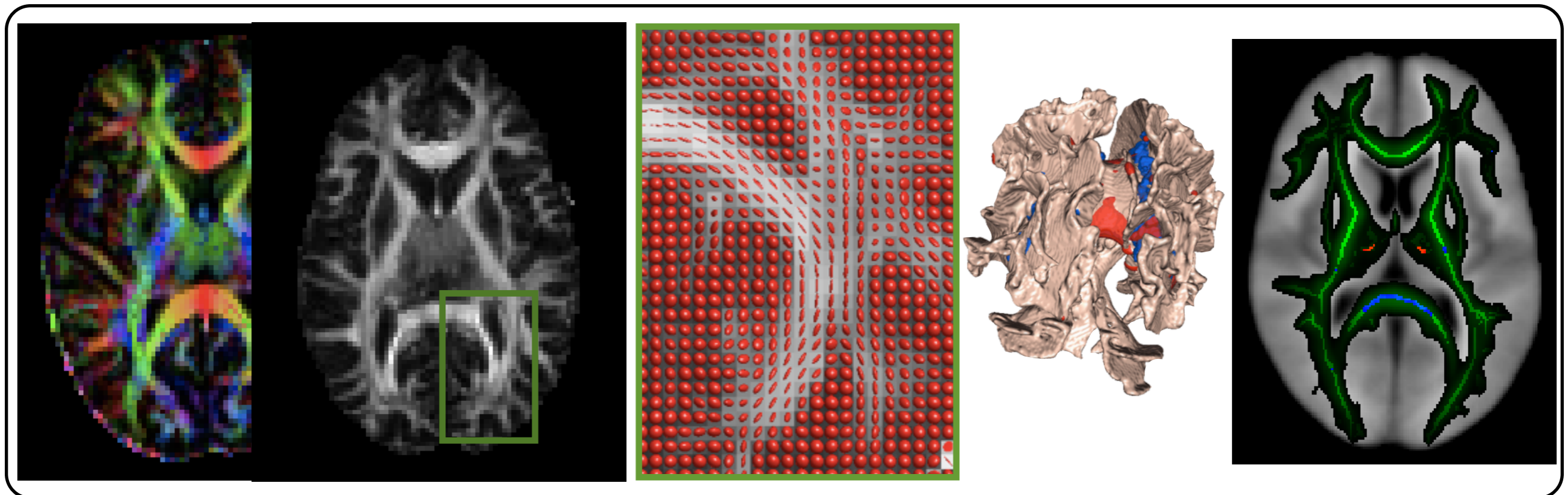




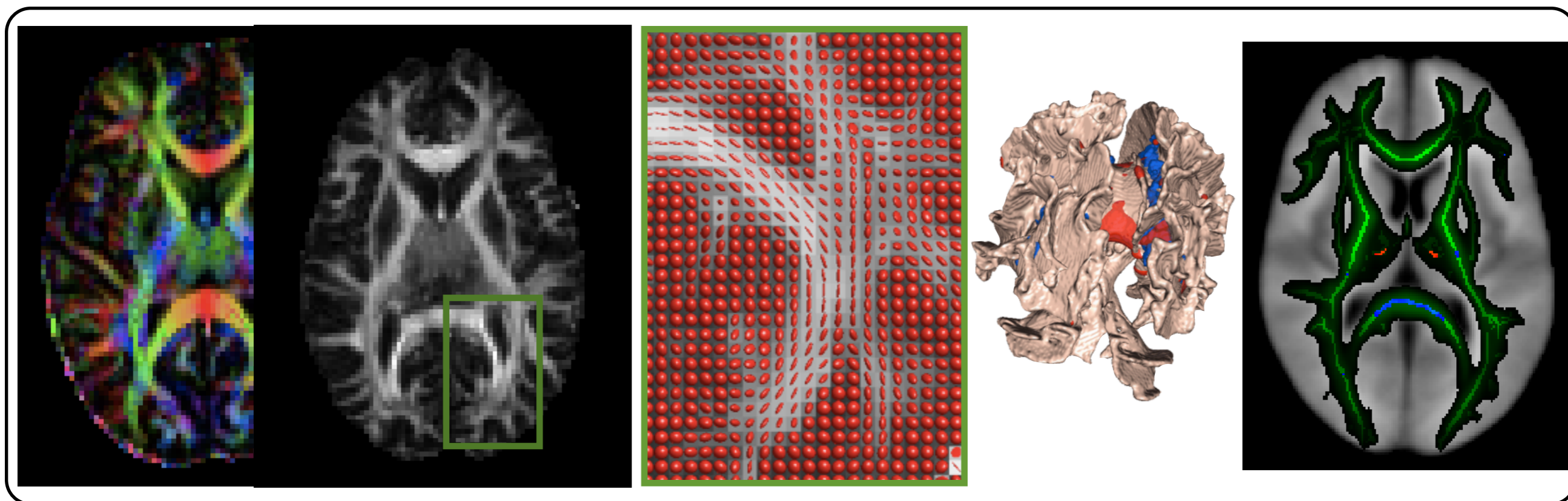
Diffusion MRI Processing and Analysis





Overview

- What is Diffusion? Diffusion-weighting in MRI
- Diffusion Tensor Model and DTI
- Tract-Based Diffusion analysis (TBSS)
- Distortion Correction for Diffusion MRI

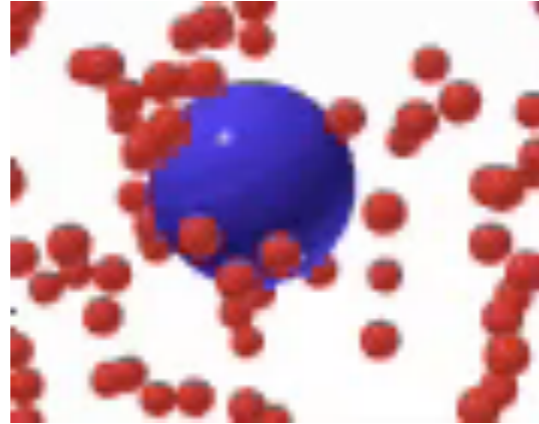




Diffusion - Brownian Motion



Robert Brown (1773-1858)



Molecules are in constant motion at non-zero absolute temperatures ($> -273^{\circ}\text{C}$)

Diffusion = thermally-driven random motion



Diffusion - Brownian Motion



Albert Einstein (1879-1955)

How can we describe this motion?
For an ensemble of molecules, in n -dimensional space:

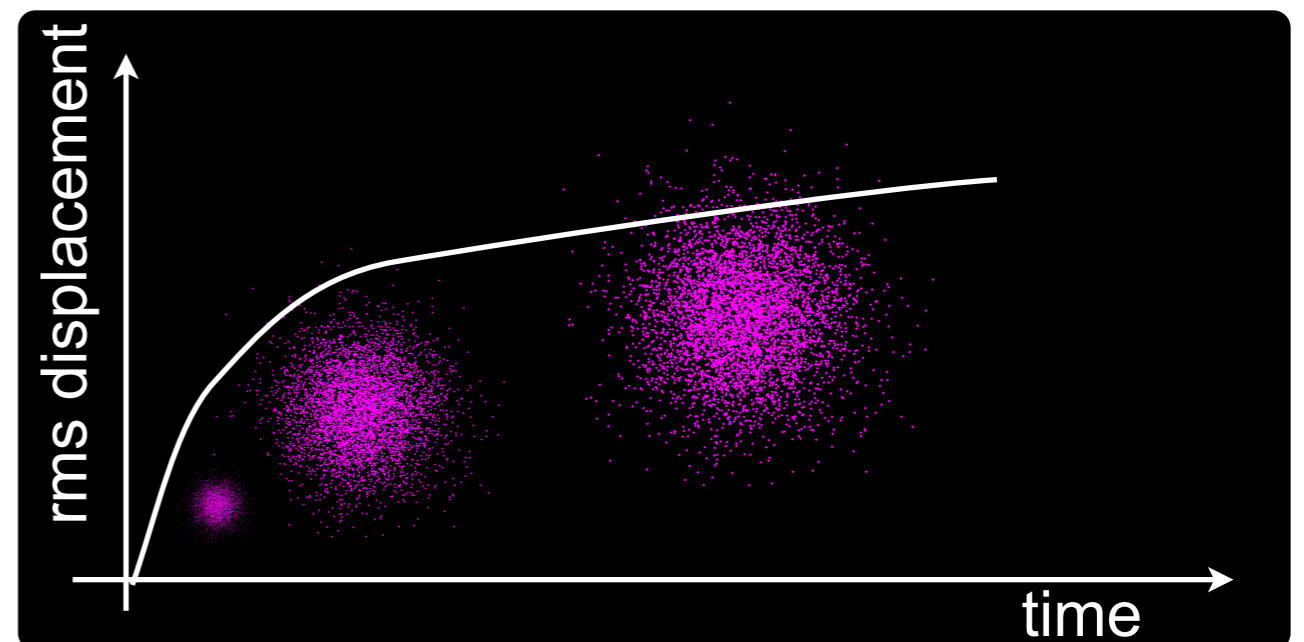
$$\langle x^2 \rangle = 2nDt$$

mean squared displacement

Diffusion coefficient

time

Valid for a homogeneous, barrier-free medium.





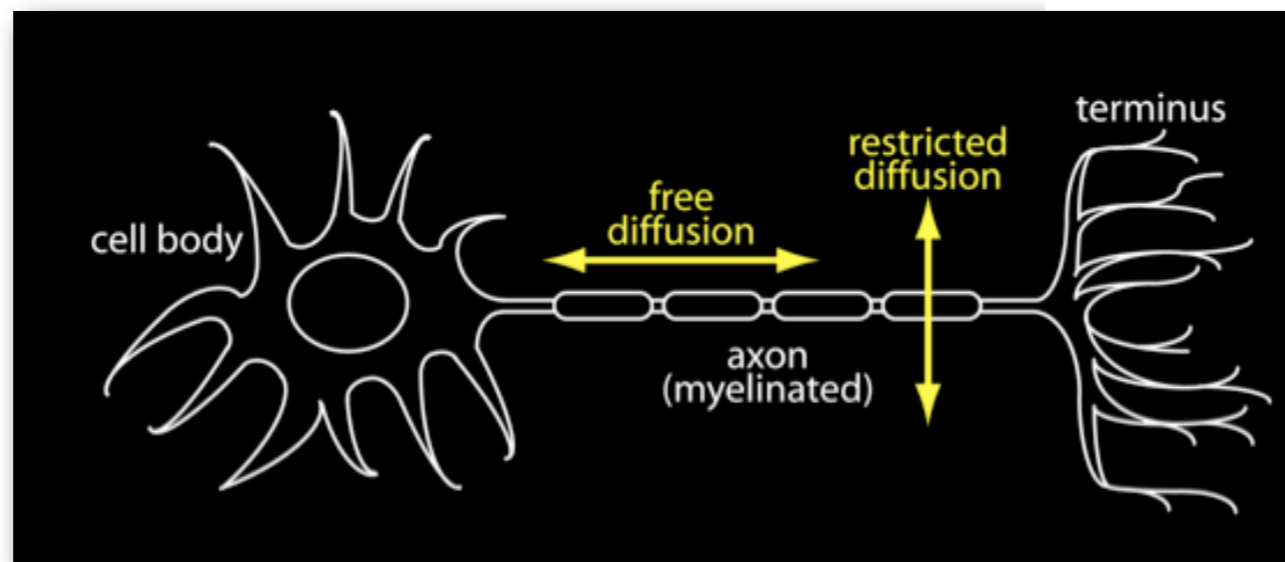
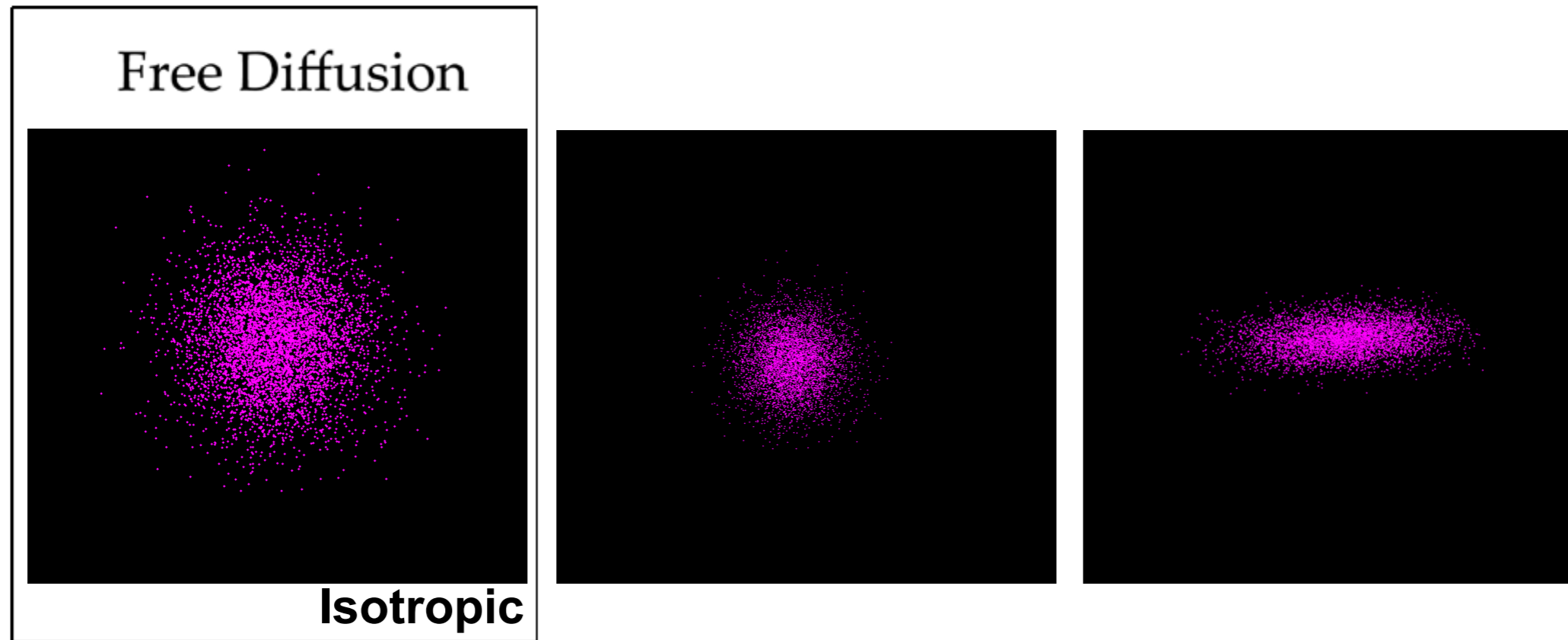
Diffusion - Brownian Motion

Another way to describe Einstein's equation:

For a barrier-free medium, **diffusion displacements of an ensemble follow a Normal distribution** with $N(0, 2tD)$:

- Zero-mean displacement
- Variance proportional to time and the diffusion coefficient

Water Diffusion in the Brain. Why is it Interesting?

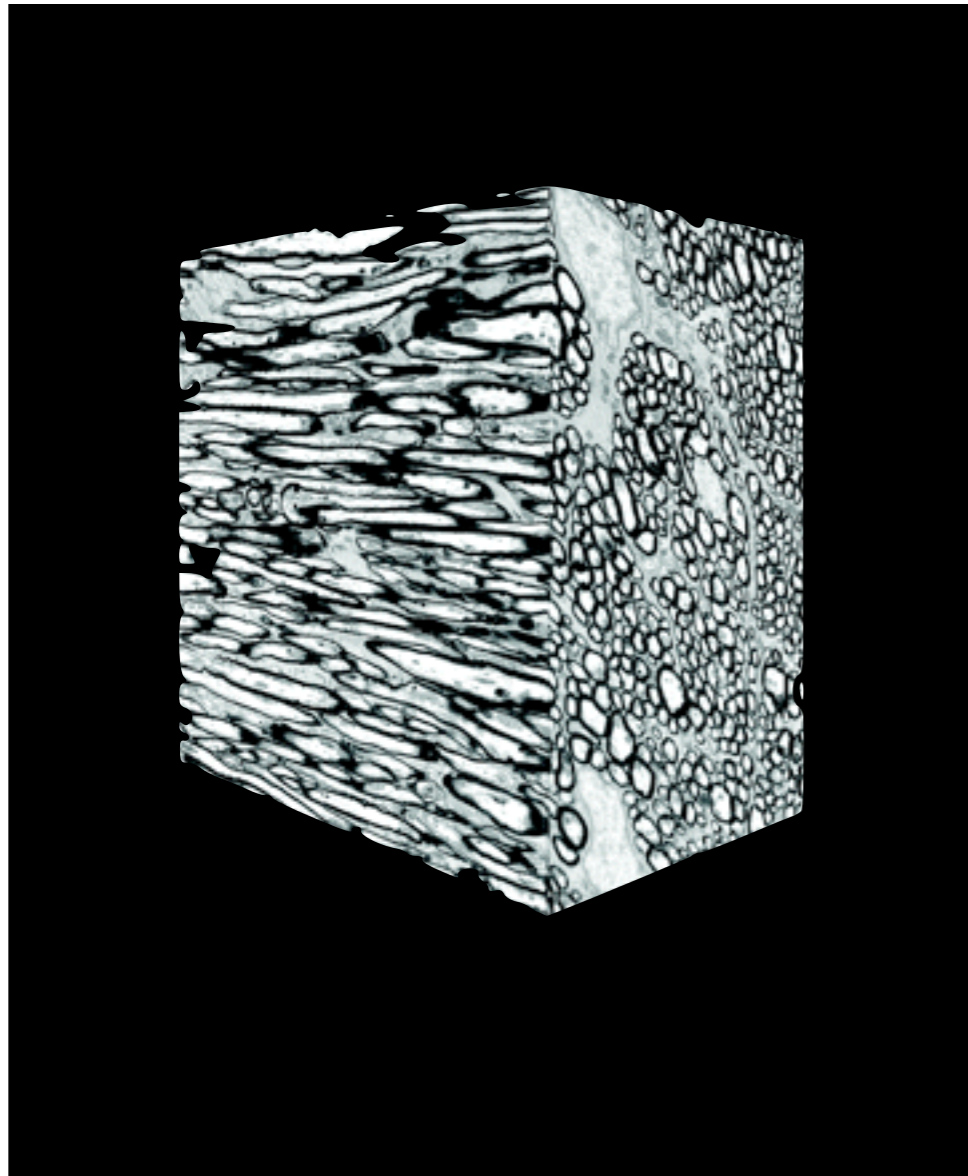


Diffusion is restricted by tissue boundaries, membranes, etc.
Marker for tissue microstructure (healthy and pathology)
Diffusion is **anisotropic** in white matter

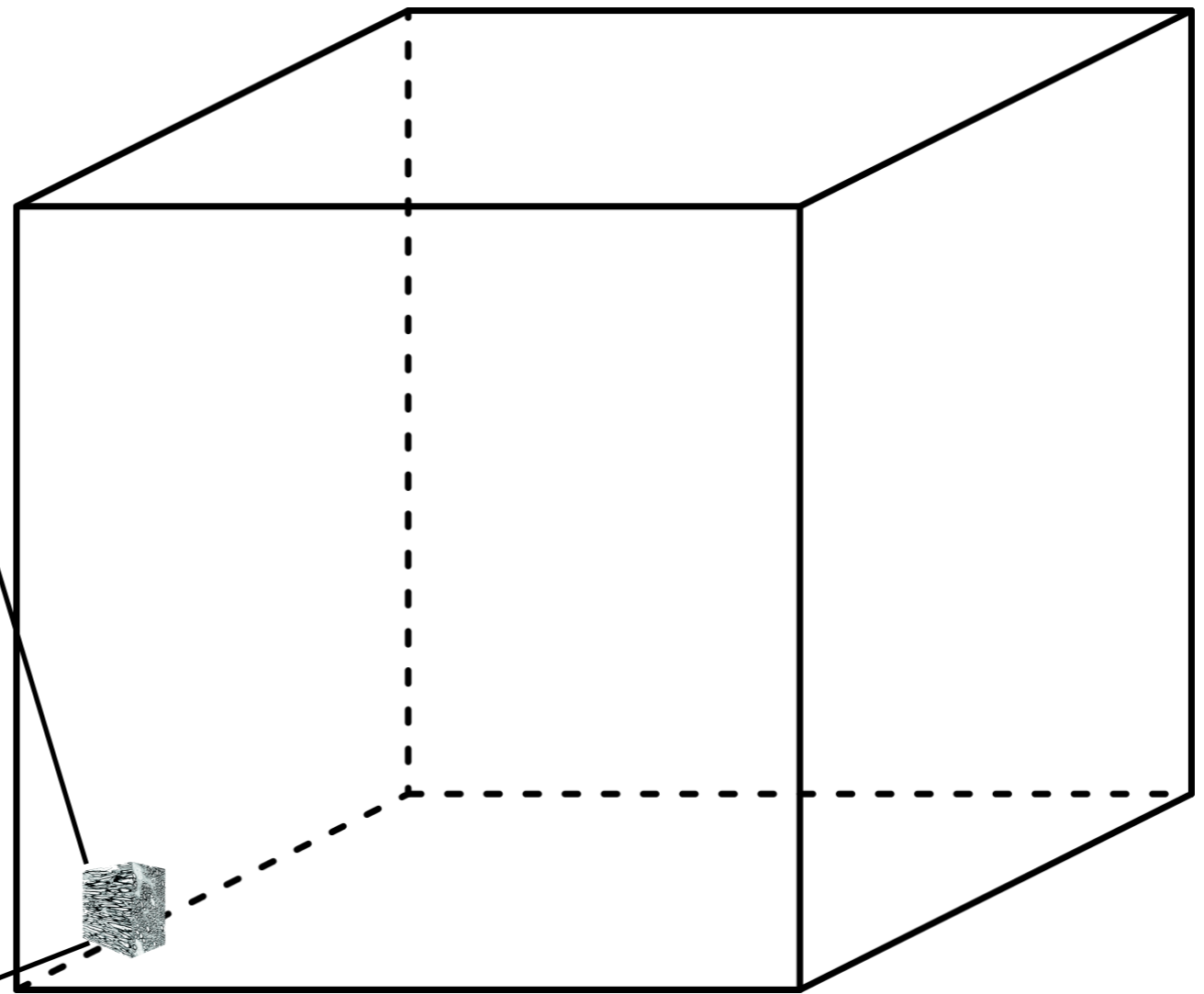
[Beaulieu, NMR Biomed, 2002]

Problems of scale

Microscopic view of white matter axon size ($\sim\mu\text{m}$)



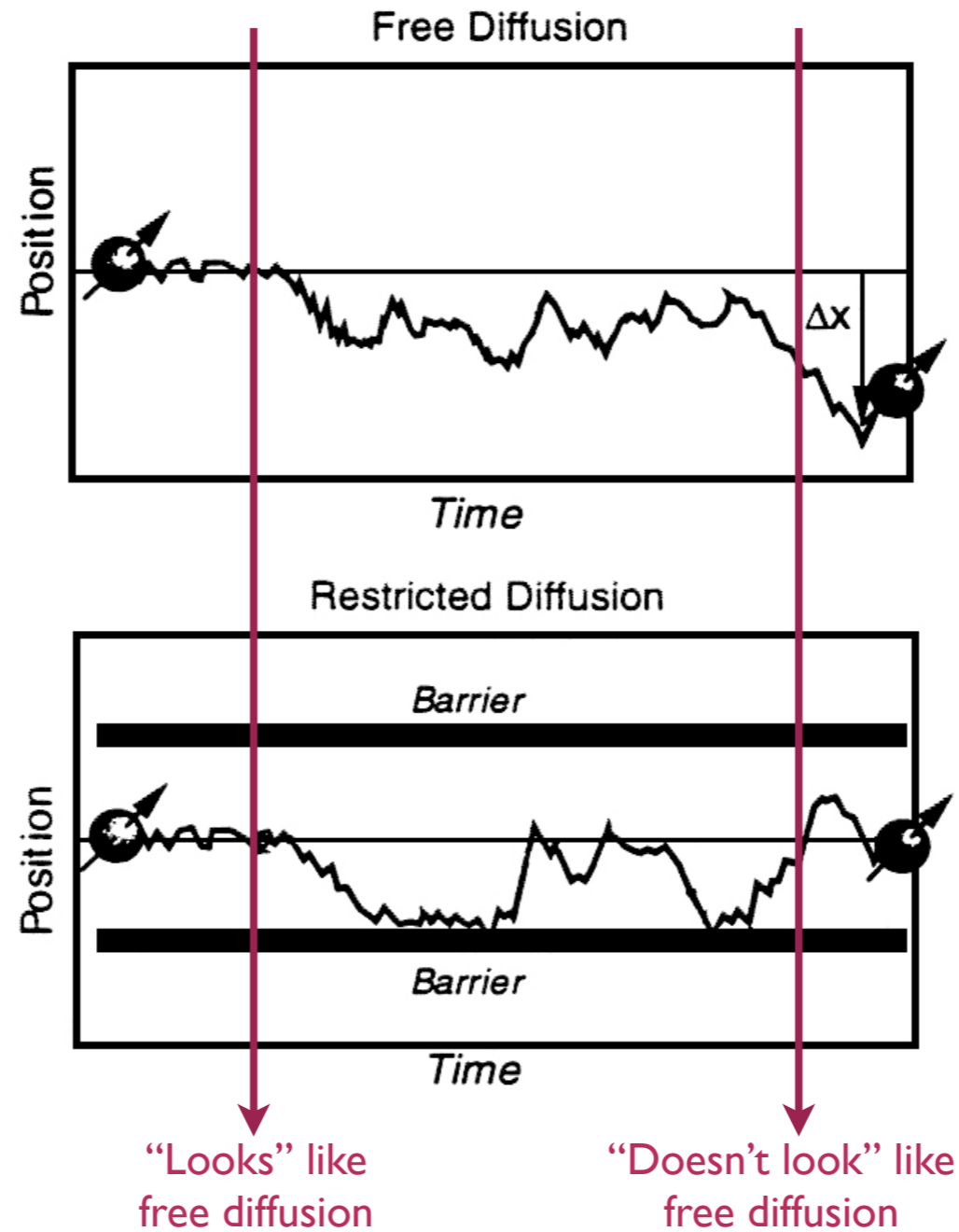
MRI voxel size ($\sim\text{mm}$)



Ohno et al. 2013



Apparent Diffusion



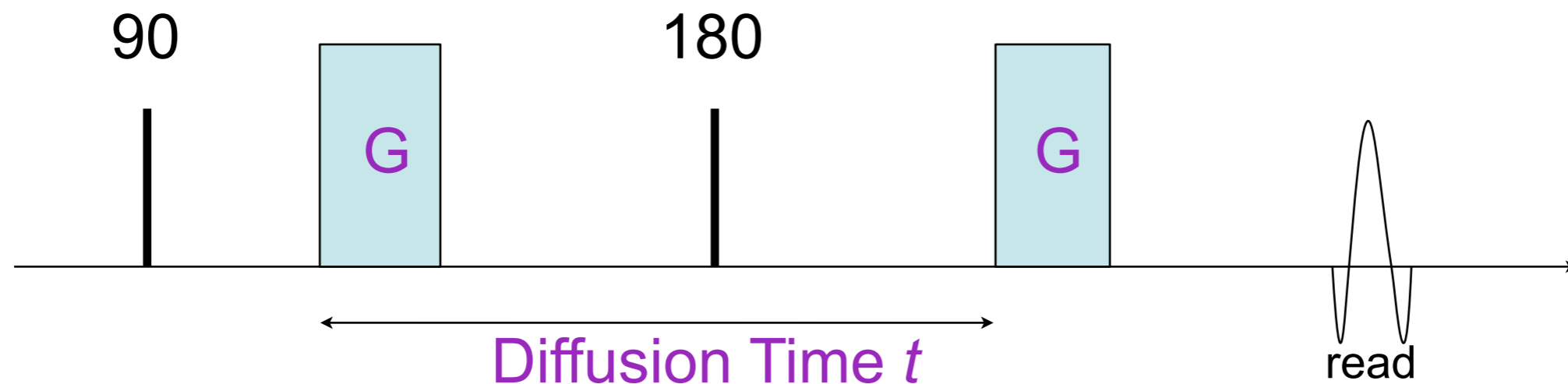
Observed diffusion in tissues depends on the experiment =
"Apparent diffusion" &
"Apparent diffusion coefficient" (ADC)



Measuring Diffusion with MRI: Diffusion MRI (dMRI)

Pulsed-Gradient Spin-Echo Sequence:

To achieve diffusion-weighting along a direction \mathbf{x} , apply strong magnetic field gradients along \mathbf{x} .



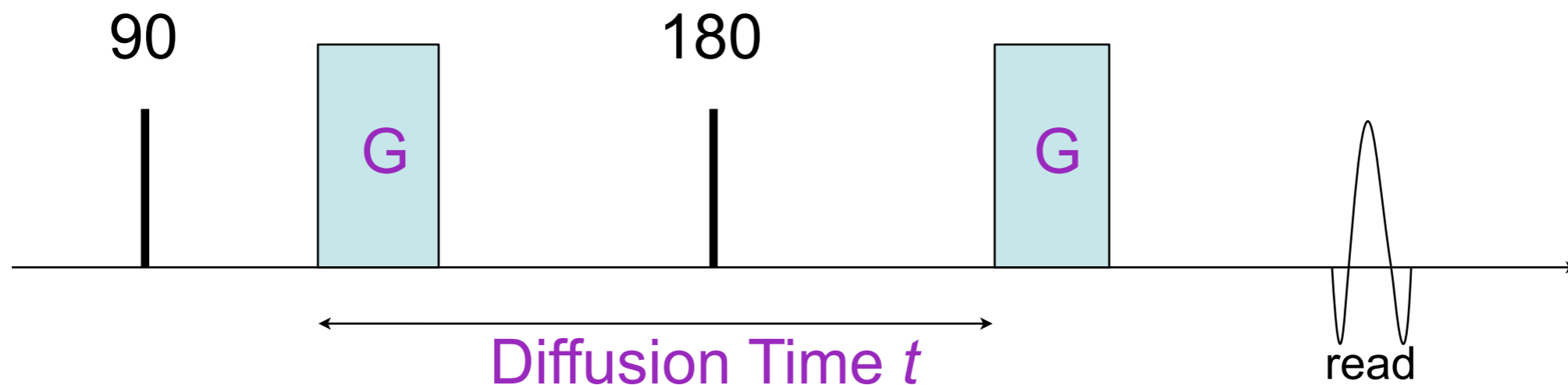
If particles diffuse along \mathbf{x} during the allowed time (DiffTime), a signal attenuation is observed, compared to the signal with $G=0$.



Measuring Diffusion with MRI: Diffusion MRI (dMRI)

Pulsed-Gradient Spin-Echo Sequence:

To achieve diffusion-weighting along a direction \mathbf{x} , apply strong magnetic field gradients along \mathbf{x} .



$D \sim 2.4 \mu\text{m}^2/\text{ms}$
 $t \sim 50\text{ms}$

$\Rightarrow x = \sqrt{6Dt} \sim 27\mu\text{m}$

st. deviation of displacements

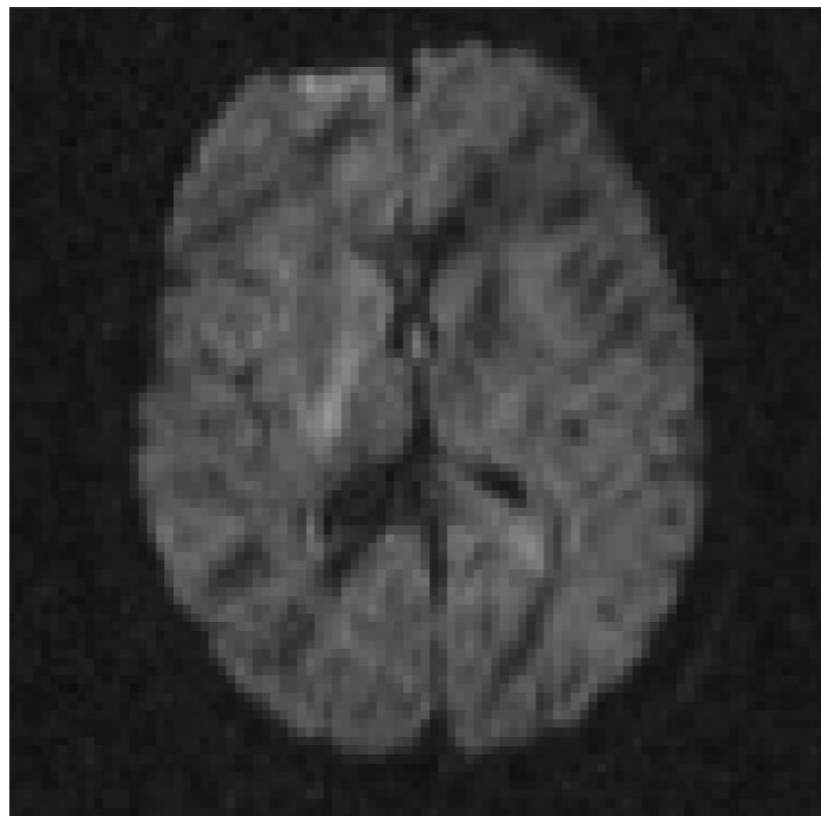


Measuring Diffusion with MRI: Diffusion MRI (dMRI)

T2w Image
No Diffusion-weighting
($G=0$)
 S_0



Diffusion-weighted
Image
 S



Ratio
 S/S_0



Removes T2w contrast



Measuring Diffusion with MRI: Diffusion MRI (dMRI)

Diffusion contrast can be modulated by:

A) Diffusion weighting: Gradient **strength**, Diffusion **time**

$$\mathbf{b\ value} \sim G^2 \cdot \text{DiffTime} \quad (\text{units in s/mm}^2)$$

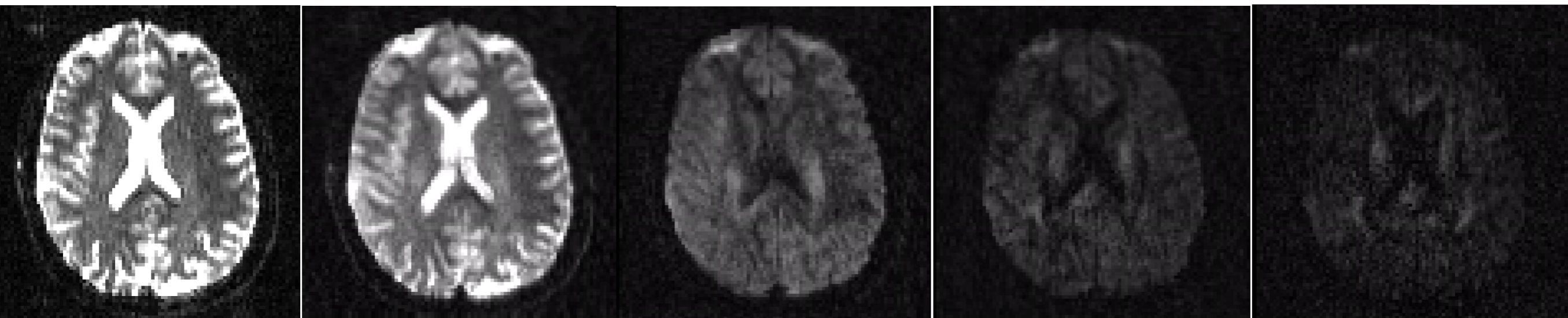
b=0

b=300

b=1000

b=2000

b=3000

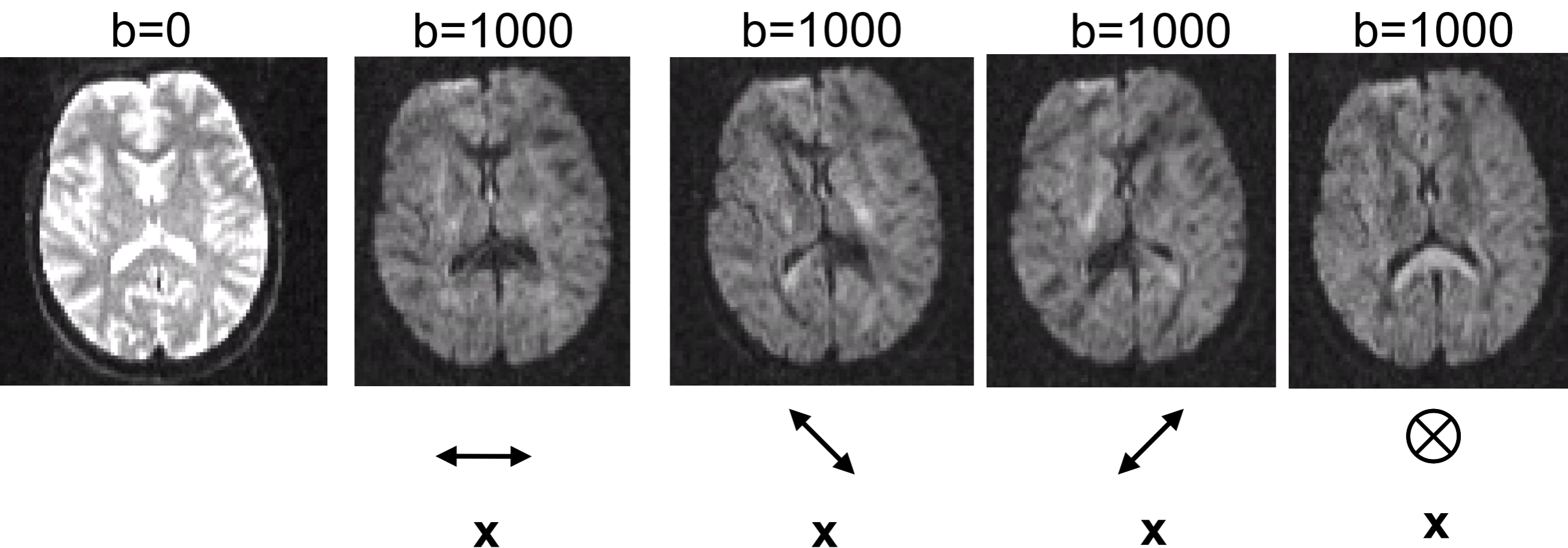


More diffusion contrast with higher b :)
...But less signal left - exponential decay :(



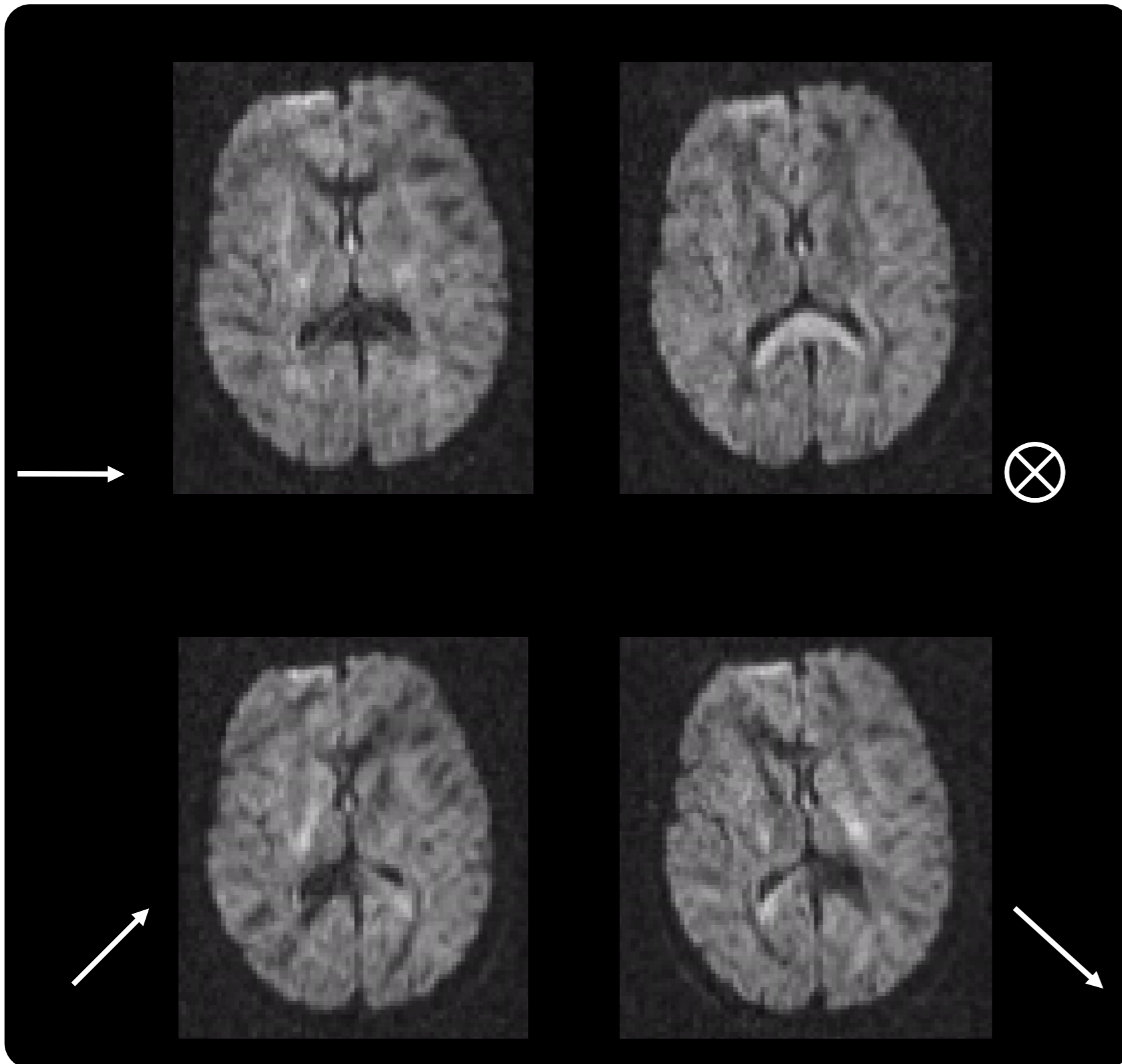
Measuring Diffusion with MRI: Diffusion MRI (dMRI)

Diffusion contrast can be modulated by:
B) Gradient Direction \mathbf{x}



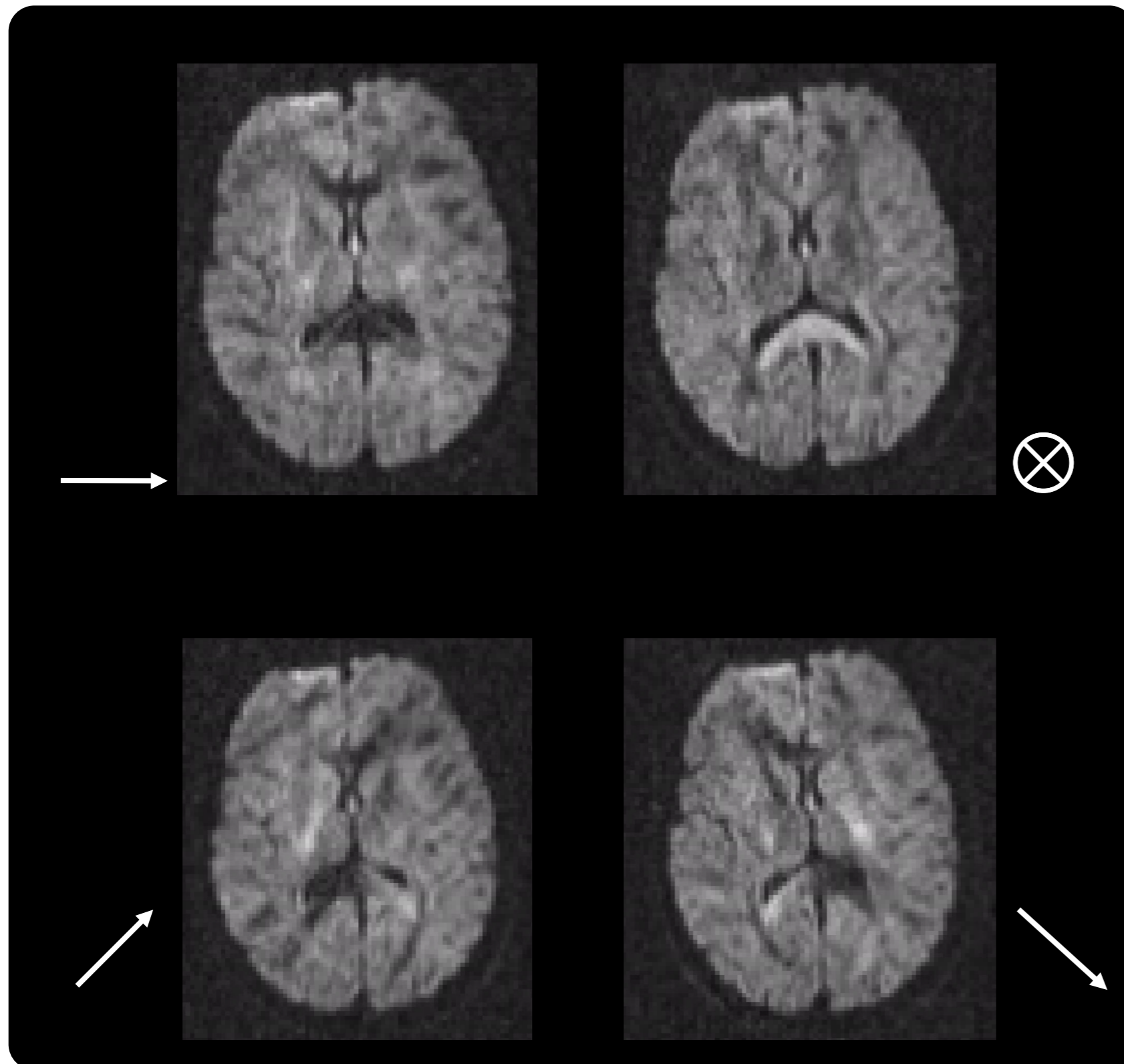


Orientation Contrast in dMRI





Orientation Contrast in dMRI



Because diffusion is anisotropic in WM, applying a gradient G along different directions \mathbf{x} , gives different contrast in WM.

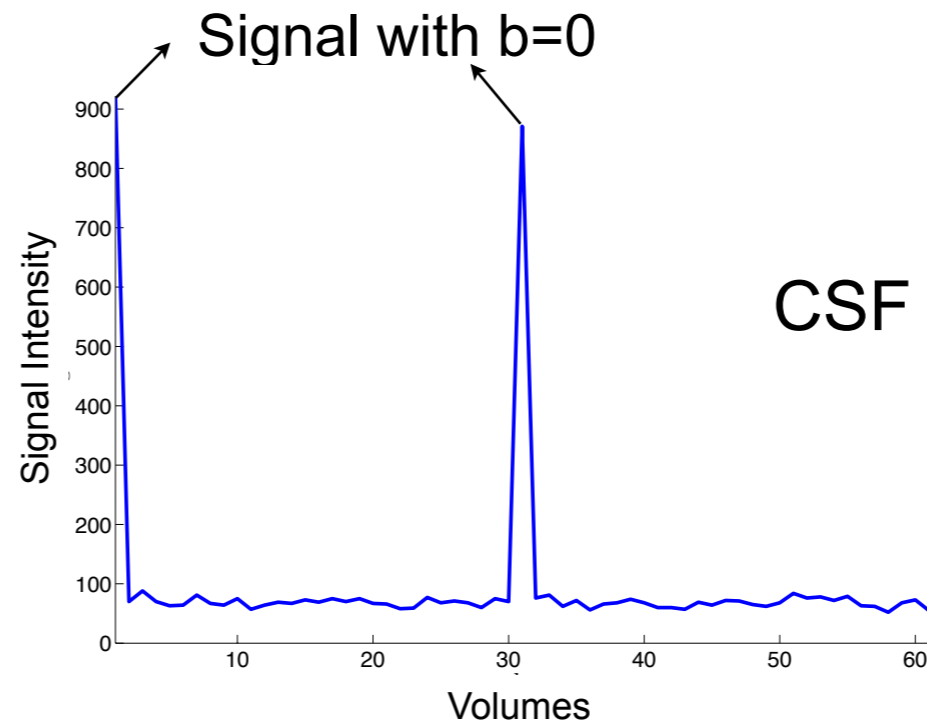
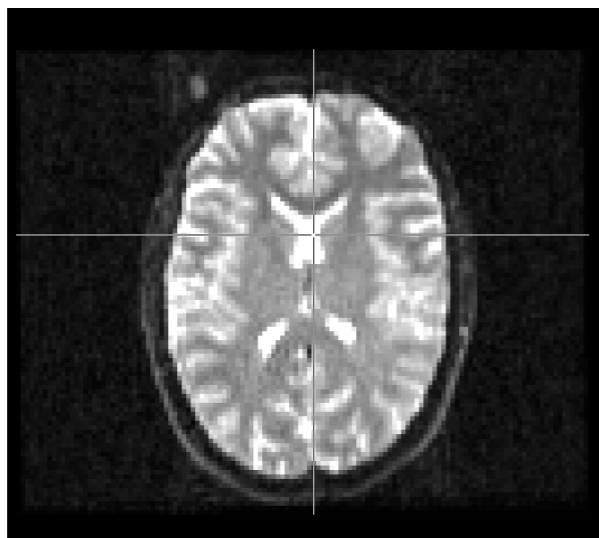
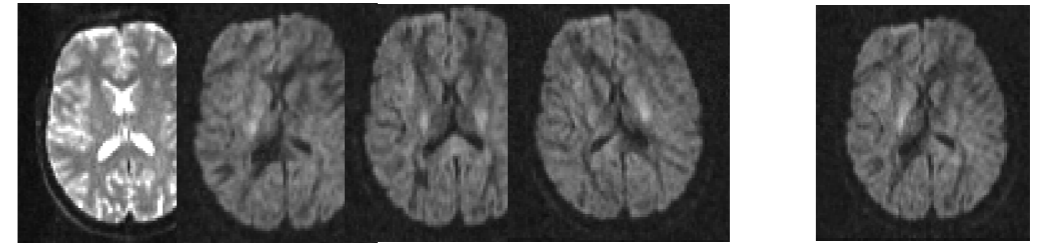
Anisotropic measurements in WM!

Roughly **Isotropic** in GM and CSF.

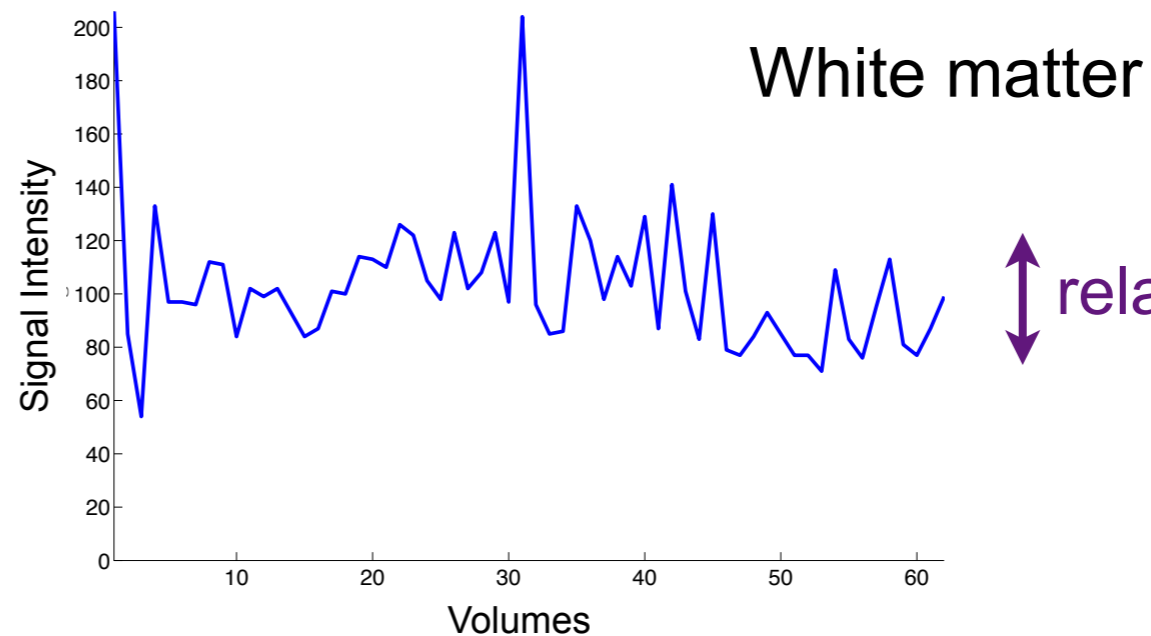
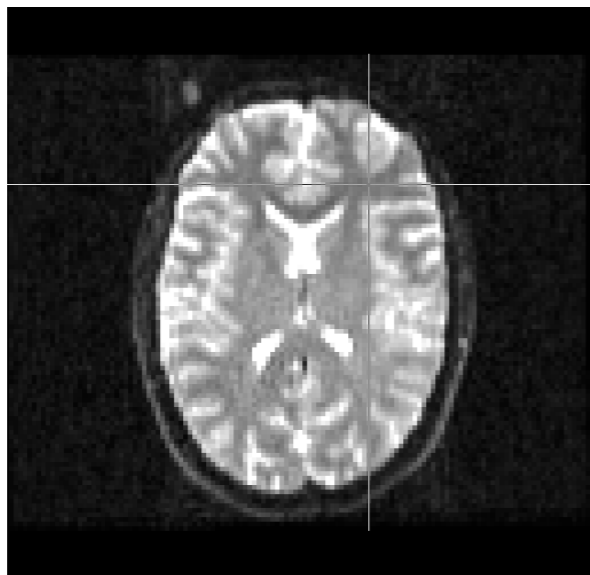


A Typical dMRI Protocol

- Normally a few (at least one) $b=0$ volumes acquired, along with volumes at higher b (~ 1000 s/mm^2).
- Different gradient directions are applied for the high b volumes.



relates to ADC



relates to anisotropy

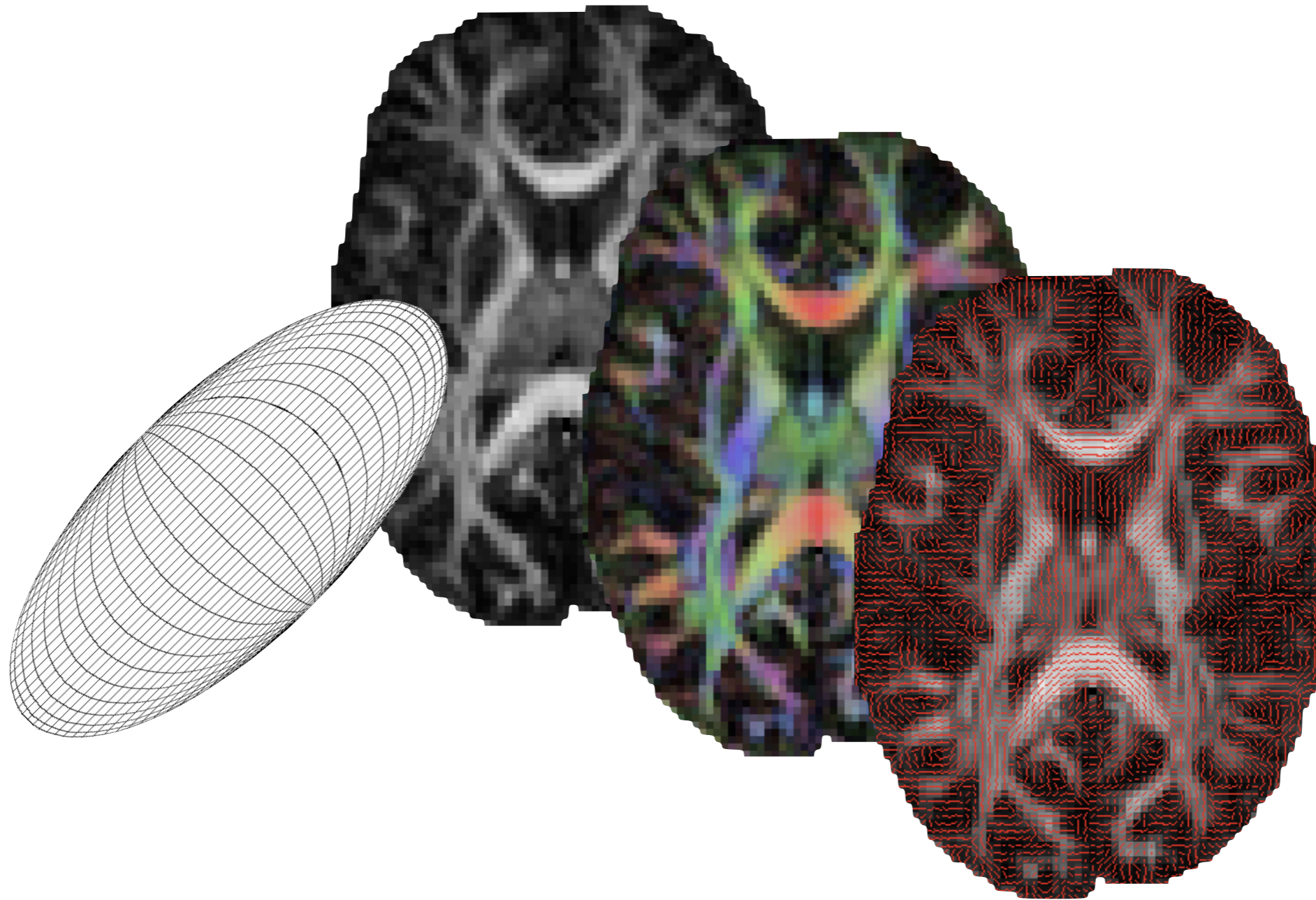


dMRI Summary

- Images acquired with a Gradient along \mathbf{x} , have contrast that is sensitive to diffusion of water molecules along \mathbf{x} .
- When diffusion occurs, signal is attenuated compared to the one with no diffusion-weighting.
- In WM, measurements are anisotropic.
- In GM and CSF, measurements are roughly isotropic.



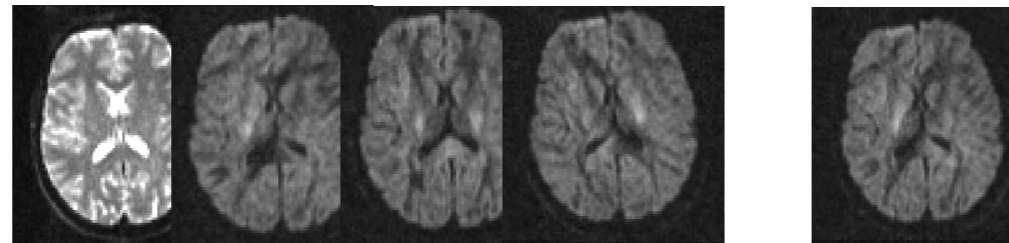
Diffusion Tensor Imaging - basic principles





Diffusion Tensor Imaging (DTI)

- Apply **the diffusion tensor model** to a set of dMRI images.



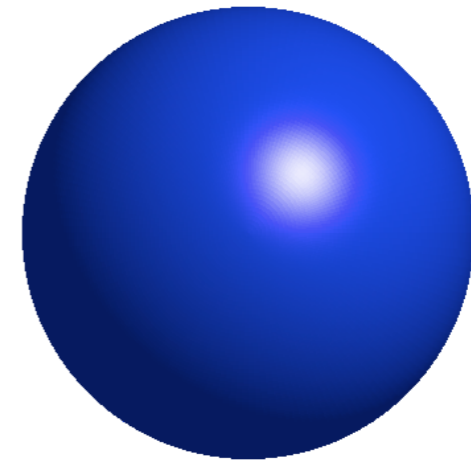
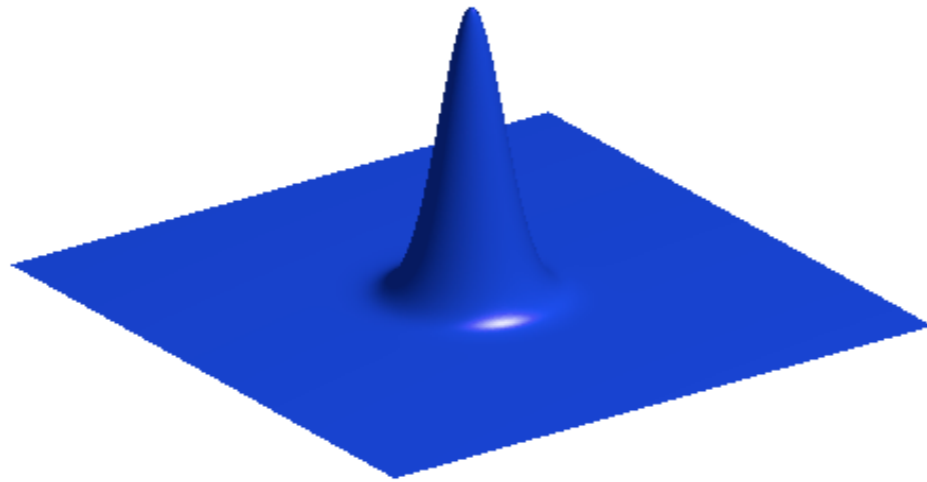


Diffusion Tensor Imaging (DTI)

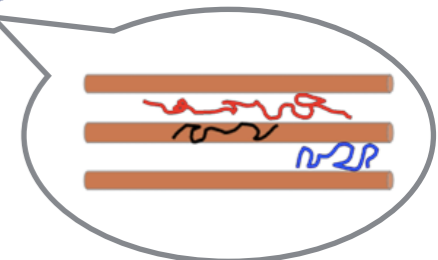
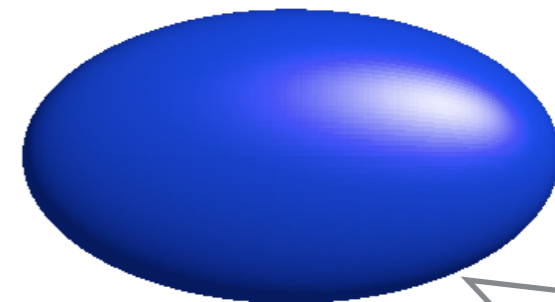
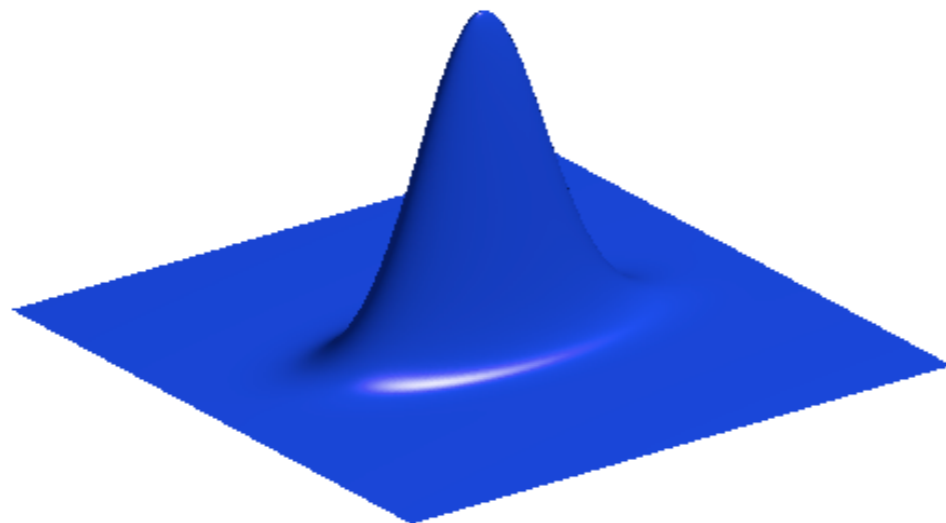
Two dimensions

Three dimensions

Scalar D (same D for all directions)



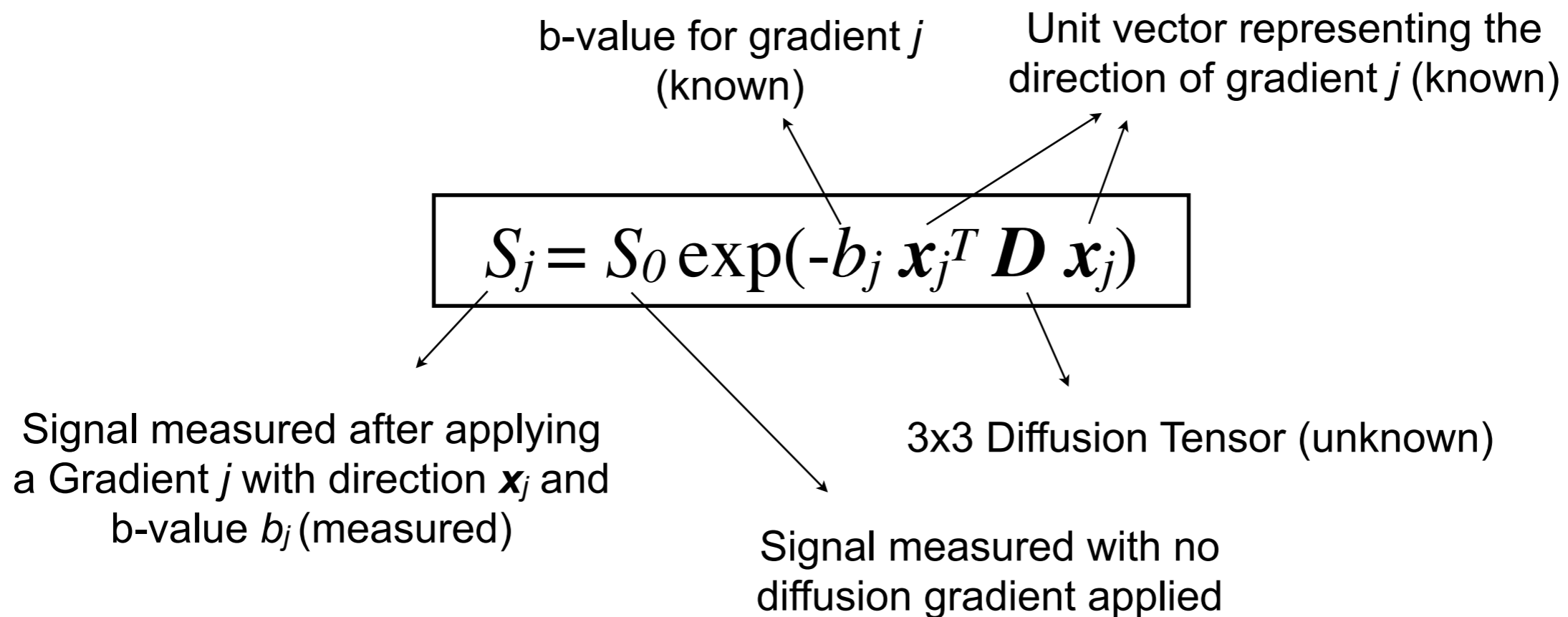
Tensor D - DTI (D can be different for different directions)

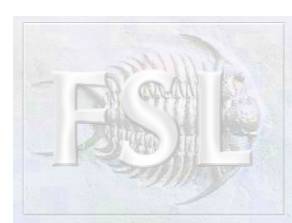




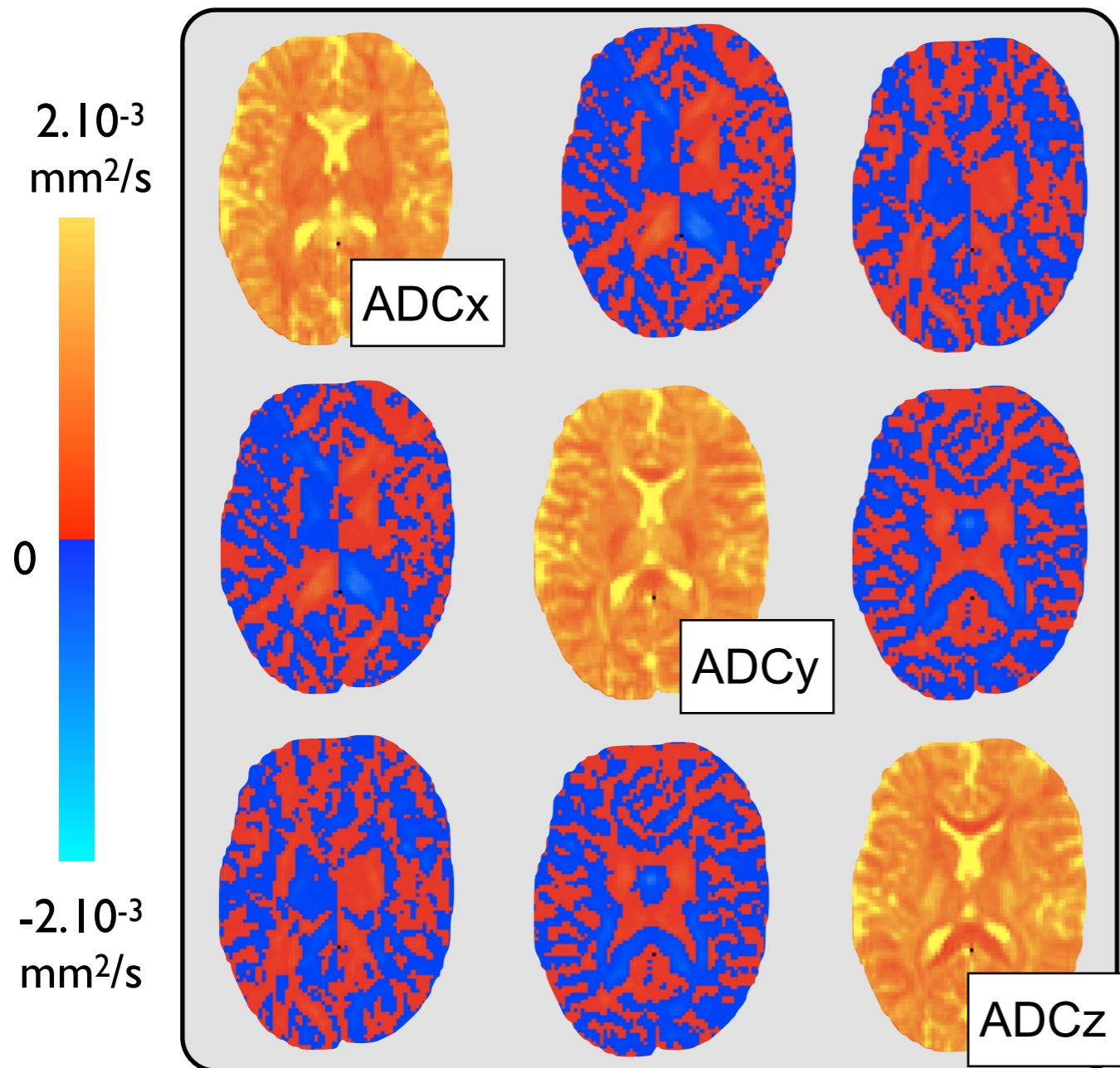
Diffusion Tensor Imaging (DTI)

Diffusion Tensor Model. In each voxel:





The Elements of the Diffusion Tensor



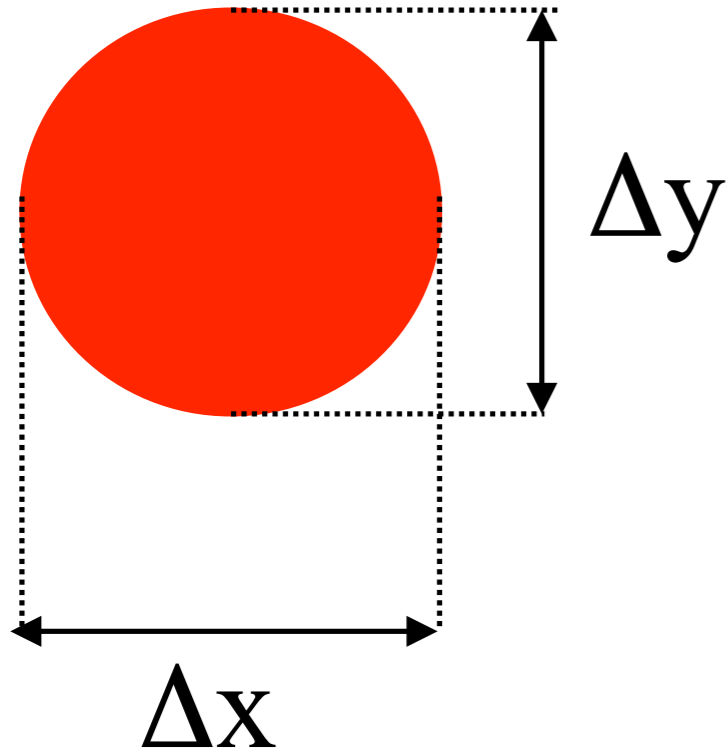
$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

- Tensor is **symmetric** (6 unknowns)
- **Diagonal Elements** are proportional to the diffusion displacement variances (**ADCs**) along the three directions of the experiment coordinate system
- **Off-diagonal Elements** are proportional to the **correlations** (covariances) of displacements along these directions

$$N_3(0, 2t\mathbf{D})$$

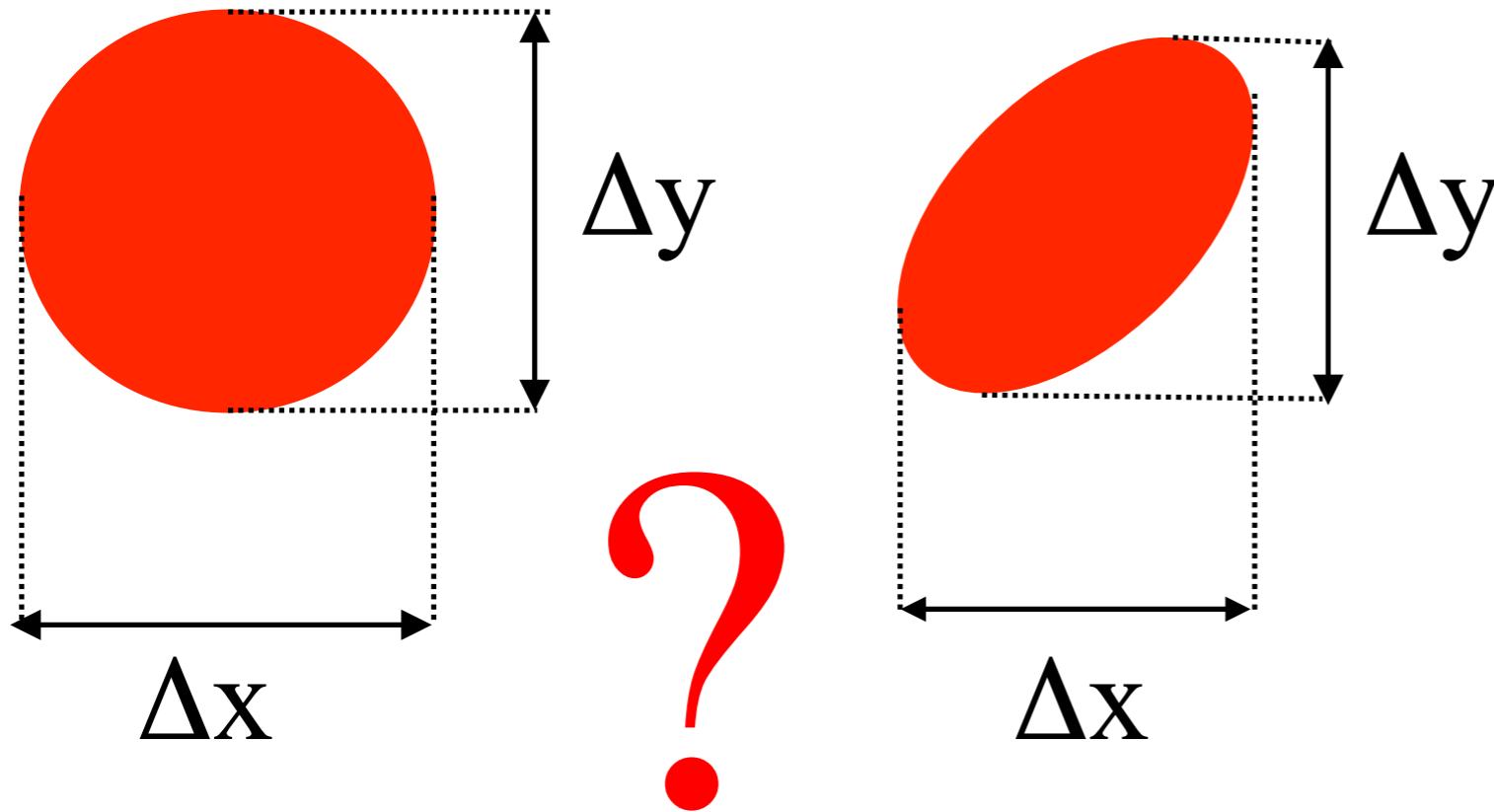


Why do we need a tensor?



