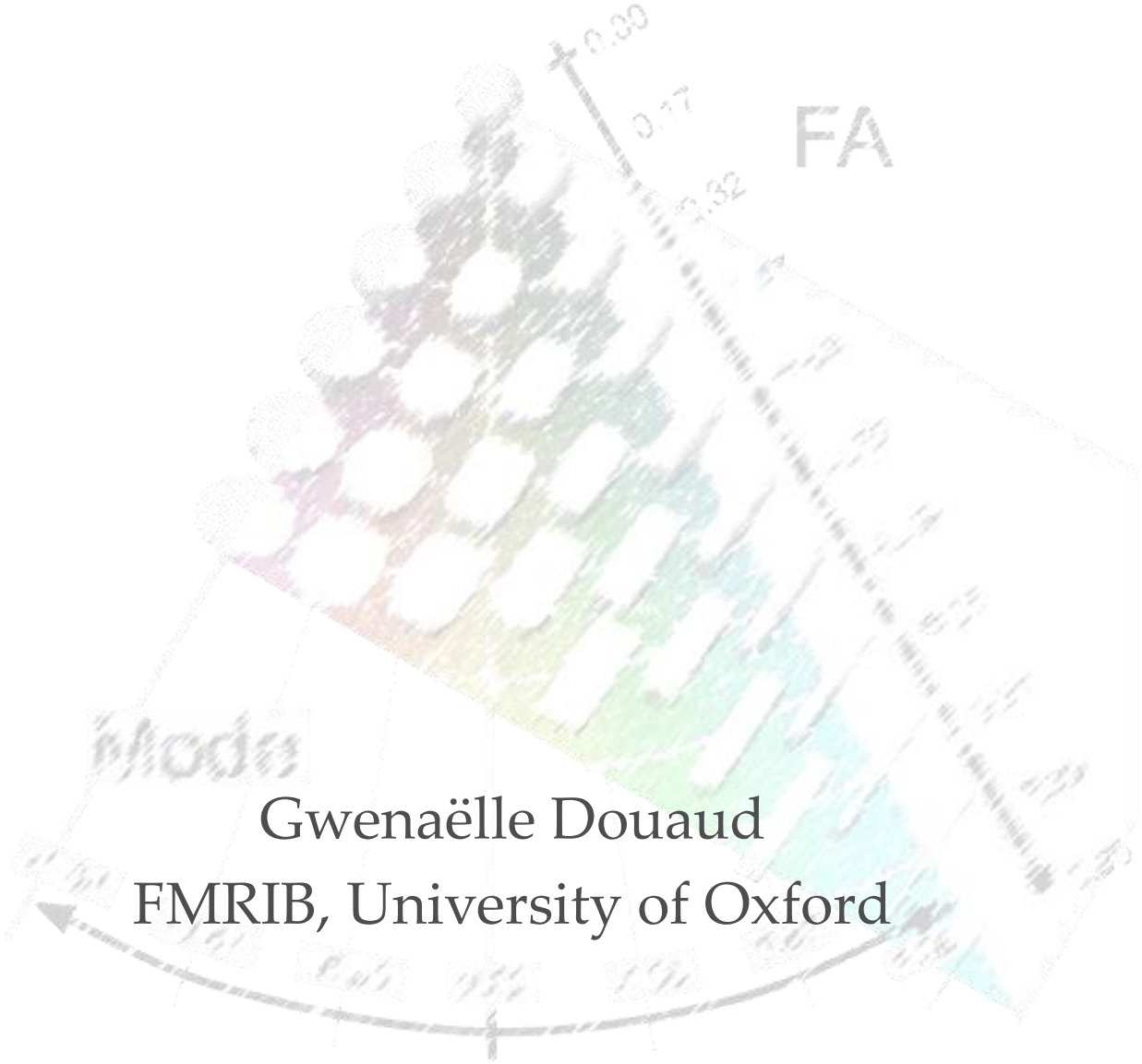
Practical Analysis and Interpretation: DTI and tractography



Gwenaëlle Douaud

FMRIB, University of Oxford

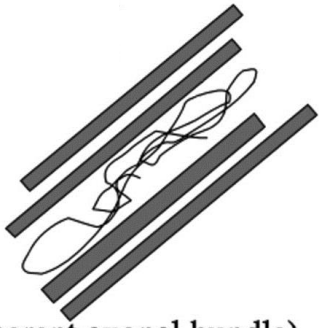
Historical description of the diffusion tensor

- Formalised by Peter Basser and colleagues *(1994a; 1994b)*

$$\frac{S(b)}{S_0} = e^{-bD}$$

Diffusion Trajectory

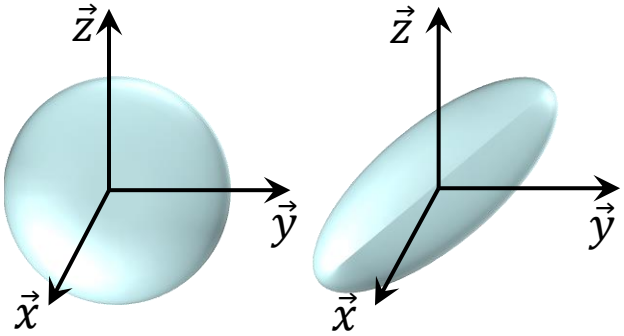
(free water)



(coherent axonal bundle)

- In an isotropic, unconstrained environment:
  D = scalar
- In an anisotropic, constrained environment:
  D = 3×3 definite symmetric positive
  D = "diffusion tensor"

Diffusion Ellipsoid

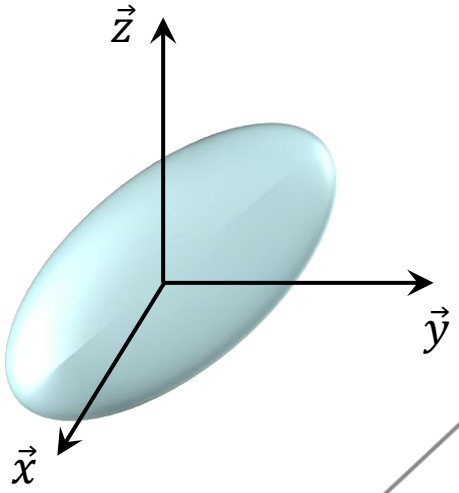


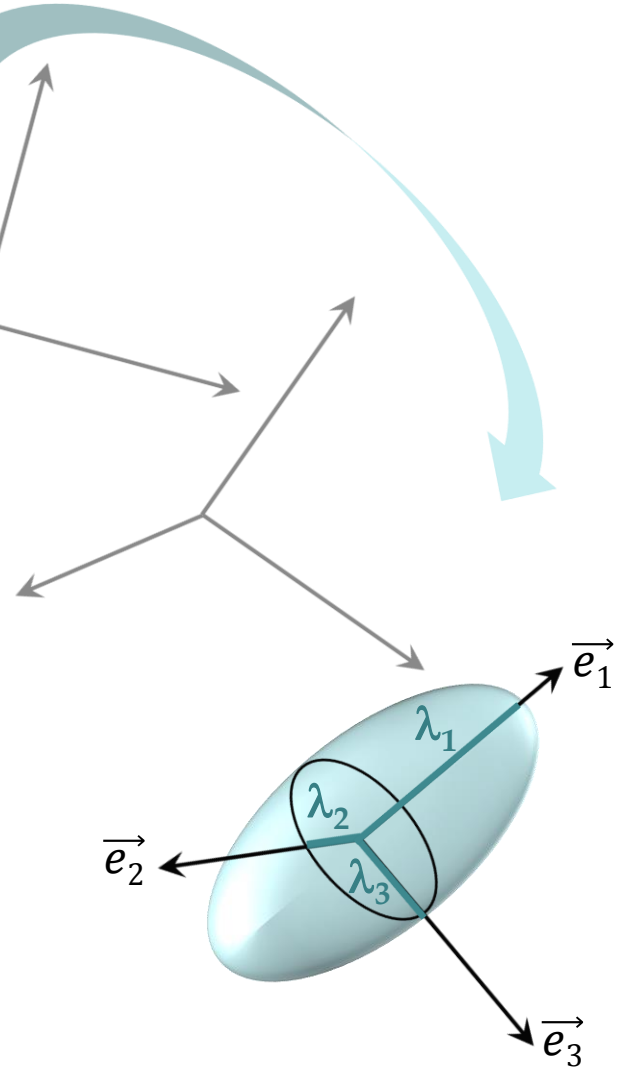
Diffusion Tensor

$$\begin{bmatrix} D & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & D \end{bmatrix} \rightarrow \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}$$

Historical description of the diffusion tensor

$$\mathbf{D} = \begin{matrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{matrix}$$





- In an anisotropic, constrained environment:
  - **D** = 3×3 definite symmetric positive
  - **D** = "diffusion tensor"

$\vec{e_i}$ = "eigenvector"
λ_i = "eigenvalue"
with $\lambda_1 \geq \lambda_2 \geq \lambda_3$

$$\mathbf{D}\,\vec{e_i} = \lambda_i\,\vec{e_i}$$

with $i \in \{1,2,3\}$

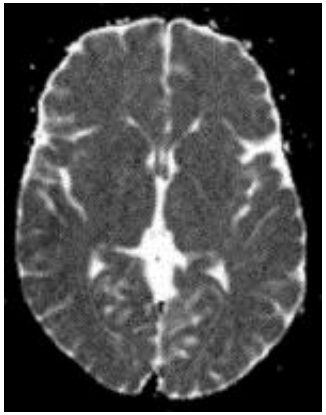
Diffusion tensor indices: Mean Diffusivity

- Formalised by Peter Basser and Carlo Pierpaoli *(1995; 1996)*

  ➢ **Magnitude of diffusion**

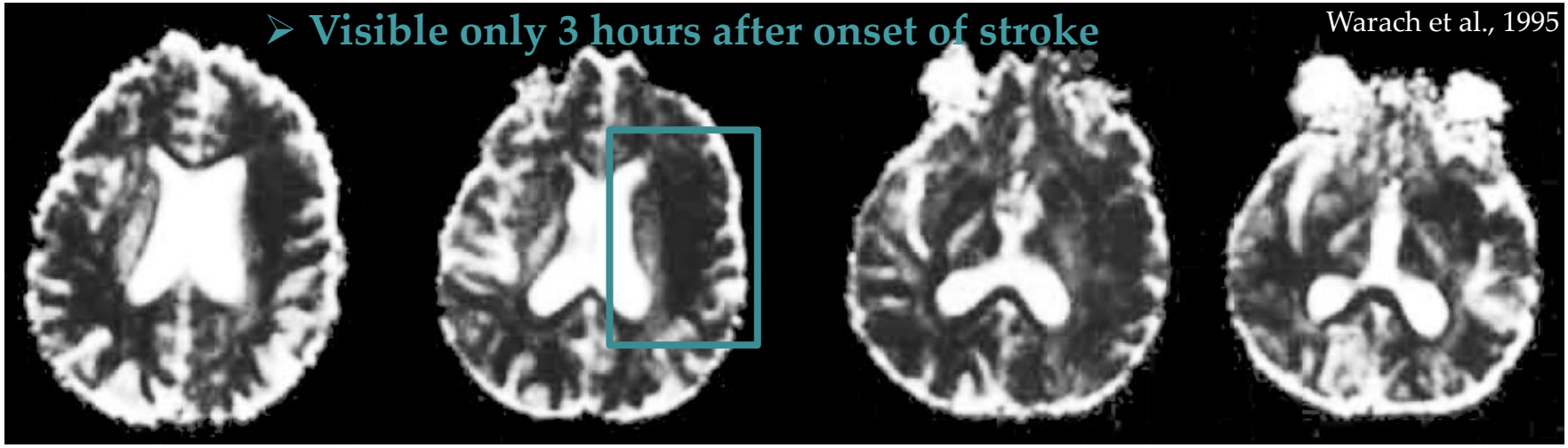
  MD = "Mean Diffusivity"

  $$MD = \frac{\text{Trace}(D)}{3} = \frac{\lambda_1+\lambda_2+\lambda_3}{3}$$



Bammer, 2003

- First clinical application: brain ischemia *(Moseley et al., 1990; Warach et al., 1992)*



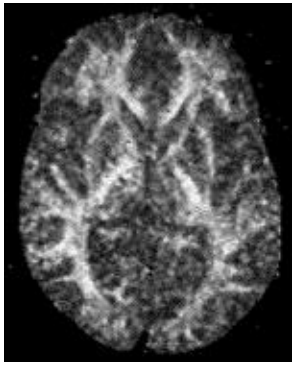
Diffusion tensor indices: diffusion anisotropy

- Formalised by Peter Basser and Carlo Pierpaoli *(1995; 1996)*

  - **Anisotropy of diffusion**

FA = "Fractional Anisotropy"

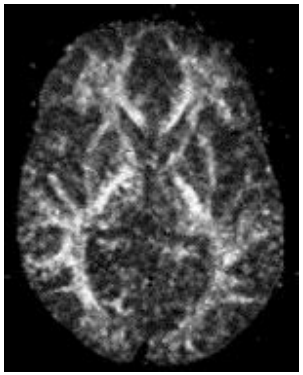
$$FA = \sqrt{\frac{3Var(\lambda)}{2(\lambda_1^2+\lambda_2^2+\lambda_3^2)}}$$



Bammer, 2003

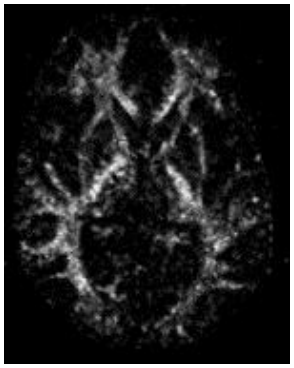
RA = "Relative Anisotropy"

$$RA = \frac{\sqrt{Var(\lambda)}}{3MD}$$



VR = "Volume Ratio"

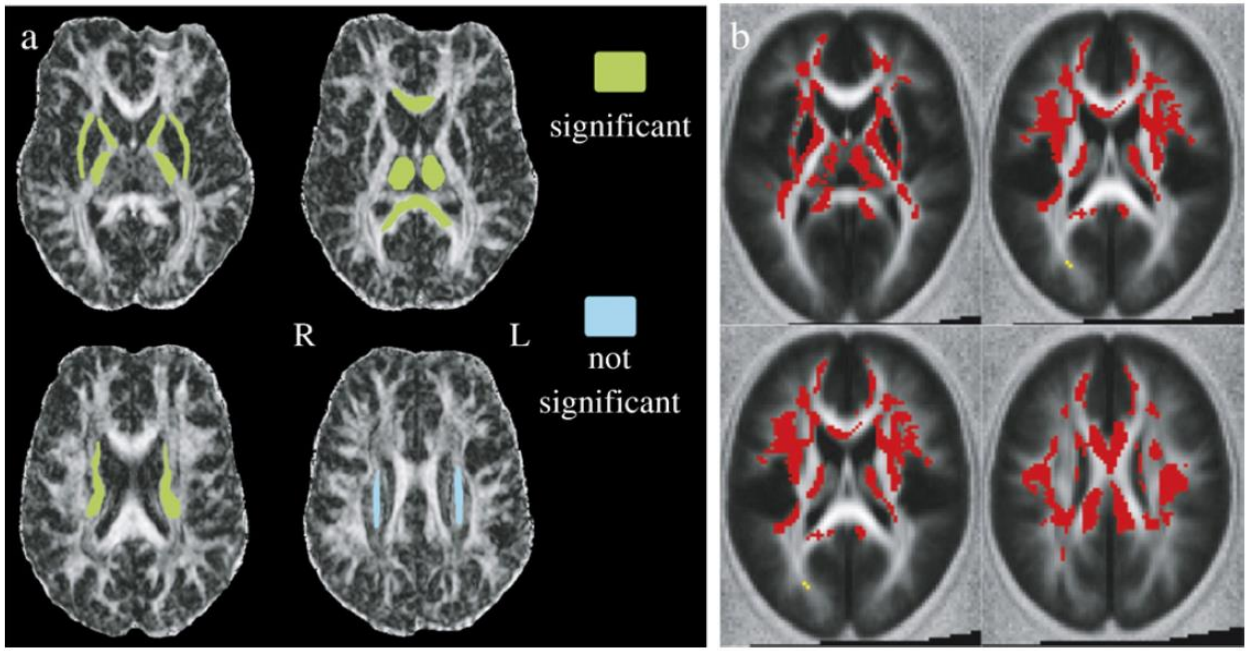
$$VR = \frac{\lambda_1\lambda_2\lambda_3}{MD^3}$$



- Formal comparison of three anisotropy indices *(Papadakis et al., 1999)*

Fractional Anisotropy and Mean Diffusivity: region-of-interest (ROI) vs voxel-wise analysis

