

# fMRI Methods Journal Club: DTI

Cabeza, Diaz, and Madden Labs

02/04/13

# Outline for today's discussion

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- ▶ **Theoretical overview of DTI**
  - ▶ What is DTI?
  - ▶ Advantages/Disadvantages to this technique
  - ▶ Some applications of DTI in the literature
- ▶ **Implementing DTI in your lab**
  - ▶ Introduction of available software packages w/ examples
  - ▶ DTI analysis
  - ▶ BIAC pipeline: Connectome Mapper Tool Kit
- ▶ **A complementary tool for investigating white matter**
  - ▶ Lesion Segmentation Tool
- ▶ **Useful papers/links**



# What is DTI?

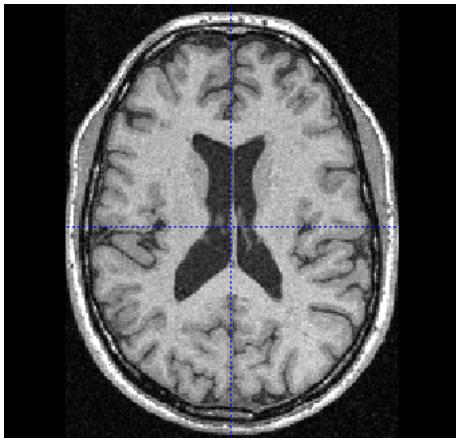
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- ▶ “Diffusion tensor magnetic resonance imaging (DTI) is a non-invasive method to determine the underlying composition and integrity of nerves, neural fibers, etc.”

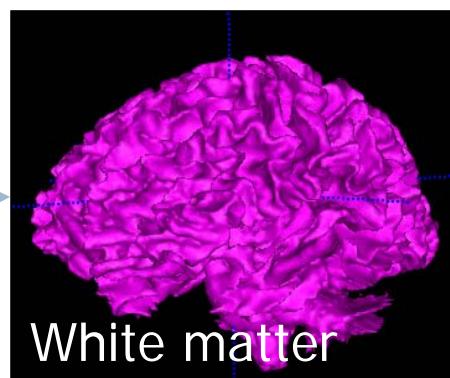
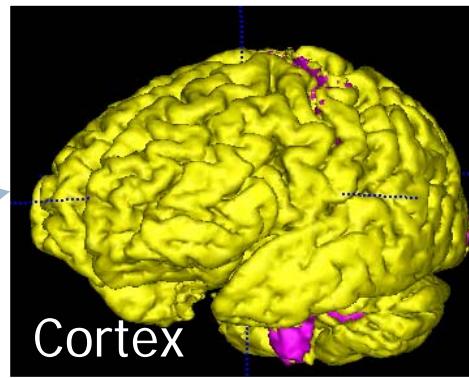
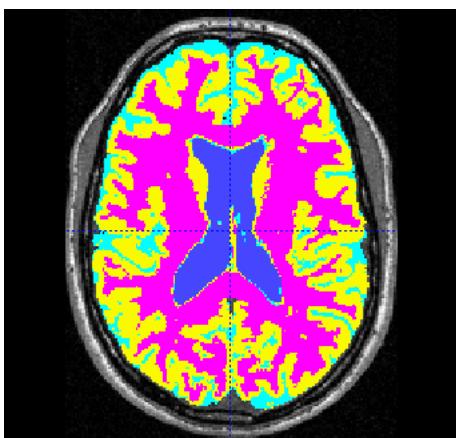
*Beaulieu, NMR Biomed, 2002*



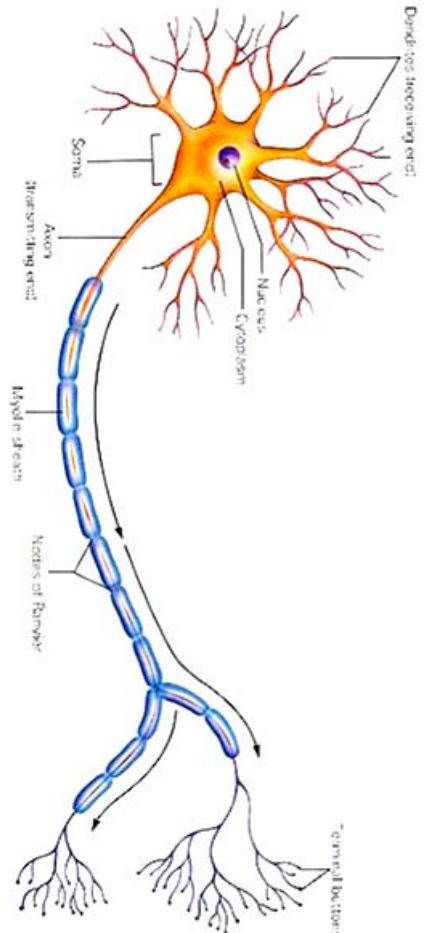
- ▶ Provides a way to look at the other “tissue”, white matter



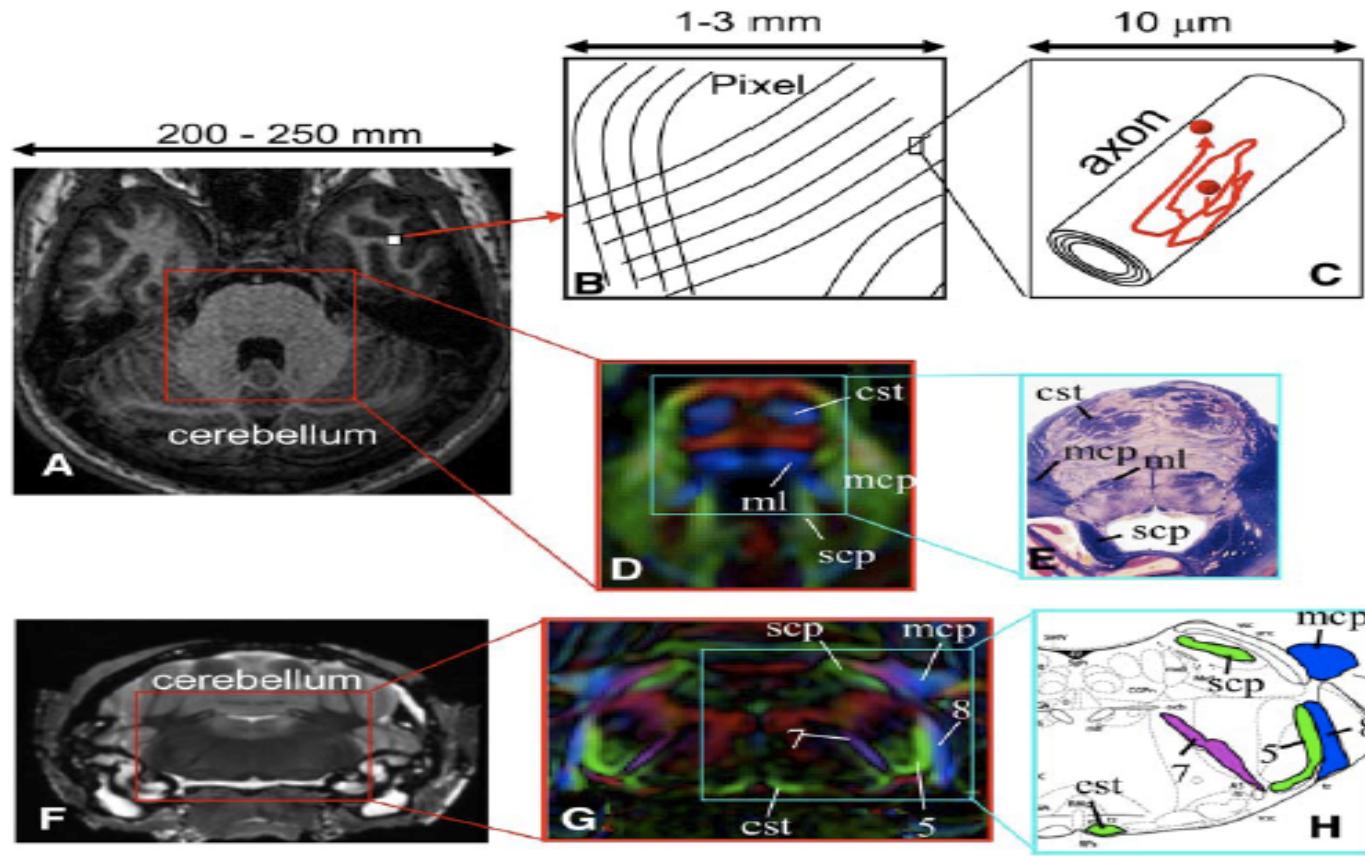
Segmentation



Gray Matter      White Matter  
Cortex              Fibers



# A quick comparison of MRI and DTI images...



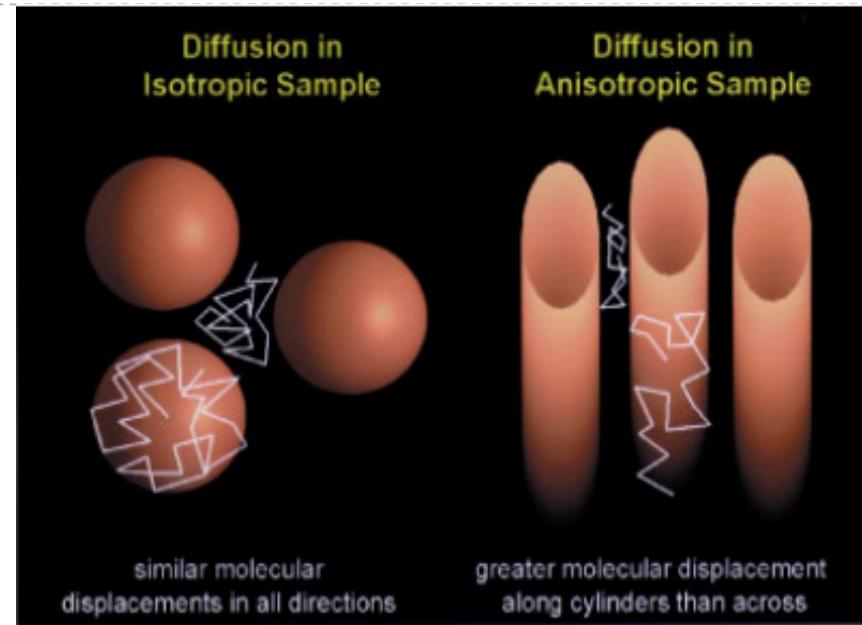
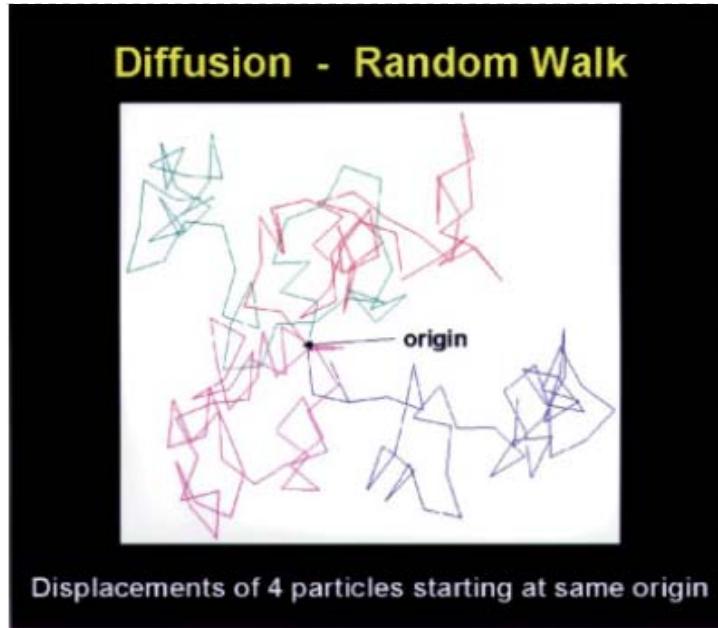
Mori et al, Neuron,  
2006

