Unraveling brain pathways with diffusion MRI

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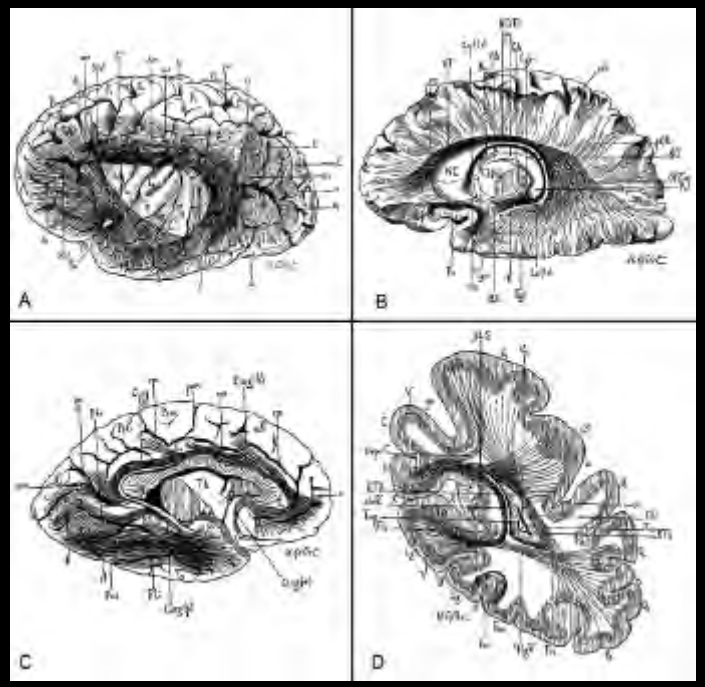
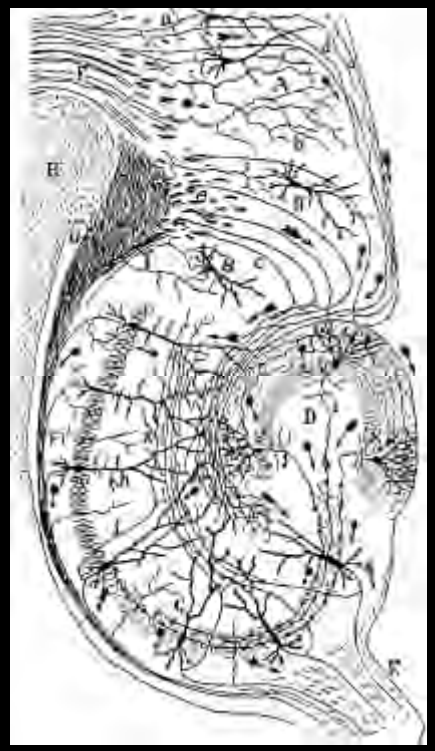
While gray matter has been mapped successfully for 100 years, white matter and connectivity remain problematic

Dejerine 1895



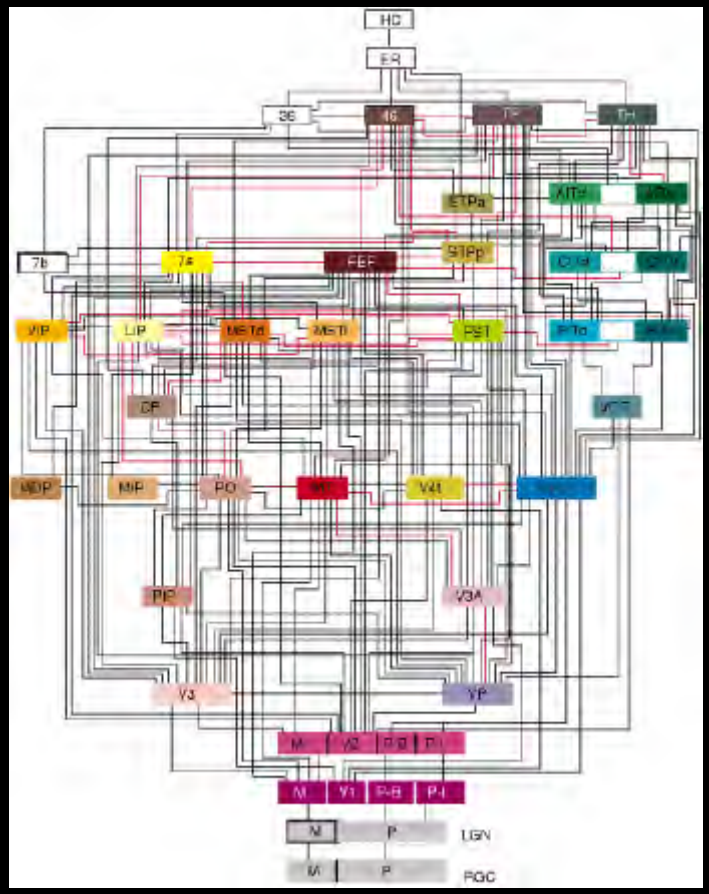
Brodmann 1909

Cajal 1911



"It is <u>intolerable</u> that we do not have a knowledge of the connectivity of the human brain"

- Crick & Jones, 1993

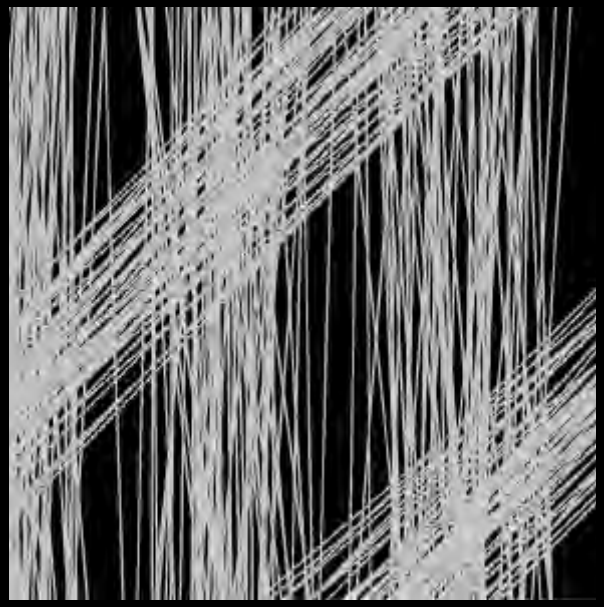


Felleman & Van Essen, 1989
rhesus visual system

Diffusion MRI - tissue structure is traced by 3D patterns of water diffusion

1994: diffusion tensors show average fiber directions

tissue



diffusion tensor

DTI tractography - invention and critique

Wedeen et al ISMRM 1995

WHITE MATTER CONNECTIVITY EXPLORED BY MRI

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Introduction

Water diffusion assessed by MRI accurately portrays the local tissue anisotropy of living tissue. In the CNS, MRI of diffusion anisotropy can provide dramatic images of the orientation fields of cerebral white matter. In order to map neocortexatomic connectivity, we have investigated the feasibility of deducing from these orientation fields the large scale trajectories of cerebral white matter tracts.

Methods

MRI measurements of the water diffusion anisotropy tensor D were performed using the pulsed gradient spin echo method of Stejskal and Tanner. Diffusion data were acquired on 5 normal subjects using a GE-ANMR echo-planar 1.5T imaging system. Acquisitions used 3 mm isotropic spatial resolution for 20-30 contiguous slices. Data were produced of SNR ≥ 30:1, defining the direction of principal diffusivity at each voxel with 3D angular accuracy of ±10°. White matter fiber trajectories were reconstructed as described below, and compared with known anatomy.

Putative white matter tracts were derived by numerical integration of the diffusion anisotropy tensor field. Two approaches were investigated. The first approach postulates fiber tracts parallel with the principal orientation of diffusivity at each location. Then fiber position $x^\alpha(s)$, see [1,2,3], will satisfy the first order differential equations

$$dx^\alpha/ds \pm e_1(x)\, v_1^\alpha(x) = 0 \qquad [1]$$

where e_1 denotes the maximal eigenvalue of the diffusion tensor and v_1^α is its respective eigenvector. The sign ambiguity of Eq. [1] is resolved by an arbitrary, but locally consistent, choice. The second approach considers the distance in tissue defined by the mean diffusion times between points. This distance defines a non-Euclidean geometry in which the role of a metric tensor is played by the negative of the diffusion tensor, and it is natural to postulate that fiber tracts are the minimal paths between points. Such paths satisfy the second order geodesic equation:

$$d^2x^\alpha/ds^2 + \Gamma^\alpha_{\beta\gamma}(dx^\beta/ds)(dx^\gamma/ds) = 0 \qquad [2a]$$

with repeated indices summed, where Γ represents the connection coefficients of $D = D_{\alpha\beta}$:

$$\Gamma^\alpha_{\beta\gamma} = 1/2\,(D^{-1})^{\alpha\lambda}\,(\partial D_{\lambda\beta}/\partial x^\gamma + \partial D_{\lambda\gamma}/\partial x^\beta + \partial D_{\beta\gamma}/\partial x^\lambda) \qquad [2b].$$

Eq. [2] may be solved given an initial point x^α and an initial slope dx^α/ds.

Results

Fiber tracts reconstructed via Eq. [1] were in good agreement with known anatomy. Fig 1 shows fibers of the left *corona radiata* traced from diencephalon to cortical mantle; fiber data are superposed upon parasagittal magnitude MRI; right is ventral.

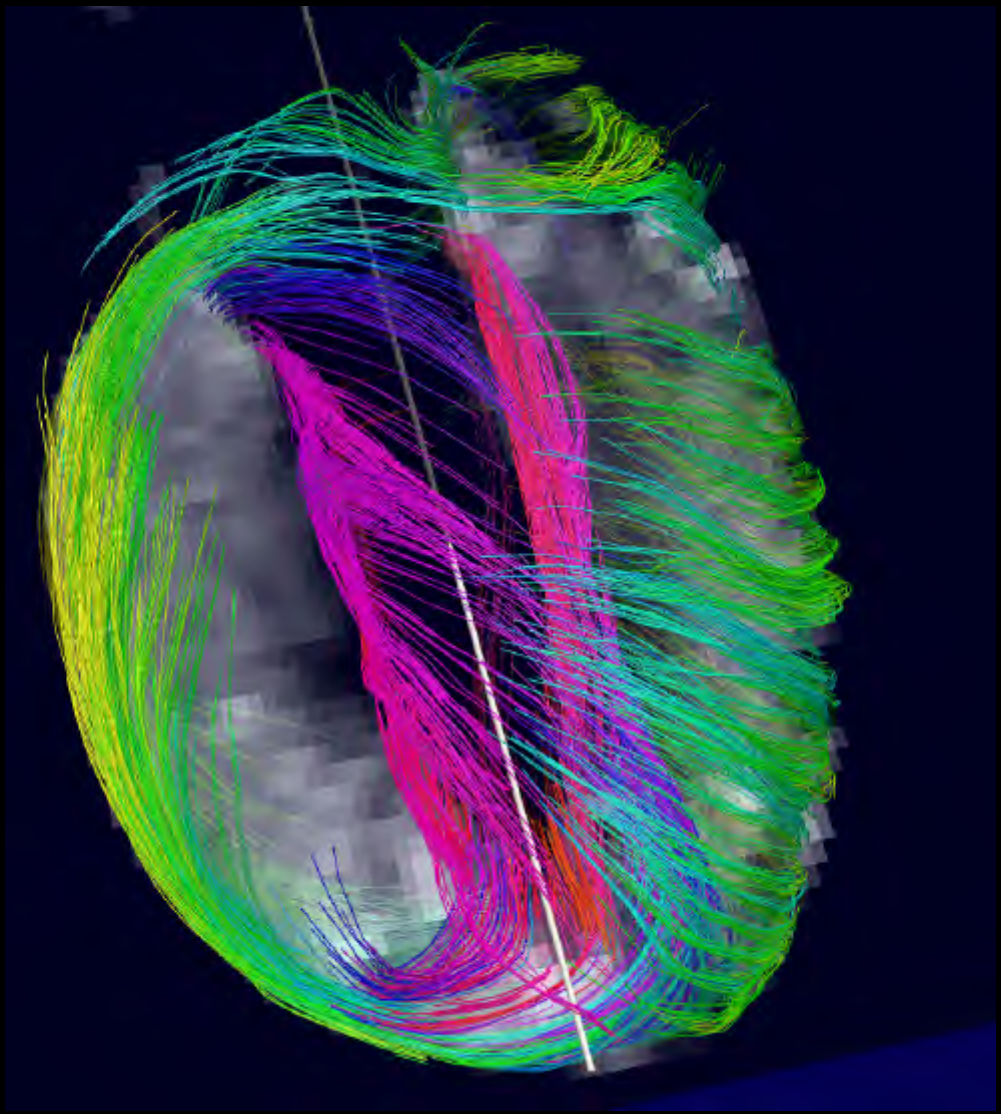
Solution of the geodesic Eq. [2a-2b] is less robust. In the *corpus callosum*, fewer than 50% of computed geodesics tracked known white matter anatomy for more than 3 cm. Abrupt divergences of solutions from expected trajectories suggest numerical instability.

Discussion

Reconstruction of white matter tracts by vector field integration successfully indicates known large-scale white matter anatomy in prototypical cases. This technique may allow for integration in an individual of activated neural systems with their underlying connectivity.

Fig 1. Stereo pair of 3D fiber tracts.

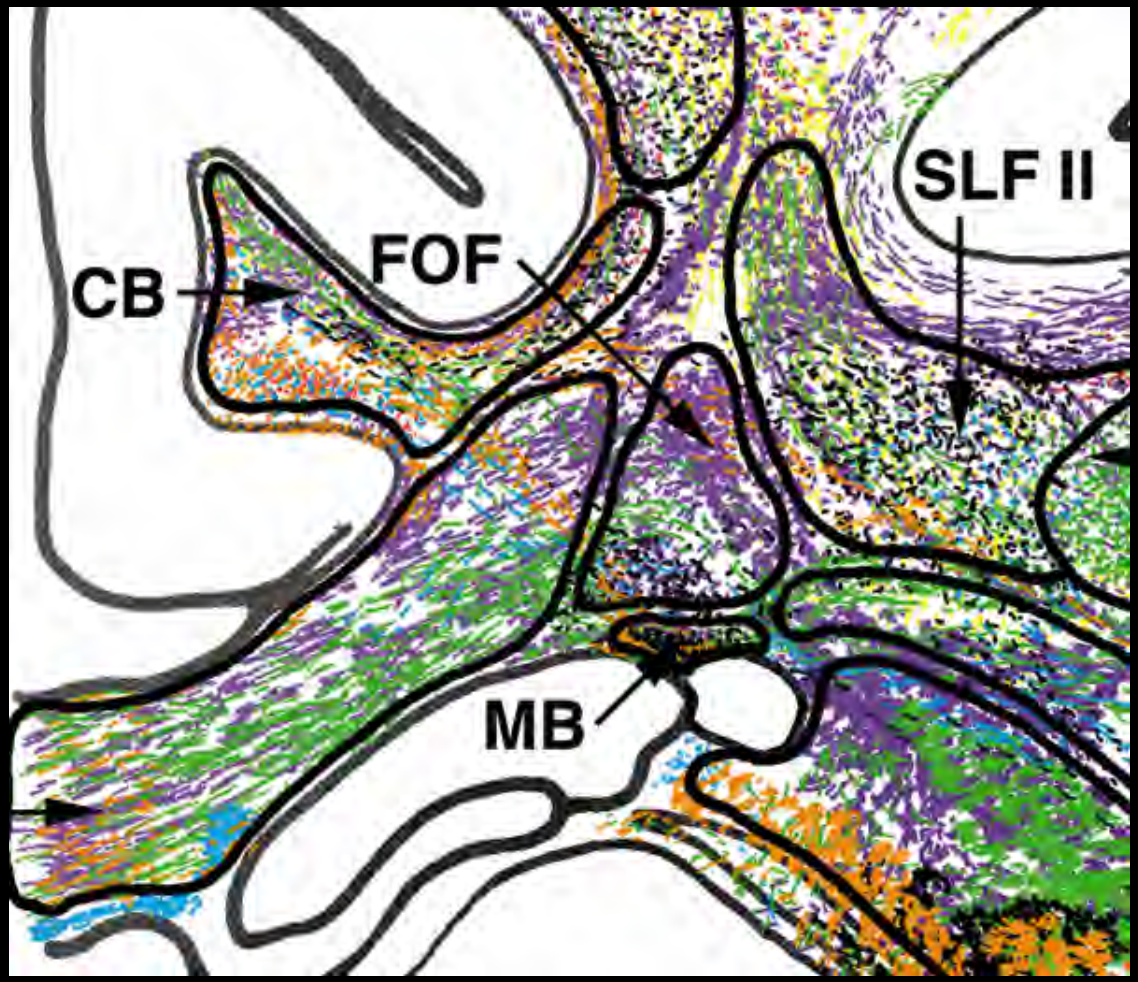
Myocardial fiber geometry for optimum efficiency



The main reason neuro anatomy is more difficult to figure out than other kinds of anatomy - "fiber crossing" or overlap of structures in 3D

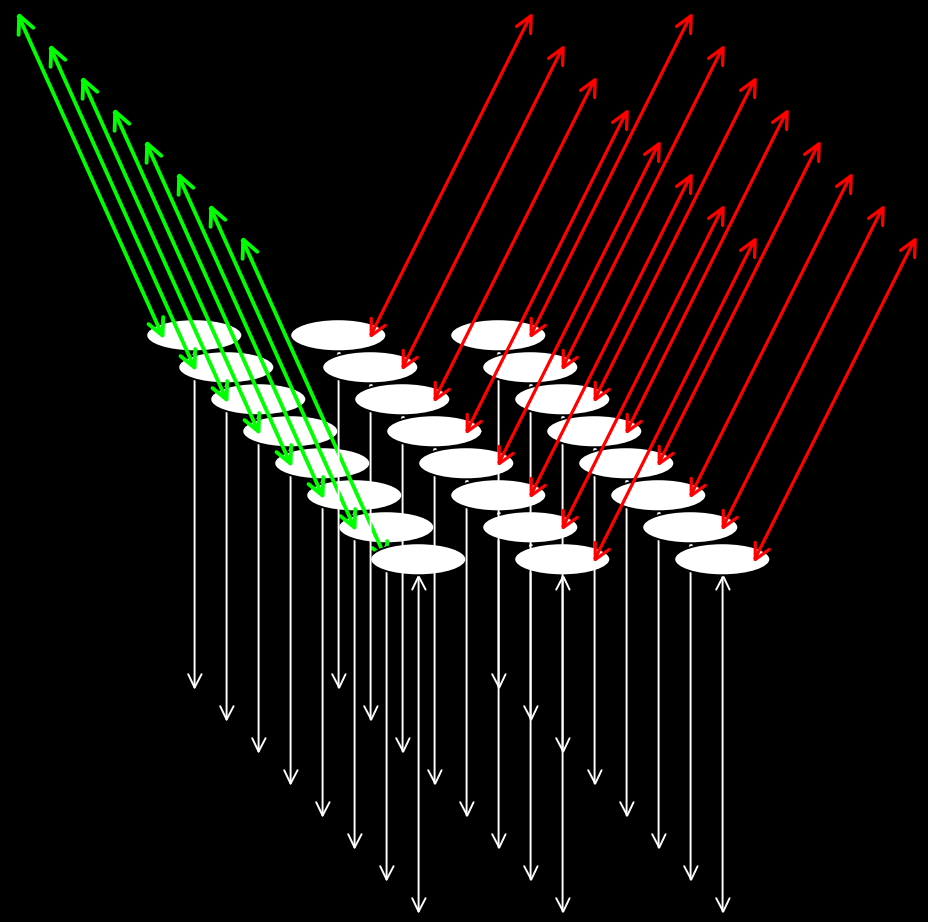
Neuroanatomy is hard because neural structures freely overlap in 3D

