An Introduction to Diffusion Tensor Imaging, with Applications

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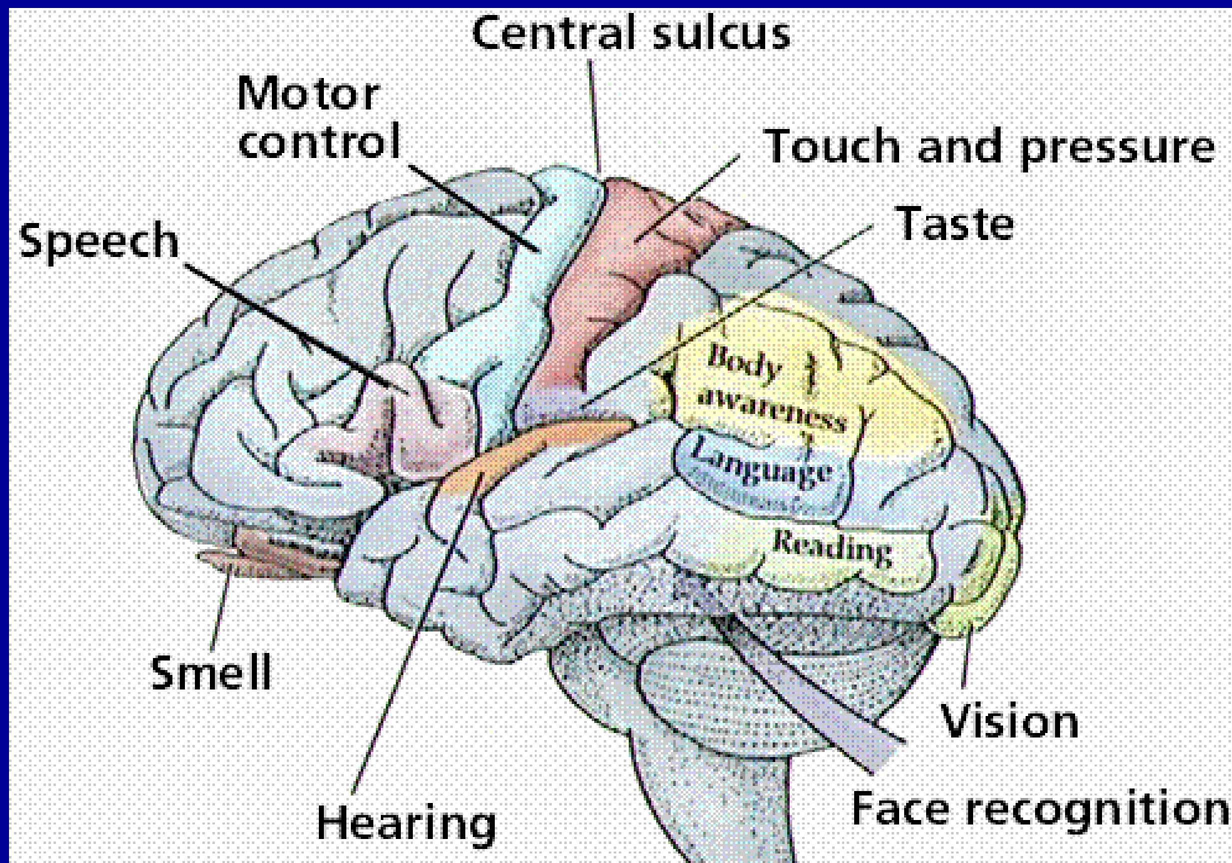
Outline

- Structural connectivity overview
- Diffusion weighted imaging (DWI)
  - Data acquisition
  - Diffusion tensor imaging (DTI) model
  - Basic quantities
- Tractography: estimating white matter connections
- Applications
  - Research studies-- studying WM properties
  - Clinical use-- electrode placement, surgical planning

Function and Structure: Network Motivation

The brain is both regionally specialized and globally operative.
At its highest level, it is organized as networks of separate ROIs.



Functional and *structural* connectivity are complementary paradigms for describing the interactions within (and between) networks, quantifying GM and WM properties, respectively.

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DTI is a particular kind of magnetic resonance imaging (MRI) modality based on diffusion weighted imaging (DWI) acquisitions

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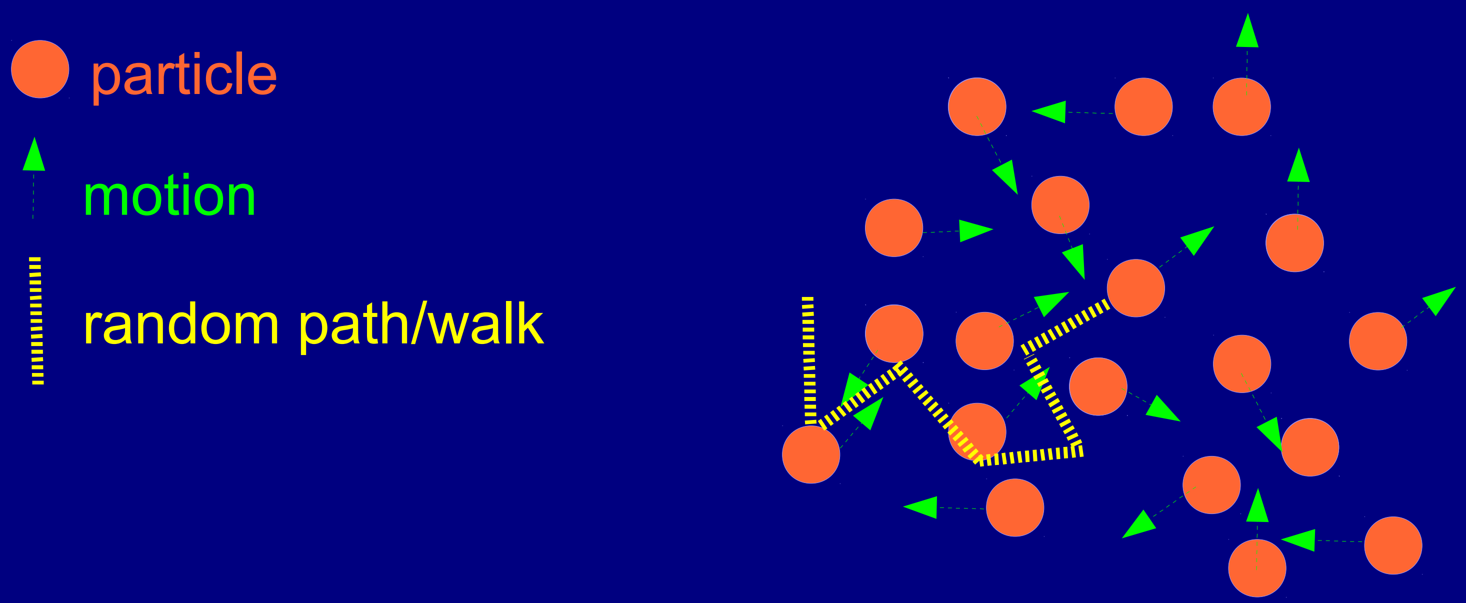
$\longrightarrow$ here, hydrogen atoms in aqueous brain tissue



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*T*ensor: a mathematical object (a matrix) to store information

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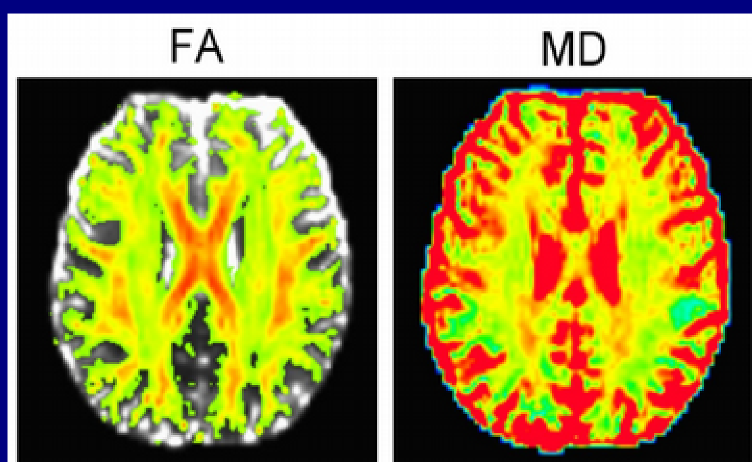
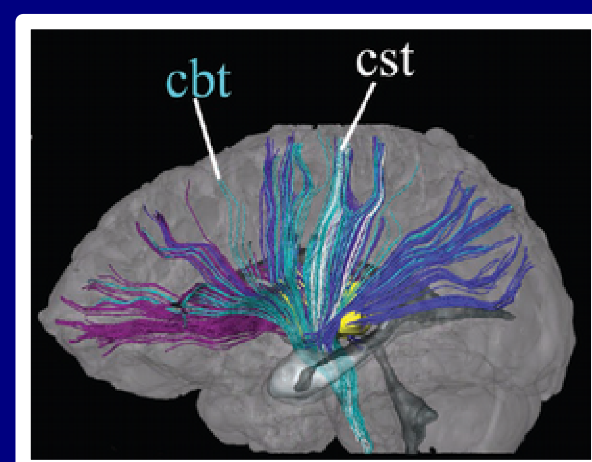
*I*maging: quantifying brain properties

$\rightarrow$ here, esp. white matter properties





Diffusion as environmental marker

Diffusion: random (Brownian) motion of particles $\rightarrow$ mixing or spreading

<u>Ex: unstirred, steeping tea (in a large cup):</u>

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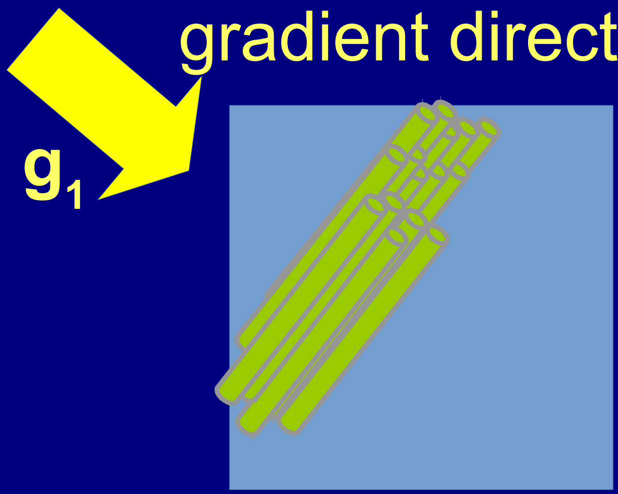
Diffusion shape tells of structure presence and spatial orientation

Acquiring data for DTI modeling:
diffusion weighted gradients in MRI

DWI

Purpose: view diffusion along a particular direction

View diffusion along
gradient direction, **g**



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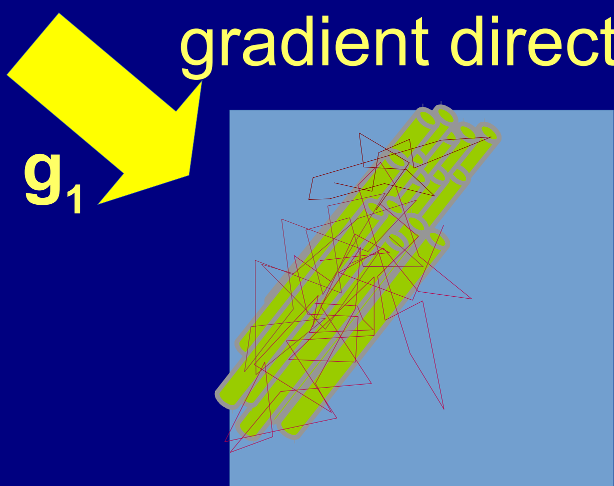

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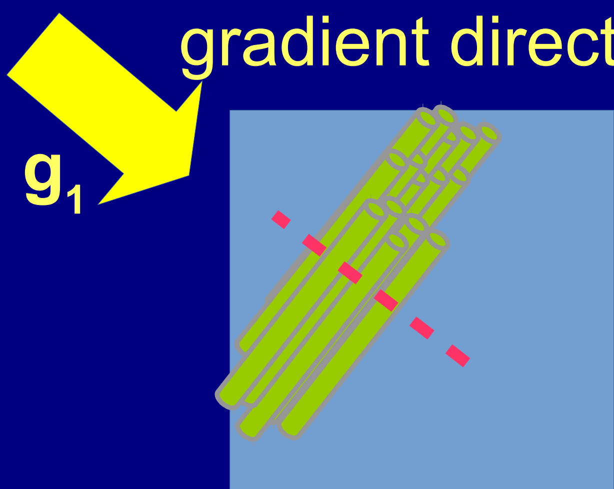
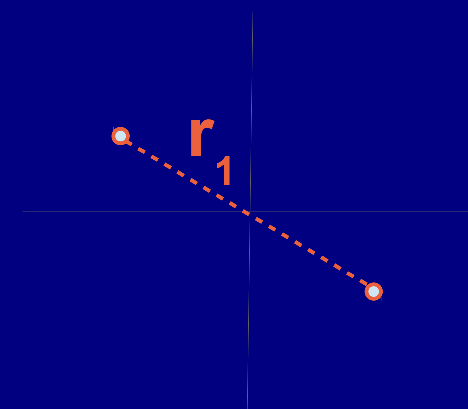


Calculate and store average diffusion radius, **r**



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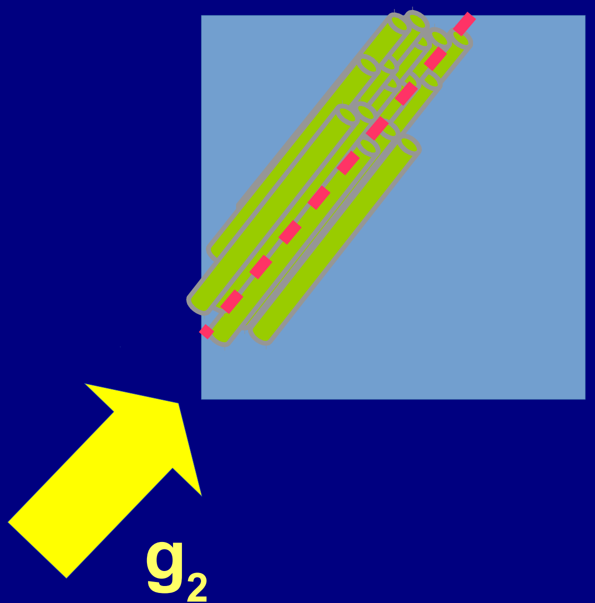

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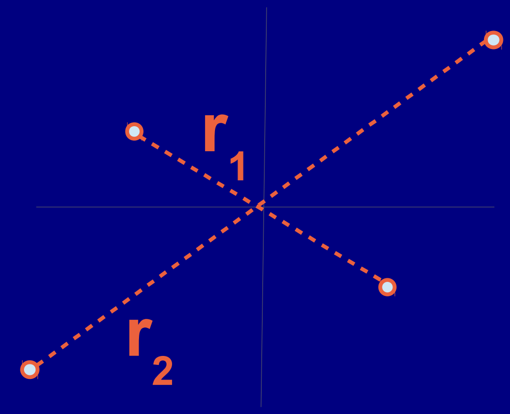

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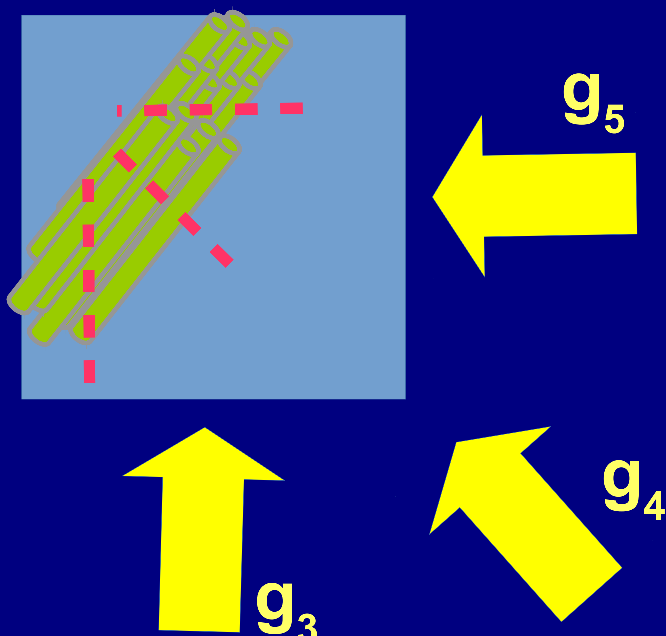

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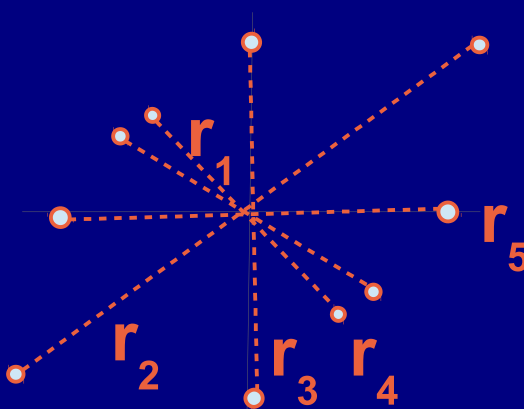

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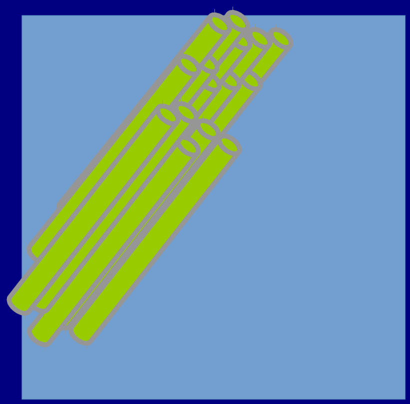

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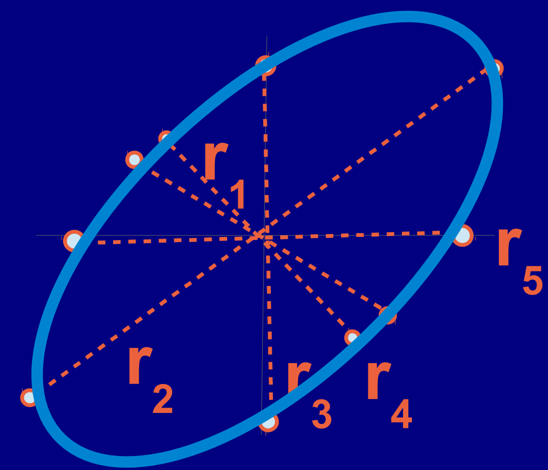

Fit ellipsoid

DWI $\rightarrow$ DTI

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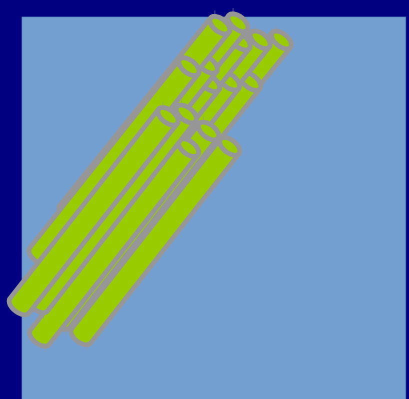

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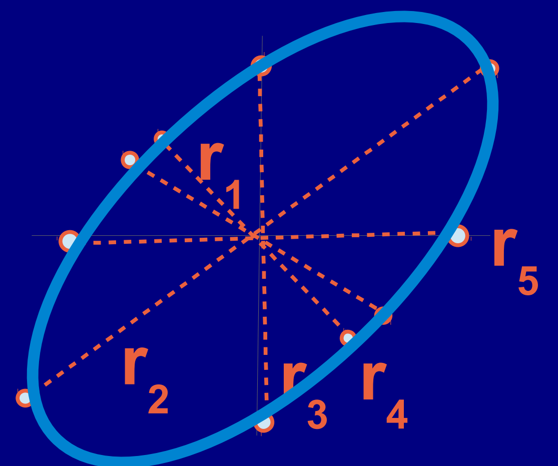

The diffusion tensor model: Solve for **D** = Fit ellipsoid

DWI → DTI

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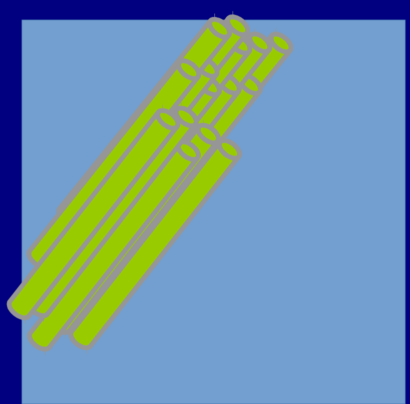

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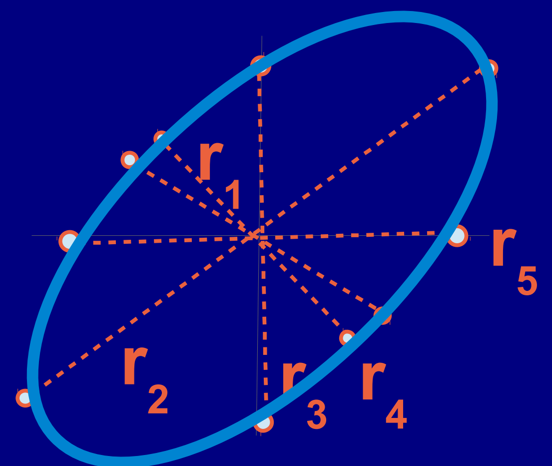

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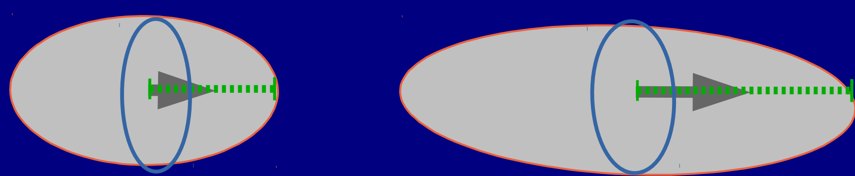
The geometric properties of the DTI ellipsoid are used to characterize WM structure!

