Diffusion Imaging II

By:
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Review

- Introduction.
    - What is diffusion?
    - Diffusion and signal attenuation.
    - Diffusion imaging.
- How to capture diffusion?
  - Diffusion sensitizing gradients.
    - Spin Echo.
    - Gradient Echo.
    - Quantitative description.
    - What is the *b*-value?
    - High *b*-value problems.
- Diffusion imaging pulse sequence.
    - Pulsed Gradient Spin Echo.
    - Single shot EPI.
    - RARE
      - RARE with crushers
      - Split Acquisition of fast spin echo (SPLICE) – diffusion preparation.
    - Split echoes of FSE or STEAM.
- Diffusion basics.
  - Einstein equation.
  - Factors that affect diffusion.
  - Diffusion tensor.
  - Anisotropic vs. isotropic diffusion.
- Diffusion Imaging techniques:
  - Introduction
  - Family of techniques
    - Diffusion weighted imaging (DWI).
    - Quantitative apparent diffusion coefficient (ADC).

Ref: Handbook of MRI pulse sequences (P. 274-280 and 830-853)

Review
Diffusion weighted (DW) image

- An MRI image acquired in the presence of diffusion weighting gradient (at single *b*-value).

$$S=S_0\exp(-bD)$$

- Its contrast depends on the **direction** of the applied gradient.
- To remove orientation dependence, three DW images with gradients applied along three orthogonal directions can be geometrically averaged to give an Isotropic (or Trace weighted) diffusion weighted image

$$S_{xyz} = \sqrt[3]{S_x S_y S_z} = S_0 e^{-b(D_{xx}+D_{yy}+D_{zz})/3} = S_0 e^{-b\, D_{trace}/3}$$

Apparent diffusion coefficient (ADC)

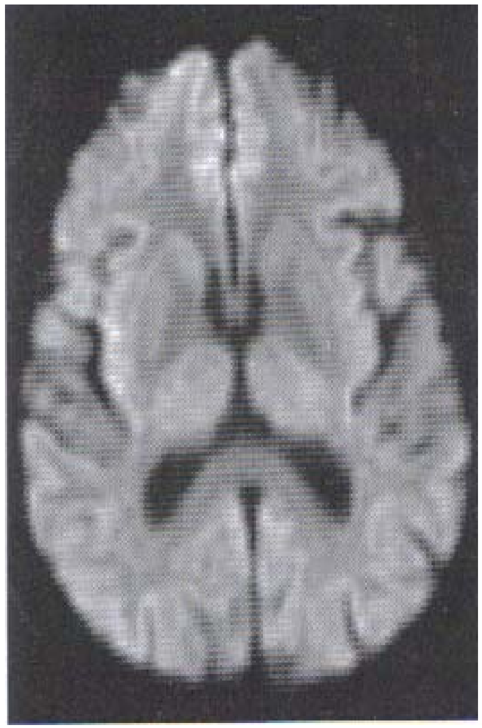
- Constructed from more than one DW image (at least two DW images), with different b-values.

$$S_1 = S_0 e^{-b_1 D}, S_2 = S_0 e^{-b_2 D} \ldots S_n = S_0 e^{-b_n D}$$

- The first image should be calculated without diffusion weighting (S_0) and the rest with different *b*-values (i.e., different gradients amplitudes in the **same direction**). Then the ADC map can be constructed by means of Linear fitting (approximation) or a Nonlinear fitting.

- The resulted ADC map contrast is inverted compared to DW image

DW image



ADC map

Biexponential Decay

- In some tissues (e.g. brain), diffusion signal follows a biexponential signal decay according to:

$$S = S_0(\zeta e^{-bD_f} + (1-\zeta)e^{-bD_s})$$

Where:

- ξ and (1-ξ) are the compartmental fractions.
- D_f is the fast diffusing component.
- D_s is the slow diffusing component.

Lecture 2 outline

- Family of diffusion techniques, cont'd
  - Diffusion tensor imaging
    - Quantitative description.
    - Finding the diffusion tensor.
    - Scalar and vector parameters extracted from the diffusion tensor (RA, FA, MD, PE, and Tractography)
  - q-space imaging
    - Quatitative description.
    - Definition of q.
    - How to conduct a q-space experiment?
- Quick paper discussion:

  Assaf et al 2002: "High b-value q-space analyzed diffusion-weighted MRI: Application to multiple sclerosis". Magn Reson Med 47:115-126, 2002 Wiley-Liss, Inc.

III. Diffusion Tensor Imaging (DTI)

- Many tissue structures imposes a non-spherical geometry on water diffusion boundaries, i.e., diffusion *anisotropy.*
- To fully describe diffusion anisotropy, diffusion tensor notation is used.

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

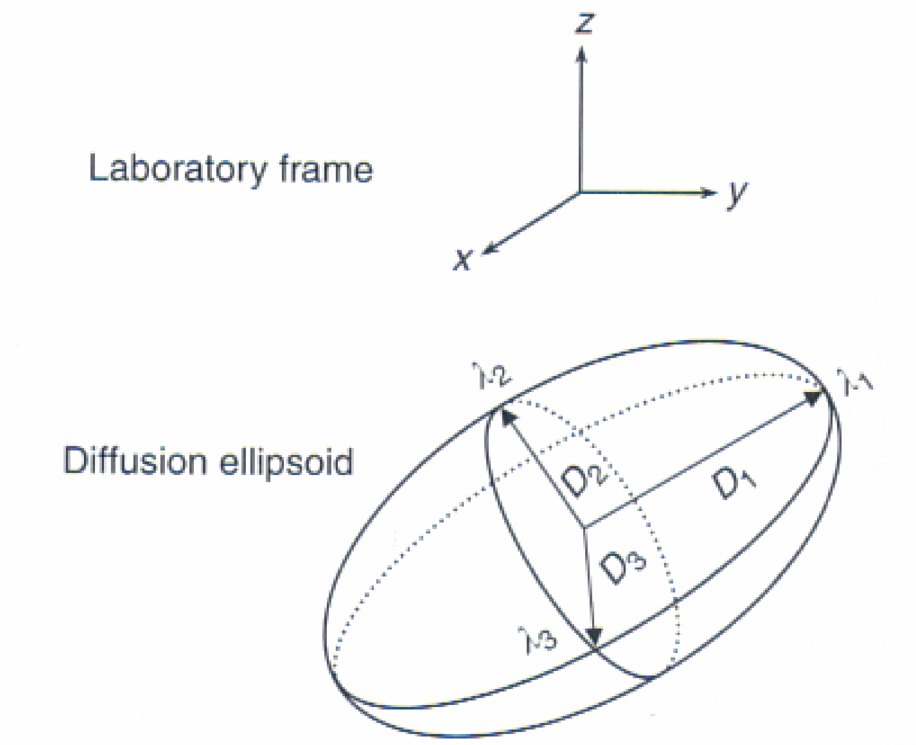
- It maps diffusion anisotropy at each spatial location,

Diffusion tensor

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

Eigenvalues

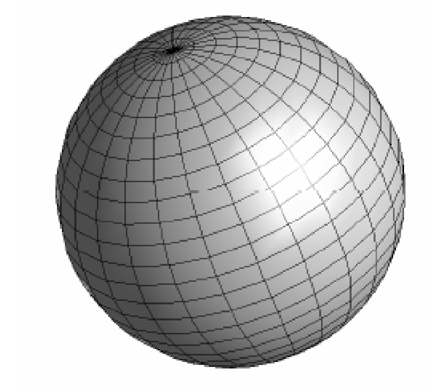
$$\overset{\Rightarrow}{D} = \begin{bmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{bmatrix}$$



Diffusion models

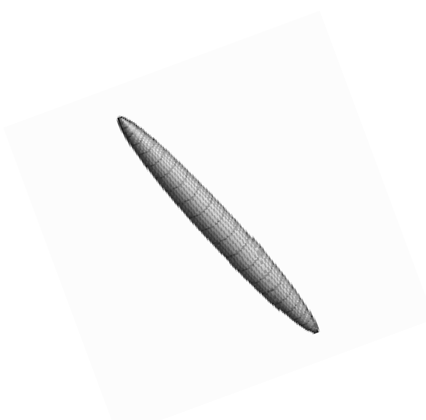
- Isotropic
  - No orientation dependence.