# What is DTI?

- ▶ Diffusion tensor magnetic resonance imaging (DTI) is a non-invasive method to determine the underlying composition and integrity of nerves, neural fibers, etc.
- ▶ Primarily dependent on the way water diffuses within different brain structures
- ▶ What factors influencing how water diffuses?
  - ▶ Underlying tissue micro-structure (neurons, glia, etc.)
  - ▶ Changes in Temperature (heat)
  - ▶ Viscosity as indexed by the number of molecular-molecular interactions
- ▶ The “difficulty” in the mobility of water molecules to travel may reveal the underlying structure of the tissue



# Two different forms of diffusion...

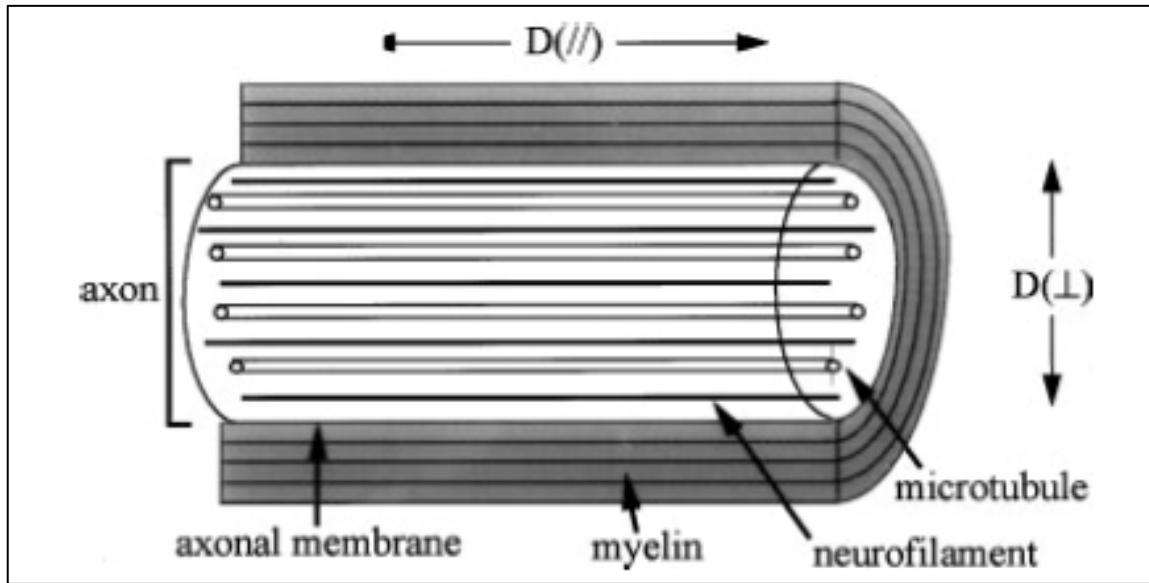


Beaulieu, NMR Biomed, 2002

Beaulieu, NMR Biomed, 2002

- The mobility of molecules is referred to a physical constant, the *diffusion coefficient*, and when measured by DTI, yields a measure called ***apparent diffusion coefficient***
- In isotropic diffusion, diffusion of the molecules is equal in all directions whereas anisotropic diffusion refers to diffusion that is greater in one direction than the rest

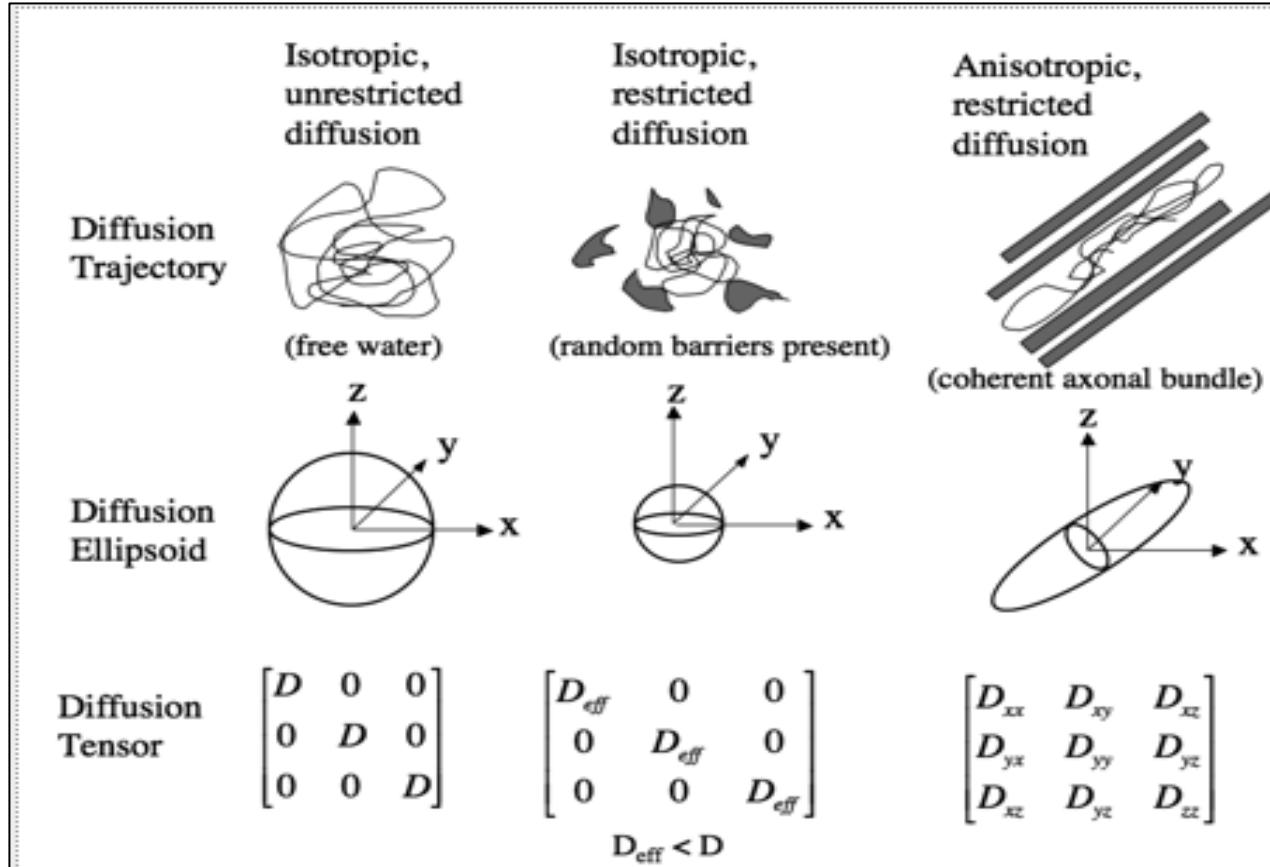
# Potential sources of this anisotropy?



Beaulieu, NMR Biomed, 2002

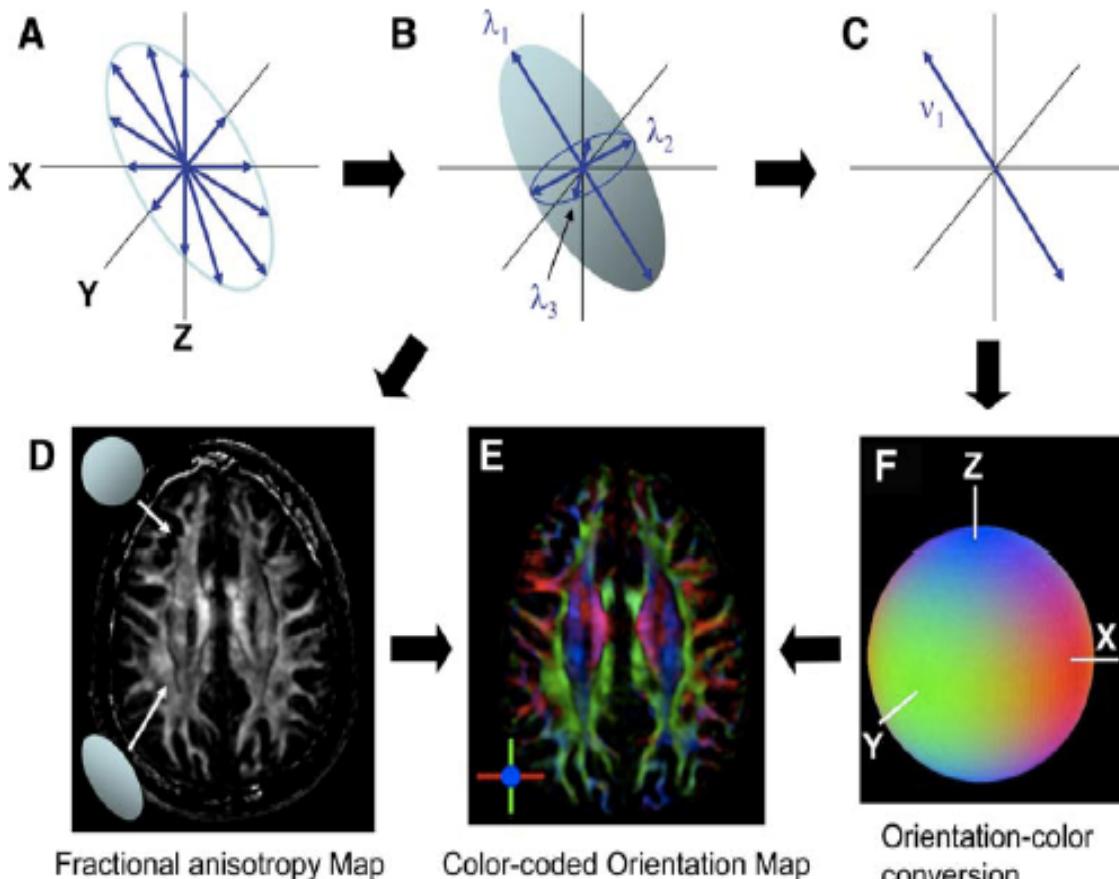
- “Barriers” to optimal mobility to water diffusion perpendicular to the axon could be as shown in this schematic, the axonal membrane, neuro-filament, and microtubule structures