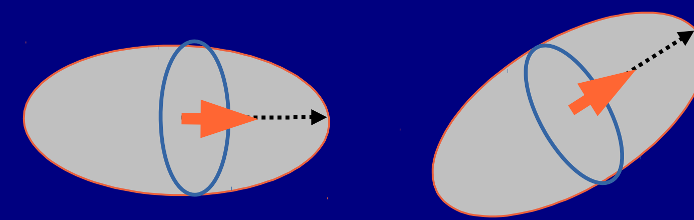
“Big 5” DTI ellipsoid parameters

first eigenvalue, L1 (=“parallel diffusivity”)



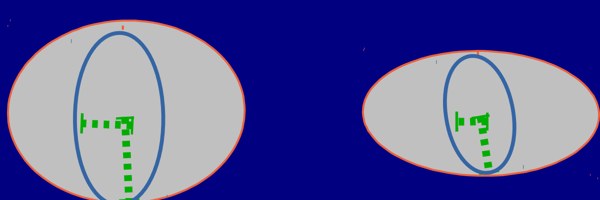
$L1_1$ < $L1_2$

first eigenvector, e_1



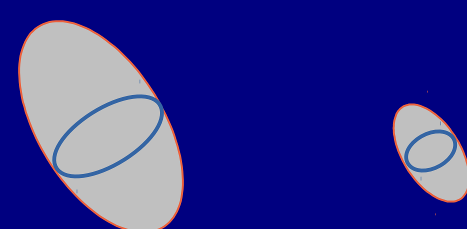
e_1 e_1

Radial diffusivity, RD (=“perpendicular diffusivity”)



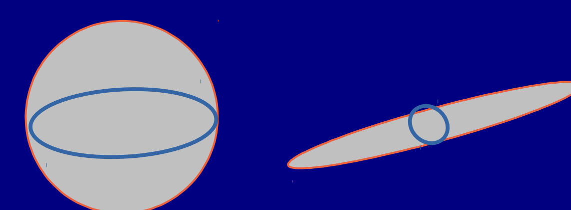
RD_1 > RD_2

Mean diffusivity, MD



MD_1 > MD_2

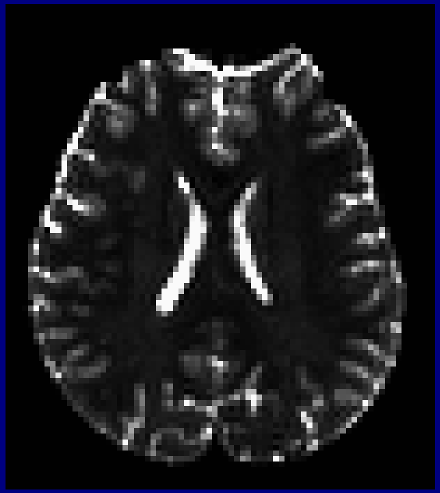
Fractional anisotropy, FA



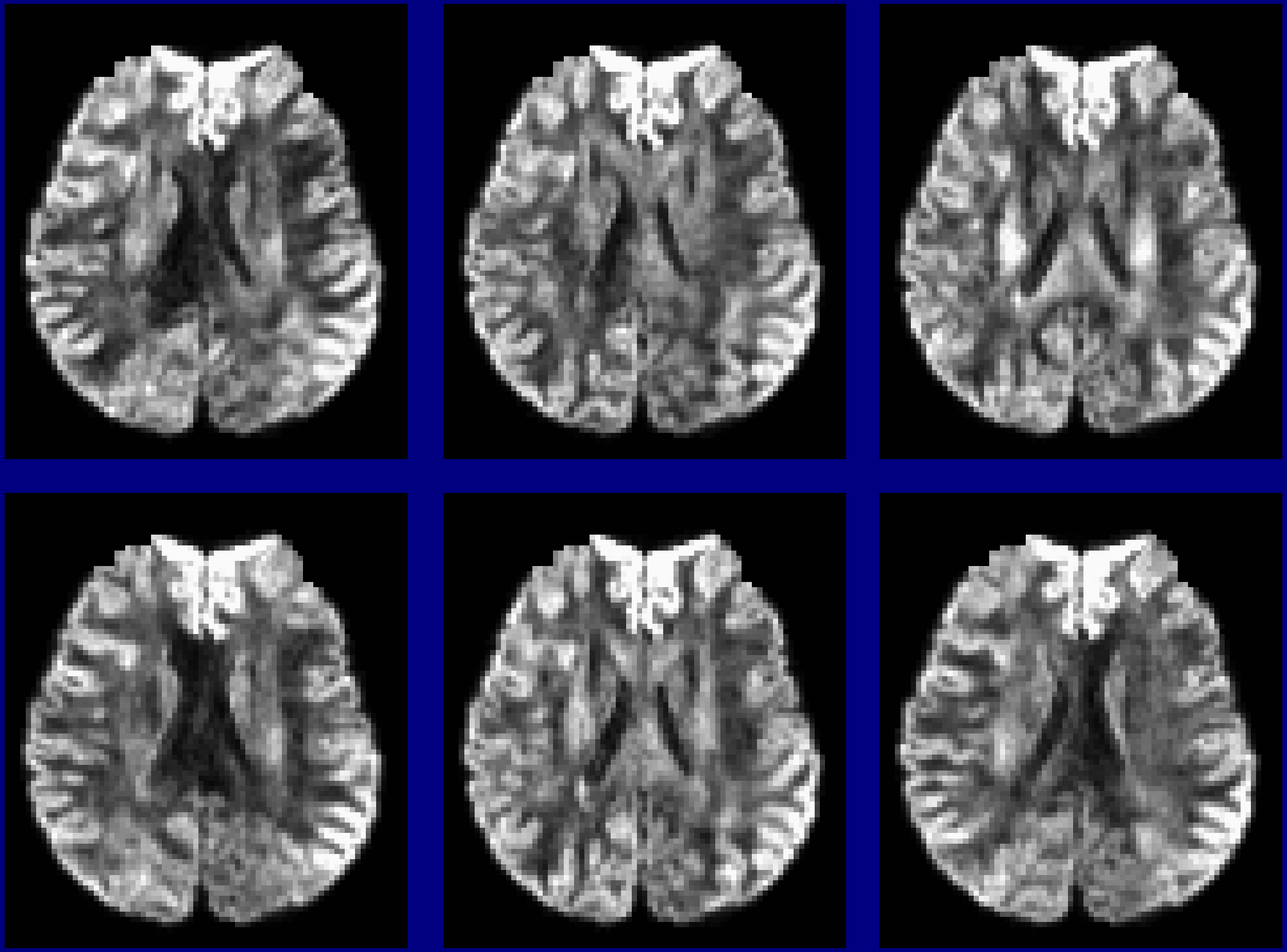
FA≈0 FA≈1

Sidenote: what DWIs look like

Unweighted
reference
b=0 s/mm^2



Diffusion weighted images
(example: b=1000 s/mm^2)



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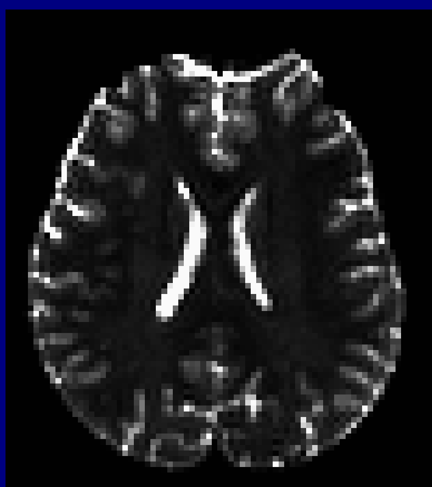

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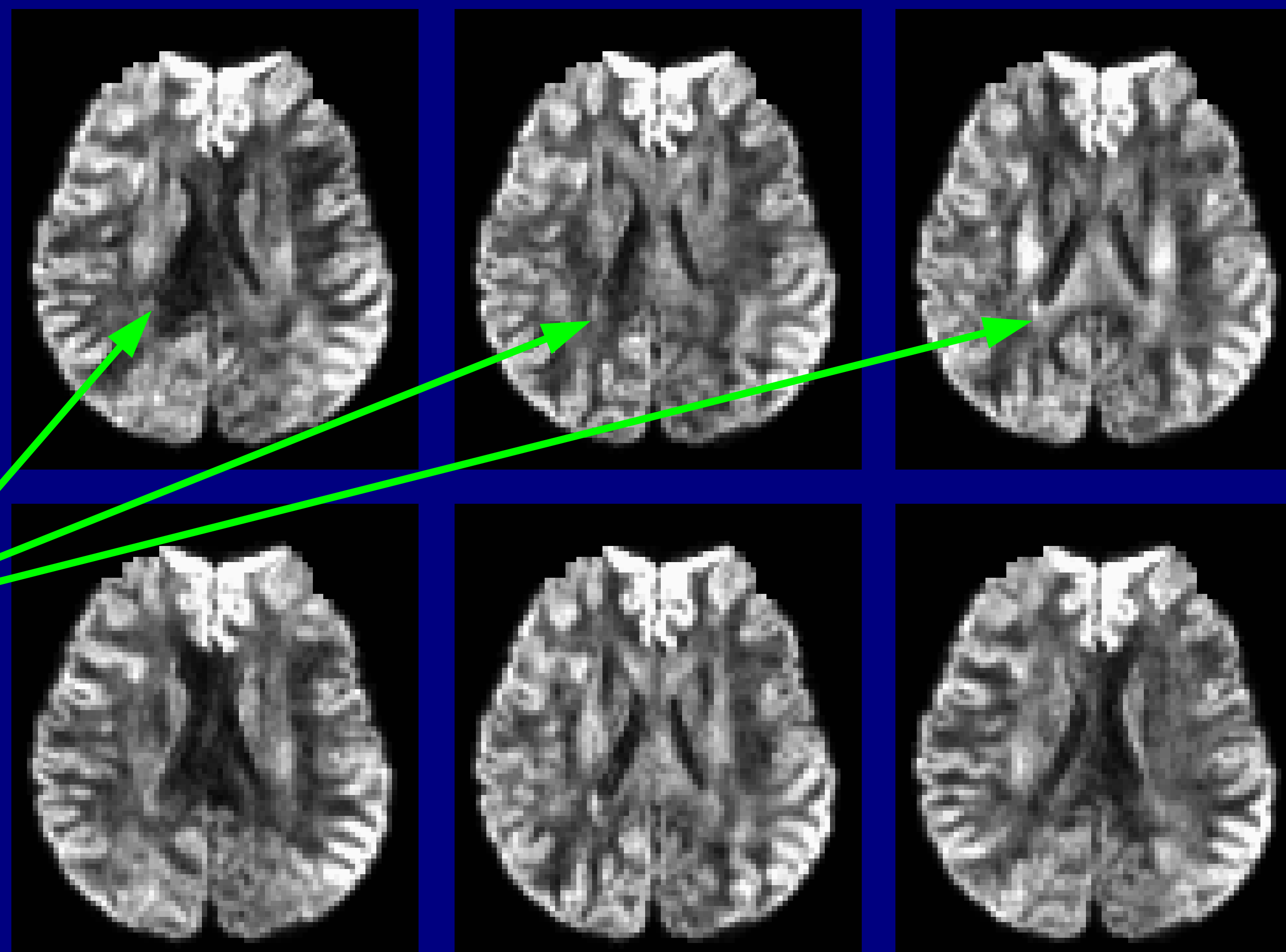
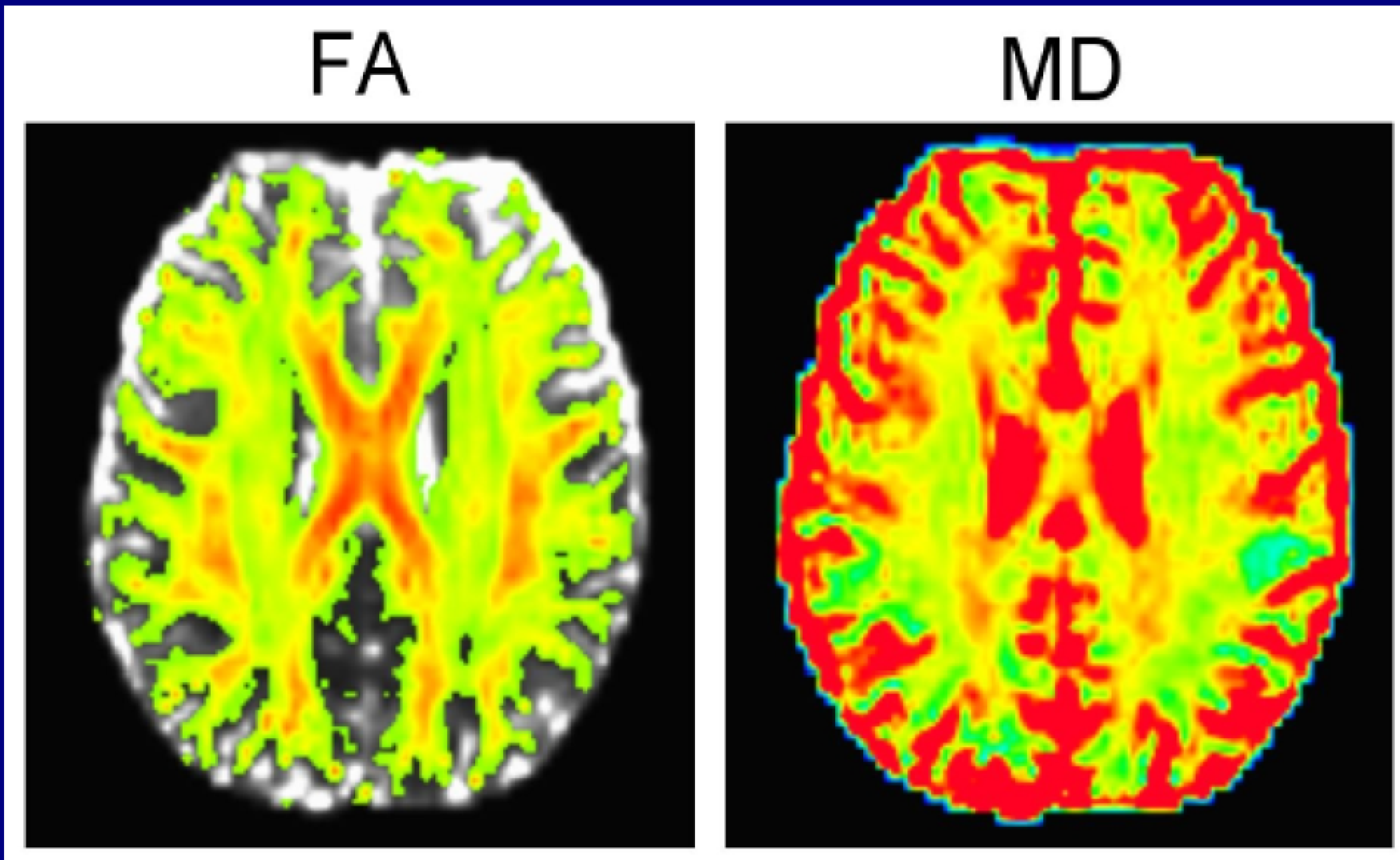


(Each DWI has a different brightness pattern: viewing structures from different angles.)

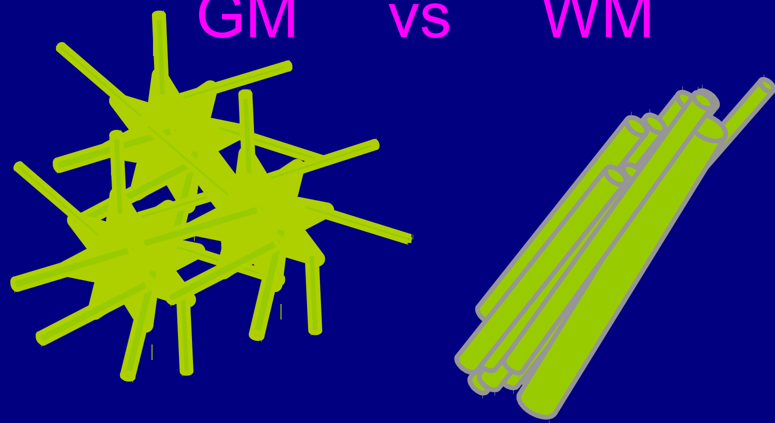
Sidenote: what DTI parameters look like



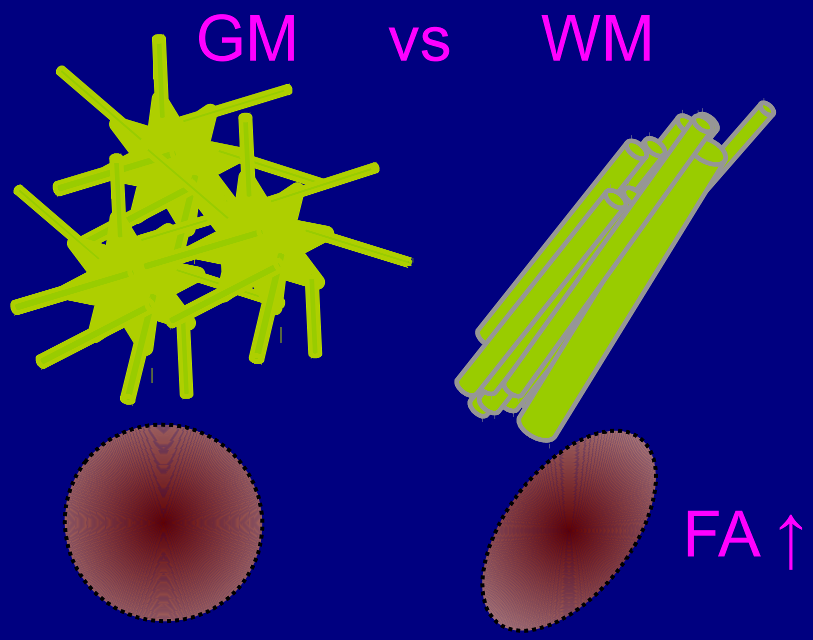
(FA>0.2)

Cartoon examples: white matter $\leftrightarrow$ FA

GM vs WM



Cartoon examples: white matter ↔ FA



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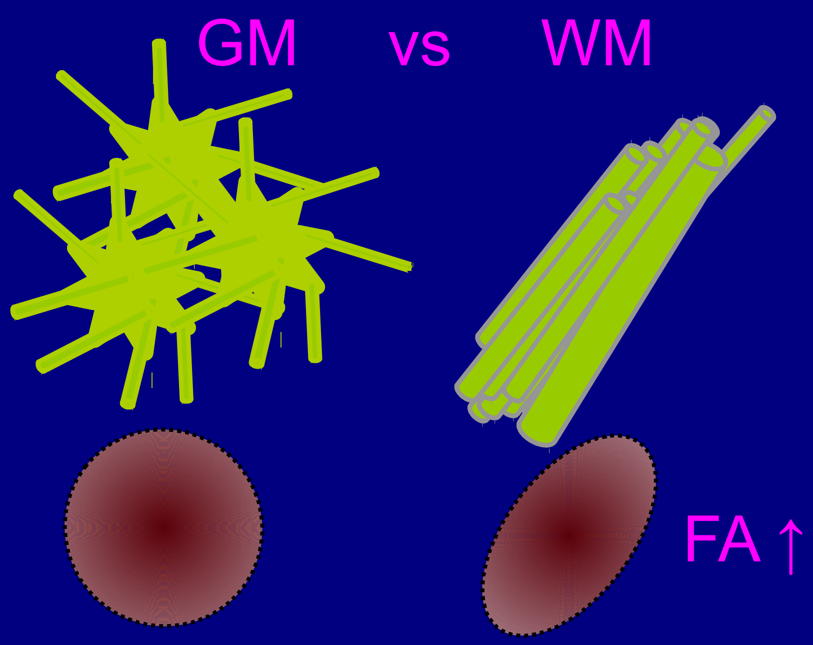