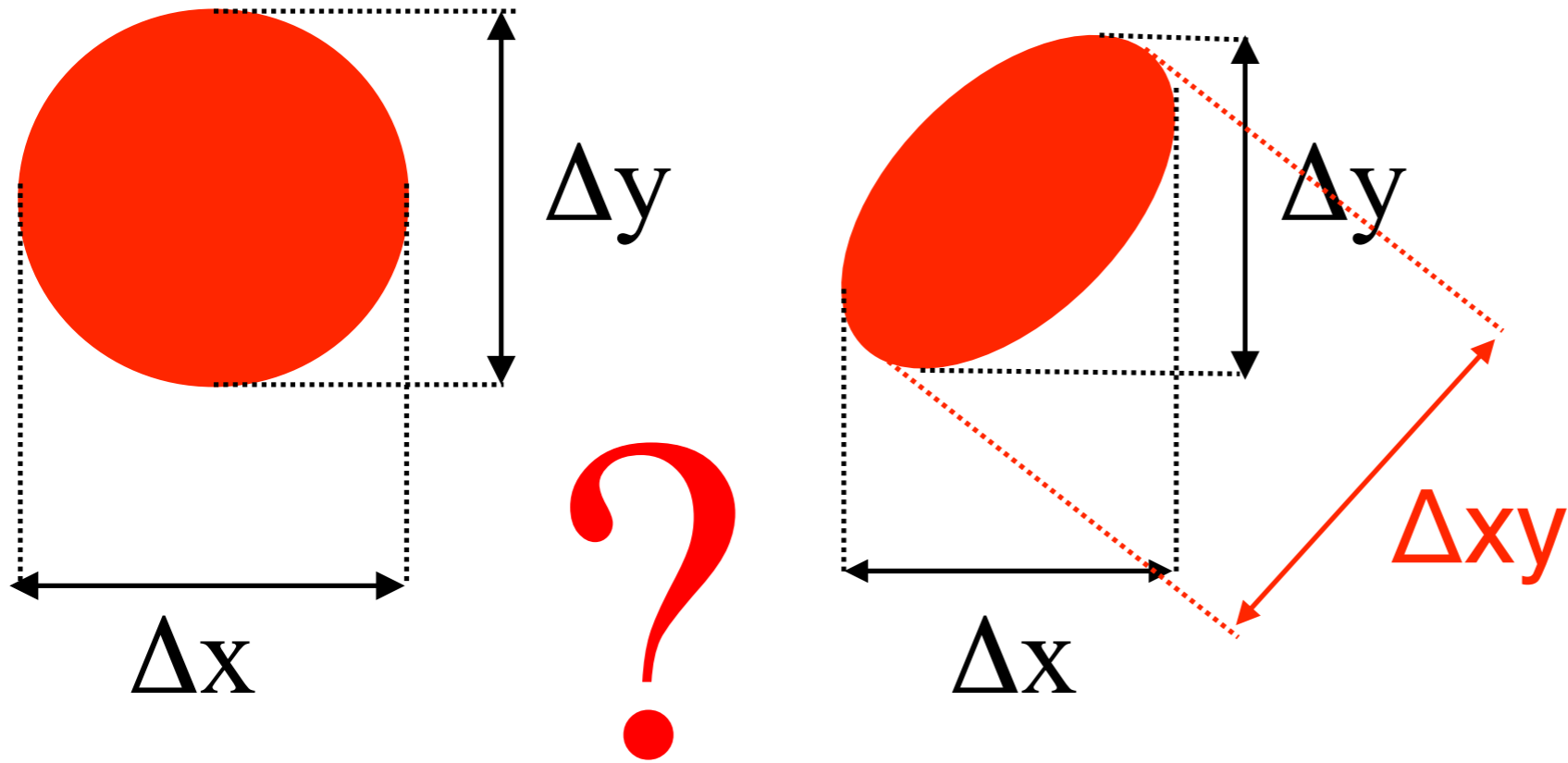


Why do we need a tensor?

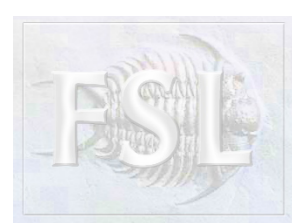




Why do we need a tensor?



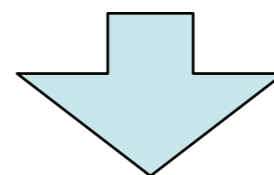
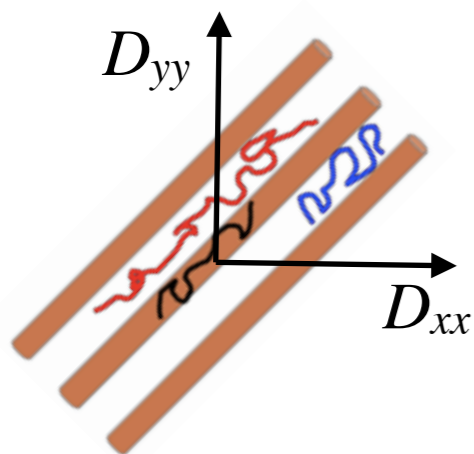
$$\begin{bmatrix} D_x & D_{xy} \\ D_{xy} & D_y \end{bmatrix}$$



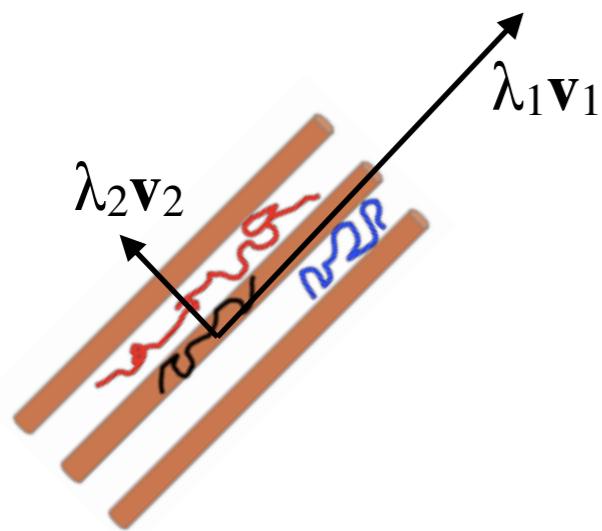
The Diffusion Tensor Eigenspectrum

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

Once \mathbf{D} is estimated, we get ADCs along the scanner's coordinate system. But we want ADCs along a local coordinate system in each voxel, determined by the anatomy.



Diagonalize the estimated tensor in each voxel



$$\mathbf{D} = [\mathbf{v}_1 | \mathbf{v}_2 | \mathbf{v}_3]^T \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} [\mathbf{v}_1 | \mathbf{v}_2 | \mathbf{v}_3]$$

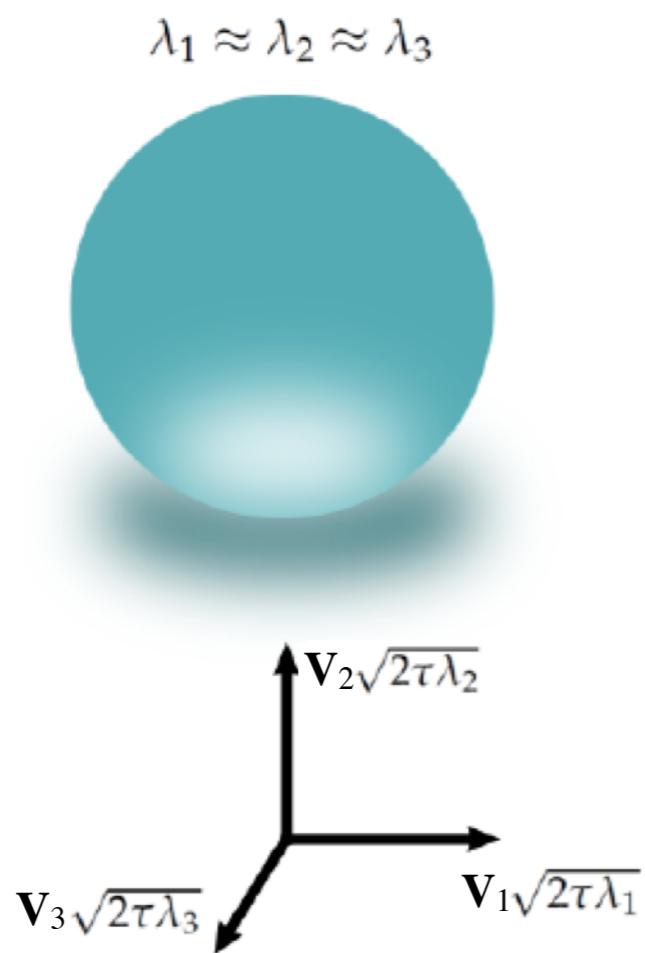
eigenvalues: ADCs along $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$

eigenvectors - \mathbf{v}_1 = direction of max diffusivity

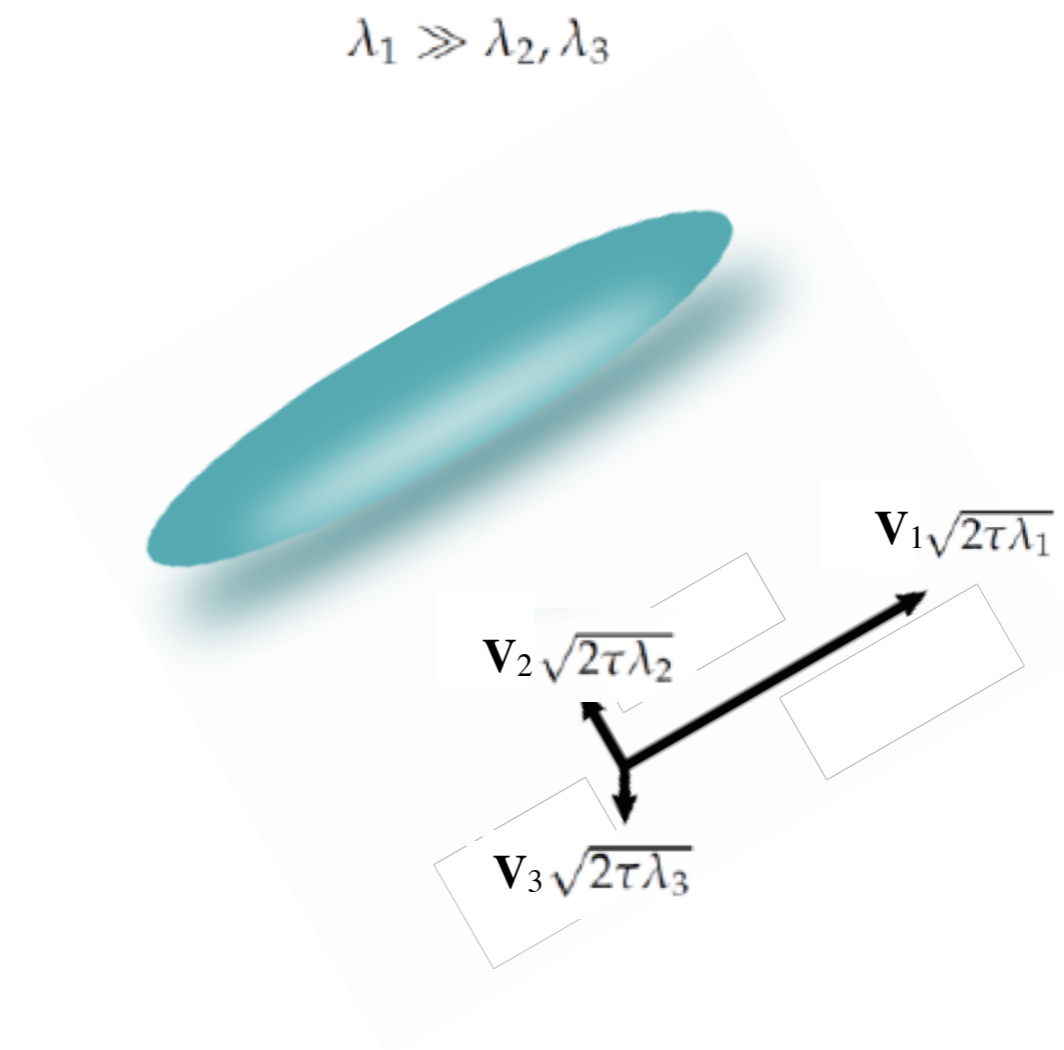


The Diffusion Tensor Ellipsoid

Isotropic voxel

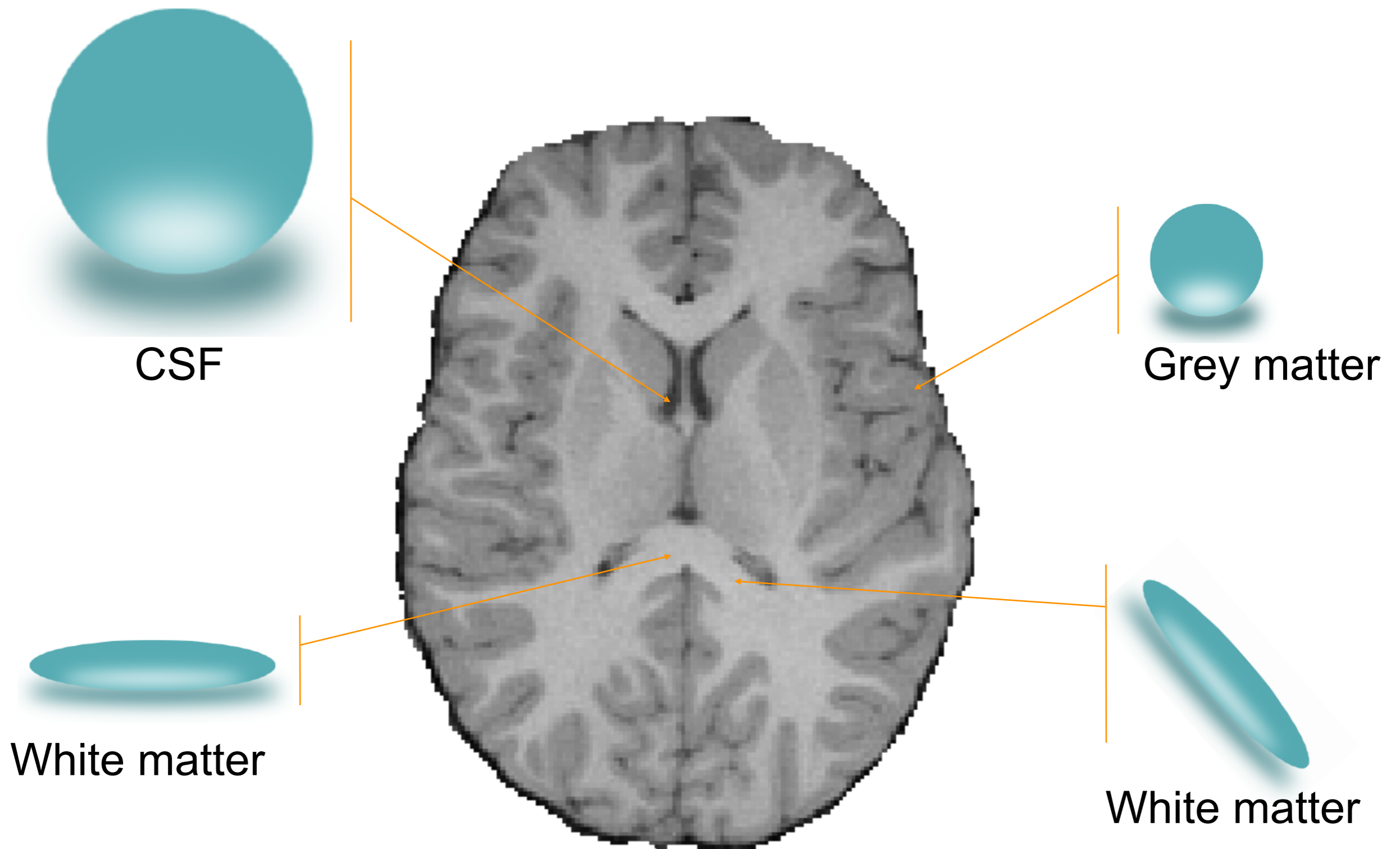


Anisotropic voxel





The Diffusion Tensor Ellipsoid





Quantitative Diffusion Maps

Fractional Anisotropy (FA) ~ Eigenvalues Variance (normalised)
Mean Diffusivity (MD) = Eigenvalues Mean

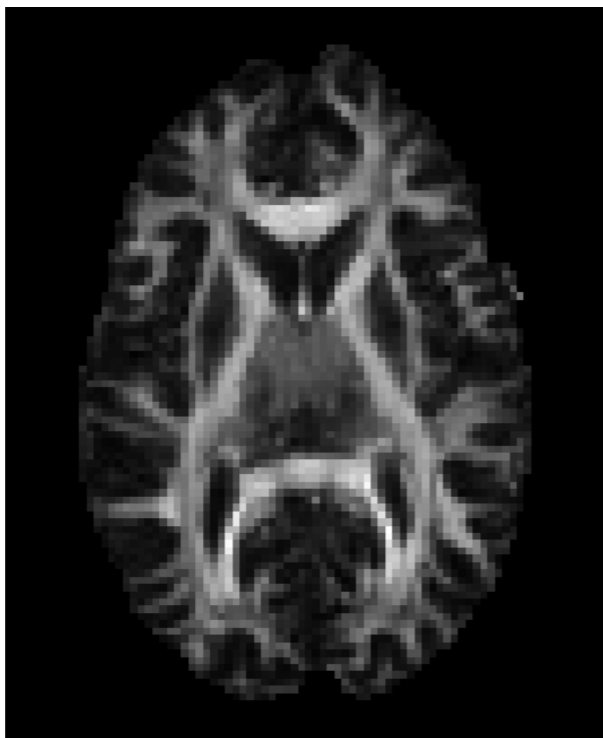
$$FA = \sqrt{\frac{3 \sum_{i=1}^3 (\lambda_i - \bar{\lambda})^2}{2 \sum_{i=1}^3 \lambda_i^2}}, \quad FA \text{ in } [0,1]$$

$$MD = \frac{D_{xx} + D_{yy} + D_{zz}}{3} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}$$



Quantitative Diffusion Maps

FA



MD



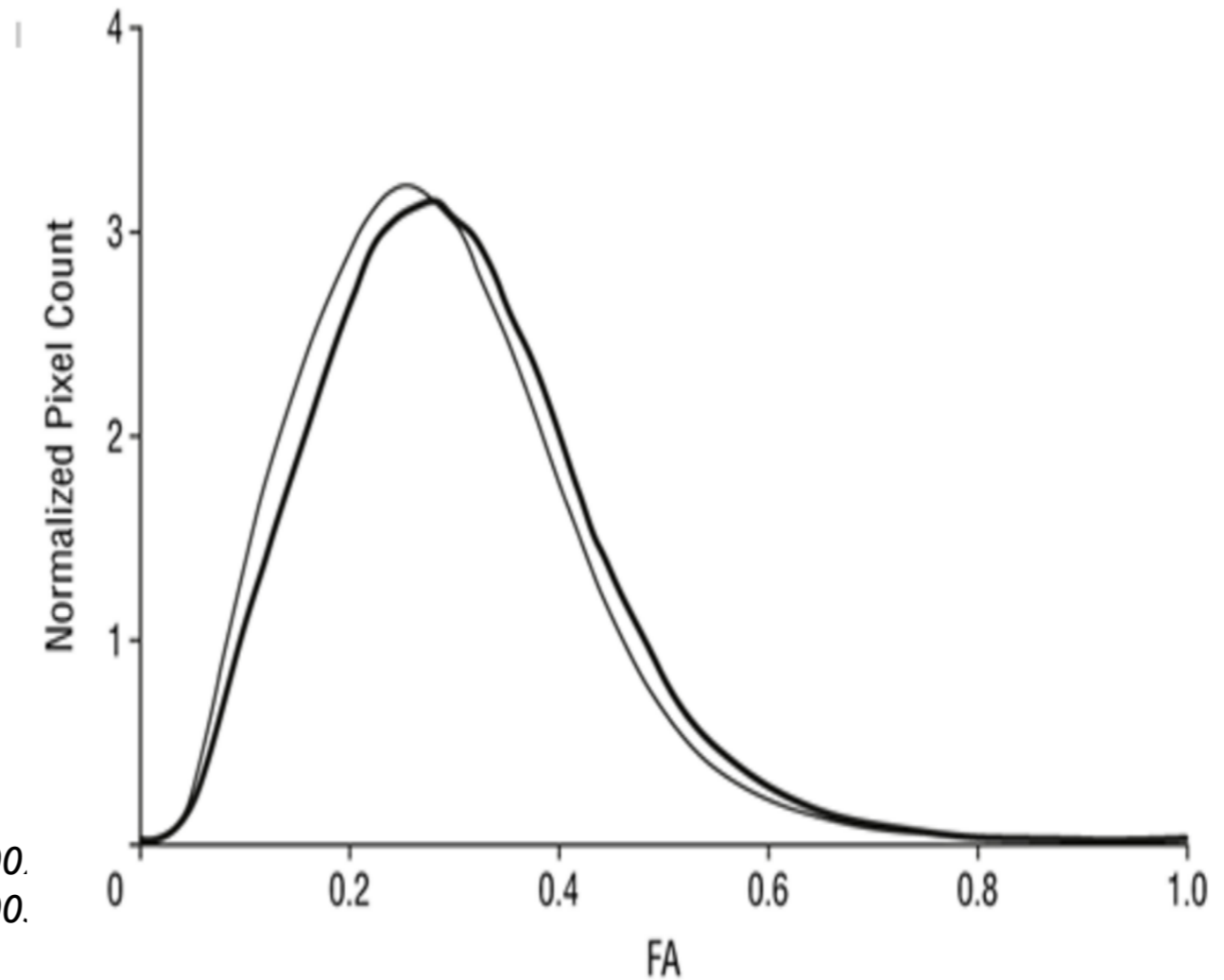


Quantitative Diffusion Maps

FA decrease/ MD increase has been associated in many studies with tissue breakdown (loss of structure).



Rovaris et al, Arch Neurol 200.
Gallo et al, Arch Neurol 200.

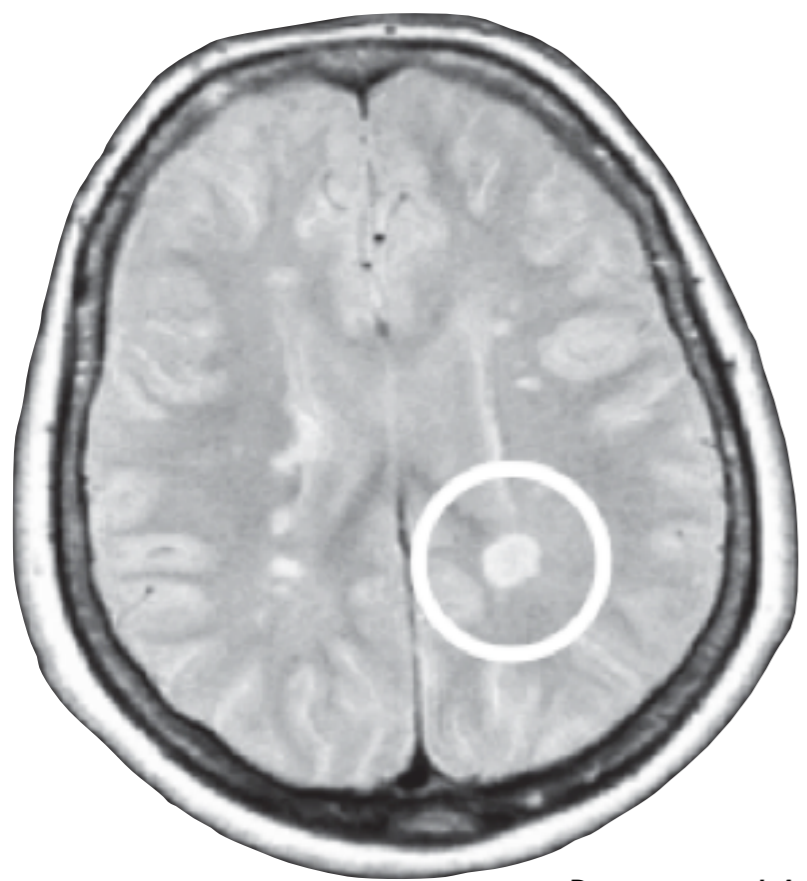


Fractional Anisotropy changes in MS normal appearing white matter

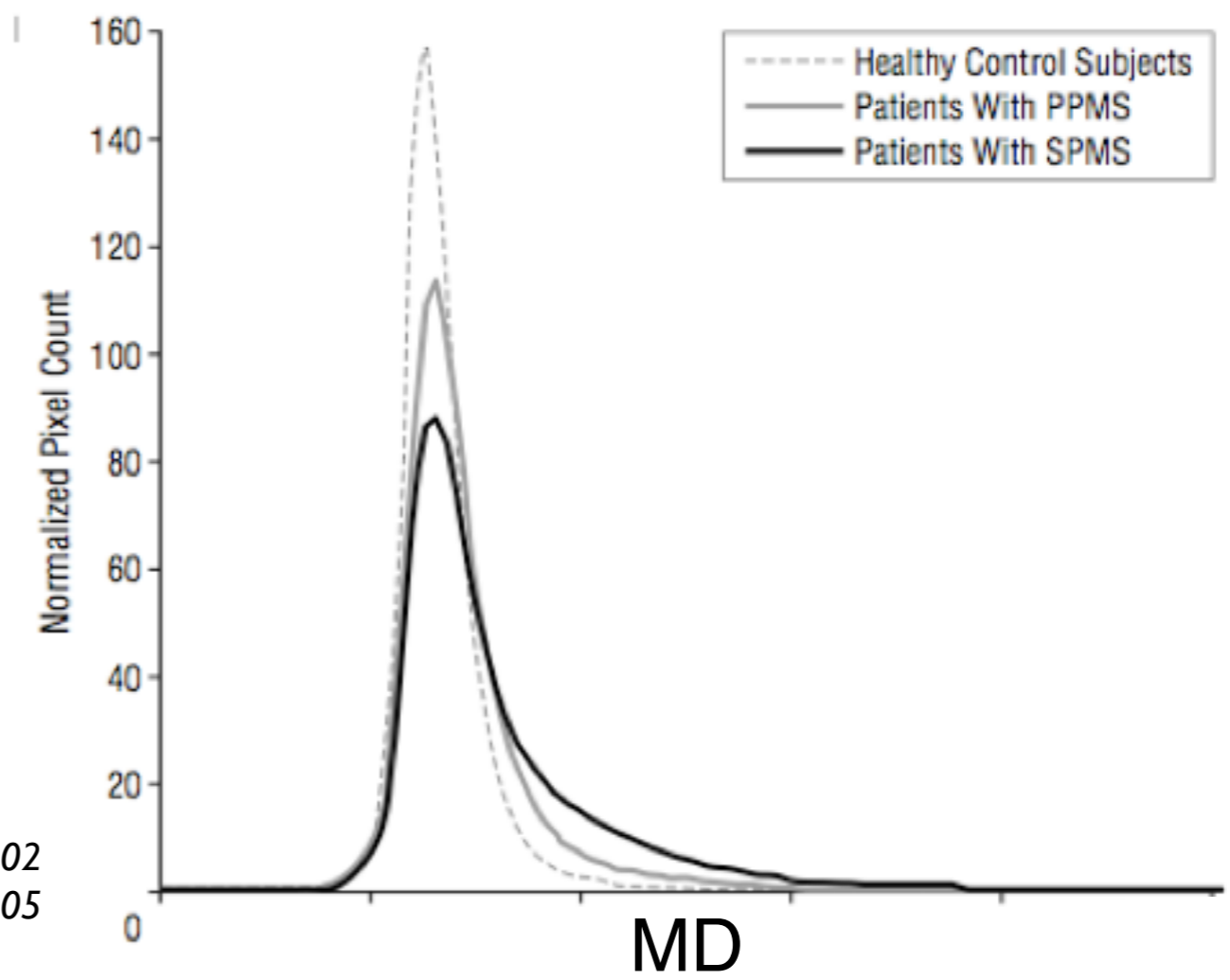


Quantitative Diffusion Maps

FA decrease/ MD increase has been associated in many studies with tissue breakdown (loss of structure).



Rovaris et al, Arch Neurol 2002
Gallo et al, Arch Neurol 2005

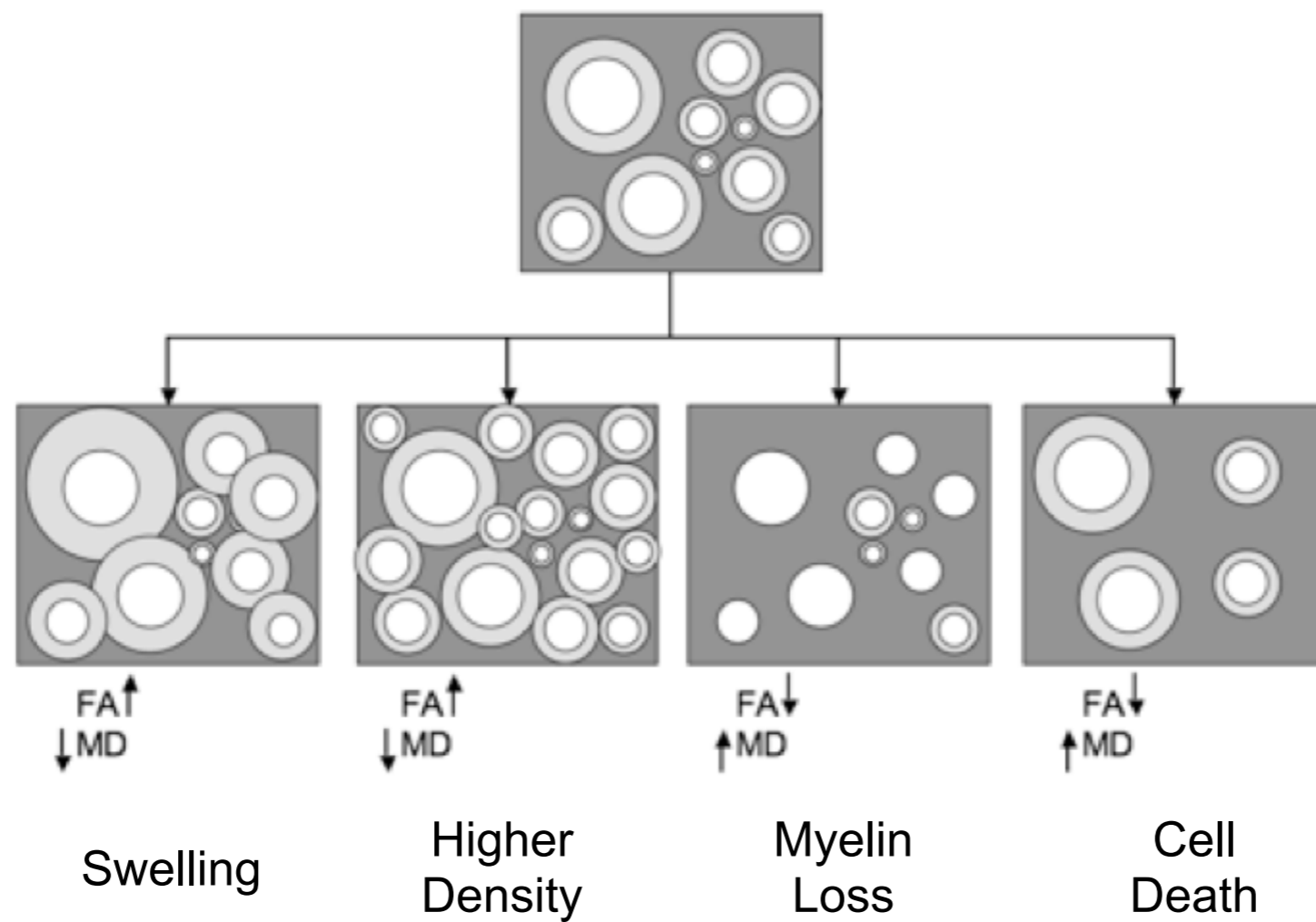


Fractional Anisotropy changes in MS normal appearing white matter



Quantitative Diffusion Maps

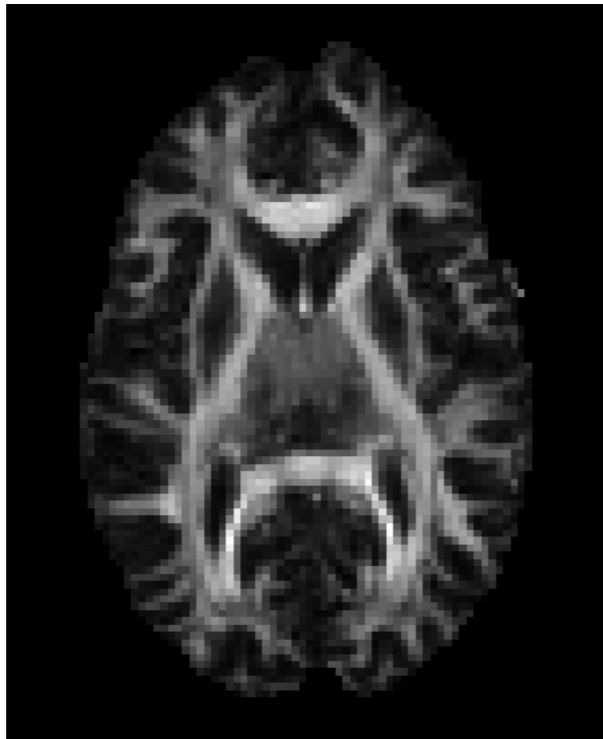
Different scenarios can have same effect on FA, MD





Quantitative Diffusion Maps

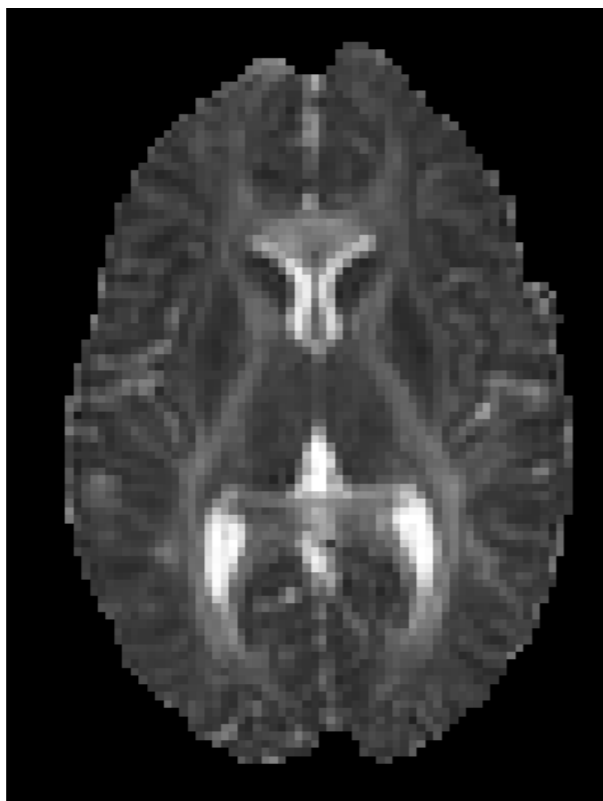
FA



MD



Longitudinal ADC
(λ_1)



Transverse ADC
($(\lambda_2 + \lambda_3)/2$)





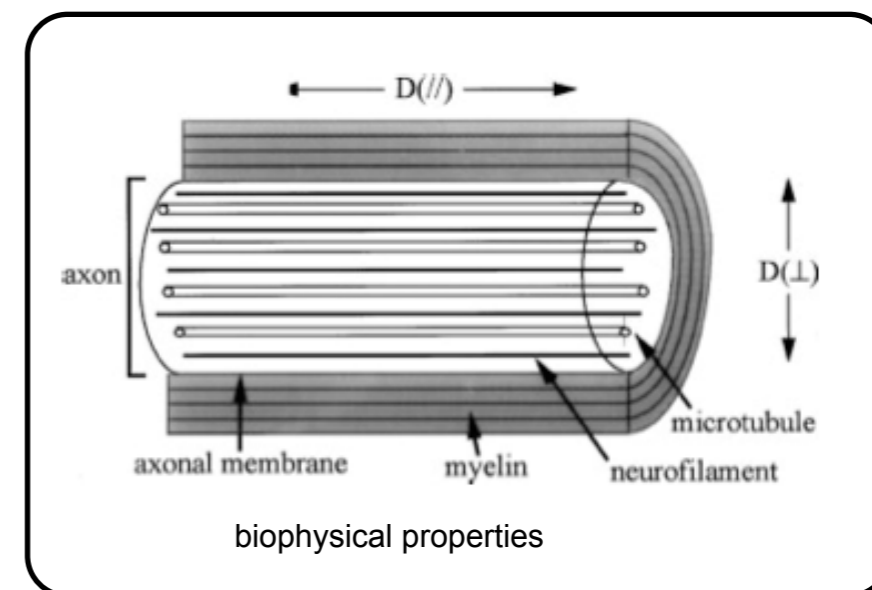
Quantitative Diffusion Maps

FA decrease in WM can be caused:

a) Decrease of longitudinal ADC.
Axonal breakdown?

b) Increase of transverse ADC.
Myelin breakdown?

But do not over-interpret your results.
Always keep in mind that the DTI
model is an oversimplification of
reality





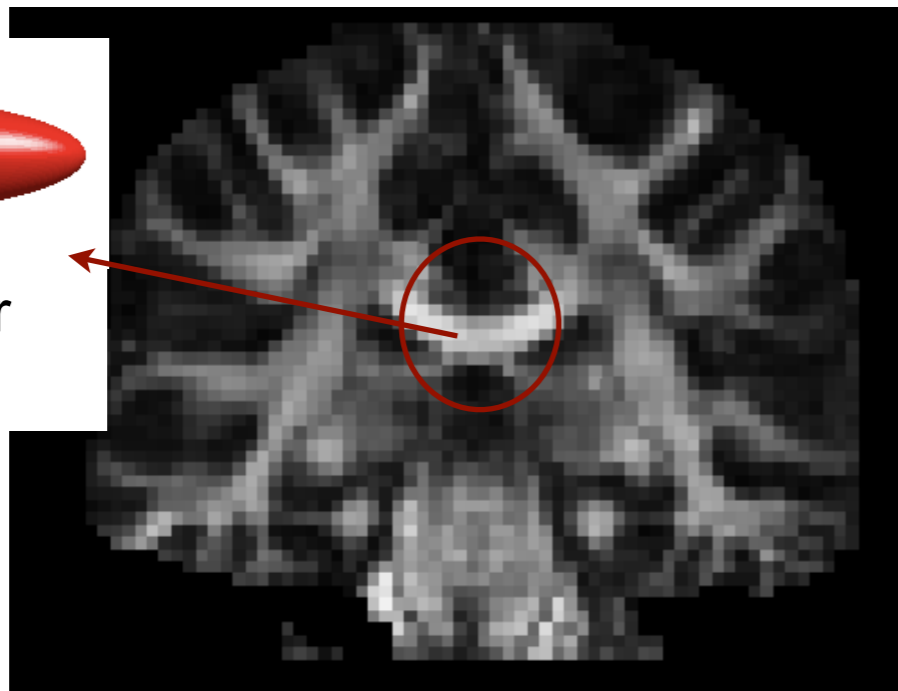
Tensor and FA in Crossing Regions

- In voxels containing two crossing bundles, FA is low and the tensor ellipsoid is pancake-shaped (oblate, planar tensor).



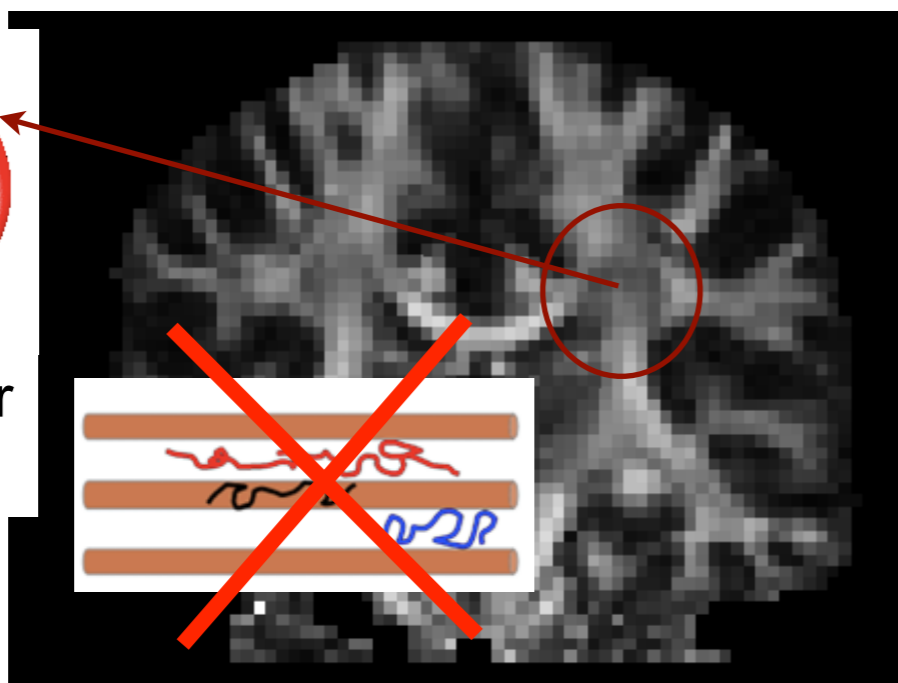
Prolate Tensor

$$\lambda_1 \gg \lambda_2, \lambda_3$$



Oblate Tensor

$$\lambda_1 = \lambda_2 \gg \lambda_3$$

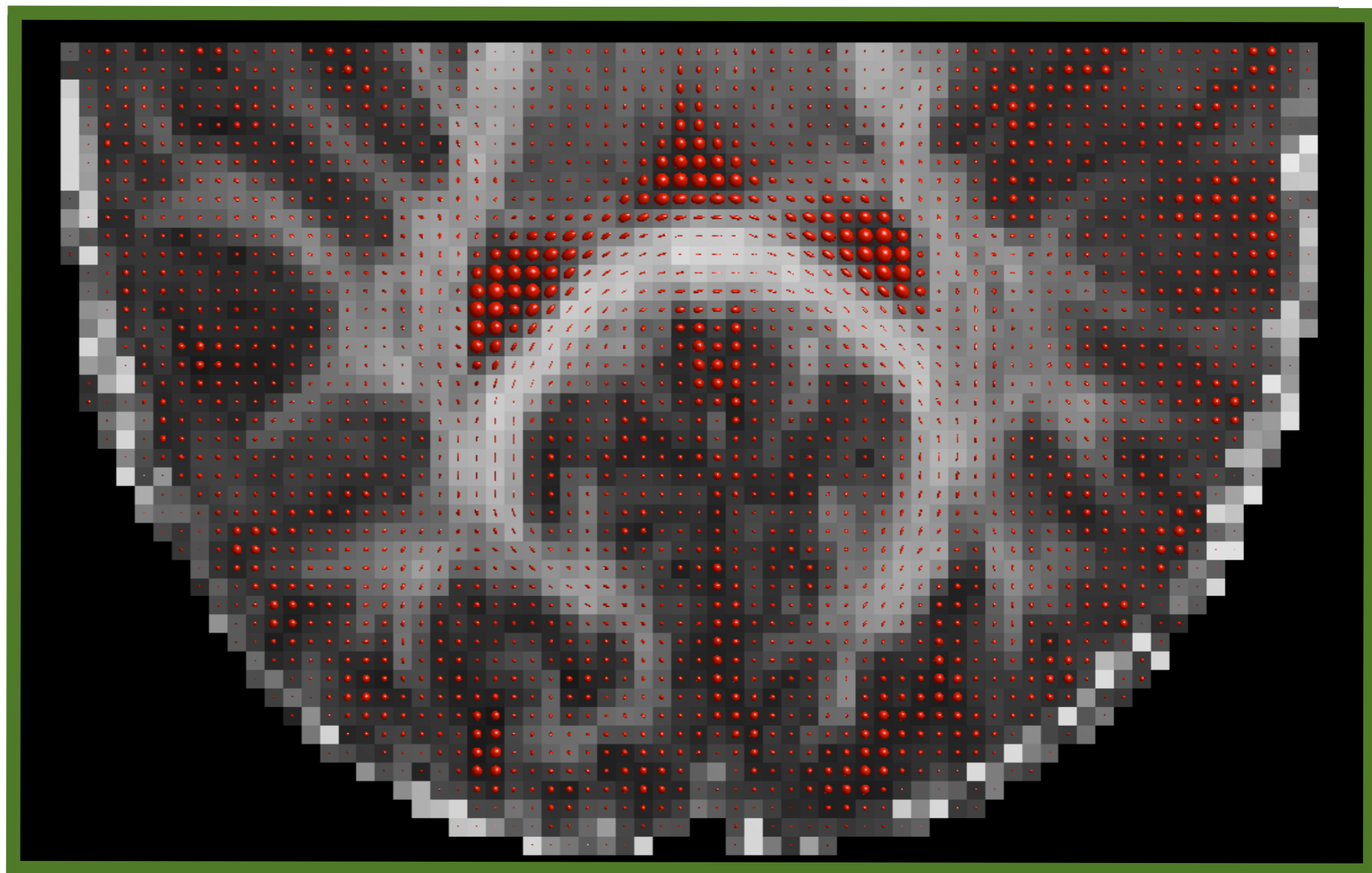
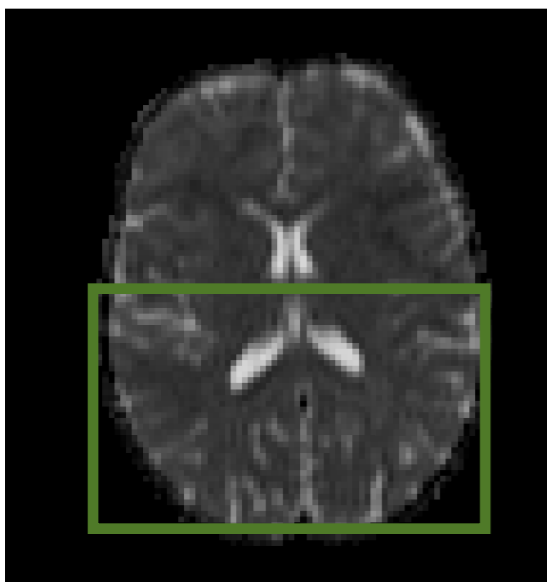
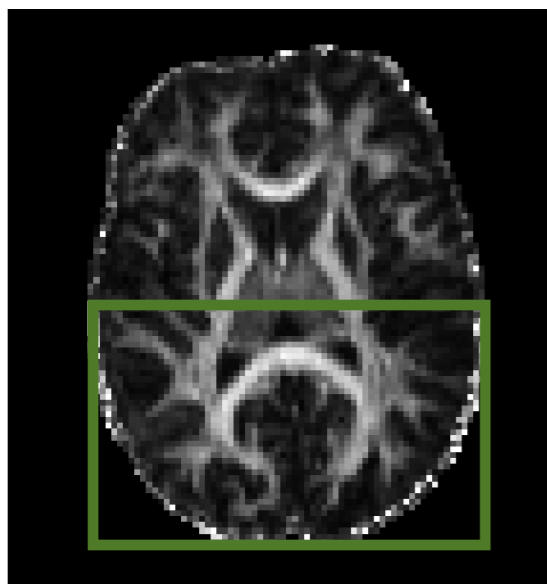


Consequences:

- PDD not necessarily = direction of fibres
- FA changes difficult to interpret



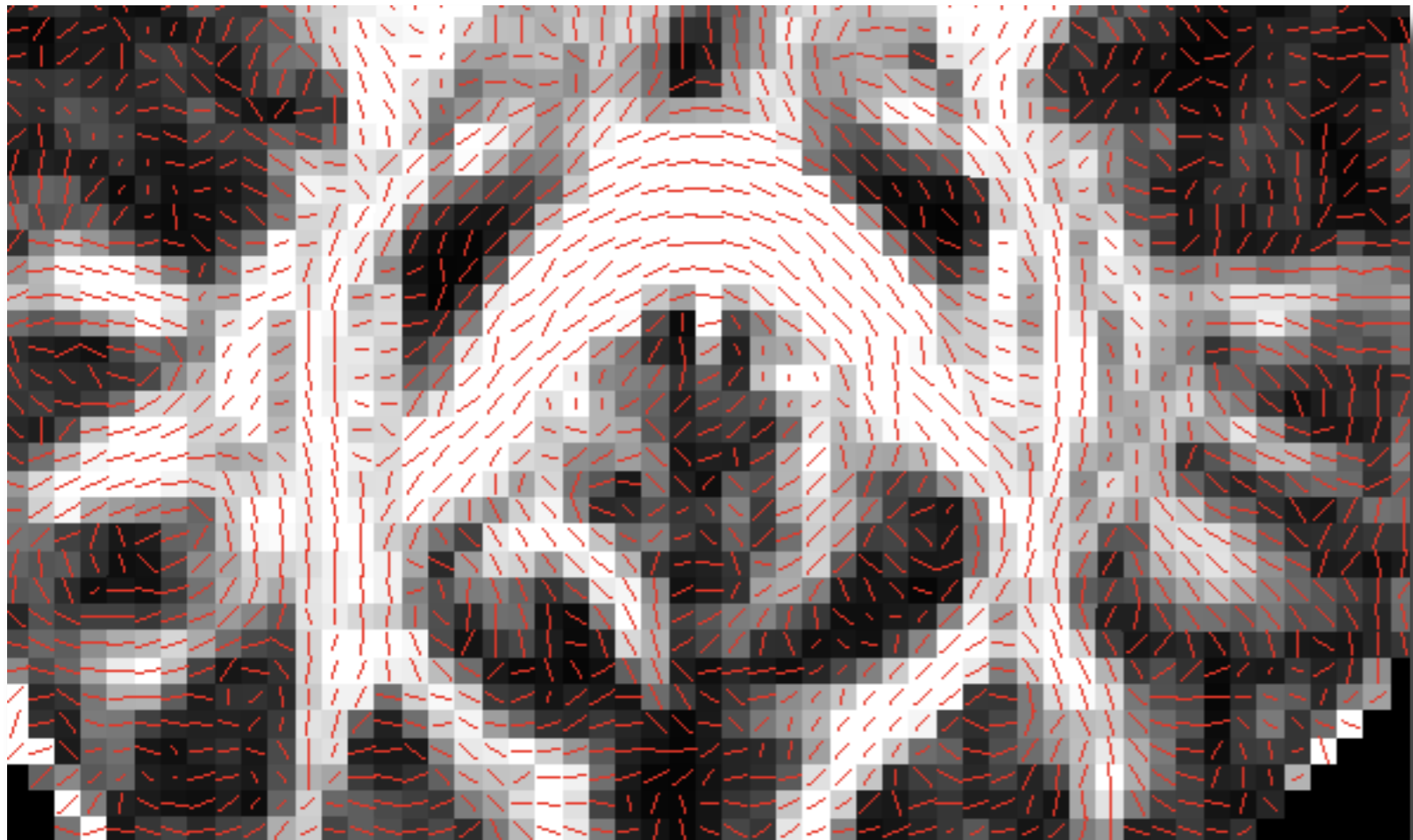
Diffusion Tensor Ellipsoids



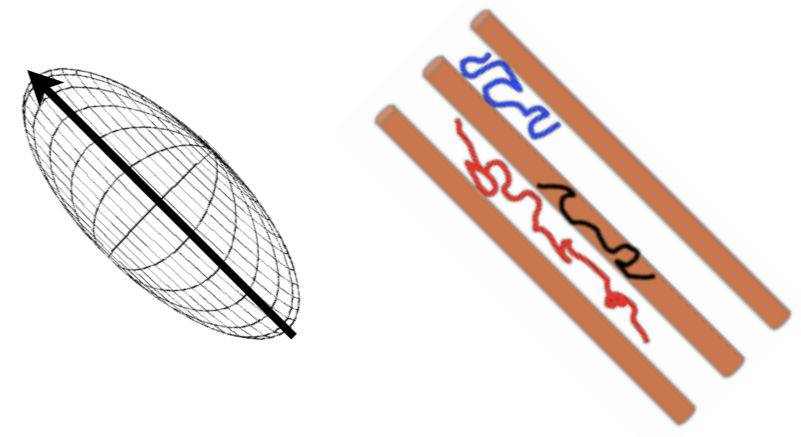


Estimates of Principal Fibre Orientation in WM

v_1 map
Principal Diffusion Direction



Principal Diffusion
Direction

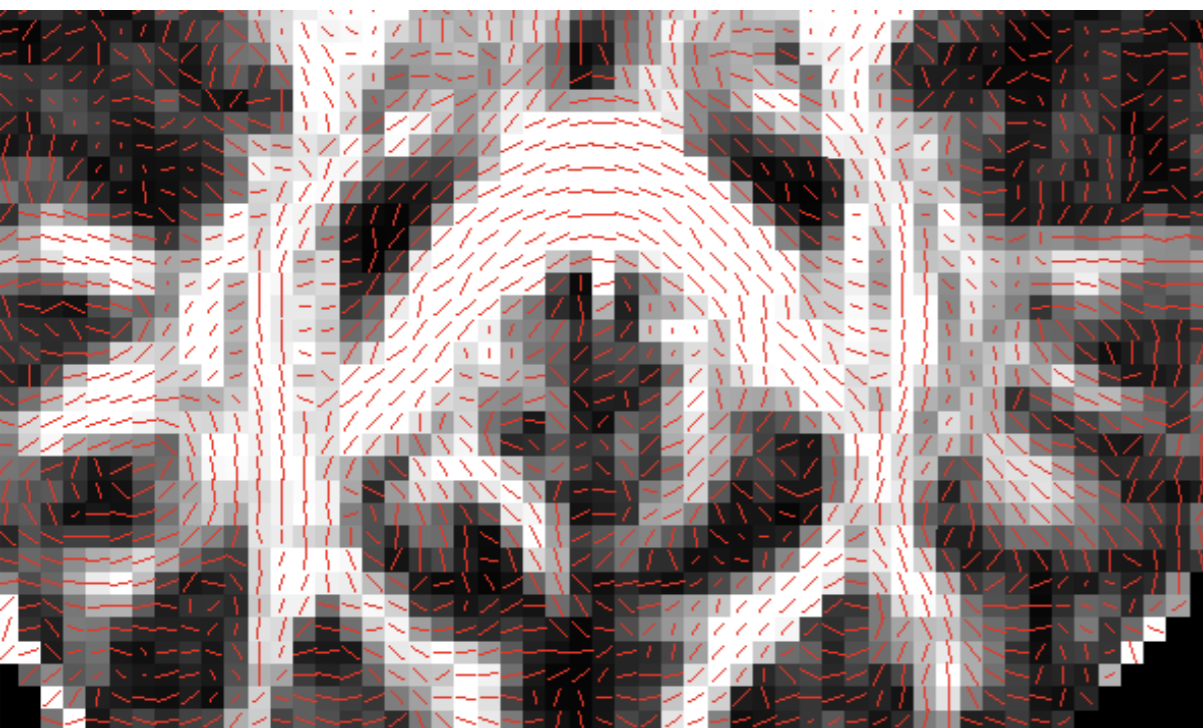


Assumption!!

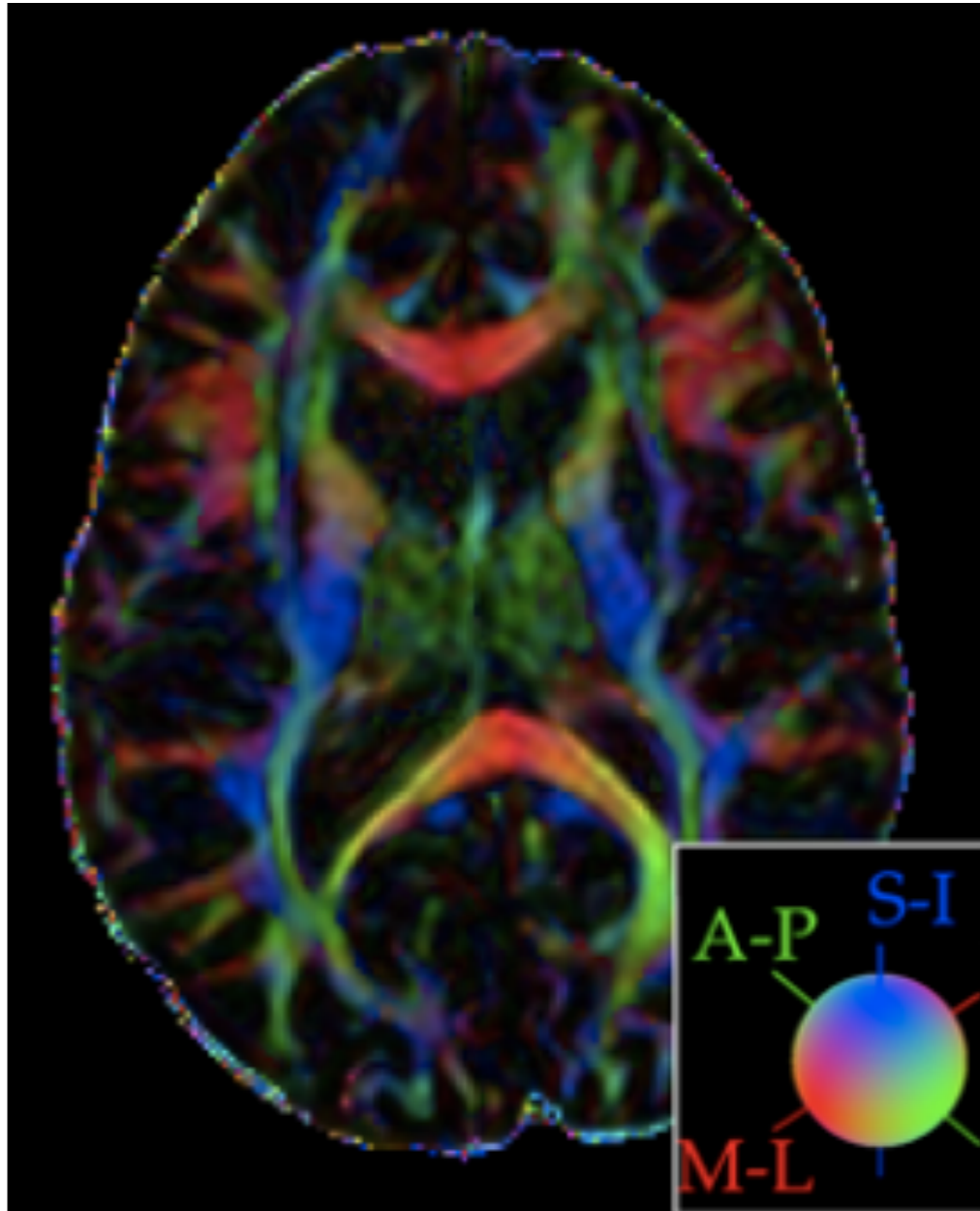
Direction of maximum diffusivity in voxels with anisotropic profile is an estimate of the major fibre orientation.



Estimates of Principal Fibre Orientation in WM

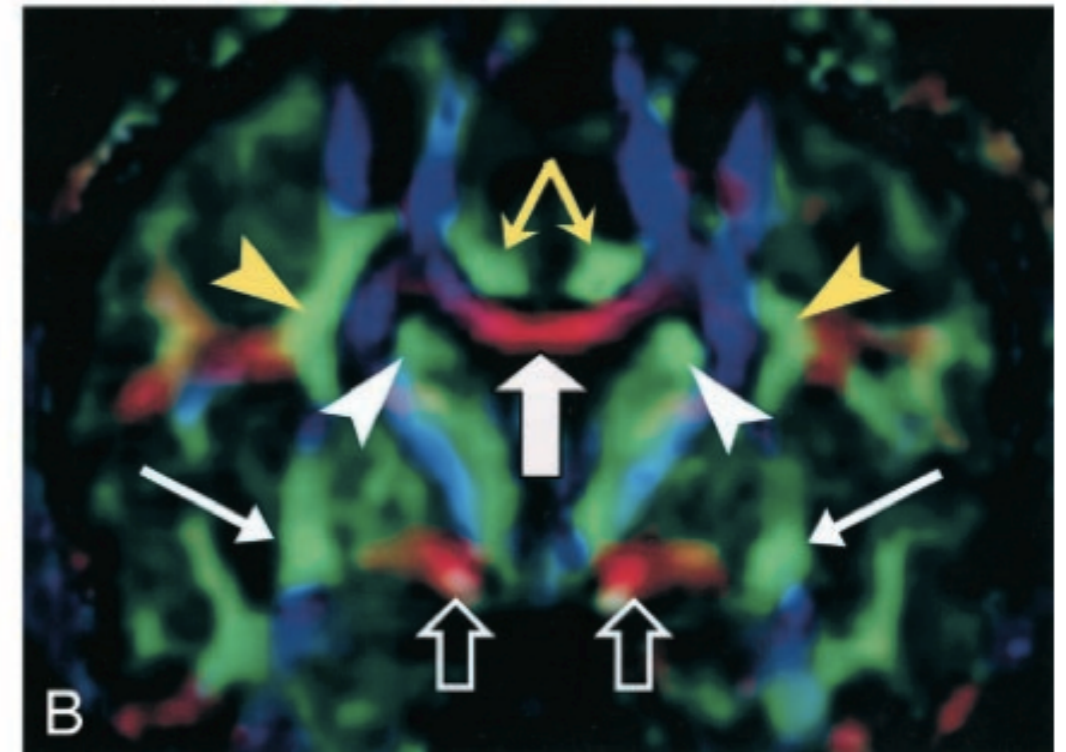
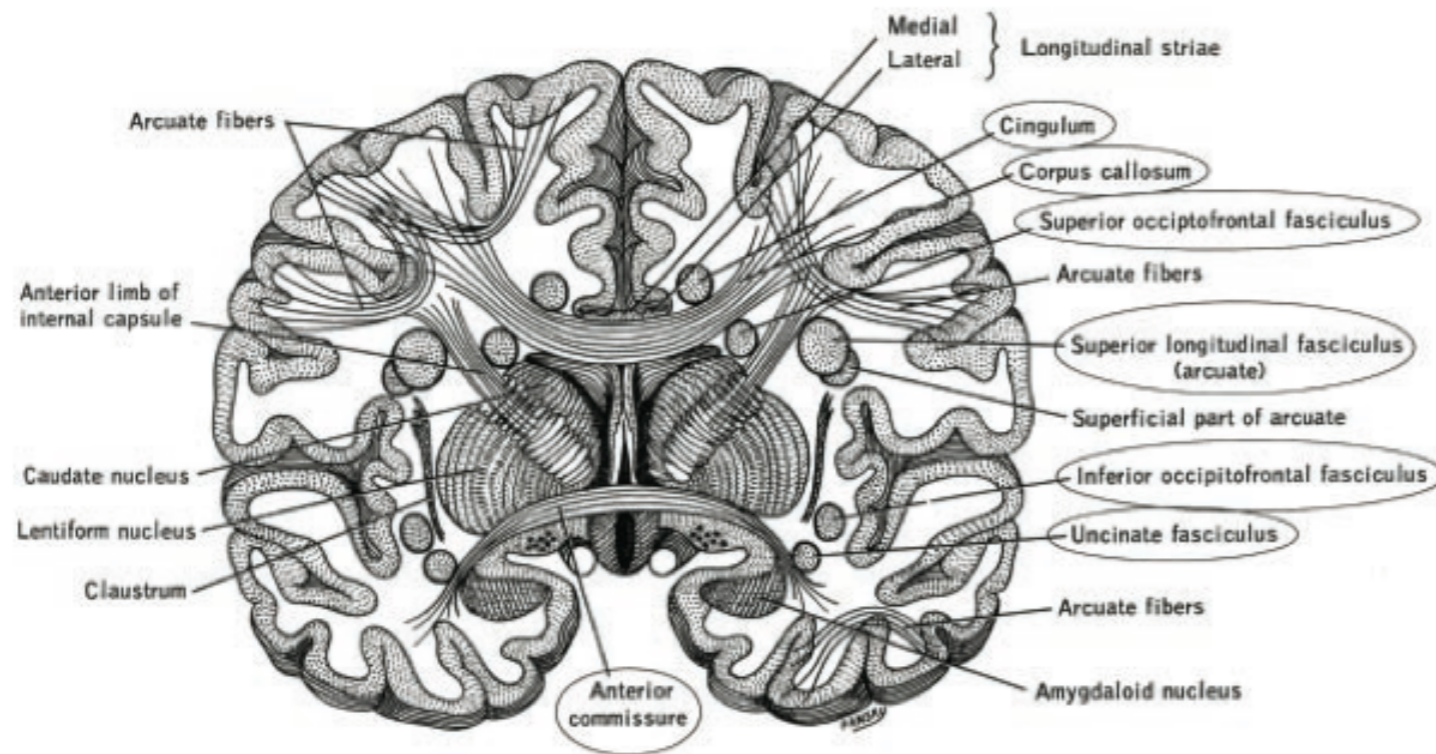


Colour-coded v_1 map



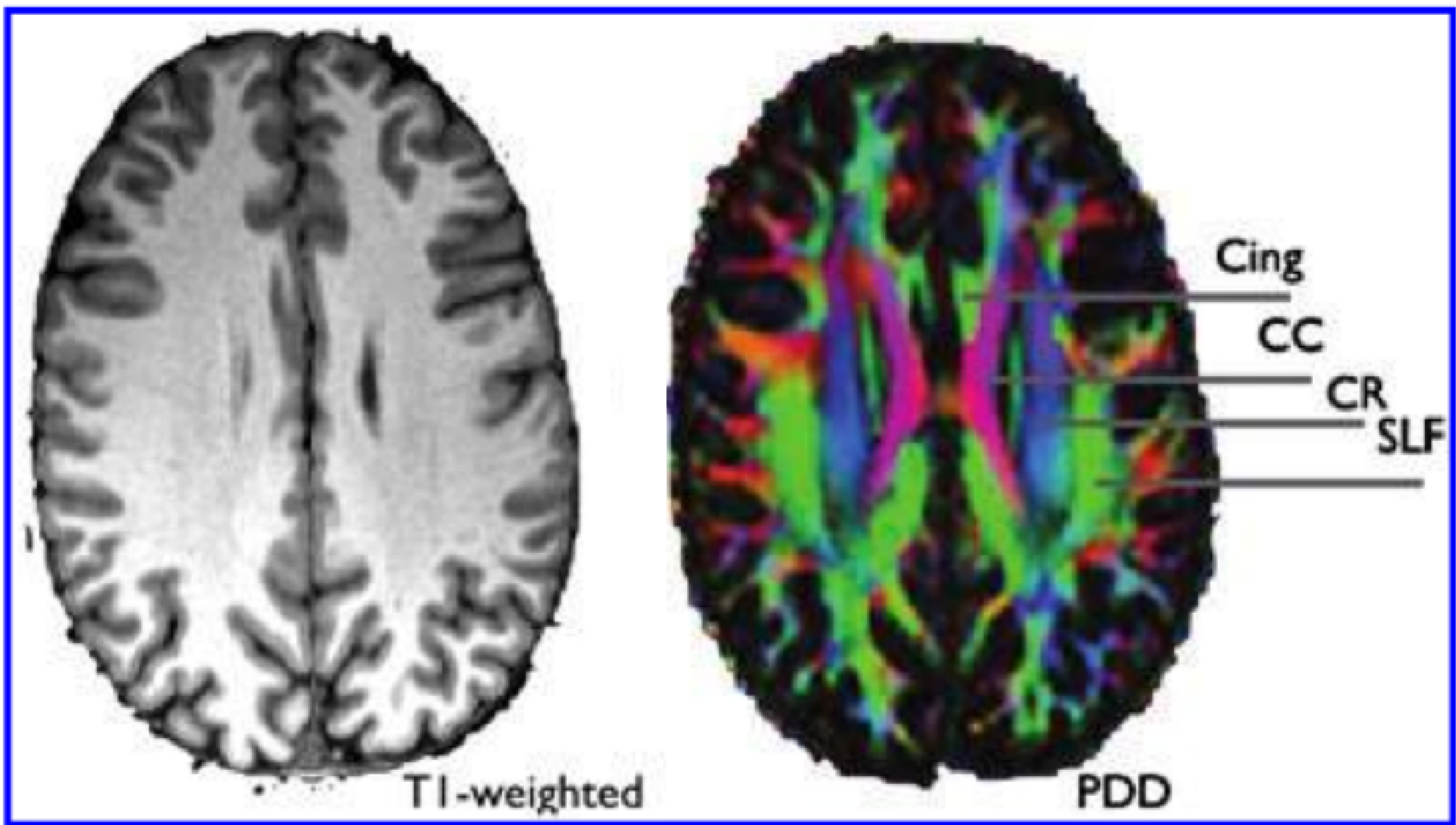


Estimates of Principle Fibre Orientation in WM





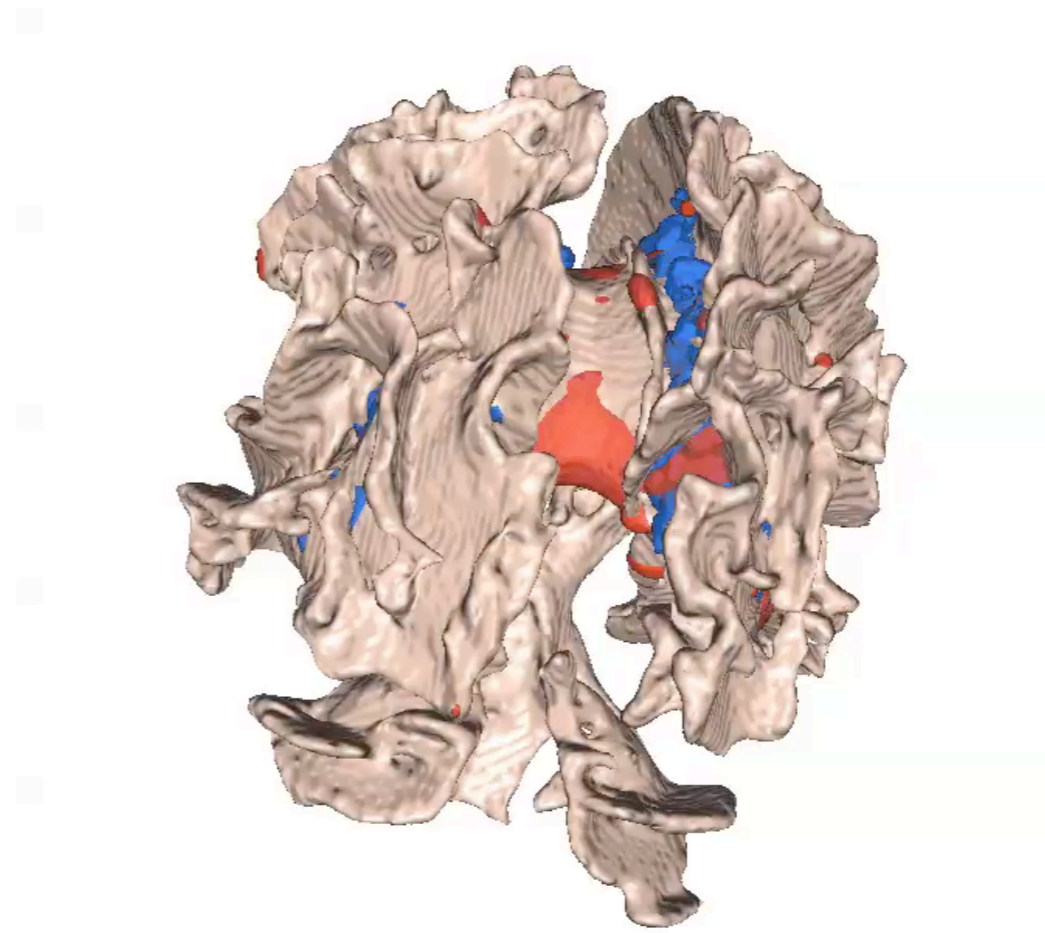
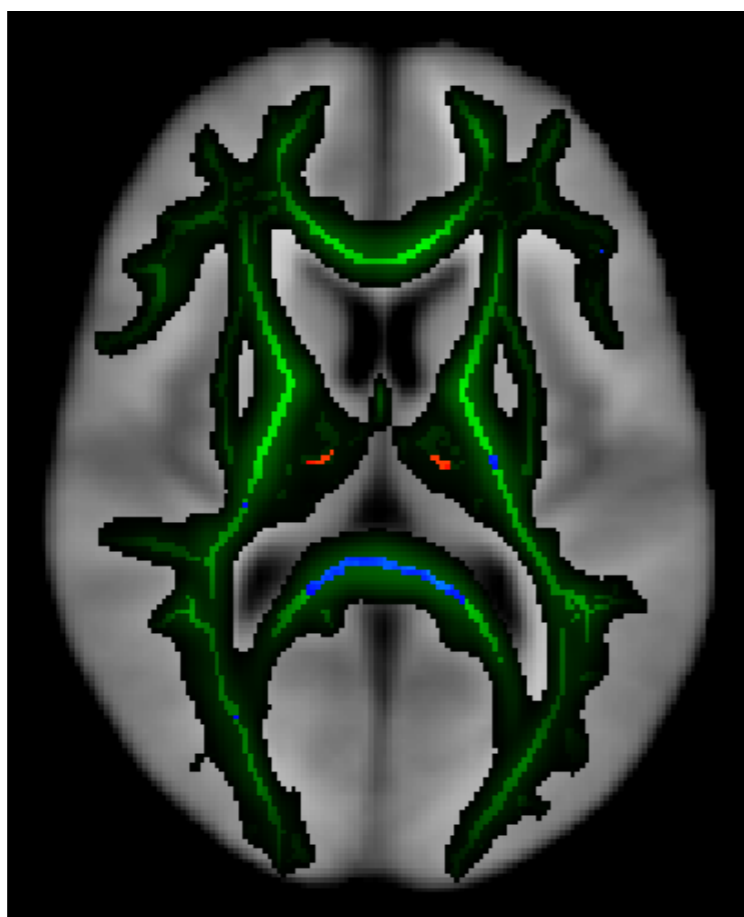
Directional contrast in DTI

