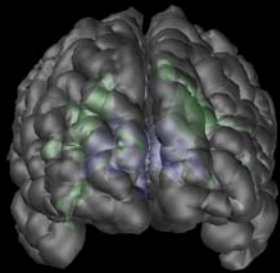


# The use of MRI to measure degeneration and progression: Lessons learned from MS



Douglas Arnold MD  
Neuro*Rx* Research

# Three lessons

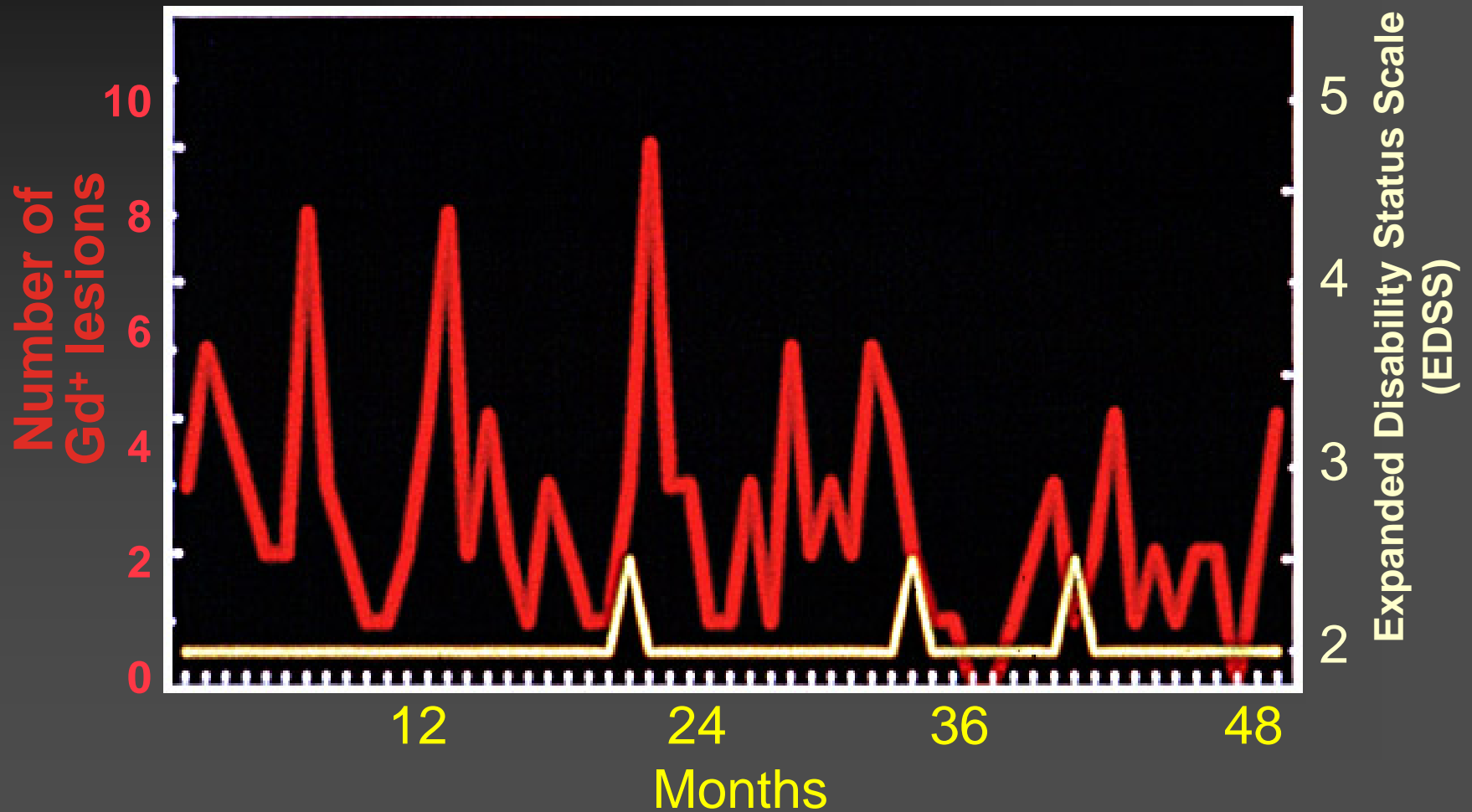
1. MRI shows the pathology of the disease  
Some of which will be new(s)
2. MRI may dissociate from the clinical  
May challenge concepts of pathogenesis
3. MRI will be predictive

MS: Focal white matter inflammatory lesions occur much more frequently than clinical relapses

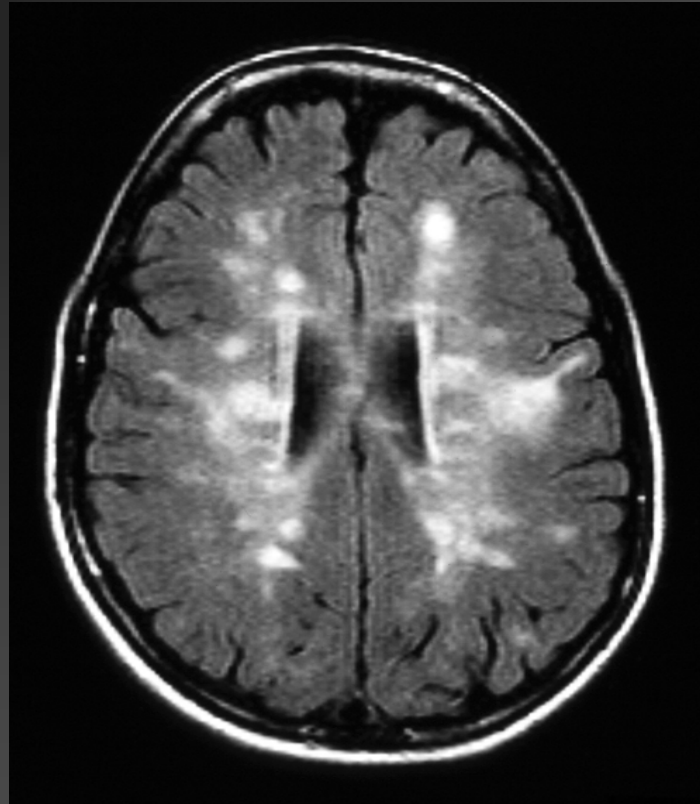
QuickTime™ and a decompressor are needed to see this picture.

Gd-Enhanced MRI

# Gd<sup>+</sup> Lesion Frequency vs Relapse



Sub / pre-clinical disease accumulates



Optic neuritis

# Links to AD

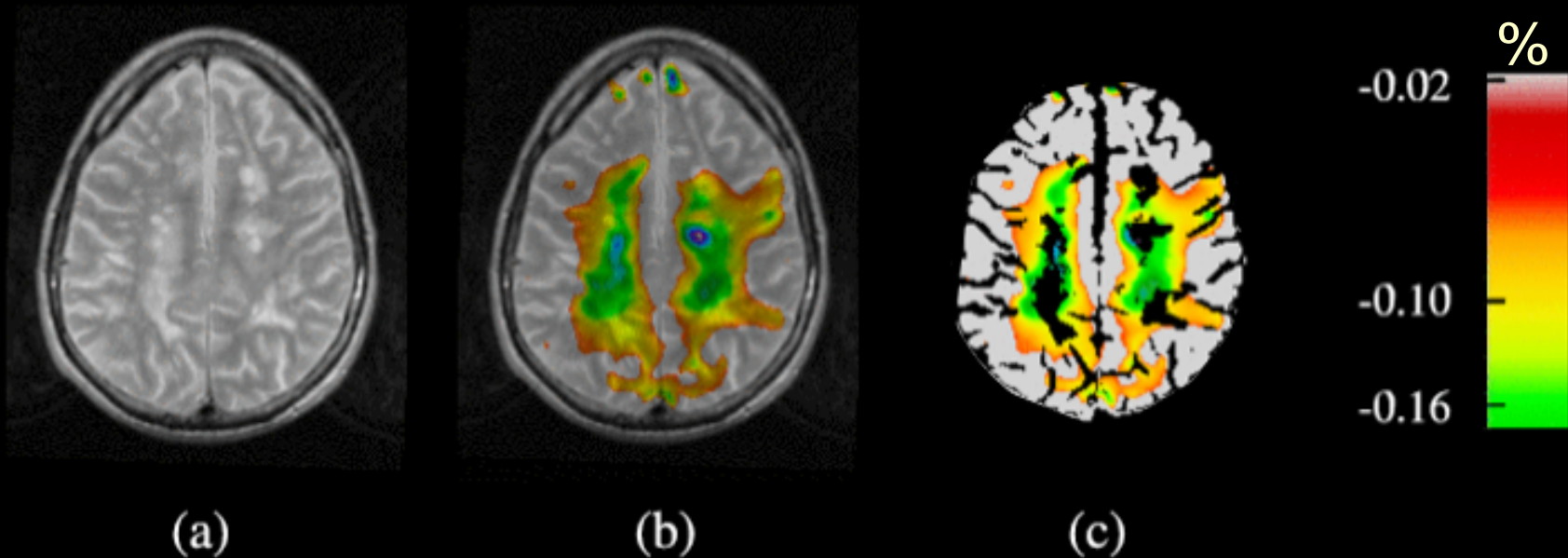
- MRI can provide markers that are more sensitive to disease than clinical markers
- Pre-clinical disease
- More responsive to early Rx

# MS lesions can dissociate from the clinical:

- Are we looking at the right thing?



