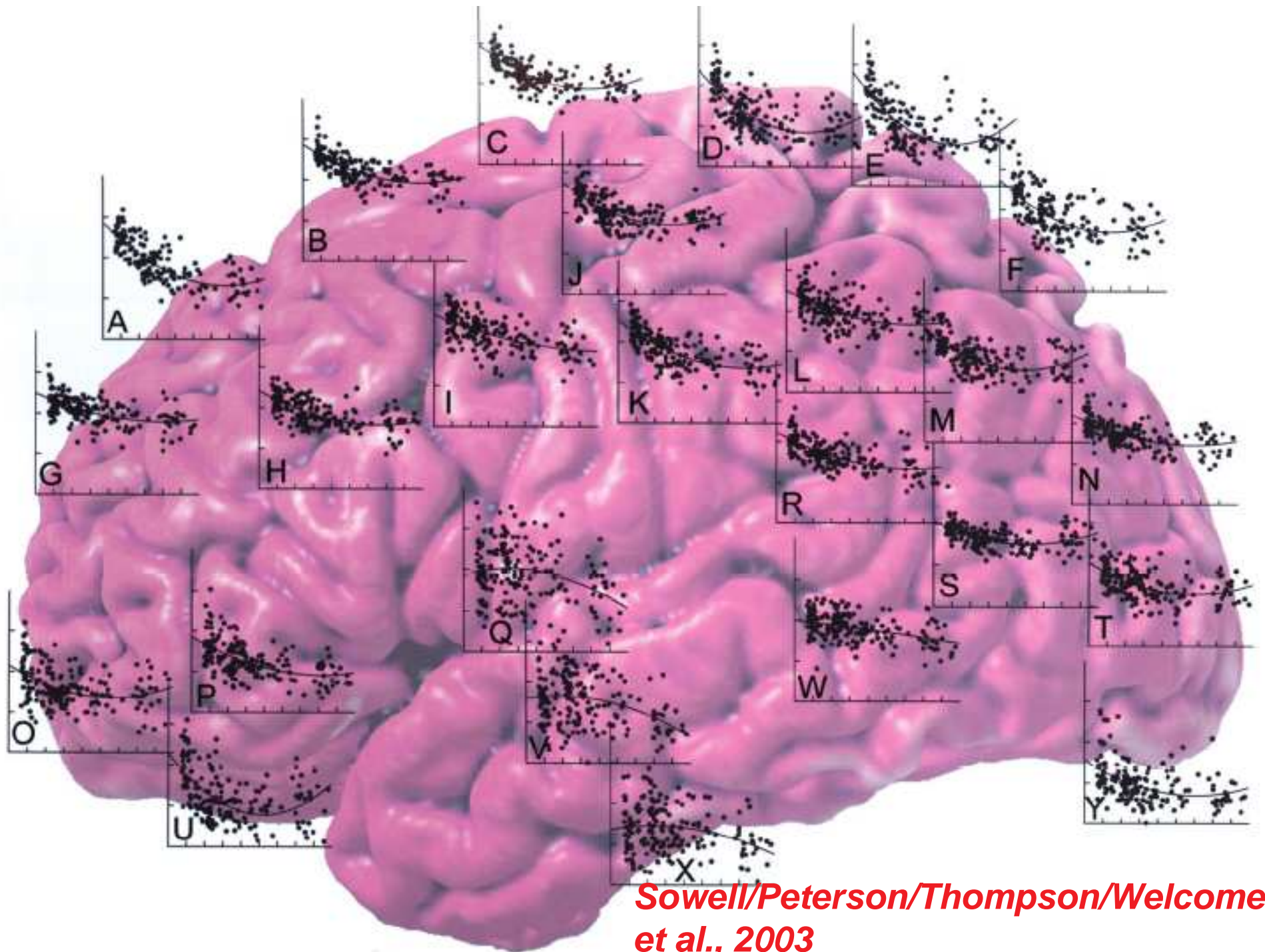
age at peak?

Correlate with functional, cognitive/clinical change (e.g. SANS, SAPS, IQ), meds.

Nonlinear Loss (N=176 normal subjects)



Sowell/Peterson/Thompson/Welcome et al., 2003, Nature Neuroscience



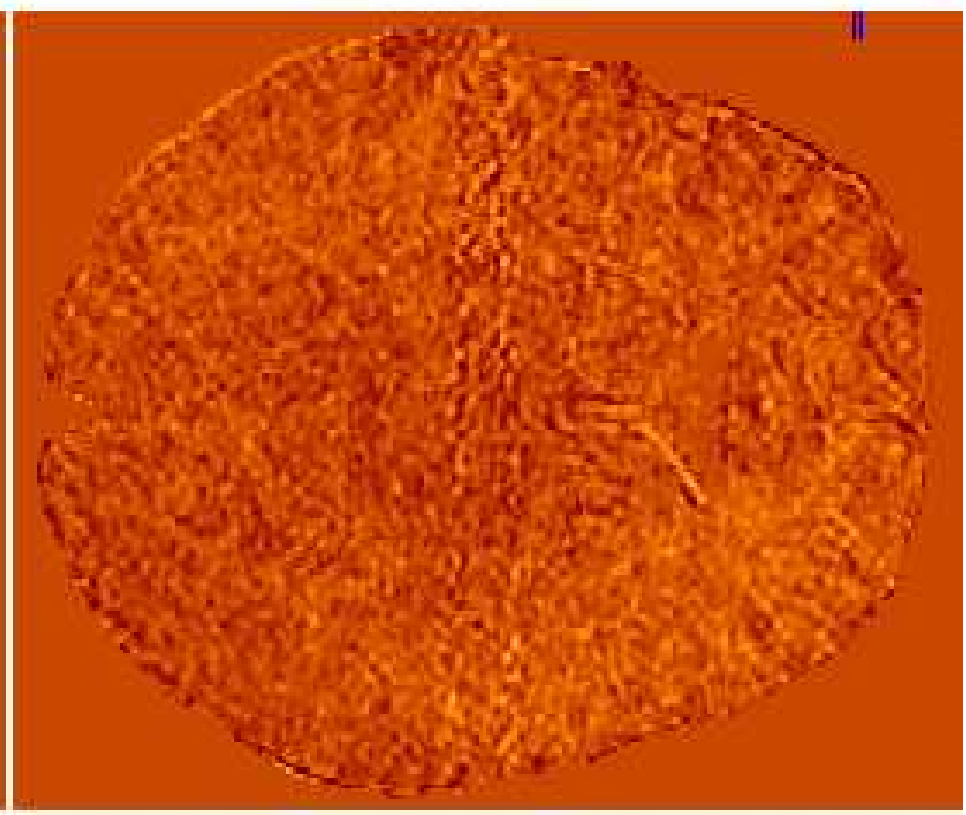
*Sowell/Peterson/Thompson/Welcome
et al., 2003*

WHAT ARE THE SUBTLEST BRAIN CHANGES WE CAN DETECT?

Detecting Anatomical Change

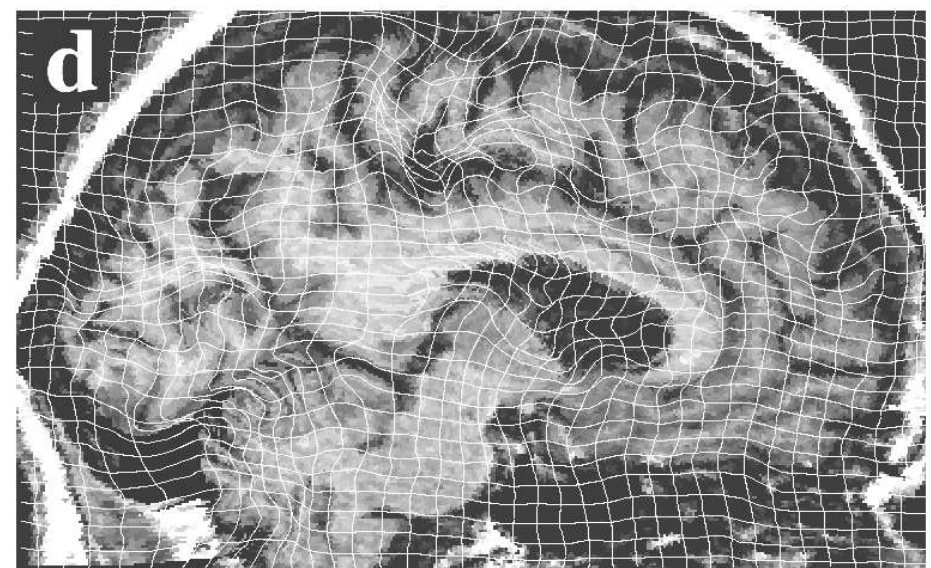
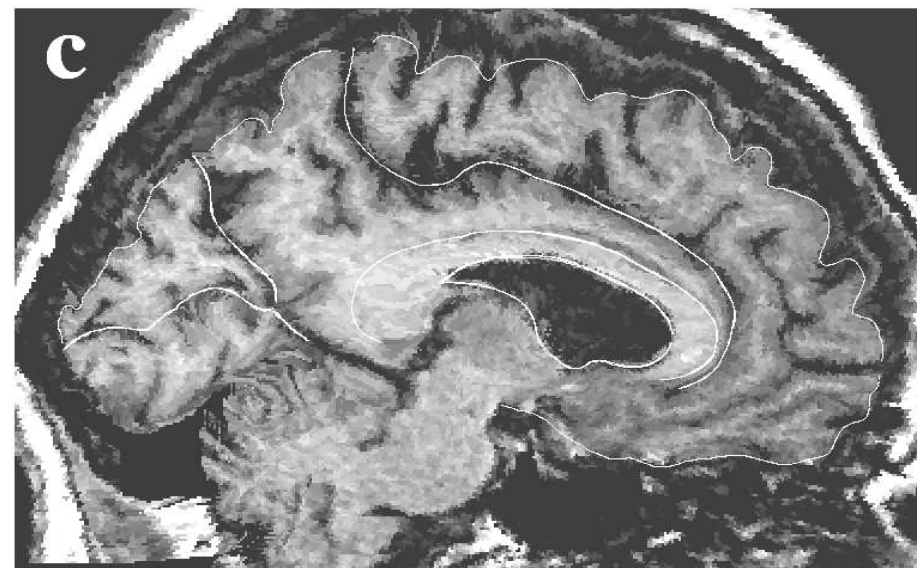
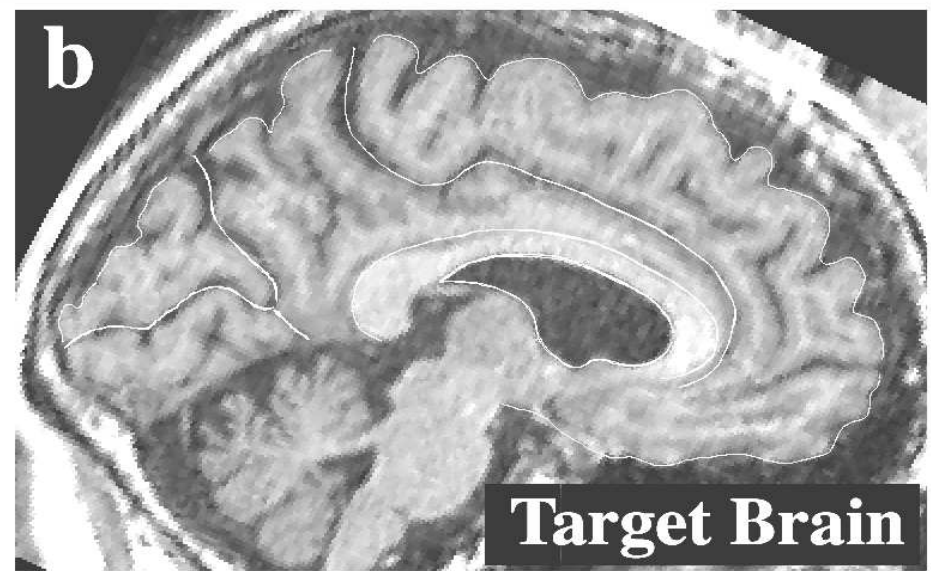
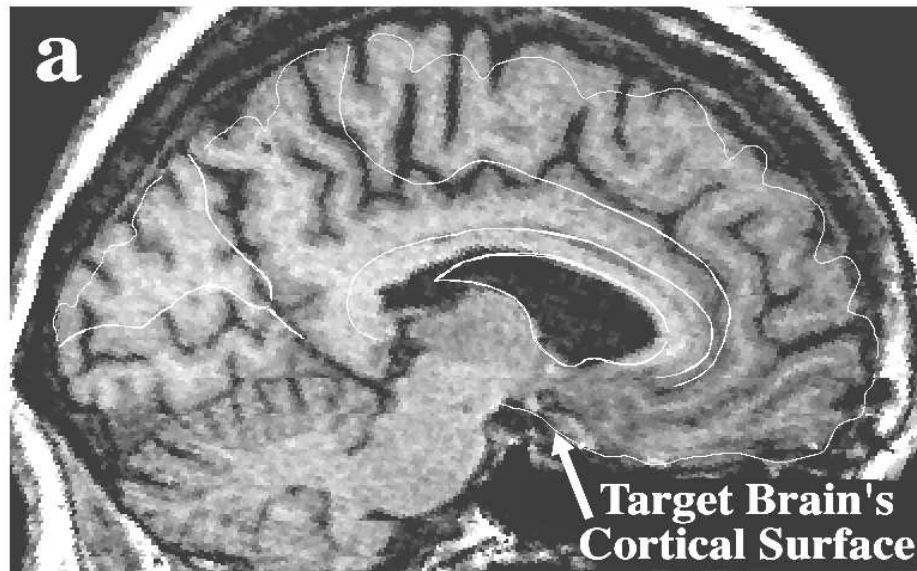