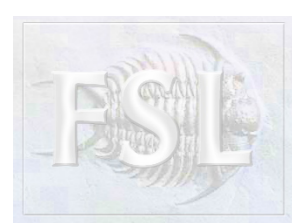




TBSS : Tract-Based Spatial Statistics

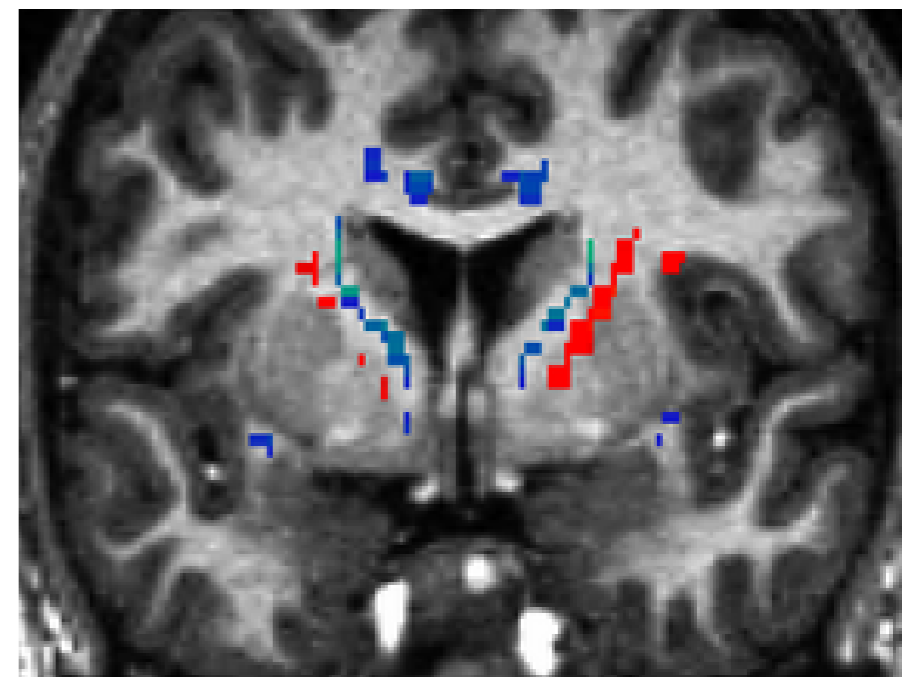
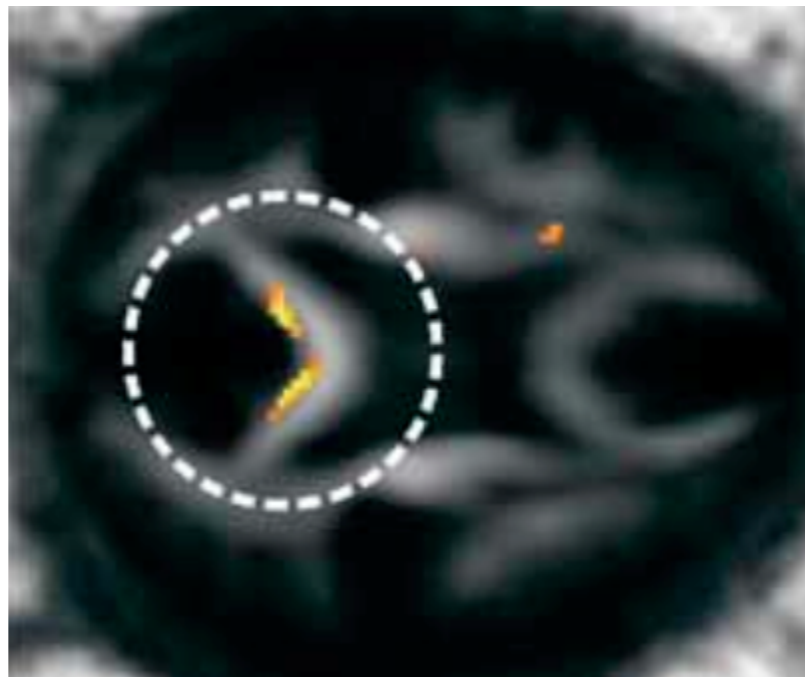
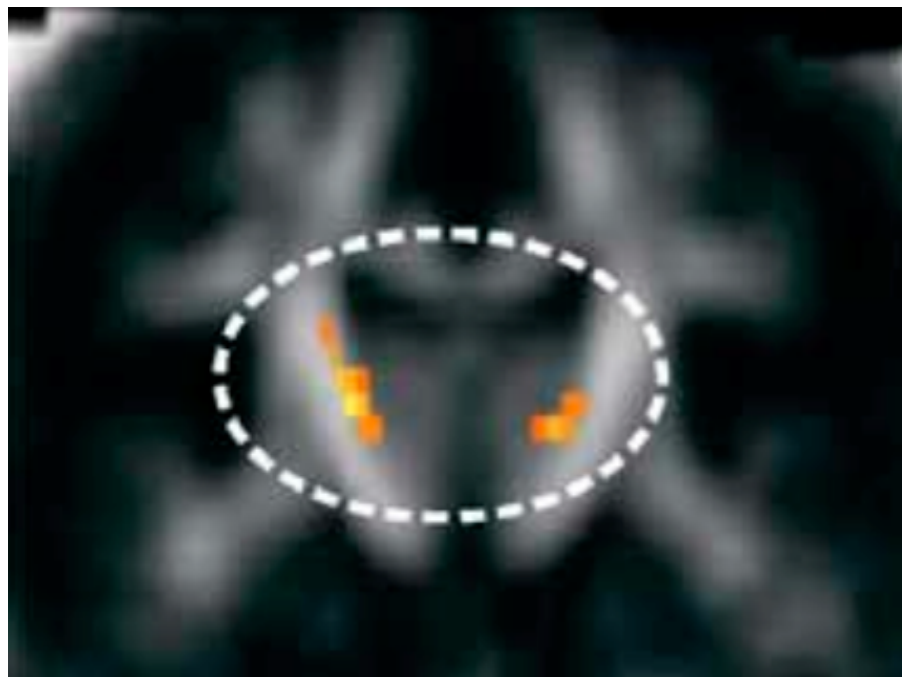
Robust “voxelwise” cross-subject stats
on diffusion-derived measures





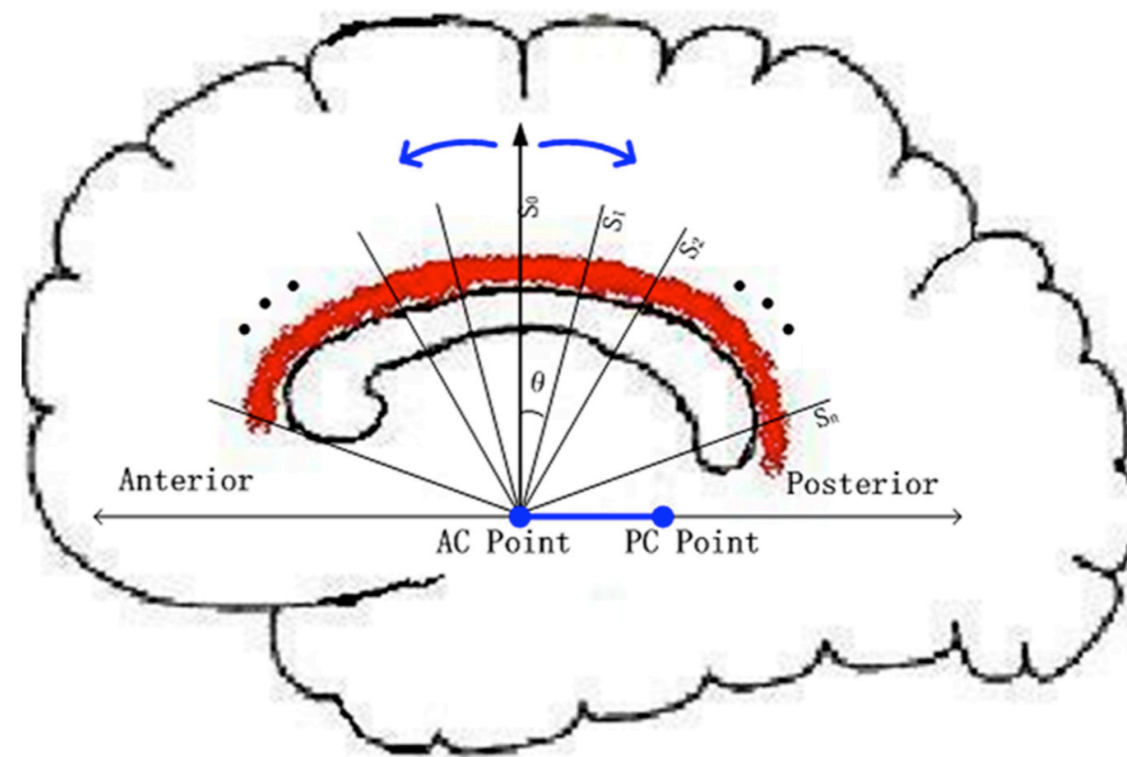
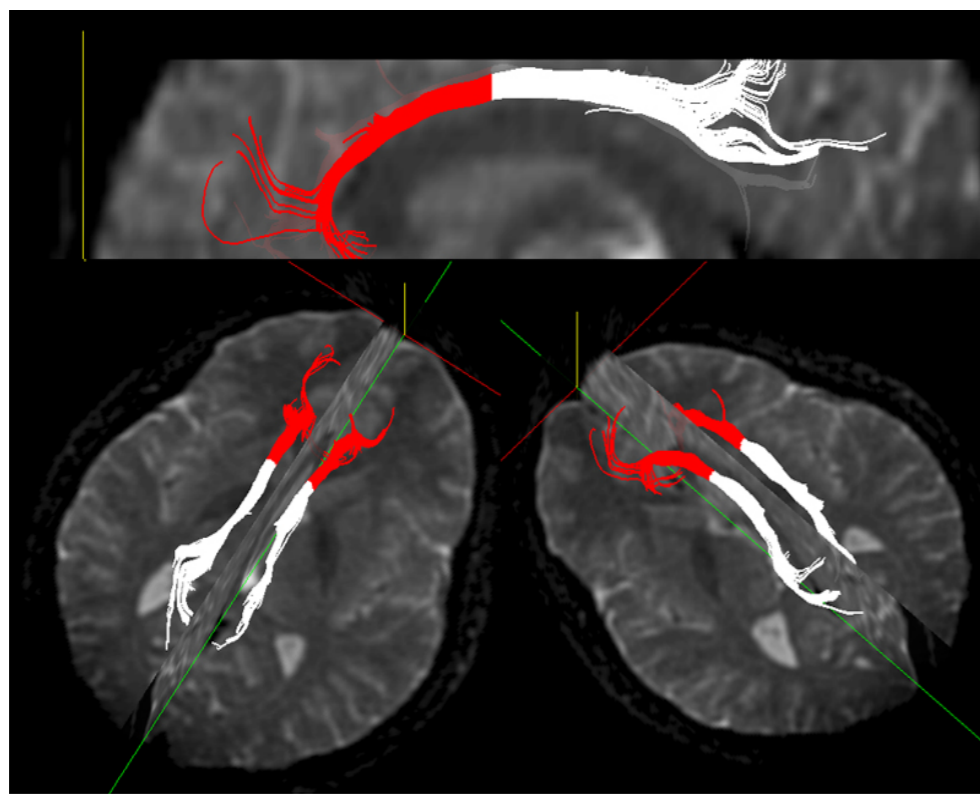
Voxelwise Analysis of FA

- Strengths
 - Fully automated & quick
 - Investigates whole brain
- Problems [Bookstein 2001, Davatzikos 2004, Jones 2005]
 - Alignment difficult; smallest systematic shifts between groups can be incorrectly interpreted as FA change
 - Needs accurate registration





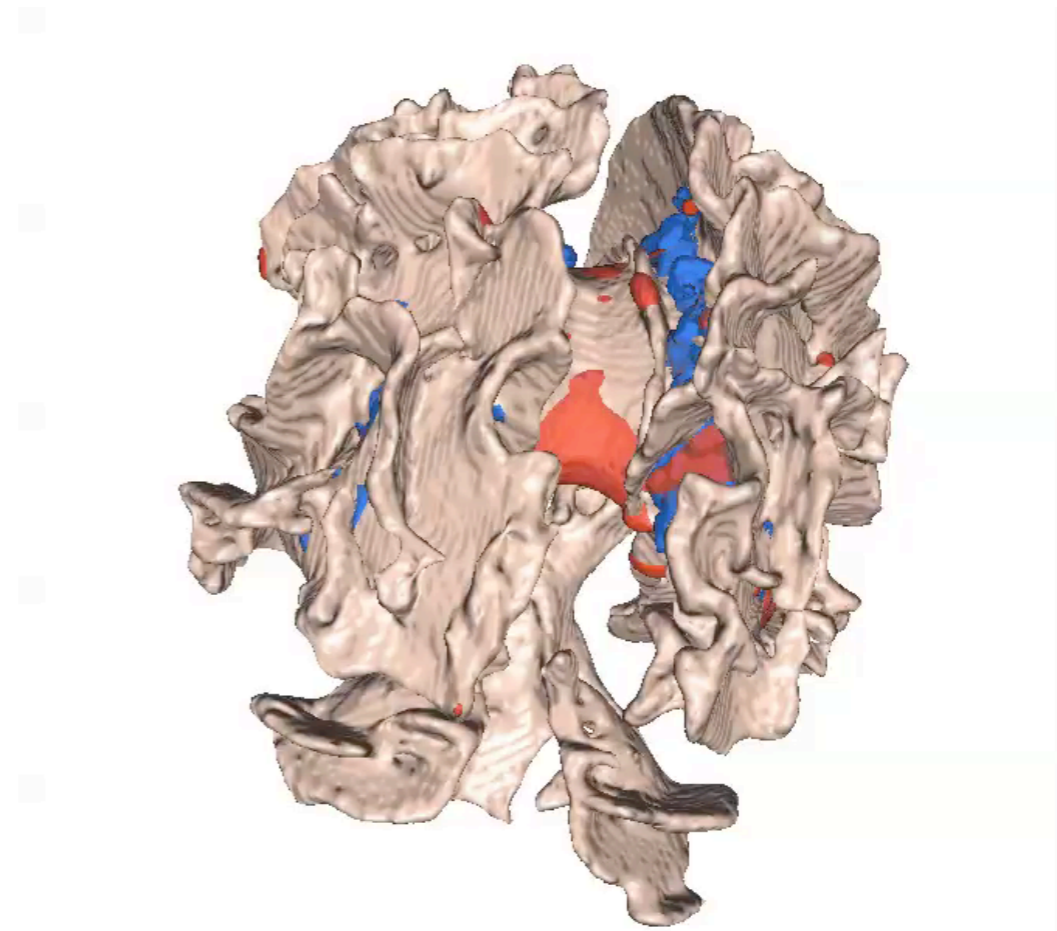
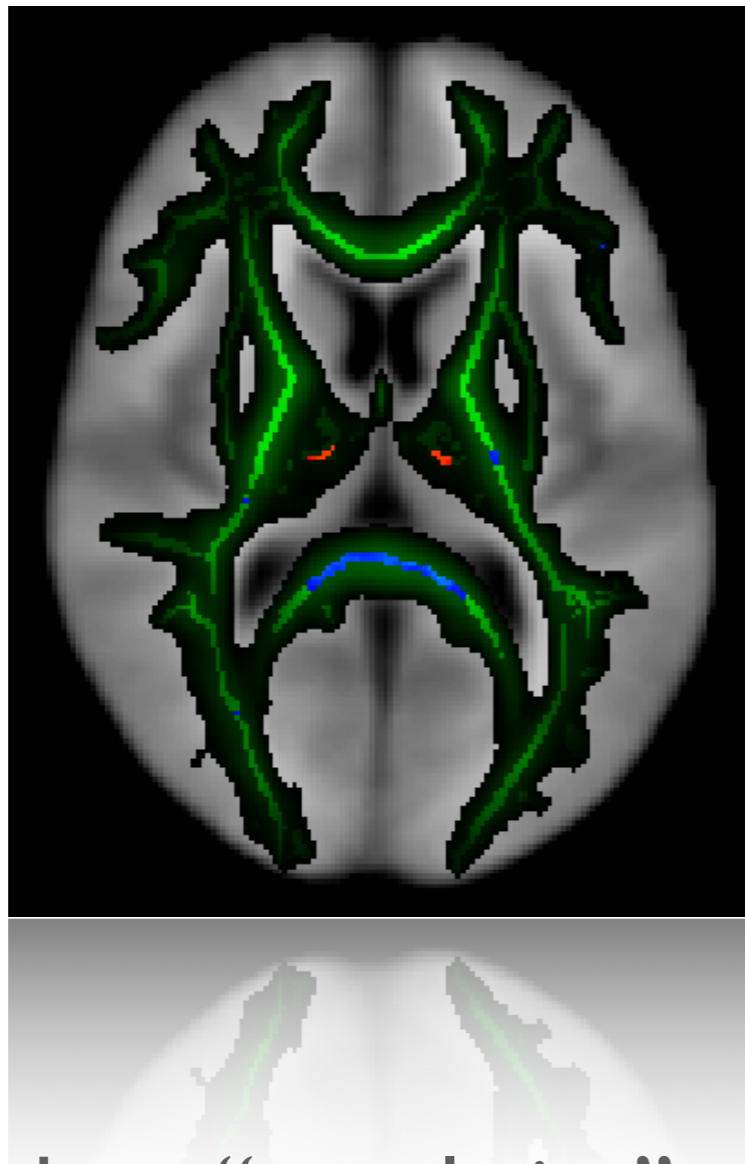
Tractography-Based FA Comparison



- Method [Gong 2005, Corouge 2006]
 - Define a given tract in all subjects
 - Parameterise FA along tract
 - Compare between subjects
- Strength: correspondence issue hopefully resolved
- Problems
 - Currently requires manual intervention to specify tract
 - Hence doesn't investigate whole brain
 - Projection of FA onto tract needs careful thought



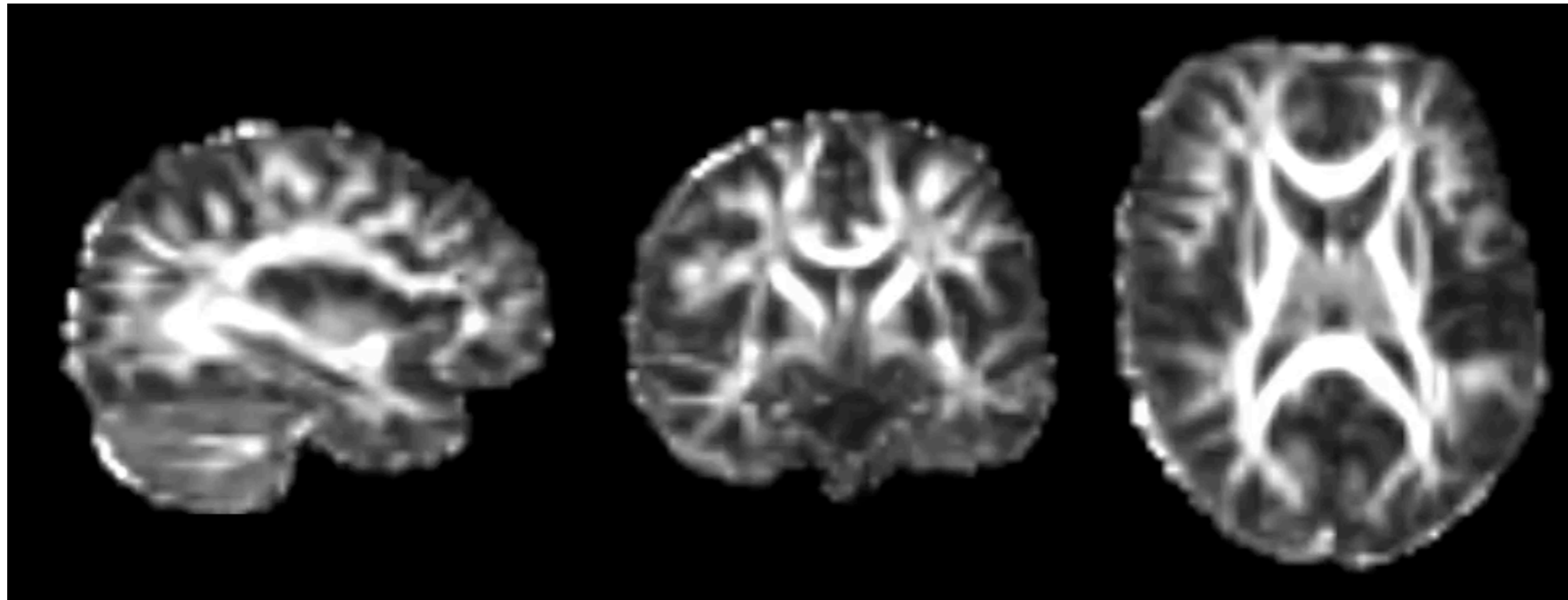
TBSS : Tract-Based Spatial Statistics



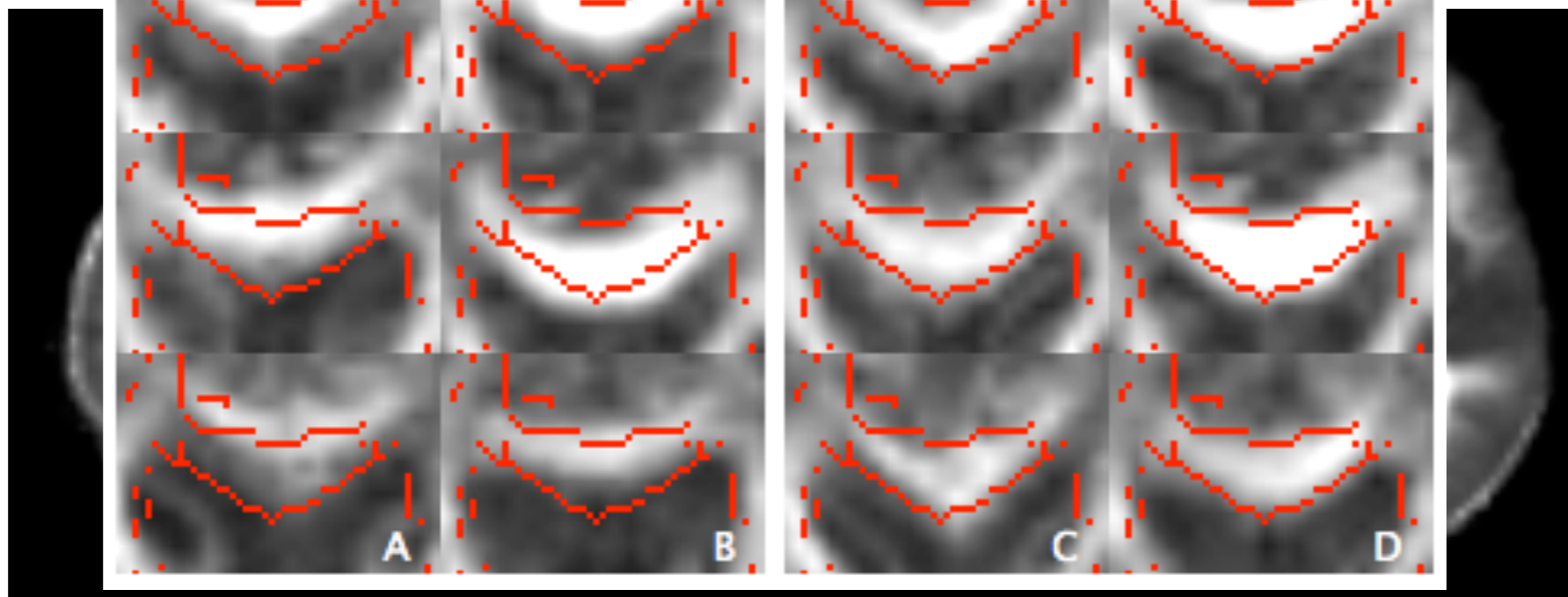
- Need: robust “voxelwise” cross-subject stats on DTI
- Problem: alignment issues confound valid local stats
- TBSS: solve alignment using alignment-invariant features:
- Compare FA taken from tract centres (via skeletonisation)



1. Use medium-DoF nonlinear reg to pre-align all subjects' FA (nonlinear reg: FNIRT)

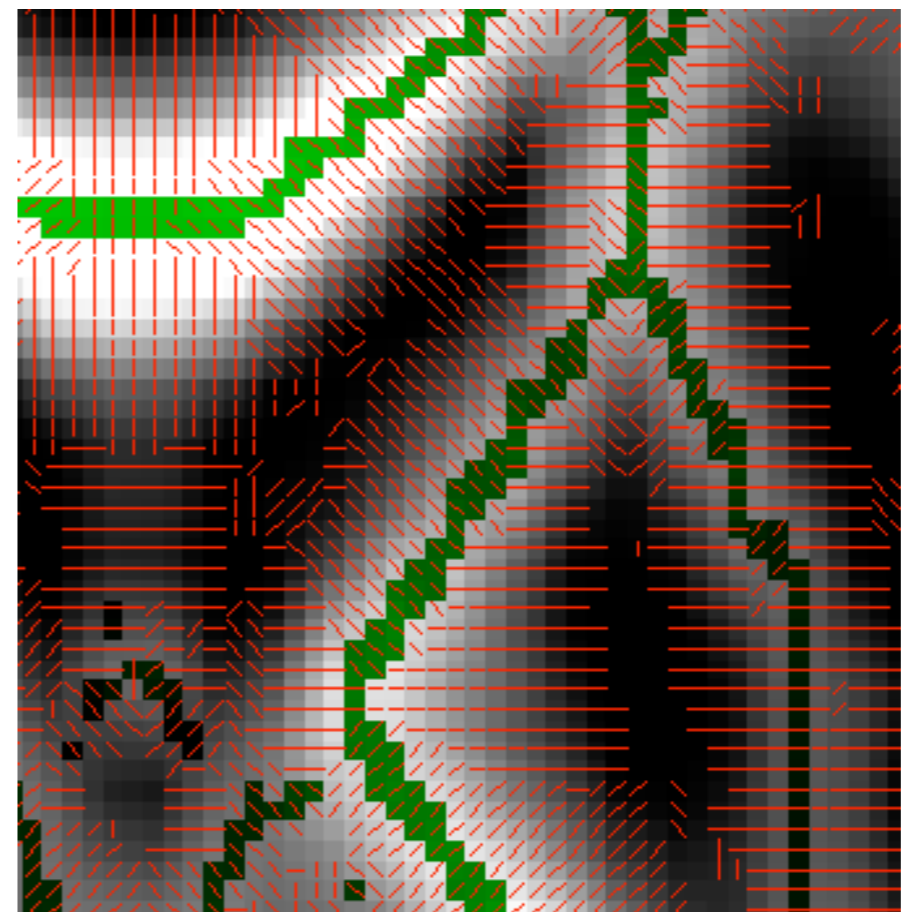
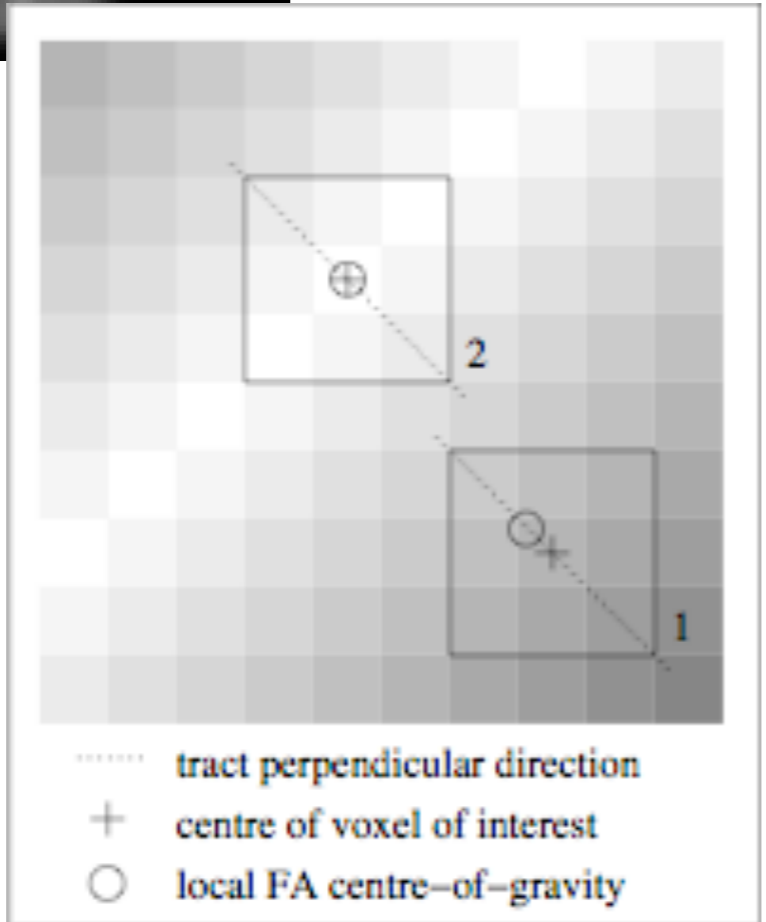
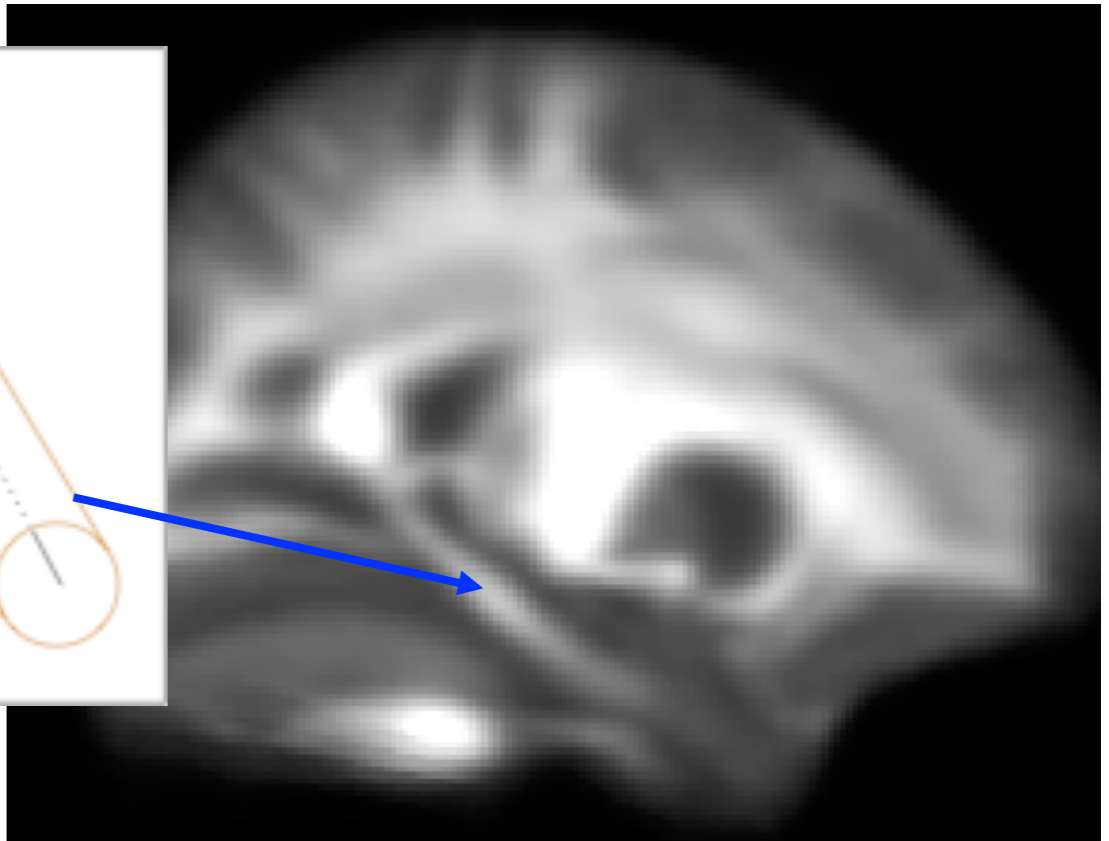
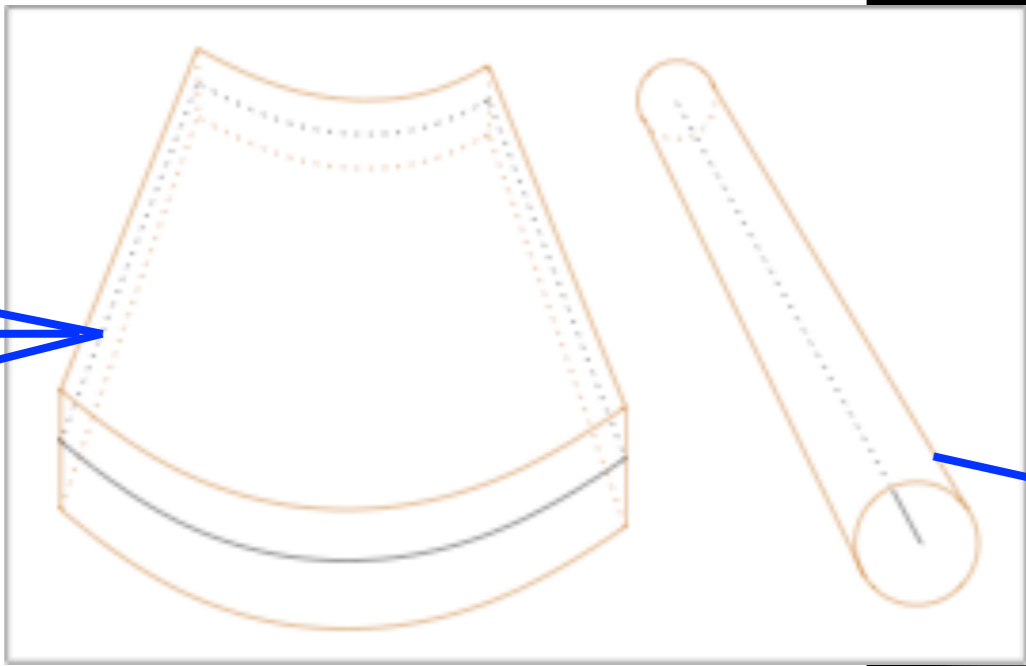
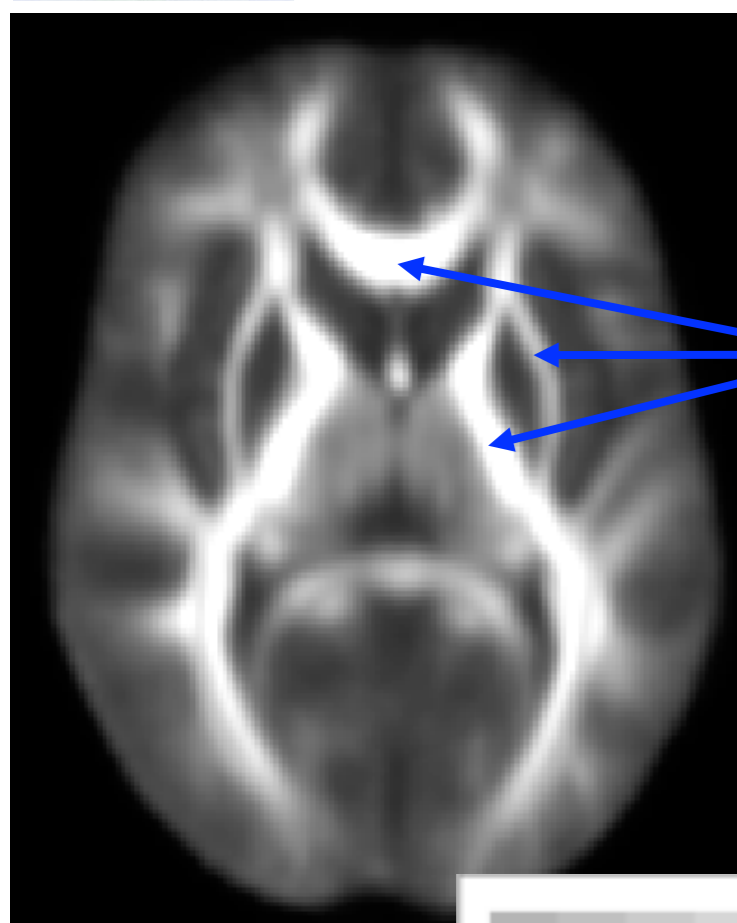


2. Cr (hinging)





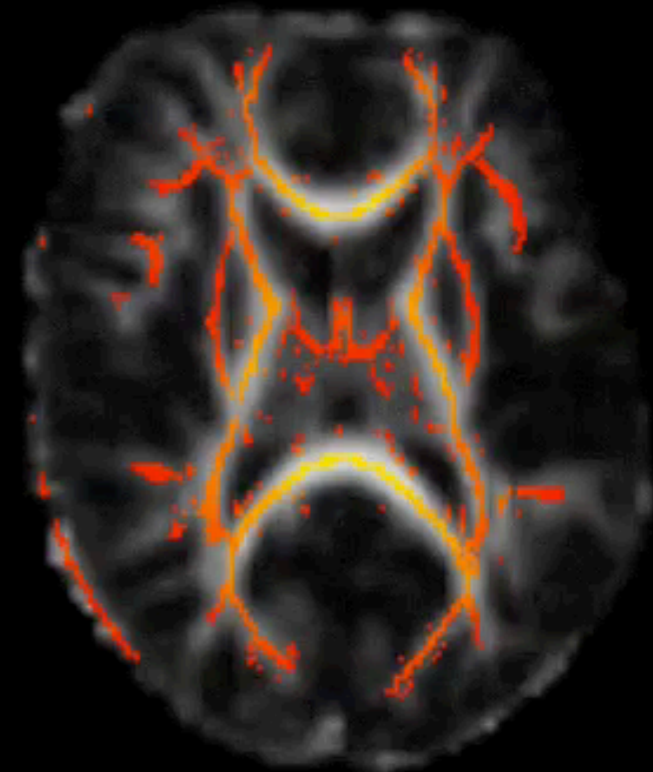
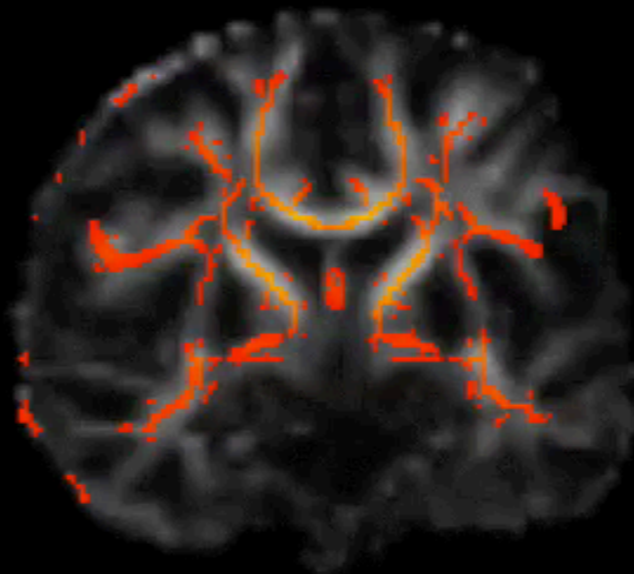
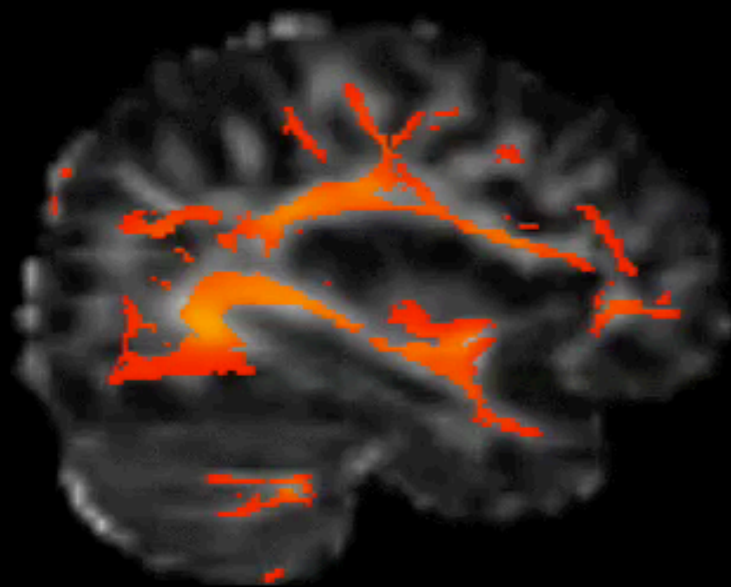
2. "Skeletonise" Mean FA





3. Threshold Mean FA Skeleton

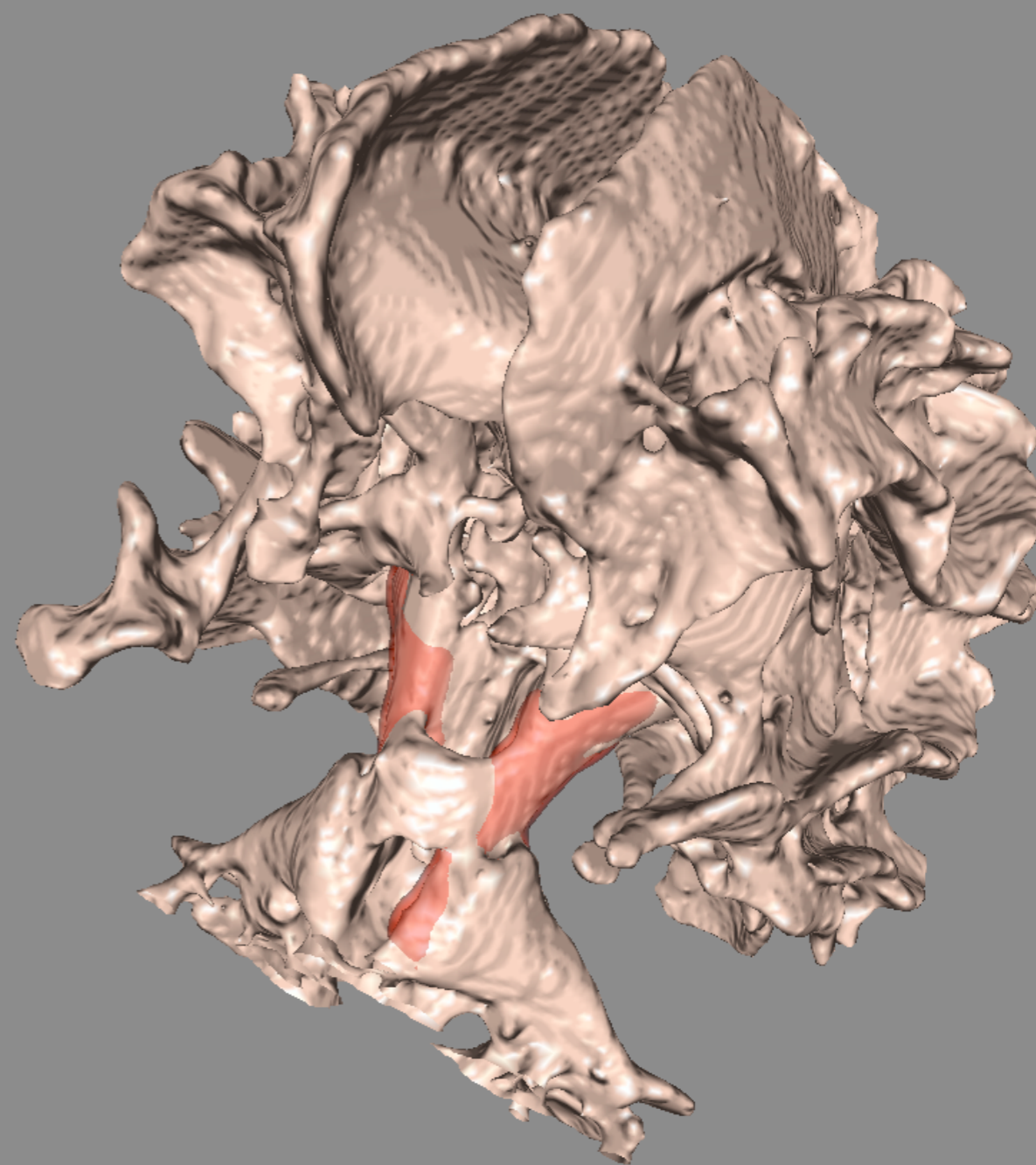
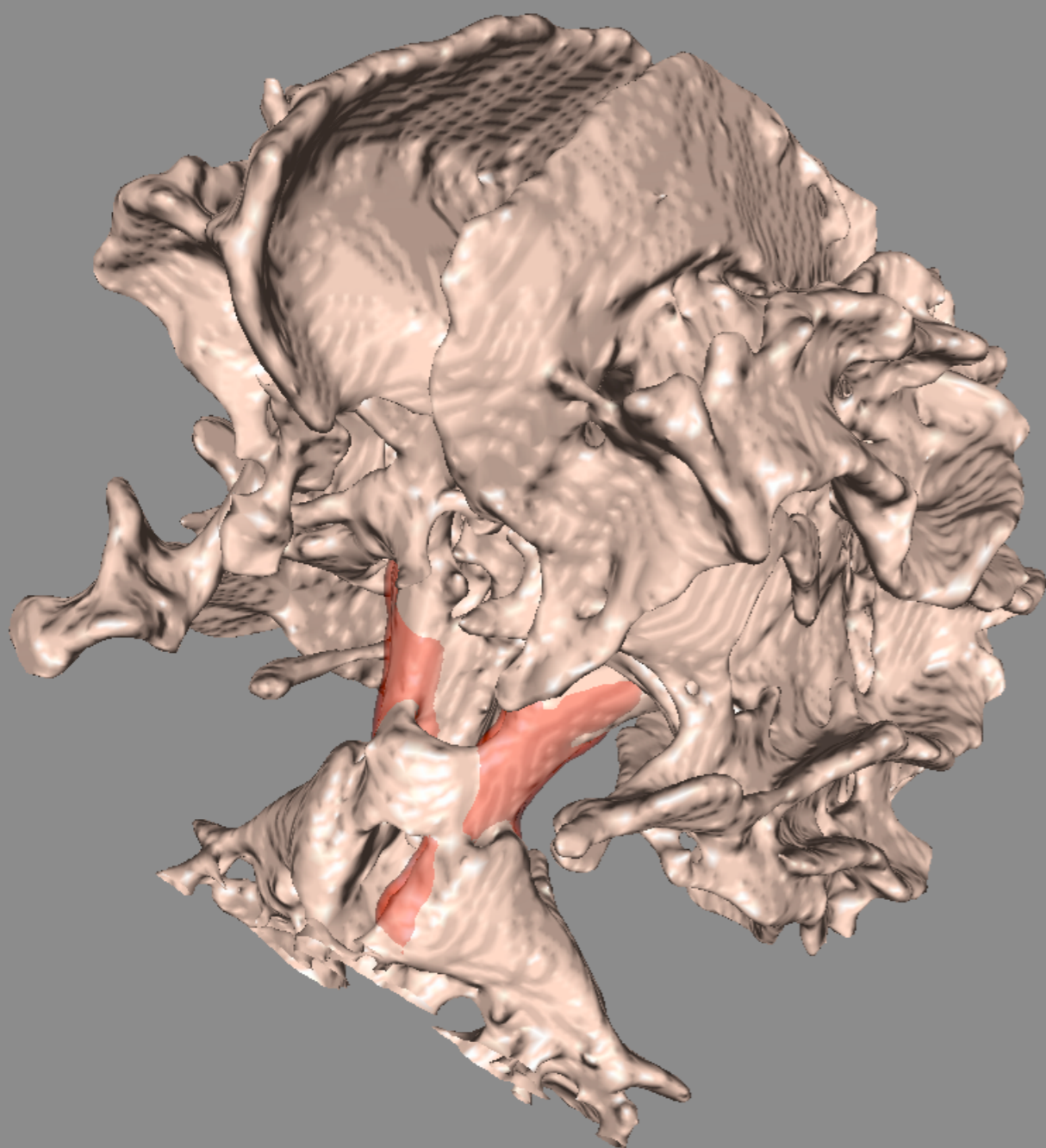
giving “objective” tract map





3. Threshold Mean FA Skeleton

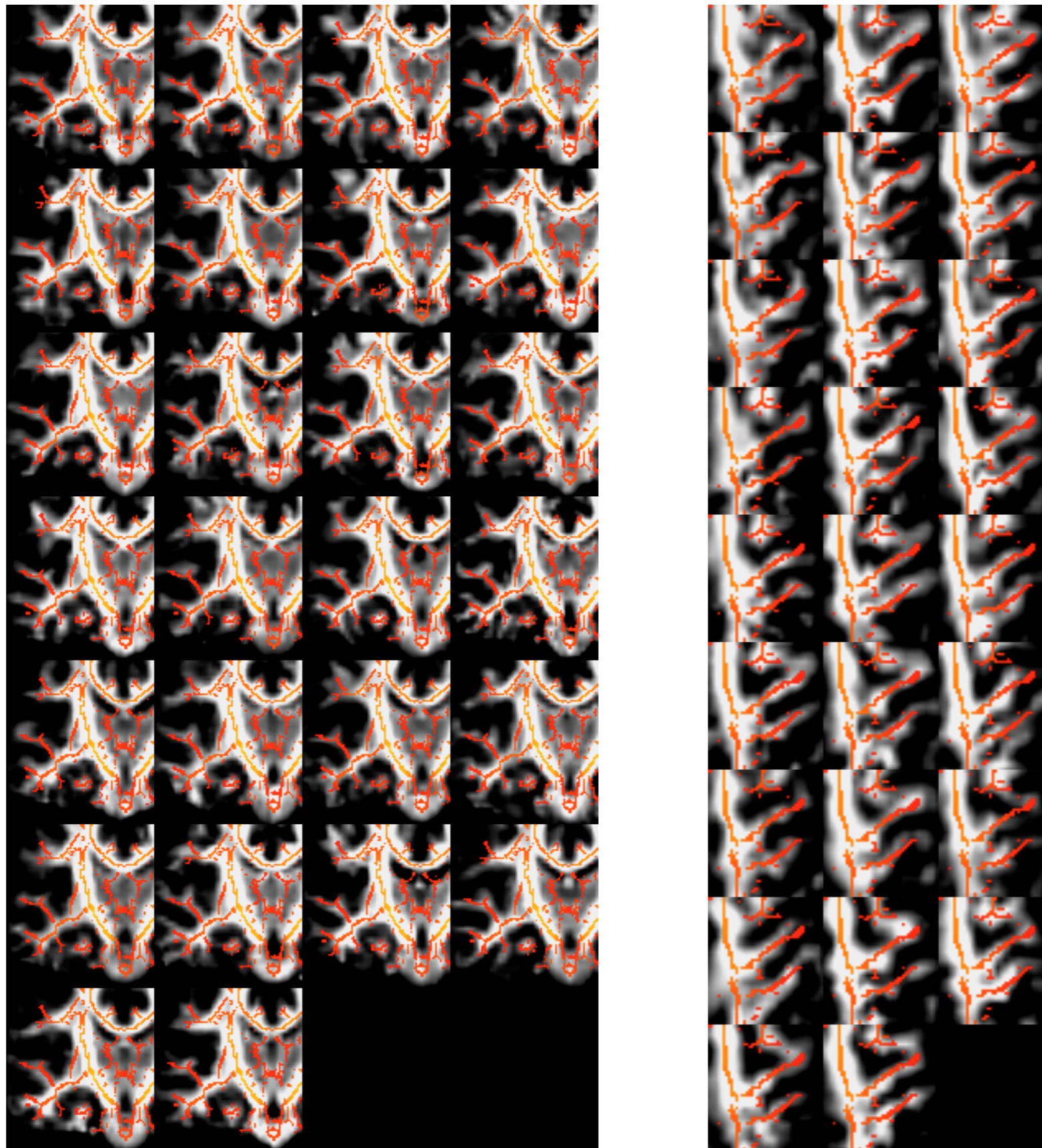
giving “objective” tract map





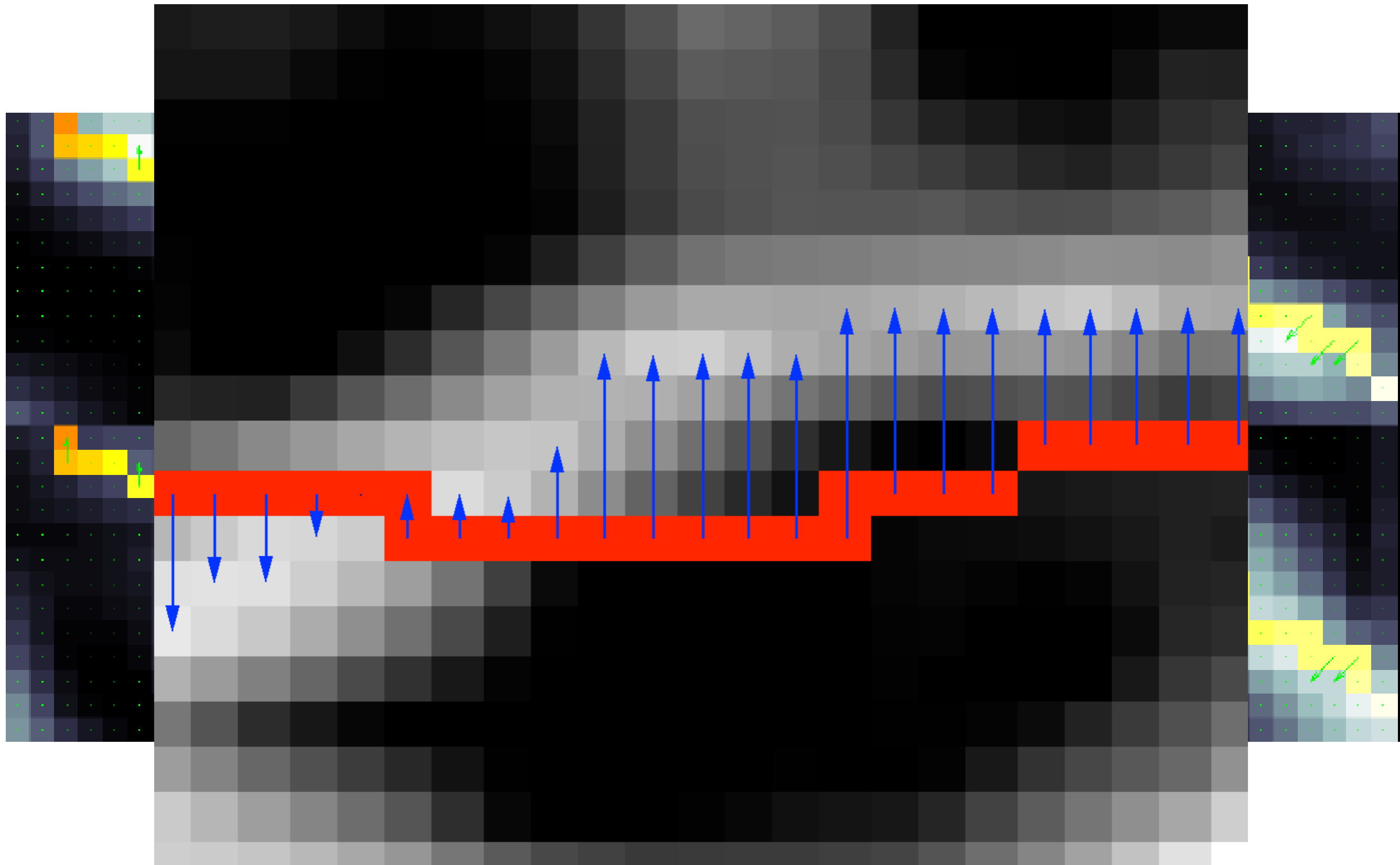
3. Threshold Mean FA Skeleton

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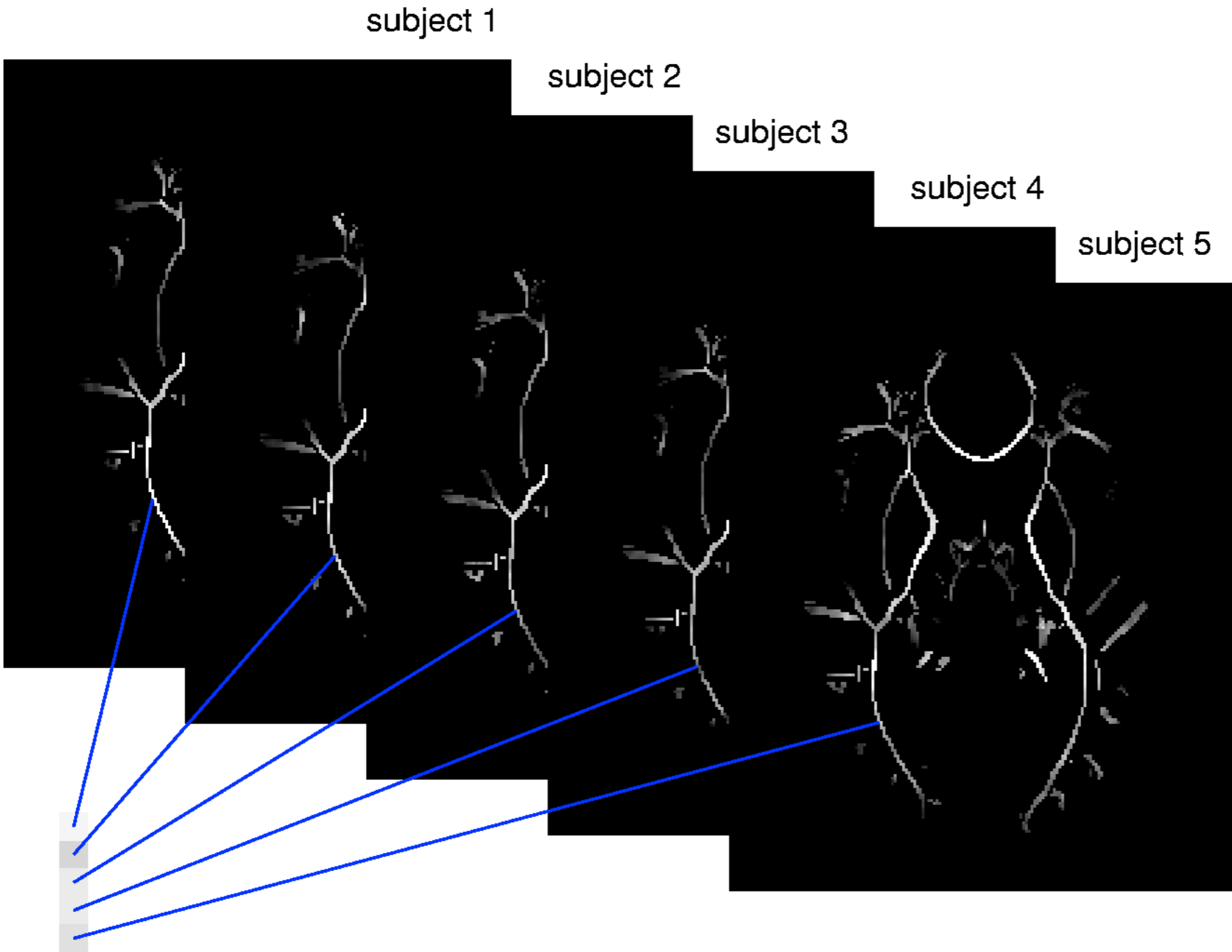


4. For each subject's warped FA, fill each point on the mean-space skeleton with nearest maximum FA value (i.e., from the centre of the subject's nearby tract)

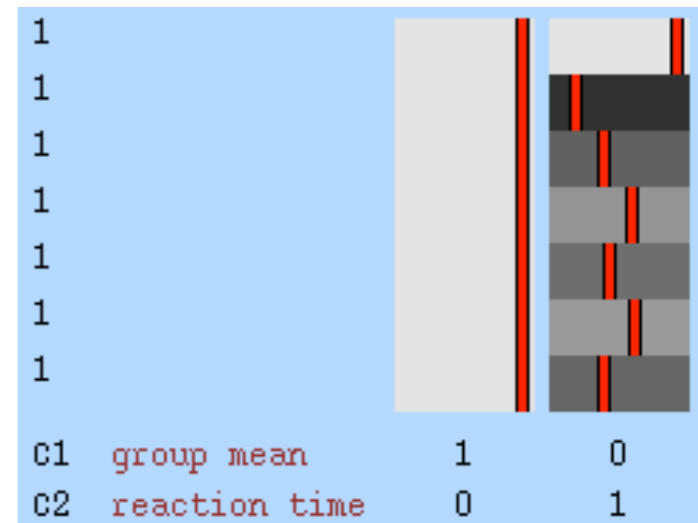
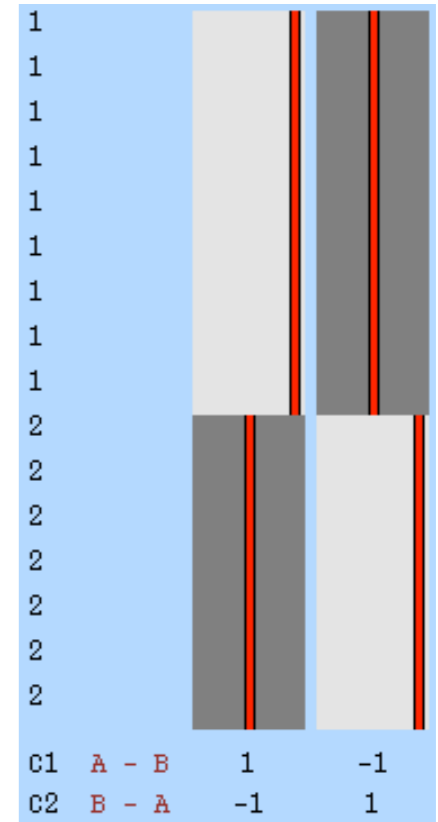




5. Do cross-subject voxelwise stats on skeleton-projected FA and Threshold, (e.g., permutation testing, including multiple comparison correction)



one skeleton voxel's data vector (to be fed into GLM)

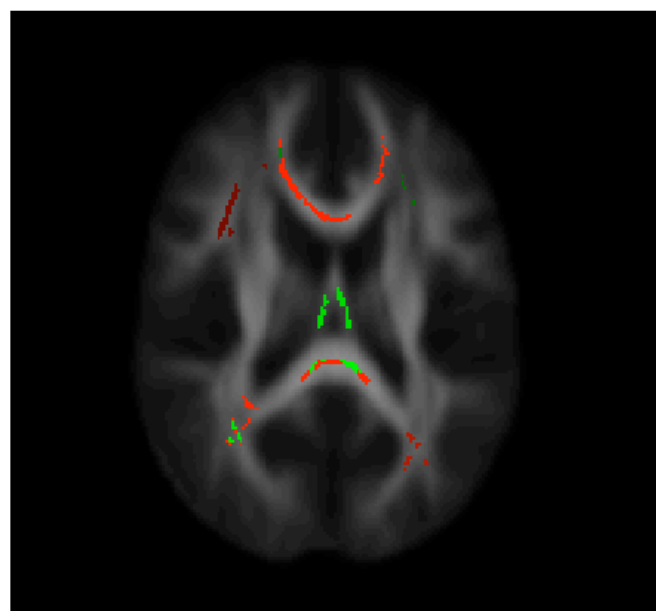
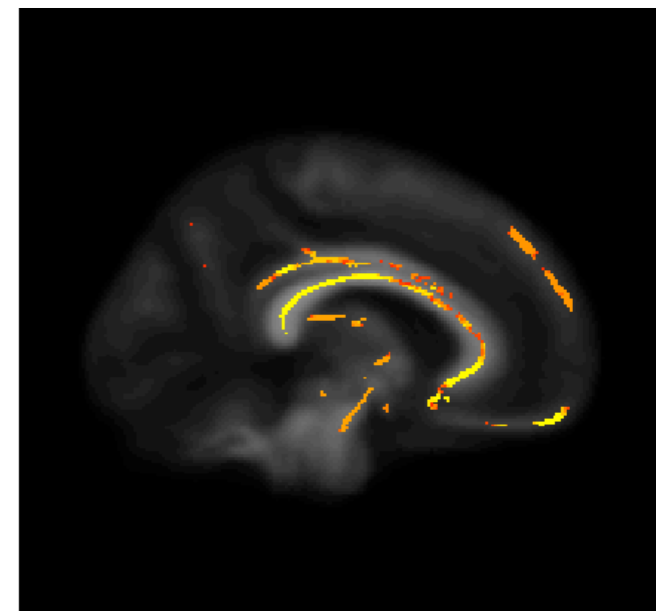
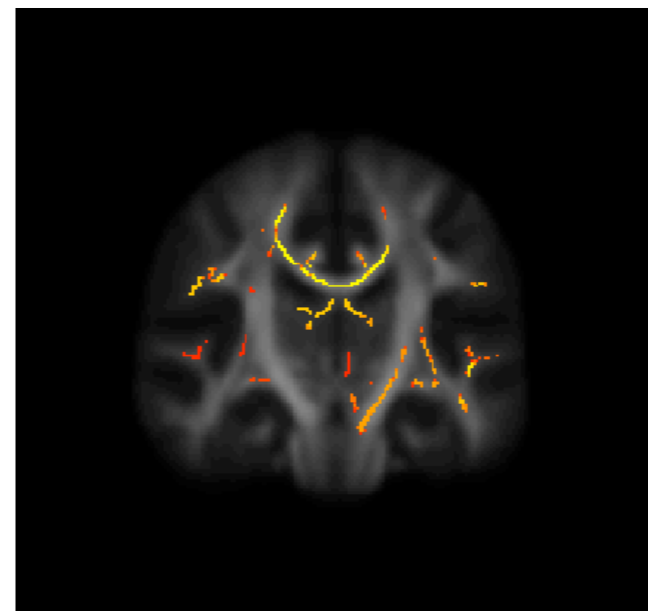
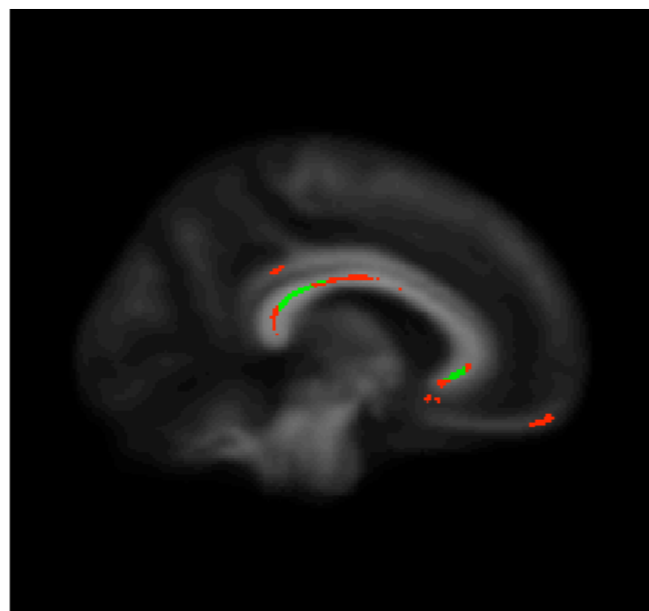
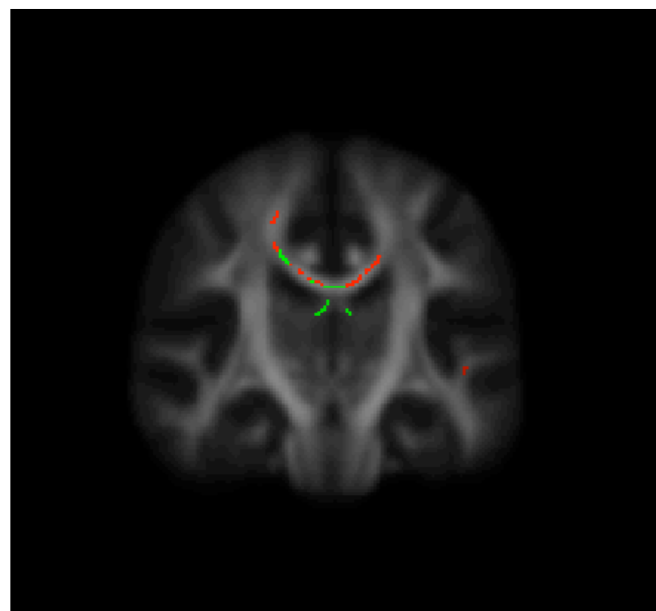




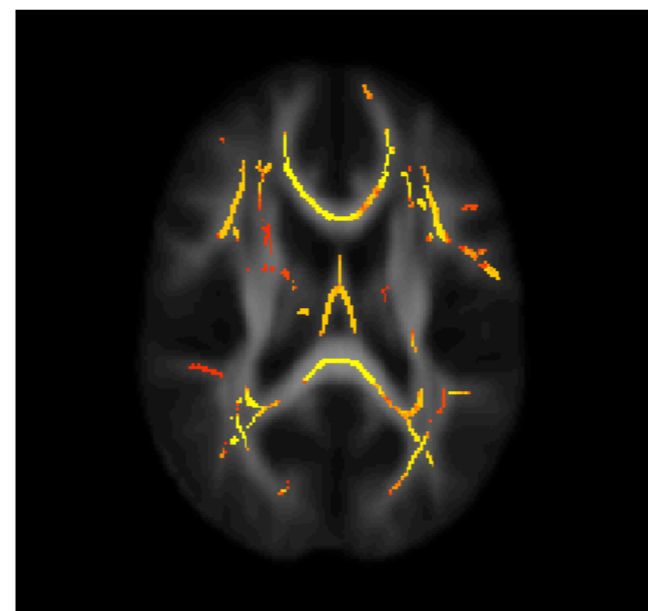
TFCE for TBSS

controls > schizophrenics

$p < 0.05$ corrected for multiple comparisons across space,
using randomise



cluster-based:
cluster-forming
threshold =
2 or 3



TFCE



Schizophrenia (Mackay)

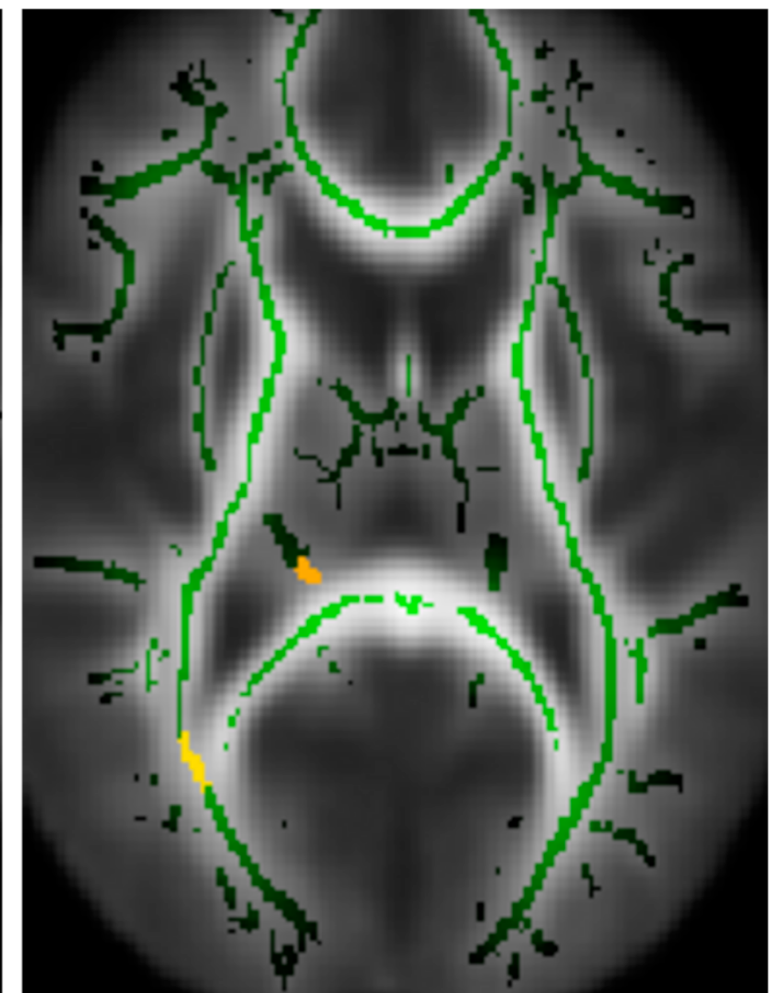
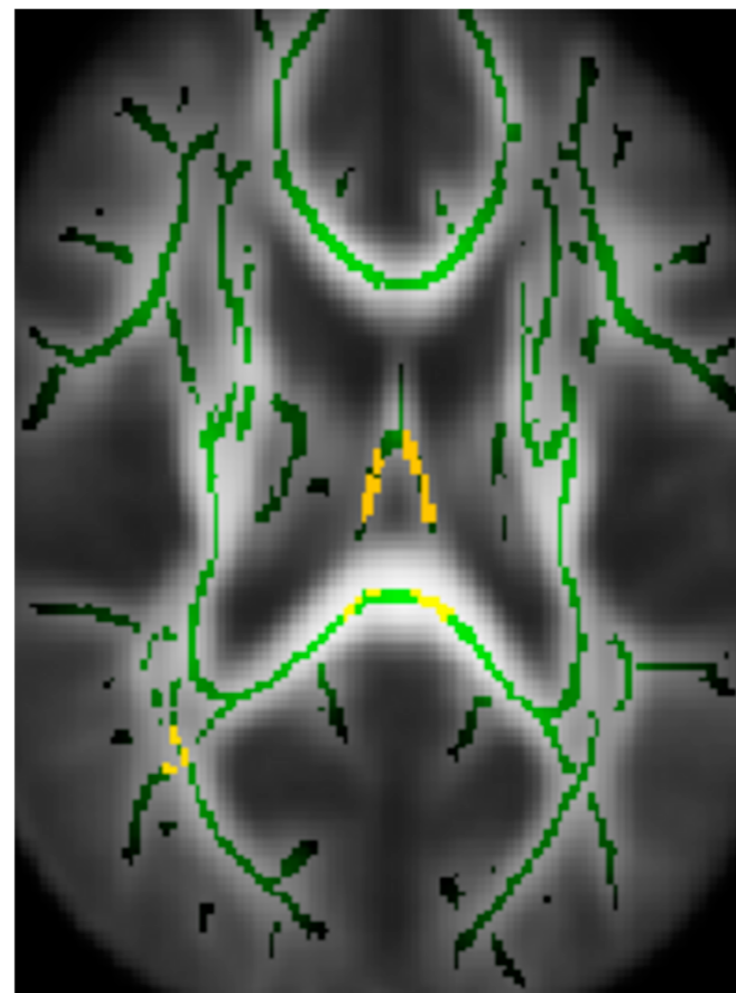
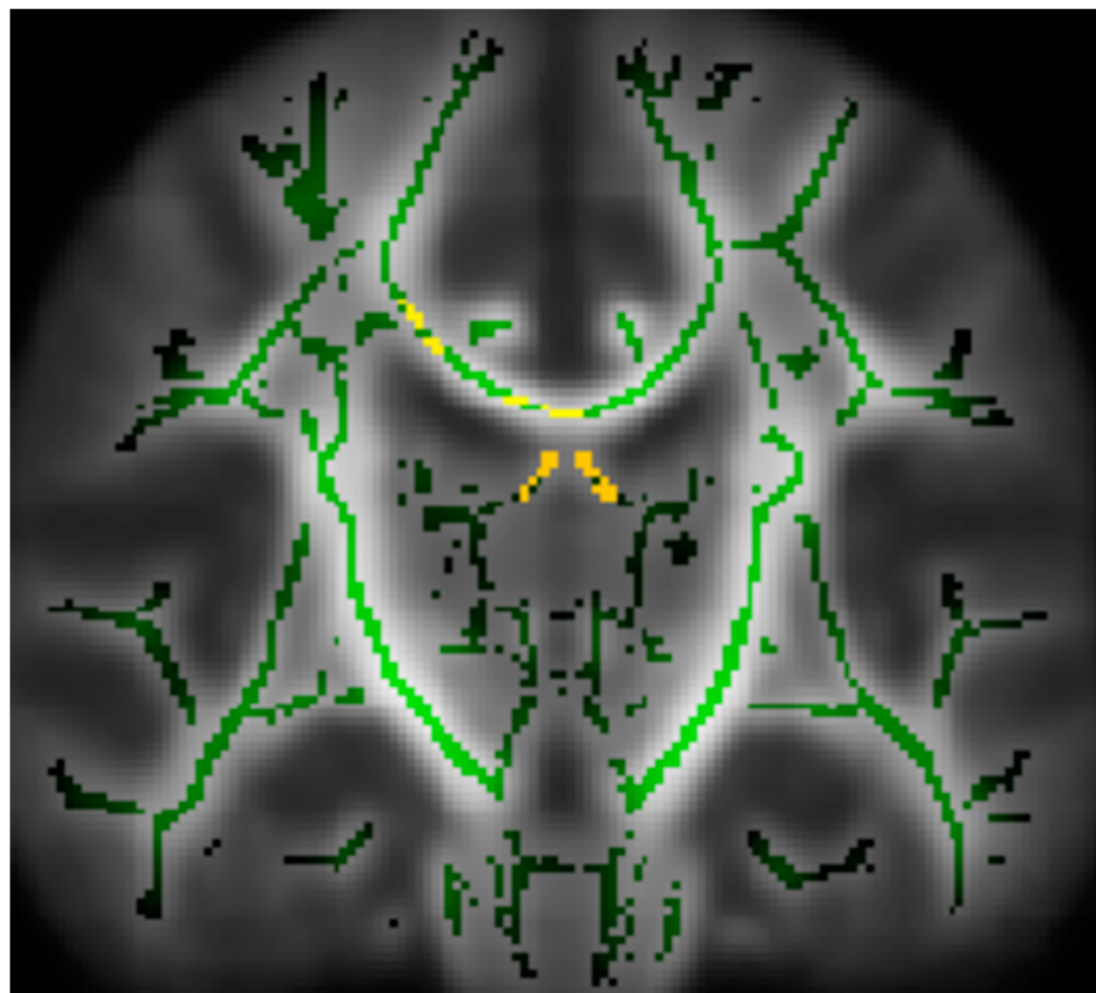
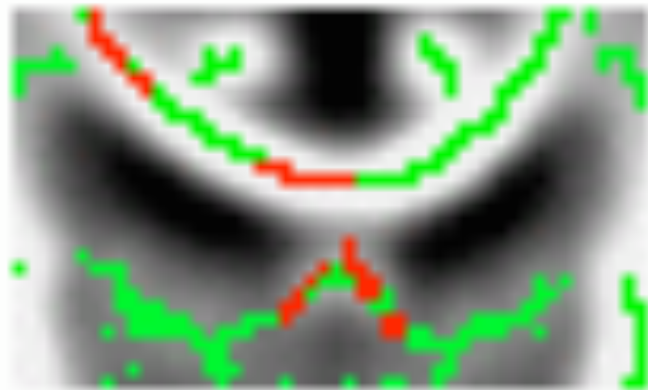
TBSS & VBM show reduced FA in corpus callosum & fornix
VBM shows spurious result in thalamus due to increased ventricles in schiz.

