Fibre Orientation Models & Tractography Analysis

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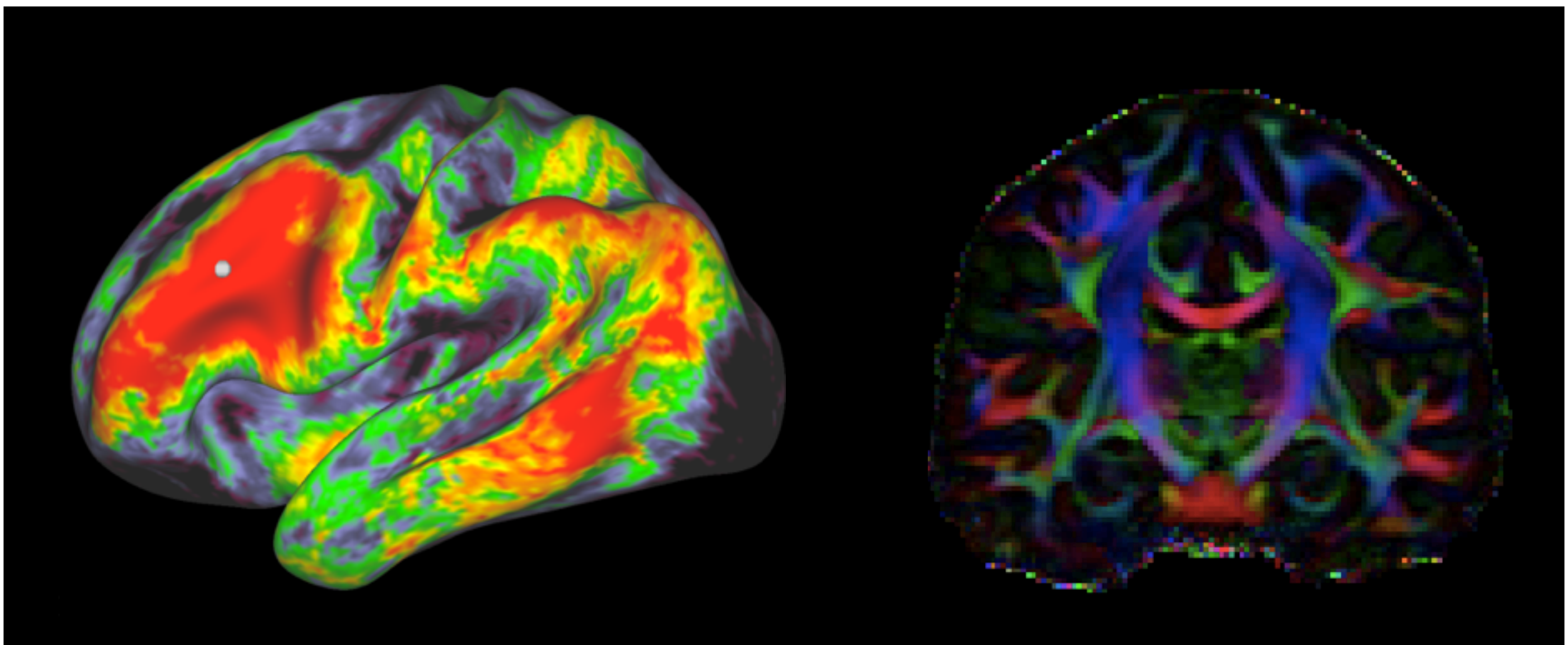

Overview

- Why DTI is not enough?
- Estimating Crossing Fibre Orientations - bedpostX
  Adding spatial information - RubiX
- Probabilistic Tractography - probtrackX
- Applications & Connectomes

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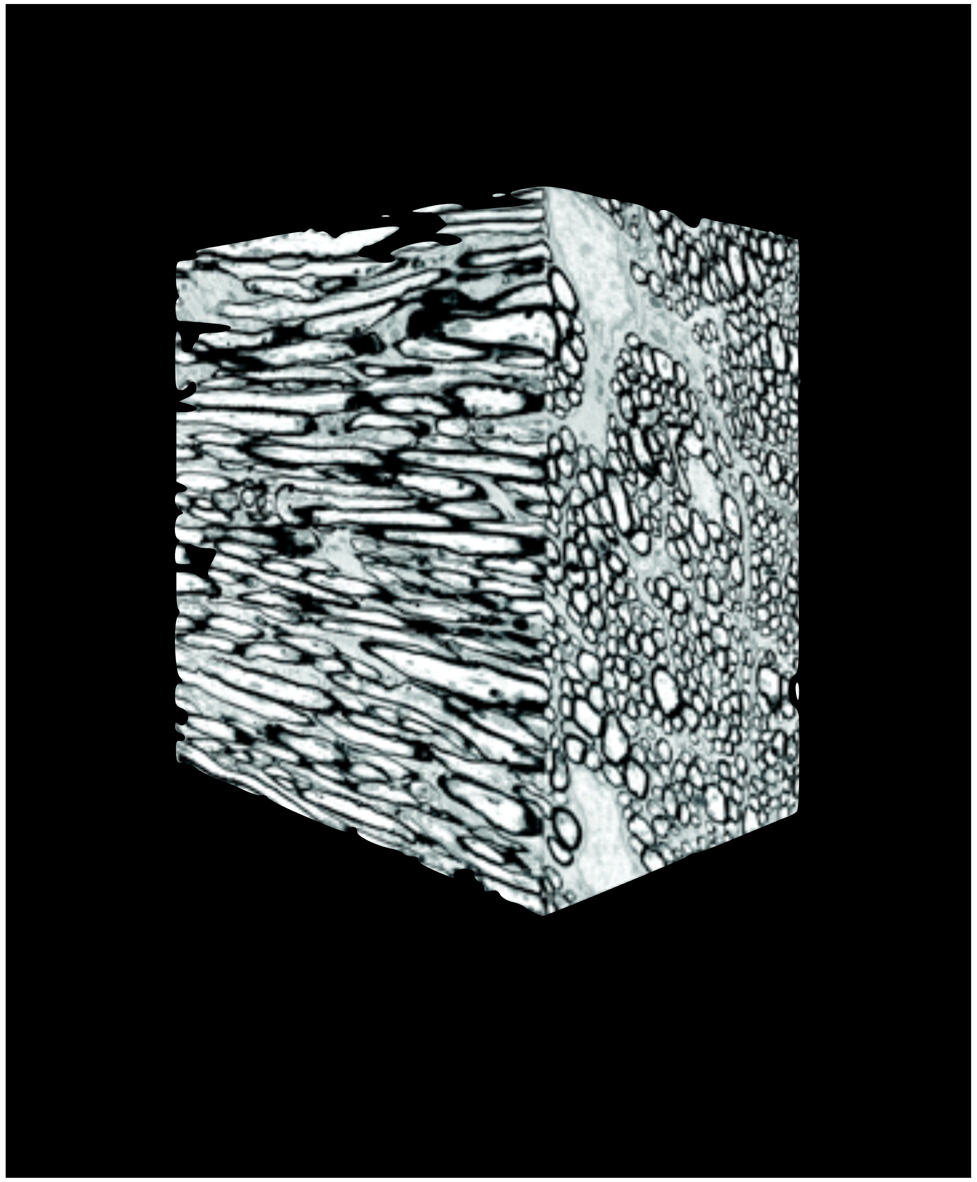
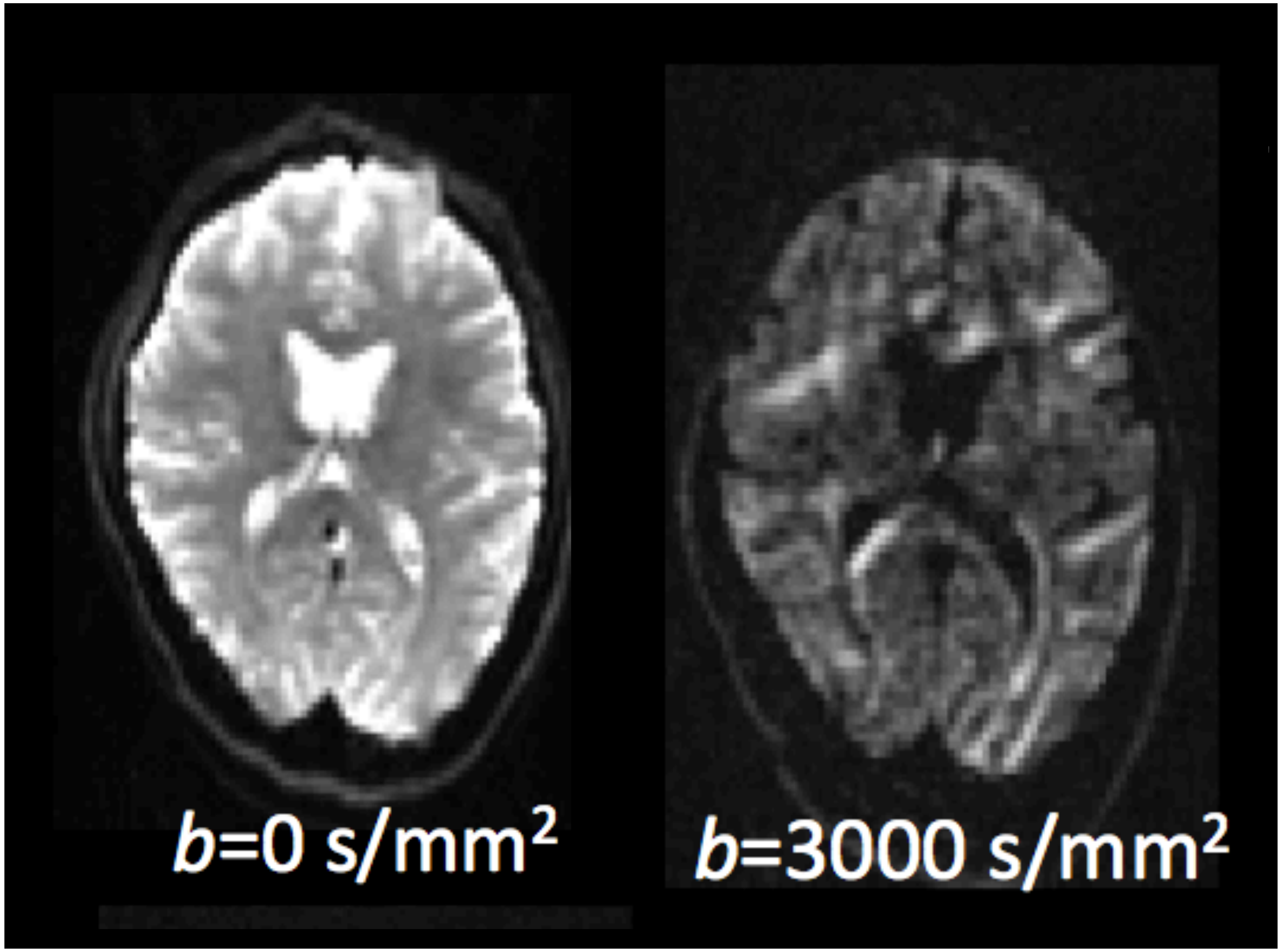
Why do we need modelling?

Micro-structure
Ex-vivo Electron Microscopy
Direct Imaging of Axons

Macro-structure
Whole-brain In-vivo Imaging
Direct Imaging of Water Diffusion =>
Need a model to infer connections



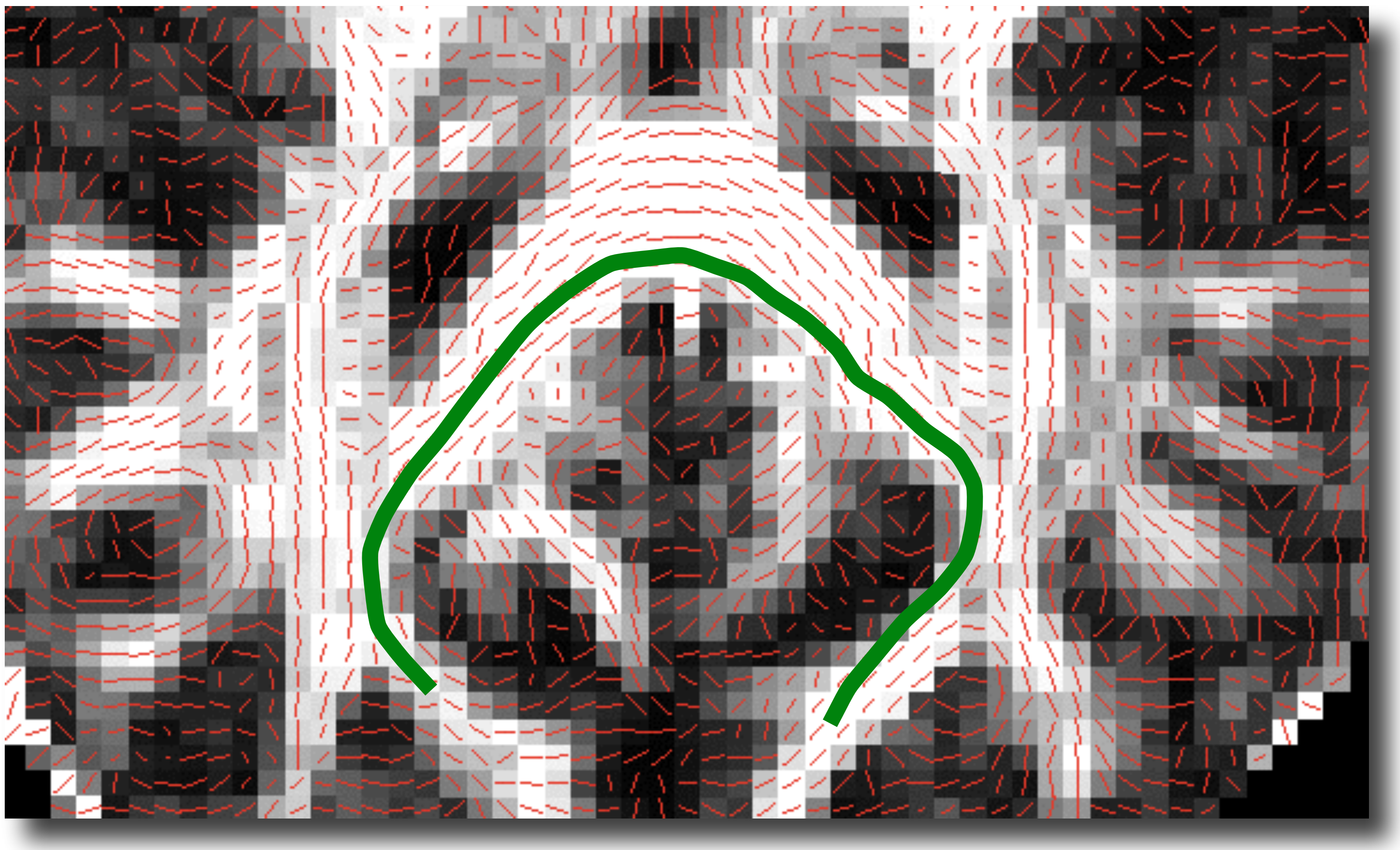
Ohno et al. 2011



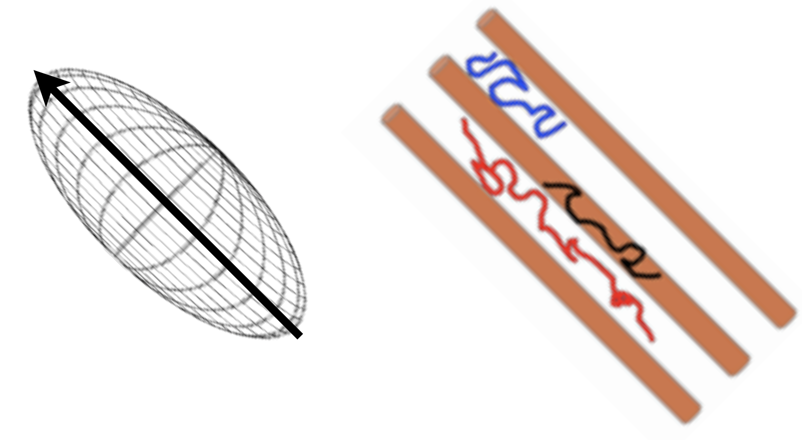
3T Skyra Connectome
(32ch Coil, 84 mT/m)

DTI Estimates of Principle Fibre Orientation in WM

$\mathbf{v}_1$ map
Principal Diffusion Direction



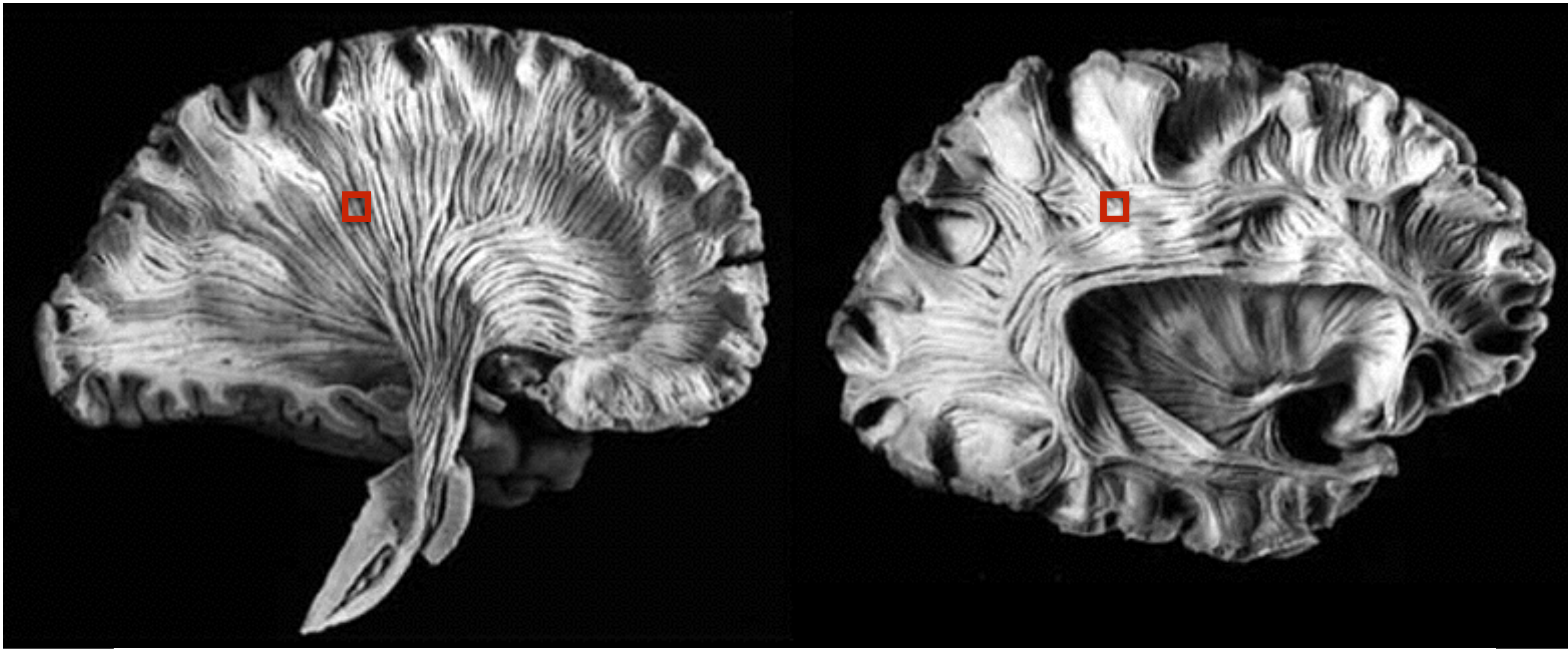
Principal Diffusion Direction



<u>Assumption</u>:

Direction of maximum diffusivity
(in anisotropic voxels)
is an **<u>estimate</u> of the major fibre orientation**.

But is WM always coherently organised within a voxel?

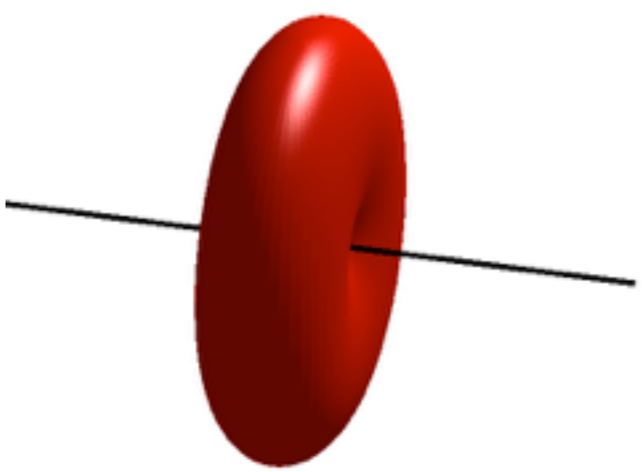


Unfortunately not, complex fibre patterns (e.g. crossings) are very common at the voxel scale.

Predictions from the tensor model
no crossing fibres

One orientation

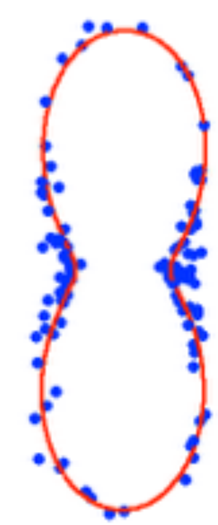
Measured
Signal
Shape



Predicted
Signal
Shape

DTI
Ellipsoid

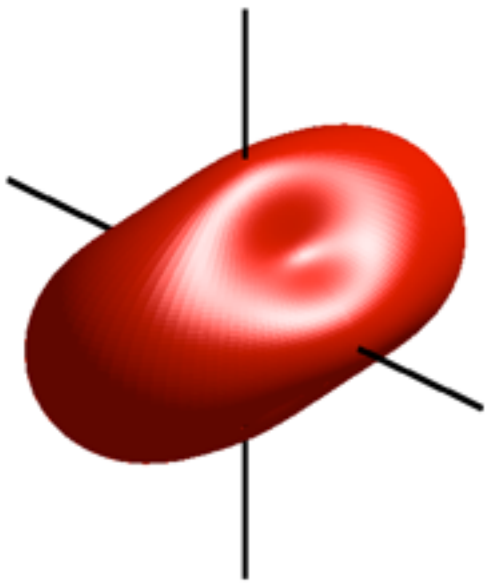
Prediction &
Measurements
in 2D



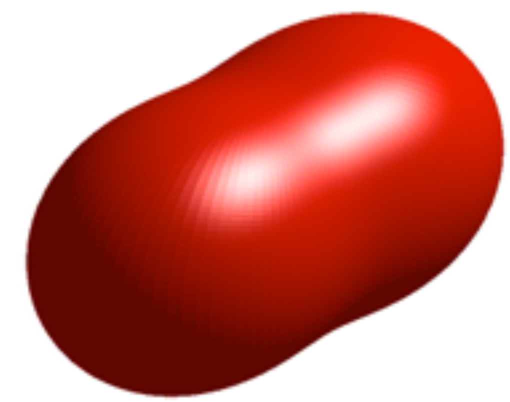
Predictions from the tensor model crossing fibres

Two orientations

Measured Signal Shape

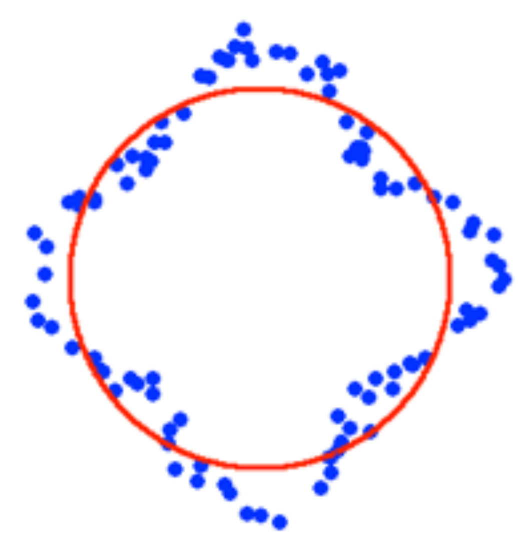


Predicted Signal Shape



DTI Ellipsoid

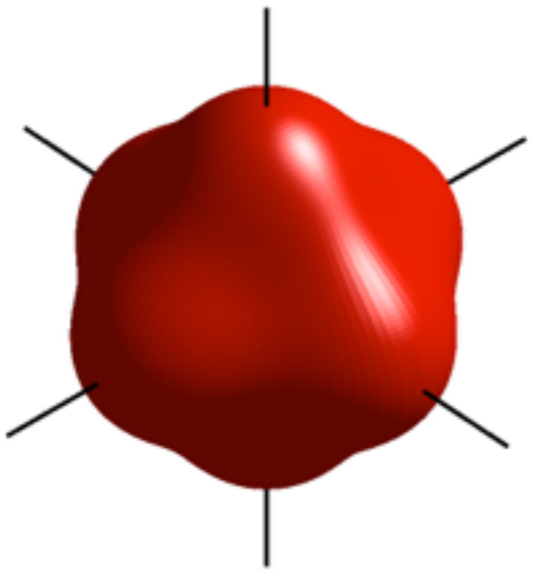
Prediction & Measurements in 2D



Predictions from the tensor model crossing fibres

Three Orientations

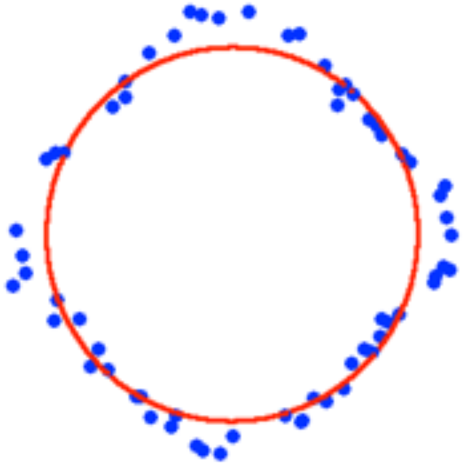
Measured Signal Shape



Predicted Signal Shape

DTI Ellipsoid

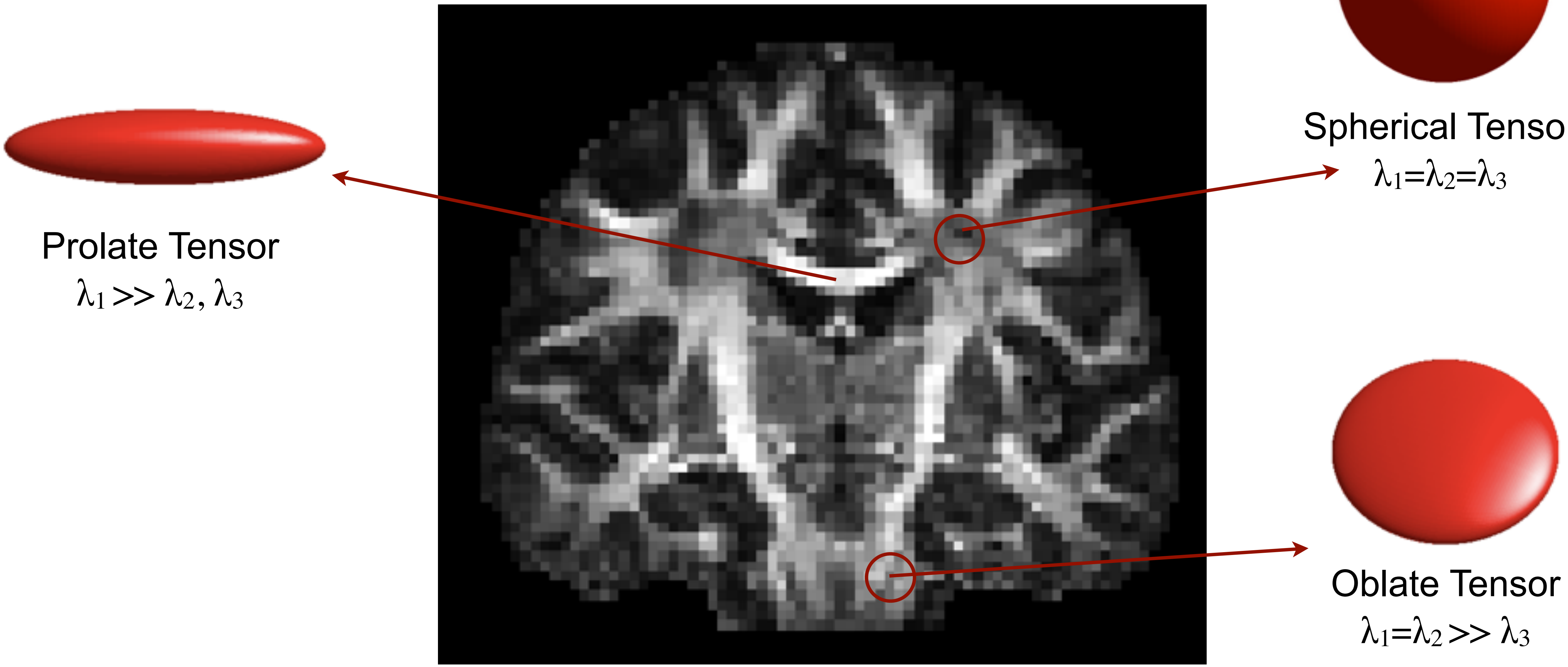
Prediction & Measurements in 2D



How good is the DTI Model in regions with crossing fibres?

- In voxels containing two crossing bundles, the tensor ellipsoid is pancake-shaped (oblate, planar tensor).
- In voxels containing three crossing bundles, the tensor ellipsoid is spherical.

- In these areas, DTI $\mathbf{v_1}$ is meaningless and FA is biased.