macaque tracers - Pandya & Schmahmann

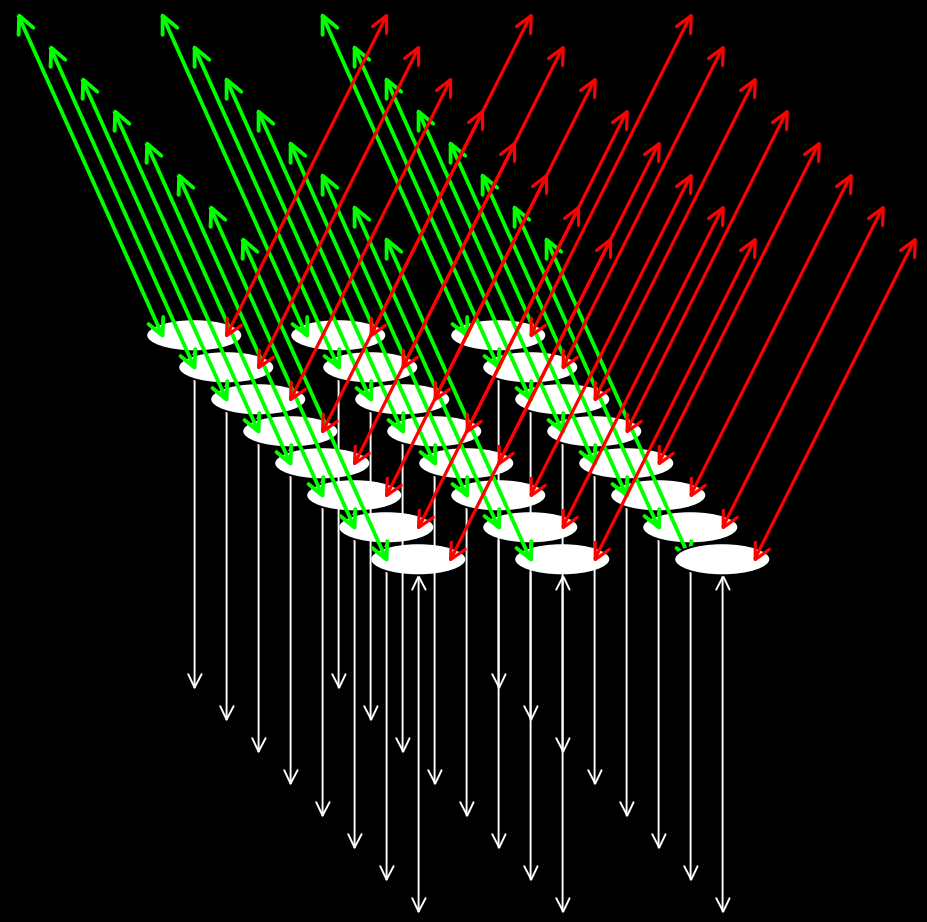


Pathway overlap is a defining characteristic of the brain

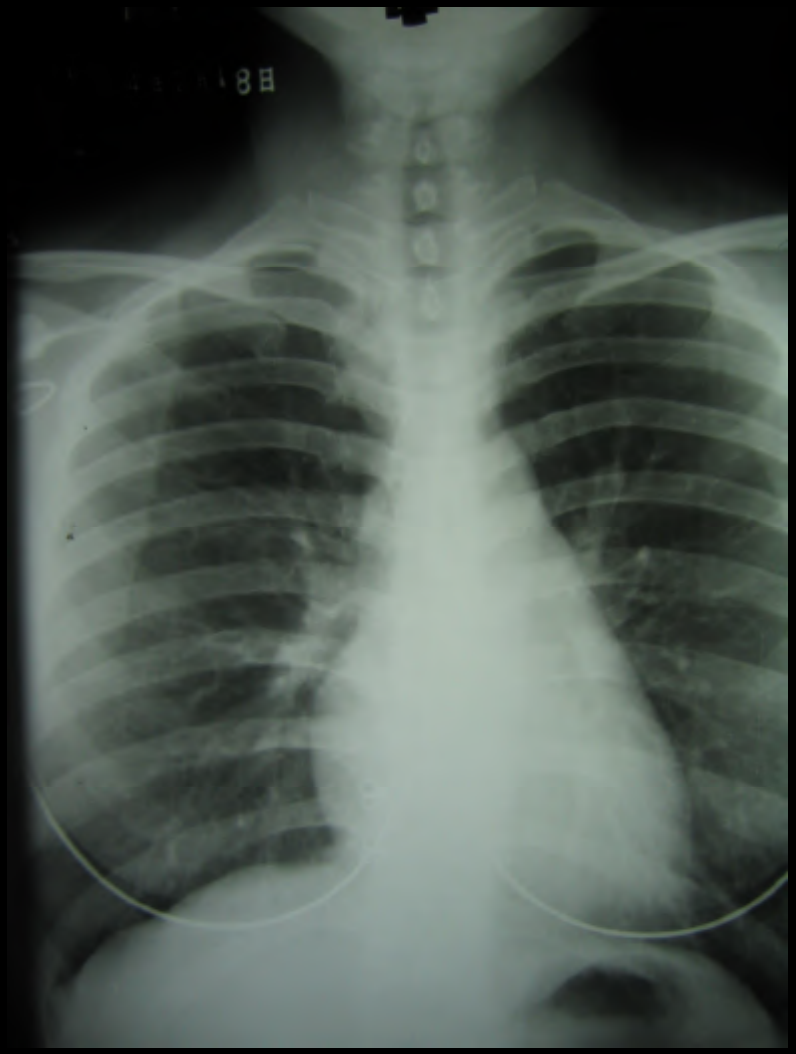
not brainy



brainy



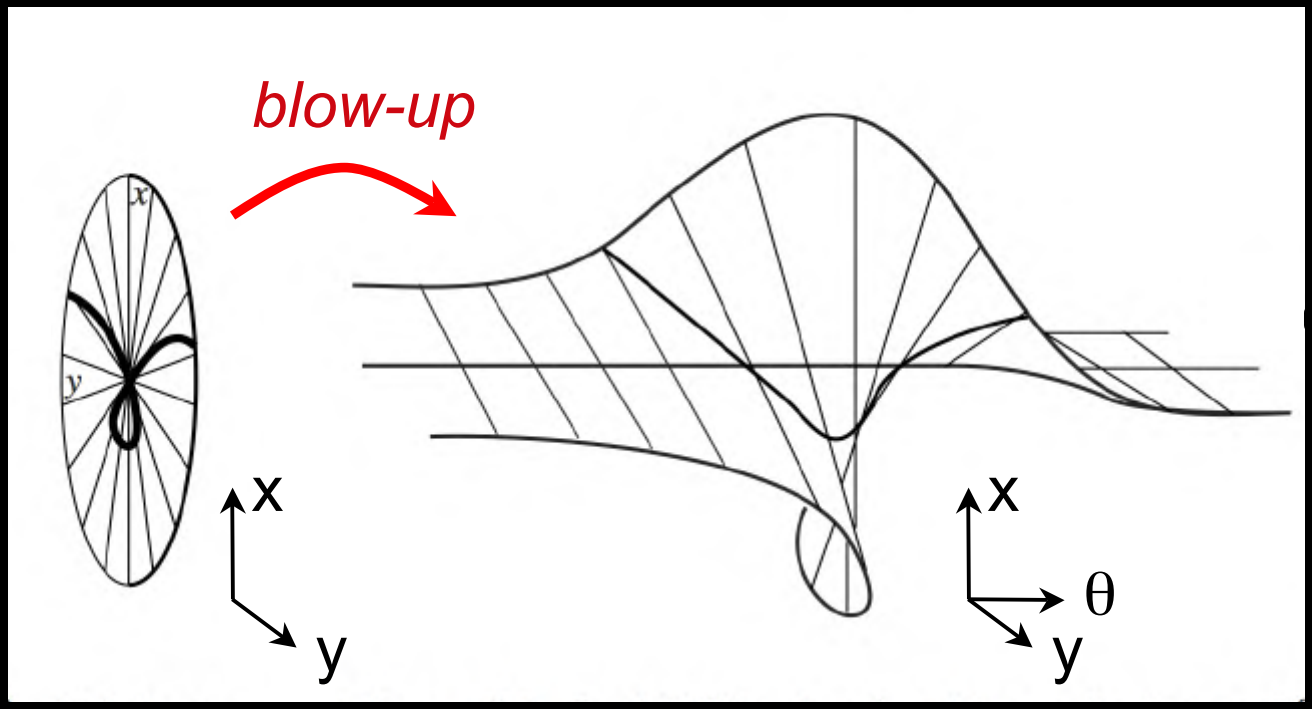
x-ray, overlap



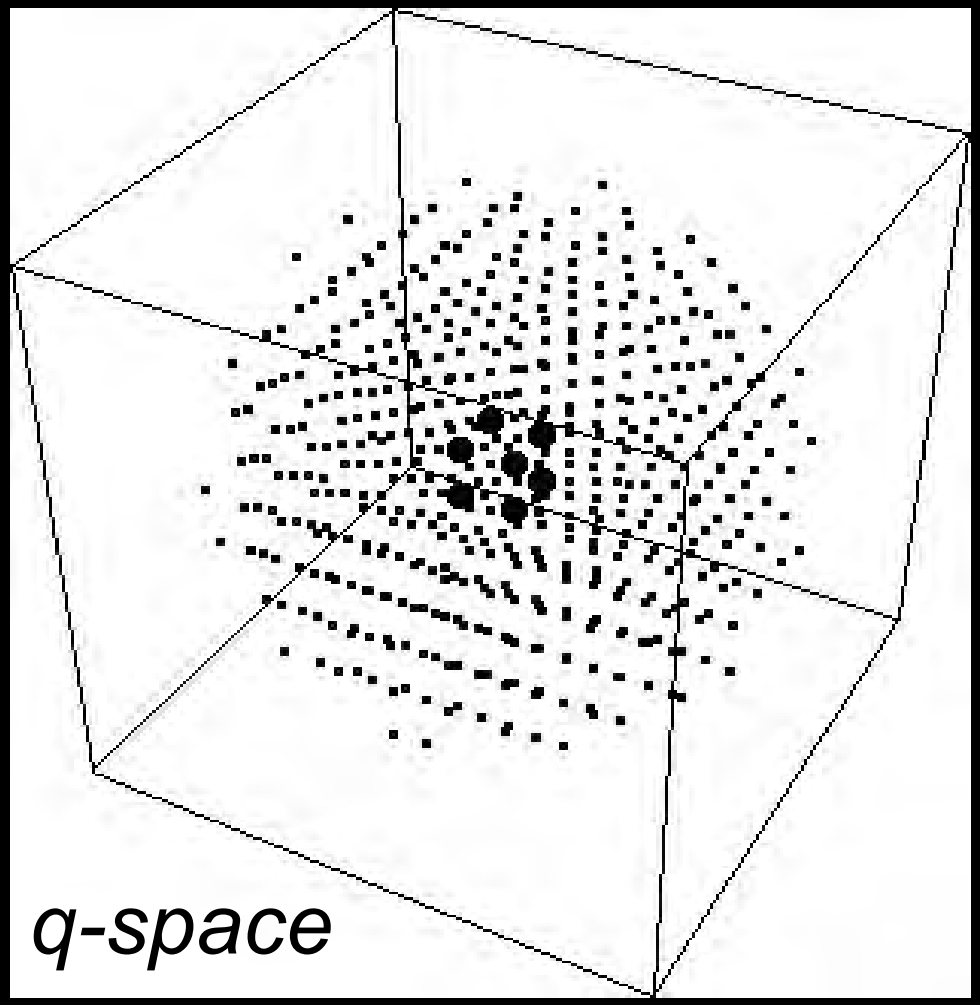
CT, overlap resolved

To un-cross a curve, map it into a position-orientation space with a "blow-up" transform

$$\{x, y\} \rightarrow \{x, y, dy/dx\} = \{x, y, \theta\}$$



1. *DSI - imaging the 6-dimensional brain*
2. *The connectome*
3. *Limbic system and hippocampus*
4. *Prospects*

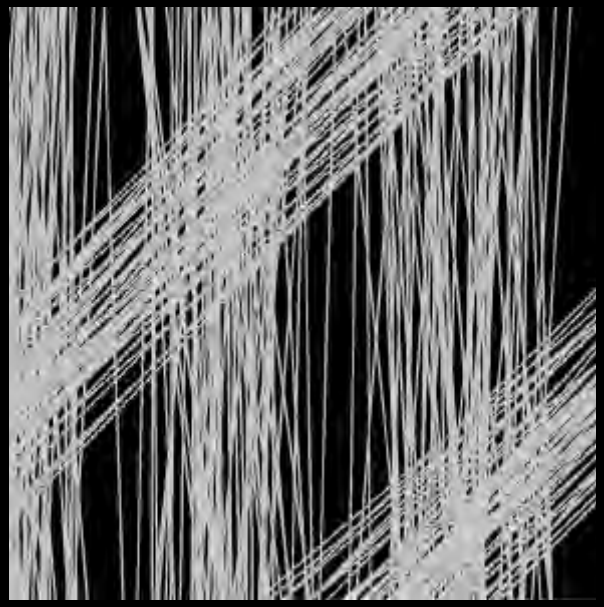


DTI: 7 q-samples, recon with tensor fit
DSI: 500 q-samles, recon with 3DFT

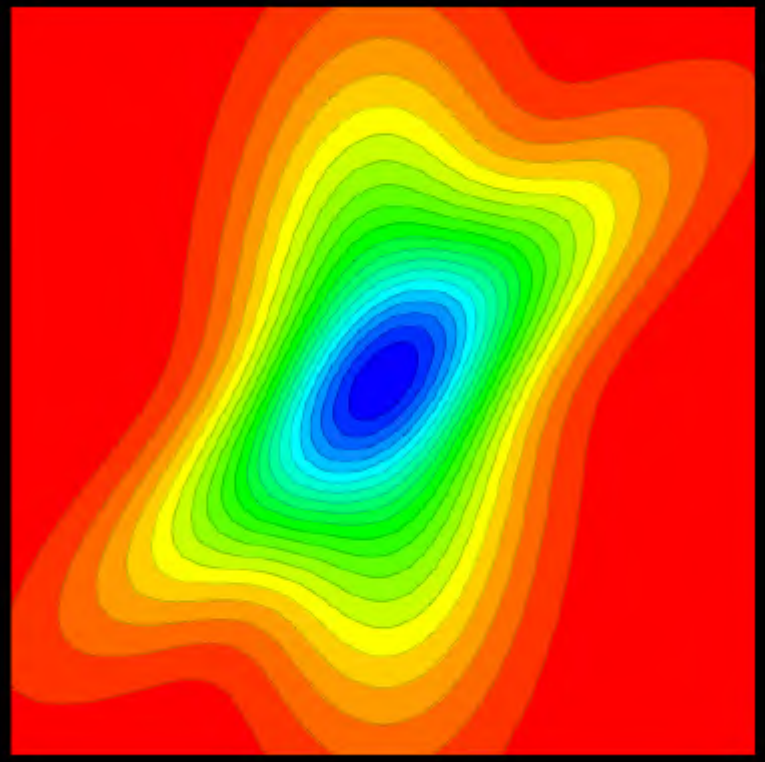
Water diffusion traces tissue fiber structure

2000: breakthrough diffusion spectrum MRI (DSI) resolves overlapping fiber pathways

brain tissue



diffusion spectrum



Diffusion-limited diffusion MRI. Resolution of diffusion MRI for tissue microstructure R_{eff} is limited by two factors:

- *diffusion "camera resolution" $q = GT$*
- *"motion blur" $\sqrt{2DT}$ due to diffusion itself*

hence $R_{eff} = (q^{-2} + 2DT)^{1/2}$

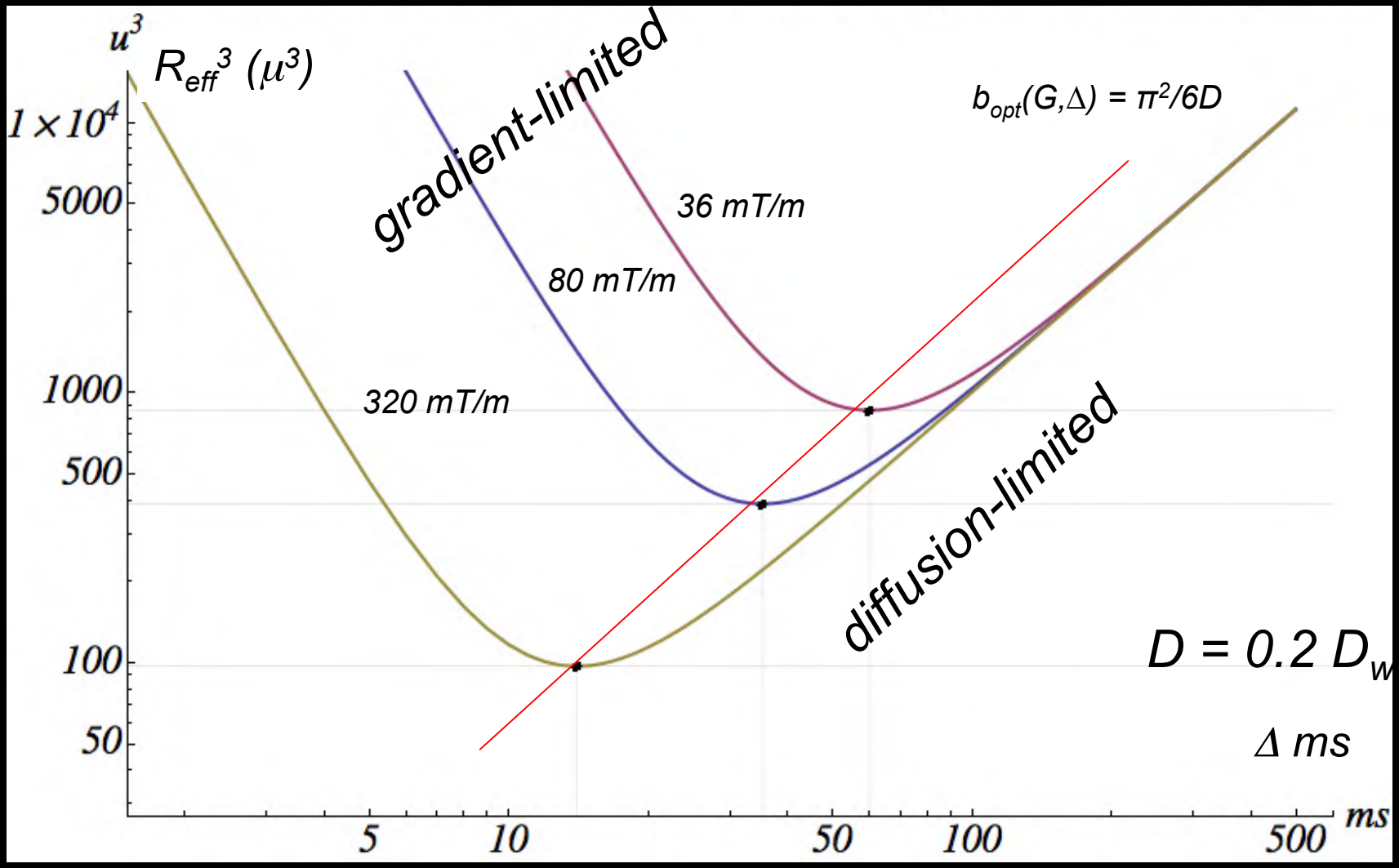
Consequences:

For any gradient G, there is a <u>best-possible</u> micro-resolution

$$R_{eff} \approx (D/G_{max})^{1/3}$$

For any diffusion D, there is a <u>universal optimum b-value</u>

$$b_{opt} \approx \pi^2/6D$$


u^3
R_{eff}^3 (μ^3)
1×10^4
5000
1000
500
100
50
5
10
50
100
500
ms
gradient-limited
diffusion-limited
36 mT/m
80 mT/m
320 mT/m
$b_{opt}(G,\Delta) = \pi^2/6D$
$D = 0.2\ D_w$
Δ ms

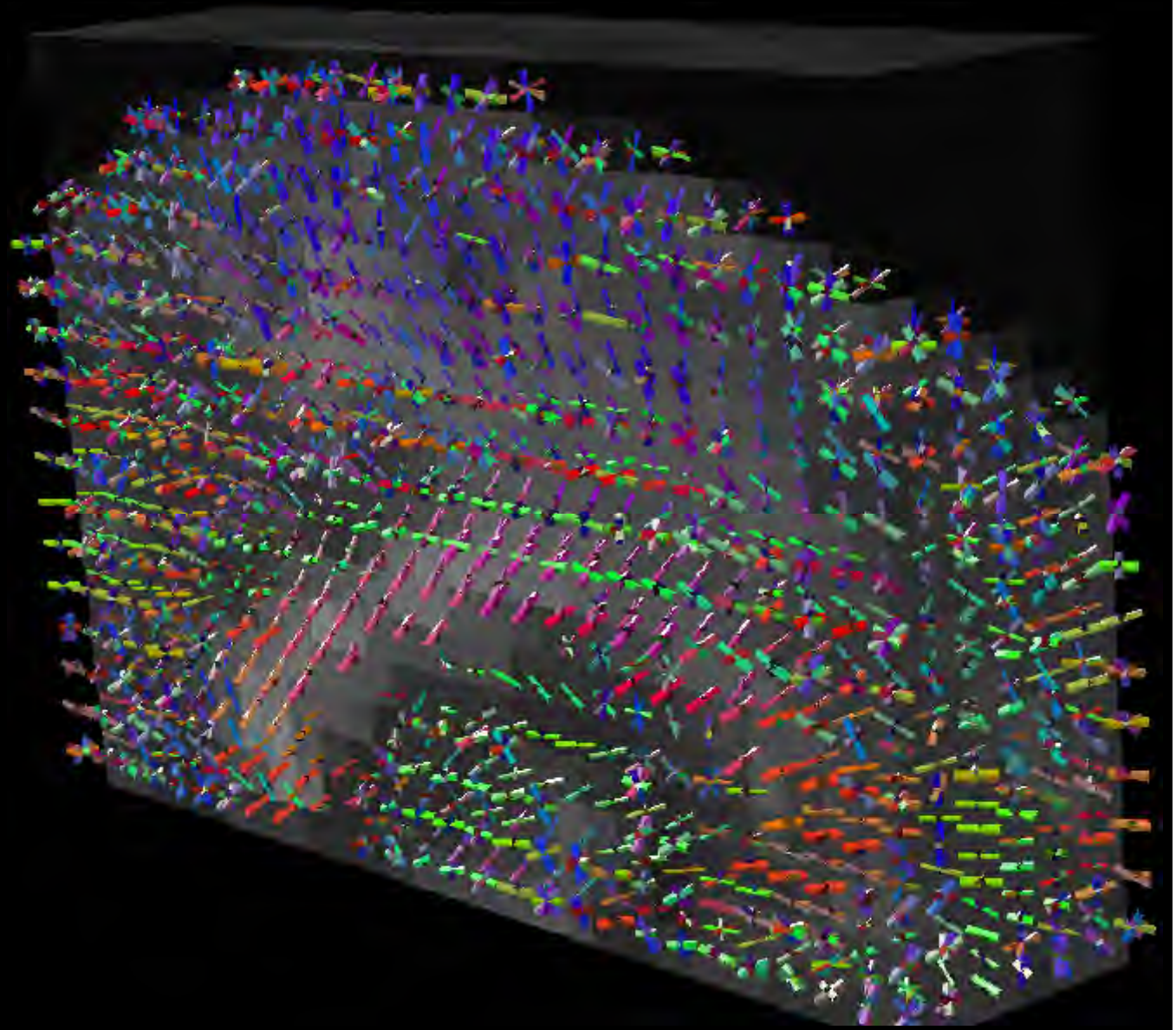
Heresy:

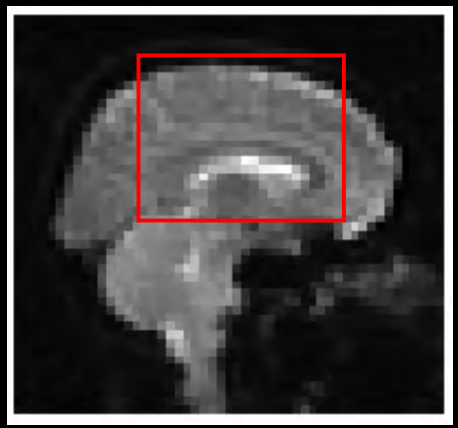
Angular resolution is a useless idea, because it's model-dependent

In other words, it means whatever somebody wants it to mean.

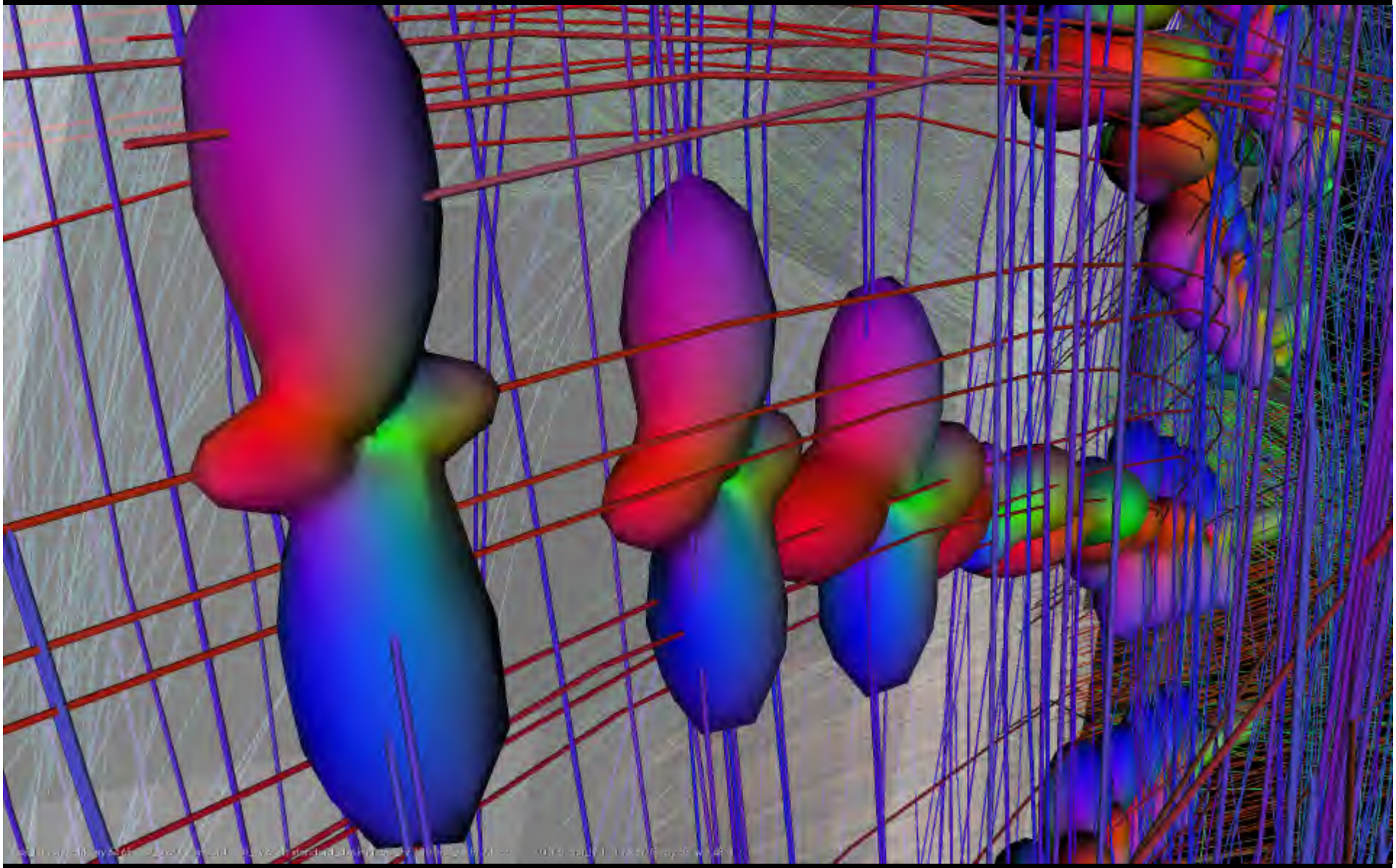
That's why it's so useful.