4-year Interval



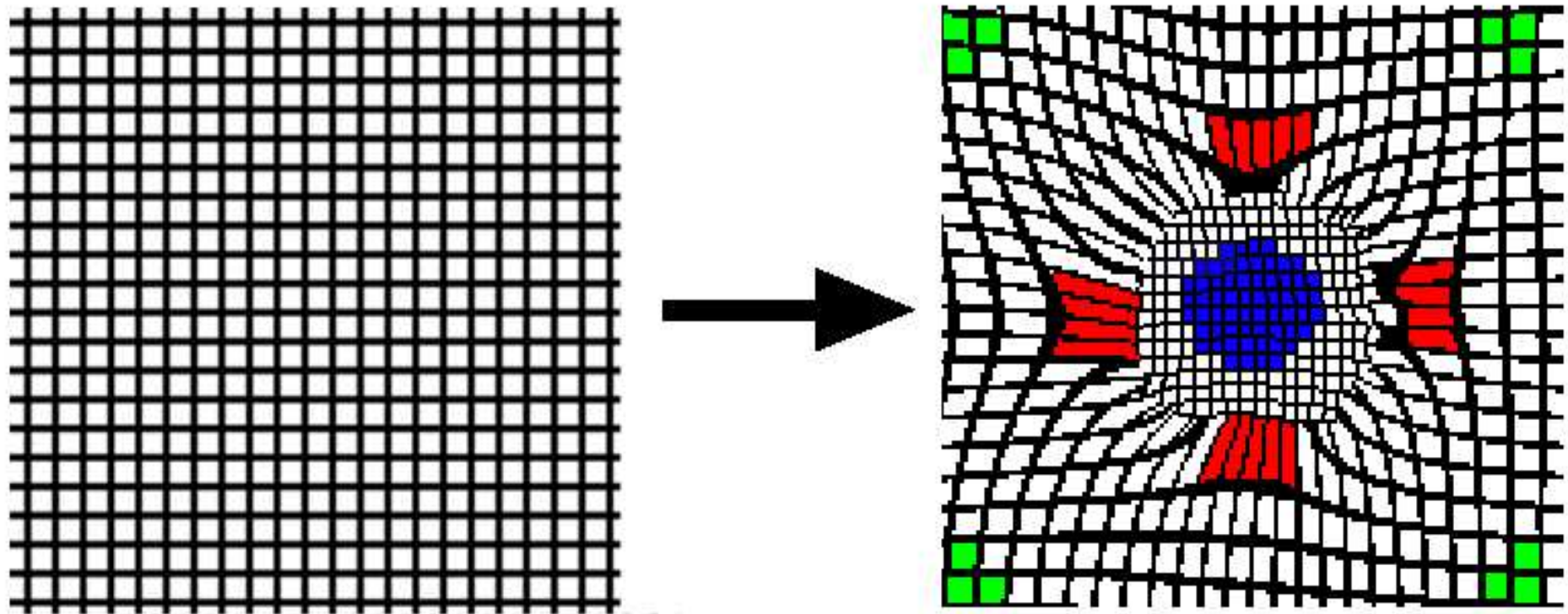
2 weeks

Warping/Morphing Brain Scans



Thompson et al., Nature 404:190-193 (2000).

Mapping Growth



 *Growth*

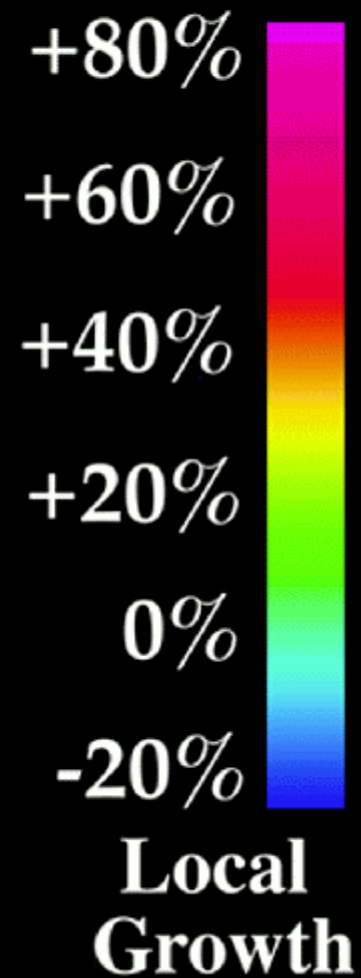
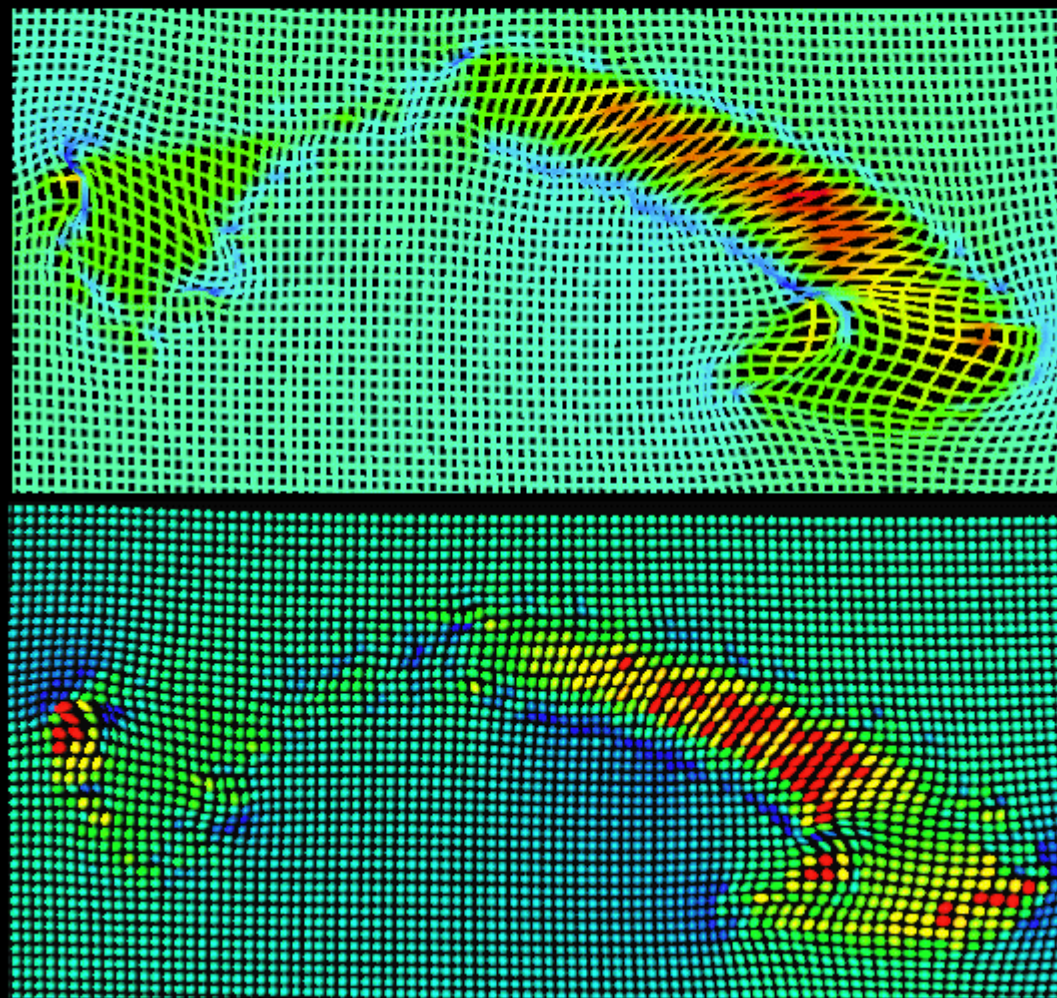
 *Loss*