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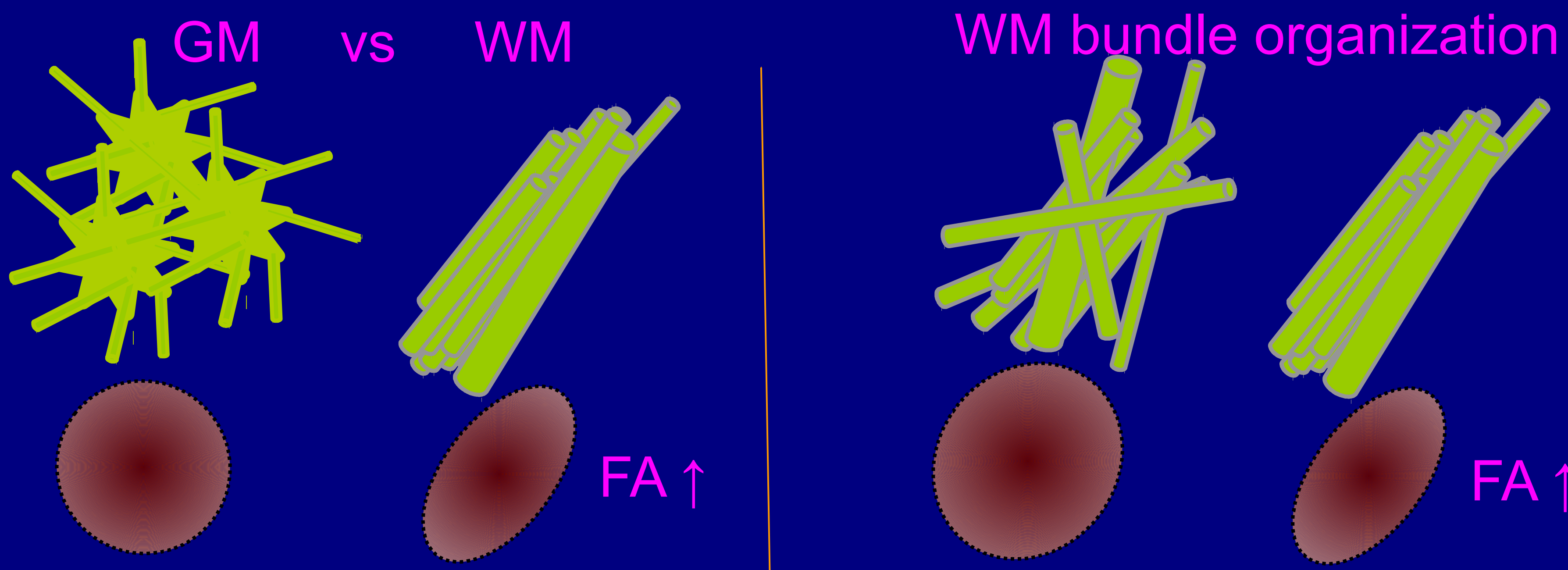

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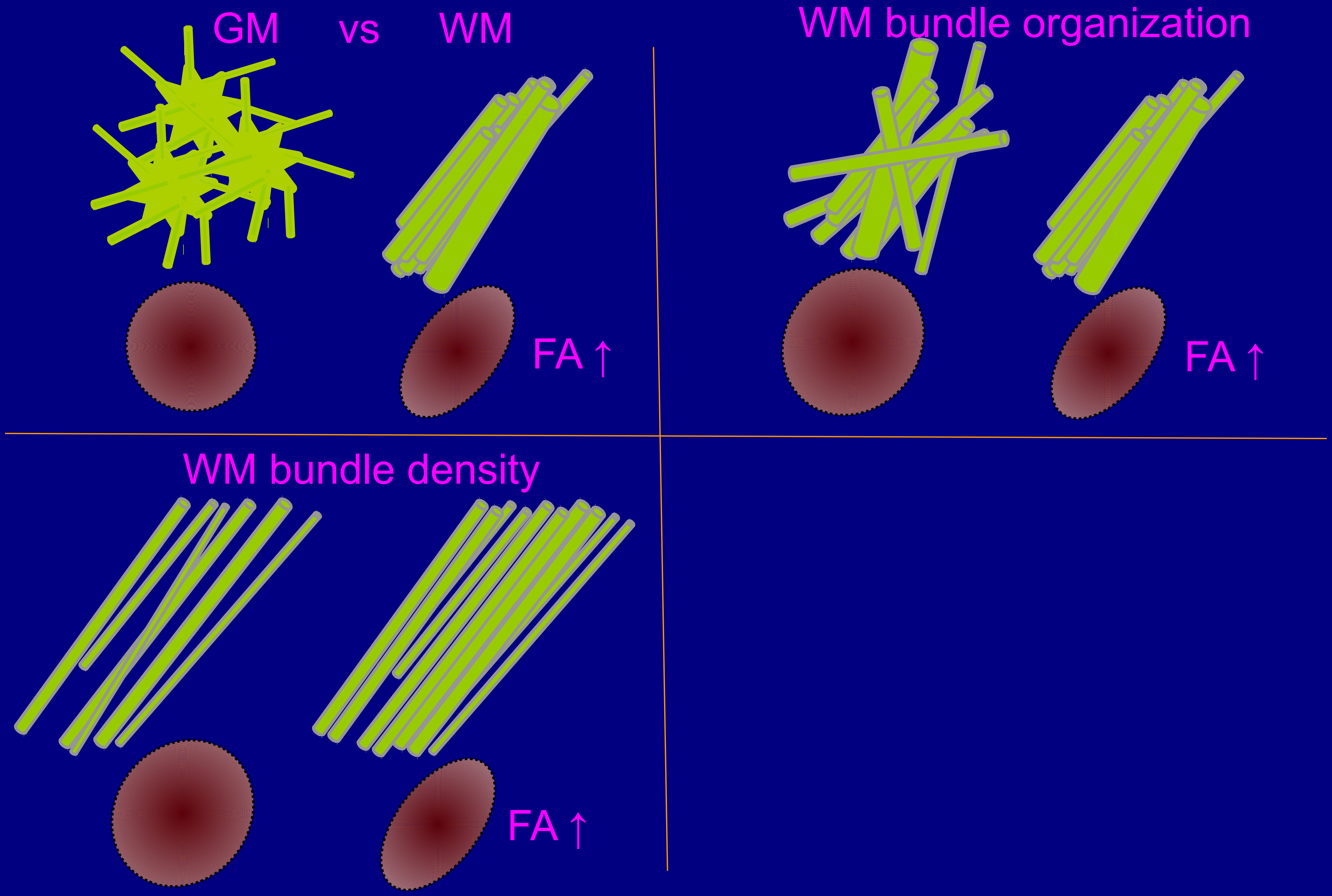

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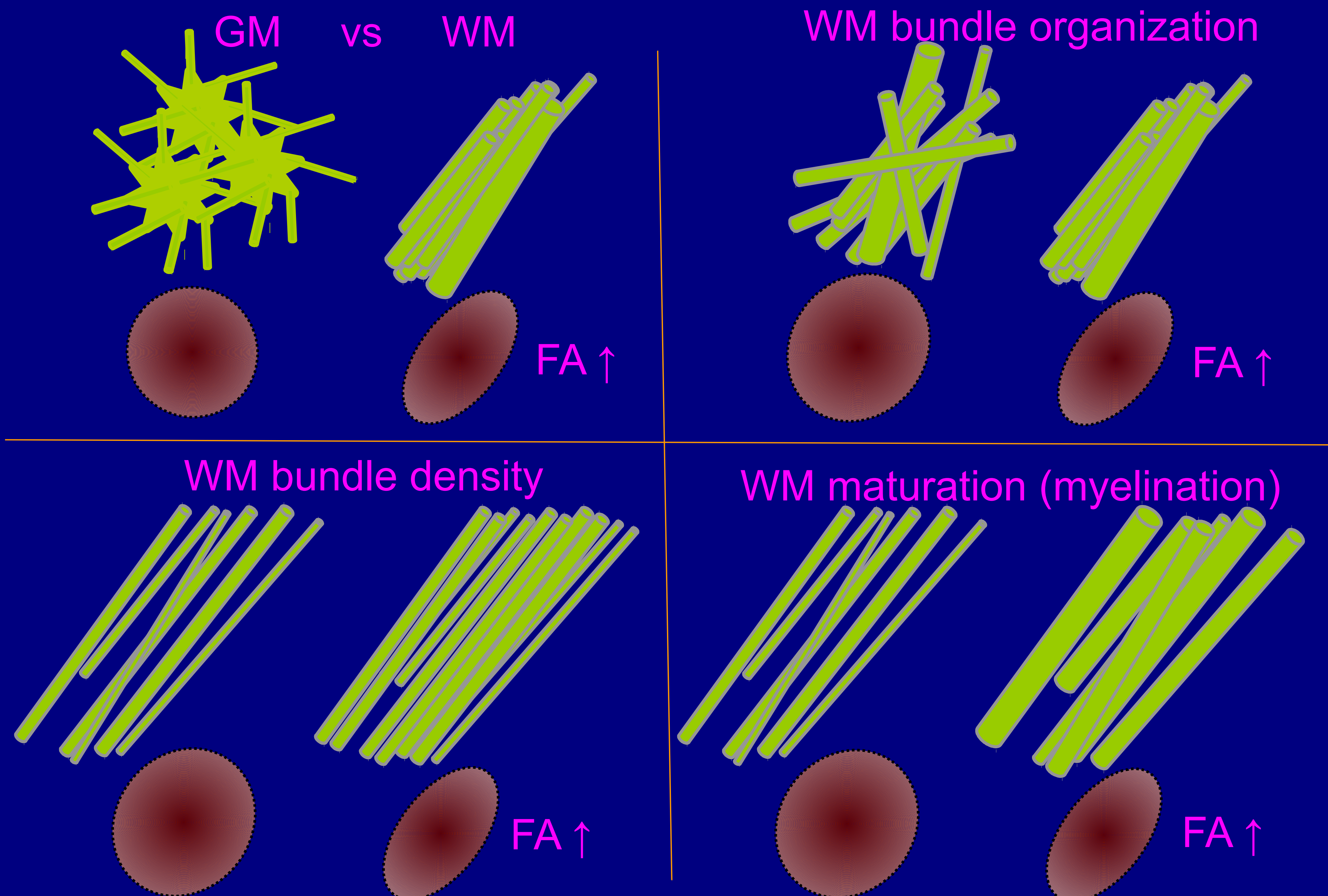

Interpreting DTI parameters

General literature:

FA: measure of fiber bundle coherence and myelination

- in adults, FA>0.2 is proxy for WM

MD, L1, RD: local density of structure

e_1: orientation of major bundles

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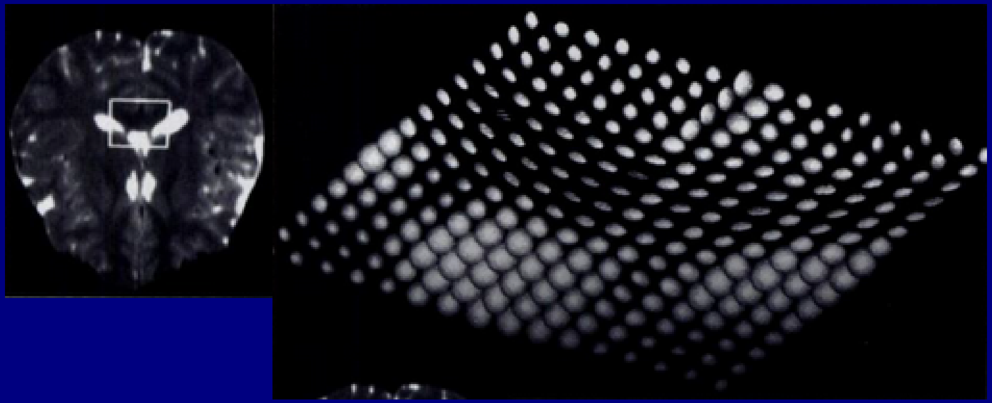
Cautionary notes:

- Degeneracies of structural interpretations
- Changes in myelination may have small effects on FA
- WM bundle diameter << voxel size
  - don't know location/multiplicity of underlying structures
- More to diffusion than structure-- e.g., fluid properties
- Noise, distortions, etc. in measures

Now discuss using *local* structure information
to generate/estimate *nonlocal* structures:
WM tractography

Local DTs $\rightarrow$ extended tracts

Field of local diffusion parameters



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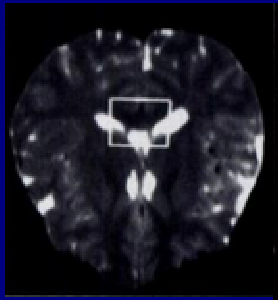
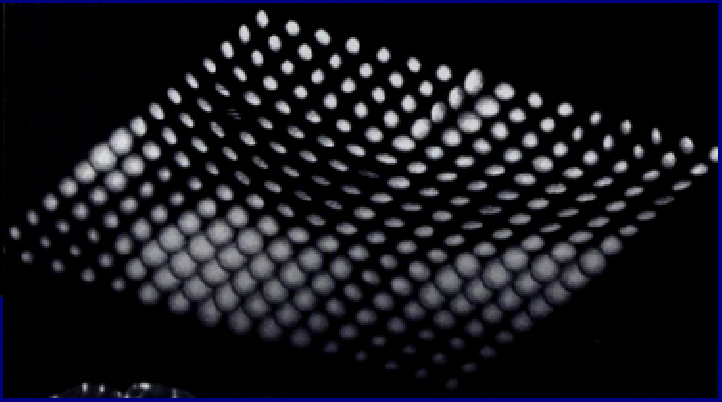




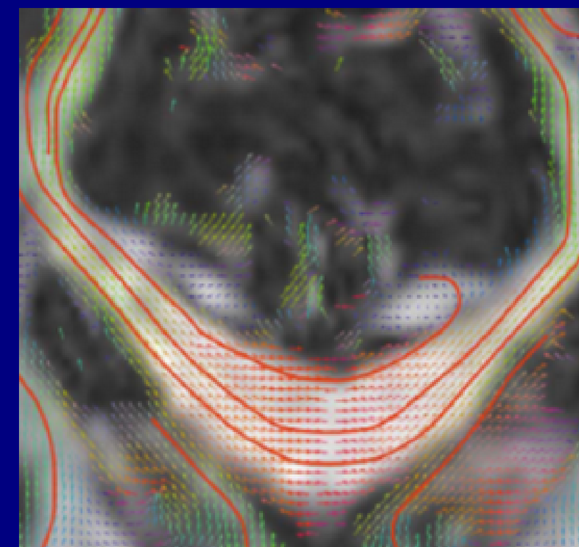
$\longrightarrow$ individual ellipsoids

Local DTs → extended tracts

Field of local diffusion parameters

→ individual ellipsoids

Connect to form extended tracts



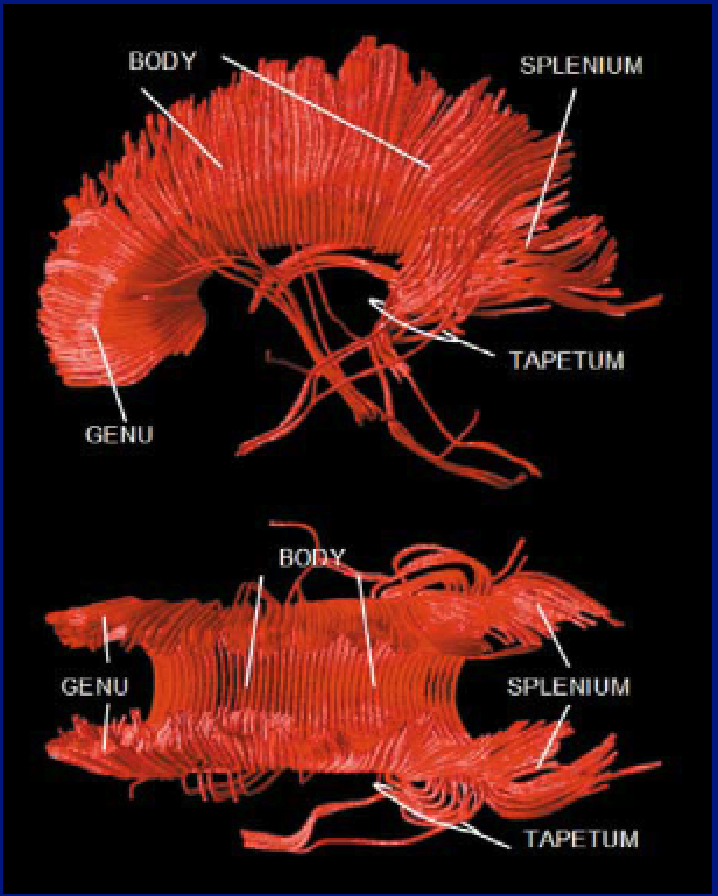
→ linked structures

Tractography in brief

old, invasive

stain and preserve brain, get some
Idea of structure… non-ideal:
brain physiology changes postmortem,
also `mortem' aspect

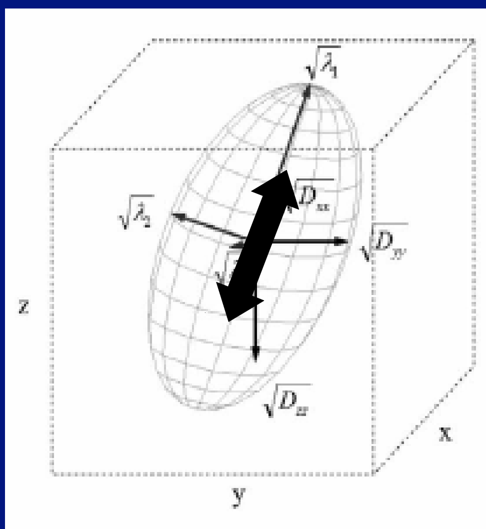
new(er), theoretical



(images from Iowa Virtual Hospital
and Bammer et al. 2003)

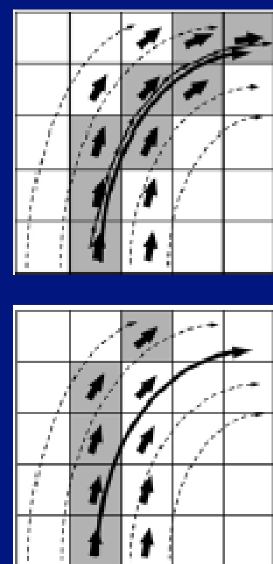
Tractography

Estimate WM structure (fiber tract locations)



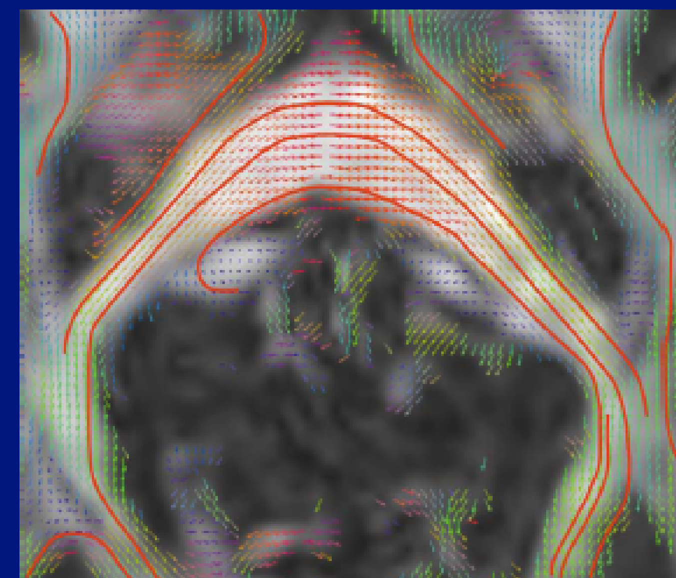
ellipsoid measures (~*smoothing of real structures*)