DSI directions of maximum diffusion 3T human in vivo



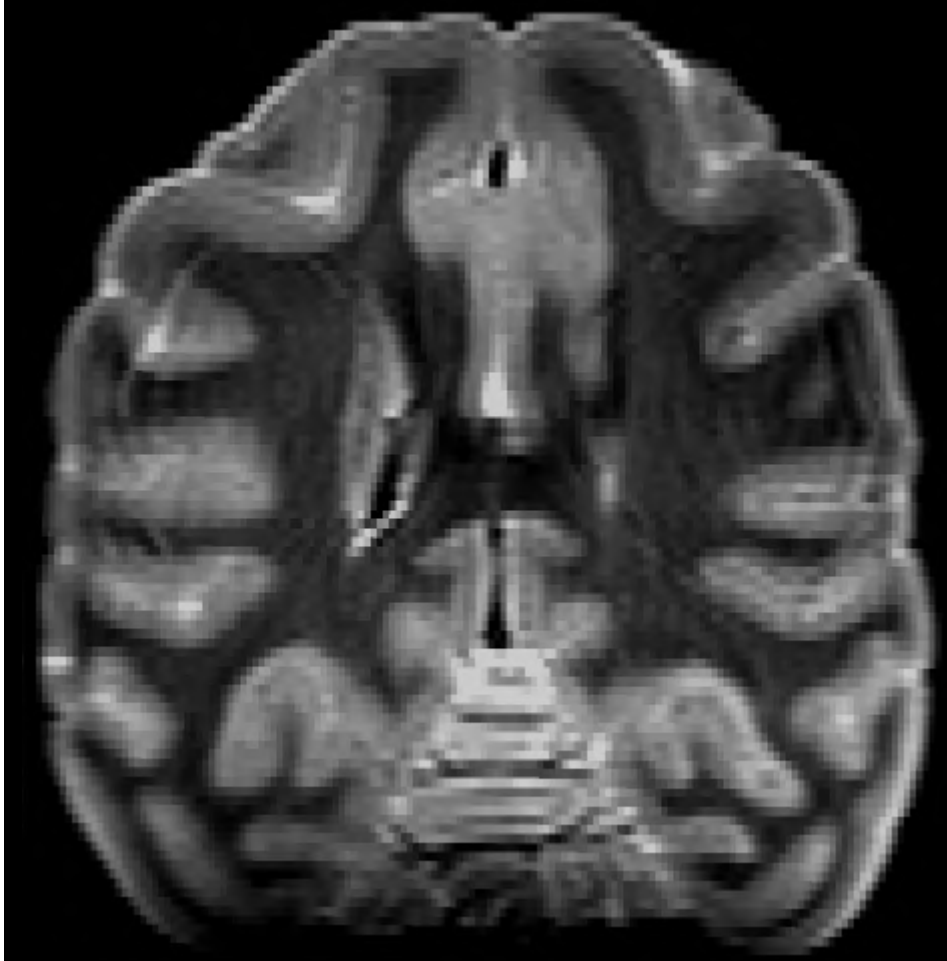


Diffusion spectrum MRI and computed fiber paths (human pons)