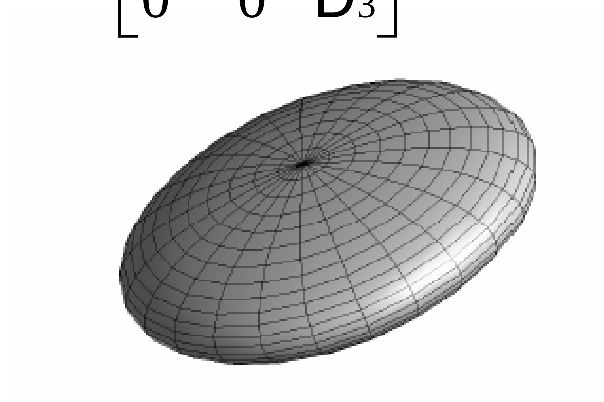
$$\overset{\Rightarrow}{D} = \begin{bmatrix} D & 0 & 0 \\ 0 & D & 0 \\ 0 & 0 & D \end{bmatrix}$$



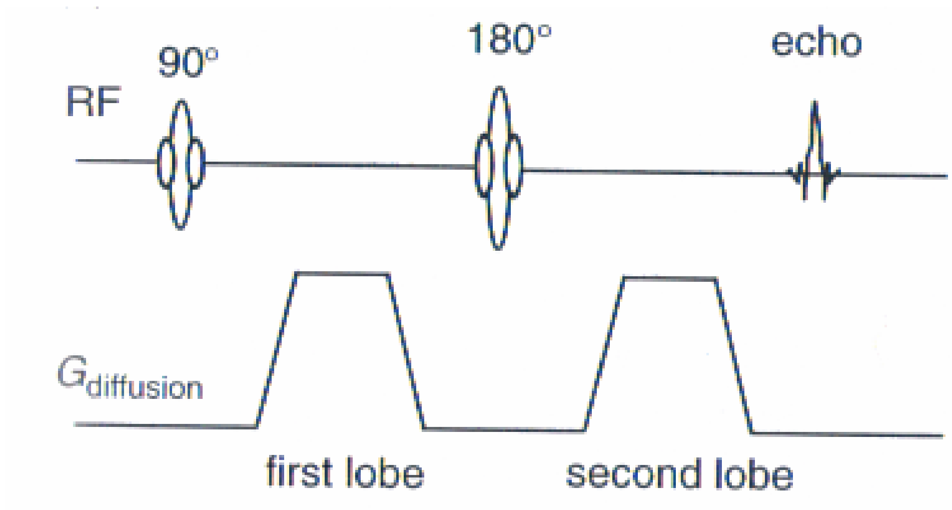
- Anisotropic
  - Diffusion depends on spatial orientation.

$$\overset{\Rightarrow}{D} = \begin{bmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{bmatrix}$$





- Stejskal and Tanner (1965) solved Bloch equation with diffusion weighting in a pulsed gradient spin echo (PGSE) experiment, which made this sequence amenable for describing free diffusion in anisotropic medium.



- They related the applied gradient, **G**(t)

$$\mathbf{G_j}(t) = G_j\,[u_j\;\; v_j\;\; w_j] \quad \textit{and} \quad \vec{k}(t) = \frac{\gamma}{2\pi}\int_{o}^{t} \vec{G}(t')\,dt'$$

to the echo intensity, *S*, in a spin echo experiment according to:

$$\frac{S}{S_0} = \exp\left(-\int_0^{TE} [k(t') - 2U(t' - \frac{TE}{2})\vec{k}(\frac{TE}{2})]^{T} D\; [k(t') - 2U(t' - \frac{TE}{2})\vec{k}(\frac{TE}{2})]dt'\right)$$

"U" is the step function (unit Heaviside function)

[*uj vj wj] are unit vectors in the direction of the applied gradient field.*

- Basser, Mattiello and Le Bilhan (1994) defined the effective diffusivity tensor, D_{eff}, to be the mean value of the exponent in Stejskal's equation. Re-writing it in term of the new parameter:

$$\frac{S}{S_0} = \exp\left(-4\pi^2 \int_0^{TE} \vec{k}_j \cdot \overline{\overline{D}}_{eff} \cdot \vec{k}_j^{\,T} \, dt\right)$$

$$\vec{k}_j(t') = \frac{\gamma}{2\pi} \int_o^t \vec{G}_j(t')\,dt'$$

- Neglecting the contribution from imaging gradients, we obtain the previous equation in matrix form:

$$\frac{S_j}{S_0} = \exp(-b\,.[u_j\ v_j\ w_j].\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}.\begin{bmatrix} u_j \\ v_j \\ wj \end{bmatrix})$$

$$IM_j = \ln(S_j / S_0) = -bQ_j$$

Q_j is the quadratic form of the diffusion tensor matrix.

$\mathbf{G_j} = G_0\,[u_j\ v_j\ w_j]$ *and* $b = c_1.G_0$

$$c_1 = \gamma^2[\delta^2(\Delta - \frac{\delta}{3}) + \frac{\zeta^3}{30} - \frac{\delta\xi^2}{6}]$$

Calculating the diffusion tensor

- Requires at least two *b*-values, one of them without diffusion weighting (*b*~0).
- Acquire six DW images with gradients applied along *at least six noncolinear, noncoplanar directions at any nonzero b*-values.
- In total, at least seven images are needed: one with *b*=0 which gives S_0, and six images with nonzero *b-values , giving* S_1, S_2, …, S_6

- We have a system of six linear equations with six unknowns, (the six independent elements of *D*):

$$IM_j = -b\,.\,[u_j\ v_j\ w_j]\,.\begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix}.\begin{bmatrix} u_j \\ v_j \\ wj \end{bmatrix}$$

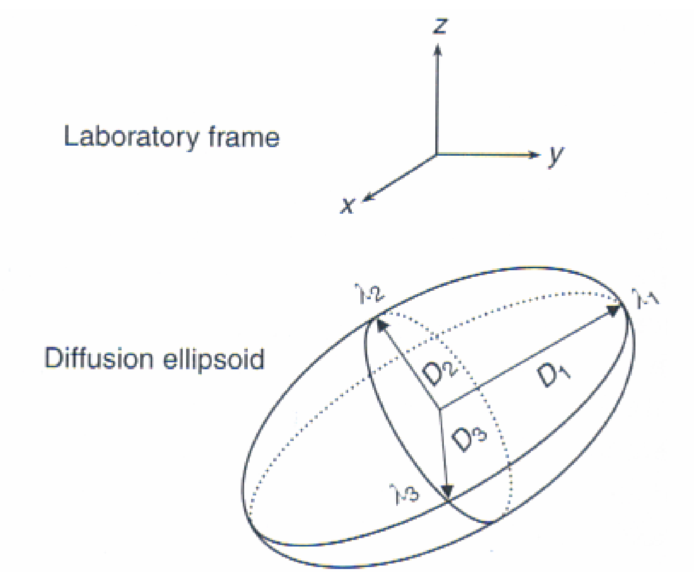
Solving this system of linear equations will yield the diffusion tensor at each voxel.

Diffusion tensor anisotropy-maps

- Scalar maps:
  - Can be exploited in Visualizing location, size and integrity of fibrous structures (white matter).
  - Examples: Mean diffusivity, relative anisotropy (RA), fractional anisotropy (FA) and Volume ratio (VR)
- Vector maps
  - Provide information on diffusion spatial orientation that can infer fiber tracts connectivity.
  - Examples: Eigenvectors and Tractography.

Scalar diffusion anisotropy calculations

- In order to remove patient orientation dependence, the diffusion tensor matrix will not be used directly, instead, its eigenvalues will be used.

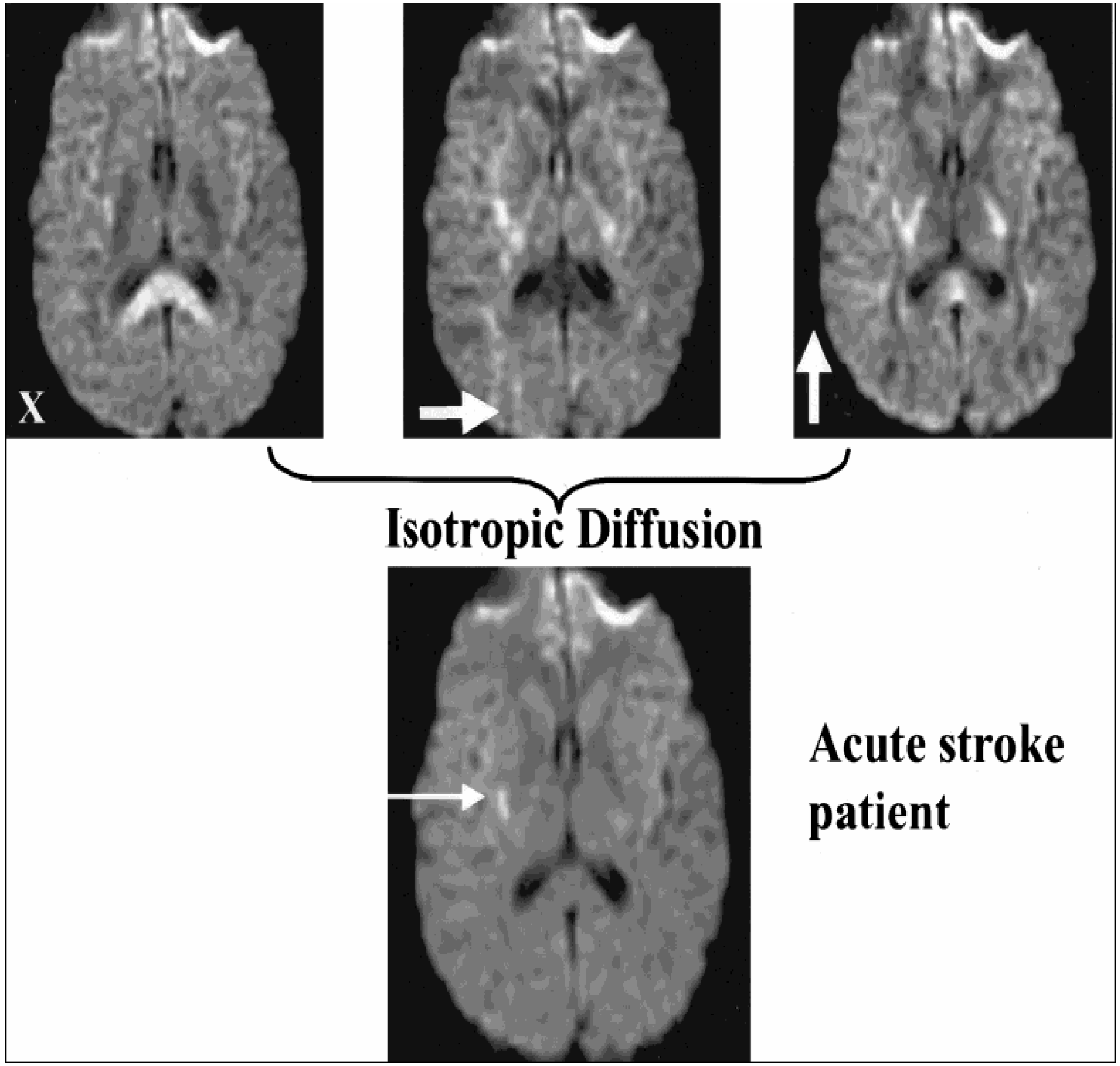


$$\vec{D} = \begin{bmatrix} D_1 & 0 & 0 \\ 0 & D_2 & 0 \\ 0 & 0 & D_3 \end{bmatrix}$$

