UNIVERSITÉ PAUL SABATIER TOULOUSE III

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LONGITUDINAL STUDY TO ASSESS THE PREDICTIVE VALUE OF DTI PARAMETERS IN RRMS PATIENTS

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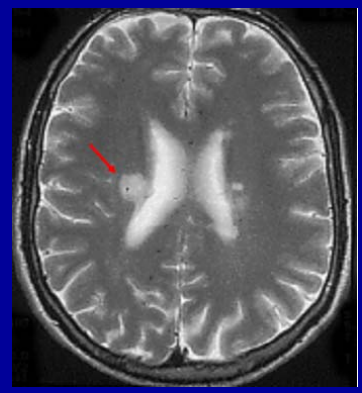
INTRODUCTION

- cMRI: diagnosis and management of multiple sclerosis (MS)

  → lesions in the central nervous system (CNS)



- Correlations between lesion load (LL) and EDSS weak
- Non-conventional MRI techniques: pathological process in NAWM and GM
- **Diffusion tensor imaging (DTI):** sensitive in detecting occult MS-related brain abnormalities
- No marker monitor or predict progression of MS
- **Aim:** potential of quantitative DTI parameters and LL to predict

MULTIPLE SCLEROSIS AND DTI

1. DTI

- Microscopic random motion of water molecules:

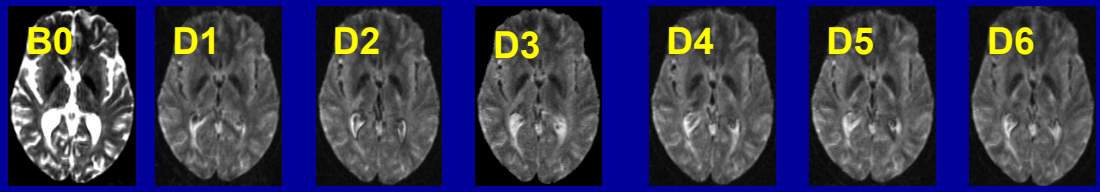
  → Brownian motion

- Diffusion is not the same in all directions: WM tracts

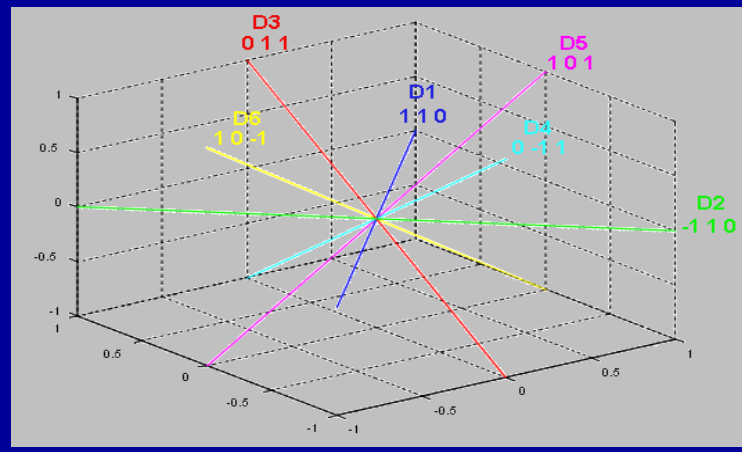
  → Anisotropy

- **Tensor:**

$$D = \begin{pmatrix} Dxx & Dxy & Dxz \\ Dyx & Dyy & Dyz \\ Dzx & Dzy & Dzz \end{pmatrix}$$



g_1=(1 0 -1) g_2=(1 -1 0) g_3=(0 -1 1) g_4=(1 0 1) g_5=(1 1 0) g_6=(0 1 1)