# Atrophy is greater near lesions, but is not due solely to lesions

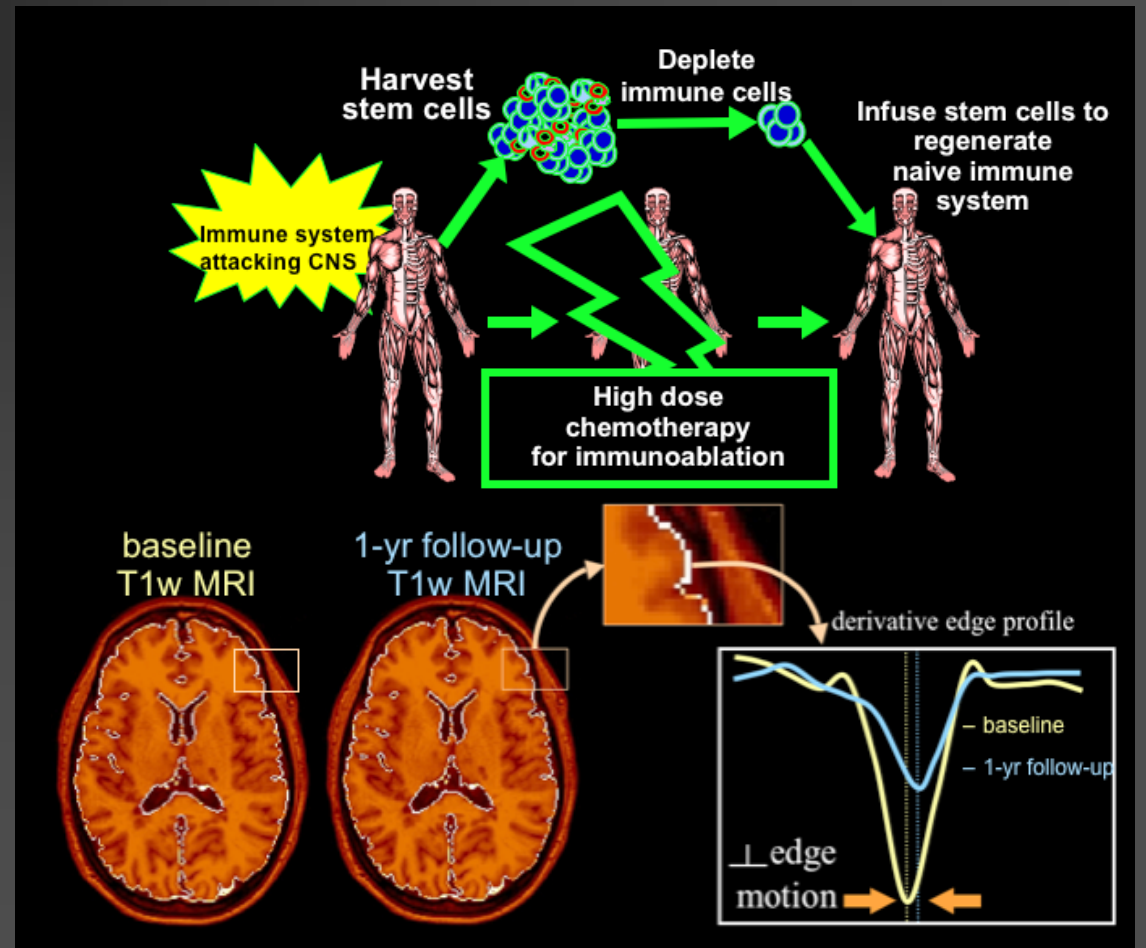


There is a degenerative component to MS that involves normal-appearing brain tissue

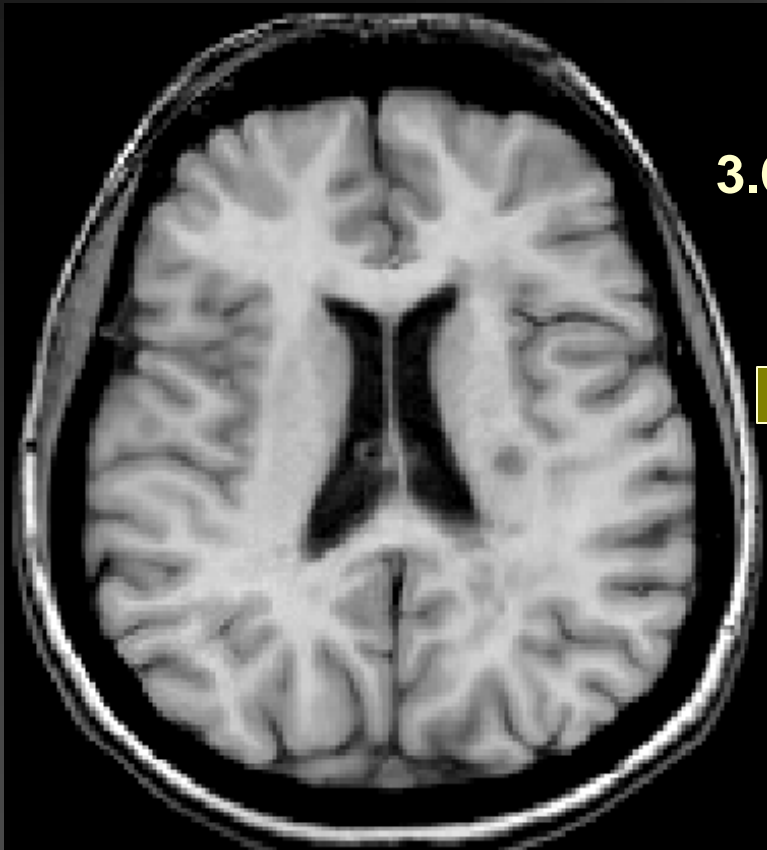
MRI can be used to  
understand pathogenesis

# Treating MS with immunoablation & autologous stem cell transplantation

Longitudinal measurement of brain atrophy:

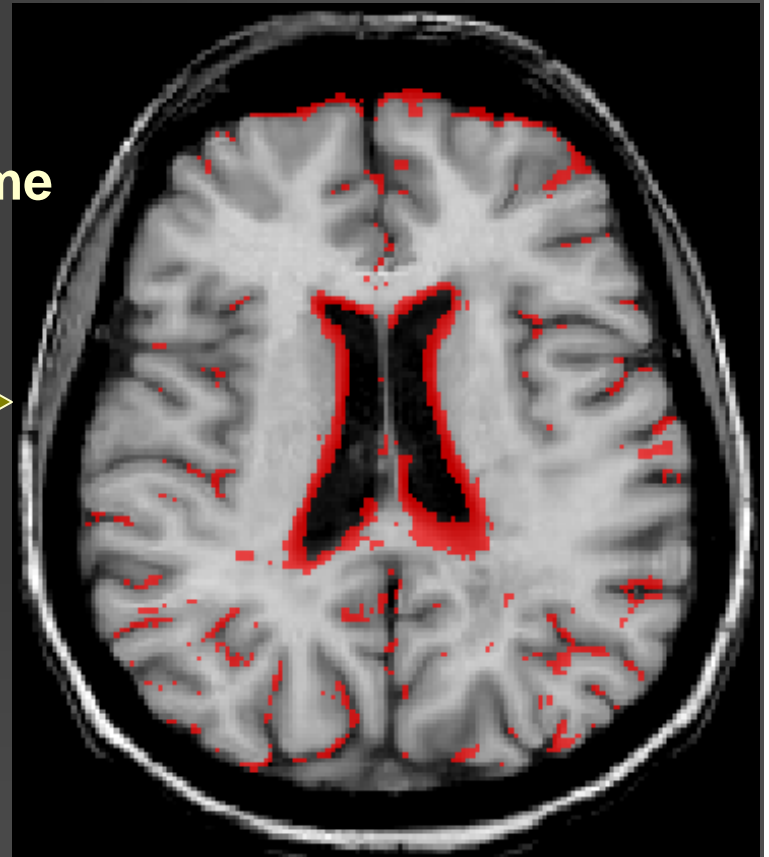


# Brain volume loss after immunoablation & AHSCCT



baseline

3.6 % brain volume  
loss over 6 mo



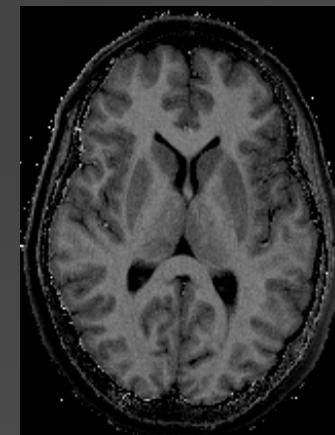
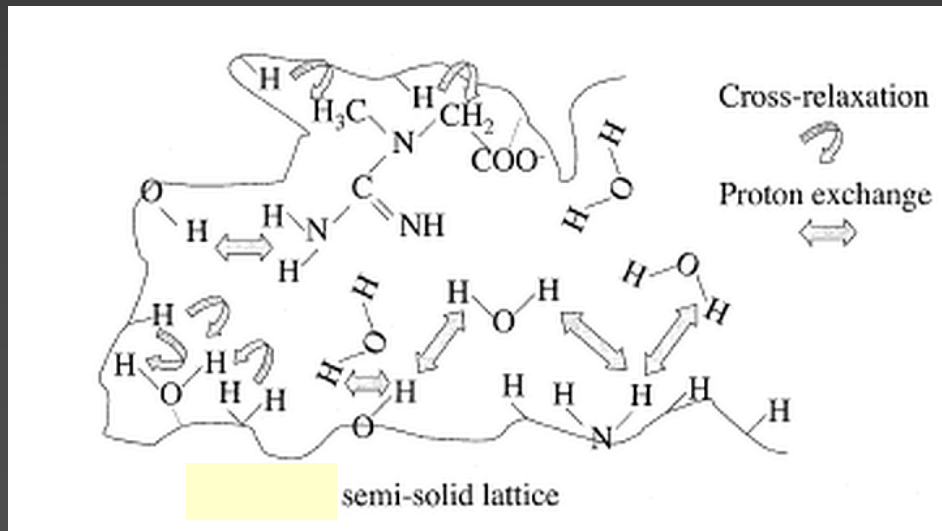
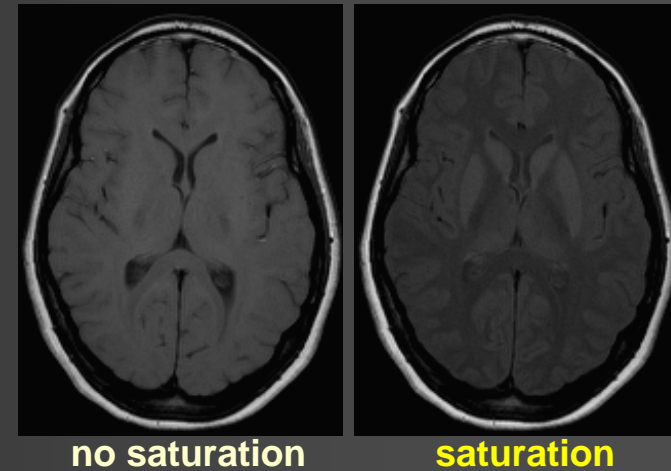
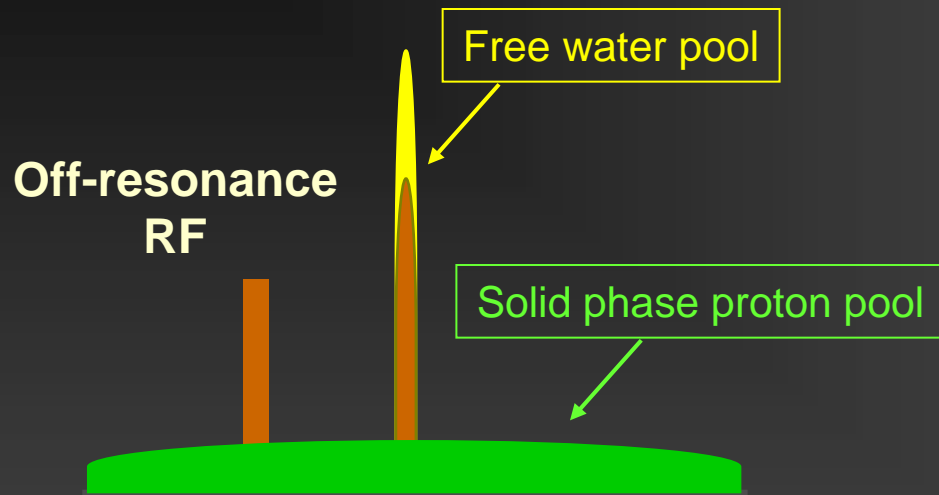
1 mo after therapy

# Atrophy or Pseudoatrophy?

Is the loss of brain volume due to resolution of inflammatory edema or therapy-related tissue injury?

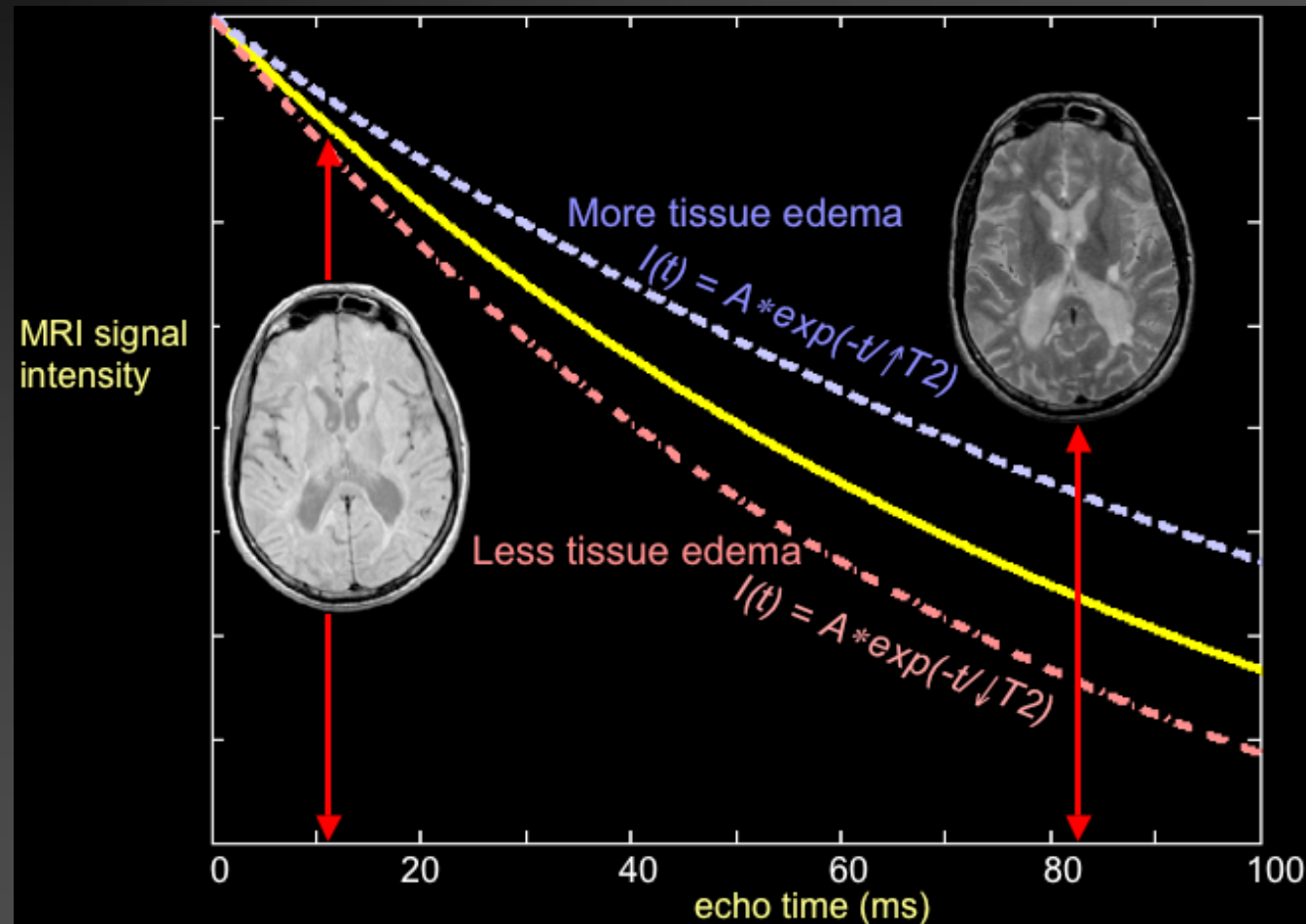
- Non-conventional MRI can provide increased pathological specificity
  - Examples
    - MTR
      - myelin content / tissue integrity / remyelination
    - T2 relaxation time
      - Water content
    - MRS
      - Neuro-axonal integrity