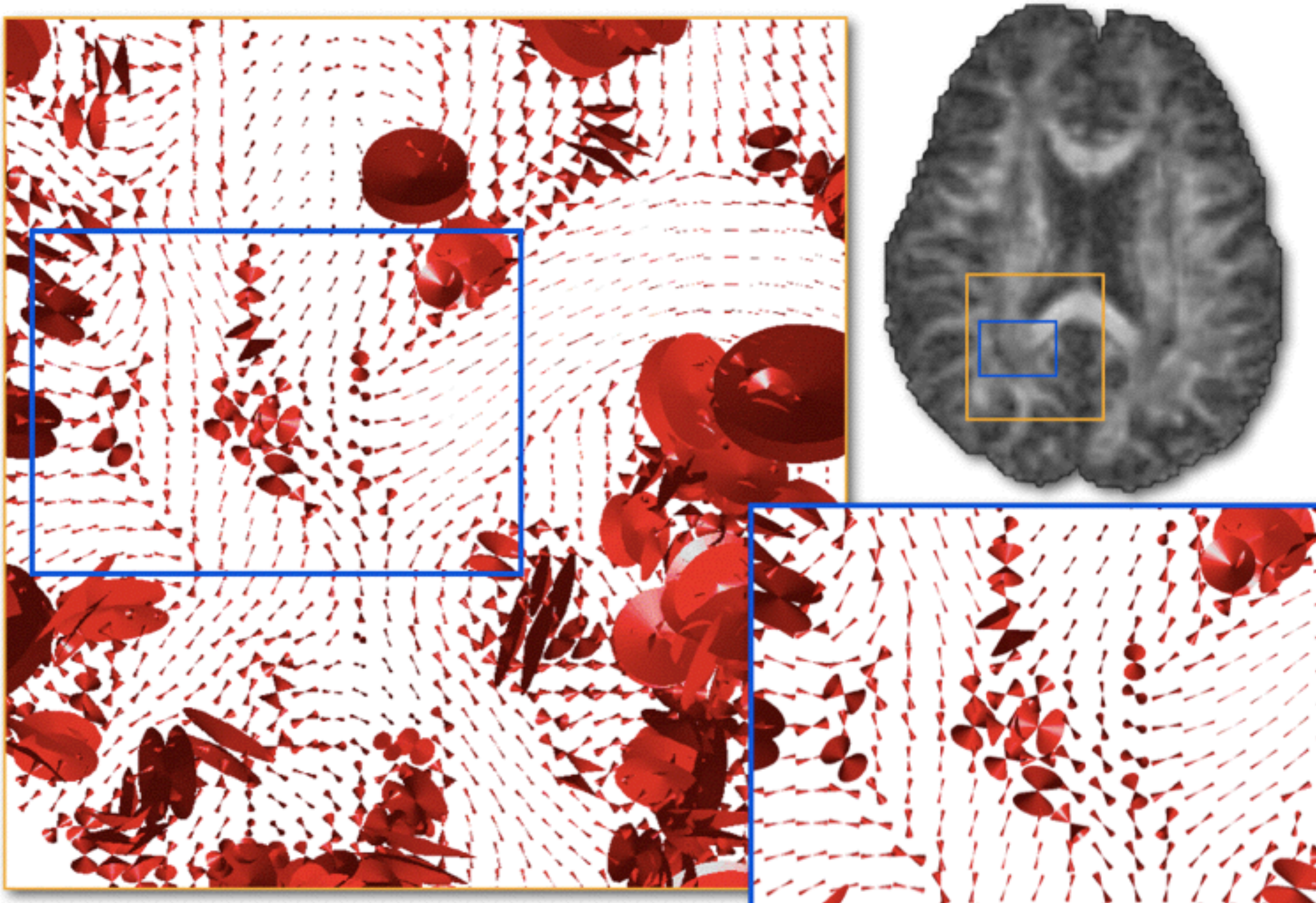


Uncertainty on DTI Fibre Orientation Estimates

Repeat an acquisition many times and obtain the variability in $\mathbf{v}_1$ from the different datasets.

Uncertainty Sources

- Modelling errors
- Noise



Cones of uncertainty on DTI $\mathbf{v}_1$

Jones, 2002

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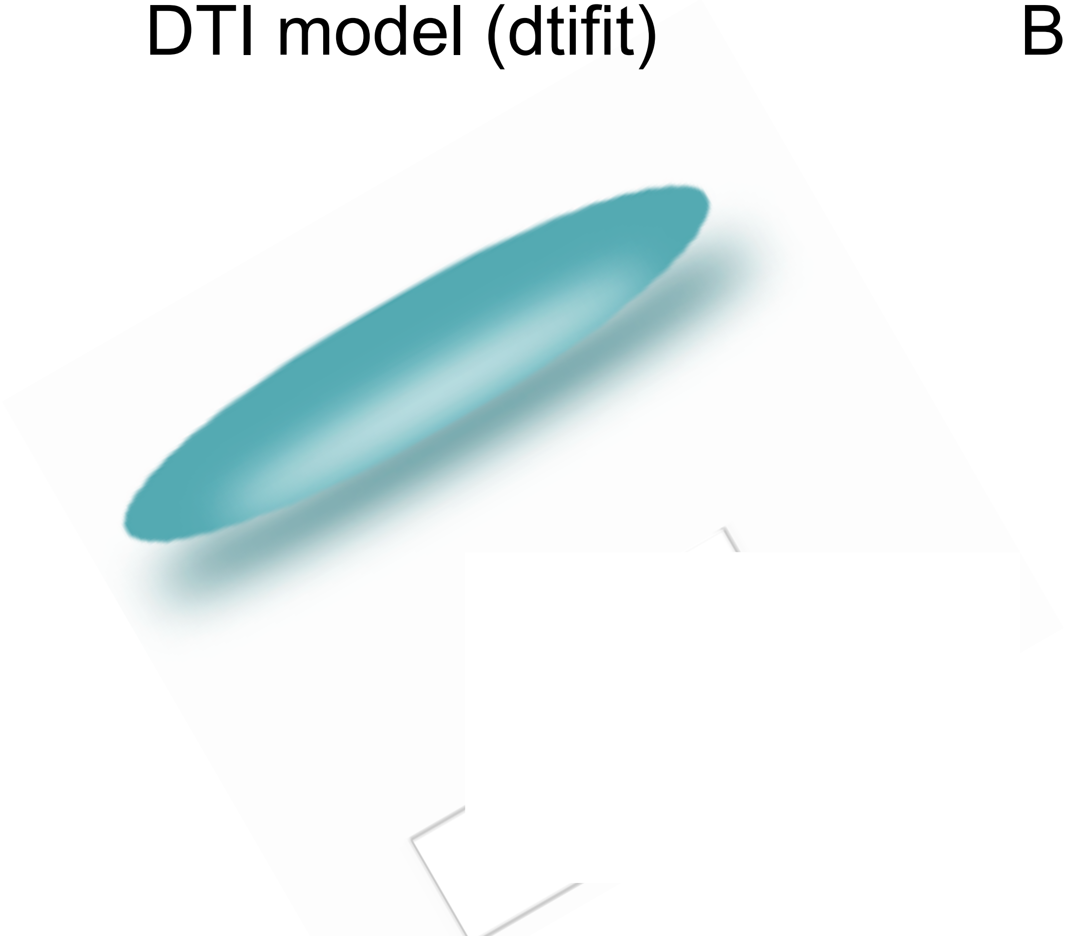
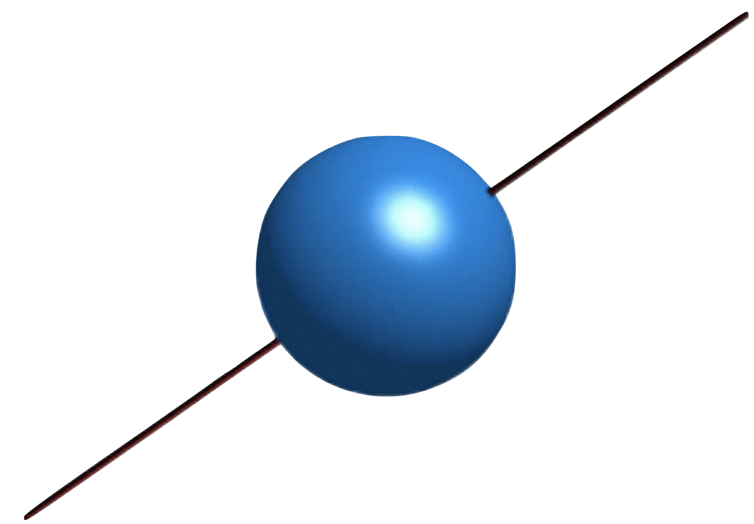
Do we have to use the DTI model to estimate orientations? Not really, many models exist

DTI model (dtifit)



Ball & sticks model (bedpostX model1)



Anisotropic Volume Fraction (unknown)

Diffusivity (unknown)

Fibre Orientation (unknown)

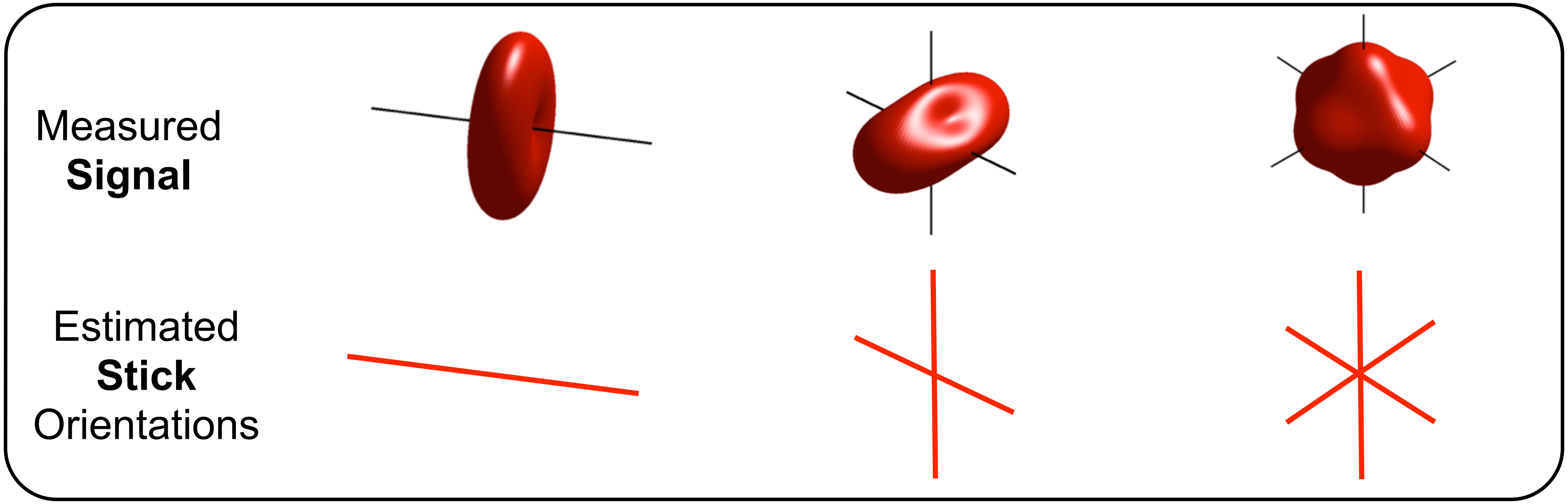
$$s_j = s_0 \left[(1-f)\exp(-b_j\, d) + f \exp(-b_j\, d (\mathbf{x}_j^{T} \mathbf{v})^2) \right]$$

Measured Signal for Gradient *j*

b-value for gradient *j* (known)

Unit vector representing the direction of gradient *j* (known)

Ball & Sticks Model
Unlike the DT model, it can represent many orientations



- Anisotropic tensors (sticks) with isotropic background (ball)
- Fibre Orientations modelled explicitly and separated from isotropic partial volumes

Anisotropic Volume Fractions (unknown)

Diffusivity (unknown)

Max number of sticks (user-defined)

Fibre Orientation (unknown)

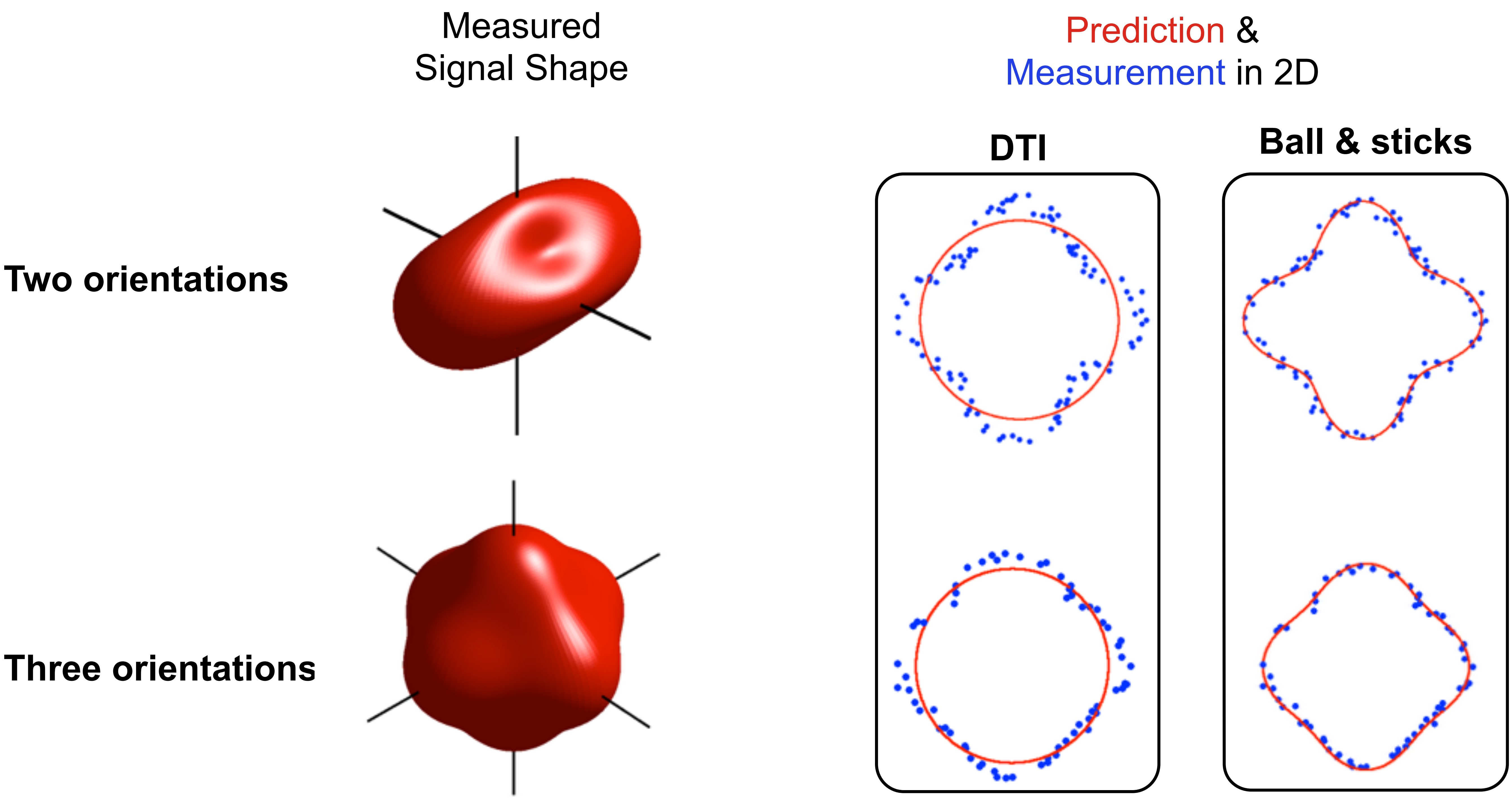
$$s_j = s_0\,[(1-\Sigma f_n)\exp(-b_j\, d)+\Sigma f_n \exp(-b_j\, d(\mathbf{x}_j^{\mathrm{T}}\mathbf{v}_n)^2)]$$

Measured Signal for Gradient *j*

b-value for gradient *j* (known)

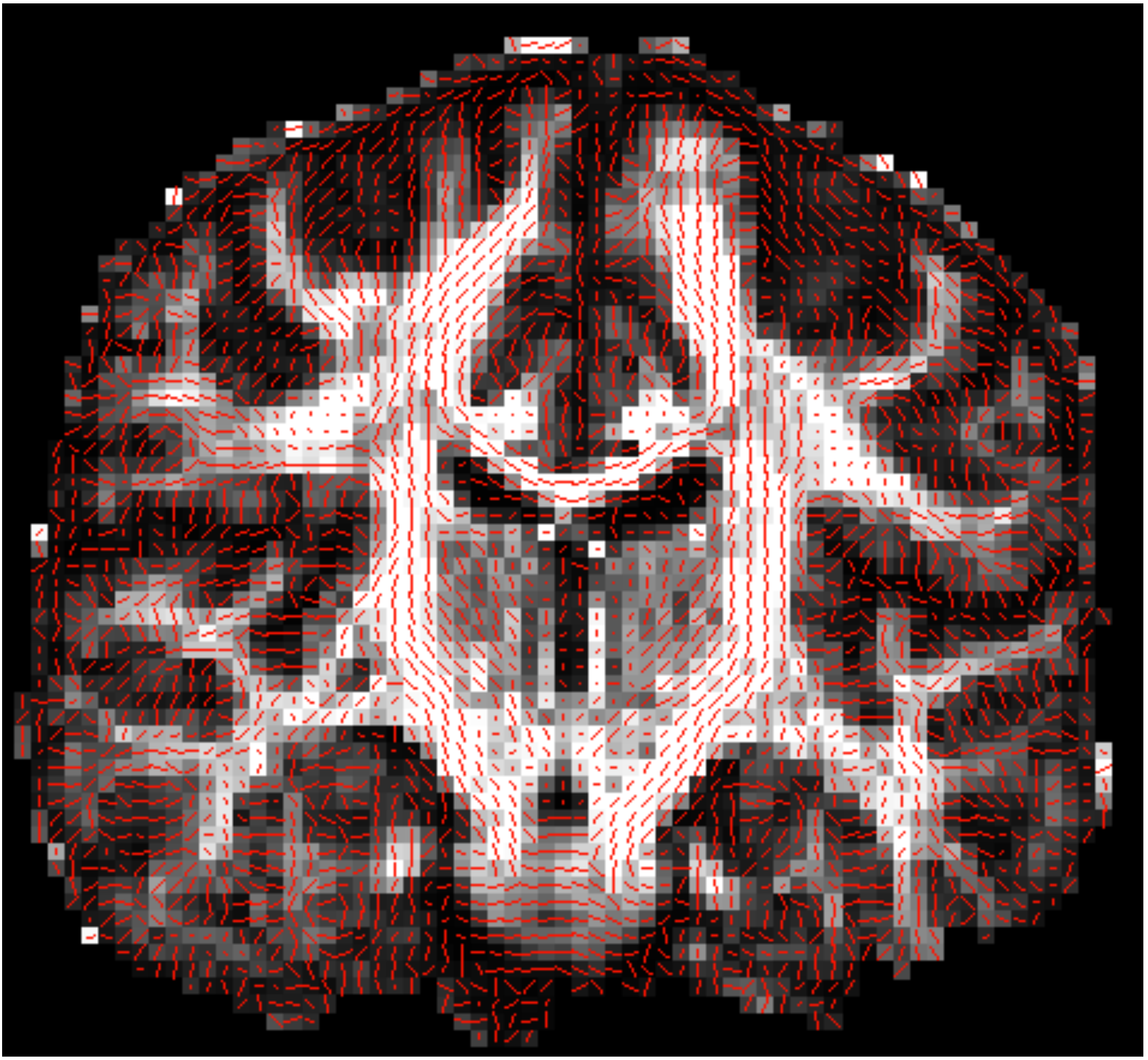
Unit vector representing the direction of gradient *j* (known)

Predictions from the ball and sticks model
crossing fibres

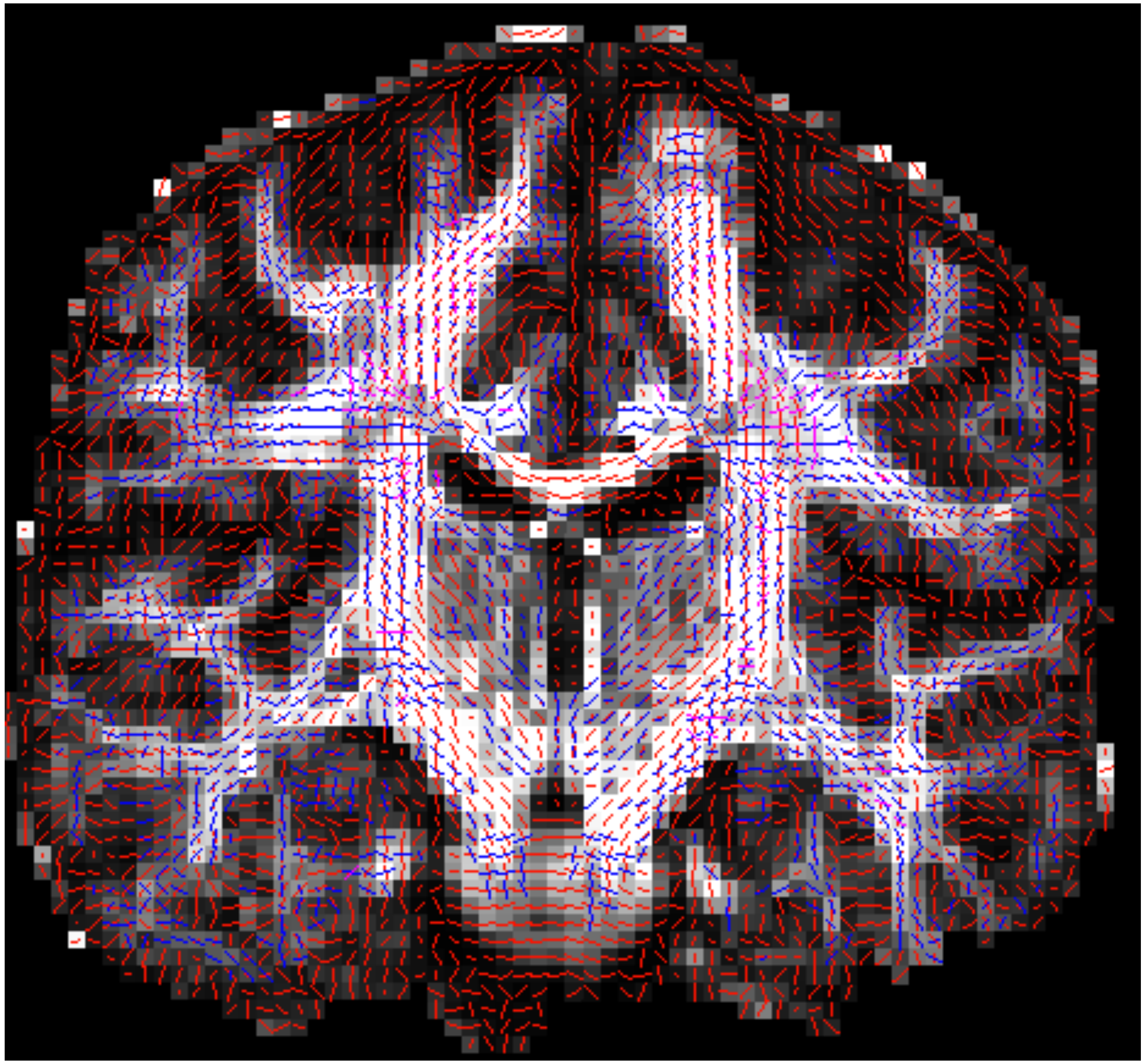


DTI vs Ball & Sticks Orientations

DTI



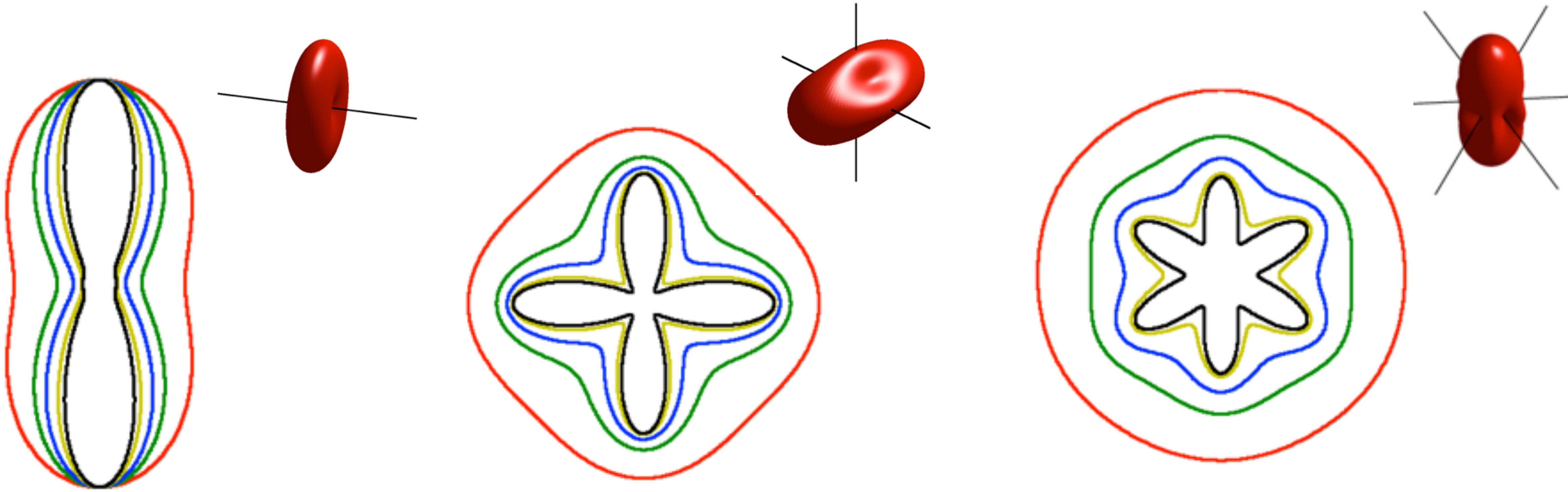
Ball & Sticks



Multi-Shell Diffusion Acquisitions
Why bother?

One Orientation | Two Orientations | Three Orientations

Signal at different b values (s/mm^2)
b=1000
b=2000
b=3000
b=4000
b=5000

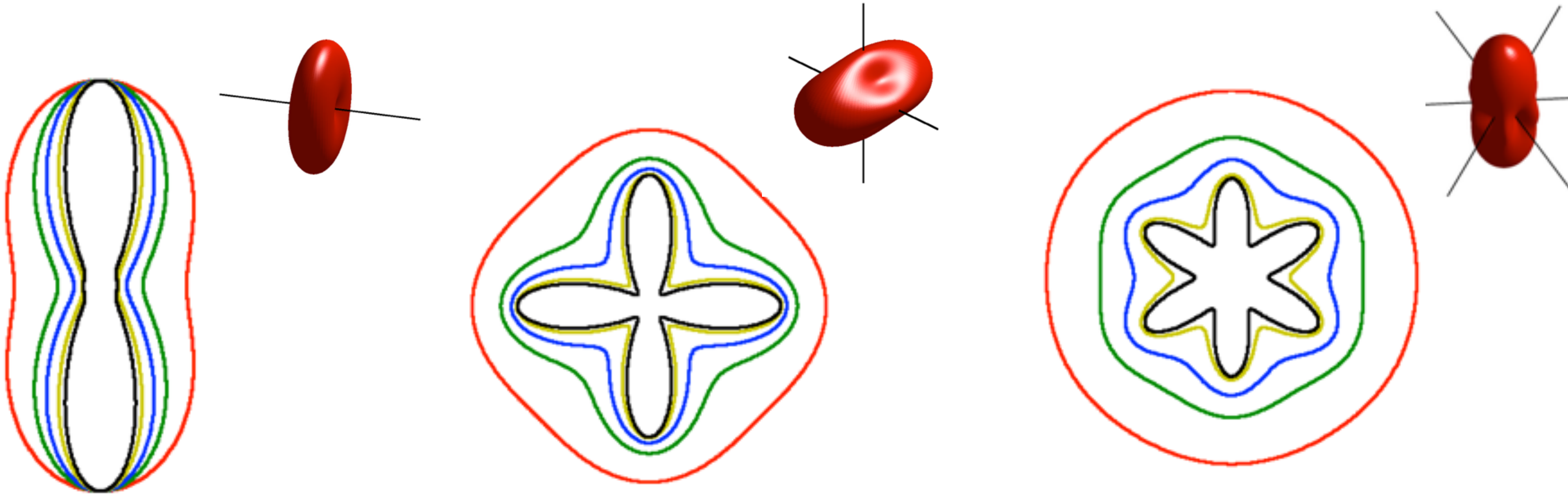


Higher b value gives us more angular contrast!!!

Multi-Shell Diffusion Acquisitions
Why bother?

One Orientation | Two Orientations | Three Orientations

Signal at different b values (s/mm²)
b=1000
b=2000
b=3000
b=4000
b=5000



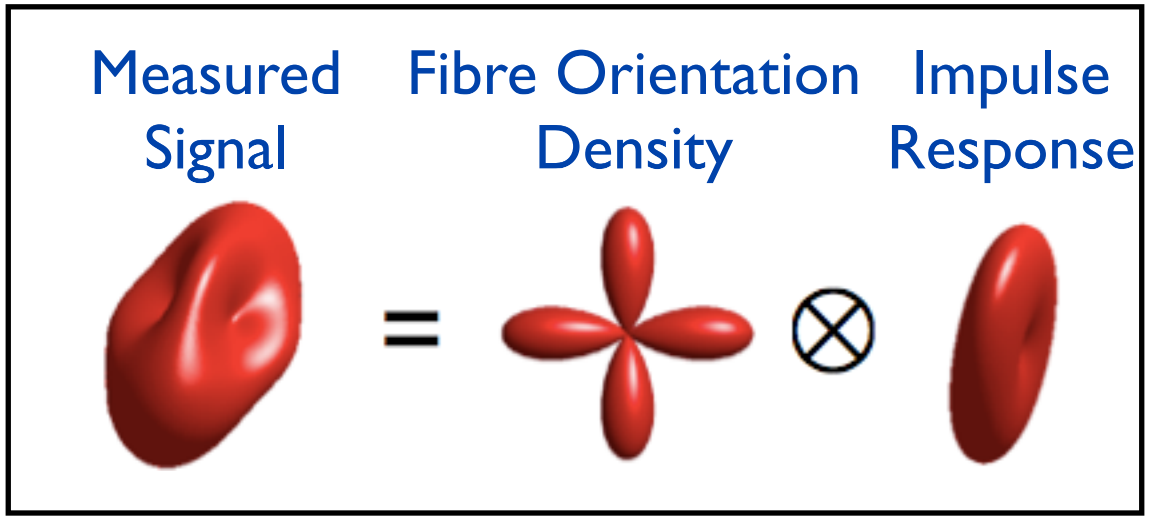
b=300 | b=1000 | b=2000 | b=3000

But SNR goes down very quickly with b… ☹

Generalised Parametric Deconvolution
Gets best of both worlds by combining multiple shells

Parametric spherical deconvolution:

In every **voxel**



- **Multi-shell** model in bedpostX (model=3).
  Allows representation of multiple diffusivities within a voxel (rather than just one).
  => More accurate model for multi-shell data & partial volume effects.

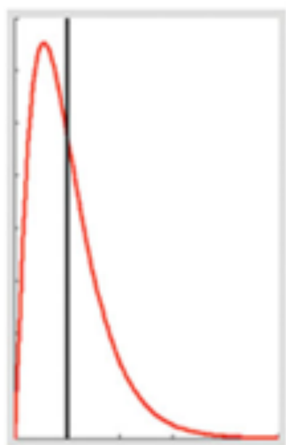
- Instead of representing a **fibre** compartment as a “stick” (perfectly anisotropic),
  it has a more realistic description (a “**zeppelin**”).
  I.e. a very anisotropic compartment, which however has some width.

