Group comparisons using diffusion imaging

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Declaration of Financial Interests or Relationships

Speaker Name: Konstantinos Arfanakis, Ph.D.

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.

Introduction

- Diffusion imaging reveals brain architecture and structural integrity in health and disease.

- The purpose of this presentation is to offer:
  - an overview of approaches for group comparison of diffusion imaging data
  - advantages and disadvantages of each approach
  - tips for enhancing the accuracy of group comparisons

- DTI will be the basis for our discussion.
- Close with corresponding approaches for other diffusion imaging models.

Outline

- Spatial normalization in DTI:
  registration, templates and data quality considerations
- Traditional voxel-based group comparisons
- Voxel-based group comparisons along the white matter skeleton
- ROI-based group comparisons
- Group comparisons for other diffusion imaging models

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- Spatial normalization in DTI:
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- Traditional voxel-based group comparisons

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- ROI-based group comparisons

- Group comparisons for other diffusion imaging models

Spatial Normalization in Diffusion Imaging

- Spatial normalization plays a central role in group comparison of diffusion imaging data.
- Accurate group comparison of diffusion imaging data requires accurate spatial normalization.
- The accuracy of spatial normalization depends on the:

  - registration algorithm
  - template
  - data quality

Registration of DTI Data

- Most commonly used approaches for registration of DTI data.

First approach

Step 1: Register T_1 or T_2-weighted data.
Step 2: Apply the resulting transformations to FA or trace maps.
Step 3: Perform tensor reorientation to allow comparisons of orientation-dependent quantities.

Problems

- Imperfect spatial matching between diffusion and anatomical data (e.g. due to distortions).
- Registration is based on anatomical features which are different than the features of diffusion data (e.g. FA map vs. T_1-weighted image).
- Rotations calculated from T_1- or T_2-based registration does not guarantee matching of tensor orientation.

Registration of DTI Data

Second approach

Step 1: Register maps of tensor-derived scalar quantities (e.g. FA, trace).
Step 2: Perform tensor reorientation to allow comparisons of orientation-dependent quantities.

Problem

- Rotations calculated from registration of tensor-derived scalar quantities do not guarantee matching of tensor orientation.

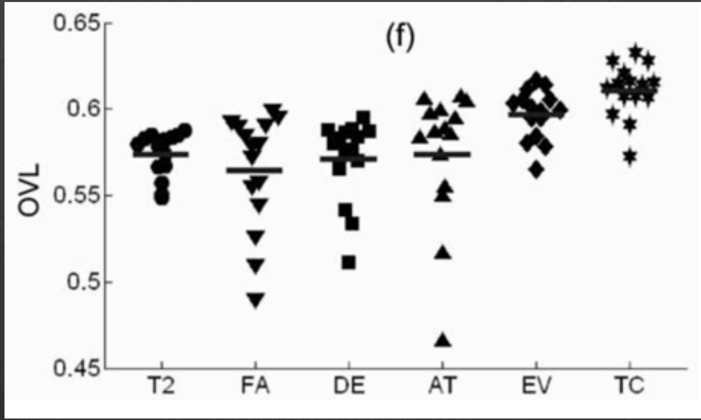
Registration of DTI Data

Third approach

Step 1: Register tensors.

Problem

- More time-consuming.

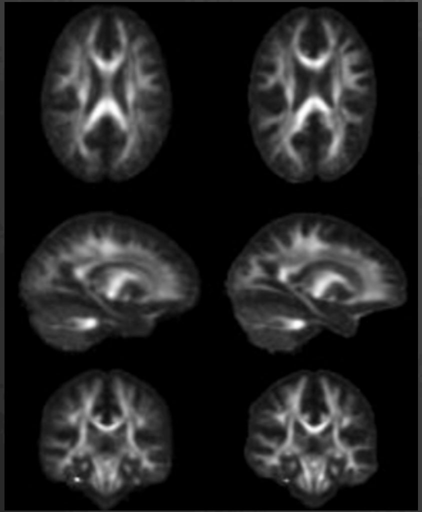


Park et al., Neuroimage, 2003

Registration of DTI Data

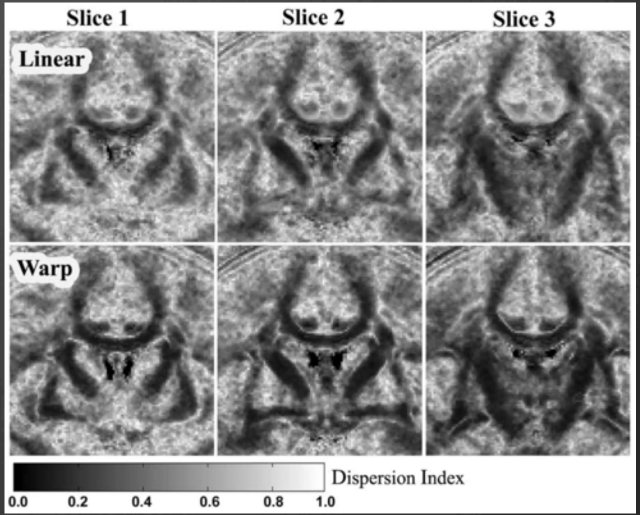
Rigid body, affine, or non-linear?

rigid non-linear



Rohde et al., ISBI, 2004

Tensor orientation dispersion

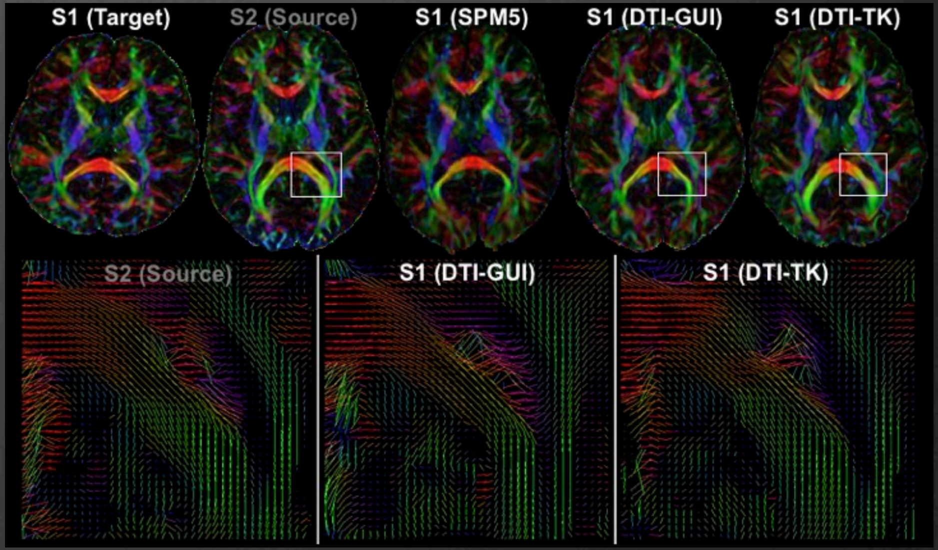


Park et al., Neuroimage, 2003

Registration of DTI Data

Answer: Tensor-based non-linear registration

- Examples: DTI-TK
  Zhang et al., Med Imag Anal, 2006
  Medinria
  Yeo et al., ISBI, 2008
  F-TIMER
  Yap et al., IEEE Trans Med Imaging, 2010



Diffusion Imaging Brain Templates

- Diffusion imaging brain templates are typically used as references for spatial normalization.

- Different types of diffusion brain templates:

a) standardized

b) study-specific

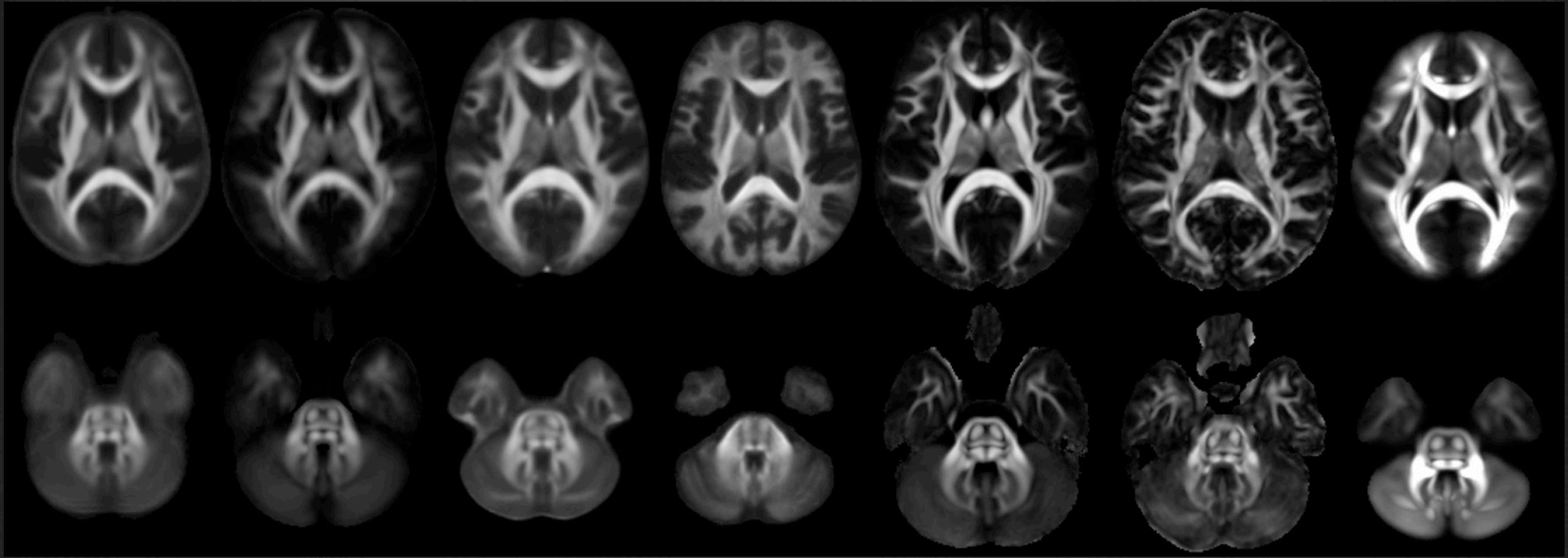
contents

i) full-tensor
ii) FA-only

construction

i) single-subject
ii) multi-subject average

Standardized DTI Brain Templates



	Enigma	ICBM81	FMRIB58	SRI24	IIT v.4.0	Eve	HCP488
contents:	FA	tensors	FA	tensors	tensors	tensors	tensors
subjects:	400	81	58	24	72	1	488
age:	18-85 y.o.	18-59 y.o.	20-50 y.o.	19-84 y.o.	20-40 y.o.	32 y.o.	22-35 y.o.

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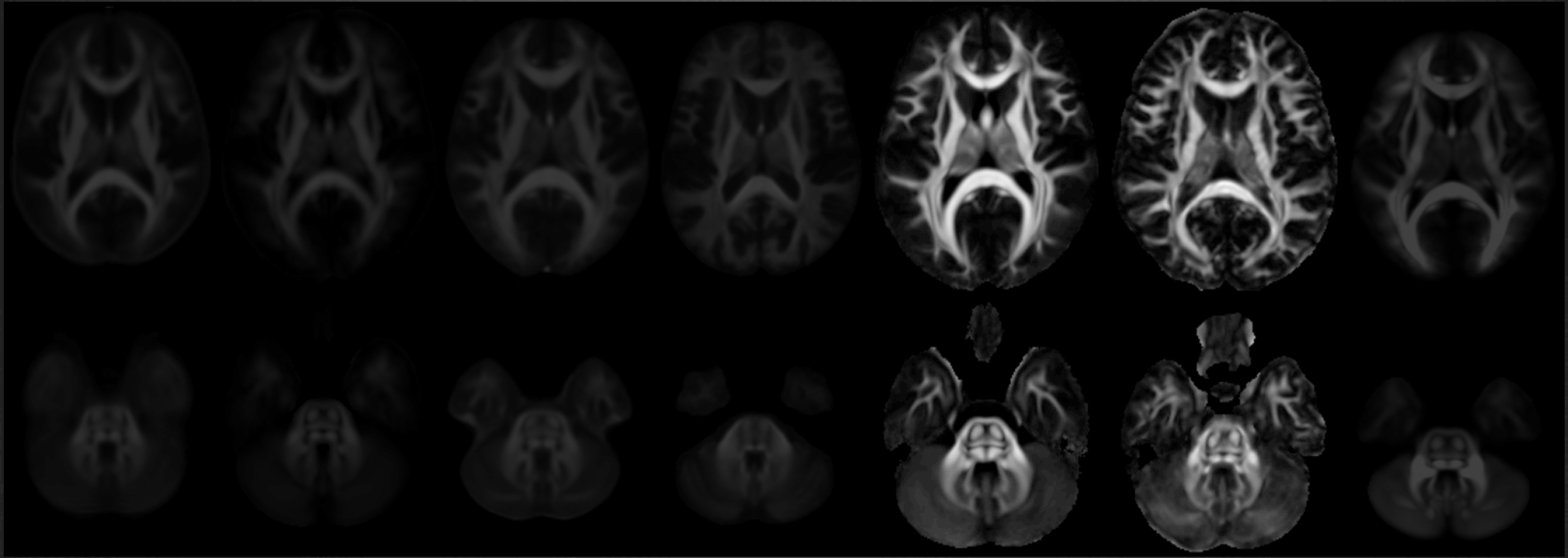

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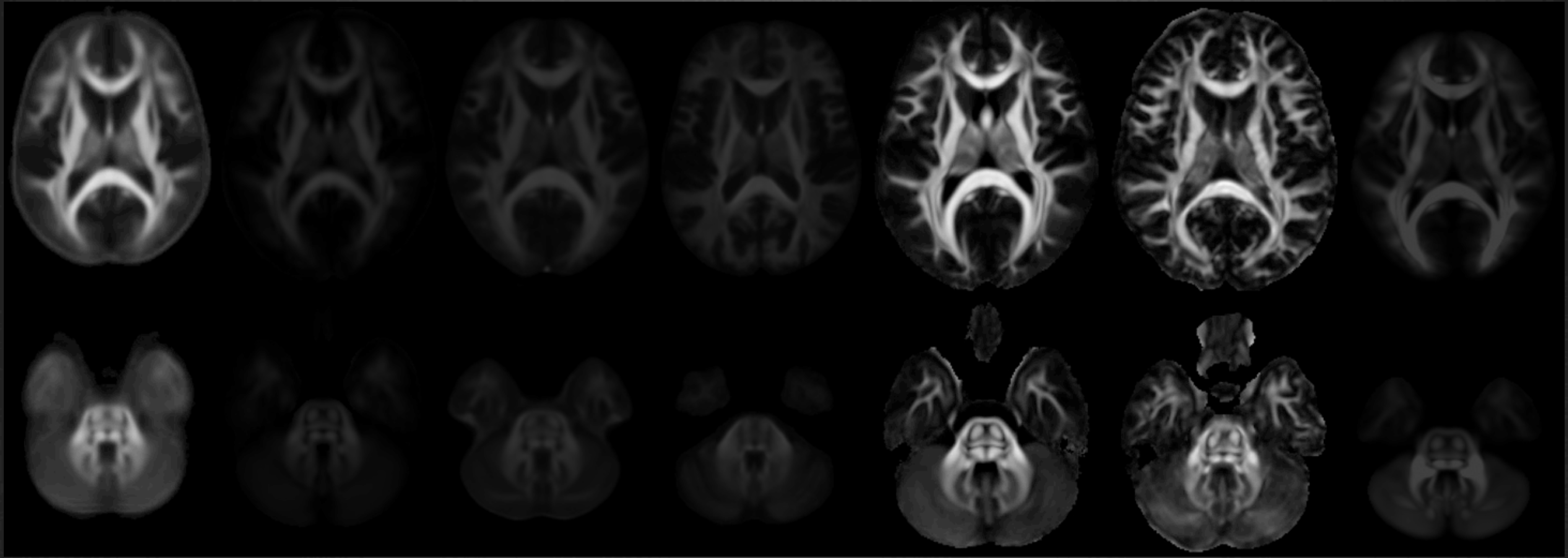

