MRI in drug development: Lessons from MS

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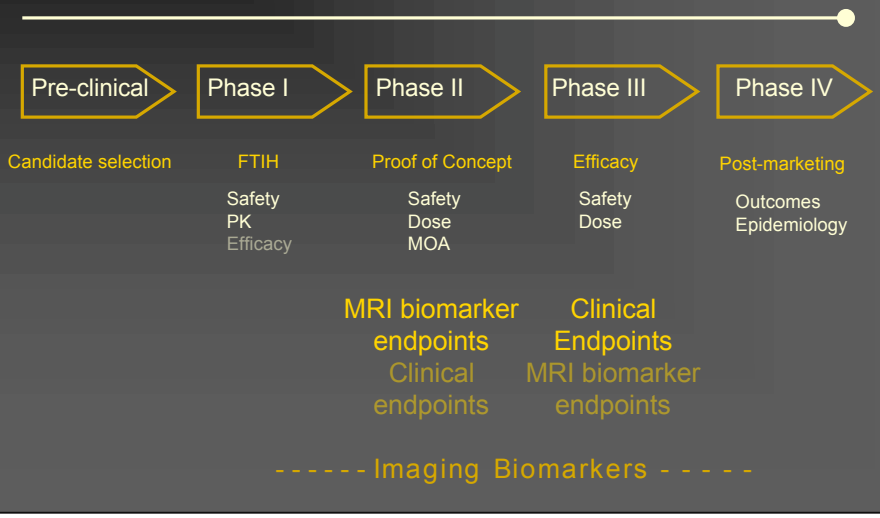
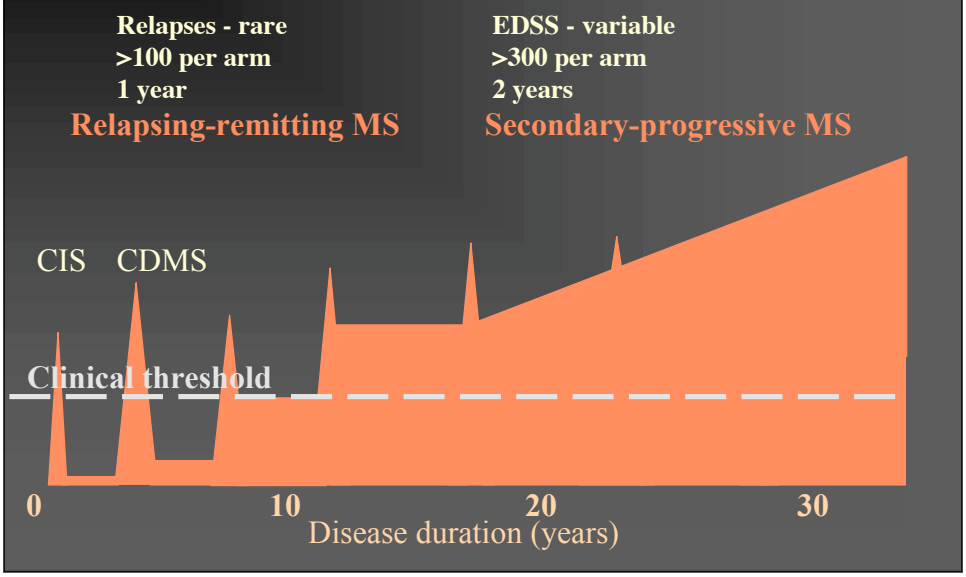
Drug development