  Width estimated from the data, but constrained through Prior knowledge learned fron
  data!

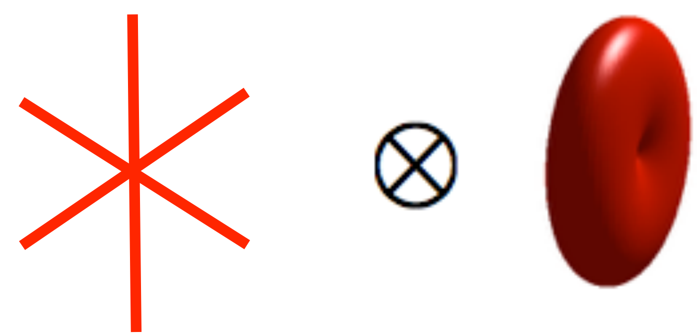
Generalised Parametric Deconvolution
Gets best of both worlds

$$S_k/S_0 = (1 - f_{WM})\boxed{E_k^{PV}} + f_{WM}\boxed{E_k^{WM}}$$

Partial Volume



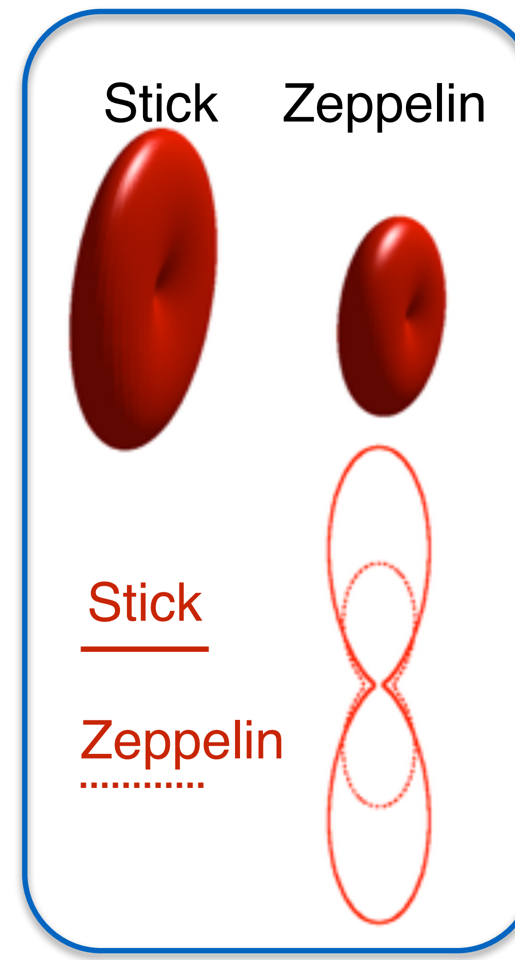
Fibre (WM) Compartment



fODF (estimate its local maxima directly)

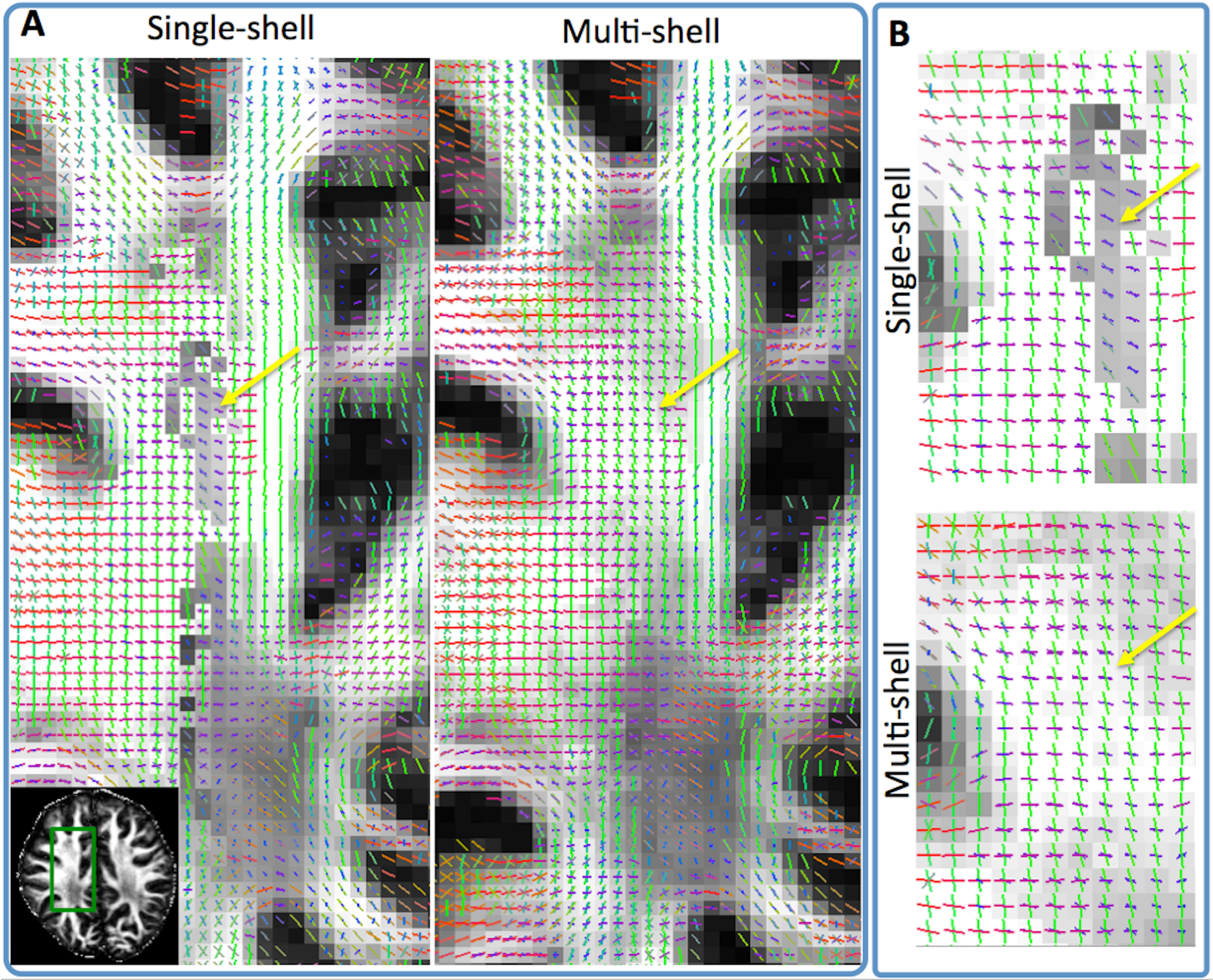
Impulse Response from a tensor

Impulse Responses



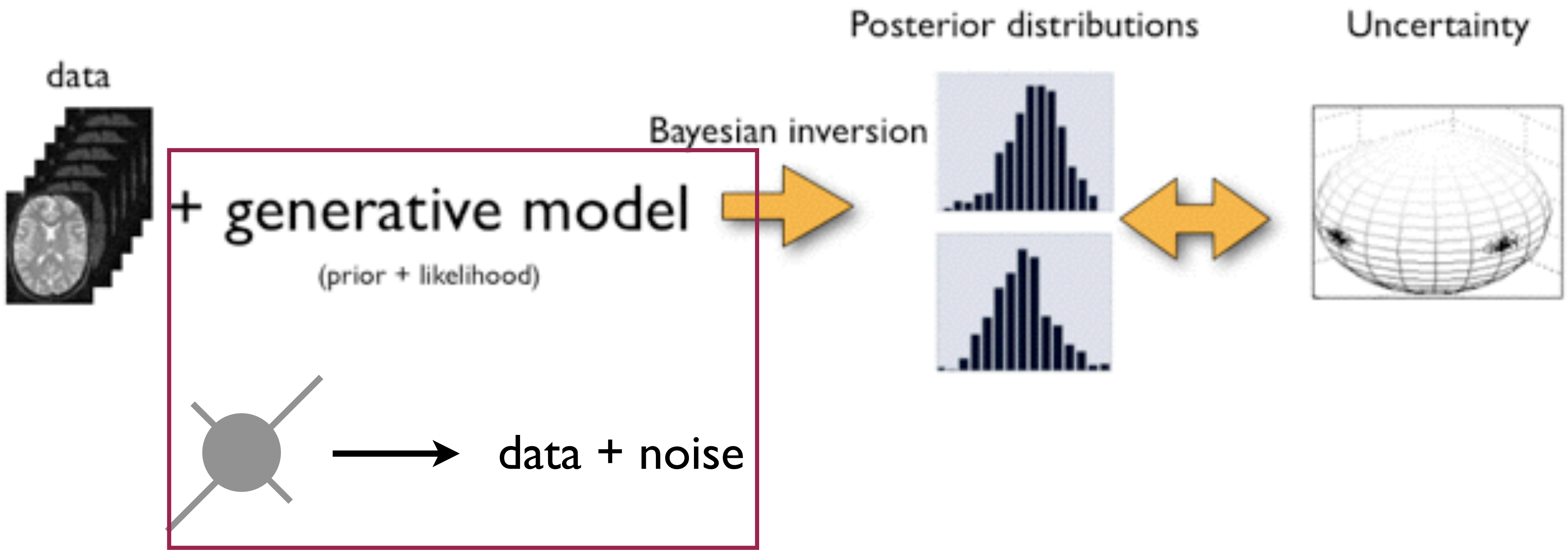
- Sum of Diracs for fODF
- Gamma distribution of diffusivities in the partial volume compartment
- Axially symmetric anisotropic tensor (i.e., “zeppelin”) in the Impulse Response kernel
- Bayesian Inference Framework.

Generalised Parametric Deconvolution

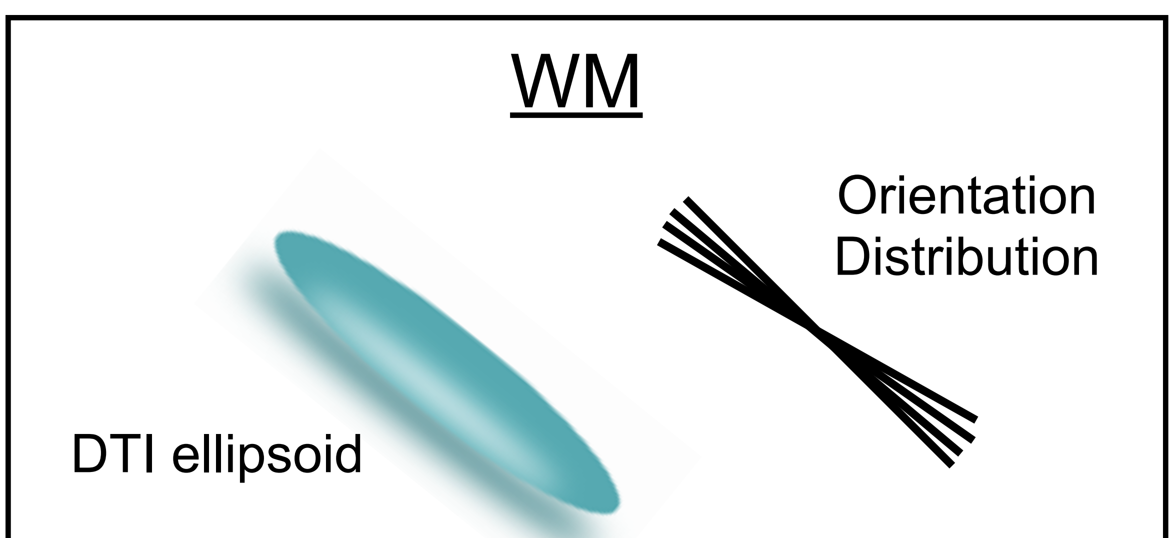


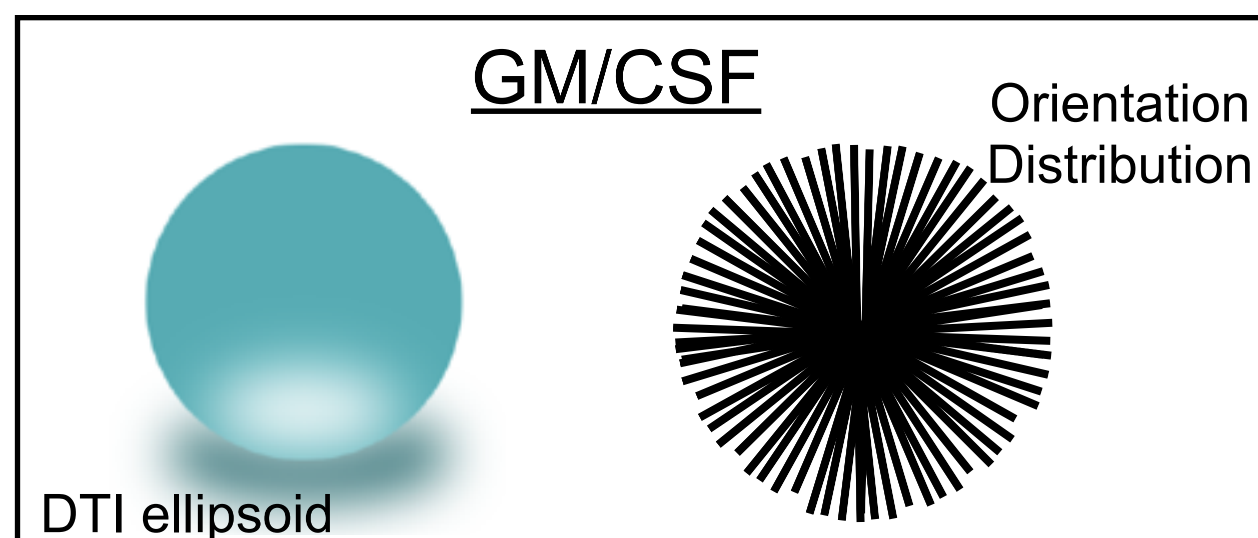
Sotiropoulos et al, NeuroImage 2013

Quantifying Uncertainty
Bayesian Modelling in bedpostX

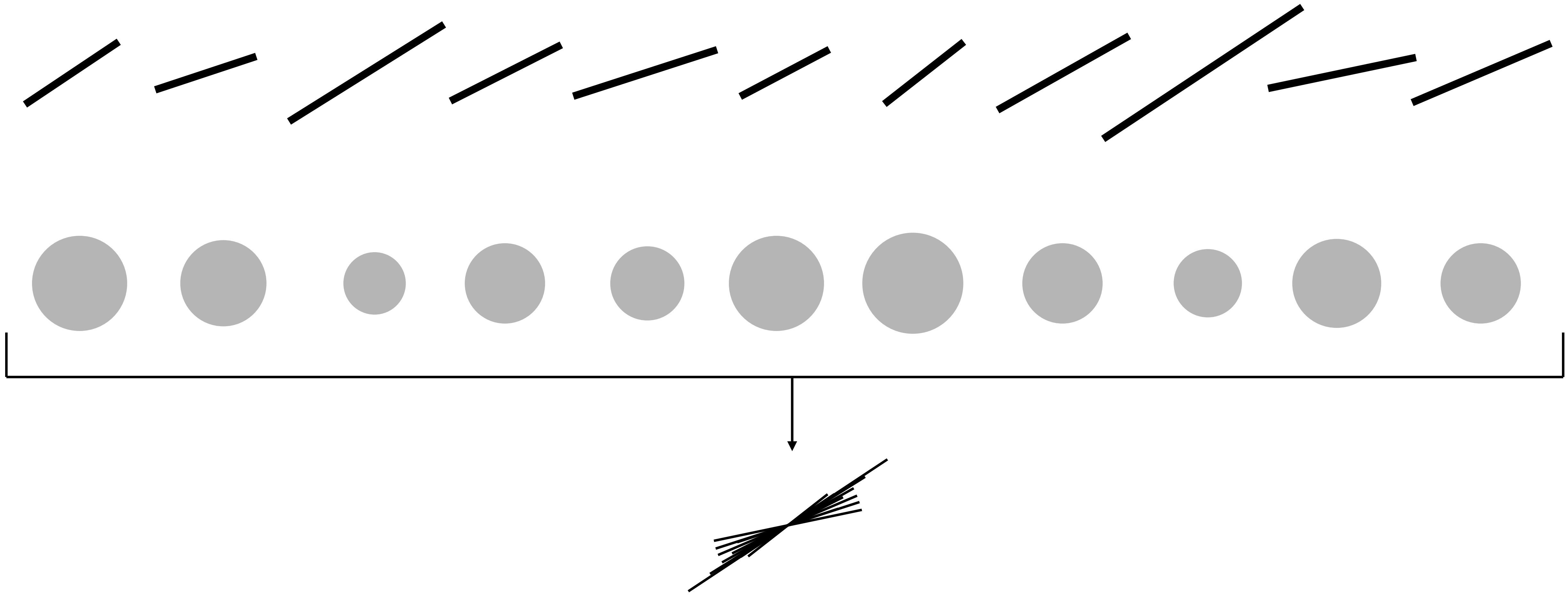


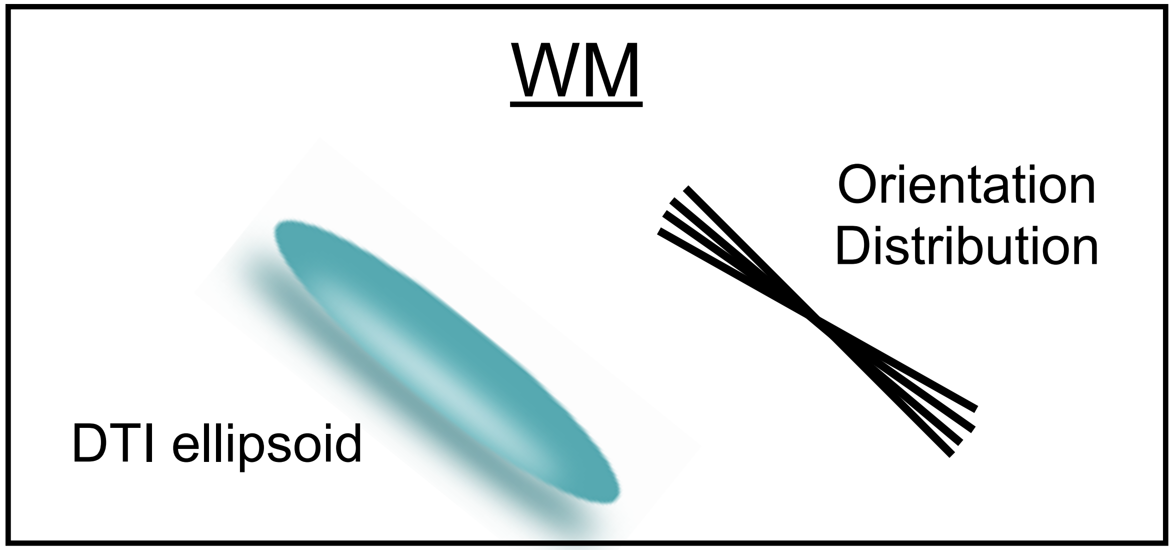
- Uncertainty can be quantified from a single data set
- Instead of a single orientation estimate, infer a **distribution** of orientations in each voxel. (and for every model parameter)

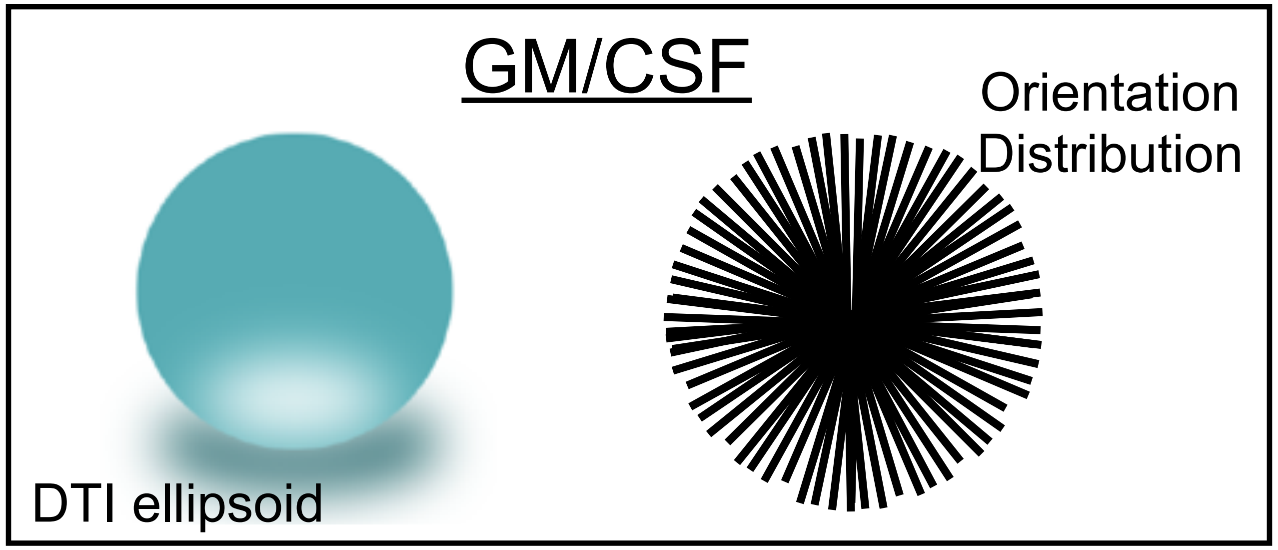




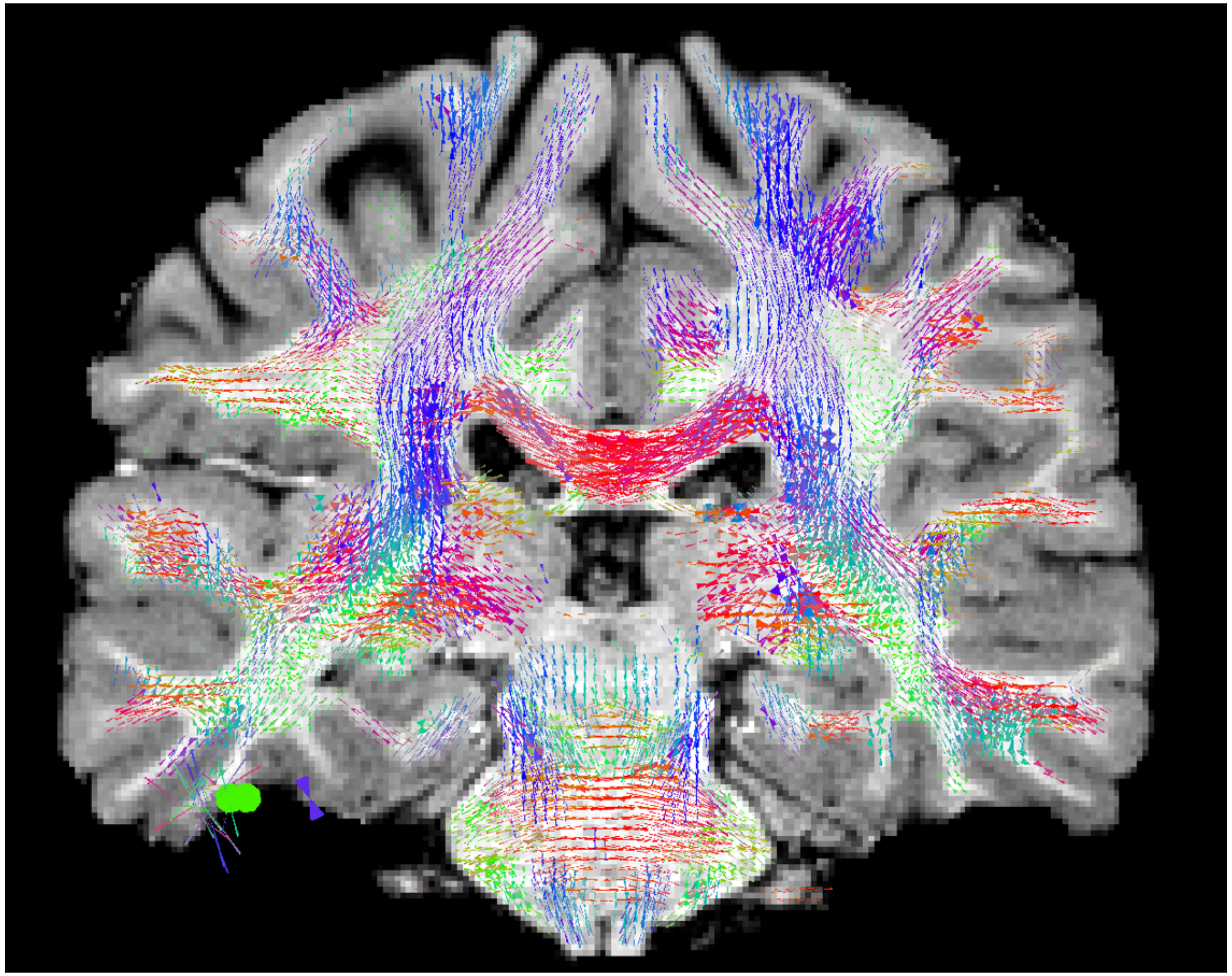
Output in Each voxel = Distributions of Parameters

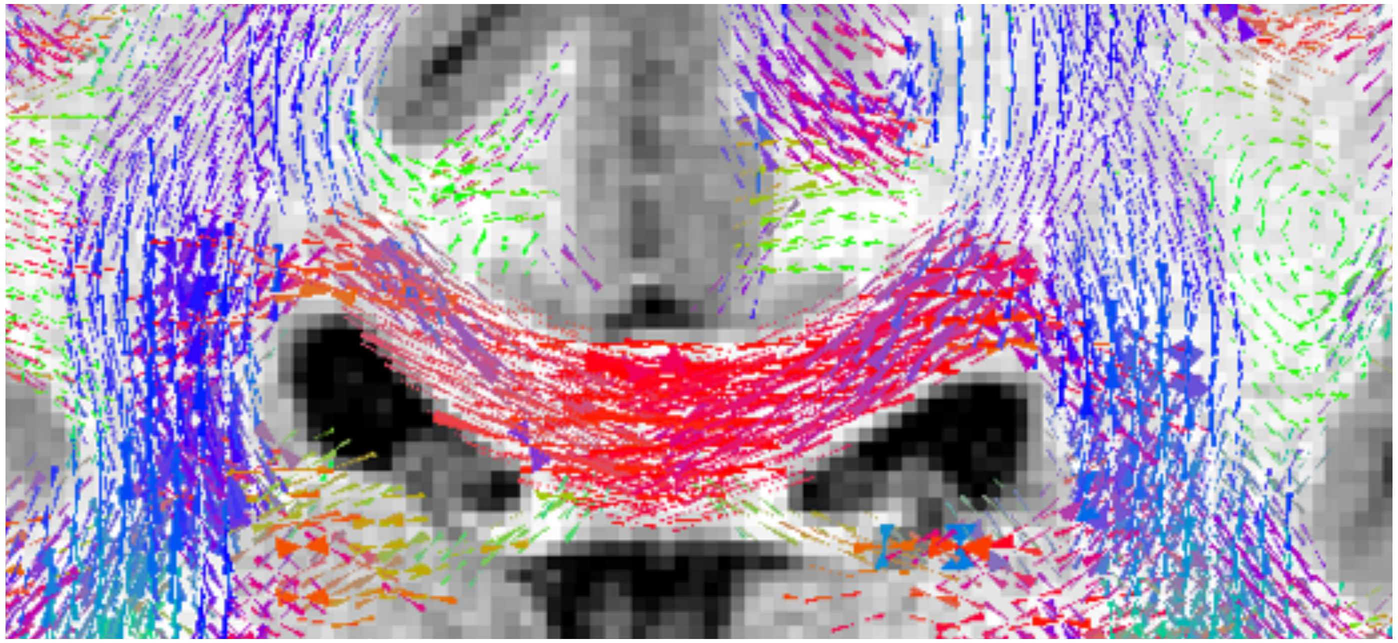






Visualisation of Orientation Uncertainty in Workbench





*See Practical
for various options
to visualise these
distributions

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Fusing 3T & 7T HCP dMRI

3T

1.25 mm, 3 shells

90 dir / shell (x2)

MB3

100 mT/m

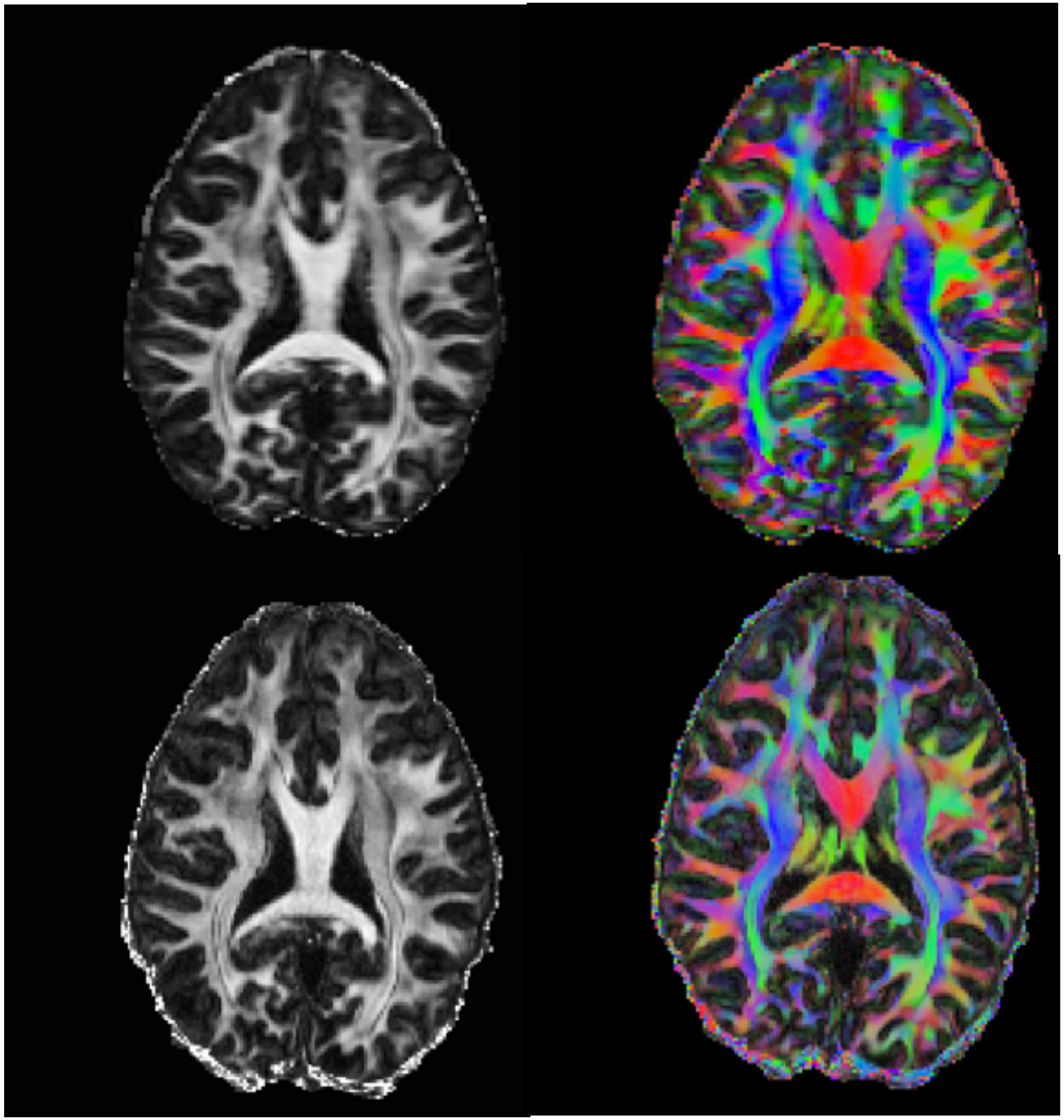
7T

1.05 mm, 2 shells

65 dir / shell (x2)