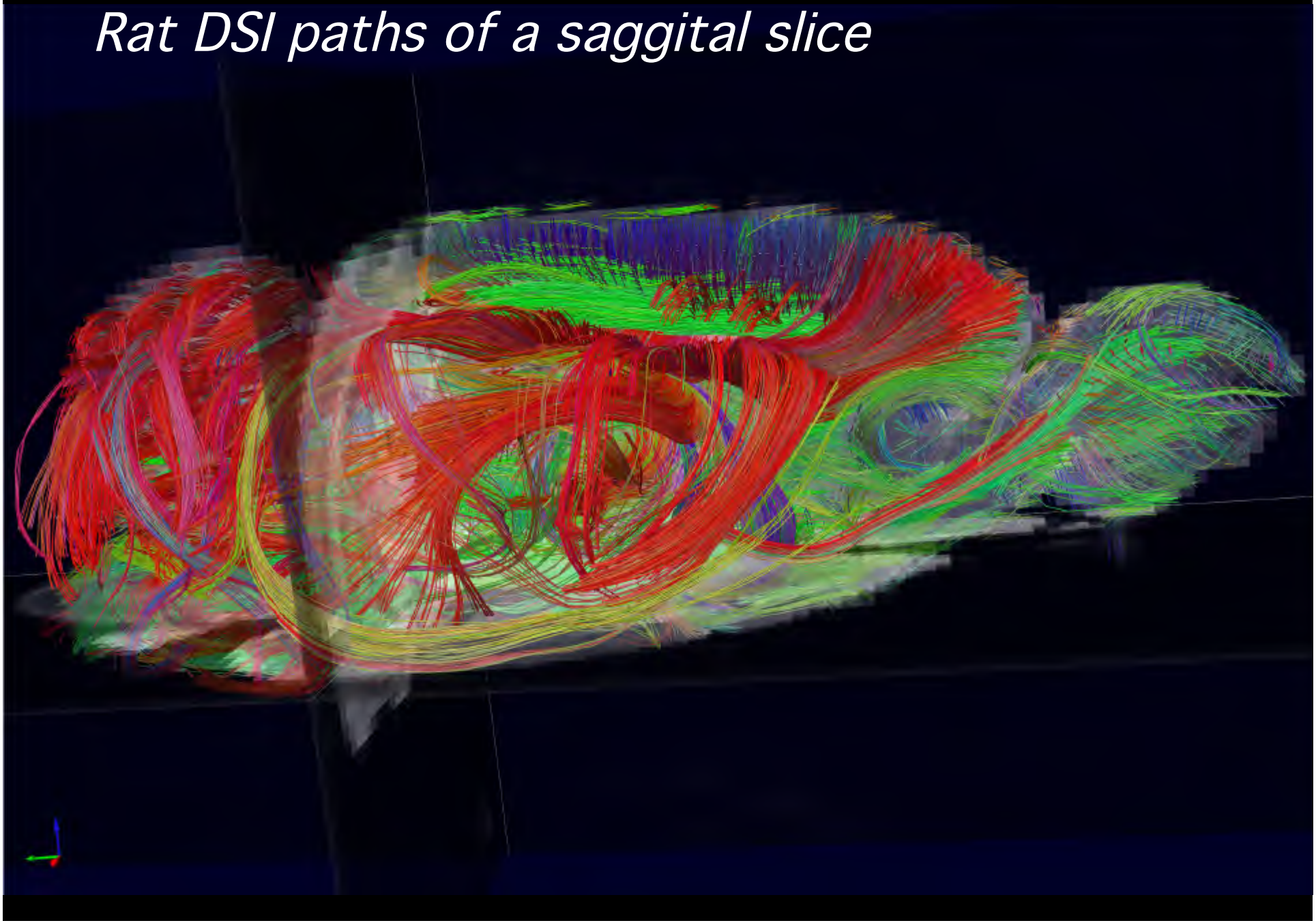
Macaque

3D MRI - paths superimpose



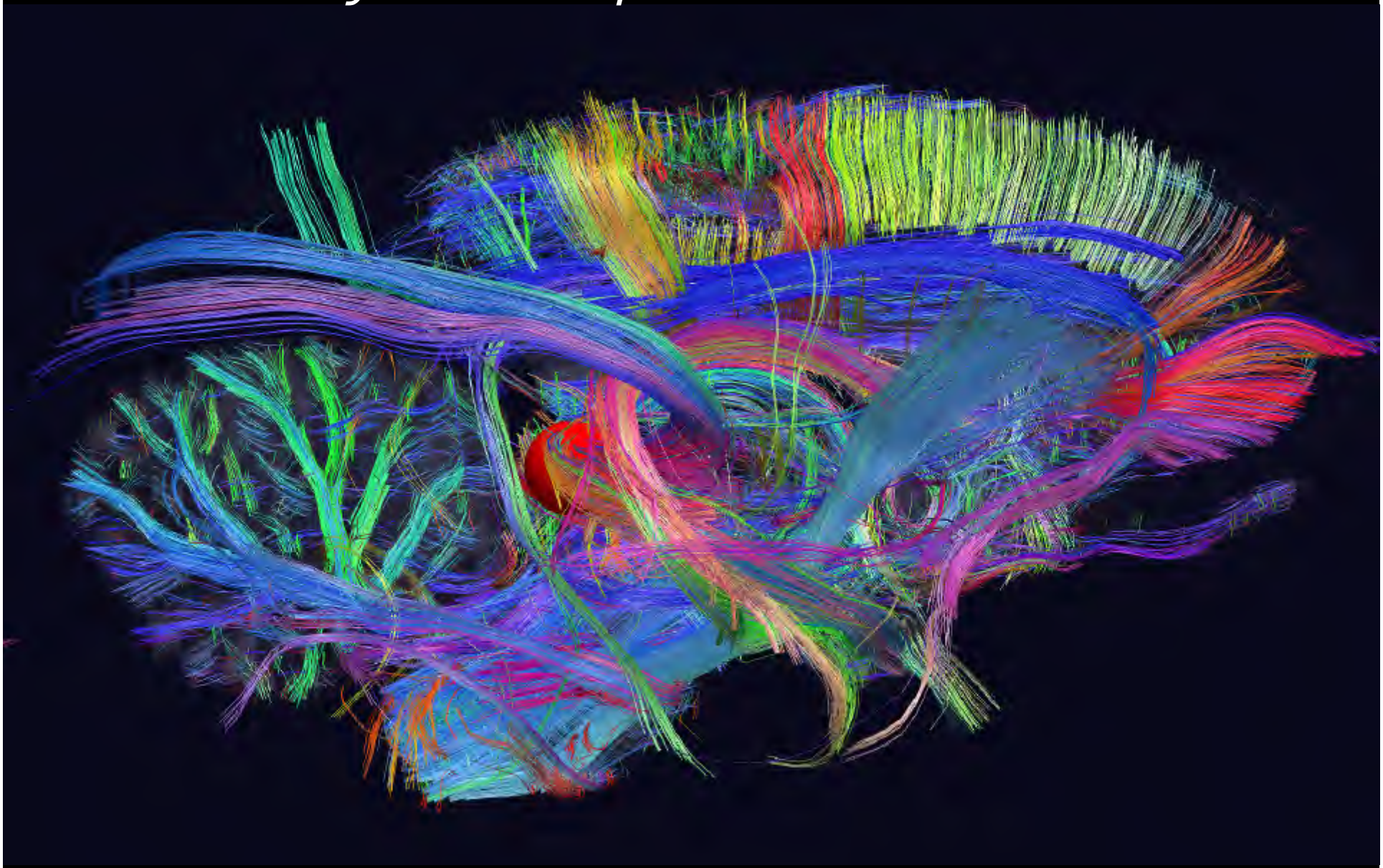
6D DSI - paths resolved

Rat DSI paths of a saggital slice

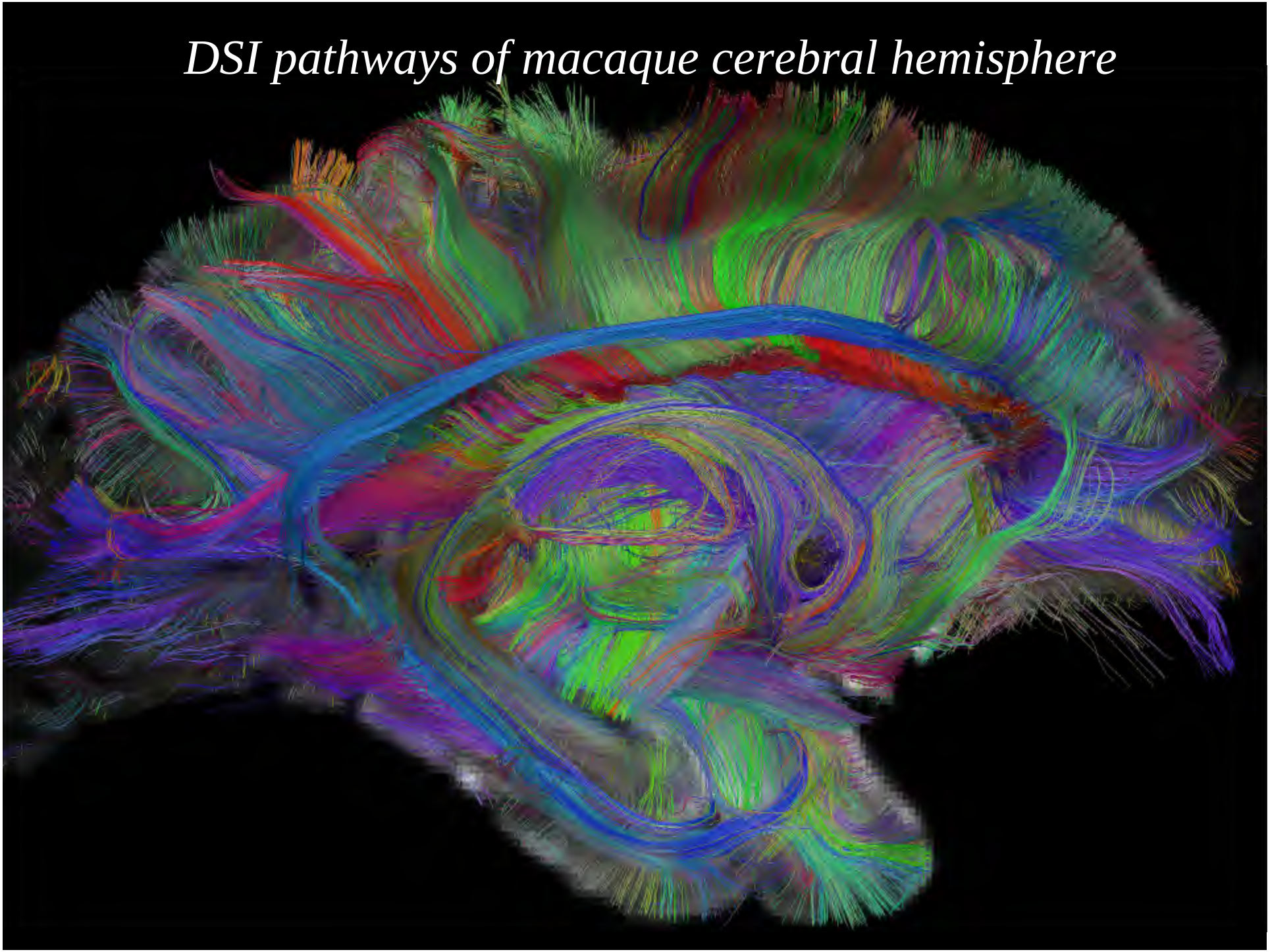


Cat and mouse

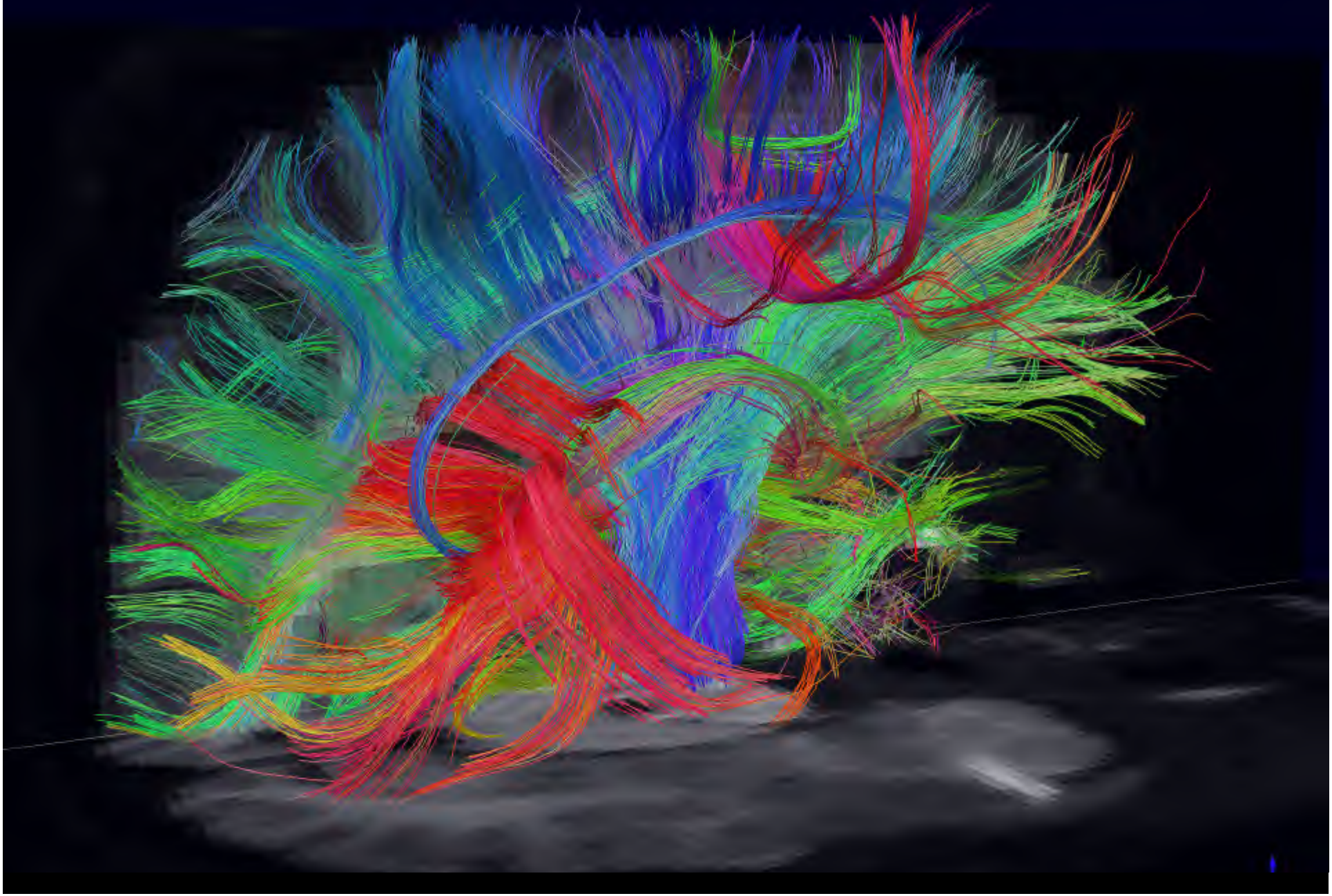
Owl monkey DSI - 3D paths of 1 slice



DSI pathways of macaque cerebral hemisphere

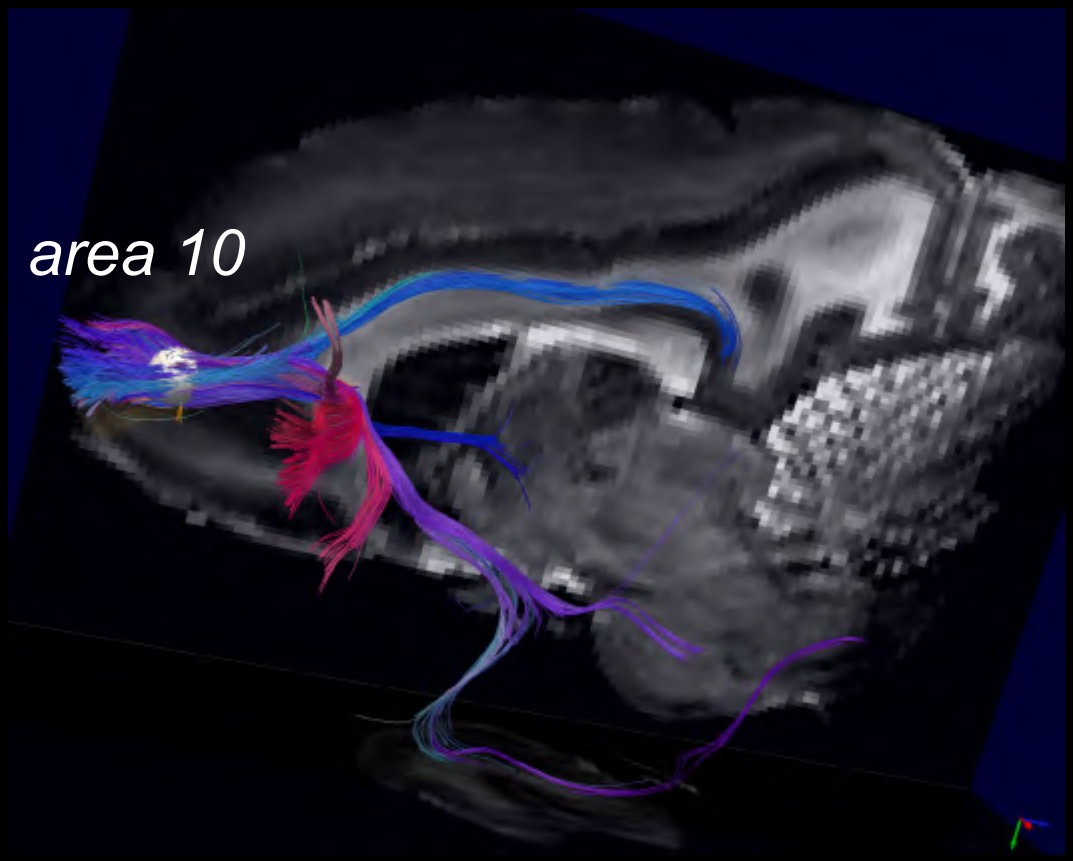


DSI human in vivo 3T

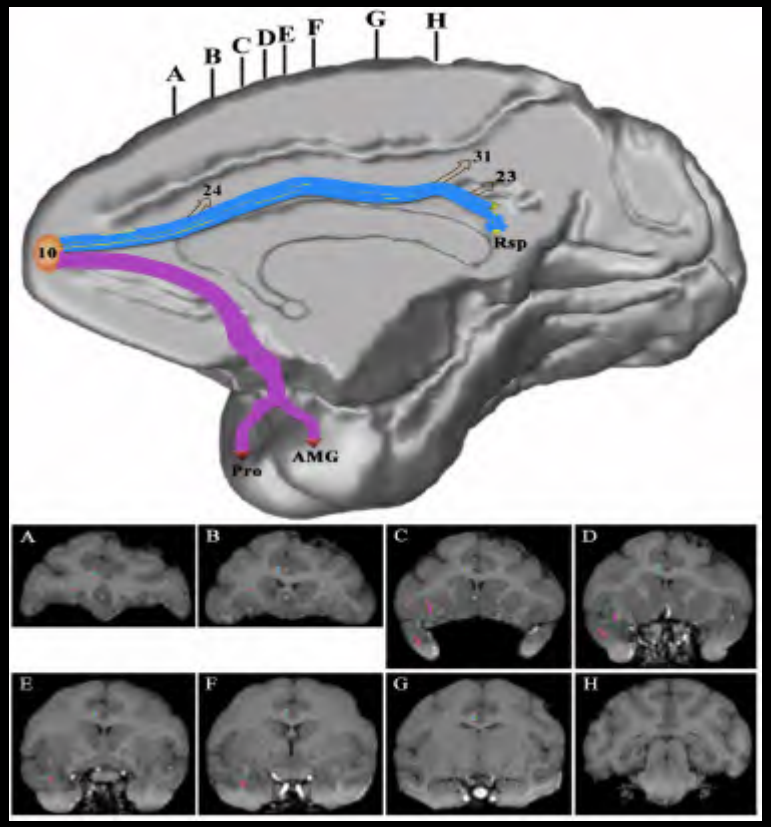


DSI cortical connectivity in macaque

DSI



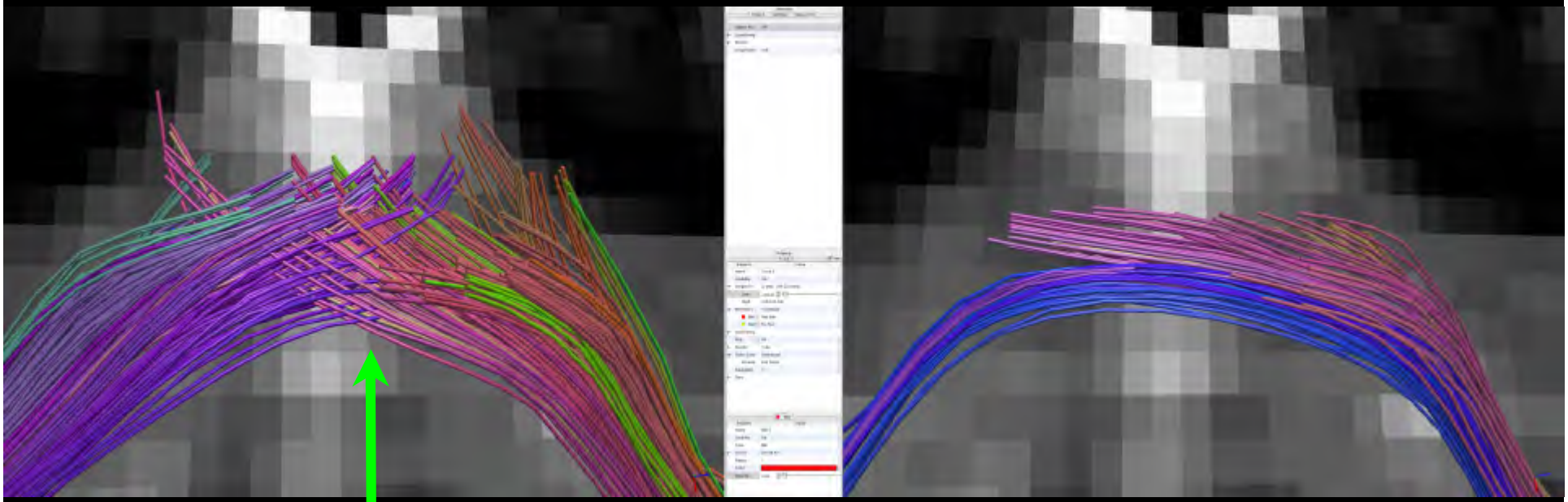
Petrides & Pandya



BA10 important in schizophrenia, language

Optic chiasm

DSI *DTI*

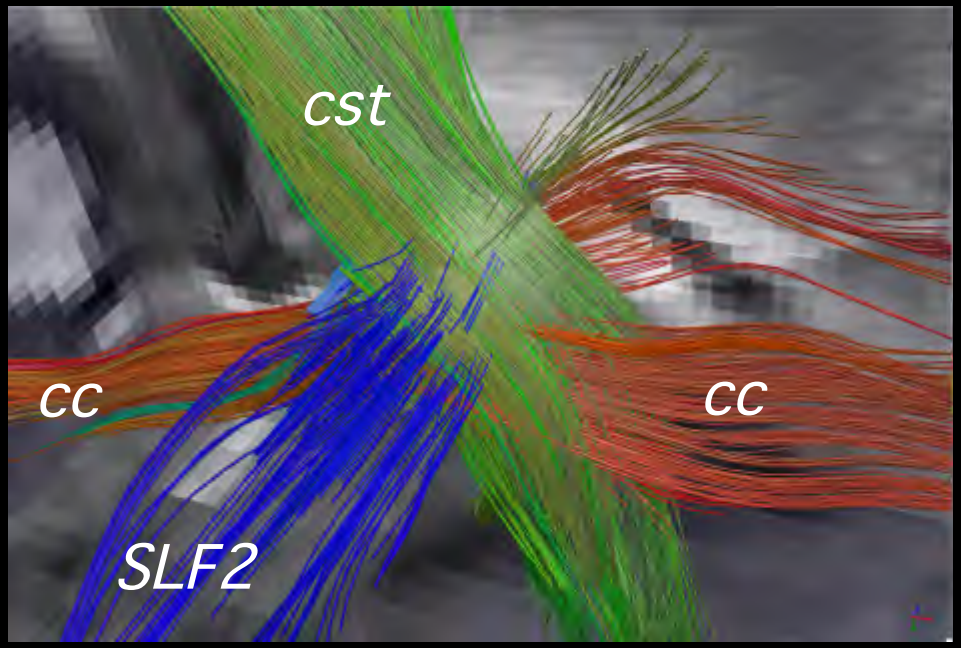


descusation

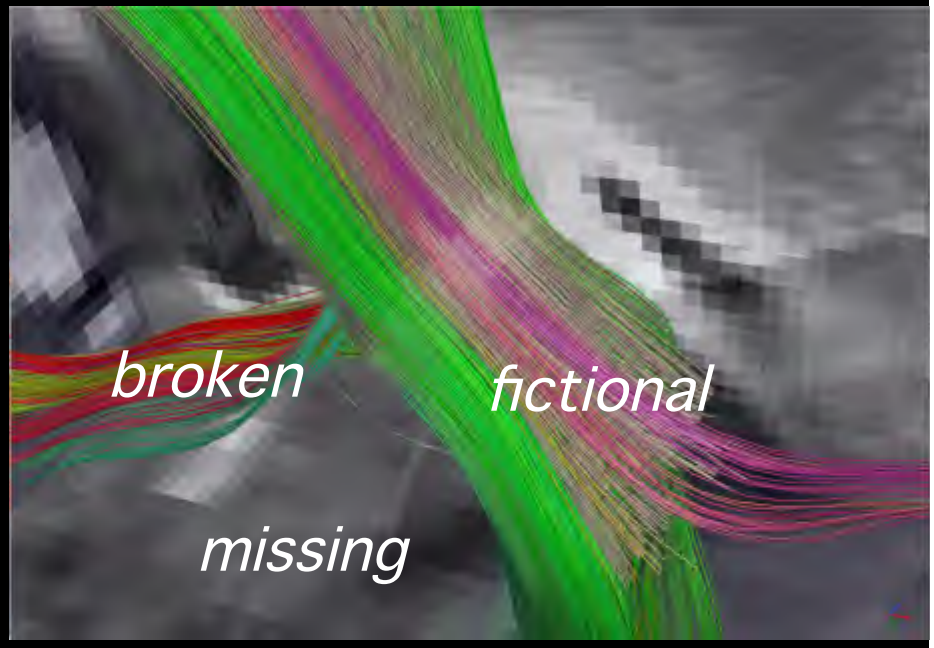
Wedeen et al Neruoimage 2008 in press

DSI vs DTI - centrum semiovale of macaque

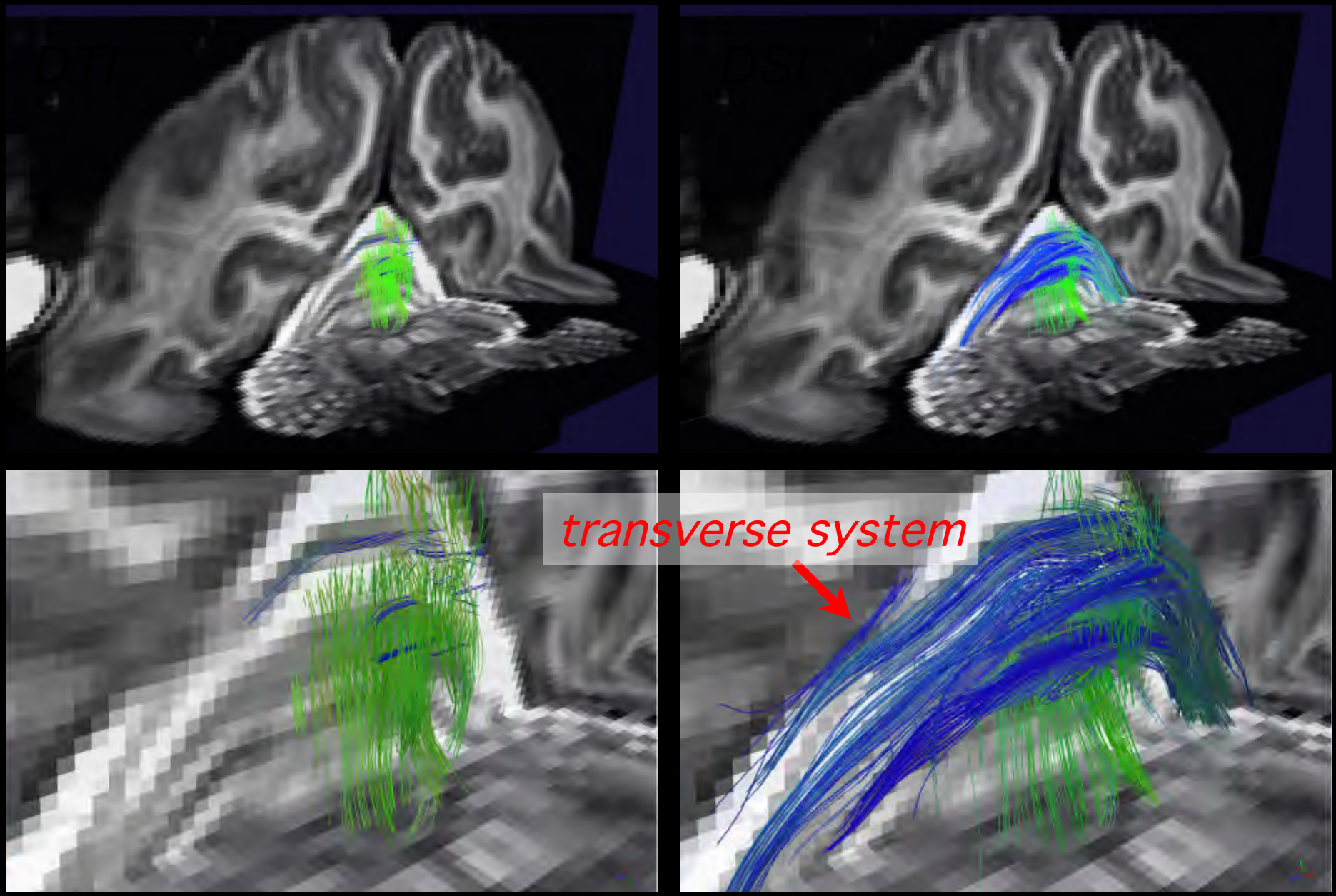
DSI



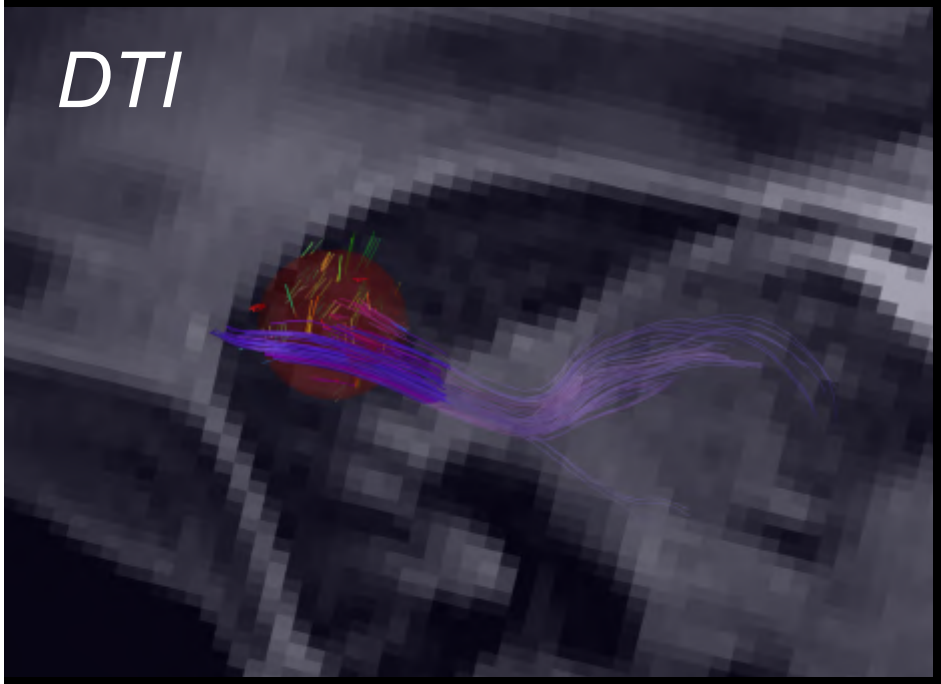
DTI

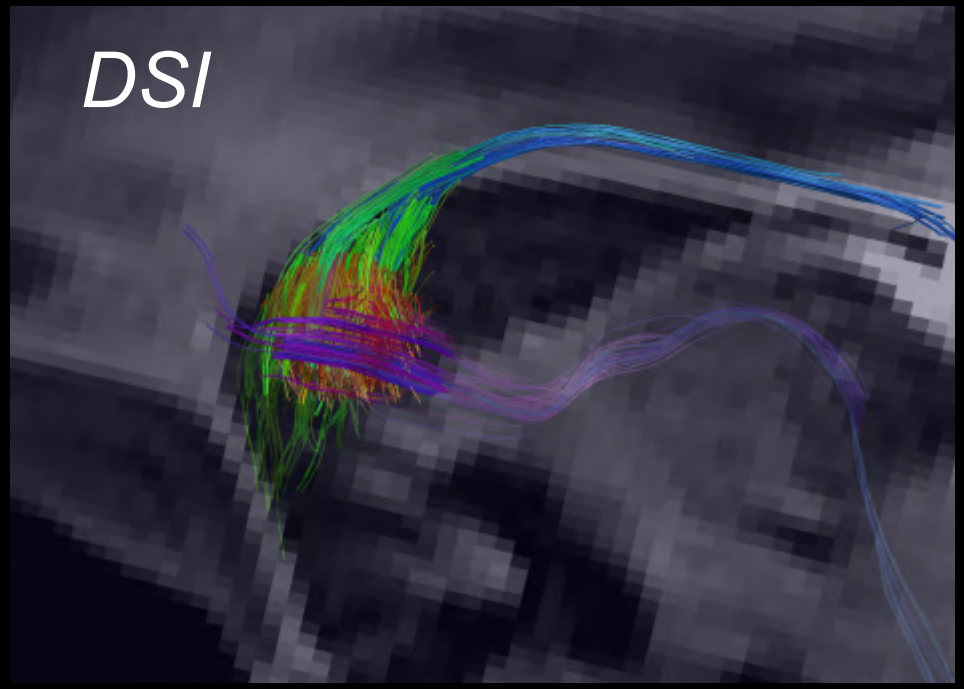


Cerebellum



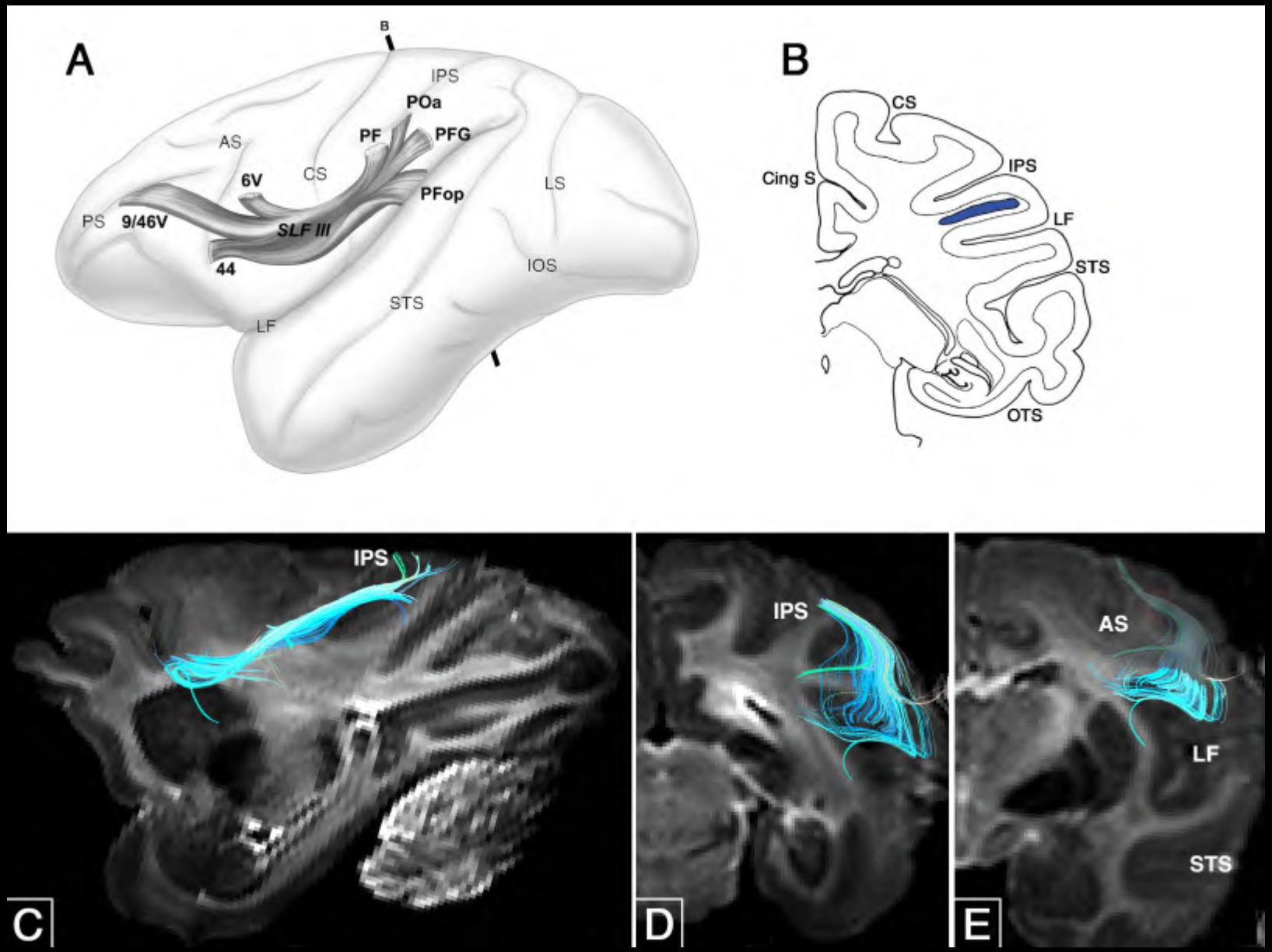
Tractography in caudate nucleus - Amygdalo-striate bundle of Muratoff





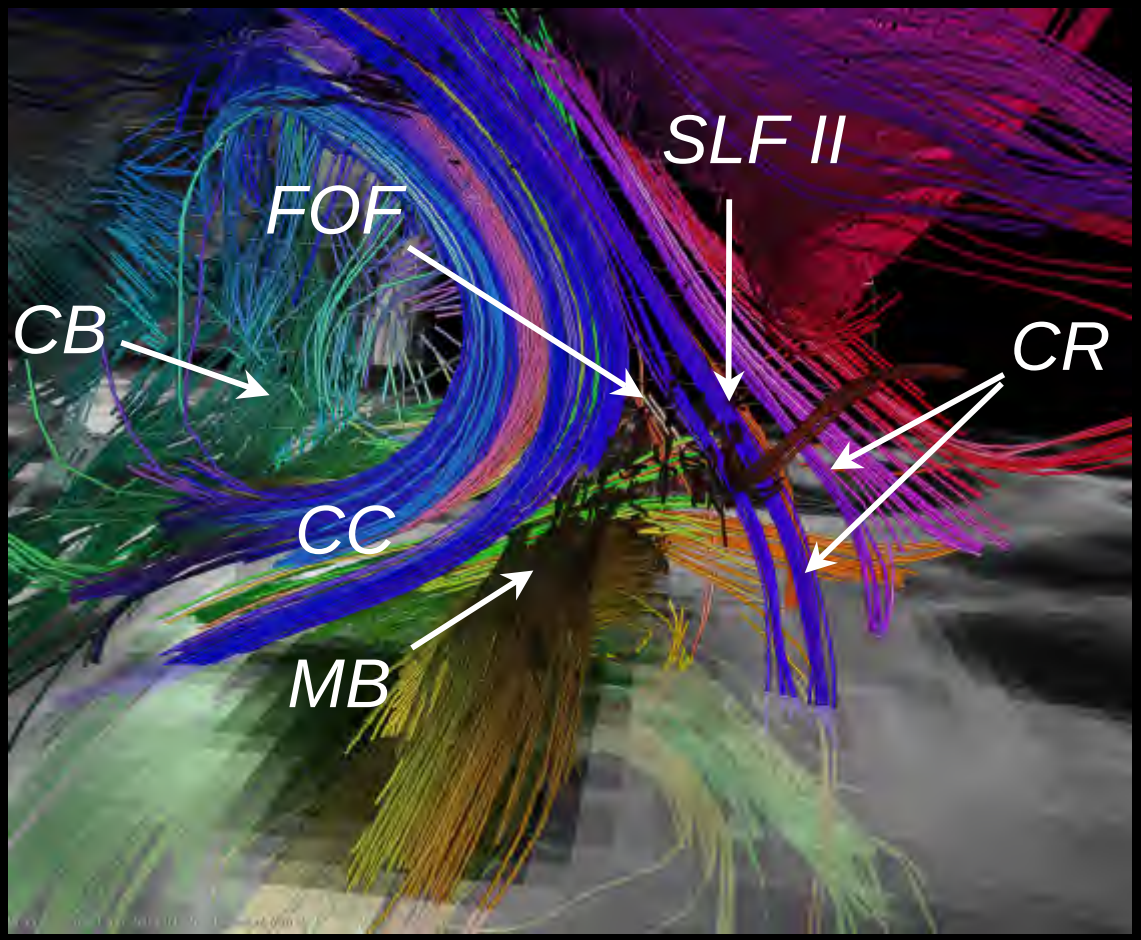
Wedeen et al Neruoimage 2008 in press

Tracer and DSI - SLFIII

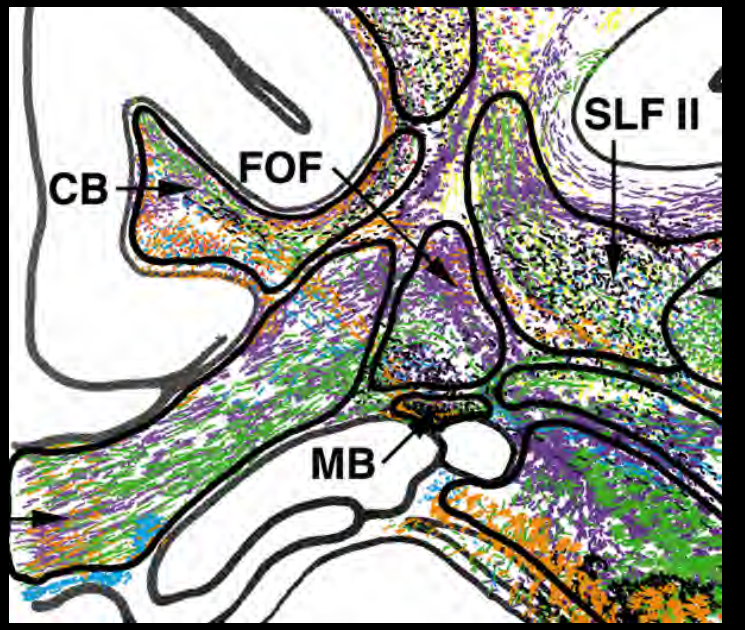


Macaque DSI and isotope gold standard

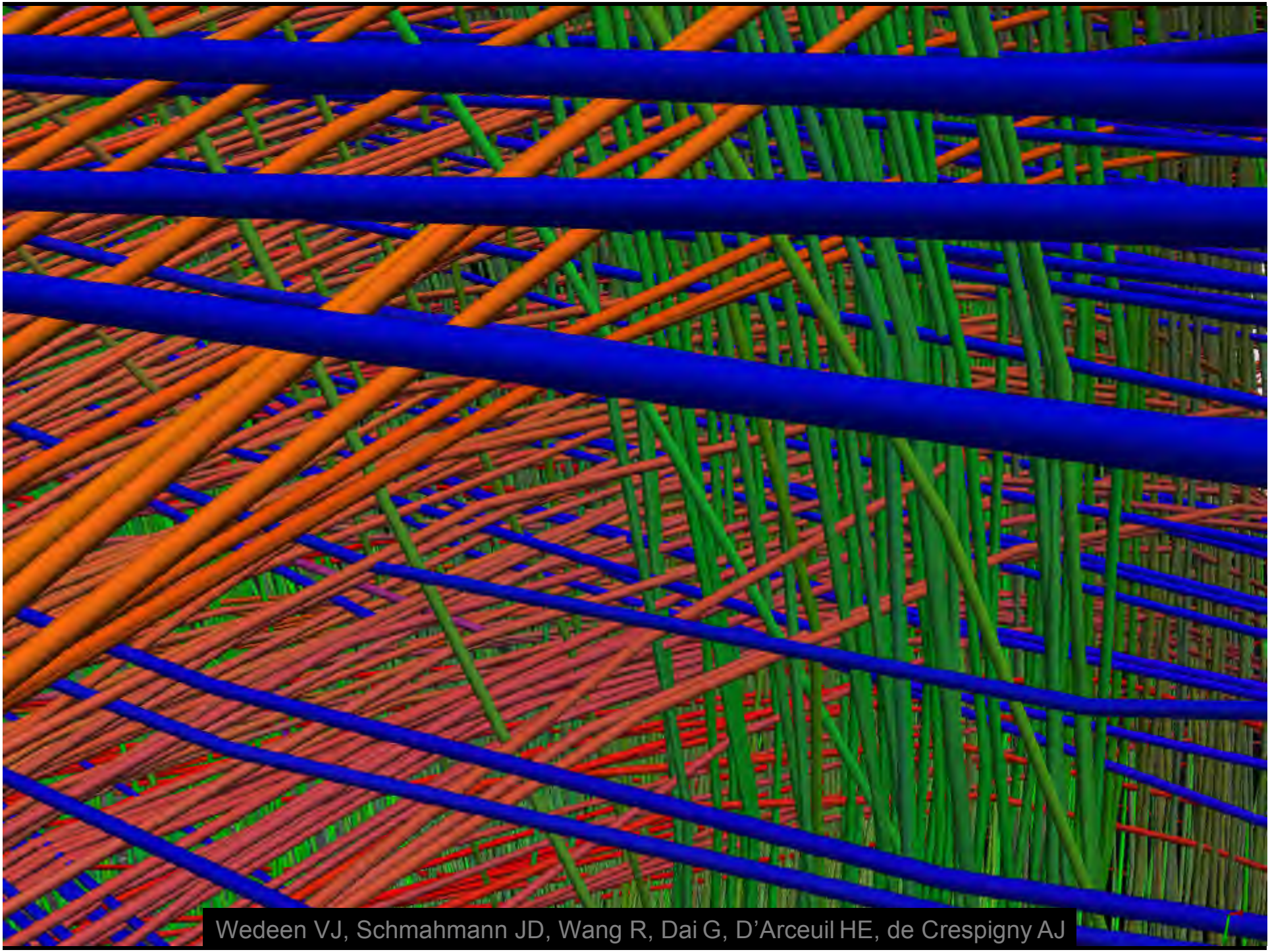
Muratoff bundle in context



Pandya & Schmahmann



Schmahmann et al Brain 2007



Wedeen VJ, Schmahmann JD, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ

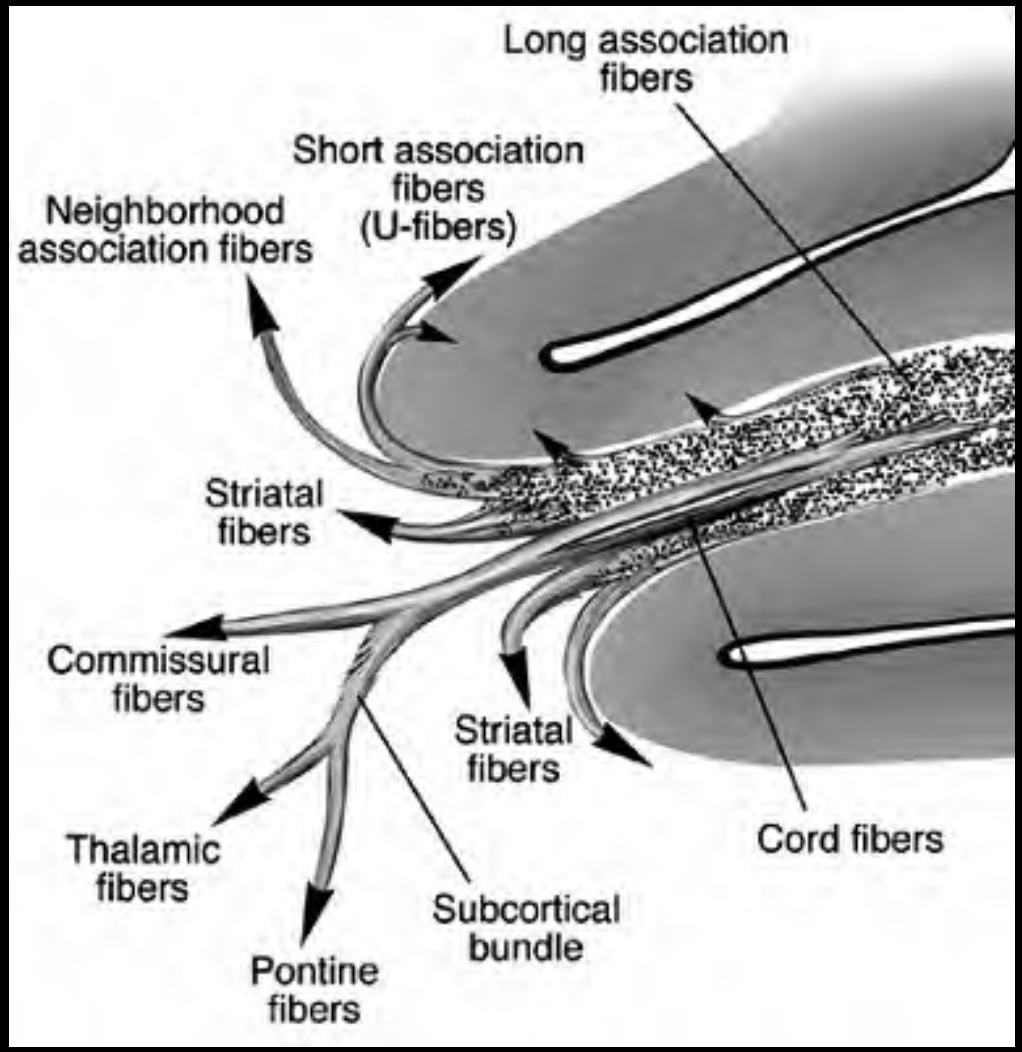
1. *DSI - imaging the 6-dimensional brain*
2. *The connectome*
3. *Limbic system and hippocampus*
4. *Prospects*