# Diffusion Tensor aids in measuring diffusion along different directions



Mukherjee et al., AJNR, 2008

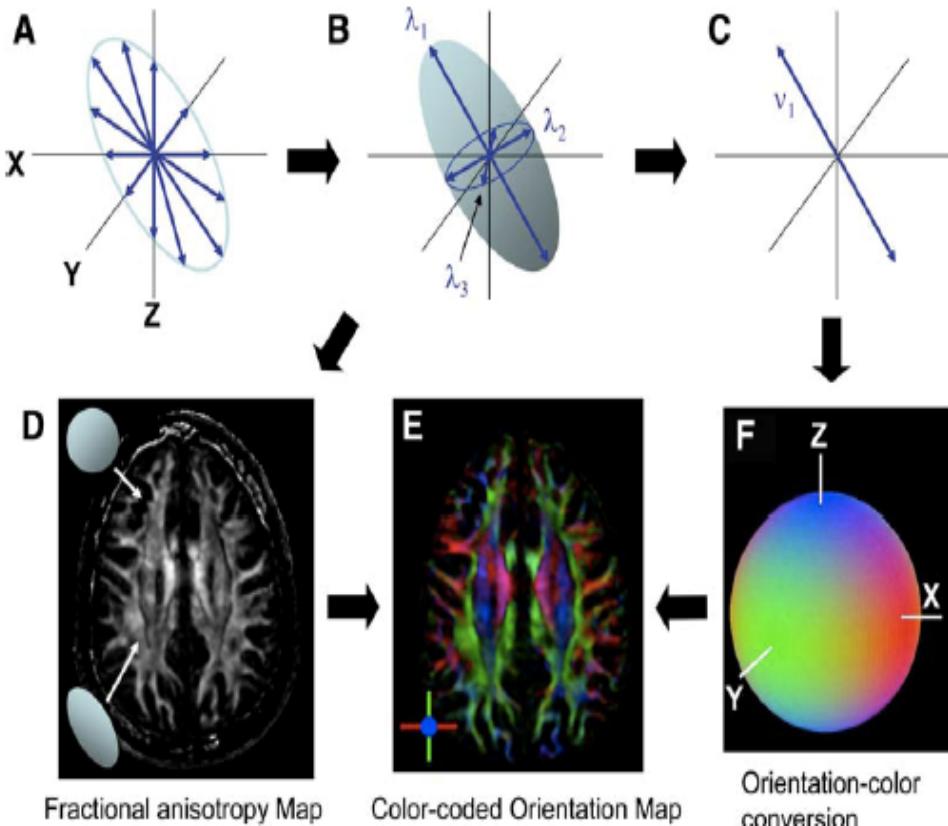
# Anisotropy & Color-coded Orientation



Mori et al, Neuron, 2006

- From a diffusion measurement along multiple axes a “diffusion ellipsoid” is created
- One can get an FA map with darker regions more isotropic than lighter more anisotropic regions
- From this “diffusion ellipsoid” one can get the local fiber orientation by identifying the longest axis
- Color-coded orientation map can then be created; R (left-right), B (sup-inf), G (ant-post)

# Indices one can get from DTI...

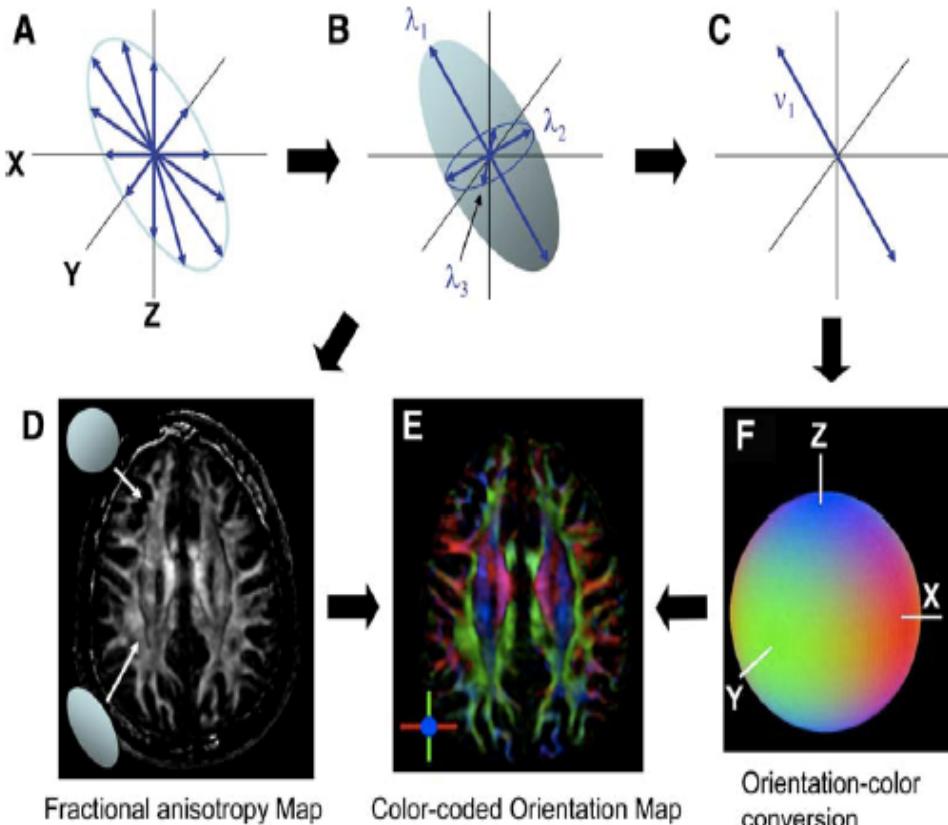


Mori et al, Neuron, 2006

- **Axial Diffusivity (AD)**
  - Reflects diffusivity along the longitudinal/main axis ( $\lambda_1$ )
- **Radial Diffusivity (RD)**
  - Reflects average of the two minor axes ( $\lambda_2 + \lambda_3)/2$
- **Mean Diffusivity (MD)**
  - Reflects average of all three eigenvectors ( $\lambda_1 + \lambda_2 + \lambda_3)/3$
- **Fractional Anisotropy (FA)**
  - Measure that ranges from **0** (isotropic) to **1** (very anisotropic)

$$\sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}$$

# Indices one can get from DTI...



Mori et al, Neuron, 2006

- **Axial Diffusivity (AD)**
  - Reflects diffusivity along the longitudinal/main axis ( $\lambda_1$ )
- **Radial Diffusivity (RD)**
  - Reflects average of the two minor axes  $(\lambda_2 + \lambda_3)/2$
- **Mean Diffusivity (MD)**
  - Reflects average of all three eigenvectors  $(\lambda_1 + \lambda_2 + \lambda_3)/3$
- **Fractional Anisotropy (FA)**
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$$\sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}}}$$

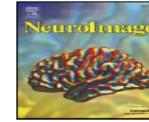
# Examples of studies using DTI...



Contents lists available at ScienceDirect

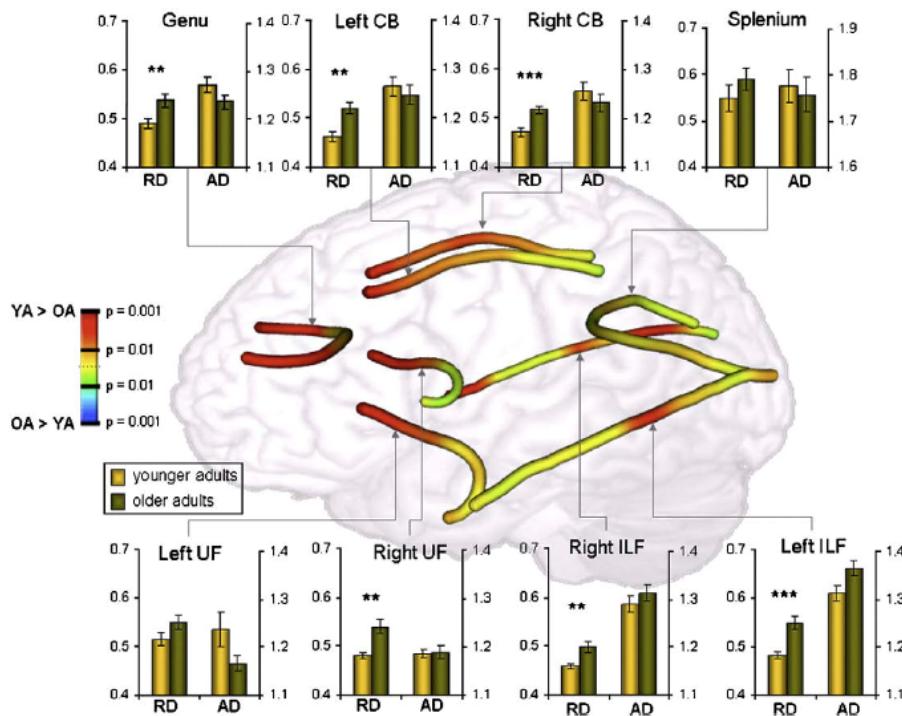
NeuroImage

journal homepage: [www.elsevier.com/locate/ynimsg](http://www.elsevier.com/locate/ynimsg)



## Assessing the effects of age on long white matter tracts using diffusion tensor tractography

Simon W. Davis <sup>a,b,\*</sup>, Nancy A. Dennis <sup>a,c</sup>, Norbou G. Buchler <sup>a,d</sup>, Leonard E. White <sup>c,e</sup>,  
David J. Madden <sup>c,d</sup>, Roberto Cabeza <sup>a,b,c,d</sup>



- Davis and colleagues employed DTI using manual/deterministic tractography and TBSS to look at age-related deficits on long-white matter tracts
- Looked at DTI measures of RD and AD for each of the tracts in younger and older adults
- Study also included neuropsych measures

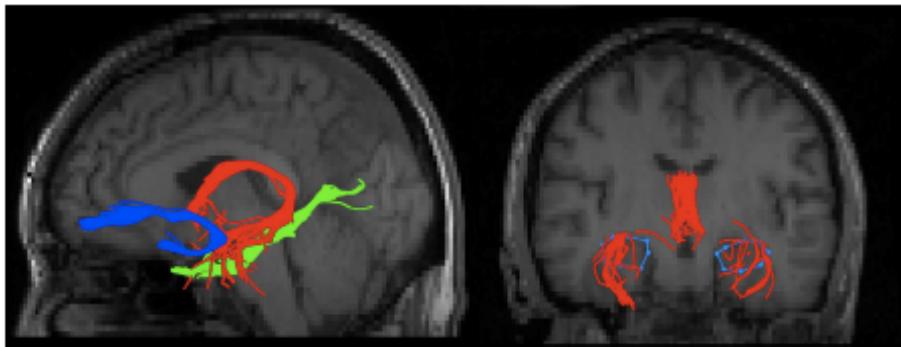
# Examples of studies using DTI...