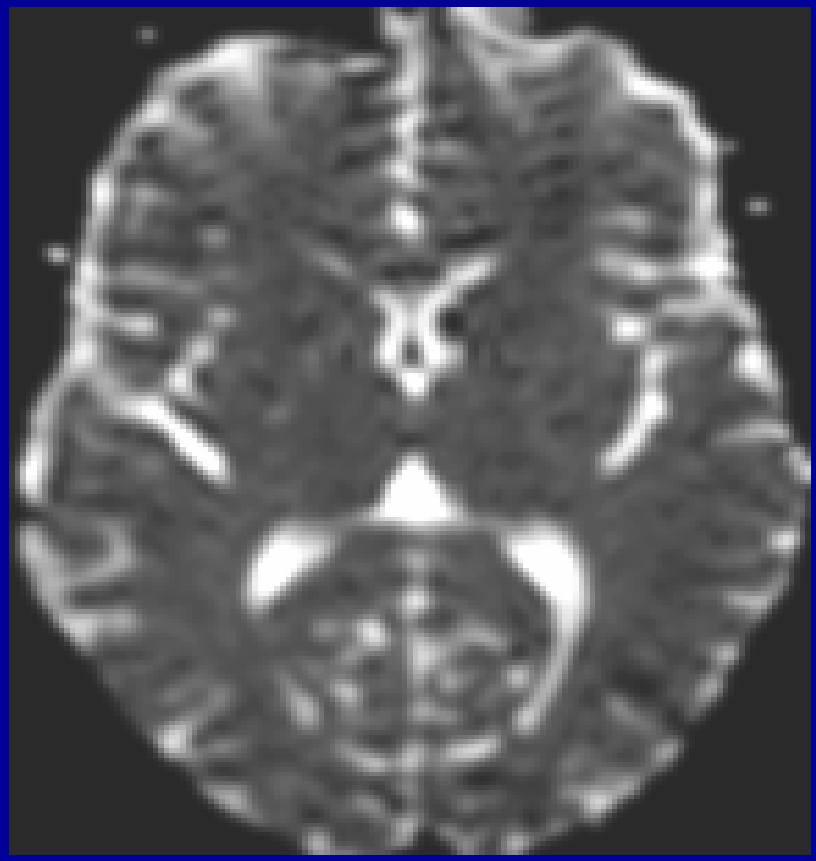
- 6 weighted diffusion images in 6 ≠ directions of gradient + 1 non weighted diffusion image

$$\begin{pmatrix} Dxx & Dxy & Dxz \\ Dyx & Dyy & Dyz \\ Dzx & Dzy & Dzz \end{pmatrix} \xrightarrow{\text{Diagonalisation}} \begin{pmatrix} \lambda 1 & 0 & 0 \\ 0 & \lambda 2 & 0 \\ 0 & 0 & \lambda 3 \end{pmatrix}$$

V1, V2, V3: eigen vectors associated with the main diffusion directions

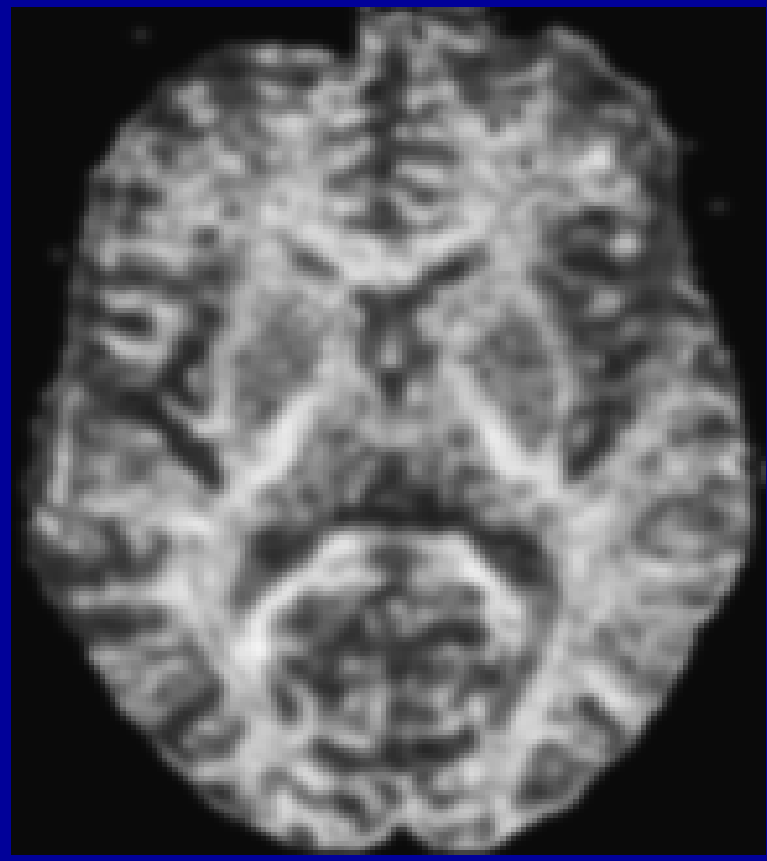
$\lambda 1$, $\lambda 2$, $\lambda 3$: eigen values associated with eigen vectors