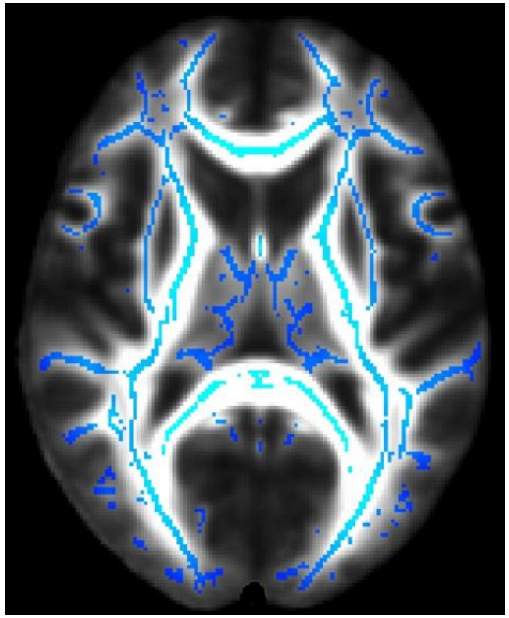
- Developmental study: comparison between ROI and voxel-based diffusion analysis (VBD) *(Snook et al., 2007)*

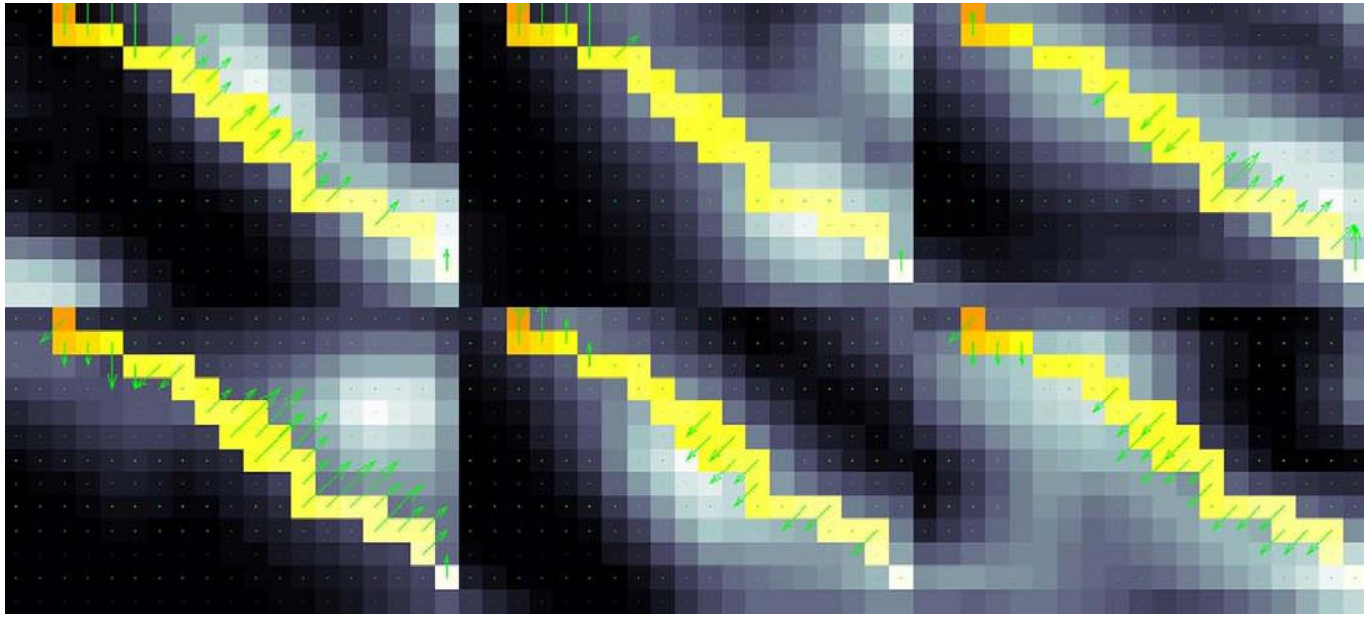


➢ The discrepancies related to:
- ROI approach inherently limited – FIRST, FreeSurfer etc. but bias?
- Issues with the spatial normalisation for VBD analysis (*)
- Averaging out localised changes within a ROI (**)

Fractional Anisotropy and Mean Diffusivity: (*) region-of-interest (ROI) vs voxel-wise analysis

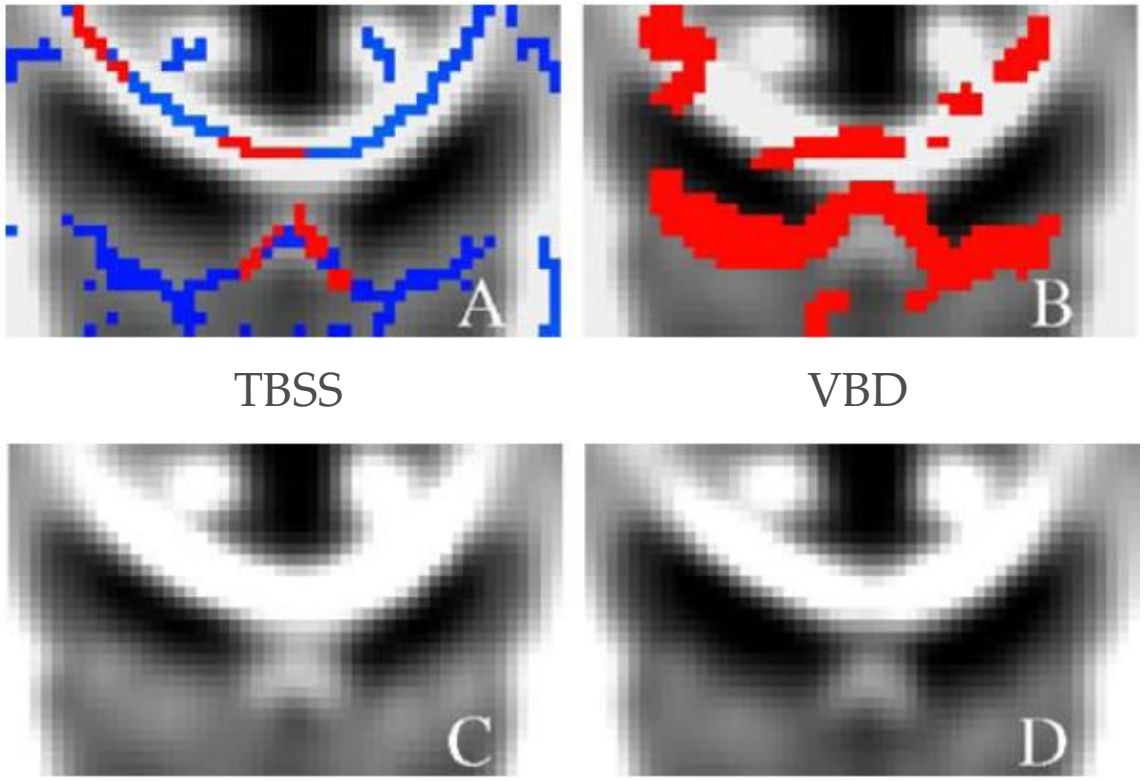
- Increasing sensitivity and interpretability of results compared with VBD
  - TBSS *(Smith et al., 2006)*





Fractional Anisotropy and Mean Diffusivity: (*) region-of-interest (ROI) vs voxel-wise analysis

- Increasing sensitivity and interpretability of results compared with VBD
  - TBSS *(Smith et al., 2006)*

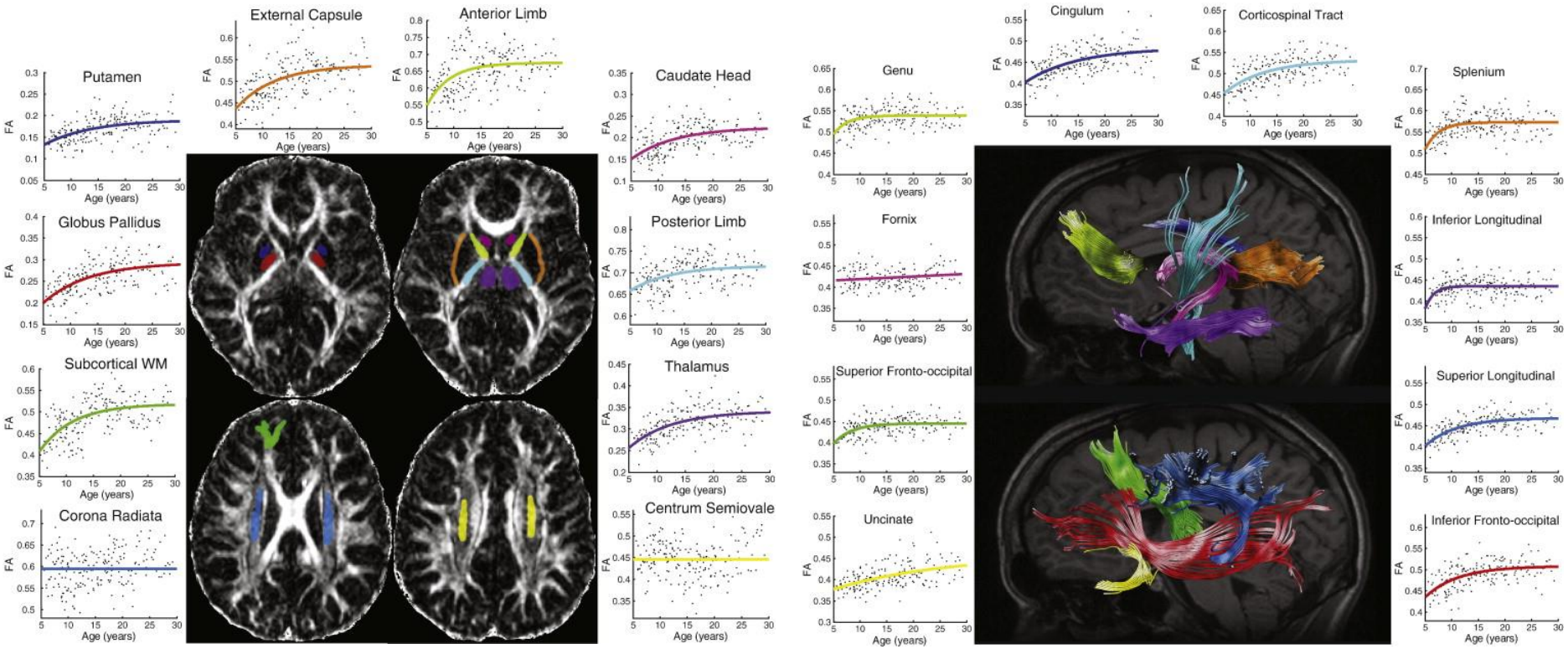


TBSS | VBD

Mean Control | Mean Patient

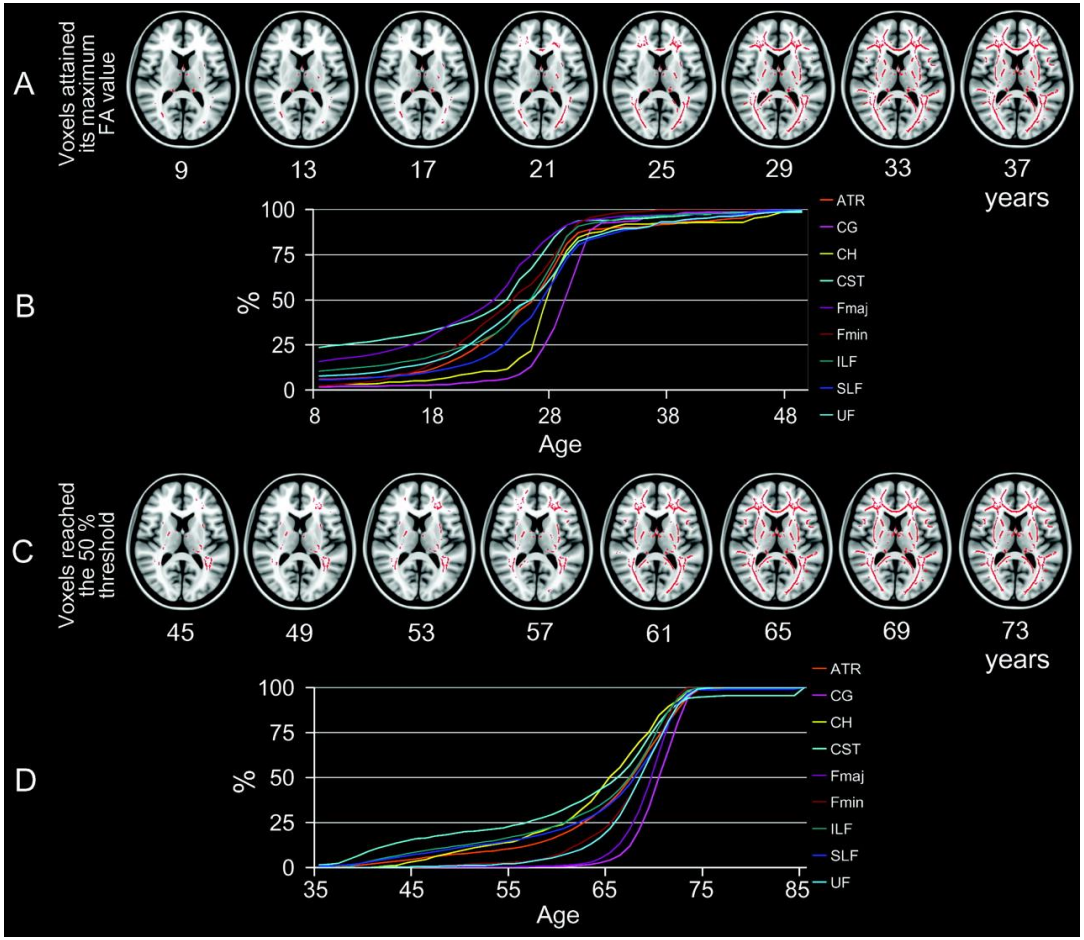
Fractional Anisotropy and Mean Diffusivity: region-of-interest (ROI) & voxel-wise analysis

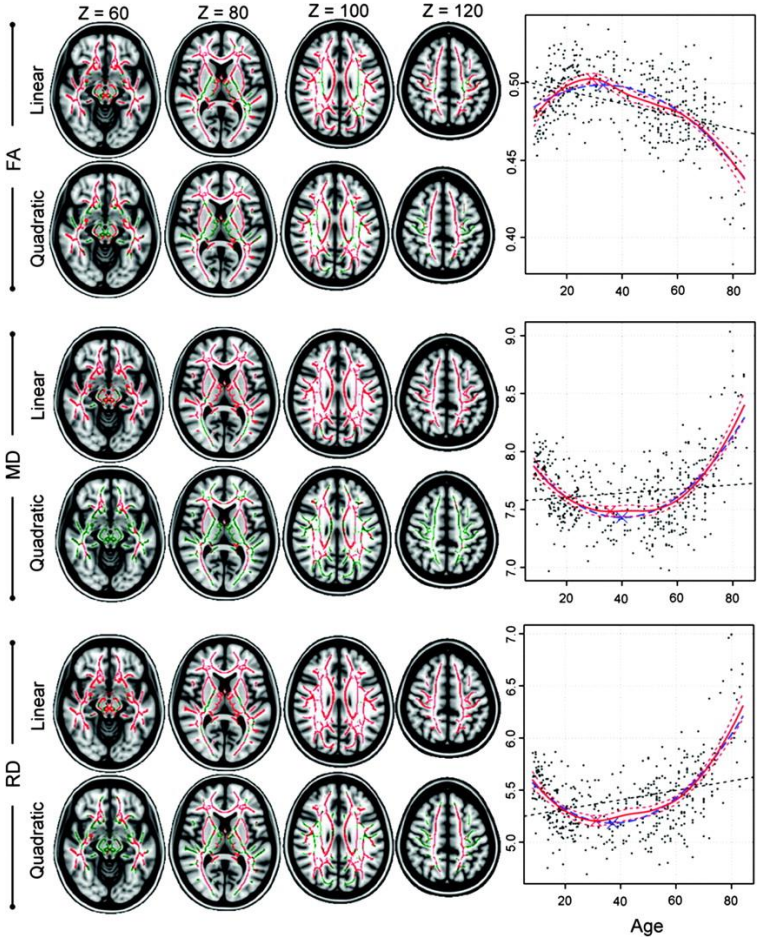
- Developmental study: anatomical and tractography-defined ROI *(Lebel et al., 2008)*



Fractional Anisotropy and Mean Diffusivity: region-of-interest (ROI) & voxel-wise analysis