MB2, GRAPPA3

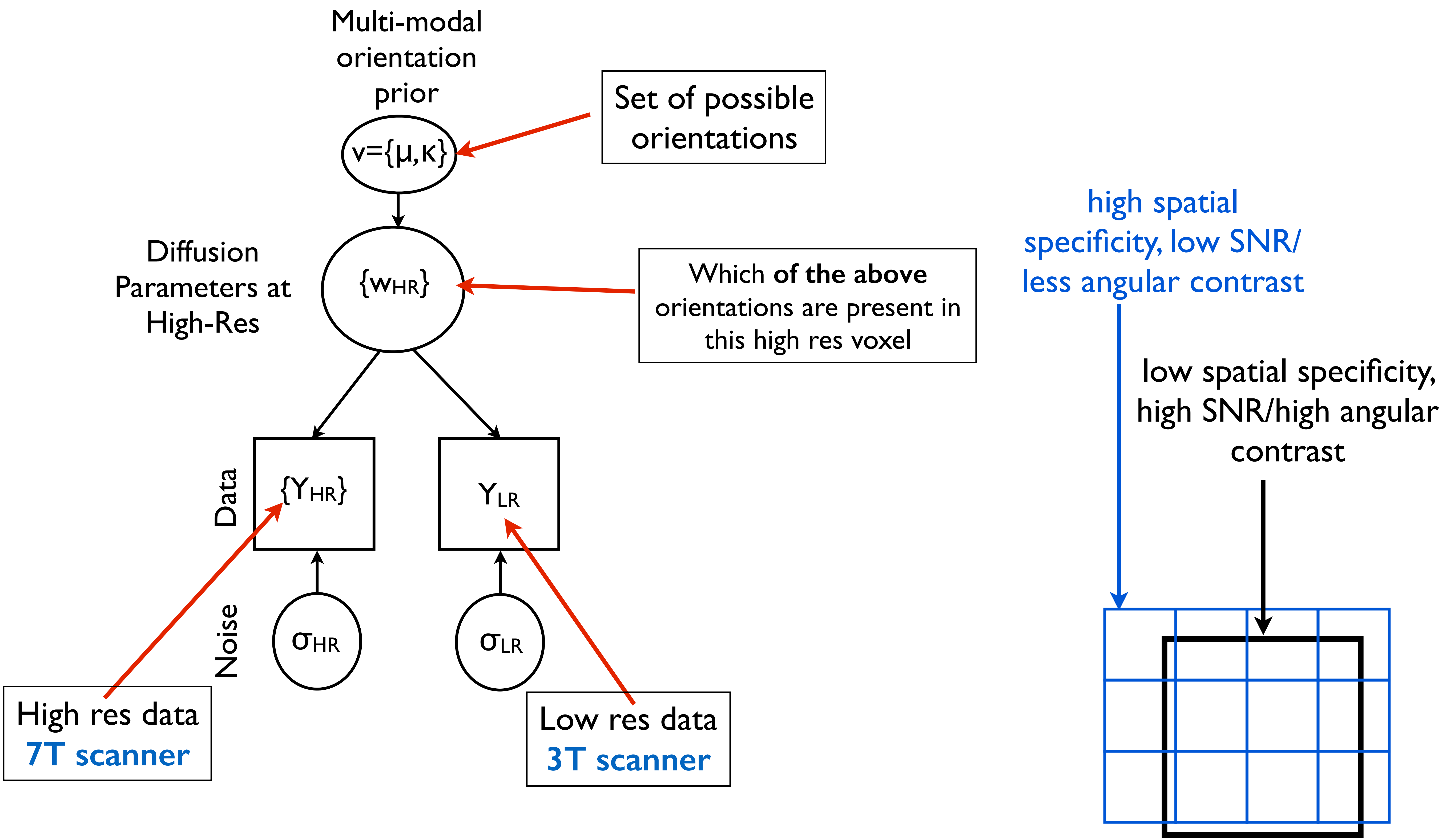
70 mT/m



3T: Better Angular Contrast, Better SNR => **better sensiticity to complex fibre patternsns**

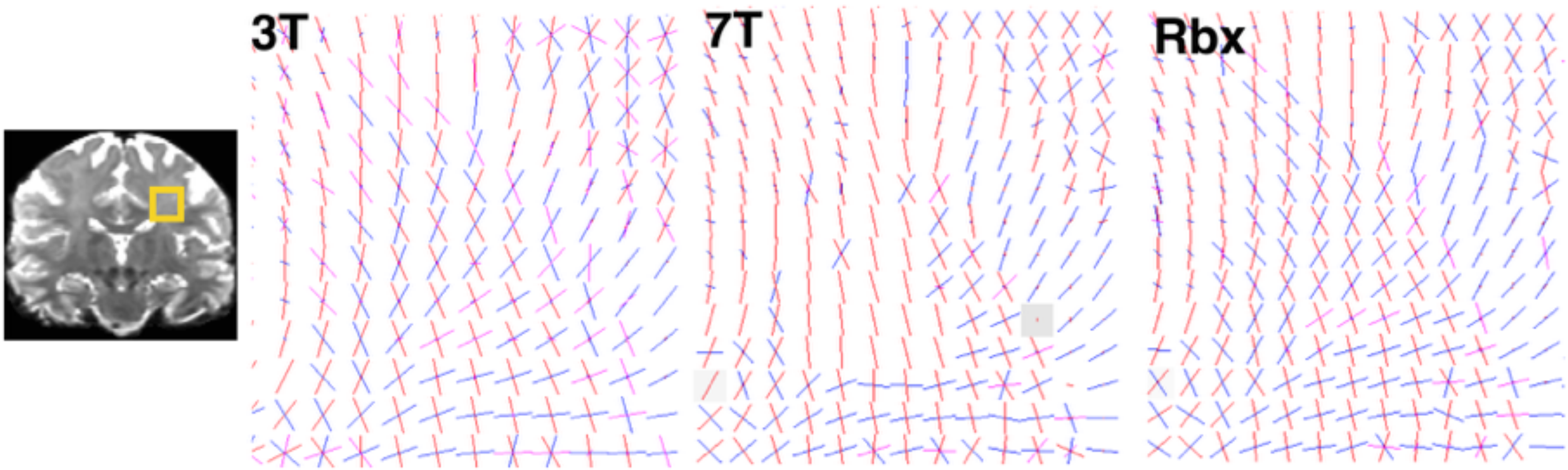
7T: Better Spatial Resolution
(considering total readout and PSFs, 7T voxels ~40% of 3T voxels)

RubiX - Spherical Deconvolution of dMRI acquired at different spatial resolutions



(Sotiropoulos et al, IEEE TMI 2013)

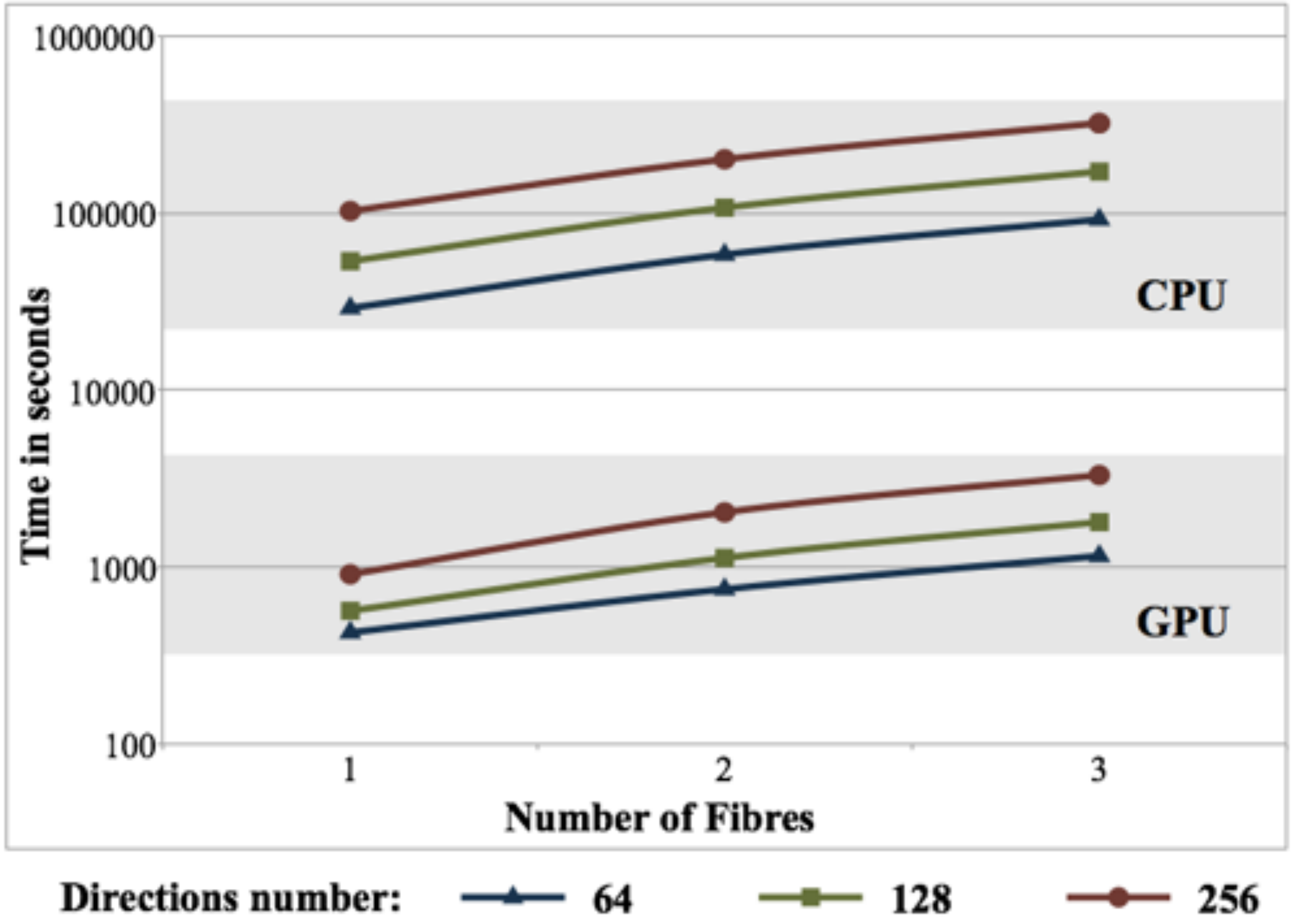
In deep WM, RubiX can achieve similar level of complexity as 3T, at the 7T resolution grid



(Sotiropoulos et al, ISMRM 2015)

The Need for Speed! … bedpostx_gpu

- Sampling-based Inference takes very long on dMRI datasets.
- It is even worse for HCP dMRI datasets, which are huge compared to conventional dMRI.
- Do not run bedpostX on a desktop with HCP data, unless you are happy to wait for weeks…
- **GPU** non-trivial **implementations allow massive speed-ups (x150)**.



Hernandez et al, Plos One 2013

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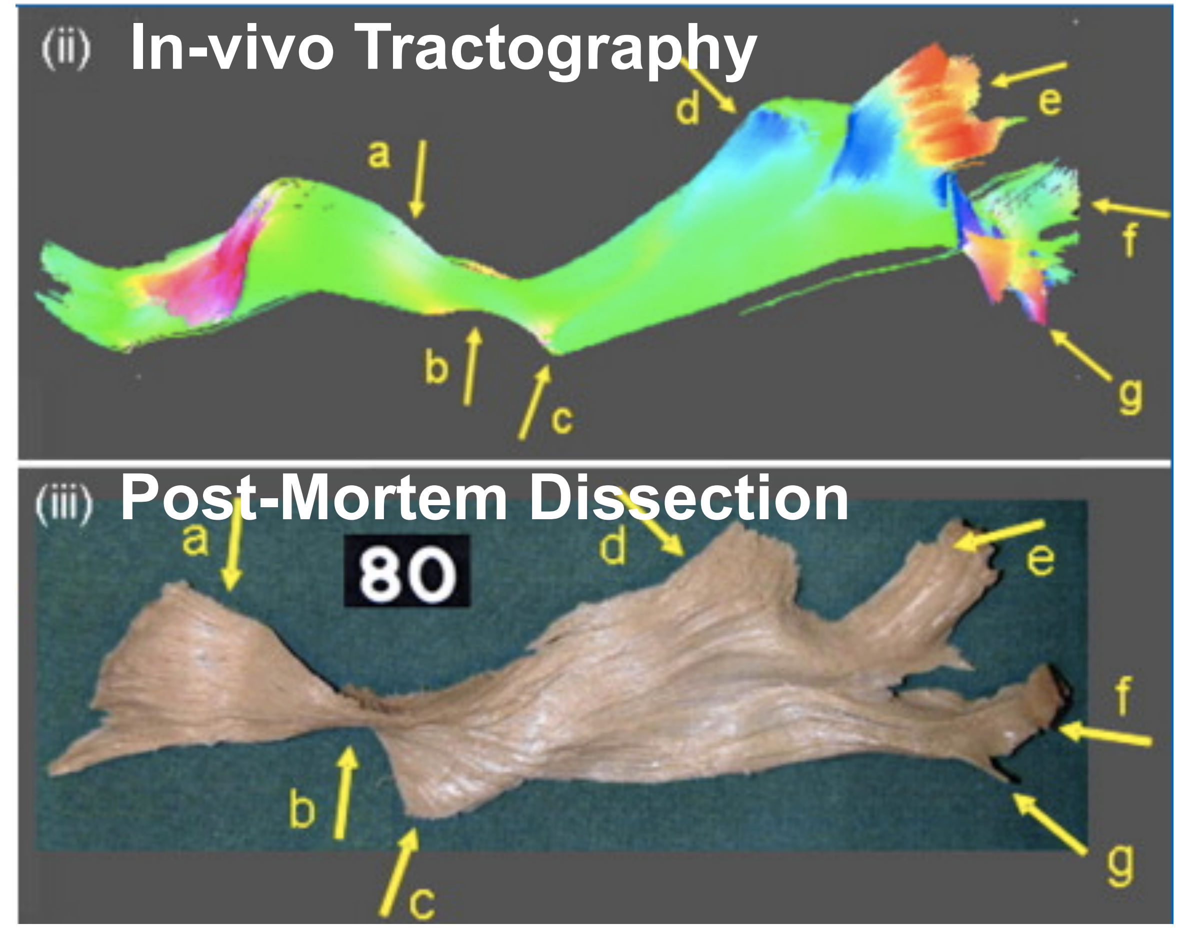
What does tractography offer?

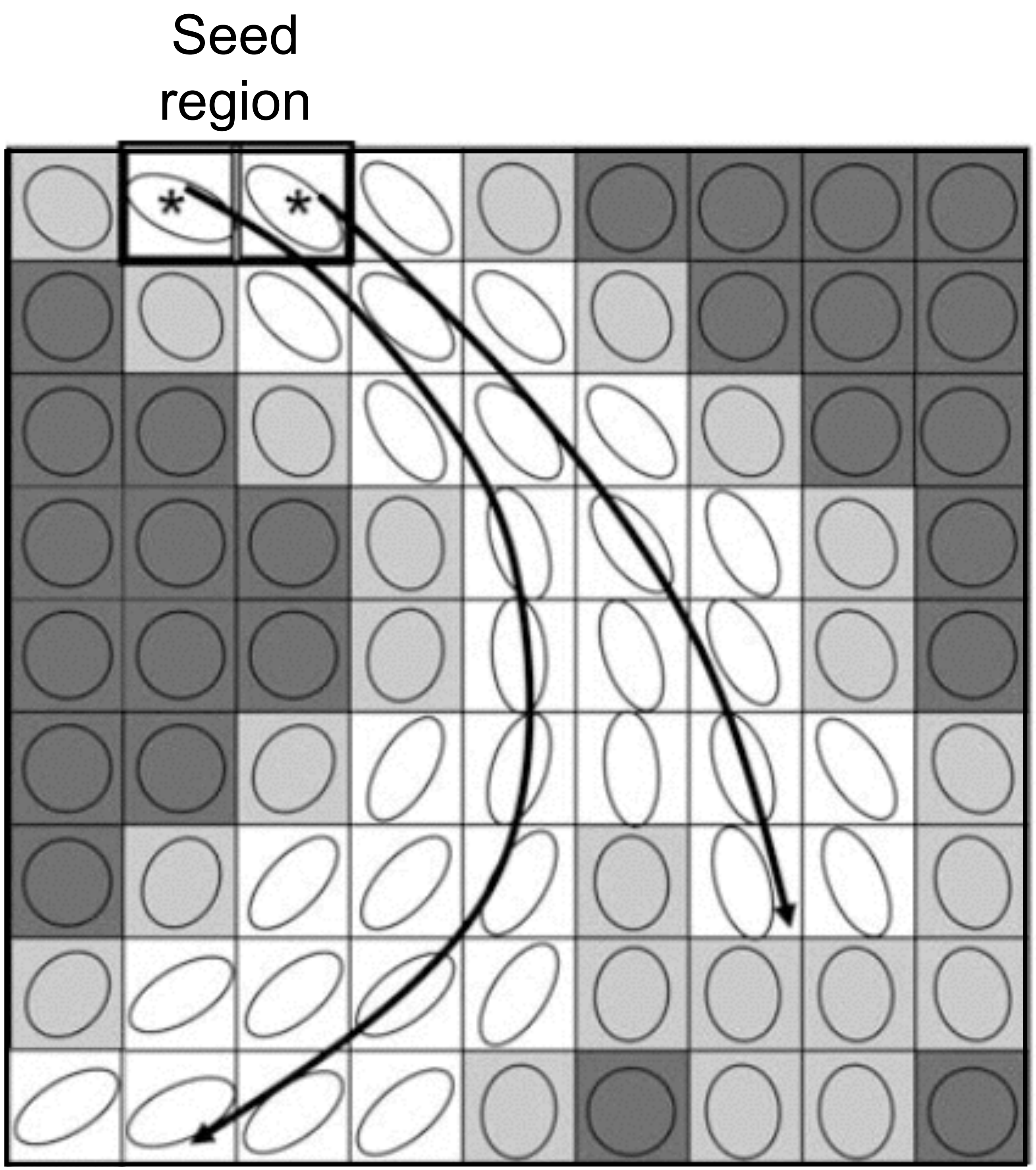
+ non-invasive
+ in-vivo
+ whole brain
+ can address new questions and associate with function & behaviour



Lawes et al. 2008

...But
- realtively low resolution (large bundles)
- indirect (diffusion paths)
- error prone (MRI is noisy)
- difficult to interpret quantitatively

DTI Streamline Tractography



Mori S, Neuron 2006

Formally, we solve numerically the differential equation:

$$\boxed{\frac{d\mathbf{r}(s)}{ds} = \mathbf{v_1}(\mathbf{r}(s)), \quad \mathbf{r}(0) = \mathbf{r}_0}$$

Position along a curve

Principal eigenvector $\mathbf{v_1}$ at position $\mathbf{r}(s)$

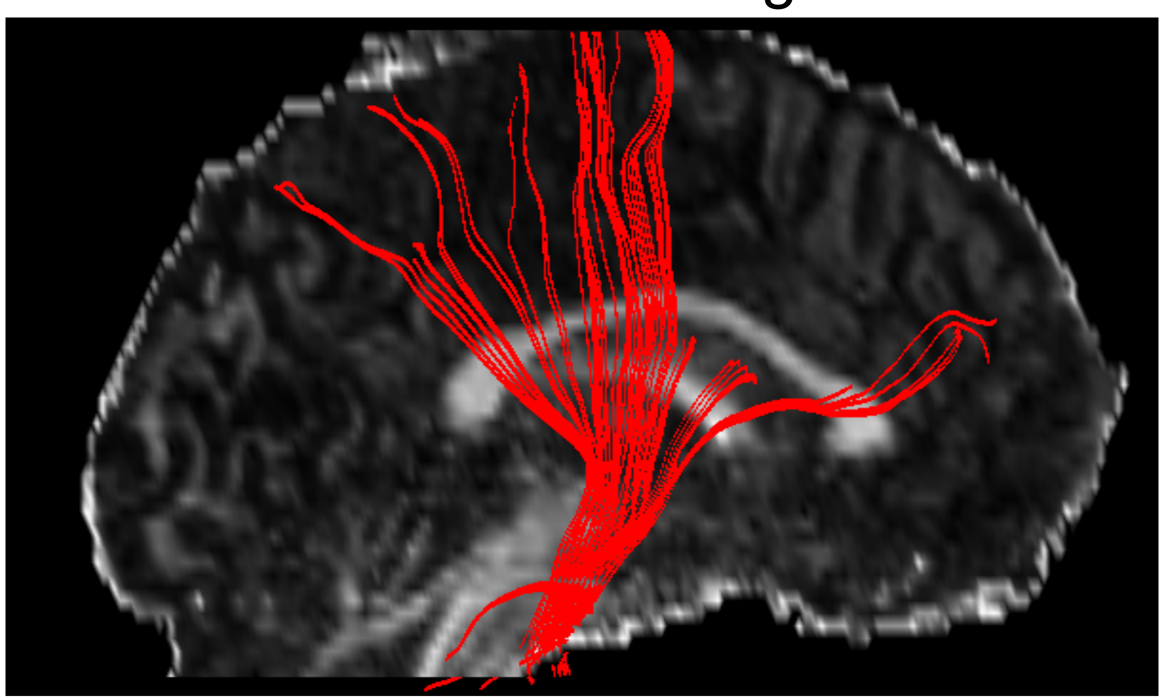
Starting Position

Streamlining reproducibility

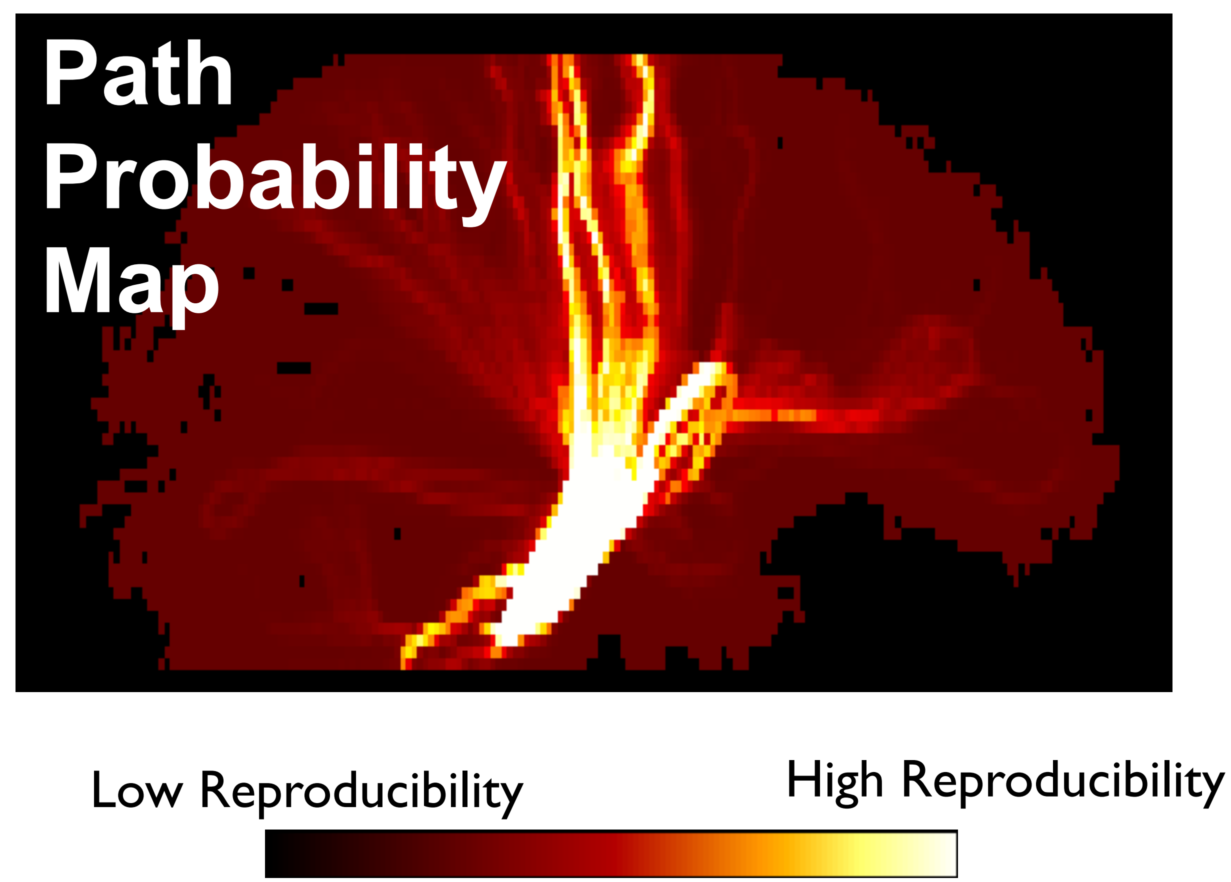
-> By following a deterministic orientation estimate per voxel, deterministic tracking will always produce the same deterministic result.

-> But due to uncertainty in the estimates, curves will not perfectly overlap if we repeat an experiment. So, what if we are interested in a spatial distribution describing this path estimate?

Streamlines from a single dataset



Map that shows where results across datasets overlap



Probabilistic Tractography

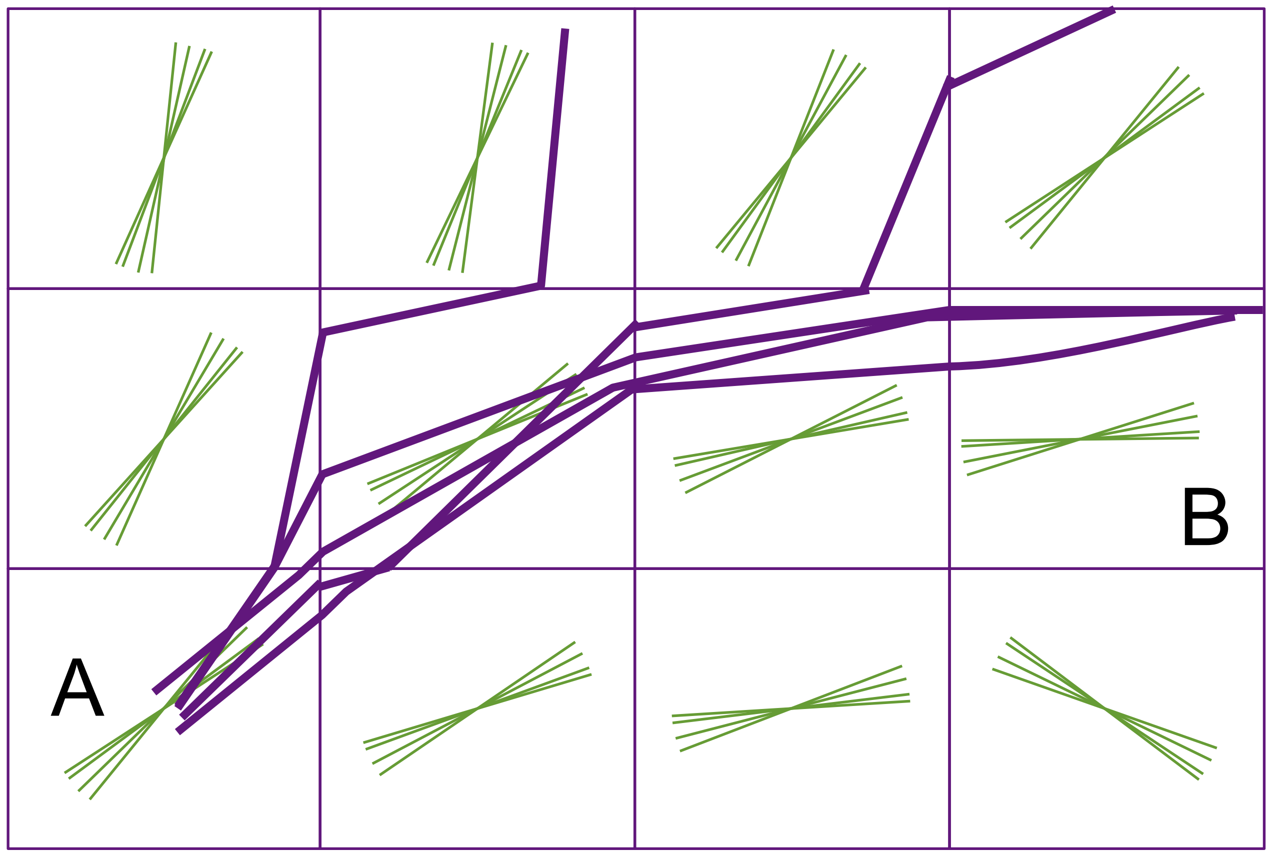
- We normally have one dataset per subject, not many.