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	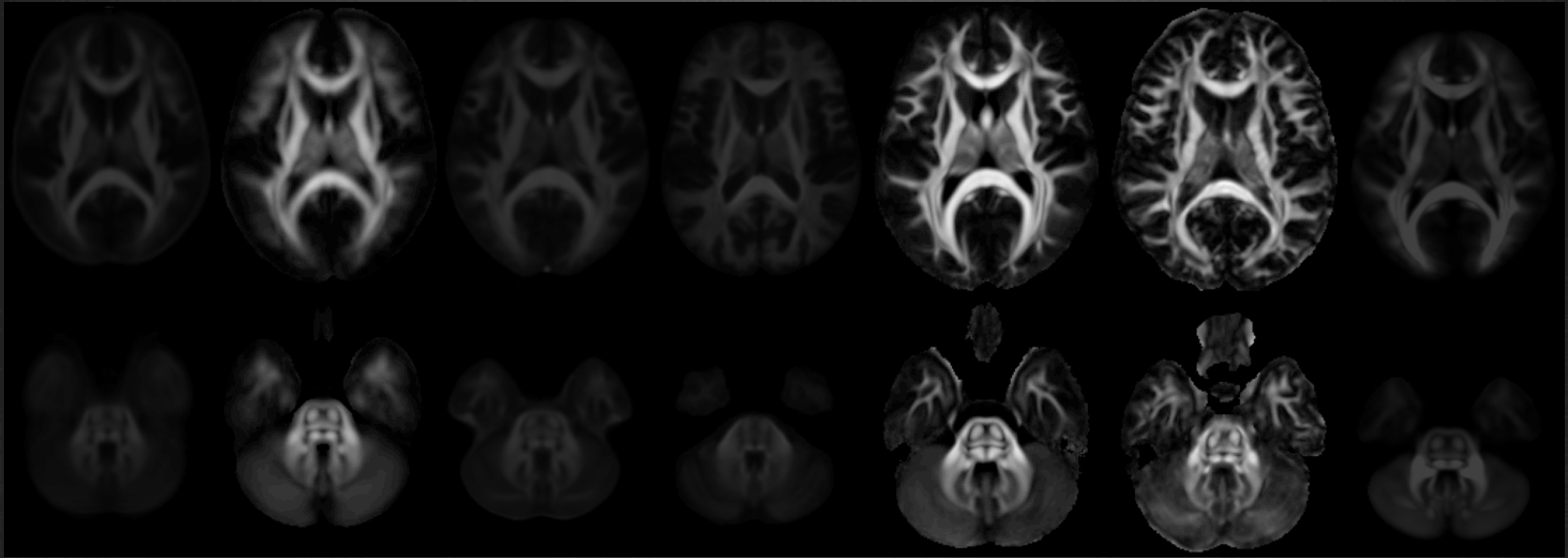						
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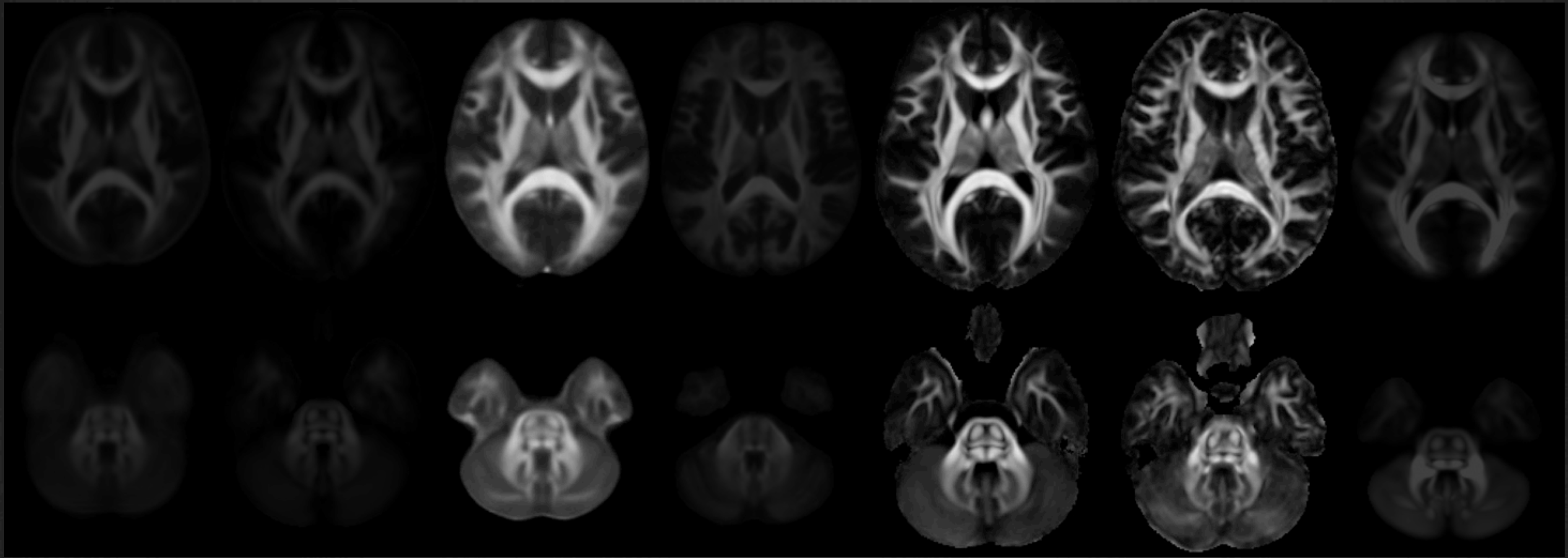

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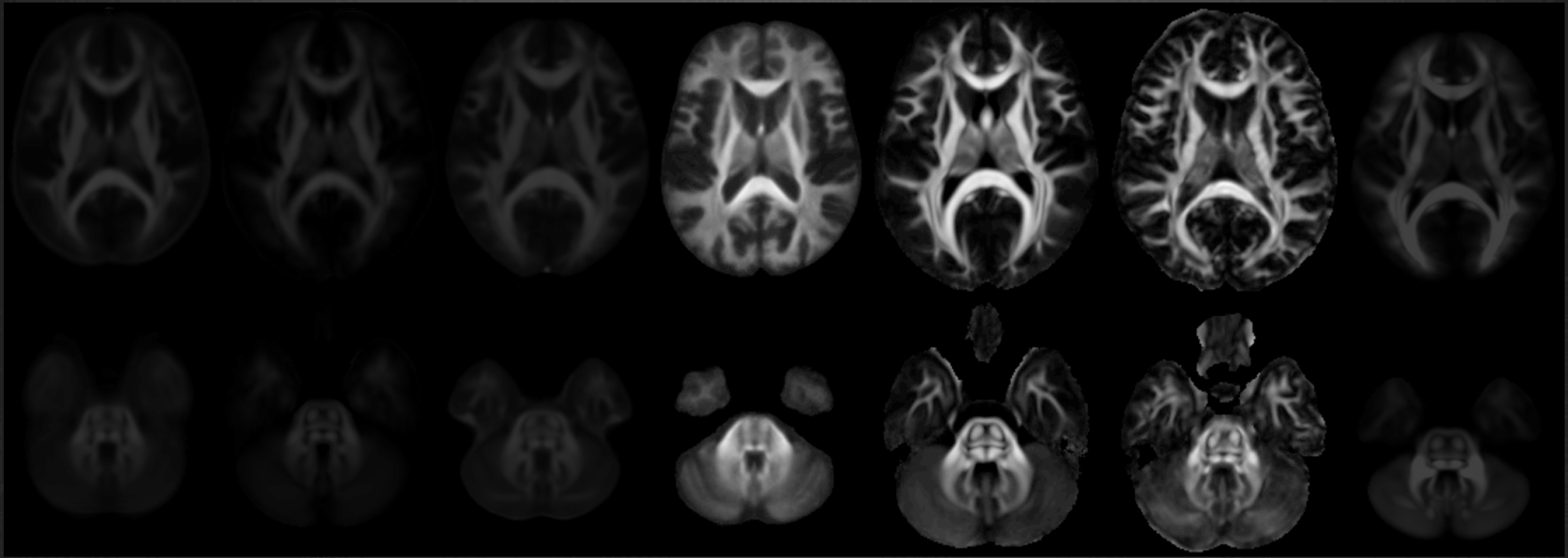

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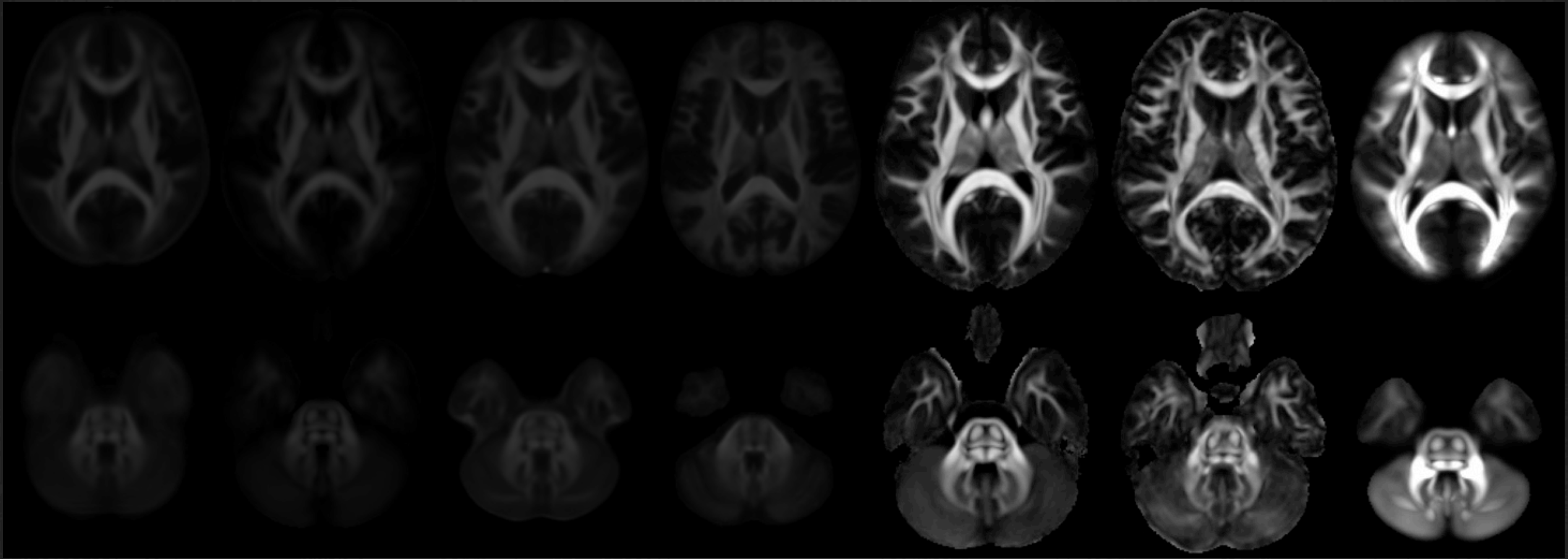

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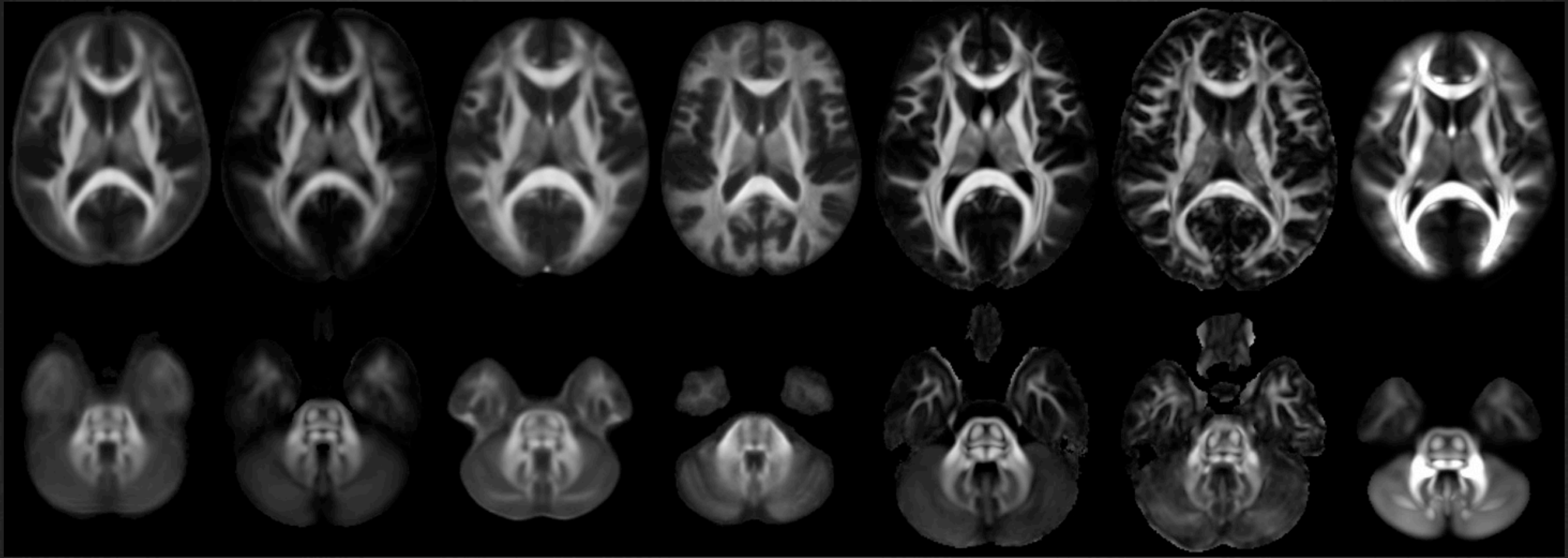

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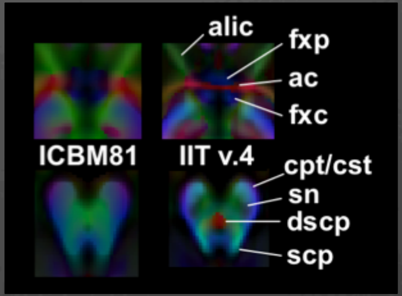
Standardized DTI Brain Templates

<u>Eve</u> Oishi et al., Neuroimage, 2009

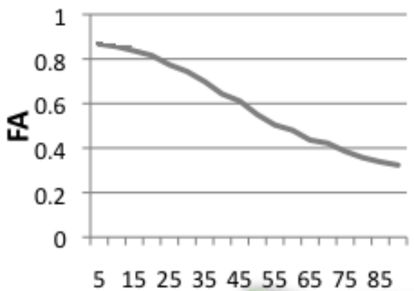
- High image sharpness, high SNR
- Single subject (bias)

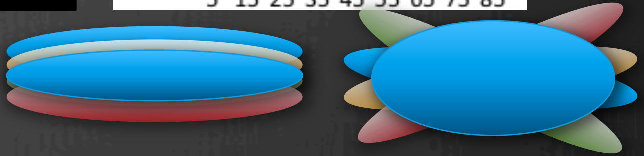
<u>IIT v.4.0</u> Varentsova et al., Neuroimage, 2014

- High image sharpness, high SNR
- Population-based
- Representative of data on individual subjects
- In ICBM-152 space