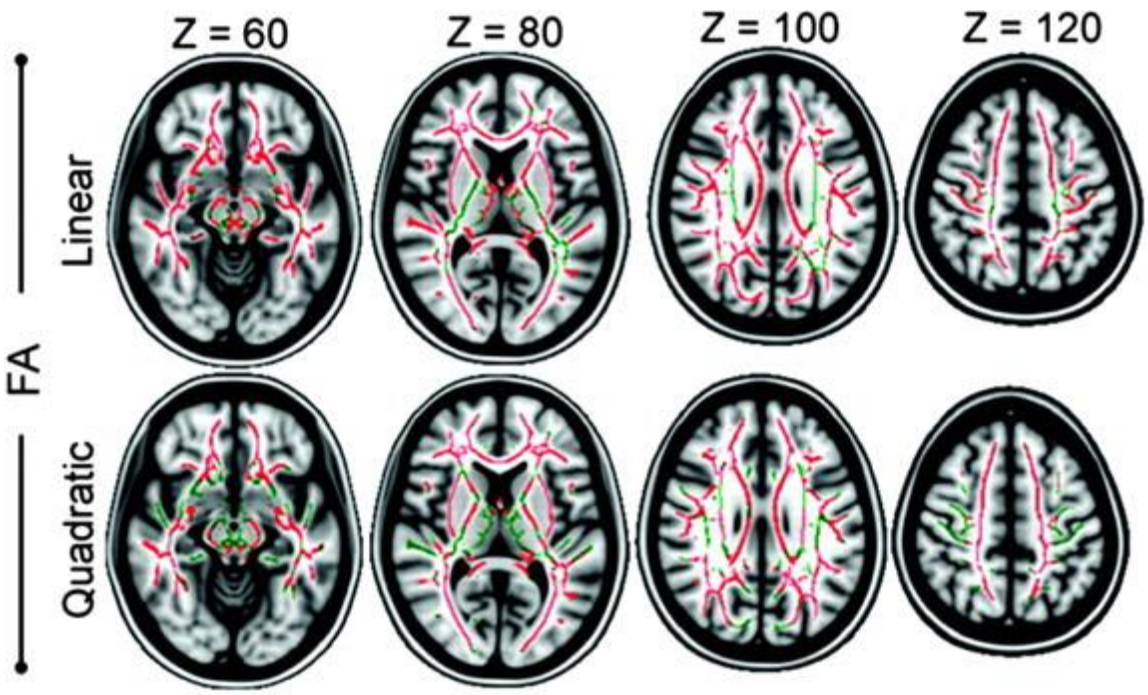
- Large developmental and ageing study using TBSS *(Westlye et al., 2010)*

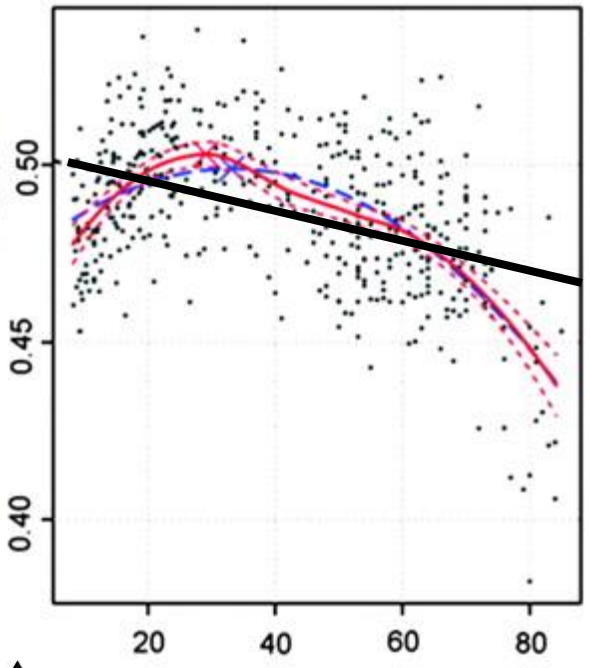




Fractional Anisotropy and Mean Diffusivity: region-of-interest (ROI) & voxel-wise analysis

- Large developmental and ageing study using TBSS *(Westlye et al., 2010)*

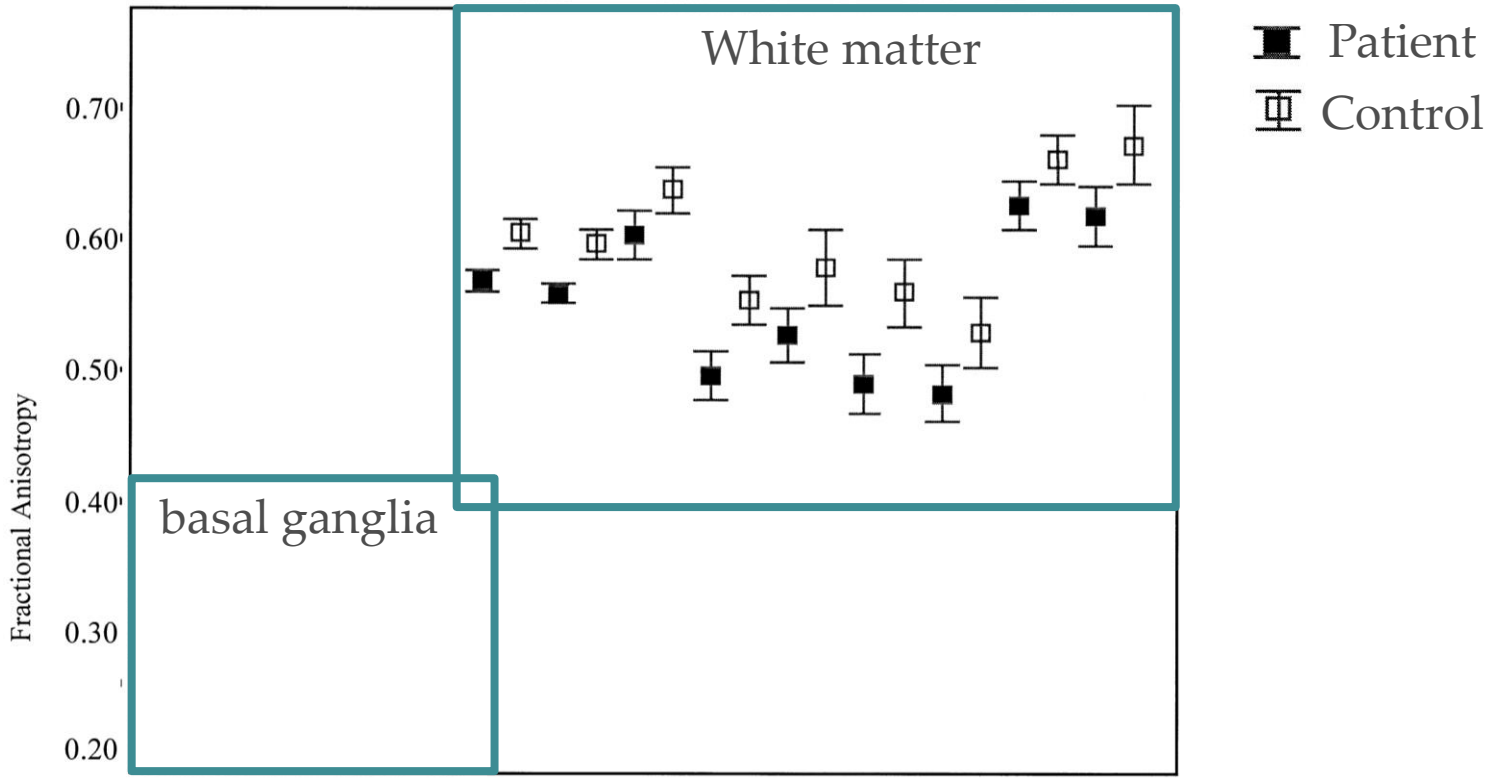




➢ Limits of the general **linear** model (GLM)

Fractional Anisotropy and Mean Diffusivity: two complementary measures

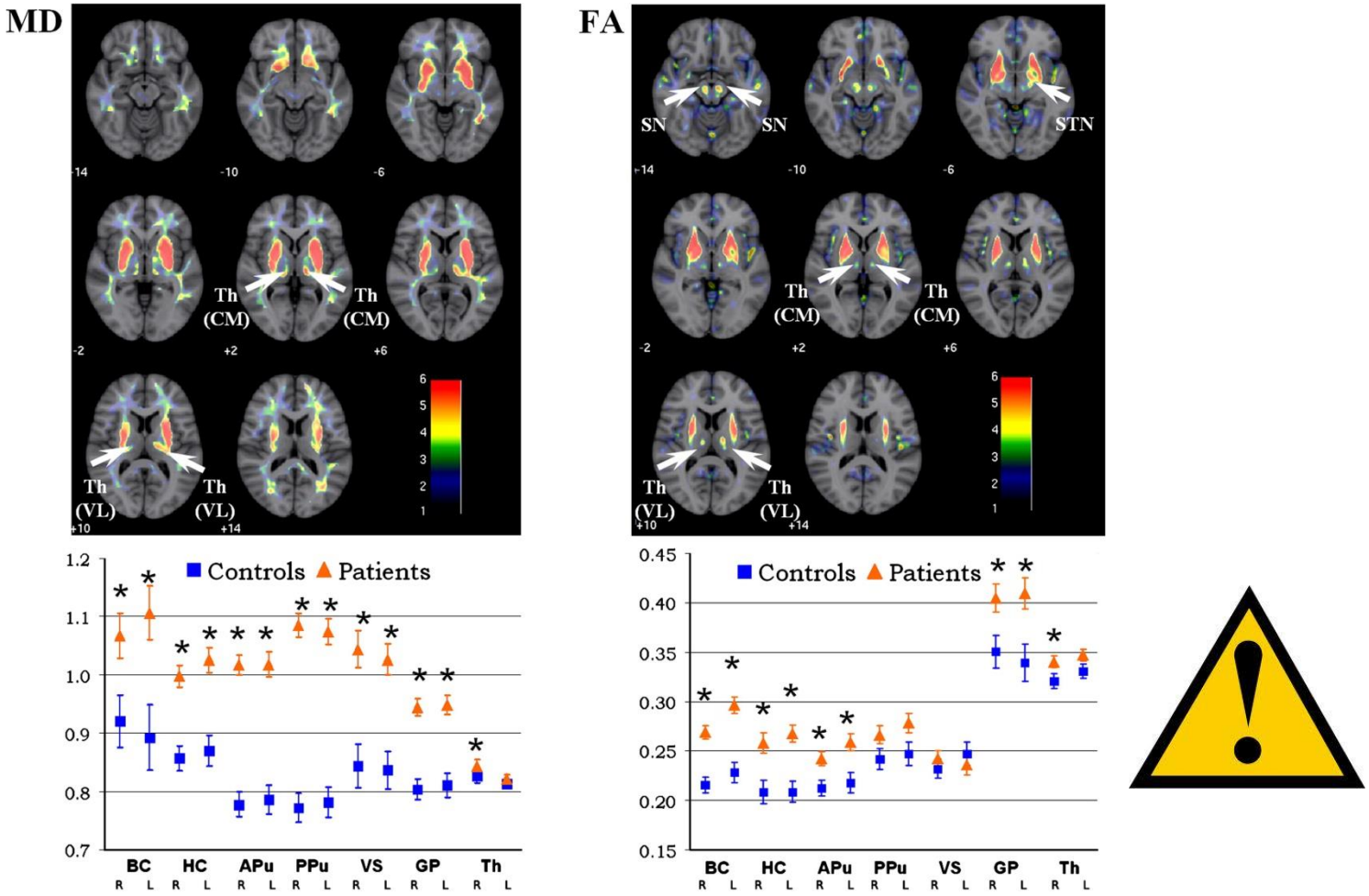
- An intriguing finding in multiple sclerosis *(Ciccarelli et al., 2001)*



➢ Increased FA in the basal ganglia in MS
= selective Wallerian degeneration, making it appear "more organised"?

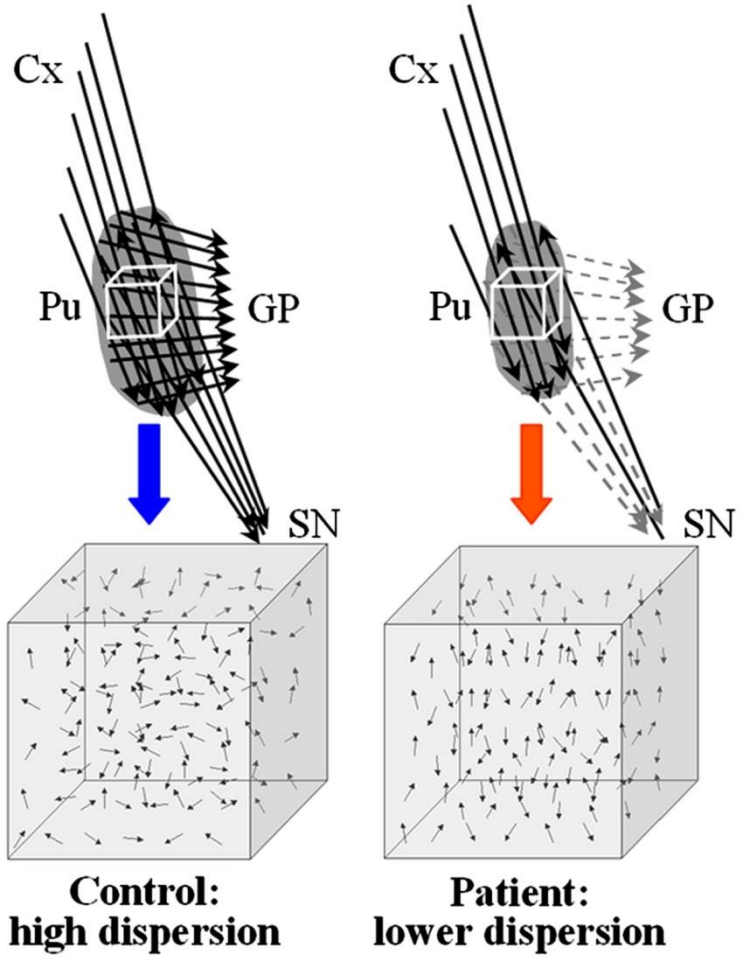
Fractional Anisotropy and Mean Diffusivity: two complementary measures

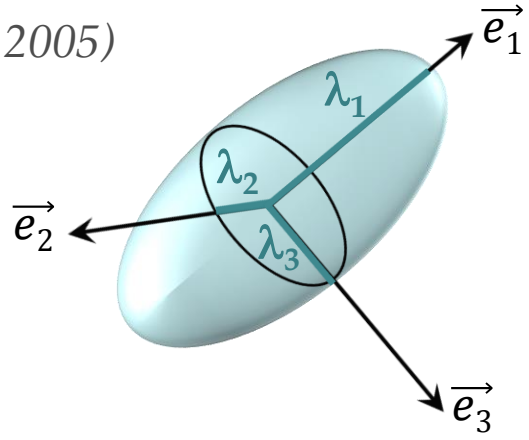
- Same findings seen in the basal ganglia in Huntington's disease *(Douaud et al., 2009)*



Beyond Fractional Anisotropy and Mean Diffusivity: Principal Diffusion Direction ($\vec{e_1}$)

- Using the information from the PDD *(Schwartzmann et al., 2005)*

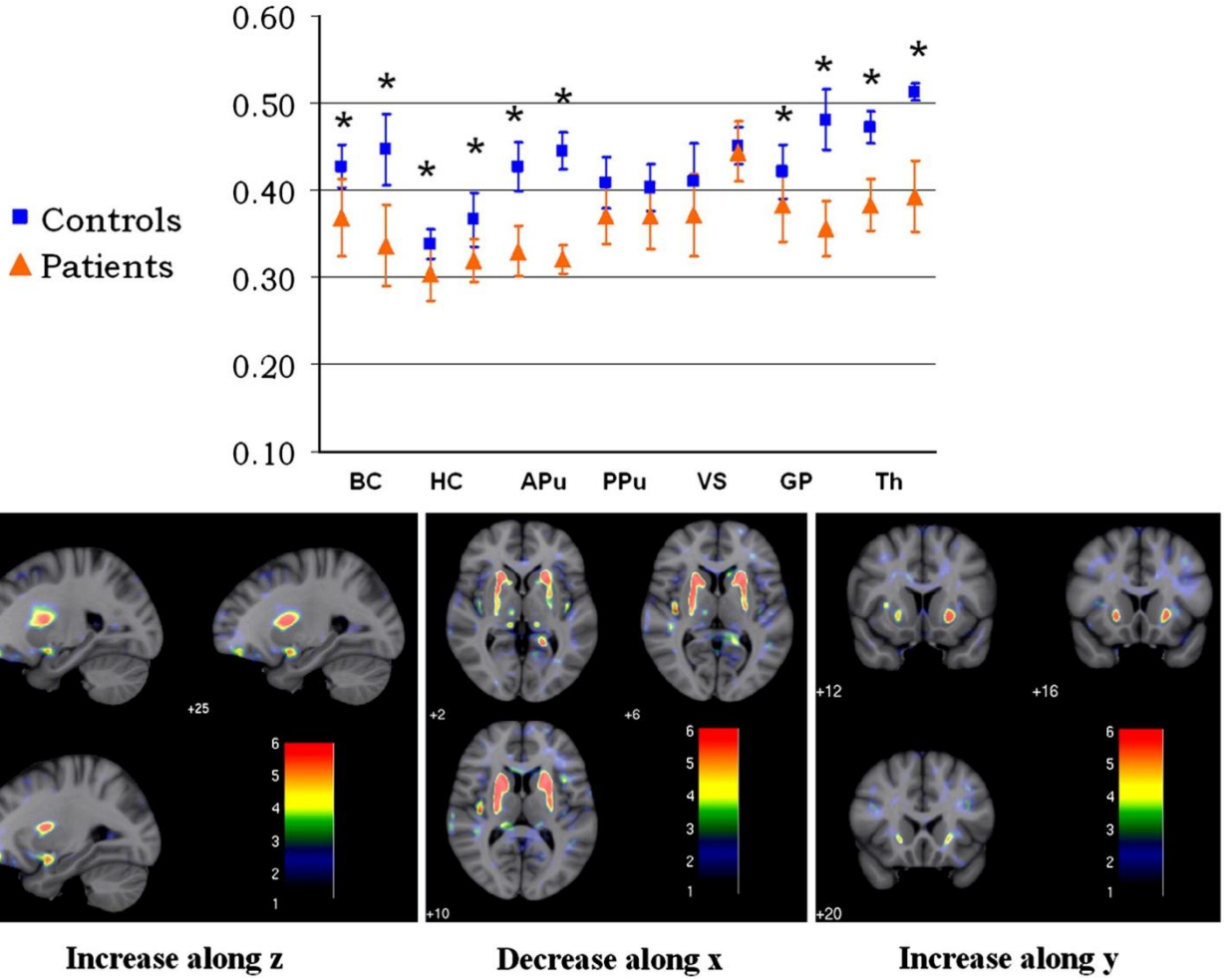




Douaud *et al.*, 2009

Beyond Fractional Anisotropy and Mean Diffusivity: Principal Diffusion Direction ($\vec{e}_1$)