- Probabilistic Tractography as a two-step process:

a) Use DWI data and a model to infer a fibre orientation **and its uncertainty** in each voxel.

b) Use the estimates **and the uncertainty to build a path probability map** to a seed
(i.e. it estimates a spatial distribution of possible connections vs a deterministic estimate)

Probabilistic Tractography - Propagating the Uncertainty

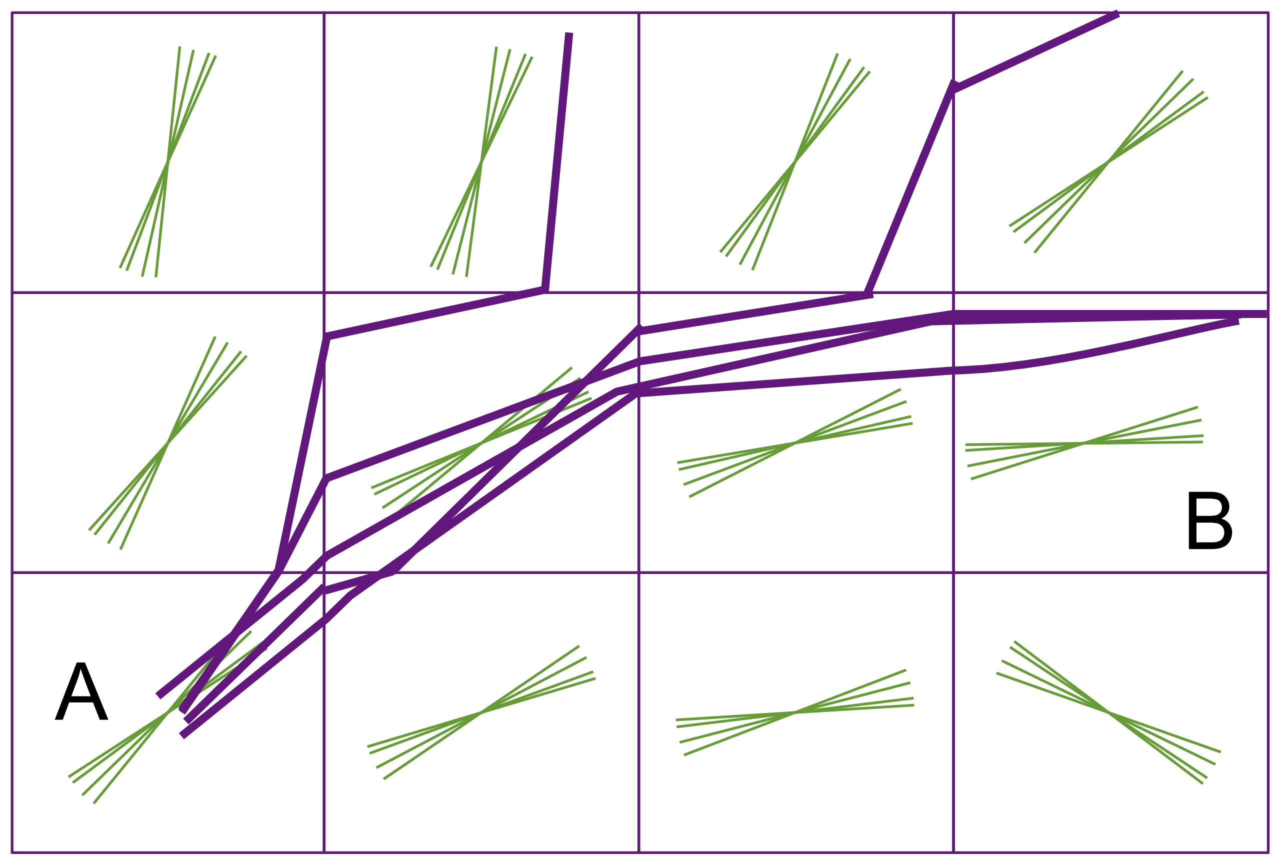


Behrens et al, 2003
Parker et al, 2003

- Propagate N streamlines from a seed, but for each propagation step choose randomly an orientation from the underlying distribution.

- Build a spatial distribution of curves that mimics the overlapped results from multiple deterministic tracking on multiple scans

Probabilistic Tractography - Propagating the Uncertainty



Behrens et al, 2003
Parker et al, 2003

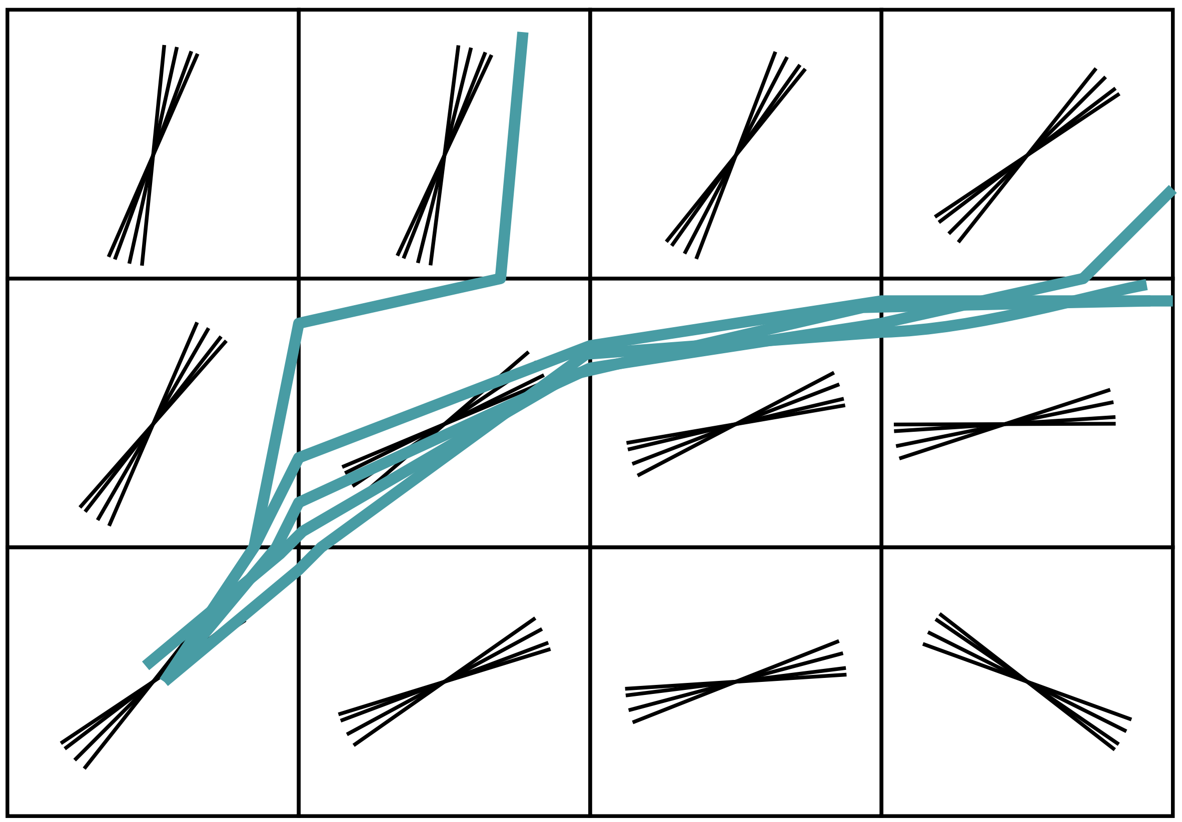
Define the degree of overlap at each location B, as:

$$\boxed{P_{AB} = M/N}$$

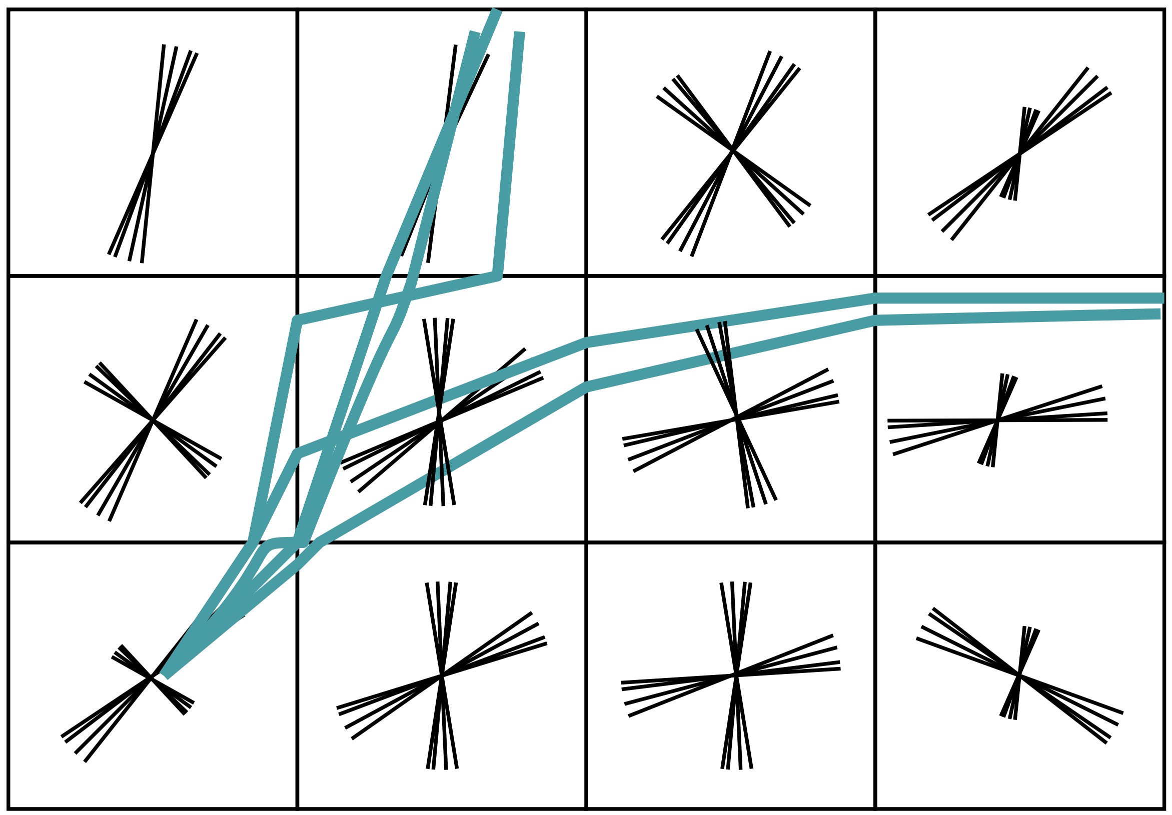
M:number of streamlines that go through B
N: total streamlines generated from A

This is the probability of a curve starting at A and going through B.

Probabilistic Tractography in Multi-Fibre Fields



Behrens et al, 2003, Parker et al. 2003,
Hagmann et al 2003, Jones et al. 2004



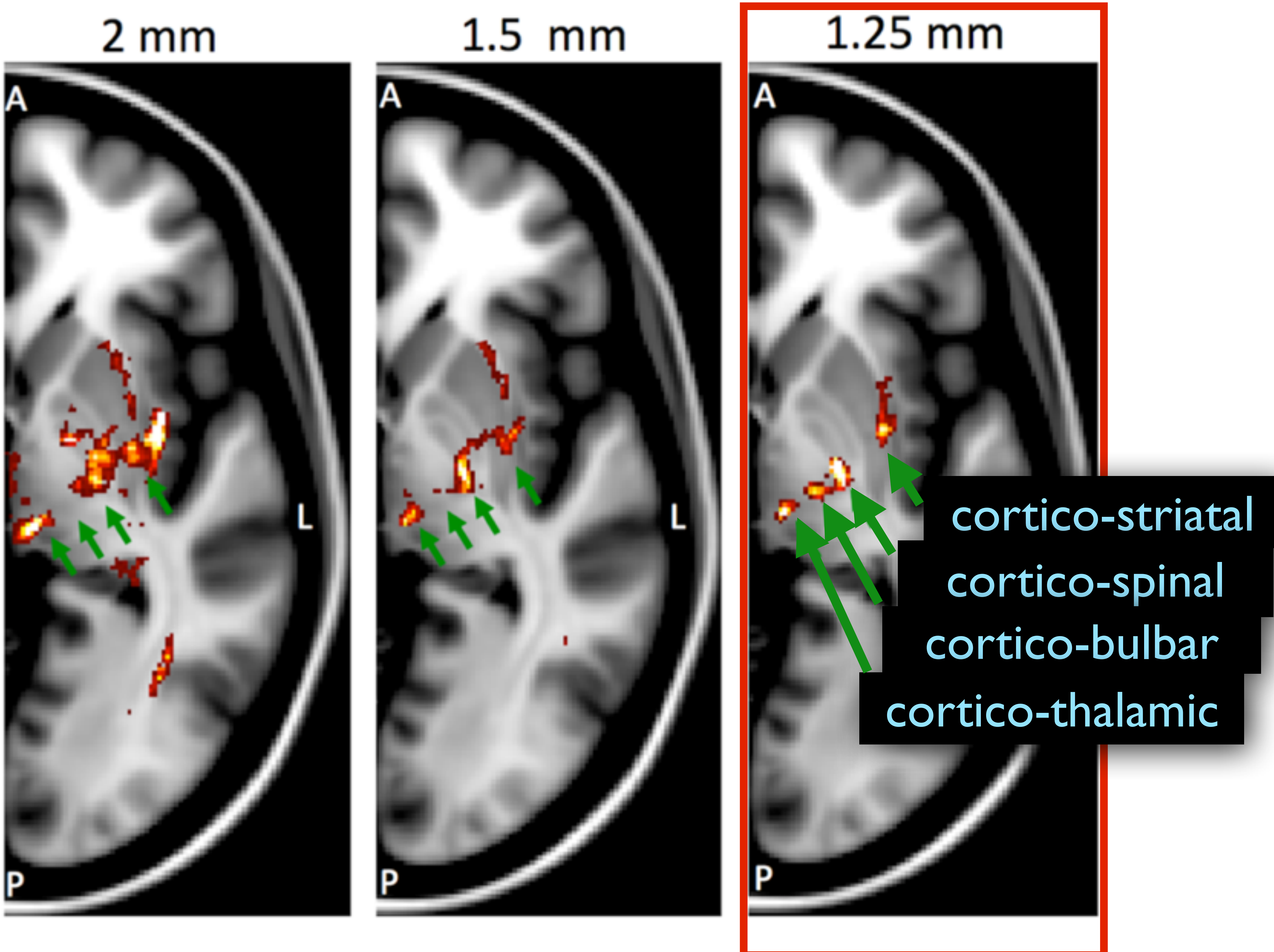
Parker & Alexander 2003,
Behrens et al, 2007

When multiple fibre orientations exist in a voxel, choose the one that is most compatible with the incoming trajectory.

Examples of Probabilistic Tractography in HCP data

The Importance of spatial resolution

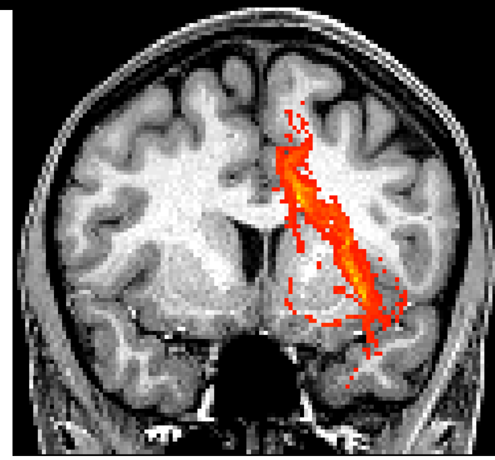
Seed:
Hand Area M1

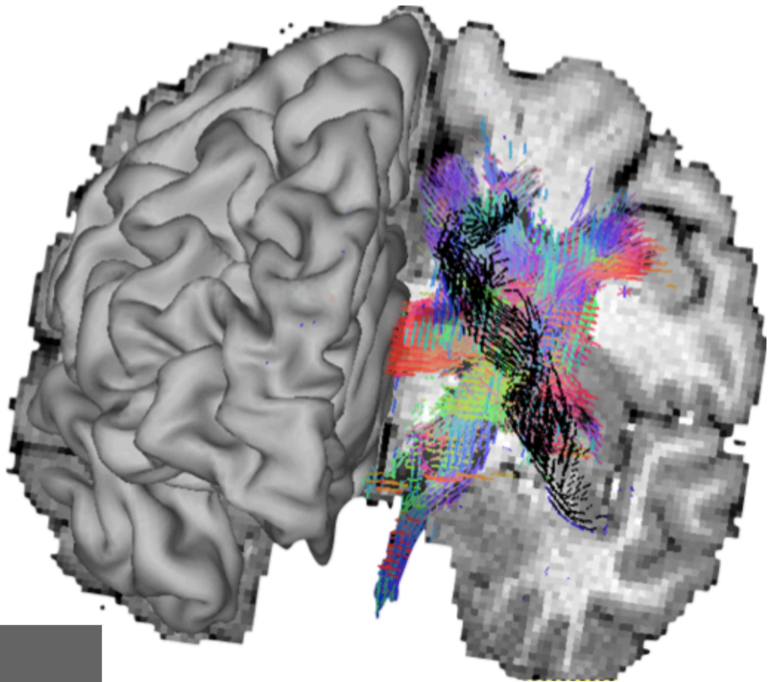


Sotiropoulos et al, NeuroImage 2013

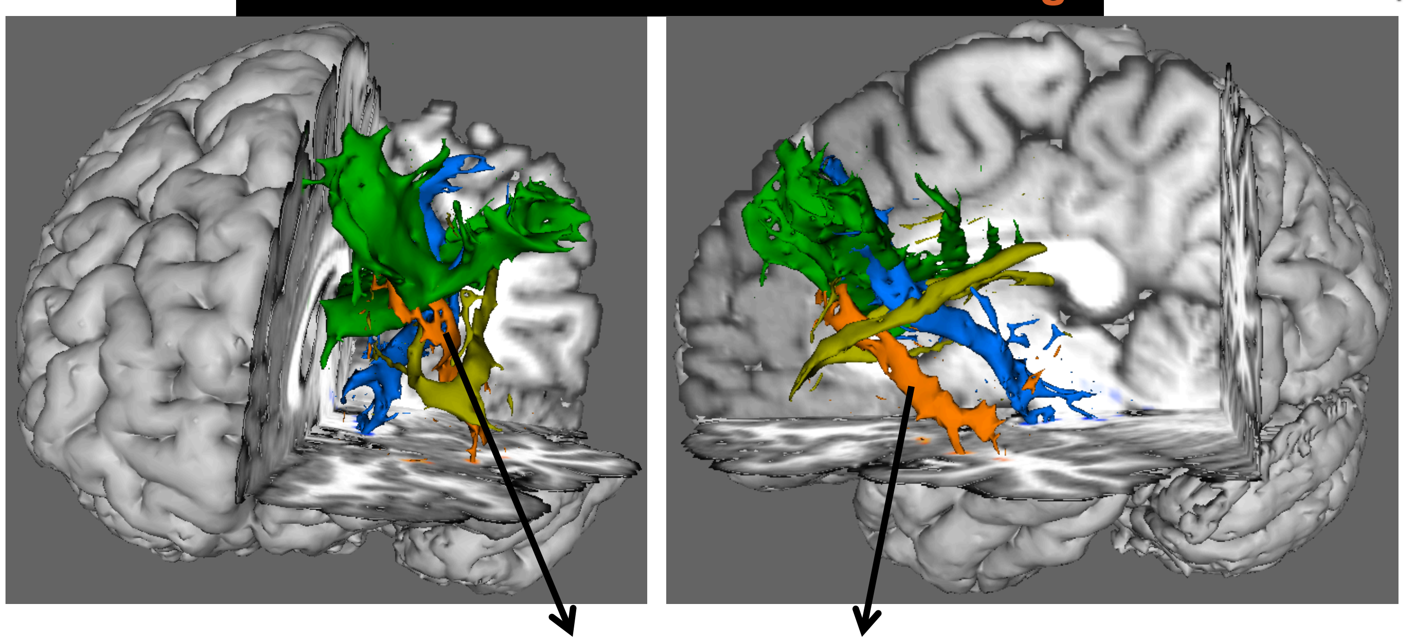
Examples of Probabilistic Tractography in HCP data

Insula-cingulate connection (Maximum Intensity Projection)





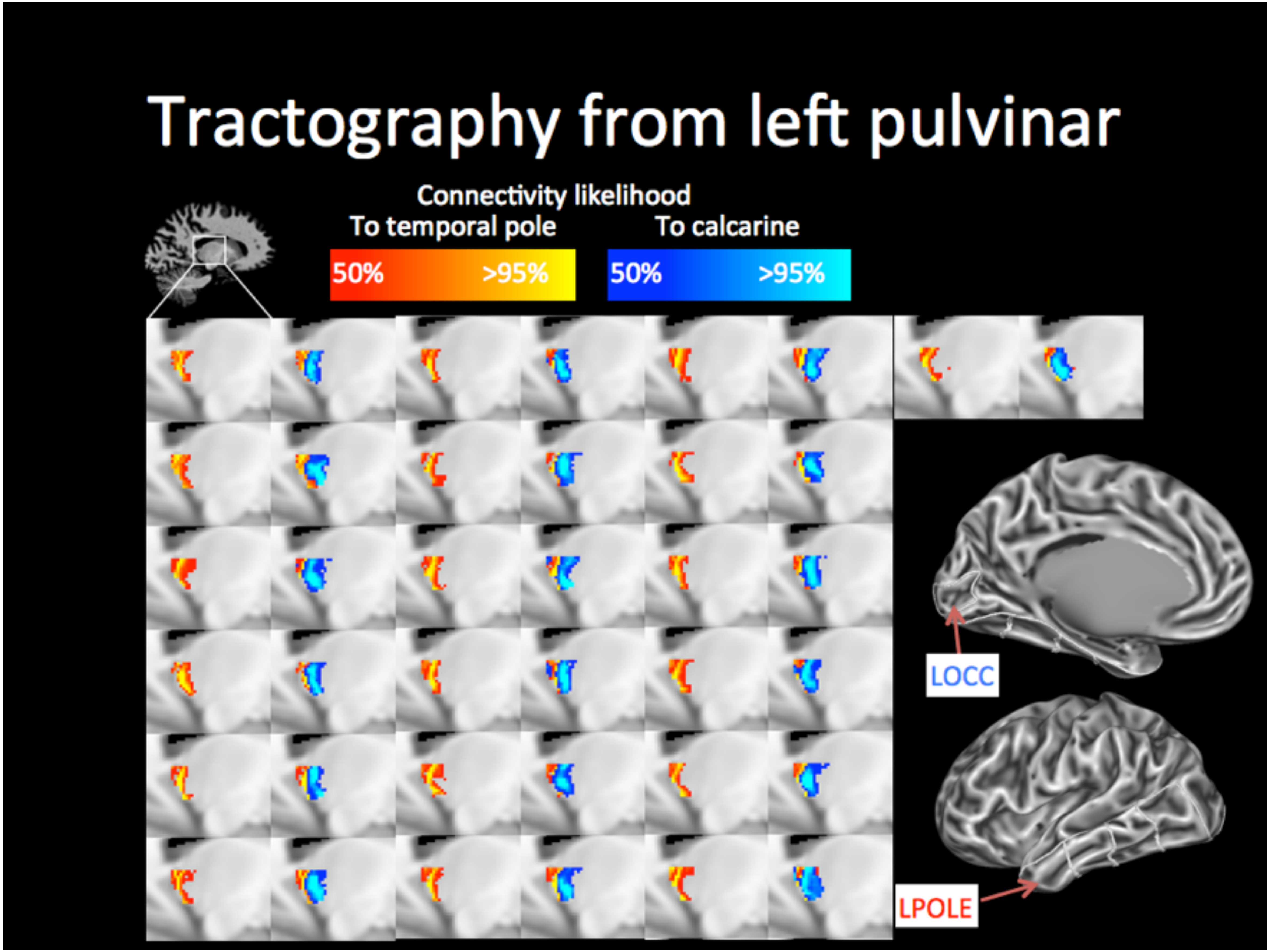
Callosum + CST + SLF + Insula-Cing



Route taken by insula-cingulate connection, crossing the centrum semiovale

If one fibre is modelled and we track through a crossing, a) we may not make it through the crossing, b) if we make it, the connectivity index will be relatively low.

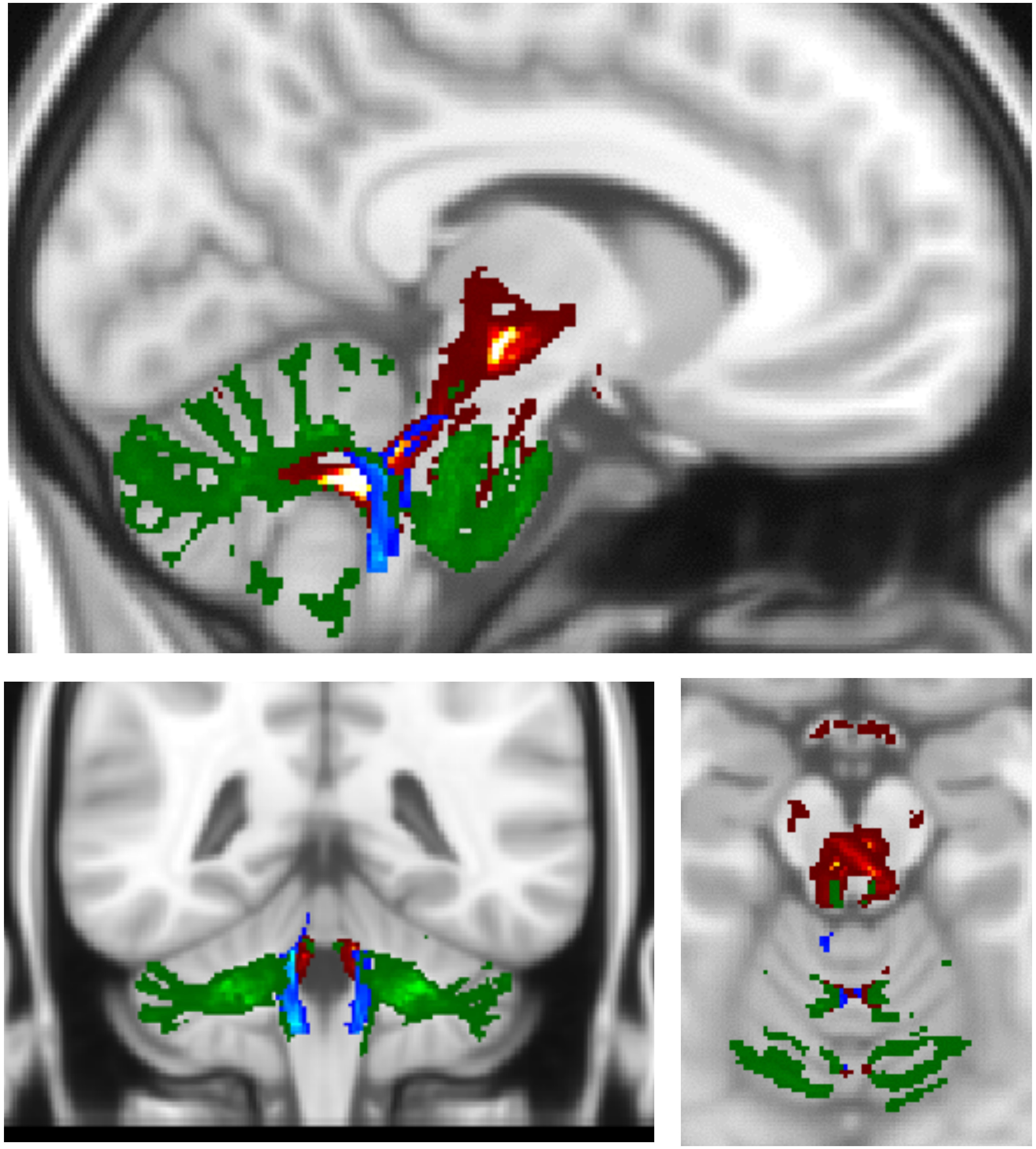
Examples of Probabilistic Tractography in HCP data

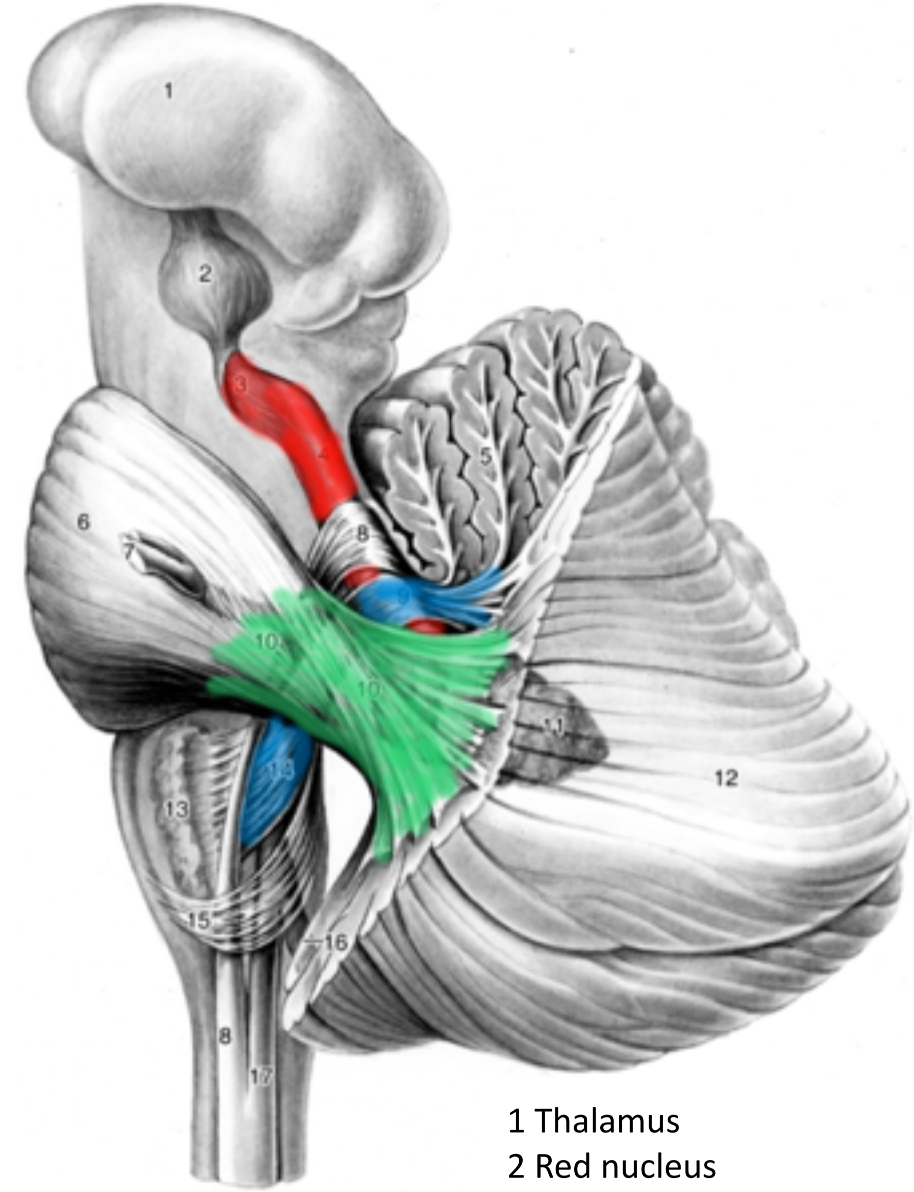


Courtesy of Johannes Klein

Examples of Probabilistic Tractography in HCP data

Resolving the cerebellar peduncles and the decussation of the SCP





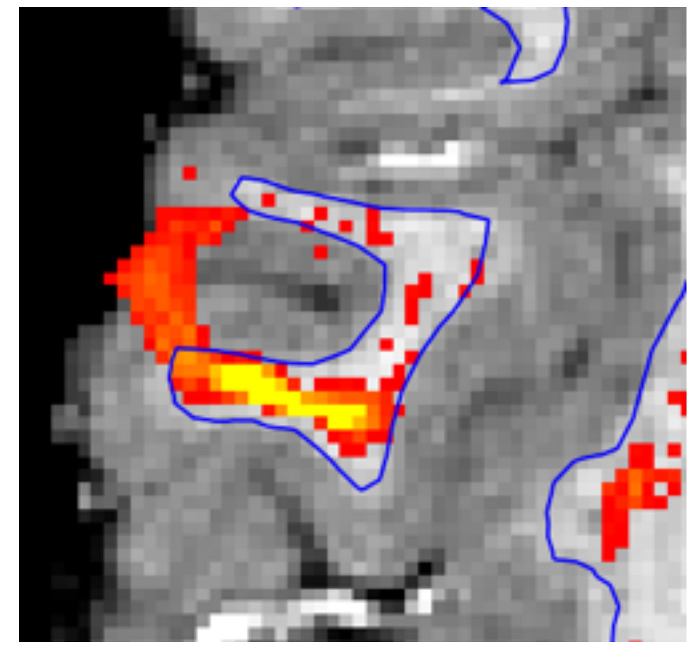
1 Thalamus
2 Red nucleus
3 Decussation
4 Superior cerebellar peduncle
5 Vermis
6 Pons
7 Trigeminal nerve
8 Ventral spinocerebellar tract
9 Inferior cerebellar peduncle
10 Middle cerebellar peduncle
11 Dentate
12 Inferior olive
14 Olivocerebellar fibres
15 External arcuate fibres

Kirsten van Baarsen & Michiel Kleinnijenhuis

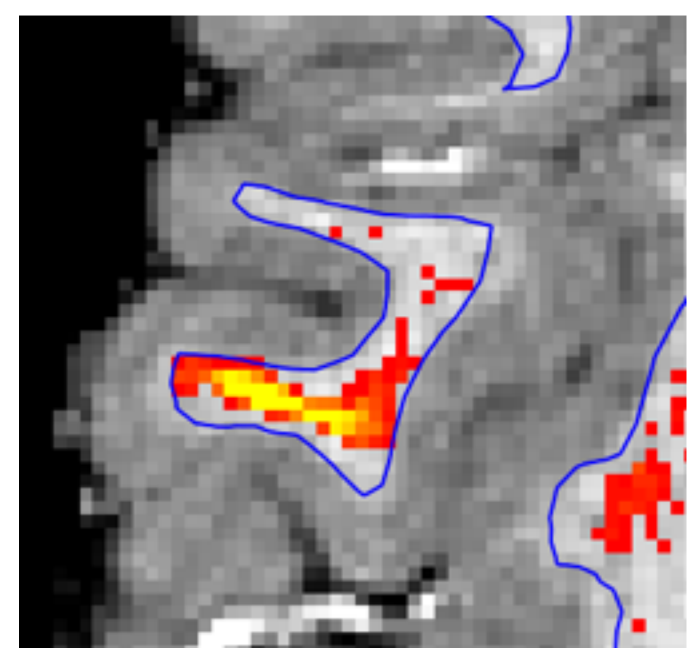
Using Surfaces in Tractography and probtrackX

Using 2D surfaces allow more realistic constraints and seeds in tractography.