Behavioral/Systems/Cognitive

## Frontotemporal Connections in Episodic Memory and Aging: A Diffusion MRI Tractography Study

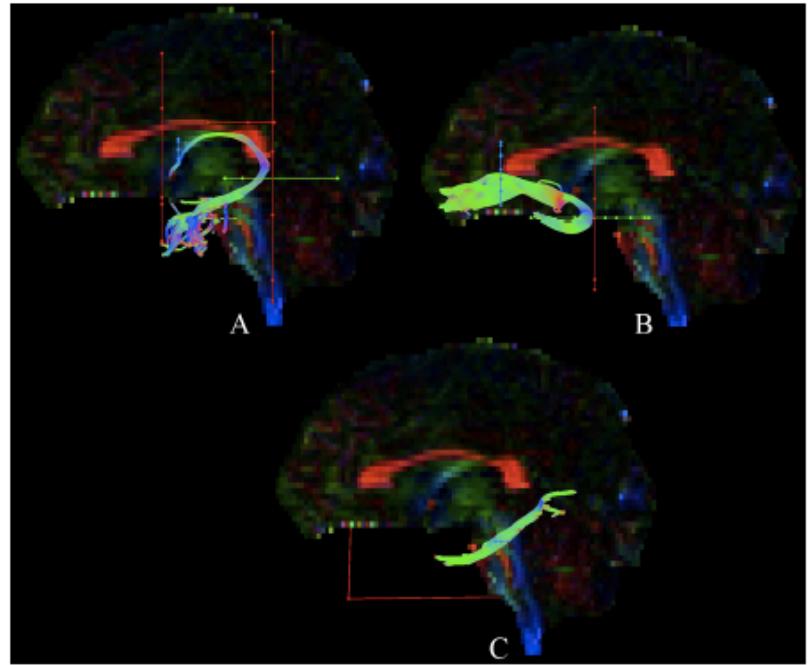
Claudia Metzler-Baddeley,<sup>1</sup> Derek K. Jones,<sup>1</sup> Boubakeur Belaroussi,<sup>2</sup> John P. Aggleton,<sup>1</sup> and Michael J. O'Sullivan<sup>1</sup>

<sup>1</sup>Cardiff University Brain Research Imaging Centre, School of Psychology, and Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff CF10 3AT, United Kingdom, and <sup>2</sup>BioClinica SAS, F-69008 Lyon, France



**Figure 1.** Example of the reconstruction of the fornix (red), uncinate fasciculus (blue), and parahippocampal cingulum (green), registered on a T1-weighted image of one participant in sagittal view. The coronal image shows the fornix in relation to the hippocampus outlined in blue.

➤ Metzler-Baddeley et al., traced tracts (fornix, PHG cingulum, uncinate fasciculus) involving regions that were functionally known to be involved in episodic memory and looked at the underlying structural integrity of the three tracts



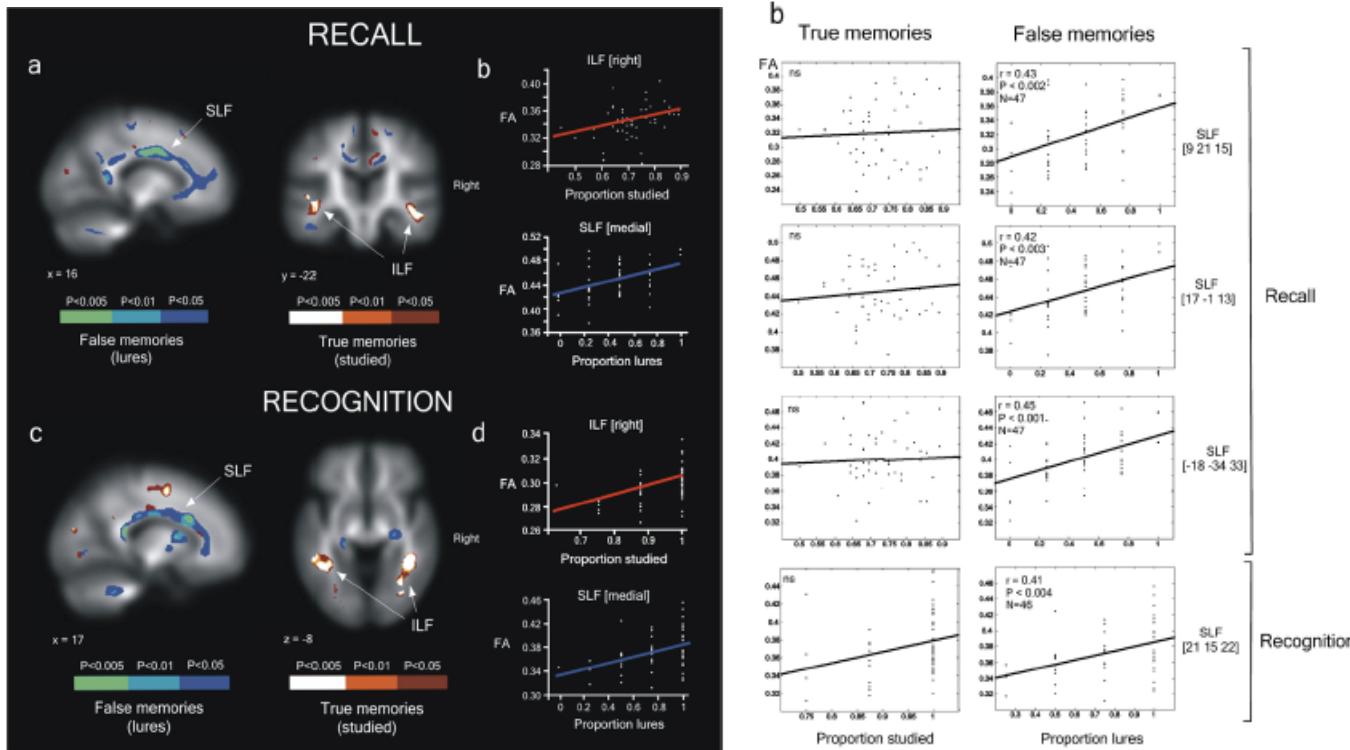
**Figure 2.** Tractography using ROI waypoints (blue, seed point ROIs; green, AND ROIs; red, NOT ROIs; for further details, see Materials and Methods) for the fornix (A), uncinate fasciculus (B), and parahippocampal cingulum (C) in the native space of one participant.

# Examples of studies using DTI...

Brief Communications

## Individual Differences in True and False Memory Retrieval Are Related to White Matter Brain Microstructure

Lluís Fuentemilla,<sup>1,\*</sup> Estela Càmara,<sup>1,2,\*</sup> Thomas F. Münte,<sup>2,3</sup> Ulrike M. Krämer,<sup>2</sup> Toni Cunillera,<sup>1</sup> Josep Marco-Pallarés,<sup>2</sup> Claus Tempelmann,<sup>4</sup> and Antoni Rodriguez-Fornells<sup>1,5</sup>



➤ Fuentemilla et al., were interested in looking at how differences in the accuracy of memory could be driven by anatomical differences as gauged by white matter integrity in “memory-relevant” tracts

# Some Advantages & Disadvantages to DTI...

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## ▶ Advantages

- ▶ Non-invasive and Requires the use of no contrast agents or tracers
- ▶ Works within the existing fMRI framework – no major additional setup required
- ▶ Allows for a more refined understanding of the underlying structural fidelity
- ▶ How does structural connectivity inform functional connectivity and vice versa → DTI via FA indices could help w/ structural connectivity

## ▶ Disadvantages

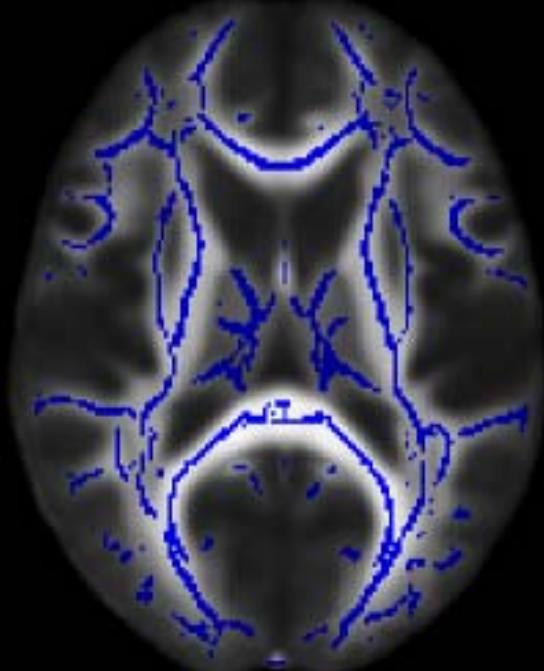
- ▶ DTI is sensitive to noise and motion impacting SNR & tractography
- ▶ Problems with tensor fitting and diffusion-weighting gradients



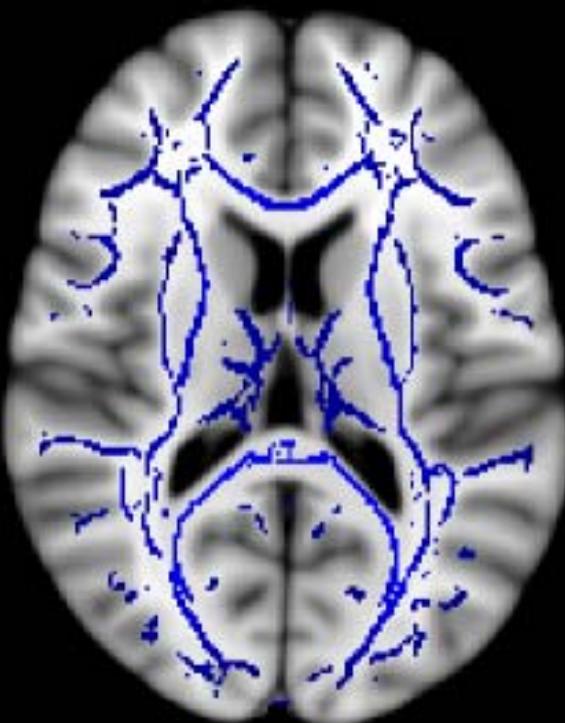
# FSL's TBSS: Tract-Based Spatial Statistics