# Magnetization transfer as a marker of myelin content



$$MTR = 100 \times \frac{\text{No Sat} - \text{Sat}}{\text{No Sat}}$$

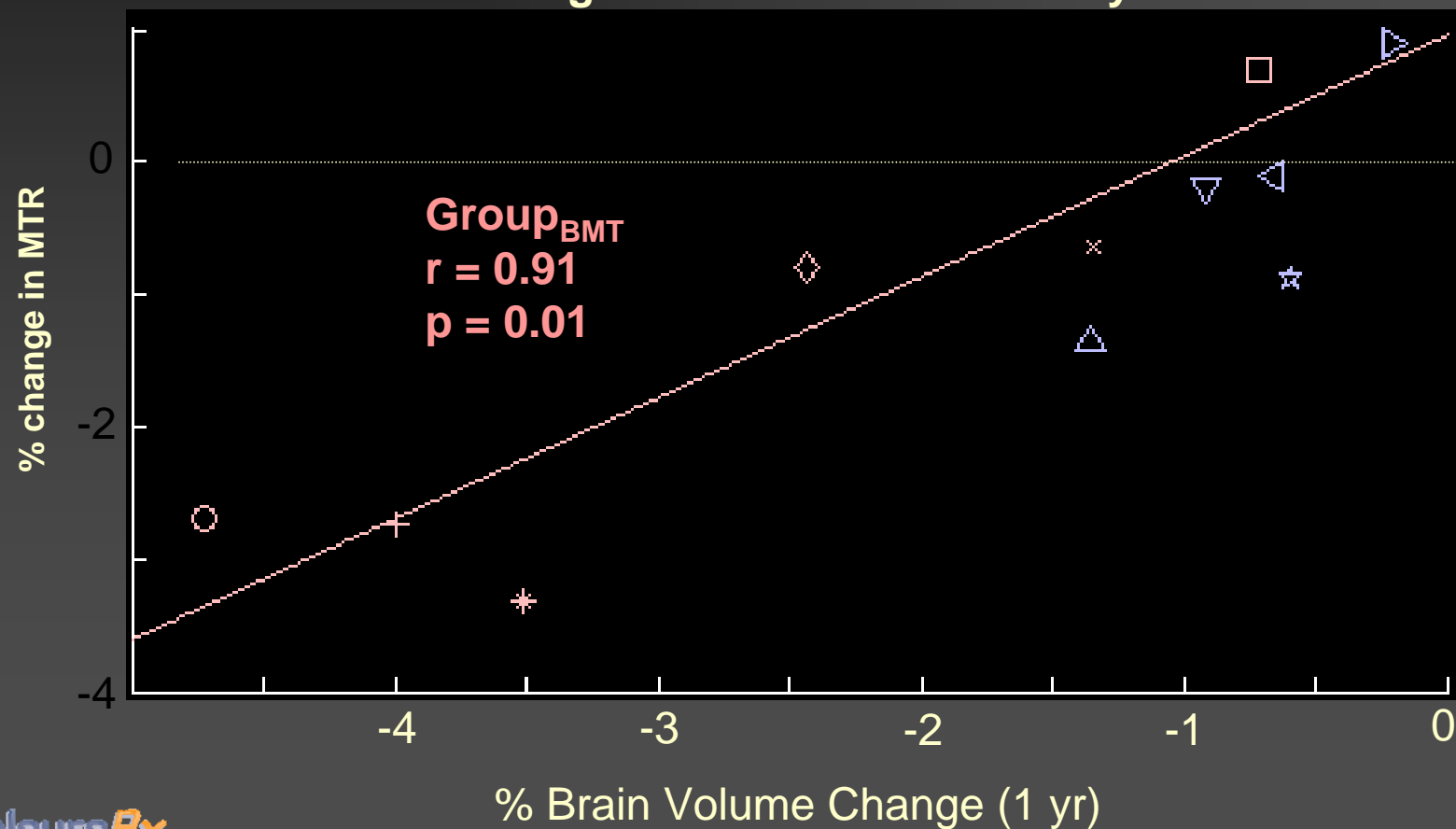
# T2 relaxation time change as a marker of brain water content



Measurement of change in  
parenchymal edema:

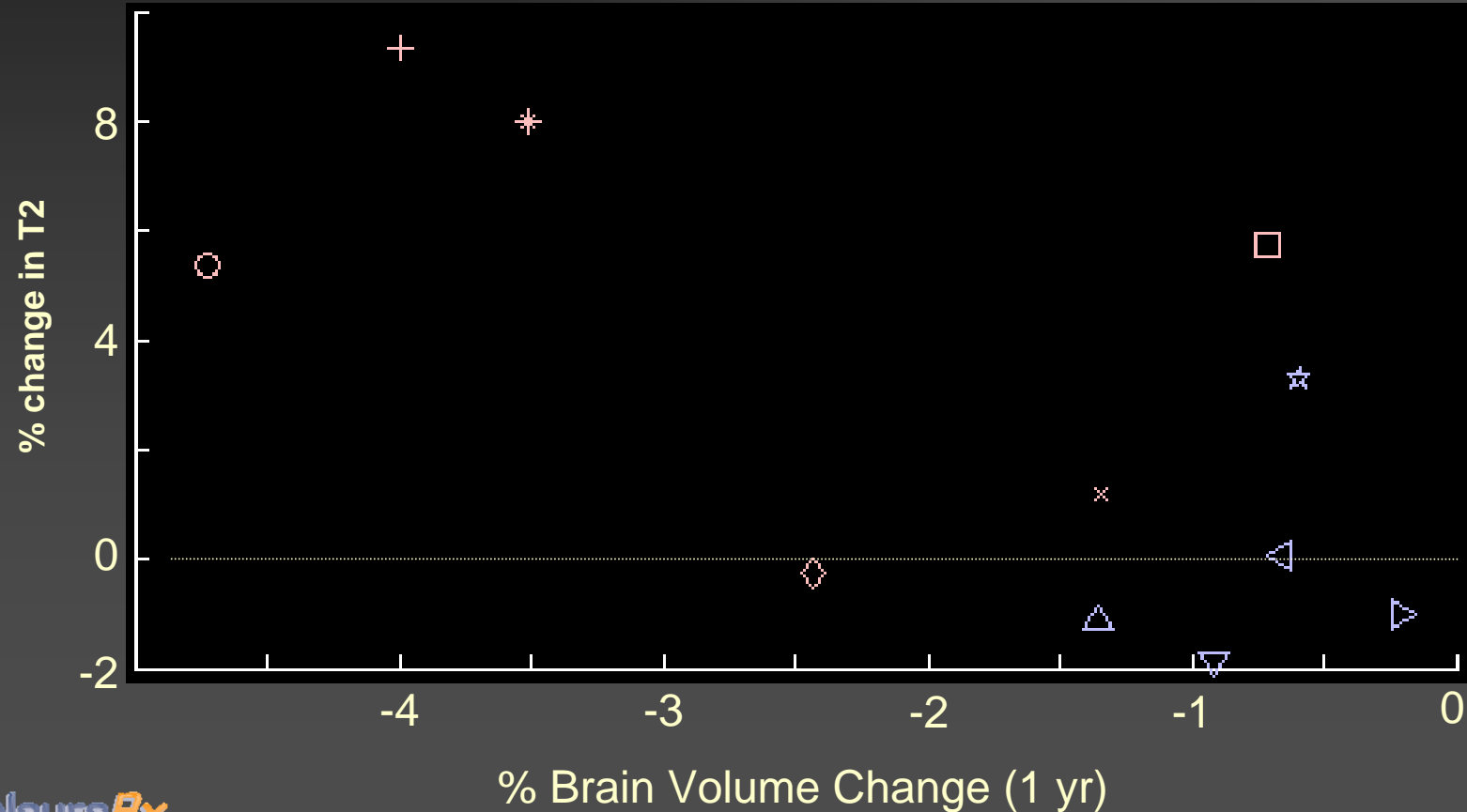
# ↑ atrophy after therapy *is* associated with ↓ MTR