- Decrease of the dispersion of the PDD in Huntington's disease *(Douaud et al., 2009)*



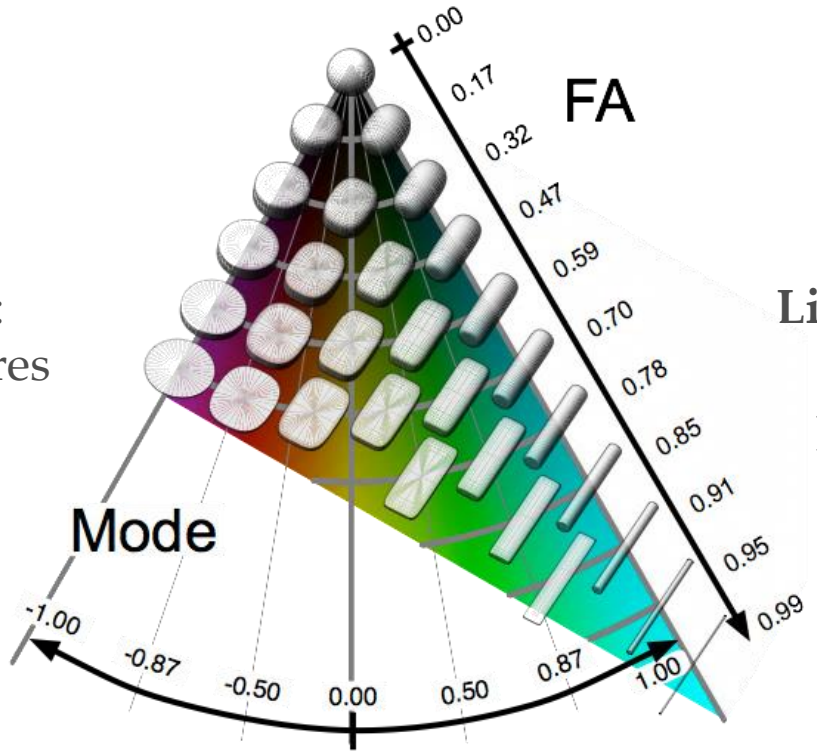
Beyond Fractional Anisotropy and Mean Diffusivity: the MOde of anisotropy (MO)

- No difference in the white matter of mild cognitive impairment (MCI) patients using MD or FA *(Douaud et al., 2011)*

➢ Mode of anisotropy (MO): 3rd moment of the tensor, introduced by Basser *(1997)*, formalised by Ennis and Kindlamnn *(2006)*.

-1

Planar, disc-like $\lambda_1 \sim \lambda_2$: e.g., areas of crossing fibres

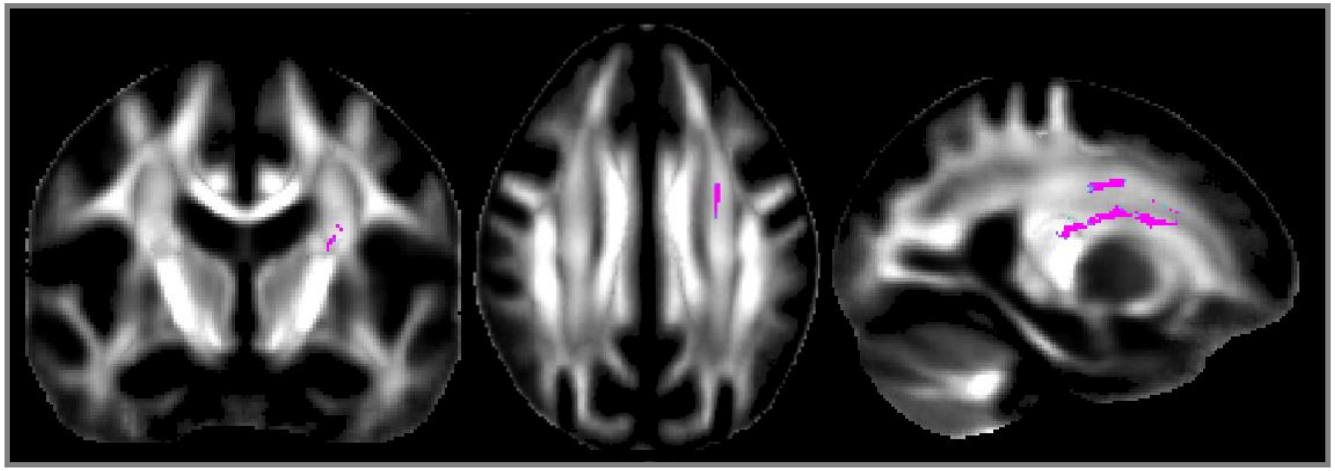


+1

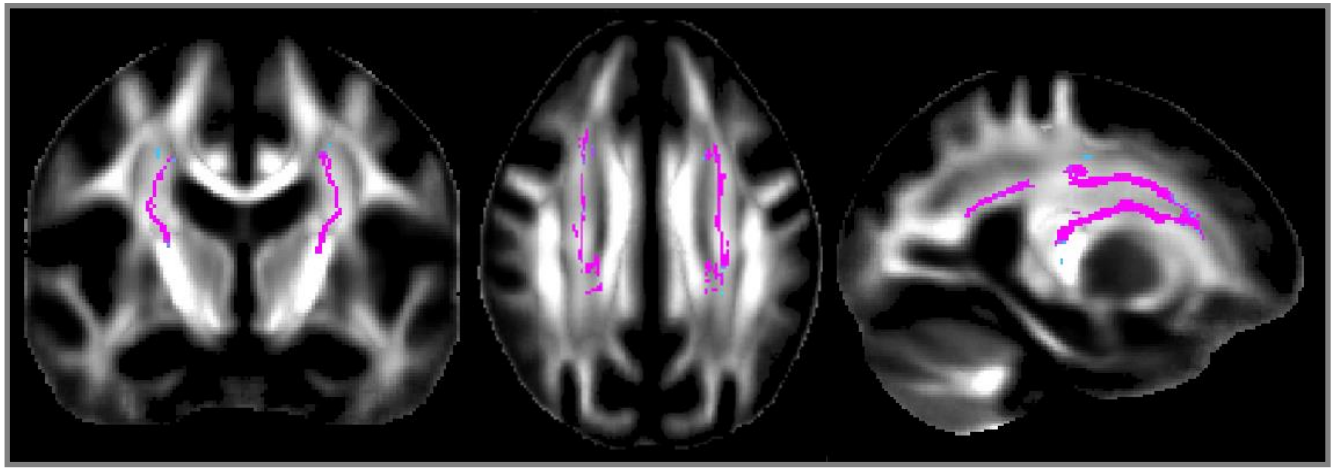
Linear, cigar-like $\lambda_2 \sim \lambda_3$: e.g., areas of one predominating fibre population

Beyond Fractional Anisotropy and Mean Diffusivity: the MOde of anisotropy (MO)

- Significant difference in the white matter of MCI patients, with an **increase** of MO



MCI>CON

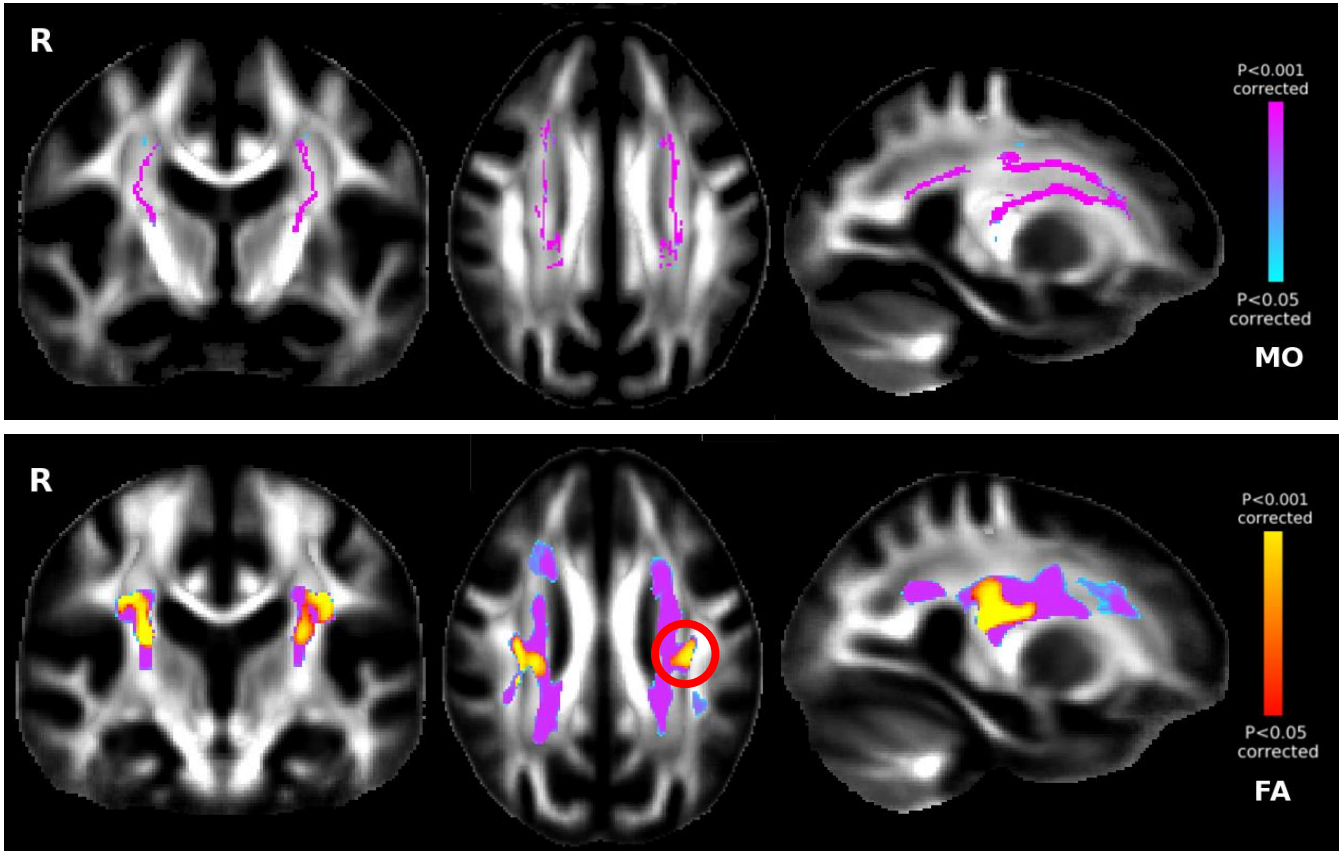


AD>CON

Douaud *et al.*, 2011

Beyond Fractional Anisotropy and Mean Diffusivity: the Mode of anisotropy (MO)

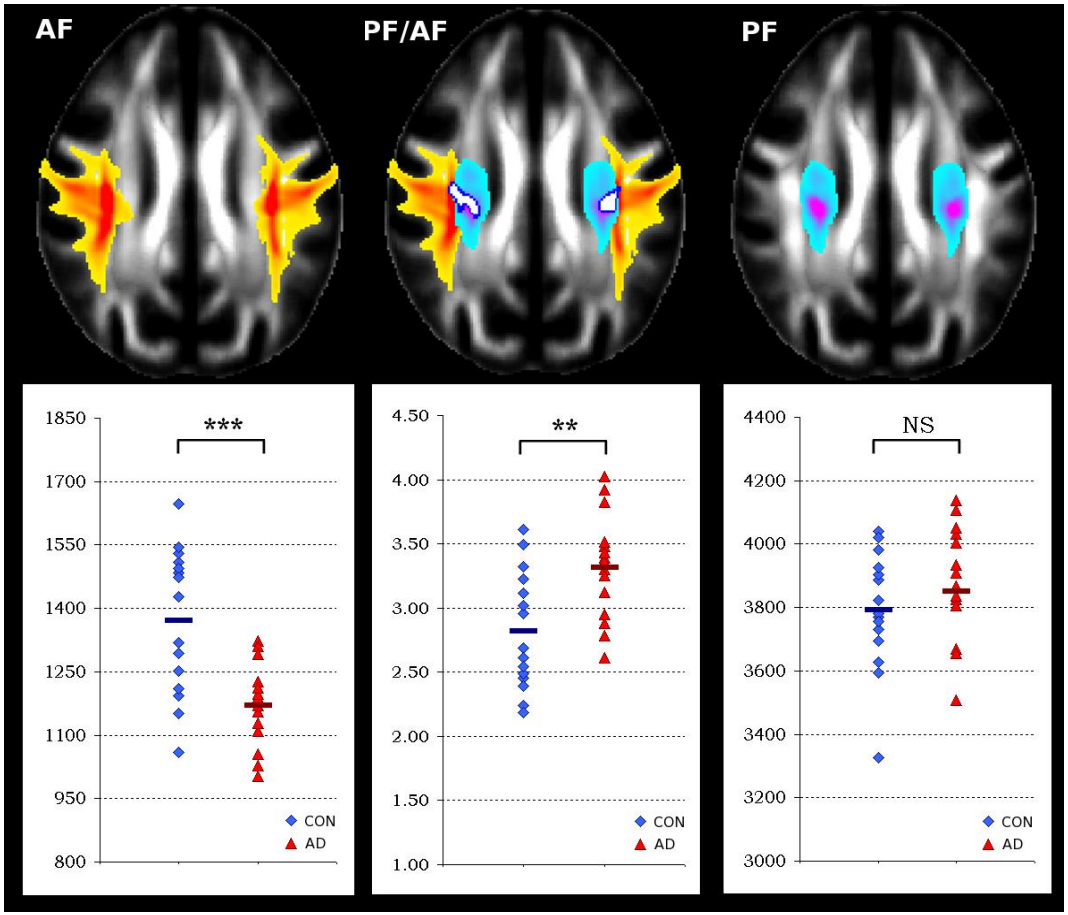
- Significant **increase** of MO in MCI and AD also related to selective degeneration in crossing fibres region (here, centrum semiovale)?