Maps



Mean diffusivity (MD)

$$DM = (\lambda 1 + \lambda 2 + \lambda 3)/3$$

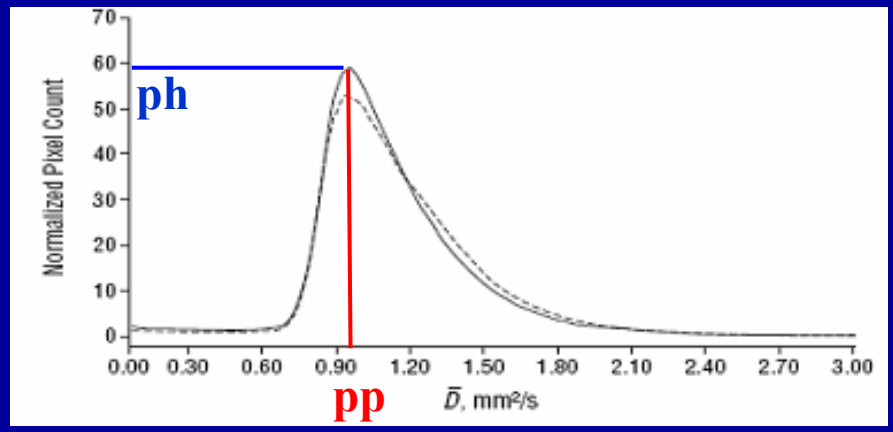


Fractional anisotropy (FA)

$$FA = \frac{1}{\sqrt{2}} \frac{\sqrt{(\lambda 1 - \lambda 2)^2 + (\lambda 2 - \lambda 3)^2 + (\lambda 1 - \lambda 3)^2}}{\sqrt{(\lambda 1^2 + \lambda 2^2 + \lambda 3^2)}}$$

FA from 0 to 1

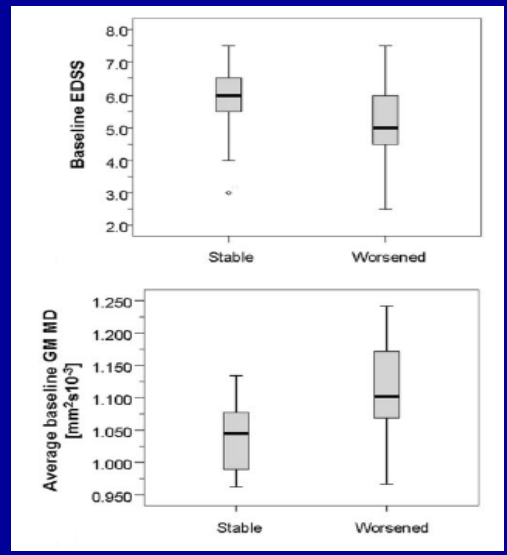
2. DTI in multiple sclerosis



(Oreja-Guevara, Arch Neurol, 2005)