No surface constraint



Surface constrained



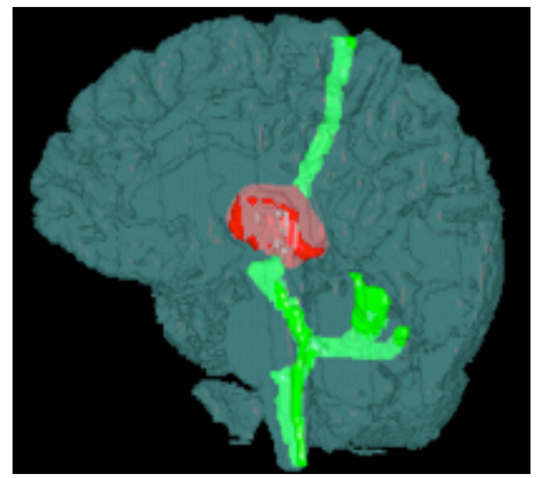
Overview

- Why DTI is not enough?
- Estimating Crossing Fibre Orientations - bedpostX
  - Adding spatial information - RubiX
- Probabilistic Tractography - probtrackX
- Applications & Connectomes

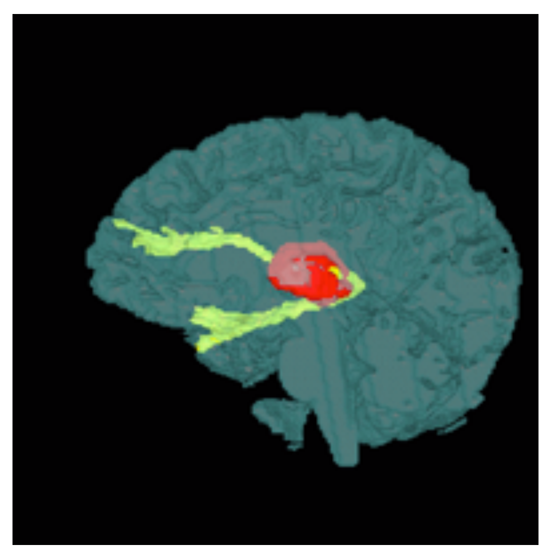
Connectional contrast

no contrast on conventional MRI

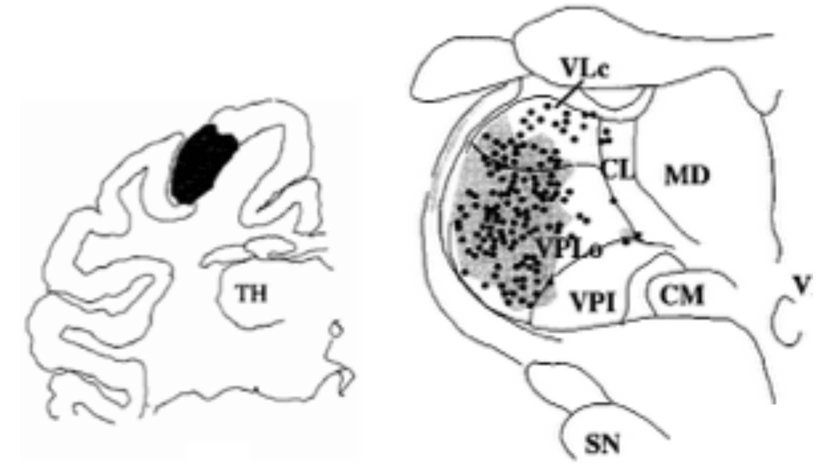
VL –> M1

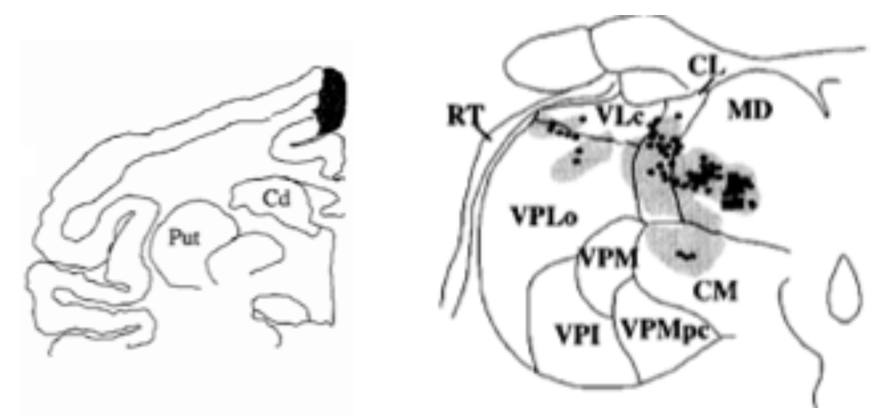


MD –> PFC



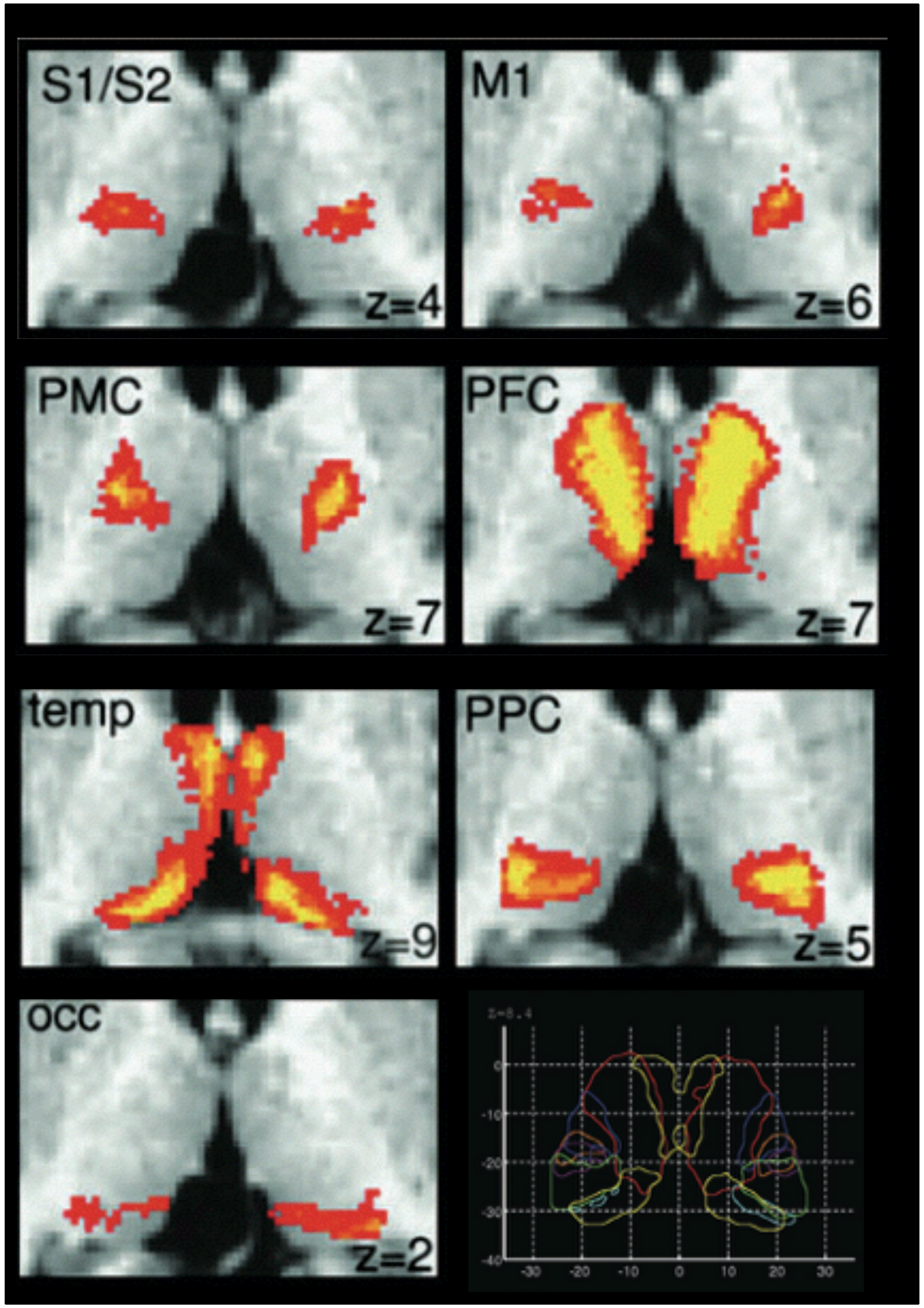
Behrens et al, 2003
(probabilistic tractography)

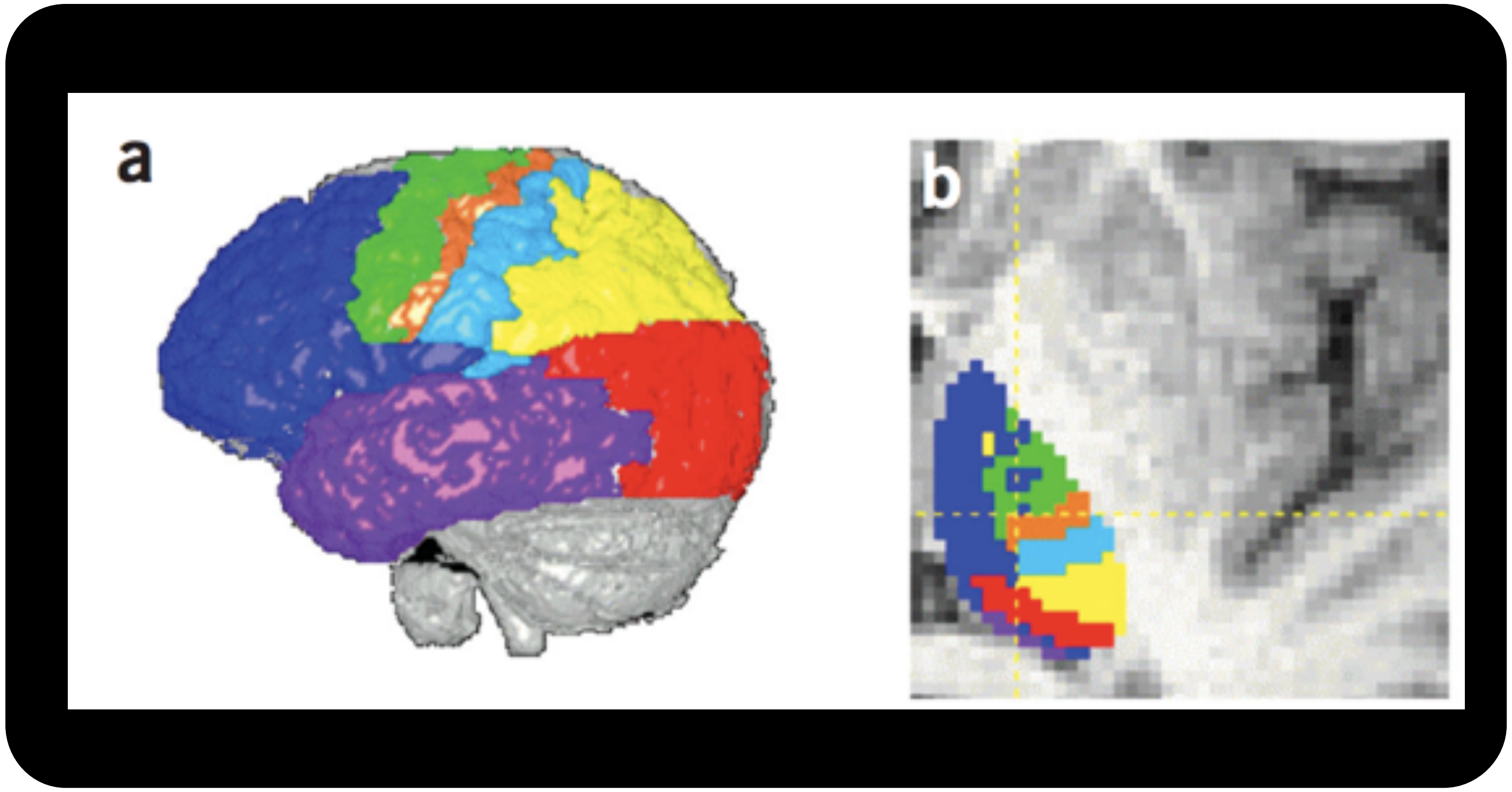




Rouiller et al, 1998
(BDA anterograde tracing)

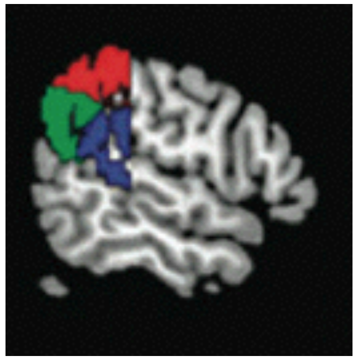
Connectional contrast in the thalamus



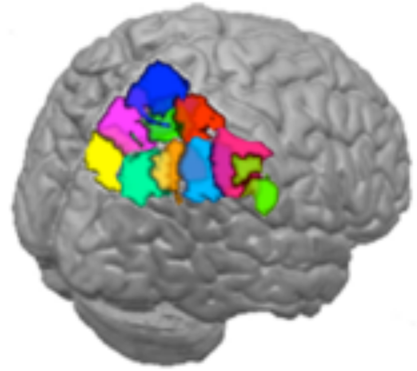


Behrens et al. Nat Neuro2003
Johansen-Berg et al. Cereb Ctx 2005

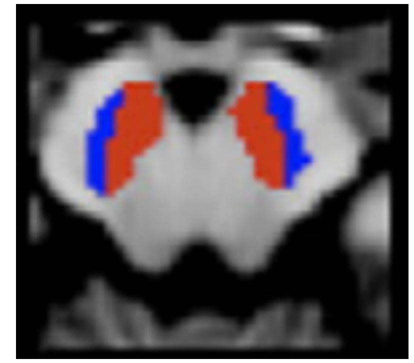
Using Tractography to extract "Connectional contrast" in GM



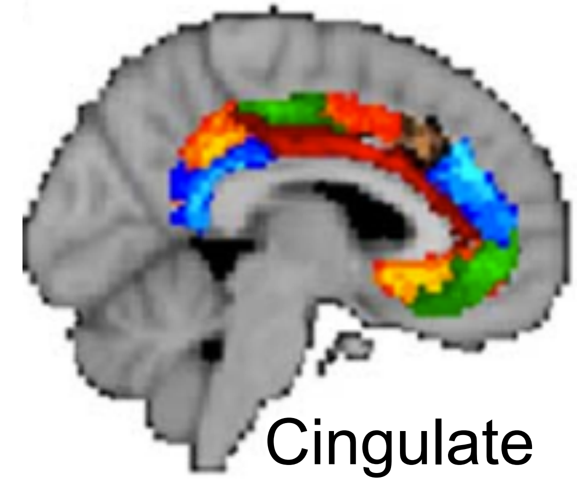
Temporo-parietal junction
Mars 2012



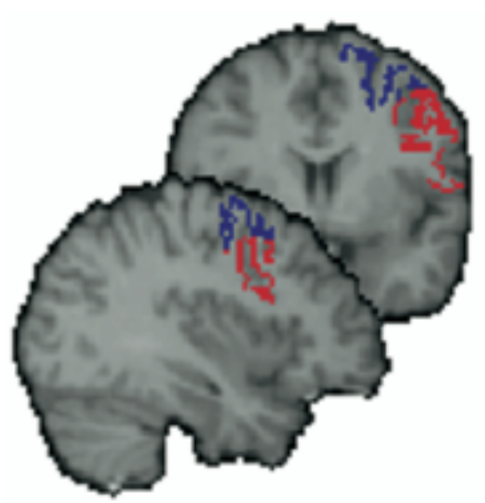
Lateral Parietal
Mars 2011



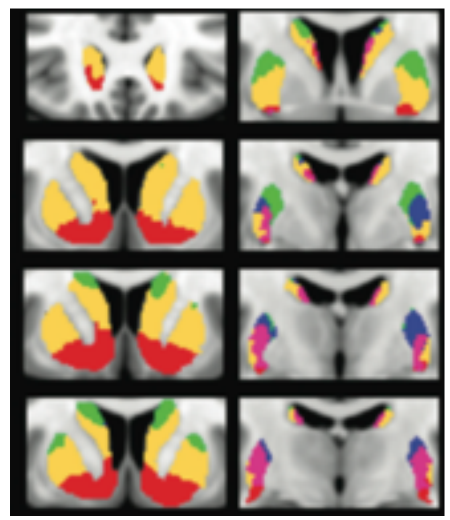
Substantia Nigra
Menke 2010



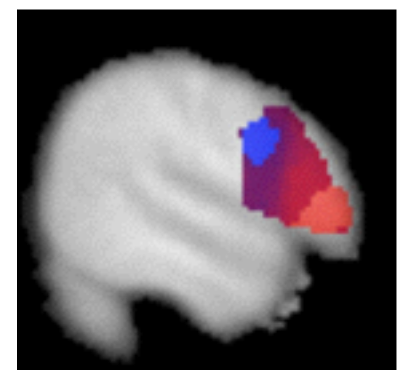
Cingulate
Beckmann 2009



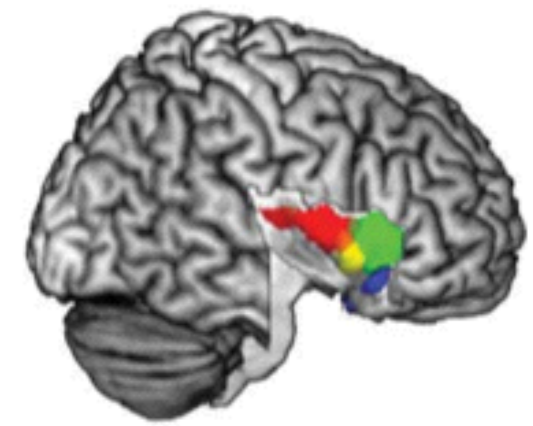
Lateral pre-motor
Tomassini 2007



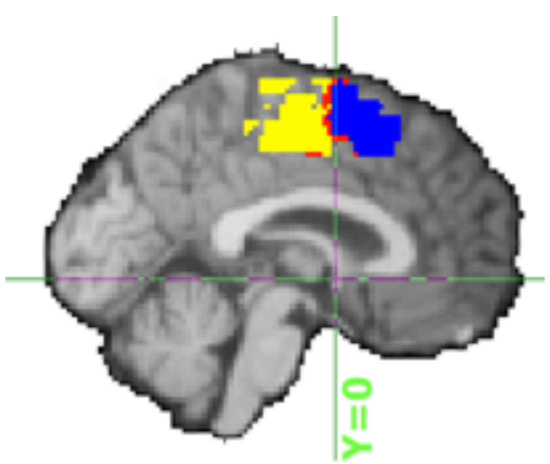
Striatum
Tziortzi 2013



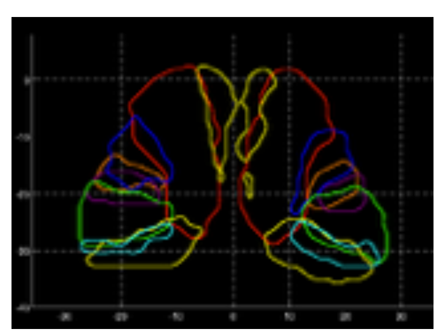
Broca's area
Klein 2007



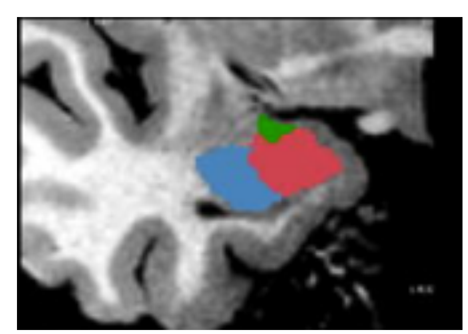
Insular cortex
Cerliani 2012



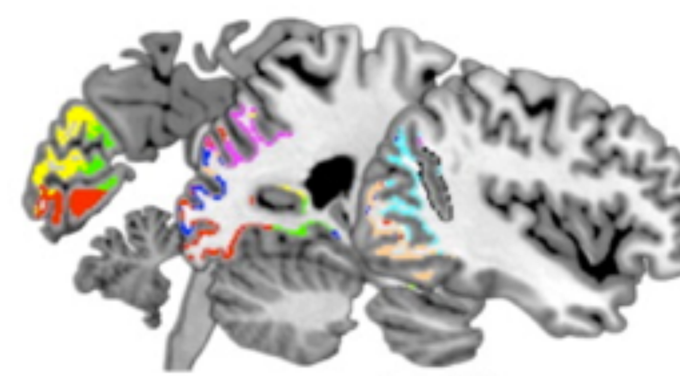
Medial prefrontal
Johansen-Berg 2004



Thalamus
Behrens 2003

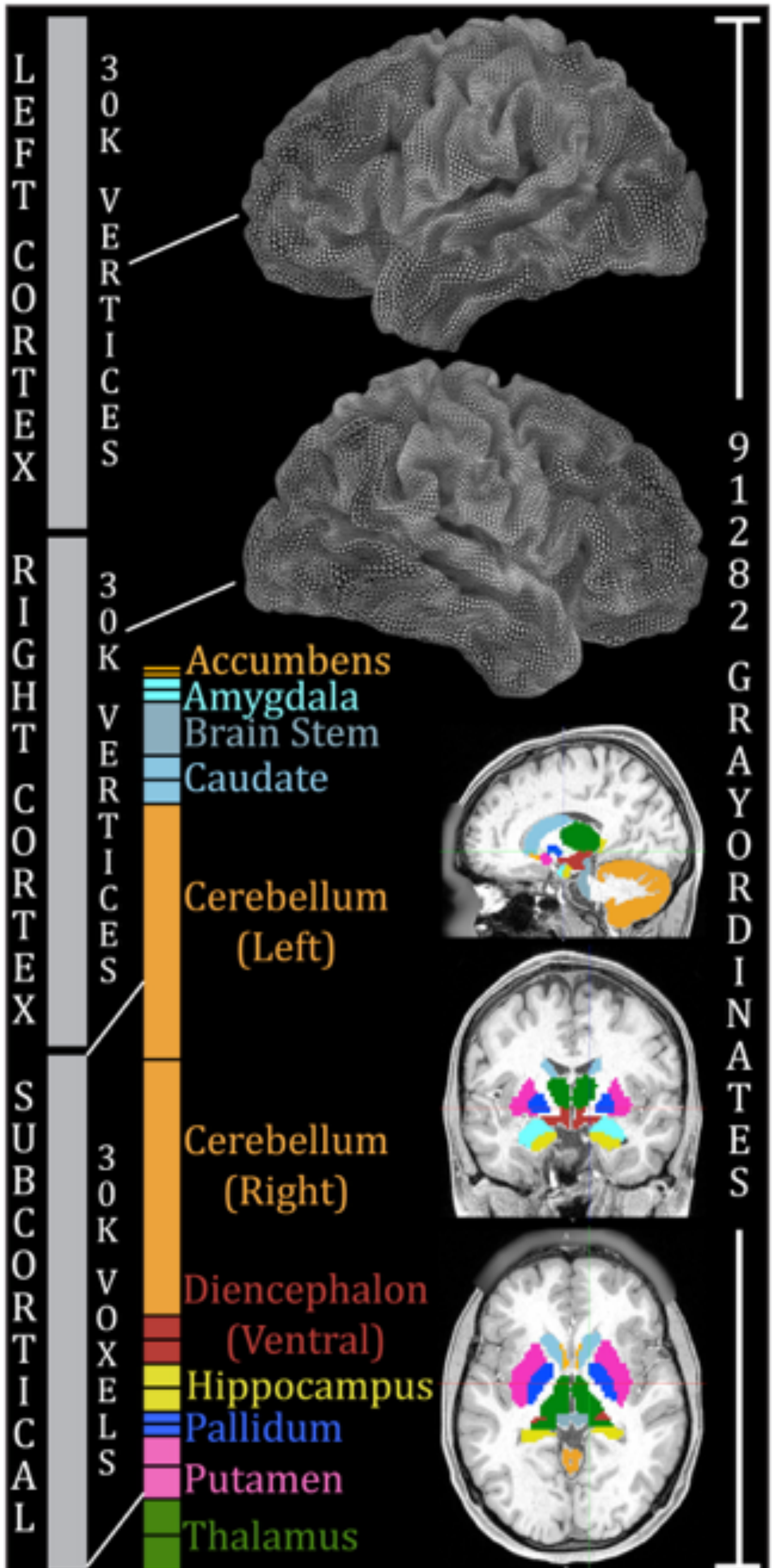


Amygdala
Saygin 2011



Occipital cortex
Thiebaut de Schotten 2013

Connectomes: Obtain complehensive “connectivity profiles” from all GM to allow exploratory analysis



Connectivity profiles for **~90k *GrayOrdinates***

~30K surface vertex coordinates for Left Cortical hemisphere (from WM/GM boundary surface)

~30K surface vertex coordinates for Right Cortical hemisphere (from WM/GM boundary surface)

~30K voxel centre coordinates for Subcortex and Cerebellum

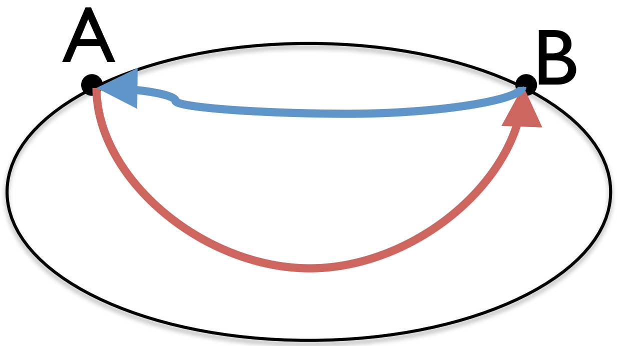
“Dense” Connectomes are huge 90k x 90k Matrices.
Each Row is a connectivity profile of each GrayOrdinate.