Douaud *et al.*, 2011

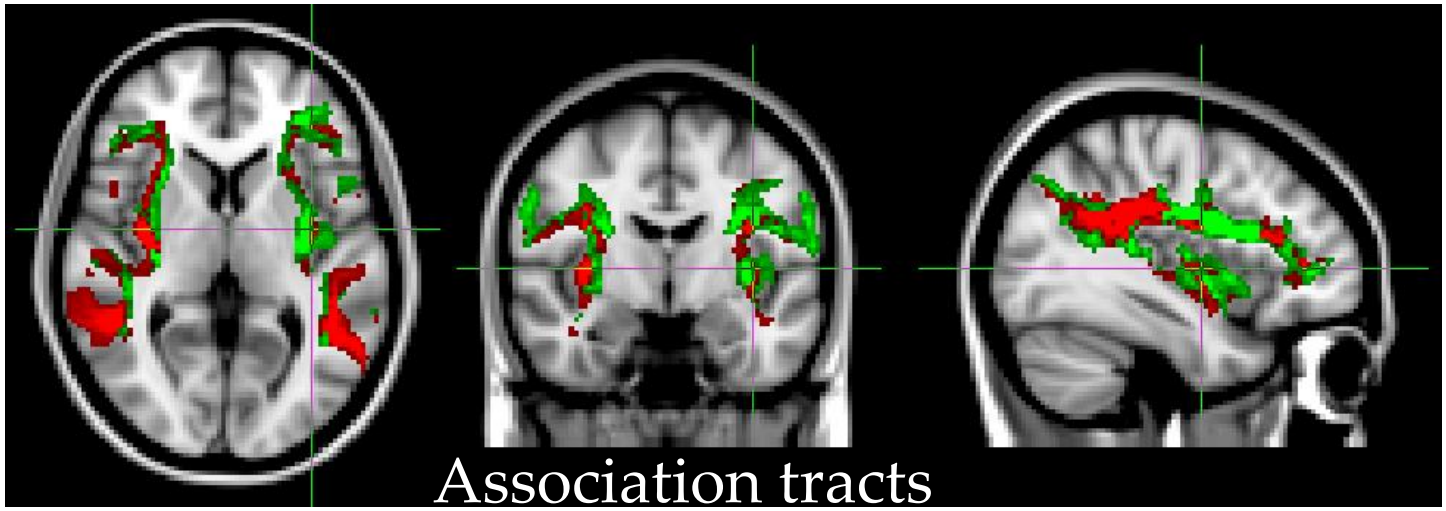
Beyond Fractional Anisotropy and Mean Diffusivity: the Mode of anisotropy (MO)

- Significant **increase** of MO in MCI and AD also related to selective degeneration in crossing fibres region (here, centrum semiovale)

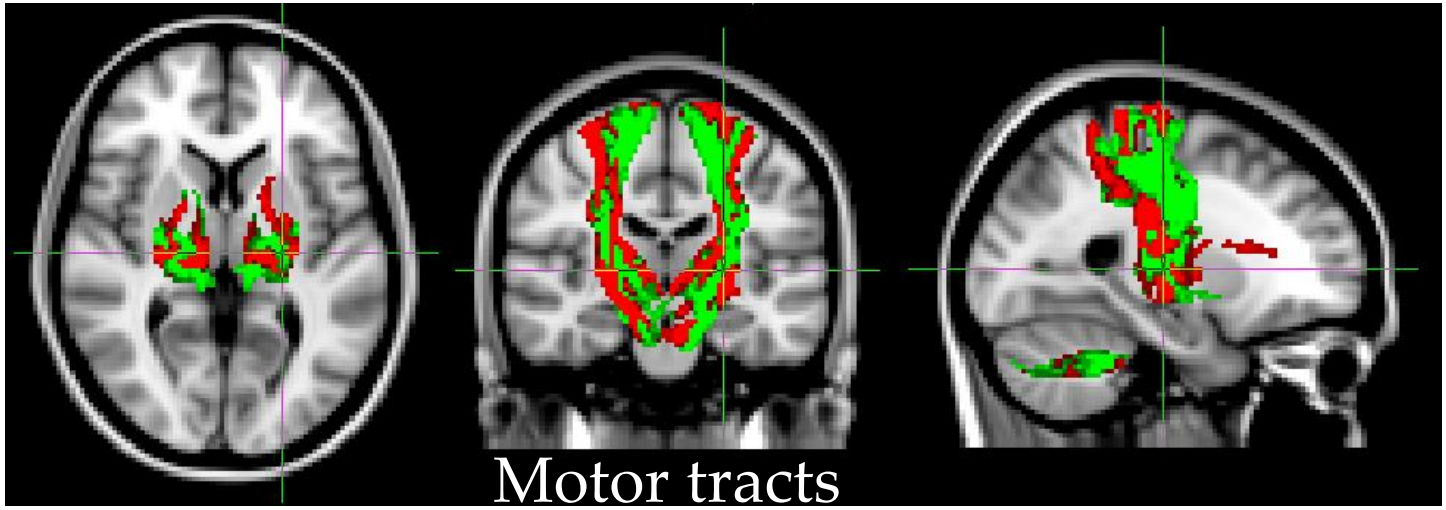


Douaud *et al.*, 2011

Tractography: think before you publish!



AD>CON

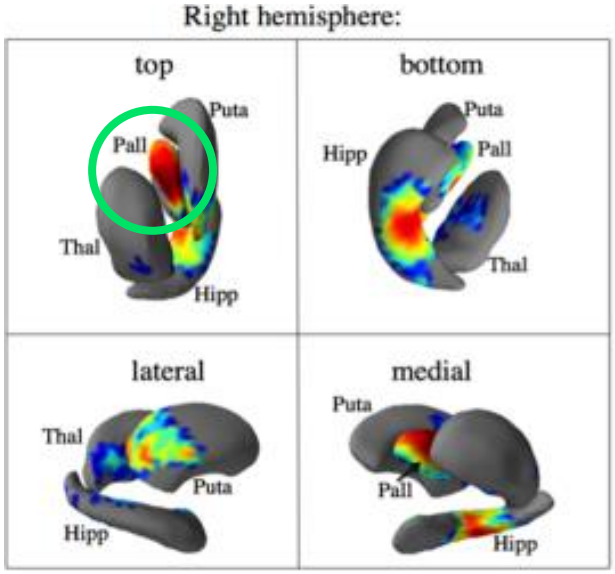


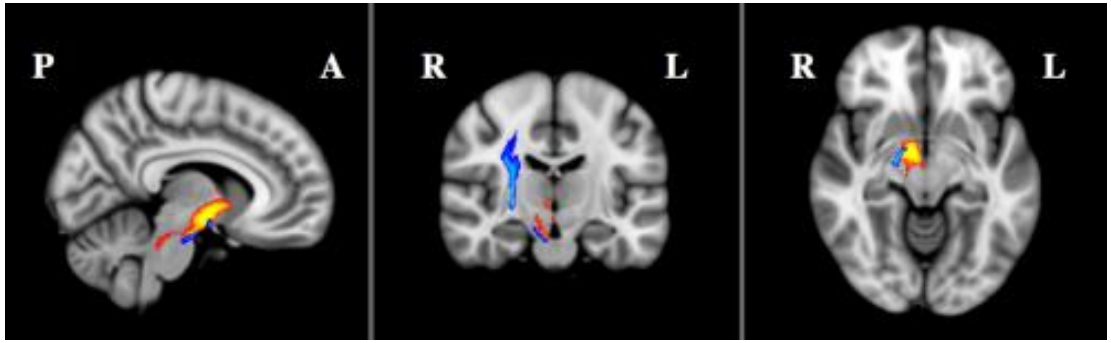
AD<CON

Tractography: what you can do

- So… you can't use tractography streamlines **directly**
- And… you can't use tractography to **prove the existence** of a tract *(Jbabdi & Johansen-berg, 2011)*

➢ But you can use tractography to:
- create ROI/parcellate
- help understand further some results: shape analysis (Parkinson's disease)



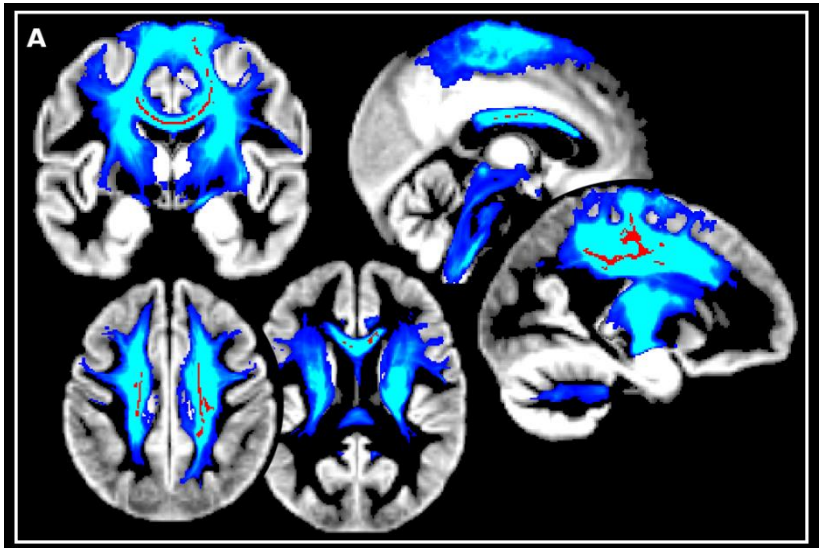


Menke *et al.*, 2013

Tractography: what you can do

- So… you can't use tractography streamlines directly
- And… you can't use tractography to **prove the existence** of a tract *(Jbabdi & Johansen-berg, 2011)*

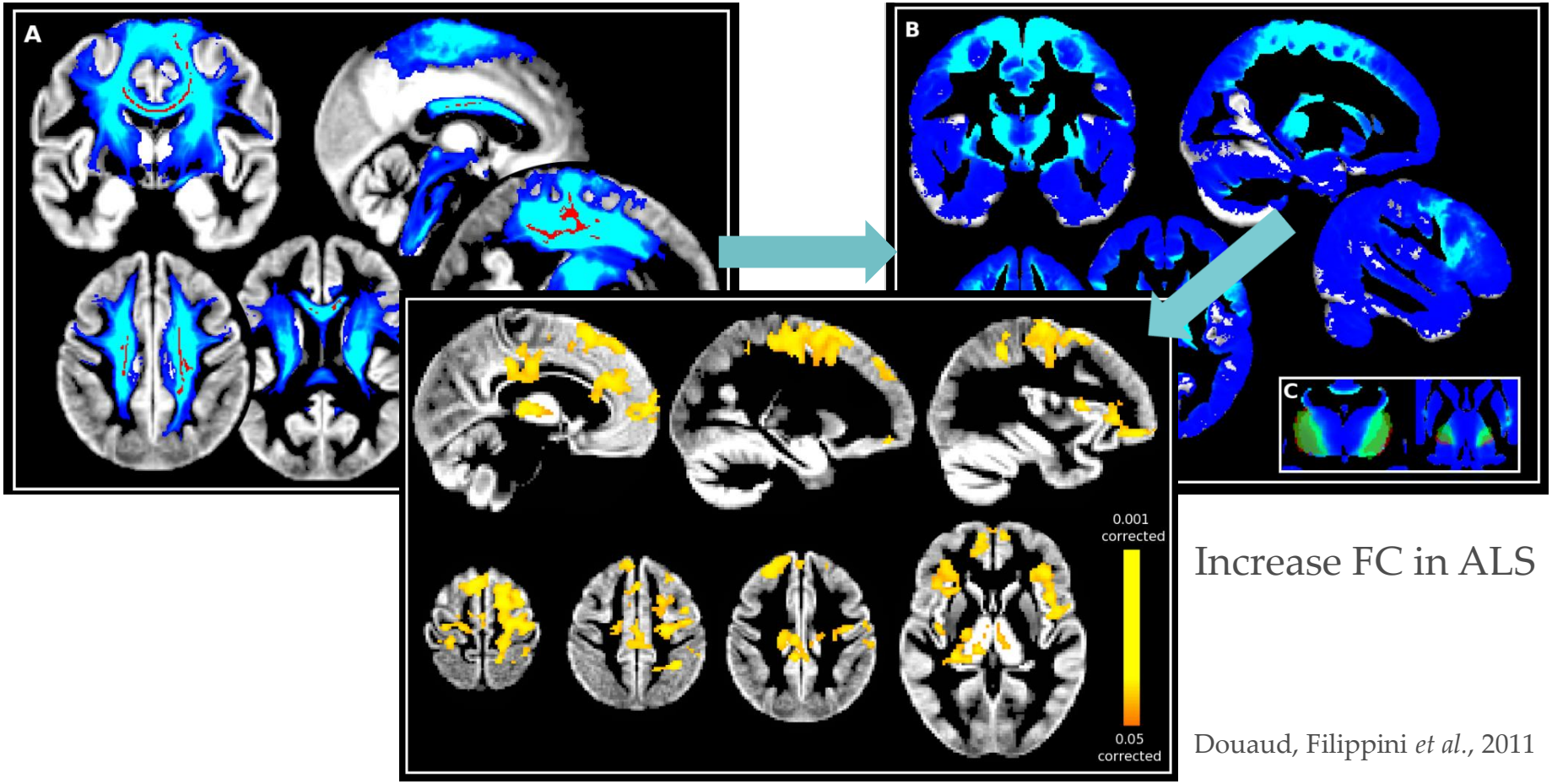
➢ But you can use tractography to:
- create ROI/parcellate
- help understand further some results: TBSS (amyotrophic lateral sclerosis)



Douaud, Filippini *et al.*, 2011

Tractography: what you can do

- Combining information of diffusion tensor and tractography with resting-state
  Example in amyotrophic lateral sclerosis

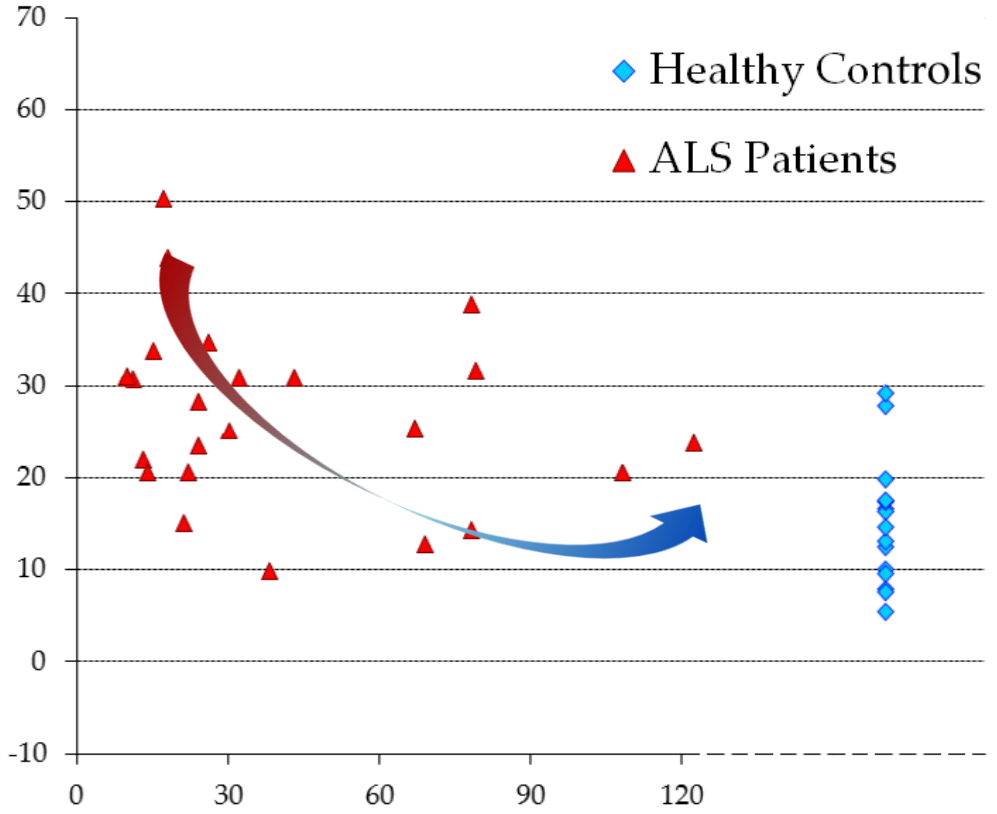


Increase FC in ALS

Douaud, Filippini *et al.*, 2011

Tractography: what you can do

- Combining information of diffusion tensor and tractography with resting-state
  Example in amyotrophic lateral sclerosis



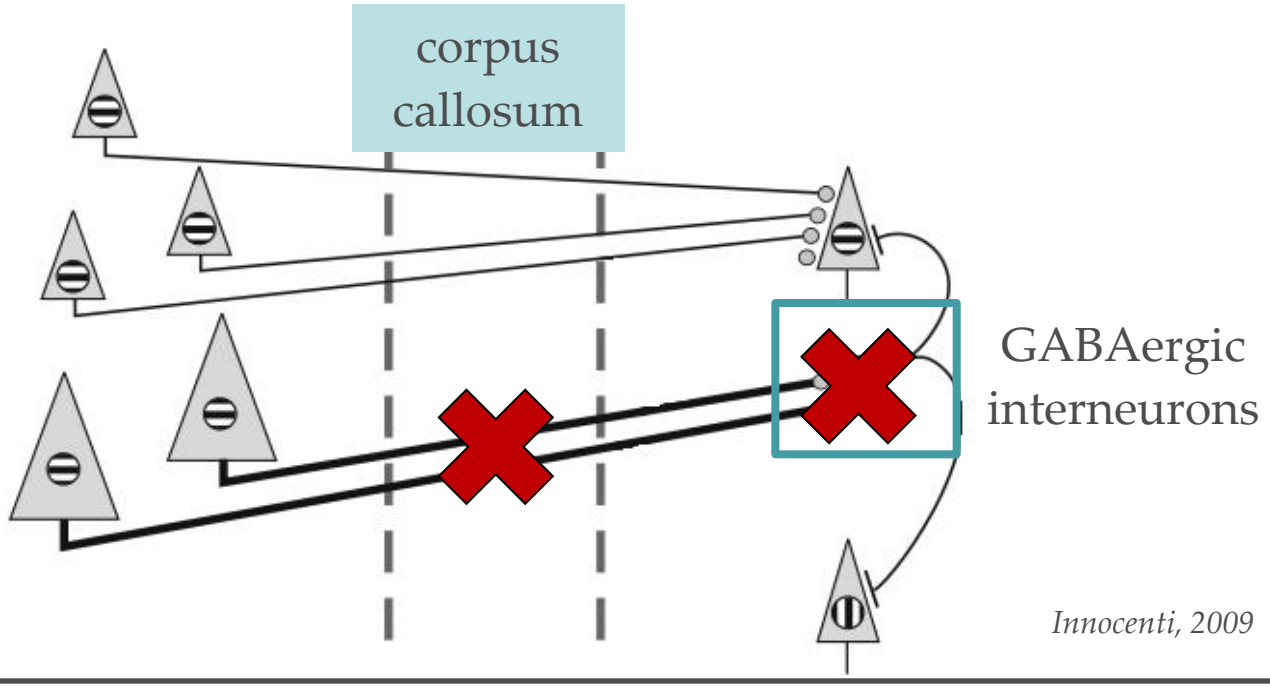
Disease duration

Tractography: what you can do

- Combining information of diffusion tensor and tractography with resting-state Example in amyotrophic lateral sclerosis

➢ Higher functional connectivity not necessarily better

- Reconciling *lower* structural connectivity (SC) with *higher* functional connectivity?