Peng et al., Neuroimage, 2009



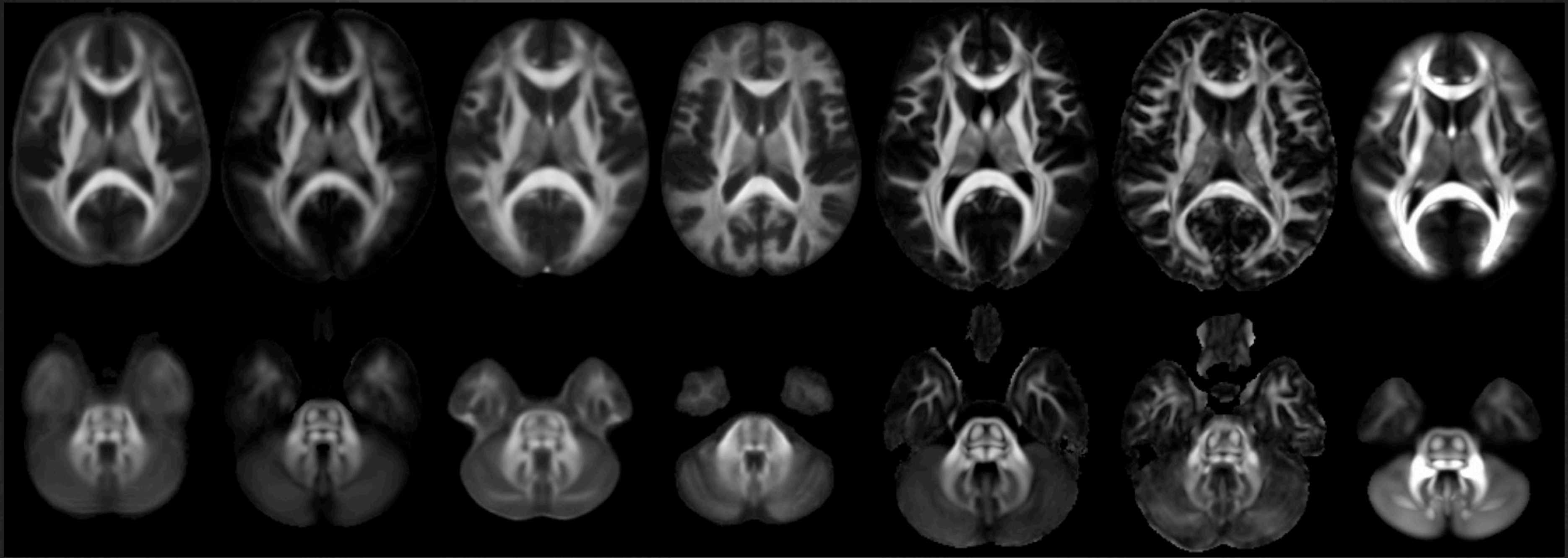


<u>Compared to IIT v.4.0</u>

- <u>ICBM81</u>: blurrier + lower FA (due to misregistration and/or wide age-range)
- <u>Enigma</u> & <u>FMRIB58</u>: blurrier + lower FA + do not allow tensor-based registration
- <u>SRI24</u>: blurrier + lower FA + atypical FA map
- <u>HCP488</u>: blurrier + atypical FA map + FA > 1

Mori et al., Neuroimage, 2008; Jahanshad et al., Neuroimage, 2013; FSL (FMRIB, Oxford, UK);
Rohlfing et al., Hum Brain Map, 2010; Yeh et al., ISMRM, 2015

Standardized DTI Brain Templates



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Study-specific DTI Brain Templates

- The data collected for a certain study are used to construct the template that will be used in that study.

- Three approaches:

  - all subjects are normalized to one of the subjects

    \# of registrations = [N-1] Guimond et al., Comput. Vision Imag. Understand, 2000

  - all subjects are normalized to all others, the N-1 transformations corresponding to a subject are averaged and applied to that subject

    \# of registrations = [N × (N-1) / 2] Van Hecke et al., Neuroimage, 2008

  - all subjects are normalized to a temporary template, their mean becomes the new temporary template, and the process is repeated several times

    \# of registrations = [N × iterations] Goodlett et al., MICCAI, 2006

Study-specific DTI Brain Templates

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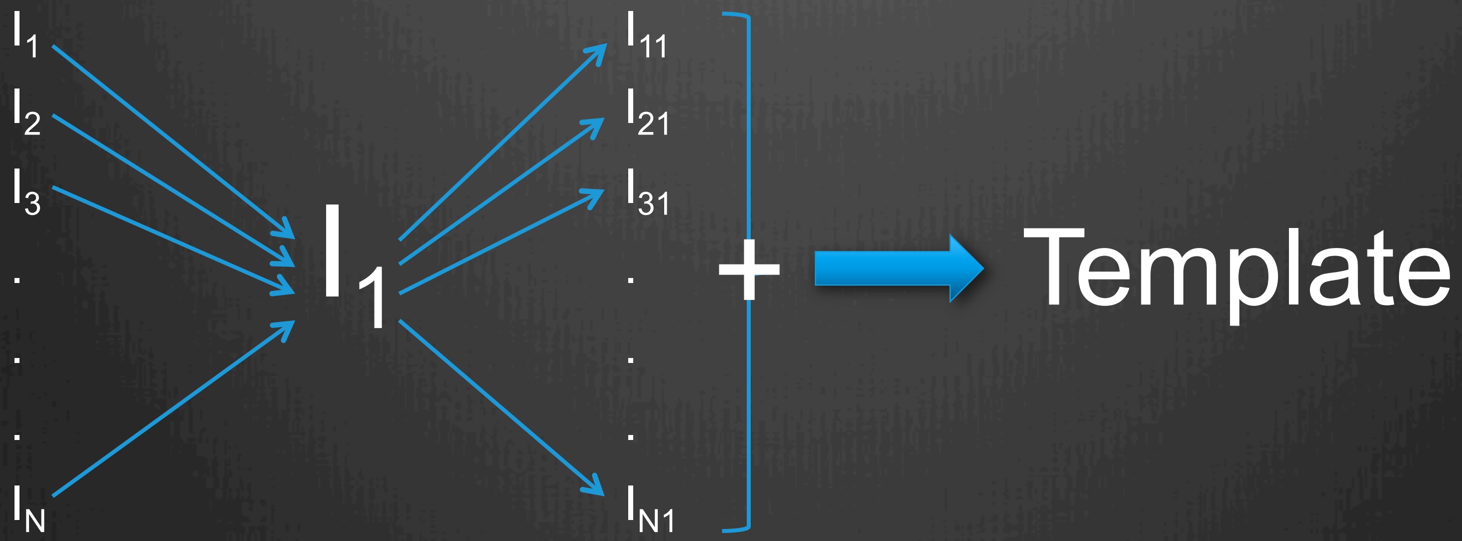

Not recommended (biased)

Study-specific DTI Brain Templates

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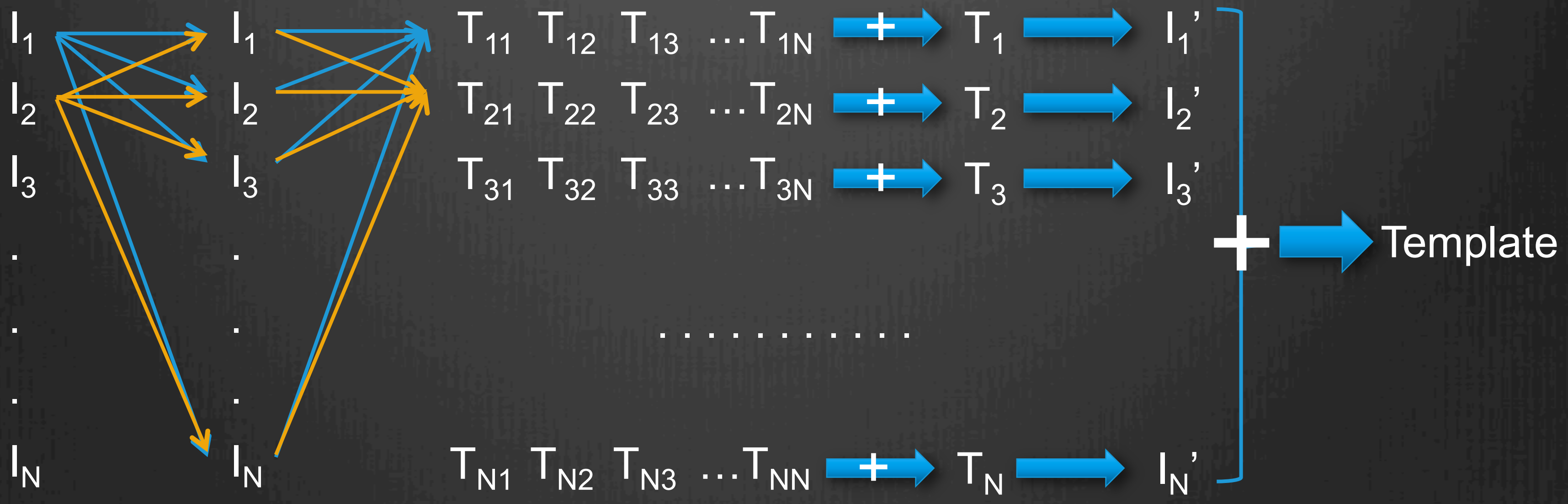
Van Hecke et al., Neuroimage, 2008



Great template but not recommended (unless you have free time)

Study-specific DTI Brain Templates

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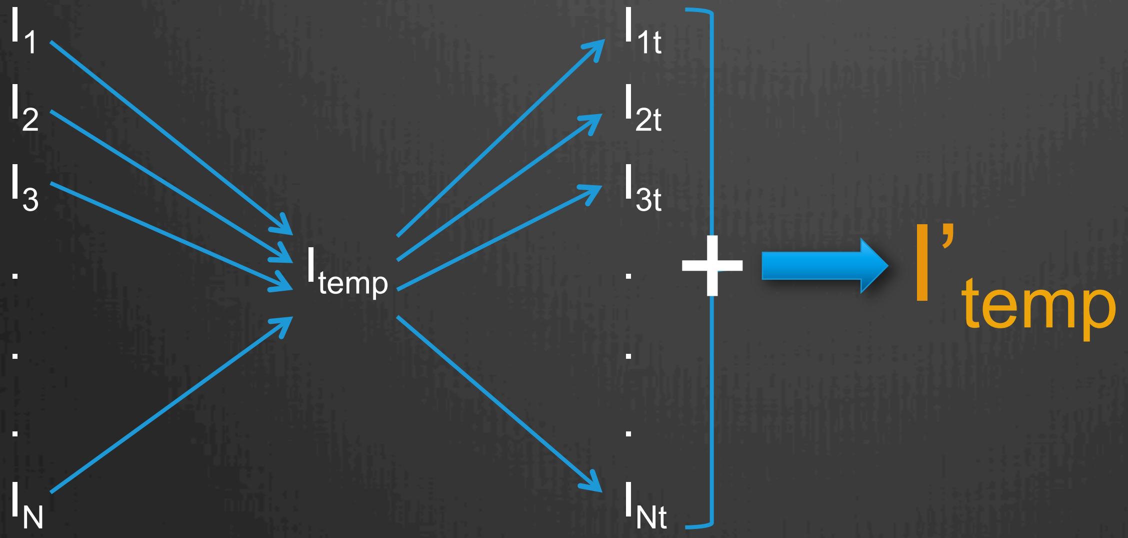
Goodlett et al., MICCAI, 2006



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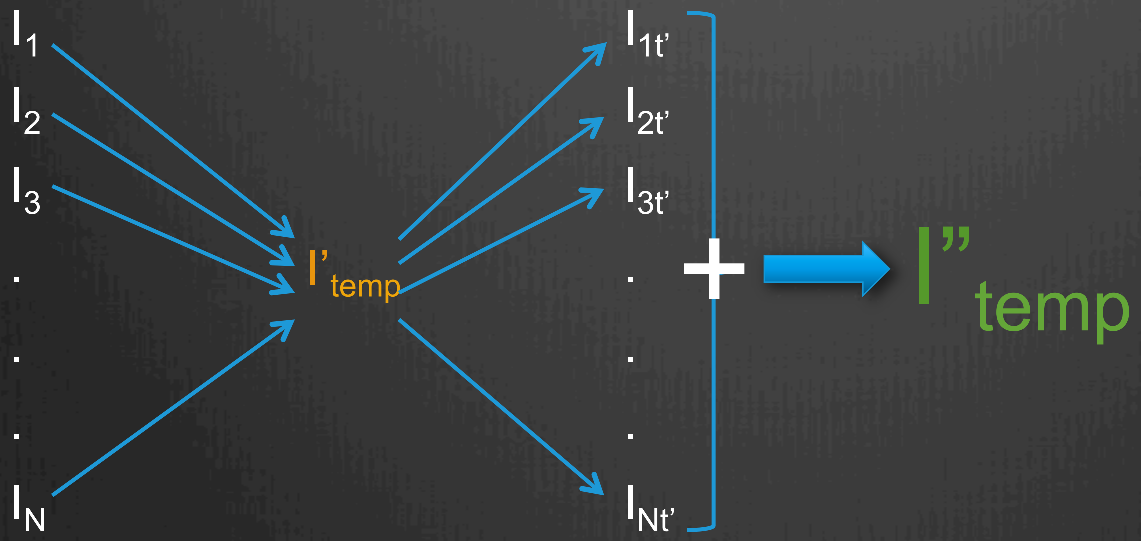

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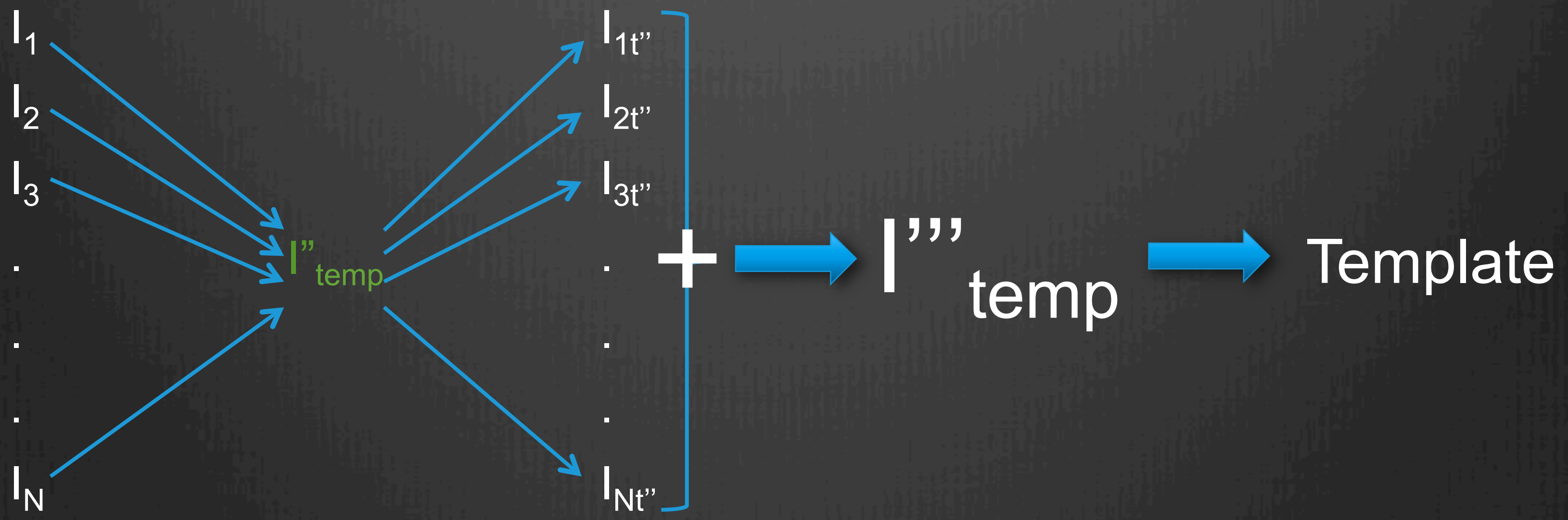
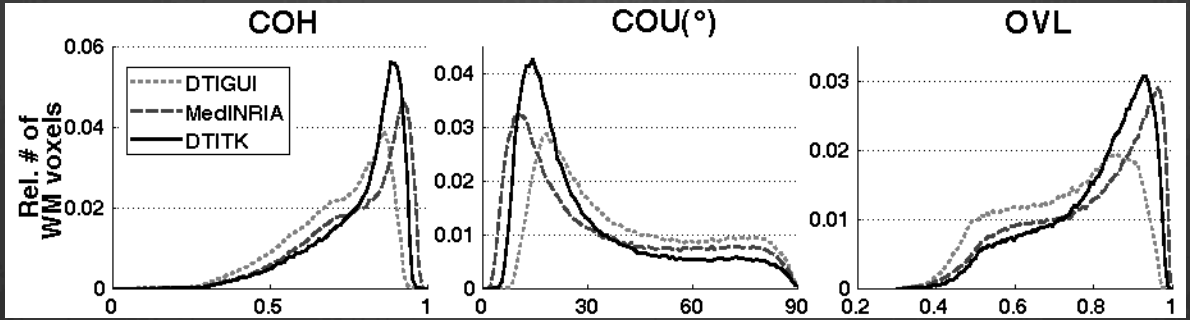


Recommended. Great template, fast.