+



some kind of algorithm for connecting

=



estimate spatial extents of WM 'tracts' in vivo

(images from Bammer et al. 2003)

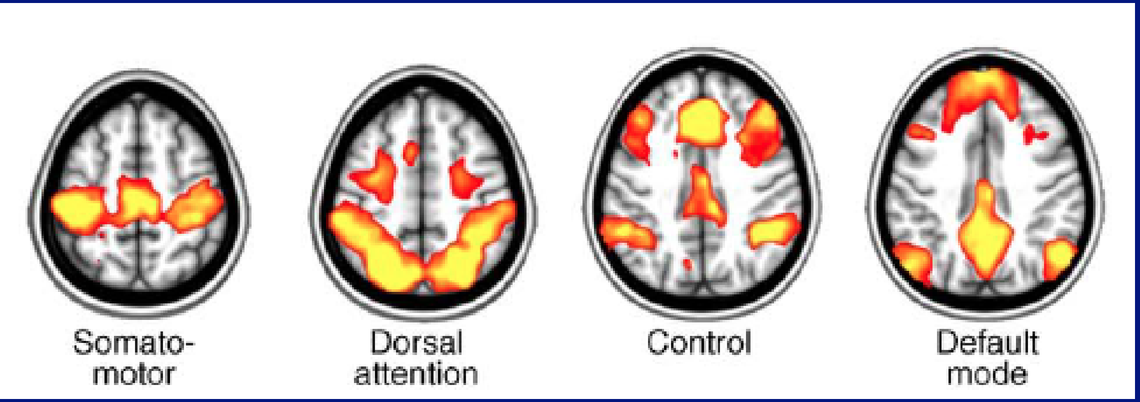
Applying tractography

Structure + Function

Simple example:

FMRI provides:
maps of (GM) regions working together

GM ROIs network:



Raichle (2010, TiCS)

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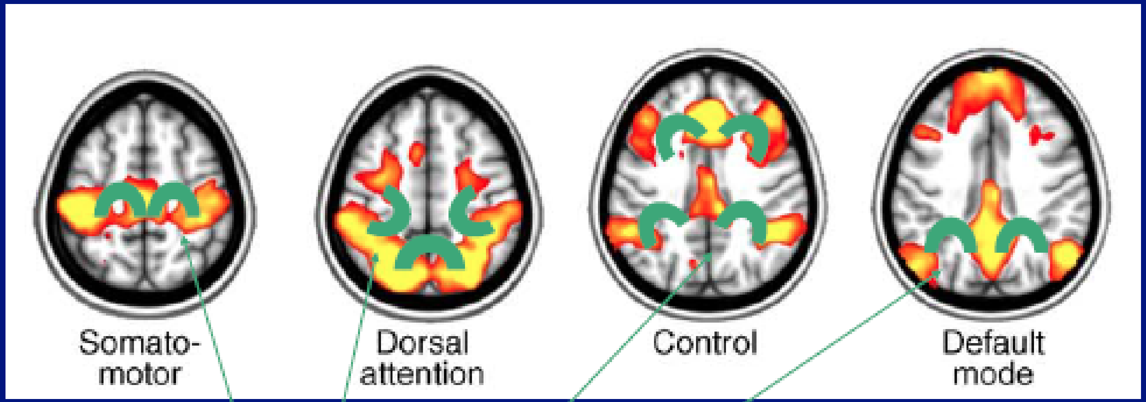

Raichle (2010, TiCS)

Associated WM ROIs

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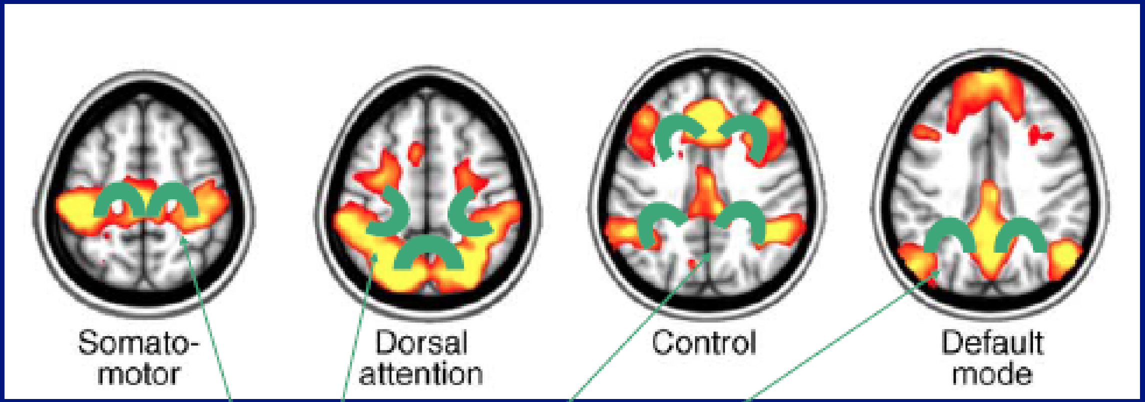


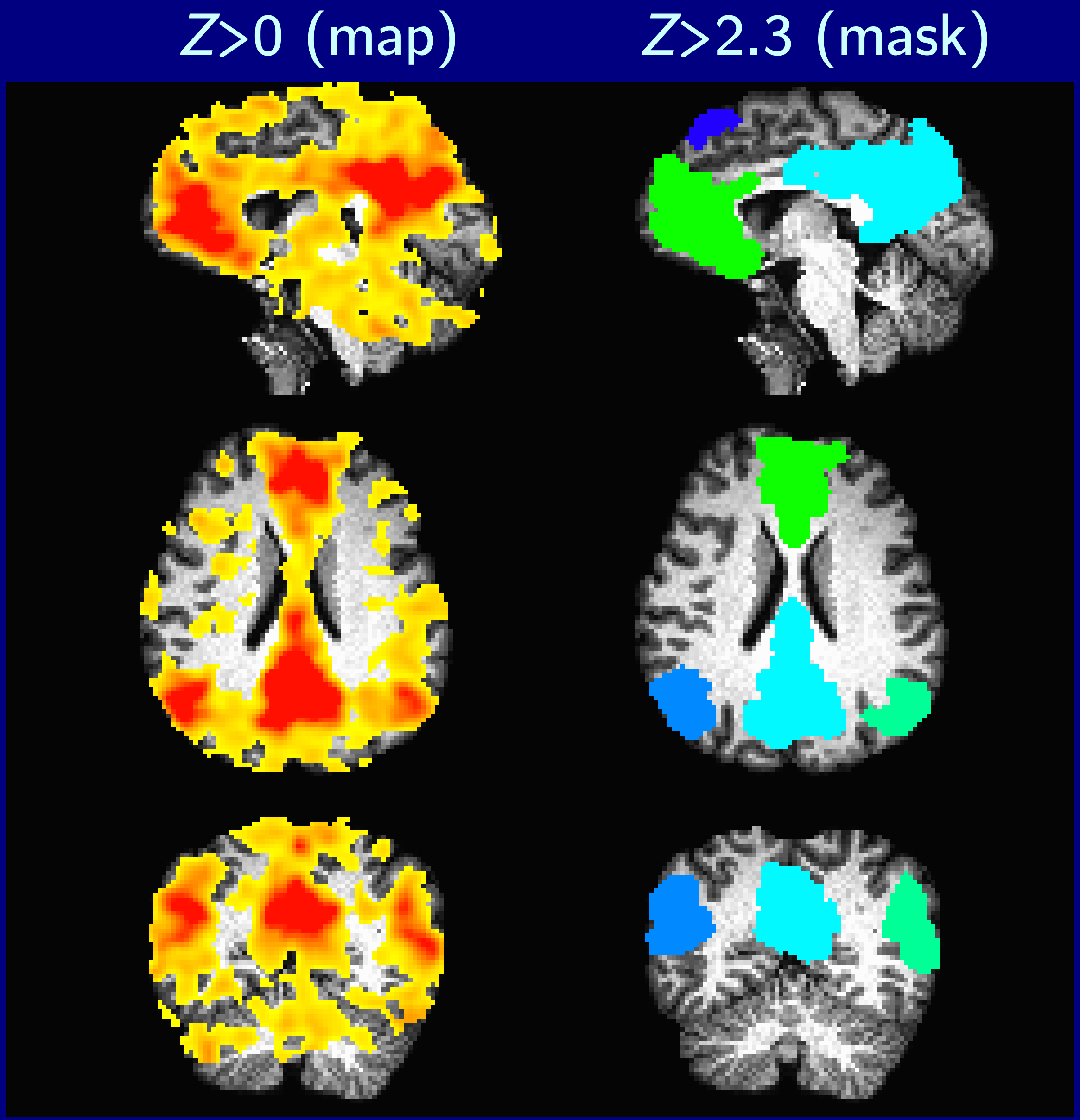
Raichle (2010, TiCS)

Associated WM ROIs

Our goal for tractography->
estimate likely/probable locations of WM associated with GM, and relate ROI quantities with functional/GM properties

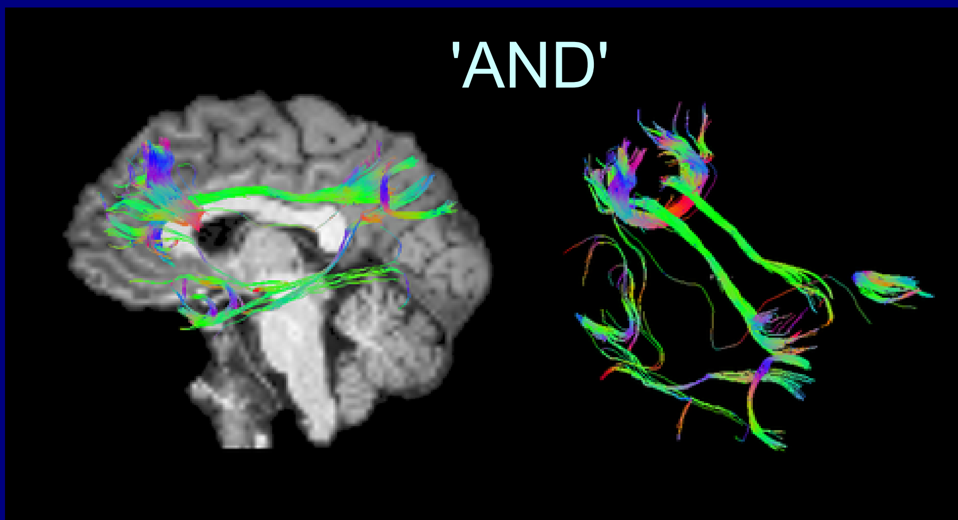
Example: Tractographic selections of WM

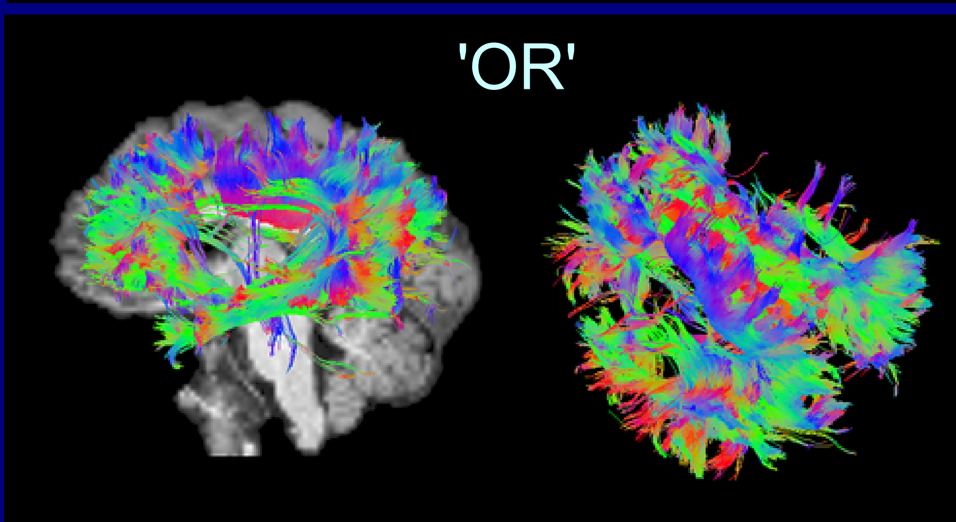
1) Start with FMRI:
$\rightarrow$ threshold to obtain
networks of GM ROIs

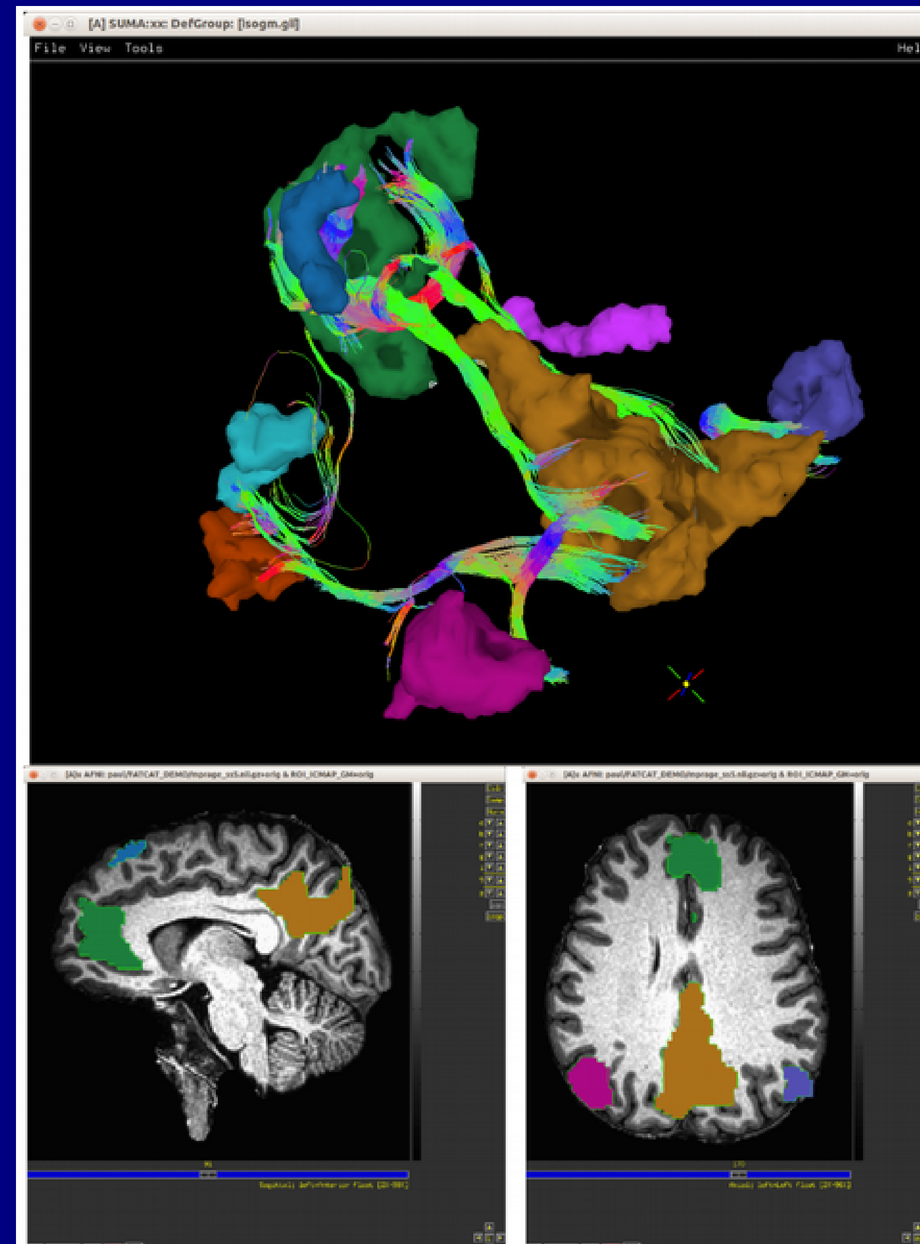


Example: Tractographic selections of WM

2) Use DTI-tractography to find likely location of WM associated with these 'targets'





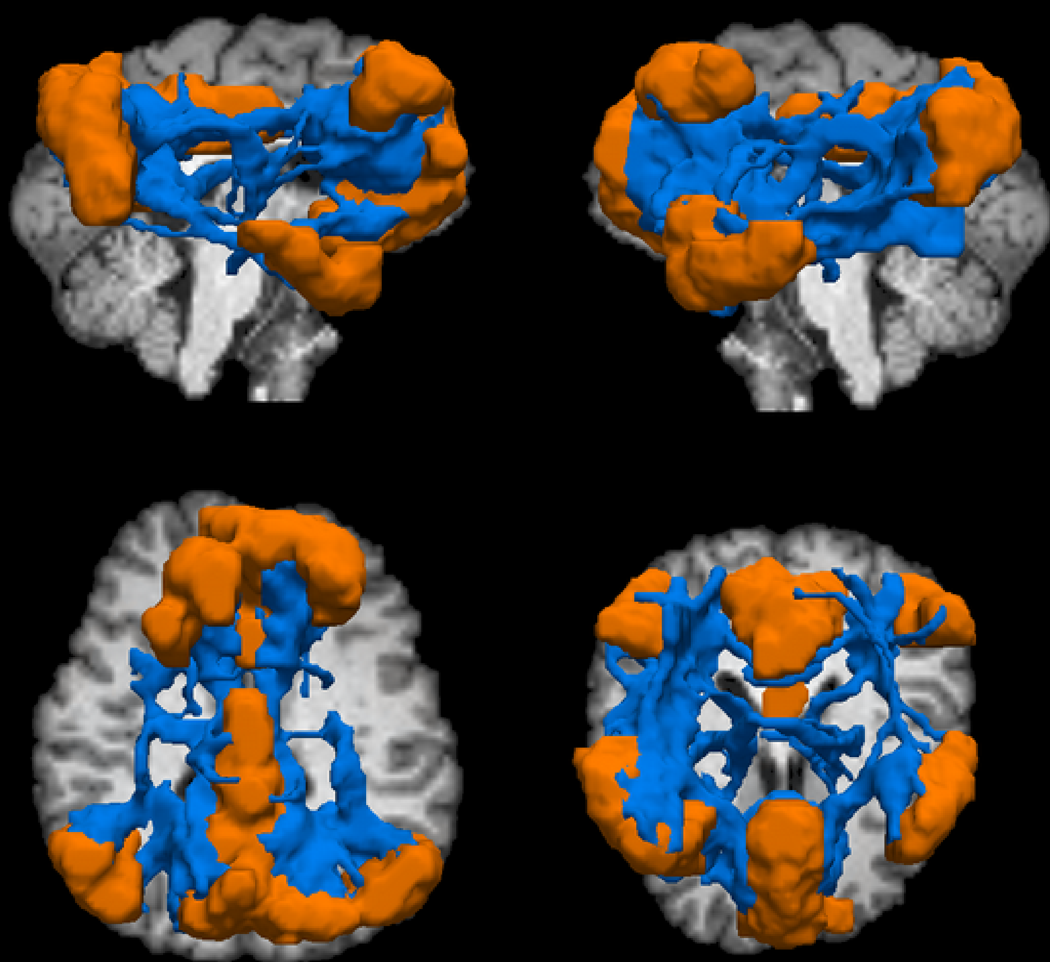


(Deterministic tracking using publicly available AFNI-FATCAT software)

Example: Probabilistic tractography

More robust tracking method (many Monte Carlo iterations)