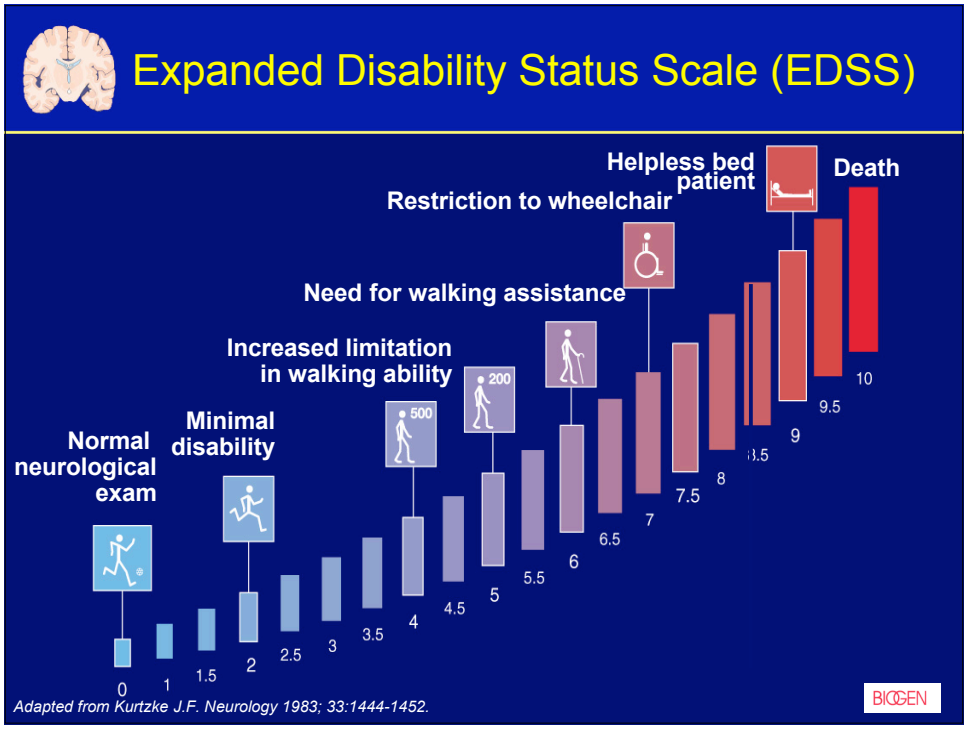


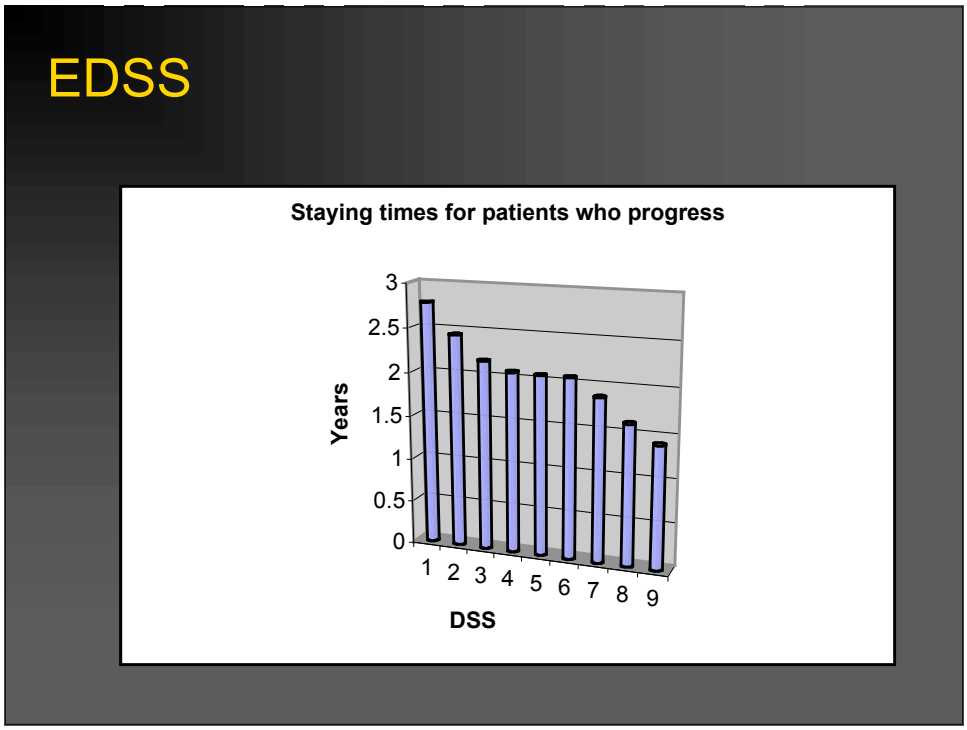
Value of imaging outcome measures

- Increased precision & sensitivity to change
  - smaller, more efficient studies
- Can be related to pathophysiology:

MS clinical outcomes




Expanded Disability Status Scale (EDSS)
Normal neurological exam
Minimal disability
Increased limitation in walking ability
Need for walking assistance
Restriction to wheelchair
Helpless bed patient
Death
0
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
9.5
10
500
200
Adapted from Kurtzke J.F. Neurology 1983; 33:1444-1452.
BIOGEN

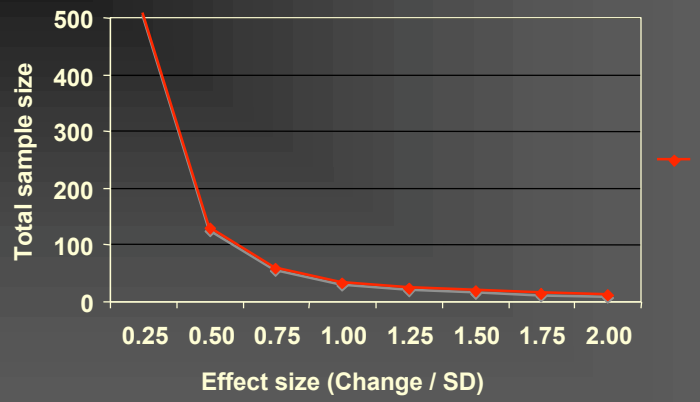

EDSS
Staying times for patients who progress
Years
3
2.5
2
1.5
1
0.5
0
1 2 3 4 5 6 7 8 9
DSS

EDSS

- Inter-rater agreement low
  - Kappa 0.3 - 0.5

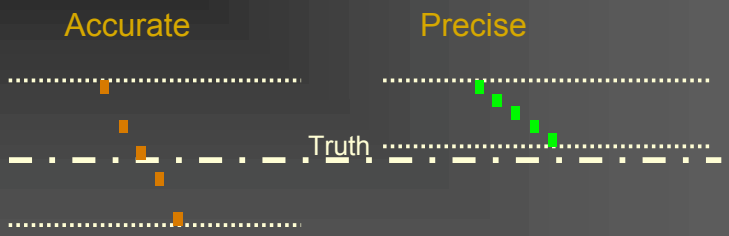
NeuroRx RESEARCH

Sample size vs Effect size (Untreated 1 year)



Atrophy MTR Gd MRS

Precision is king when looking for change over time



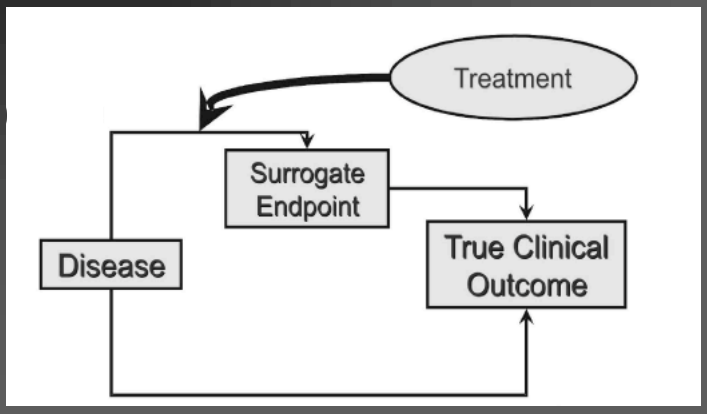
The attraction & challenge of MRI surrogates

Surrogate endpoint (FDA)

- Substitute for a clinically meaningful endpoint
  - direct measure of how a patient feels, functions, or survives &
  - is expected to predict the effect of the therapy

An ideal surrogate

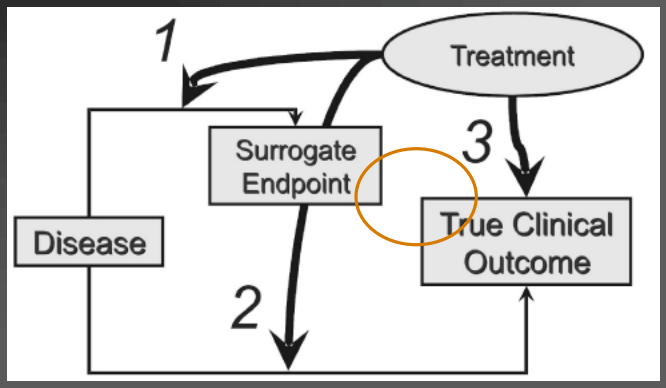
Treatment acts only through the surrogate