- Maps:
  - Apparent diffusion coefficient
    - $ADC_1 = D_1$, $ADC_2 = D_2$, $ADC_3 = D_3$
    - ADC_1/ADC_2 or $\max[ADC_1, ADC_2, ADC_3]/\min[ADC_1, ADC_2, ADC_3]$
  - Trace weighted image

$$\mathit{Trace}(D) = D_1 + D_2 + D_3$$

  - Mean diffusivity = *Trace(D) / 3*



DTI in acute stroke (7 hours). Acute ischemic regions appear bright in diffusion-weighted images. As normal white matter regions may also appear bright in some orientations (indicated by the bold arrows) due to anisotropic diffusion effects, the use of images weighted by the trace of the diffusion tensor is more adequate (the ischemic lesion is indicated by the thin arrow).

- Relative Anisotropy (RA)
  - Normalized standard deviation:
  - Represents the ratio of the anisotropic part of **D** to its isotropic part.

$$\mathrm{RA} = \frac{1}{\sqrt{3} D_{avg}} \sqrt{\sum_{i=1}^{3} (D_i - D_{avg})^2}$$

  - Ranges from 0 (isotropic diffusion) to $2^{1/2}$ (infinite anisotropic)
- Fractional Anisotropy (FA)
  - Normalized standard deviation:
  - FA measures the fraction of the “magnitude” of **D** that can be ascribed to anisotropic diffusion

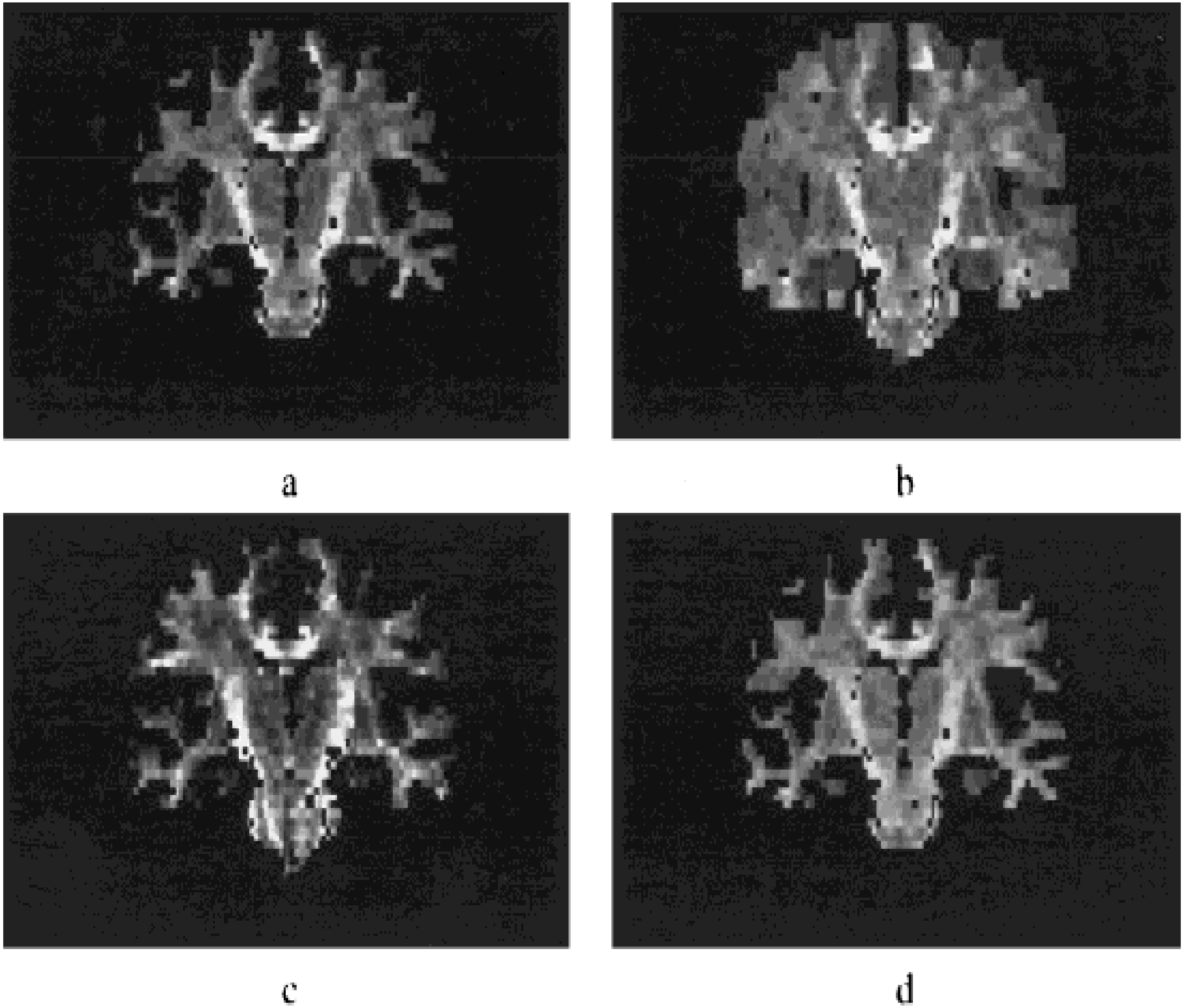
$$\mathrm{FA} = \sqrt{1.5} \frac{\sqrt{\sum_{i=1}^{3} (D_i - D_{avg})^2}}{\sqrt{\sum_{i=1}^{3} D_i^2}}$$

  - Ranges from 0 (isotropic diffusion) to 1 (infinite anisotropic)

- Volume Ratio (VR)

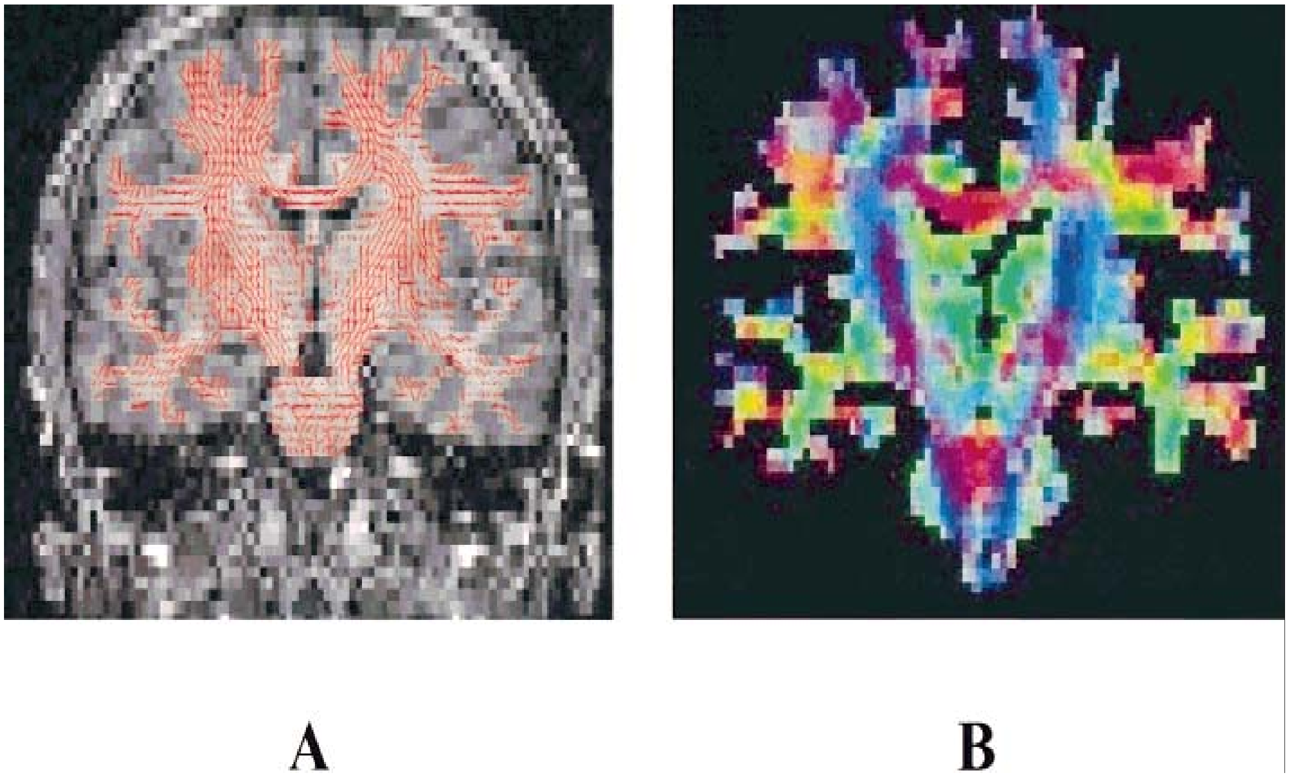
$$\mathrm{VR} = \frac{D_1 D_2 D_3}{D_{\mathrm{avg}}^3}$$

  - Represents the ratio of the ellipsoid volume to the volume of a sphere of radius D_{avg}.
  - Ranges from 1 (isotropic diffusion) to 0 (infinite anisotropic), hence, (1-VR) may be used.