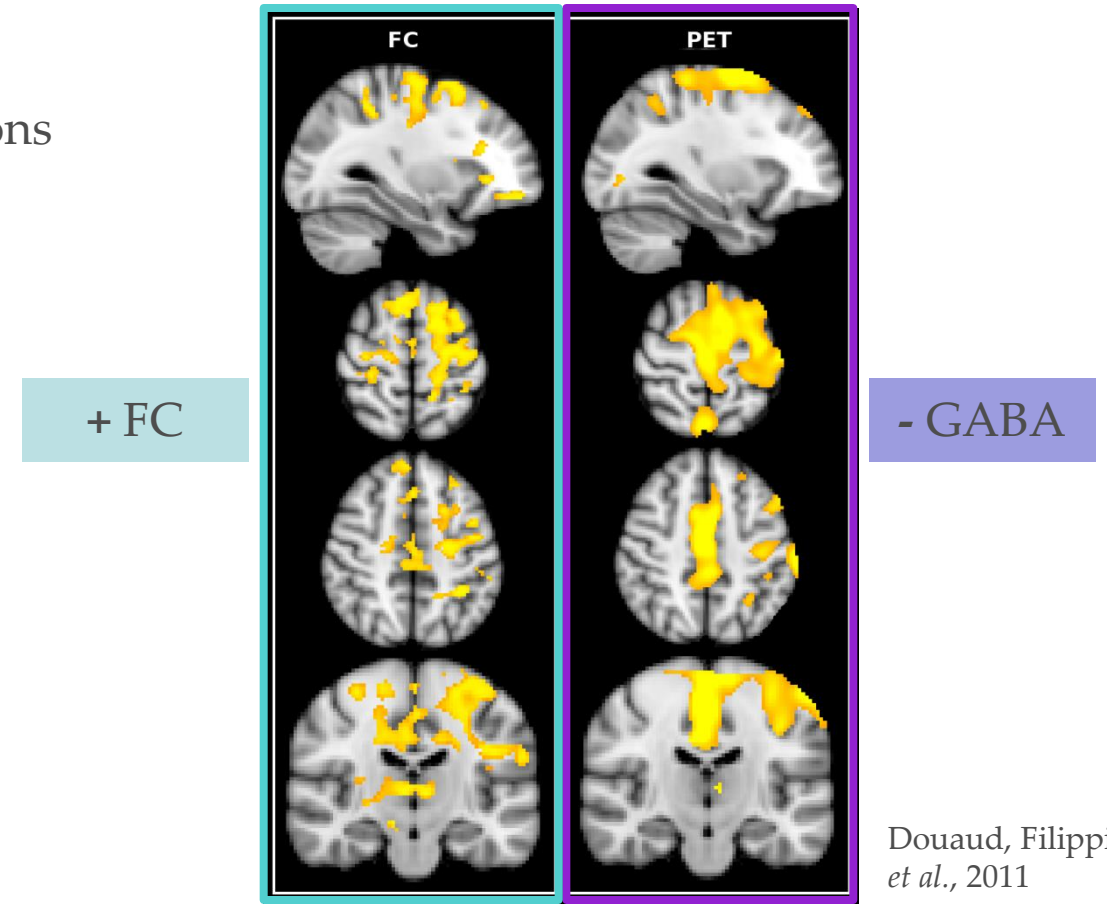


Innocenti, 2009

Tractography: what you can do

- Combining information of diffusion tensor and tractography with resting-state
  Example in amyotrophic lateral sclerosis

➢ Low SC + high FC in ALS
  = loss of GABA interneurons

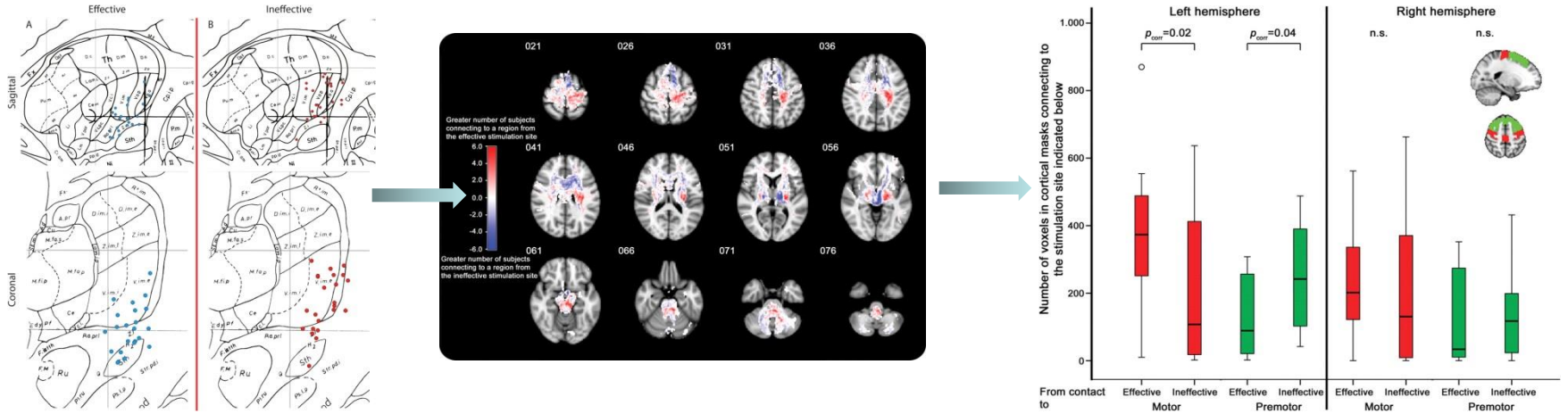


Douaud, Filippini *et al.*, 2011

Tractography: what you can do

- So… you can't use tractography streamlines directly
- And… you can't use tractography to **prove the existence** of a tract *(Jbabdi & Johansen-berg, 2011)*

➢ But you can use tractography to:
- create ROI/parcellate
- help understand further some results: deep brain stimulation *(Klein et al., 2012)*

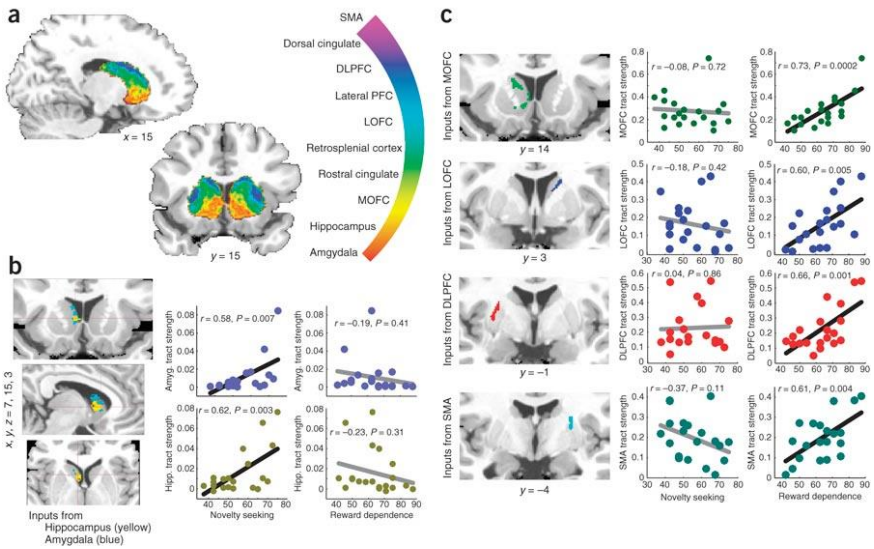


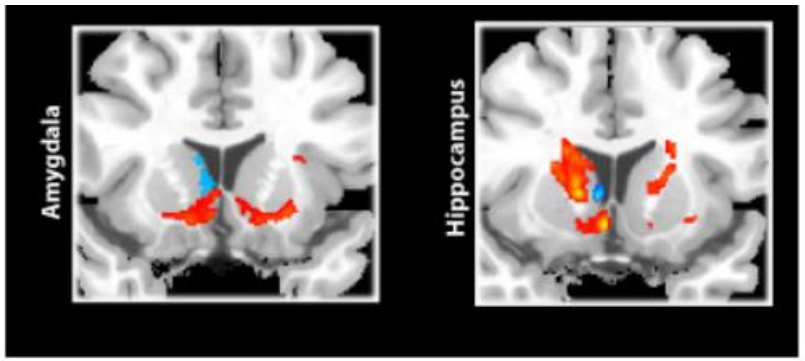
*"Our data suggest that the optimum target for tremor suppression is defined by its **remote connections rather than spatial coordinates**"*

Tractography: what you can do

- So… you can't use tractography streamlines directly
- And… you can't use tractography to **prove the existence** of a tract *(Jbabdi & Johansen-berg, 2011)*

➢ But you can use tractography to:
- create ROI/parcellate
- help understand further some results
- correlate "seeds-to-target" with behaviour/compare between populations





Cohen *et al.*, 2009

Beyond Fractional Anisotropy and Mean Diffusivity: Parallel and Perpendicular Diffusivity

- Validated in animal models by Song and colleagues *(2002; 2005)*

  - **Parallel diffusivity or axial diffusivity:** assessing axonal injury

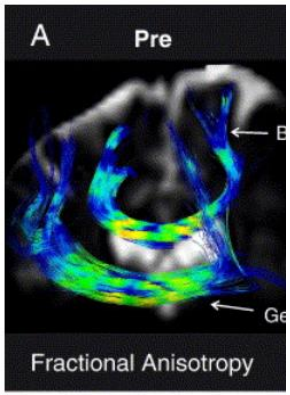
    $$\lambda_{||} = \lambda_1$$

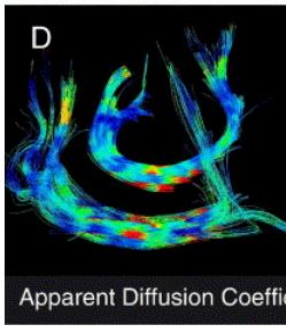
  - **Perpendicular diffusivity or radial diffusivity:** assessing myelin injury

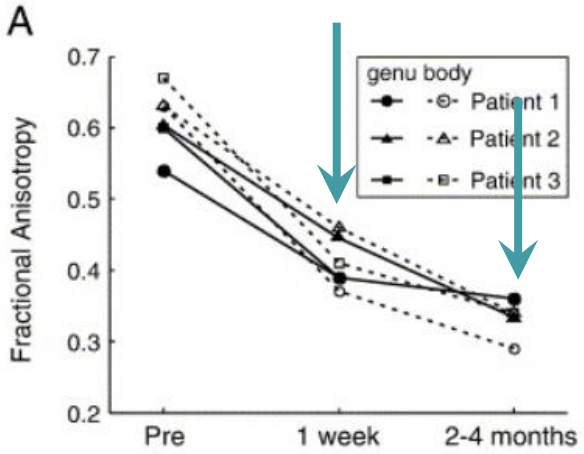
    $$\lambda_{\perp} = \frac{\lambda_2 + \lambda_3}{2}$$

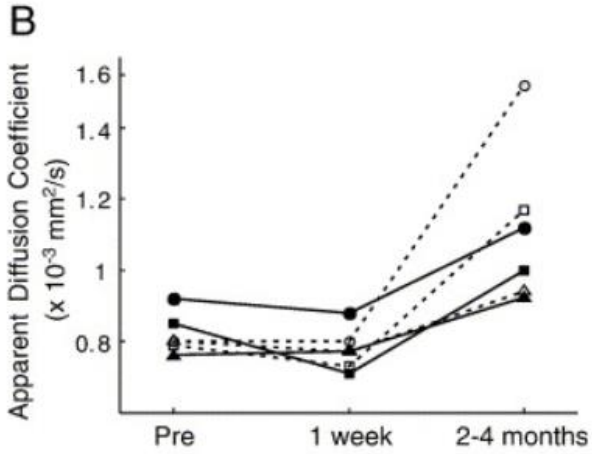
Beyond Fractional Anisotropy and Mean Diffusivity: Parallel and Perpendicular Diffusivity

- Validated in humans using the model of callosotomy *(Concha et al., 2006)*

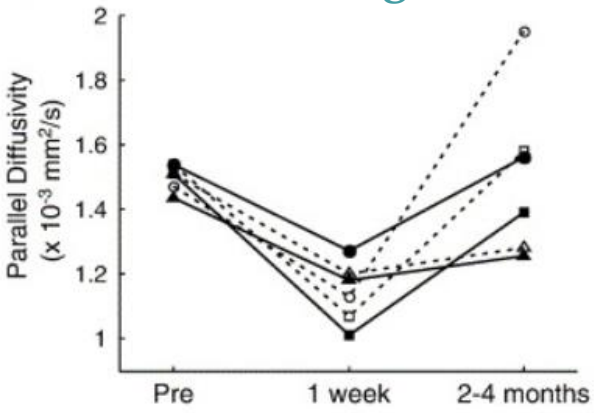




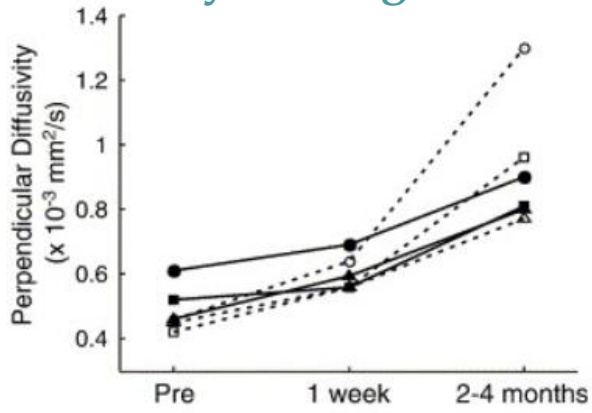


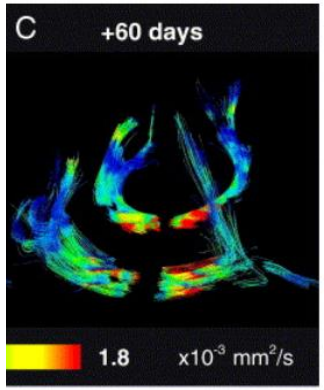


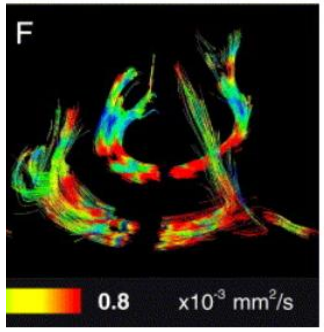
C ➢ **Axonal degradation**



D ➢ **Myelin degradation**





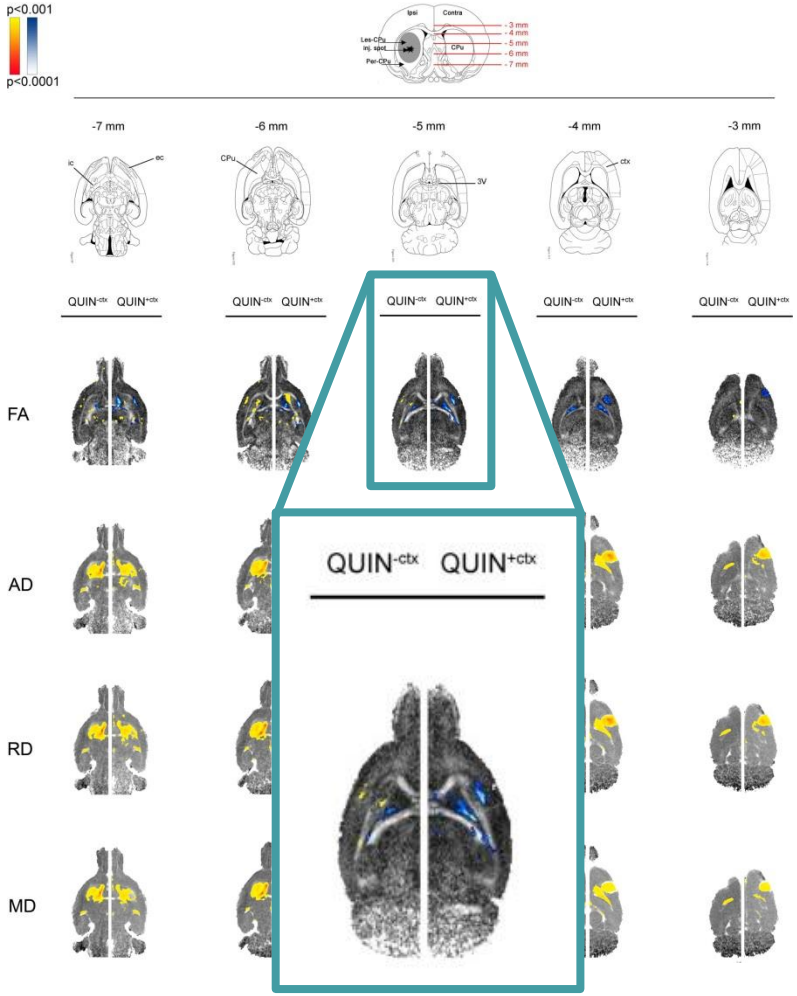


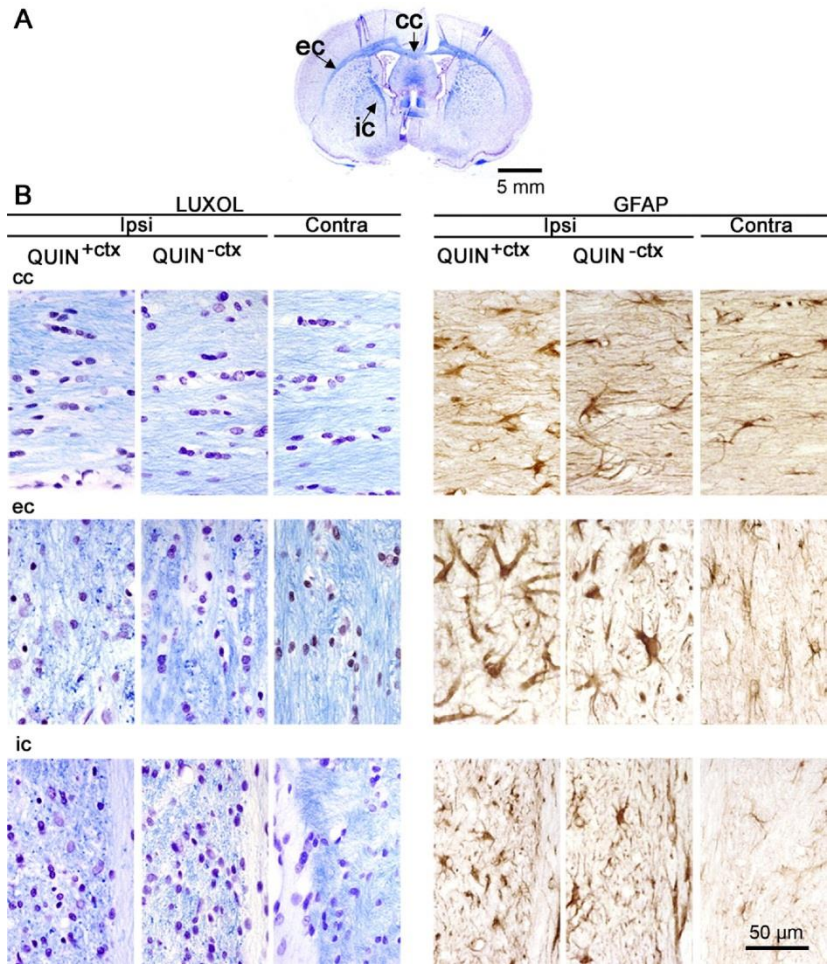
Diffusion tensor indices: *in vivo* models and histological validation