Principles of organization common to all cortical areas

Association fibers
- *Local*
- *Neighborhood*
- *Long*

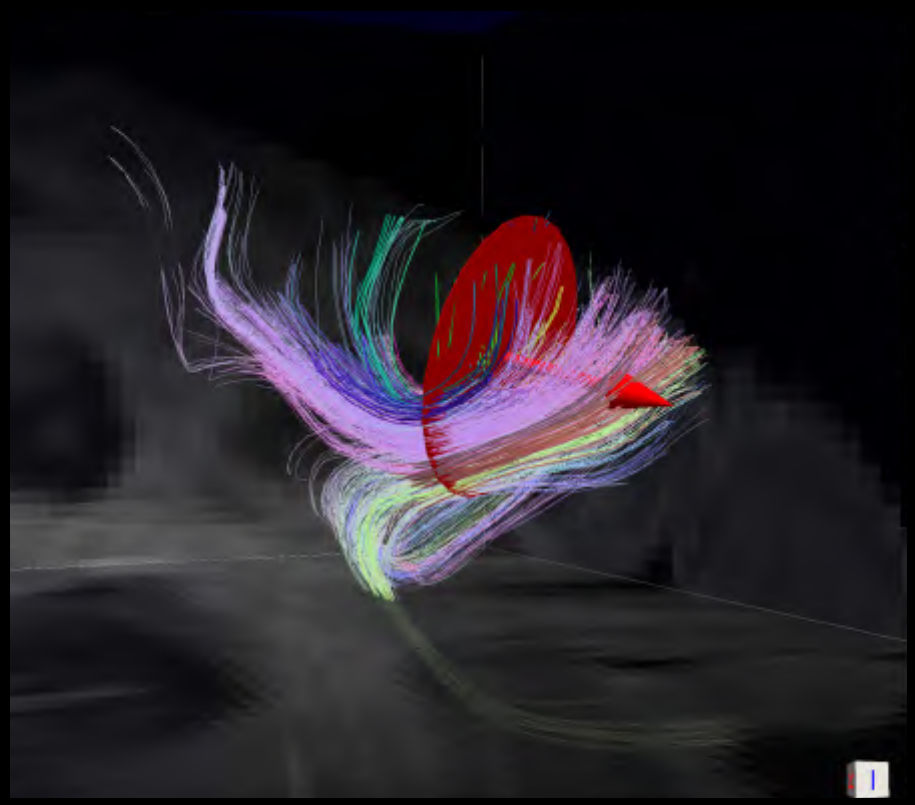
Cord
- *Commissural fibers*
- *Subcortical bundle*

Striatal fibers
- *Muratoff bundle*
- *External capsule*

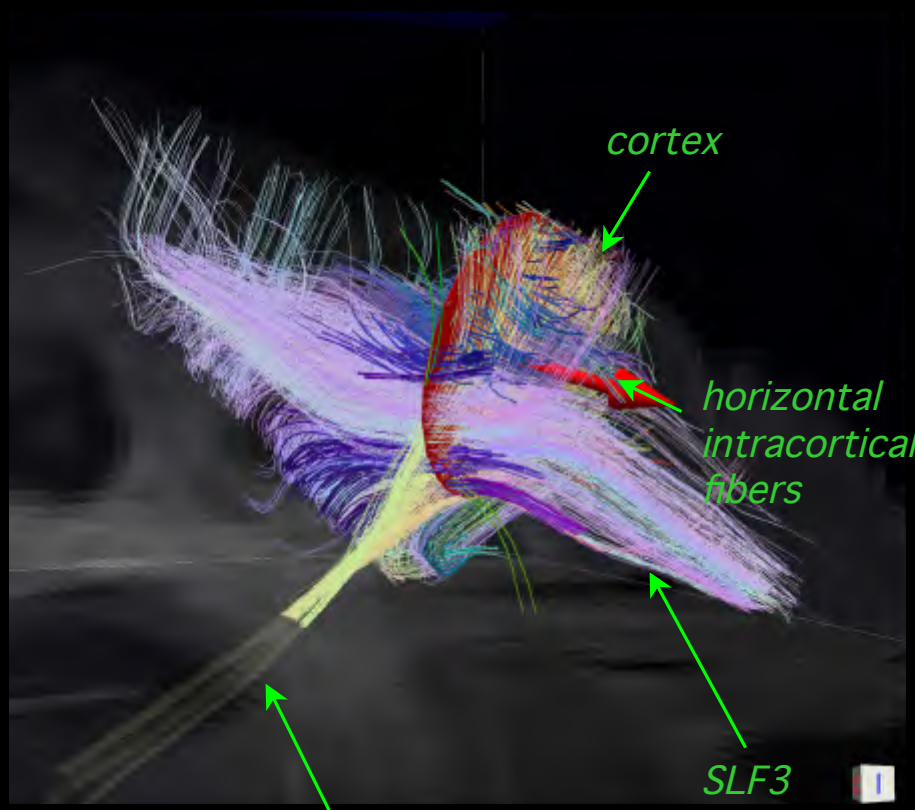


Rhesus motor cortex connections of DTI vs DSI

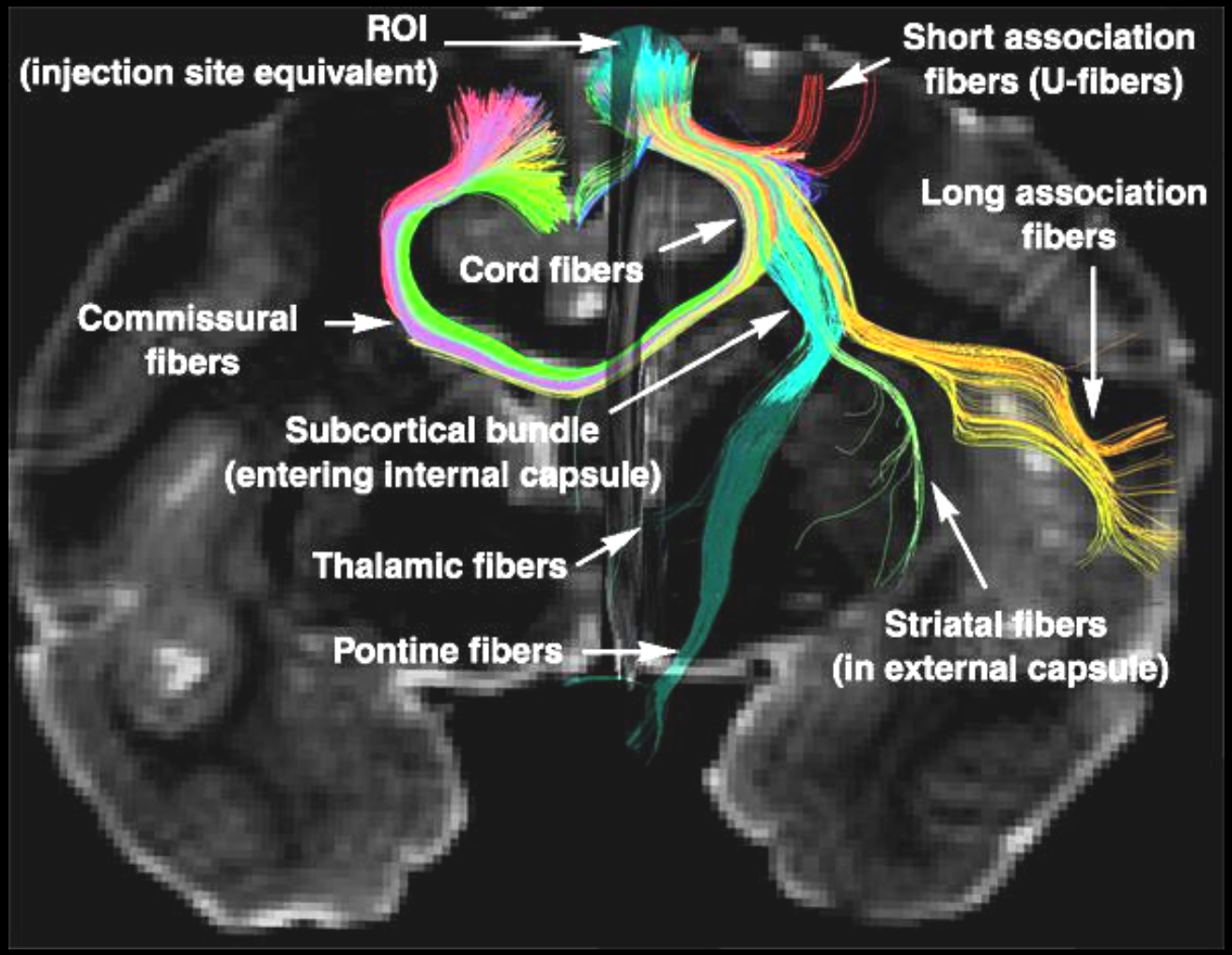
DTI



DSI

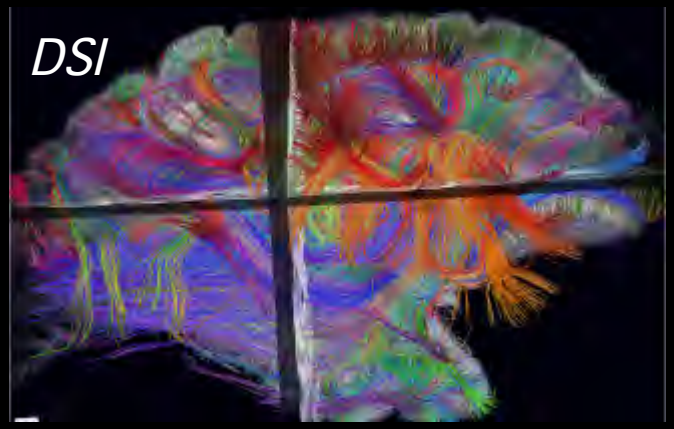


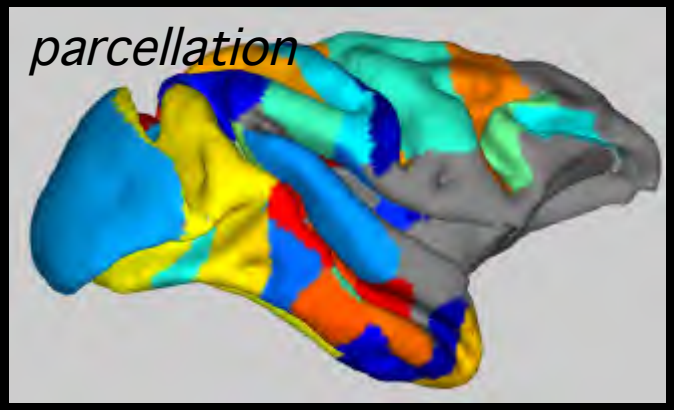
DSI connectivity of macaque superior frontal gyrus

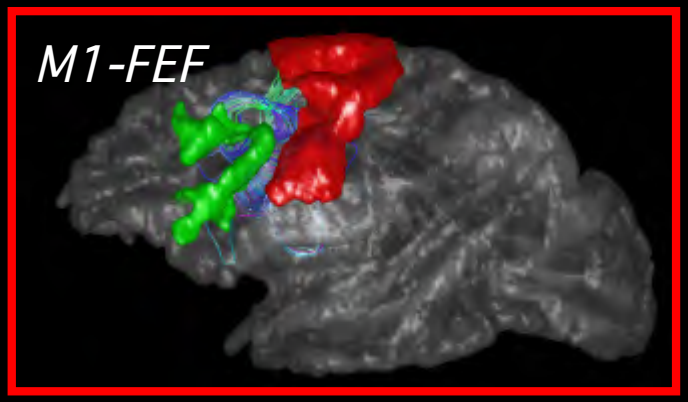


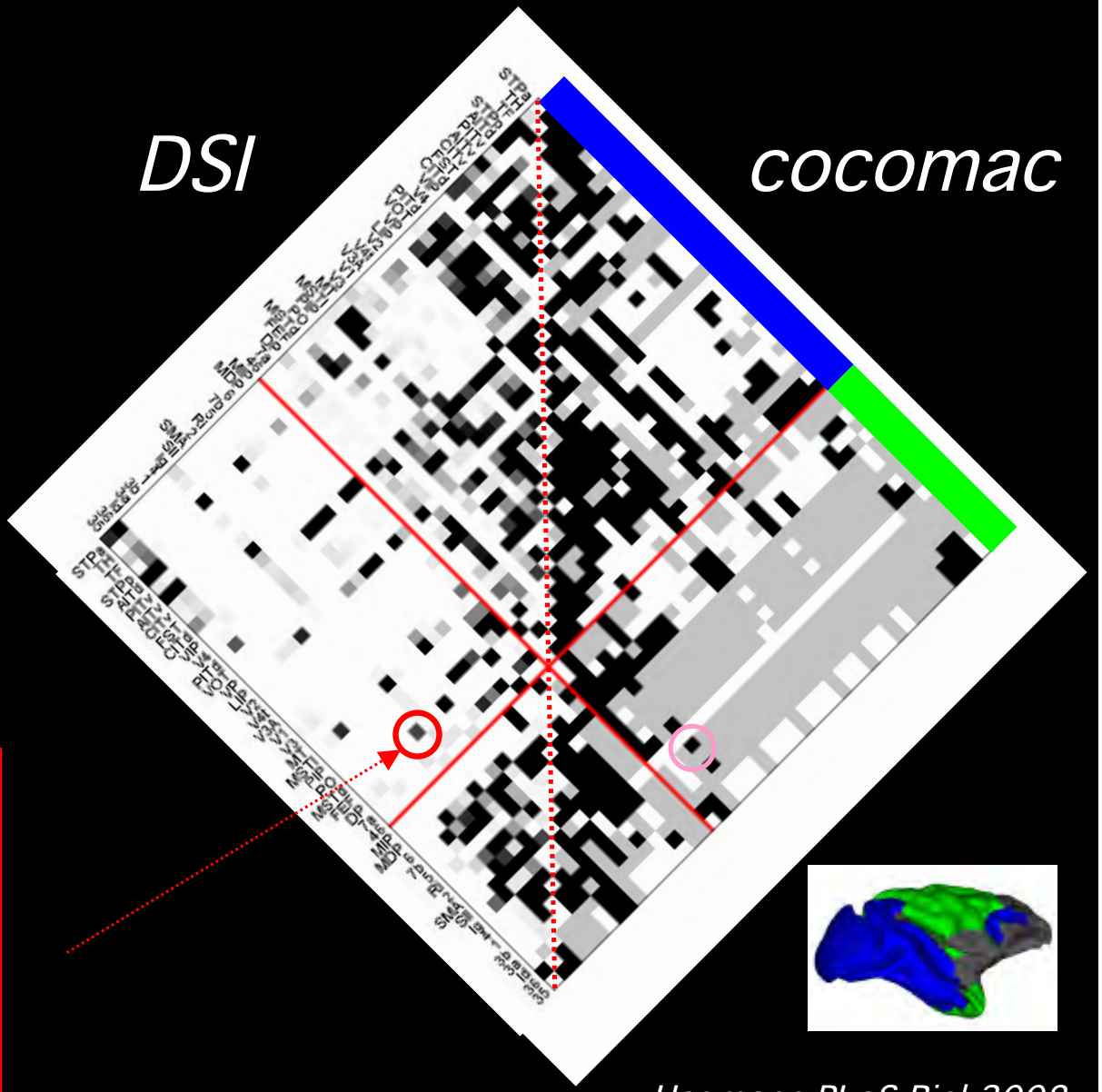
Schmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ

Macaque connectomes



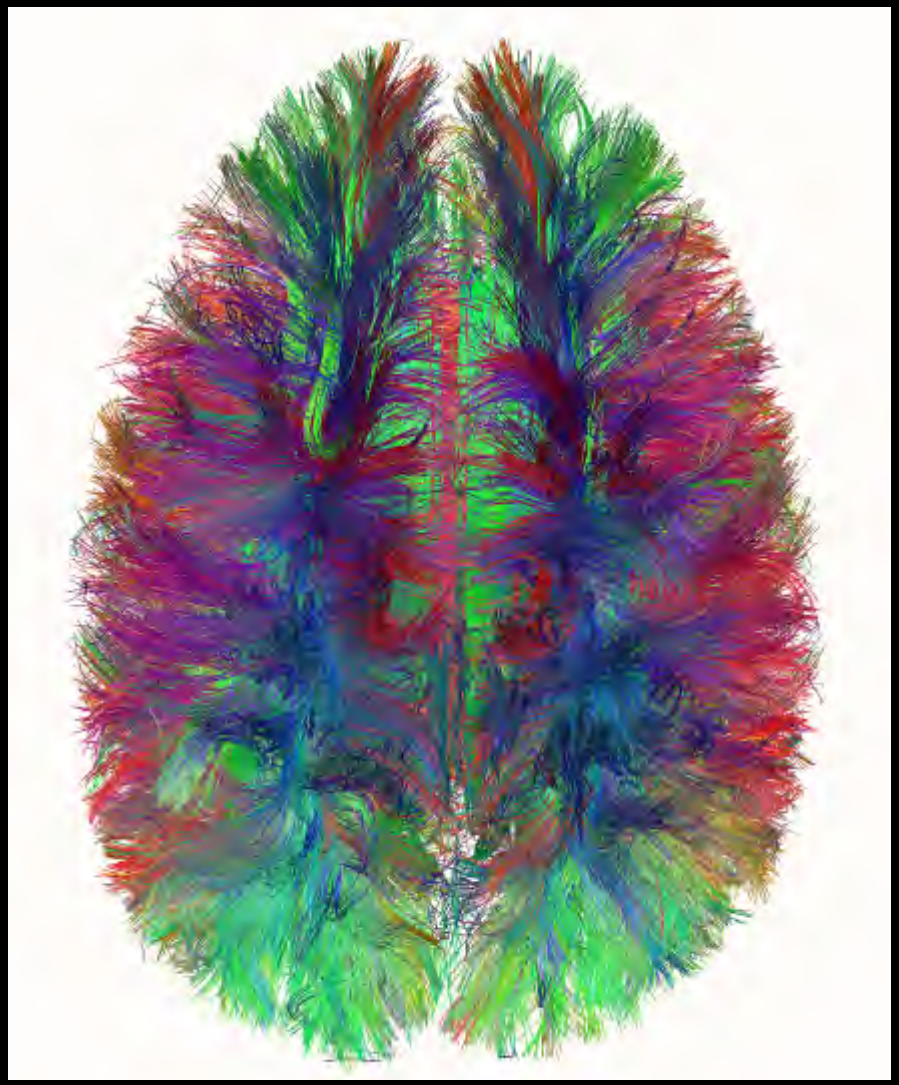




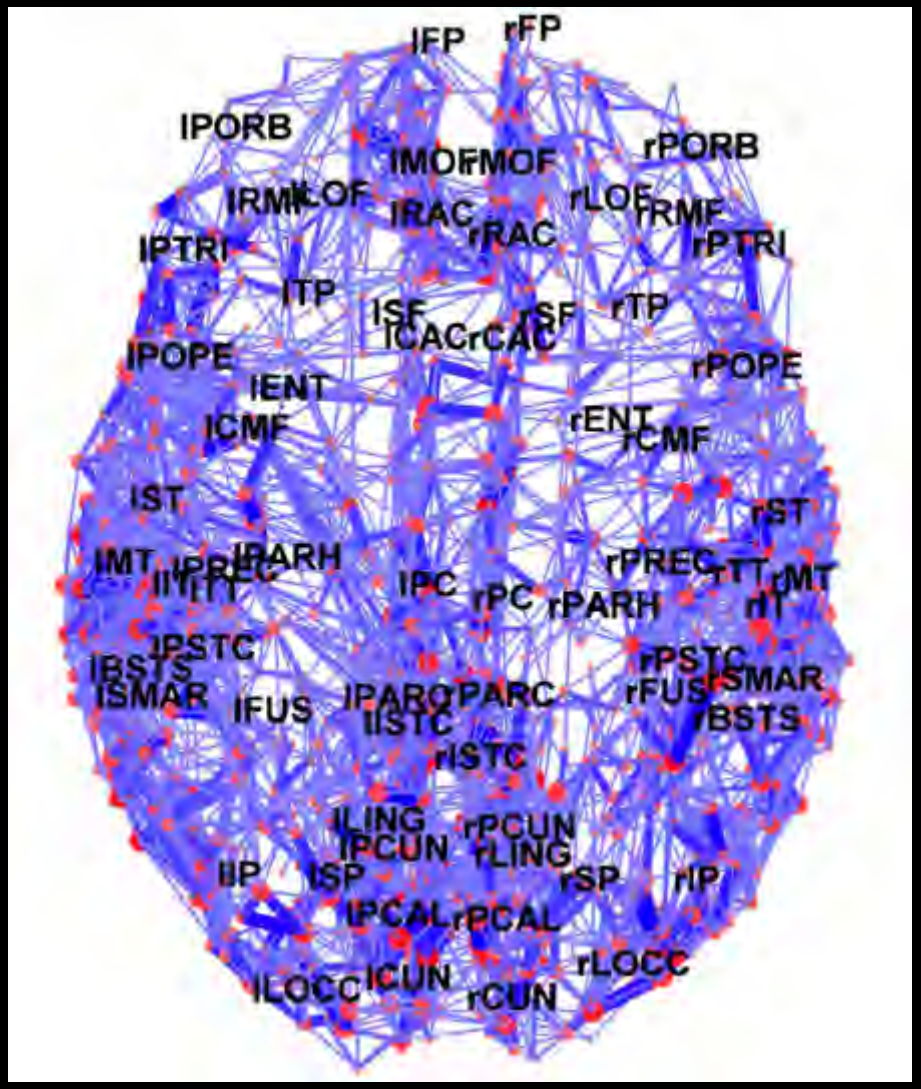


Hagmann PLoS Biol 2008

DSI in vivo human

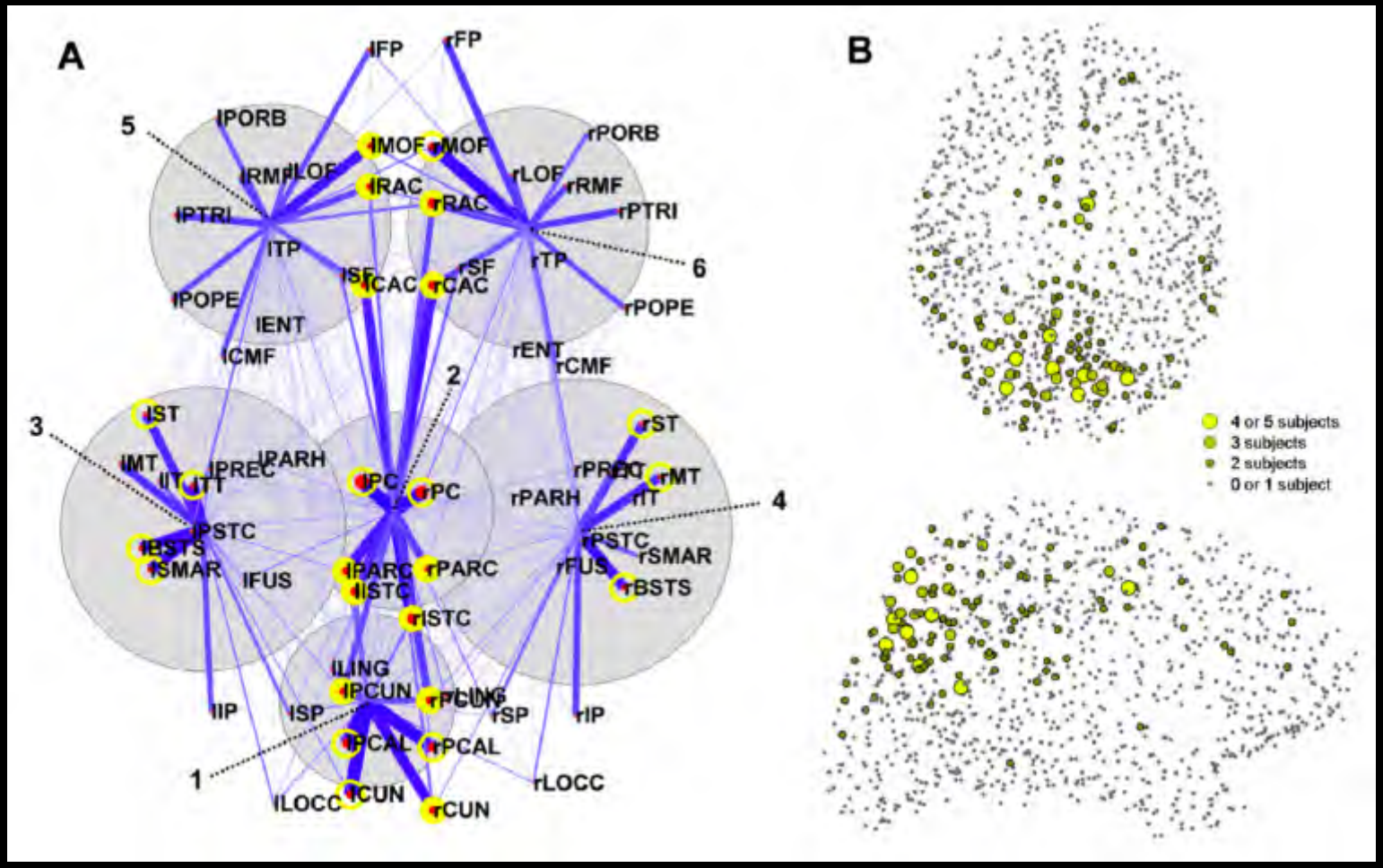


human connectome



Hagmann et al PLoS Biol 2008

Human connectome hubs and core



Hagmann et al PLoS Biol 2008

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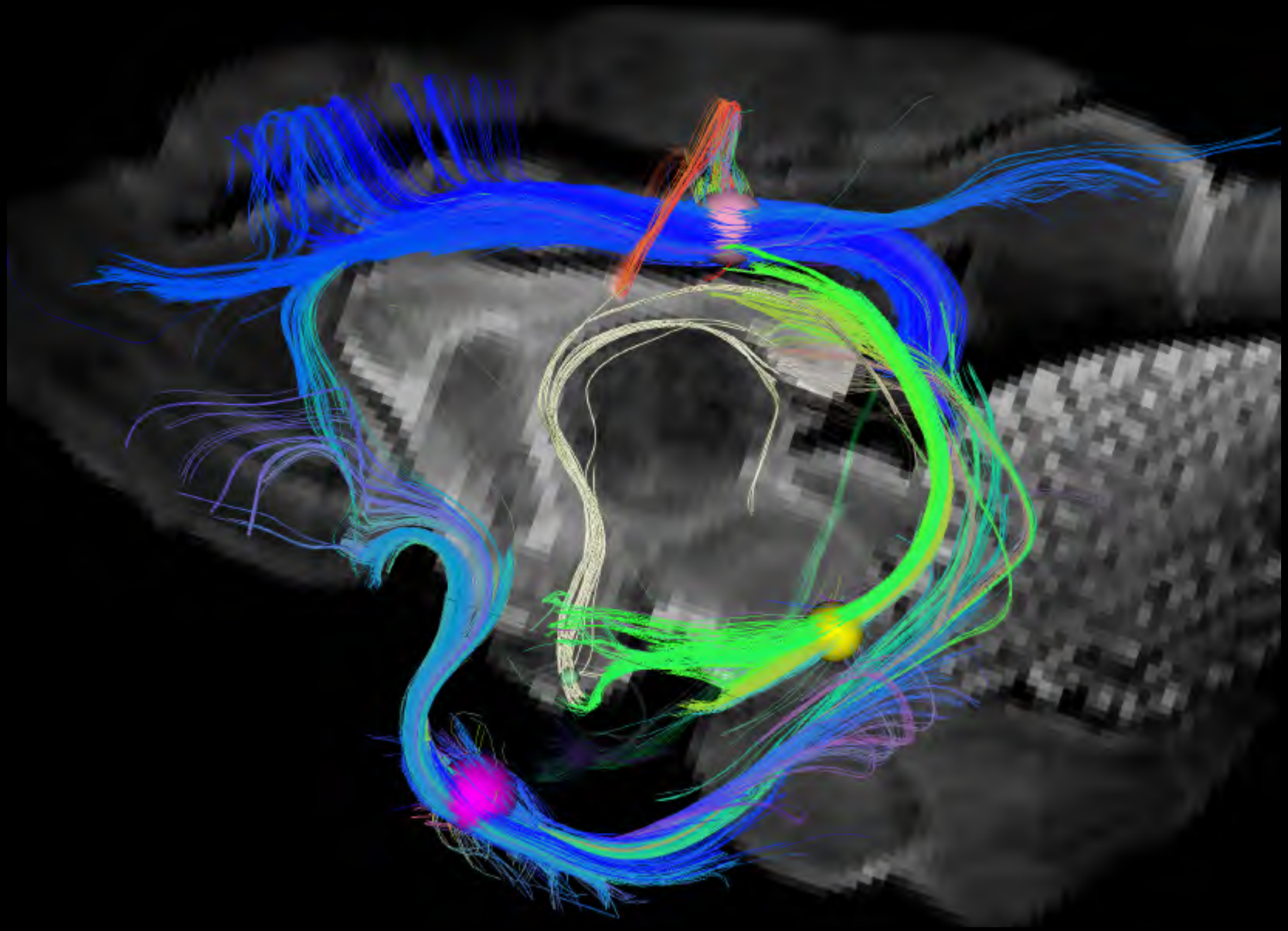
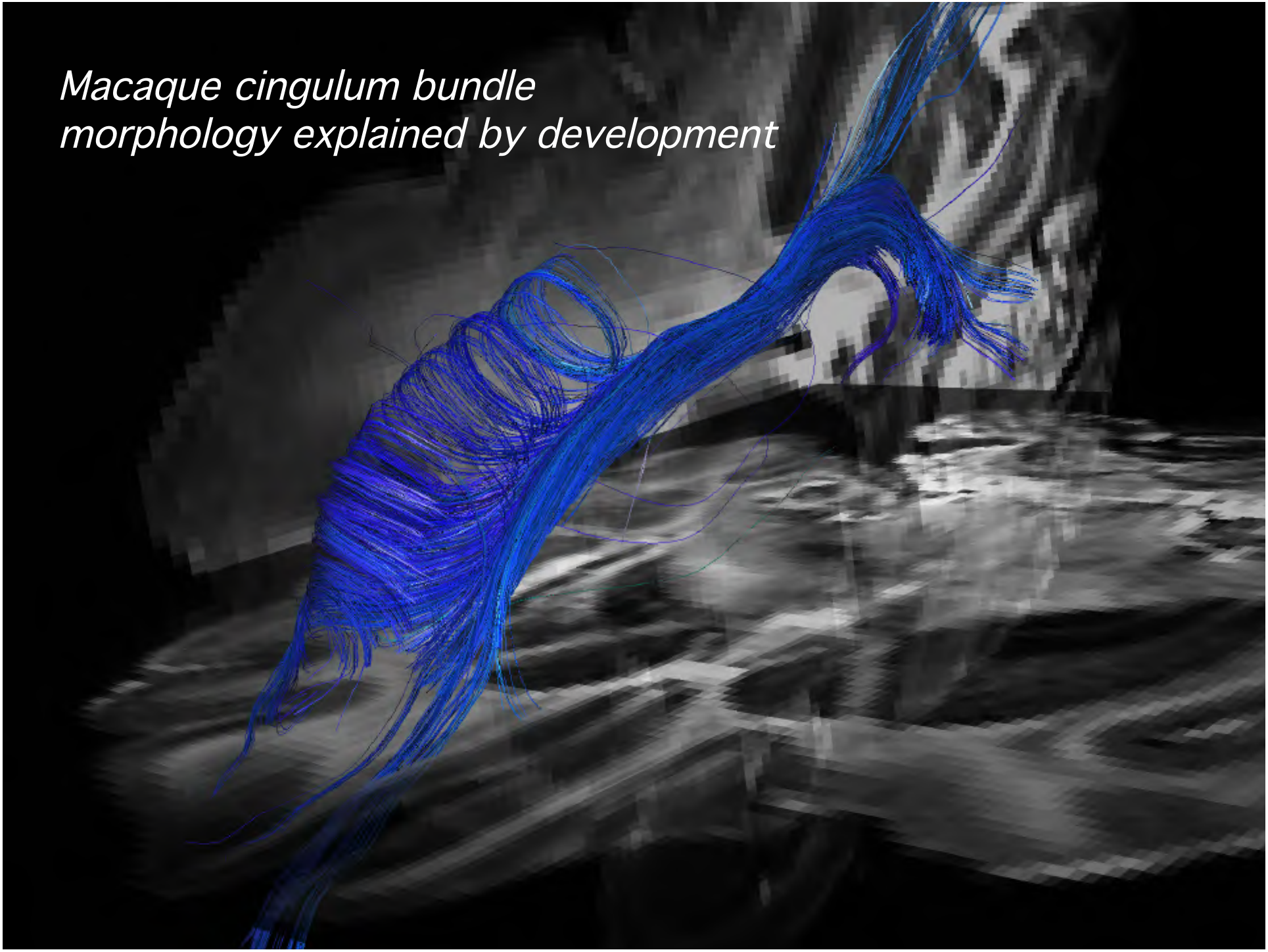
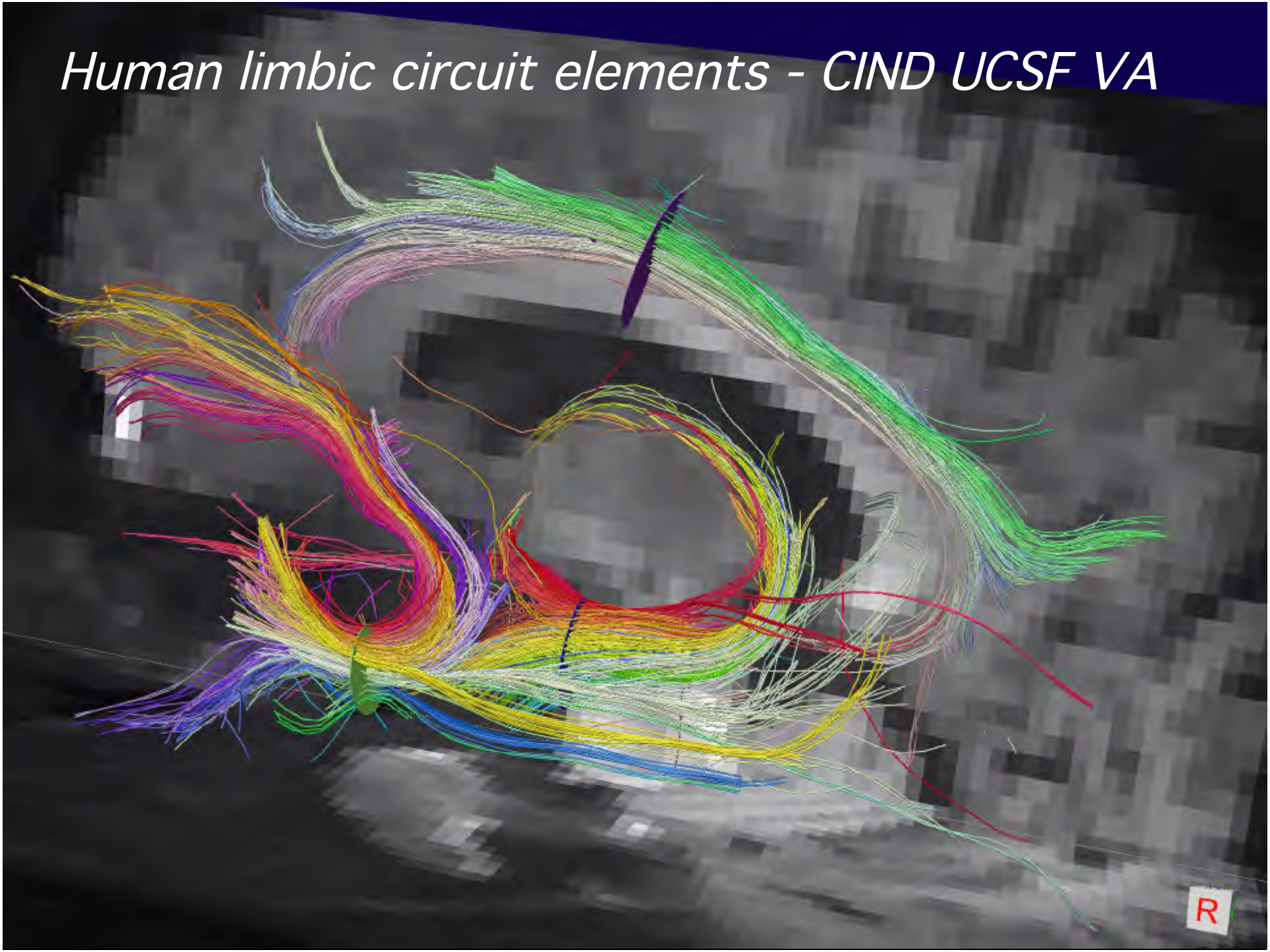
Macaque circuit of Papez ex vivo

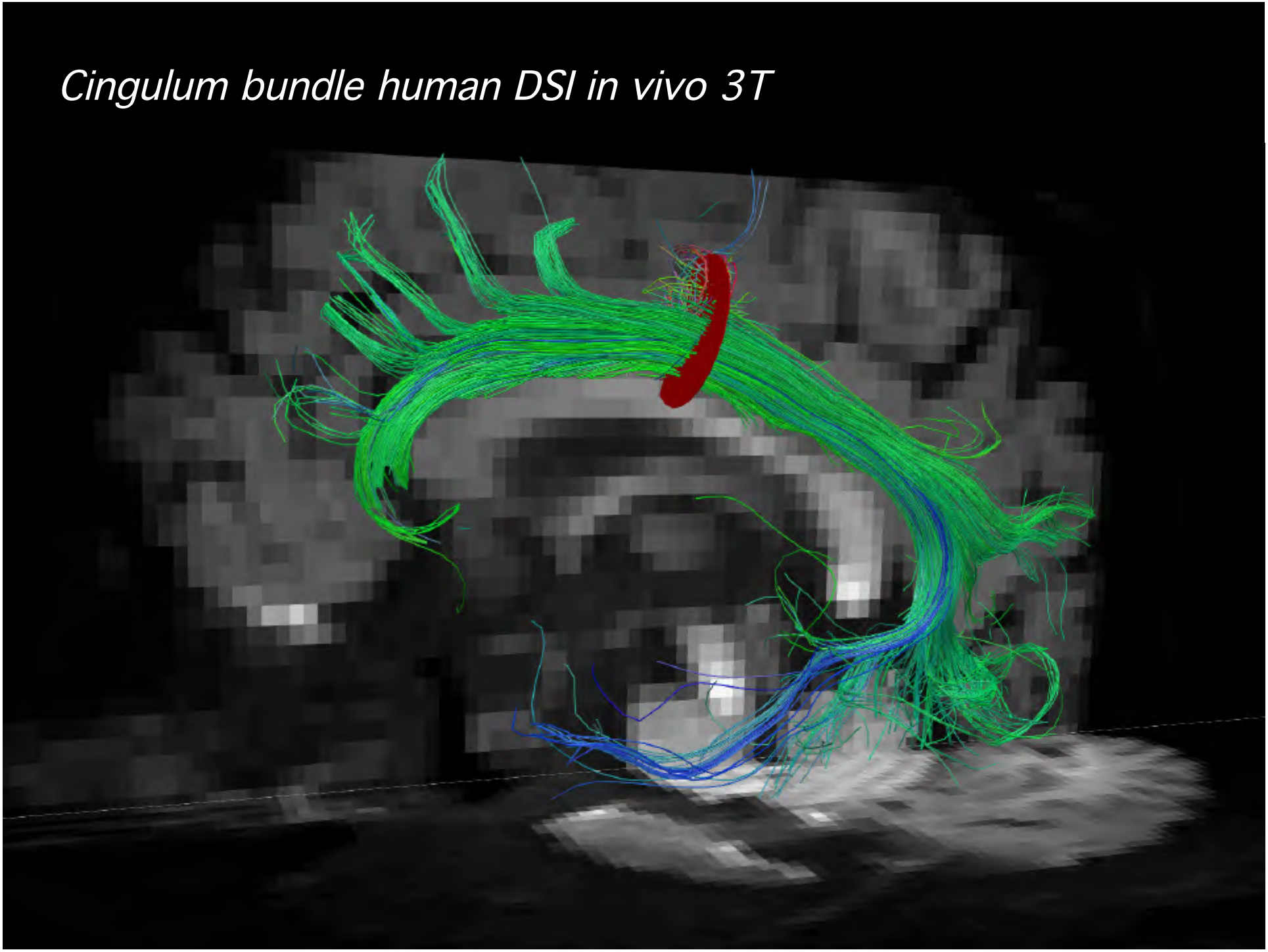



Macaque cingulum bundle
morphology explained by development

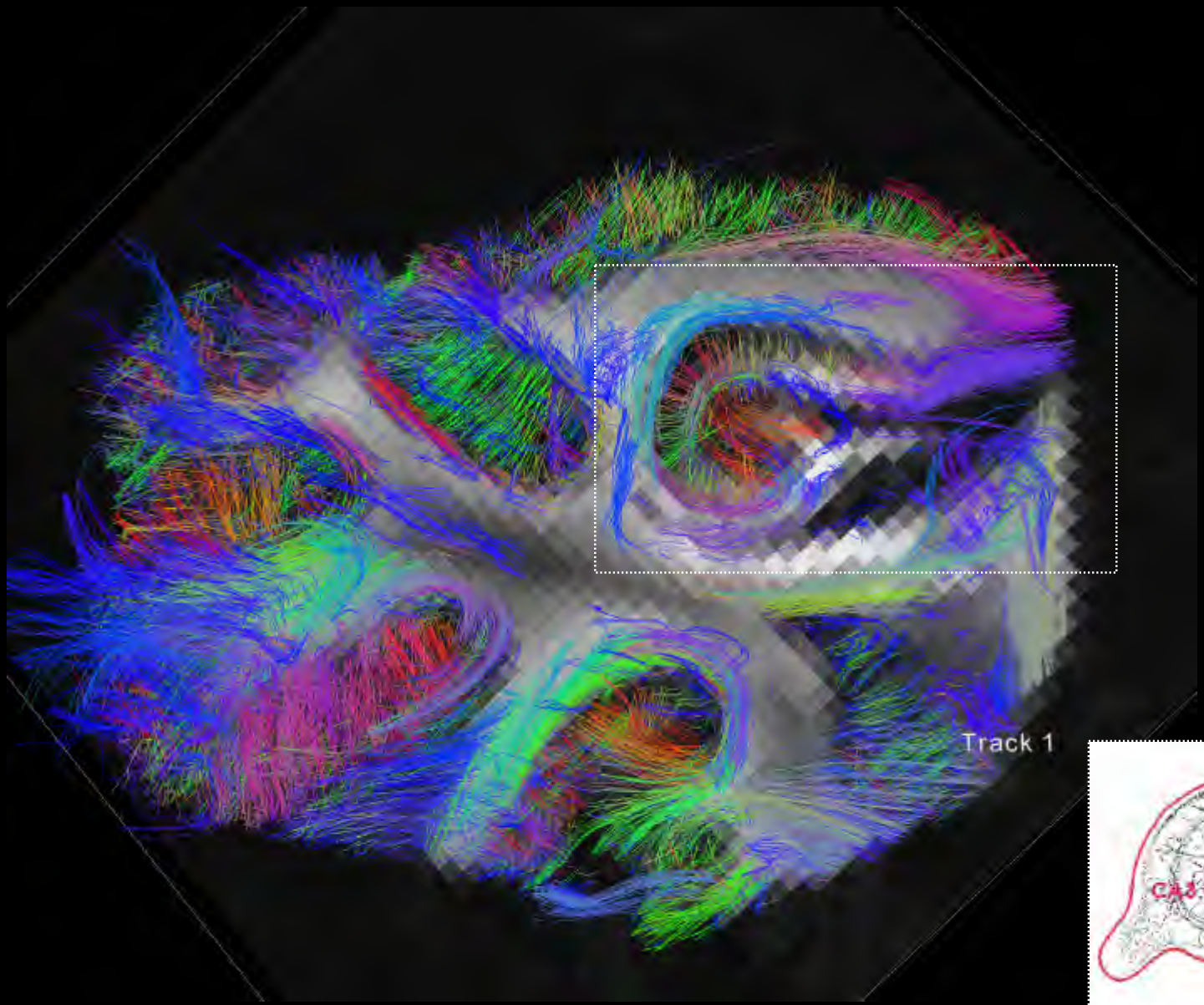
Human limbic circuit elements - CIND UCSF VA