Comparison of various anisotropy indices. a: Simple anisotropy index given by: $(D/D_{avg}-1)/2$. b: Relative anisotropy index (RA). c: Volume ratio index (VR). d: Fractional anisotropy index (FA).

Principal eigenvector



Two-dimensional display of the diffusion tensor. A: Projection of the main eigen-vector on a high-resolution T2-weighted image. B: Representation of the main eigenvector direction using a color scale (red = x axis, green = y axis, blue = z axis).

Tractography

- Maps the tissue fiber orientation and connectivity in three directions, *in vivo*.
- The assumption is that the direction of the fibers is colinear with the direction of the eigen-vector, $\vec{\lambda}_1$, associated with the largest eigen diffusivity.

Quantitative Description

- It was proposed that a white matter fiber tract trajectory could be represented as a 3D space curve, i.e., a vector, **h**(r), parameterized by the arc length, r, of the trajectory.
- The Frenet equation describing the evolution of **h**(r) is:

$$\frac{dh(r)}{dr} = t(r)$$

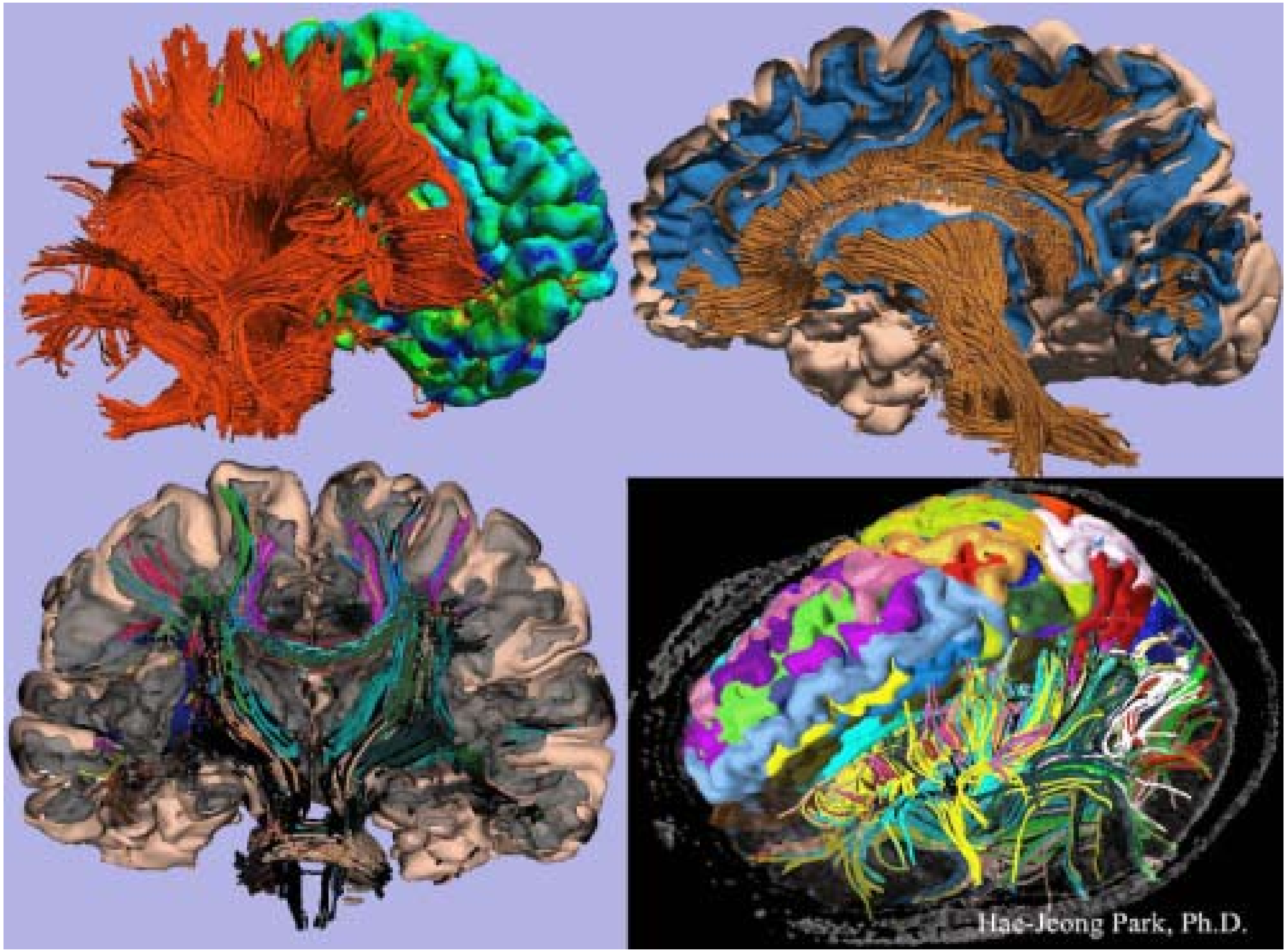
  - Where t(r) is a unit tangent vector to h(r) at r.

- Let $\vec{\lambda}_1$ be the eigenvector associated with the largest eigenvalue at location *r.*
- *Since* $\vec{\lambda}_1$ *is assumed to be parallel to the fiber tracts, then it is equal to the tangent of the 3D space curve* ***h****(r):*

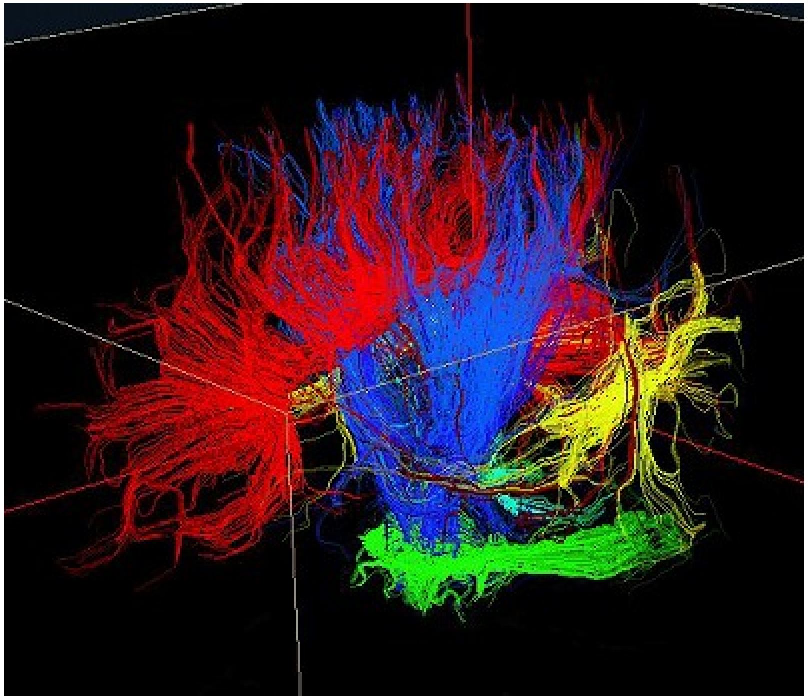
$$\vec{\lambda}_1 = t(r) = \frac{dh(r)}{dr}$$

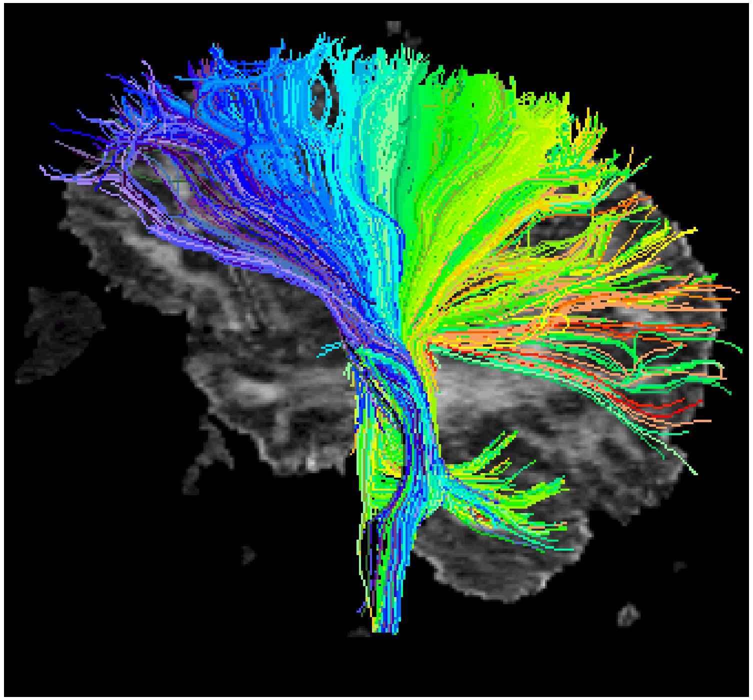
- Solving this equation can be done using iterative methods based on Euler's Method or more robustly Runge-Kutta Method, to interpolate the **h**(r) curve.