- Basis of diffusion anisotropy in the brain: comprehensive review by Beaulieu *(2002)*
  - Anisotropy due to membrane, not myelin
  - Myelin modulates anisotropy
  - Axonal cytoskeleton does not contribute to anisotropy

Diffusion tensor indices: *in vivo* models and histological validation

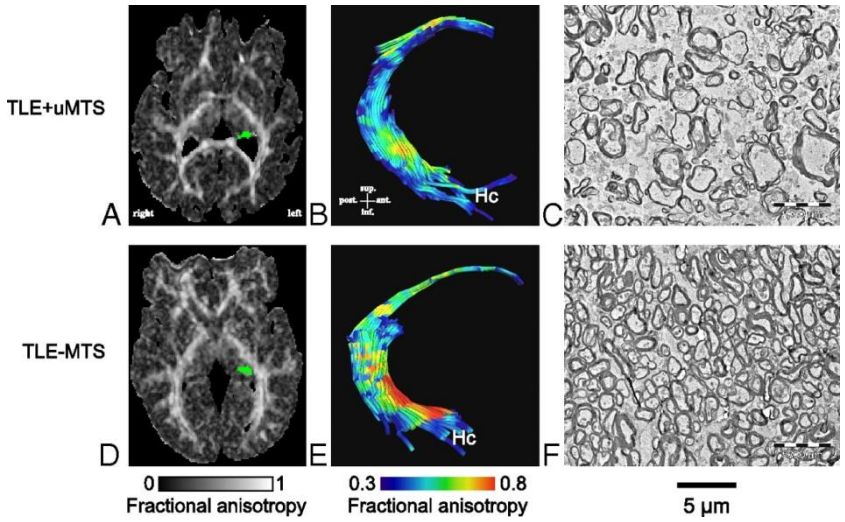
- Combined *in vivo* diffusion/histological study: animal model *(van Camp et al., 2012)*

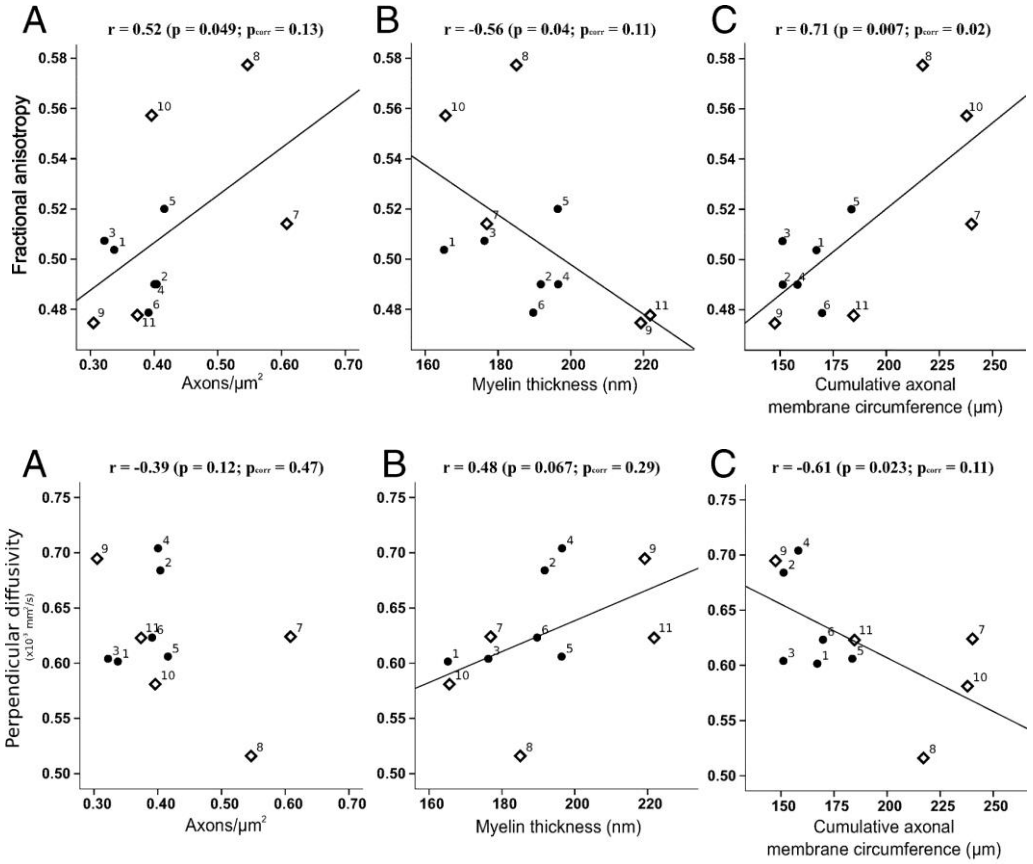




Diffusion tensor indices: *in vivo* models and histological validation

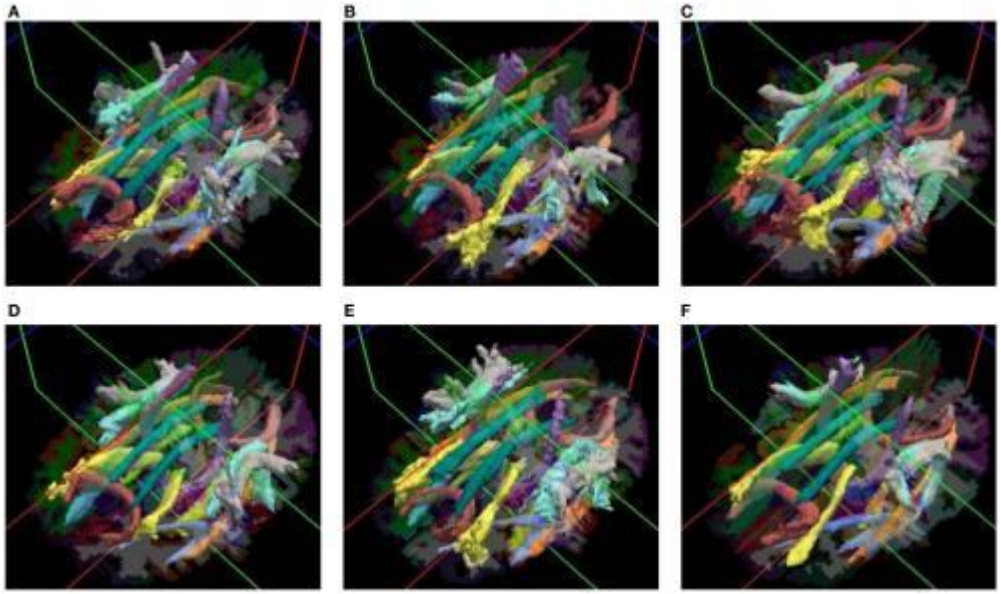
- Combined *in vivo* diffusion/histological study: epilepsy *(Concha et al., 2010)*





The take-home message slides

- Voxel-wise (VBD) results depend on the accuracy of the registration
  - TBSS
- TBSS doesn't cover the basal ganglia and regions of crossing fibres
  - VBD!
  - ROI

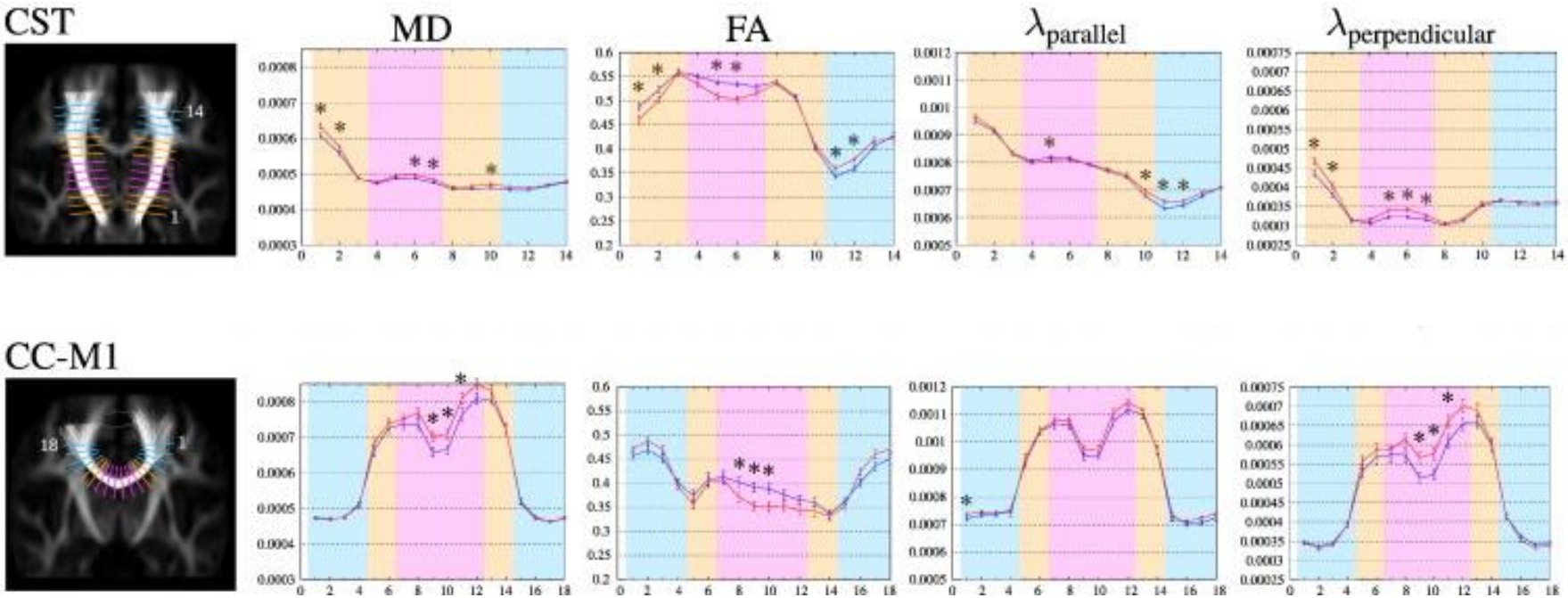


"Tracula!"

Yendiki *et al.*, 2011

The take-home message slides

- (**) Tractography/atlas ROI of tracts: effects can be averaged out
  - Look *along* the tract, or only in regions with one dominating fibre population

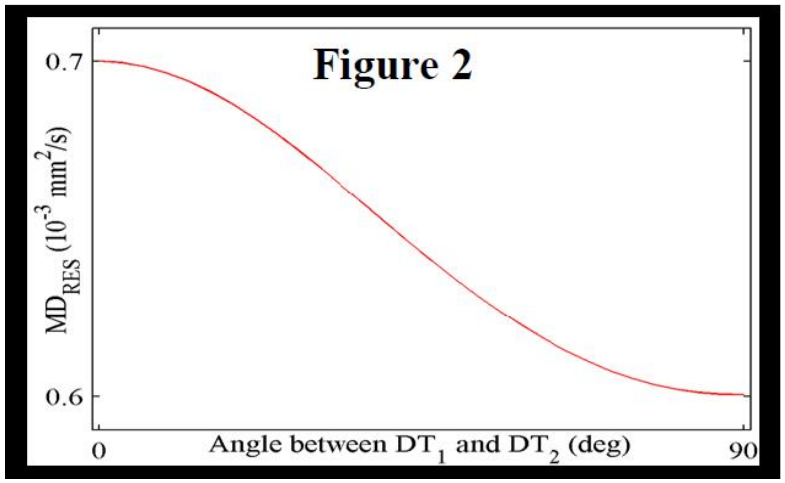


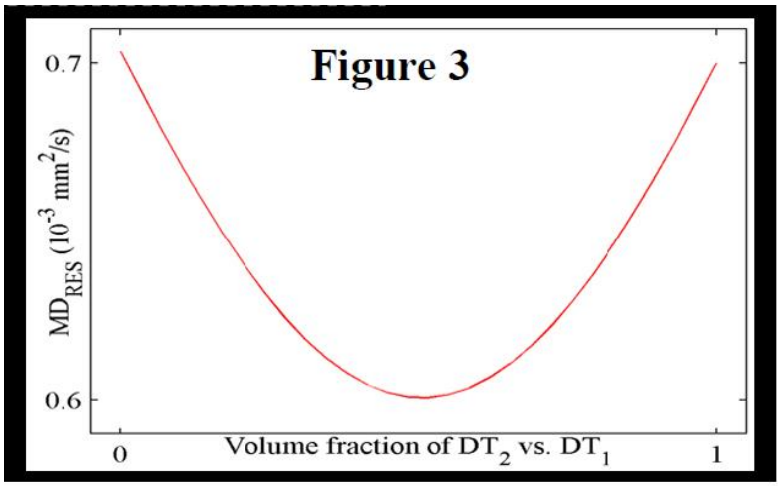
Groeschel *et al.*, 2014

The take-home message slides

- Higher (FA, streamlines etc.) is not always better and it is not always compensatory!
  - Use MD: it's complementary to FA
  - Think crossing fibres!