Petkau et al. 2008

When surrogates fail

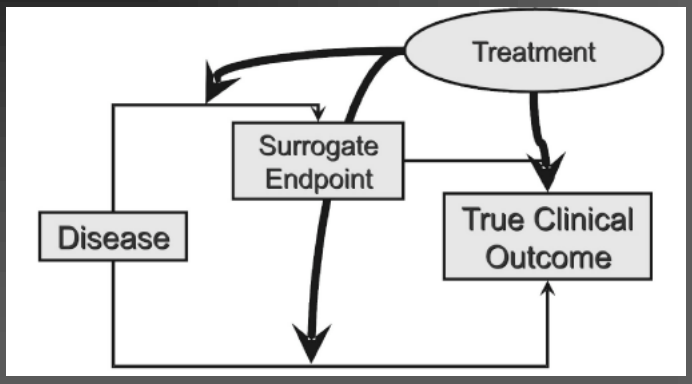
Treatment acts *only* through other pathways



Petkau et al. 2008

Weak surrogates

Treatment acts through the surrogate & other pathways

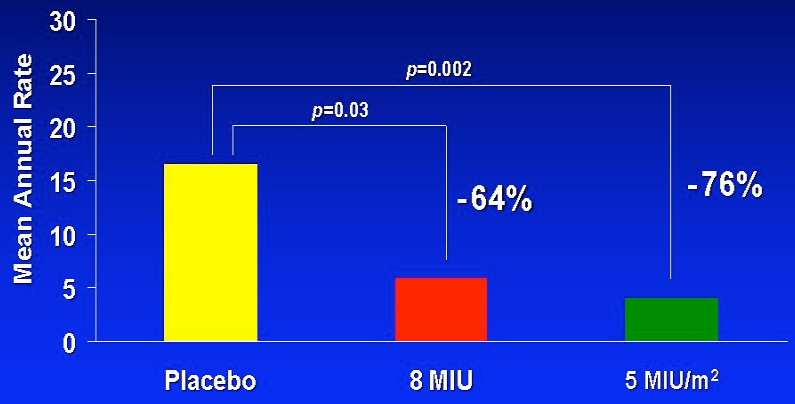


Petkau et al. 2008

Example of a failed MRI surrogate for disability (EDSS) progression

NASP 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.

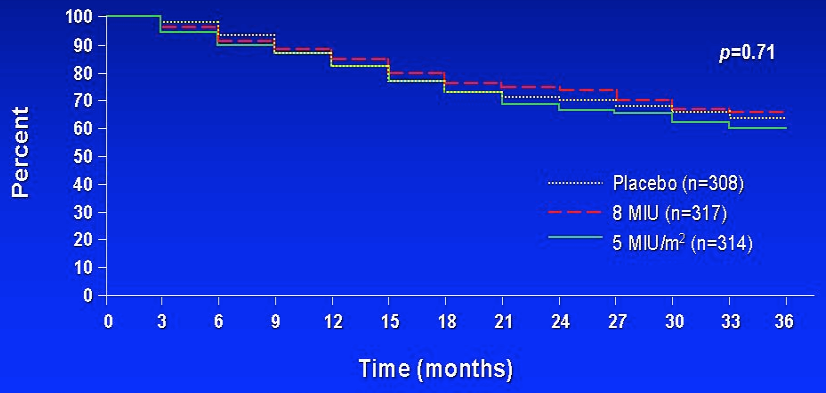
Goodkin et al. Annual Meeting of the American Academy of Neurology. 2000.

Example of a failed MRI surrogate for disability (EDSS) progression

NASP Betaseron® Trial

Disability Progression

Time to Confirmed Disability Progression



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

Prentice Criteria for surrogacy

1. Rx is effective on the surrogate
2. Rx is effective on the clinical outcome
3. Surrogate and clinical are correlated
4. Effect of Rx on clinical outcome is mediated through an effect on the surrogate

No residual variance!