- Usually, color mapping is used to represent the tract directions:
    - Red: left-right
    - Green: anterior-posterior
    - Blue: Superior-inferior



Upper left panel displays fiber tractography combined with cortical thickness map obtained with Free Surfer. Upper right panel demonstrates a sagittal cross-sectional view of brain parenchyma segmented into white and gray matter combined with fiber tractography map. Lower left figure shows a coronal cross-sectional view of automatic parcellation of white matter overplayed with the gray matter surface. Lower right figure shows the parcellation of gray matter surface and corresponding white matter fibers.





IV. q-space imaging

- Proposed by D. Cory and N. Garroway (1990) and P. Callaghan (1991).
- It can provide *structural* information on samples with a higher spatial resolution compared to an MR image.
- What is q-space?

- What is k-space?

Fourier transformation of MRI *image* (spin density) in the spatial domain with respect to "k-vector" (1/cm) , defined as :

$$\vec{k}(t) = \frac{\gamma}{2\pi}\int_{o}^{t} \vec{G}_d(t')dt'$$

Yielding the Echo Intensity S(k)

- What is q-space?

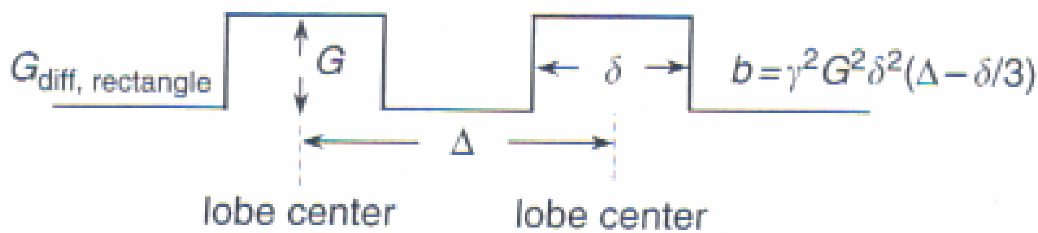
Fourier transformation of the the Diplacement Probability Profile, $P_s(R,\Delta)$, with respect to "reciprocal spatial vector," q (1/cm), defined as:

$$q = \frac{\gamma}{2\pi}\delta G_d$$

Yielding the Echo Intensity S(q)

• The Stejskal's equation, with a rectangular pulse,

$$S / S_0 = \exp(-bD) = \exp[-\gamma^2 g^2 \delta^2 (\Delta - \delta / 3) D]$$



•Using the definition of q,

$$q = \frac{\gamma}{2\pi} \delta G_d$$

We get:

$$S(q) / S_0 = \exp[-4\pi^2 q^2 D(\Delta - \delta / 3)]$$

- Taking the FFT of the previous equation, we will get the *Displacement Probability profile:*

$$F(\mathrm{r}) = FT\{S(\mathrm{q})\} = \alpha.exp(-\beta.r^2)$$

r is the Fourier conjugate of *q*

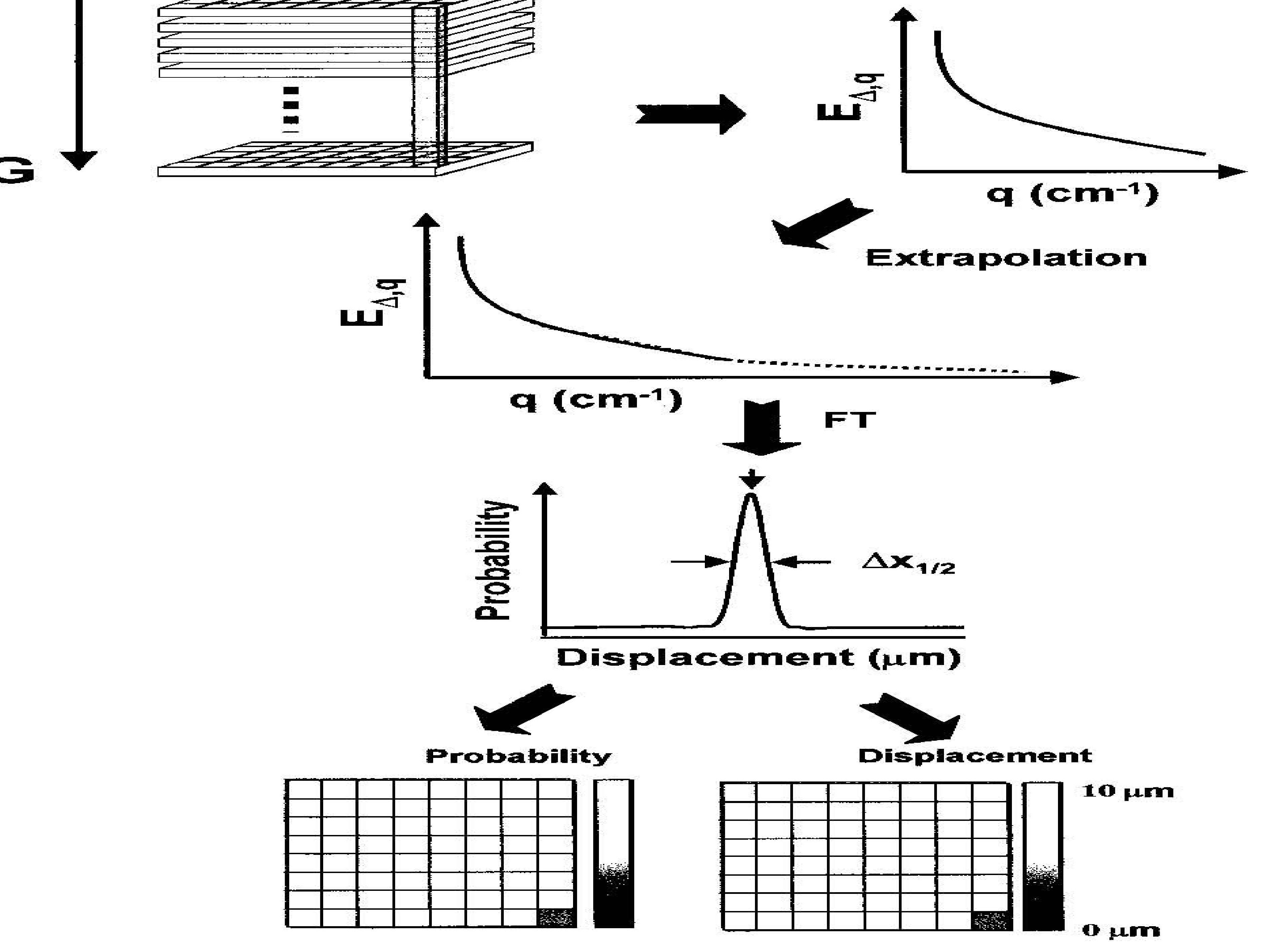
α and ß are diffusion dependent parameters

The displacement probability profile is a Gaussian profile.

How to conduct a *q*-space experiment?

- Acquire a set of DW images (16 for example), with increasing the gradient amplitude. The applied gradients must be in the same direction.
- For the diffusion weighting gradient: Short pulse gradient approximation (or Long time scale limit) should be met.