TBSS

VBM

mean FA (controls)

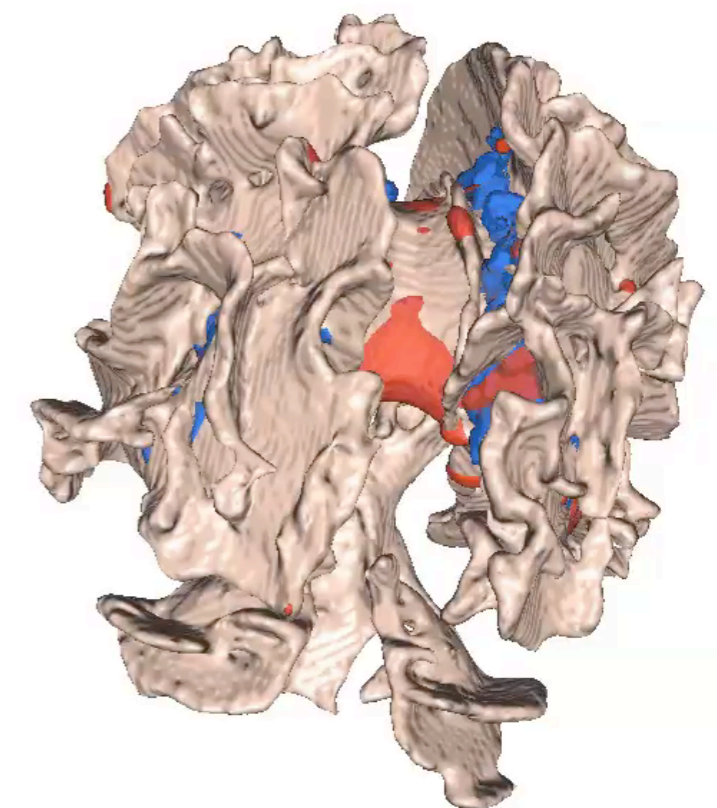
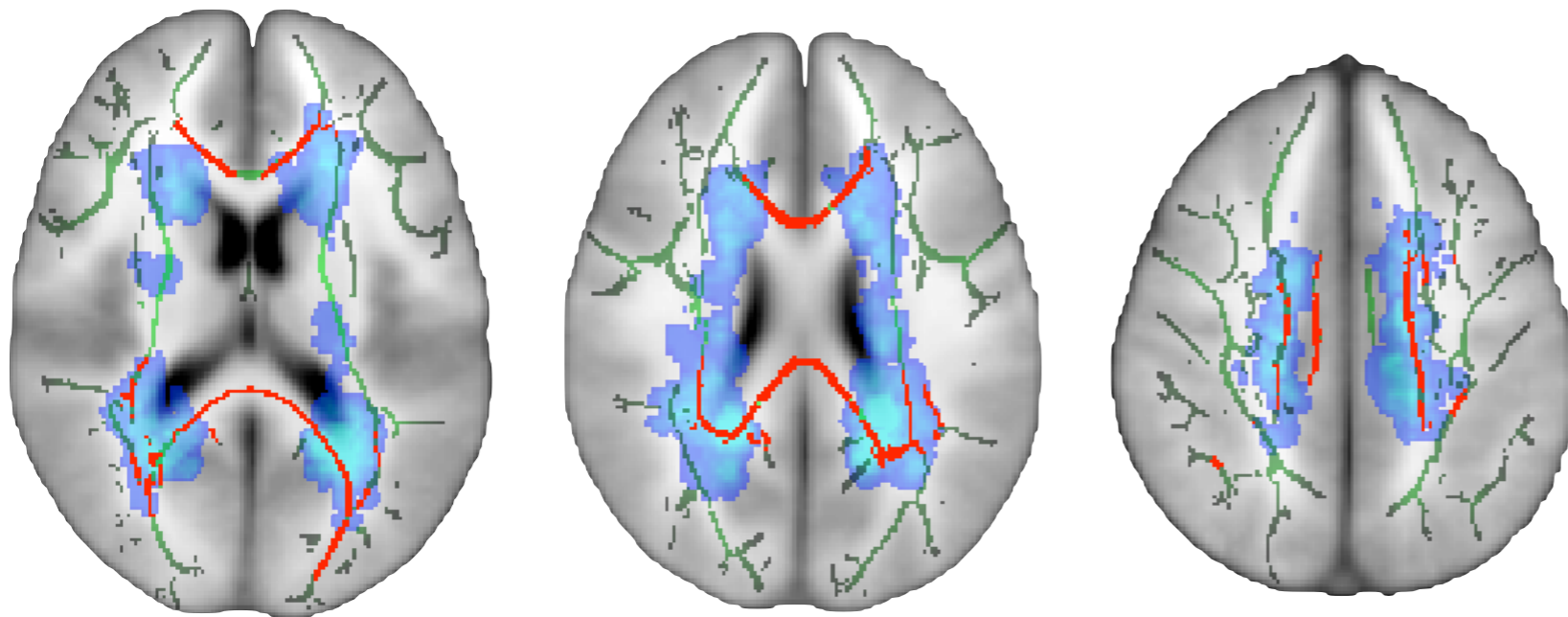
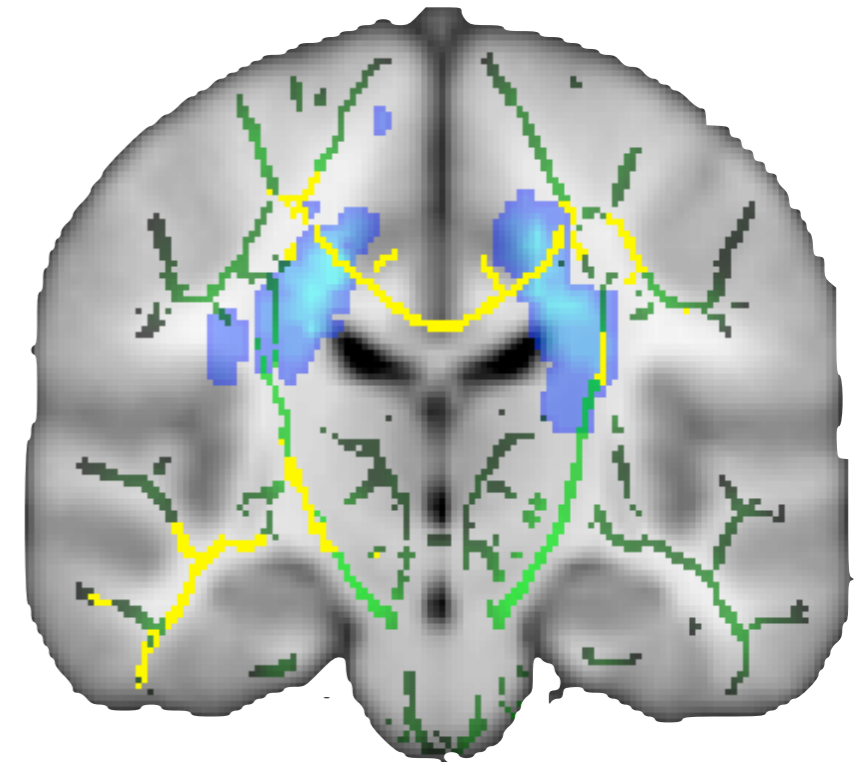
mean FA (schiz.)





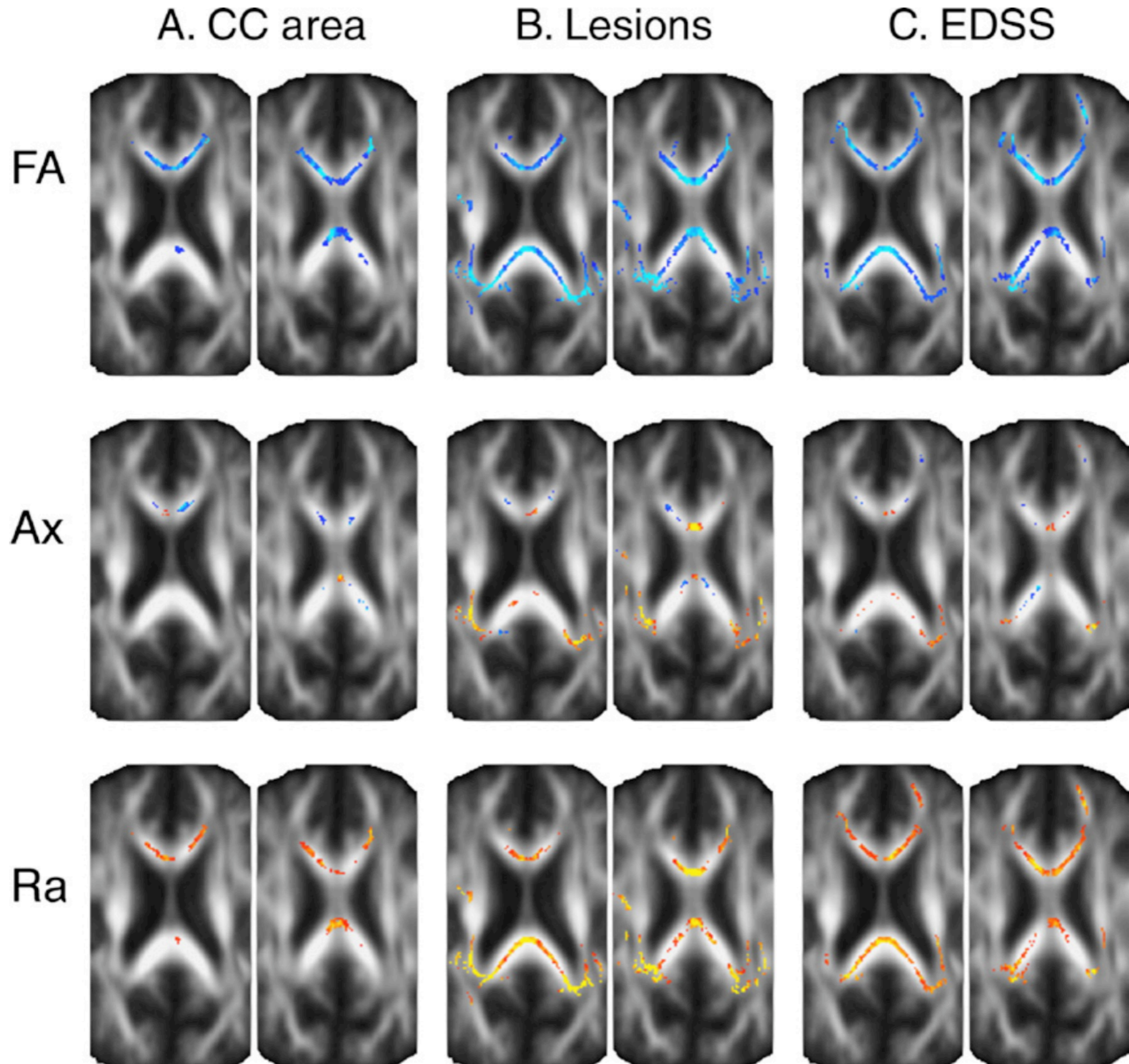
Multiple Sclerosis (Cader, Johansen-Berg & Matthews)

- 15 MS patients
 - **Yellow** = -ve corr. FA vs EDSS
 - **Blue** = group lesion probability (50%)
 - **Red** = -ve corr. FA vs lesion volume
- Note reduced FA away from lesions





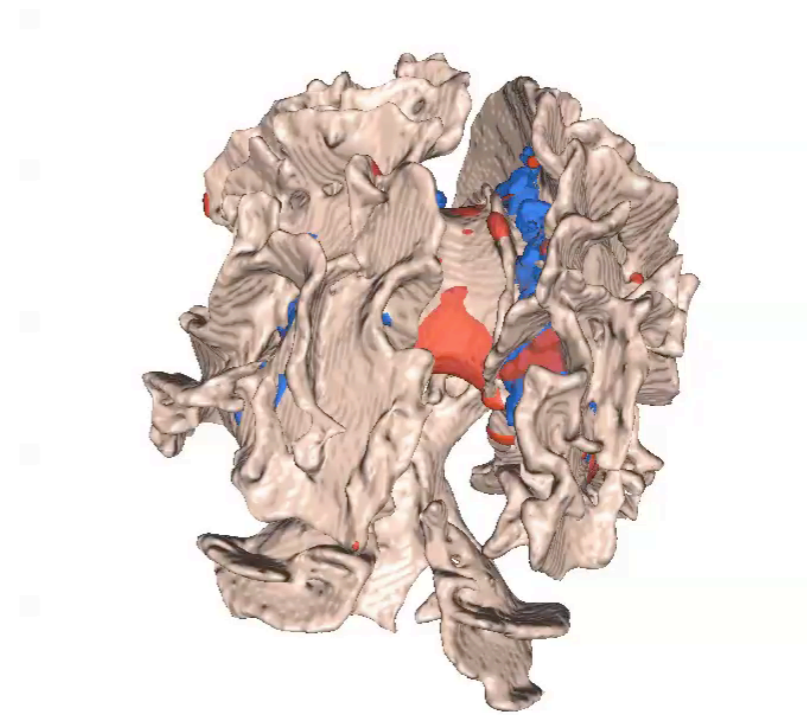
Multiple Sclerosis (Cader, Johansen-Berg & Matthews)

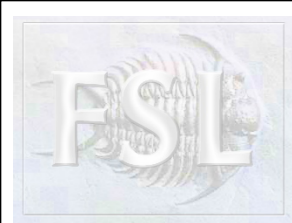




TBSS - Conclusions

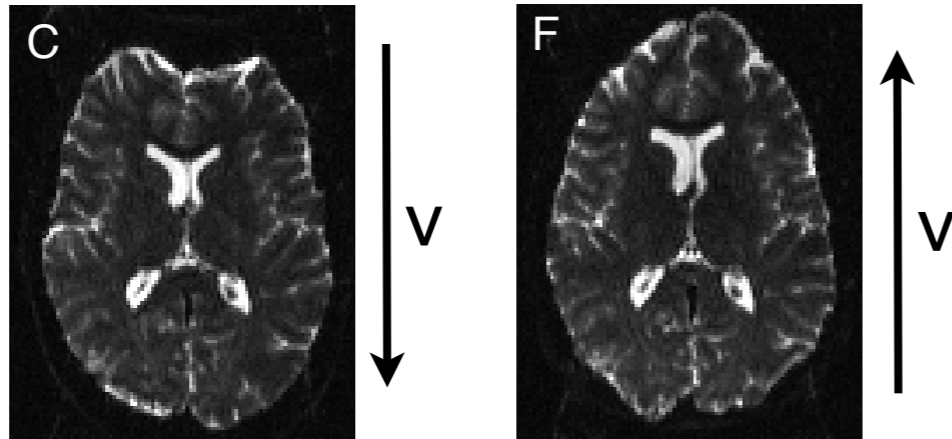
- Attempting to solve correspondence/smoothing problems
- Less ambiguity of interpretation / spurious results than VBM
- Easier to test whole brain than ROI / tractography
- Limitations & Dangers
 - Interpretation of partial volume tracts still an issue
 - Crossing tracts?



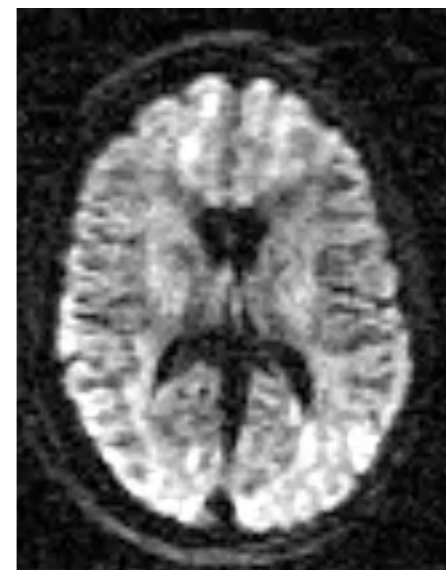
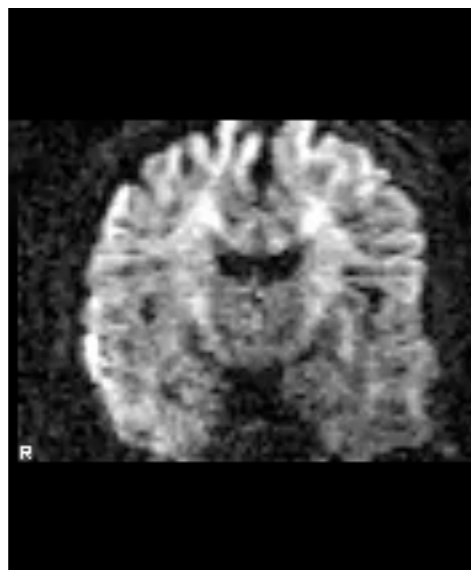


...But what about dMRI distortions?

Susceptibility-induced (EPI) Distortions

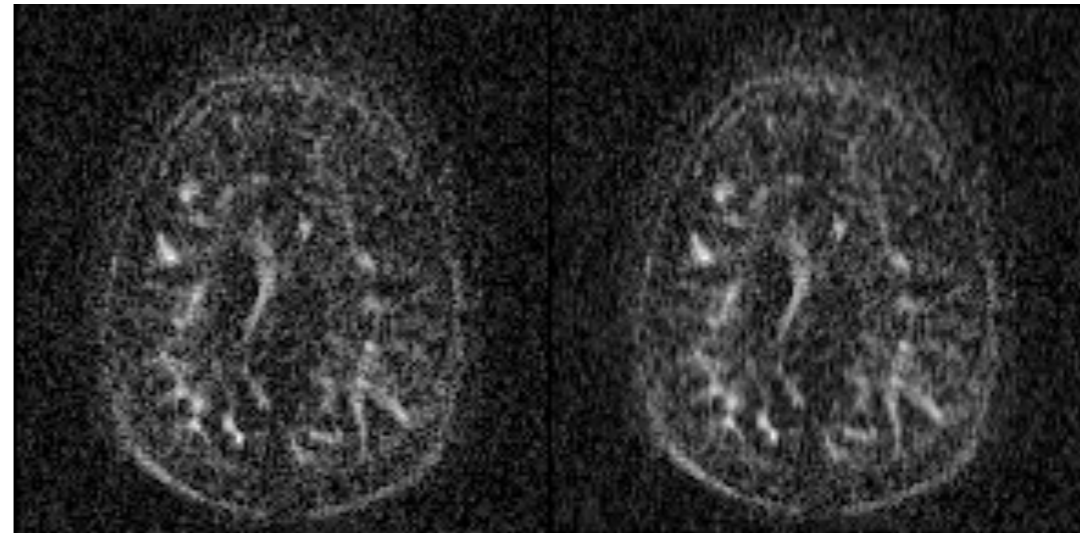
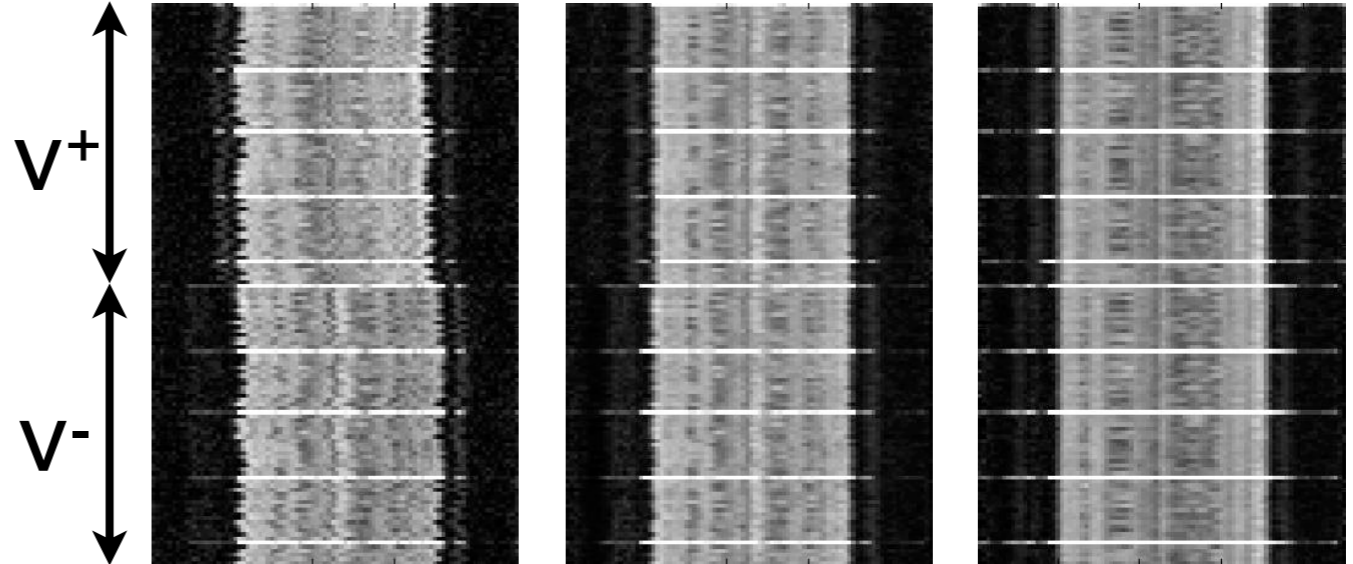
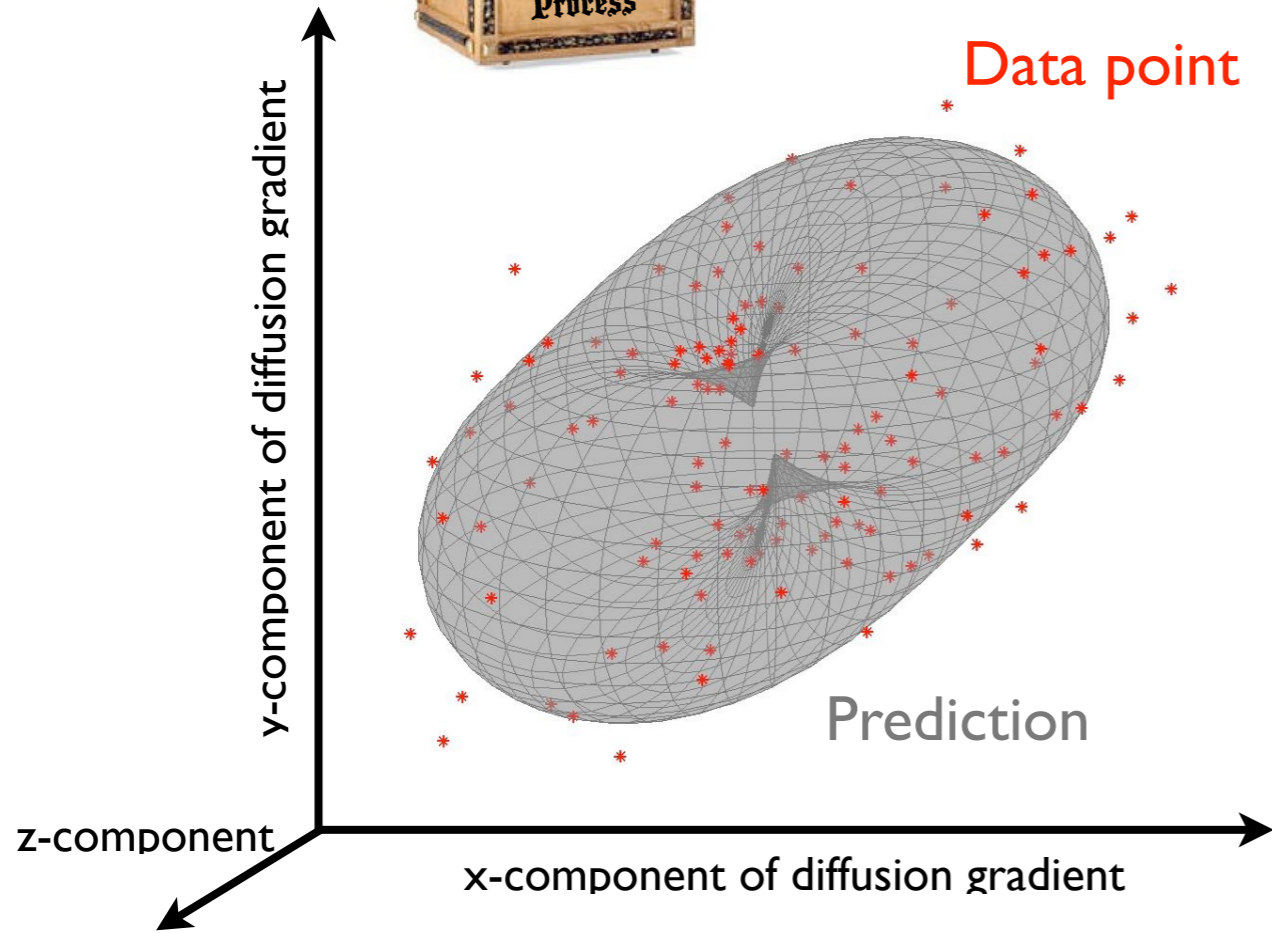


Eddy Current-induced Distortions





eddy and topup - tools for processing of diffusion data





Outline of the talk

- What is the problem with diffusion data?
- Off-resonance field
 - How does it cause distortions?
 - Where does it come from?
- Registering diffusion data
 - How topup works
 - How eddy works
- Practicalities
- Some results
- Quality control
- “New” eddy features

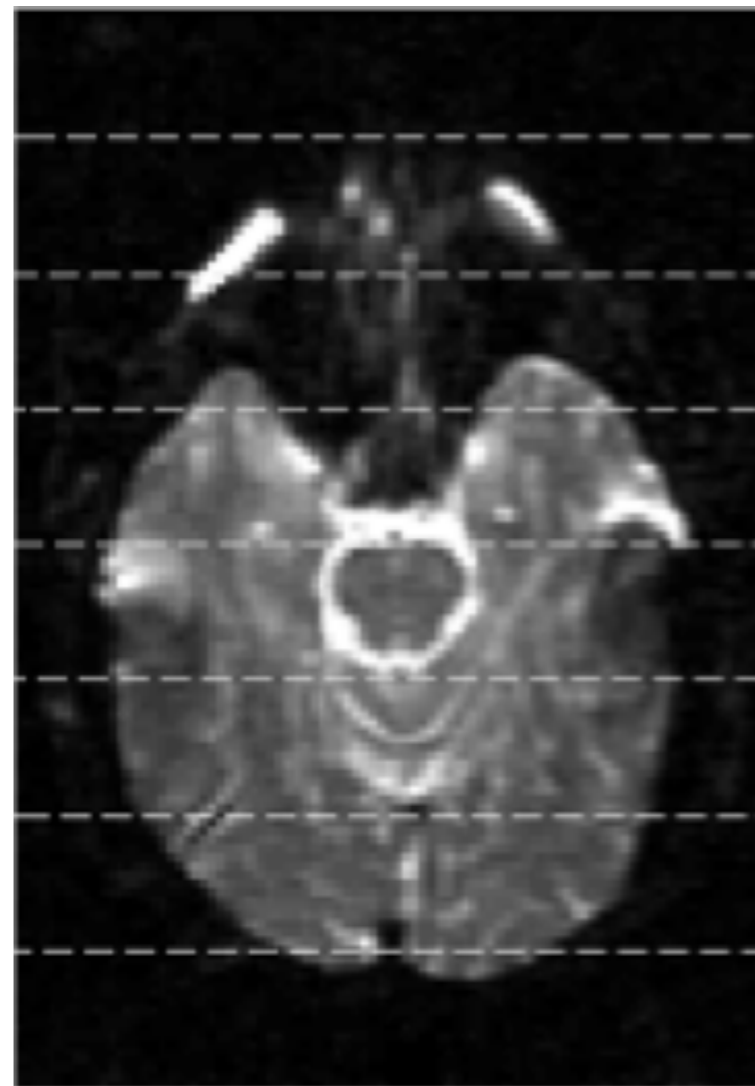
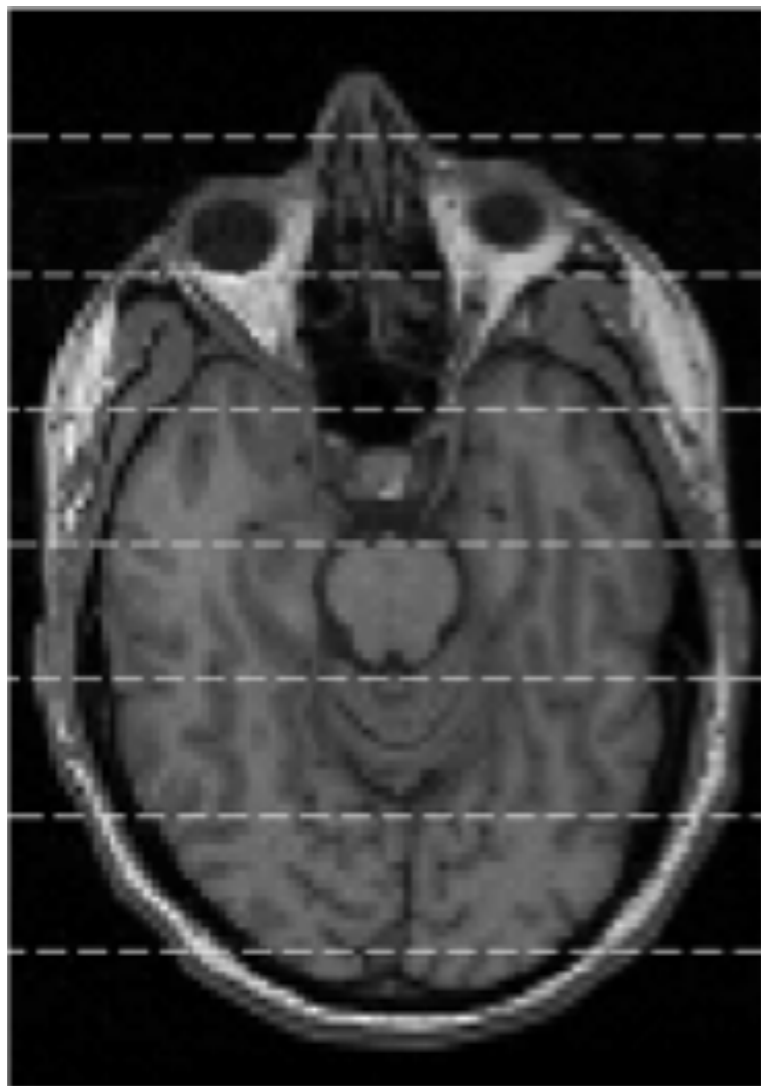


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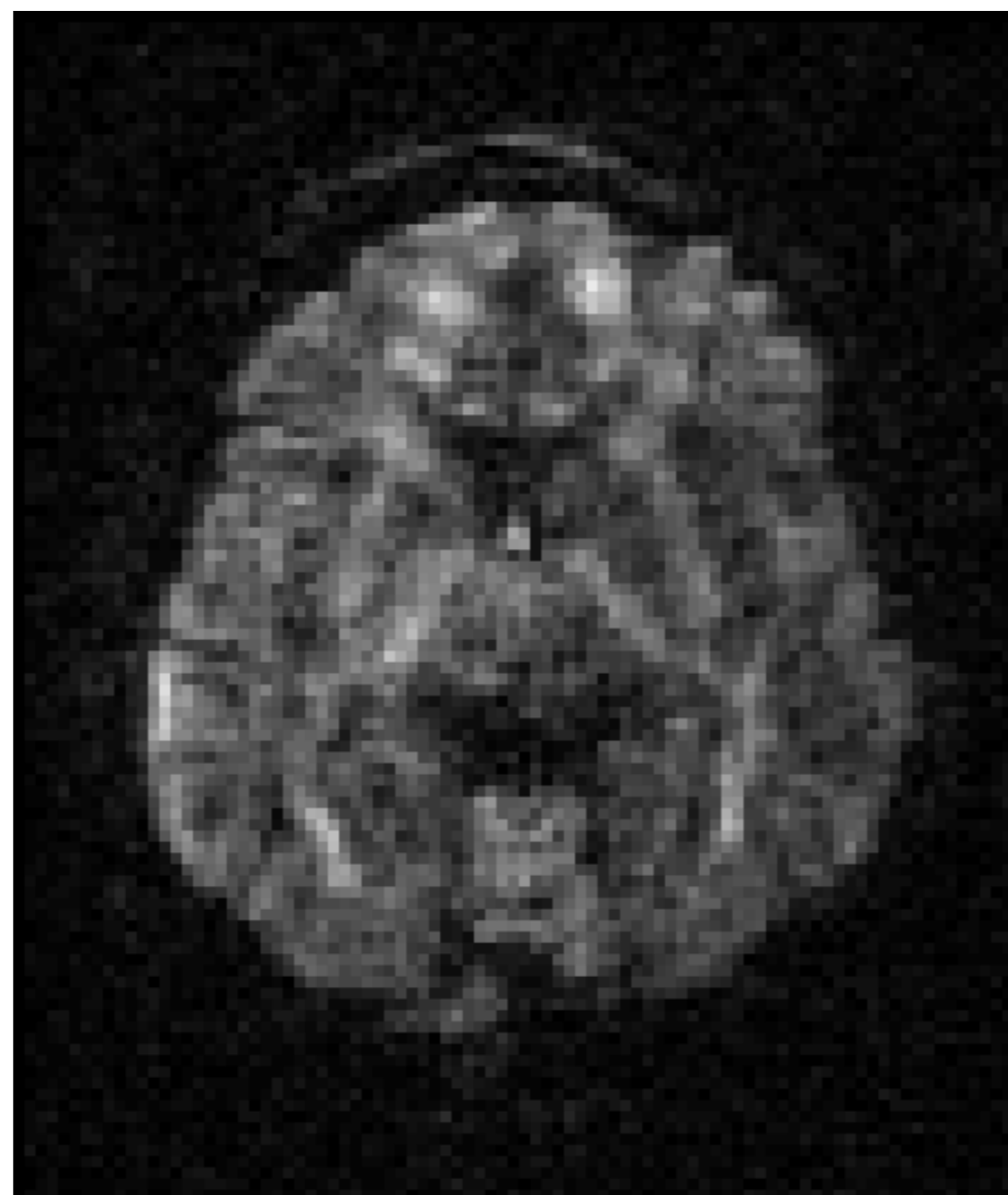
What is the problem with diffusion data?



Well, it isn't very anatomically faithful



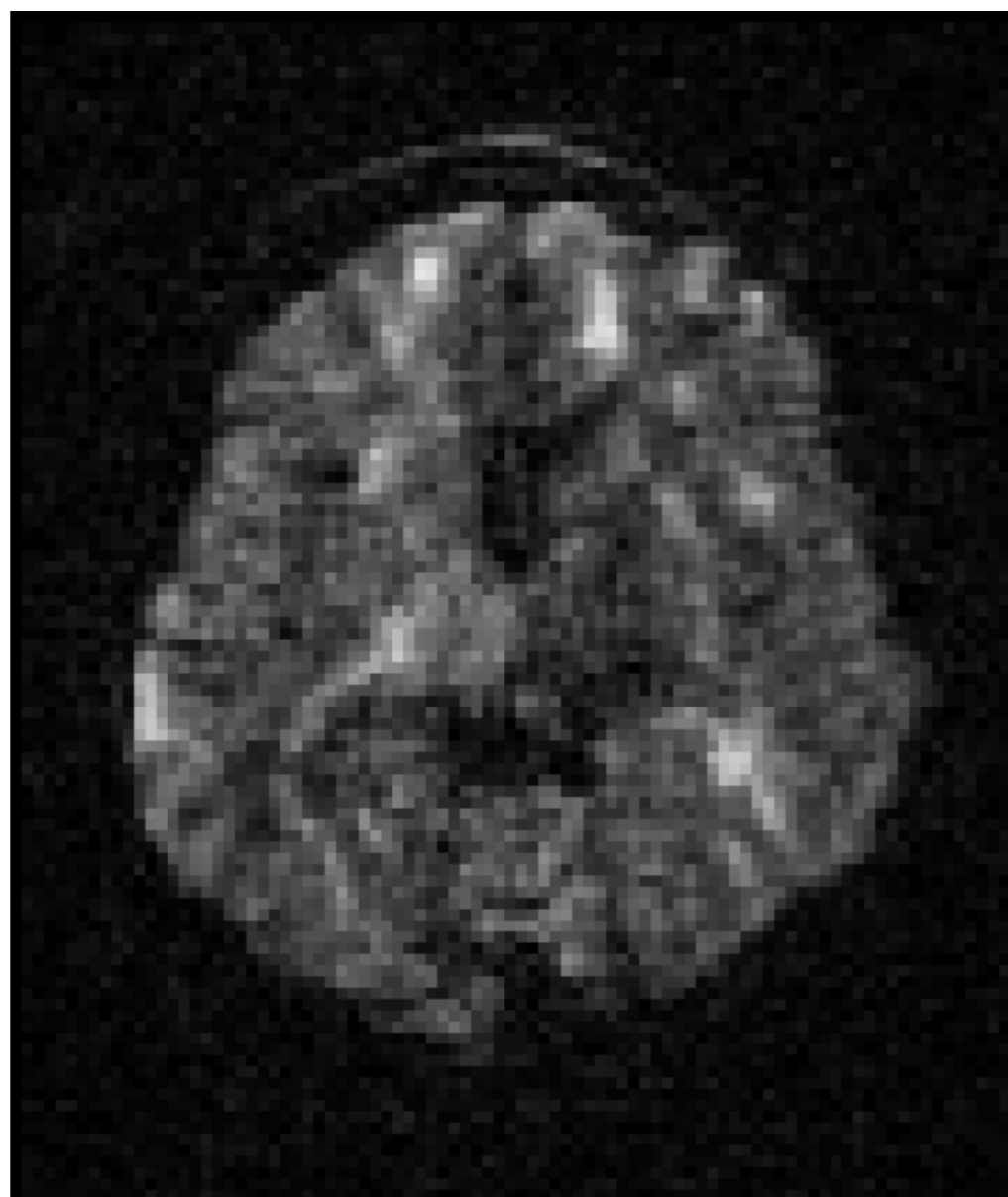
What is the problem with diffusion data?



In fact, it isn't even internally consistent



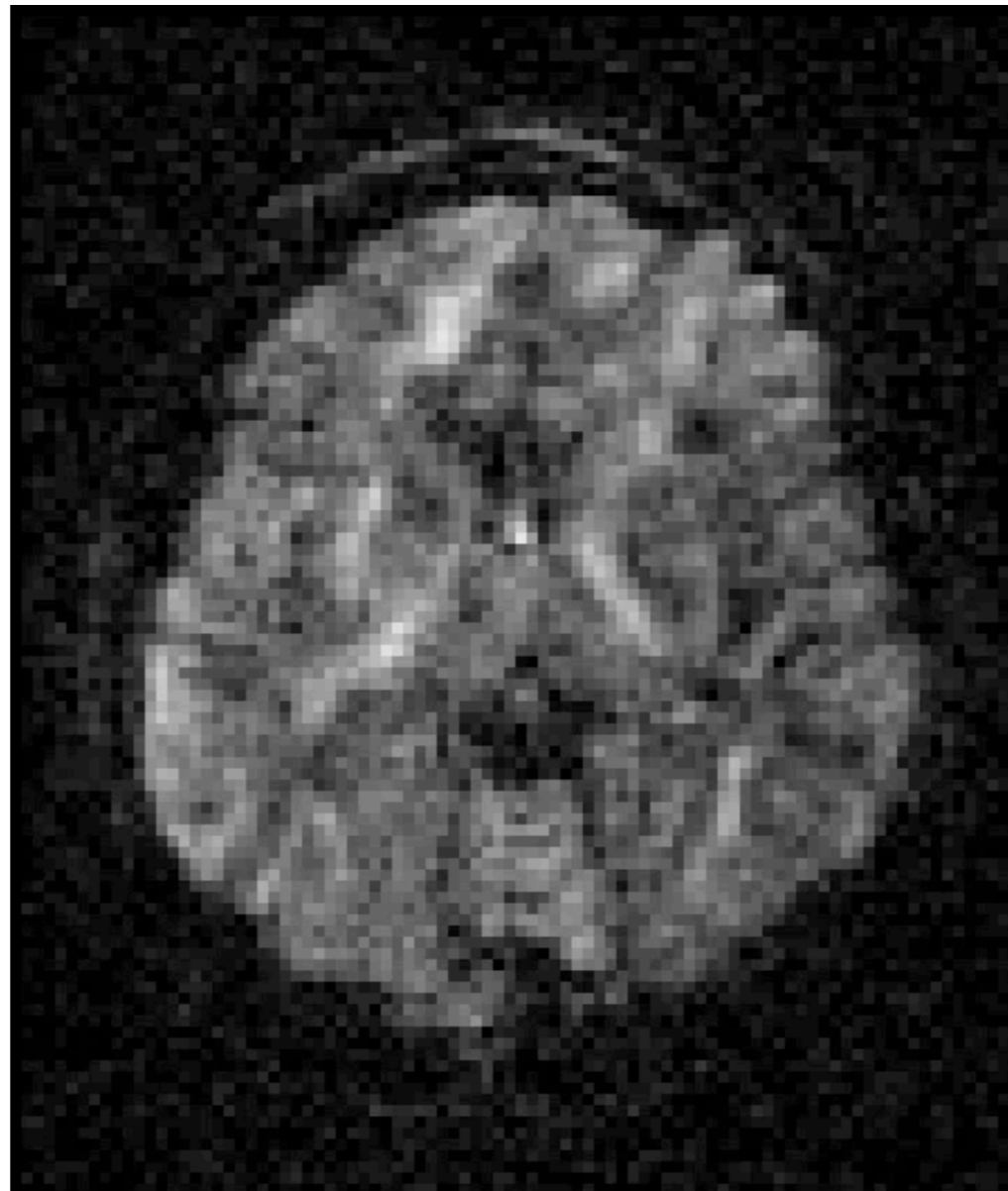
What is the problem with diffusion data?



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What is the problem with diffusion data?



In fact, it isn't even internally consistent



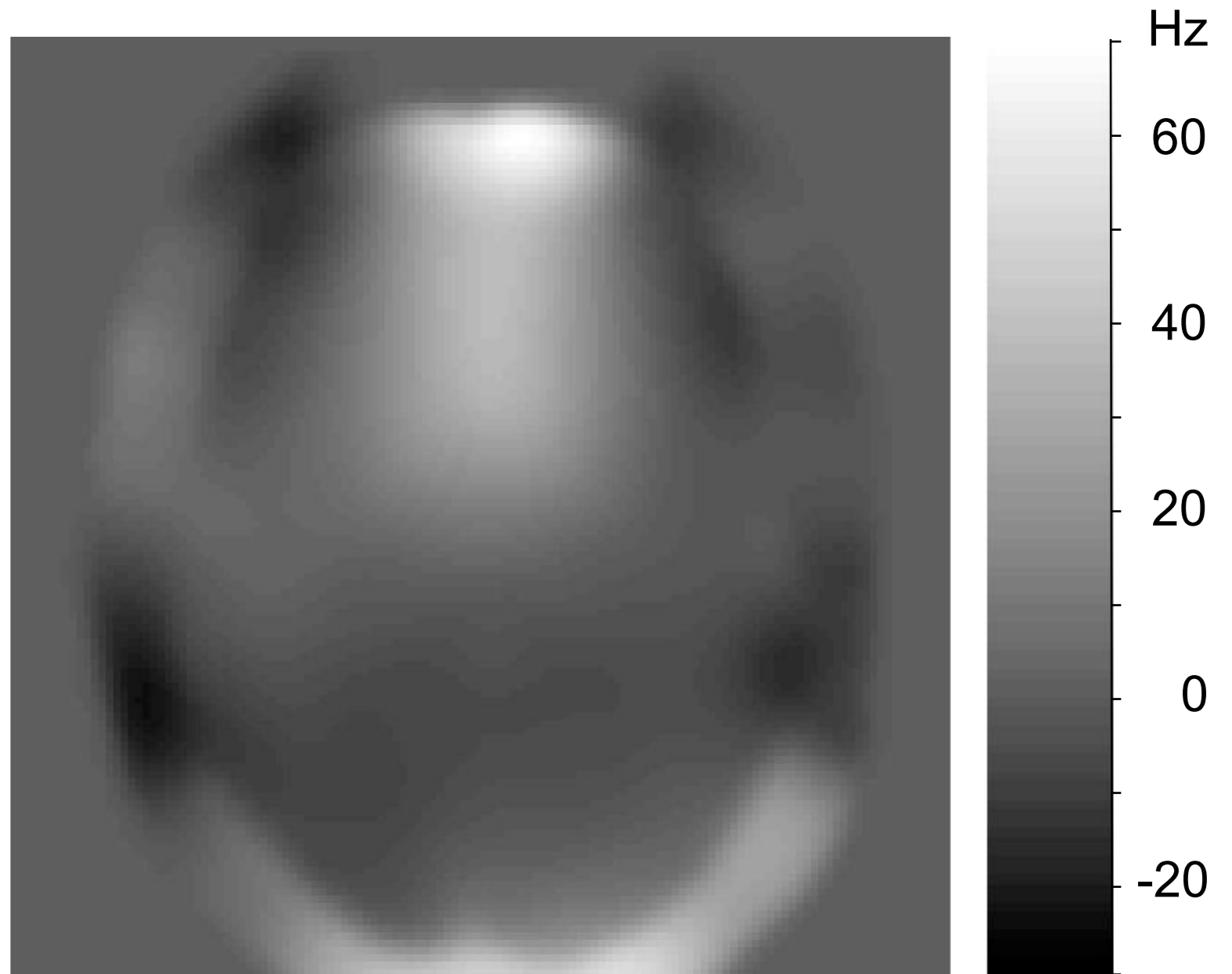
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Off-resonance field \Rightarrow Distortions

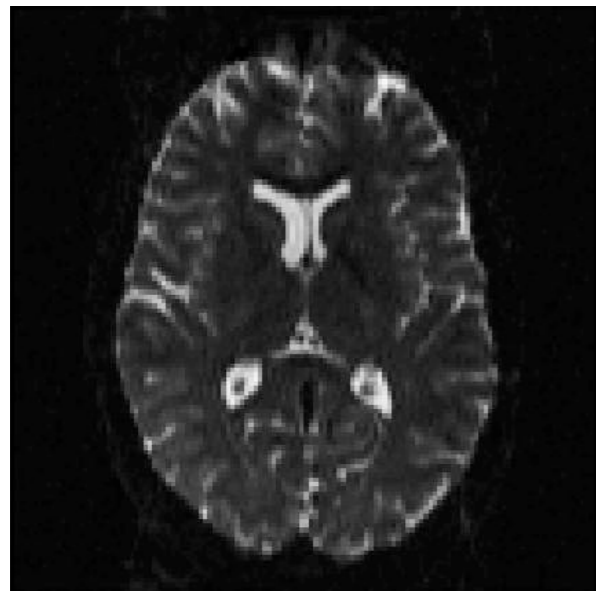
An “off-resonance” field is a map of the difference between what we think the field is and what it really is.



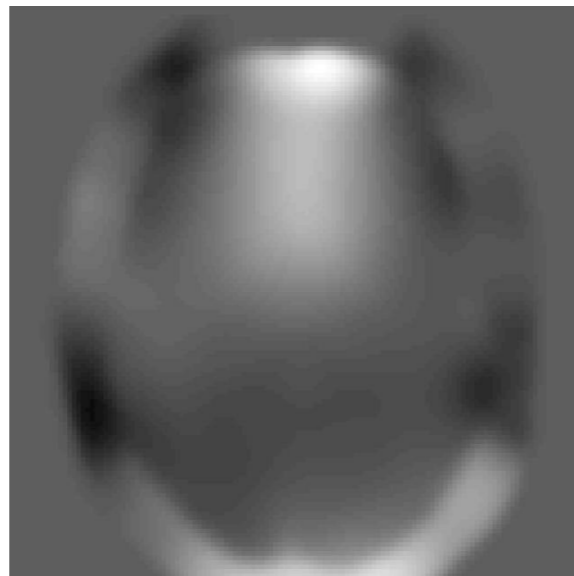
It is all caused by an “off-resonance” field



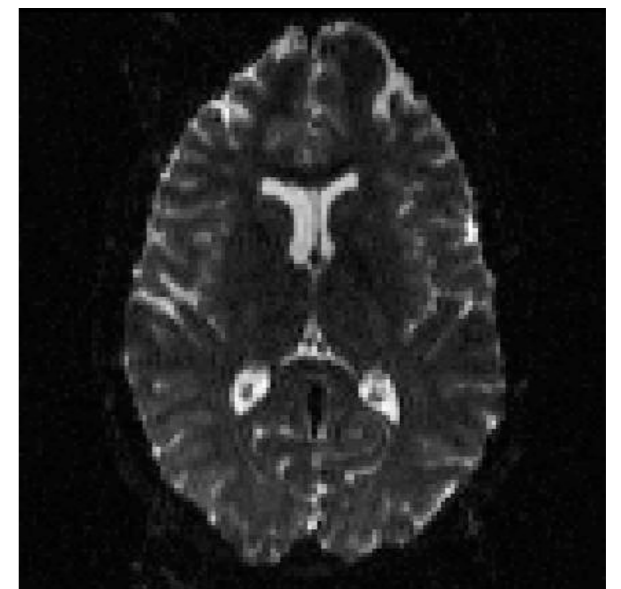
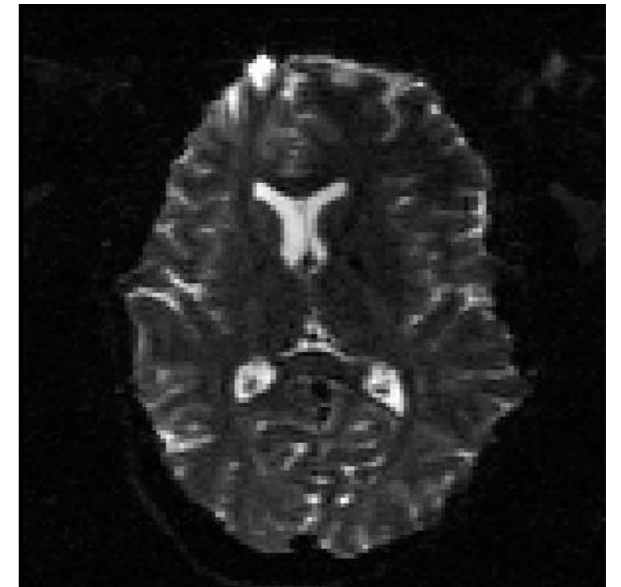
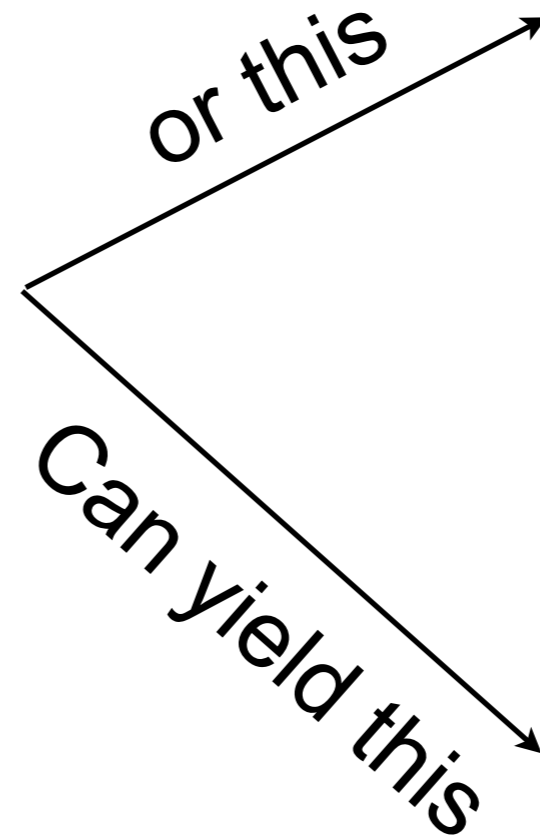
Off-resonance field \Rightarrow Distortions



But this object



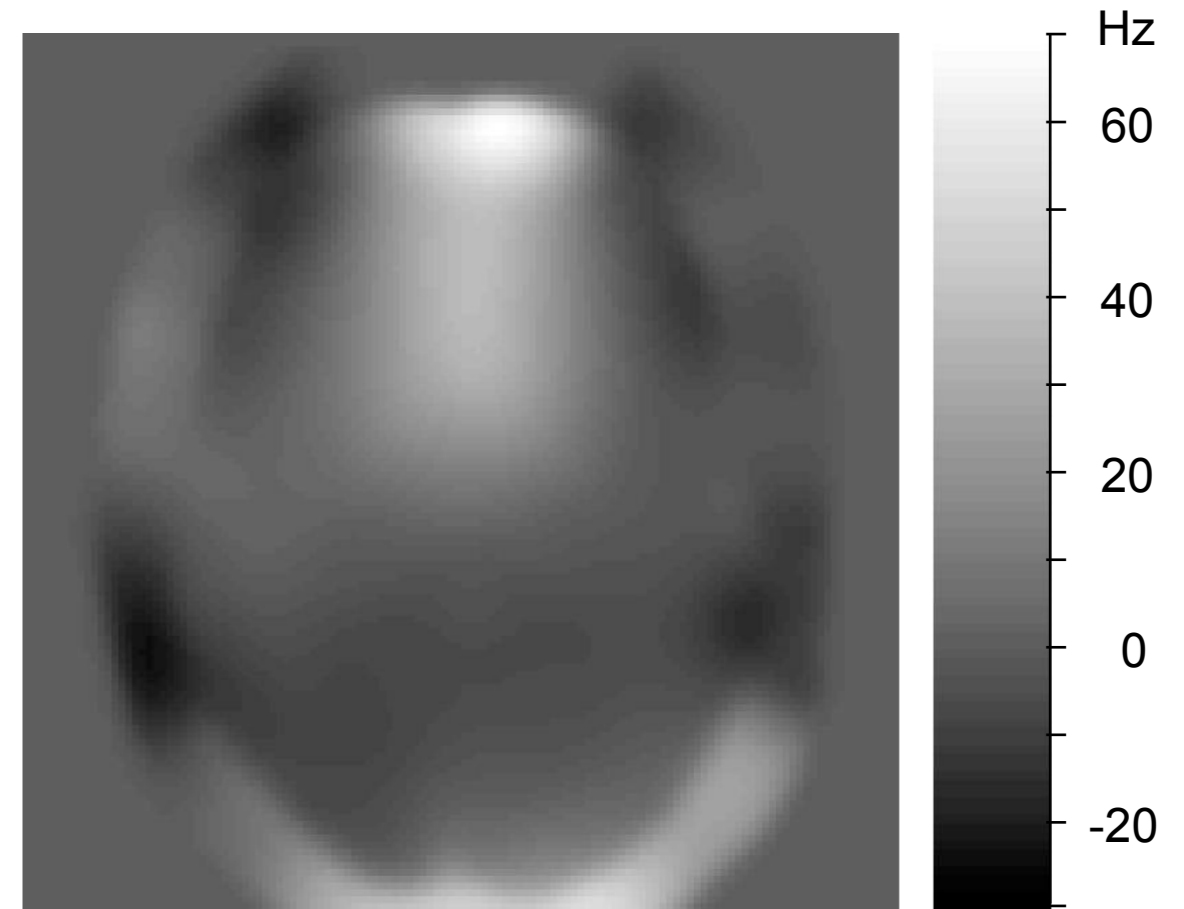
scanned in
this field



So there is clearly more to this story...



Off-resonance field \Rightarrow Distortions

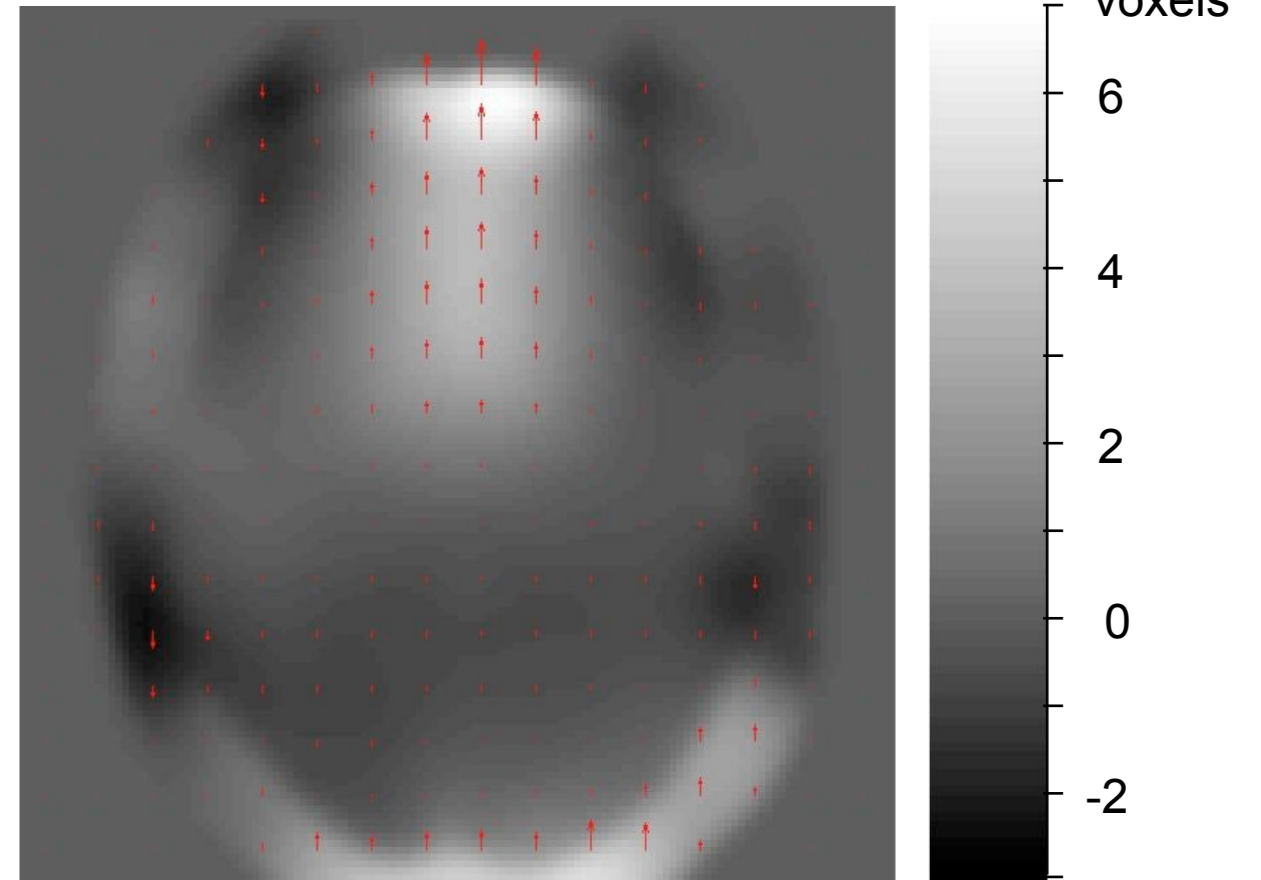
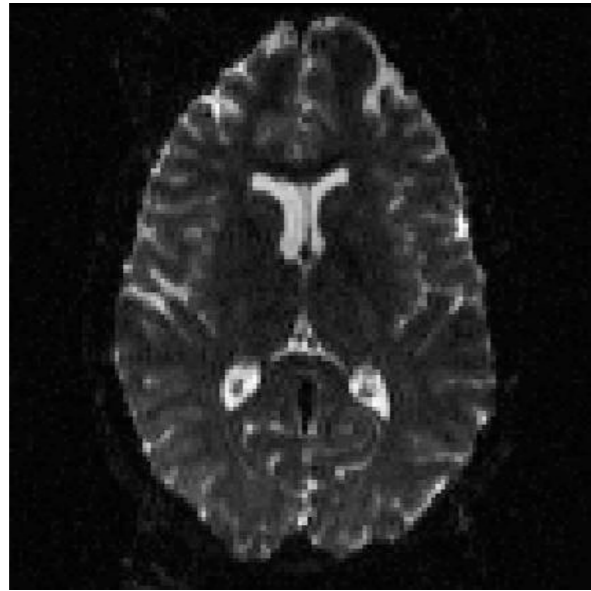


An off-resonance field is effectively a scaled voxel-displacement map.

If we know the imaging parameters we can do the translation.



Off-resonance field \Rightarrow Distortions



And know what to expect

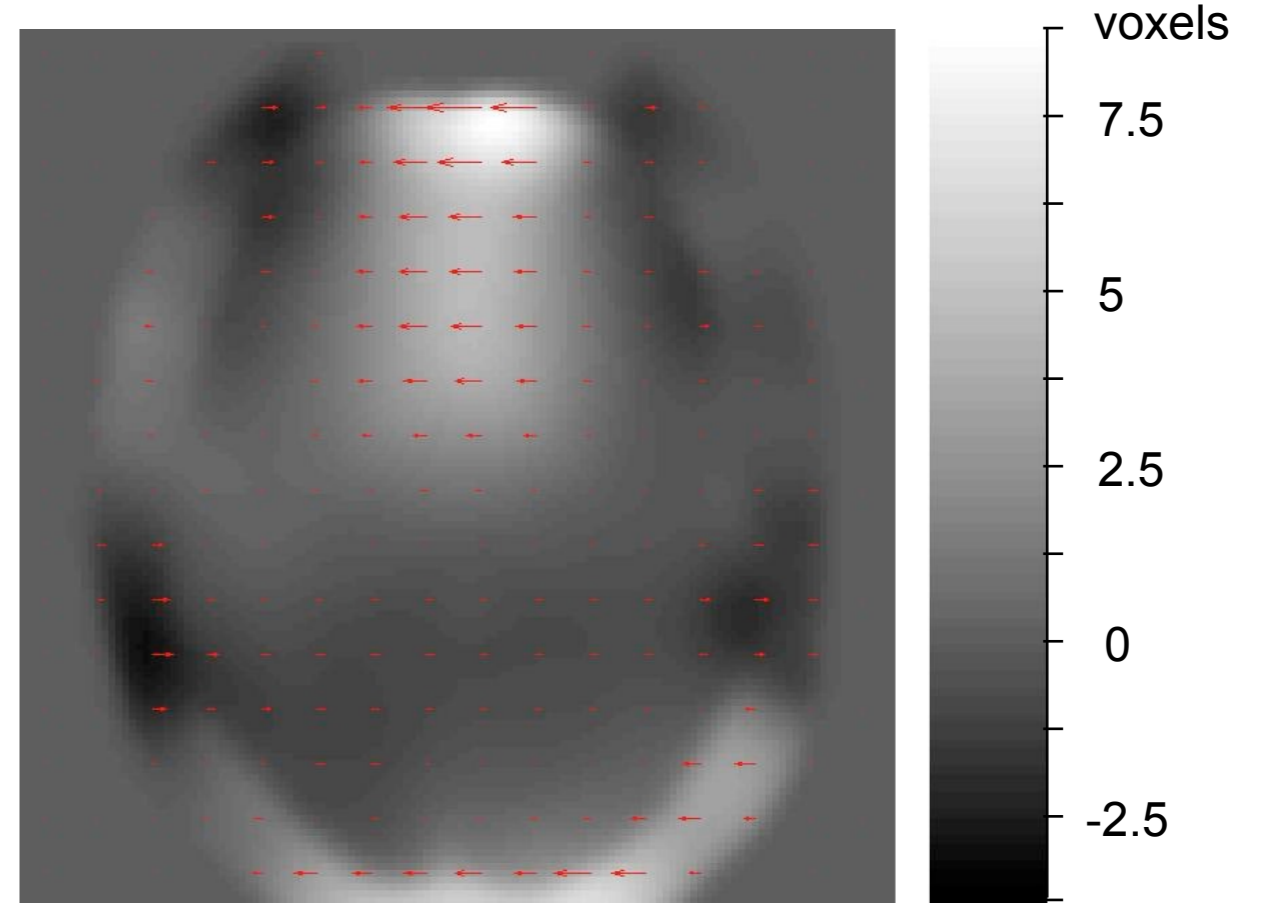
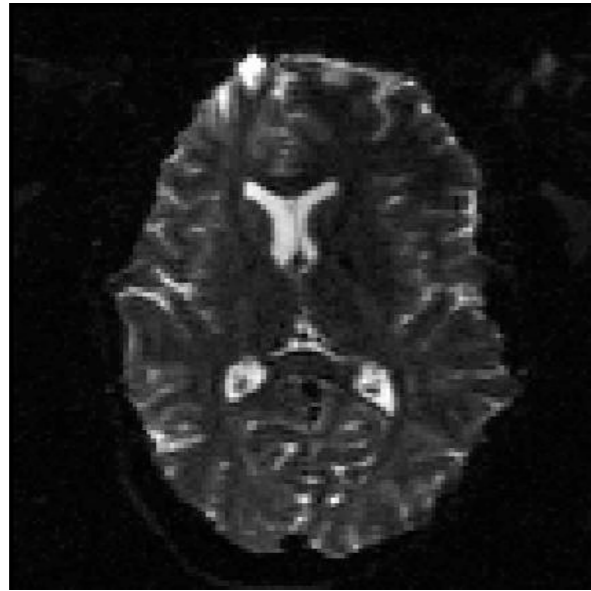
An off-resonance field is effectively a scaled voxel-displacement map.