Spatial Normalization Accuracy: Registration Algorithms



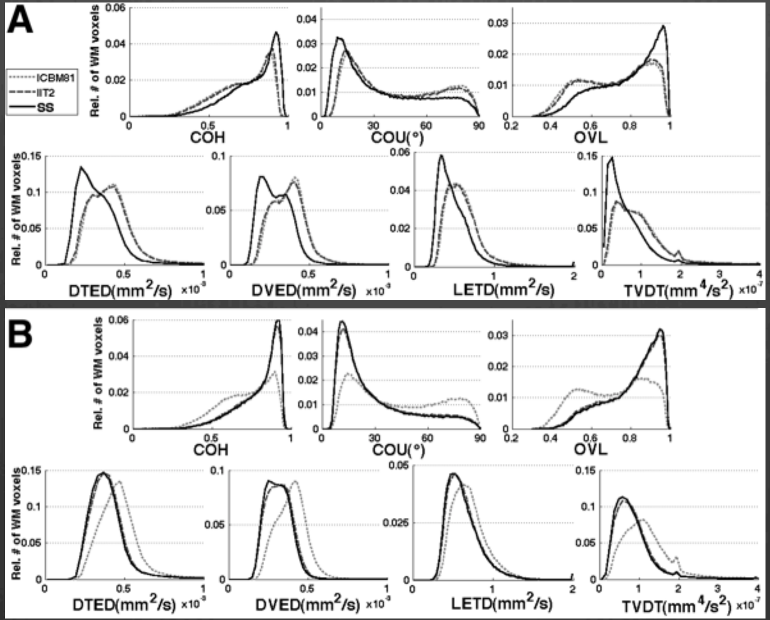
Zhang & Arfanakis, J Magn Reson Imaging, 2012

DTI-TK resulted in highest spatial normalization accuracy

Spatial Normalization Accuracy: Standardized vs. Study-specific DTI Brain Templates

For DTI data with susceptibility artifacts

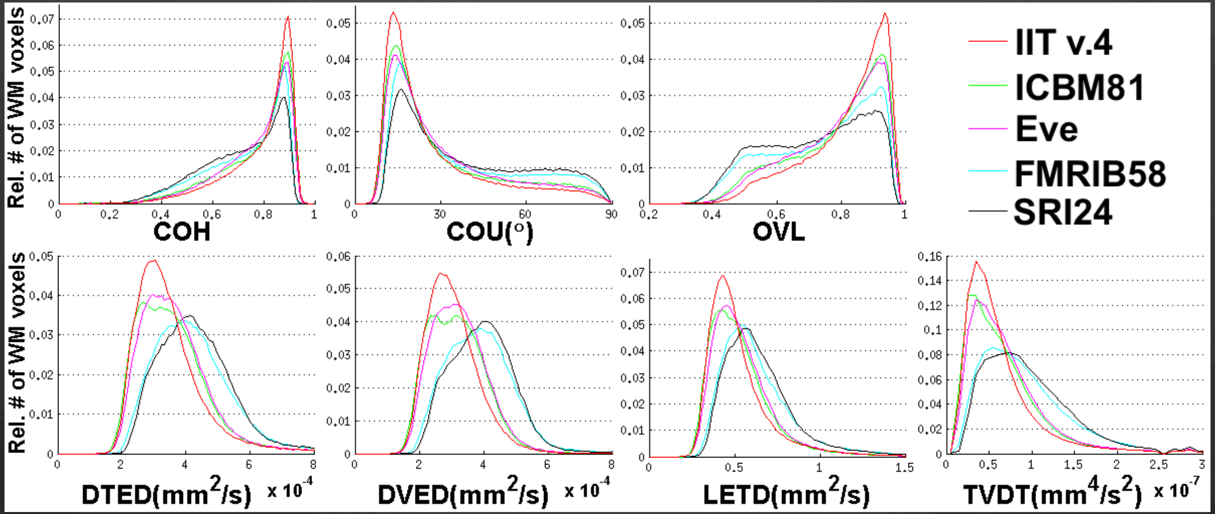
For artifact-free DTI data



Zhang & Arfanakis,
J Magn Reson Imaging, 2012

- As DTI data quality improves, a high quality standardized template results in similar normalization accuracy as a study-specific template.

Spatial Normalization Accuracy: Standardized DTI Brain Templates



IIT v.4.0 resulted in highest spatial normalization accuracy

Spatial Normalization Accuracy: Standardized vs. Study-specific DTI Brain Templates

<u>Study-specific templates</u>

Advantages: a) Most representative of the data under study.

Disadvantages: a) Poorly constructed study-specific templates have low performance (e.g. for small # of subjects, or inaccurate spatial normalization, etc.).

b) Time consuming.

c) Lack labels and other features of an atlas.

d) Differences in study-specific templates complicate integration of results across studies.

Spatial Normalization Accuracy: Standardized vs. Study-specific DTI Brain Templates

<u>Standardized templates</u>

Advantages:

a) Consistently high accuracy.

b) Minimize complexity.

c) Facilitate integration of findings across studies.

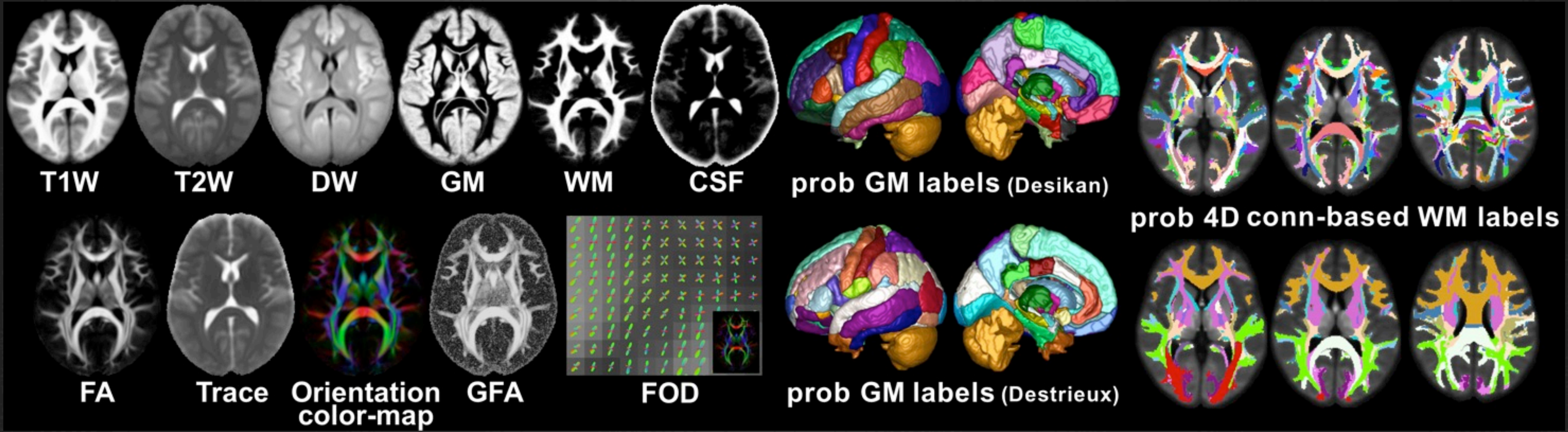
d) Labels and other resources may be available (if part of an atlas).

Disadvantages:

a) In the presence of artifacts, may not be the most representative of the data under study, but as DTI data quality improves, this is corrected.

Spatial Normalization: Summary

- Registration algorithm: Tensor-based non-linear (DTI-TK). www.nitrc.org/projects/dtitk
- Template: Study-specific. CAUTION
- Template: Standardized (IIT v.4.0). www.nitrc.org/projects/iit2



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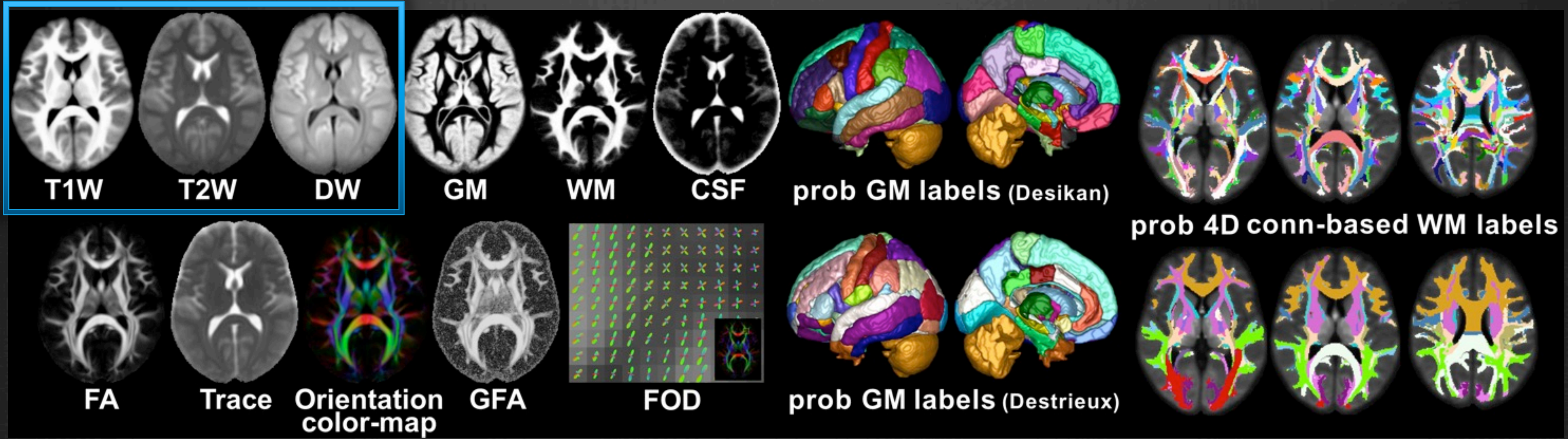

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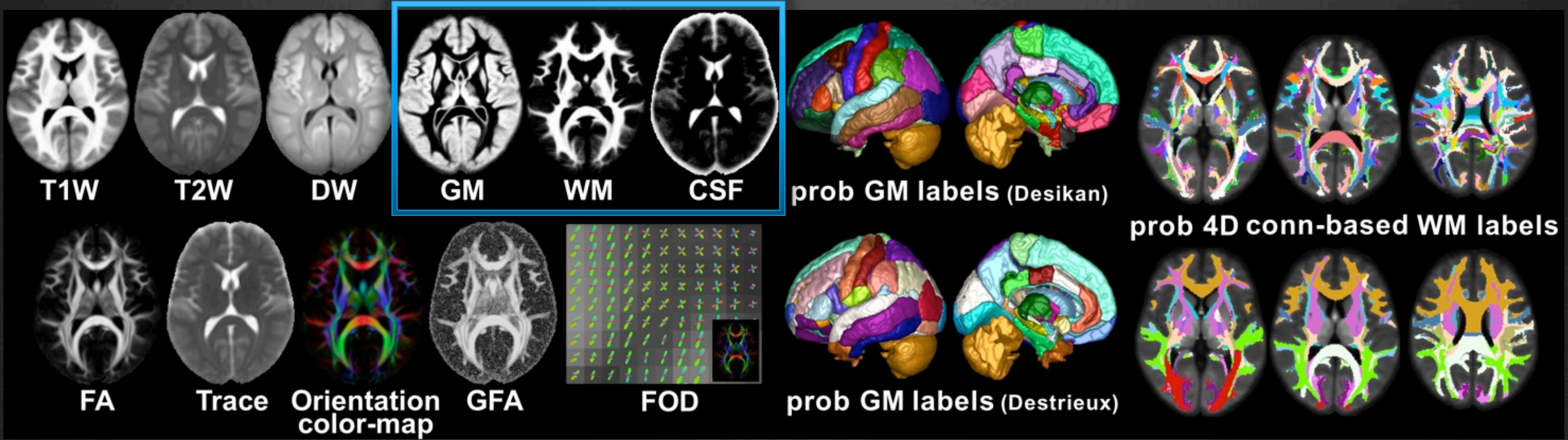

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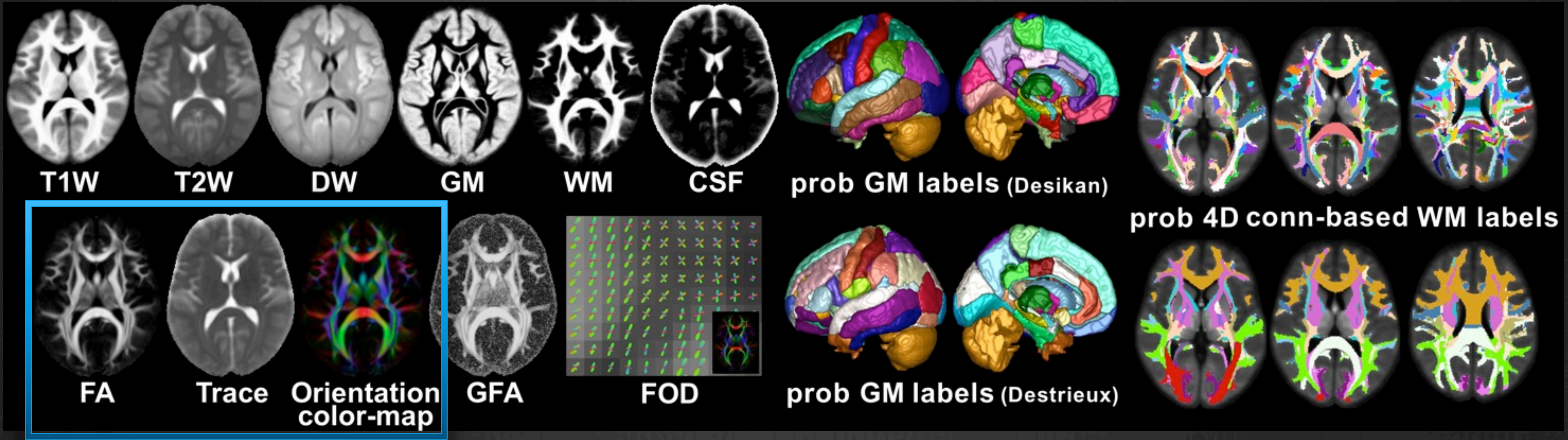