$$\boldsymbol{\delta \ll \Delta}$$

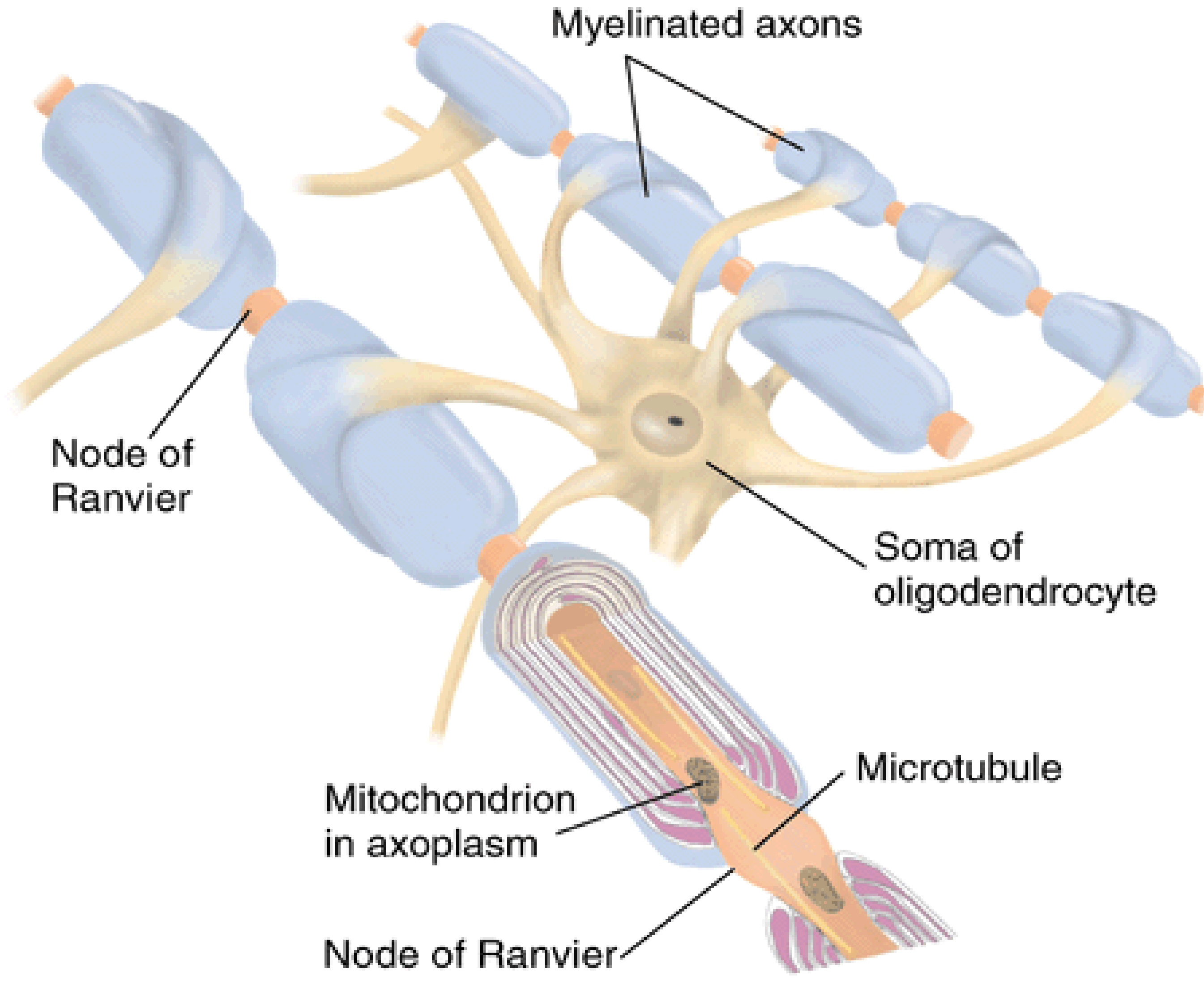

G
$E_{\Delta,q}$
q (cm^{-1})
Extrapolation
$E_{\Delta,q}$
q (cm^{-1})
FT
Probability
$\Delta x_{1/2}$
Displacement (μm)
Probability
Displacement
10 μm
0 μm

Paper Discussion

High b-value q-space analyzed diffusion-weighted MRI: Application to multiple sclerosis

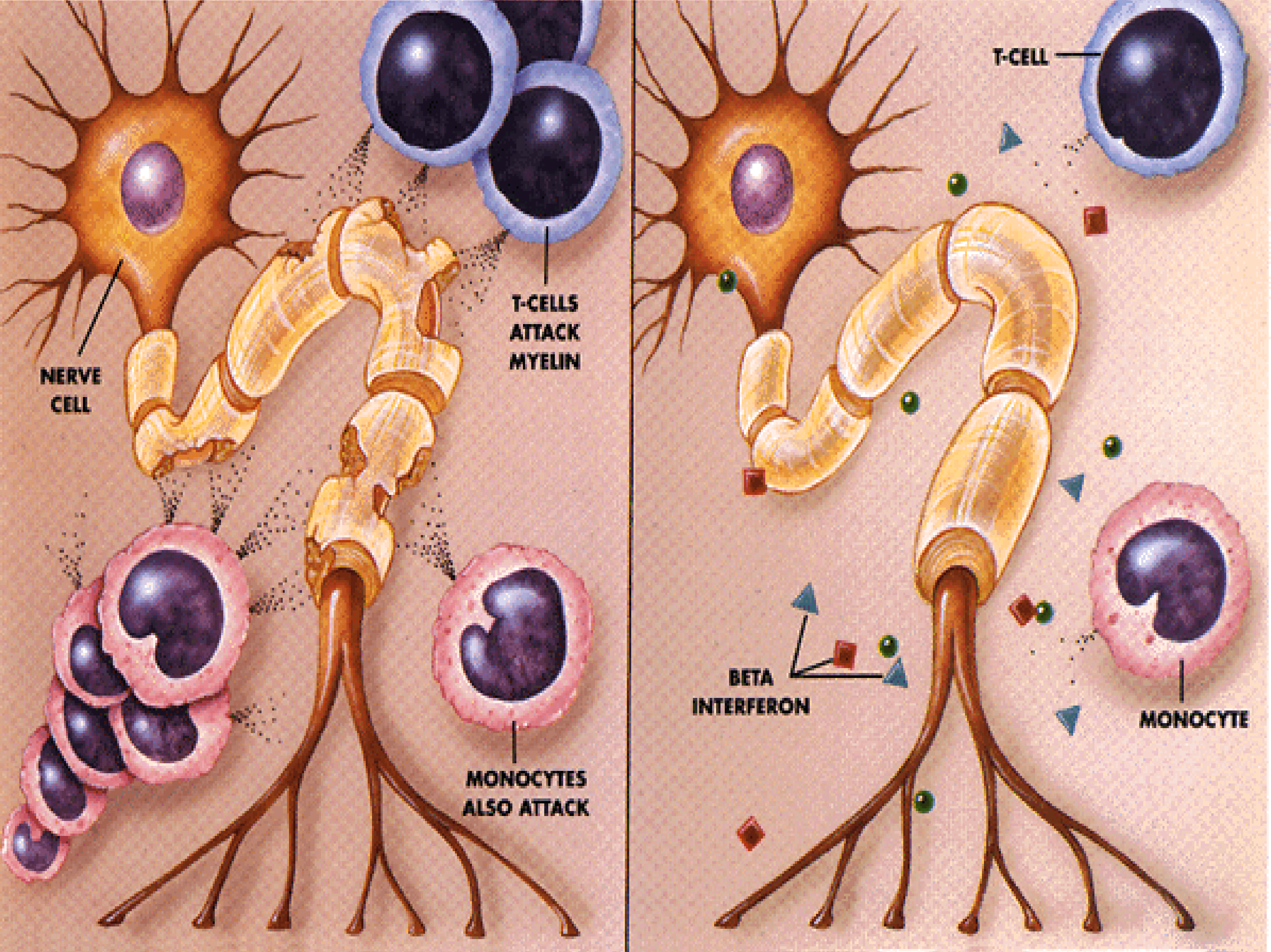
- By: Y. Assaf, et al 2002.
- Magnetic Resonance in Medicine 47:115-126, Wiley-Liss, Inc.

► An Oligodendrocyte



Multiple Sclerosis (MS)

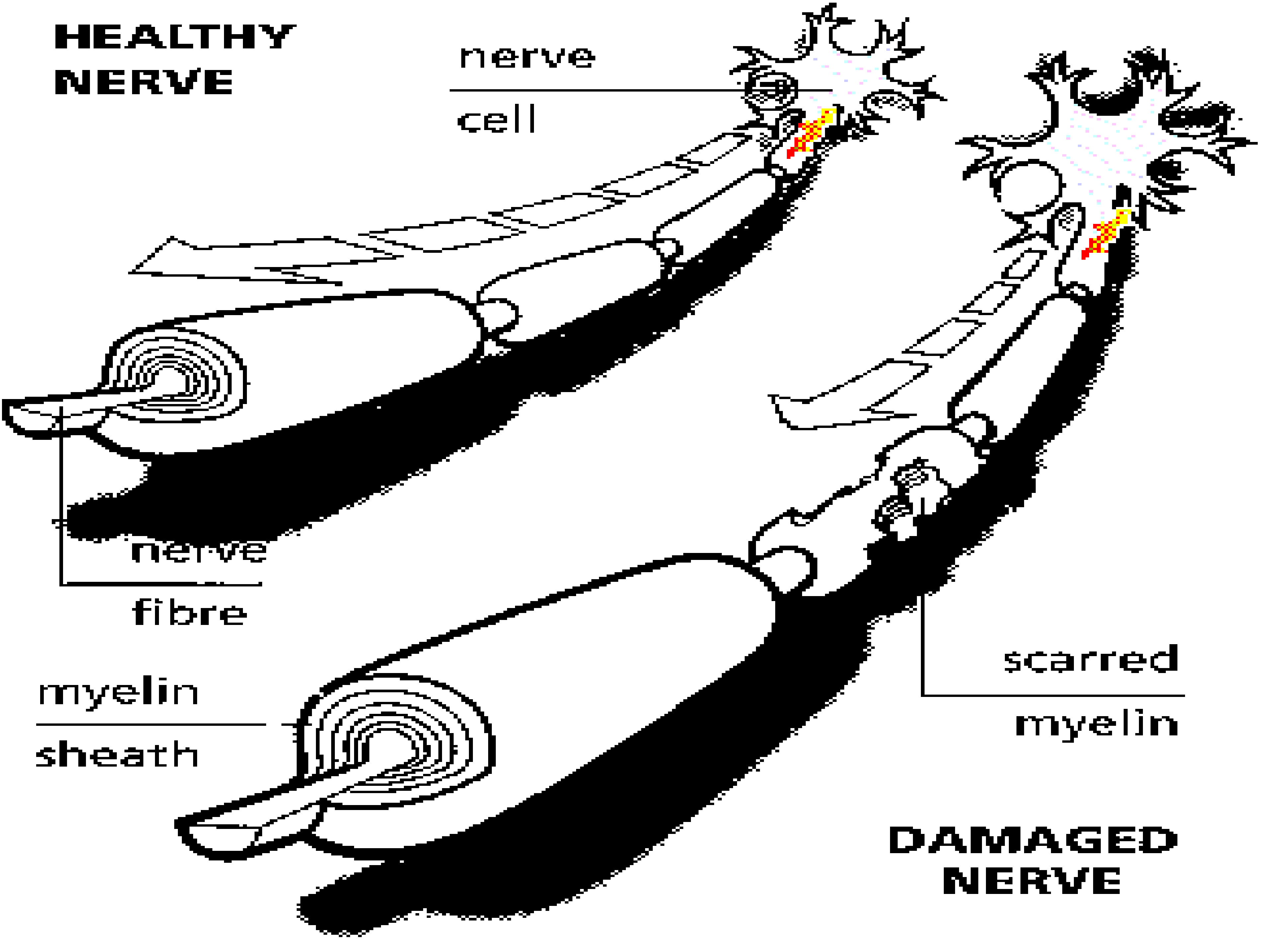
- MS is an autoimmune-mediated disease of the Central Nervous System (CNS) characterized by:
  - 1. Demyelination of axons
  - 2. Focal inflammatory reactions in the MS lesions