If we know the imaging parameters we can do the translation.

$$BW/\text{voxel} = 10\text{Hz}, \mathbf{p} = [0 \ 1 \ 0]$$



Off-resonance field \Rightarrow Distortions



And know what to expect

So, an off-resonance field is effectively a scaled voxel-displacement map.

And if we know the imaging parameters we can do the translation.

$$BW/\text{voxel} = 8\text{Hz}, \mathbf{p} = [-1 \ 0 \ 0]$$



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Where does the off-resonance field come from?

- There are two sources
- The first is the object (head) itself.

(CT of) Human head

$B_0 \odot$



Resulting field



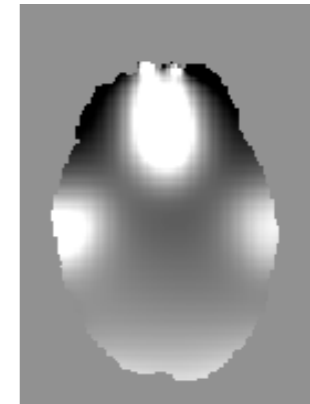
PPMs

Must fulfil $\begin{cases} \nabla \times \mathbf{H} = 0 \\ \nabla \cdot \mathbf{B} = 0 \end{cases}$ (still)

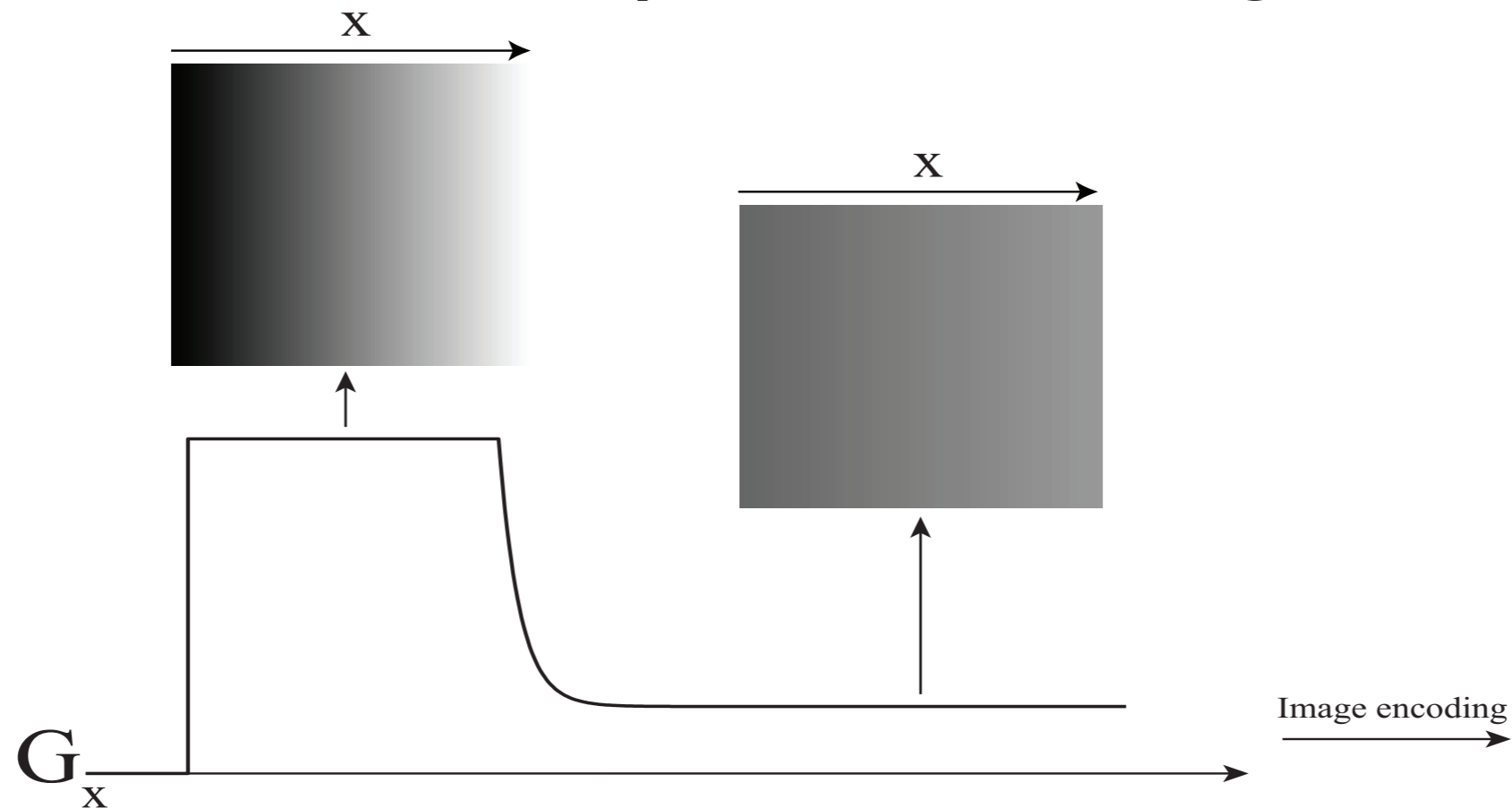


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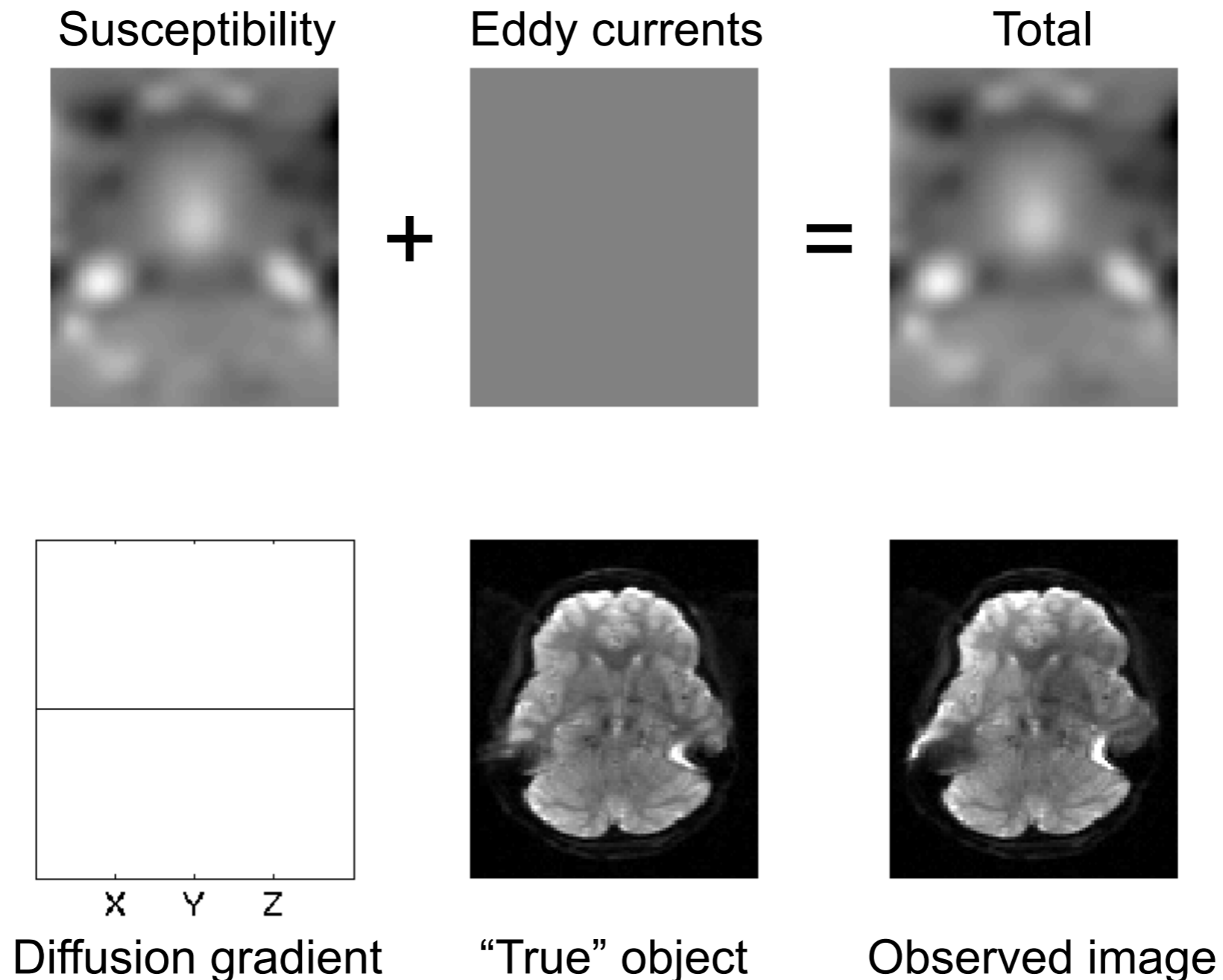
- The second is caused by the diffusion gradient





Where does the off-resonance field come from?

So for any diffusion weighted volume the off-resonance field is the sum of these two contributions

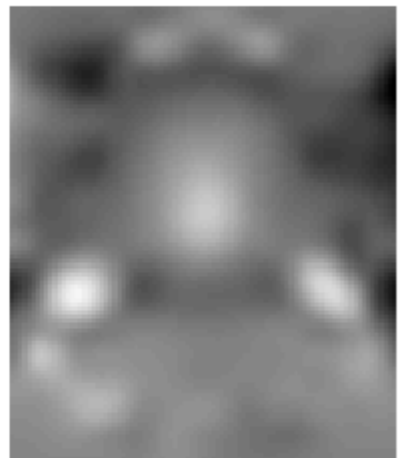




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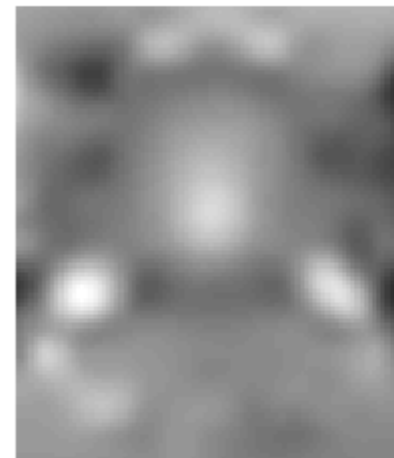
Susceptibility



Eddy currents

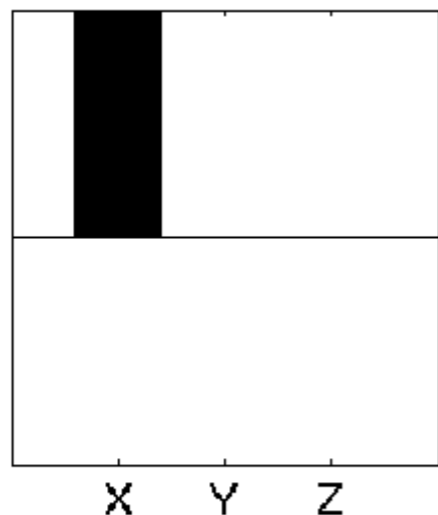


Total

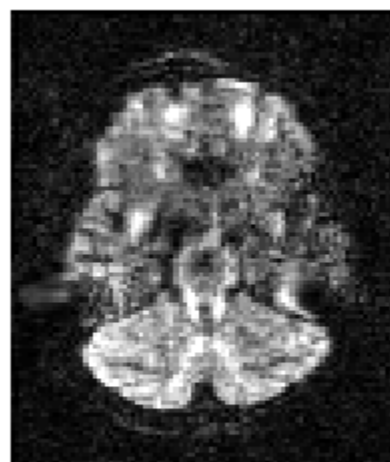


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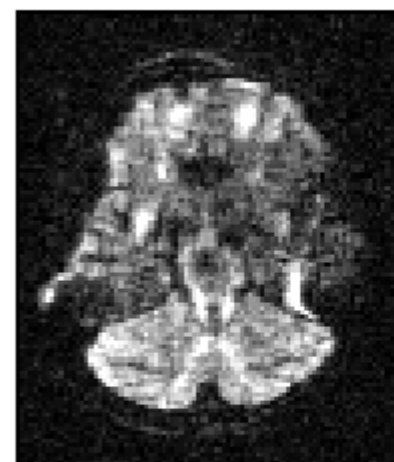
=



Diffusion gradient



"True" object



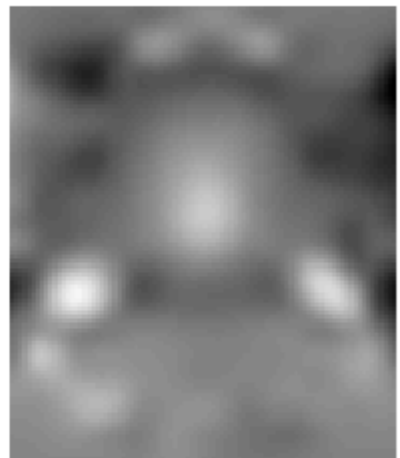
Observed image



Where does the off-resonance field come from?

So for any diffusion weighted volume the off-resonance field is the sum of these two contributions

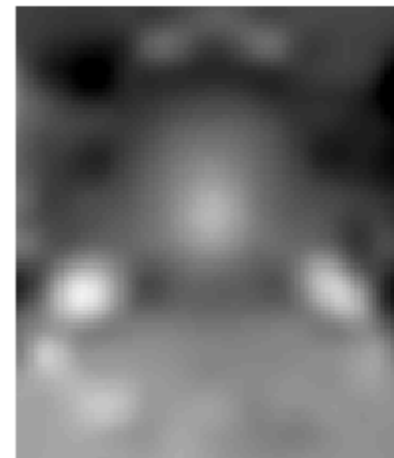
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Eddy currents

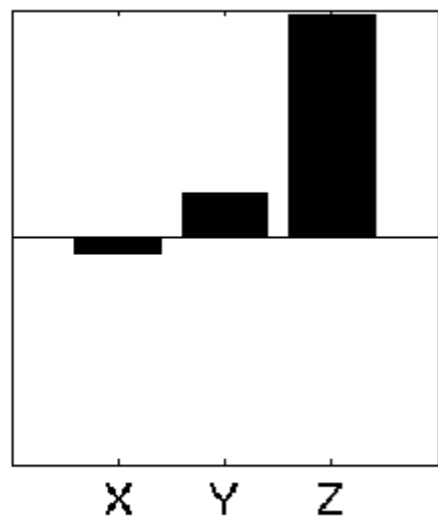


Total

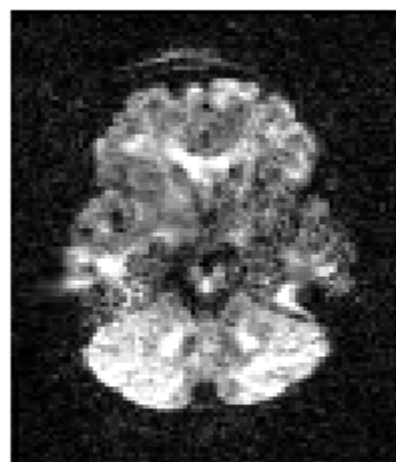


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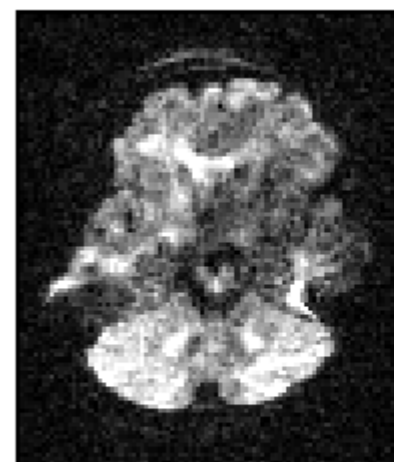
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Diffusion gradient



"True" object



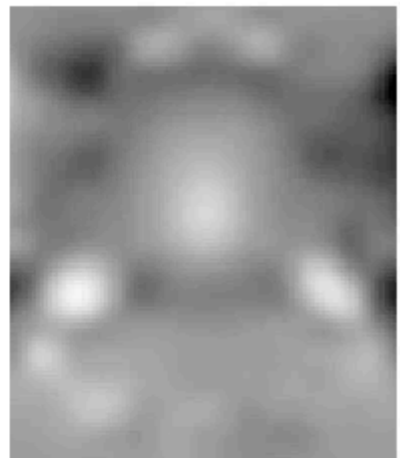
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Where does the off-resonance field come from?

So for any diffusion weighted volume the off-resonance field is the sum of these two contributions

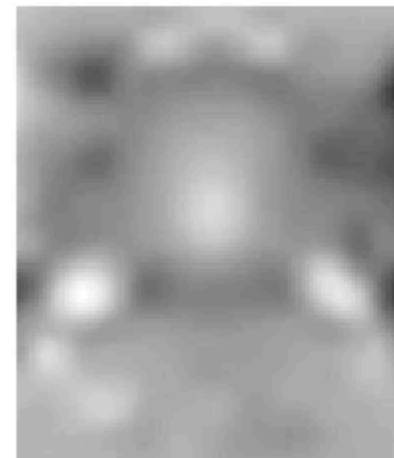
Susceptibility



Eddy currents

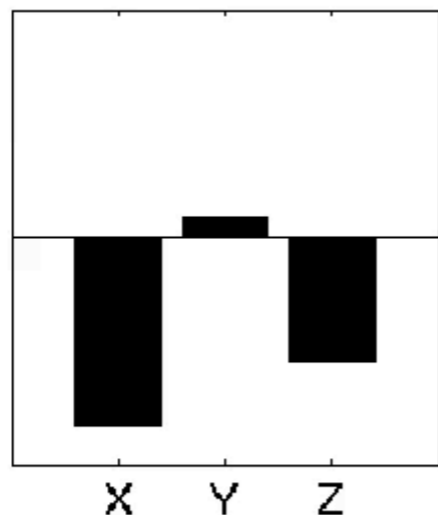


Total

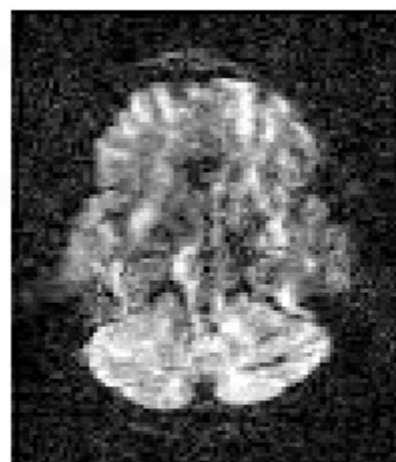


+

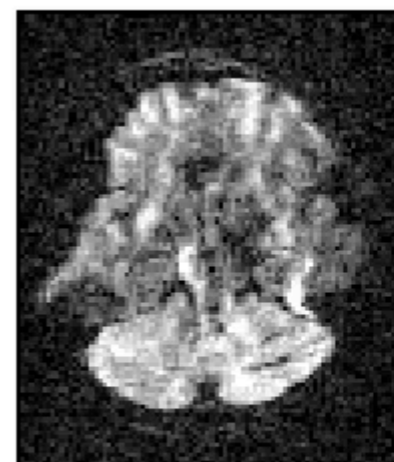
=



Diffusion gradient



"True" object



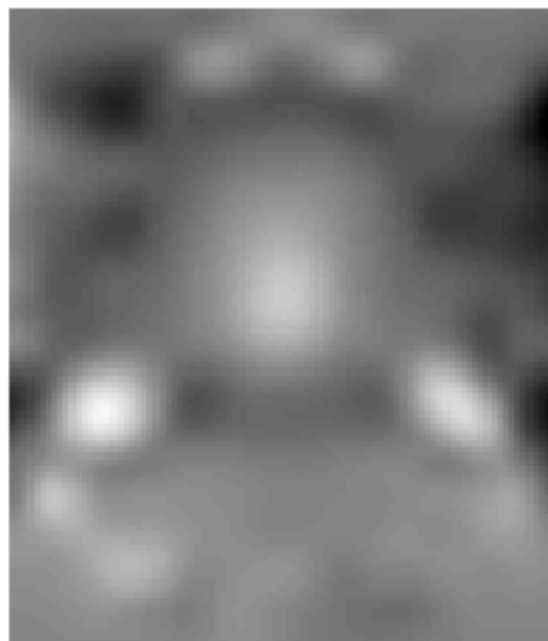
Observed image



Separate estimation of susceptibility- and eddy current-fields

So, what we need to estimate is

One of these per
subject



One of these per
volume



FSL-tools:

topup

eddy

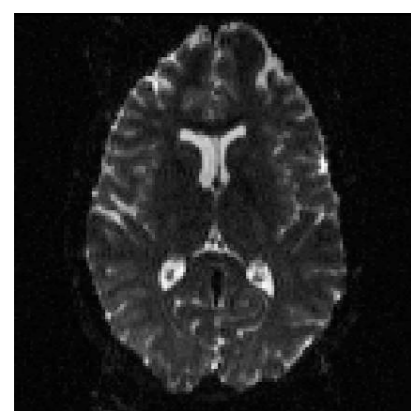


Outline of the talk

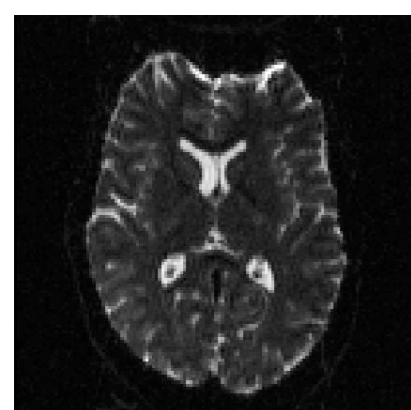
- What is the problem with diffusion data?
- Off-resonance field
 - How does it cause distortions?
 - Where does it come from?
- Registering diffusion data
 - **How topup works**
 - How eddy works
- Practicalities
- Some results
- Quality control
- “New” eddy features



How topup works (very briefly)



$p=[0 \ 1 \ 0]$

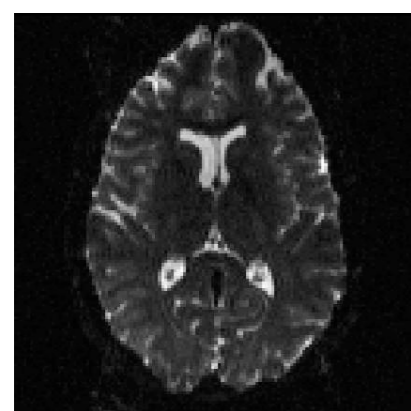


$p=[0 \ -1 \ 0]$

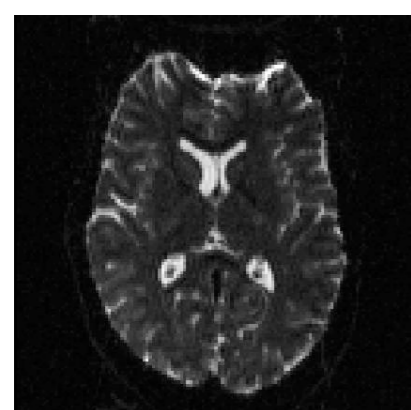
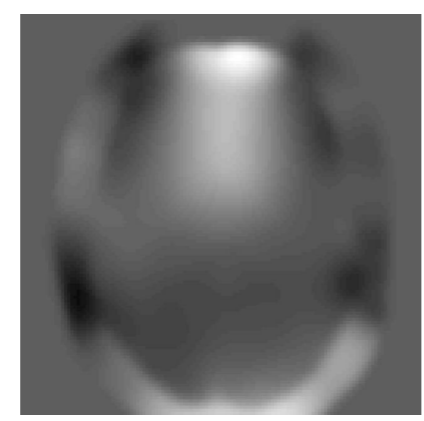
Given two images acquired with different phase-encoding



How topup works (very briefly)



$p=[0 \ 1 \ 0]$

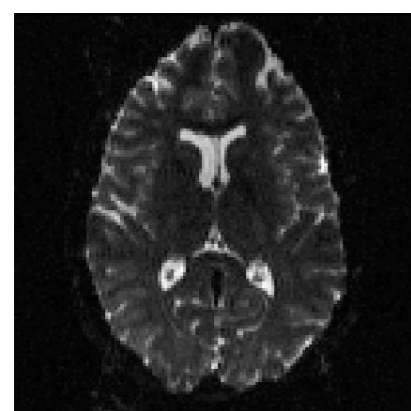


$p=[0 \ -1 \ 0]$

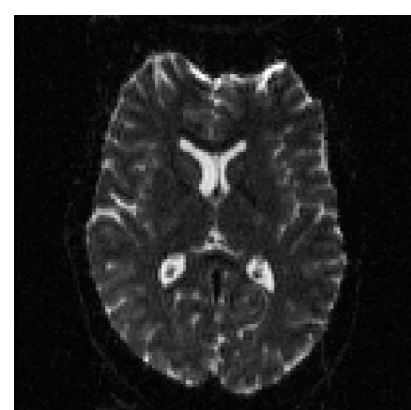
And we know what the off-resonance field is



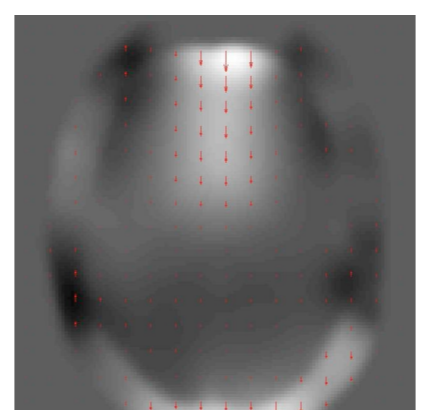
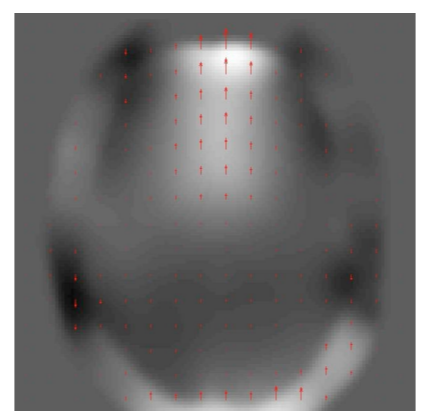
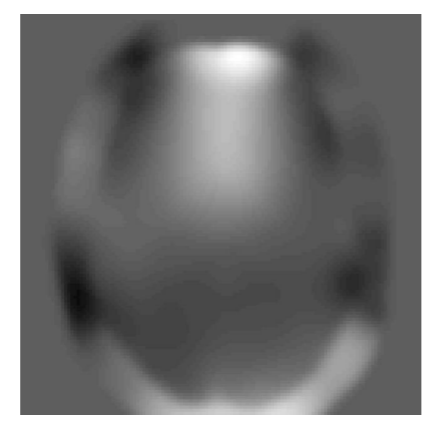
How topup works (very briefly)



$p=[0 \ 1 \ 0]$



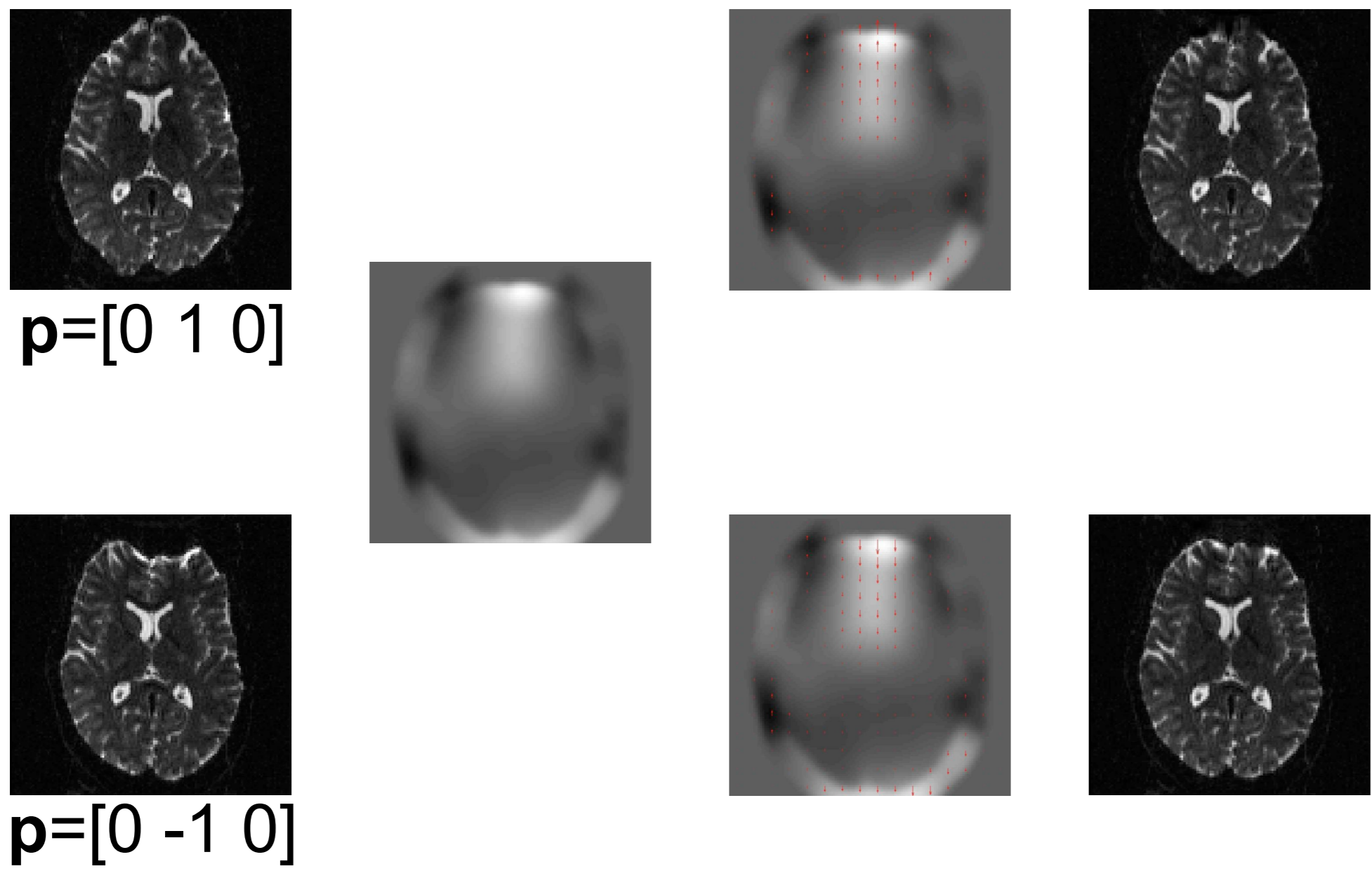
$p=[0 \ -1 \ 0]$



We can combine this with the PE information to get displacement maps



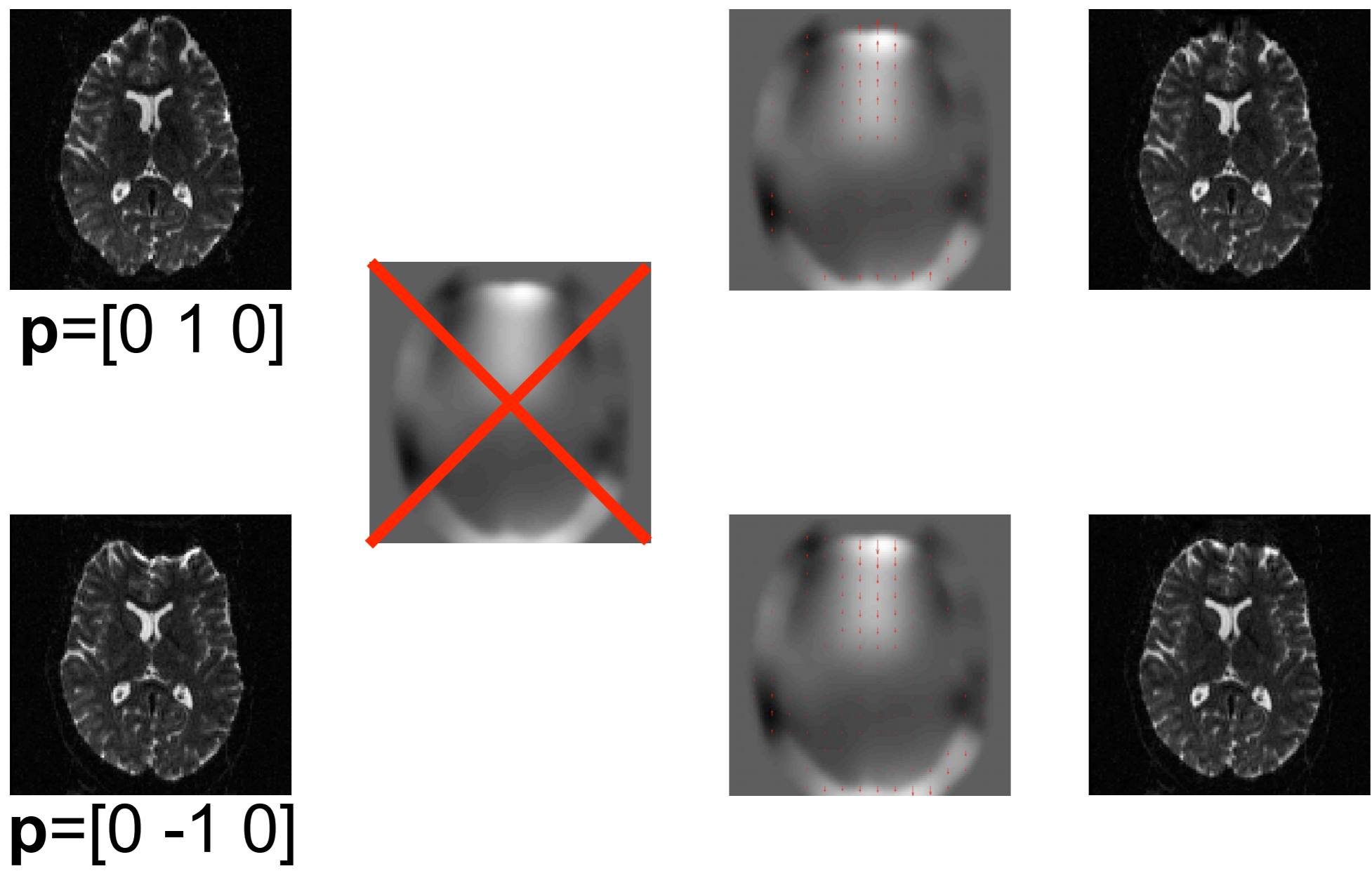
How topup works (very briefly)



And use that to correct the distortions



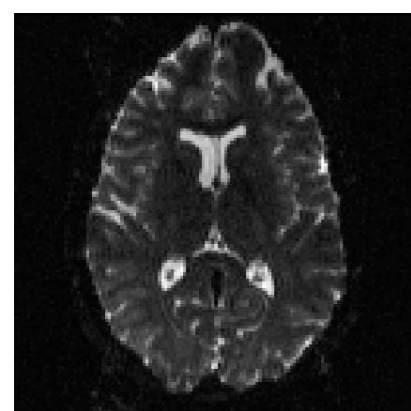
How topup works (very briefly)



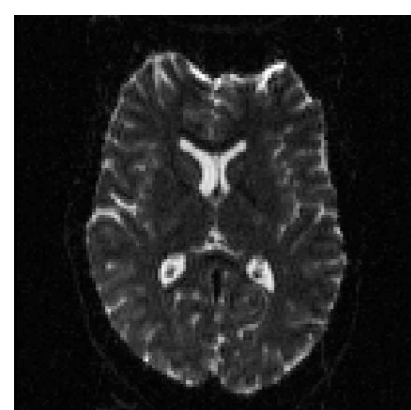
BUT we don't know the field. That is what we want topup to calculate.



How topup works (very briefly)



$p=[0 \ 1 \ 0]$

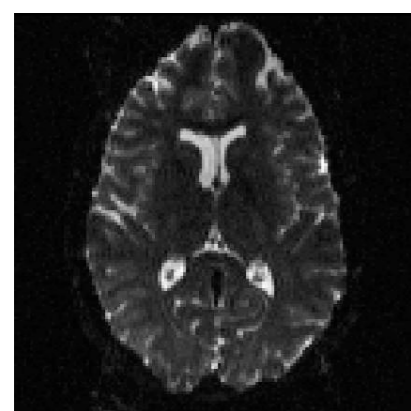


$p=[0 \ -1 \ 0]$

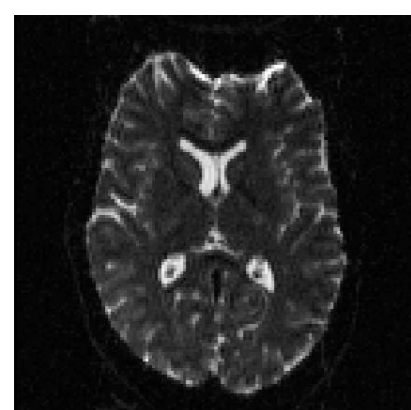
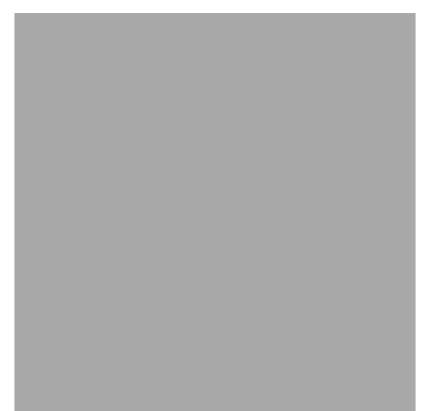
topup “guesses” a field...



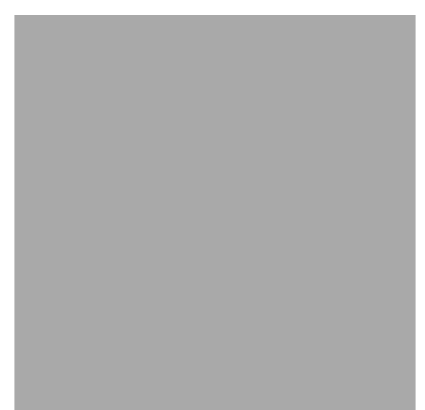
How topup works (very briefly)



$p=[0 \ 1 \ 0]$



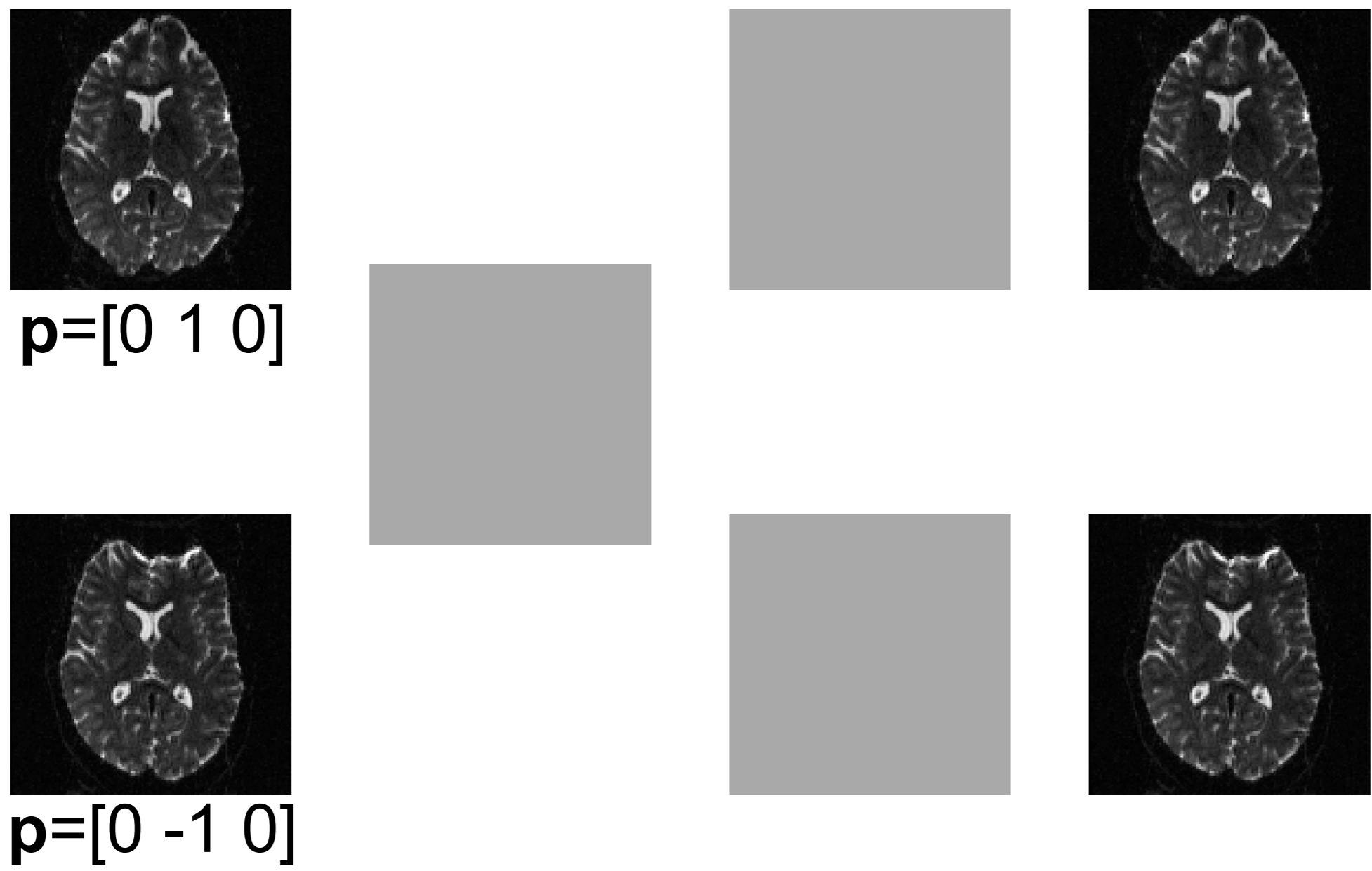
$p=[0 \ -1 \ 0]$



...calculates the displacement maps...



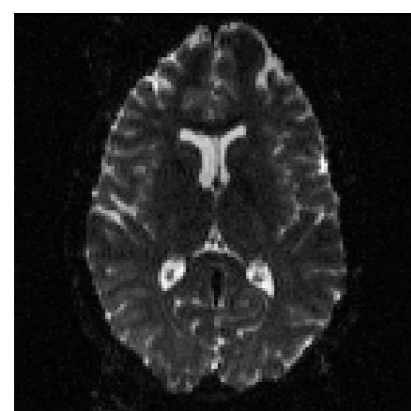
How topup works (very briefly)



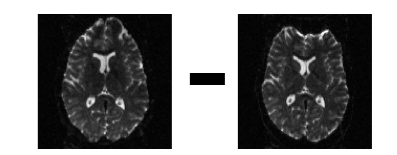
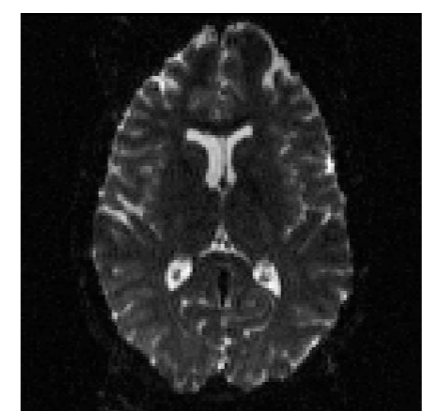
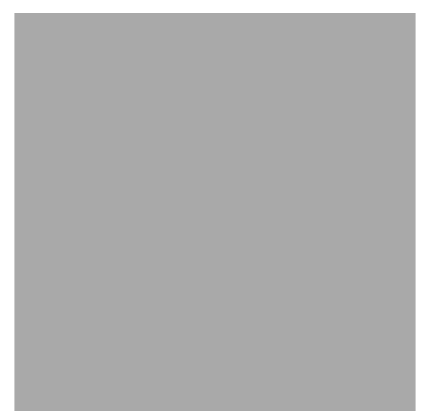
...”corrects” the images...



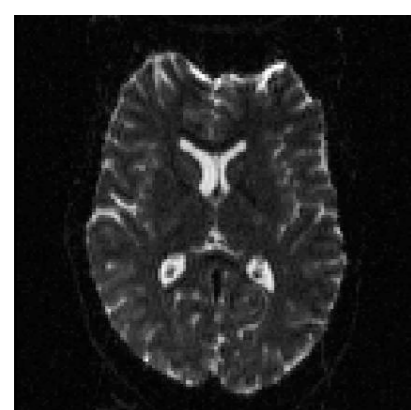
How topup works (very briefly)



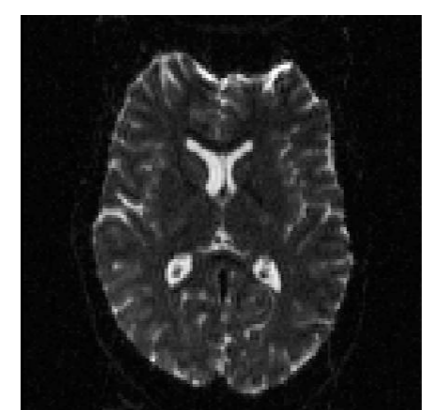
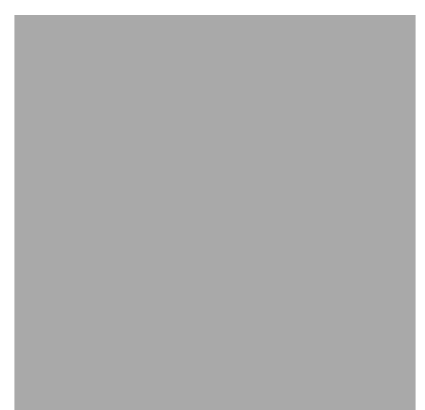
$p=[0 \ 1 \ 0]$



BAD!



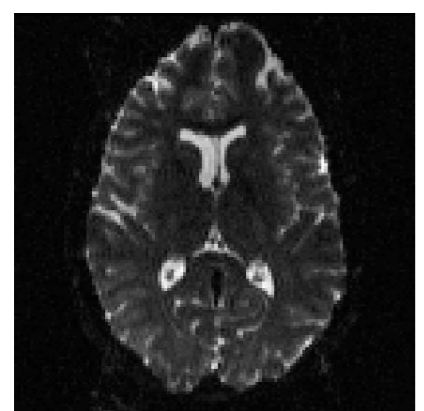
$p=[0 \ -1 \ 0]$



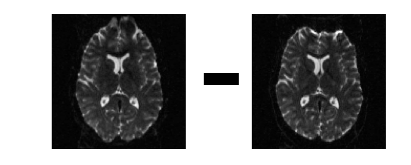
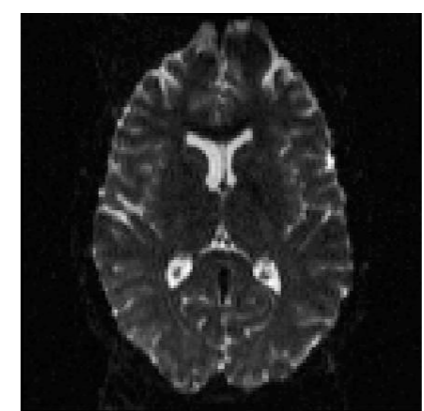
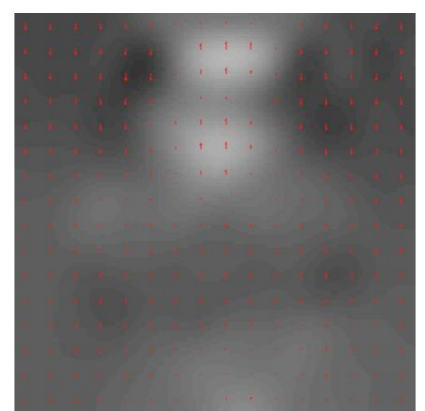
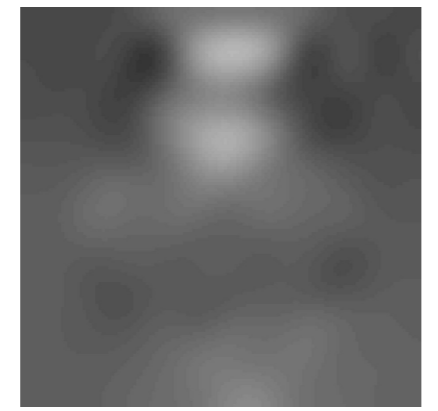
...and evaluates the results...
And **this** is the crucial bit.



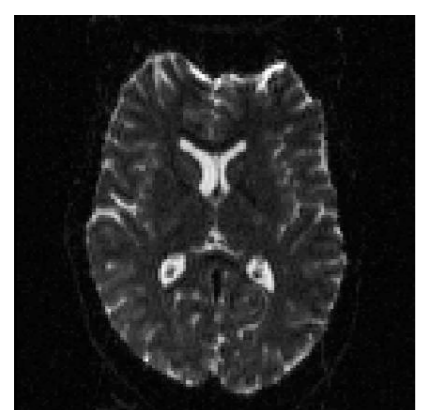
How topup works (very briefly)



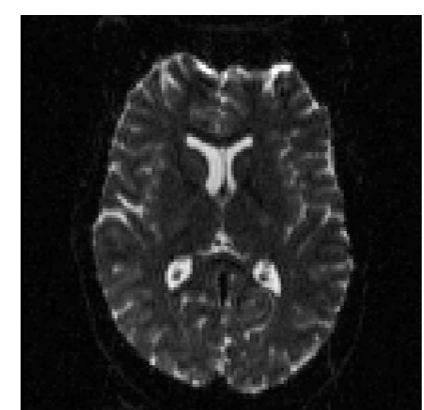
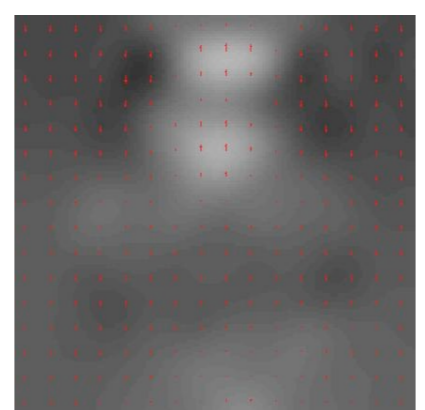
$p=[0\ 1\ 0]$



better



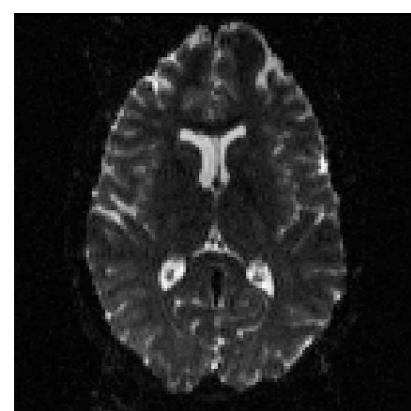
$p=[0\ -1\ 0]$



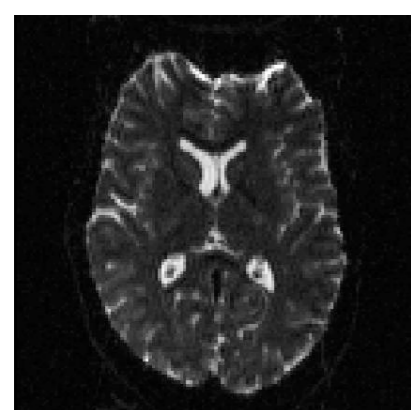
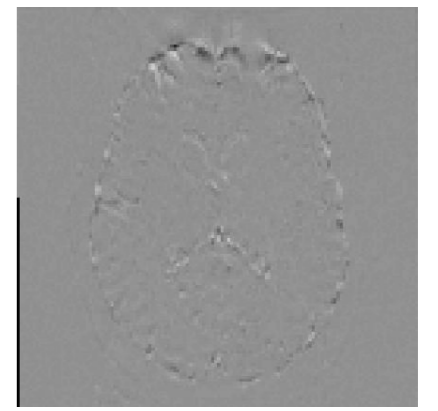
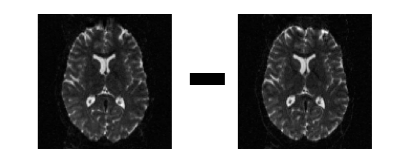
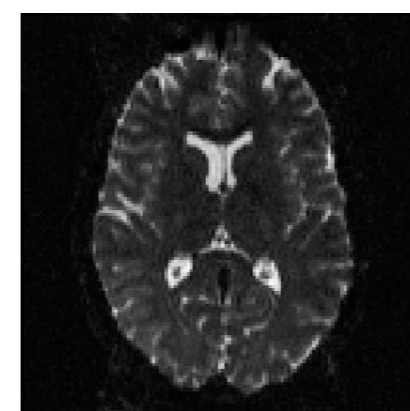
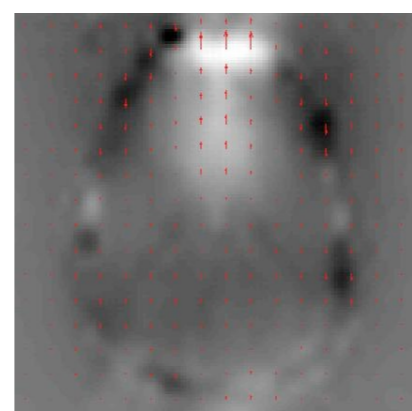
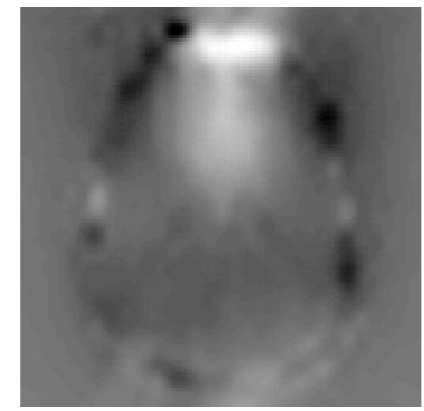
Because topup can then “guess” another field



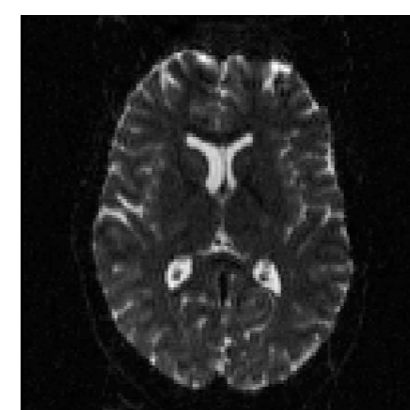
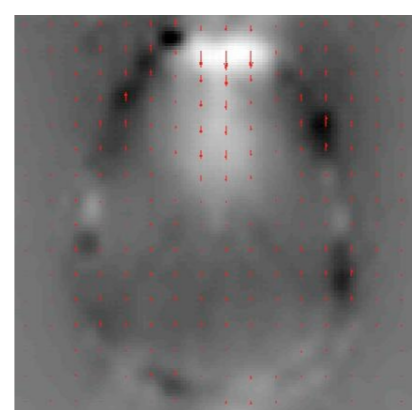
How topup works (very briefly)



$p=[0 \ 1 \ 0]$



$p=[0 \ -1 \ 0]$



even
better

...and another...until it is happy,
and then it “knows” the field

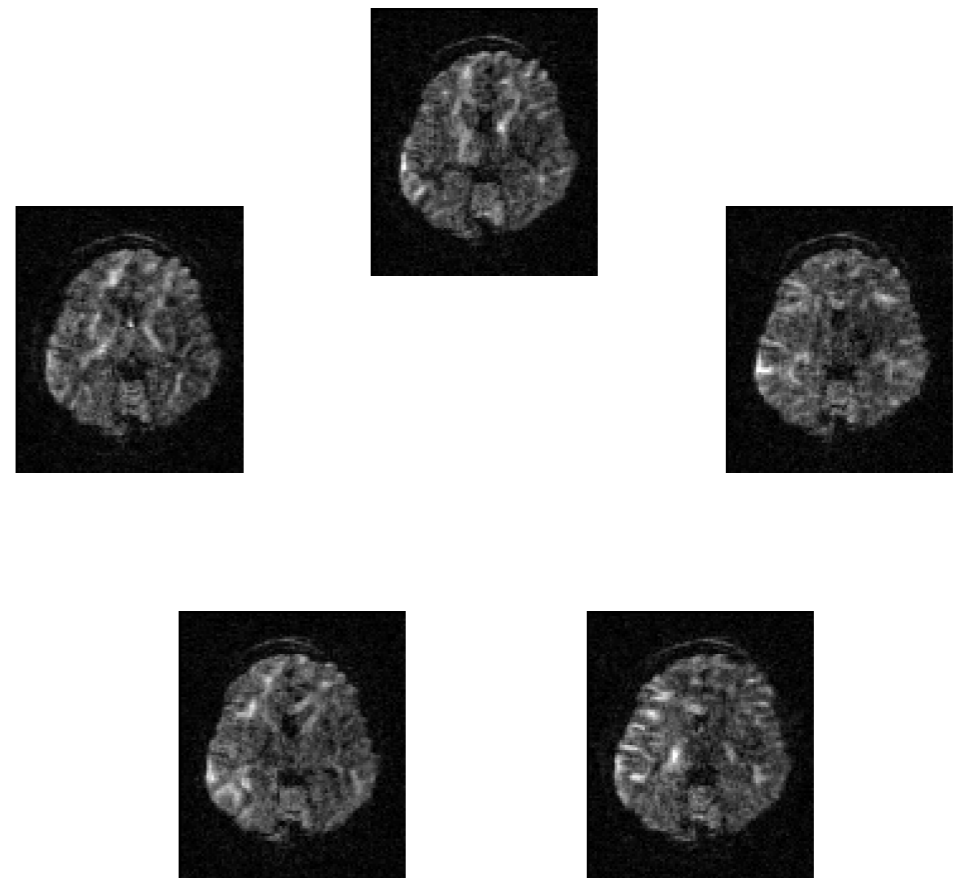


Outline of the talk

- What is the problem with diffusion data?
- Off-resonance field
 - How does it cause distortions?
 - Where does it come from?
- Registering diffusion data
 - How topup works
 - **How eddy works**
- Practicalities
- Some results
- Quality control
- “New” eddy features



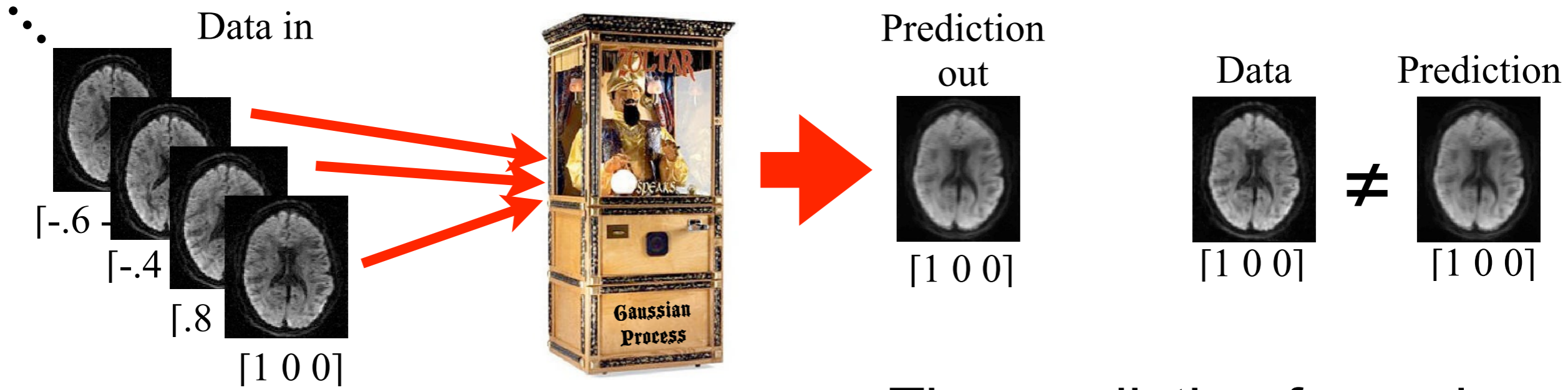
But it is not easy to register diffusion weighted images



- Each image has different distortions -> non-linear registration
- What is the reference image?



Zoltar -- The prediction maker



Given some data in, Zoltar will make a prediction what the data “should” be.

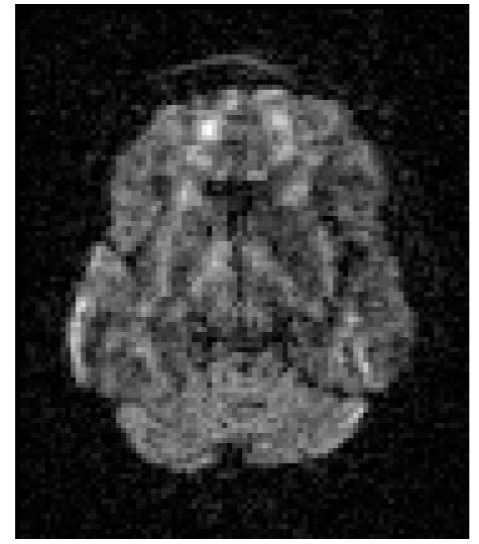
The prediction for a given dwi will not be identical to the “input” for that dwi

I know this sounds crazy, but please trust me on this.
(Zoltar is actually a Gaussian Process)



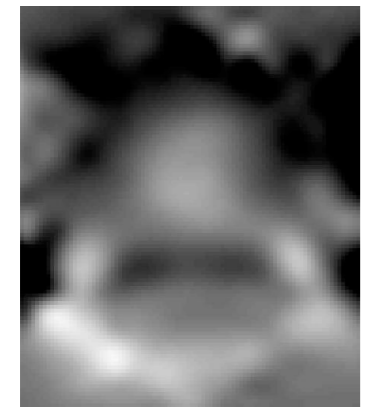
How eddy works: Loading step

Pick the first dwi

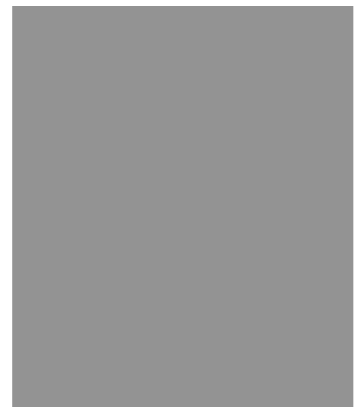


Use current estimates of

Susc



EC

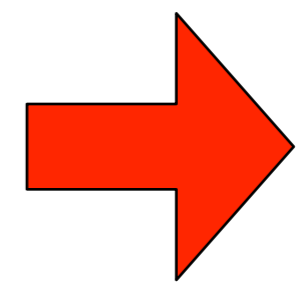
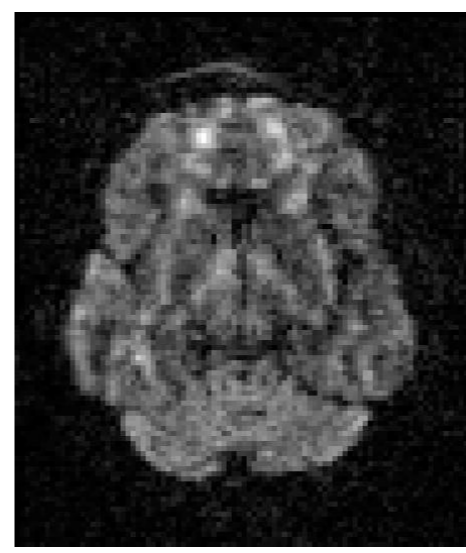


MP

$$\begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$



To correct image



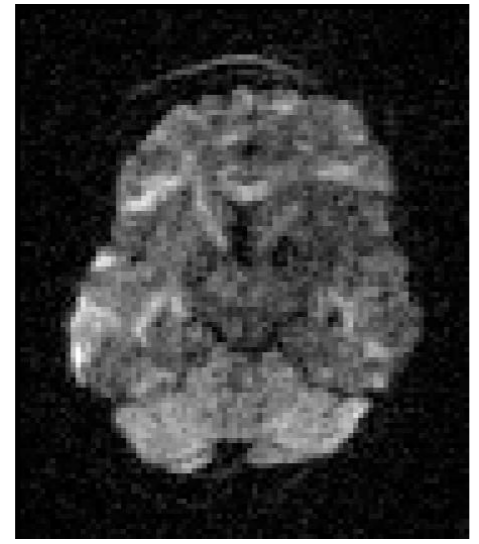
And load into prediction maker





How eddy works: Loading step

then the 2nd dwi

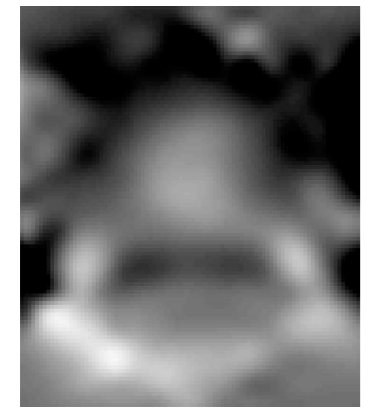


Use current estimates of

Susc

EC

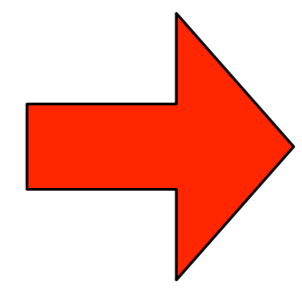
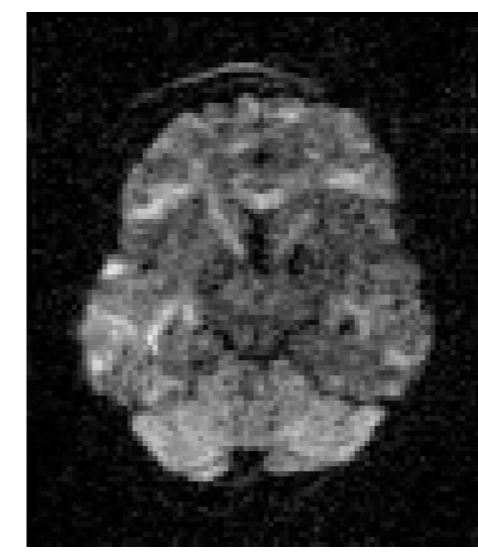
MP



$$\begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$



To correct 2nd image



And load into prediction maker

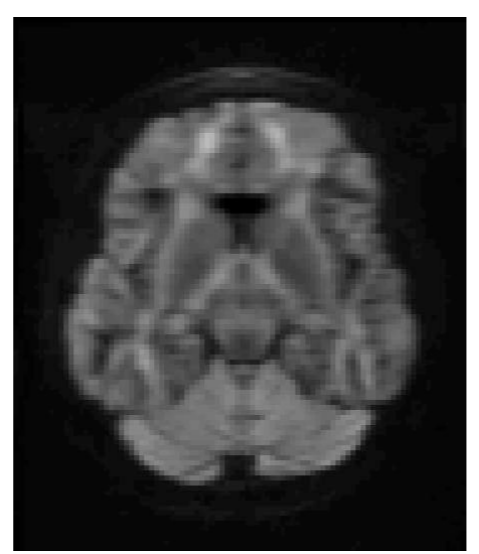
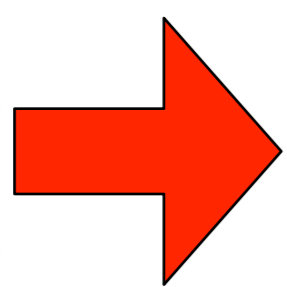


Until we have loaded all dwis

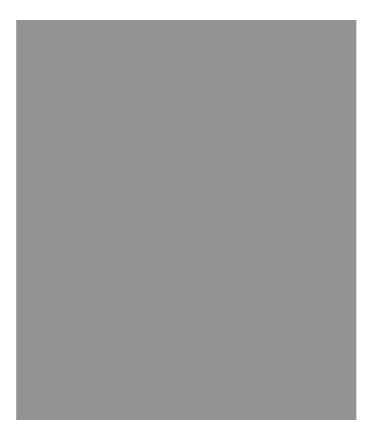


How eddy works: Estimation step

Draw a prediction for first dwi

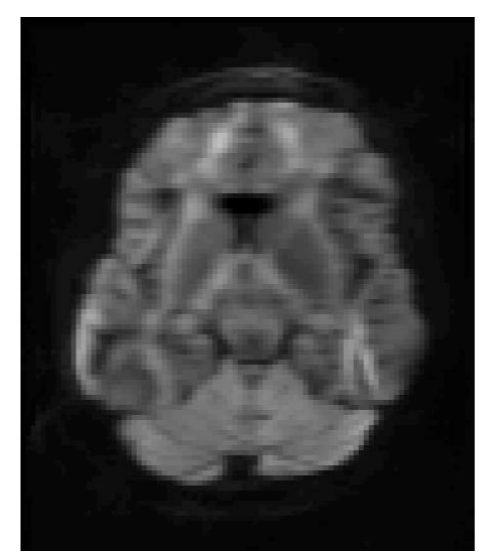


Use current estimates of
SusC EC MP

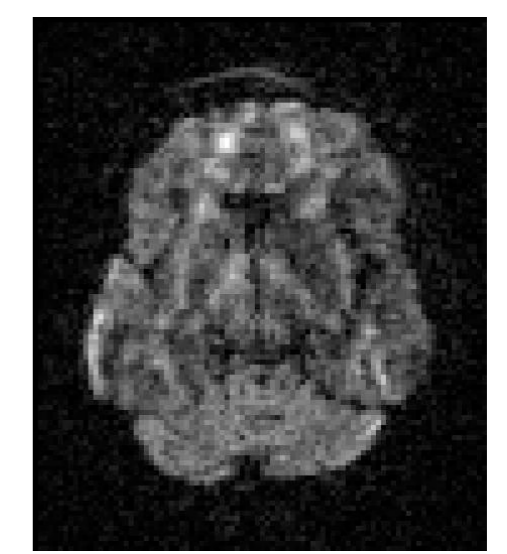


$$\begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

Invert



To get prediction in "observation space"

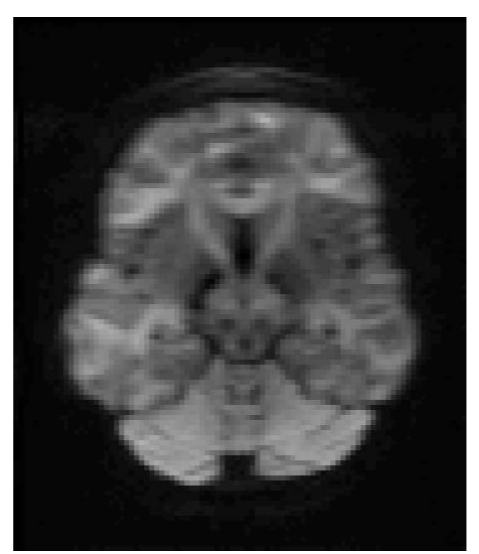
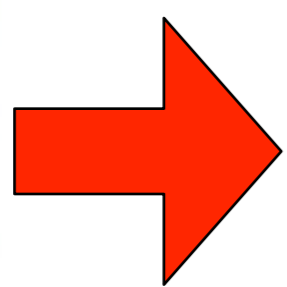


And compare to actual observation

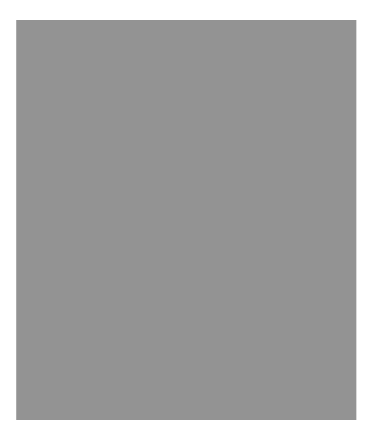


How eddy works: Estimation step

Draw a prediction
for 2nd dwi

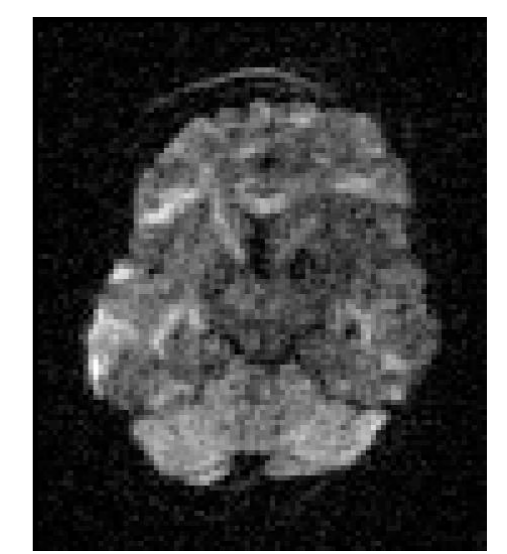
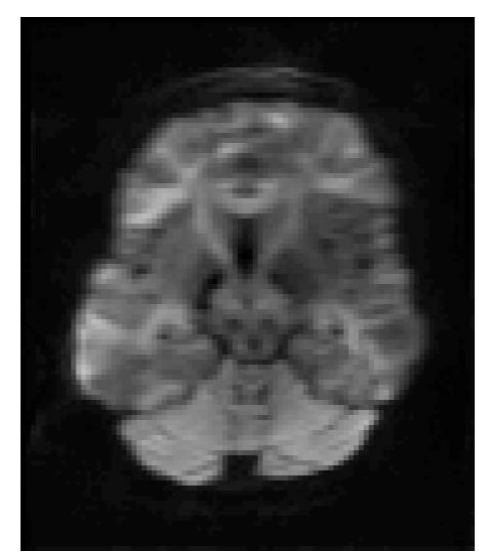


Use current estimates of
SusC EC MP



$$\begin{bmatrix} 0 \\ 0 \\ \vdots \\ 0 \end{bmatrix}$$

Invert



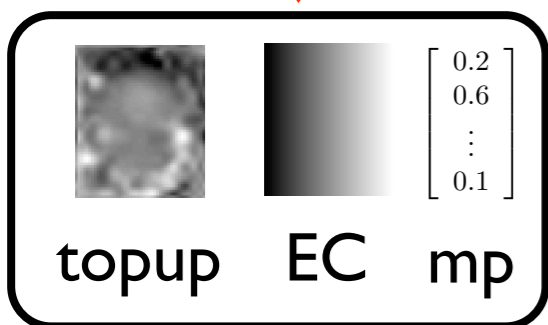
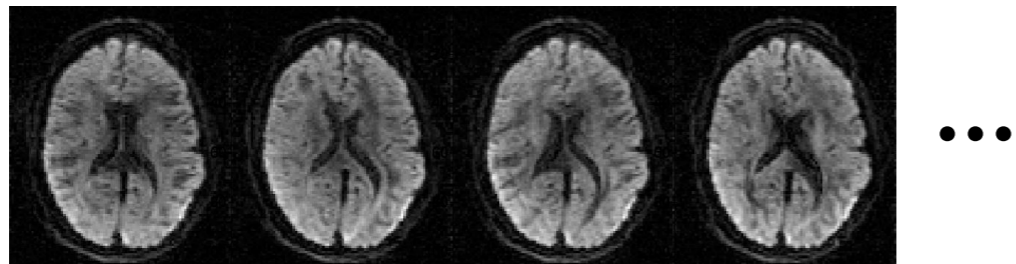
And then we repeat
the procedure for the
next dwi ...