- ↗ MD and ↘ FA in NAWM and GM compared with healthy subjects

- Association abnormal MD values with disease progression (Rovaris et al., 2006)



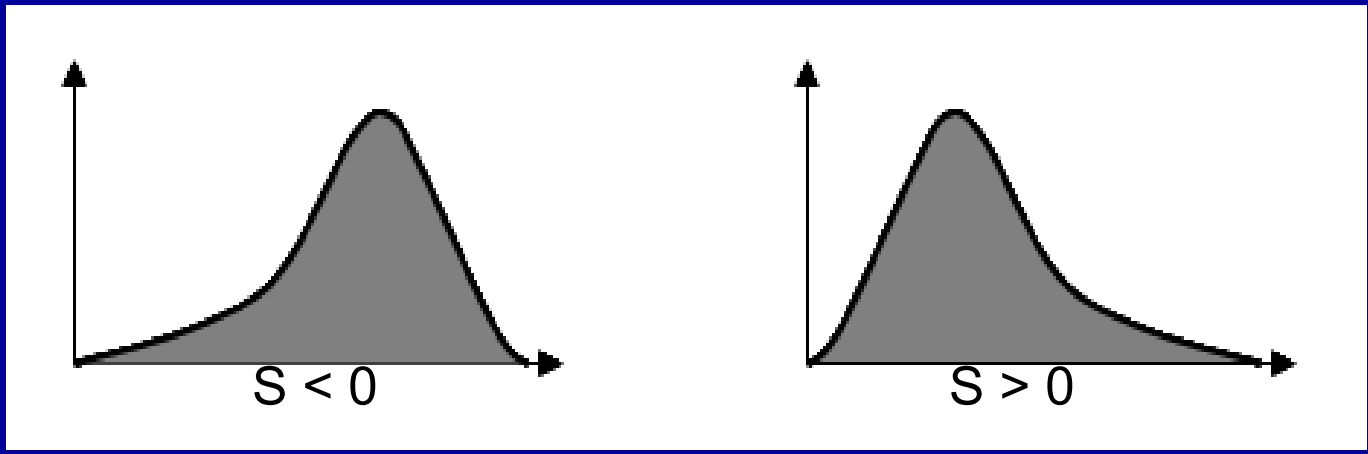
Previous DTI study over 3 months on a group of RRMS patients

(Graulieres E., Lotterie J.A., Cassol E., Gerdelat A., Clanet M., Berry I. Relevance of the Skewness index in DTI exploration of multiple sclerosis. Magma. submitted)