- <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>

FMRI58\_FA-skeleton\_1mm.nii.gz



FMRI58\_FA\_1mm.nii.gz



MNI152\_T1\_1mm\_brain.nii.gz

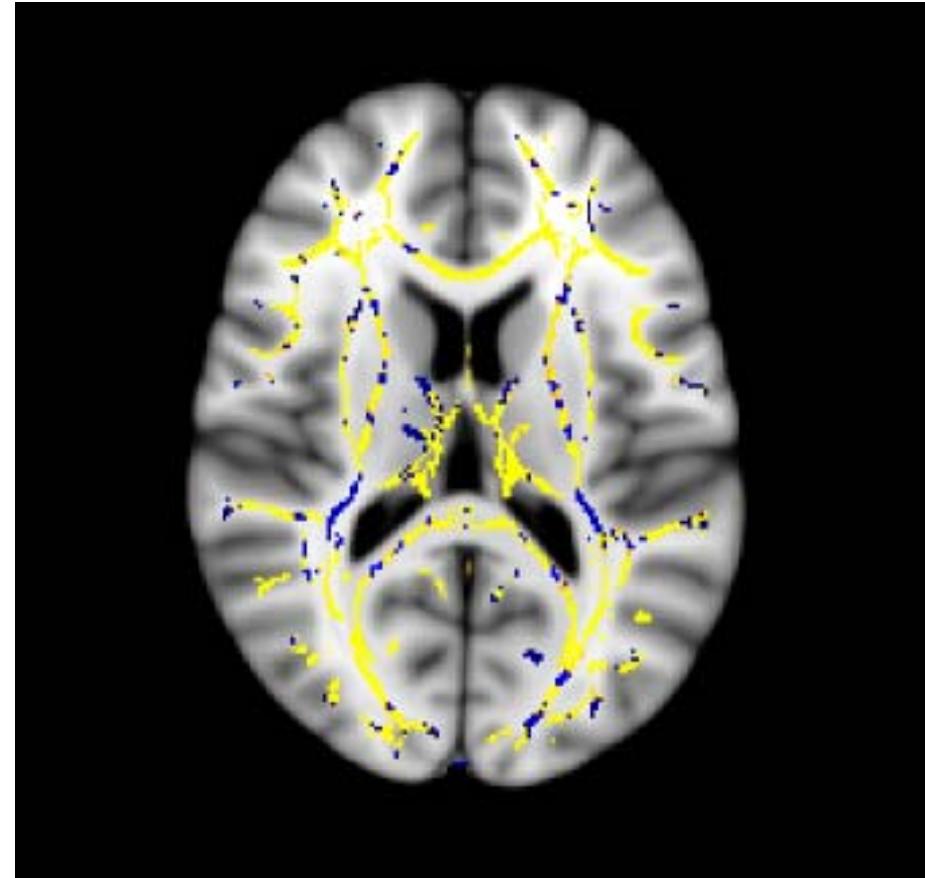
# Skeleton-based stats with FSL's *randomise*

<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise>

<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>

design\_ttest2 design 4 4

<u>test_groups.mat</u>	<u>test_groups.con</u>
/NumWaves 2	/NumWaves 2
/NumPoints 8	/NumContrasts 2
/PPheights 1 1	/PPheights 1 1
/Matrix	/Matrix
1 0	1 -1
1 0	-1 1
1 0	
1 0	
0 1	
0 1	
0 1	
0 1	



**Example of code to run "randomise"**

```
randomise -i all_FA_skeletonised.nii.gz -o test_groups
-m mean_FA_skeleton_mask.nii.gz -d test_groups.mat
-t test_groups.con -n 1000 -T2 -V
```

test\_groups\_tfce\_corrp\_tstat2.nii.gz

# TBSS code

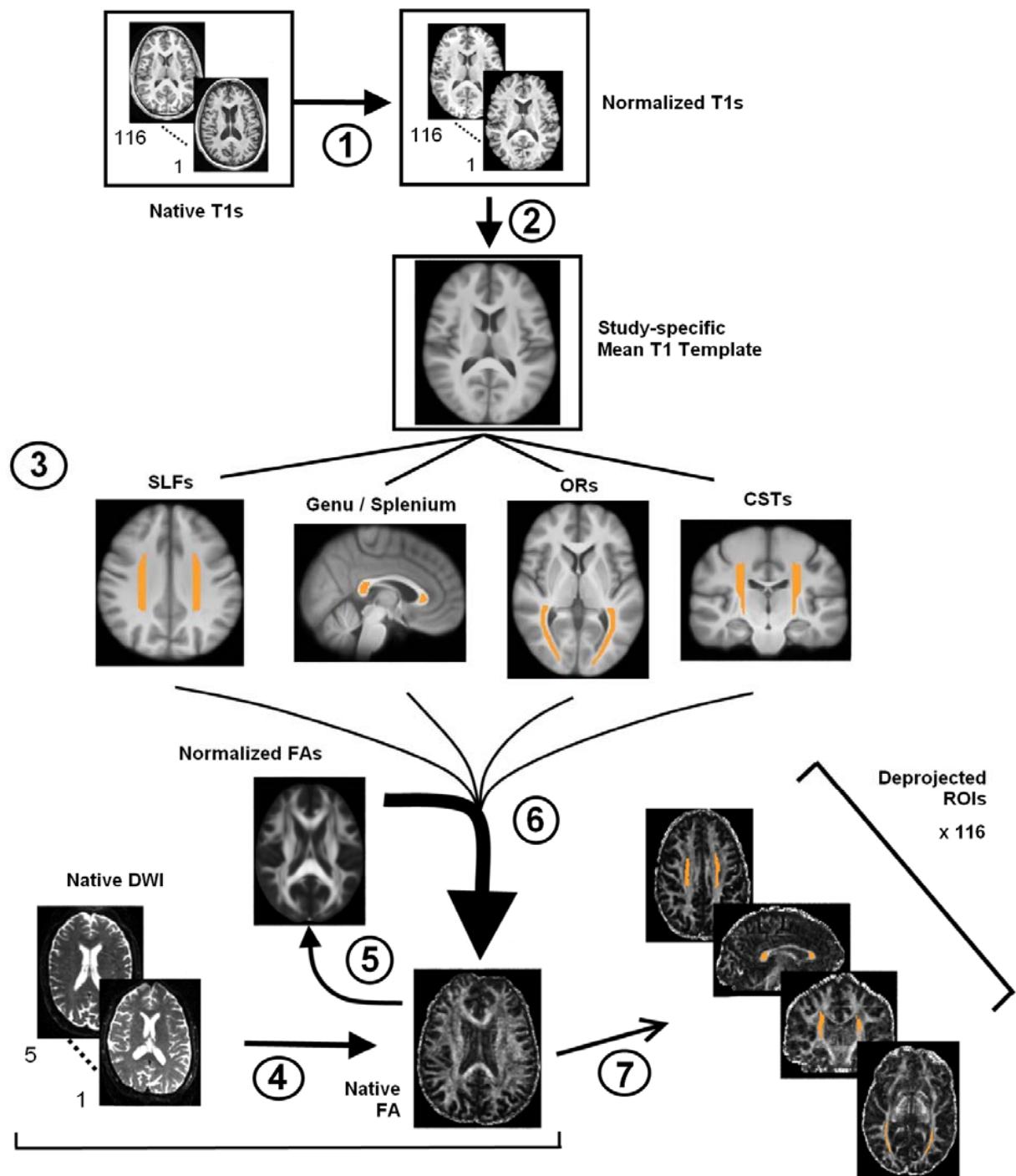
<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>

- 1) tbss\_1\_preproc \*.nii.gz
- 2) tbss\_2\_reg -T
  - Or, tbss\_2\_reg -n (for study-specific option, see website)
- 3) tbss\_3\_postreg -T
  - Or, tbss\_3\_postreg -S (for study-specific option, see website)
- 4) tbss\_4\_prestats 0.2 (to threshold meanFA skeleton and create all\_FA\_skeletonised.nii.gz)

Alternatively, for Steps 2 & 3, you could use the following FSL functions:

- fsl\_reg \${subj}\_FA \${FSLDIR}/data/standard/FMRIB58\_FA\_1mm \${subj}\_to\_FMRIB58\_FA
  - For registration, which is what the tbss\_2\_reg is doing anyway
- fslmerge -a all\_FA \*to\_FMRIB58.nii.gz
  - creates a 4D file with all subjects' registered FA images
- fslmaths all\_FA -max 0 -Tmin -bin mean\_FA\_mask -odt char
  - Create mean\_FA\_mask.nii.gz
- # ## to use the TBSS mean\_FA template (FMRIB58) and create skeleton
- fslmaths \$FSLDIR/data/standard/FMRIB58\_FA\_1mm -mas mean\_FA\_mask mean\_FA
- fslmaths mean\_FA -bin mean\_FA\_mask
- fslmaths all\_FA -mas mean\_FA\_mask all\_FA
- \$FSLDIR/bin/imcp \$FSLDIR/data/standard/FMRIB58\_FA-skeleton\_1mm mean\_FA\_skeleton

# Semi-automated ROI definition and deprojection method



# ROI deprojection code

- \* NOTE: FOR ALL THESE FSL FUNCTIONS, TO LEARN MORE ABOUT THE FUNCTION OR PARAMETER OPTIONS, TYPE THE NAME OF THE FUNCTION IN AN INTERACTIVE NODE
- **Register all subjects' T1 images (e.g., "...\_anat\_...nii.gz") to MNI T1 template**
  - for j in `\$FSLDIR/bin/imglob \*\_anat\_\*` ; do
  - flirt -ref \${FSLDIR}/data/standard/MNI152\_T1\_1mm\_brain -in \$j -omat \${OUTPUTDIR}/\${j}\_to\_MNI\_aff.mat -out \${OUTPUTDIR}/\${j}\_flirted
  - fnirt --in=\$j --aff=\${OUTPUTDIR}/\${j}\_to\_MNI\_aff.mat --  
cout=\${OUTPUTDIR}/\${j}\_to\_MNI\_nonlin\_warps --config=T1\_2\_MNI152\_2mm --  
ref=\${FSLDIR}/data/standard/MNI152\_T1\_1mm\_brain --  
refmask=\${FSLDIR}/data/standard/MNI152\_T1\_1mm\_brain\_mask
  - applywarp --ref=\${FSLDIR}/data/standard/MNI152\_T1\_1mm\_brain --in=\${j} --  
warp=\${OUTPUTDIR}/\${j}\_to\_MNI\_nonlin\_warps --out=\${OUTPUTDIR}/\${j}\_in\_MNI
  - done
- **Register (nonlinearly) a subject's FA image to MNI's FA template**
  - Fsl\_reg subj\_FA \${FSLDIR}/data/standard/FMRIB58\_FA\_1mm subj\_to\_FMRIB58\_FA
- **Get the inverse nonlinear registration transformation parameters**
  - invwarp --ref=subj\_FA -- warp=subj\_to\_FMRIB58\_warp --out=FMRIB58\_into\_subj\_warp
- **Deproject an ROI using the inverse warp**
  - applywarp –ref=subj\_FA –in=ROI.nii.gz –warp=FMRIB58\_into\_subj\_warp –out=ROI\_in\_subj\_FA