The challenge of surrogacy

- No MS therapy has been approved based on MRI markers since Betaseron (1998)

The attraction of biomarkers

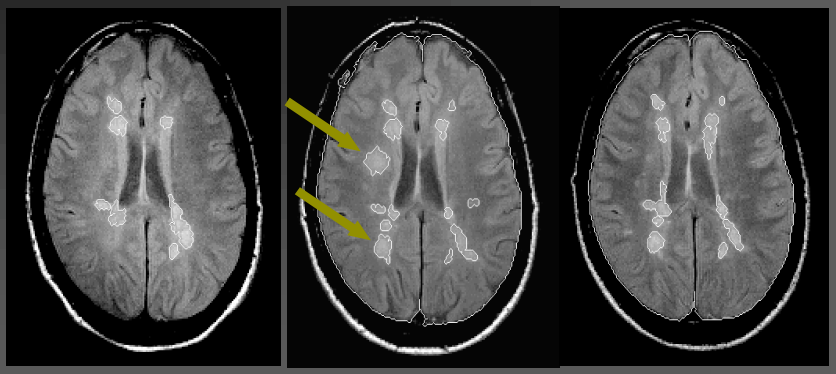
- Every MS therapy that has been approved has used MRI biomarkers during its development (phase II)

MRI Biomarkers: WM lesions

- Disease “activity” -
  - “Active” lesion counts
    - Gd+, new T2
- Disease “burden”
  - Accumulated Lesion volumes
    - T2, T1w

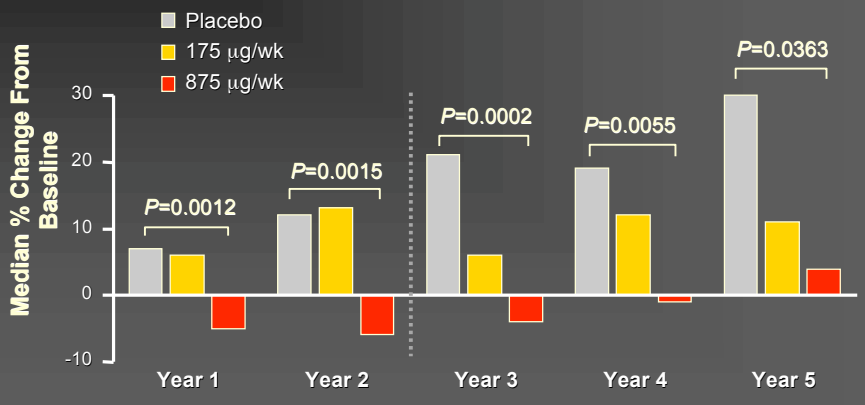
Lesion volume:

" Burden of Disease"