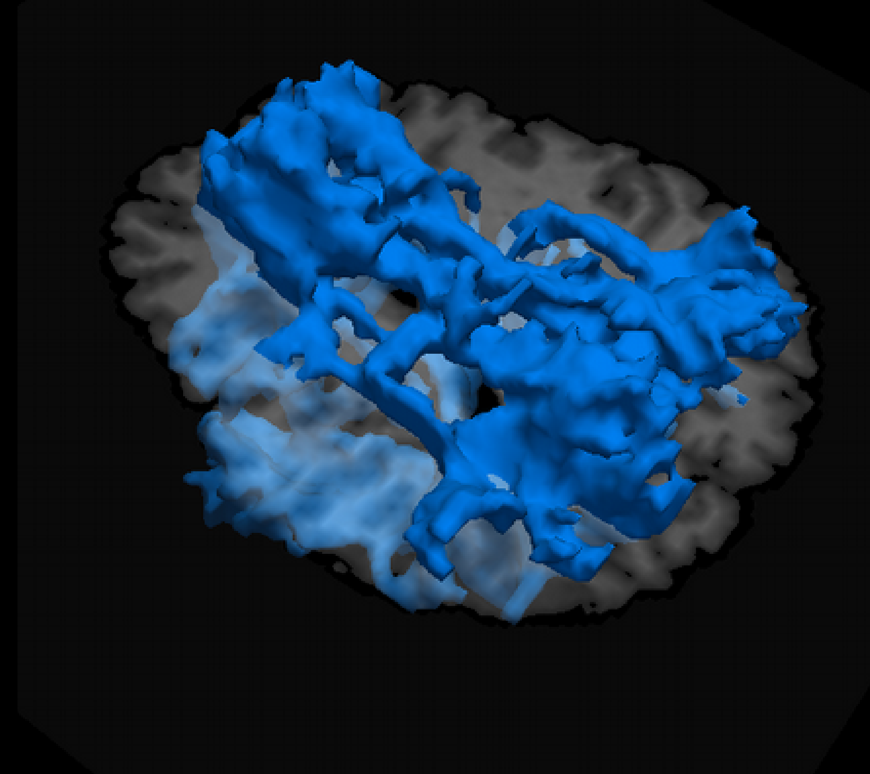
→ '***most likely***' locations of WM



orange = GM ROIs

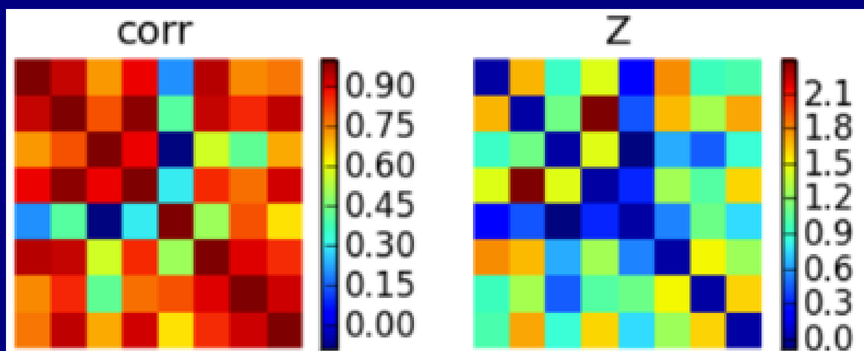
blue = WM estimates

(via AFNI-FATCAT)

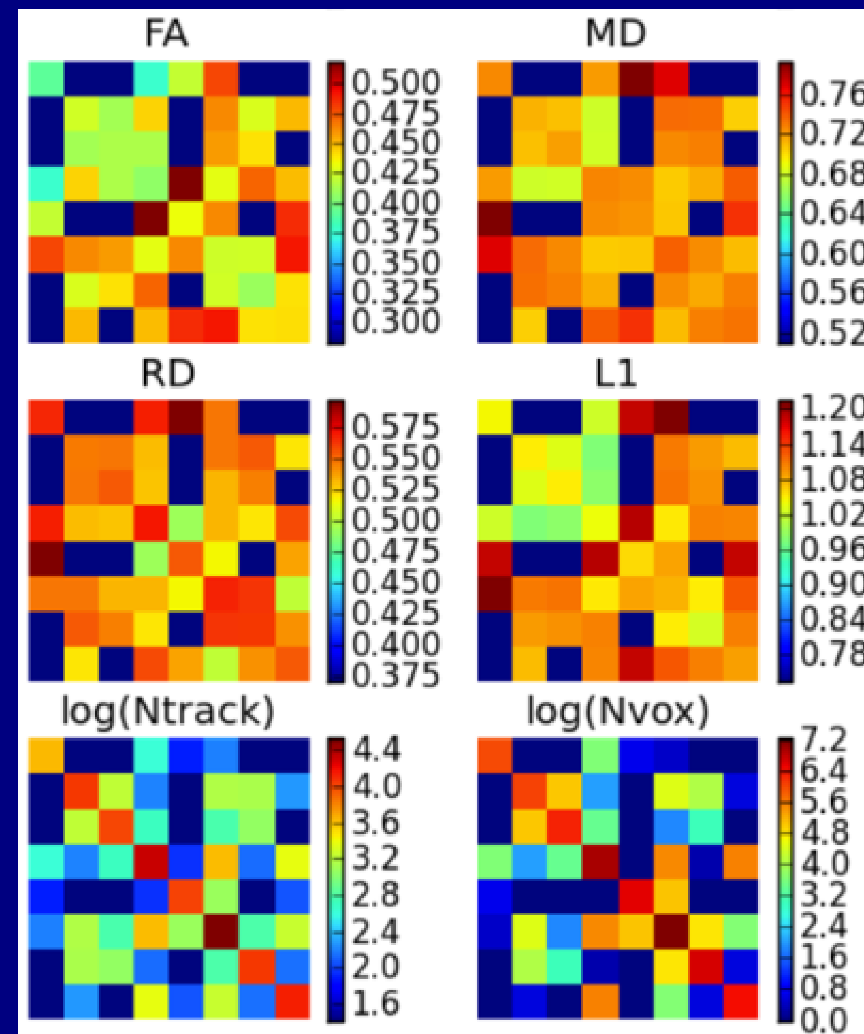


Network quantities: connectivity matrices

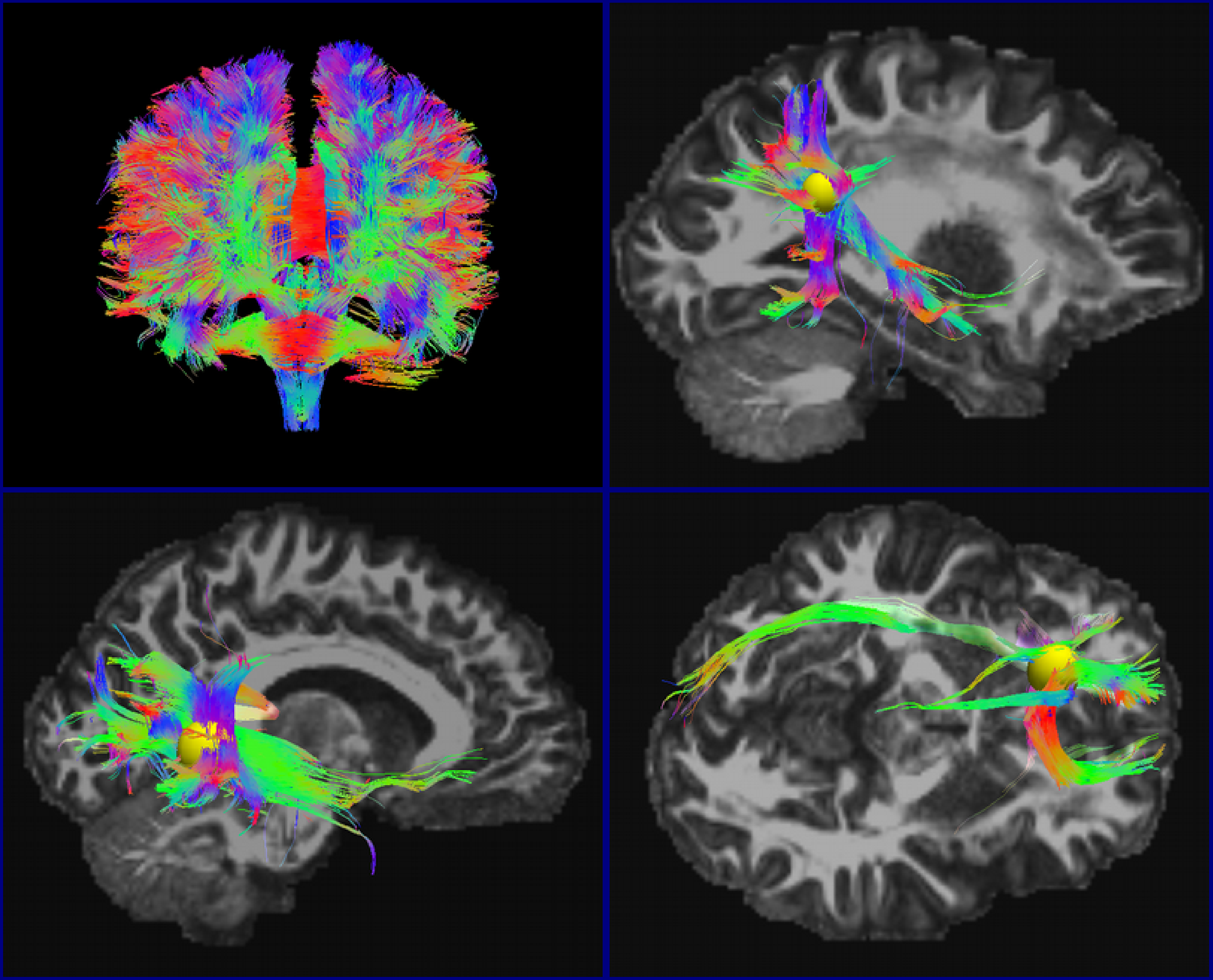
FMRI: correlation matrices quantify functional connectivity in GM



DTI: Structural connectivity matrices quantify properties in WM



Investigate tracts in 3D



Human Connectome Project subject, 288 grads, HARDI reconstructed with GQI in DSI-Studio, tracking in AFNI-FATCAT, visualized in SUMA.

Application 1:

Network-based group analysis,
applied to a DTI + tractography study
of newborns with prenatal alcohol exposure

Taylor PA, Jacobson SW, van der Kouwe AJW, Molteno C, Chen G, Wintermark P, Alhamud A, Jacobson JL, Meintjes EM (2015). *A DTI-Based Tractography Study of Effects on Brain Structure Associated with Prenatal Alcohol Exposure in Newborns.* Human Brain Mapping 36(1):170-186.

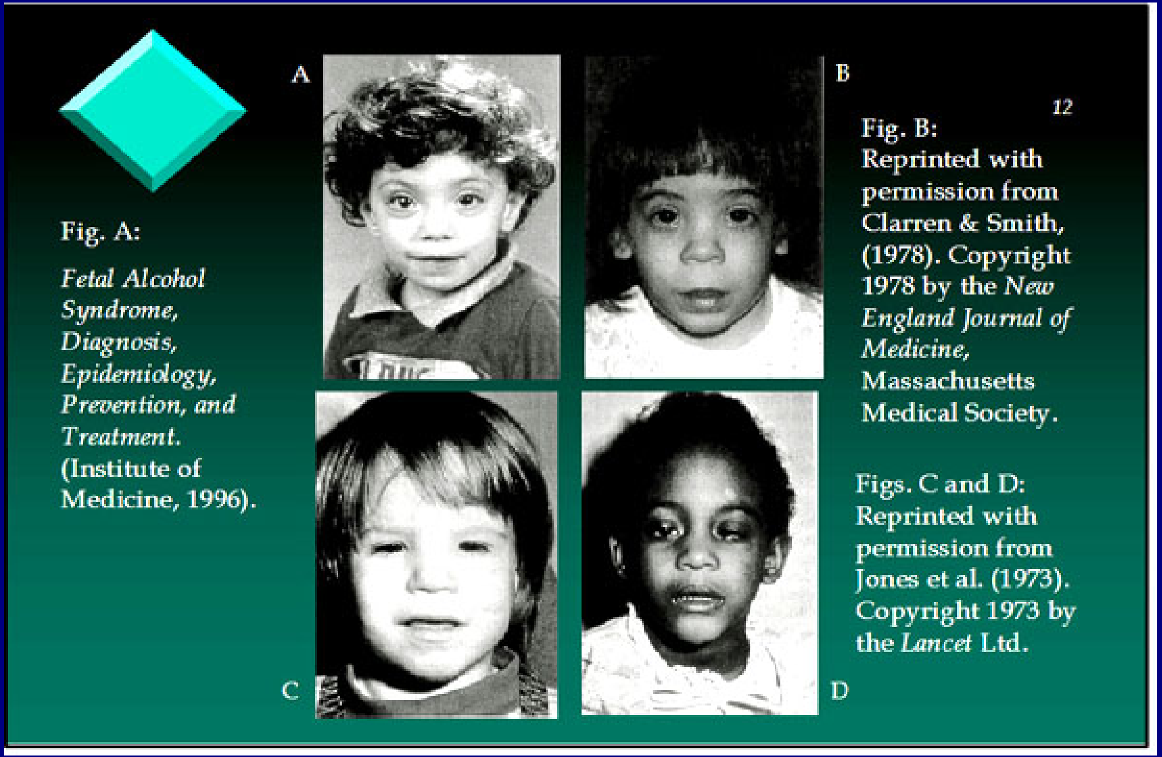
Prenatal alcohol exposure (PAE)

- Alcohol is a teratogen, disrupting healthy development.
  $\rightarrow$ leads to various Fetal Alcohol Spectrum Disorders (FASD)

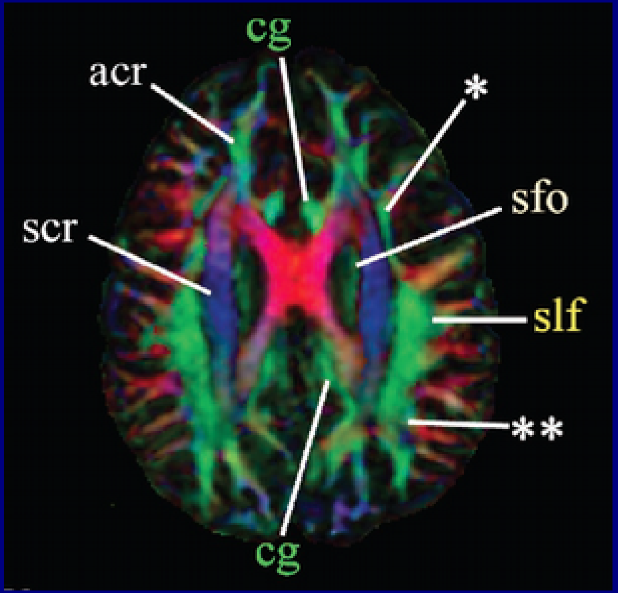
- FASD often occurs in children whose pregnant mothers binge drank
  - e.g., ≥4 drinks/occasion and/or ≥14 drinks/wk

- Results in *poor*:
  - academic performance
  - language/math skills
  - impulse control
  - abstract reasoning
  - memory, attention

  and facial and skeletal dysmorphology



Goals of this study



Use DTI and tractography to:

1) Delineate similar WM across all subjects

2) Compare brain development in PAE newborns with controls.
   i. which WM shows strongest association with PAE?
   ii. which DTI parameter is most sensitive to alcohol exposure?
   (while controlling for factors of age, maternal cig, etc.)

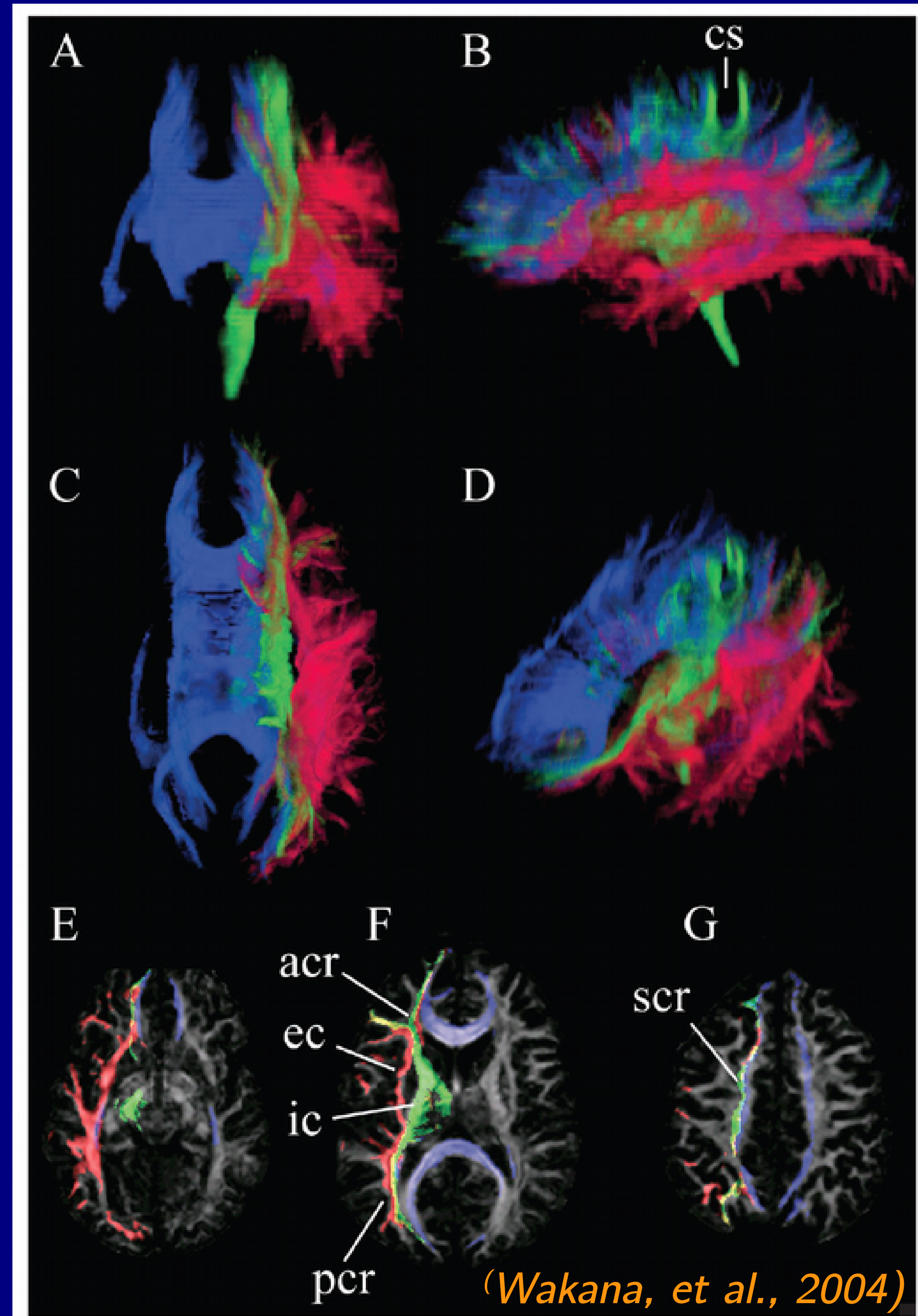
Tracking WM fibers

Tracking can be a useful alternative to maps/atlases for finding characteristic subsets, families or networks of the same WM bundles within each subject, for example:

Transcallosal

Projection

Association

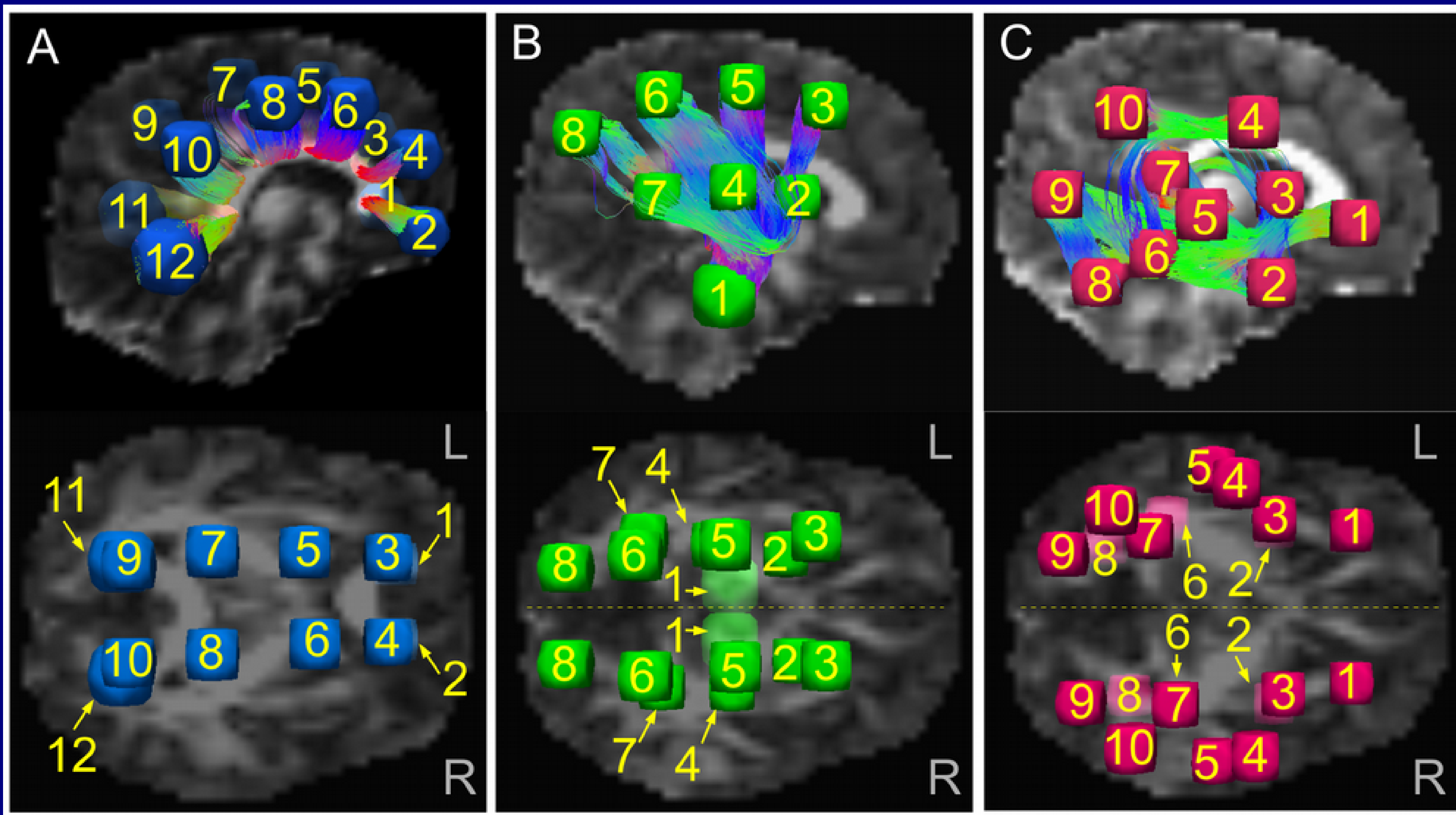


(Wakana, et al., 2004)