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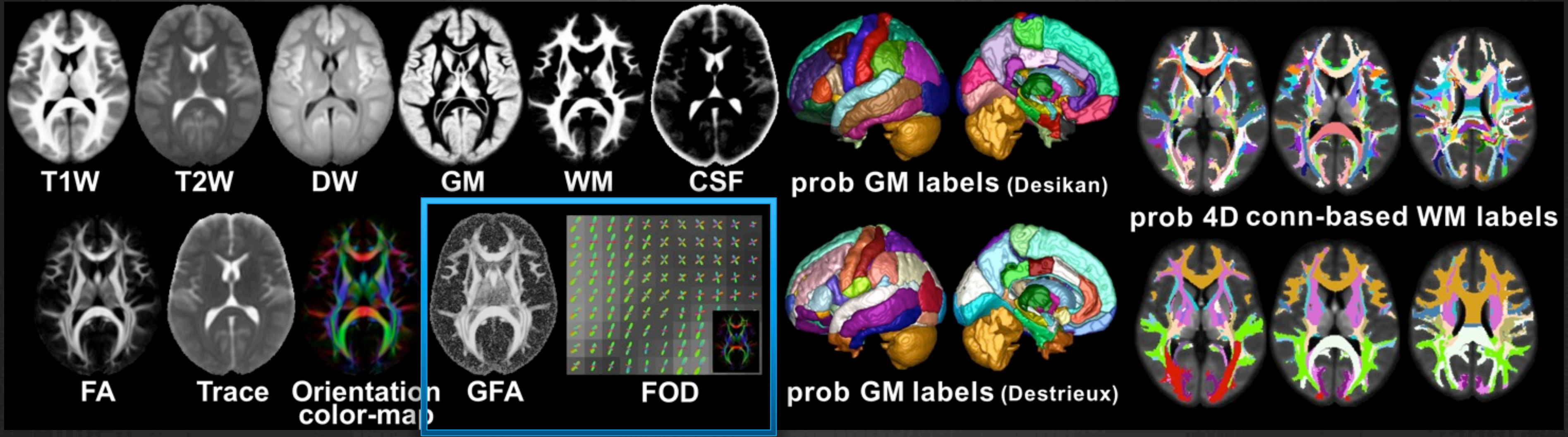

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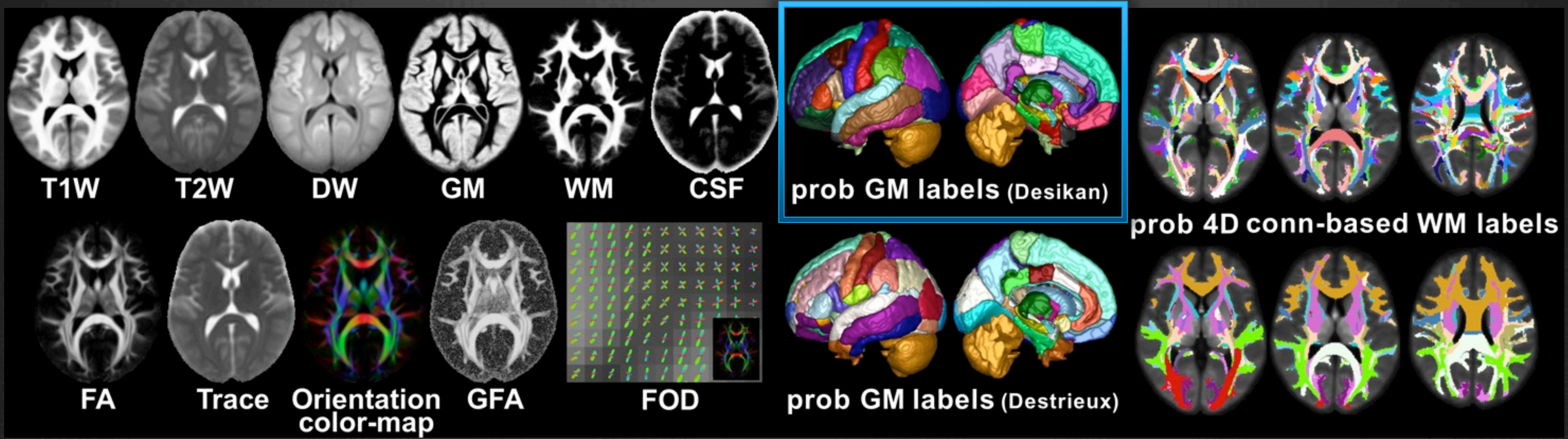

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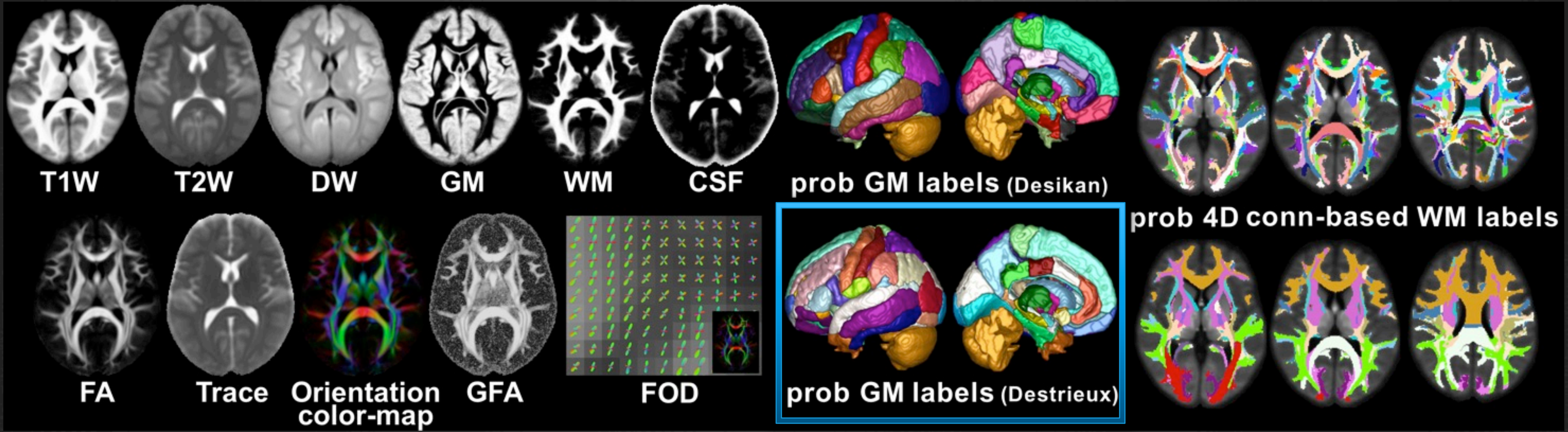

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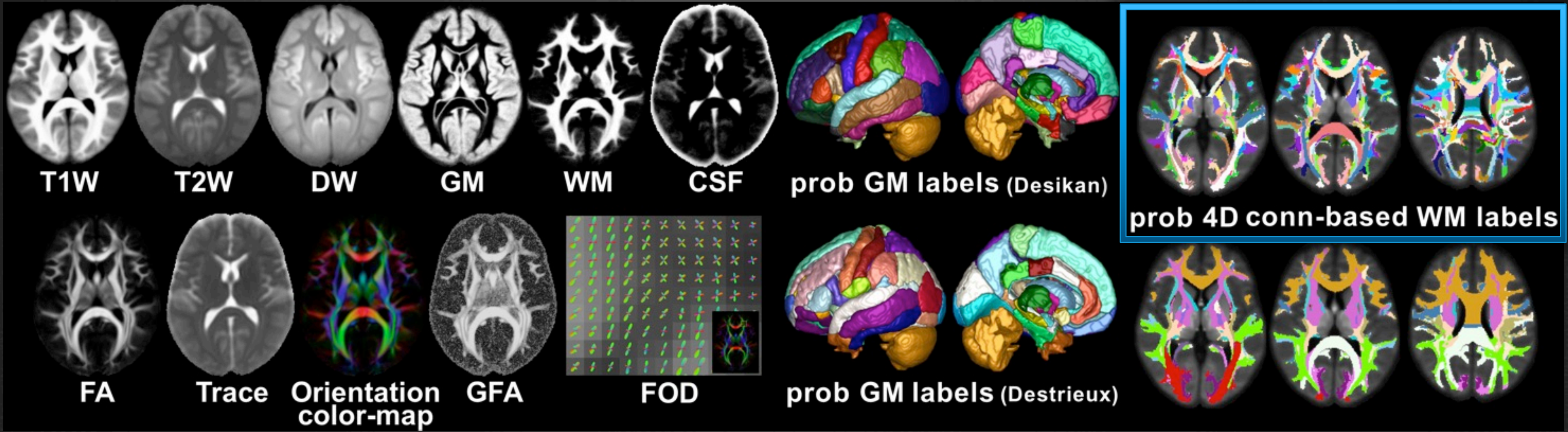

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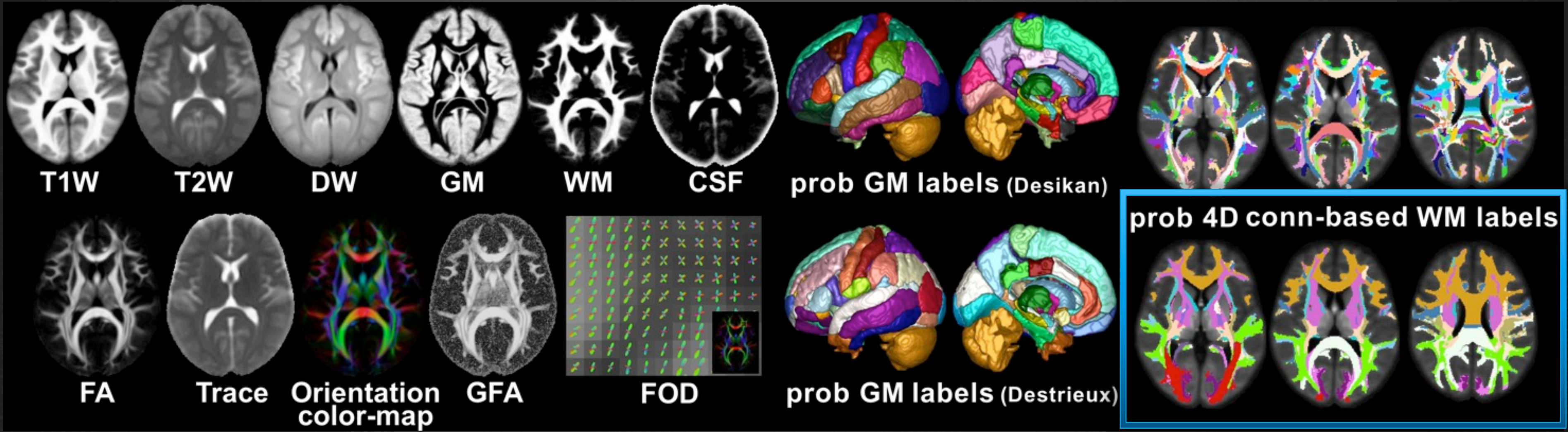

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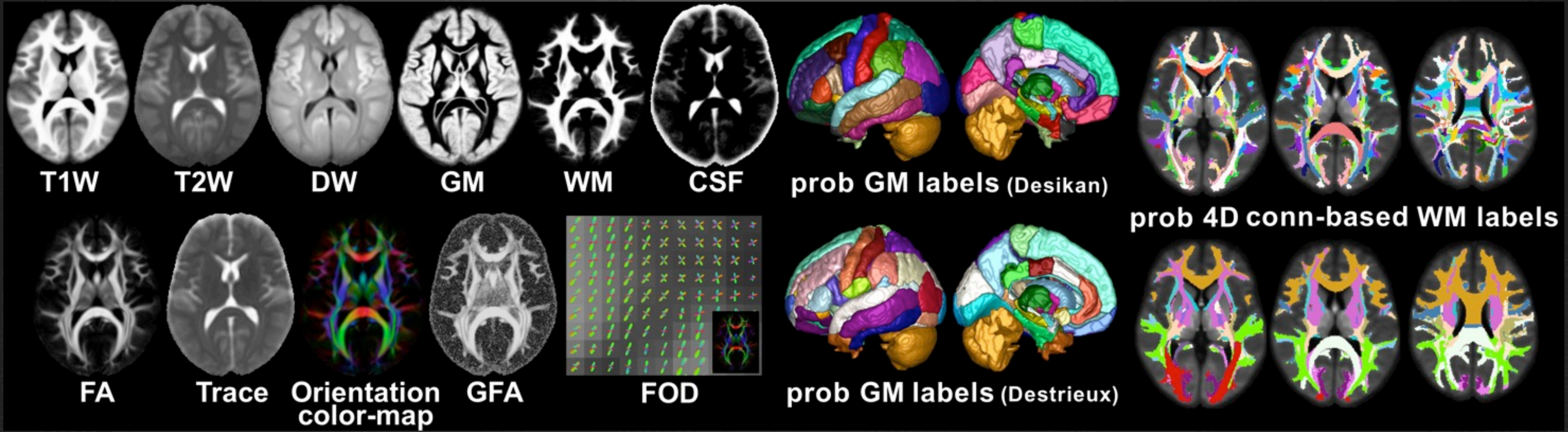

- Data quality: Influences normalization accuracy.

Outline

- Spatial normalization in DTI:
  registration, templates and data quality considerations
- Traditional voxel-based group comparisons
- Voxel-based group comparisons along the white matter skeleton
- ROI-based group comparisons
- Group comparisons for other diffusion imaging models

Traditional Voxel-based Group Comparisons

- Traditional voxel-based group comparison.
  - Step 1: Spatial normalization.
  - Step 2: Smoothing
  - Step 3: Voxel-wise statistical analysis.