Betaseron: Extension Study

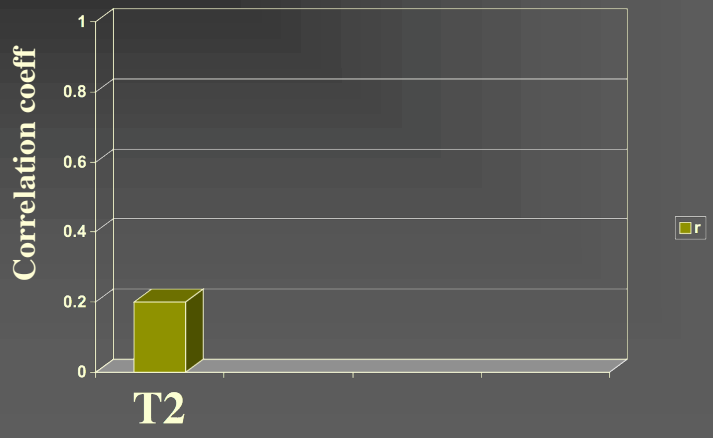
T_2 lesion burden



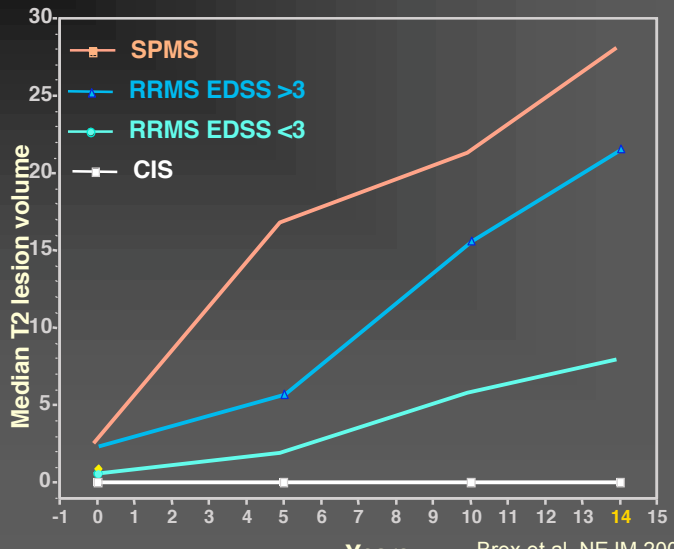
IFNβ MS Study Group et al. *Neurology*. 1995;45:1277-1285.

MRI *vs.* clinical

T2w lesion volume *vs.* EDSS in clinical trials (1-2 years)



Greater lesion volume is associated with greater disability (long term)



Brex et al. NEJM 2002;346:158-64.

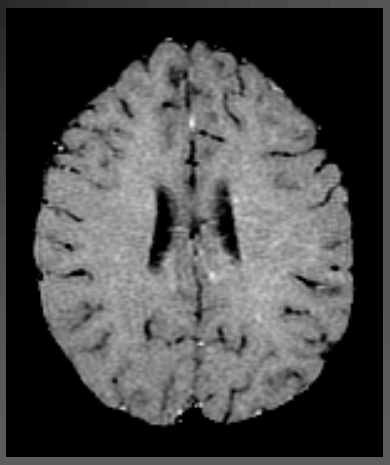
Lesion volume analysis:
Precision is the challenge

- Change = 5% / year
- Variance = 5-20%
  - Effect size 1 - 0.25 for 100% efficacy

MRI Biomarkers: WM lesions

- Disease “activity” -
  - “Active” lesion counts
    - Gd+, new T2
- Disease “burden”
  - Accumulated Lesion volumes
    - T2, T1w

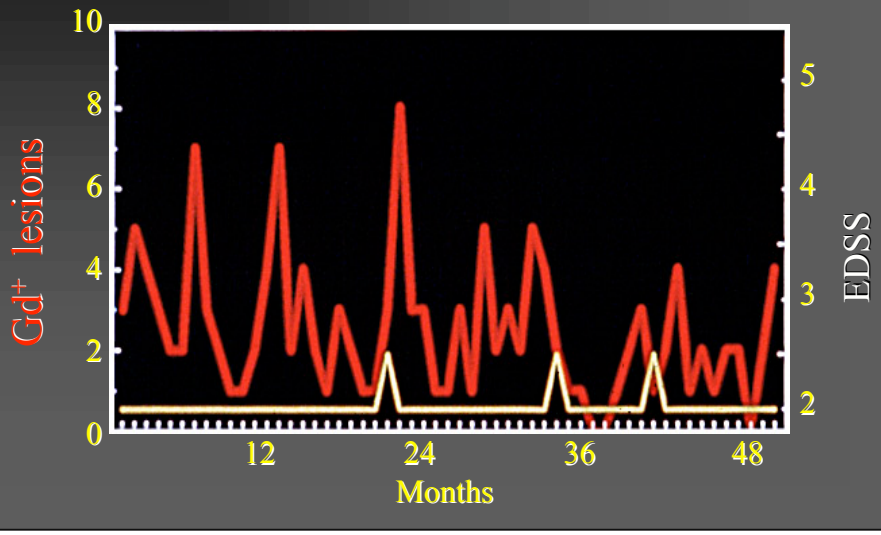
MRI shows that MS is much more active than clinically evident