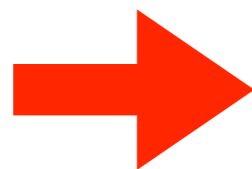
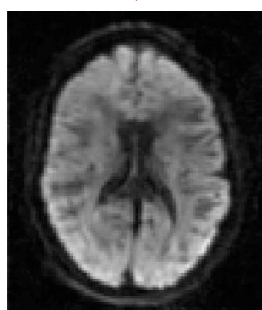
How eddy works

1. For all scans

$[1\ 0\ 0]$ $[.6\ -.4\ -.7]$ $[.8\ .6\ 0]$ $[-.4\ .9\ 0]$...



Use susceptibility field and current estimate of EC and movement to “unwarp” scan

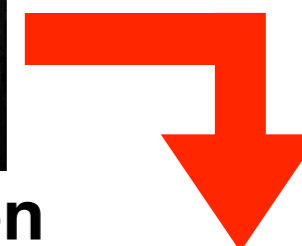
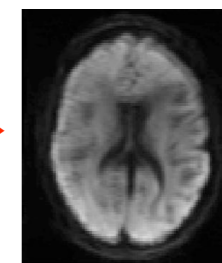


Load into prediction maker

2. For all scans

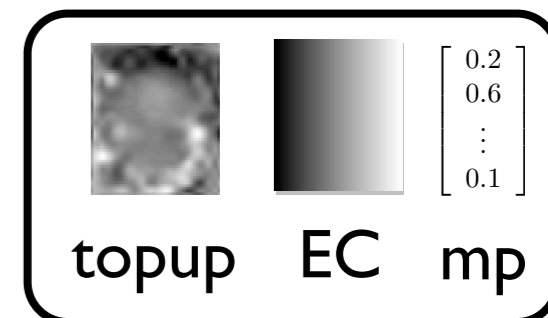


$[1\ 0\ 0]$



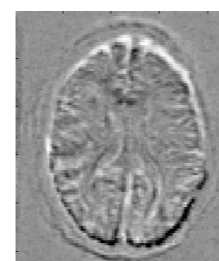
Get prediction

Invert current transform

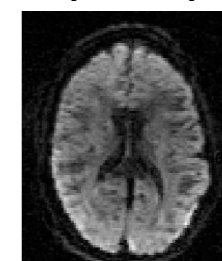


Use difference to update EC and mp

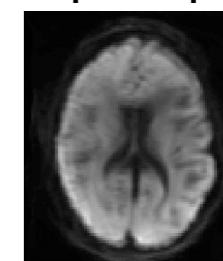
Get prediction in scan space



$[1\ 0\ 0]$



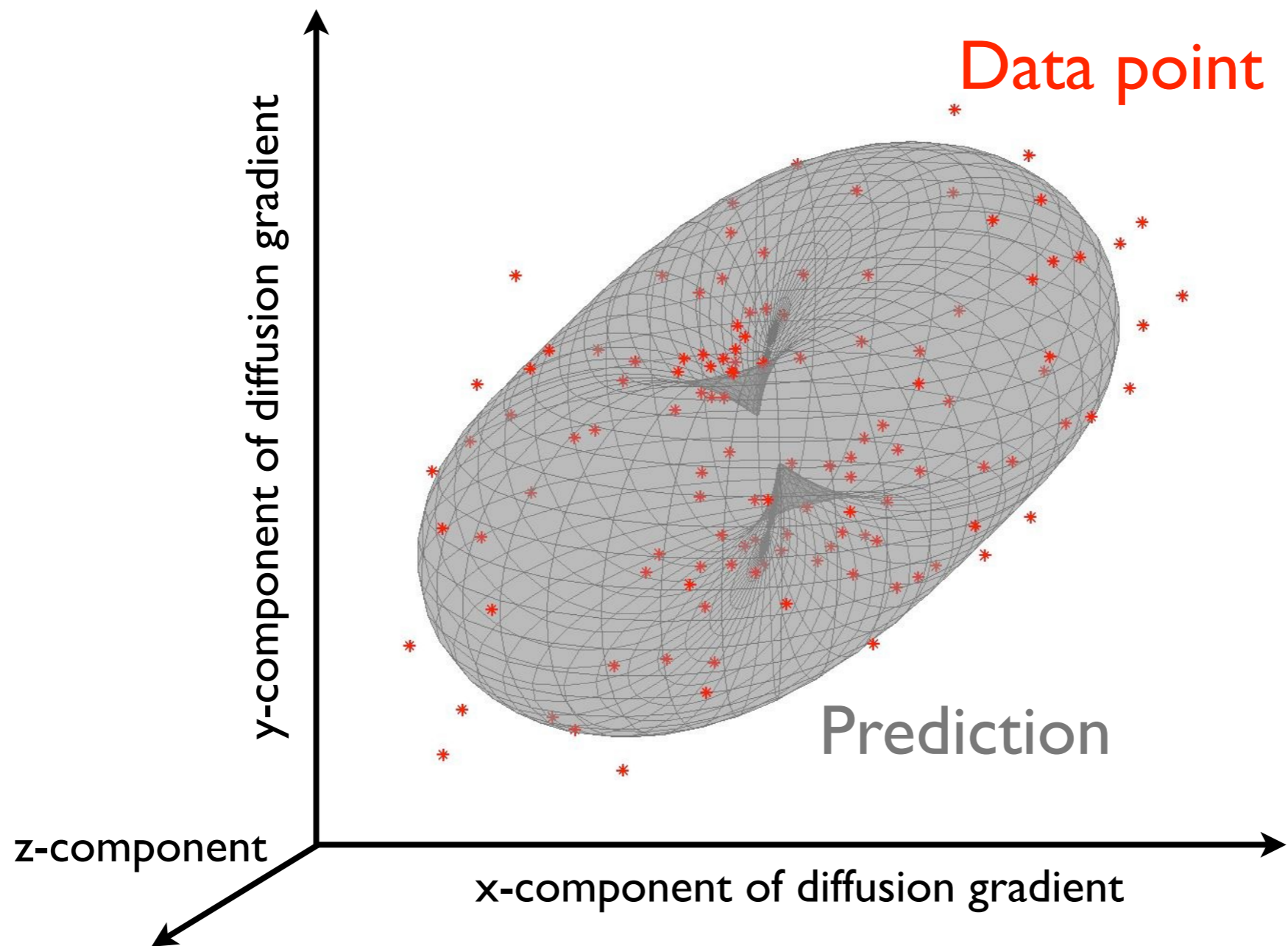
$[1\ 0\ 0]$



Compare to scan



Under the hood of Zoltar

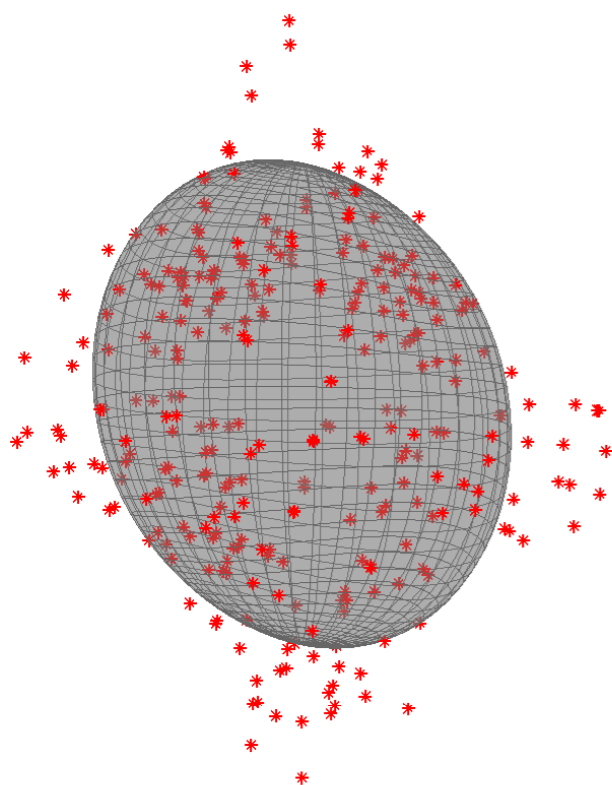


The signal is “modelled” in a data-driven fashion assuming that points close together on the unit sphere have similar signal.

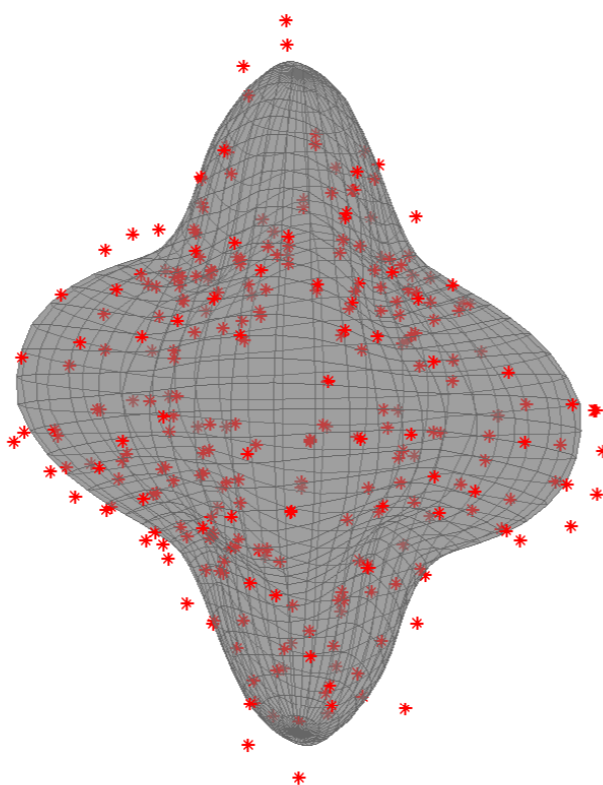


Under the hood of Zoltar

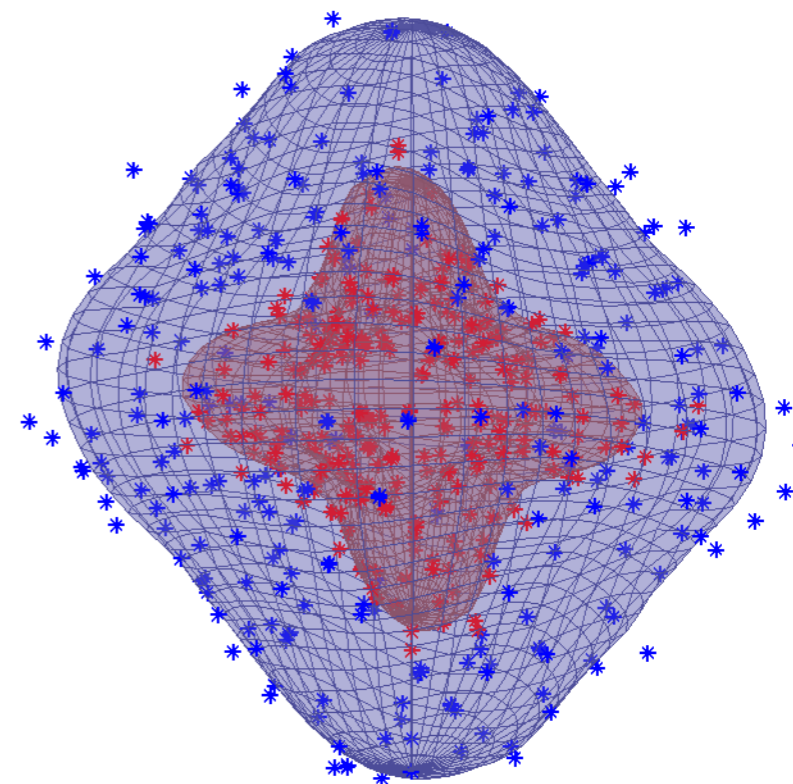
Tensor



Gaussian Process



Multi-shell predictions



The GP can model voxels with complicated anatomy while still being computationally convenient.

Shells with strong signal can help inform predictions in shells with poor signal

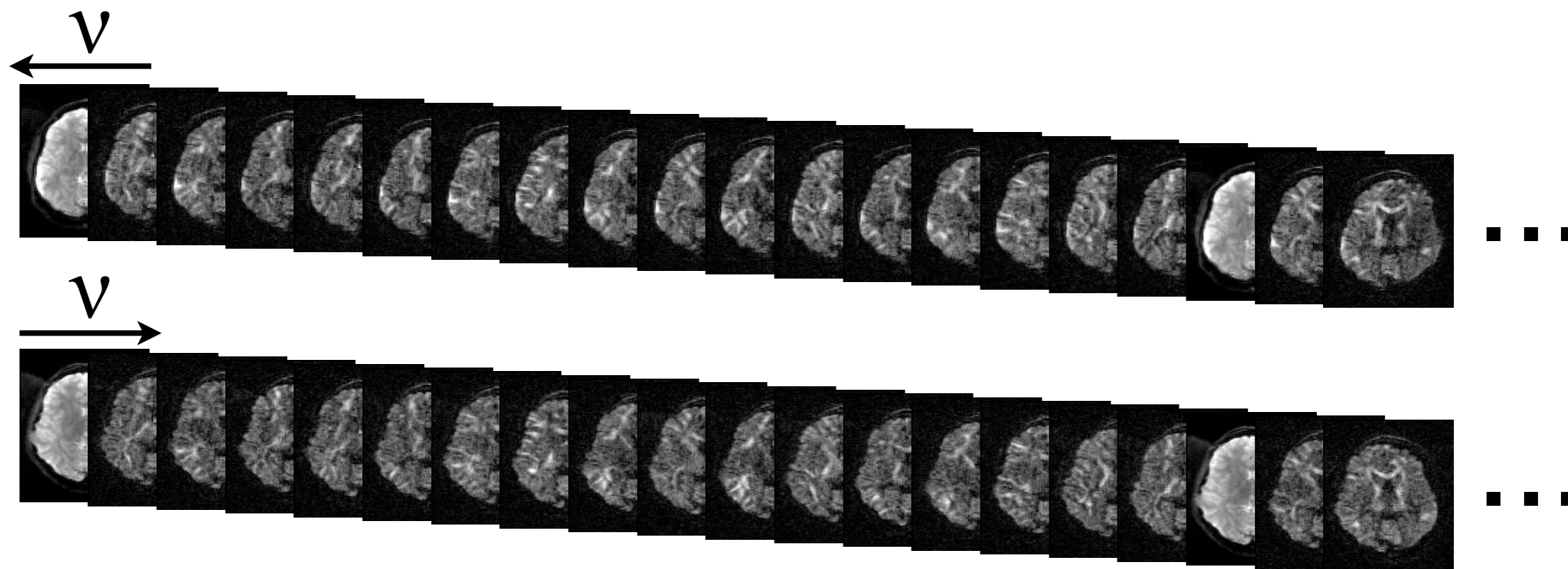


Outline of the talk

- What is the problem with diffusion data?
- Off-resonance field
 - How does it cause distortions?
 - Where does it come from?
- Registering diffusion data
 - How topup works
 - How eddy works
- **Practicalities**
- Some results
- Quality control
- “New” eddy features



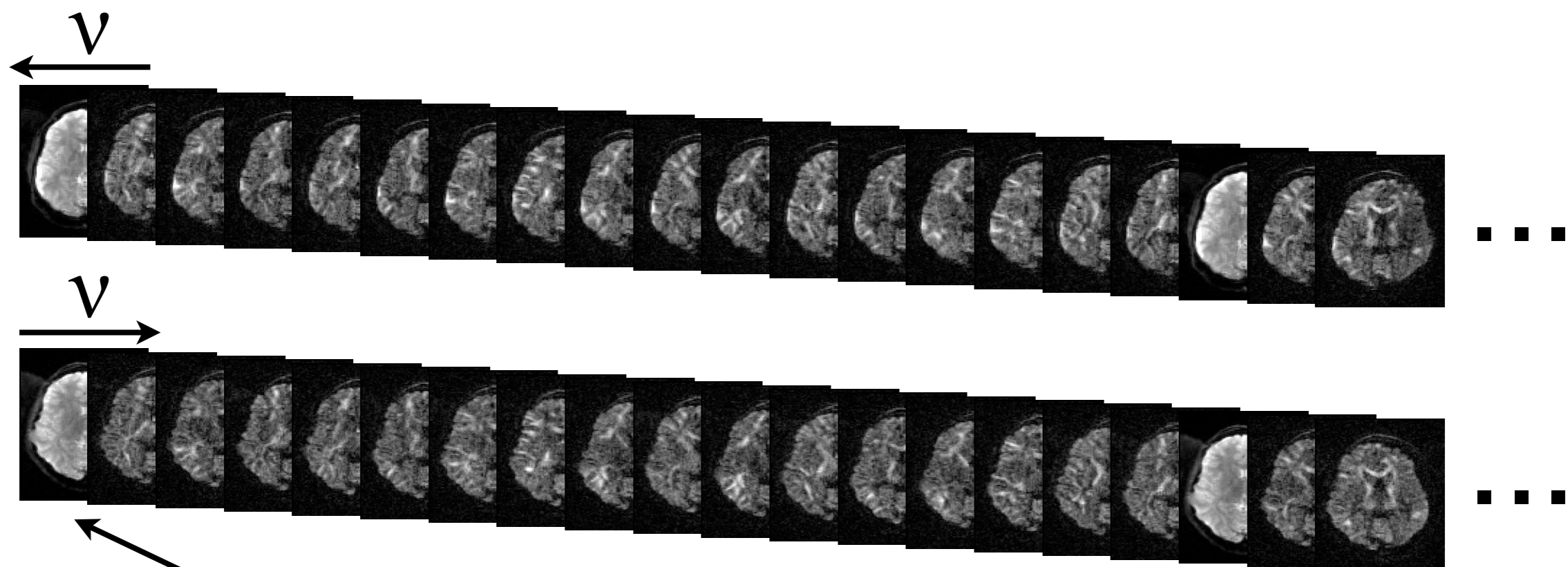
Practicalities



- Our example data consists of:
 - N diffusion weighted volumes and n $b=0$ volumes
 - $b=0$ volumes interspersed
 - Two repetitions, phase-encode $L \rightarrow R$ and $R \rightarrow L$
 - Same diffusion table for both repetitions



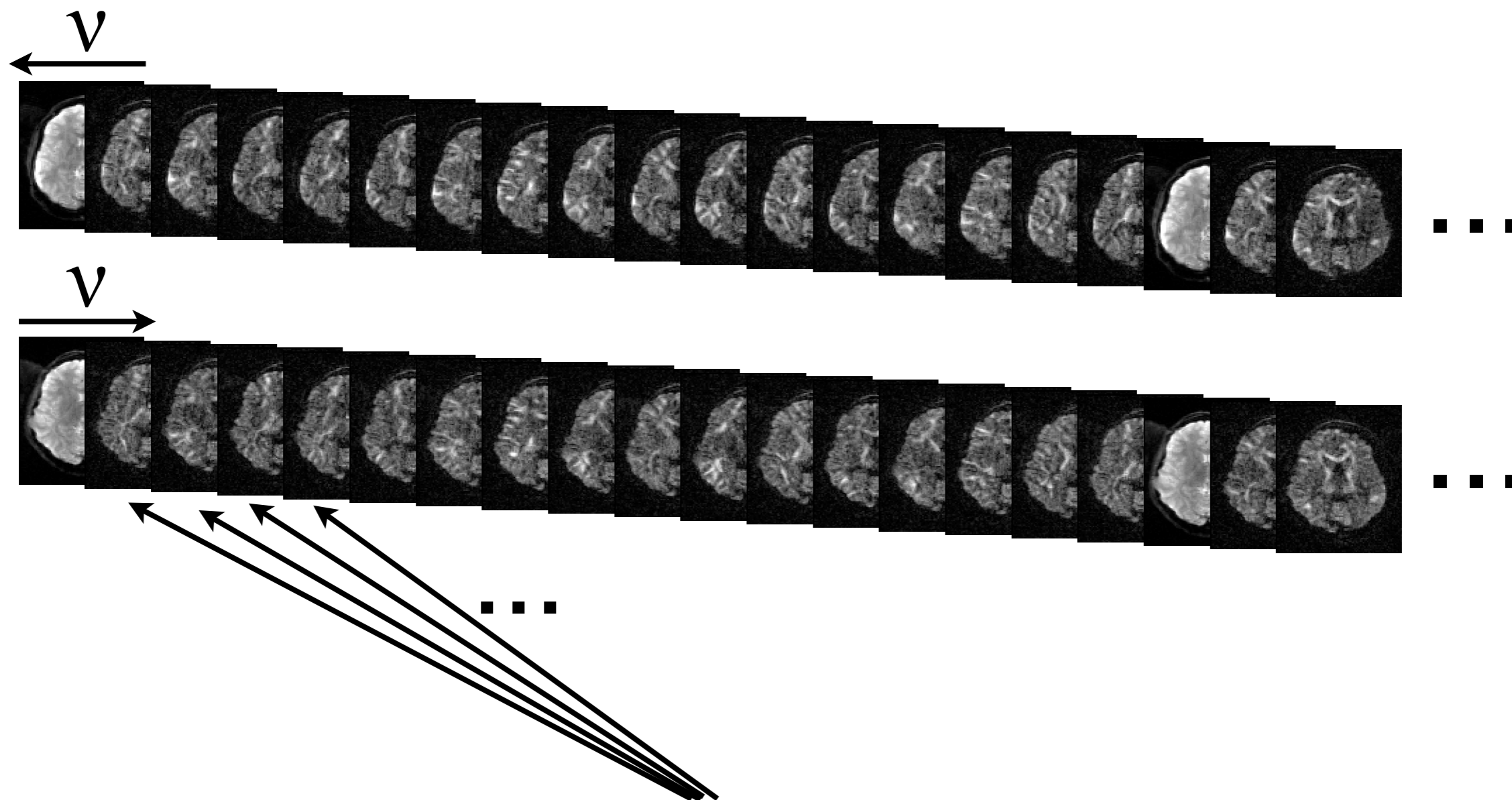
Practicalities



Affected by susceptibility distortions



Practicalities

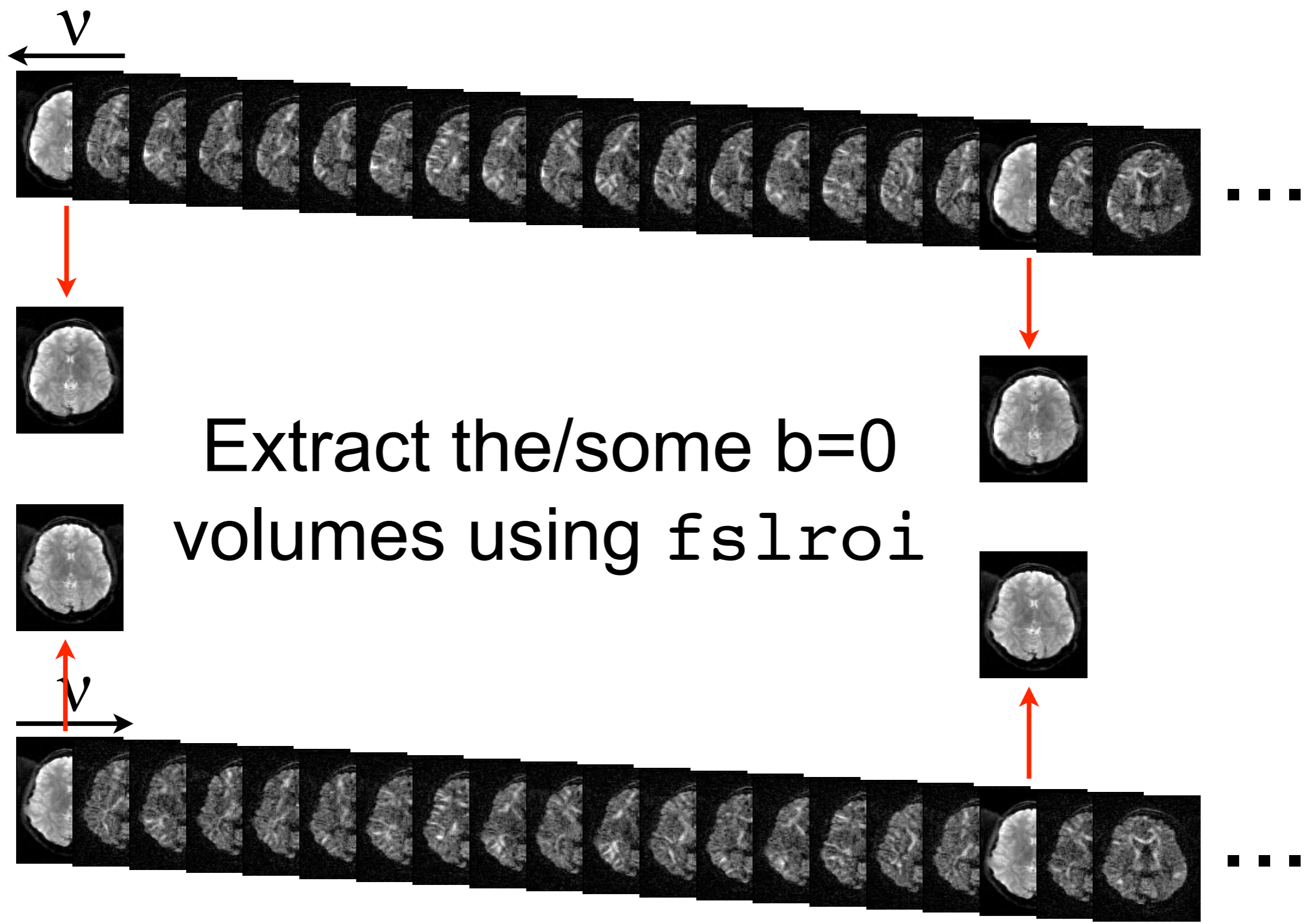


Affected by susceptibility distortions
AND eddy current distortions

And everything is of course affected by subject movement.



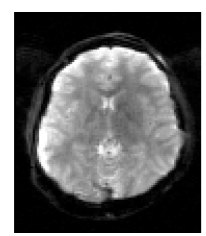
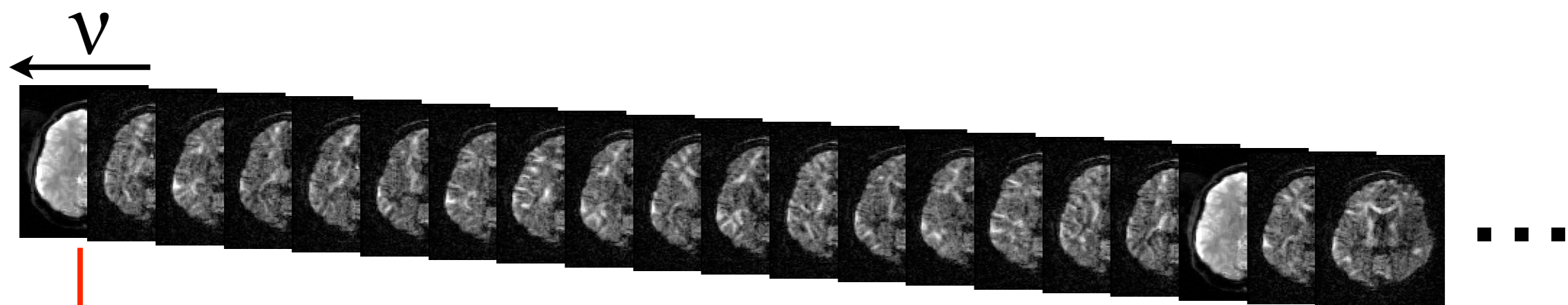
So, let's start with susceptibility



Extract the/some b=0 volumes using `fs1roi`

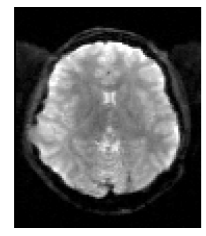


So, let's start with susceptibility



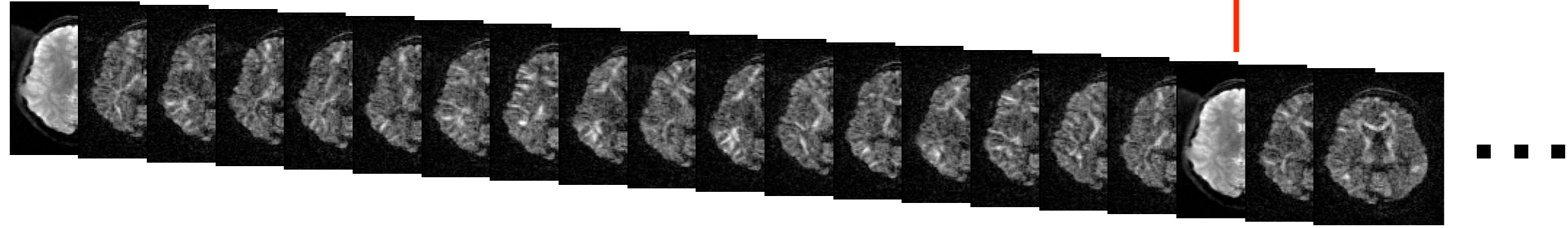
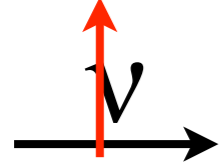
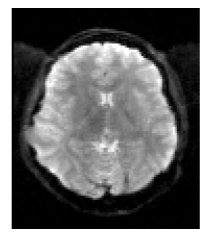
And let's call it for example `my_b0s`

Collect the `b=0` volumes



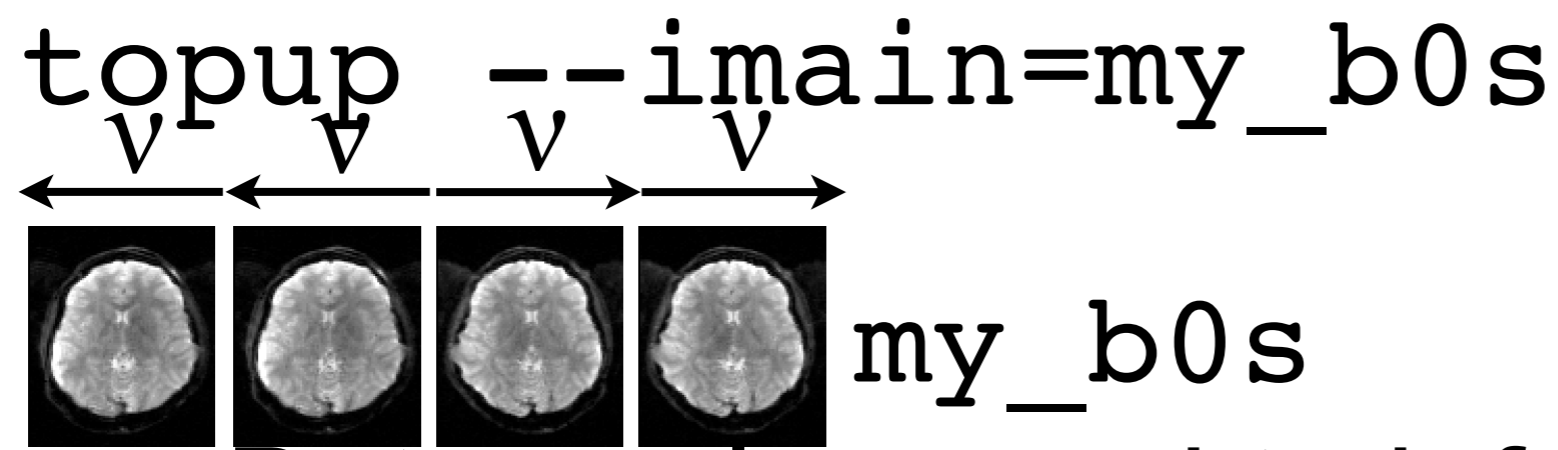
into a single file using

`fs1merge`





And the tool for that is `topup`



But we also need to inform `topup` about the acquisition parameters



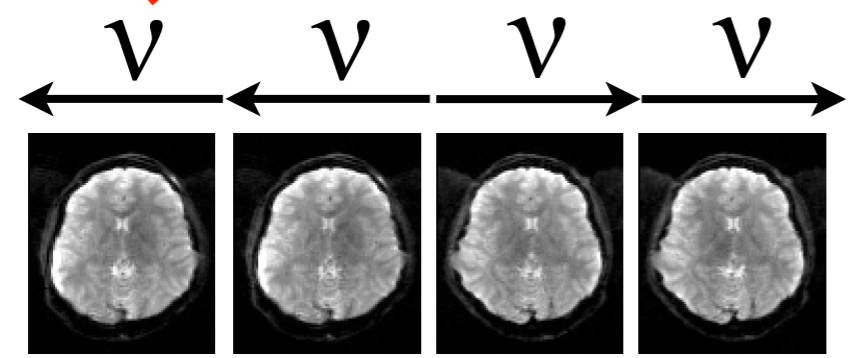
And the tool for that is `topup`

```
topup --iain=my_b0s
```

Means PE in x-direction, L→R

`-1 0 0 0.051`

Total readout time
(in seconds)



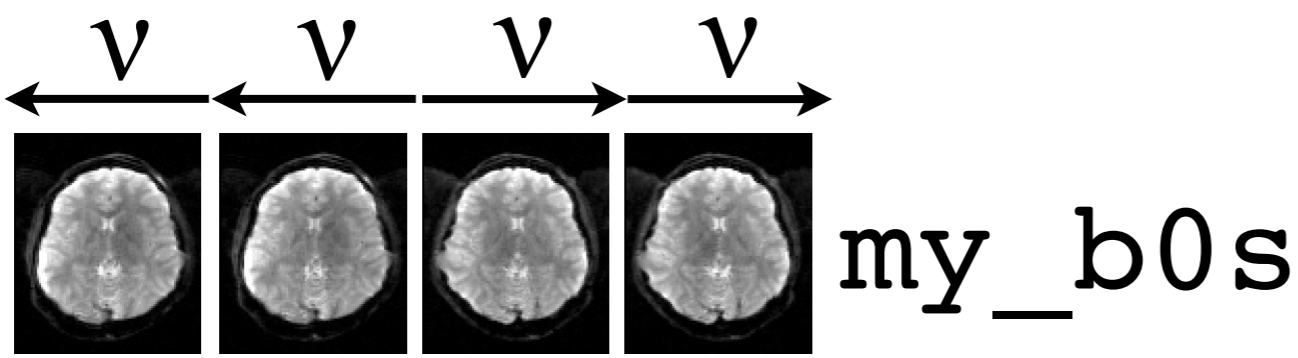


And the tool for that is `topup`

```
topup --iain=my_b0s --datain=acqparams.txt
```

```
-1 0 0 0.051  
-1 0 0 0.051  
1 0 0 0.051  
1 0 0 0.051
```

Text file that we can call for example `acqparams.txt`



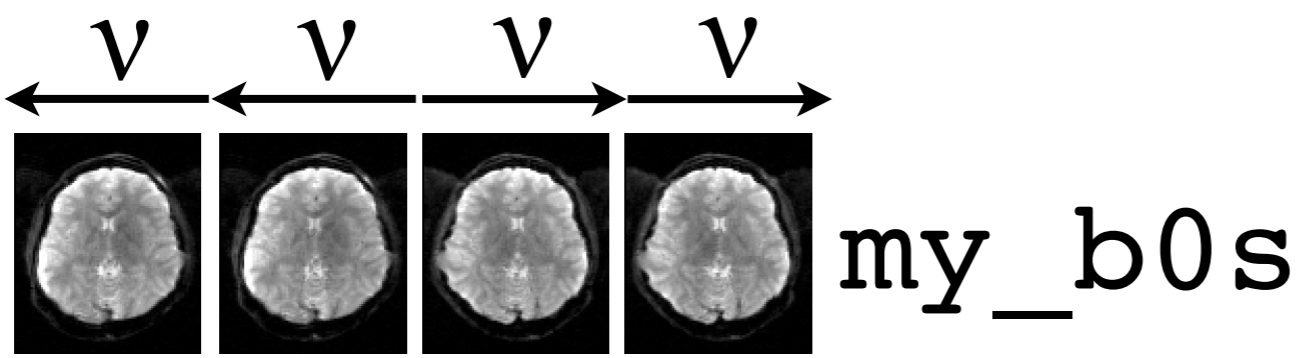


And the tool for that is `topup`

```
topup --iain=my_b0s --datain=acqparams.txt --config=b02b0.cnf
```



And then some technical details



```
-1 0 0 0.051  
-1 0 0 0.051  
1 0 0 0.051  
1 0 0 0.051
```

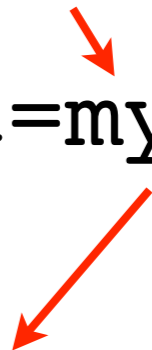
acqparams.txt



And the tool for that is topup

And finally we need to tell it where to put the results

```
topup --imain=my_b0s --datain=acqparams.txt --config=b02b0.cnf --out=my_topup
```

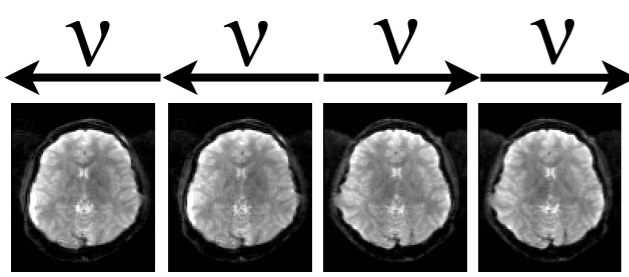


my_topup_movpar.txt

Tells position of 2nd b=0 scan relative the first



```
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```



my_b0s

```
-1 0 0 0.051
-1 0 0 0.051
1 0 0 0.051
1 0 0 0.051
```

acqparams.txt

b02b0.cnf

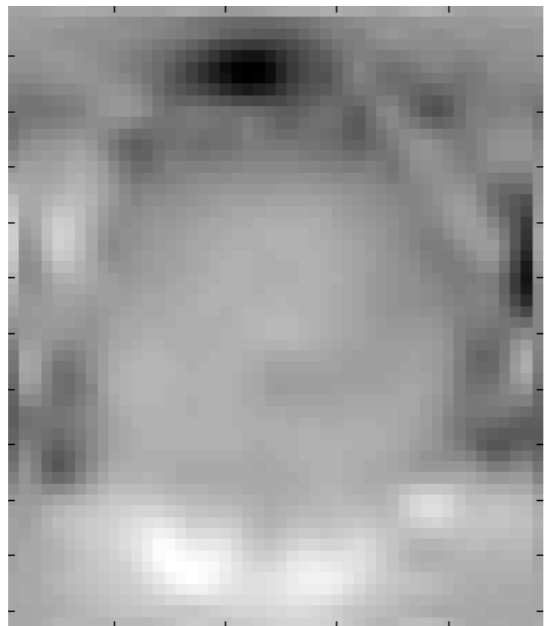


And the tool for that is topup

And finally we need to tell it where to put the results

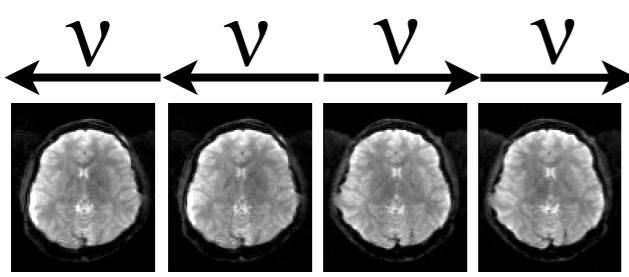
```
topup --imain=my_b0s --datain=acqparams.txt --config=b02b0.cnf --out=my_topup
```

my_topup_fieldcoef.nii



my_topup_movpar.txt

```
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```



my_b0s

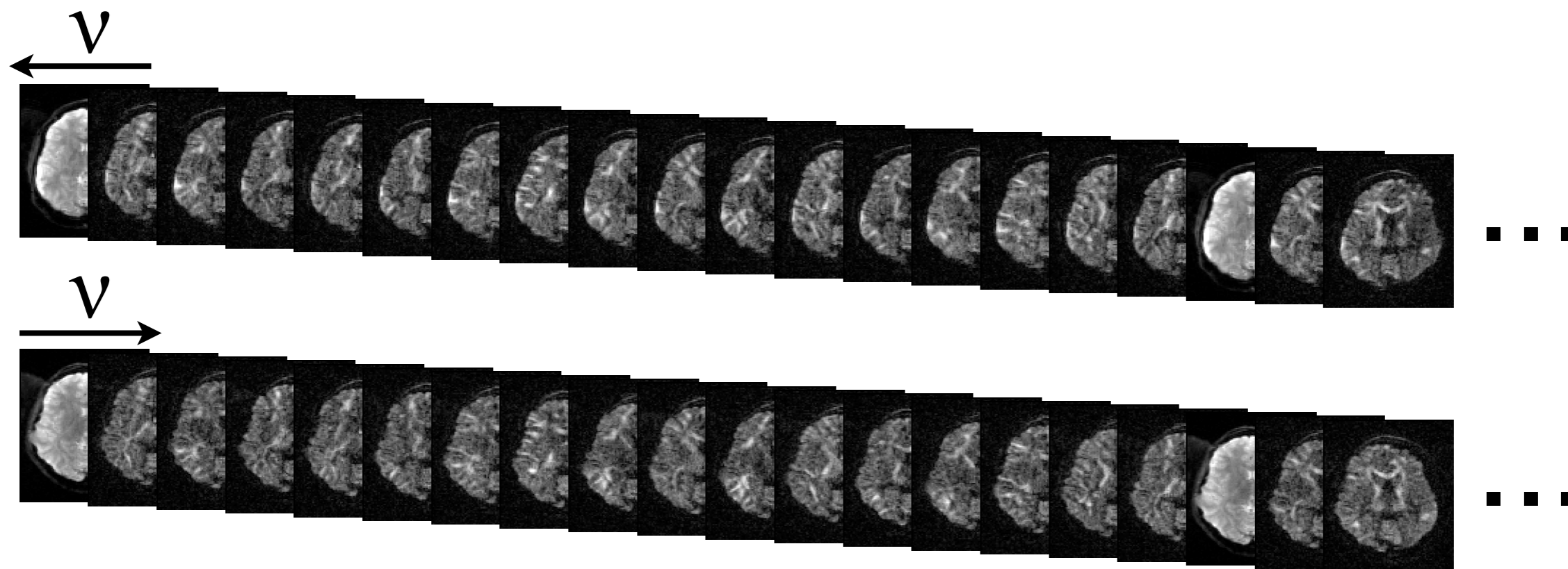
```
-1 0 0 0.051
-1 0 0 0.051
1 0 0 0.051
1 0 0 0.051
```

acqparams.txt

b02b0.cnf



Back to the full data-set

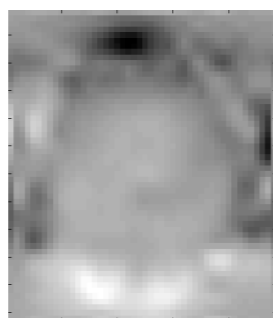


Now we want to correct the eddy current-distortions and subject movement in the whole data set.

my_topup_fieldcoef.nii

```
-1 0 0 0.051  
-1 0 0 0.051  
1 0 0 0.051  
1 0 0 0.051
```

acqparams.txt

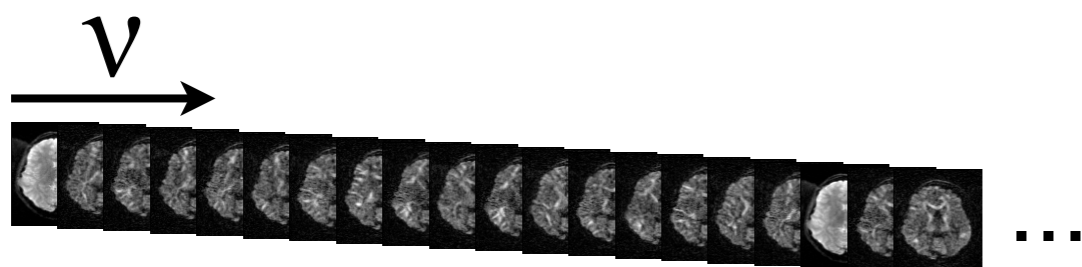
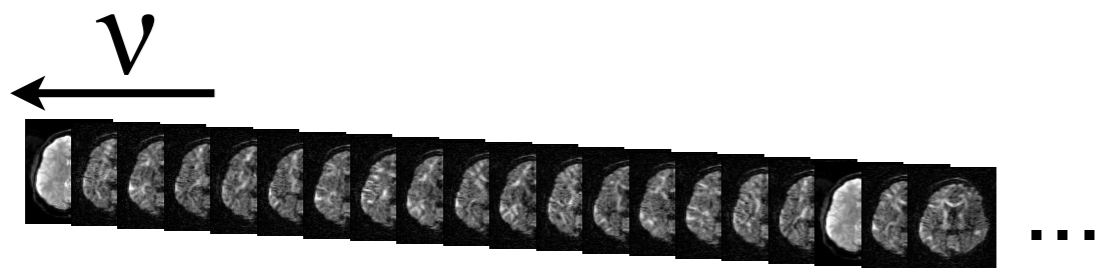


```
0 0 0 0 0 0  
0.72 -0.02 -0.07 0.002 0.000 0.002  
0 -0.11 -0.33 0.002 0.013 -0.004  
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```

my_topup_movpar.txt



Collect all data in one file



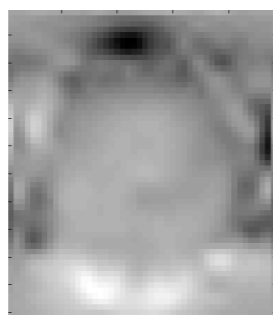
LR_RL

The first thing we do is to collect all data in a single file using `fslmerge` and call it for example LR_RL

`my_topup_fieldcoef.nii`

```
-1 0 0 0.051
-1 0 0 0.051
 1 0 0 0.051
 1 0 0 0.051
```

`acqparams.txt`

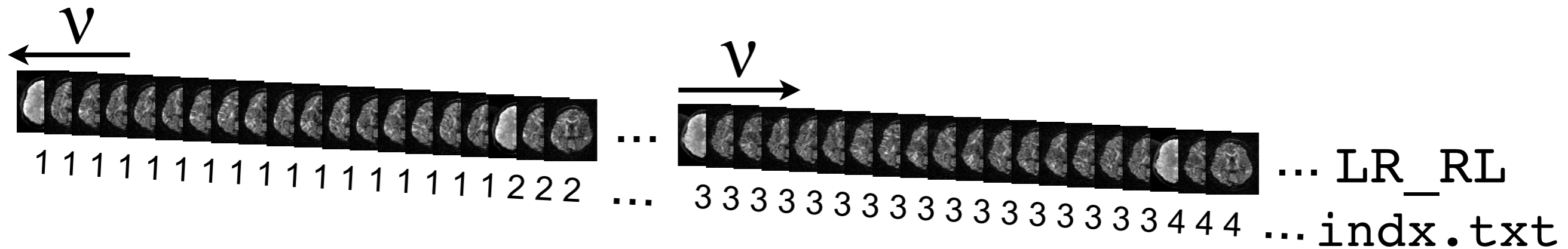


```
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```

`my_topup_movpar.txt`



Inform eddy of acquisition parameters

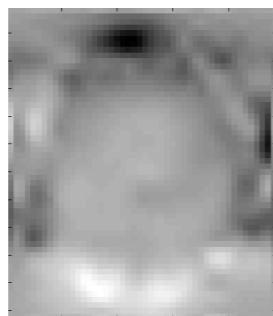


Then we make a text file with one index for each volume, and call it for example `indx.txt`

`my_topup_fieldcoef.nii`

```
-1 0 0 0.051
-1 0 0 0.051
 1 0 0 0.051
 1 0 0 0.051
```

`acqparams.txt`

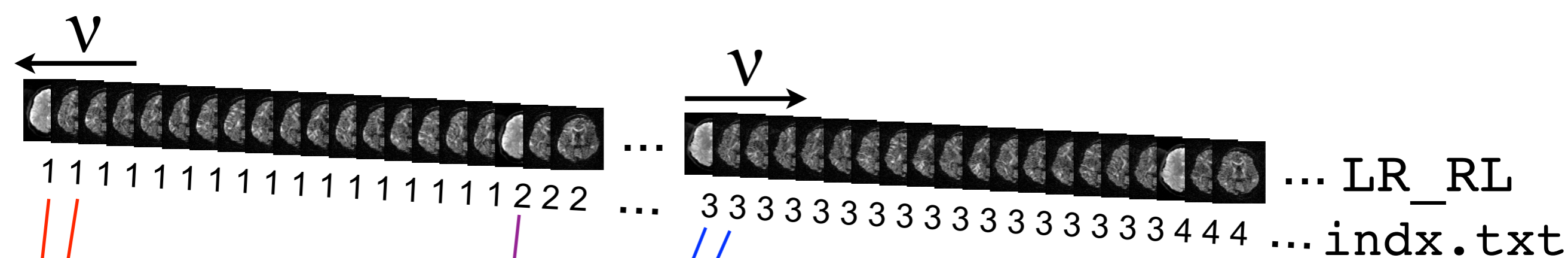


```
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```

`my_topup_movpar.txt`



Inform eddy of acquisition parameters



By referring into `acqparams.txt` this file specifies how every volume was acquired

`my_topup_fieldcoef.nii`

```

-1 0 0 0.051
-1 0 0 0.051
1 0 0 0.051
1 0 0 0.051
acqparams.txt

```

```

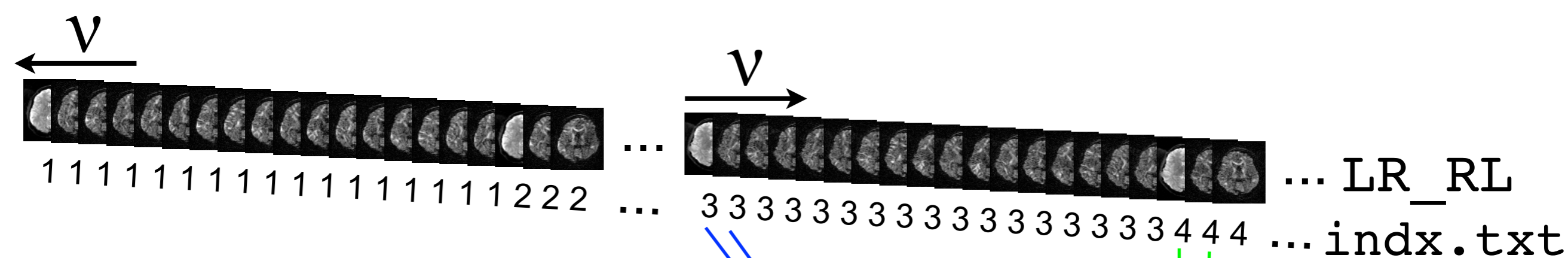
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
my_topup_movpar.txt

```





Inform eddy of acquisition parameters



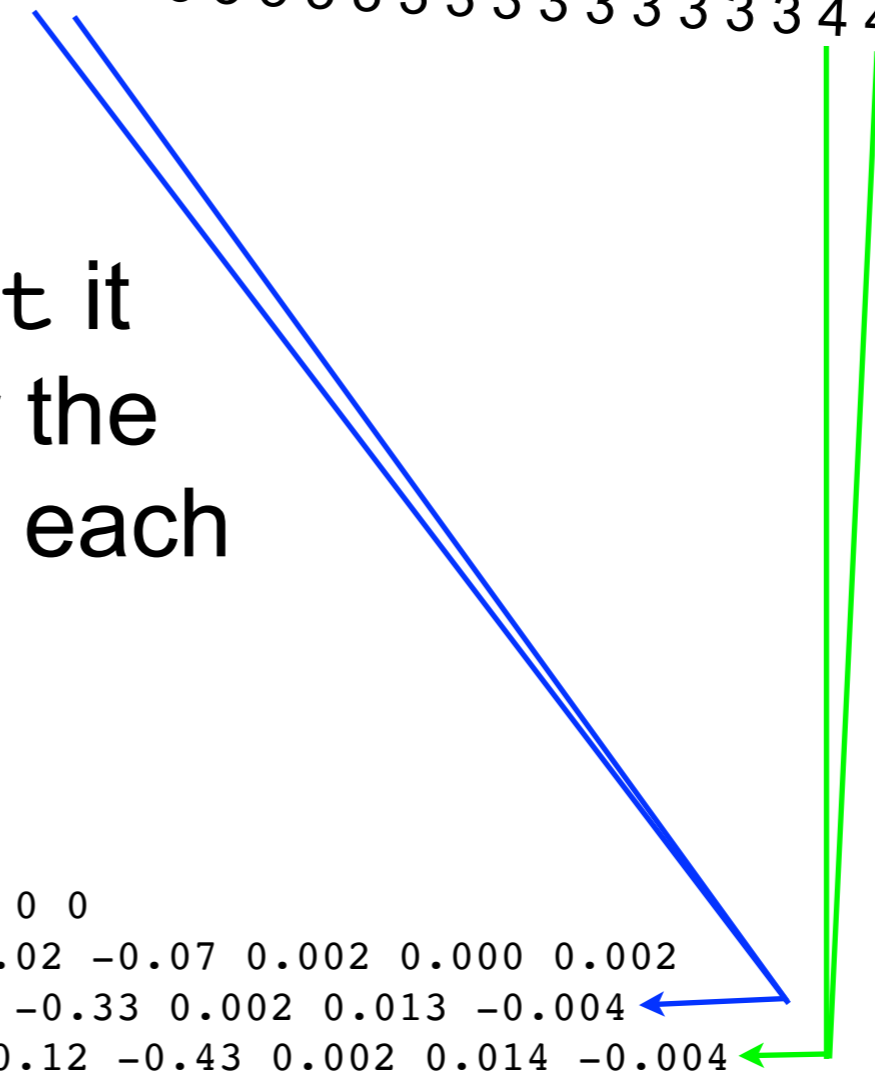
And by referring into
 my_topup_movpar.txt it
 gives a starting guess for the
 relative subject position for each
 volume

my_topup_fieldcoef.nii



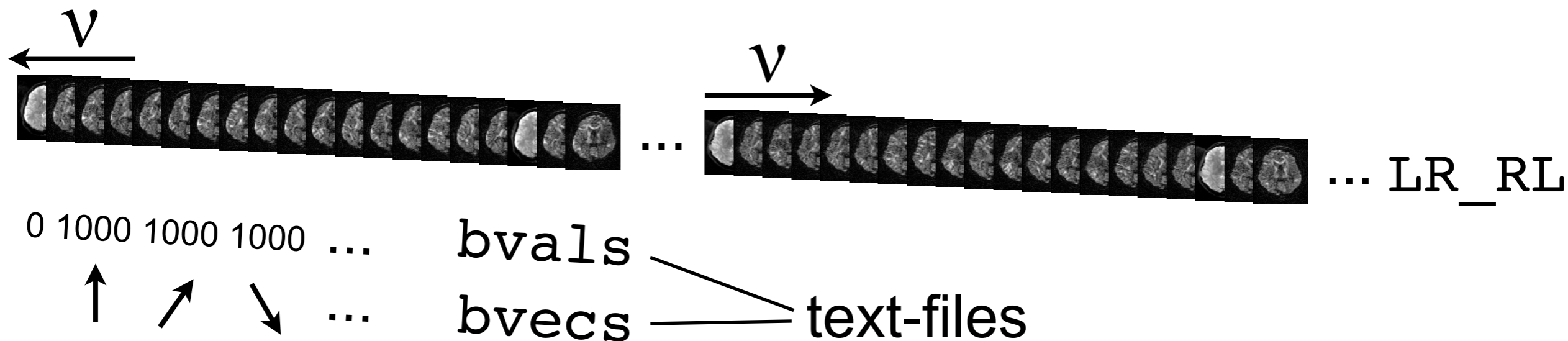
```
acqparams.txt
-1 0 0 0.051
-1 0 0 0.051
1 0 0 0.051
1 0 0 0.051
```

```
my_topup_movpar.txt
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```



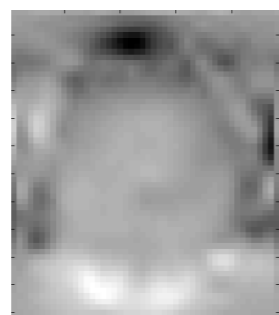


And of diffusion parameters



And we also need to know the b-value and b-vector for each volume (same as for dtifit or bedpost).

my_topup_fieldcoef.nii



```

-1 0 0 0.051
-1 0 0 0.051
 1 0 0 0.051
 1 0 0 0.051

```

acqparams.txt

```

0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004

```

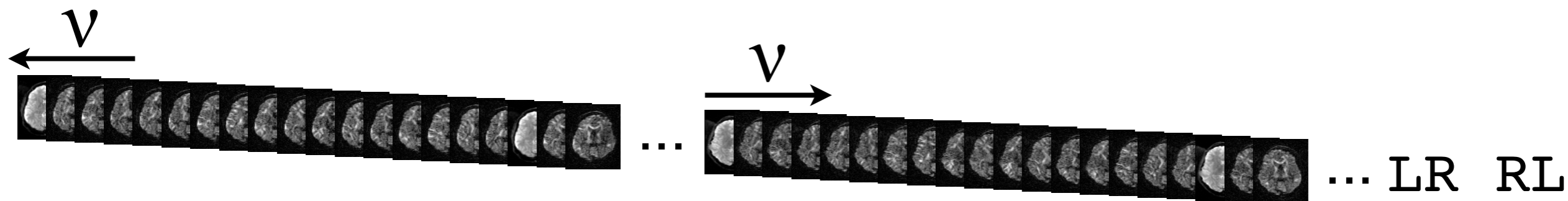
my_topup_movpar.txt

1111...

indx.txt



And where the brain is



brain_mask.nii

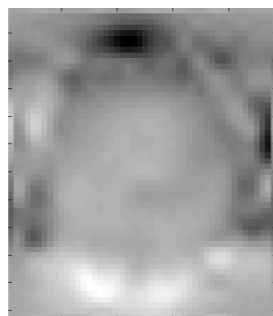
And finally a binary mask that tells eddy which voxels are brain. Also the same that is used for dtifit/bedpost.

my_topup_fieldcoef.nii

```

-1 0 0 0.051
-1 0 0 0.051
 1 0 0 0.051
 1 0 0 0.051
acqparams.txt

```



```

0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
my_topup_movpar.txt

```

```

0 1000 1000 1000 ...
bvals
1111...
↑ ↗ ↘ ...
bvecs

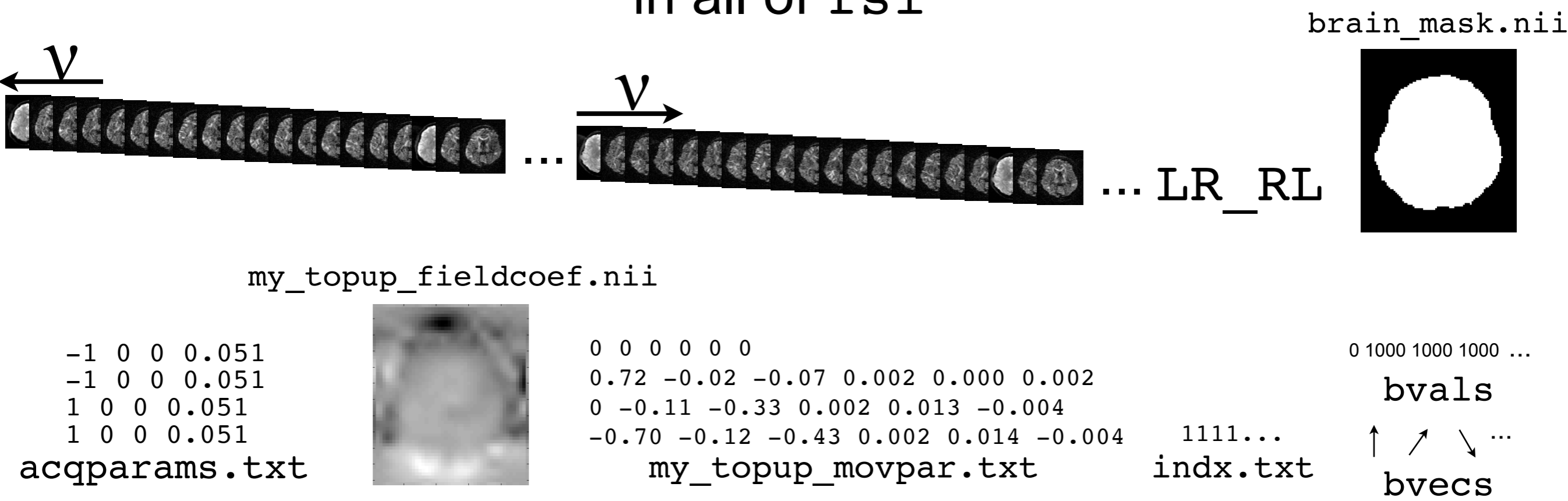
```



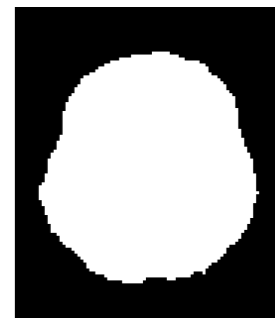
And now we can run eddy

```
eddy --imain=LR_RL --acqp=acqparams.txt
--index=indx.txt --bvecs=bvecs
--bvals=bvals --mask=brain_mask
--topup=my_topup --out=my_eddy
```

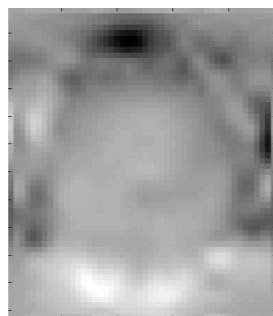
And now we are ready for the most horrible command line in all of `fsl`



`brain_mask.nii`



`my_topup_fieldcoef.nii`



```
-1 0 0 0.051
-1 0 0 0.051
 1 0 0 0.051
 1 0 0 0.051
```

`acqparams.txt`

```
0 0 0 0 0 0
0.72 -0.02 -0.07 0.002 0.000 0.002
0 -0.11 -0.33 0.002 0.013 -0.004
-0.70 -0.12 -0.43 0.002 0.014 -0.004
```

`my_topup_movpar.txt`

```
1111...
indx.txt
```

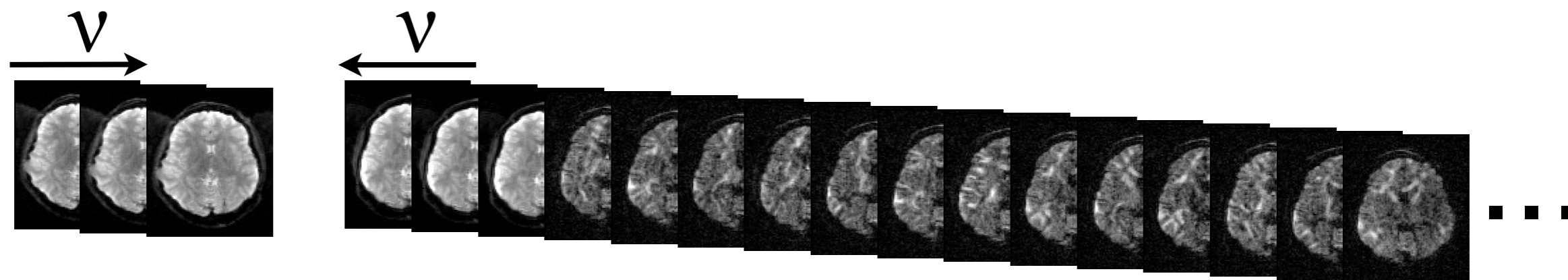
0 1000 1000 1000 ...

`bvals`

```
↑ ↗ ↘ ...
bvecs
```



A simpler (and perhaps more realistic) example

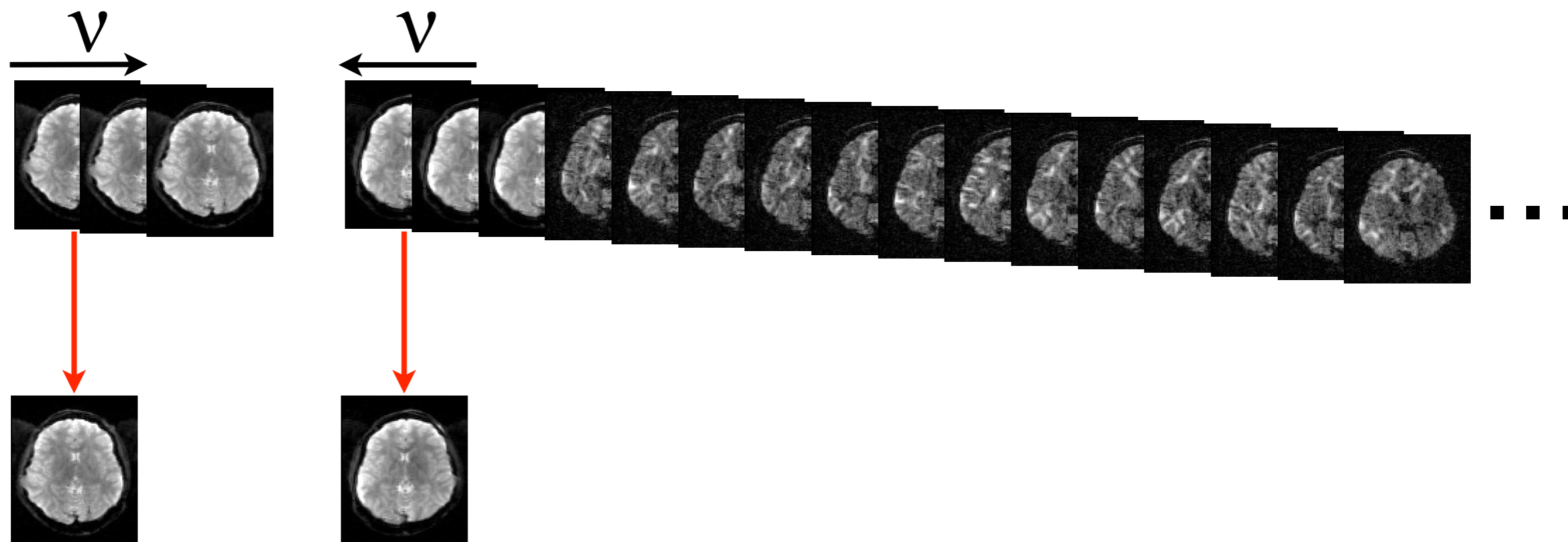


Data consists of:

- N diffusion weighted volumes and n $b=0$ volumes
- $b=0$ volumes interspersed, but 2–3 are up front.
- 2–3 $b=0$ volumes with opposing PE acquired just before the acquisition of the diffusion data set.