Traditional Voxel-based Group Comparisons

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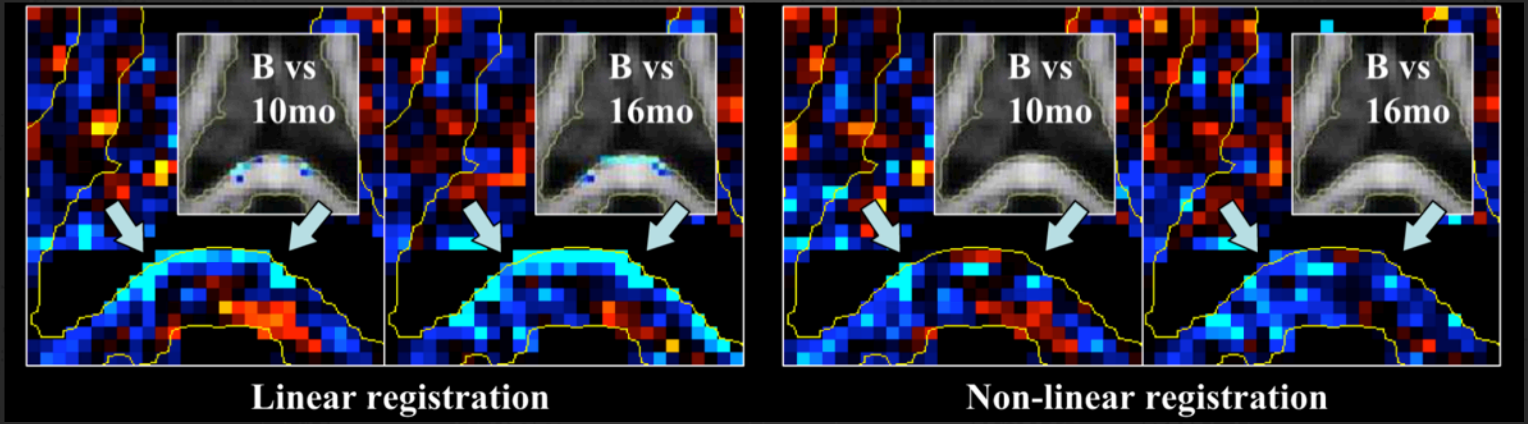
Problems

Misregistration



Chung et al., Neuroimage, 2008

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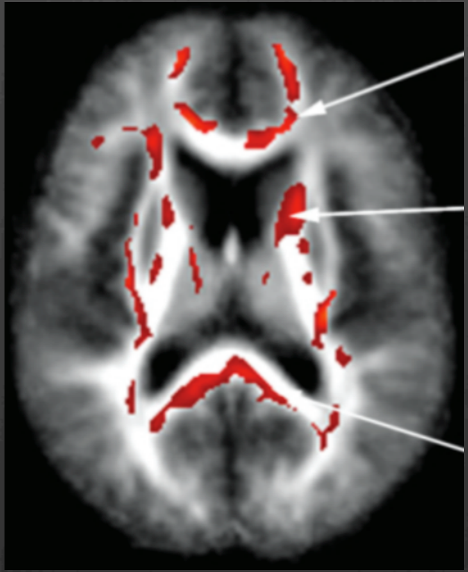
Misregistration

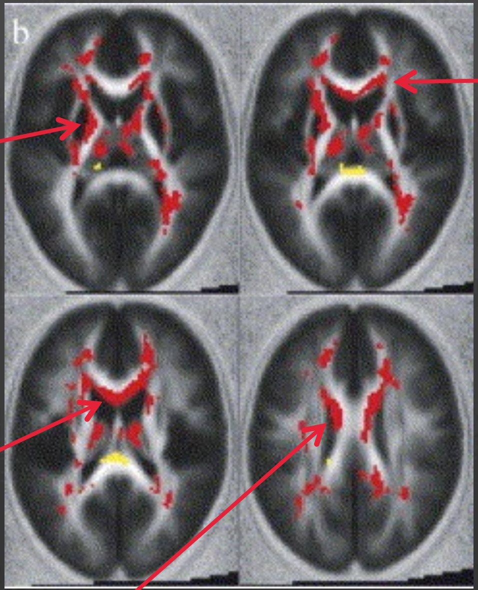


anonymous

Traditional Voxel-based Group Comparisons

- Traditional voxel-based group comparison.
  - Step 1: Spatial normalization.
  - Step 2: Smoothing
  - Step 3: Voxel-wise statistical analysis.

Problems
Misregistration



anonymous

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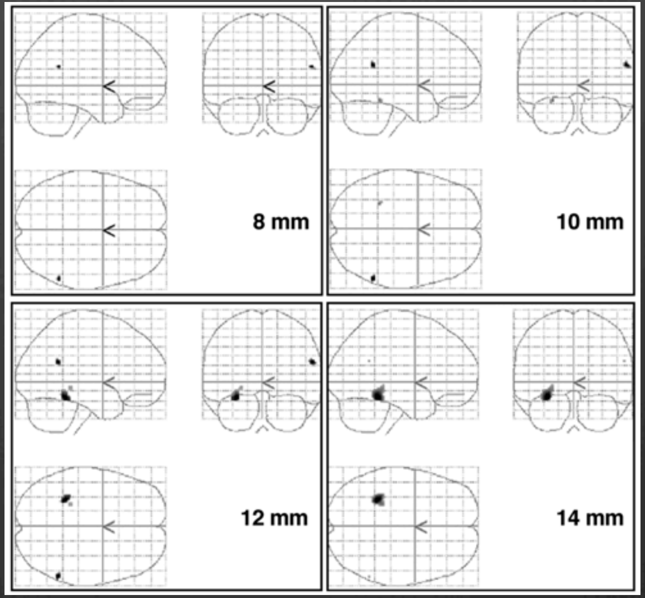
Problems
How much to smooth?



Jones et al., Neuroimage, 2005

Traditional Voxel-based Group Comparisons

Problems
- Sensitive to misregistration
- How much to smooth?

- Traditional voxel-based group comparisons are generally avoided.

Outline

- Spatial normalization in DTI:
  registration, templates and data quality considerations
- Traditional voxel-based group comparisons
- Voxel-based group comparisons along the white matter skeleton
- ROI-based group comparisons
- Group comparisons for other diffusion imaging models

Voxel-based Group Comparisons Along the White Matter Skeleton

- “Tract-based spatial statistics” (TBSS) was developed to address the problems of traditional voxel-based analyses of DTI data. Smith et al., Neuroimage, 2006

Step 1: Spatial normalization
Step 2: Skeletonization
Step 3: Projection onto the skeleton
Step 4: Voxel-wise statistics on the skeleton

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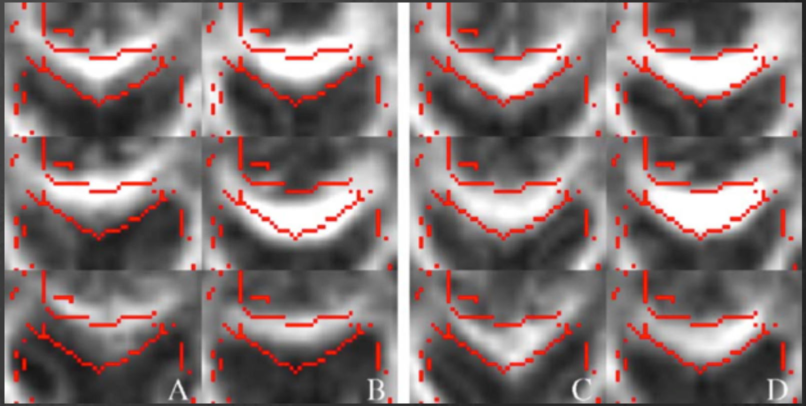

affine only affine + nonlinear

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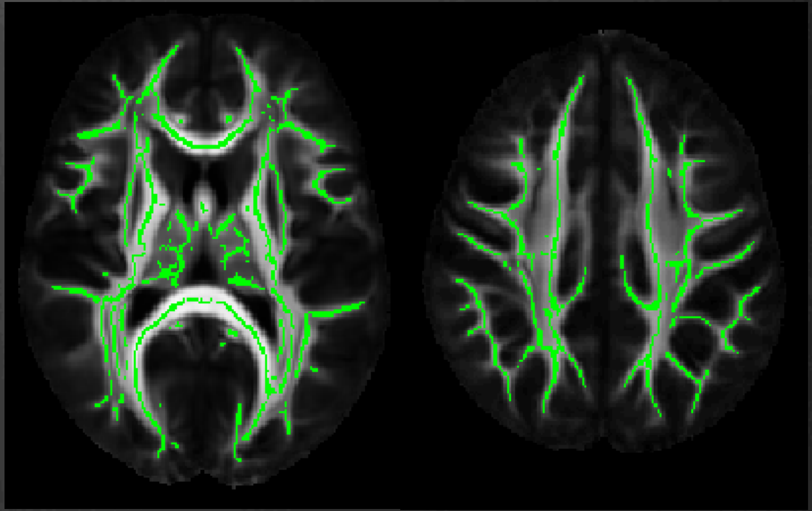

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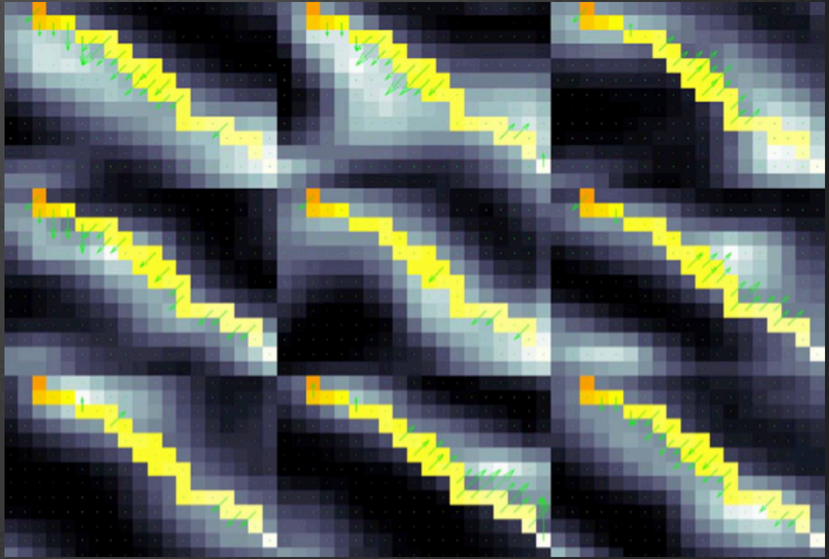

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General linear model

Gaussian distributed data
Simple parametric tests

Permutation-based approaches

Family Wise Error correction

Threshold-free cluster enhancement (TFCE)

TBSS Advantages over Traditional Voxel-based Analysis

1) Less sensitive to misregistration,
2) No smoothing necessary,
3) Smaller “multiple comparisons” problem.

TBSS Limitations & Enhancements

1) Default spatial normalization is not ideal.

de Groot et al., Neuroimage, 2013
Keihaninejad et al., PLoS ONE, 2012
Schwarz et al., Neuroimage, 2014

2) Projection to skeleton addresses ~10% of the misalignment.

Zalesky et al., Magn Reson Imaging, 2011

Standard Deviation

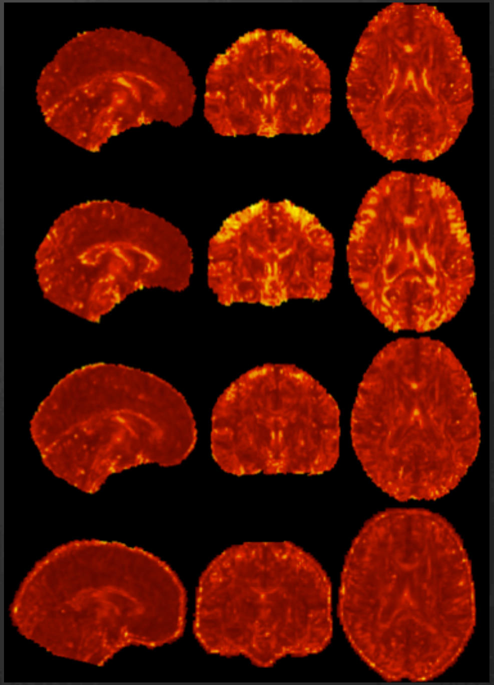
Registration to:

FMRIB58

Represent. Subj.

FMRIB58 & Ave.

Study spec.



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Zalesky et al., Magn Reson Imaging, 2011

Recommendation:

- Replace with optimal normalization strategies (e.g. tensor-based non-linear registration using high quality study-specific or standardized templates).

False Positives

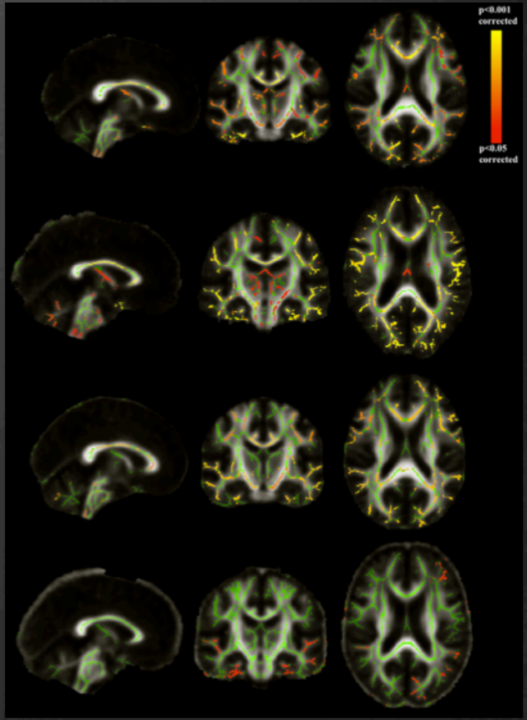
Registration to:

FMRIB58

Represent. Subj.

FMRIB58 & Ave.

Study spec.



TBSS Limitations & Enhancements

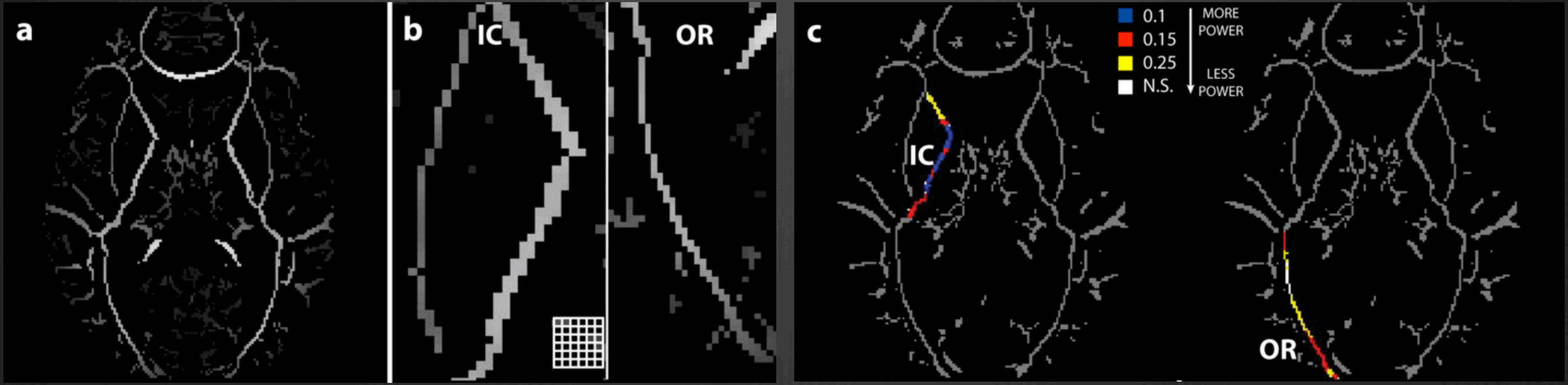
3) Only voxels at the center of tracts are studied.

Jones et al., NMR Biomed, 2010

4) Lesions may cause non-central voxels to be projected to the skeleton.

5) Higher sensitivity in diagonally-oriented tracts, because skeletonized diagonal tracts are thicker than horizontal or vertical ones.