I) Setting up DTI-tractography

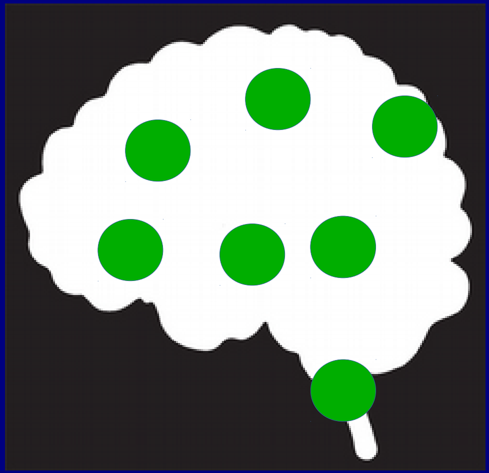
Location of “landmark” targets for tractography: 5 networks

CC and Cor. Rad. (CCCR)	Projection (L/R-PROJ)	Association (L/R-ASSOC)



II) Network-based Analysis Steps

1) Place network targets



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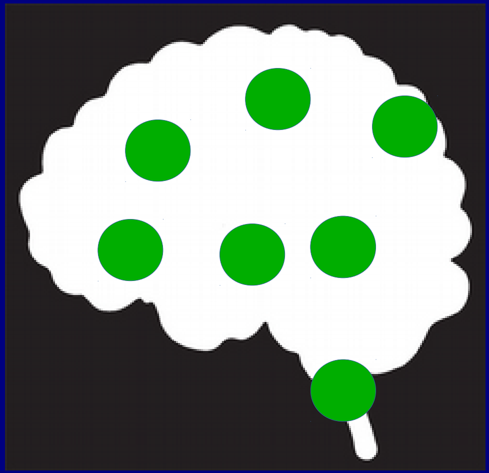
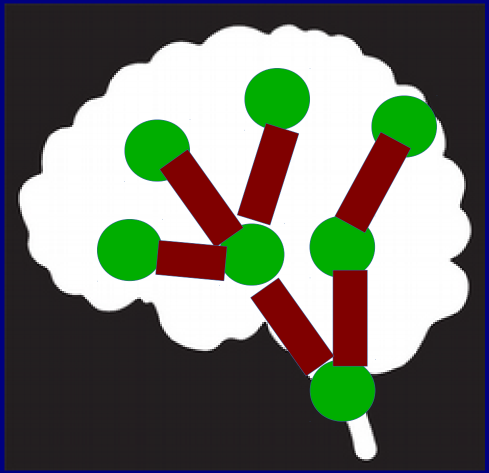
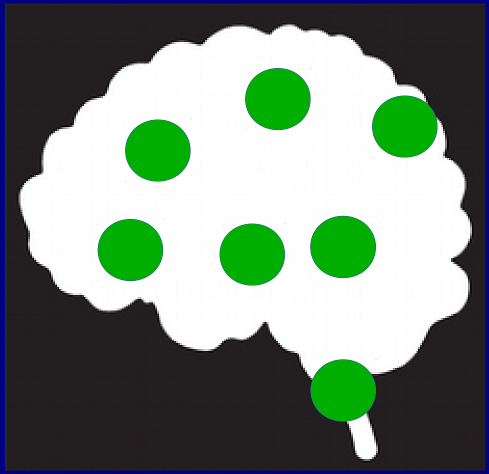


2) Probabilistic tracking

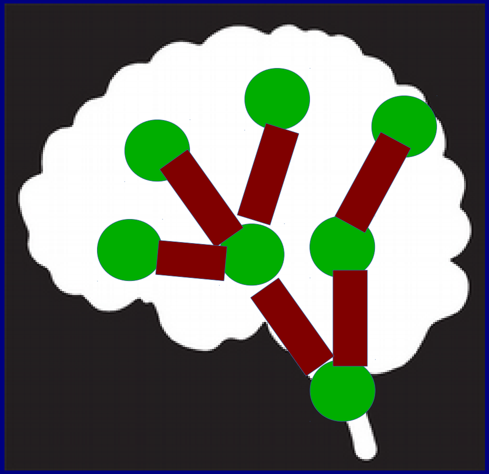


II) Network-based Analysis Steps

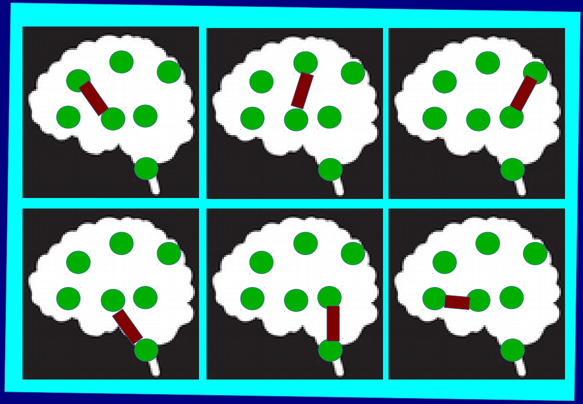
1) Place network targets



2) Probabilistic tracking



3) set of WM ROIs $\rightarrow$ set of repeated measures



II) Network-based Analysis Steps

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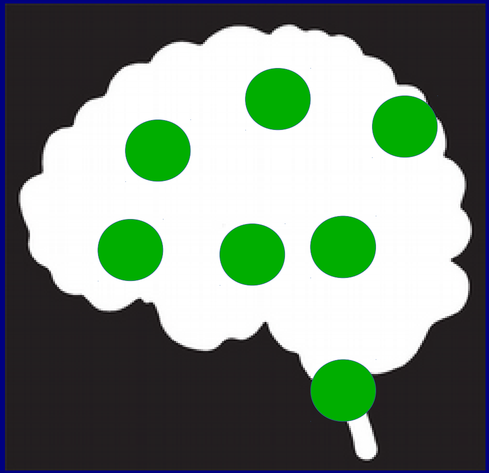
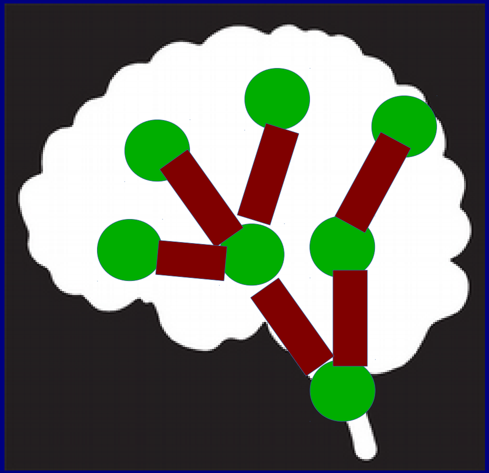


2) Probabilistic tracking



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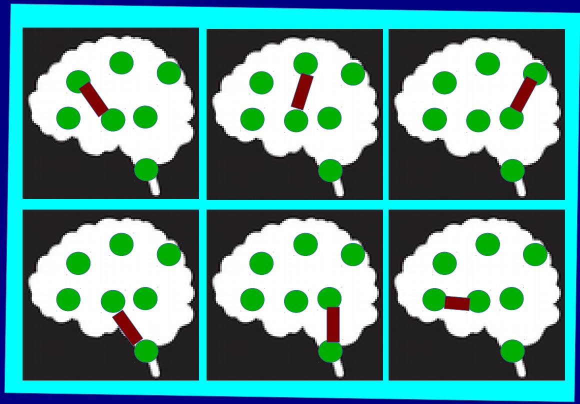
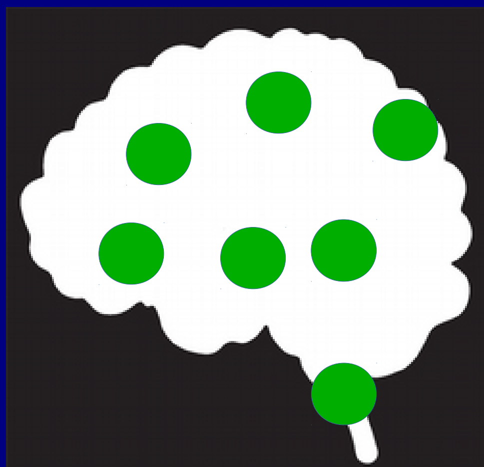


4) Multivariate model
- {FA_1, FA_2, FA_3, ...}
- alc
- infant age
- infant sex
- maternal age
- maternal cig/day

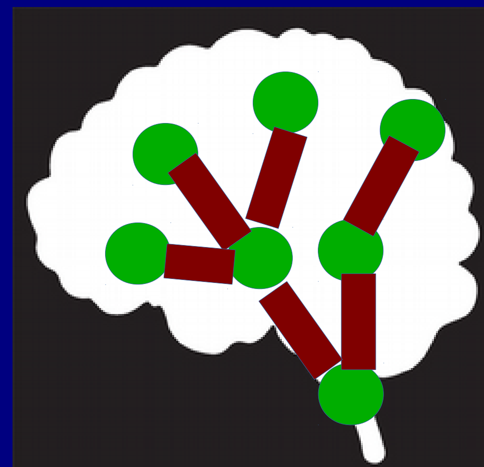
➡ AFNI's 3dMVM, written by G. Chen

II) Network-based Analysis Steps

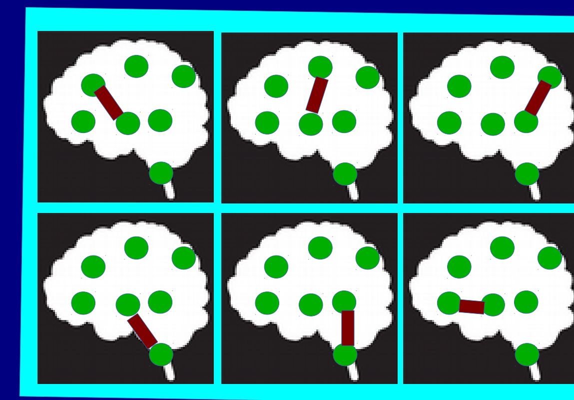
1) Place network targets



2) Probabilistic tracking



3) set of WM ROIs $\rightarrow$ set of repeated measures

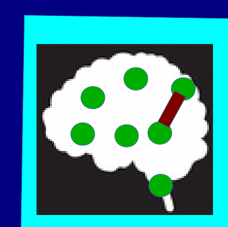
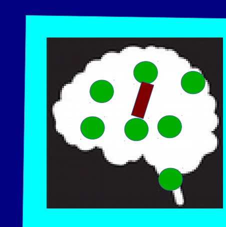


4) Multivariate model

- $\{FA_1, FA_2, FA_3, \ldots\}$
- alc
- infant age
- infant sex
- maternal age
- maternal cig/day

5) Follow-up GLM for each WM ROI

- FA
- alc
- infant age
- infant sex
- maternal age
- maternal cig/day

 ,  , ...

AFNI's 3dMVM, written by G. Chen

II) Results: network level

The questions:

1) which WM networks are affected by PAE?
2) which parameters show effects most strongly?

Answer using:

- (for each network) a multivariate GLM for
  - set of DTI parameters
  - alcohol (frequency: binge/wk)
  - infant age (wks since conception)
  - infant sex (M/F)
  - maternal age (yrs)
  - maternal cigarette smoking (cig/day).

II) Results: network level

The questions:

1) which WM networks are affected by PAE?
2) which parameters show effects most strongly?

Parameters showing at least trends ($p<0.1$) →

← Networks

	FA				MD				L1				PD			
Network	**var.**	β_{med}	$F\ (df_N, df_D)$	p	**var.**	β_{med}	$F\ (df_N, df_D)$	p	**var.**	β_{med}	$F\ (df_N, df_D)$	p	**var.**	β_{med}	$F\ (df_N, df_D)$	p
CCCR					**alc**	-0.70	8.6 (1, 14)	**0.011***	**alc**	-0.72	14.0 (1, 14)	**0.002****				
									cig	-0.27	2.5 (6, 9)	0.101	cig	0.47	3.5 (1, 14)	0.083
					mat_age	0.56	5.5 (1, 14)	**0.034***	**mat_age**	0.53	6.3 (1, 14)	**0.025***				
L-PROJ					**alc**	-0.41	3.9 (10, 140)	**0.000*****	**alc**	-0.52	4.1 (10, 140)	**0.000*****				
	cig	0.12	4.2 (11, 4)	0.091									cig	0.52	4.0 (1, 14)	0.066
					mat_age	0.37	4.4 (1, 14)	0.056	**mat_age**	0.44	6.5 (1, 14)	**0.023***				
R-PROJ					**alc**	-0.41	1.9 (12, 168)	**0.035***	**alc**	-0.45	2.7 (12, 168)	**0.002****				
													cig	0.48	3.4 (1, 14)	0.085
	age	0.33	8.6 (13, 2)	0.109	**age**	-0.41	5.8 (1, 14)	**0.031***	**age**	-0.39	5.3 (1, 14)	**0.038***				
					sex	-0.20	4.3 (1, 14)	0.056	**sex**	-0.39	5.9 (1, 14)	**0.029***				
	mat_age	-0.16	9.2 (13, 2)	0.103												
L-ASSOC					**alc**	-0.65	6.0 (7, 8)	**0.011***	**alc**	-0.66	8.1 (1, 14)	**0.013***				
													cig	0.49	3.6 (1, 14)	0.080
									age	-0.16	2.5 (6, 84)	**0.030***				
					mat_age	0.44	3.8 (1, 14)	0.071	**mat_age**	0.43	4.7 (1, 14)	**0.048***				
R-ASSOC	alc	0.23	1.8 (7, 98)	0.090	**alc**	-0.62	10.2 (1, 14)	**0.007****	**alc**	-0.67	14.1 (1, 14)	**0.002****				
									cig	-0.29	3.9 (1, 14)	0.068	cig	0.5	3.5 (1, 14)	0.082

** $p<0.05$; ** $p<0.01$; *** $p<0.001$.*

II) Results: network level

The questions:

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** $p<0.05$; ** $p<0.01$; *** $p<0.001$.*

→ Significant alcohol associations in ~every WM network

II) Results: network level

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Parameters showing at least trends ($p<0.1$) →

← Networks

	FA				MD				L1				PD			
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									cig	-0.29	3.9 (1, 14)	0.068	cig	0.5	3.5 (1, 14)	0.082

** $p<0.05$; ** $p<0.01$; *** $p<0.001$.*

→ Increased alcohol exposure: decreased L1 ("parallel diffusivity")

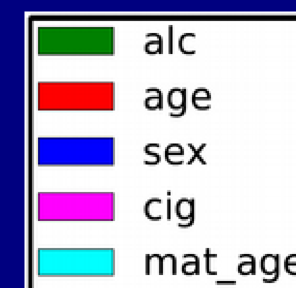
III) Results: ROI level

The question:

1) where are most significant AD-alcohol relations in each network?

Answer using:

- (for each ROI) a GLM for
  - single DTI parameter
  - alcohol (frequency: binge/wk)
  - infant age (wks since conception)
  - infant sex (M/F)
  - maternal age (yrs)
  - maternal cigarette smoking (cig/day).



III) Results: ROI level

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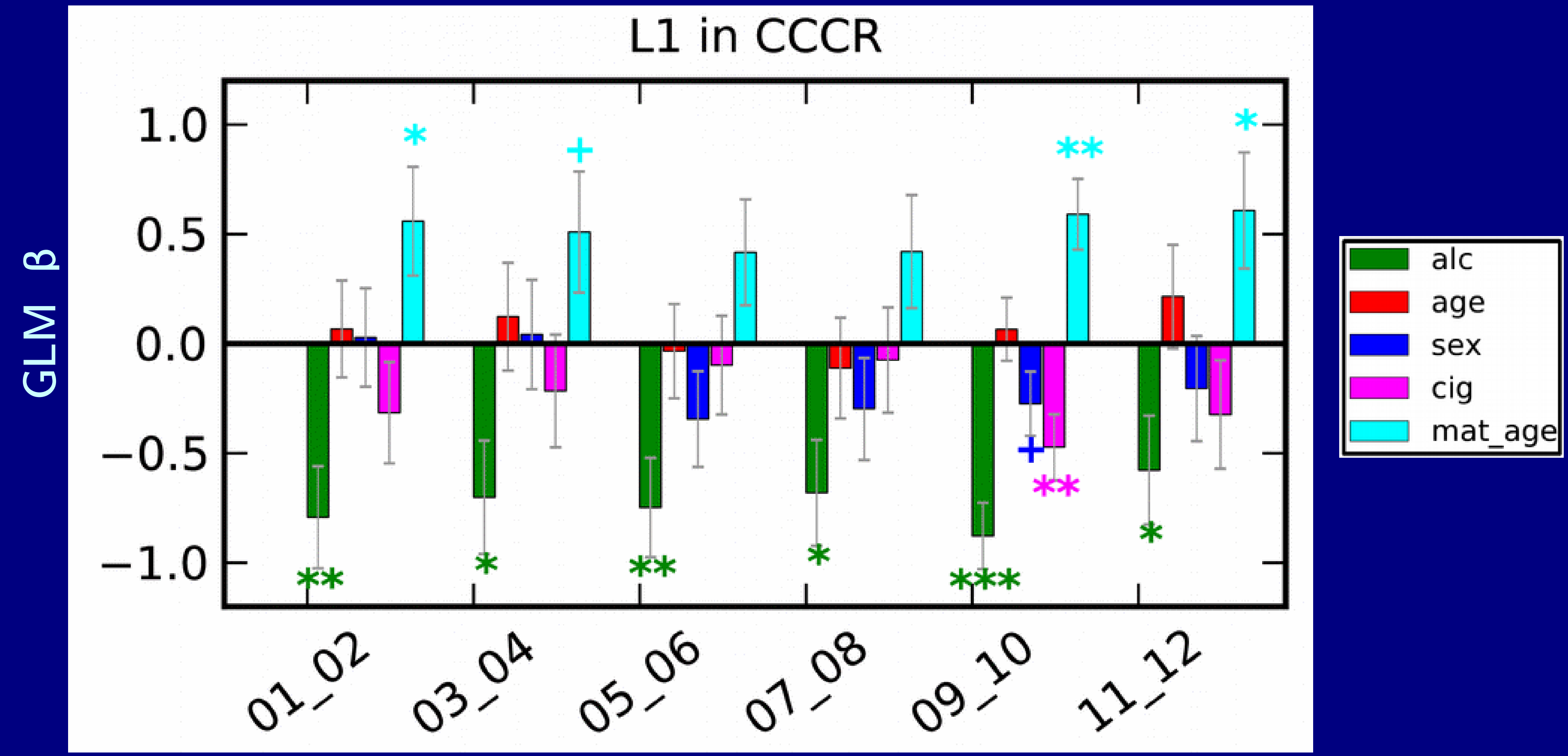
Transcallosal (CC and corona radiata)



anterior → posterior

III) Results: ROI level

The question:

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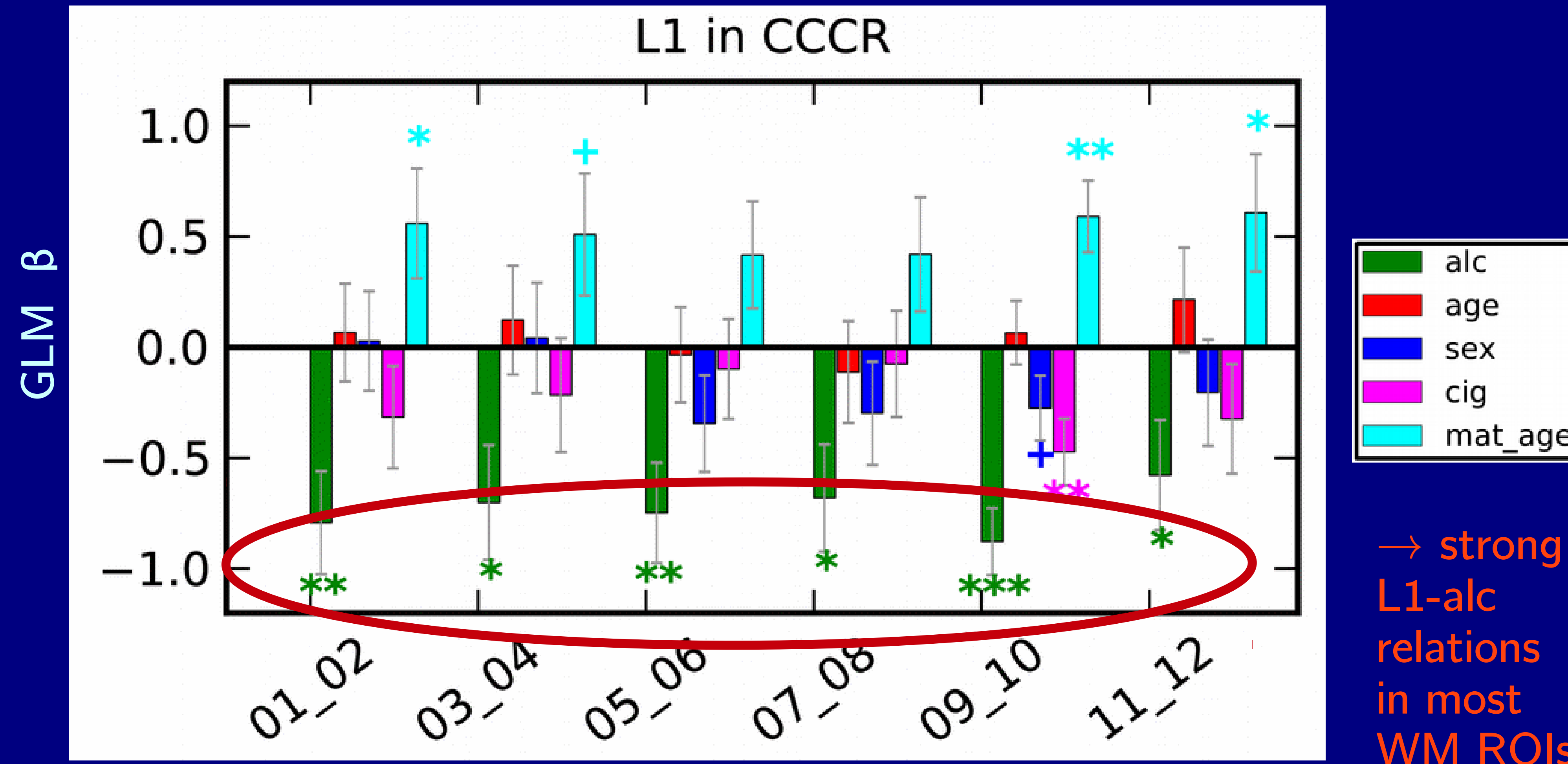
Transcallosal (CC and corona radiata)



→ strong L1-alc relations in most WM ROIs

anterior → posterior

Application 2:

Tractography to study effective placement of DBS electrodes

Application 2:

Tractography to study effective placement
of DBS electrodes

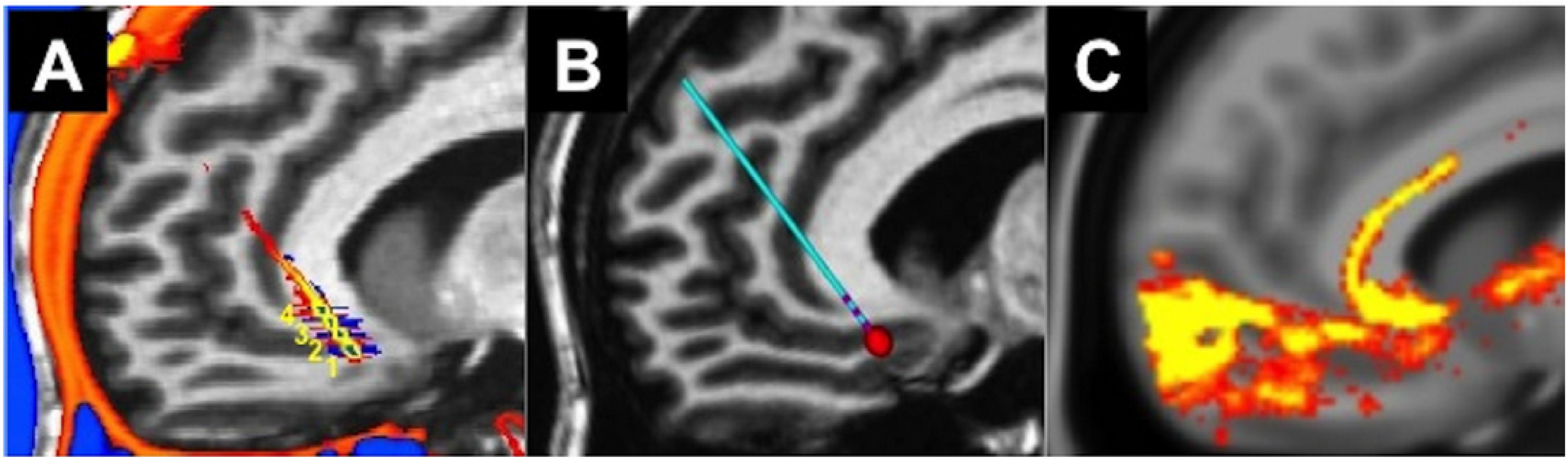
NB:
The following work has been done by Dr. Helen Mayberg's
group at Emory University, Atlanta, USA.

Following data and images taken (with kind permission) from:
Defining Critical White Matter Pathways Mediating
Successful Subcallosal Cingulate Deep Brain Stimulation
for Treatment-Resistant Depression (Riva-Posse, Choi, et al., 2014)

Initial Study: good locations for electrodes?

- 17 patients diagnosed with treatment-resistant depression (TRD)

- Electrodes were placed in subcallosal cingulate WM
  + initial placement by anatomy, from previous studies.



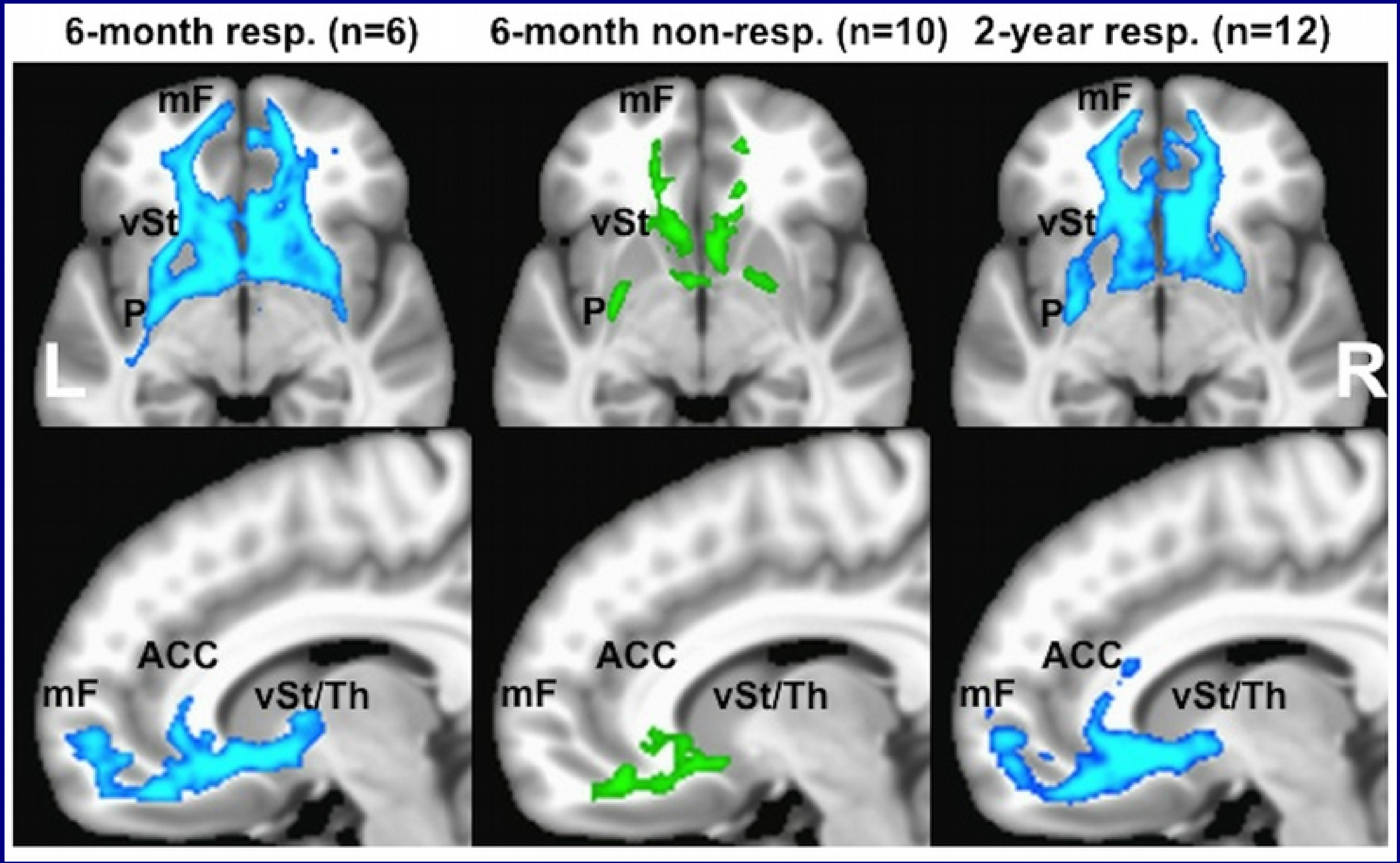
Anatomical location of electrodes

Estimated activation volume

Check: WM tracts passing through activation volume

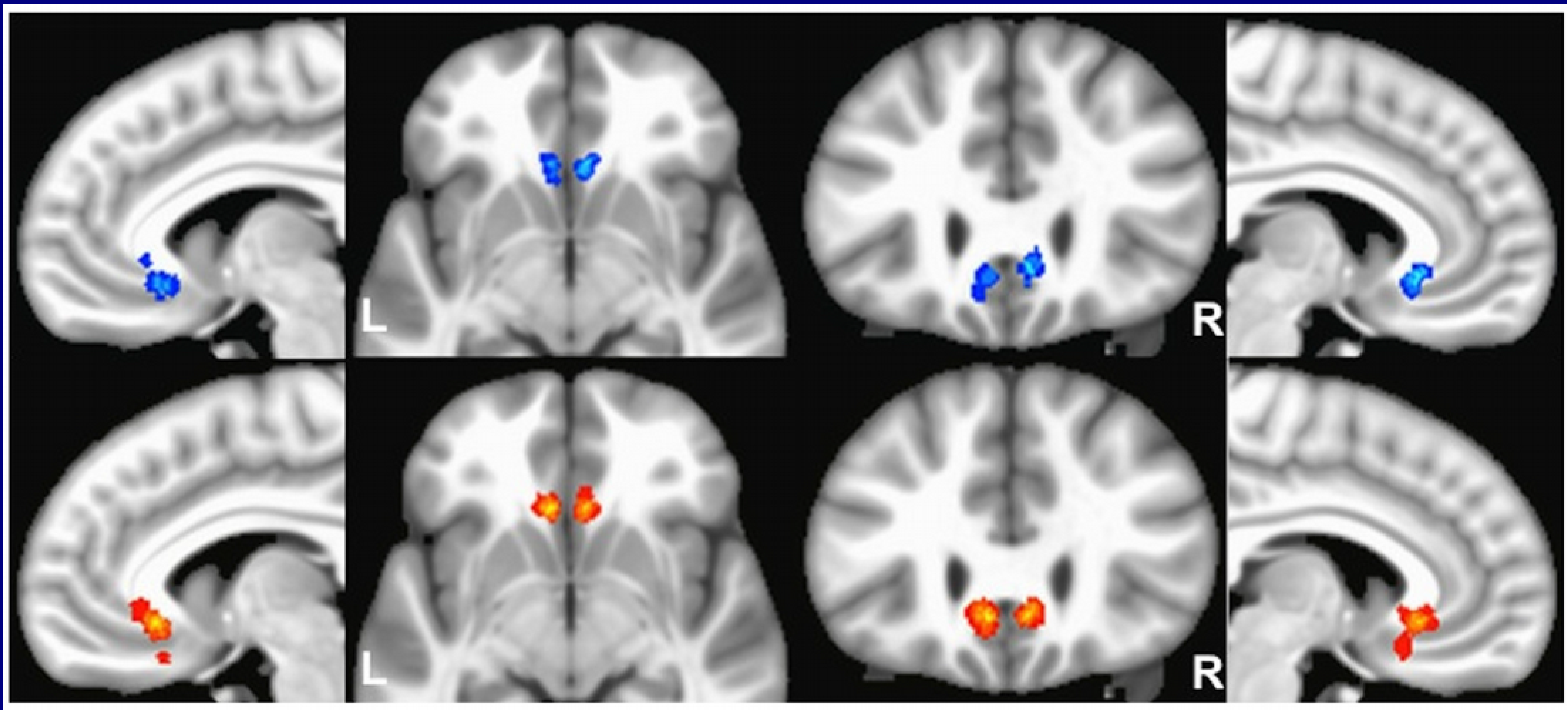
Followup with subjects: tracking

- Responses were measured at 6 mo and 2 yr.
  (17-item Hamilton Depression Rating Scale)
- Subjects categorized as 'Responders' or 'Nonresponders'
- Group comparisons of tract maps around electrodes
  → *consistent differences seen*



Followup with subjects: anatomy

- Group comparisons of anatomical electrode locations
  → *no significant difference*



(Resp. in blue, nonresp. in yellow/red)

Optimal location based on tracks

- From responder similarities in tractography paths (and differences to nonresponders), optimal location for DBS electrodes are indicated

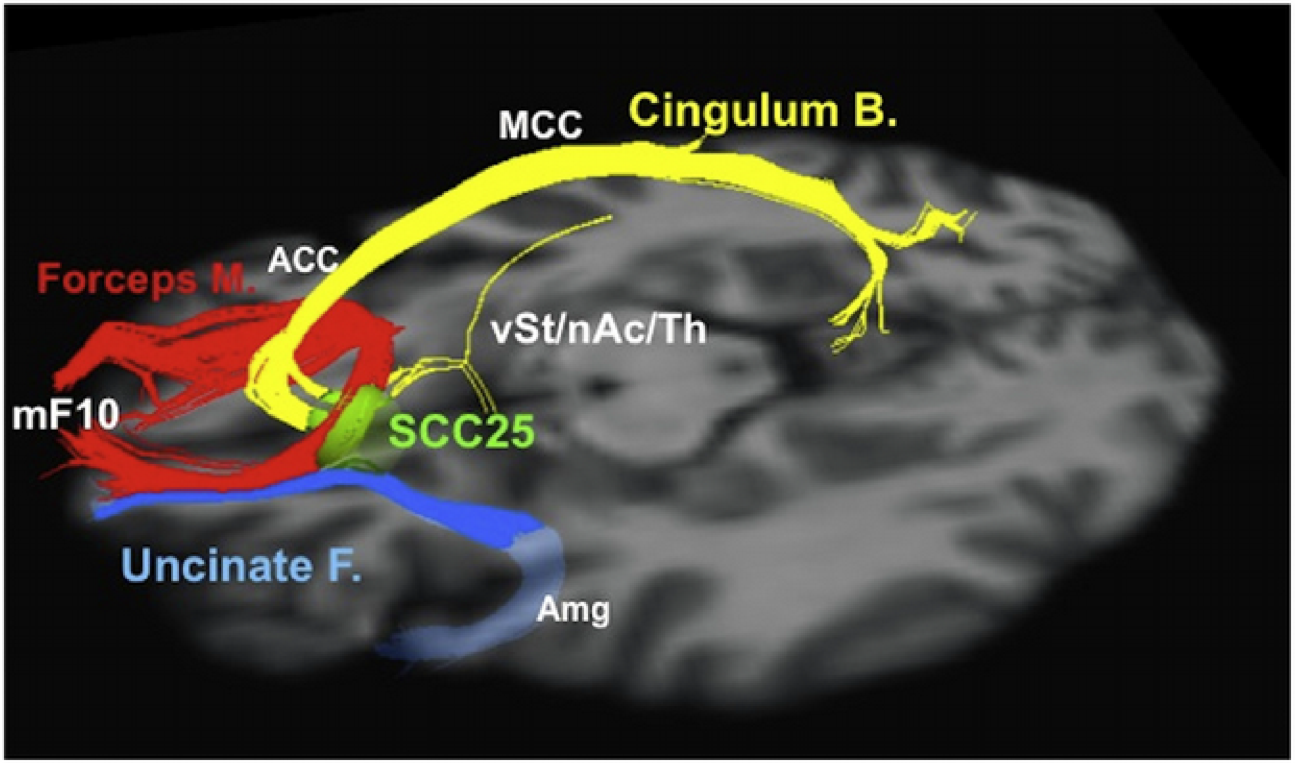


Figure 5. Optimal subcallosal cingulate deep brain stimulation fiber bundle target template. Red: forceps minor. Blue: uncinate fasciculus. Yellow: cingulate bundle. ACC, anterior cingulate cortex; Amg, amygdala; Cingulum B., cingulum bundle; Forceps M., forceps minor; MCC, middle cingulate cortex; mF10, medial frontal (Brodmann area 10); nAc, nucleus accumbens; SCC25, subcallosal cingulate cortex (Brodmann area 25); Th, thalamus; Uncinate F., uncinate fasciculus; vSt, ventral striatum.