NERVE CELL
T-CELLS ATTACK MYELIN
MONOCYTES ALSO ATTACK
T-CELL
BETA INTERFERON
MONOCYTE

Consequences of destroying the Myelin Sheath:

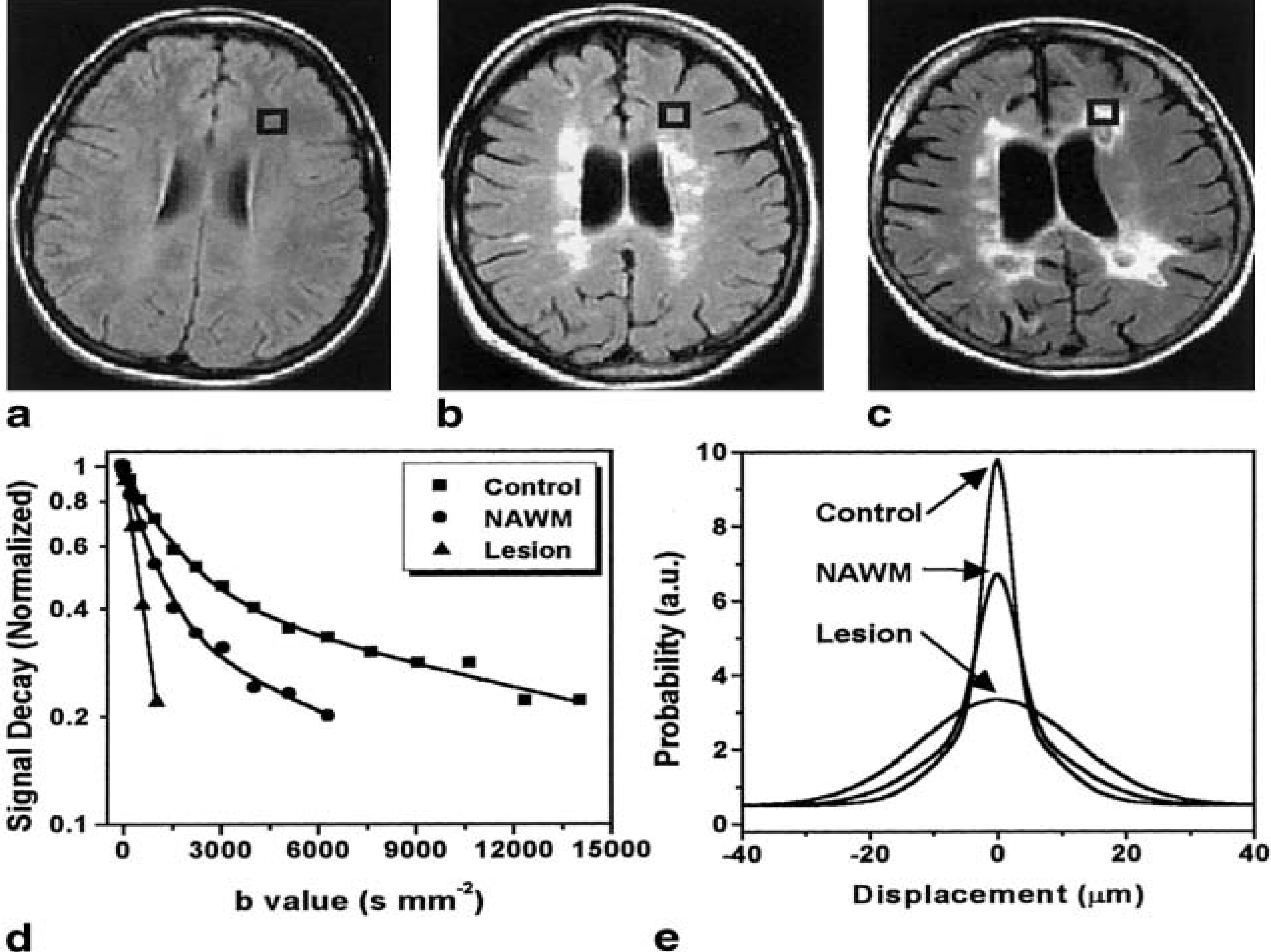
- Progressive decline of motor and sensory functions.
- Permanent disability.

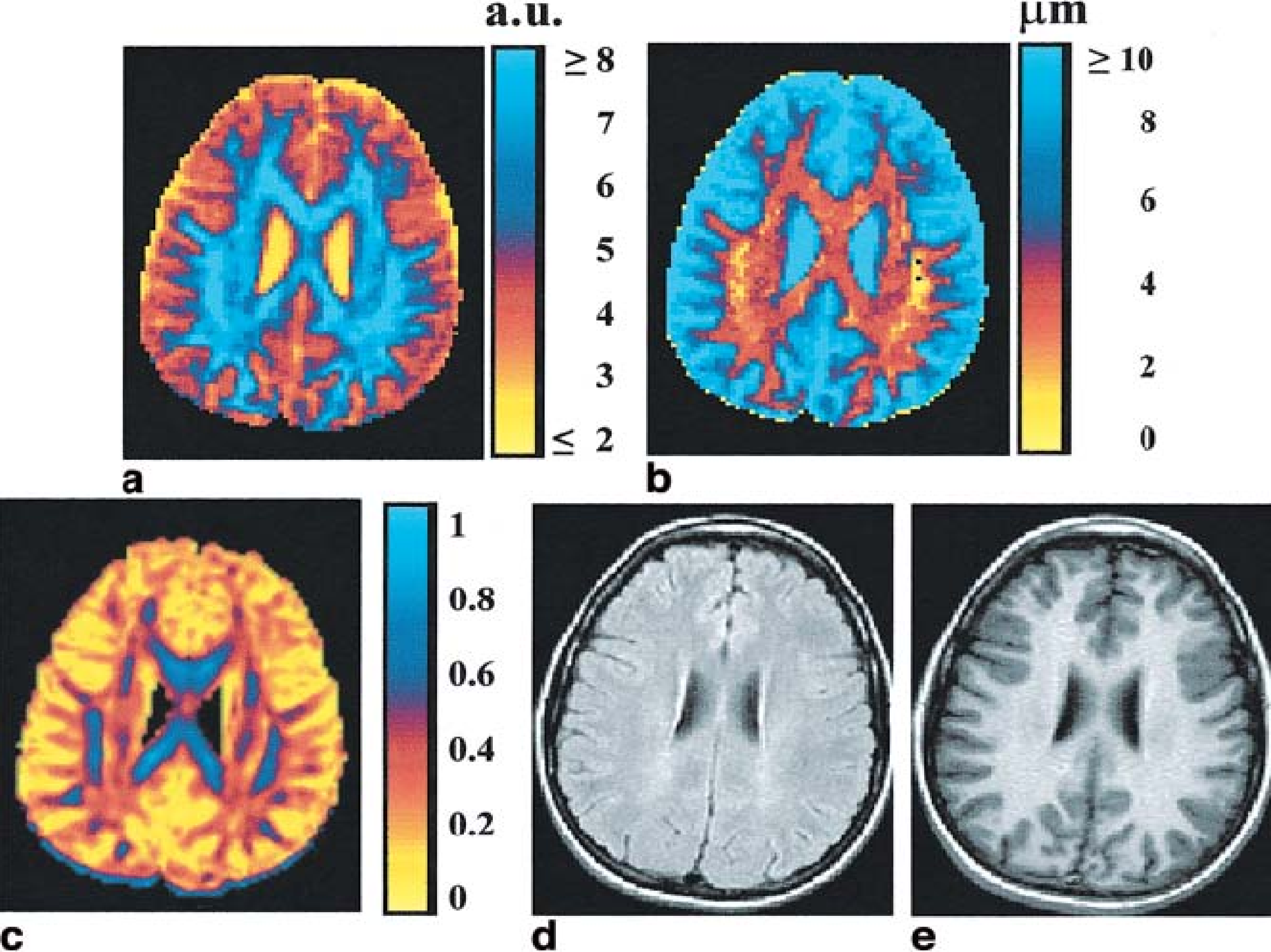

HEALTHY NERVE
nerve cell
nerve fibre
myelin sheath
scarred myelin
DAMAGED NERVE

Imaging modalities that supports the clinical diagnosis of MS:

- MRI:
  - T_1-IR weighted MRI.
  - T_2 Fluid-Attenuated Inversion Recovery (FLAIR).
  - Diffusion Tensor Imaging (DTI).
- Problems: Normal Appearing White Matter (NAWM). New imaging technique is needed.