 *No Change*

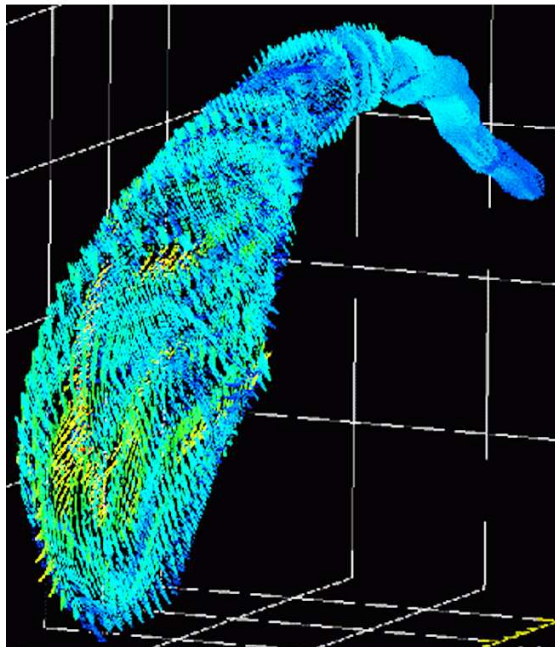
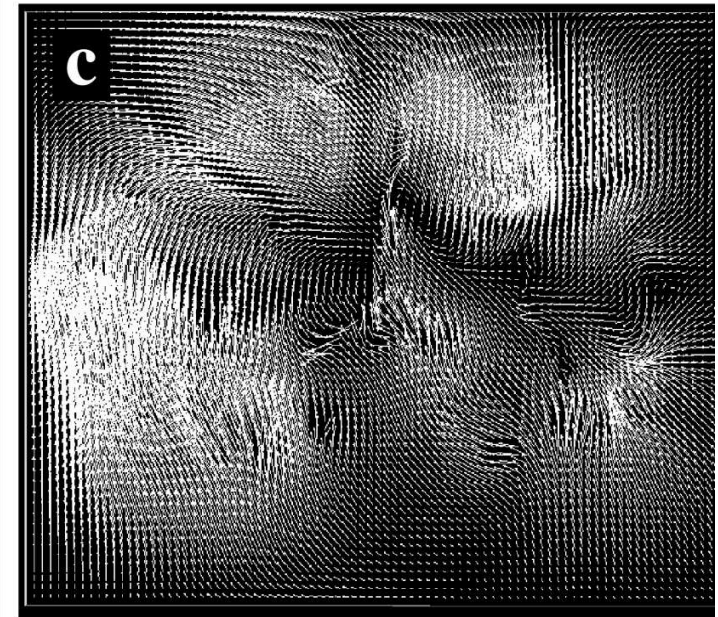
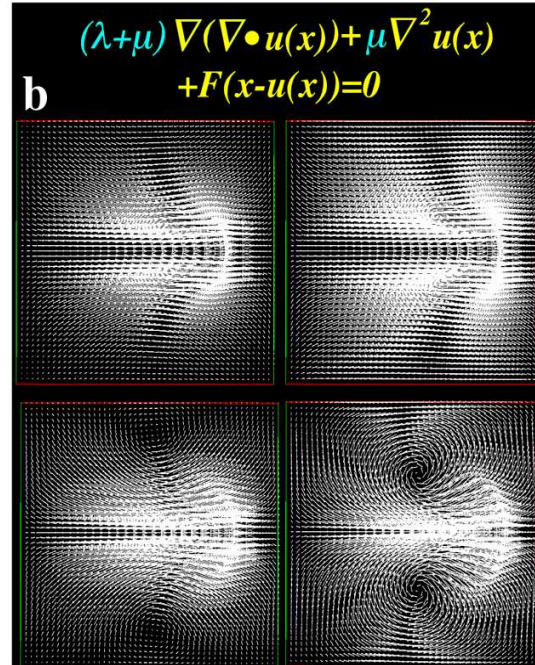
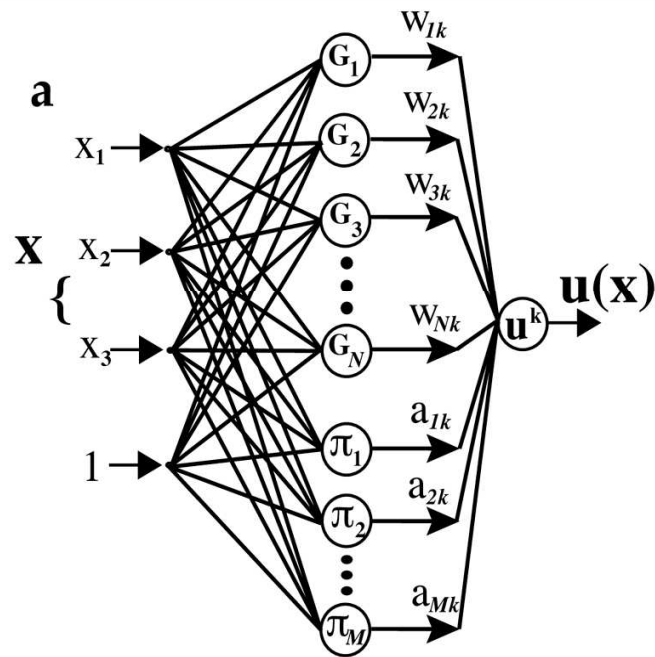
Mapping Brain Growth shape changes, signal changes



**3 year
Interval
3-6 yrs.
of age**



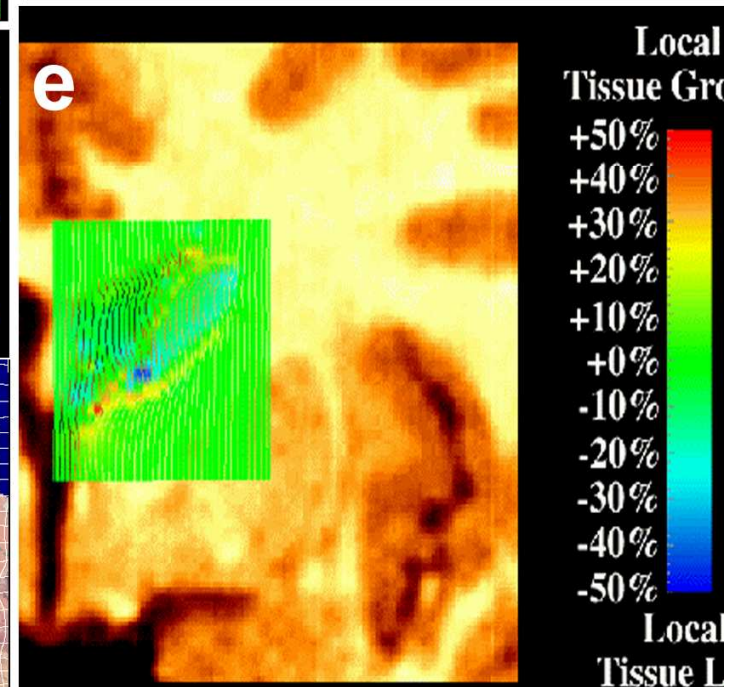
Growth Computation - Continuum-Mechanical PDE



$$(\lambda + \mu) \Delta_x^0 [\Delta_x^0 U_{i,j,k} + \Delta_y^0 V_{i,j,k} + \Delta_z^0 W_{i,j,k}] + \mu [\Delta_{xx} + \Delta_{yy} + \Delta_{zz}] U_{i,j,k} + F_i(x - u(x)) = 0$$

$$(\lambda + \mu) \Delta_y^0 [\Delta_x^0 U_{i,j,k} + \Delta_y^0 V_{i,j,k} + \Delta_z^0 W_{i,j,k}] + \mu [\Delta_{xx} + \Delta_{yy} + \Delta_{zz}] V_{i,j,k} + F_j(x - u(x)) = 0$$

$$(\lambda + \mu) \Delta_z^0 [\Delta_x^0 U_{i,j,k} + \Delta_y^0 V_{i,j,k} + \Delta_z^0 W_{i,j,k}] + \mu [\Delta_{xx} + \Delta_{yy} + \Delta_{zz}] W_{i,j,k} + F_k(x - u(x)) = 0$$