Edden & Jones, J Neurosci Methods, 2011



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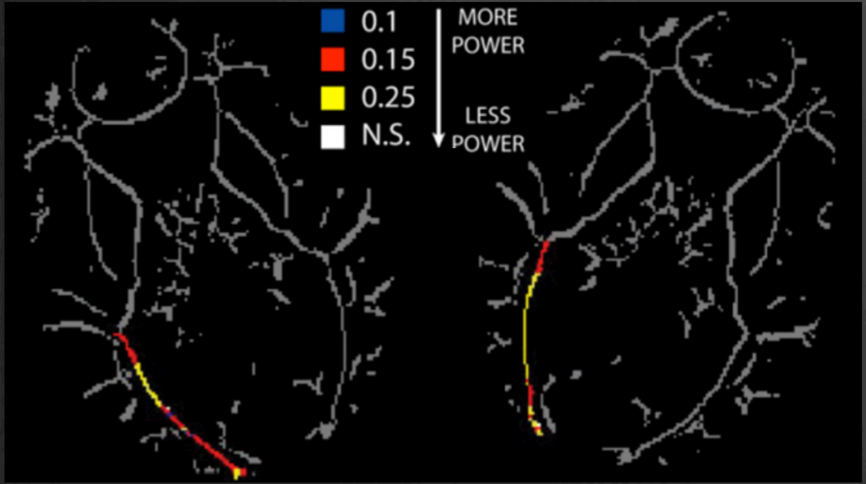
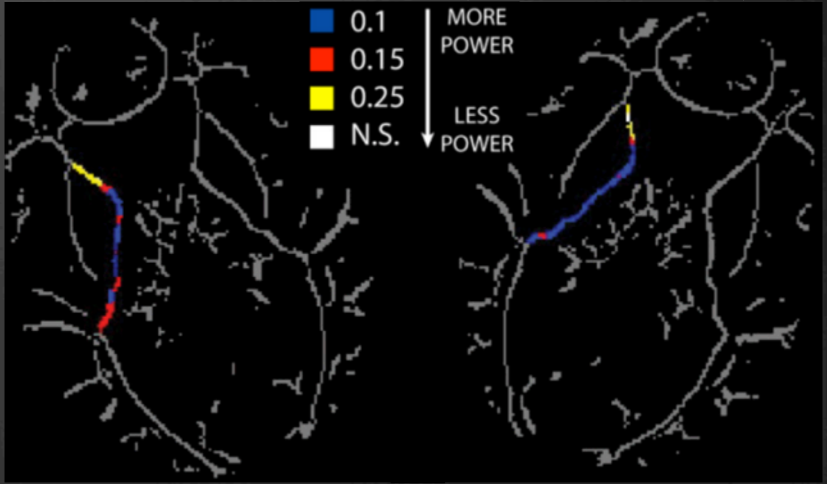




TBSS Limitations & Enhancements

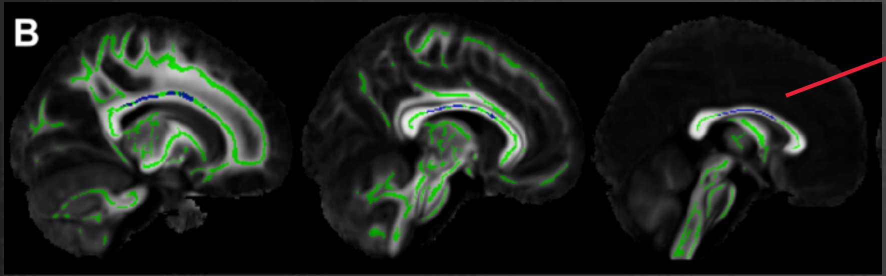
Recommendations:

- Realize which portions of the brain are included in the analysis.
- Single subject skeletons should be avoided.
- Skeletons derived from high quality study-specific or standardized templates should be preferred.
- Standardized templates and skeletons provide standard sensitivity across studies.

I can't read the skeleton….

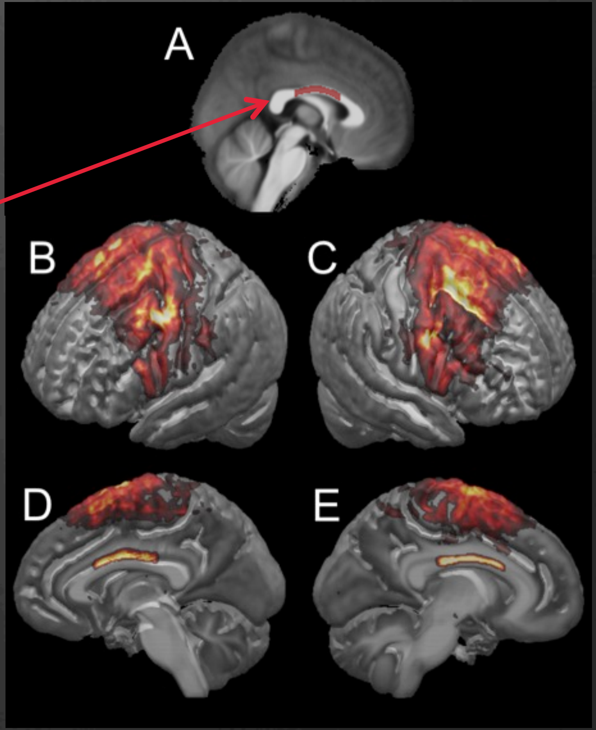
If in IIT space, then….

www.nitrc.org/projects/iit2

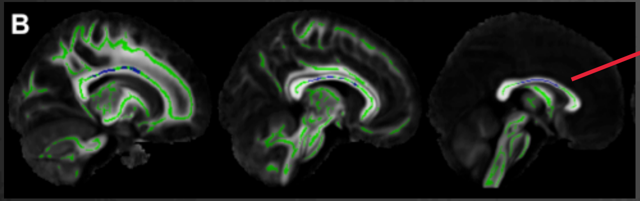


Arfanakis et al., PLoS ONE, 2013

Probabilistic tractography on the IIT HARDI template



I can't read the skeleton…
AND I don't want to run HARDI tractography
But my data are in IIT space

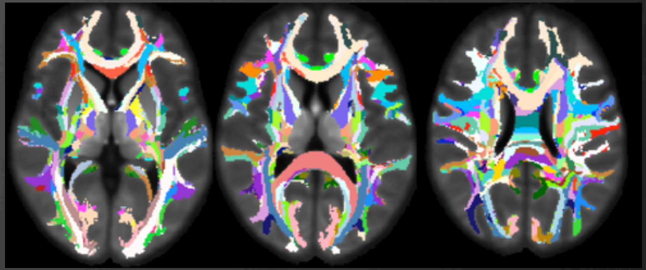


Arfanakis et al., PLoS ONE, 2013

User-defined ROI

Run provided script on the IIT 4D WM atlas

www.nitrc.org/projects/iit2



And in a few seconds:

inflammation.txt — Edited

```
98% of the selected ROI is used in this analysis
2% of the ROI is located outside white matter
49      83      22.2734
49      79      3.9707
45      79      2.5228
45      72      1.7656
49      59      1.2567
38      77      0.5293
38      72      0.3083
38      78      0.2252
48      83      0.1709
49      78      0.1356
49      72      0.1238
49      58      0.0168
44      72      0.0009
```

L Superior frontal gyrus	-	R Superior frontal gyrus	22.27%
L Superior frontal gyrus	-	R Precentral gyrus	3.97%
L Precentral gyrus	-	R Precentral gyrus	2.52%
L Precentral gyrus	-	R Paracentral gyrus	1.77%
L Superior frontal gyrus	-	R Caudal middle frontal cortex	1.26%

TBSS: Summary

- TBSS has advantages over traditional voxel-based analyses of DTI data.
- TBSS also has limitations.
- Accurate spatial normalization remains crucial (registration algorithm, template, and data quality play important roles).
- Skeleton characteristics are important.
- Standardized atlases may be particularly helpful.
- Inspect the result of each TBSS step and make necessary enhancements. Schwarz et al., Neuroimage, 2014
- Alternatives to TBSS have been proposed. Zhang et al., Med Image Anal, 2010

Outline

- Spatial normalization in DTI:
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ROI-based Group Comparisons

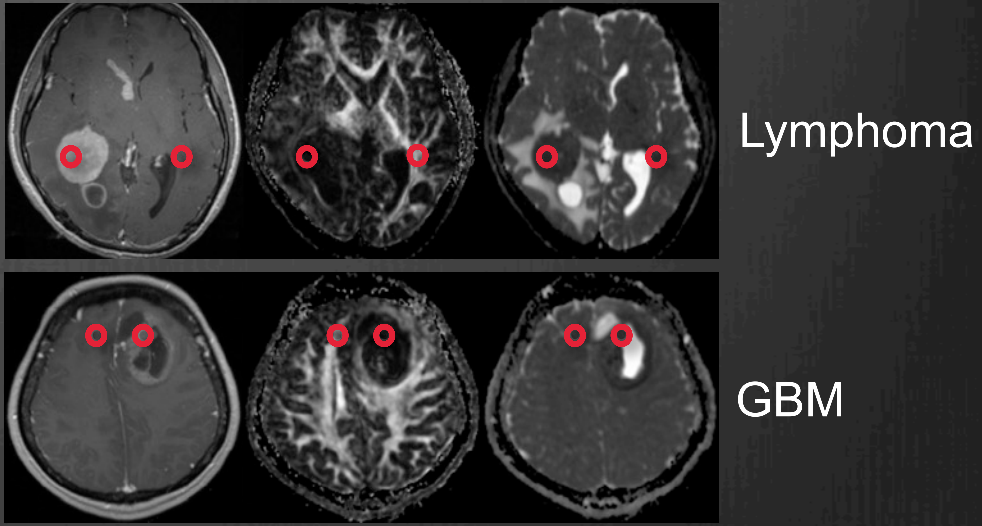
- ROI-based group comparison.
  - Step 1: ROI selection.
  - Step 2: Extract information about ROI.
  - Step 3: Statistical analysis.

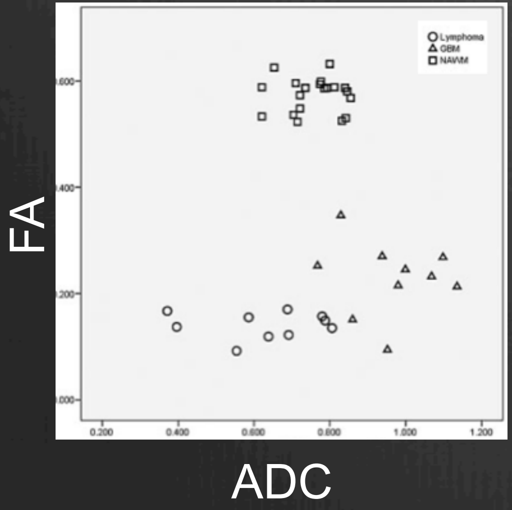
ROI is:

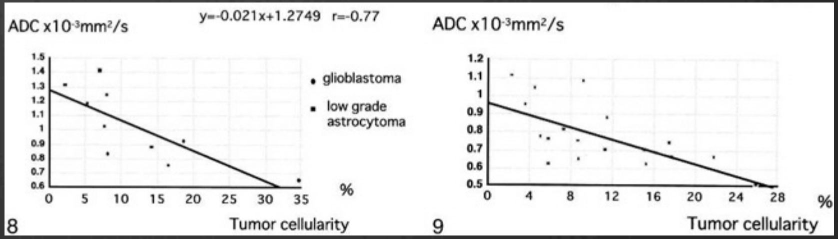
1) Lesion.
2) A fiber-bundle defined with tractography.
3) Brain structure or fiber-bundle segmented using atlas-based segmentation.
4) Part of the white matter skeleton defined with skeletonized atlas-based segmentation.

ROI-based Group Comparisons: Lesions

- Select lesion or ROI within lesion.
- Compare across subjects:
  - Summaries of diffusion characteristics.
  - Histograms, etc.



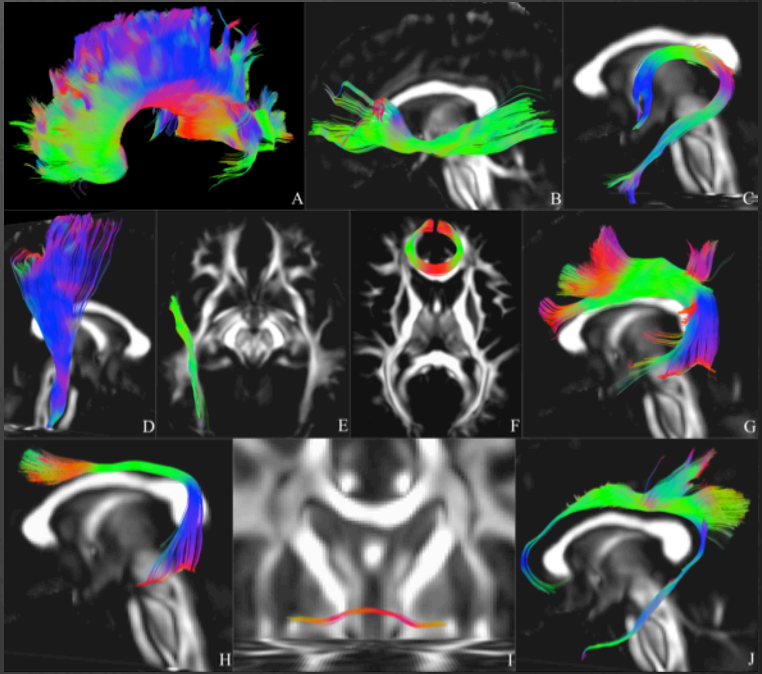




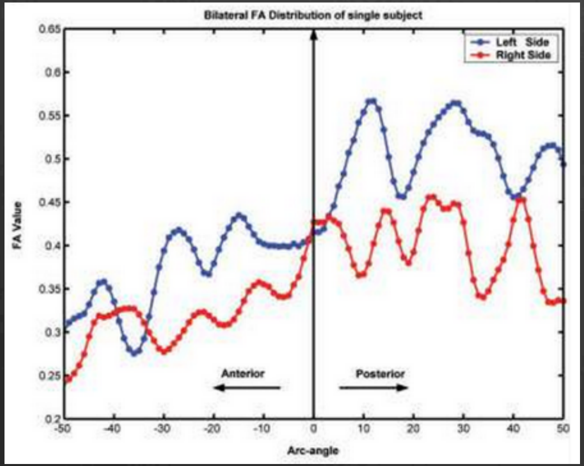
Kono et al., AJNR, 2001

ROI-based Group Comparisons: Fiber-Bundles

- Select seed ROIs in native space.
- Track fiber-bundle in native space.
- Compare across subjects:
  - Summaries of diffusion characteristics.
  - Diffusion characteristics along the bundle.



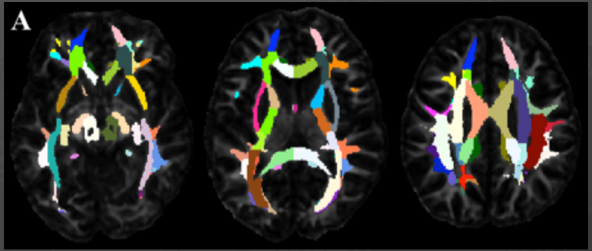
Gong et al.,
Hum Brain Mapp, 2005



ROI-based Group Comparisons: Atlas-based Segmentation

- Register atlas to individual subject.
- Transfer labels to subject space.

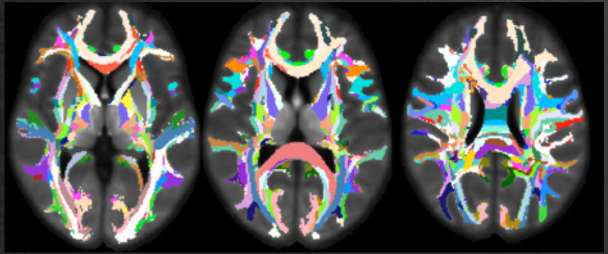
  - Anatomy-based labels: Eve



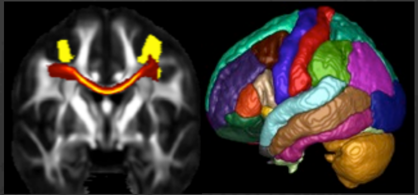
  - Probabilistic, connectivity-based labels (HARDI):

IIT v.4.0

4D WM labels



TDI for connectivity of pairs of GM regions



Major fiber bundles

ROI-based Group Comparisons: Atlas-based Segmentation

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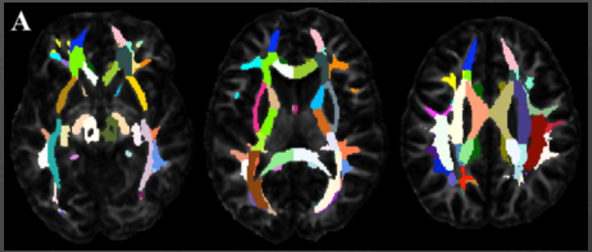

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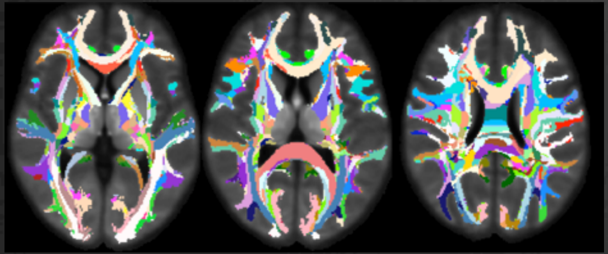
IIT v.4.0

4D WM labels



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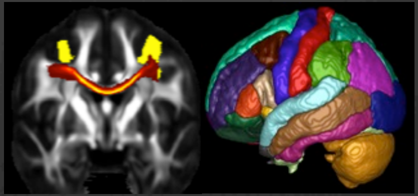
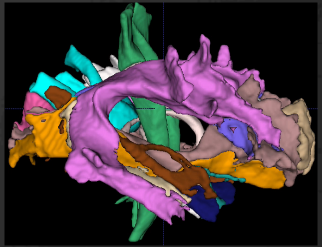


Major fiber bundles



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ROI-based Group Comparisons: Atlas-based Segmentation

- Compare across subjects:
  - Summaries of diffusion characteristics.
  - Histograms, etc.