% change in median brain MTR over 1yr  
versus  
% change in brain volume over 1yr



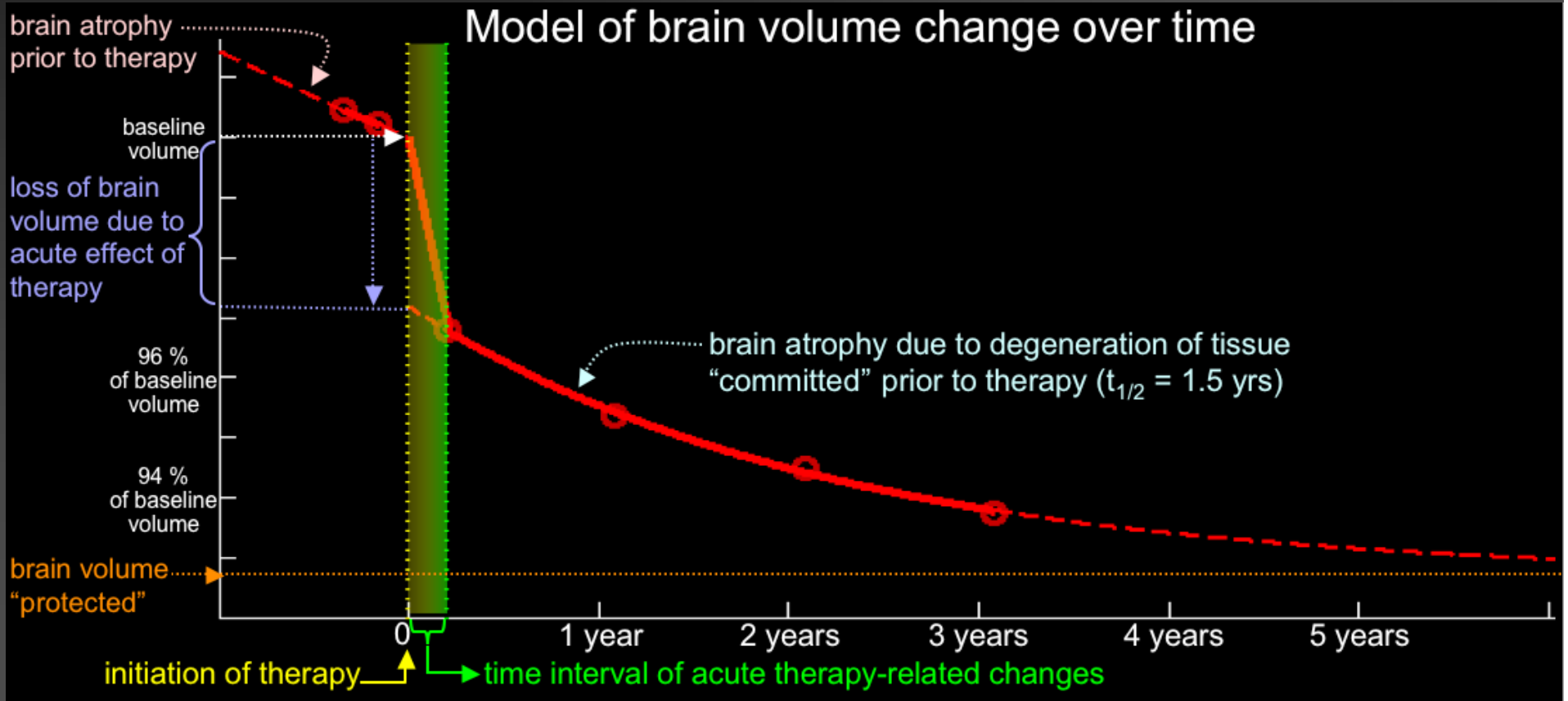
# ↑ atrophy after therapy is *not* associated with ↓ T2

% change in whole-brain T2 over 1 yr  
versus  
% change in brain volume over 1 yr

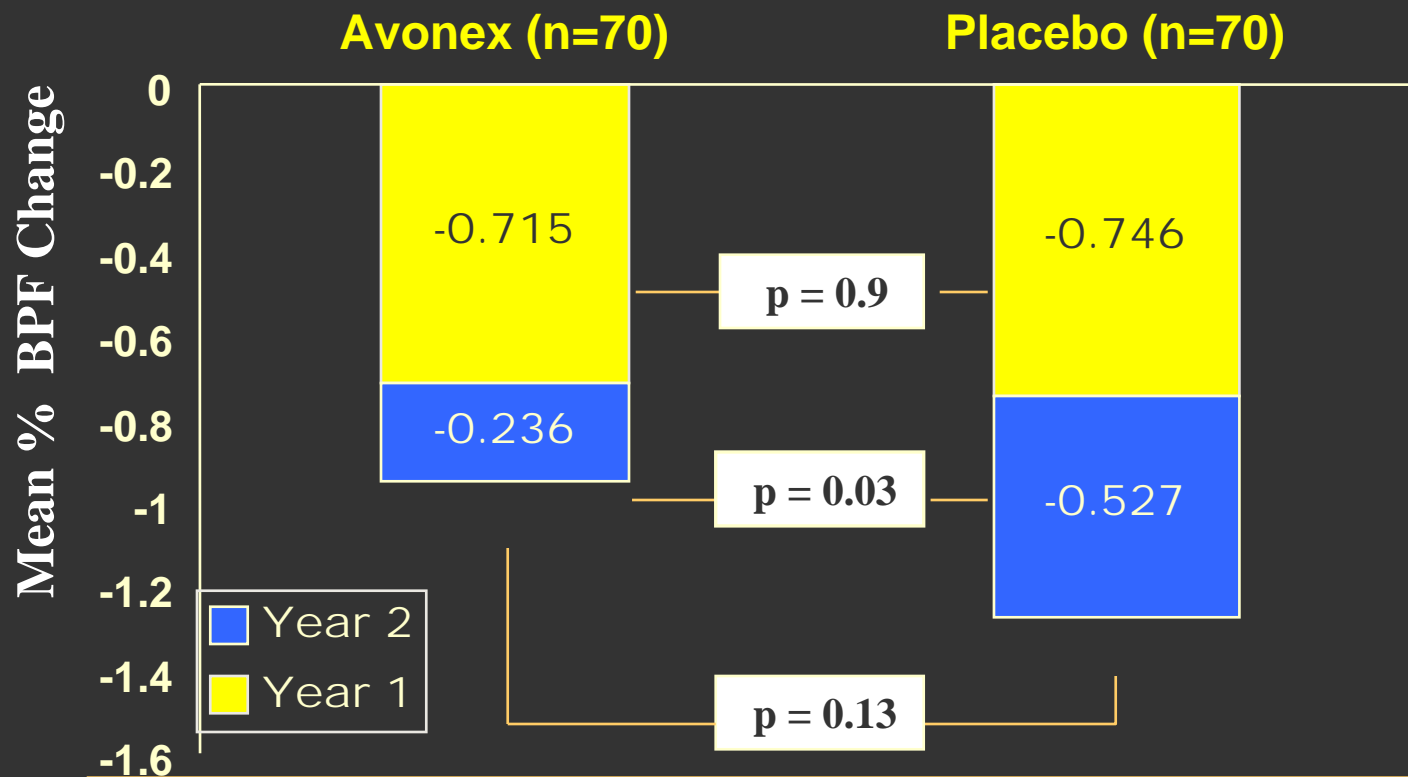


Accelerated brain atrophy after  
Chemotherapy is associated with  
a *loss of tissue* (not water)