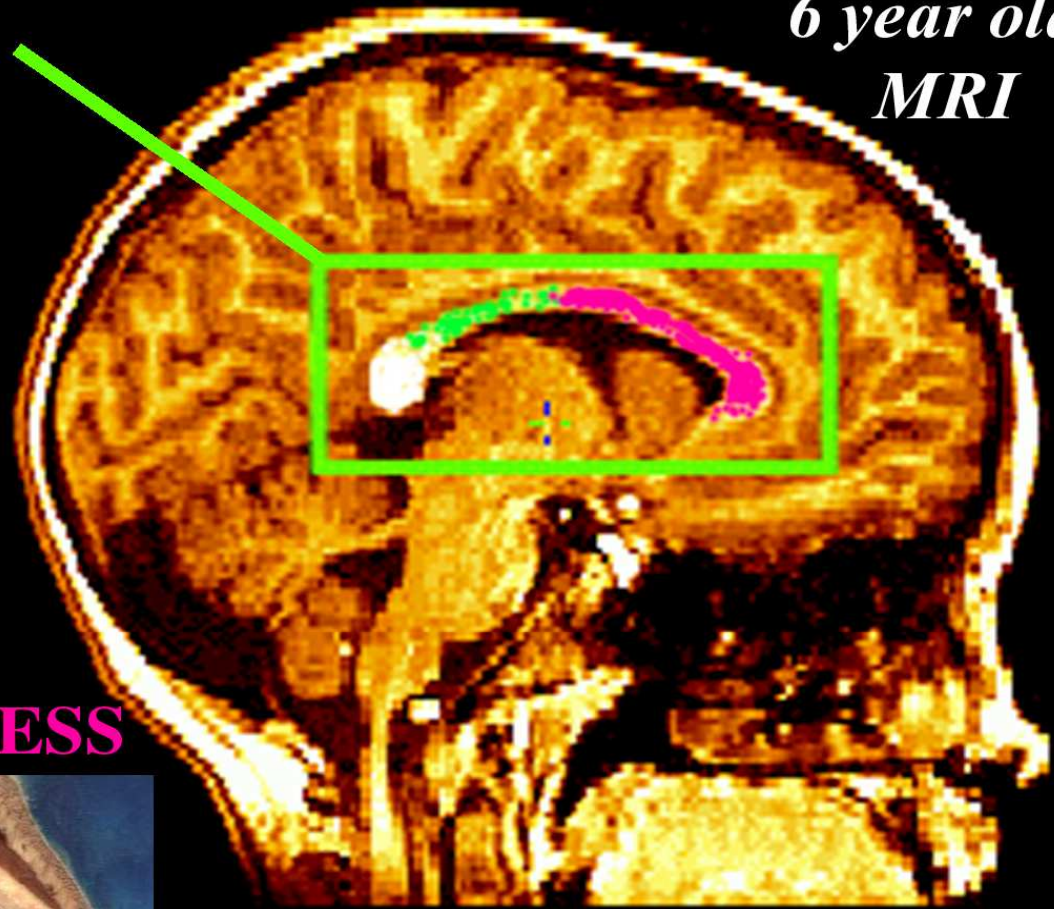
Corpus Callosum

like telephone exchange

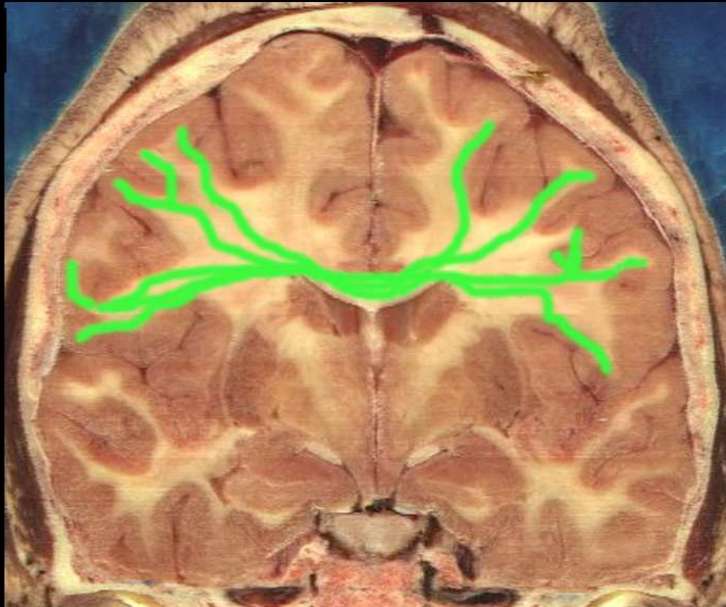
100-250 million fibers

VISION *M/F?*
LANGUAGE, MATH
ATTENTION/ALERTNESS

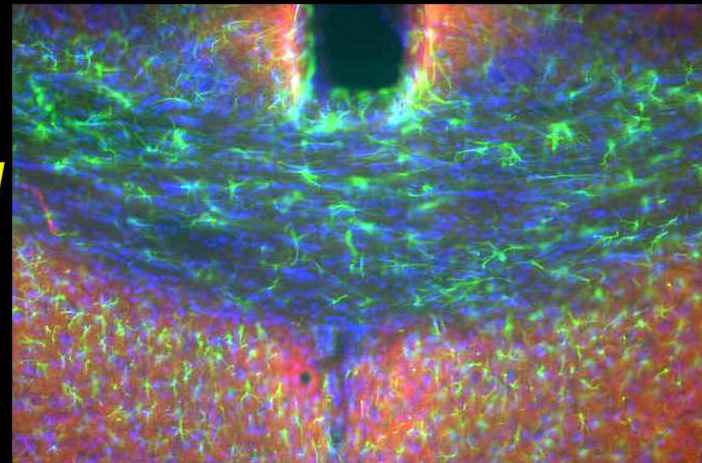
6 year old;
MRI

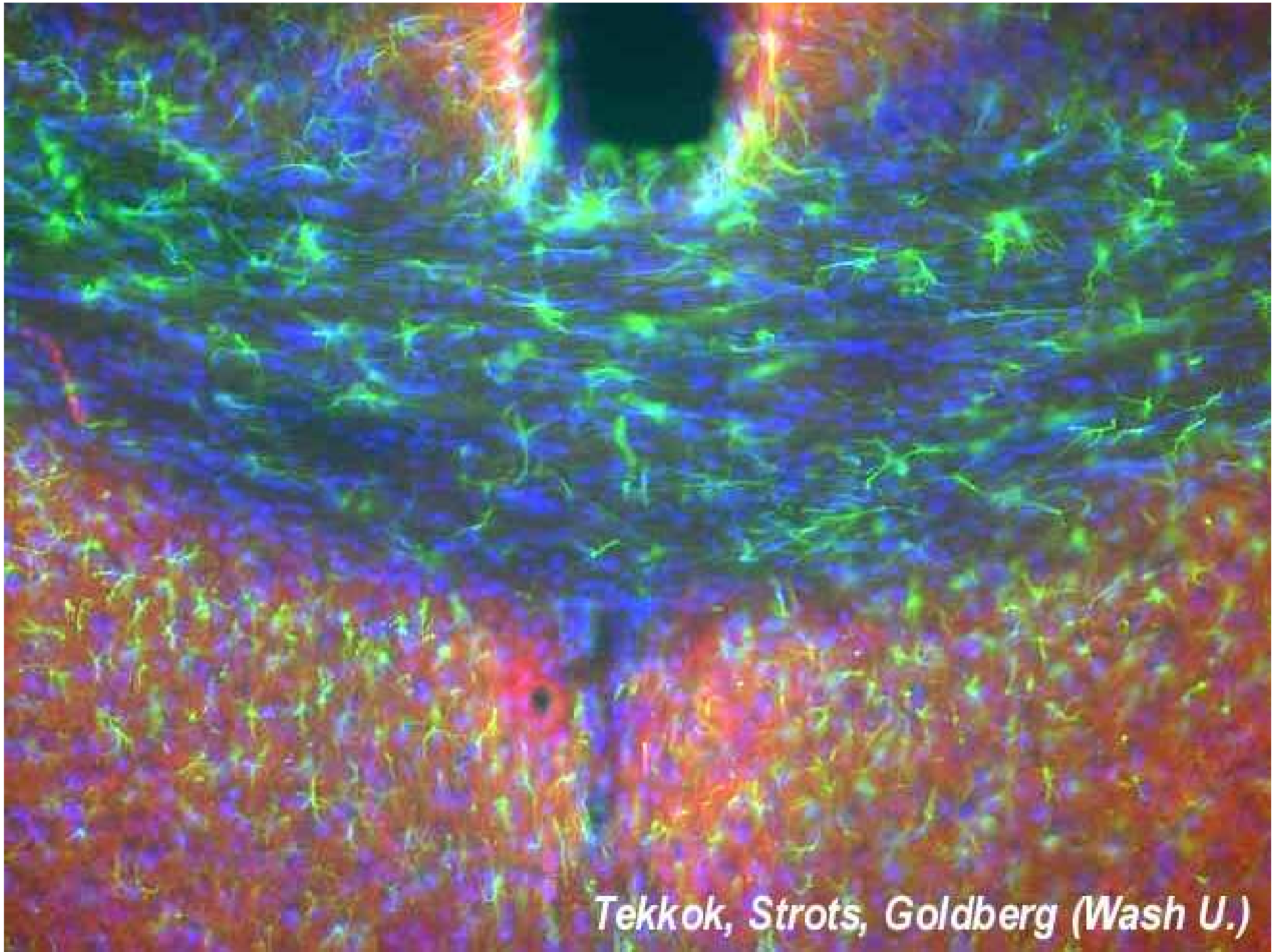


R



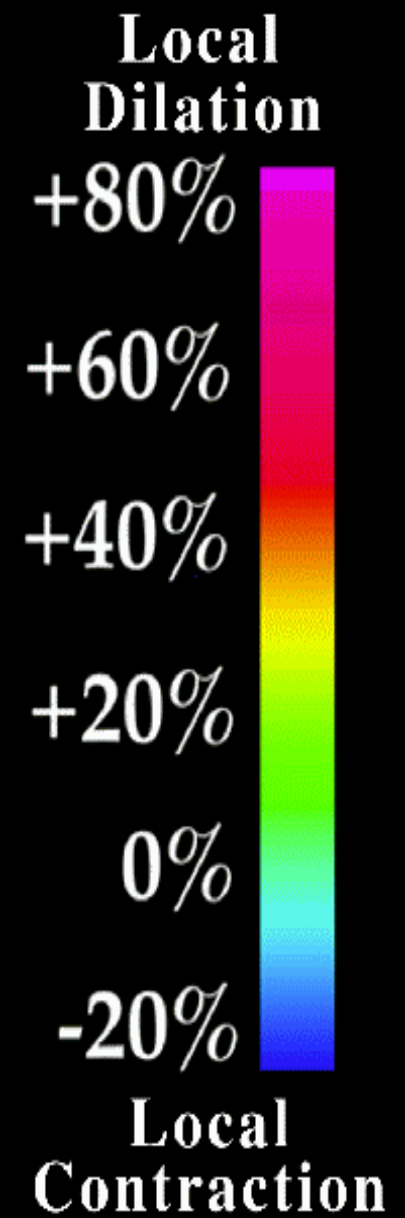
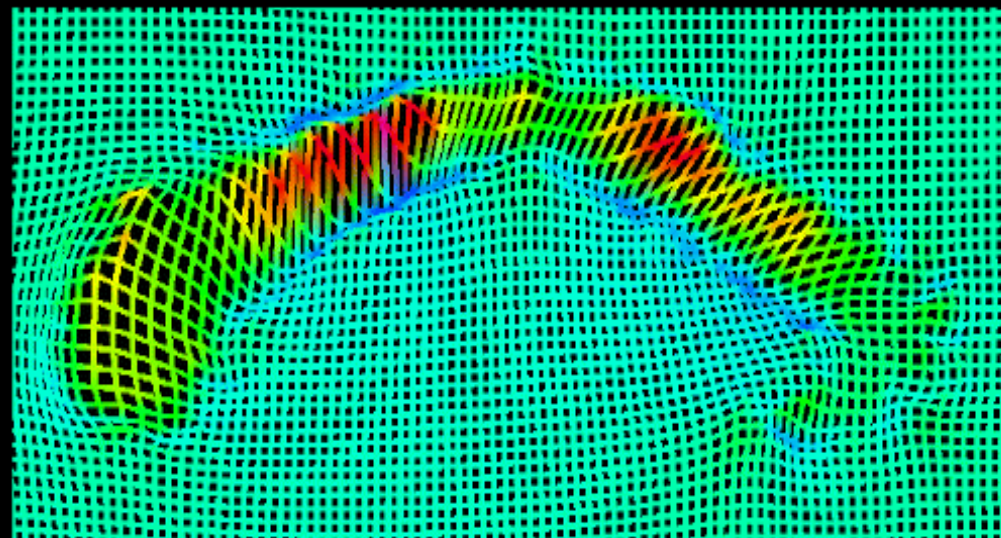
L



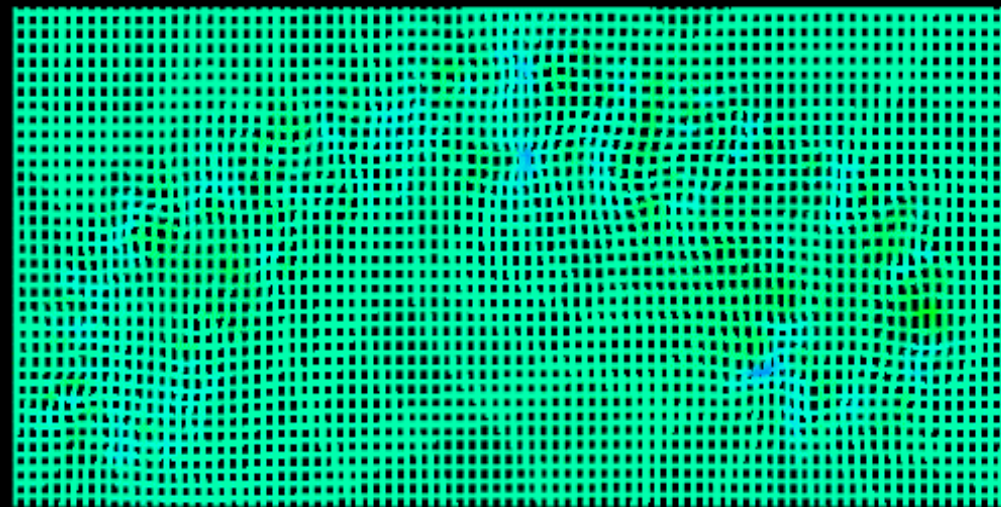


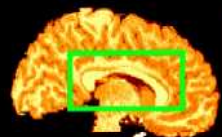
Tekkok, Strots, Goldberg (Wash U.)