→ **Skewness (S)** to describe MD and FA histograms in NAWM and GM

→ more reliable than pp and ph

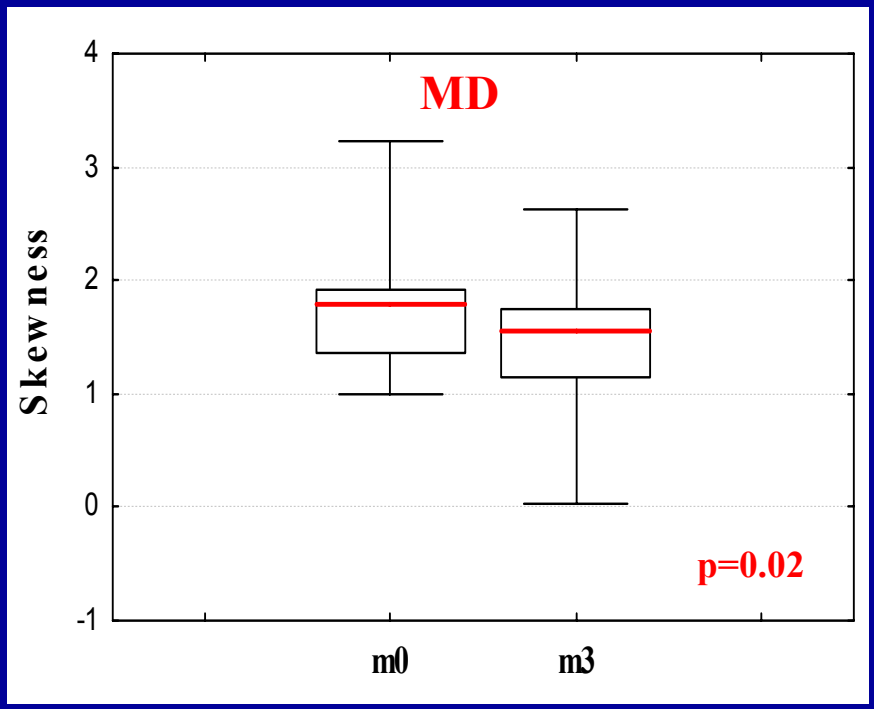
Measure of the lack of symmetry

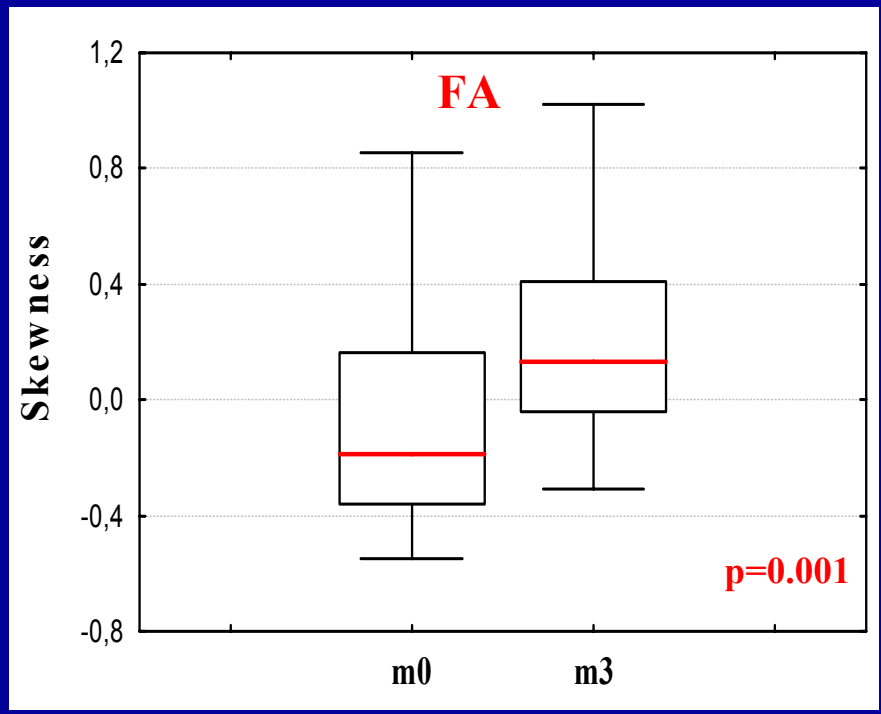


Skewed right

Skewed left

- No clinical evolution over 3 months but S in GM for both histograms showed significant change towards abnormal values





- S may be an alternative parameter to monitor disease evolution compared to EDSS

→ Objective: DTI parameters and LL have potential to predict the course of RRMS patients?