# Model of brain atrophy after immunoablation & AHSCCT



# IFN $\beta$ -1a IM Reduced Brain Atrophy By 55% In Year 2



Covariate (Baseline) Adjusted p-Values For Avonex Effect:  
Change 2 Yrs (p = 0.09); Change Yr 1 (p = 0.71); Change Yr 2 (p = 0.011)

# Links to AD

- MRI can inform on mechanisms of disease pathogenesis
  - E.g. what is responsible for changes in brain volume

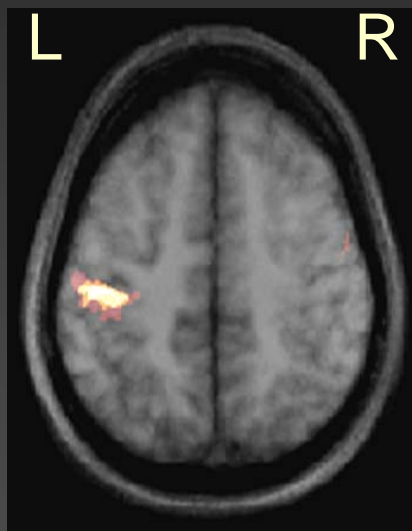
# Three lessons

1. MRI shows the pathology of the disease  
Some of which will be new(s)
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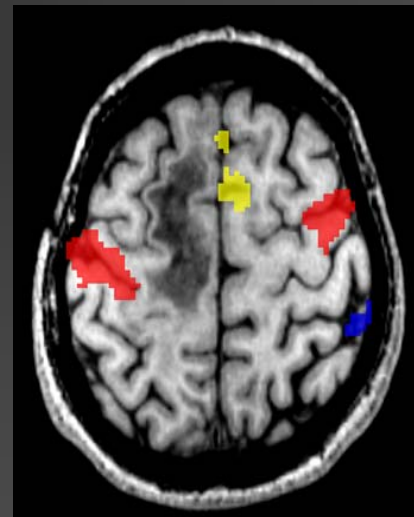
# Cerebral re-organization compensates for axonal injury

weakens association of MRI pathology and clinical expression

fMRI: R-hand motor task



Average Control  
Activation  
(Standard space)