- Crossing-fibres: not only influence on FA, but also on MD *(Vos et al., 2012)*

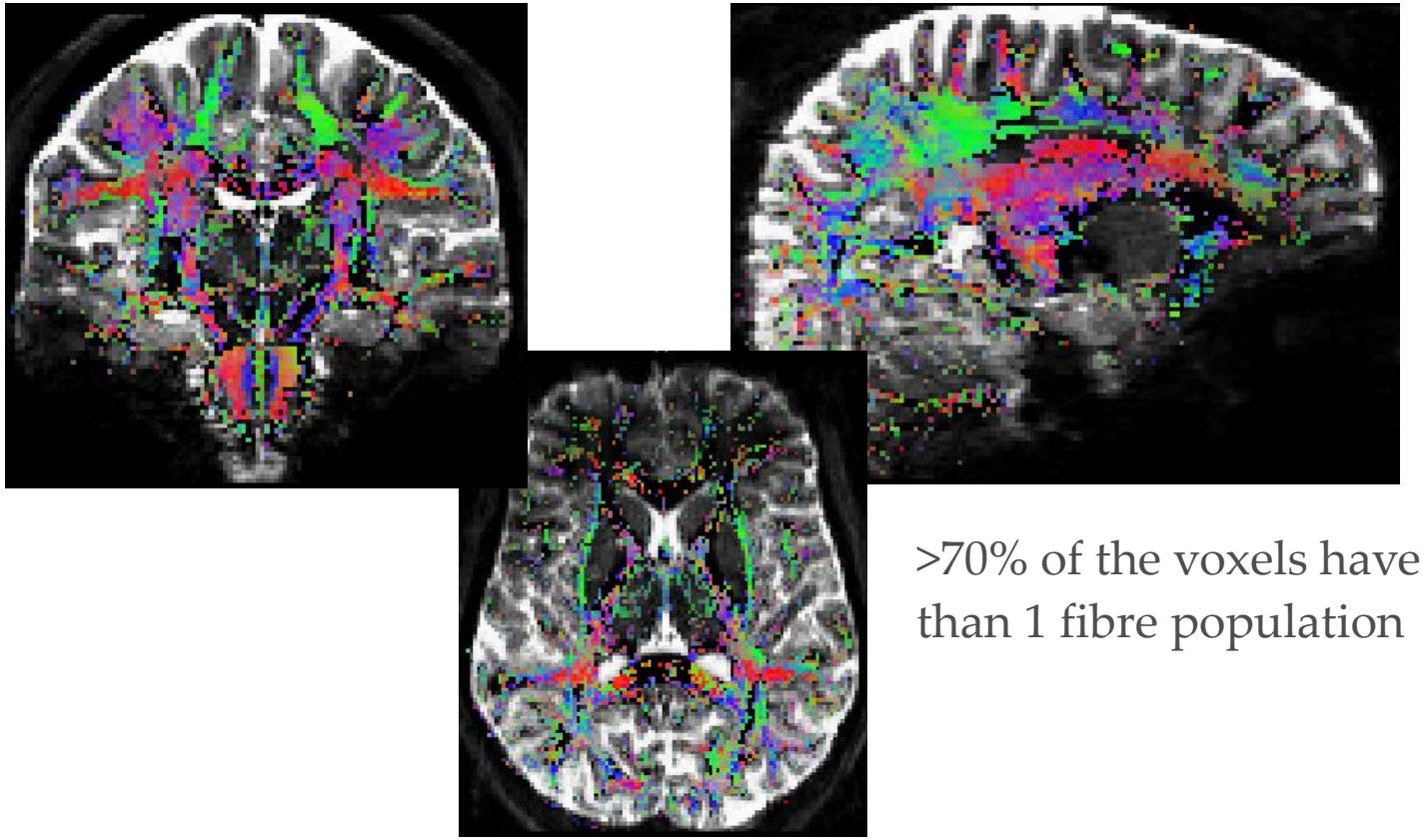




Vos *et al.*, 2012

The take-home message slides

- Crossing-fibres: problematic interpretation of $\lambda_{||}$ and $\lambda_{\perp}$

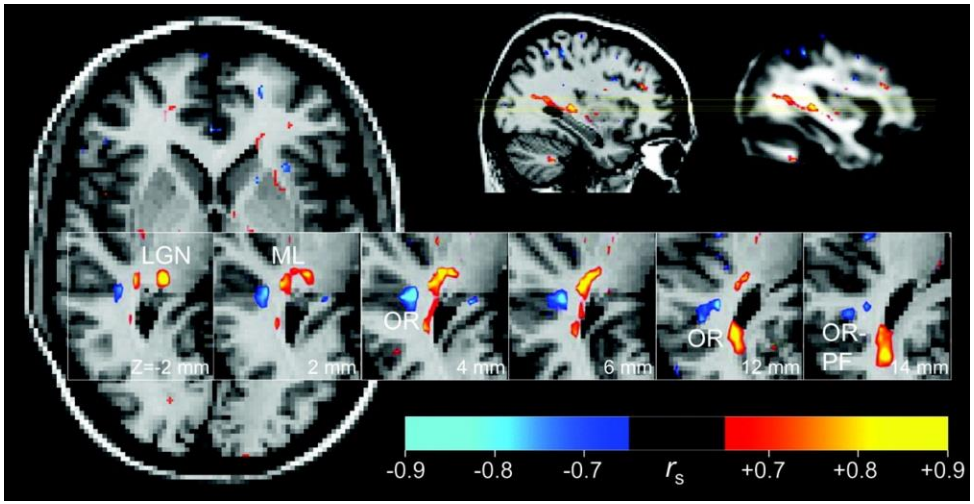


>70% of the voxels have more than 1 fibre population

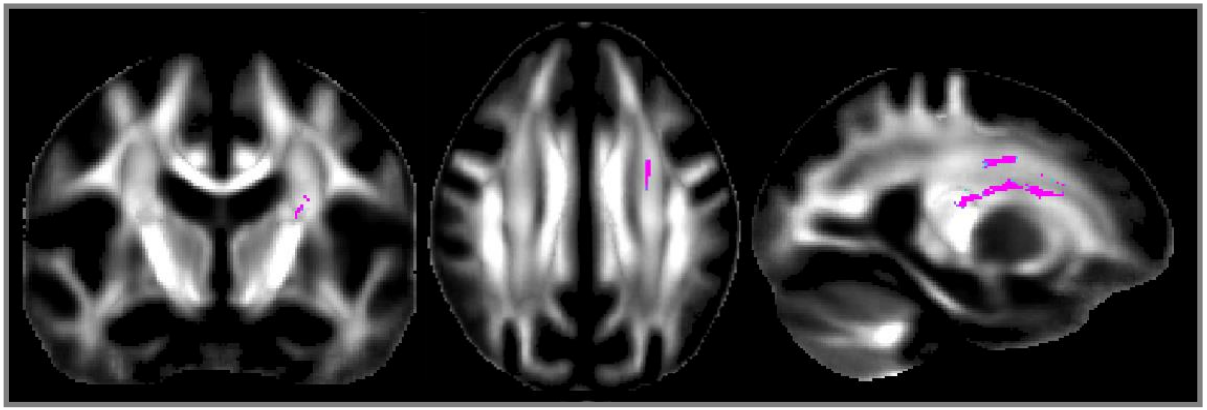
➢ If ambiguous interpretation: MO, PDD dispersion, Westin indices *(Westin et al., 1997)*

The take-home message slides

- Crossing fibres help **detect subtle differences** *(Tuch et al., 2005; Douaud et al., 2011)*



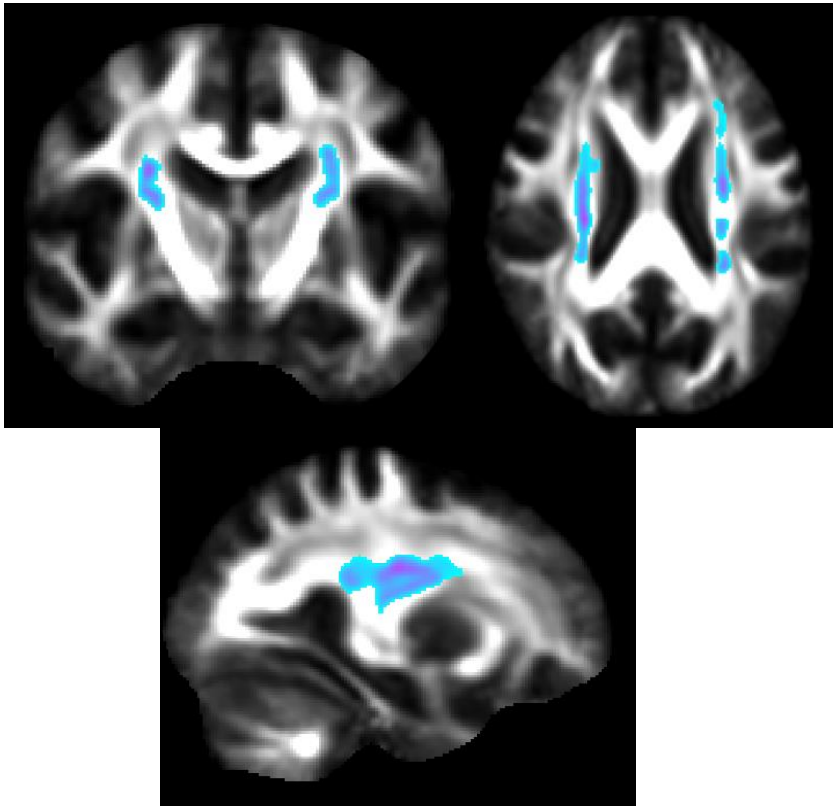
Tuch *et al.*, 2005



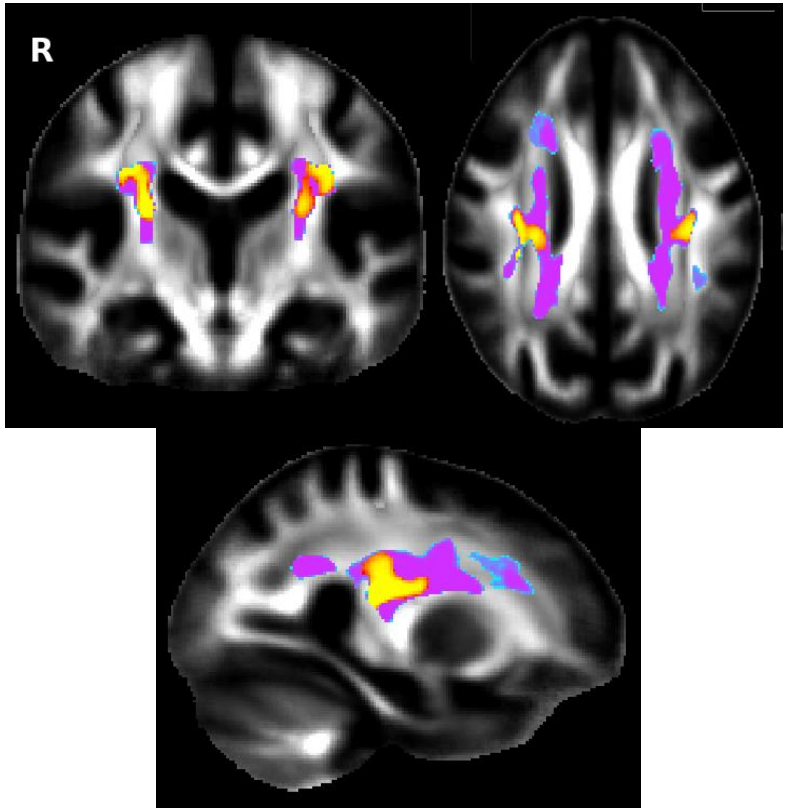
MCI>CON

Douaud *et al.*, 2011

Microstructural white matter differences between progressive MCI and stable MCI?

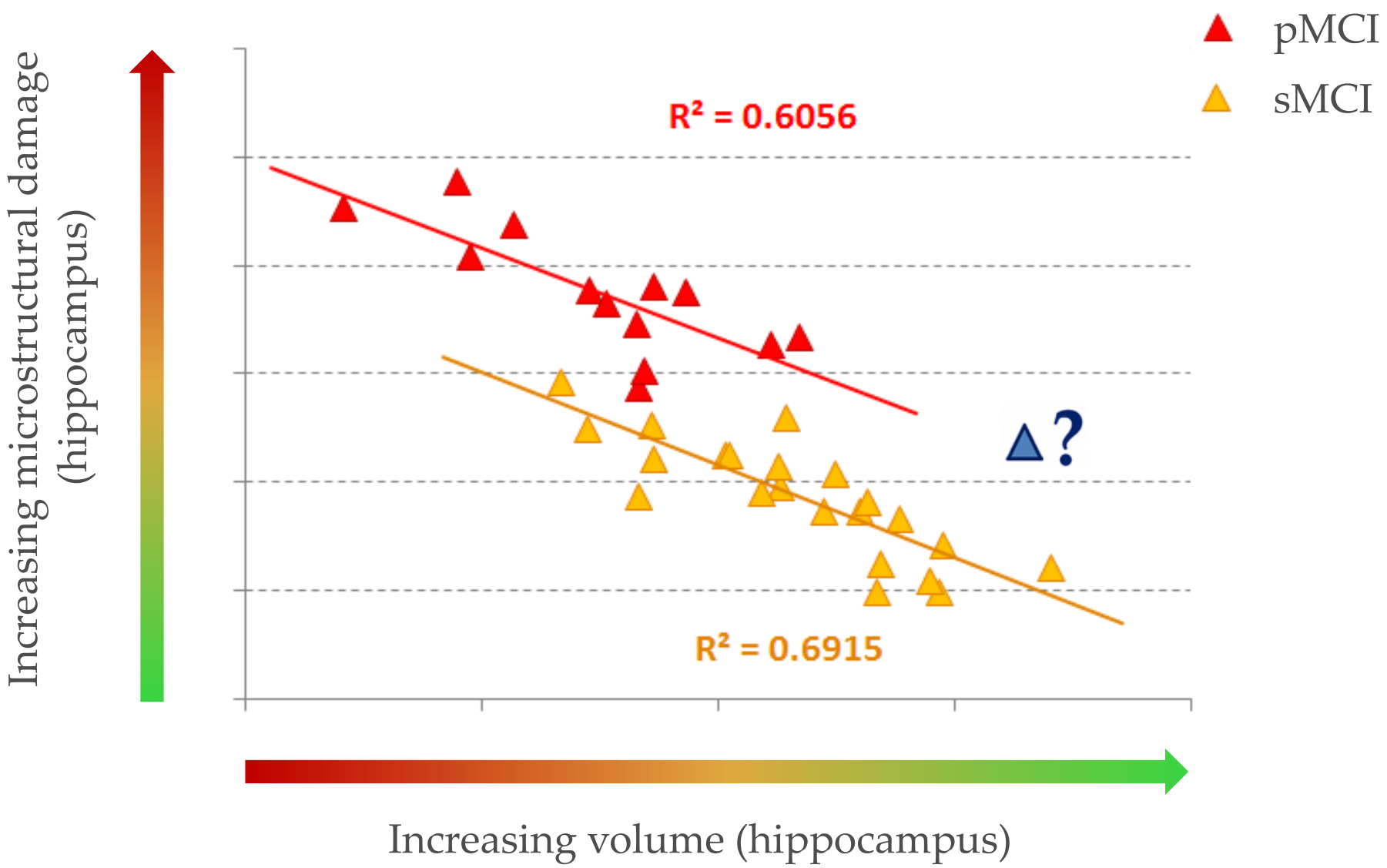


Progressing MCI – Stable MCI



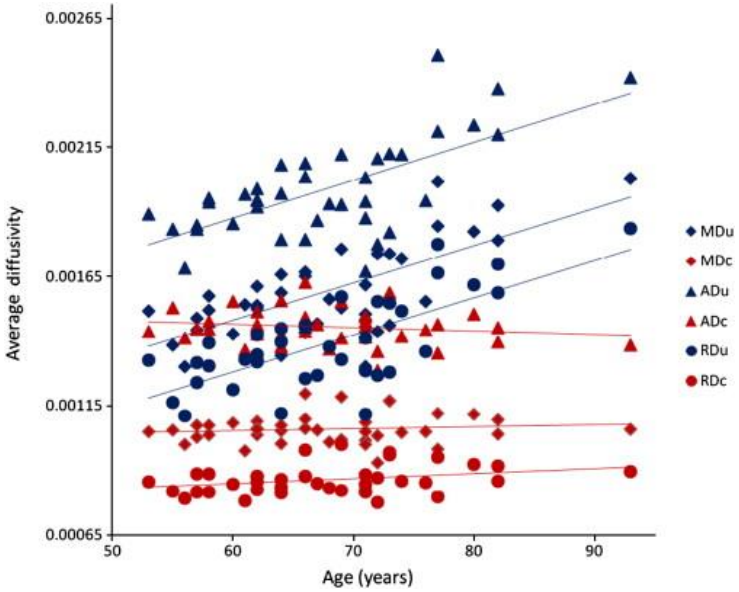
MCI – Healthy elderly

Progression to Alzheimer's disease: diffusion & GM measures are complementary



The take-home message slides

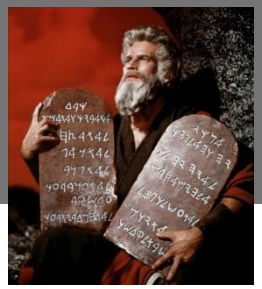
- Effect of **partial volume effect (PVE)** on FA, MD etc. *(Jones, ISMRM 2011)*
  - ➢ Correction for CSF contamination? *(Metzler-Baddeley et al., 2012)*



- **Choice of sequence:** anisotropic voxels *(Vos et al., ISMRM 2011)*

- **Choice of sequence:** 12 orientations, 5 b-values: more sensitive to ≠ using MD
  30 orientations, 2 b-values: more sensitive to ≠ using FA

The 8 commandments



- **Choice of sequence:** isotropic voxels, optimised for specific question
- **FA and MD complementary** to interpret results: **higher** FA is not necessarily better
- $\lambda_{||}$ and $\lambda_{\perp}$ give **additional information**, but are problematic in crossing-fibre regions
- Always check **opposite contrast**, it might give you the only significant results!
- Think about the right approach for your study, if necessary use **complementary** ones (ROI, TBSS, VBD, tractography…)
- Do not directly use the tractography paths for your study (ROI, classification etc.)
- Do not forget about **PVE, noise, non-linearity and X fibres** to help interpret results
- Think before you publish!

Special thanks to:

SHEL C ay

Cointe

Rivier

- Jean-Franco

matios

hothy B

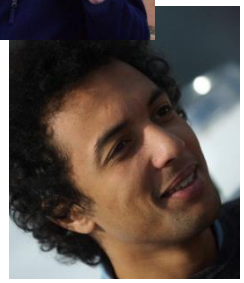
ve Smith

er Jezzard

- Saad Jbabdi

xford

s



QUESTIONS?