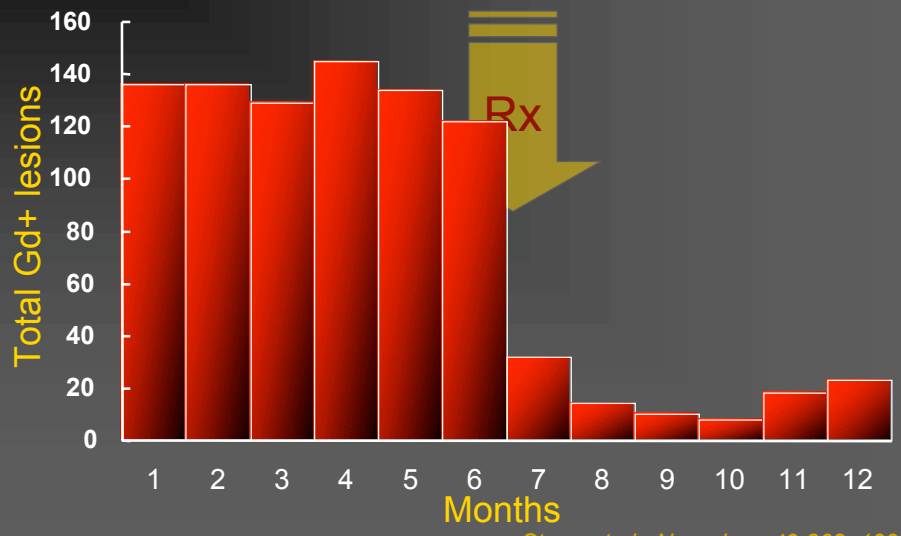
Gd-enhanced MRI: Serial scans made into movie

MRI *vs.* Clinical

Gd^+ Lesions *vs.* relapses



Effects of Interferon on Gd+ lesions:



Stone et al. Neurology 49:862, 1997

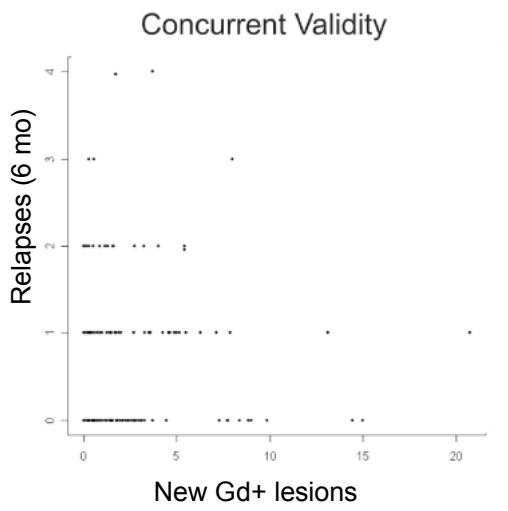
Gd: Numbers of patients needed

80% statistical power

Treatment effect	# scans (on Rx)	# patients (30-50% Gd+)
50%	Parallel group Baseline corr'd	
	3	57

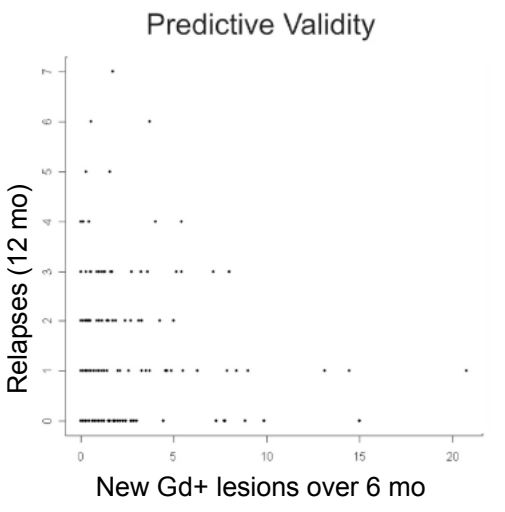
Sormani 2001

Gd is a poor “surrogate” for clinical Relapse



Petkau et al. 2008

Gd is a poor “surrogate” for clinical Relapse



Petkau et al. 2008

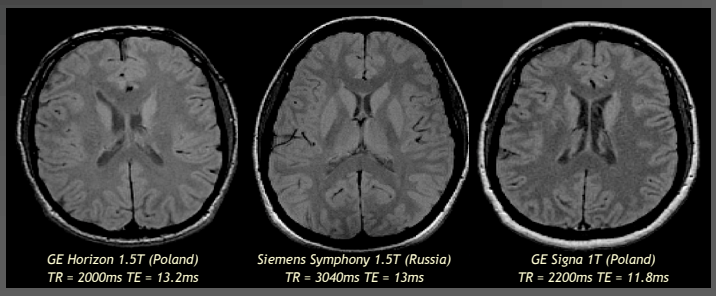
Although not a surrogate for relapses, Gd+ lesions predict drug efficacy