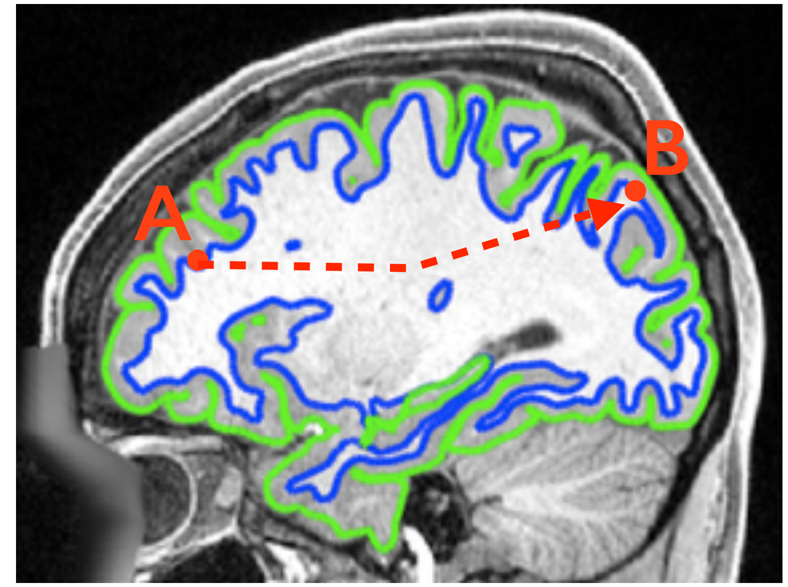
Glasser et al, NeuroImage 2013

Options for Connectome Matrices

$$Con1 = M1 + M1^T$$

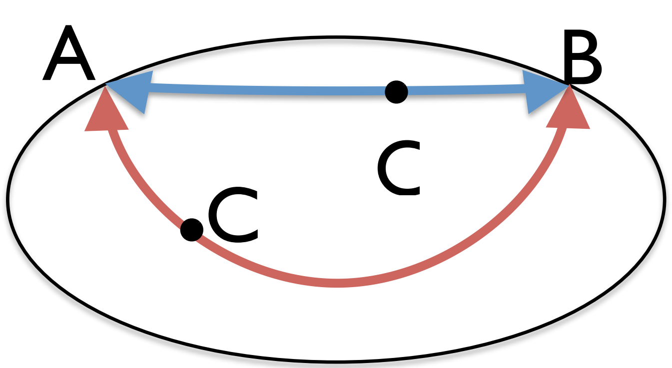
All paths starting from A ending at B
and starting from B ending at A

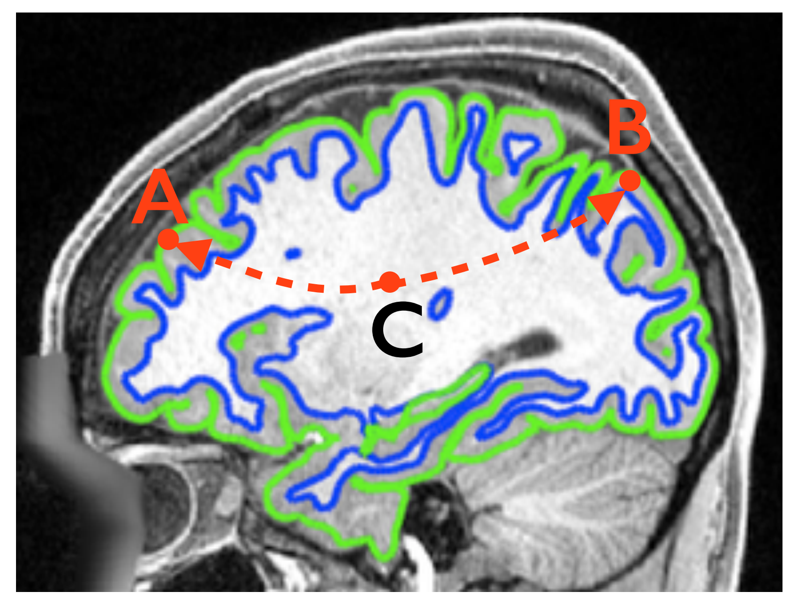




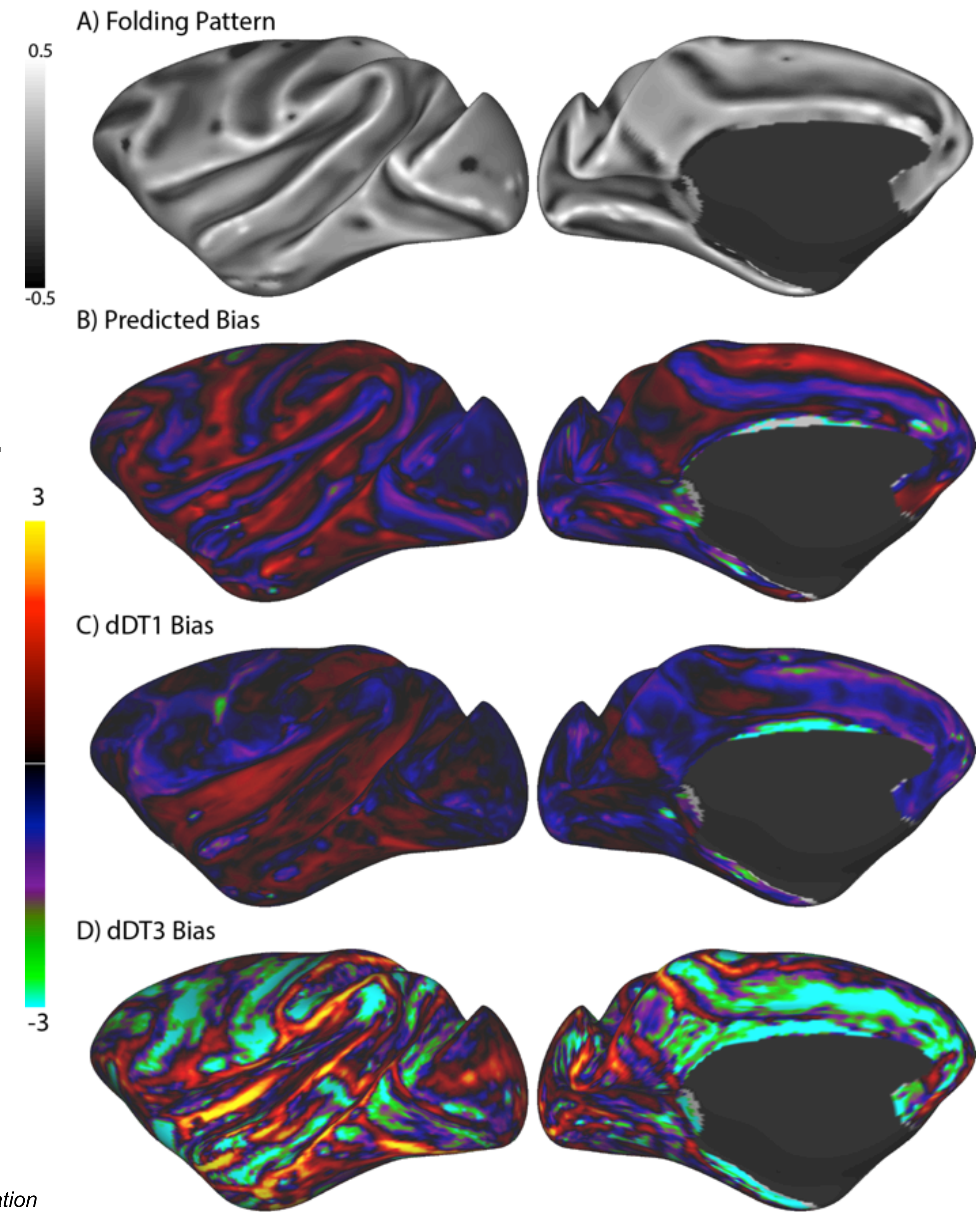
$$Con3 = M3$$

All paths starting from any point C and connect A and B





Pros & Cons of each Option



Con1: Less Gyral bias
More path-length dependent

Con3: Less path-length dependnce
More Gyral bias

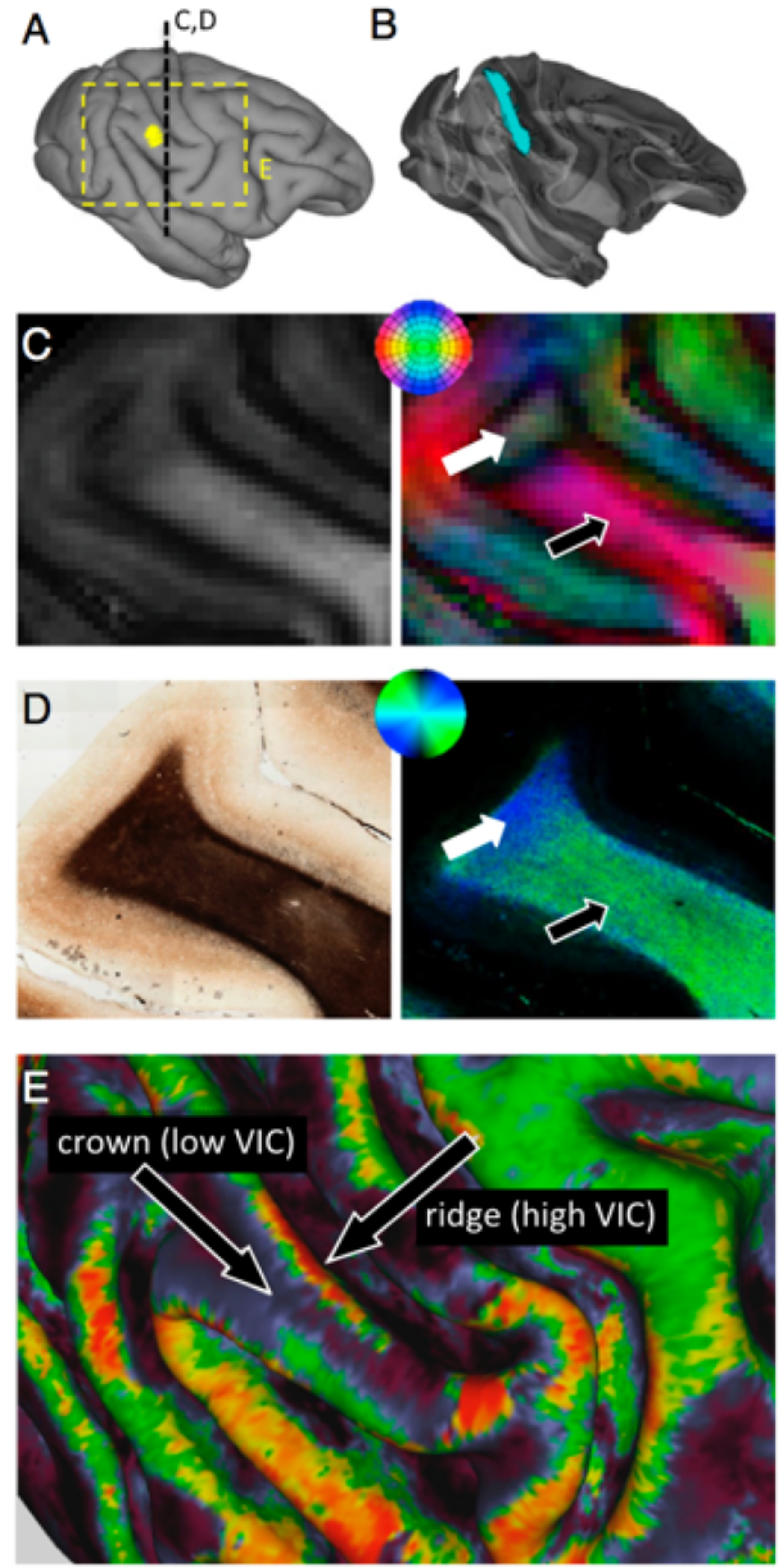
Donahue et al., *in preparation*

Superficial white matter

Complex fibre architecture close to white/grey matter boundary can bias tractography.

Need to improve:

- Diffusion models (include fibre fanning)
- Tractography algorithms



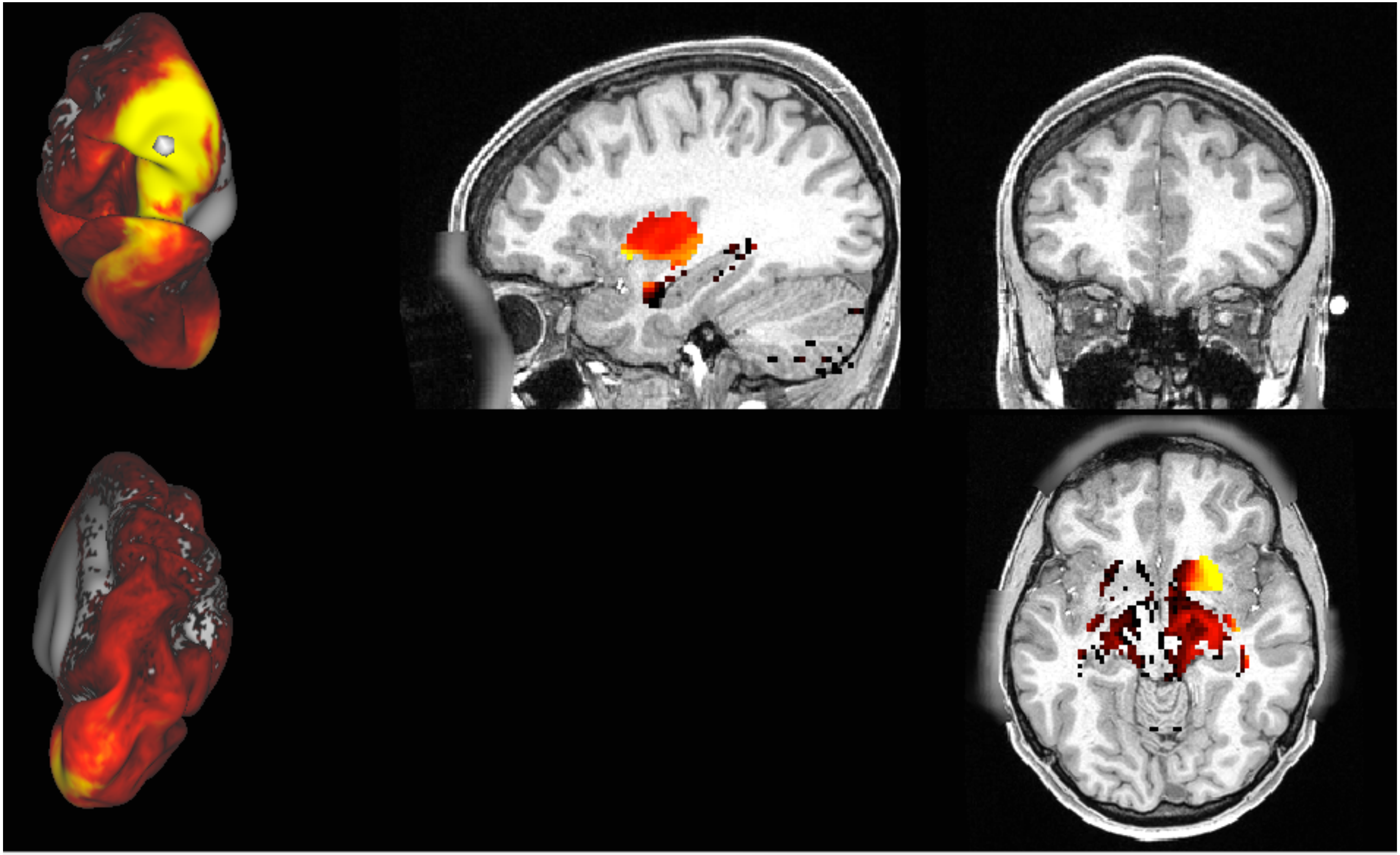
Reveley et al., *PNAS*

Some examples of known connections found

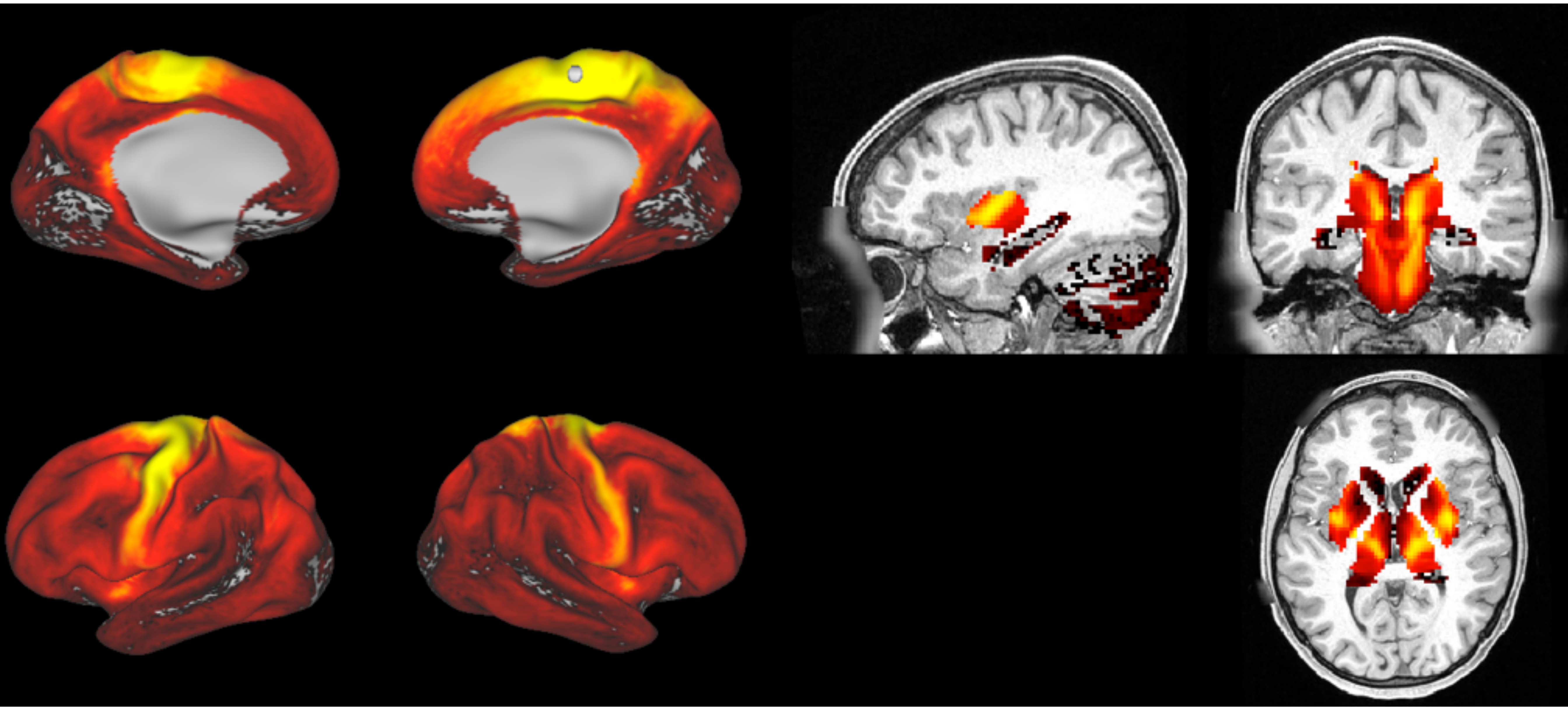
Average of 158 subjects

Conn3

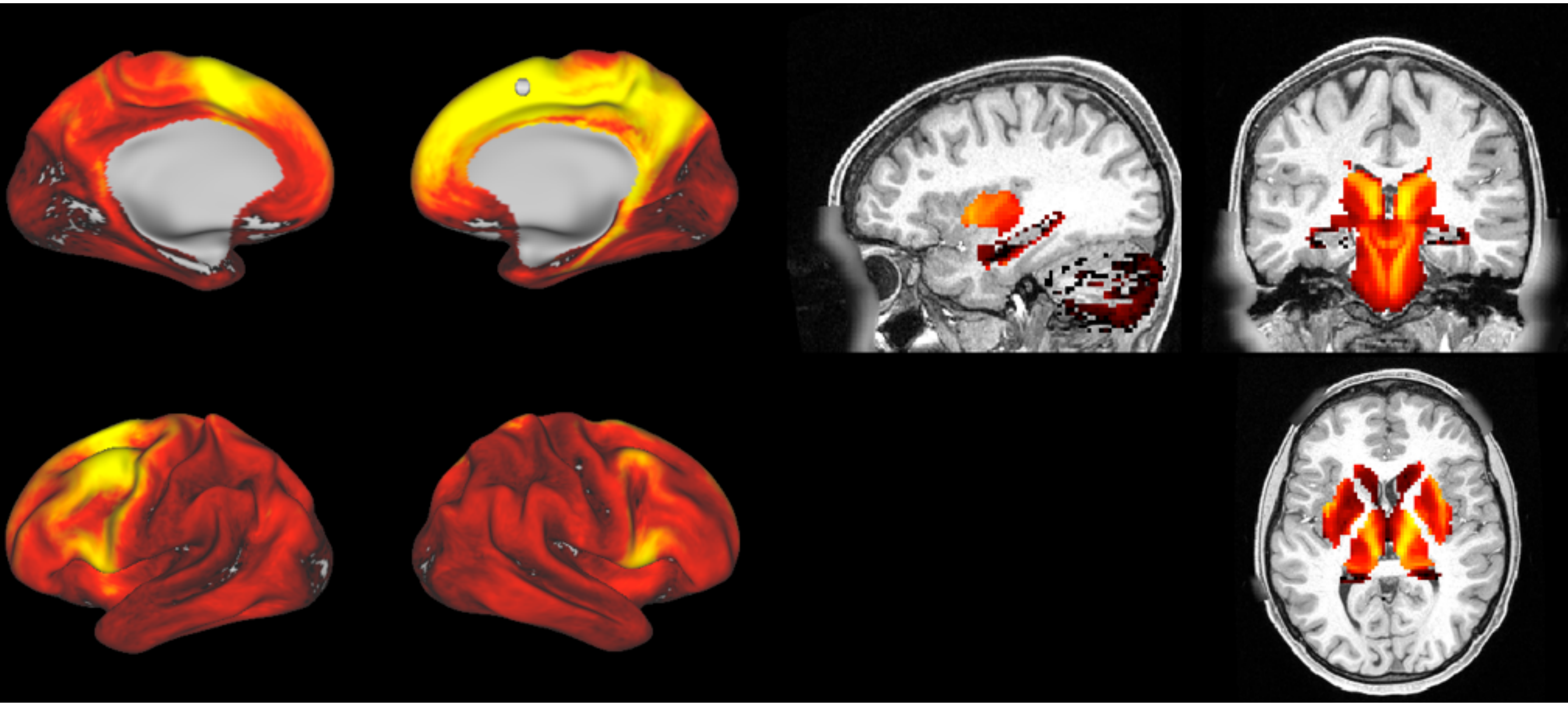
Lateral OFC to lateral Nucleus Accumbens



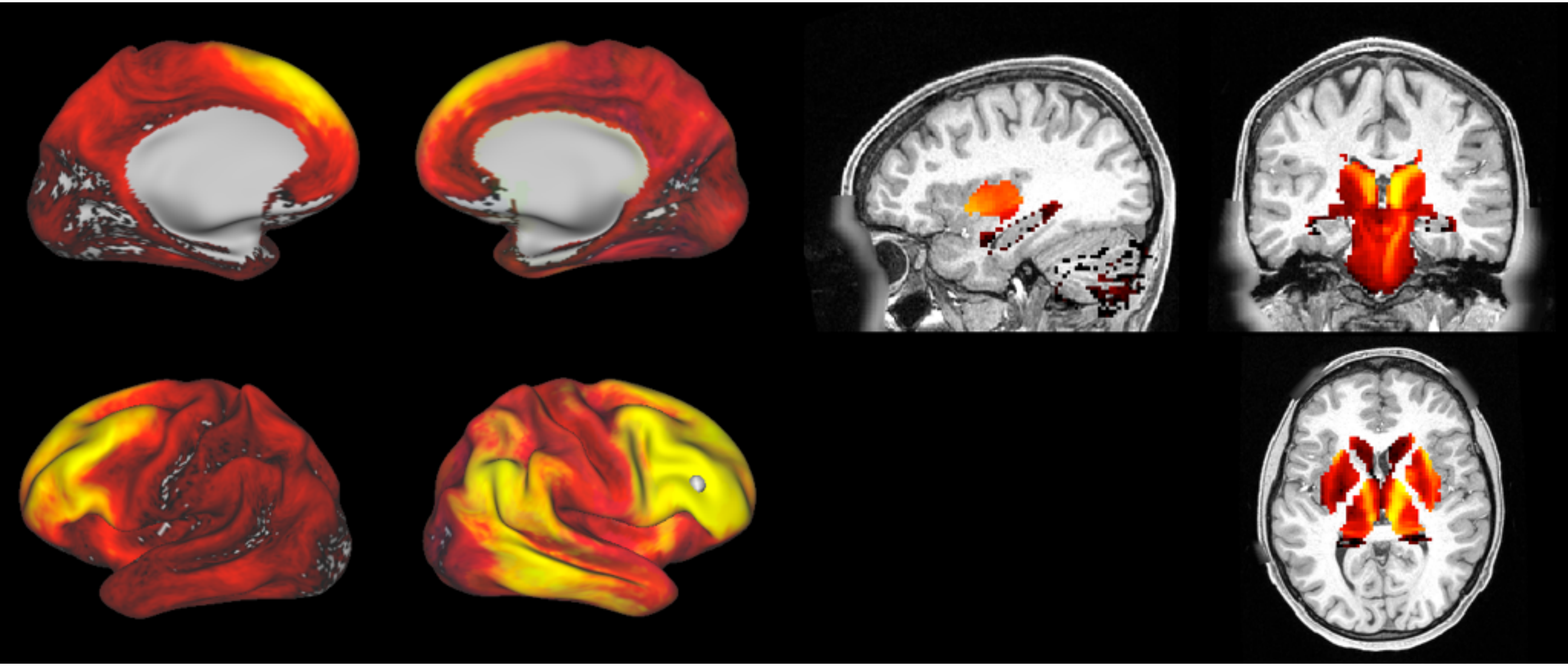
SMA to motor cortex

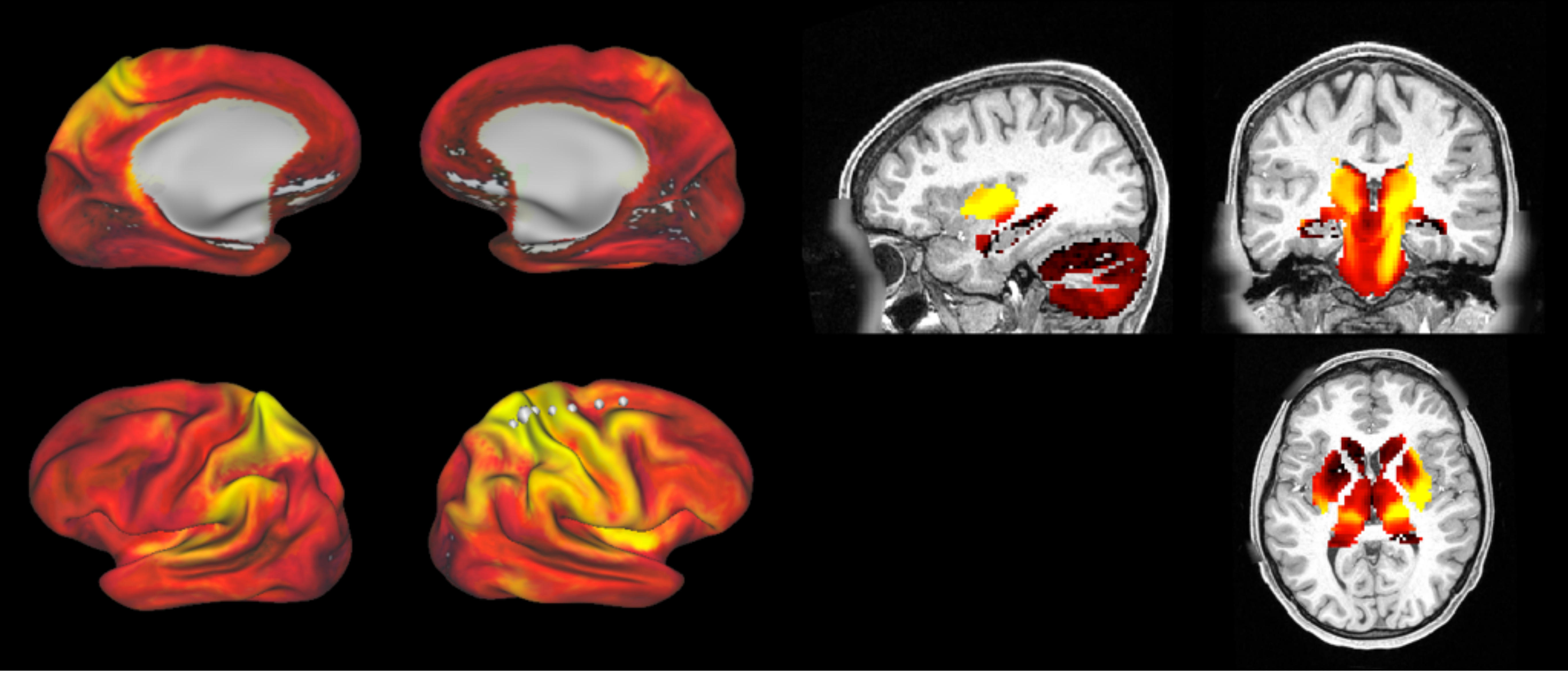


Pre-SMA to IFG



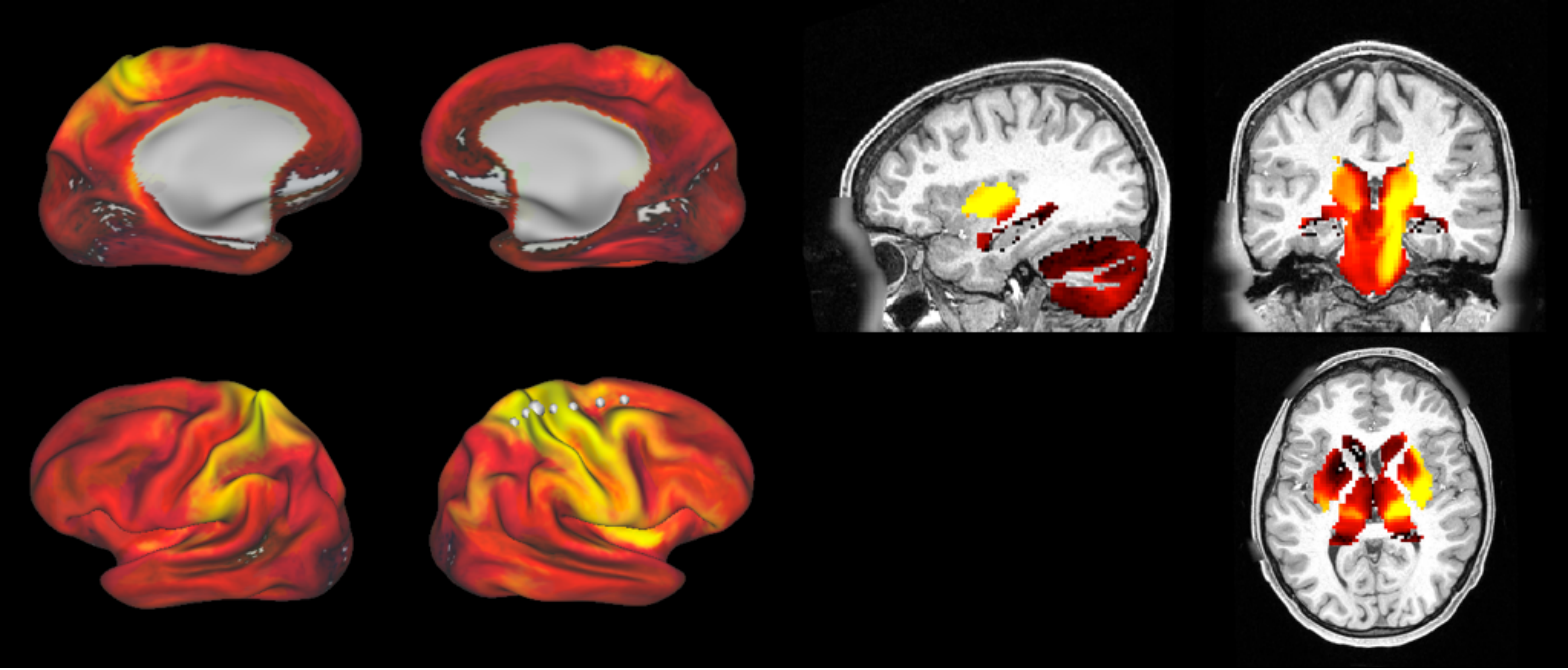
Frontal to TPJ





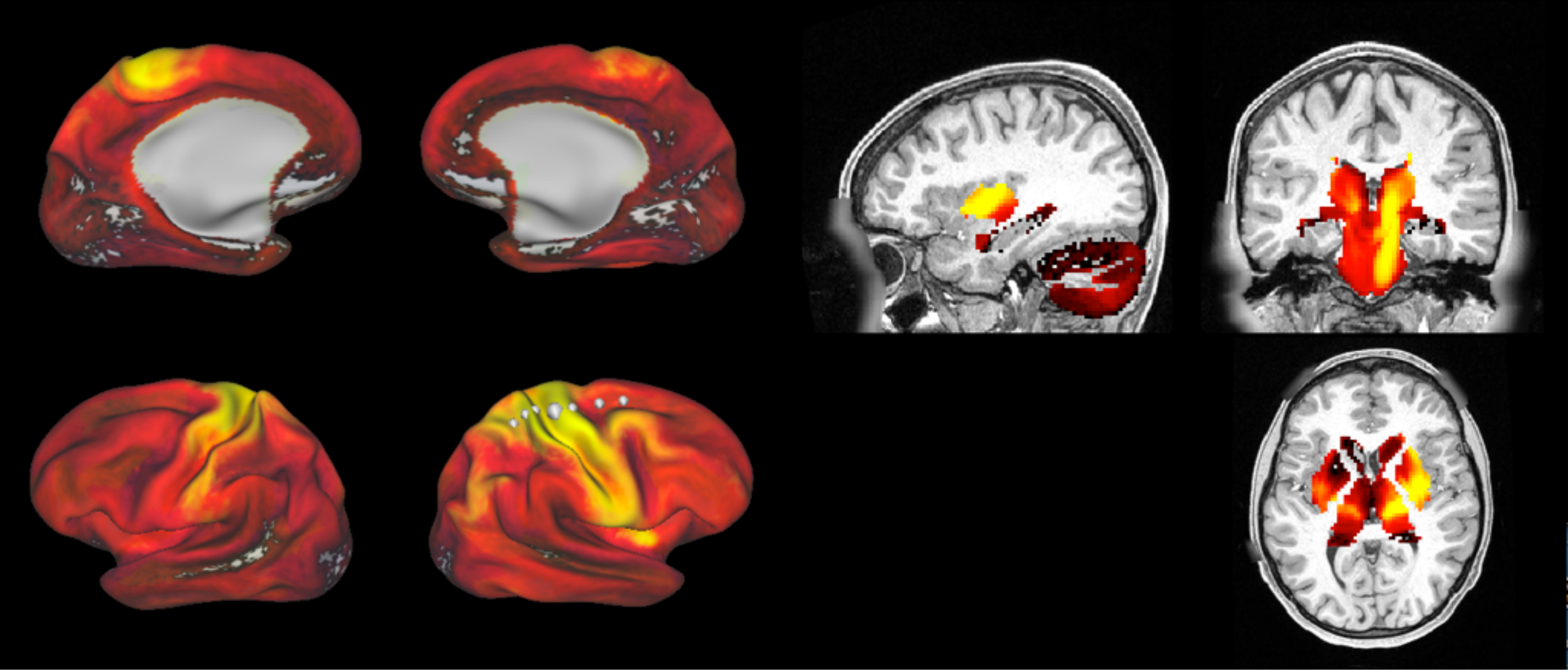
Somatosensory -> Motor -> Frontal Cortex