**4 year
Interval
(8-12 yr. old
girl)**



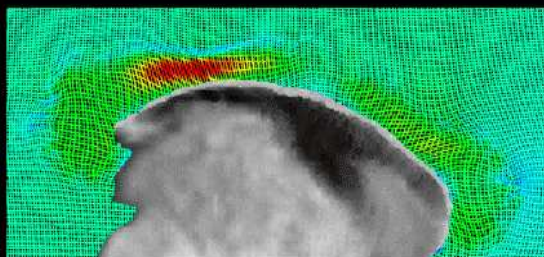
**2 week
Interval
(same
subject)**



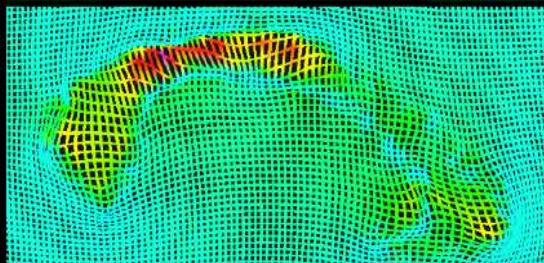


4D Growth Maps

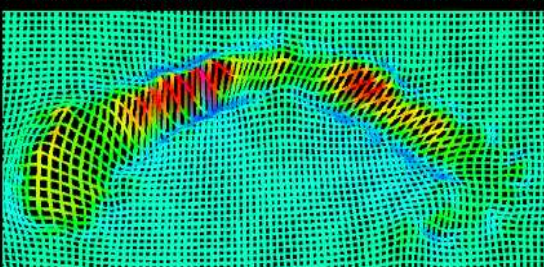
4-year Interval
7-11 years
(boy)



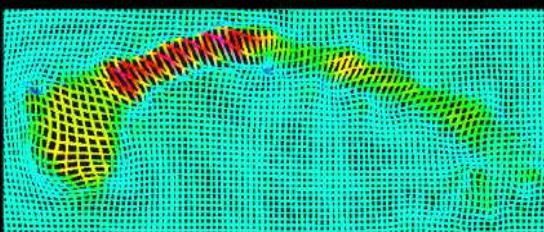
6-7 yrs.
(girl)



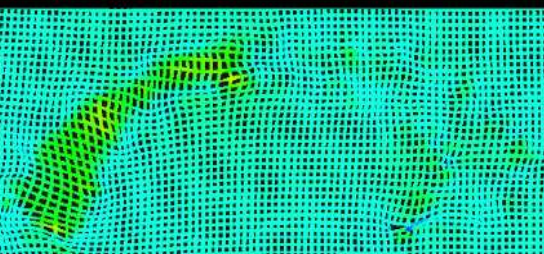
8-12 yrs.
(girl)



9-13 yrs.
(girl)

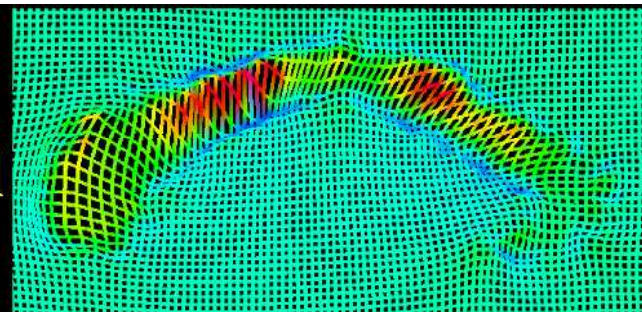


11-15 yrs.
(boy)

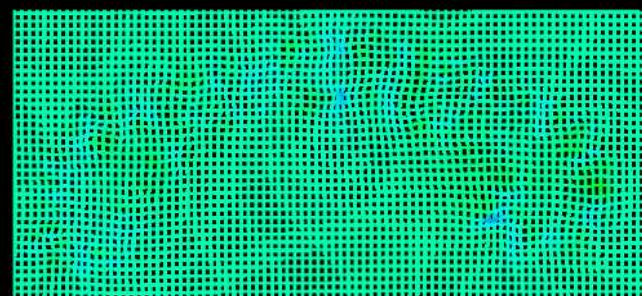


Local Growth

4 year Interval
(8-12 yr. old girl)



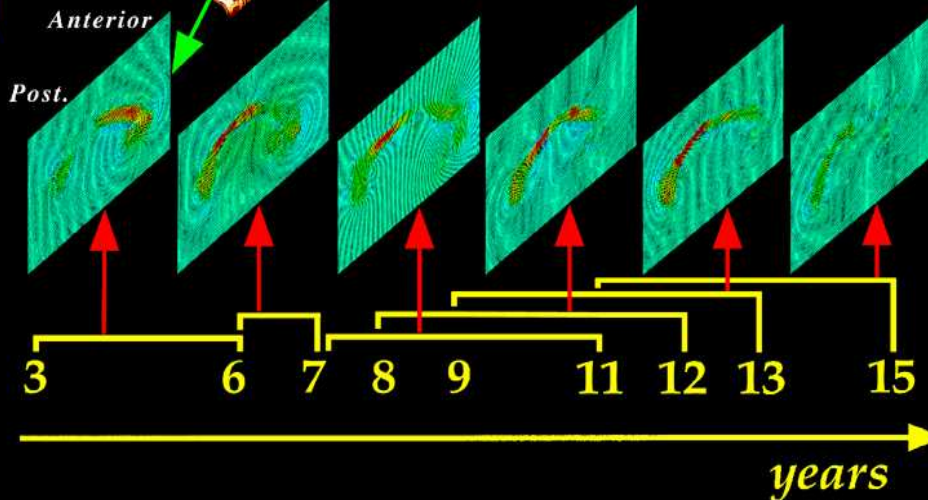
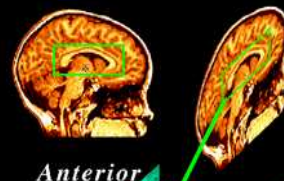
2 week Interval
(same subject)



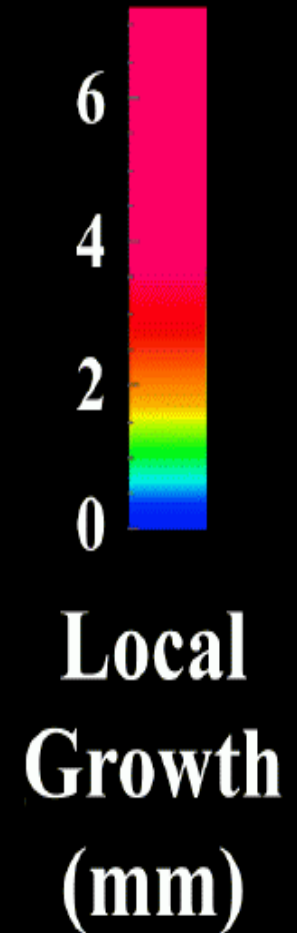
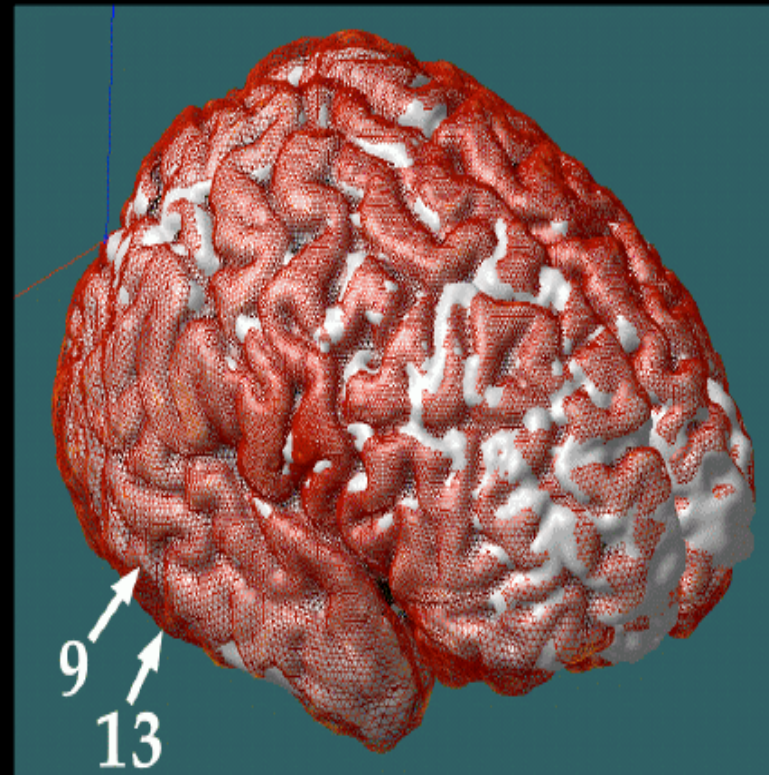
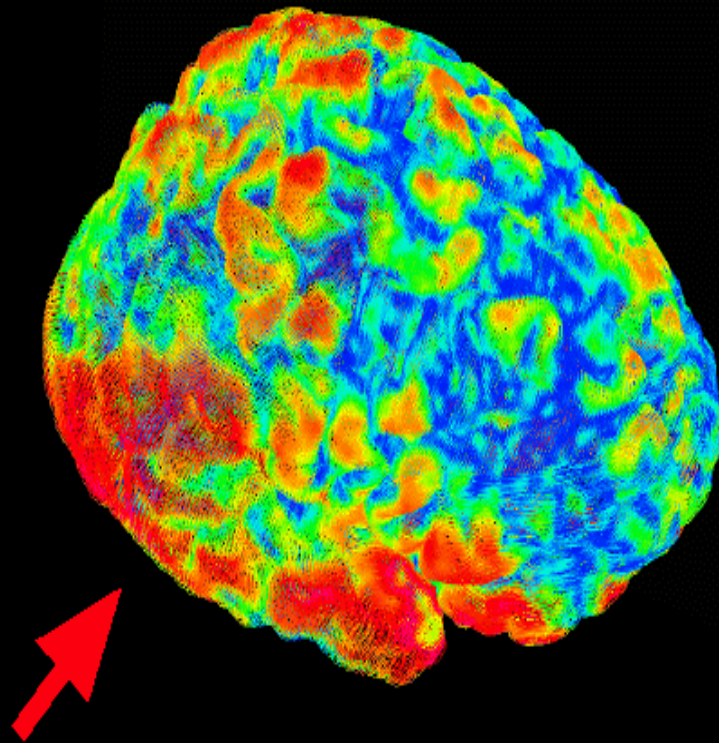
VALIDATE BUILD DYNAMIC ATLAS