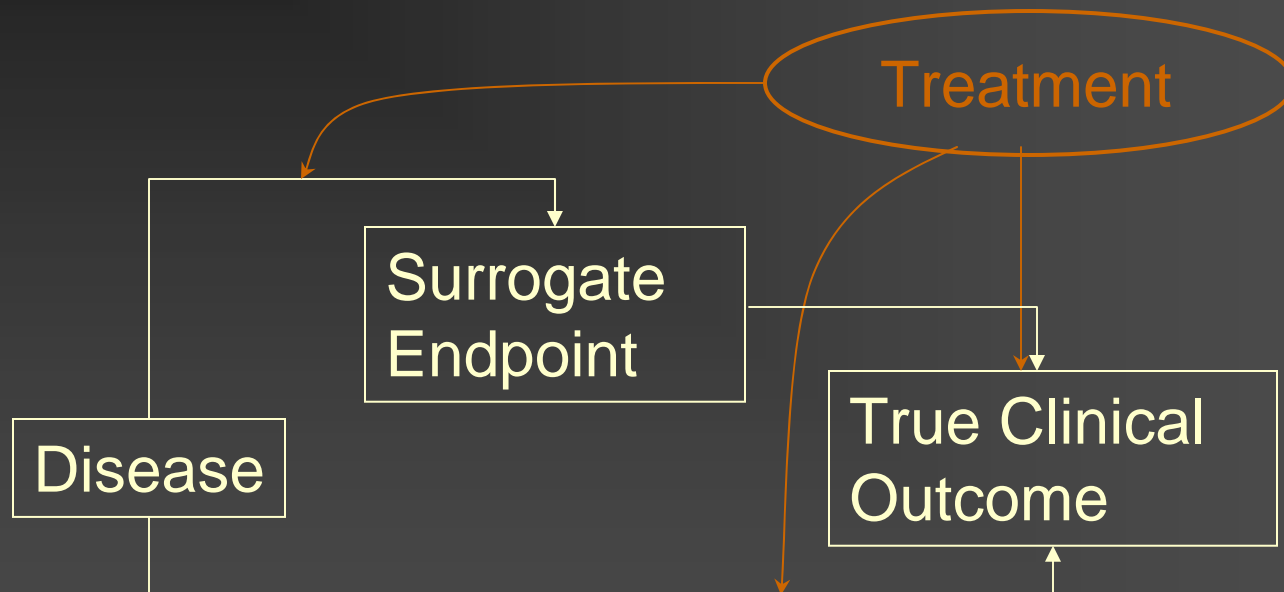
Patient at  
2 Weeks

- Motor
- SMA
- Other

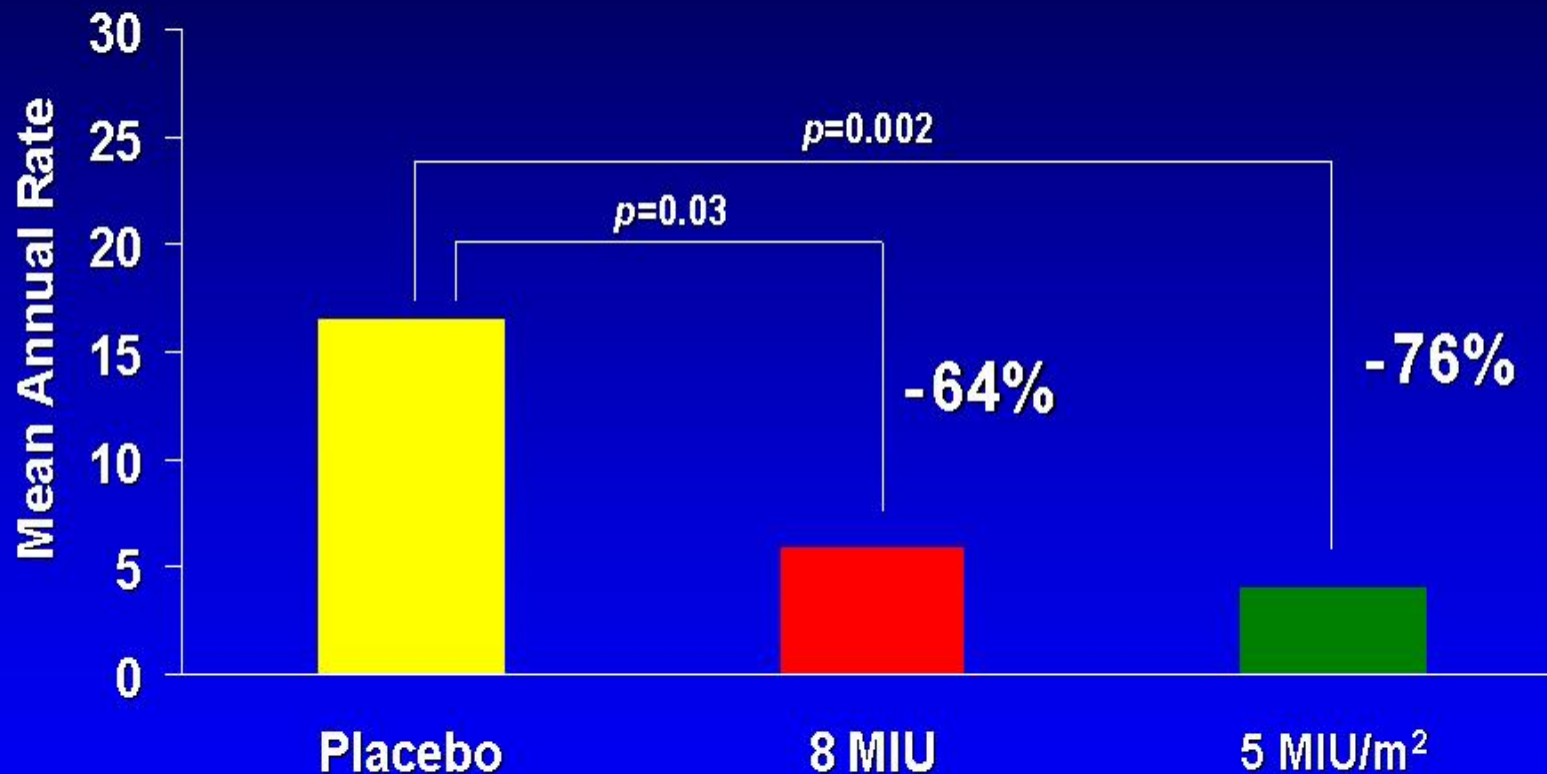
After Reddy et al., Neurology 2000

# Disease mechanisms may not be what you think

Disease or treatment may act through **other pathways**



# North American SPMS Betaseron Trial: Newly Enhancing Lesions\*

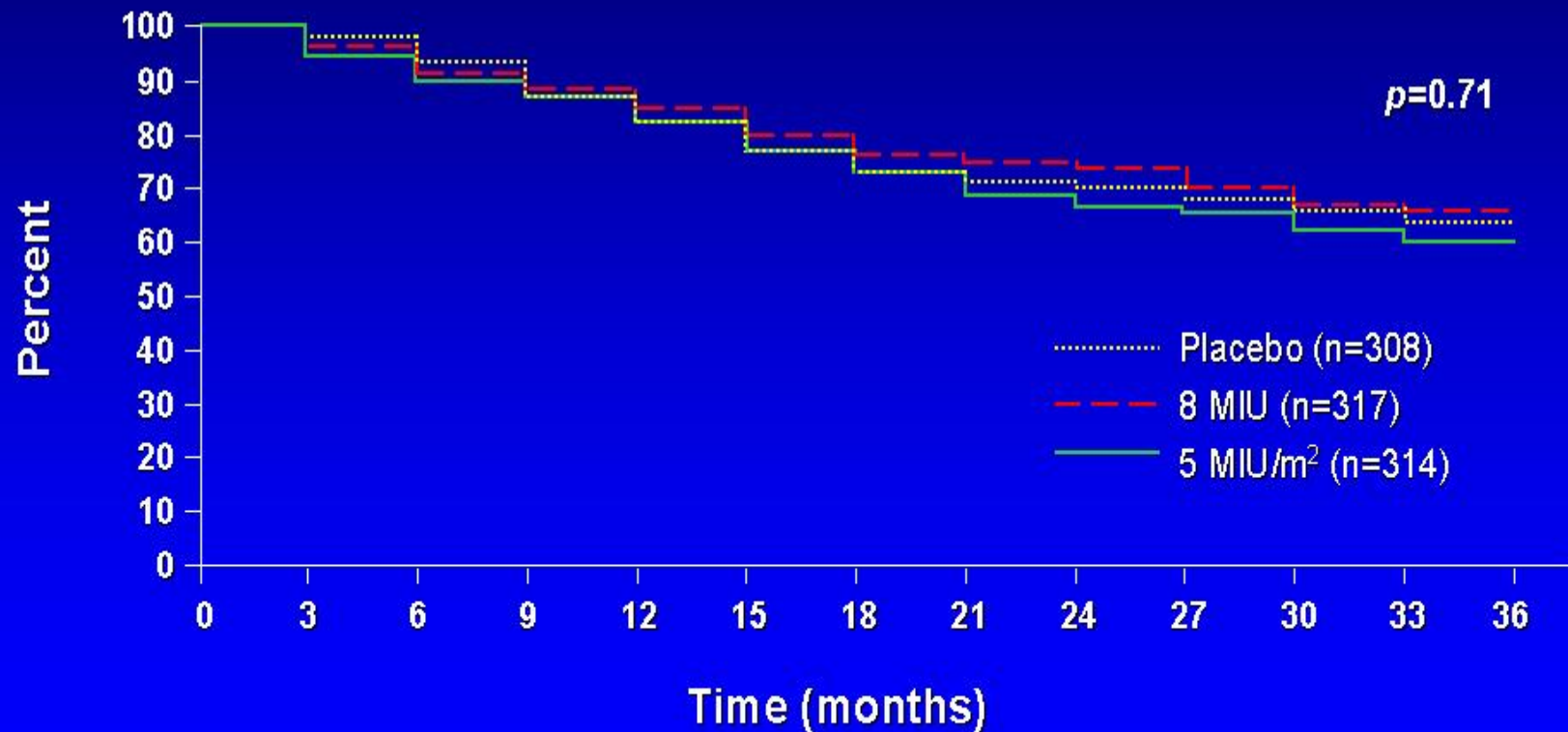


\*Count of all lesions that are enhanced on the current T1 scan and are not classified newly enhancing in the previous T1 scan.

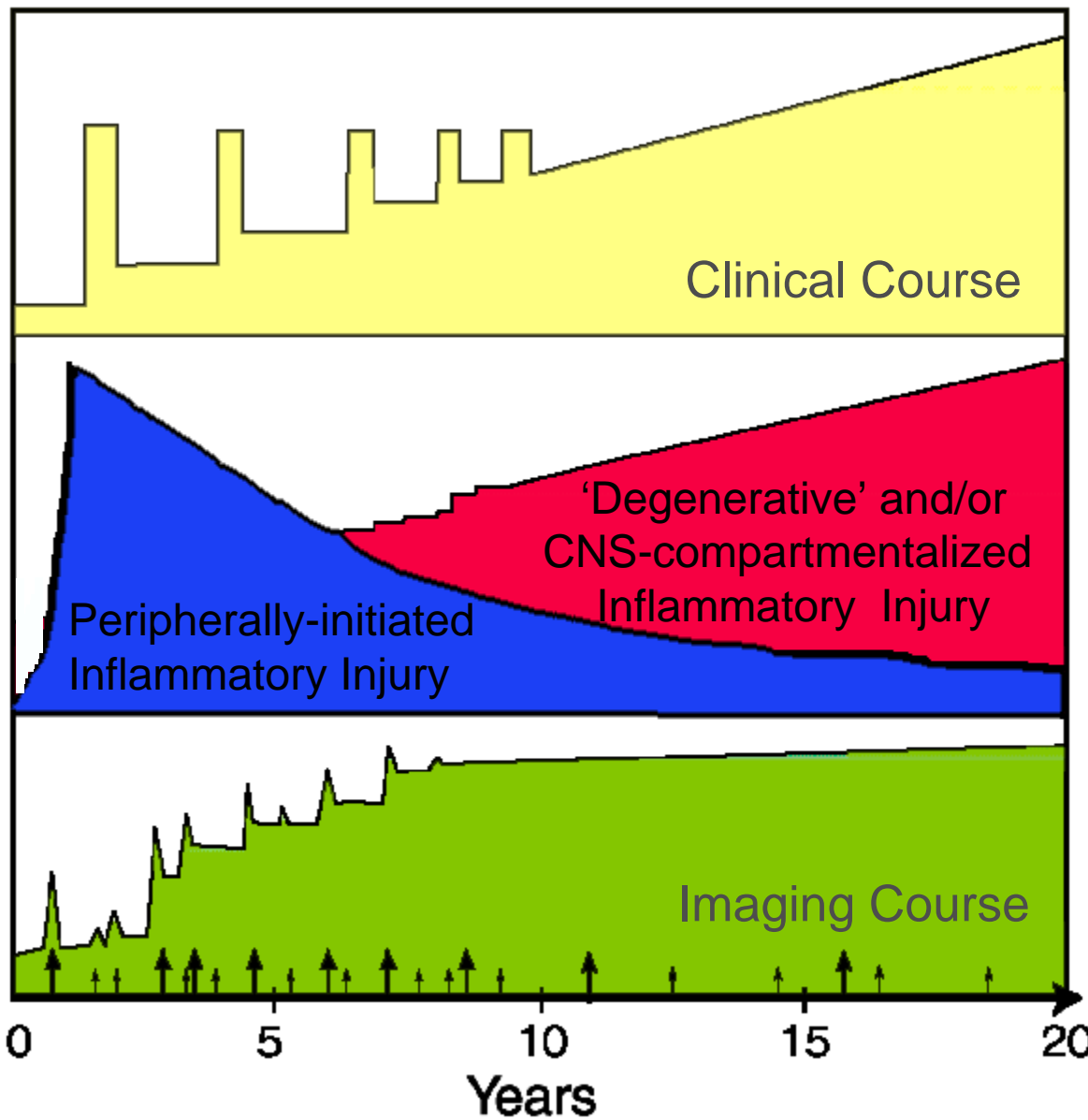
Goodkin et al. Annual Meeting of the American Academy of Neurology. 2000.