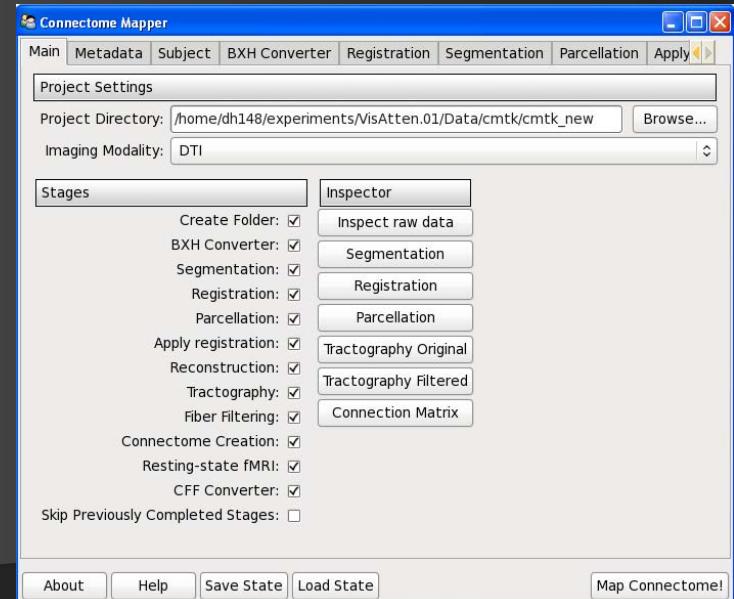
# Tractography

CMTK Pipeline -> TrackVis

# Connectome Mapping Tool Kit (CMTK)

Image processing pipeline that integrates

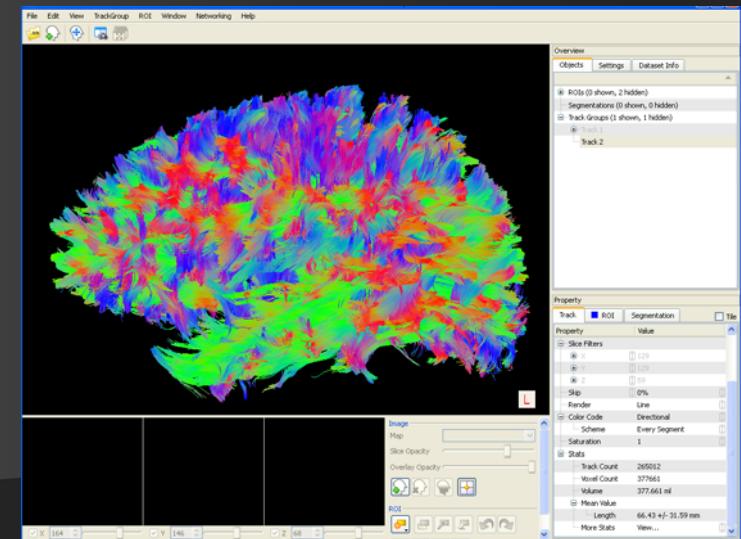
- Anatomical (T1/T2)
- Resting State fMRI
  - BIAC RS pipeline
- Diffusion Tensor Imaging
  - Via Diffusion Toolkit (DTK)
- BIAC-connectomemapper



# TrackVis

## Fiber tracking visualization and analysis

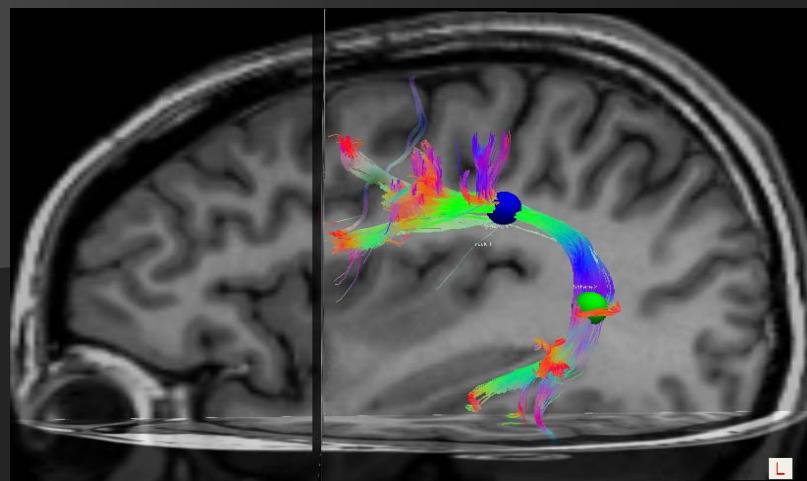
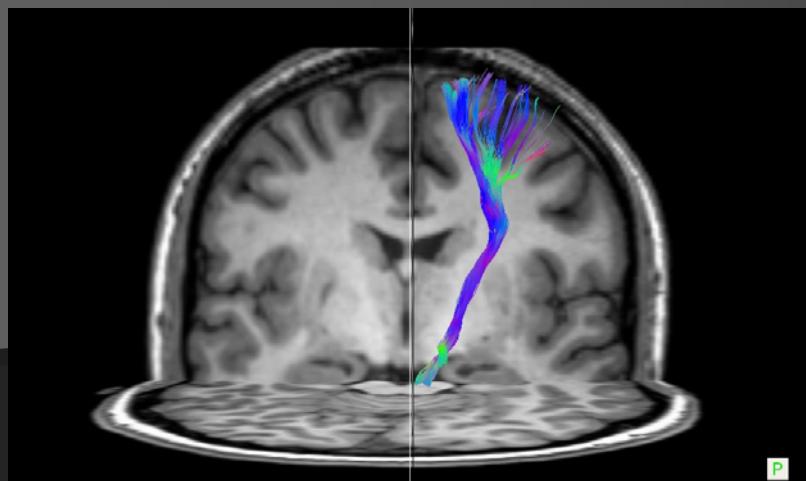
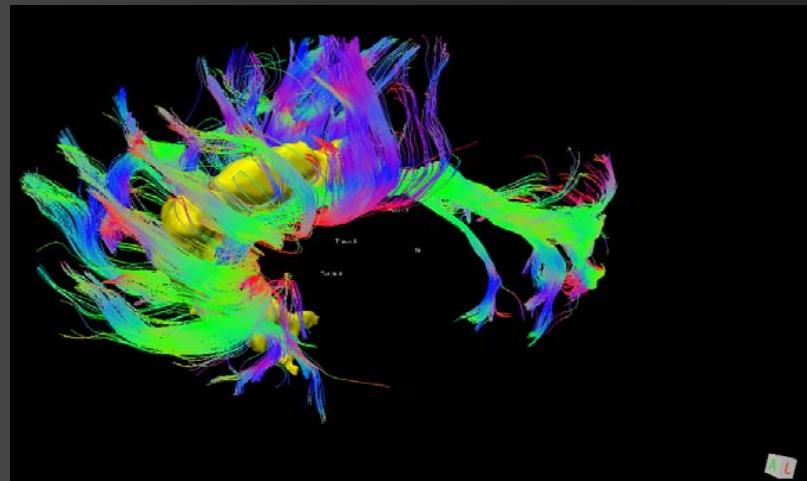
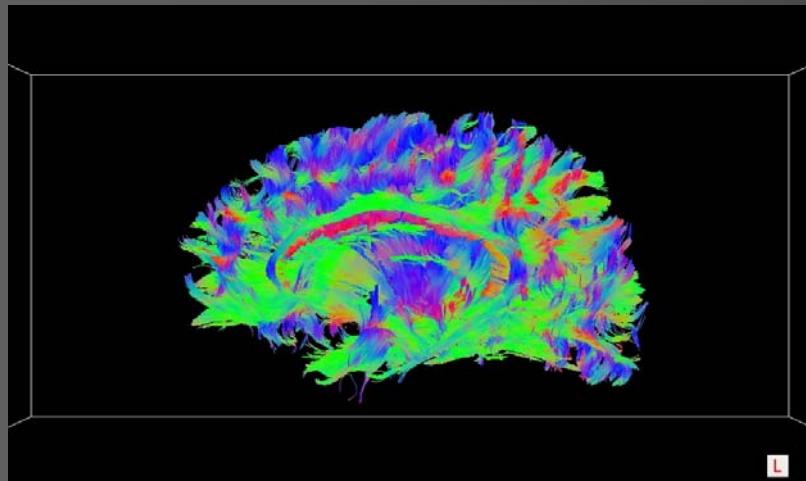
- Provides statistics such as track count, volume, and fiber length
- Numerous filtering options
- ROI placement within tracts



# What you need

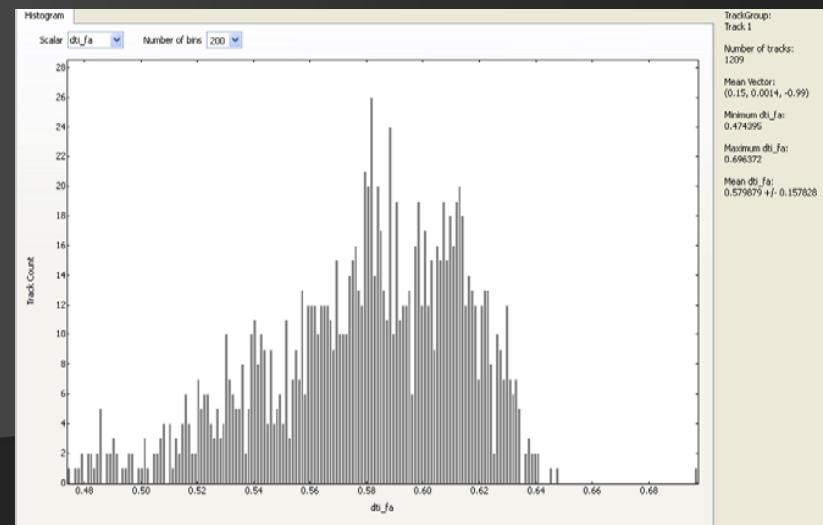
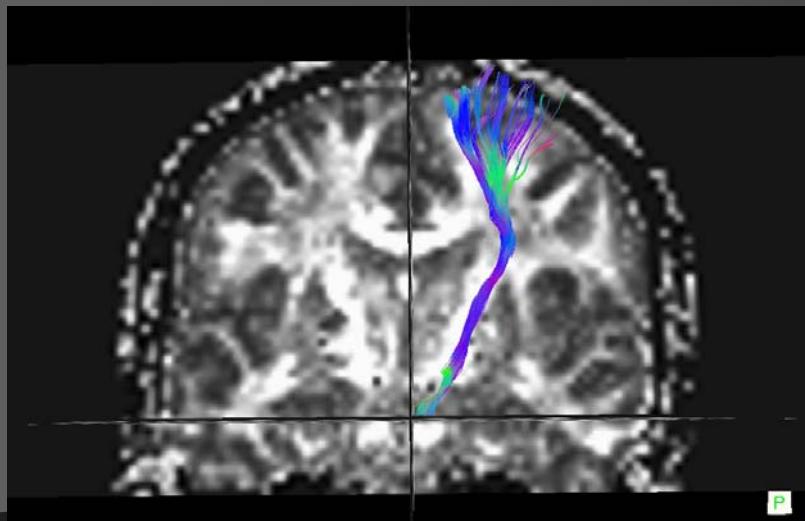
- CMTK
  - DTI data with BXH headers
  - Anatomical T1 images for registration (.bxh)
  - Cluster access
- TrackVis
  - .trk file output from CMTK
  - Newer computer with 1-2GB memory

# What you get



# TrackVis

- Overlay scalar maps generated in participant space
- Provides statistics such as FA, RD, and MD



# Limitations

- All steps must be run (12+ hours)
- Post-hoc WM seeding by default
  - Whole brain tractography using freesurfer GM atlas
- TrackVis forces  $2 \times 2 \times 2$  for visualization
- TrackVis is very memory/graphics intensive

# Helpful links

- CMTK - [connectomics.org](http://connectomics.org)
- TrackVis - [trackvis.org](http://trackvis.org)
- BIAC - [wiki.biac.duke.edu](http://wiki.biac.duke.edu)