Local Growth

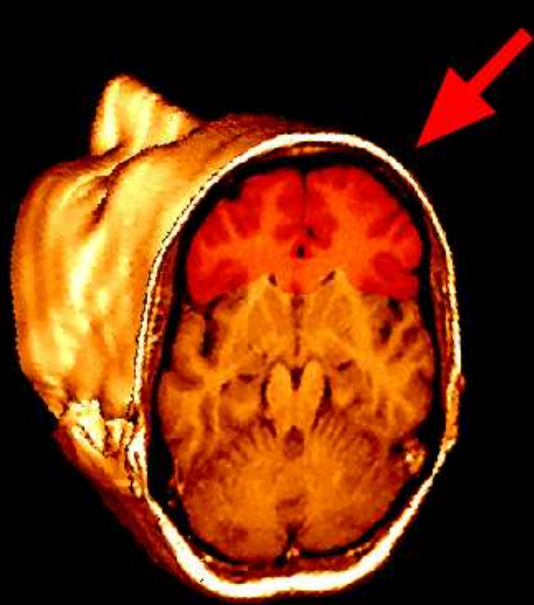
-20% 0% +20% +40% +60% +80%



Brain Growth Maps

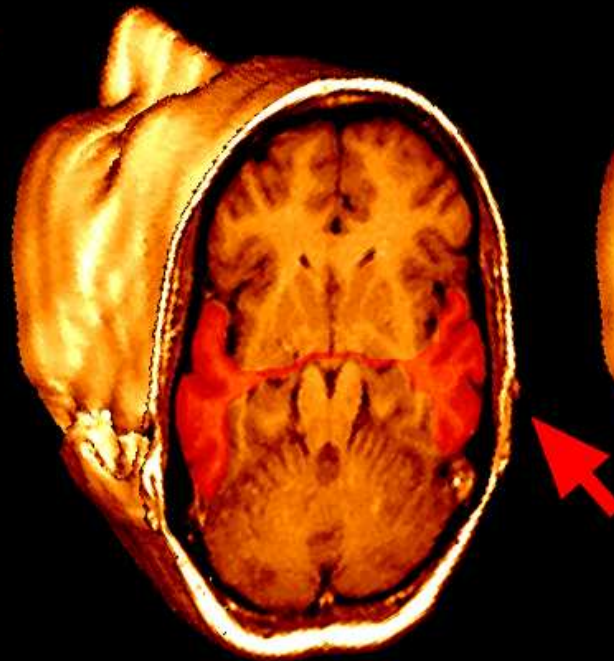


**Growth Spurt in Language Regions:
(4 year Interval: 9-13 year old girl)**



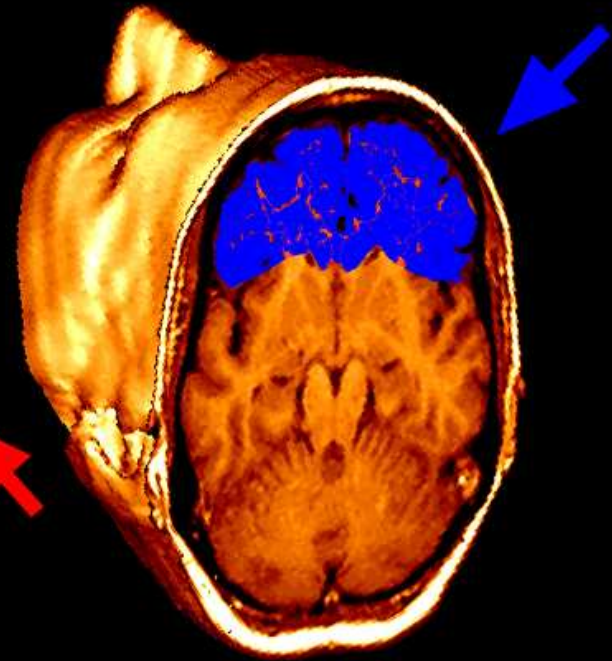
age: 3-6

**Rapid Growth in
Frontal Circuits:
attention, vigilance,
alertness**



7-15

**Growth Spurt
in temporal/
parietal lobes:
languages,
mathematics**



16-20

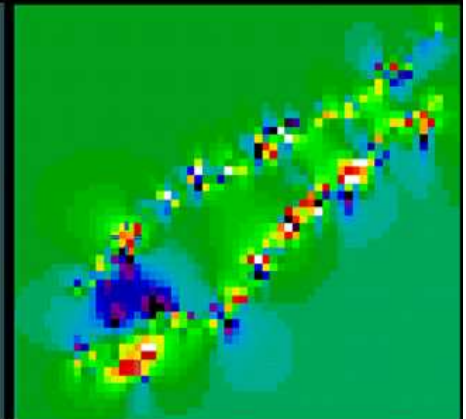
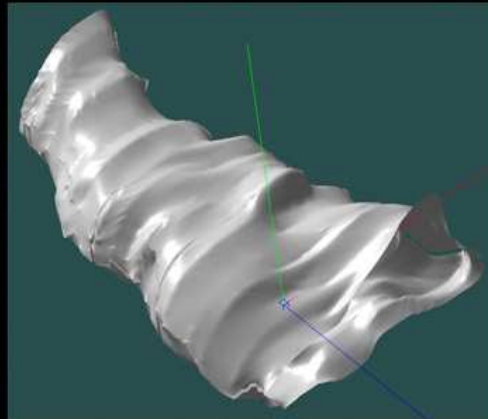
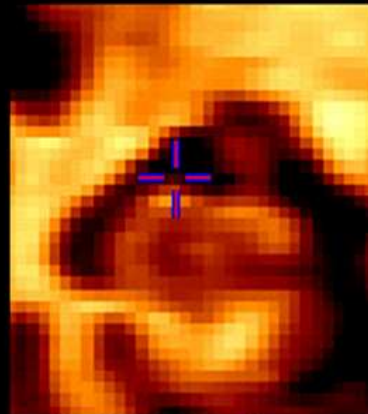
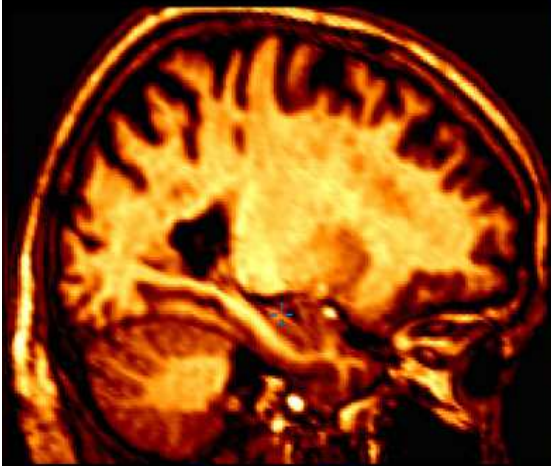
**Tissue Loss in
Frontal Circuits:
self-control,
planning, regulate
behavior**

Tensor Map

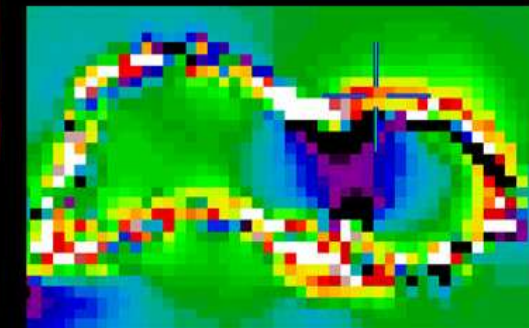
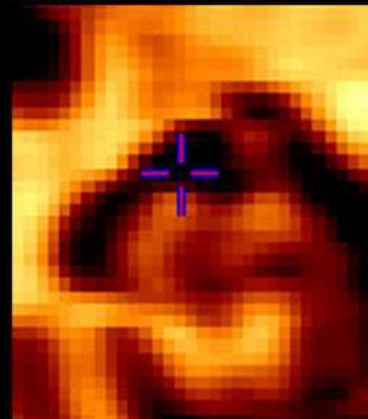
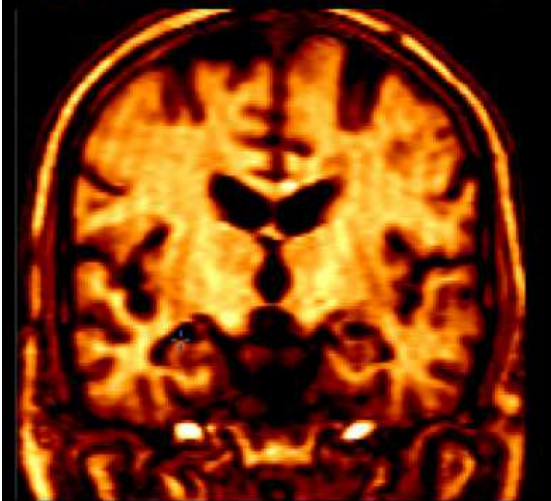
Normal Elderly Subject

73.0 y.o. M, 6 mo. interval

time 1



time 2



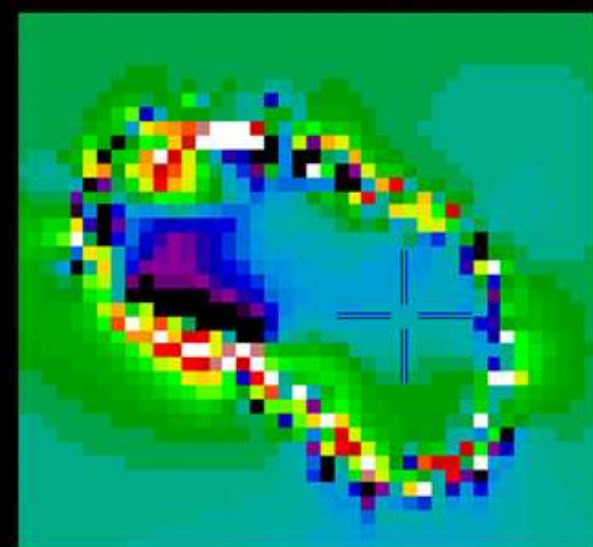
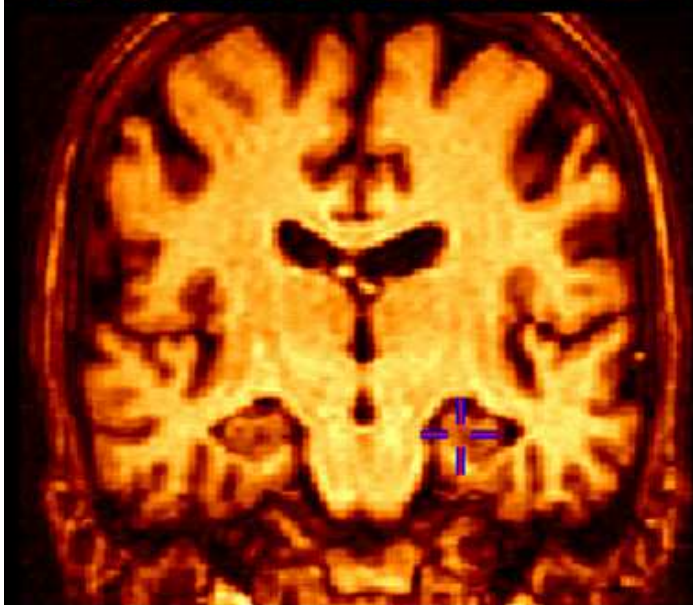
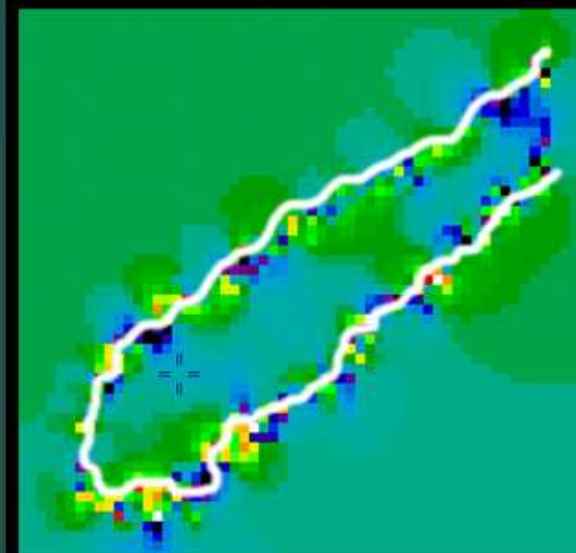
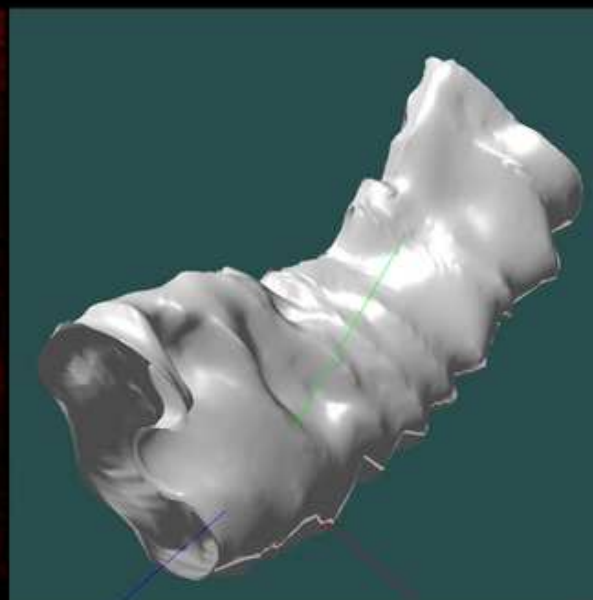
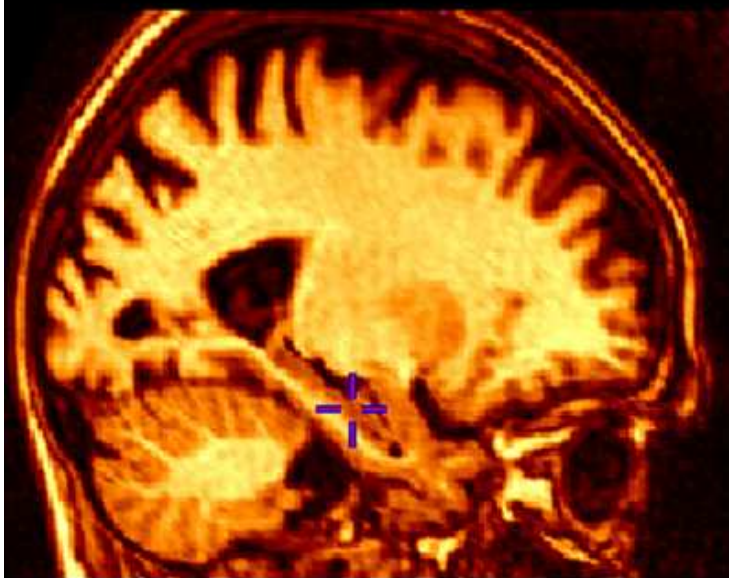
Rates of Tissue Loss