Next: feedback for electrode placement

- Next, use tractography to *prospectively* determine location for electrode placement

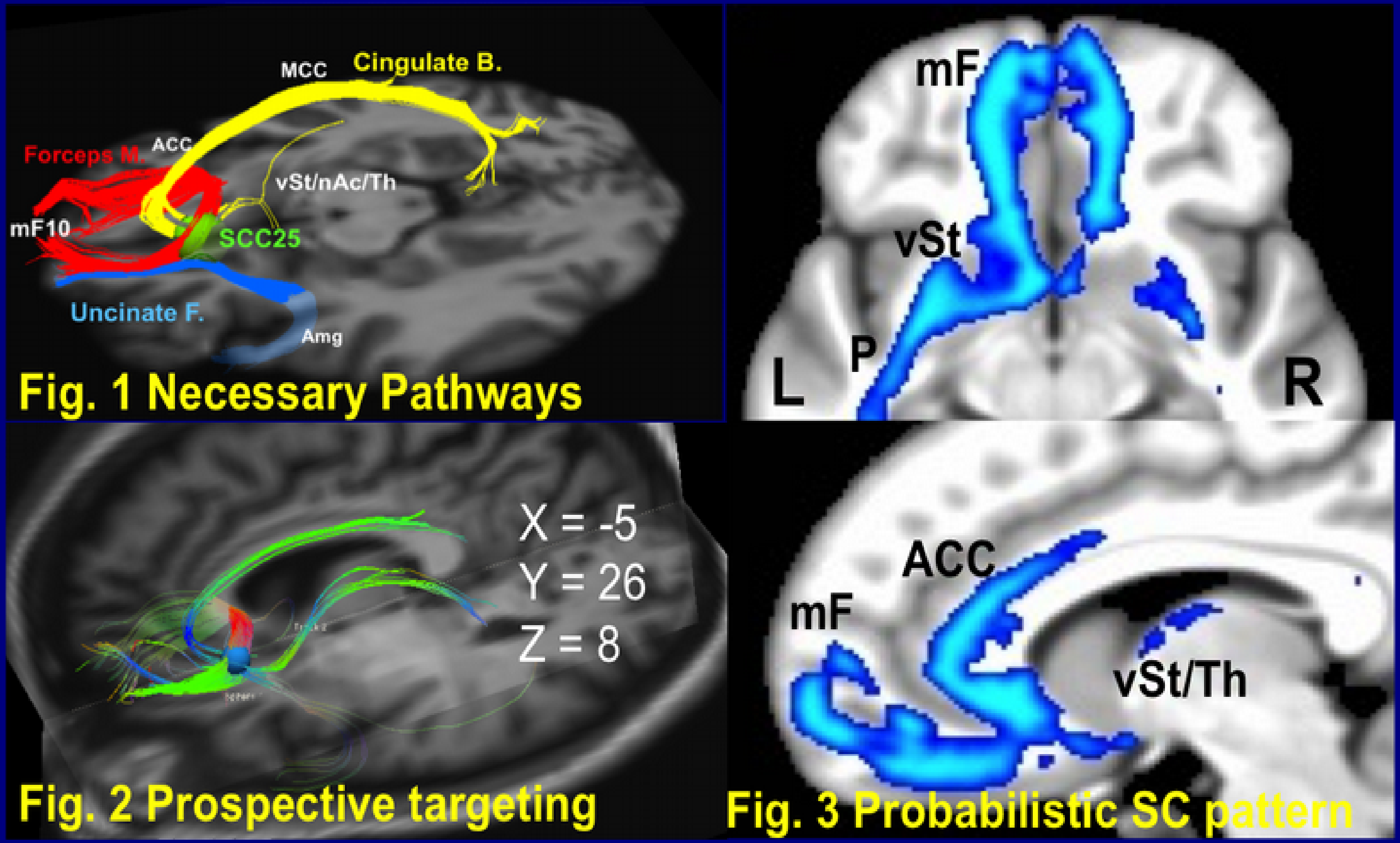
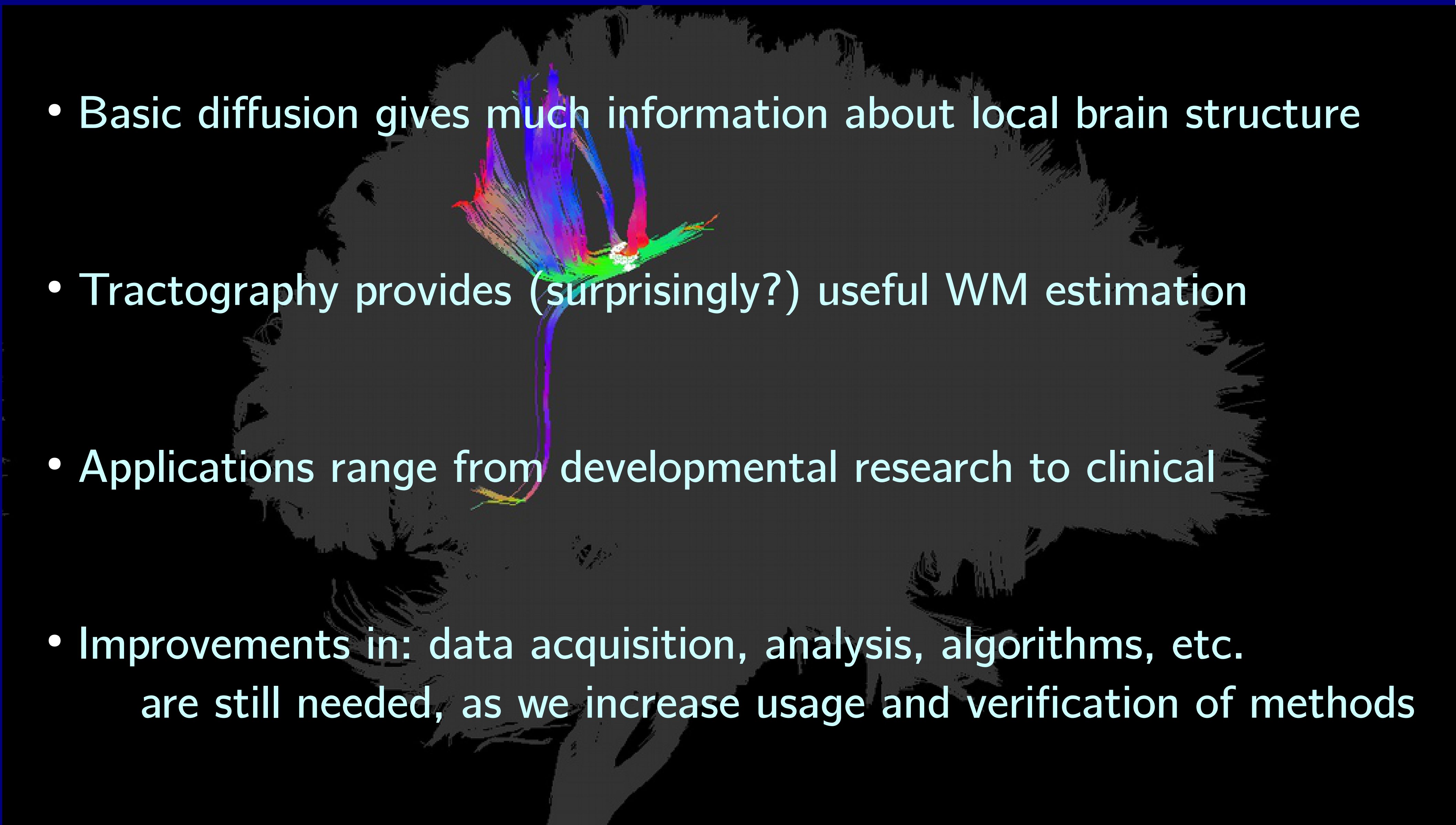


Fig. 1 Necessary Pathways
Fig. 2 Prospective targeting
Fig. 3 Probabilistic SC pattern

- Initial results (small group, N=10) are encouraging → increased fraction of responders (NB: preliminary findings)

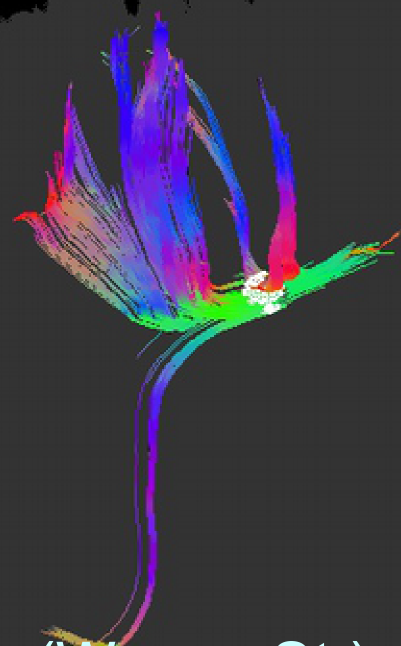
Conclusions



- Basic diffusion gives much information about local brain structure
- Tractography provides (surprisingly?) useful WM estimation
- Applications range from developmental research to clinical
- Improvements in: data acquisition, analysis, algorithms, etc.
  are still needed, as we increase usage and verification of methods

Thanks

And thanks to colleagues and collaborators:



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Pia Wintermark (Montreal Children's)

AIMS:
Johan de Villiers

NJIT:
Bharat Biswal
Suril Gohel
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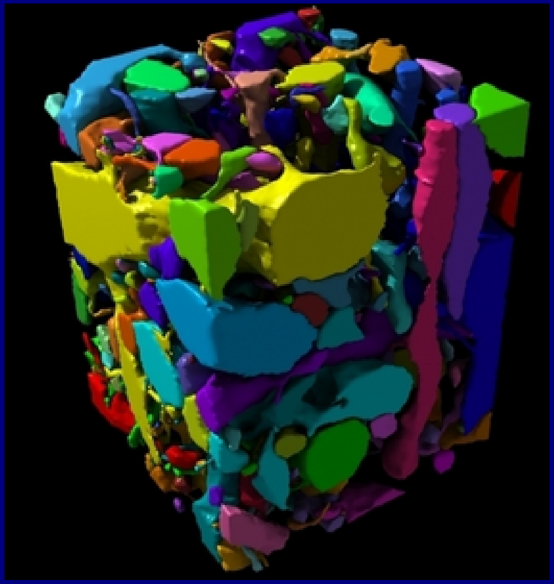
further notes

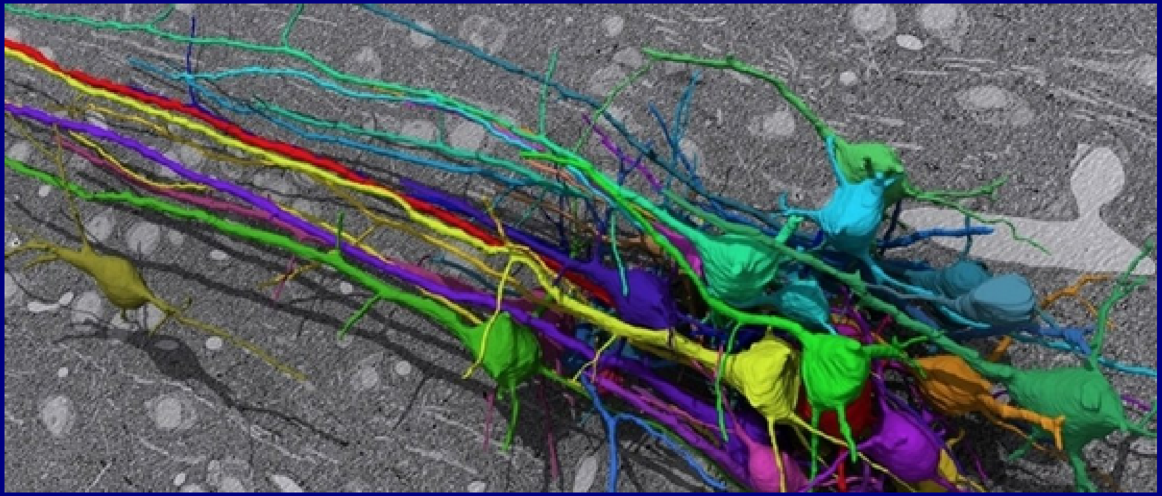
Cinematic side note:

La Belle et la Bête of tractography

Known Challenges for Tracking

+ Axon diameters are of order a few micrometers
+ MRI voxel size is of order millimeters





(images of Eyewire data via NPR website)

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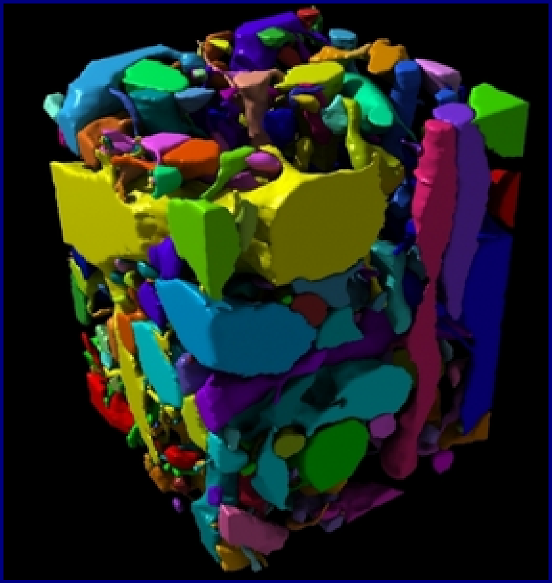
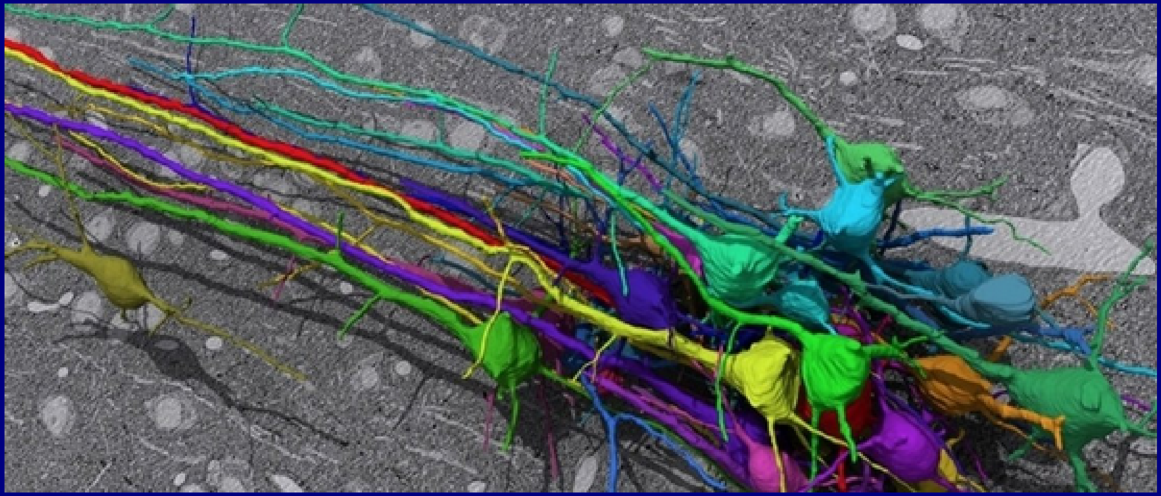
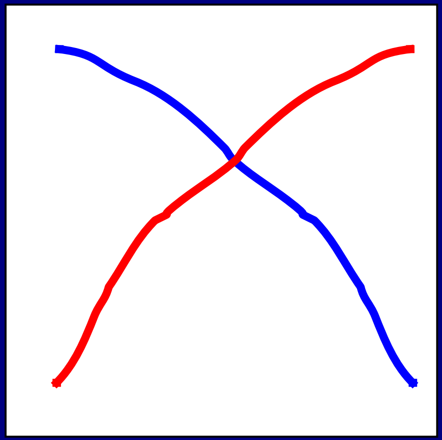
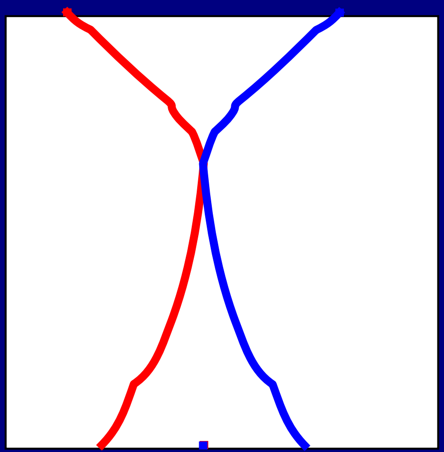




(images of Eyewire data via NPR website)

- \+ WM regions are tightly packed, with many connections and potentially complicated sub-voxel scale structure

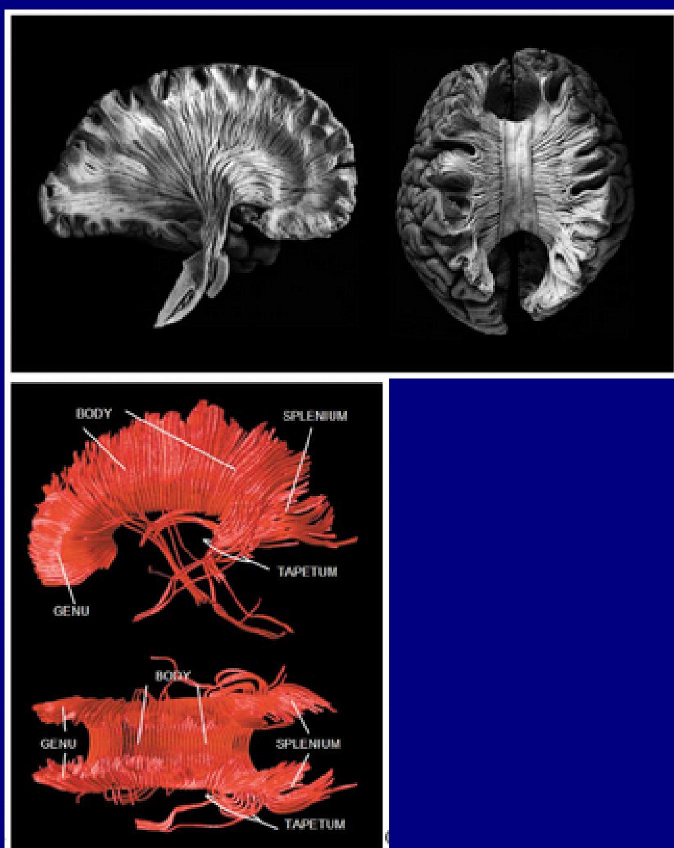




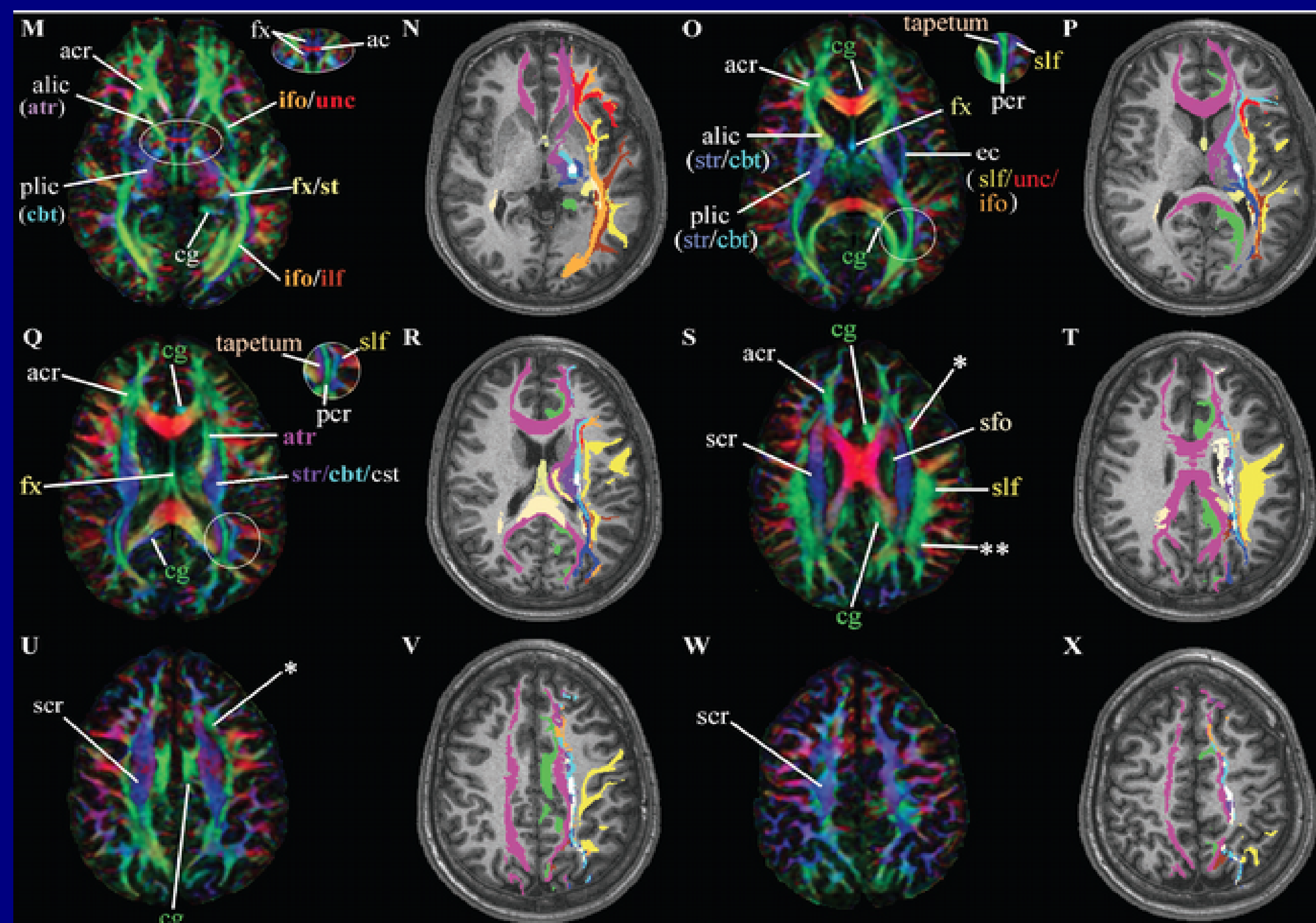
Crossing/kissing fibers can:
- Lower FA (stop tracking)
- Redirect (or *not*) tracking incorrectly.

Achievements of Tracking

+ Reproduction of many known pathways
+ In vivo vs post-mortem information



(Bammer et al., 2003)



(Wakana et al., 2004)

Light at the end of the tunnel?

Application of tractography seems useful and logically consistent as follows:

+ GM ROIs *are* connected by WM skeleton.
+ Tractography can act to parcellate the WM skeleton based on subject's own data.
+ Avoid interpreting reconstructed tracks to represent literal, underlying fibers.
+ Use tracking to estimate and highlight WM likely to be associated with GM ROIs.
+ One can then use diffusion parameters in those 'WM ROIs' for quantitative comparisons (or use ROIs as masks for other data).