MATERIALS AND METHODS

Patients

- 13 RRMS patients: 2 examinations within 3 months (m0 and m3)
- Clinical evaluation (EDSS score) and cMRI and DTI
- 7 years (y7): clinical evaluation

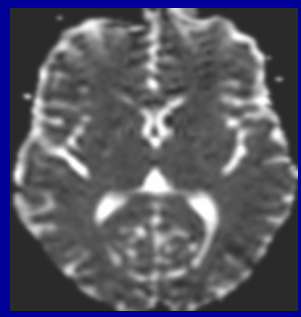
MRI acquisition and post processing

- MRI 1.5 T
- DTI: 6 non collinear directions of gradient ($b=506\ s.mm^{-2}$) ("single shot" echo planar)
- cMRI: T_2 weighted images (WI)

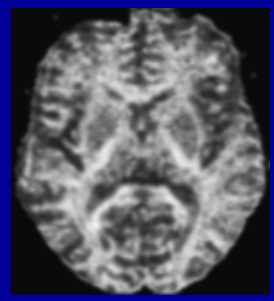
- T_2 images: calculation of LL with semi-automated process (Analyse™, Biomedical Imaging Reource, Mayo Foundation, CNSoftware Ltd, UK)

- Correction of eddy currents distorsion
(coregistration of diffusion weighted images on the diffusion un-weighted image)

- Calculation of the tensor and MD and FA values voxel by voxel
(Sisyphe, Dr Lotterie J-A, Université Paul Sabatier, Toulouse)



MD



FA

- Masks NAWM and GM
(SPM2, K. Friston, University College London, UK)

Mask NAWM

Mask GM

- Apply to MD and FA maps: histograms of MD and FA

- For each patient, at m0 and m3, from each MD and FA histogram:
  - **Skewness**
  - **pp**
  - **ph**
- For each patient, at m0, m3 and y7: EDSS

→ whole group of patients

→ 2 groups according to change in EDSS over 7 years (<2 and ≥2)

Statistical analysis

- Spearman rank: correlations between change in DTI parameters and LL over 3 months and change in EDSS over 7 years
- 2 tailed t-test power and sample size calculation
- Student t test: change over 3 months ≠ between the 2 groups

RESULTS

For the whole group of patients

		r	p	Power	N
Lesion load		0.09	0.78	0.06	>1000
NAWM MD	**S**	-0.22	0.47	0.11	213
	pp	0.13	0.68	0.07	617
	ph	0.0008	0.99	0.05	*
NAWM FA	**S**	-0.15	0.62	0.07	462
	pp	0.19	0.53	0.09	287
	ph	0.22	0.47	0.11	213
GM MD	**S**	-0.06	0.84	0.05	>1000
	pp	0.15	0.63	0.07	462
	ph	-0.03	0.93	0.05	>1000
GM FA	**S**	-0.22	0.48	0.11	213
	pp	0.22	0.48	0.11	213
	ph	-0.55	0.05	0.53	30

Correlations between change in DTI parameters and LL over 3 months and change in EDSS over 7 years

For the 2 groups of patients (EDSS <2 and ≥2)

		p
Lesion load		0.44
NAWM MD	**S**	0.82
	pp	0.1
	ph	0.66
NAWM FA	**S**	0.64
	pp	0.1
	ph	1
GM MD	**S**	0.18
	pp	0.22
	ph	0.19
GM FA	**S**	0.42
	pp	0.33
	ph	0.86

p values: change in DTI parameters and LL over 3 months ≠?

DISCUSSION

- DTI based studies: role of NAWM and GM
- No prediction of the evolution of the pathology

→ long term follow-up of RRMS patients to test DTI parameters (S) and LL

- No correlation except for ph from FA histograms in GM
- No ≠ in change of DTI parameters or LL between the 2 groups (moderate and more pronounced)

→ **limitations**

Clinical considerations

- Therapy: role in ≠ evolution of clinical score
- Not enough subjects

Methodological considerations

- Power of correlations inadequate (power<0.9) and sample size larger
- Limitation of DTI sequences:
  - image distorsions
  - patient motion artifact
  - signal to noise ratio
  - partial volume errors during segmentation

- Results show S or another parameter cannot predict evolution of MS

- Improved DTI sequences: more stable measures

→ **Further studies with larger sample size and improved DTI sequences**

Thank you for your attention

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