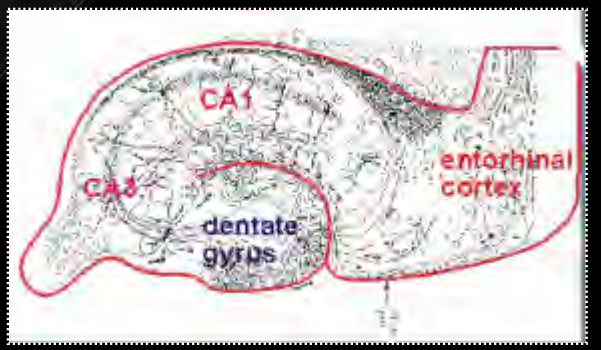


Cingulum bundle human DSI in vivo 3T

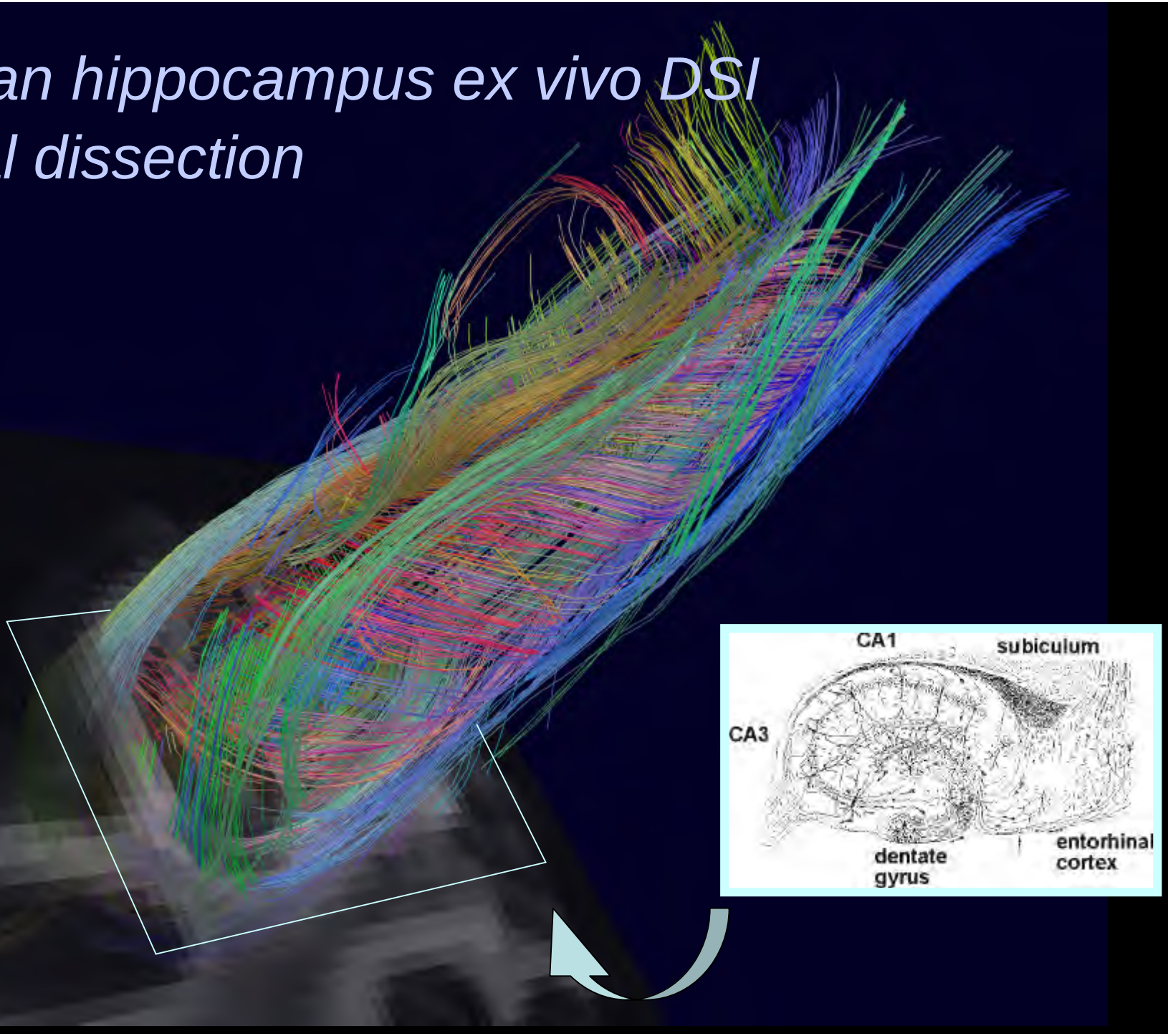


Human temporal lobe / hippocampus ex vivo

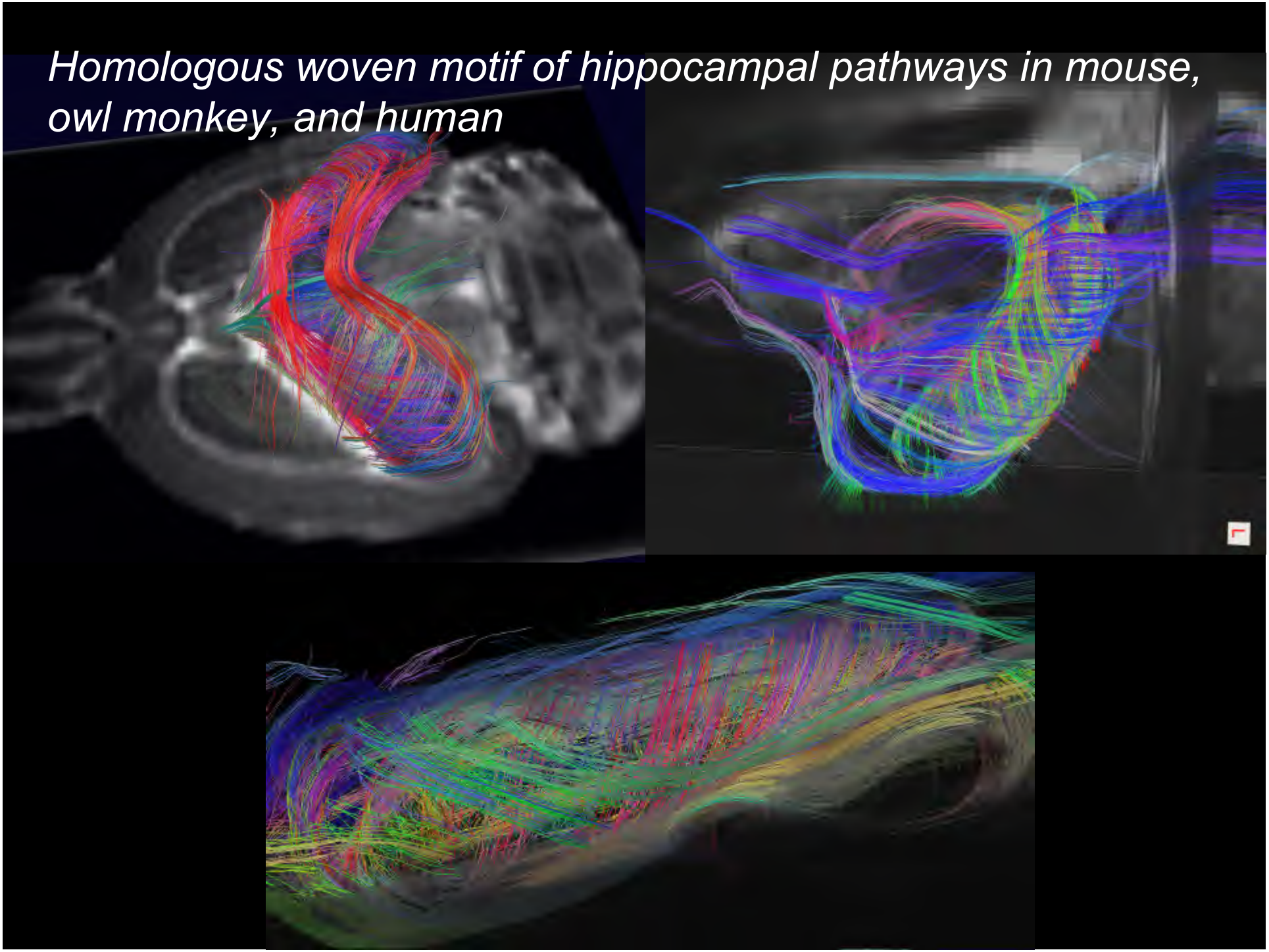




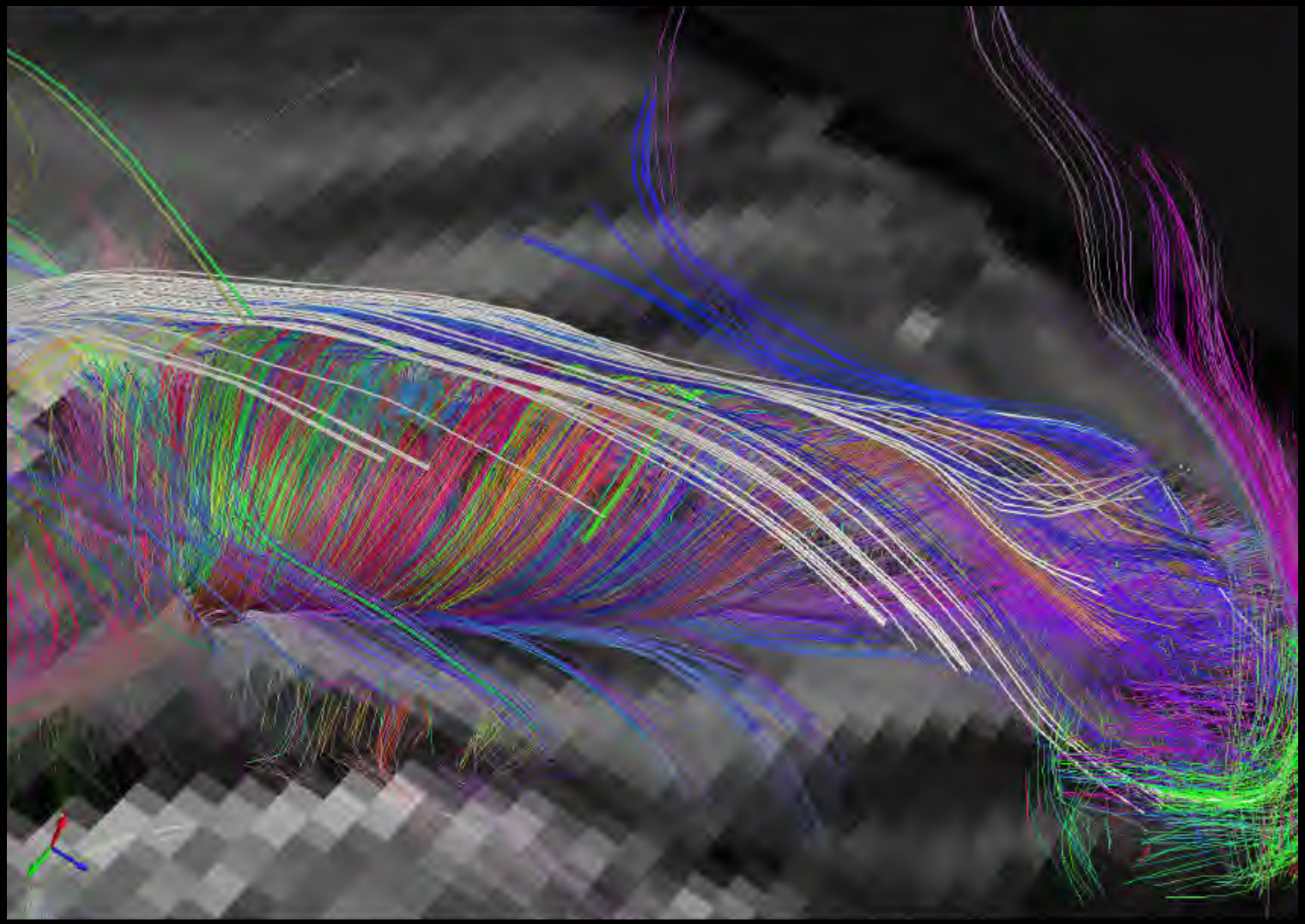
Human hippocampus ex vivo DSI digital dissection



Homologous woven motif of hippocampal pathways in mouse, owl monkey, and human



Macaque calcarine connections



1. *DSI - imaging the 6-dimensional brain*

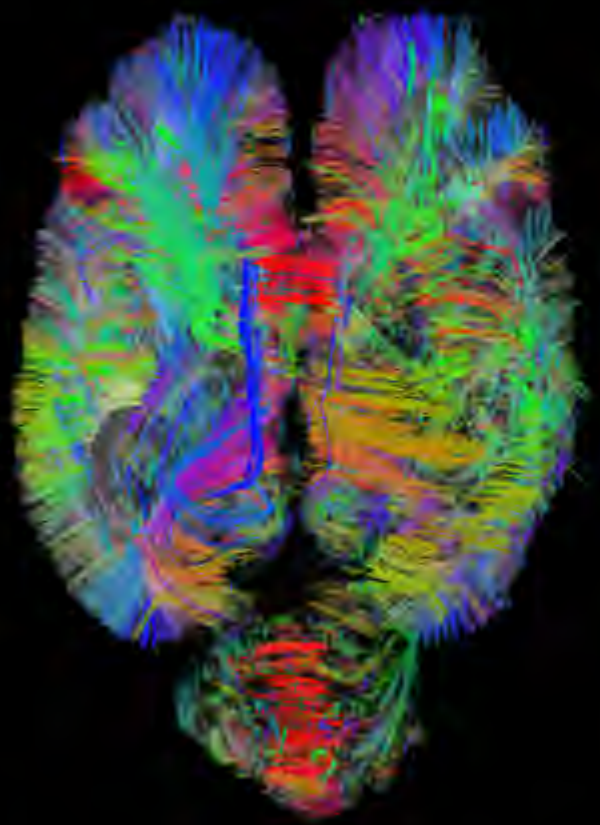
2. *The connectome*

3. *Limbic system and hippocampus*

4. *Prospects*
   - *development*
   - *cortex*

Cat DSI

birth

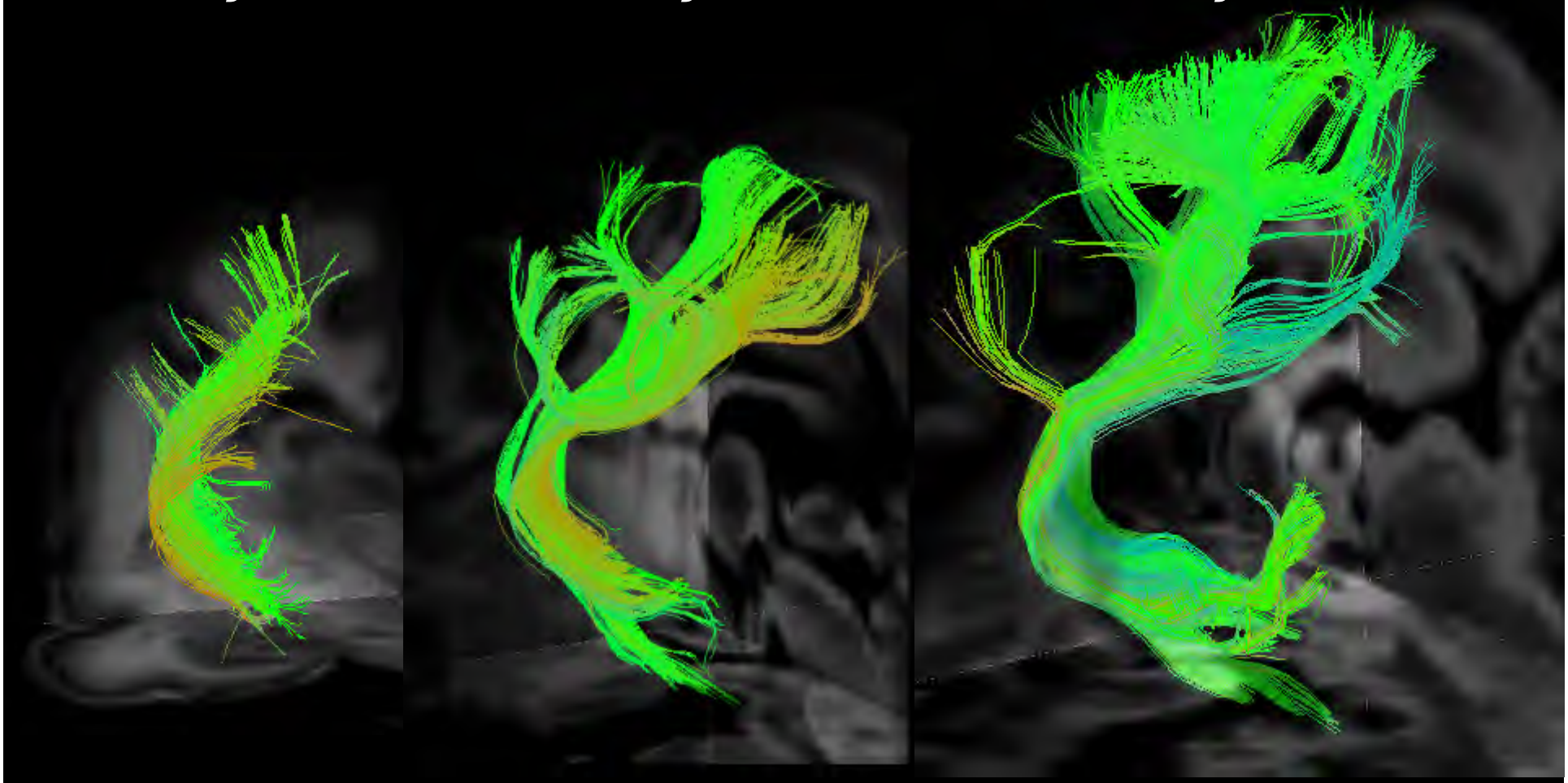


day 100

Takahasi et al ISRMR 2008

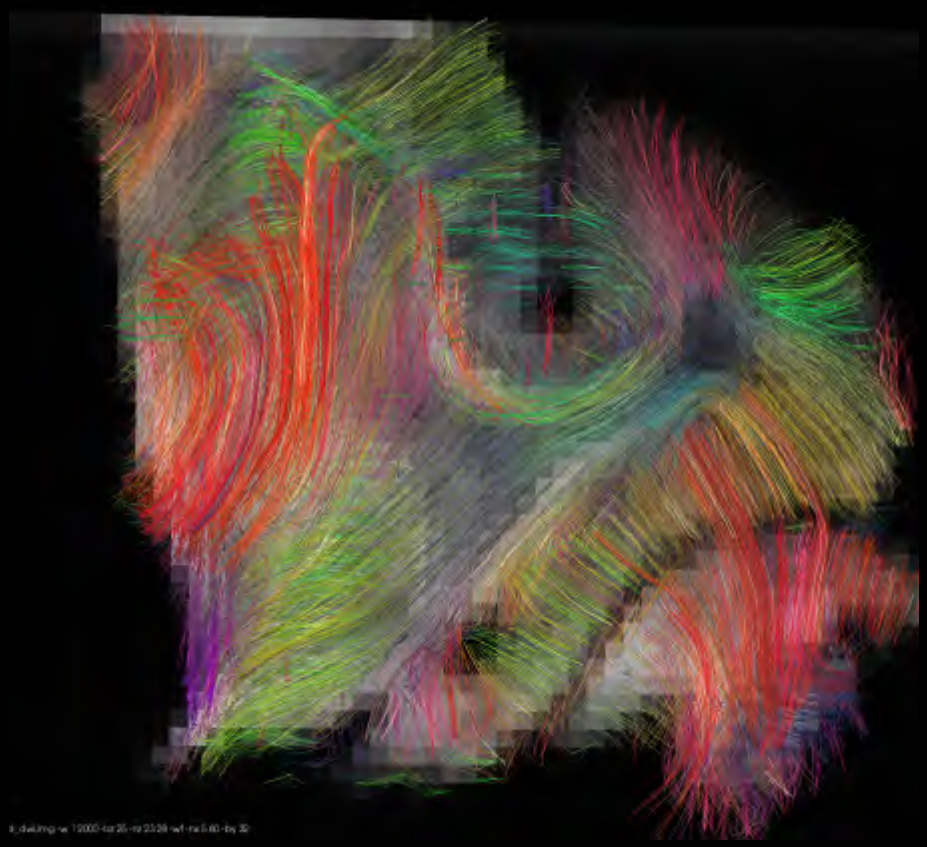
Development of cortico-thalamic tracts in cat

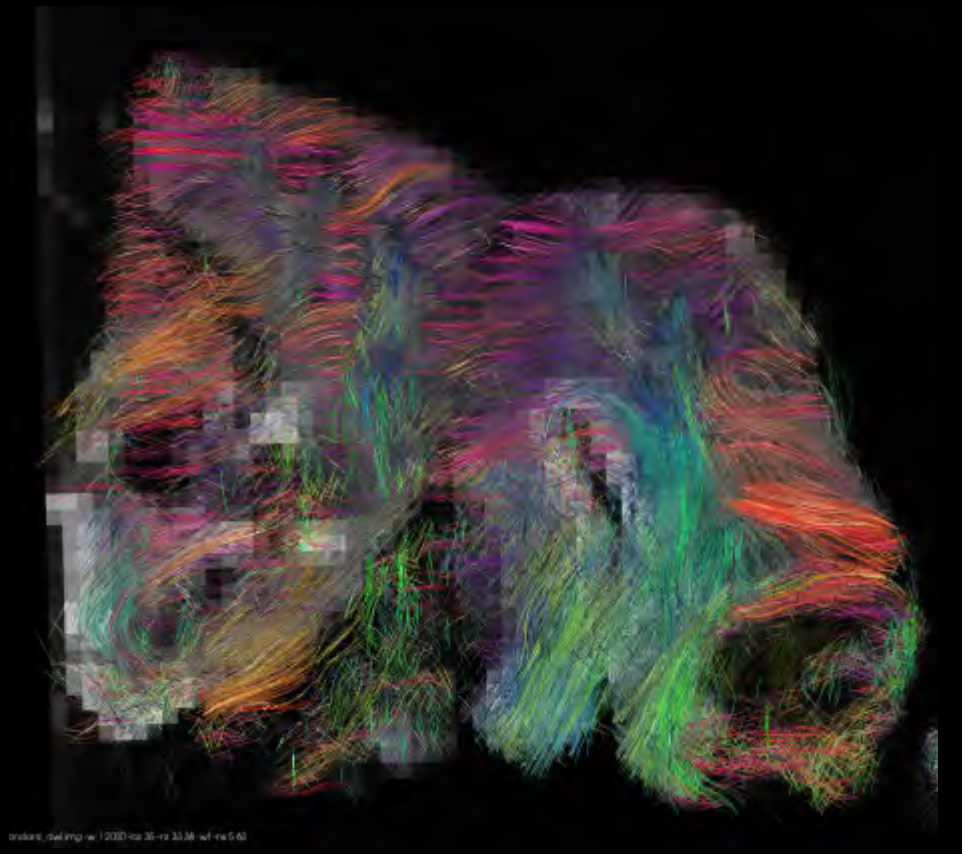
Day 0 *Day 35* *Day 100*



Takahasi et al ISRMR 2008

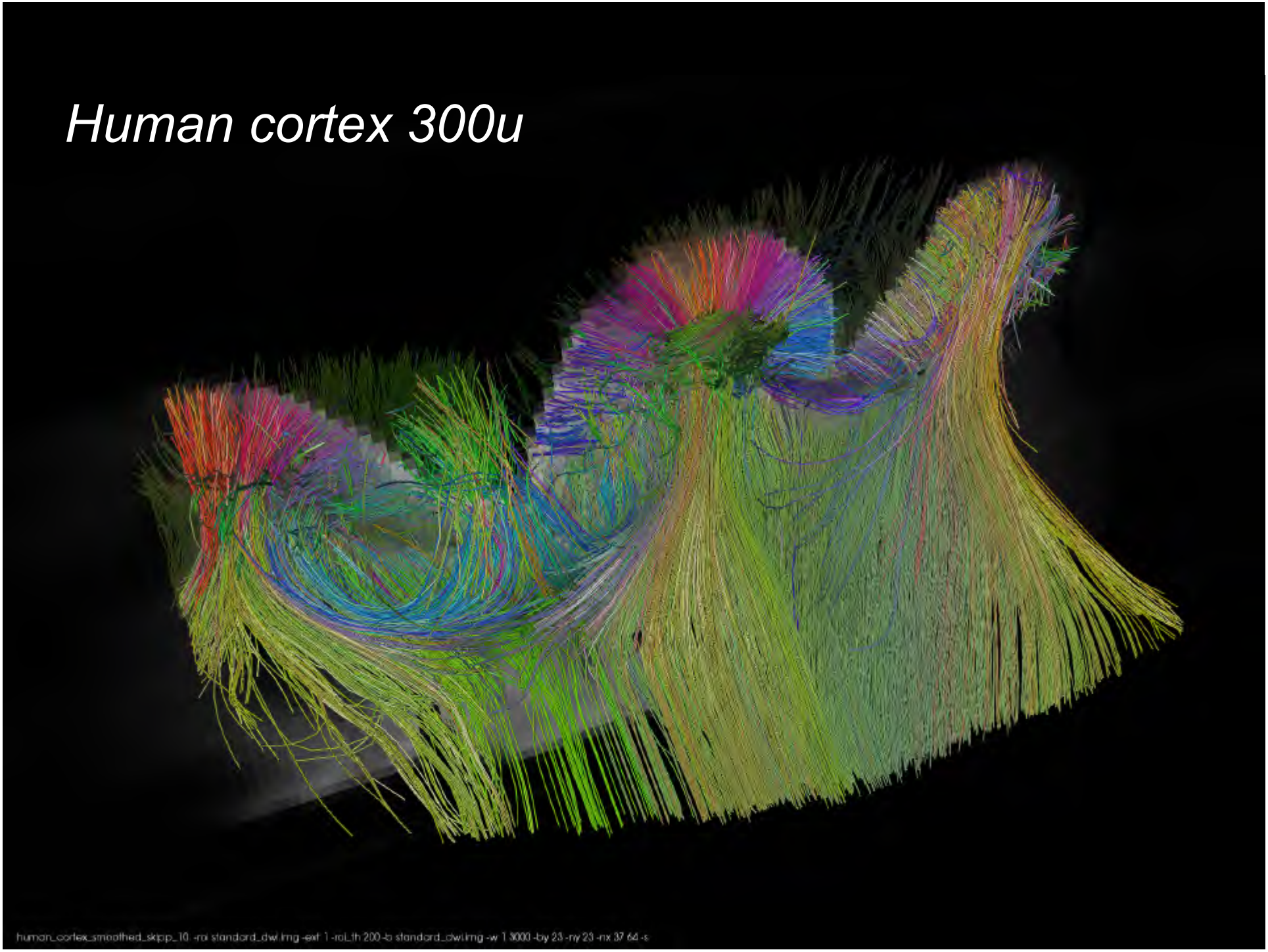
Human cortex specimens
normal control vs. polymicrogyria