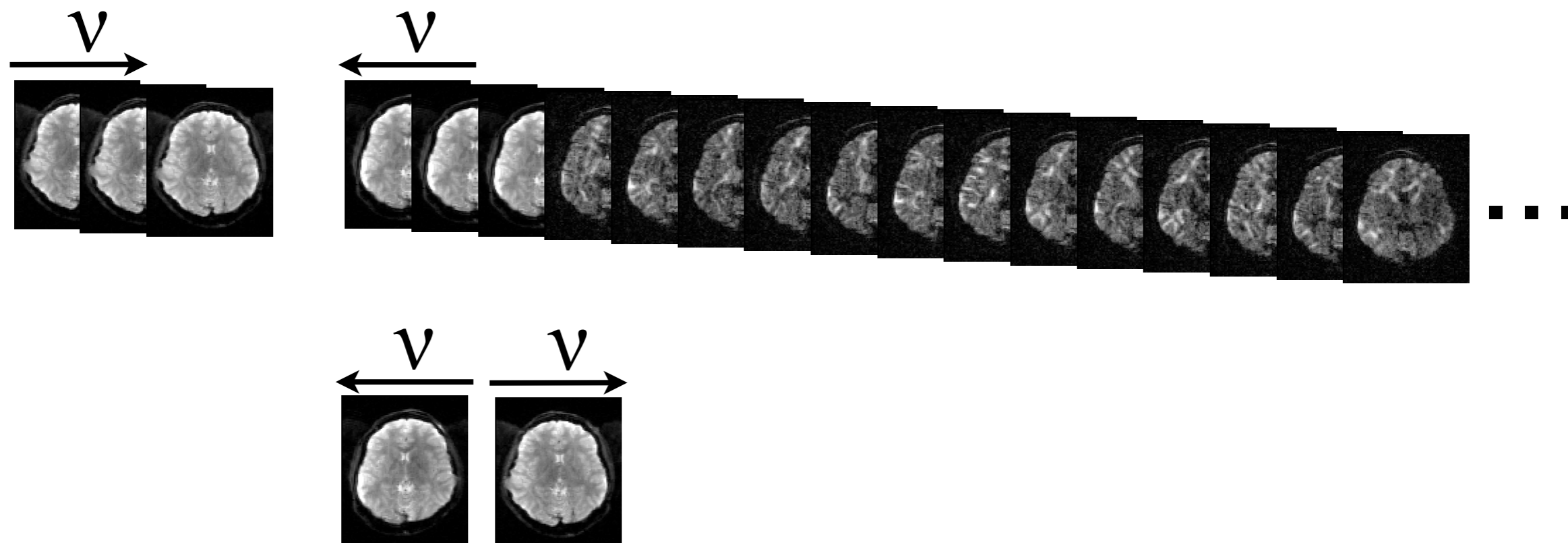
A simpler (and perhaps more realistic) example



Extract one “good” $b=0$ volume for each PE-direction using `fs1roi`



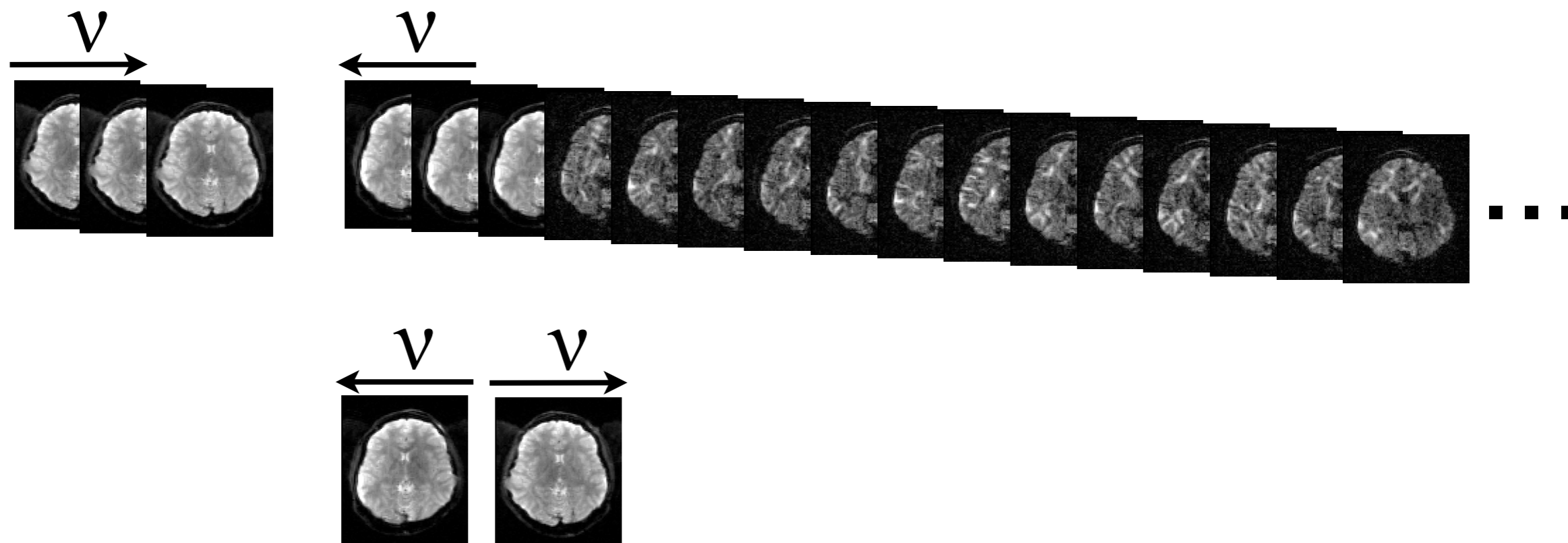
A simpler (and perhaps more realistic) example



Collect them into one 4D file using
`fs1merge`



A simpler (and perhaps more realistic) example

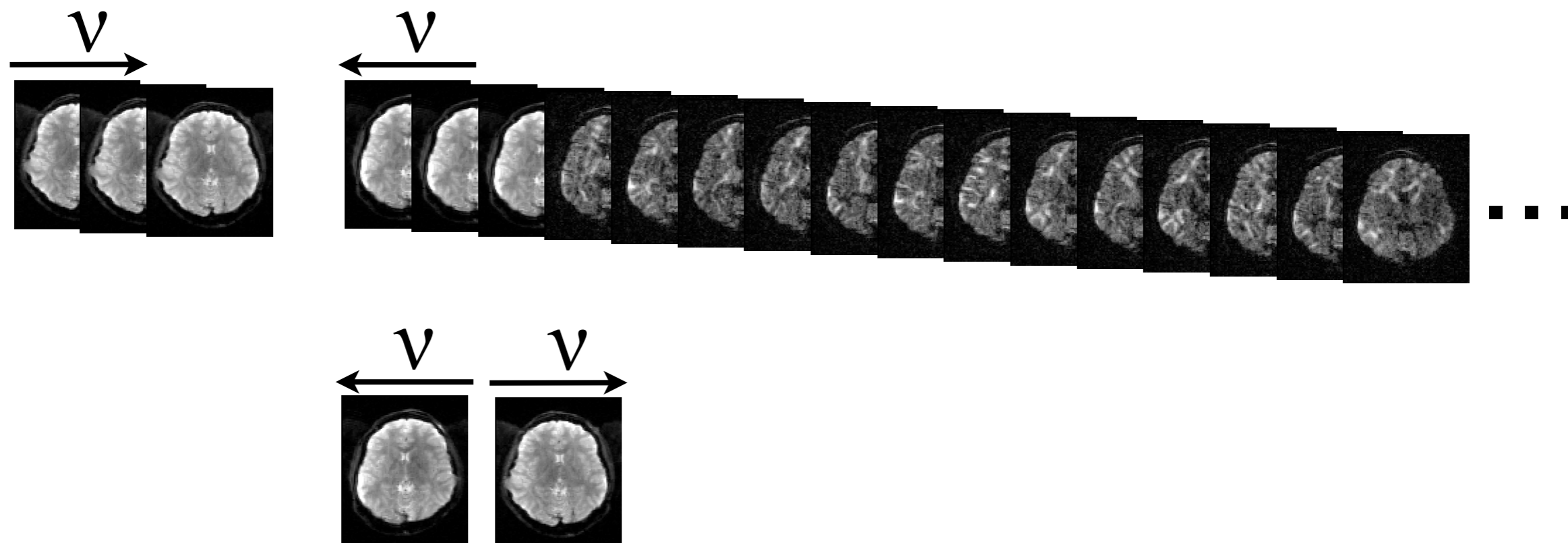


```
-1 0 0 0.051  
1 0 0 0.051
```

Create text file
acqparams.txt



A simpler (and perhaps more realistic) example



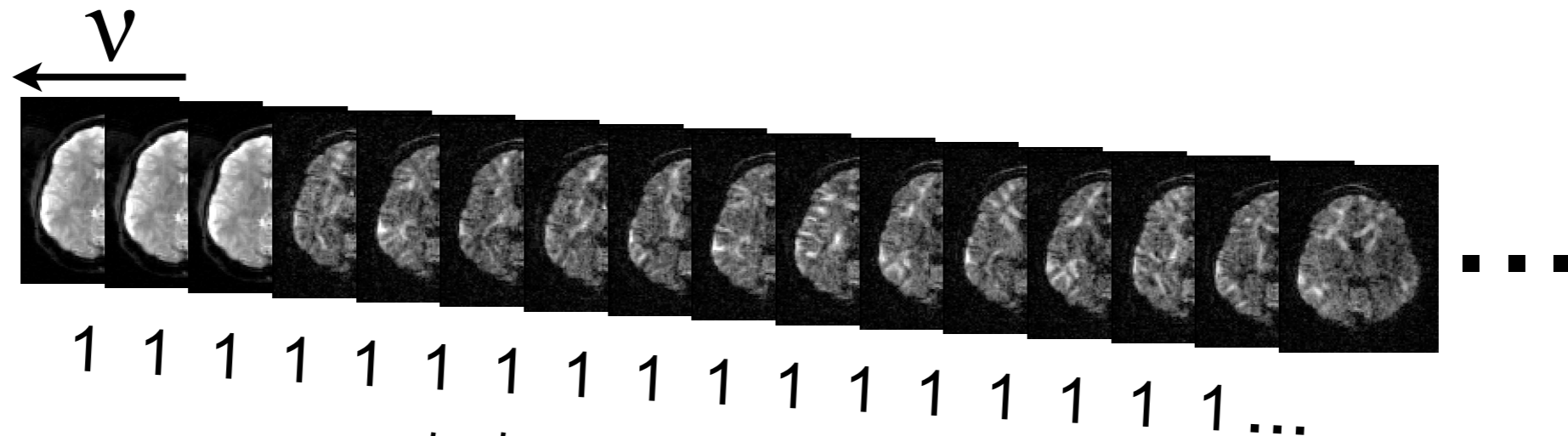
```
-1 0 0 0.051  
1 0 0 0.051
```

And run topup

```
topup --iain=my_b0s --datain=acqparams.txt  
--config=b02b0.cnf --out=my_topup
```



A simpler (and perhaps more realistic) example

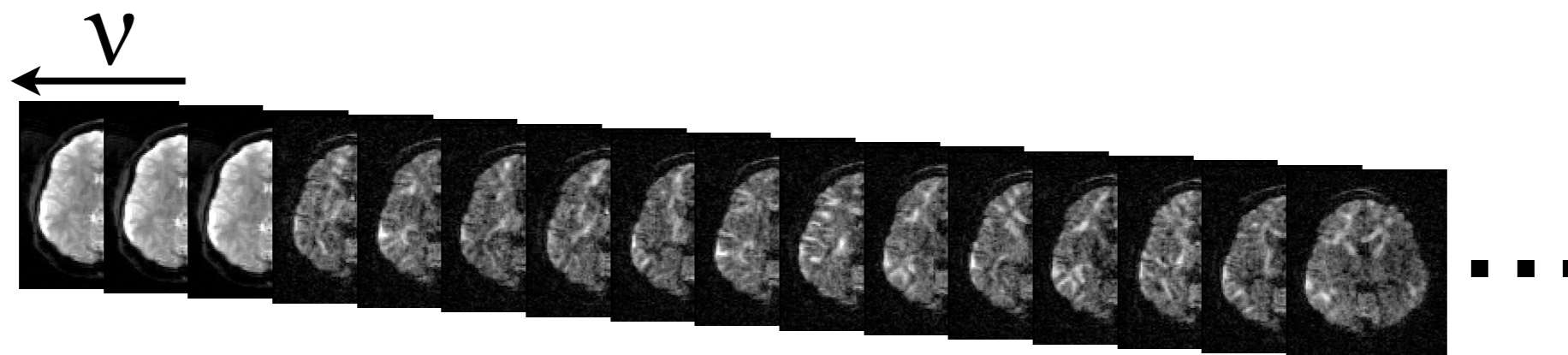


... `indx.txt` is now very simple

```
-1 0 0 0.051  
1 0 0 0.051
```



A simpler (and perhaps more realistic) example



```
eddy --iain=LR_RL --acqp=acqparams.txt  
--index=indx.txt --bvecs=bvecs  
--bvals=bvals --mask=brain_mask  
--topup=my_topup --out=my_eddy
```

And the eddy command is the same as before
(N.B. you need to create brain_mask.nii.gz in
the same way as before)

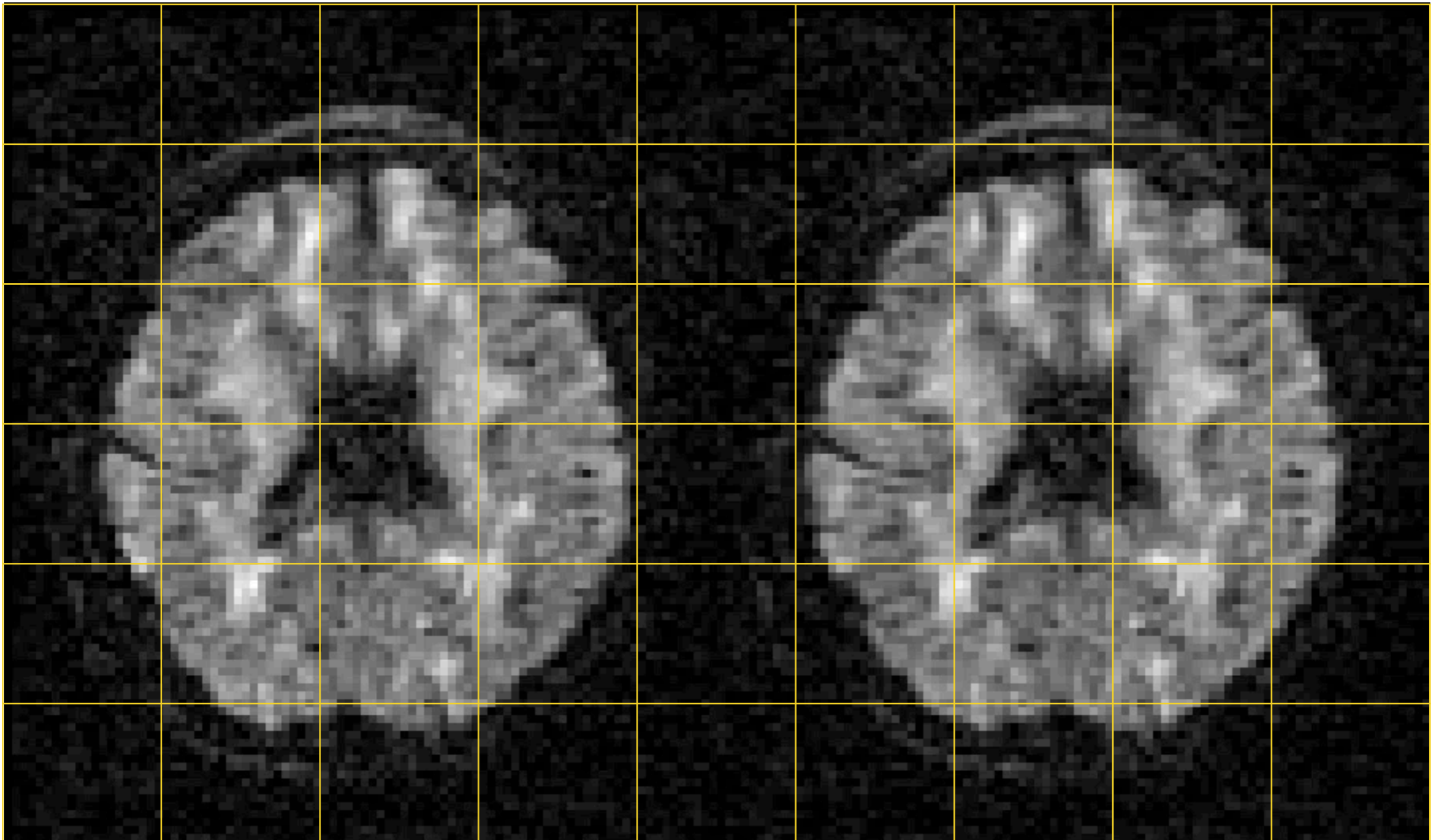


Outline of the talk

- What is the problem with diffusion data?
- Off-resonance field
 - How does it cause distortions?
 - Where does it come from?
- Registering diffusion data
 - How topup works
 - How eddy works
- Practicalities
- **Some results**
- Quality control
- “New” eddy features

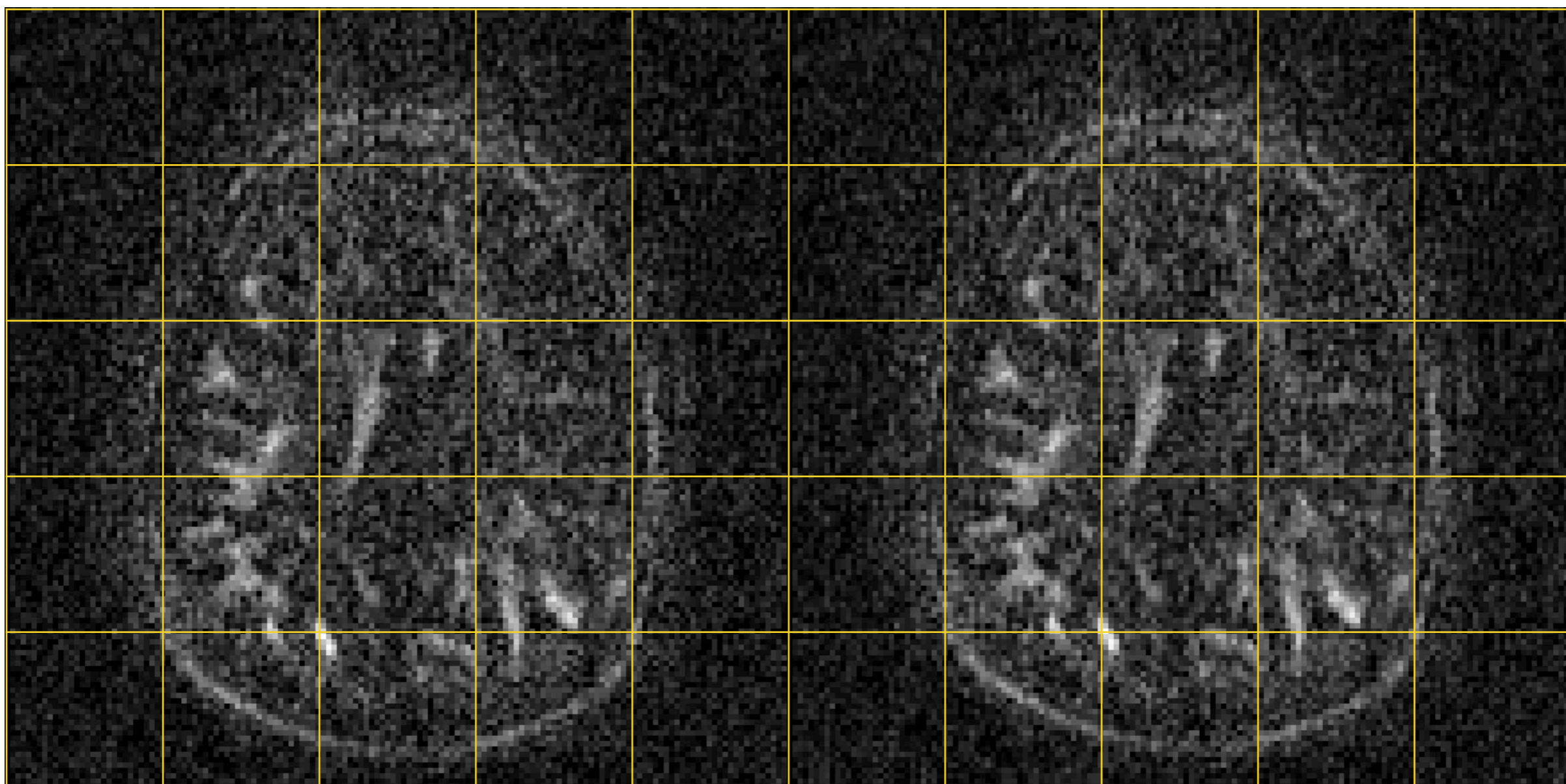


HCP-data, 150 directions, b=3000, blip-up-blip-down



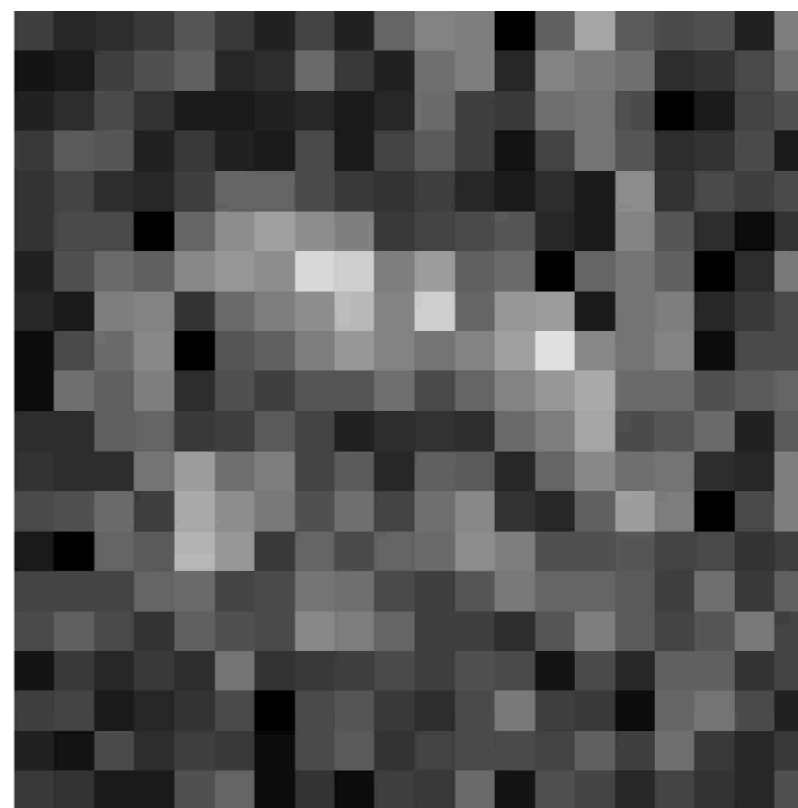
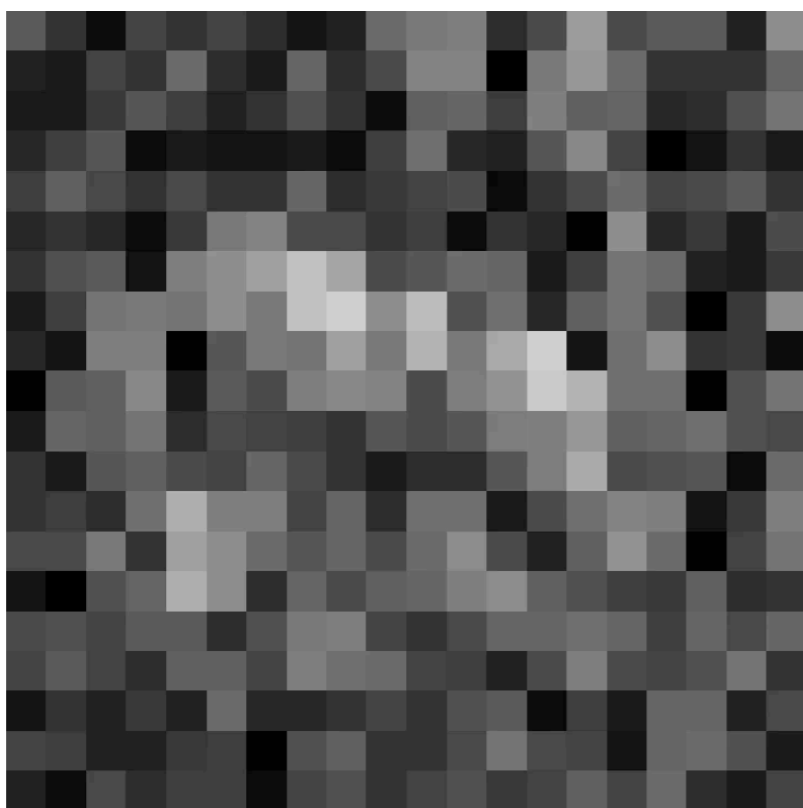
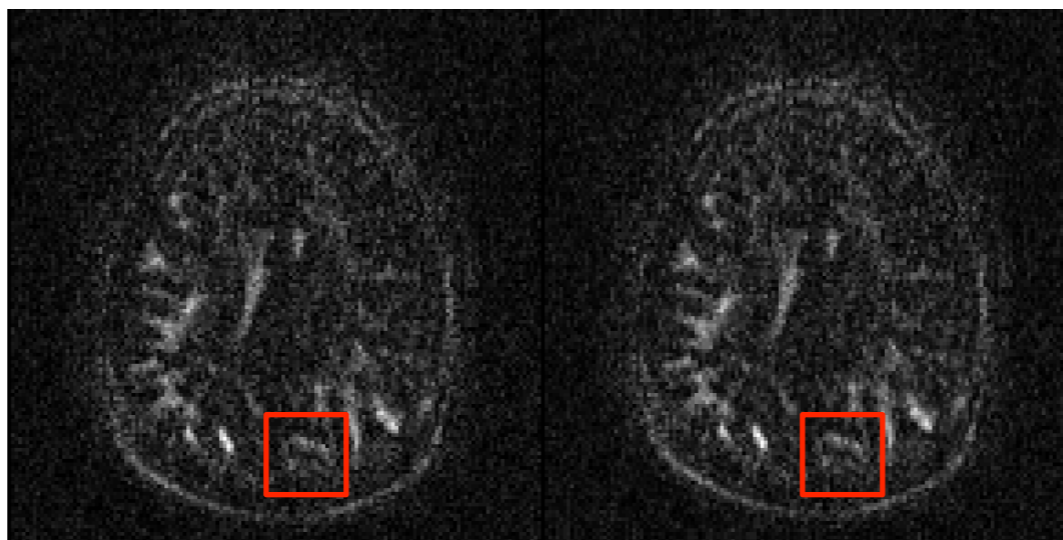


MGH-data, 198 directions, b=10000!





MGH-data, 198 directions, b=10000!









Outline of the talk

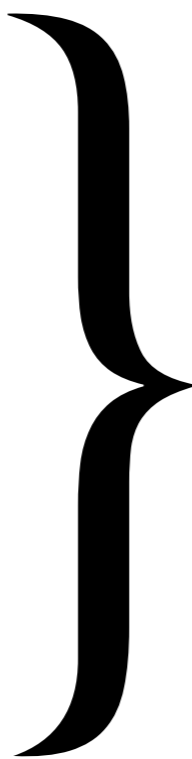
- What is the problem with diffusion data?
- Off-resonance field
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EDDY QC: data quality summary

QUAD
(subject)

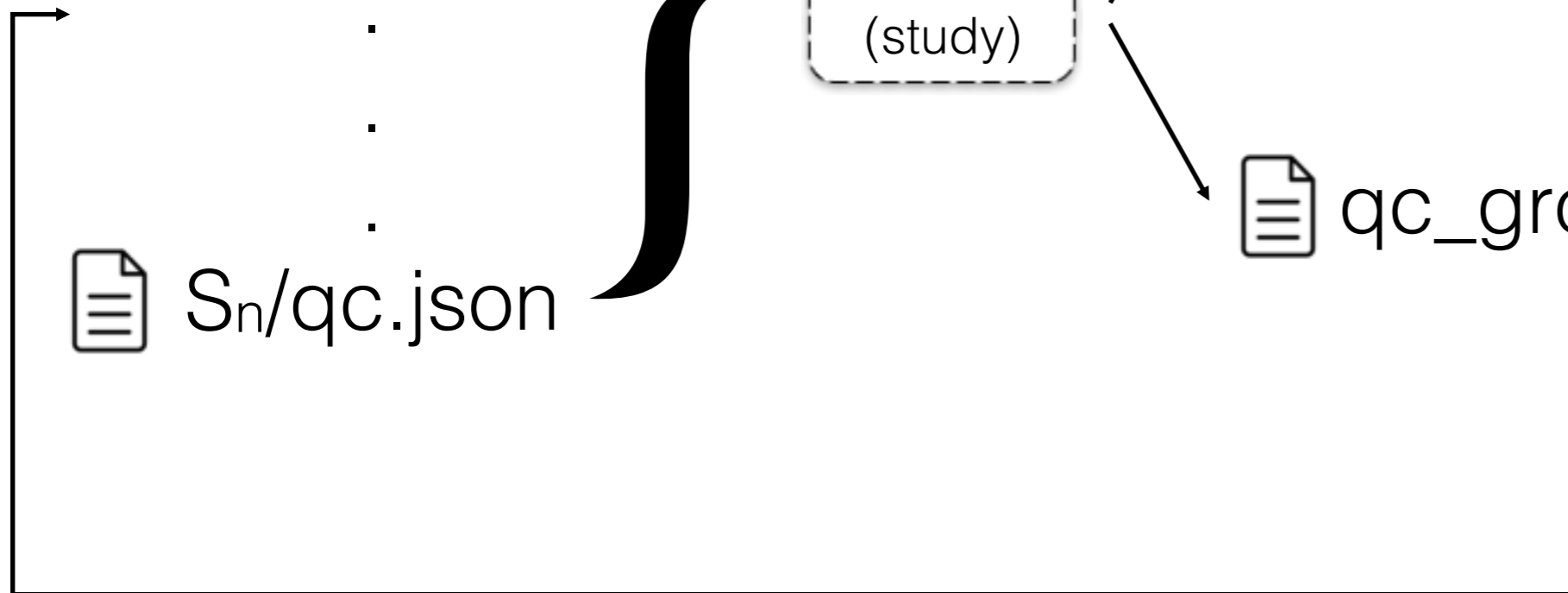
-  S1/qc.json
-  S2/qc.json
-  S3/qc.json
- ⋮
- ⋮
- ⋮
-  S_n/qc.json






SQUAD
(study)

 qc_group.pdf

 qc_group.json



-  P1/qc.json
-  P2/qc.json
-  P3/qc.json

...



EDDY QC: single-subject reports

Biobank subject A

Volume-to-volume motion

Average abs. motion (mm)	0.81
Average rel. motion (mm)	0.88
Average x translation (mm)	0.17
Average y translation (mm)	-0.10
Average z translation (mm)	-0.02
Average x rotation (deg)	0.07
Average y rotation (deg)	0.17
Average z rotation (deg)	0.15

Within-volume motion

Avg std x translation (mm)	0.02
Avg std y translation (mm)	0.11
Avg std z translation (mm)	0.04
Avg std x rotation (deg)	0.05
Avg std y rotation (deg)	0.05
Avg std z rotation (deg)	0.06

Outliers

Total outliers (%)	0.11
Outliers (b=1000 s/mm ²)	0.22
Outliers (b=2000 s/mm ²)	0.00
Outliers (PE dir=[0. 1. 0.])	0.00
Outliers (PE dir=[0. -1. 0.])	0.11

Biobank subject B

Volume-to-volume motion

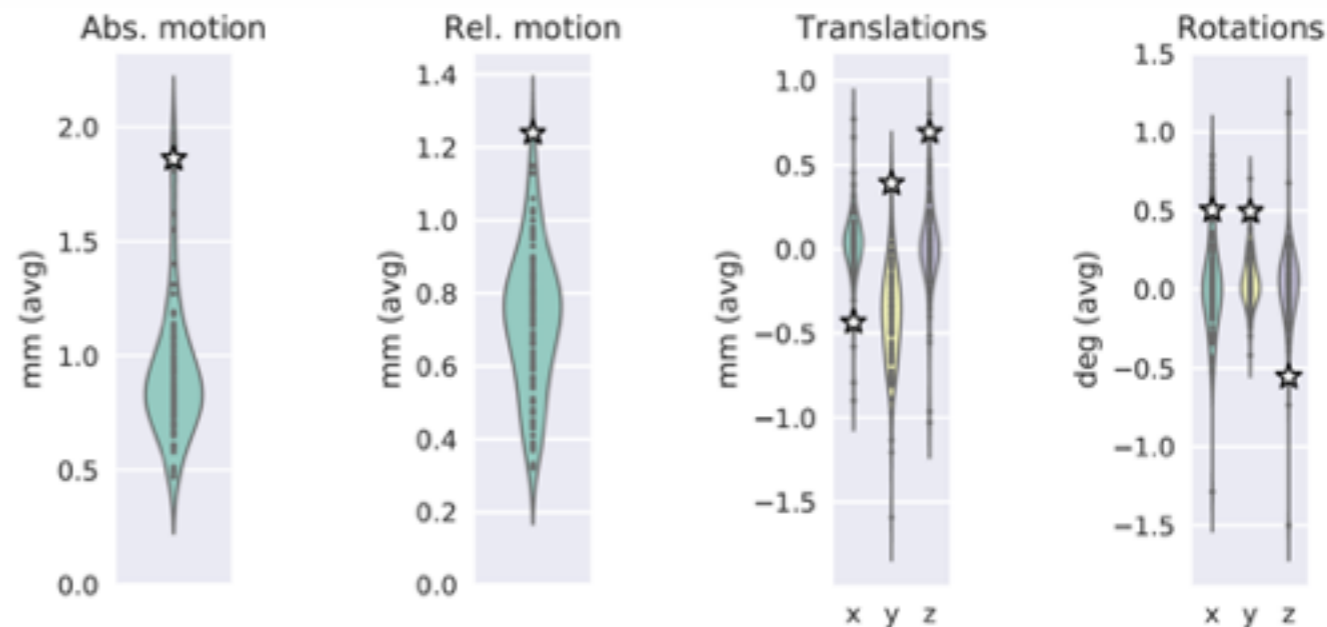
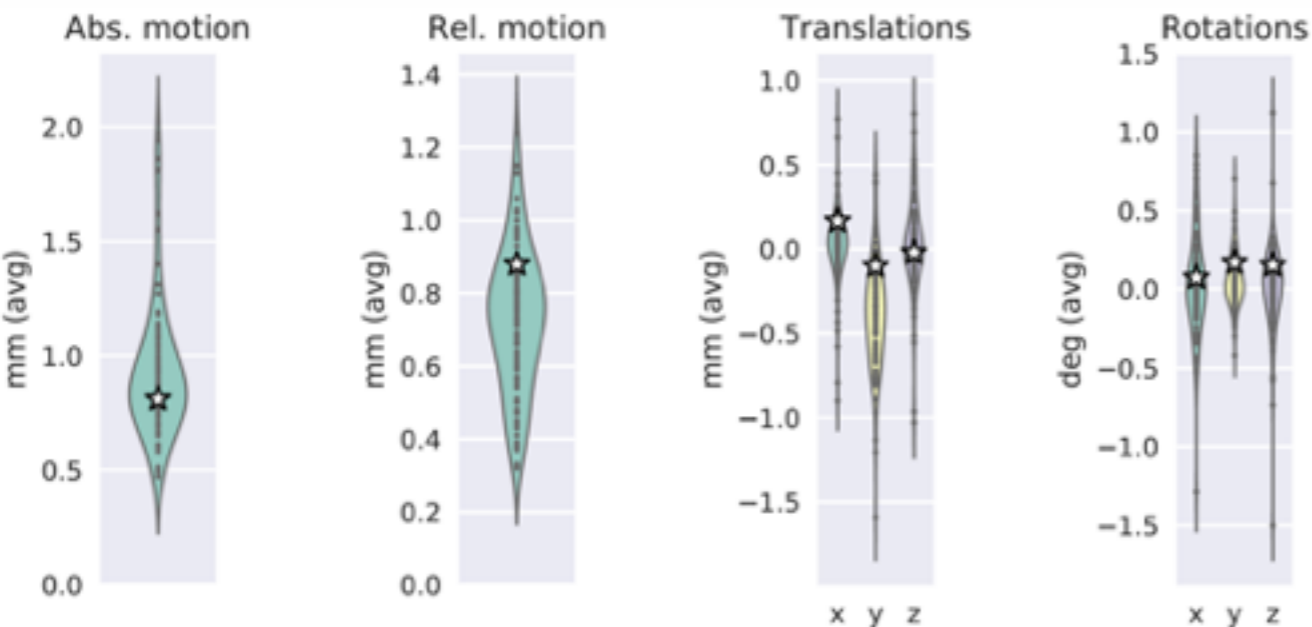
Average abs. motion (mm)	1.86
Average rel. motion (mm)	1.24
Average x translation (mm)	-0.43
Average y translation (mm)	0.39
Average z translation (mm)	0.69
Average x rotation (deg)	0.50
Average y rotation (deg)	0.49
Average z rotation (deg)	-0.55

Within-volume motion

Avg std x translation (mm)	0.08
Avg std y translation (mm)	0.22
Avg std z translation (mm)	0.13
Avg std x rotation (deg)	0.15
Avg std y rotation (deg)	0.09
Avg std z rotation (deg)	0.11

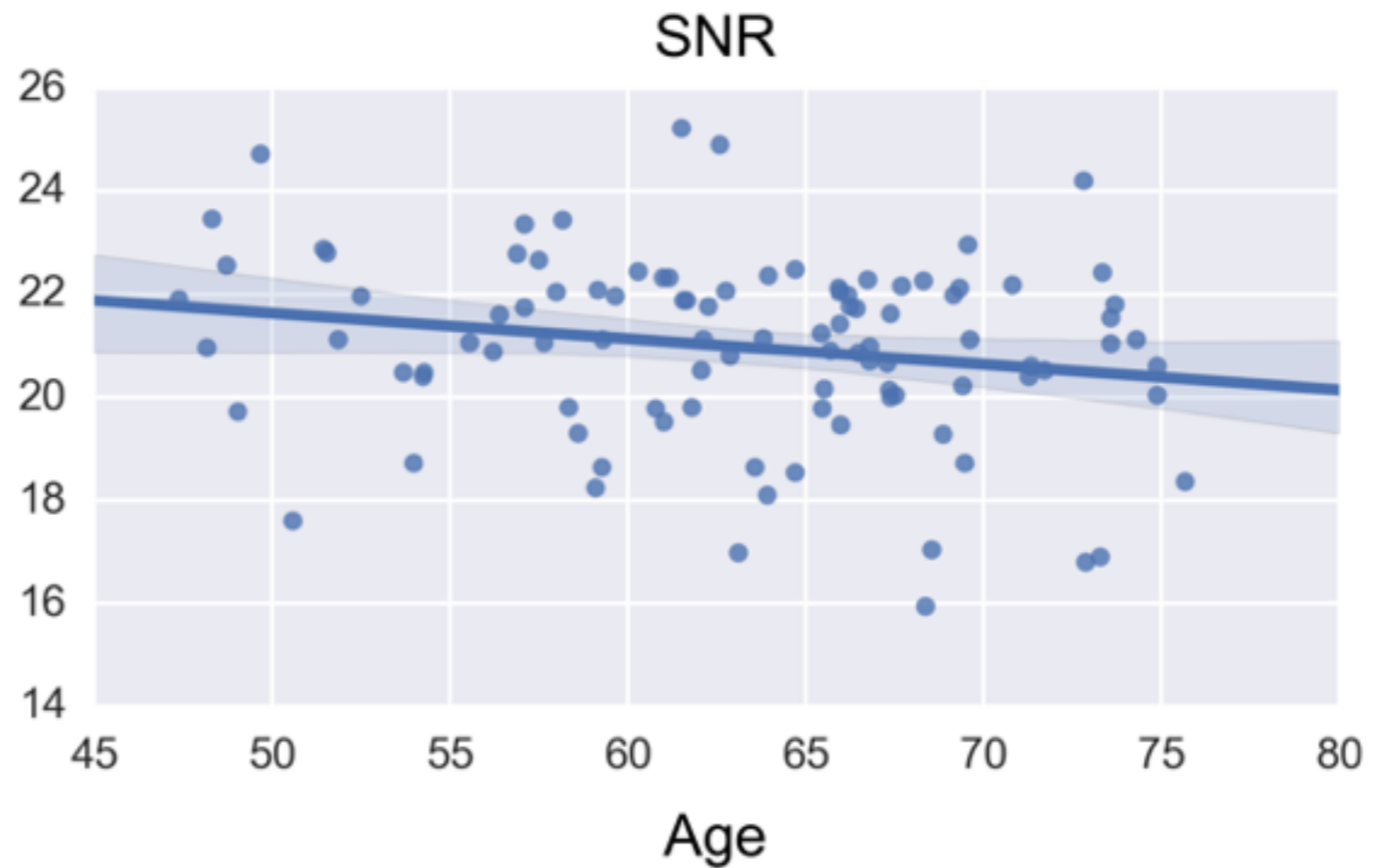
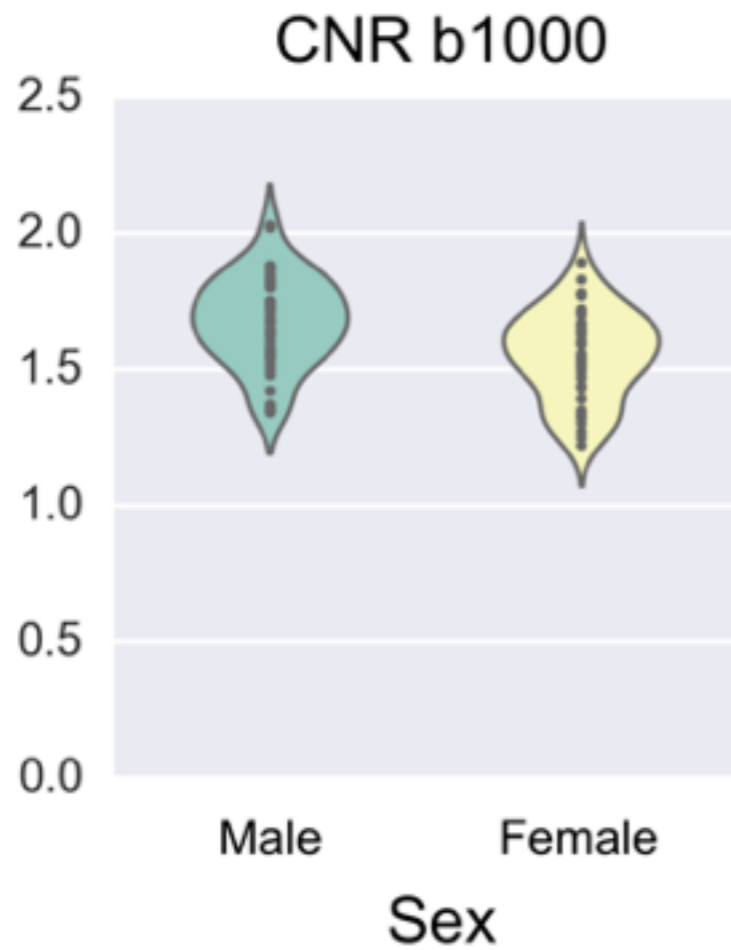
Outliers

Total outliers (%)	2.86
Outliers (b=1000 s/mm ²)	4.69
Outliers (b=2000 s/mm ²)	1.13
Outliers (PE dir=[0. 1. 0.])	2.55
Outliers (PE dir=[0. -1. 0.])	2.66



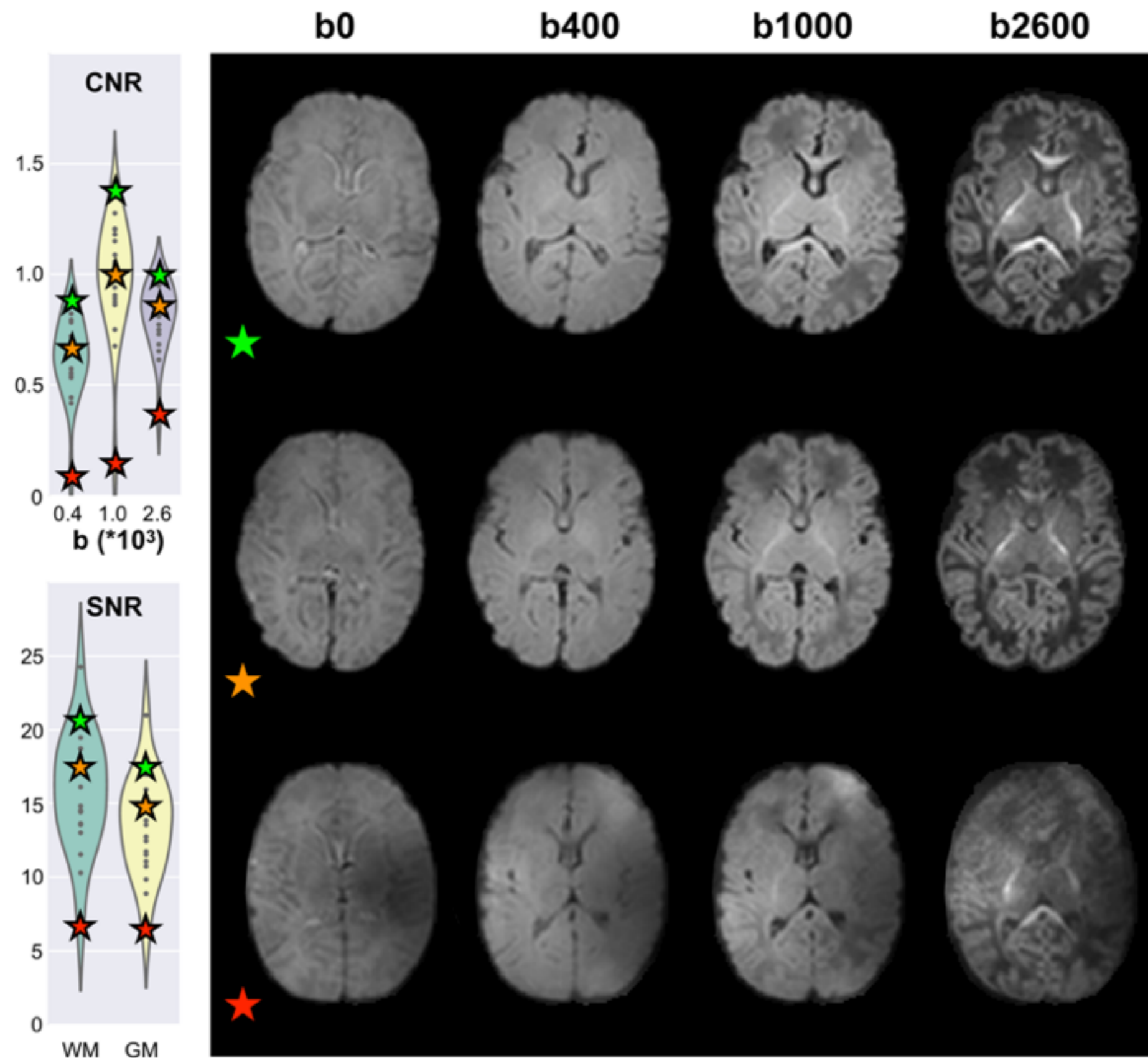


EDDY QC: group report





Data quality illustration





Outline of the talk

- What is the problem with diffusion data?
- Off-resonance field
- Registering diffusion data
- Practicalities
- Some results
- “New” eddy features
 - Movement-induced dropout
 - Intra-volume motion
 - Susceptibility-by-movement



Movement induced dropout

Diffusion encoding

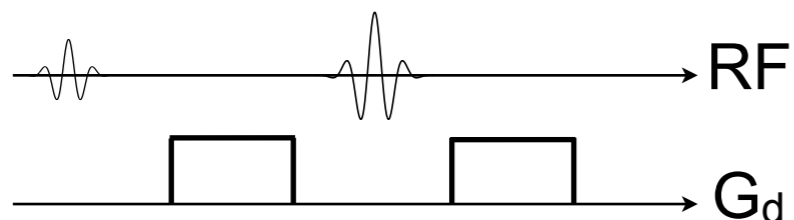
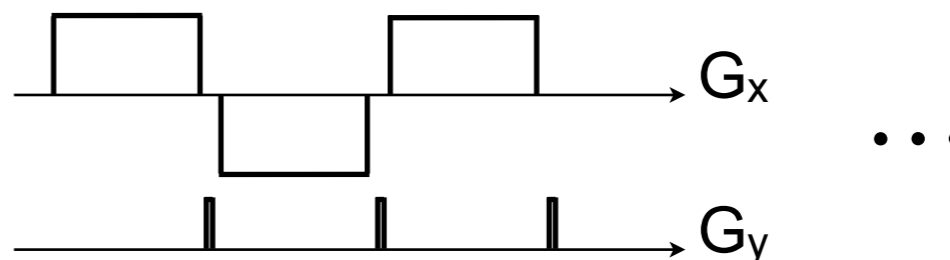
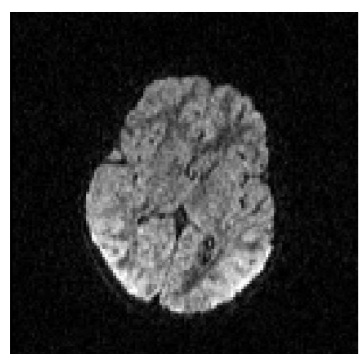


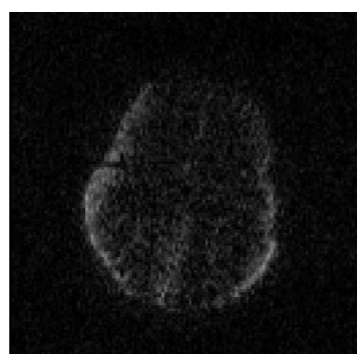
Image encoding



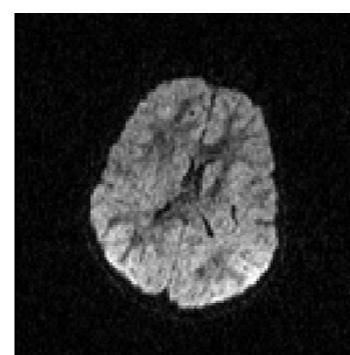
If there is movement during this part...



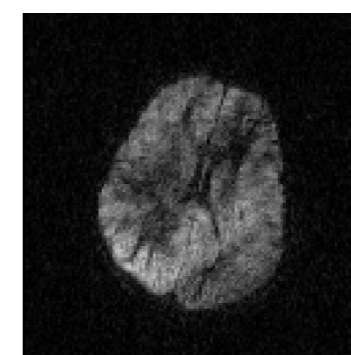
this



can turn
to this



or this



to this

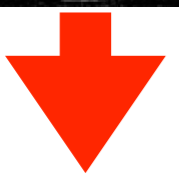
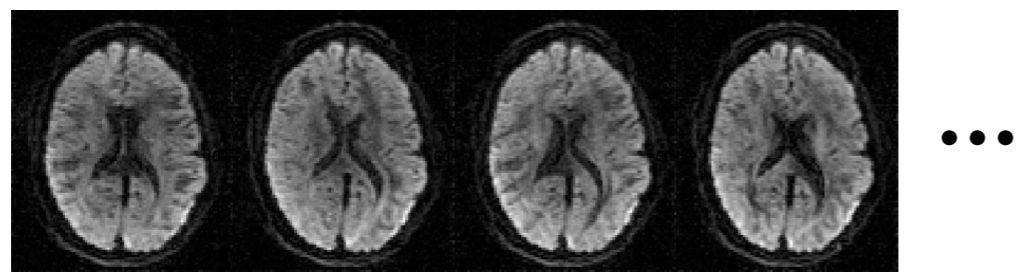


What can eddy do about it?

But first a little recap of eddy

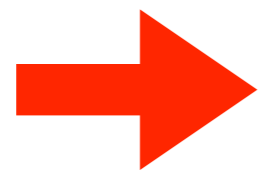
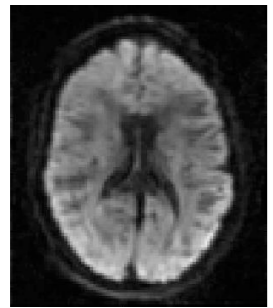
1. For all scans

$[1\ 0\ 0]$ $[.6\ -.4\ -.7]$ $[.8\ .6\ 0]$ $[-.4\ .9\ 0]$...



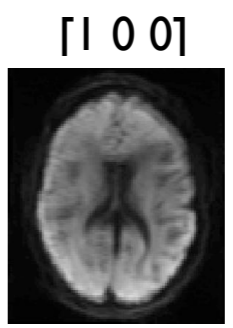
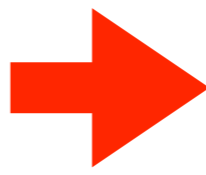
		$\begin{bmatrix} 0.2 \\ 0.6 \\ \vdots \\ 0.1 \end{bmatrix}$
topup	EC	mp

Use susceptibility field and current estimate of EC and movement to “unwarp” scan



Load into prediction maker

2. For all scans



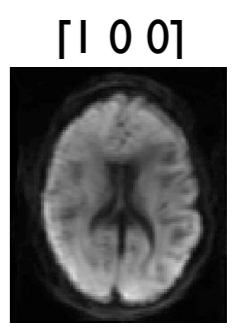
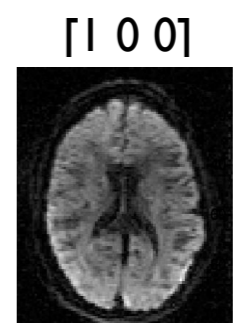
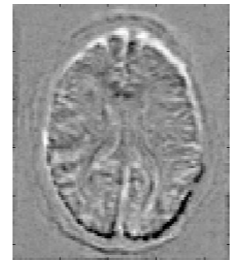
Get prediction

Invert current transform

		$\begin{bmatrix} 0.2 \\ 0.6 \\ \vdots \\ 0.1 \end{bmatrix}$
topup	EC	mp

Use difference to update EC and mp

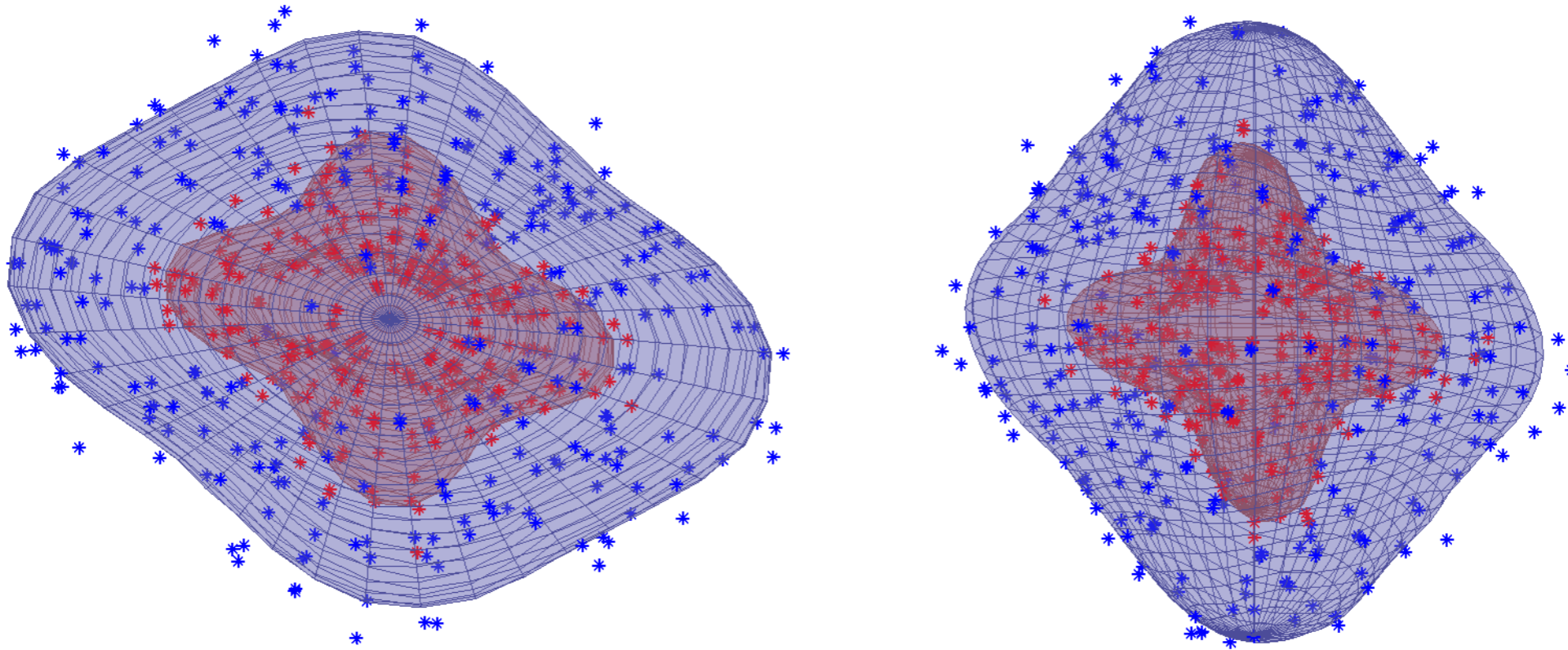
Get prediction in scan space



Compare to scan



How are the predictions made?



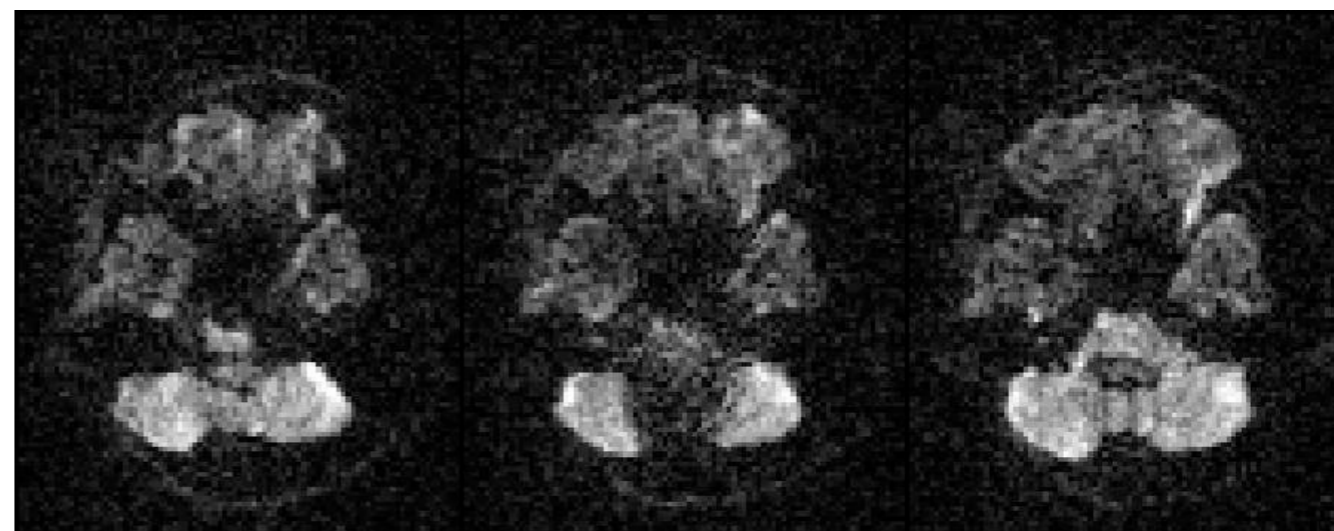
A Gaussian process that simply assumes that the signal varies smoothly as we move in Q-space
Very few assumptions. Hyperparameters calculated by leave-one-out.

$$\hat{y}_{\mathbf{g}} = K(\mathbf{g}, \mathbf{G}) [K(\mathbf{G}, \mathbf{G}) + \sigma^2 \mathbf{I}]^{-1} \mathbf{y}$$

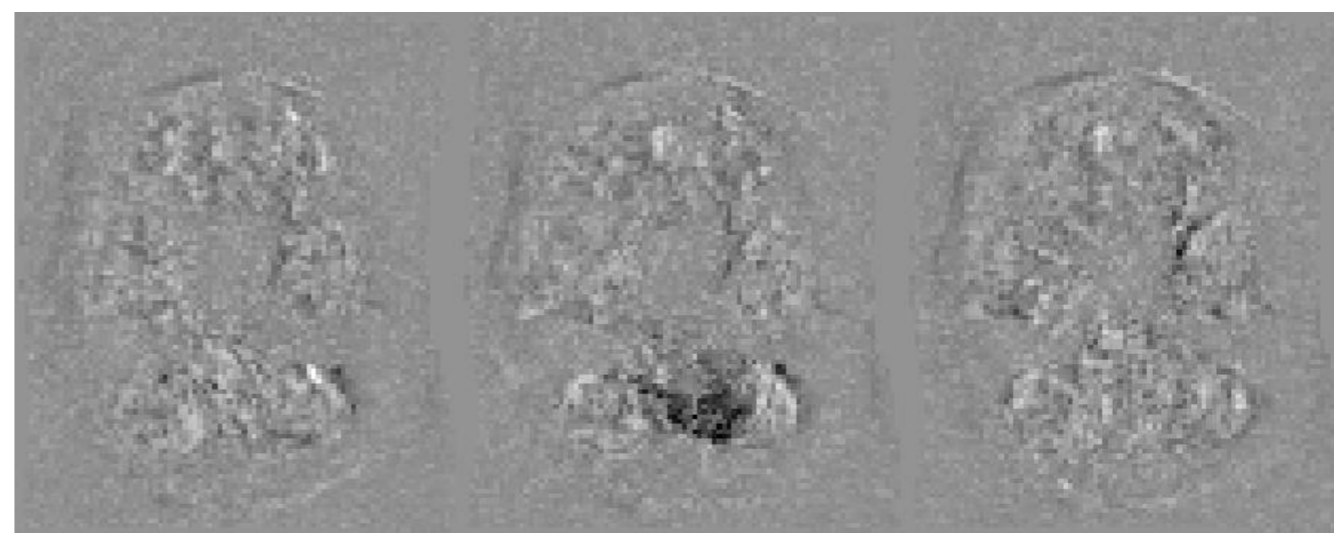


Outlier detection

Observed data



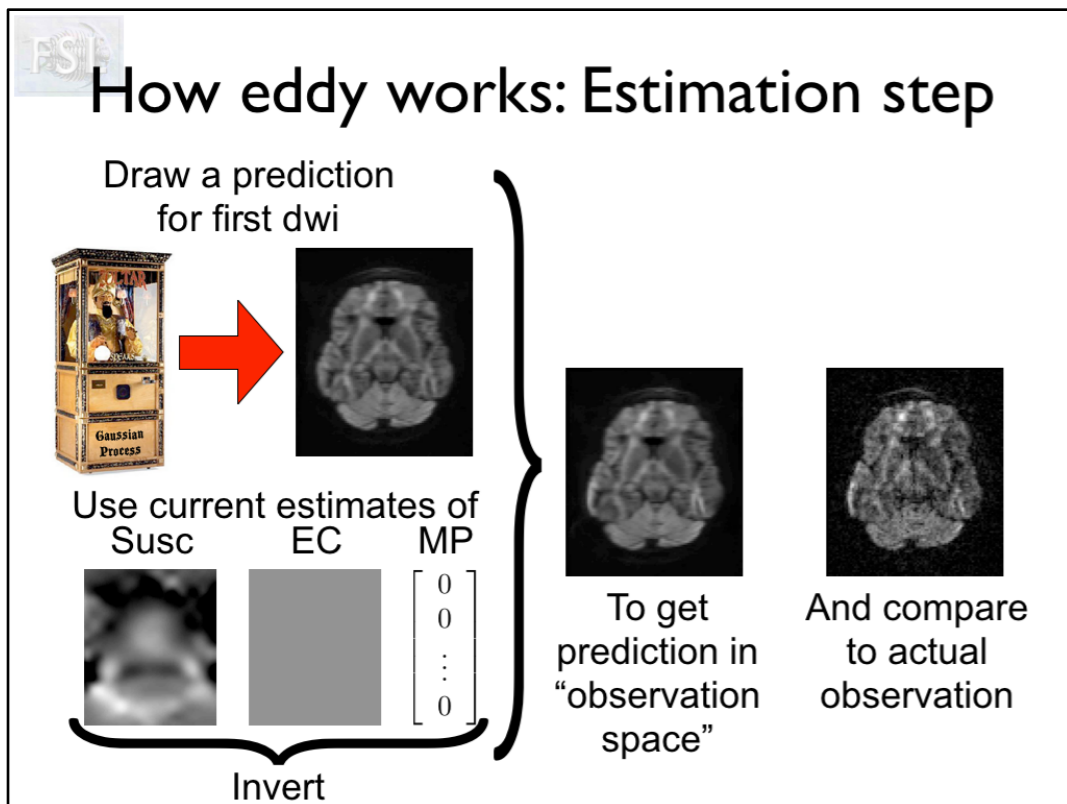
Observed - predicted



$$\bar{x} = 0.084$$

$$\bar{x} = -0.791$$

$$\bar{x} = -0.125$$

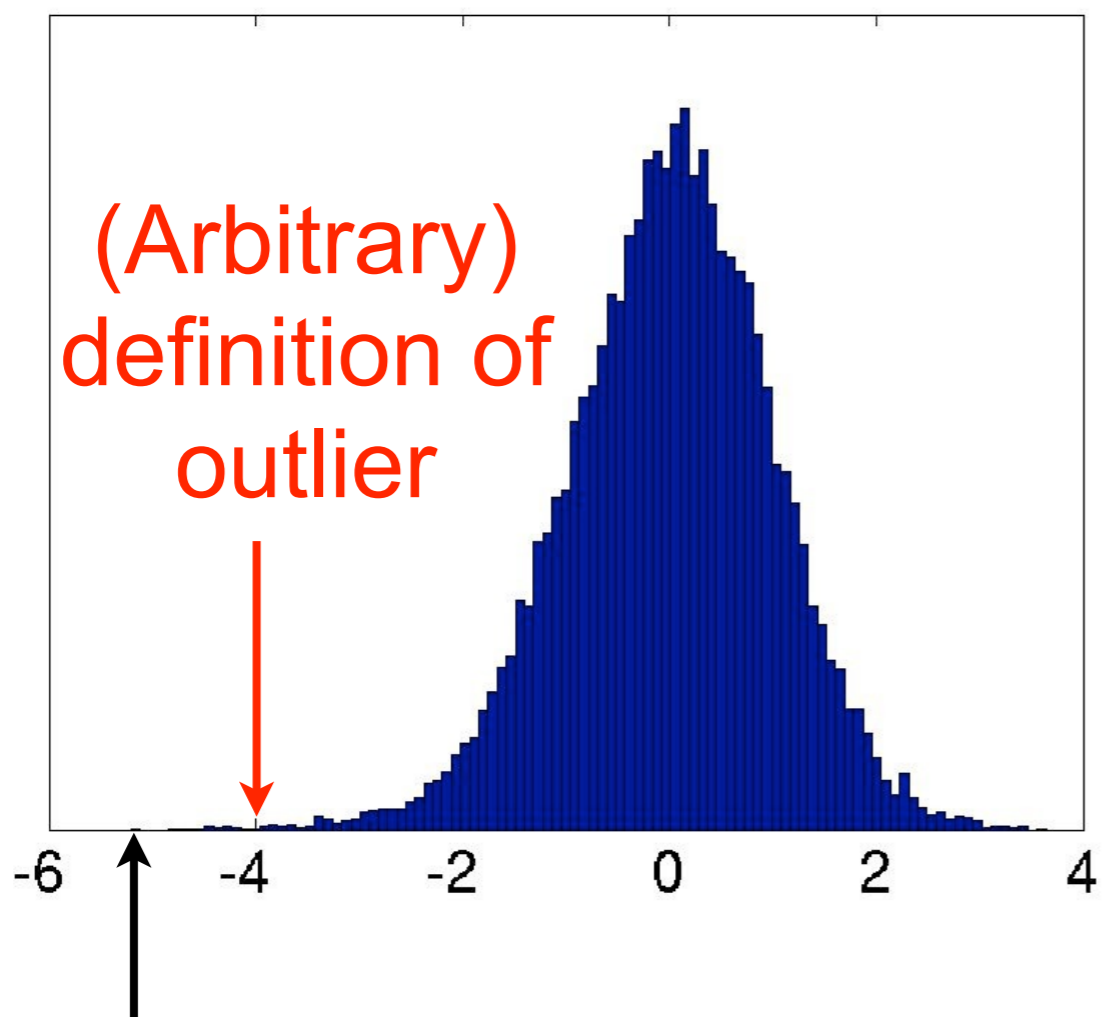


Remember that we do all comparisons in observation space.

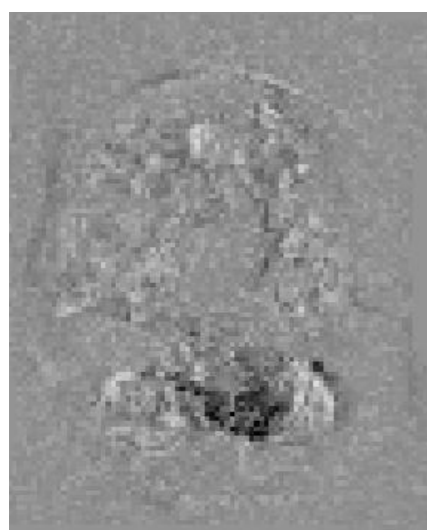
This allows us to calculate the per-slice mean difference between observation and prediction



Outlier detection



We can calculate the mean difference for every slice in every volume and get an empirical distribution that we can convert to z-scores



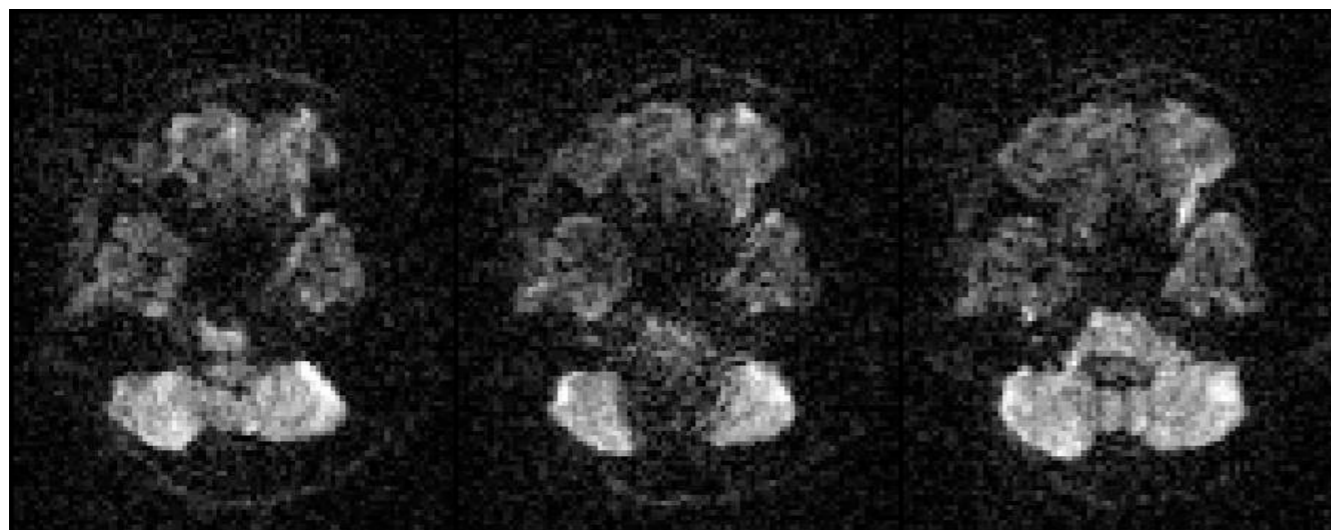
We can define an outlier slice as one with a z-score above an (arbitrary) threshold. We then have a choice of reporting outliers and/or replacing them with their predictions.

Worst slice

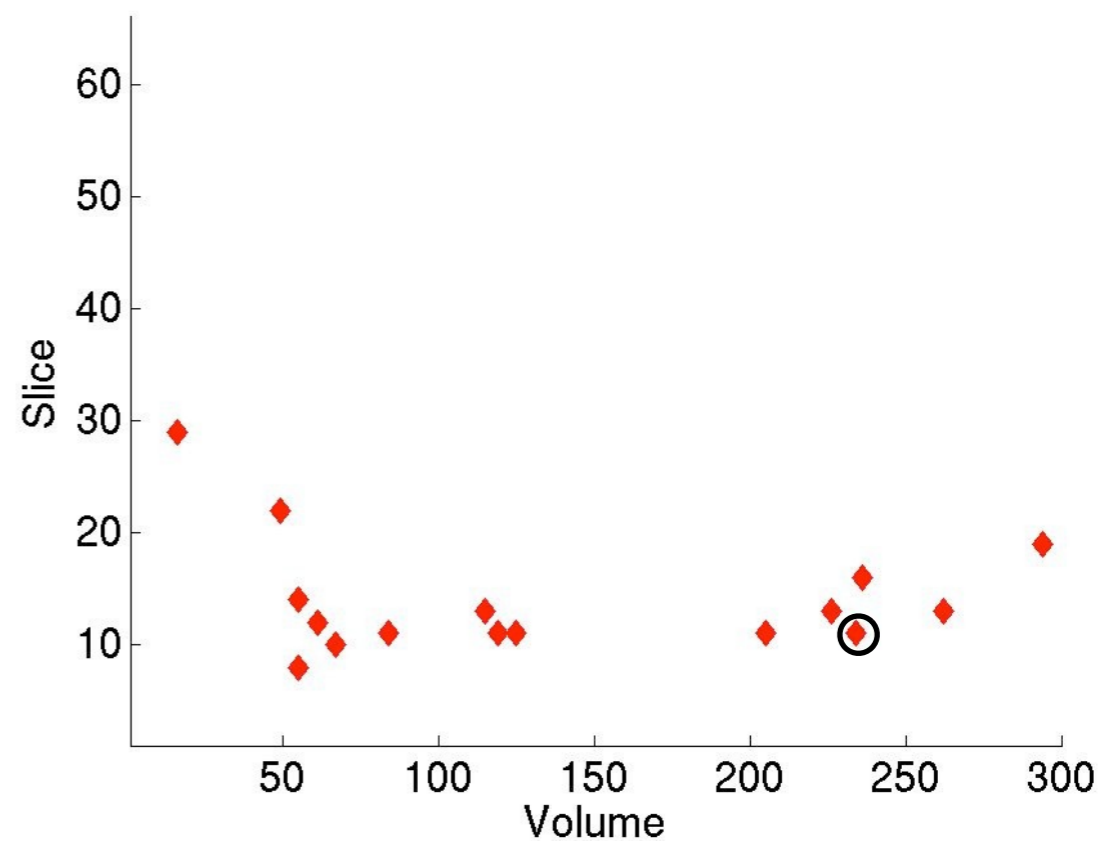
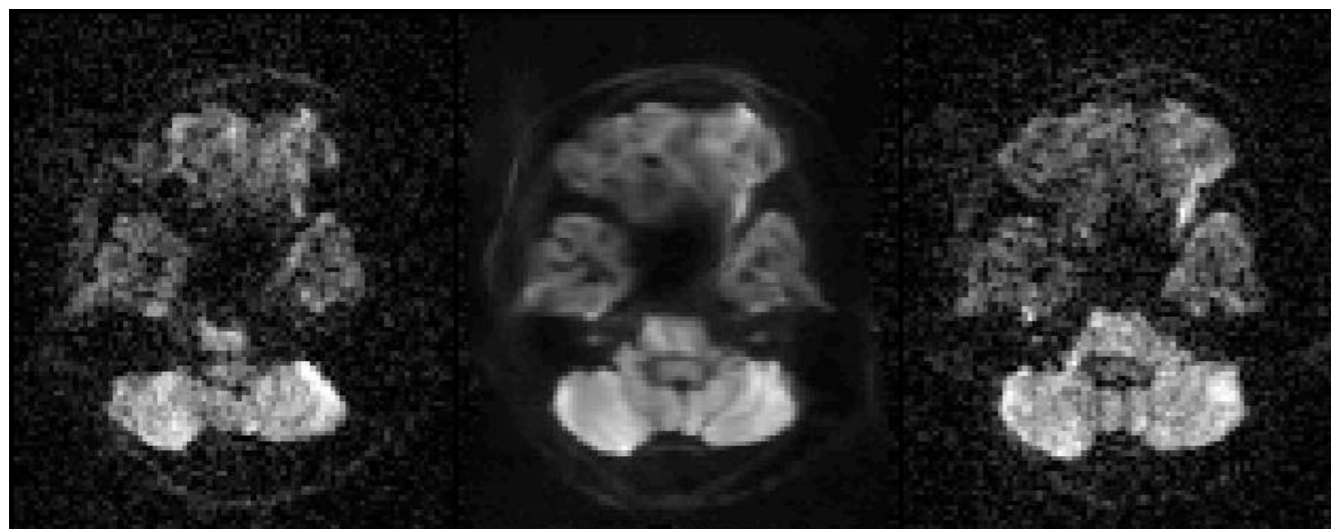


Outlier detection

Original data



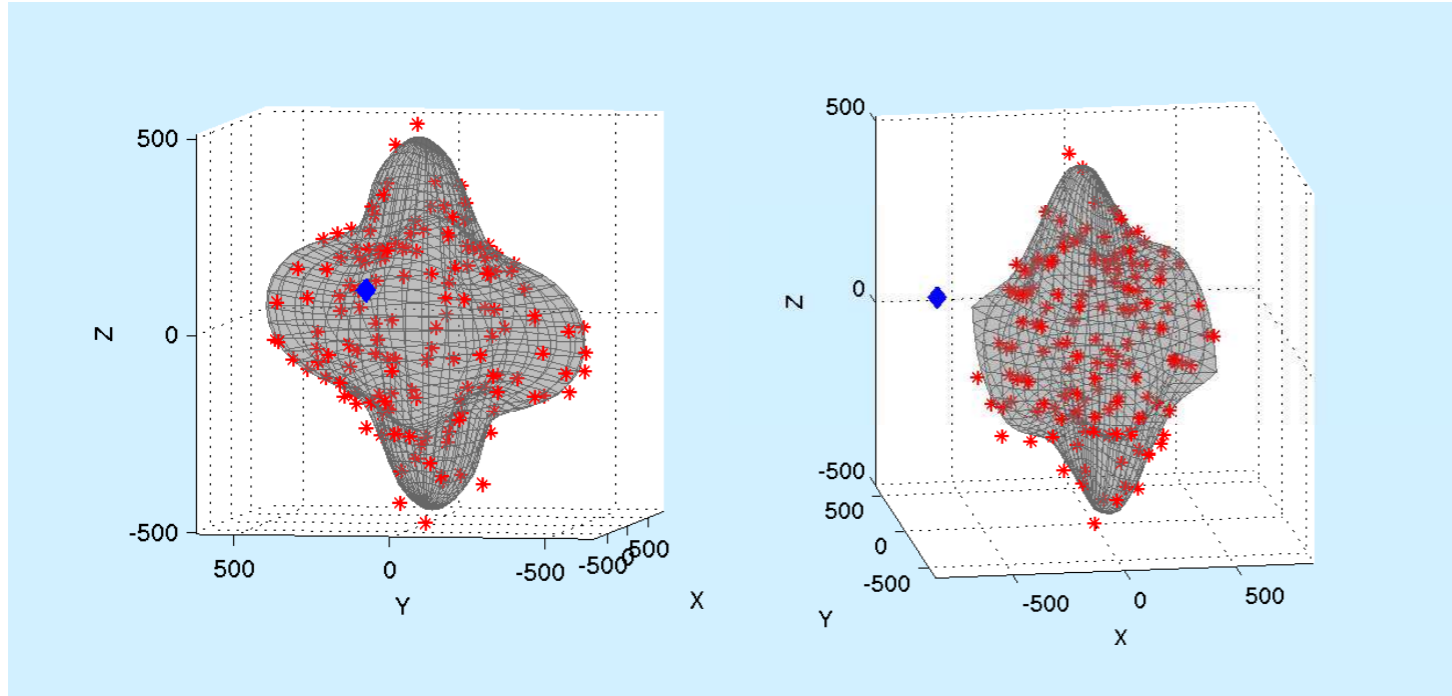
Data after replacement



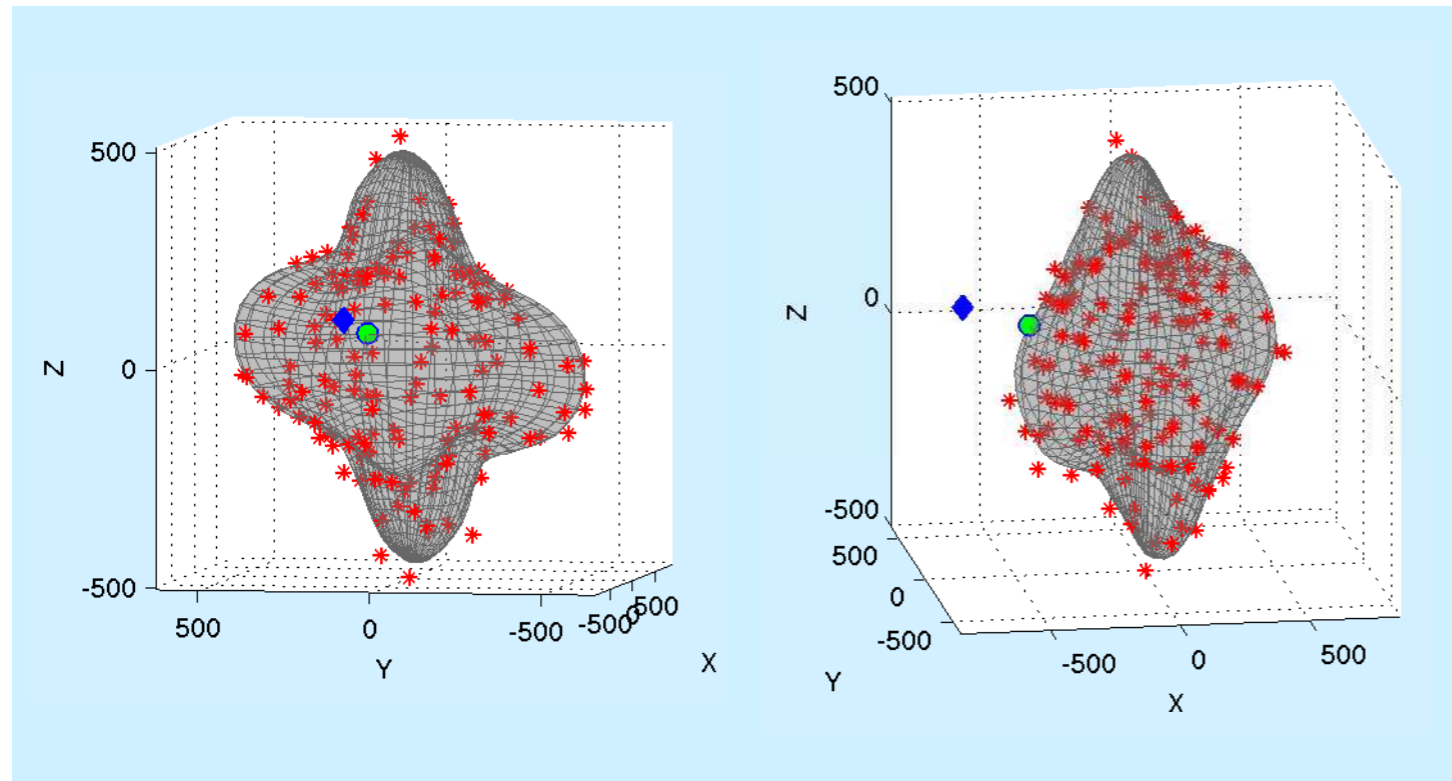
Outliers for a very still volunteer. Outliers mainly in basal slices.