Recommendations:

- Use strategies for optimal normalization (registration algorithm, template, data quality).
- Use atlases with connectivity-based instead of anatomy-based labels.

ROI-based Group Comparisons: Skeletonized Atlas-based Segmentation

- ROI studies using atlas-based segmentation are also sensitive to misregistration (similar to voxel-wise studies).
- Combine projection to a skeleton with atlas-based segmentation.

<u>Skeletonized atlas-based segmentation</u>

<u>Step 1</u>: Spatial normalization to atlas space

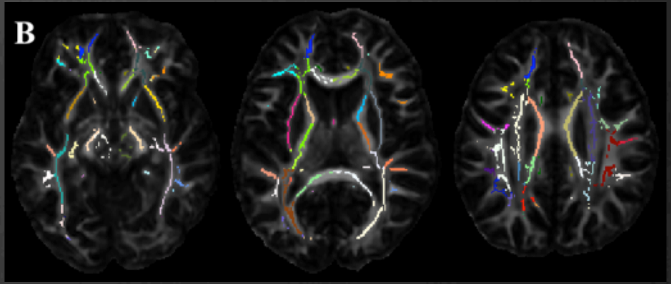
<u>Step 2</u>: Skeletonization

<u>Step 3</u>: Masking atlas labels with skeleton

<u>Step 4</u>: Projection onto the skeleton

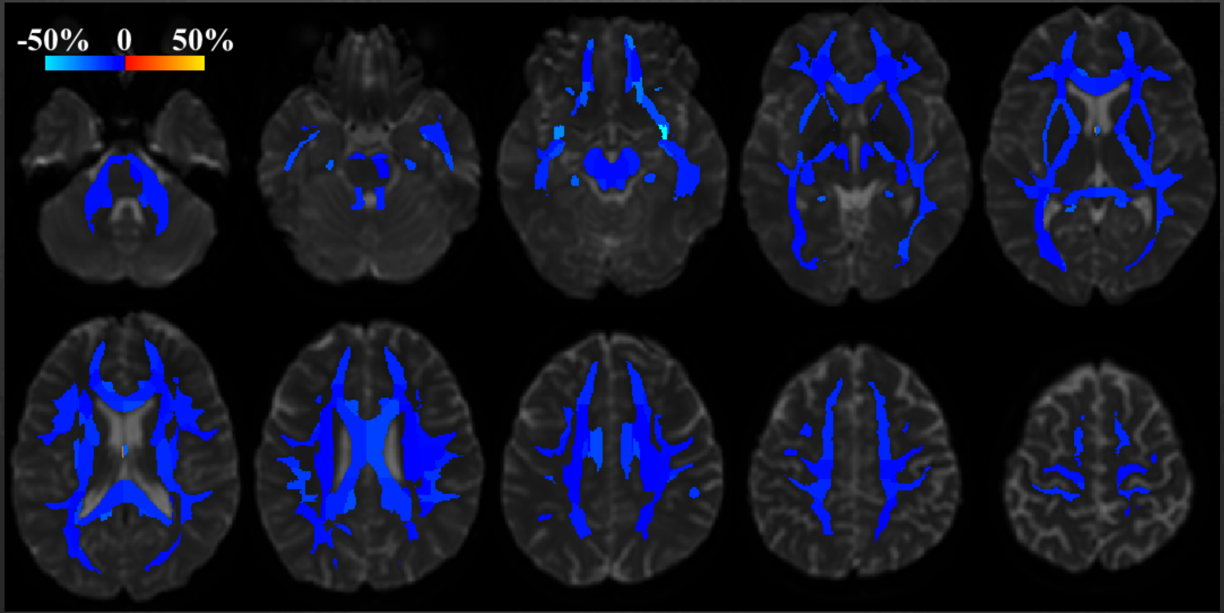
<u>Step 5</u>: Extract summary measures per skeleton segment

<u>Step 6</u>: Statistical analysis per skeleton segment



ROI-based Group Comparisons: Skeletonized Atlas-based Segmentation

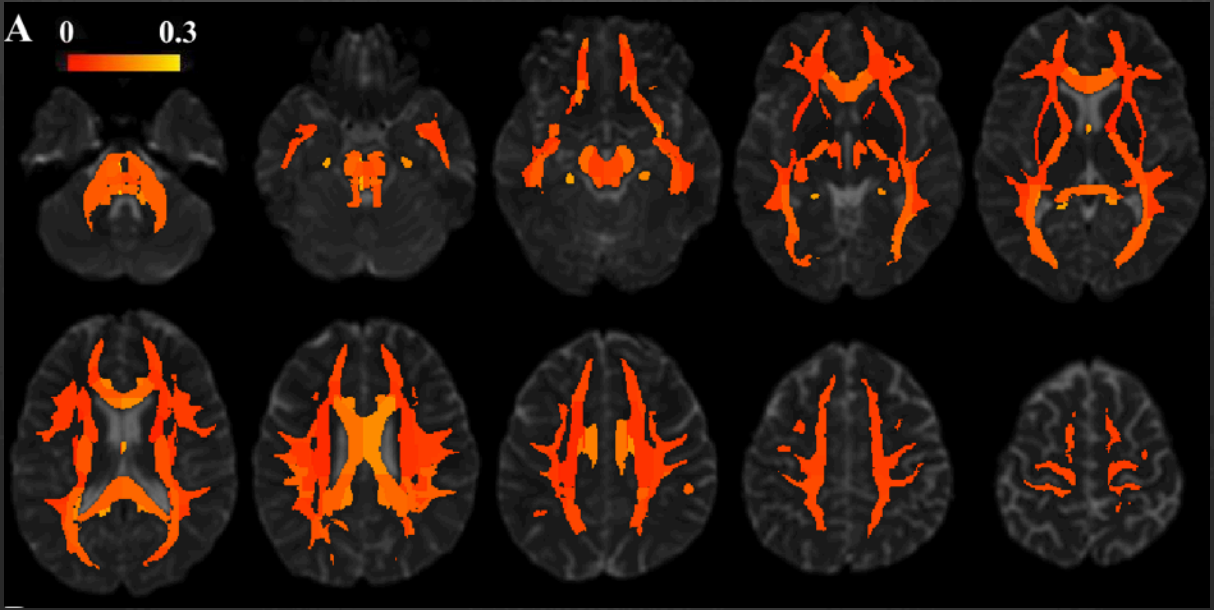
Non-WM % in skeletonized - traditional atlas-based segmentation



Zhang & Arfanakis, J Magn Reson Imaging, 2014

ROI-based Group Comparisons: Skeletonized Atlas-based Segmentation

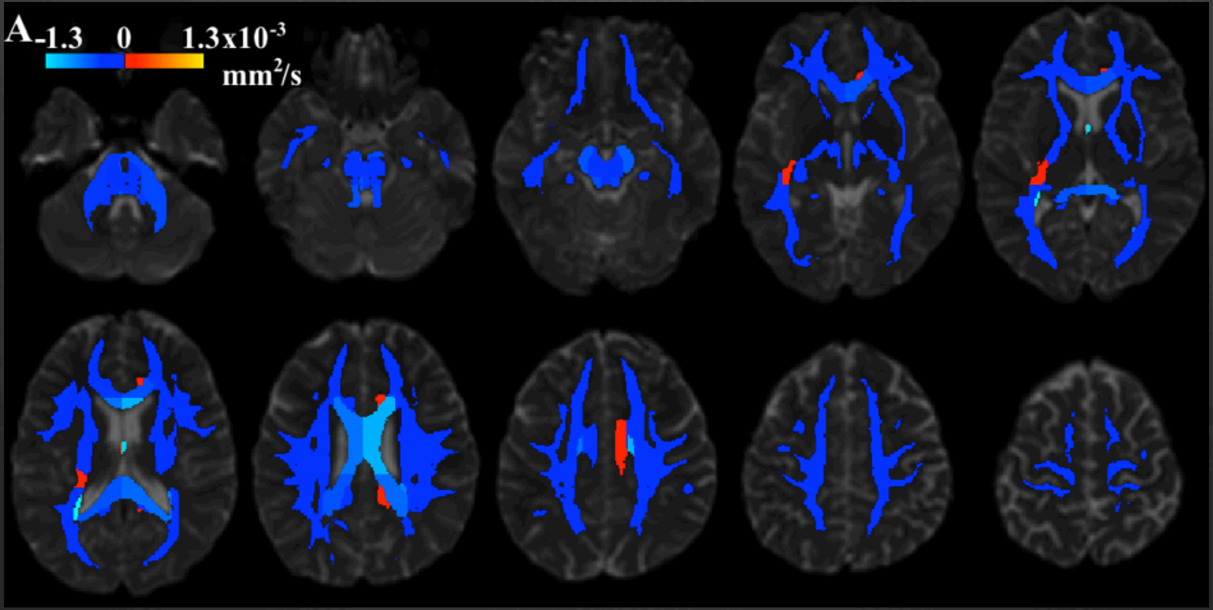
Mean FA from skeletonized - mean FA from traditional atlas-based segmentation



Zhang & Arfanakis, J Magn Reson Imaging, 2014

ROI-based Group Comparisons: Skeletonized Atlas-based Segmentation

Mean trace from skeletonized - mean trace from traditional atlas-based segmentation



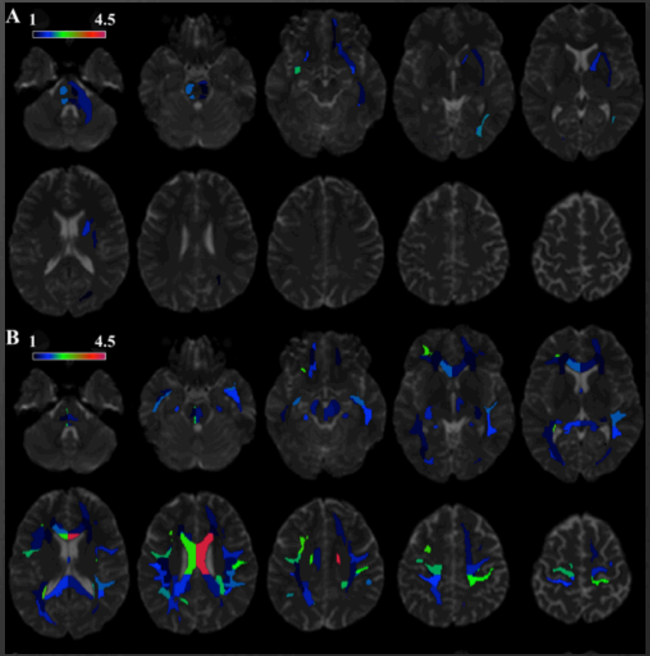
Zhang & Arfanakis, J Magn Reson Imaging, 2014

ROI-based Group Comparisons: Skeletonized Atlas-based Segmentation

Sample size comparison for detecting a 10% reduction in FA

$$\frac{\text{Sample size with skeletonized segmentation}}{\text{Sample size with traditional segmentation}} > 1$$

$$\frac{\text{Sample size with traditional segmentation}}{\text{Sample size with skeletonized segmentation}} > 1$$



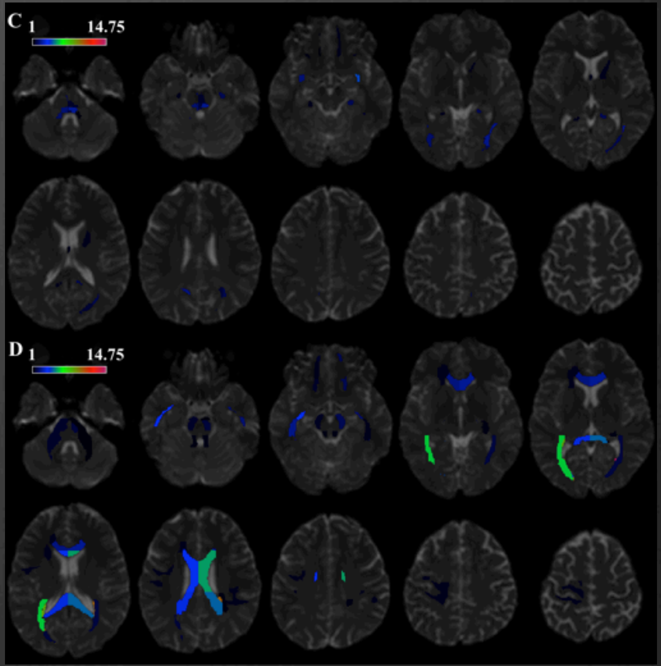
Zhang & Arfanakis, J Magn Reson Imaging, 2014

ROI-based Group Comparisons: Skeletonized Atlas-based Segmentation

Sample size comparison for detecting a 10% increase in trace

$$\frac{\text{Sample size with skeletonized segmentation}}{\text{Sample size with traditional segmentation}} > 1$$

$$\frac{\text{Sample size with traditional segmentation}}{\text{Sample size with skeletonized segmentation}} > 1$$



Zhang & Arfanakis, J Magn Reson Imaging, 2014

ROI-based Group Comparisons: Summary

- Lesions, brain structures and fiber bundles.
- Lesions: Manual segmentation. Time-consuming. Automated lesion segmentation when possible.
- Fiber-bundles: Tractography. Sensitivity to artifacts and noise, but is customized to subject-specific features.
- Brain structures or brain connections: Atlas-based segmentation.
- Standardized atlases.
- Accurate spatial normalization remains crucial (registration algorithm, template, and data quality play important roles).
- Skeletonized atlas-based segmentation reduces sensitivity to misregistration.
- Smaller multiple comparisons problem compared to voxel-wise analyses.

Outline

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Group Comparisons for Other Diffusion Imaging Models

- The concepts are the same. The methods differ.
- Spatial normalization:
  - FOD registration.
  - Non-linear.
  - Representative template.

Yap et al., Neuroimage, 2011
Raffelt et al., Neuroimage, 2011
Cheng et al., MICCAI, 2009
Hong et al., Magn Reson Med, 2009
Barmpoutis et al., MICCAI, 2007

IIT HARDI template v.4.0 www.nitrc.org/projects/iit2

Varentsova et al., Neuroimage, 2014

  - Data quality.
- Features:
  - Depends on the diffusion imaging model used.
- Analysis:
  - Voxel-based
  - ROI-based

Take Home Messages

- Spatial normalization plays a central role in group comparison of diffusion imaging data (importance of registration algorithm, template, and data quality).
- Traditional voxel-based analysis has important limitations and is generally avoided.
- Voxel-based analysis through TBSS has advantages over traditional voxel-based analyses, but several enhancements are necessary.
- ROI-based analysis is used to study lesions, brain structures and fiber-bundles.
- Skeletonized atlas-based segmentation is superior to traditional atlas-based segmentation for ROI studies.
- For other diffusion imaging models, the concepts are the same but the methods differ.

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