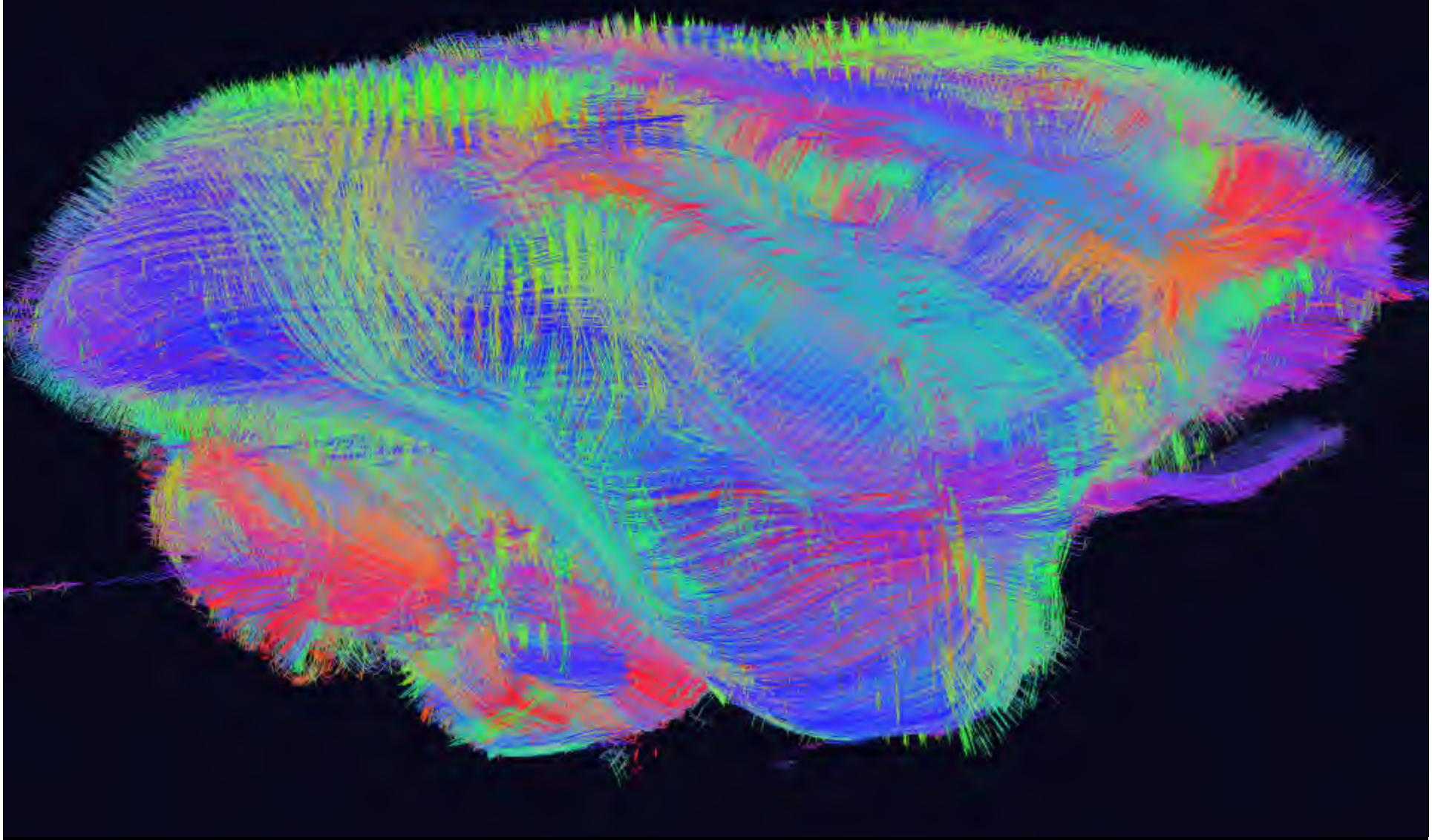


Ellen Grant, RP Wang, A deCrespigny, VJ Wedeen - MGH Radiology

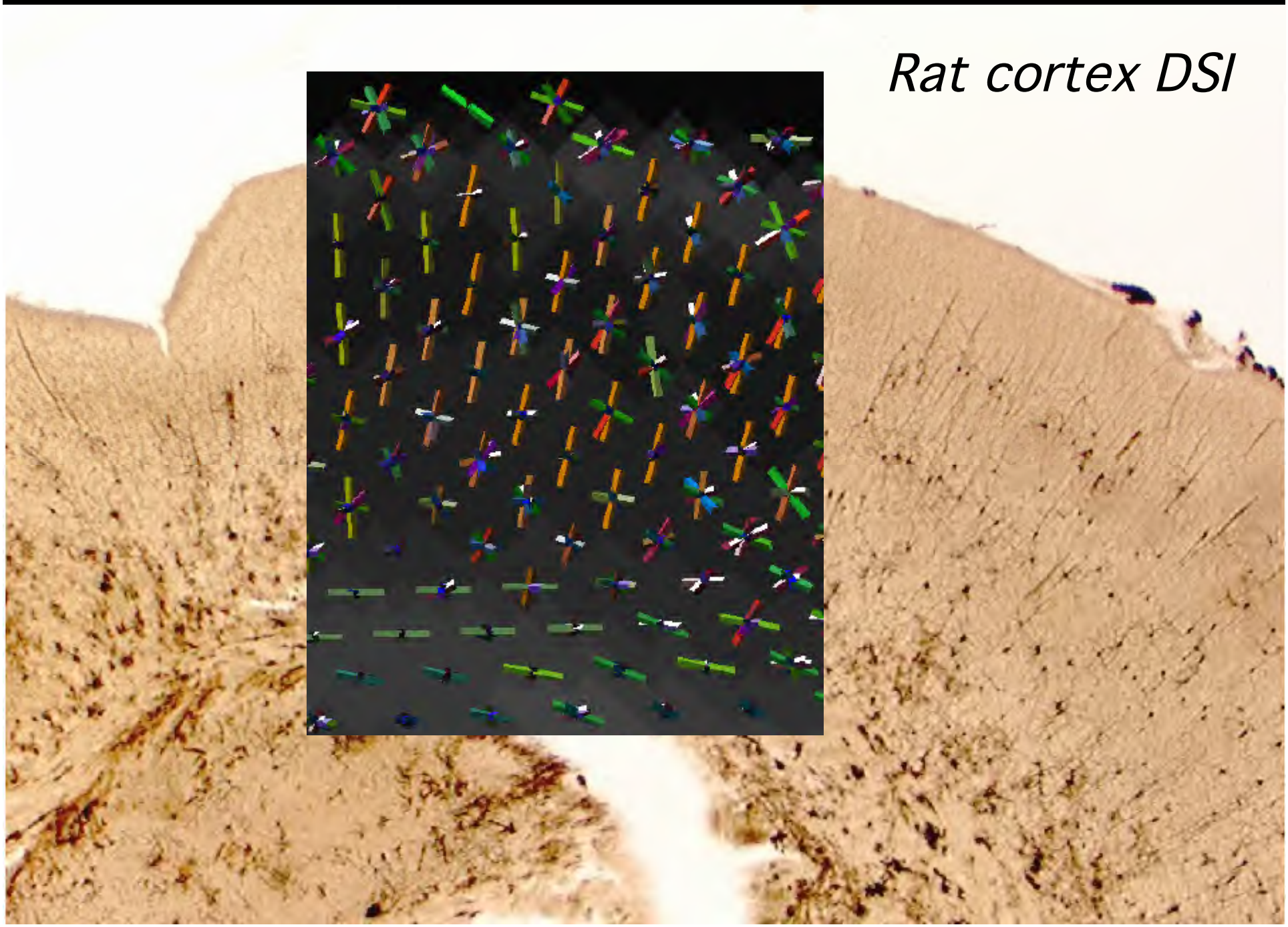
Human cortex 300u



Intracortical connectivity

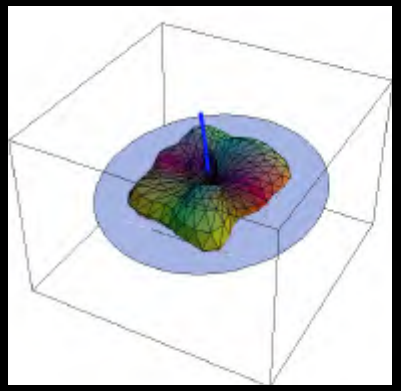


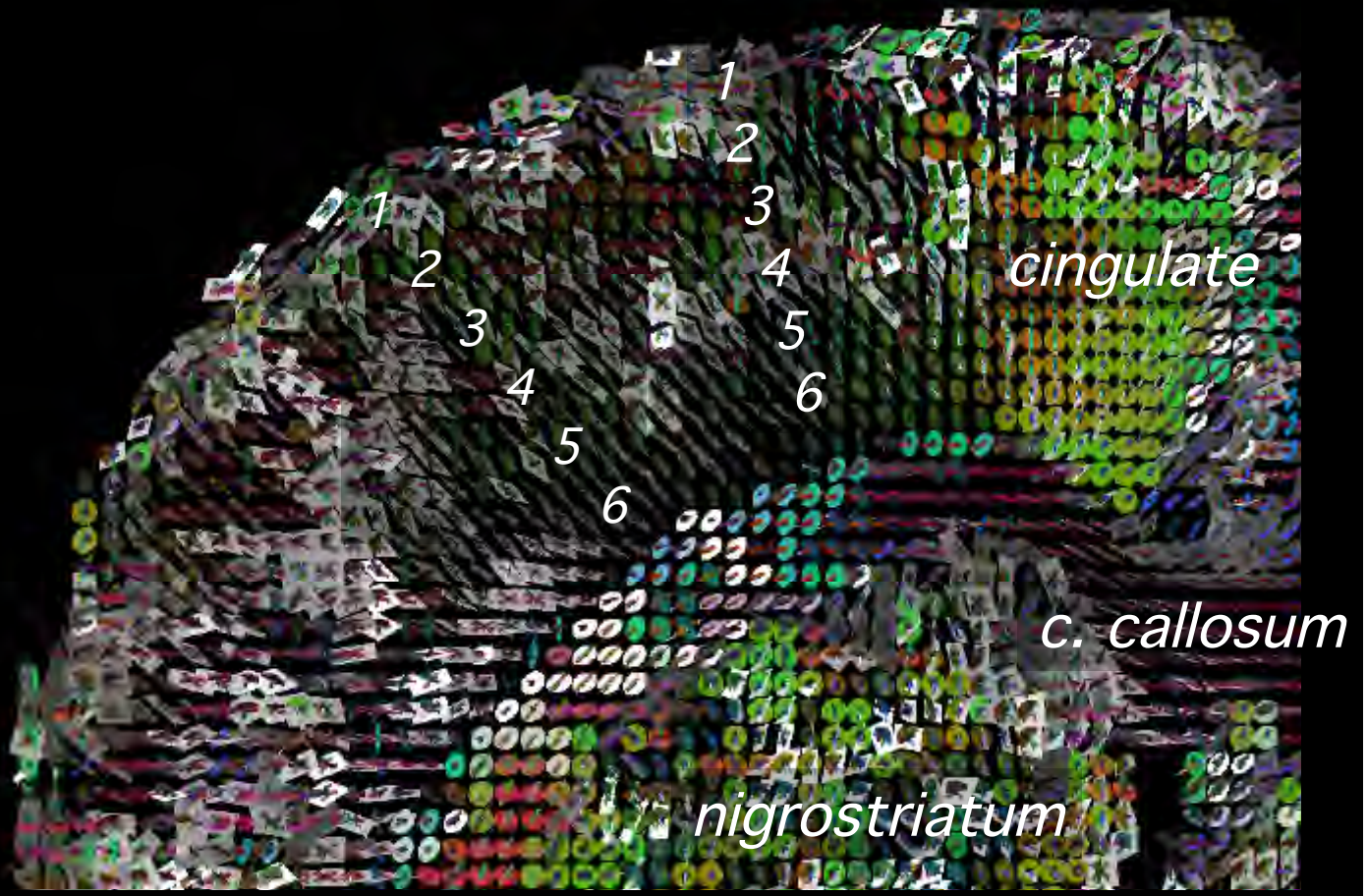
Rat cortex DSI



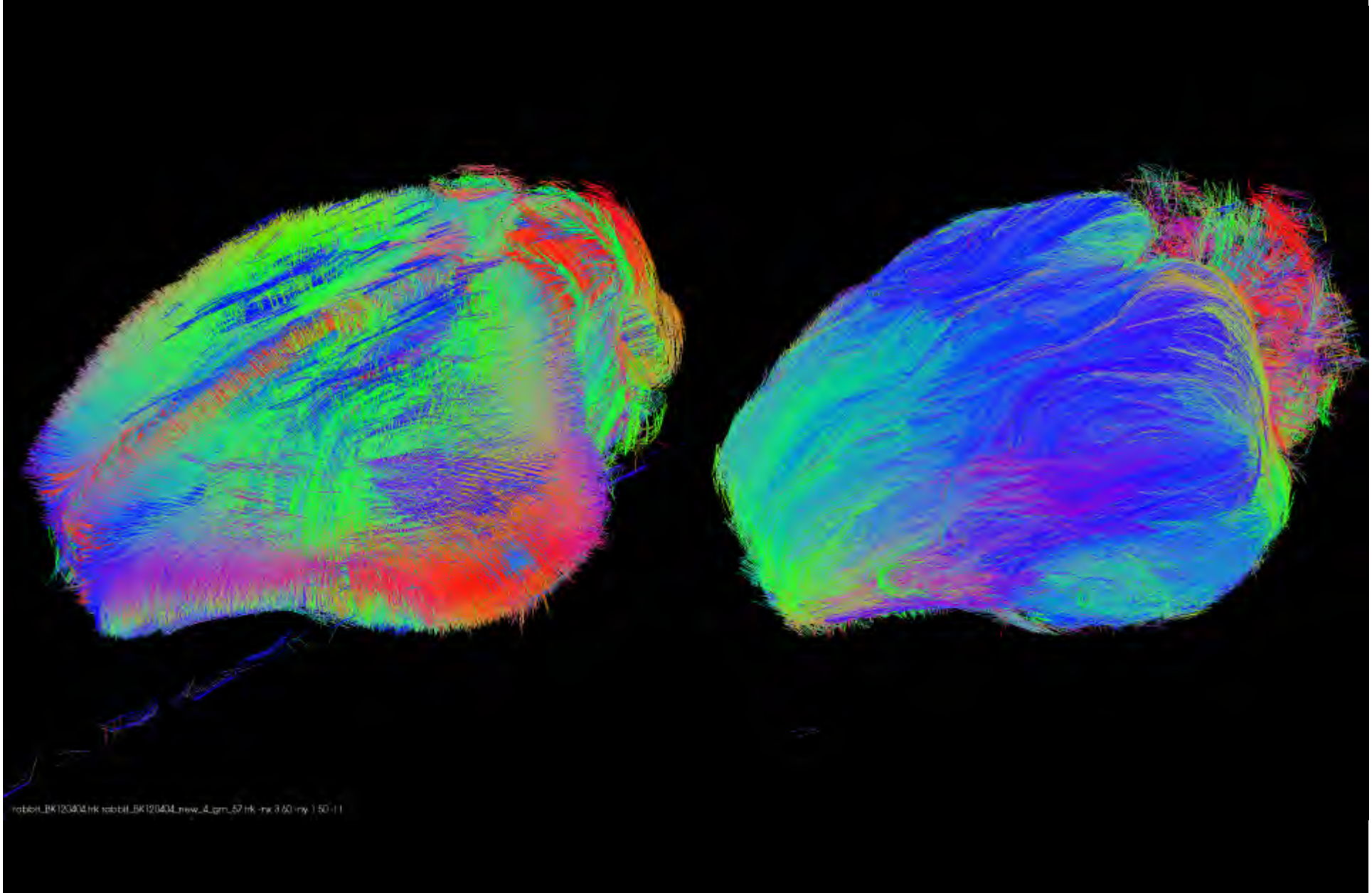
Mouse DSI - planar diffusion reveals cortical structure

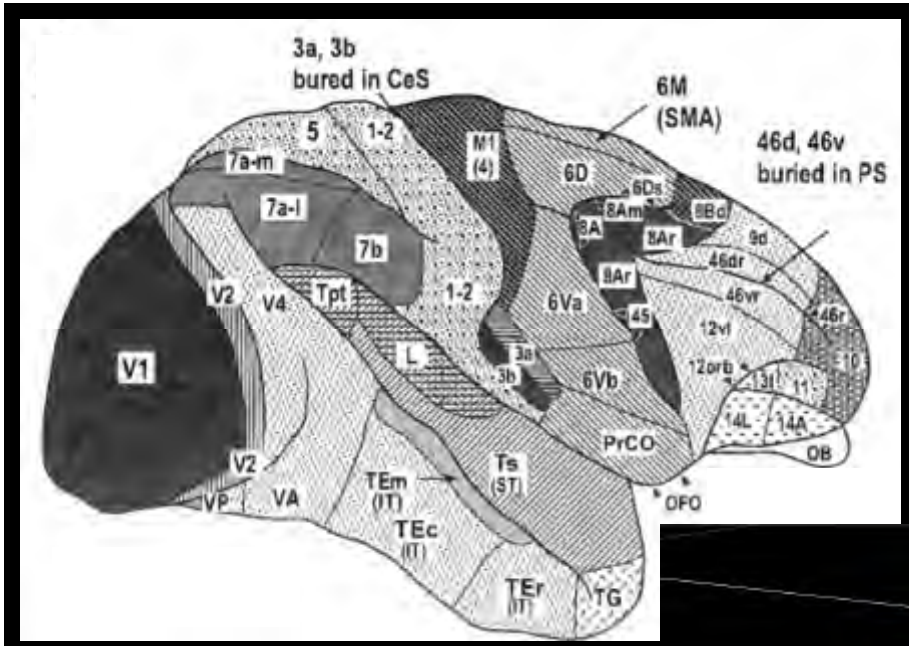
A plane of maximum diffusion





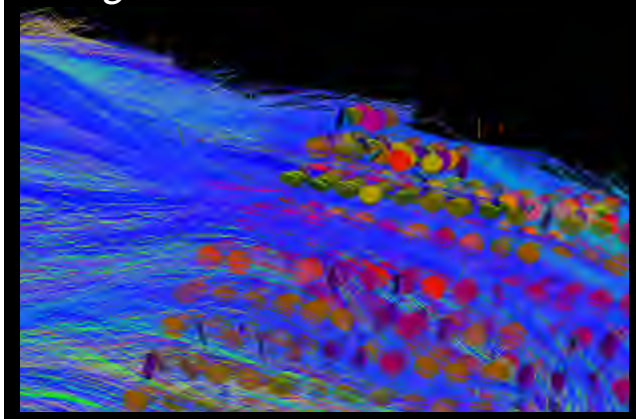
DSI tractography rabbit - conventional (L) and cortex(R)

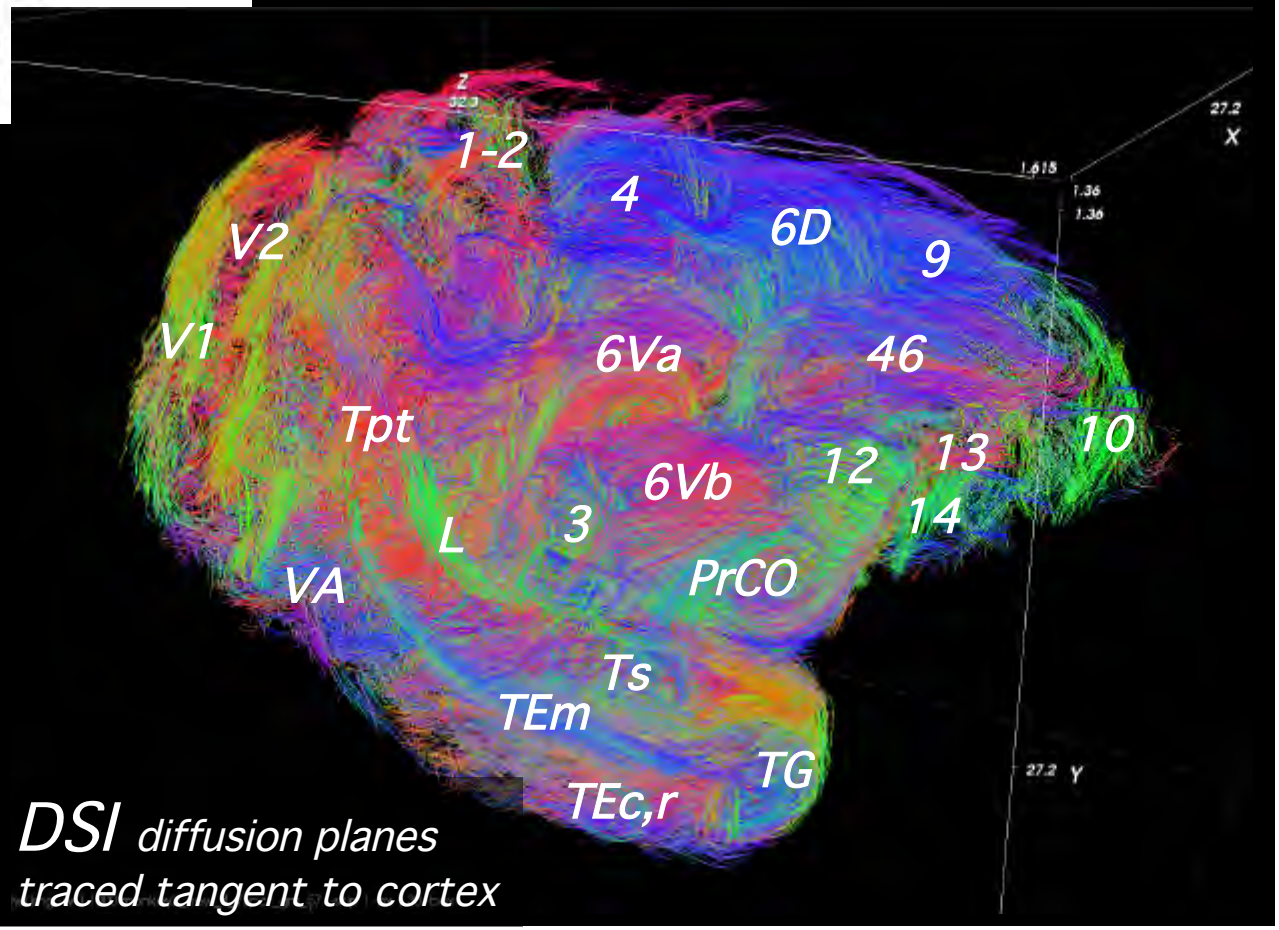




Rhesus monkey cortical paths - a noninvasive Brodmann map?

DSI diffusion planes traced tangent to cortex

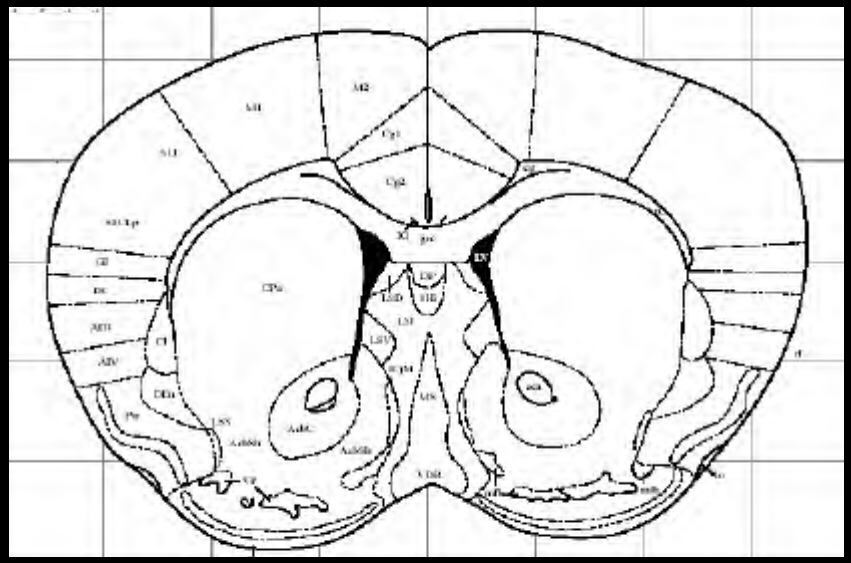




DSI diffusion planes traced tangent to cortex

Mouse brain
automated multivariate spectral segmentation of DSI planar structure

Paxinos atlas



DSI planar structure