MS and q-space


a
b
c
Signal Decay (Normalized)
1
0.8
0.6
0.4
0.2
0.1
0
3000
6000
9000
12000
15000
b value (s mm^{-2})
Control
NAWM
Lesion
d
Probability (a.u.)
10
8
6
4
2
0
-40
-20
0
20
40
Displacement (μm)
Control
NAWM
Lesion
e


a.u.
≥ 8
7
6
5
4
3
≤ 2
a
μm
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c
d
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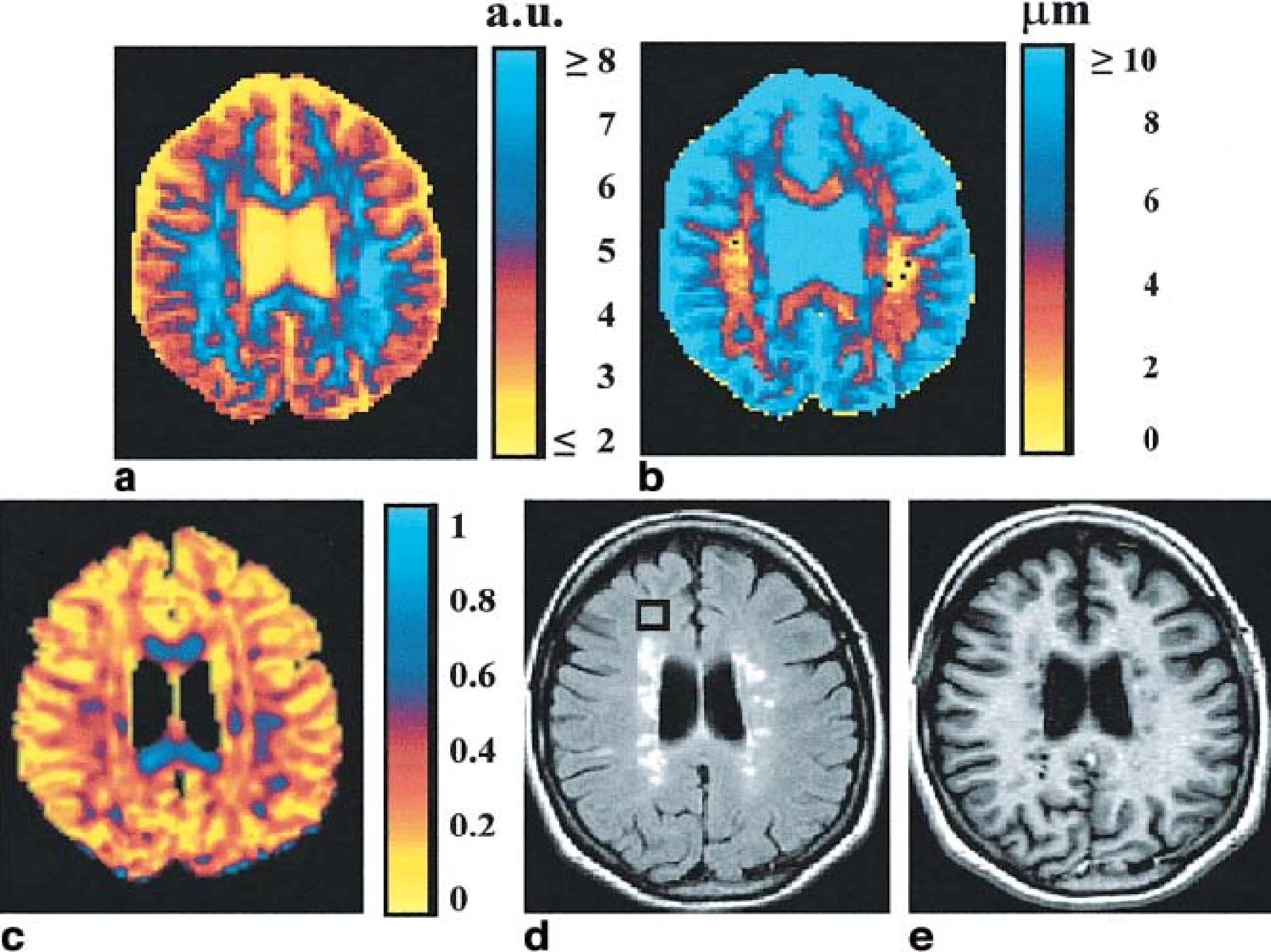

a.u.
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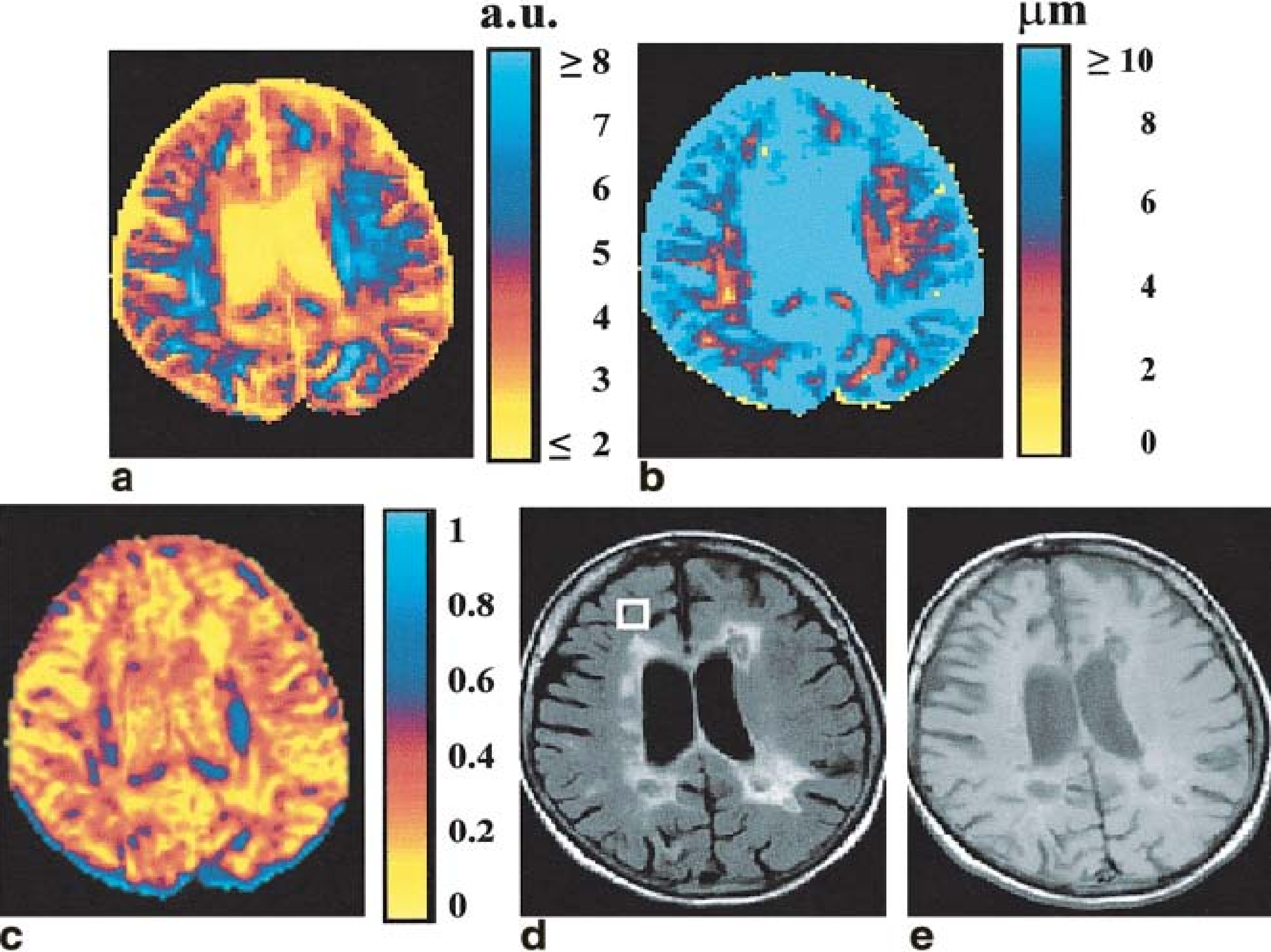

a.u.
≥ 8
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0
c
d
e

Conclusion

- The *q*-space analysis provides images displaying widespread disease load which provide evidence of abnormalities in the NAWM of MS patients that are not detected by FLAIR, T1, or even conventional DTI.

References

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