Thompson et al., 2000

Tensor Map

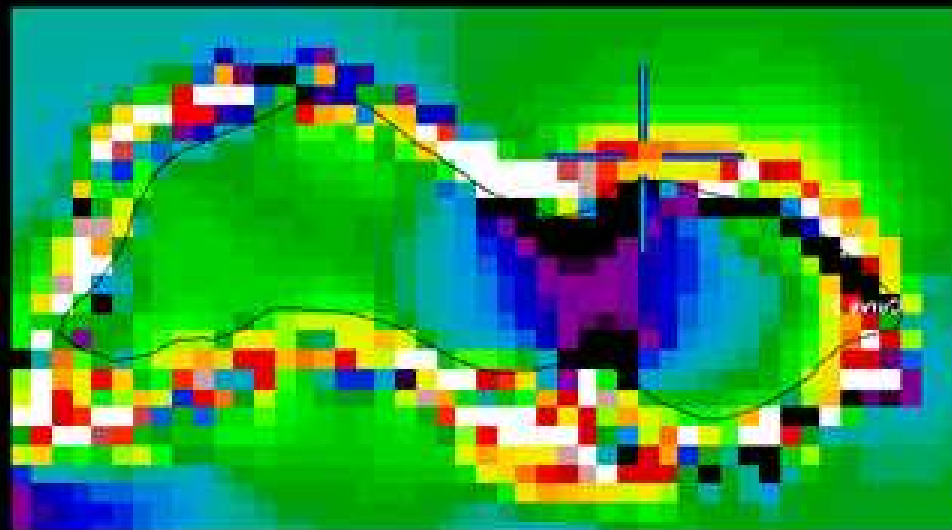
Alzheimer's Patient
62.4 y.o. F, 7 mo. interval