# North American SPMS Betaseron Trial: Disability Progression

## Time to Confirmed Disability Progression



Goodkin et al. Annual Meeting of the American Academy of Neurology. 2000.



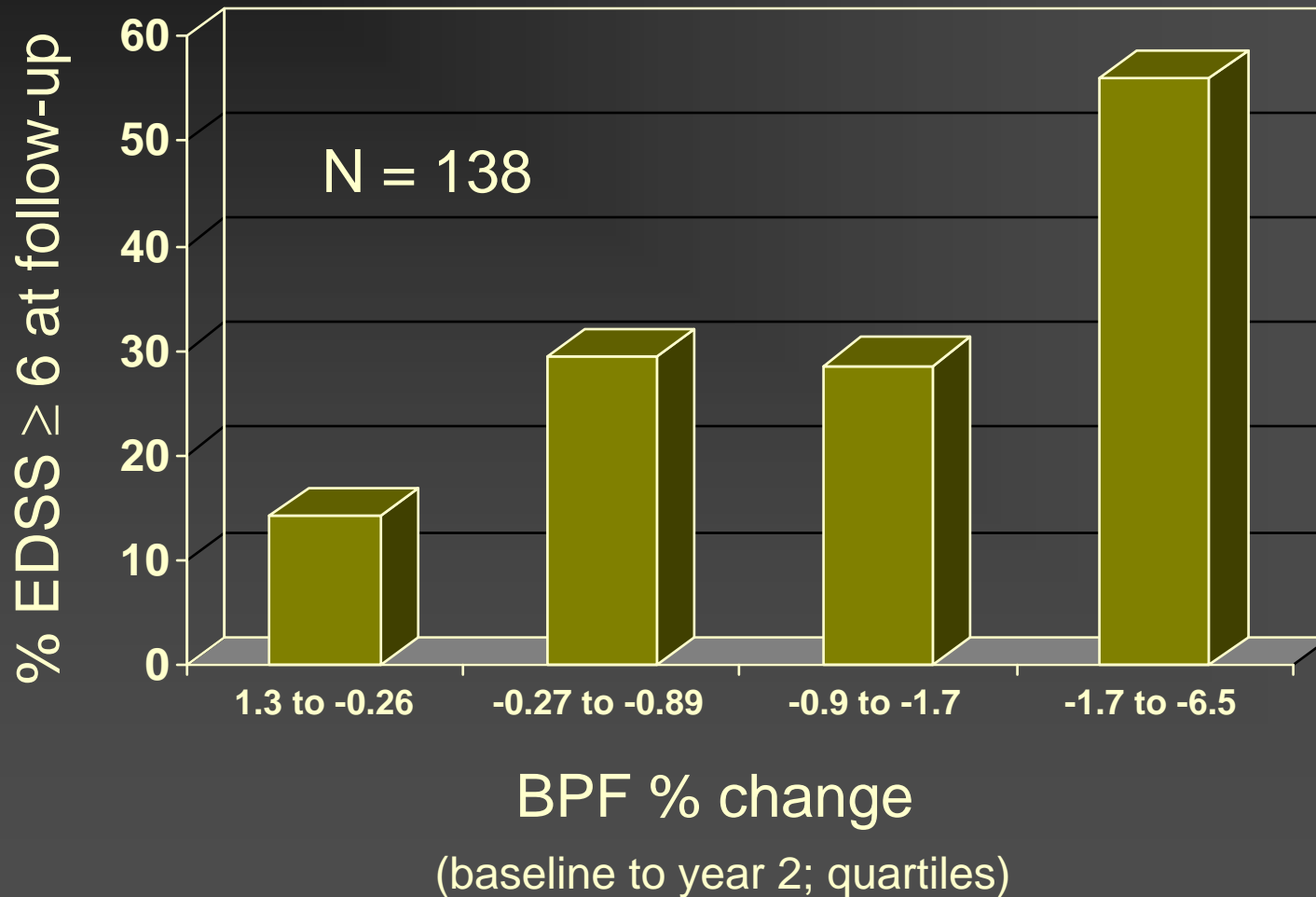
# Links to AD

- Mechanisms are not always those you thought you knew

# Three lessons

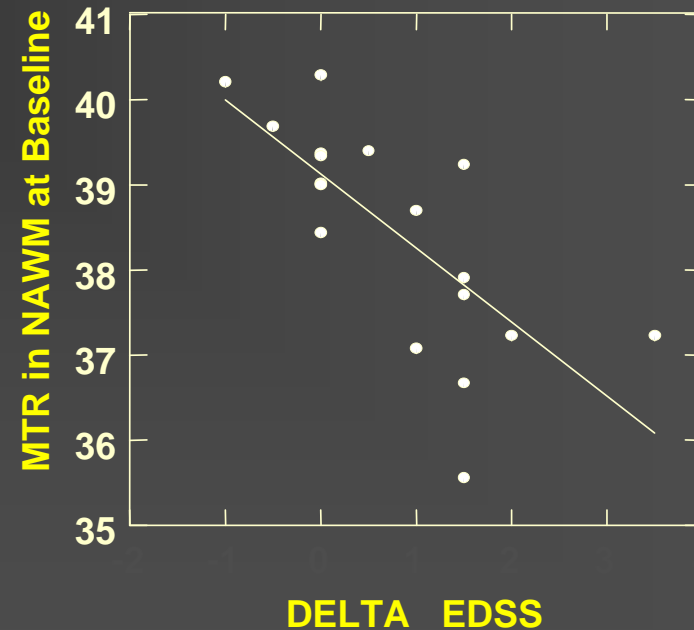
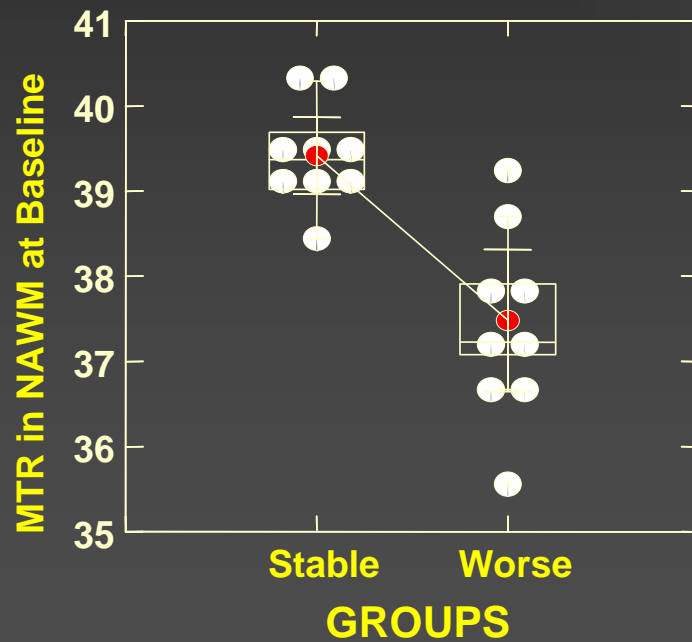
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# Atrophy predicts disability in treated RRMS



# MTR in NAWM Is Predictive of Disability

Lower MTR in NAWM – predicts worse EDSS 5 years later



# CIS: WM Lesions Are Predictive of relapse & CDMS

*Table 3 Risk of CDMS and combined CDMS/MRI outcomes*

Baseline MRI characteristics	Total patients, n	CDMS, %	CDMS/MRI, %
<b>No. of T2 lesions</b>			
2-4	10	20	
5-8	33	15	
9-12	42	33	
13-21	54	33	
22-34	38	26	
≥35	10	20	
2-8	43	16	
≥9†	144	31	
<b>No. of Gd lesions</b>			
0	133	23	
1	21	33	
≥1	46	43	
0-1	154	24	
≥2†	25	52	

Reproduced with

# MRI will be predictive of efficacy

- “trial-level” surrogacy
  - Despite a poor correlation of Gd lesions & relapses, response of Gd lesions predicts drug efficacy on relapses
  - $R^2 > 0.8$