# Lesion Segmentation Tool (LST)

fMRI Methods Journal Club  
February 4, 2013

# Automated Lesion Segmentation

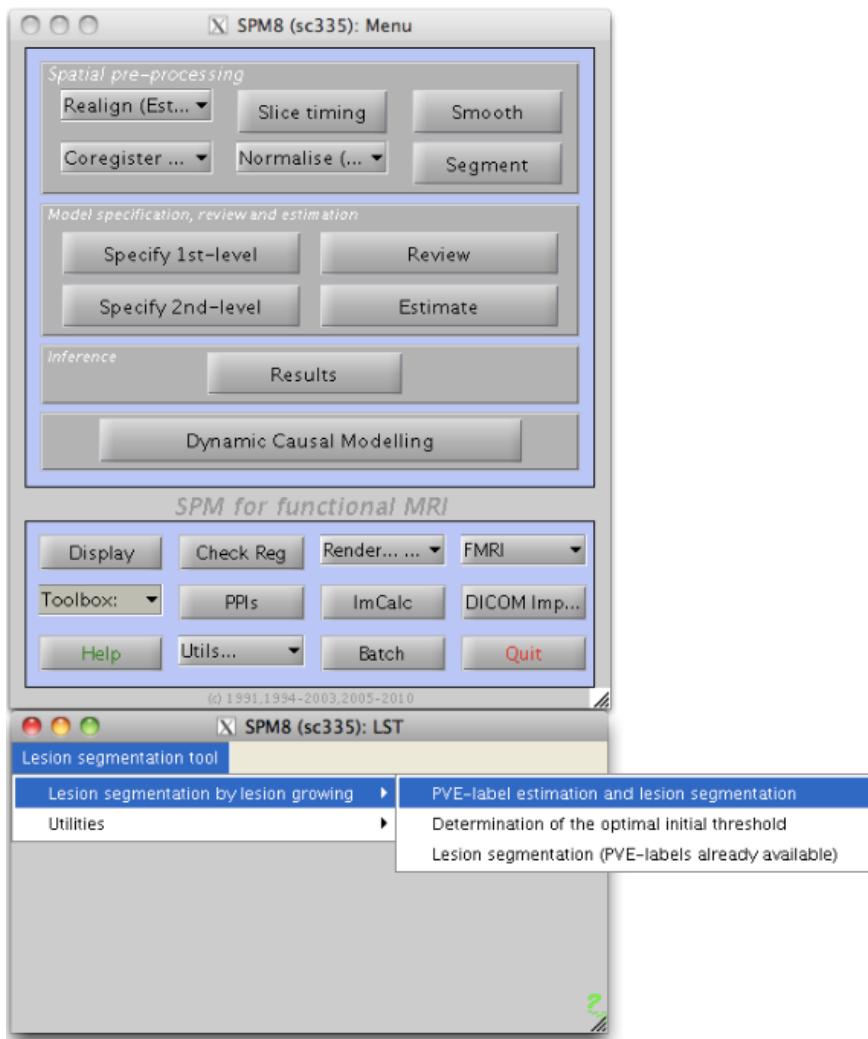
- Lesion : any abnormality in tissue due to injury or disease
- **Lesion Segmentation Tool (LST): white matter lesion detection**
  - **lesion growth algorithm**
    - Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V.J., Zimmer, C., Hemmer, B., and Muhlau, M., 2012. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage* 59, 3774-3783.
  - **open source toolbox in SPM**
  - **technical aspects:**
    - Java VM for MATLAB: Increase heap space using Java.opts
    - minimum of 10G requested on cluster

Find voxel intensities  
↓  
Segment voxels into tissue classes  
*derived from T1 image*

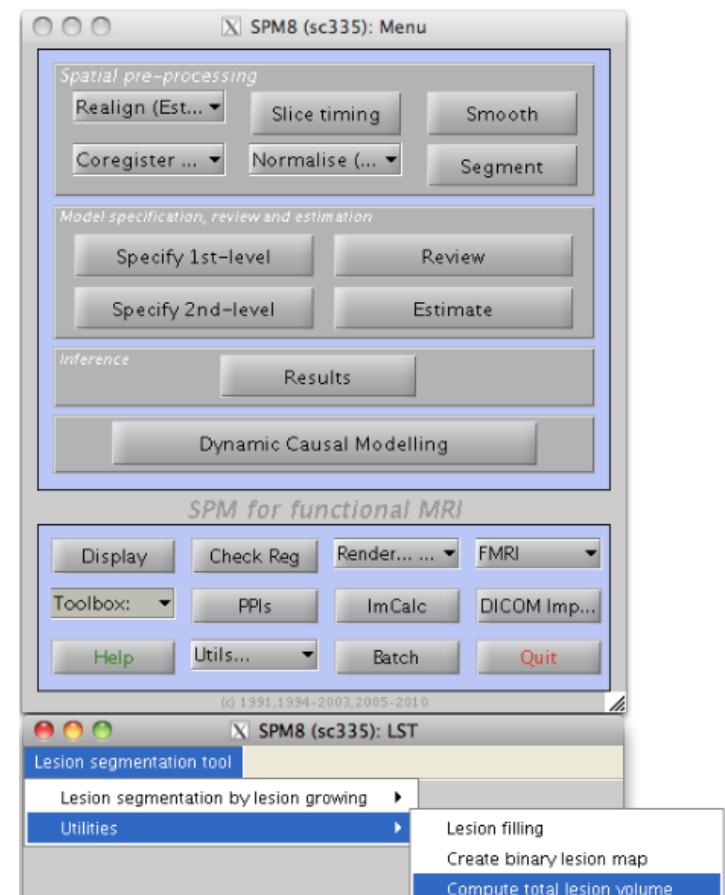
Find voxels that are hyper-intense outliers of each tissue class  
↓  
Detection of lesions  
*derived from T2 FLAIR image coregistered to T1*

# LST Module and Utilities

Lesion maps in T1 space



Volume of lesion load (mL)



# LST Input

Batch Editor

File Edit View SPM BasicIO Toy Example

Module List

PVE label estimation and lesion segmentation

Help on: PVE label estimation and lesion segmentation

T1 volumes <-X  
FLAIR volumes <-X

Options for lesion segmentation

- . Initial threshold ...ubie
- . Lesion belief map GM
- . MRF parameter 1
- . Maximum iterations 50
- . Threshold for binary lesion map 0

Writing options

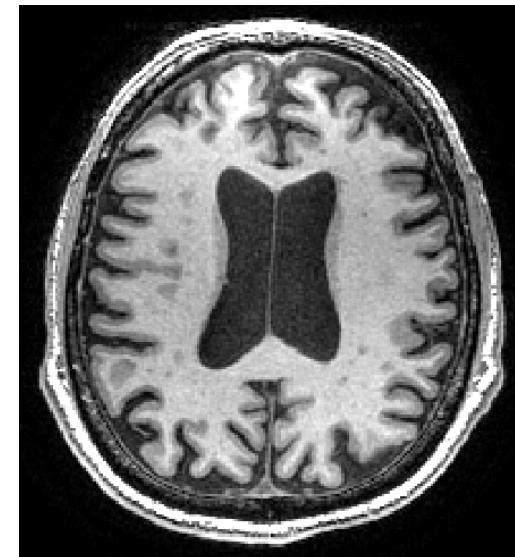
- . Lesion Map yes
- . Lesion probability map none
- . Binary lesion map none
- . Normalized lesion map yes
- . Other images

Current Item: T1 volumes

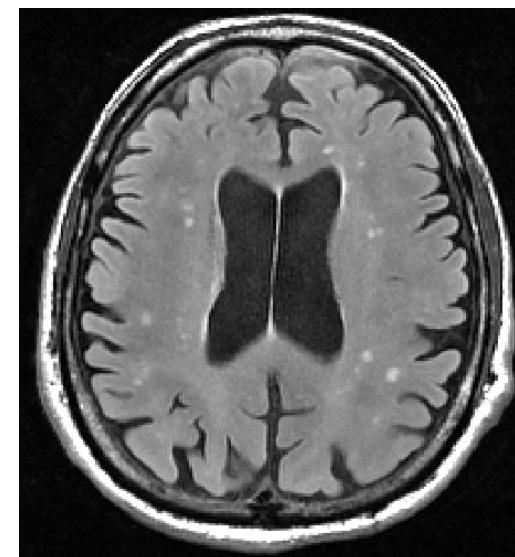
Select Files

T1 volumes

Select raw T1 images. You can select images of more than one subject. The FLAIR images must be selected in the same order.