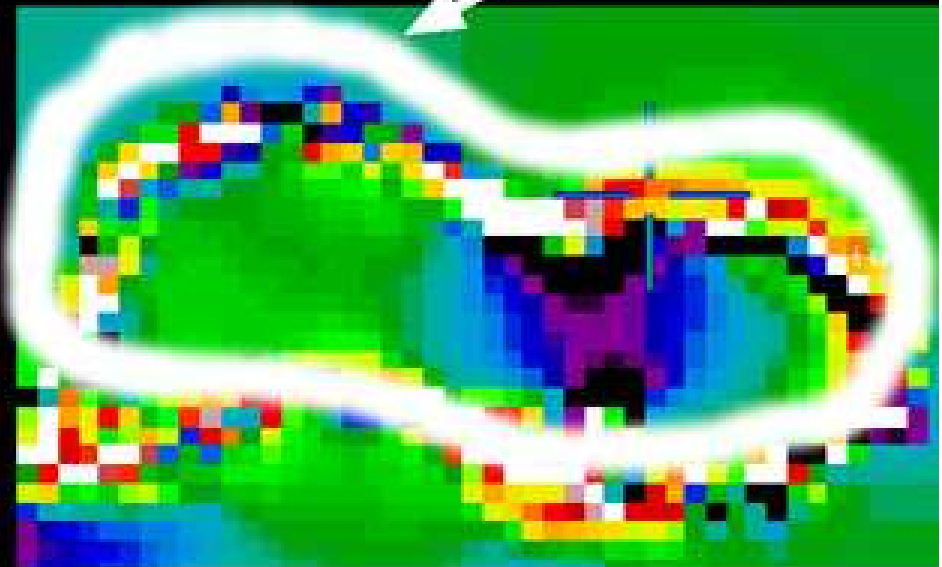
**Rates of
Tissue Loss**



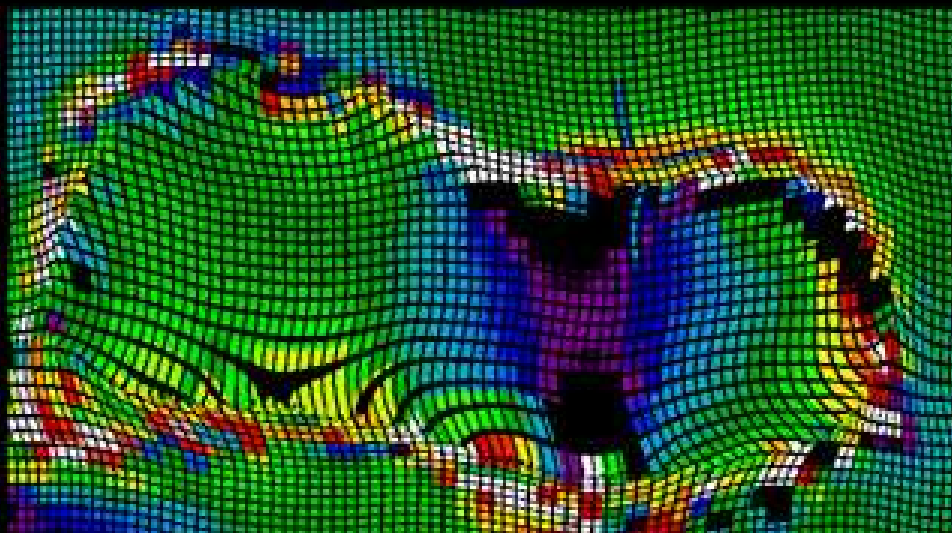
Individual Data



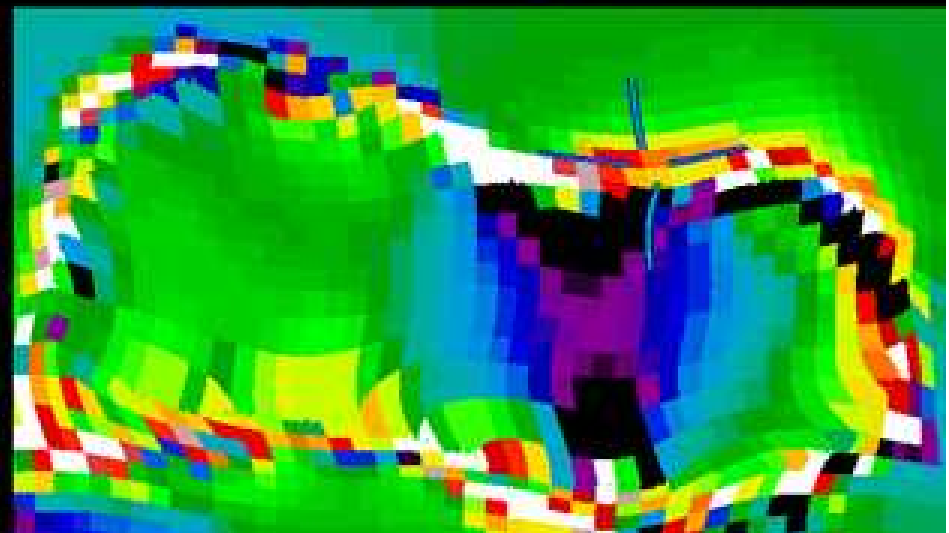
Atlas

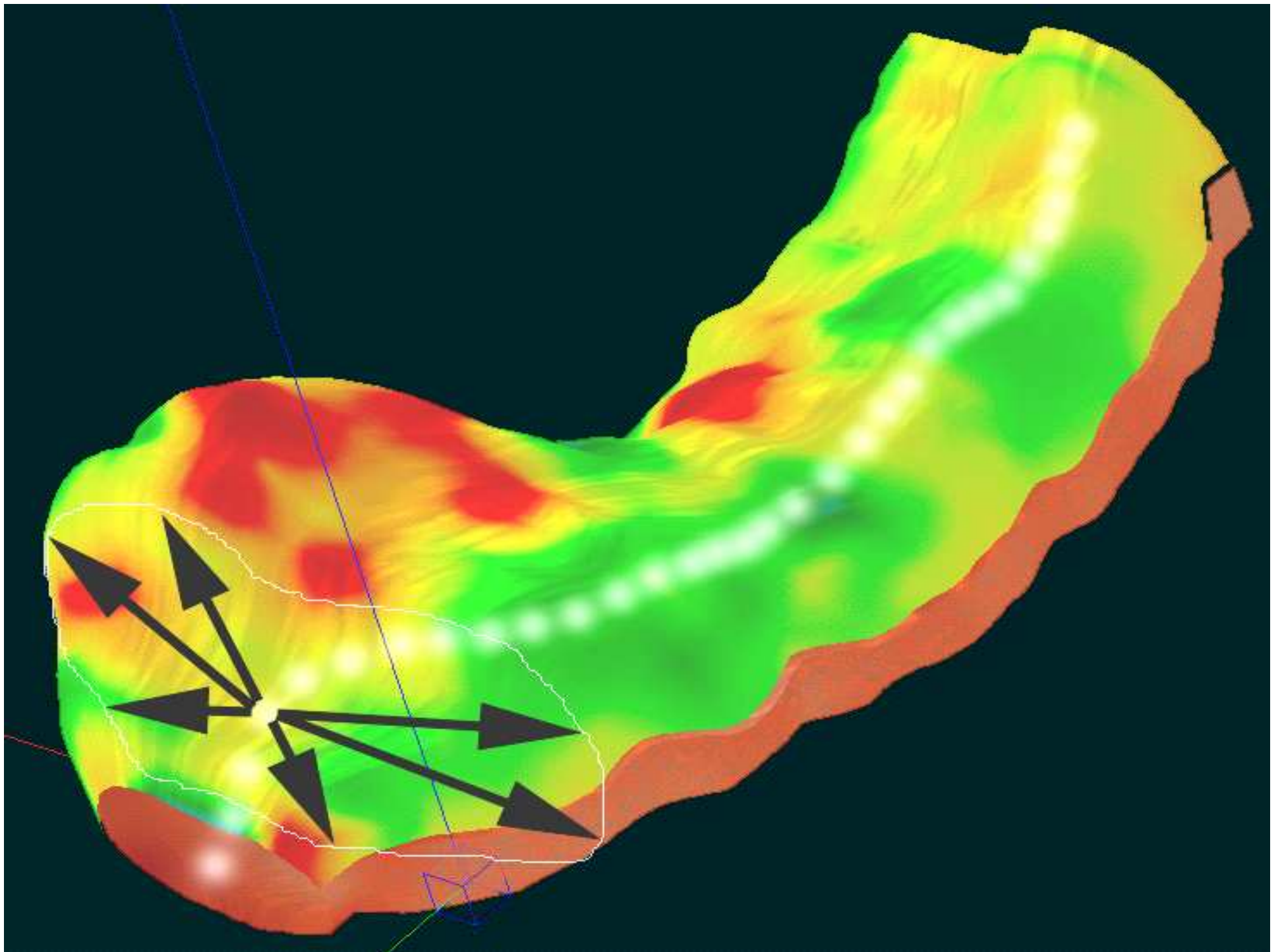


Warping Field

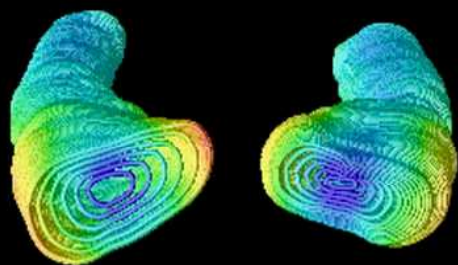


Individual Data Warped to Atlas



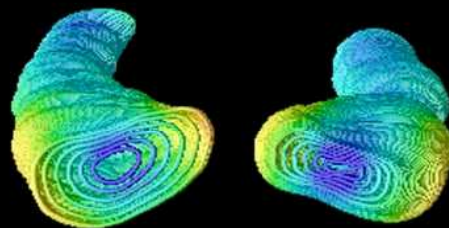


ELDERLY CONTROLS



R

L

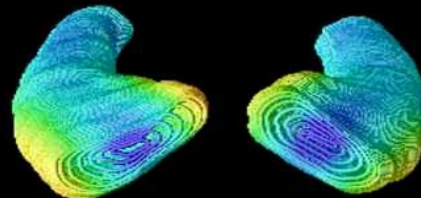
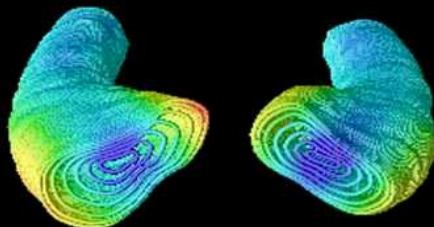


-0.2%/year -4%/year



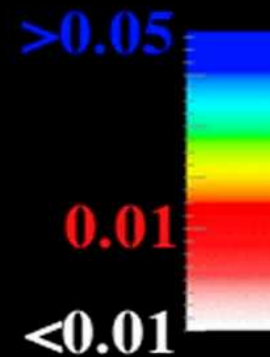
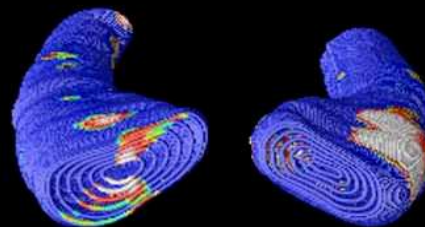
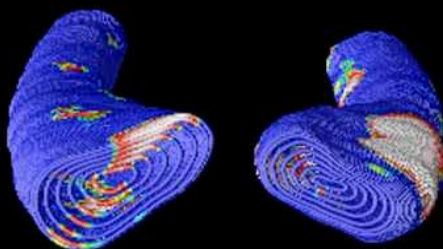
**Radial Size
(mm)**

ALZHEIMER'S DISEASE



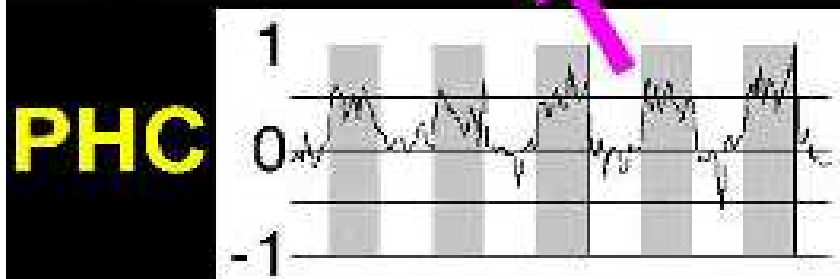
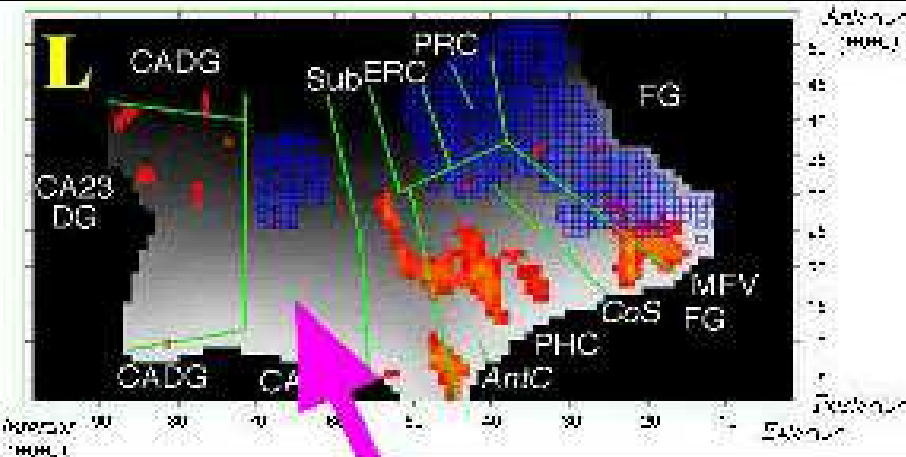
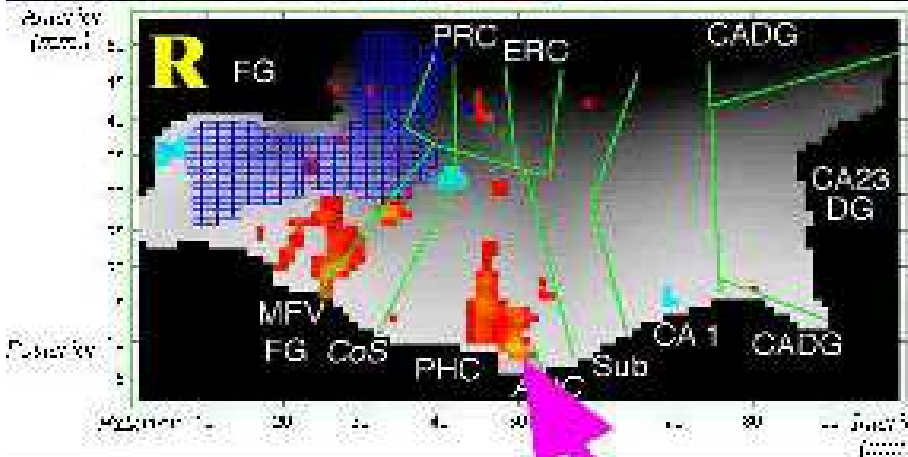
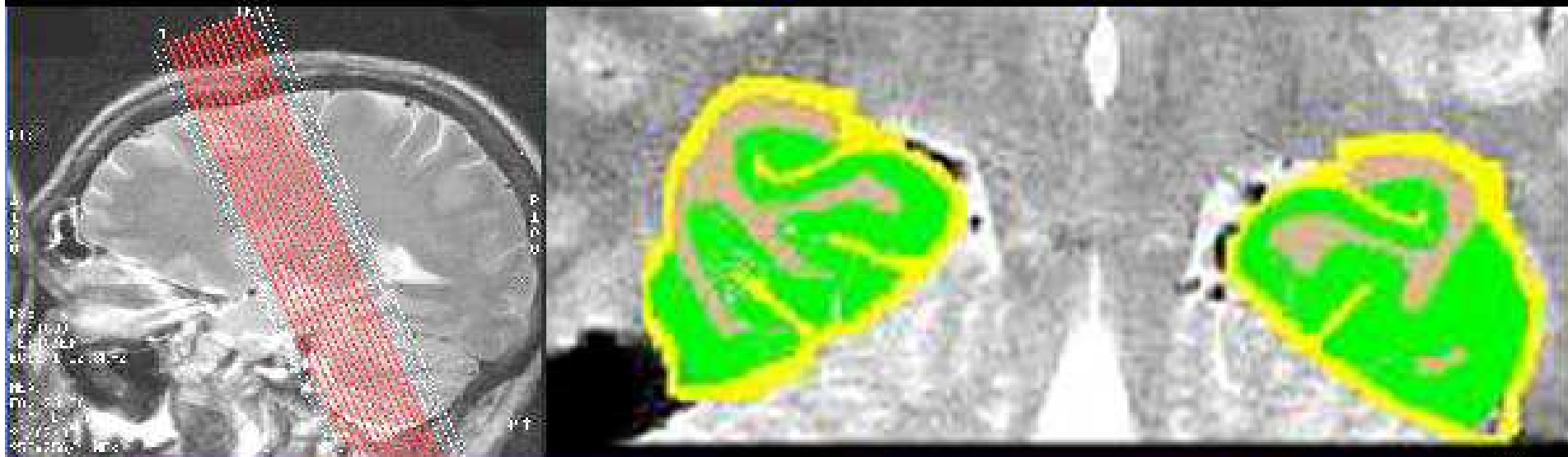
-8%/year -5%/year

DIFFERENCE

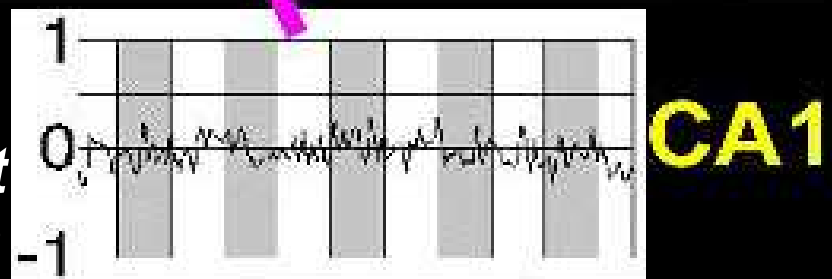


SIGNIFICANCE

Future: Unfolding the Hippocampus



Zeineh et al., 2003



Future Challenges

MATHEMATICAL:

Improved PDEs for diffeomorphic flows (level sets)

**New statistical metrics on deformations
(geodesics, random fields on manifolds)**

DYNAMIC BRAIN ATLASES:

Can now Map Diseases Spreading in the Living Brain

***Can detect altered development/accelerated brain
change vs. normative populations***

Can these techniques map therapeutic response?

GENETIC BRAIN ATLASES:

***Which genes affect brain structure and brain change?
genetic models on manifolds***