VPL -> VL -> MD in thalamus



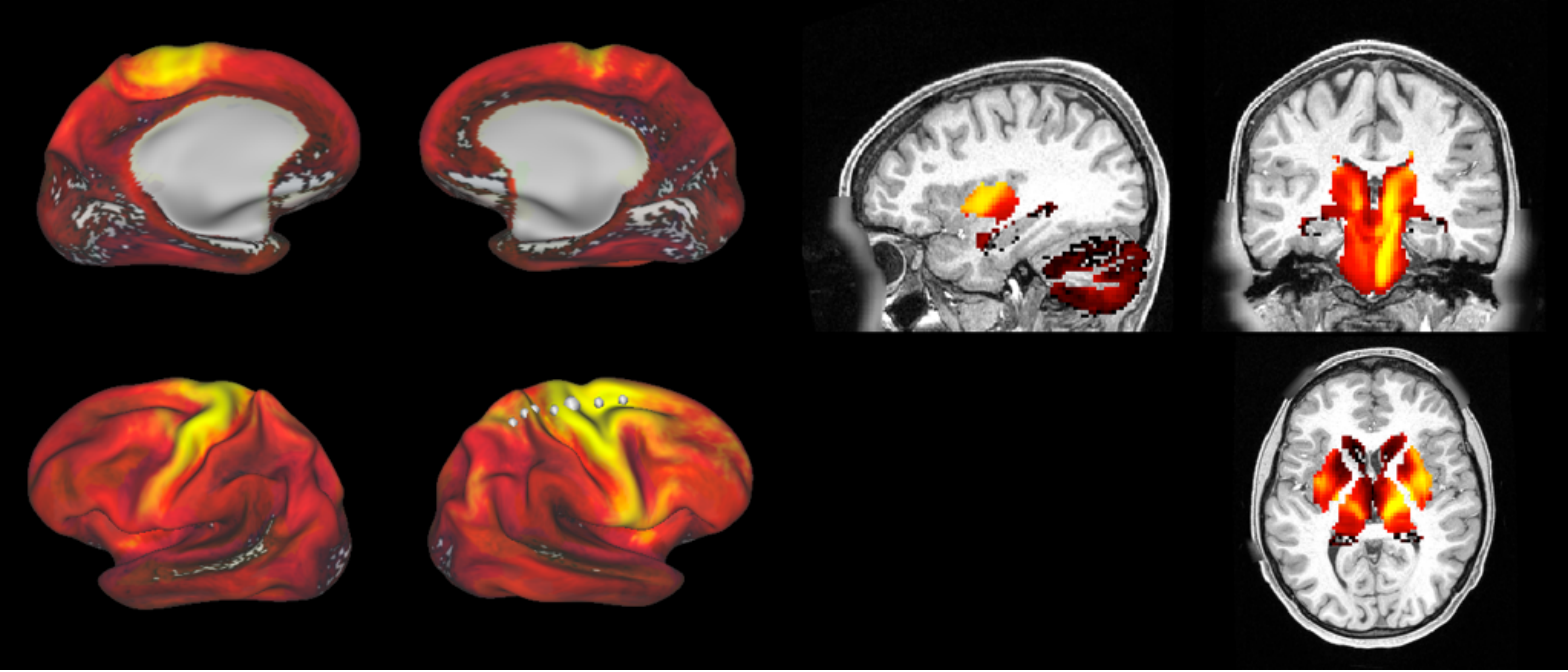
Somatosensory -> Motor -> Frontal Cortex

VPL -> VL -> MD in thalamus



Somatosensory -> Motor -> Frontal Cortex

VPL -> VL -> MD in thalamus



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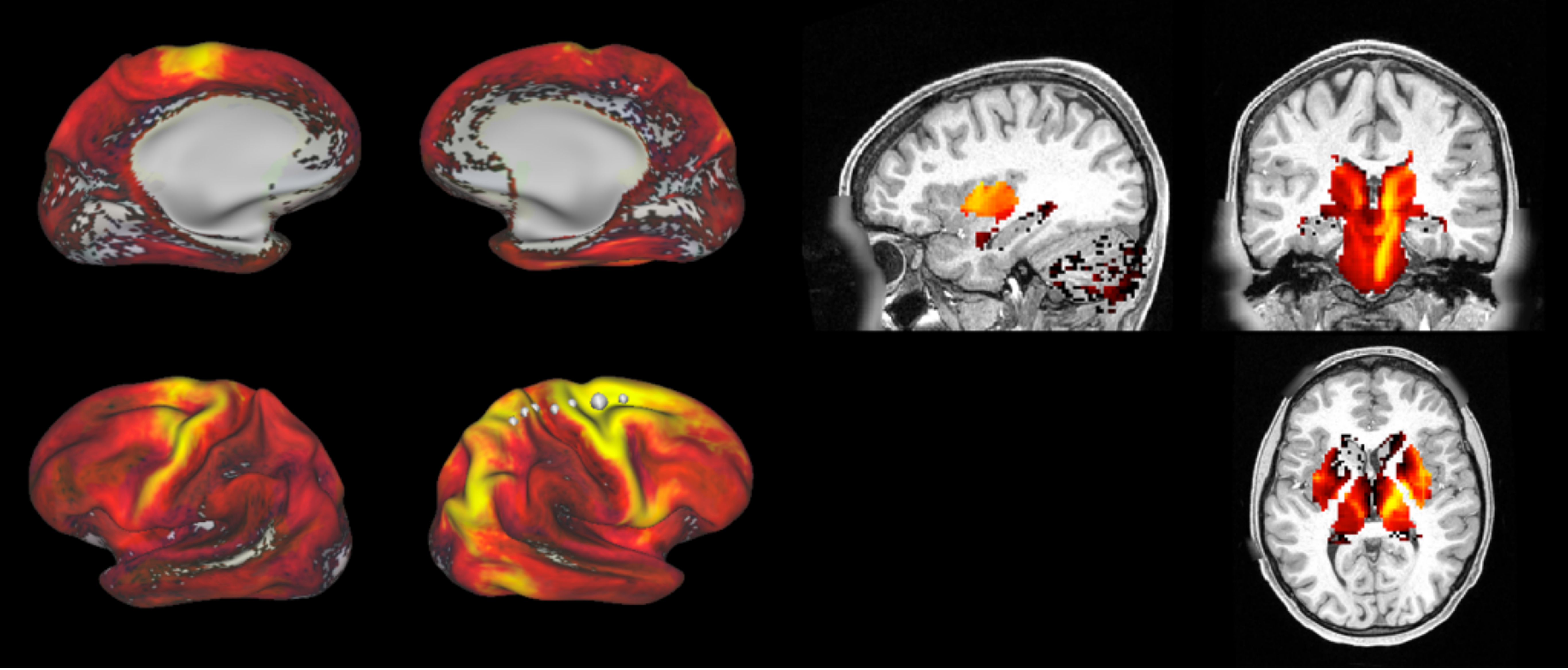

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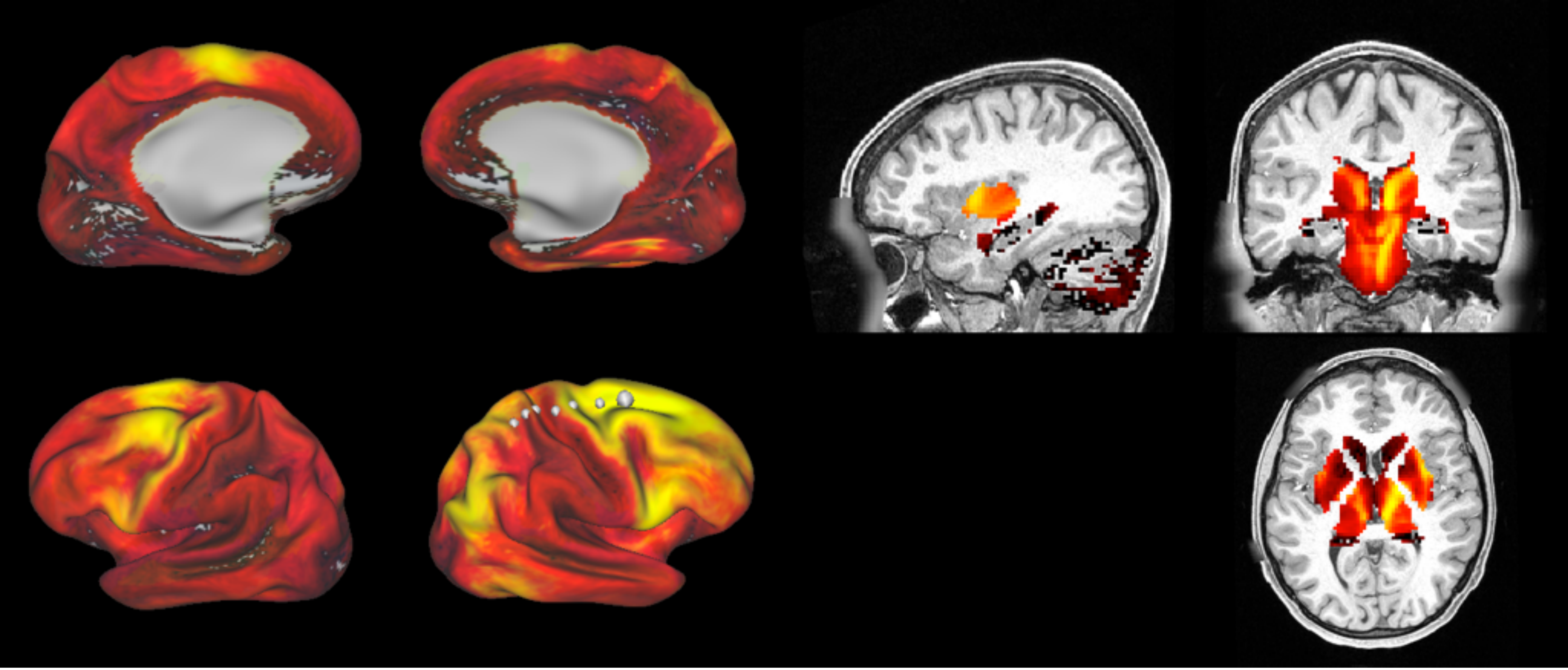

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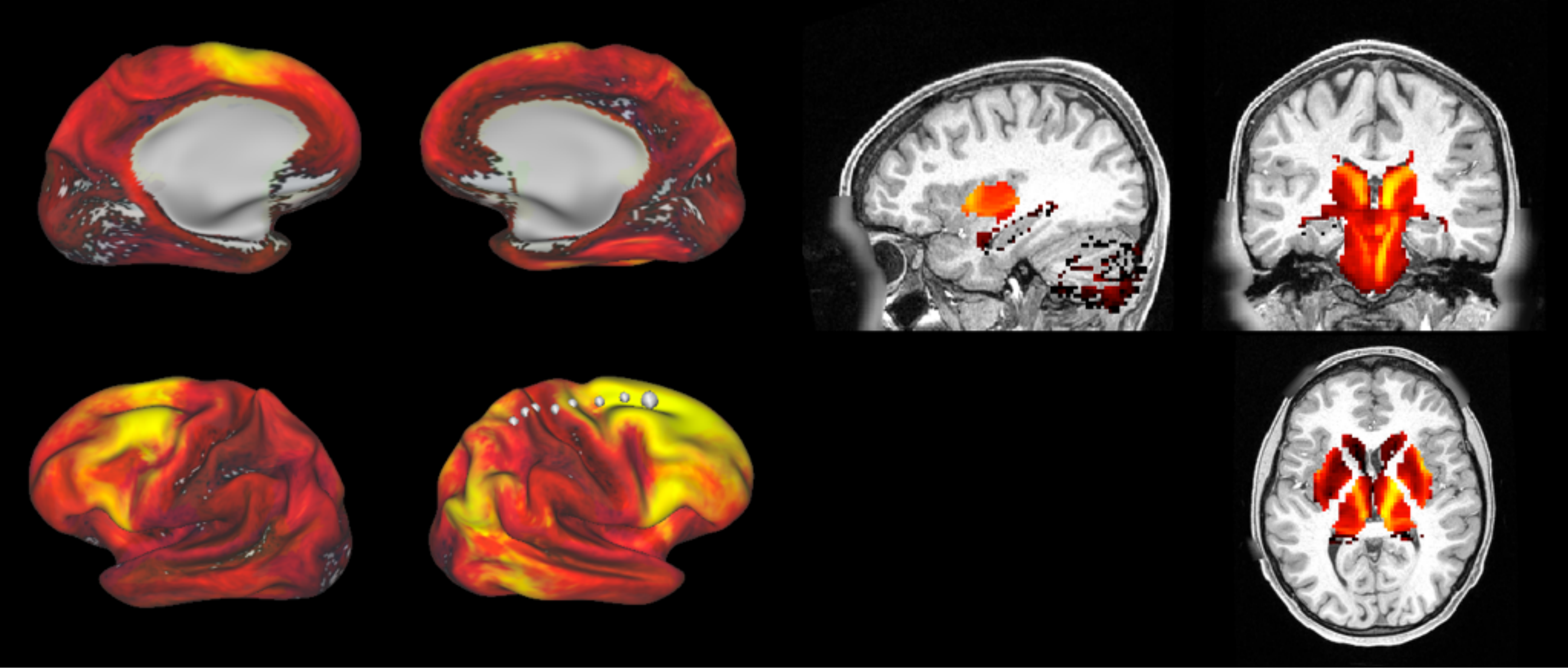
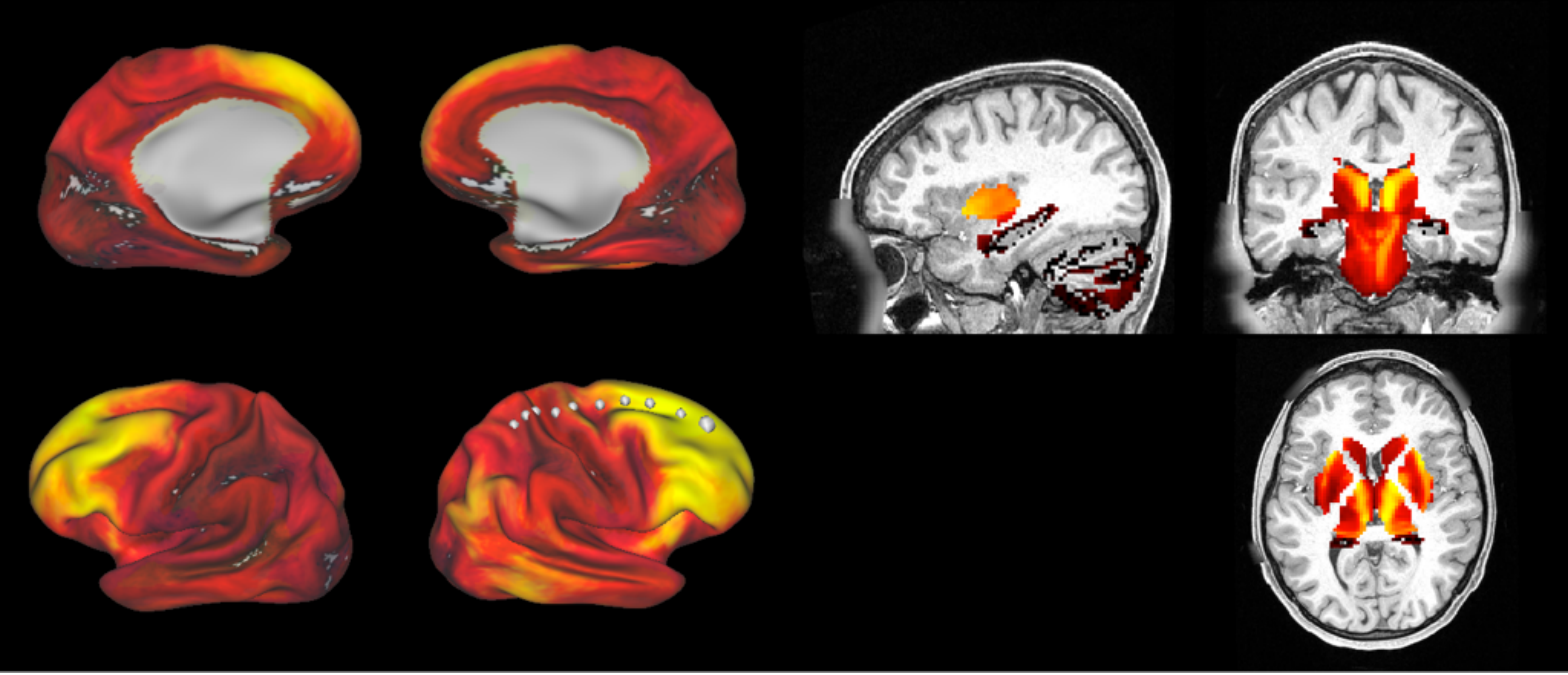


Somatosensory -> Motor -> Frontal Cortex

VPL -> VL -> MD in thalamus

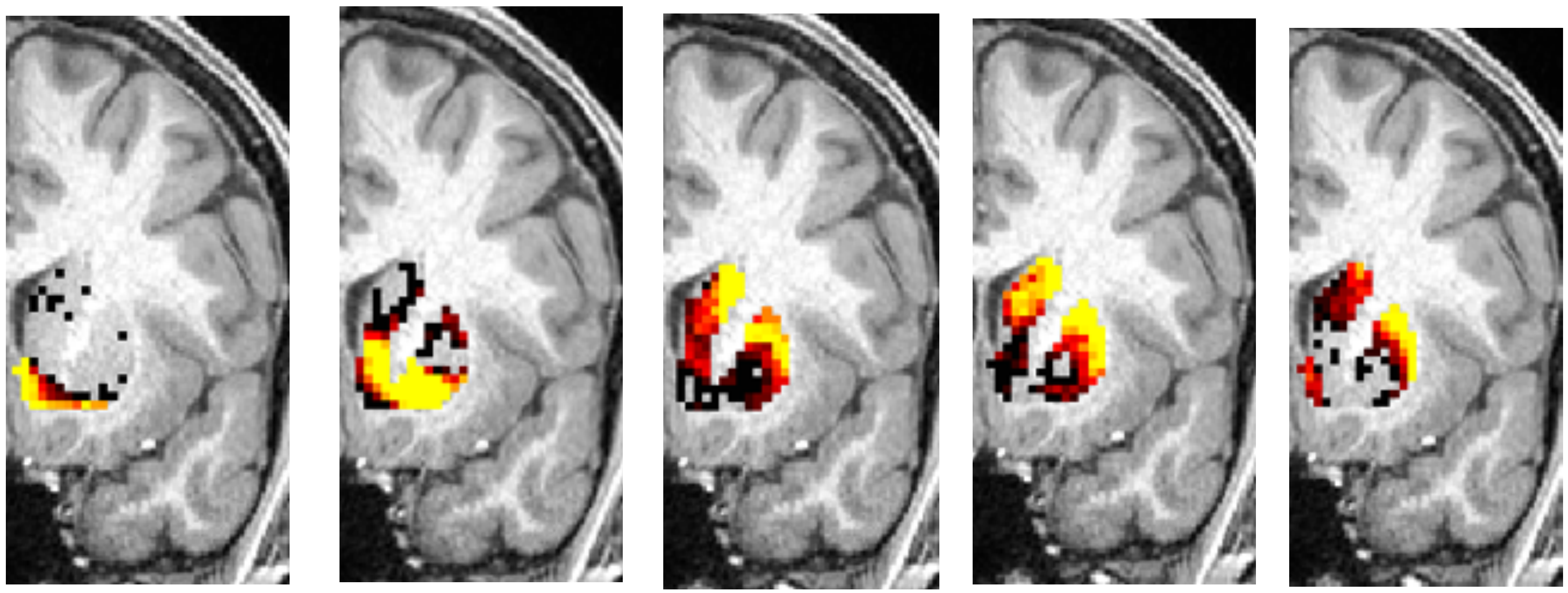


Somatosensory -> Motor -> Frontal Cortex

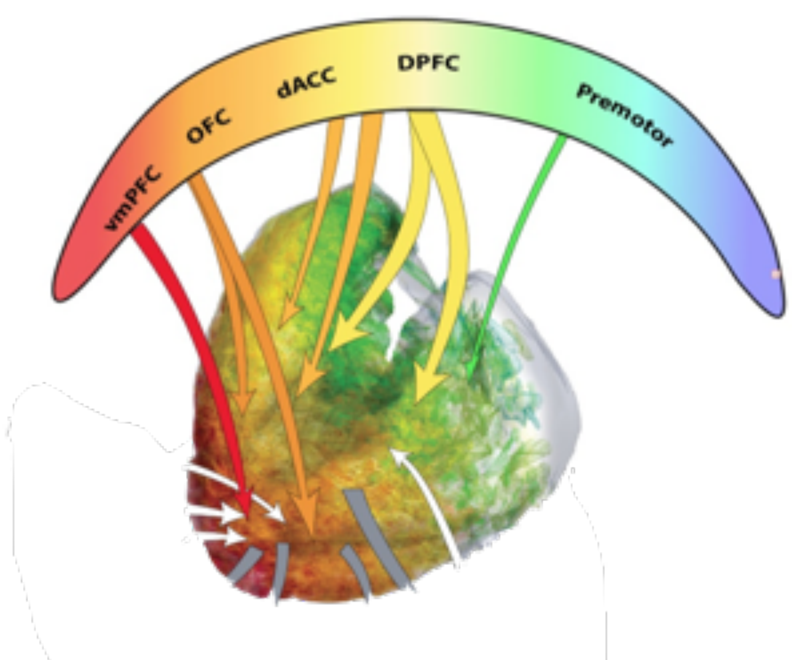
VPL -> VL -> MD in thalamus

Cortico-Striatal Connections

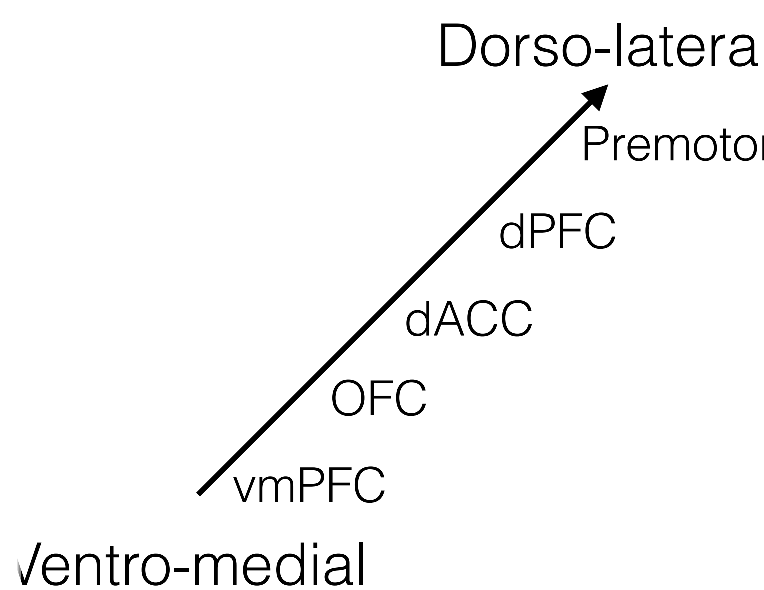
dMRI (N=15)



vmPFC OFC dACC dPFC Premotor



Tracers
(Haber & Behrens 2014)



Interpretation issues with connection probabilities

- They reflect "*Connection Strength*" (e.g. number of axons connecting two regions)

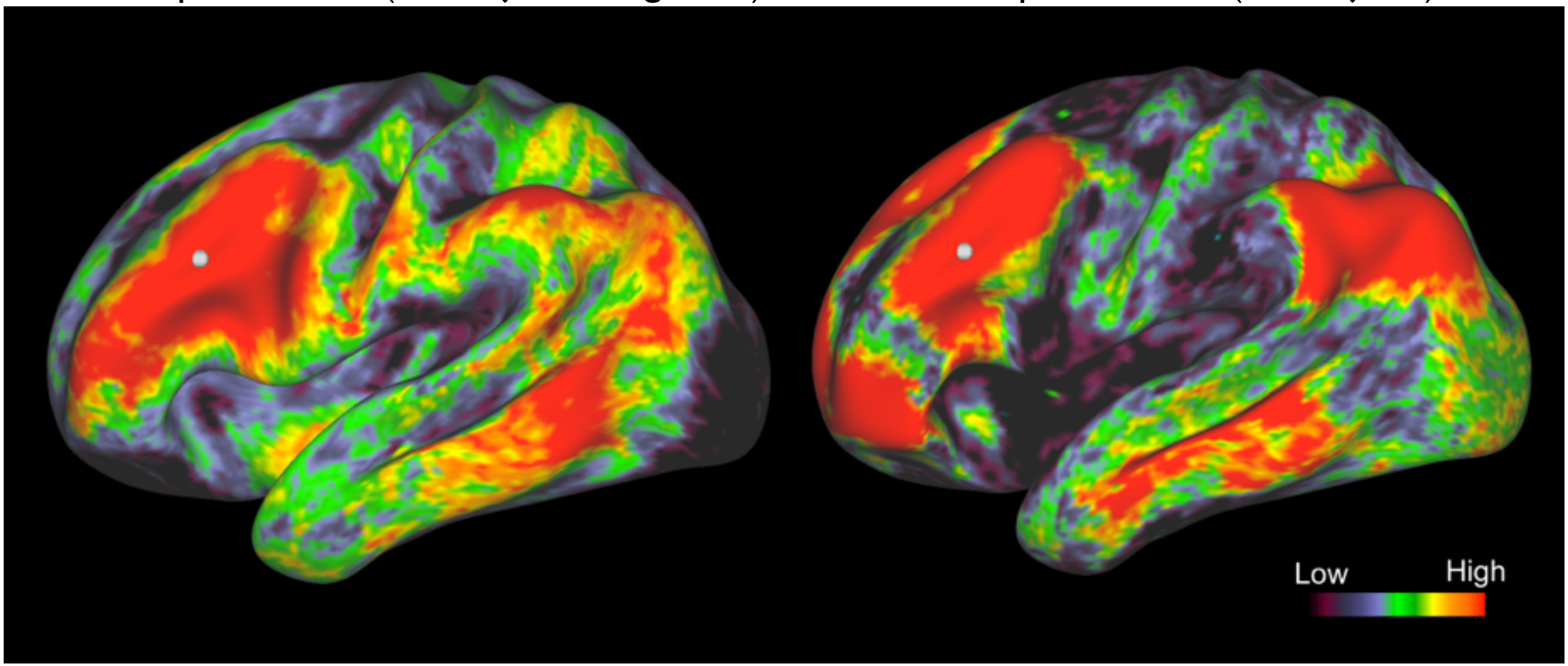
- **But** they do also reflect other uninteresting factors, such as:

<u>Connection length</u>: Longer connections have smaller probability than shorter ones (maybe that's anatomically relevant?)

<u>Geometric complexity</u>: Probabilities of connections that go through regions of complex structure will be smaller than connections than go through more coherent regions

<u>Resolution of the spatial grid</u>: Probabilities change if we change the size of "bins" for displaying the spatial histogram

Group Structural (20 subjects - log scale) Group Functional (20 subjects)



That's all folks