How to make the “right” prediction



The outlier skews the predictions, but is still recognisable as an outlier



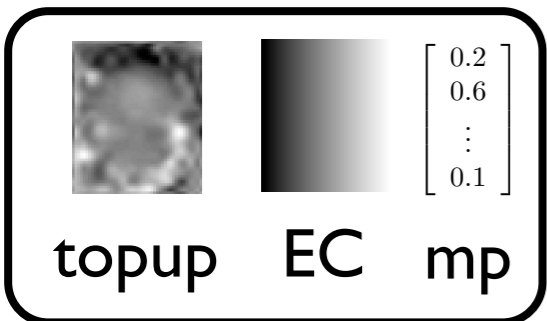
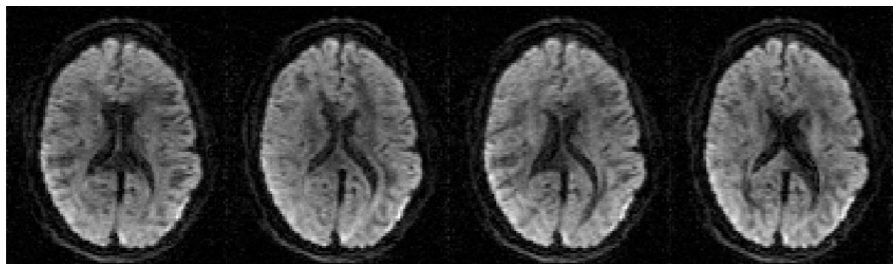
Remove the outlier and recalculate the “model”. The prediction is taken from this new “model”.



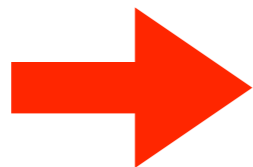
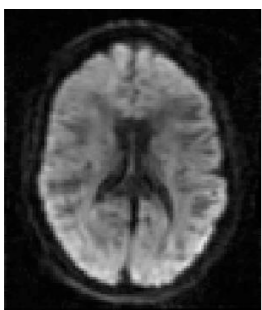
eddy revisited

1. For all scans

[1 0 0] [0.6 -0.4 -0.7] [0.8 0.6 0] [-0.4 0.9 0] ...

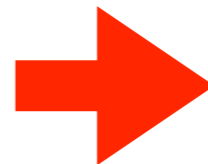


Use susceptibility field and current estimate of EC and movement to “unwarp” scan

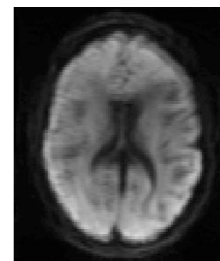


Load into prediction maker

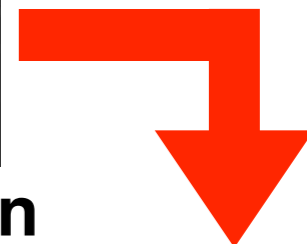
2. For all scans



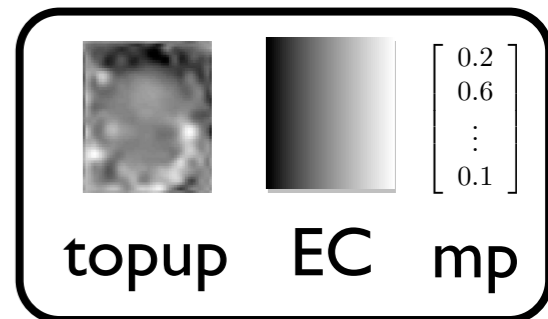
[1 0 0]



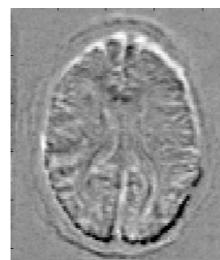
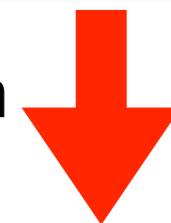
Get prediction



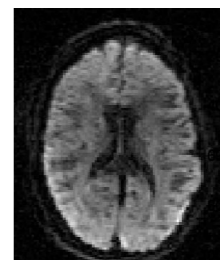
Invert current transform
Use difference to update EC, mp and outlier list



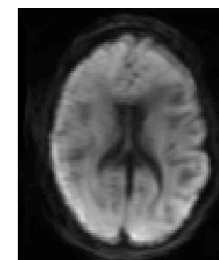
Get prediction in scan space



[1 0 0]



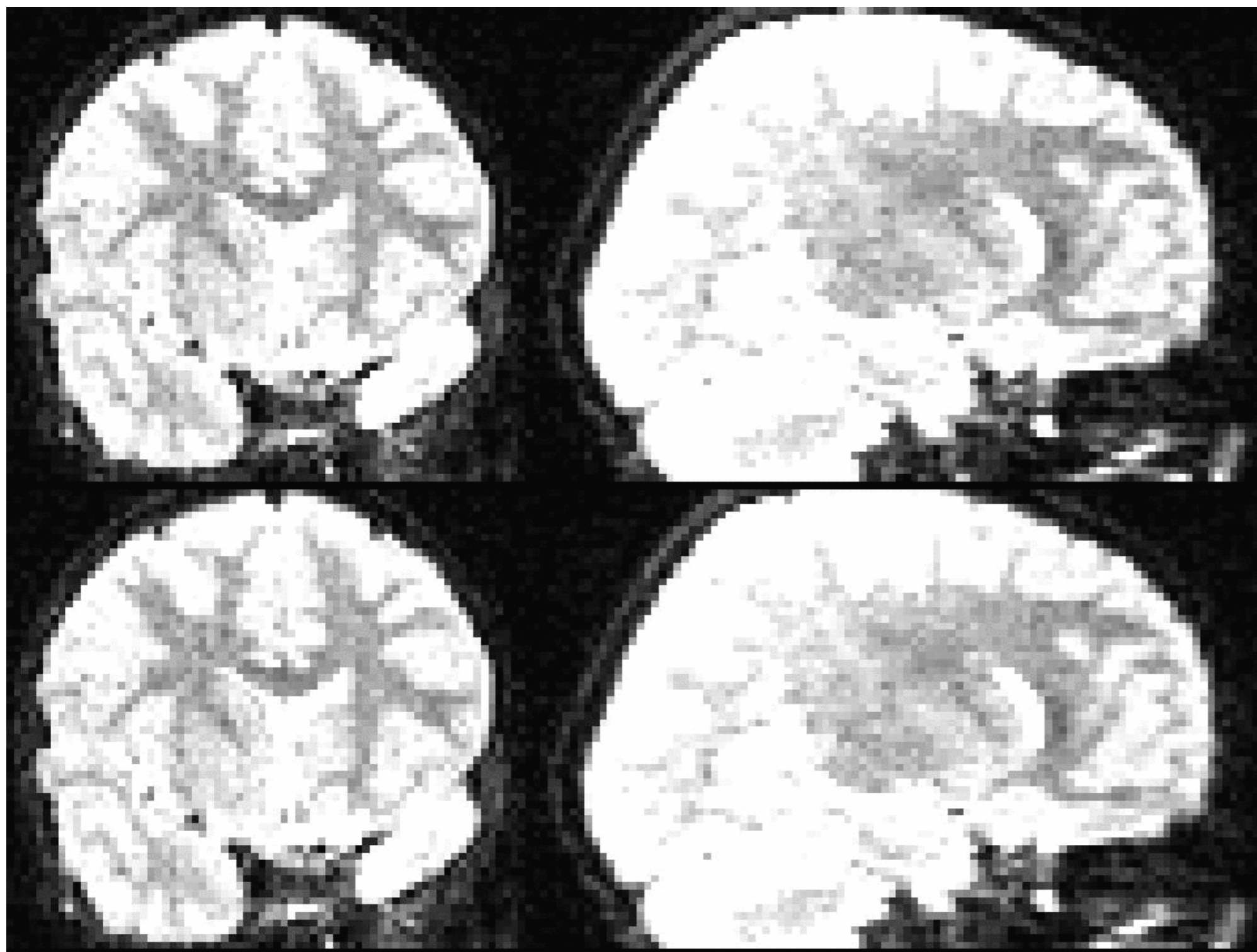
[1 0 0]



Compare to scan



Norwegian data. 32 directions. Hundreds of children.



Eight year old who gets tired towards the end of scanning

After outlier detection and replacement by eddy



Outline of the talk

- What is the problem with diffusion data?
- Off-resonance field
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 - Movement-induced dropout
 - **Intra-volume motion**
 - Susceptibility-by-movement



Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.

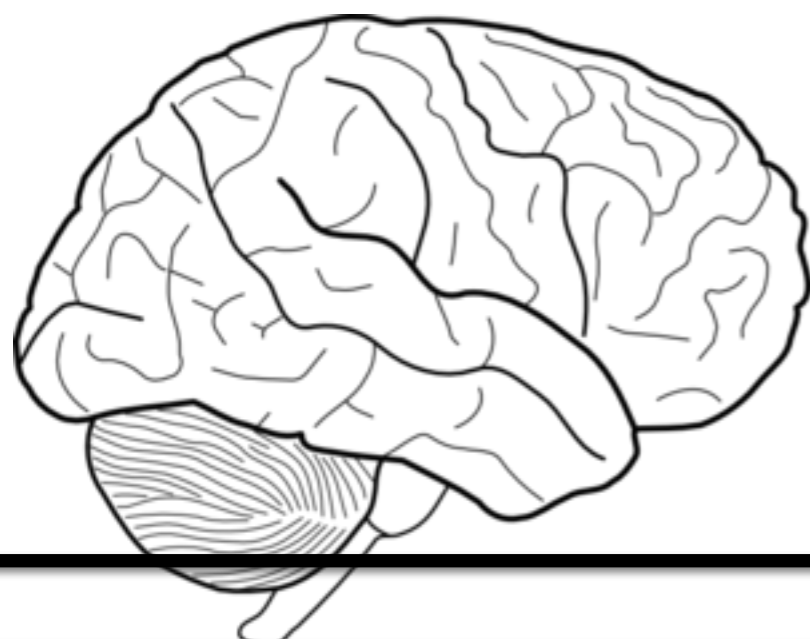


This is the brain
we set out to
image



Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.



This is the brain
we set out to
image



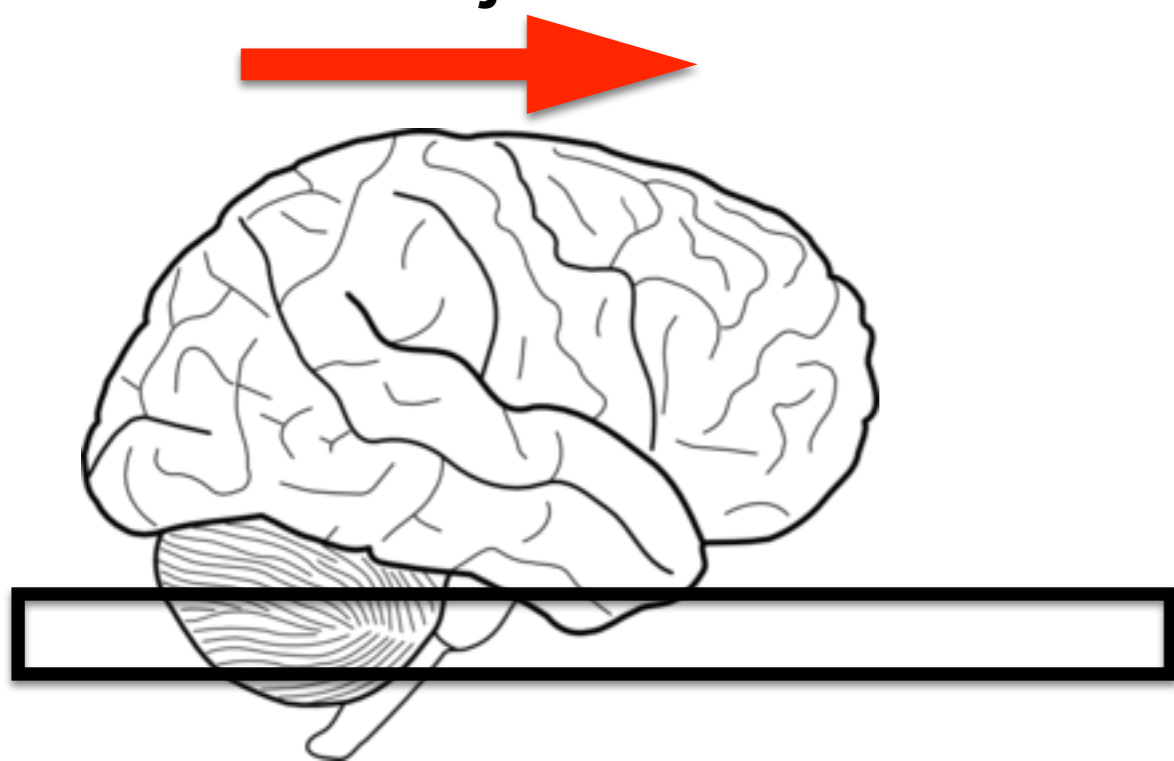
And here we have
acquired the first
slice



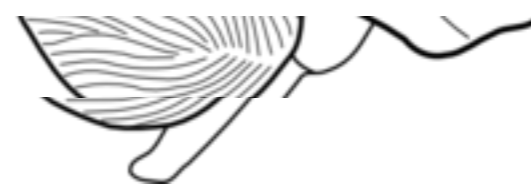
Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.

But the subject moves



This is the brain
we set out to
image



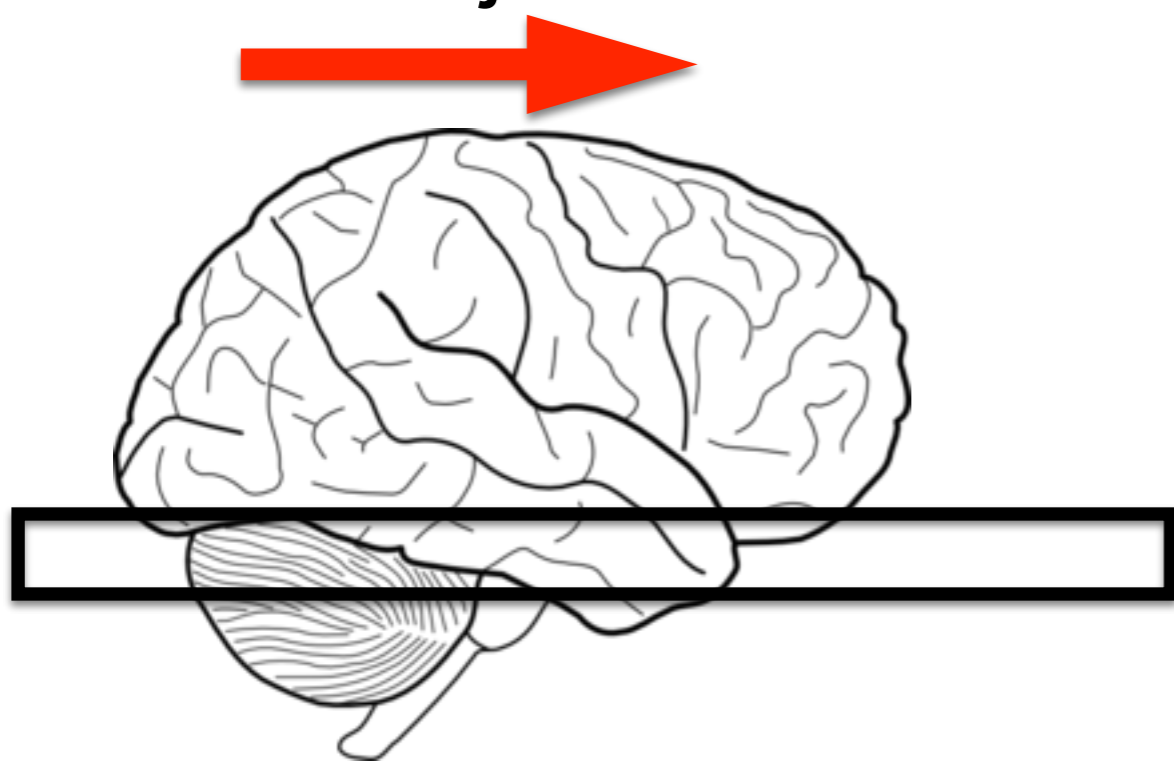
So the brain is
offset in the
second slice



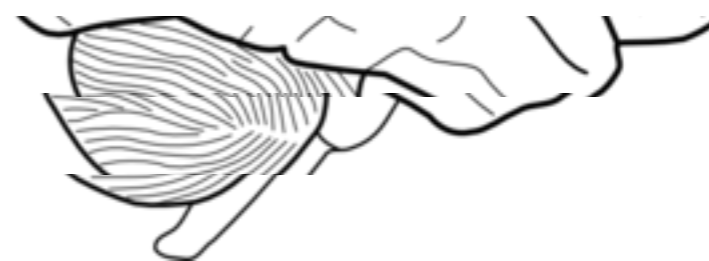
Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.

But the subject moves



This is the brain
we set out to
image



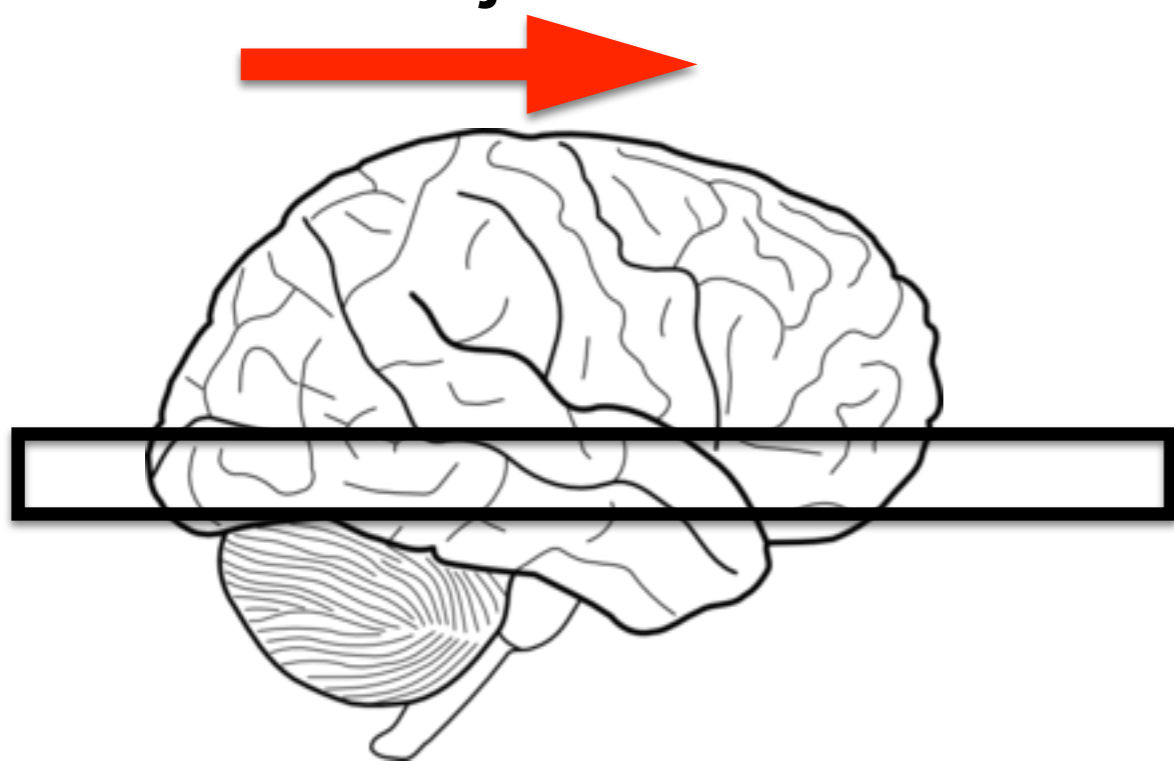
And even more so
in the third slice



Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.

But the subject moves



This is the brain
we set out to
image



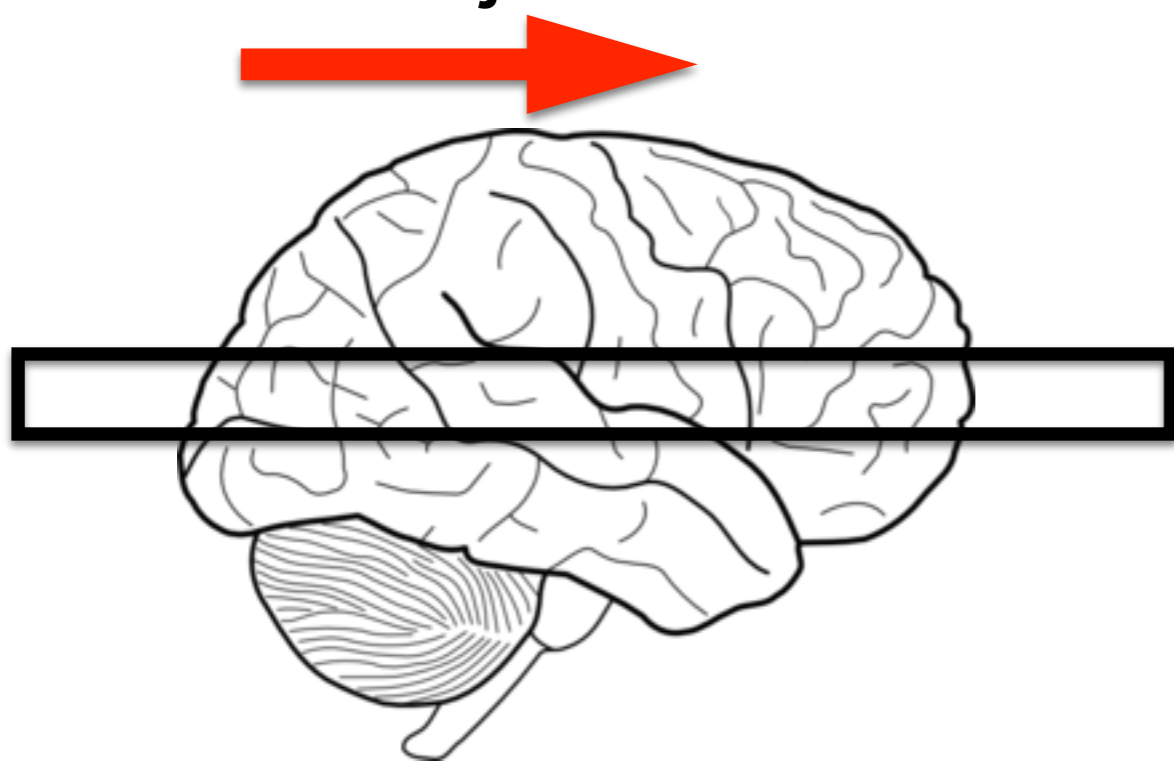
And more ...



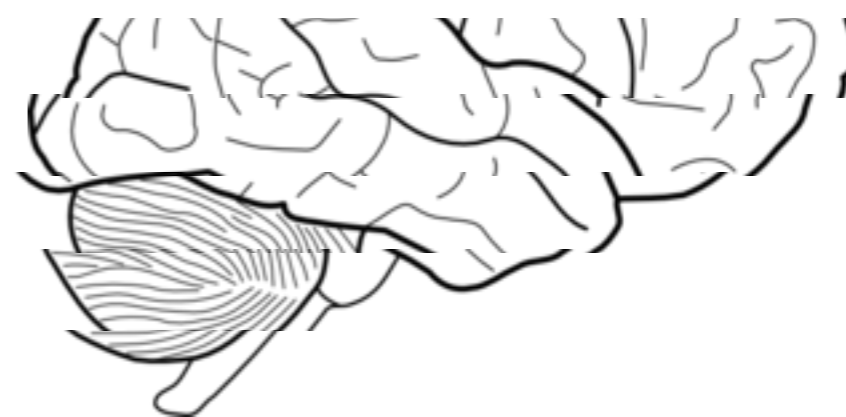
Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.

But the subject moves



This is the brain
we set out to
image

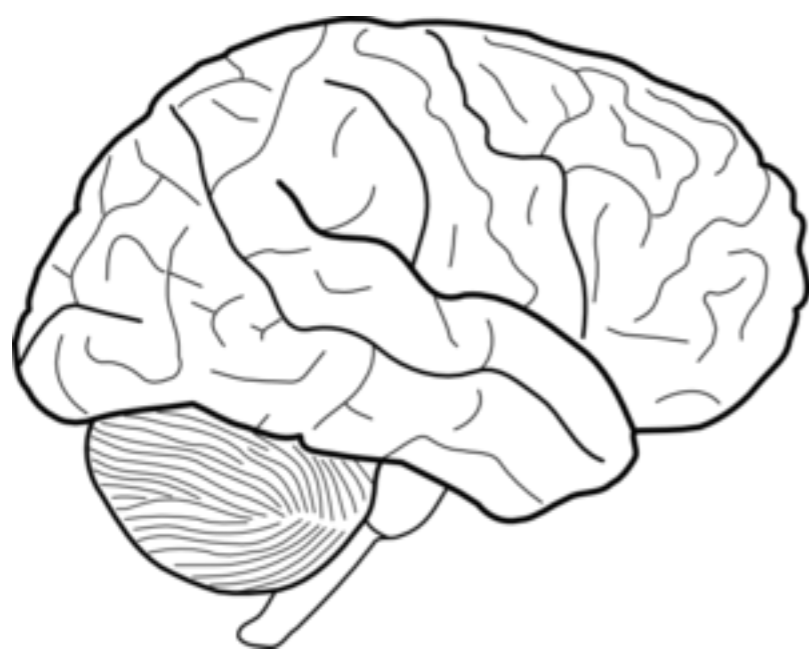


... and more ...



Intra-volume movement

One of the (possibly naive) assumptions of most movement correction is that any movement is instantaneous and occurs between the acquisition of consecutive volumes.



This is the brain
we set out to
image

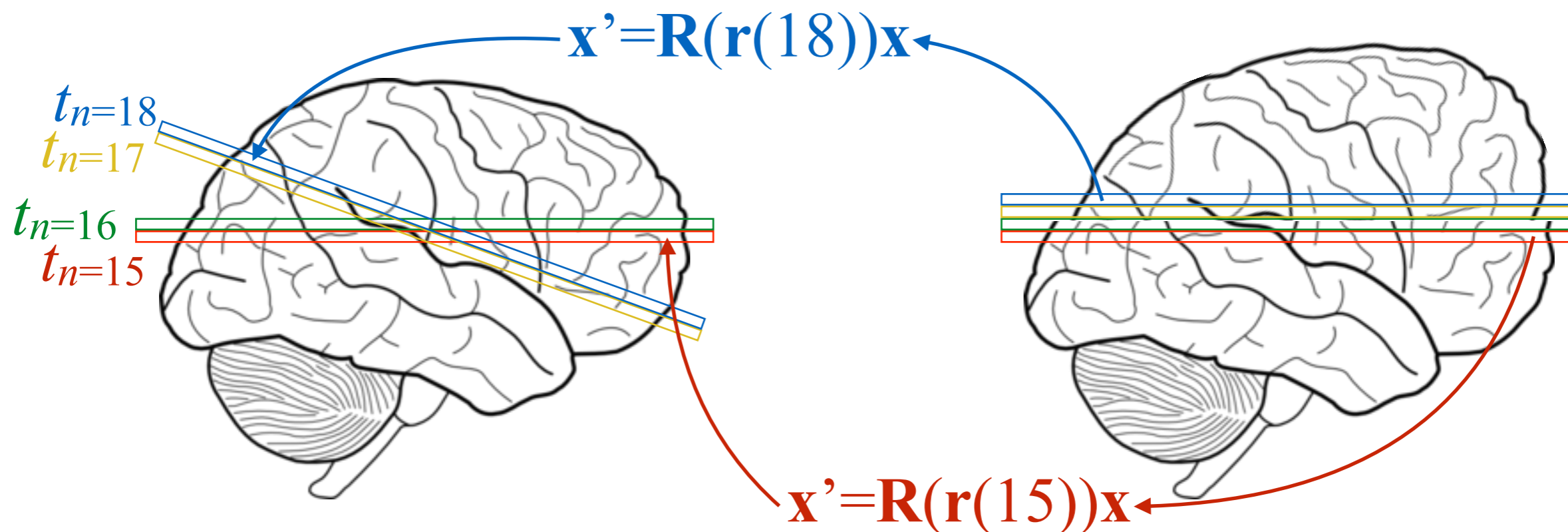


etc.



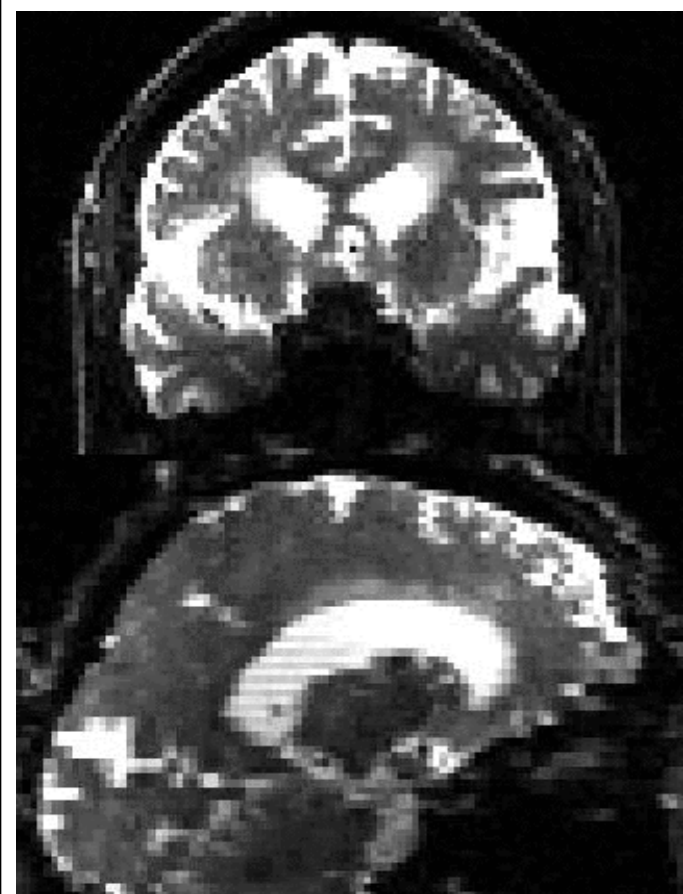
Intra-volume movement

- This is known as the “slice-to-vol” problem or the “intra-volume movement” problem.
- The new version of eddy addresses this problem.
- It estimates the slice wise movement through the same Gaussian Process based forward model.





Intra-volume movement

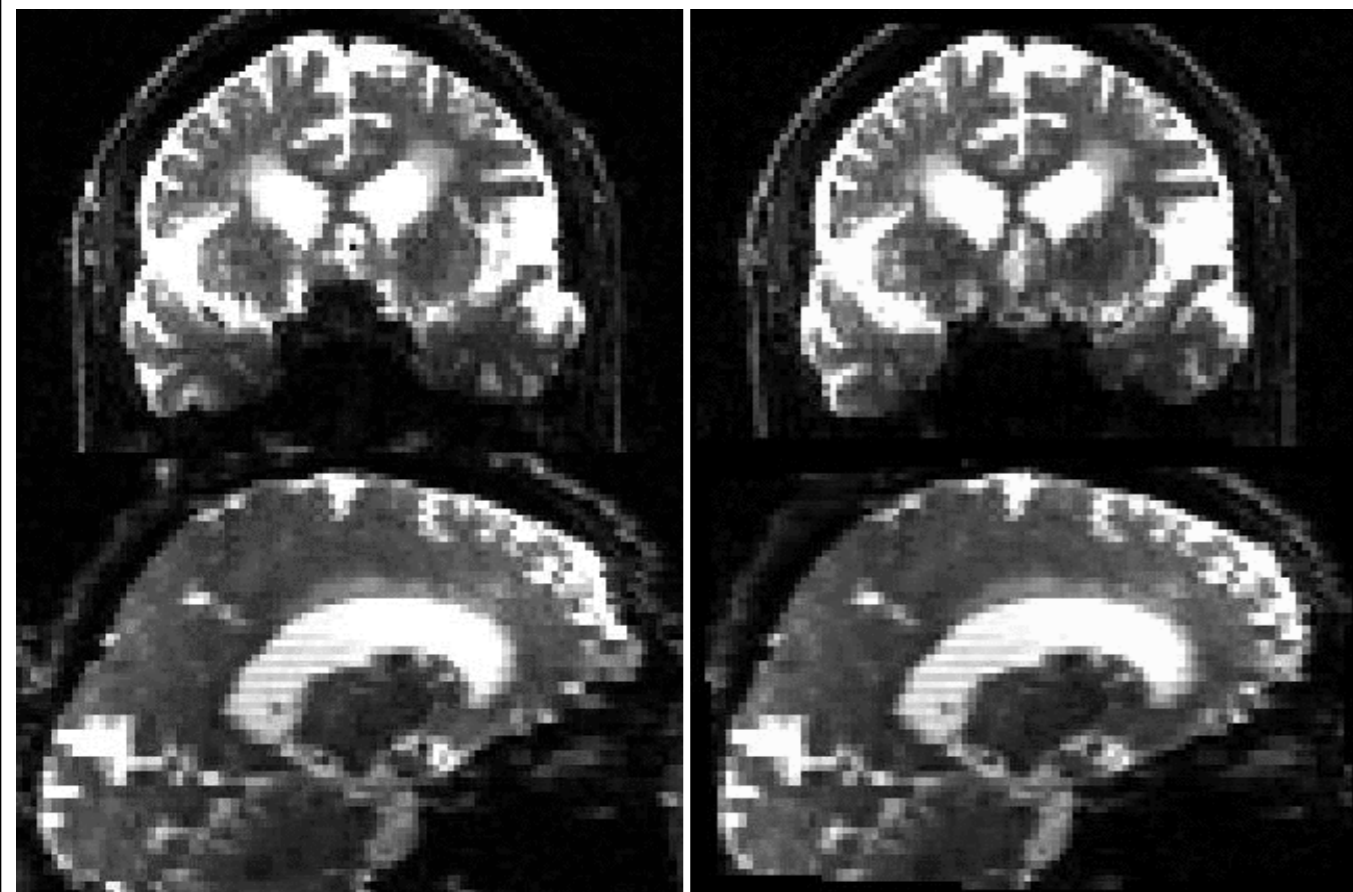


Original data

Problematic elderly subject. Lots of movement induced signal loss and intravolume movement



Intra-volume movement



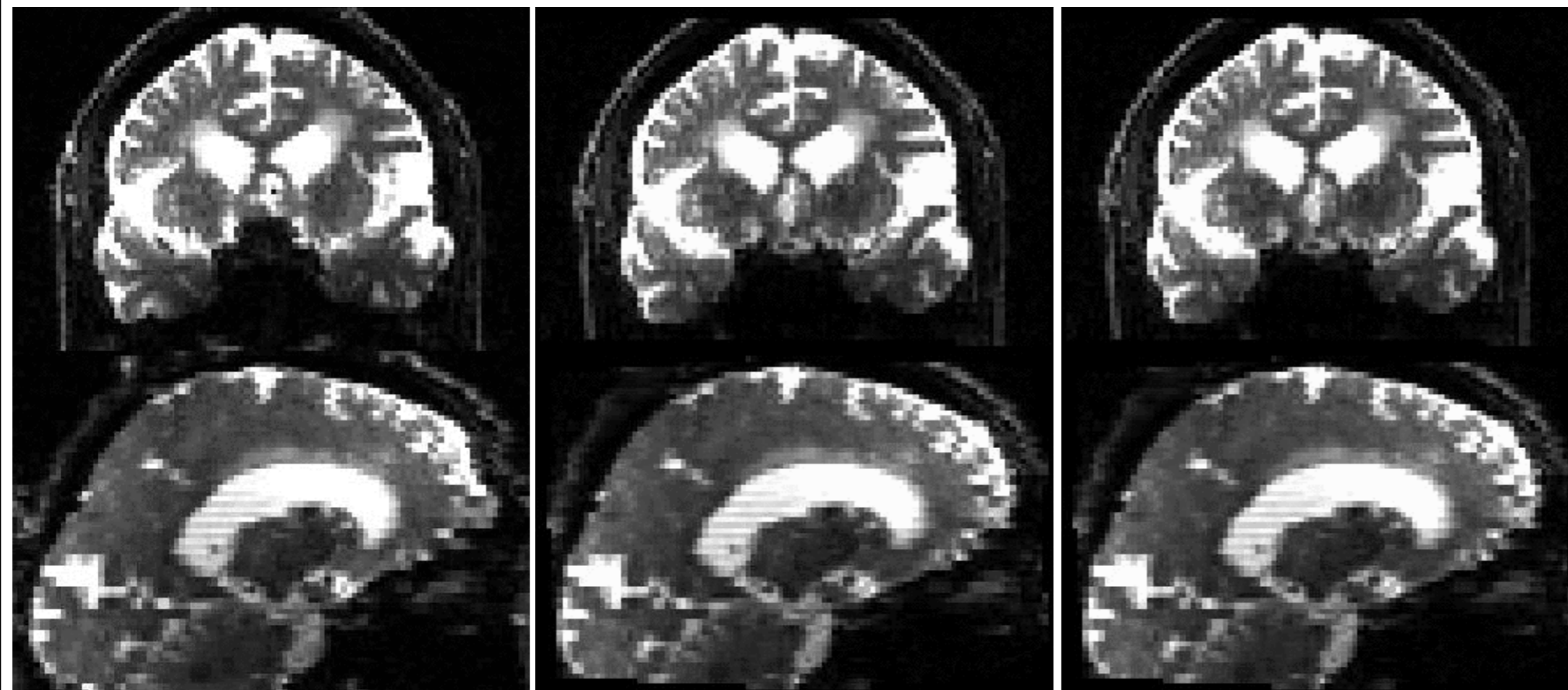
Original data

After correction
without outlier
correction

Problematic elderly subject. Lots of movement induced signal loss and intravolume movement



Intra-volume movement



Original data

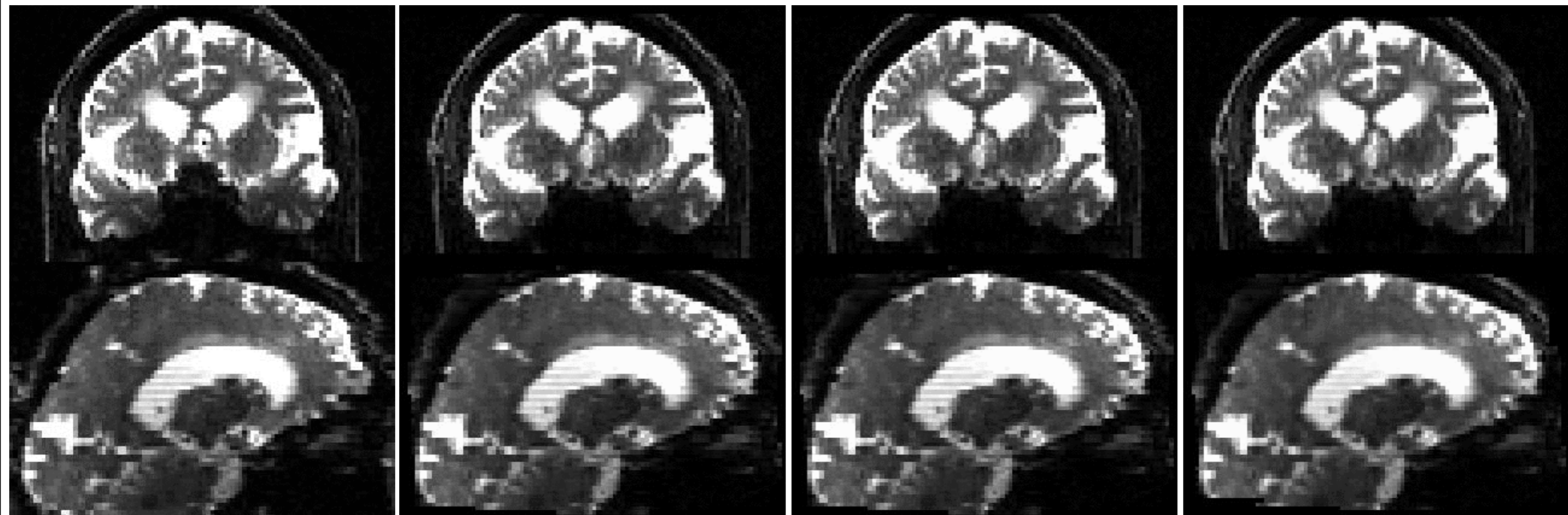
After correction
without outlier
correction

After correction
with outlier
replacement

Problematic elderly subject. Lots of movement induced signal loss and intravolume movement



Intra-volume movement



Original data

After correction
without outlier
correction

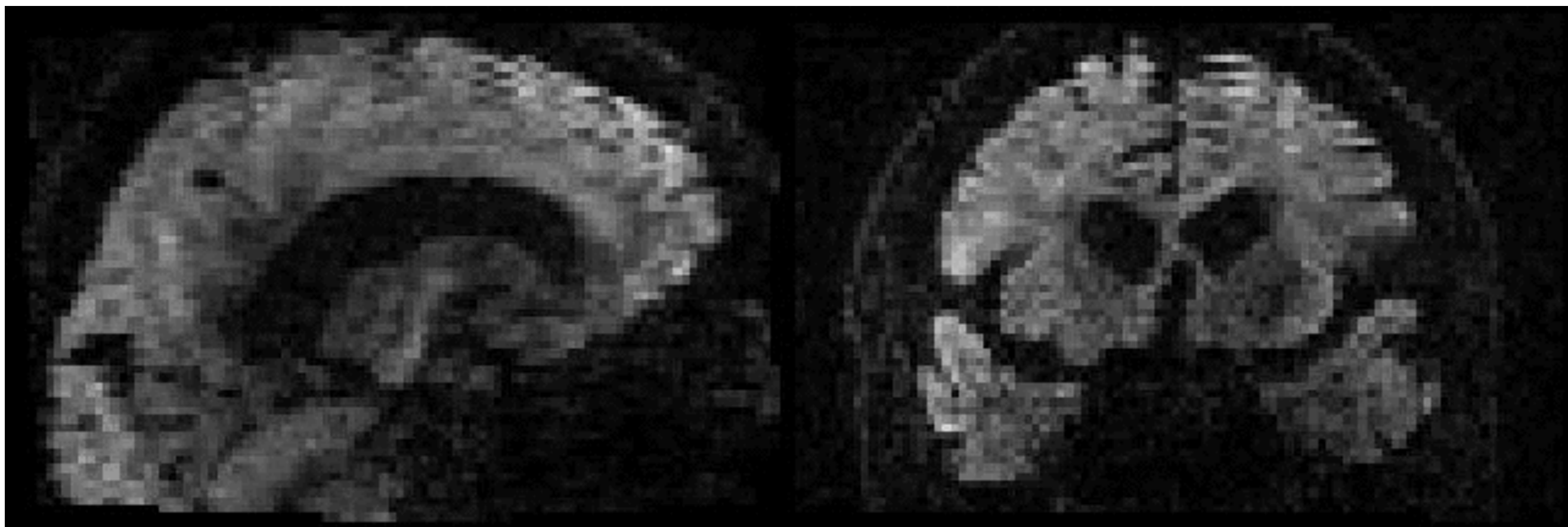
After correction
with outlier
replacement

After
intravolume
movement
correction.

Problematic elderly subject. Lots of movement induced signal loss and intravolume movement



Intra-volume movement



Highlighting the difference between just OLR and OLR combined with S2V correction

Problematic elderly subject. Lots of movement induced signal loss and intravolume movement

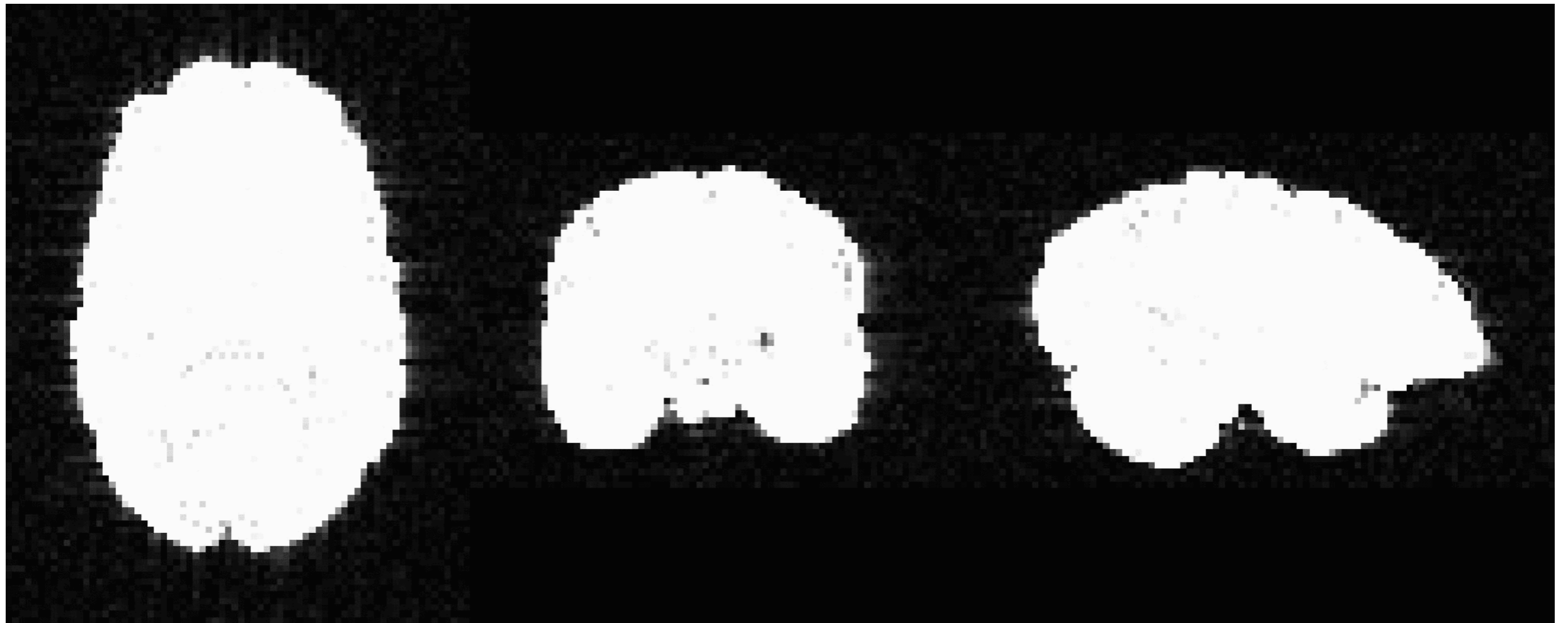


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 - Movement-induced dropout
 - Intra-volume motion
 - **Susceptibility-by-movement**



Some data with lots of movement

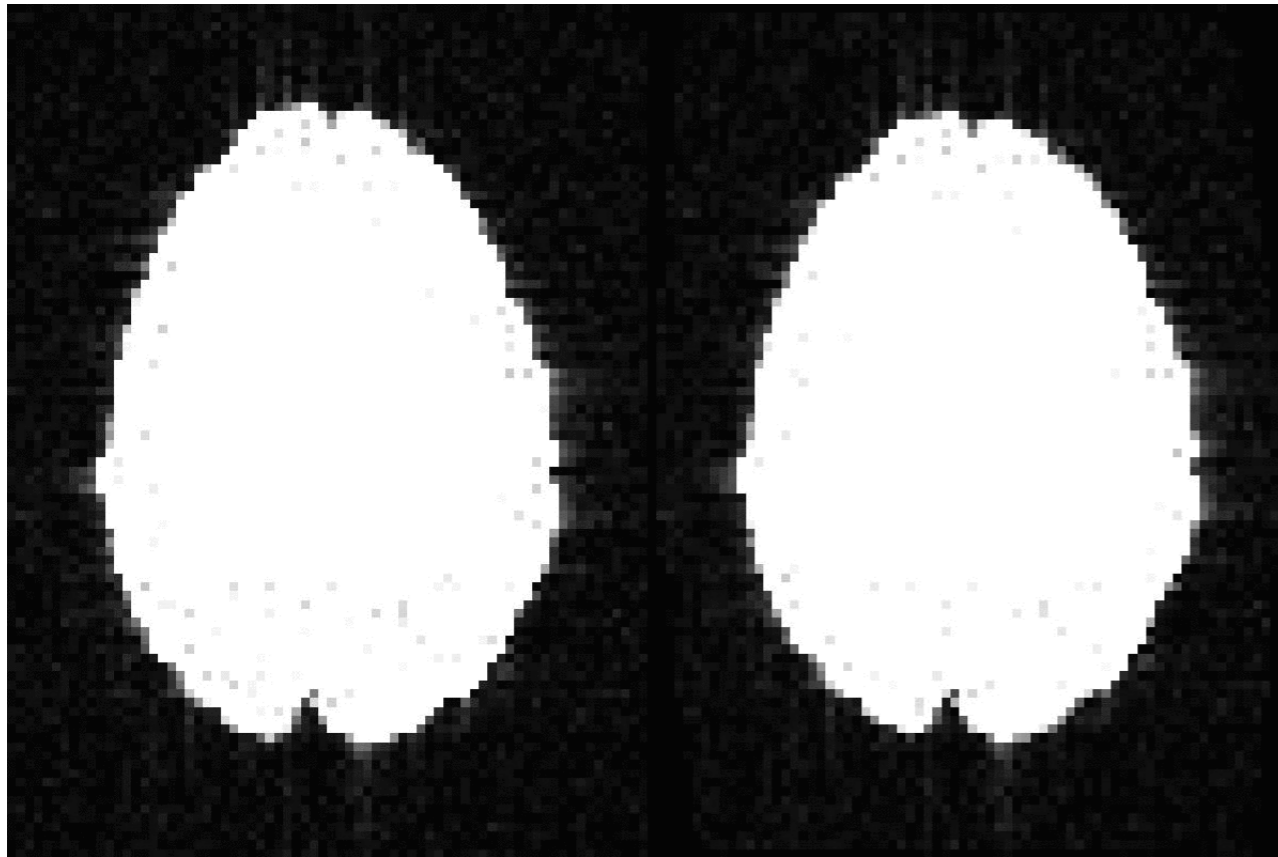




Some data with lots of movement, aligned with eddy

Before

After





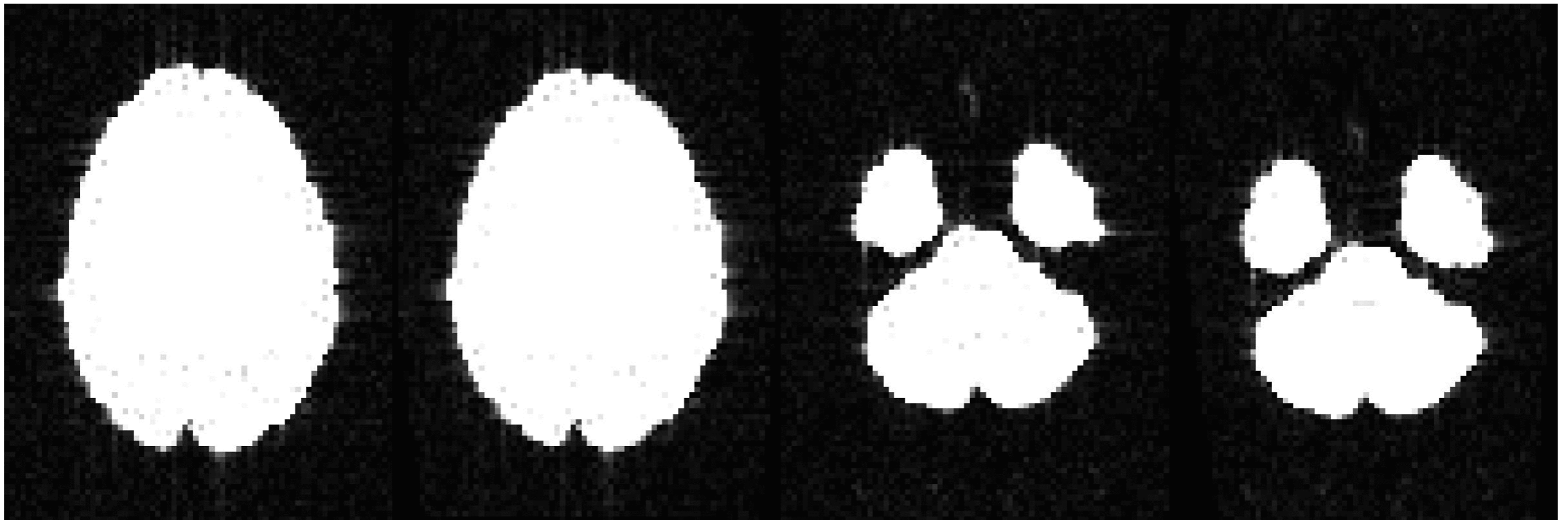
Some data with lots of movement, aligned with eddy

Before

After

Before

After





Why is that then?

Motion-induced Magnetic Field Changes Inside the Brain

Jiaen Liu¹, Jacco de Zwart¹, Peter van Gelderen¹, and Jeff Duyn¹

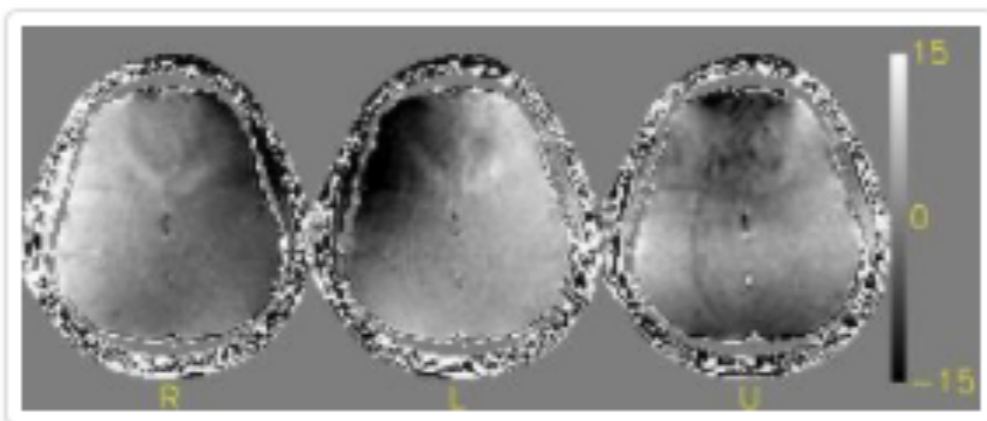


Fig. 1 Changes of field maps in four different positions relative to the field map in the reference position obtained under the “phantom shim” setting. The unit of the field maps is Hz.

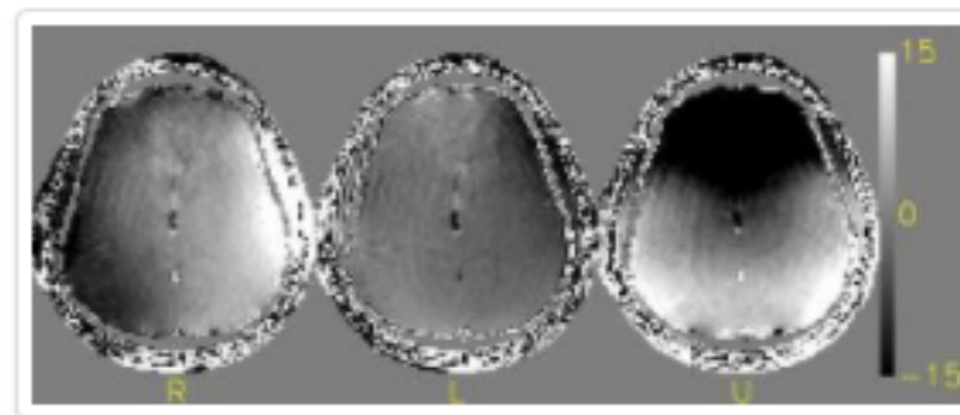
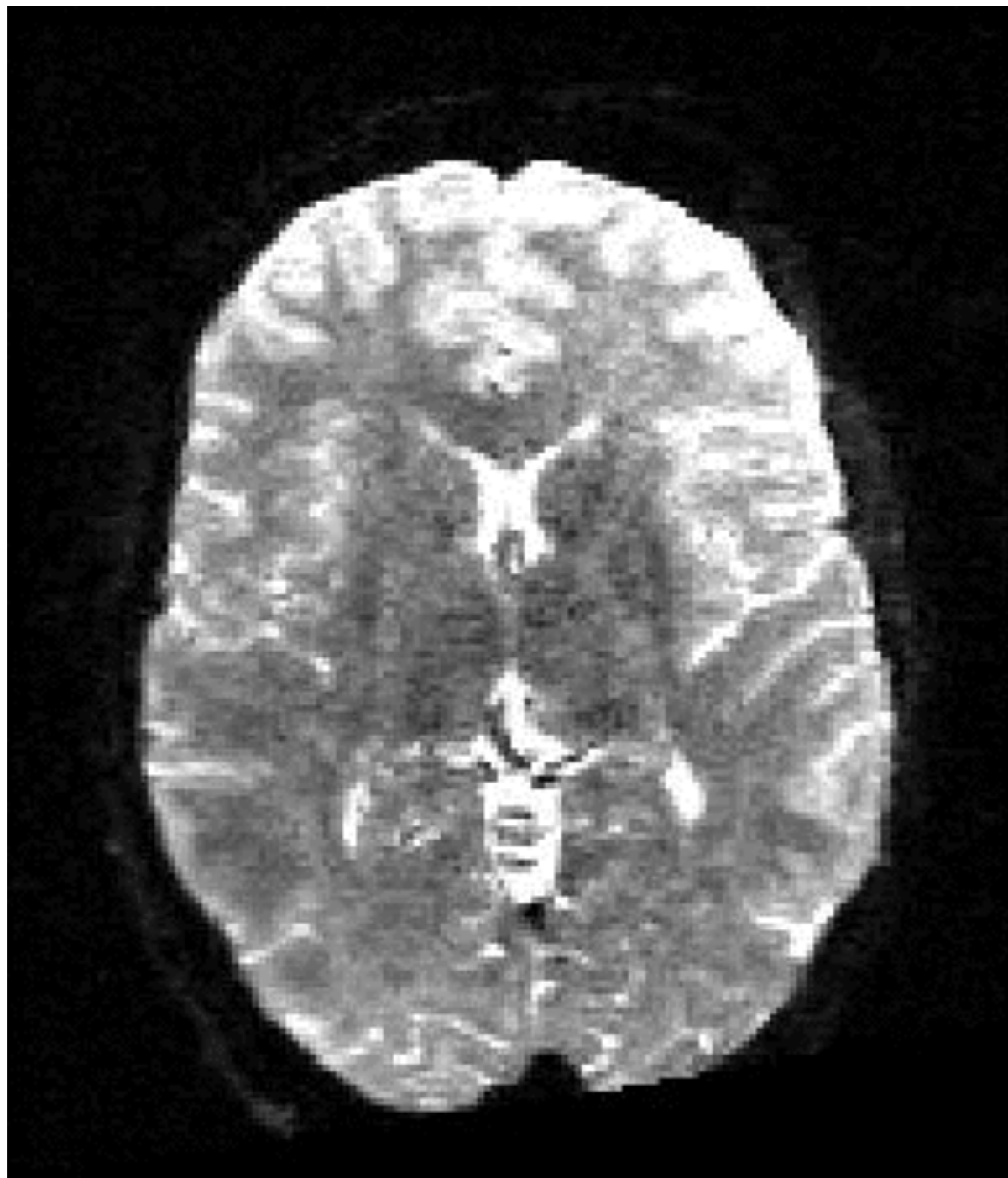


Fig. 2 Changes of field maps in four different positions relative to the field map in the reference position obtained under the “subject shim” setting. The unit of the field maps is Hz.



In case you think that was
exaggerated



Problematic
HCP subject.



Why is that then?

Richard Bowtell

Will field shifts due to head rotation compromise motion correction?

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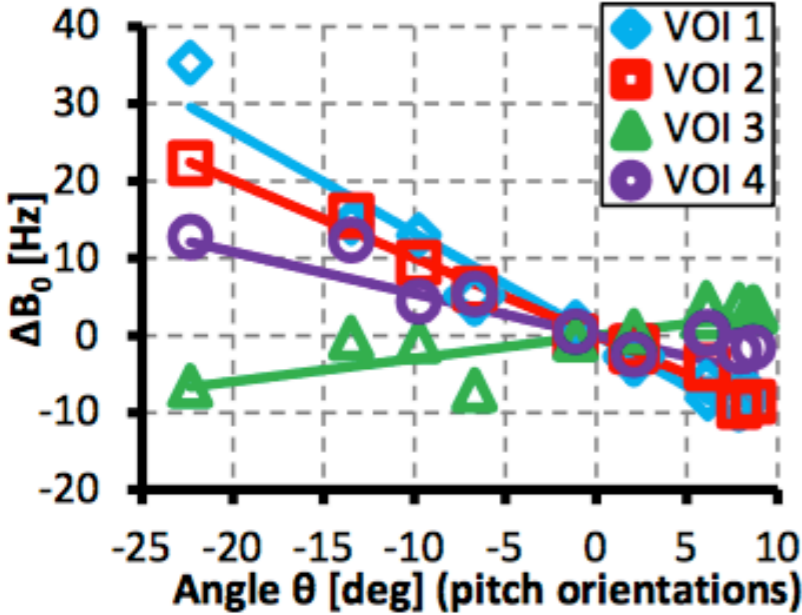


Fig. 3. Figure showing mean field shift in the VOIs during pitch rotations.

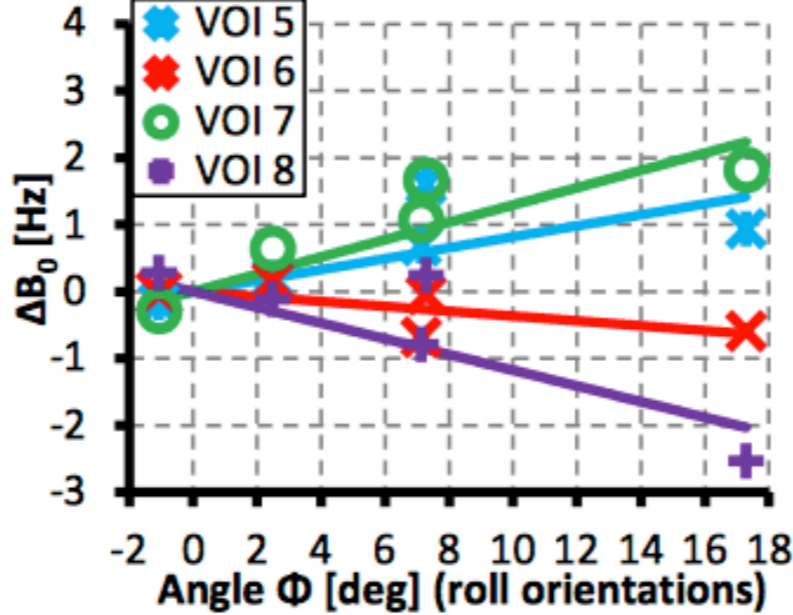


Fig. 4. Figure showing mean field shift in the VOIs during roll rotations.

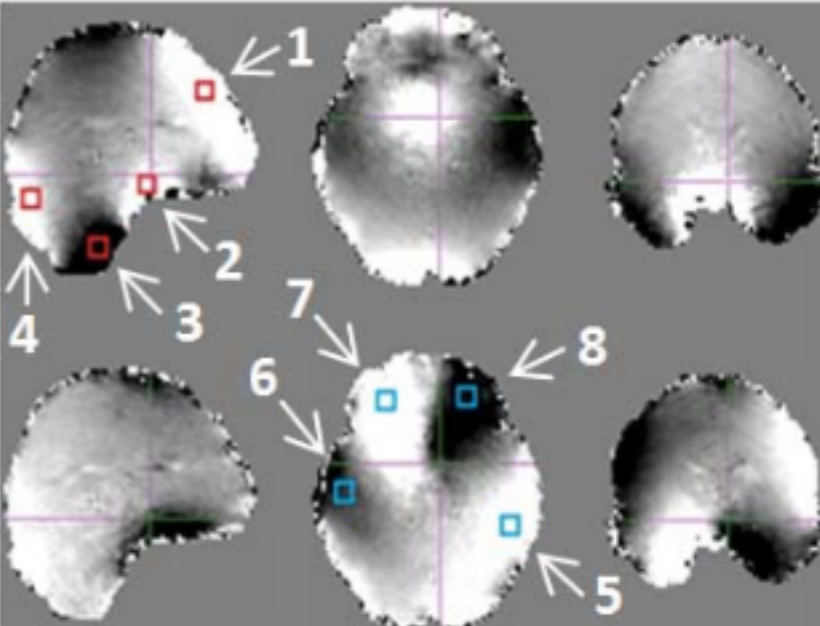


Fig. 2. B_0 field difference maps for 2 head orientations, TOP: pitch $\theta=7.87$ deg, BOTTOM: roll $\Phi=7.13$ deg. Squares indicate VOIs (red: volumes 1-4; blue: volumes 5-8). Grey scale = -5 Hz to 5 Hz.

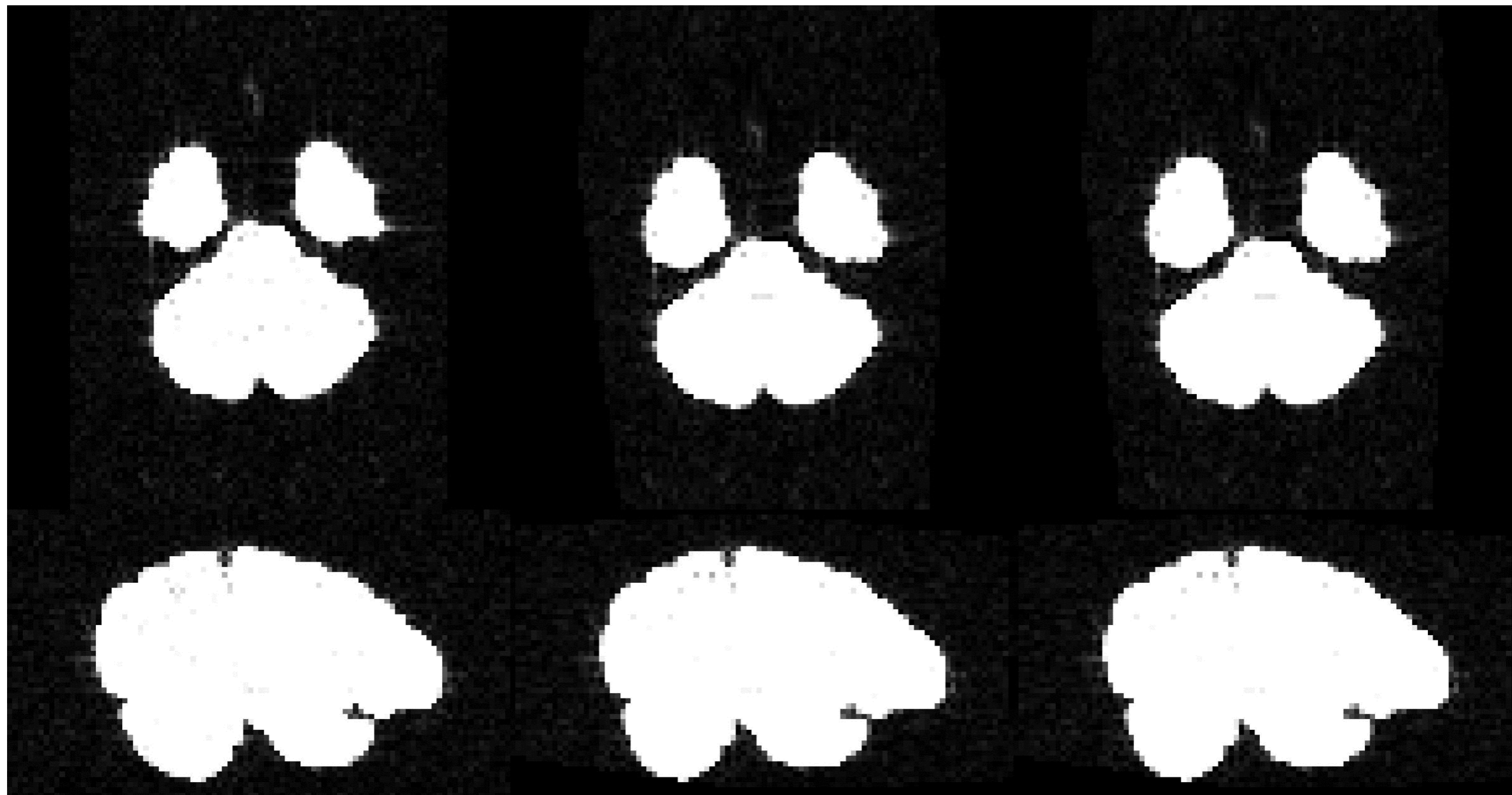


And now things look a lot better

Before

After

With Susc-by-move





And the problematic HCP subject