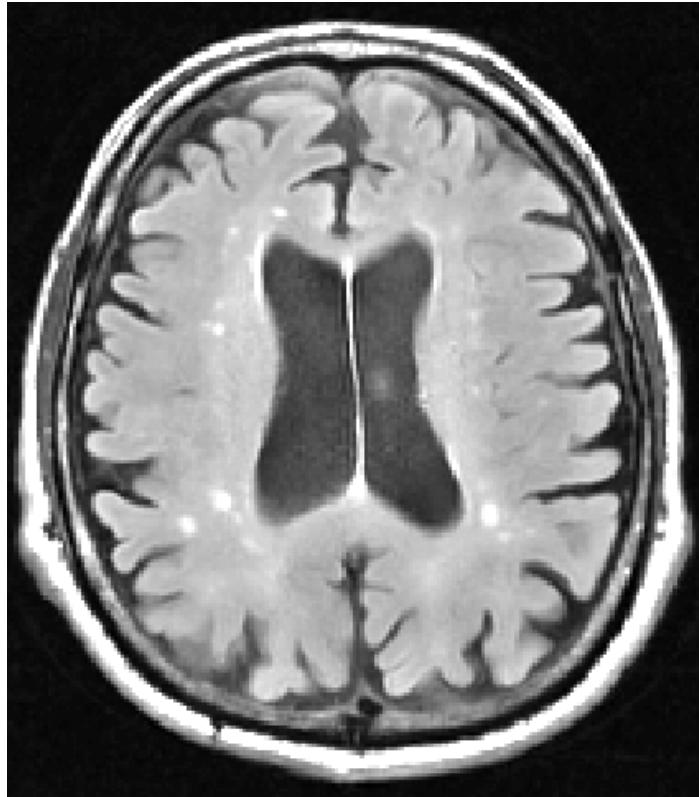


T1

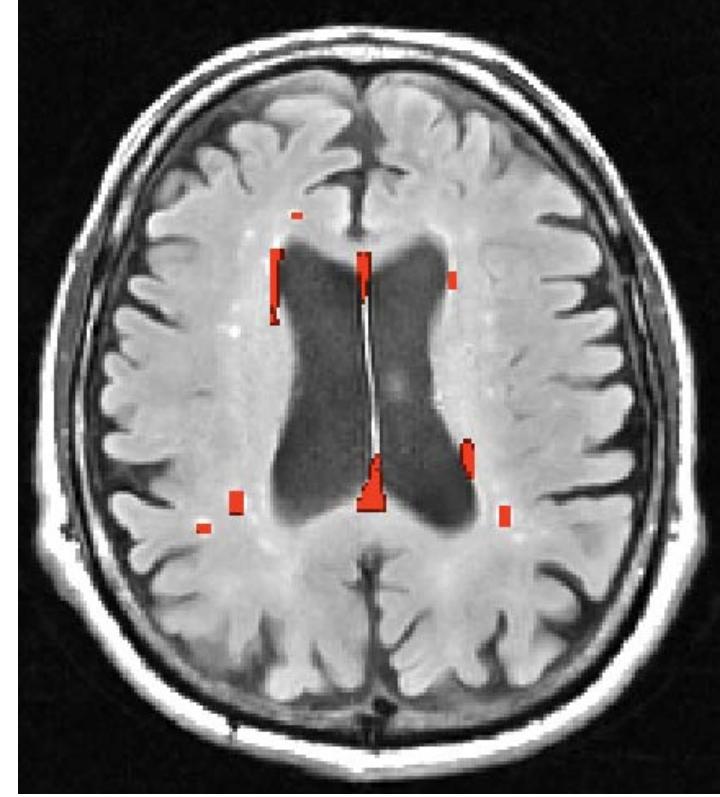


T2 FLAIR

# LST Output: Lesion map



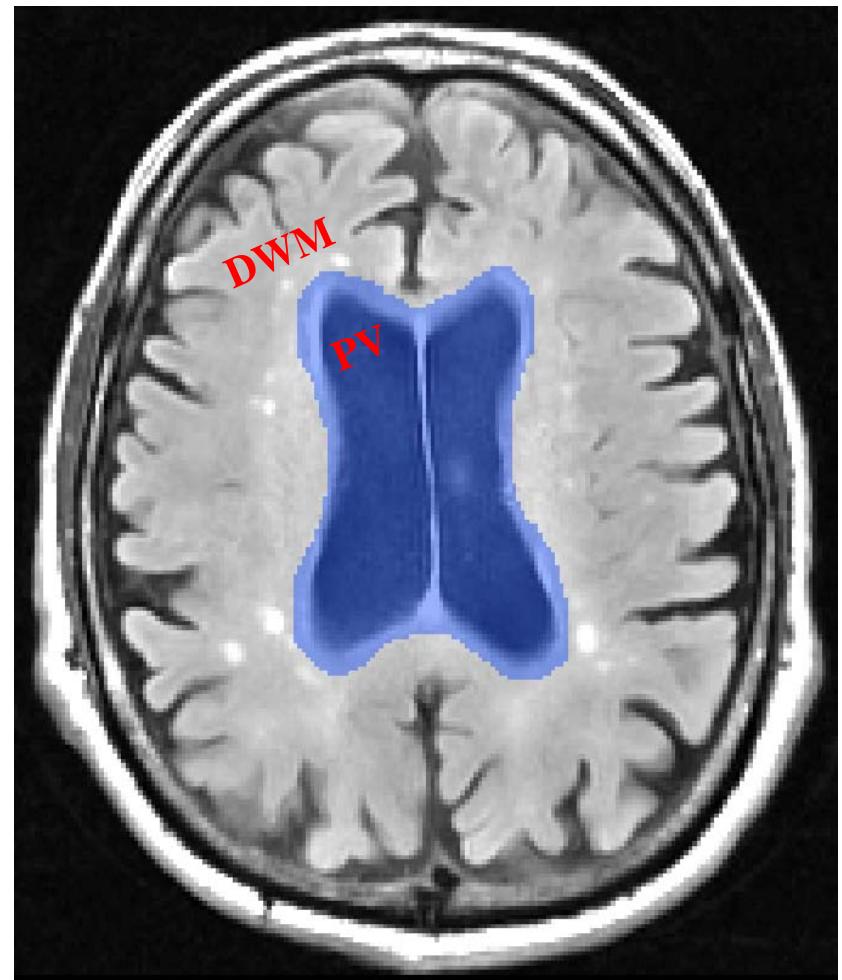
Base image: T2 FLAIR  
*bias-corrected FLAIR image in the  
space of the T1 image*



Lesion map  
(Threshold, k = 0.30)

# LST Output: Lesion map continued...

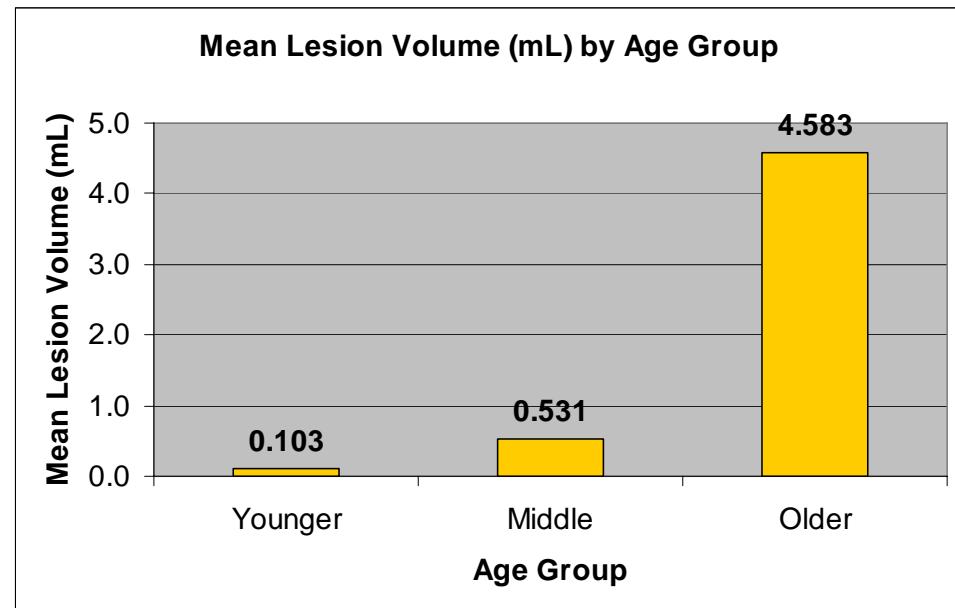
- Location is key!
  - Periventricular region
  - Deep white matter region
- Setting parameters
  - conservative and liberal thresholds
  - altering the algorithm via lesion growth initialization: GM seed vs. GM & WM seed



# LST Output: Volume

Potential for:

- Group comparisons
- Comparisons with behavioral data
- Informing threshold choice



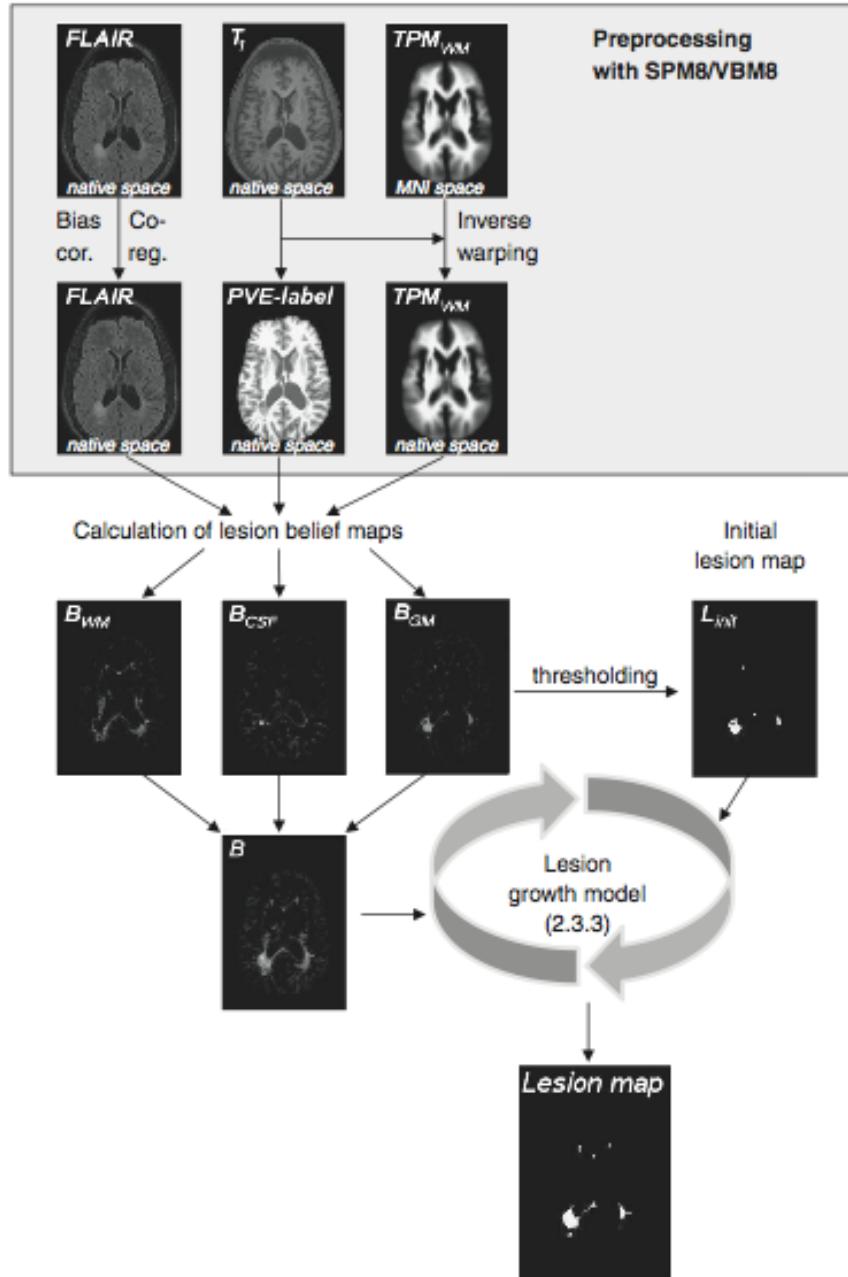
# Future ventures?

- Relating lesion data to DTI data:
  - Does lesion location correspond to measures of decreased white matter integrity?
- Relating lesion data to behavioral measures:
  - Does the amount or location of lesions predict behavioral performance?
- Group comparisons of lesion load
  - Aging

# Useful Links

- LST's website: <http://www.applied-statistics.de/lst.html>
- Schmidt, P., Gaser, C., Arsic, M., Buck, D., Förschler, A., Berthele, A., Hoshi, M., Ilg, R., Schmid, V.J., Zimmer, C., Hemmer, B., and Muhlau, M., 2012. An automated tool for detection of FLAIR-hyperintense white-matter lesions in Multiple Sclerosis. *NeuroImage* 59, 3774-3783.

## Lesion Segmentation Algorithm



## Theoretical Foundation for Lesion Growth Algorithm

- 1) Classify voxels according to intensity range of tissue classes (based on segmentation of the T1 image)
  - Individual native T1-image generates a partial volume estimate label (range: 1-3) corresponding to intensity class
 

1 = CSF
2 = GM
3 = WM
- 2) Find hyperintense-outliers of intensity distribution for each tissue class, (based on the T2 FLAIR image)
  - Standard module's generation of lesions: Hyper-intense outliers of the GM class are projected to the sum of hyper-intense outliers of CSF, GM, and WM classes