- Every approved MS therapy has used Gd as a primary outcome in phase II trials

The challenge of multicenter MRI analysis

Multisite acquisition of MRI data

- Ensure consistent across sites



MRI Intensity normalization

- Nyul
  - Intensity range normalization
  - Piecewise linear histogram matching

Intensities of WM before normalization

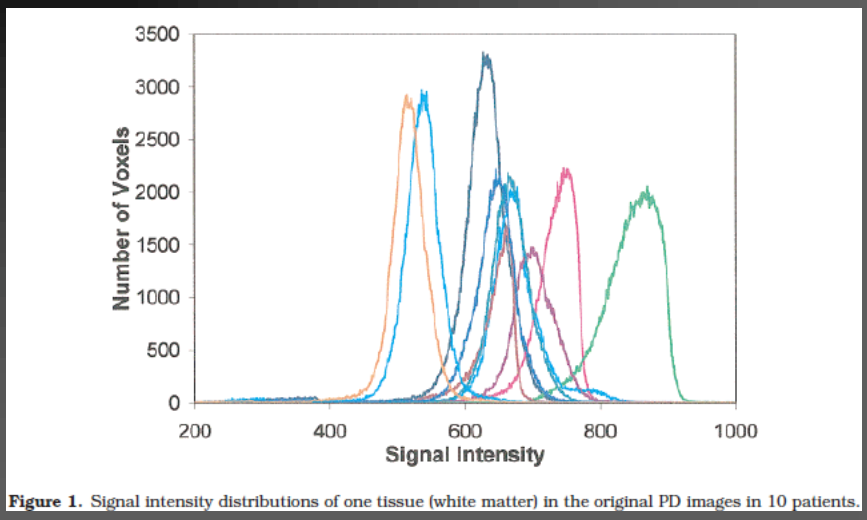


Figure 1. Signal intensity distributions of one tissue (white matter) in the original PD images in 10 patients.

Ge et al. 2000

Intensities of WM after normalization

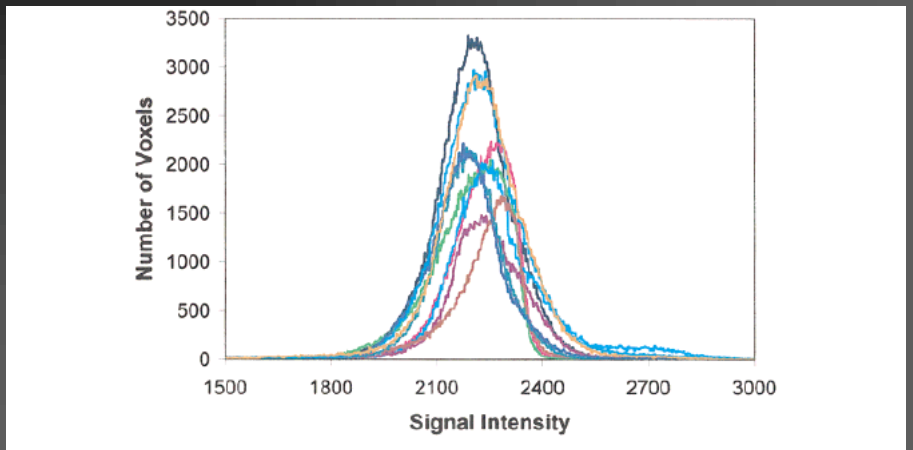


Figure 2. Signal intensity distributions of one tissue (white matter) in the standardized PD images in 10 patients.

Ge et al. 2000

Non-uniformity correction

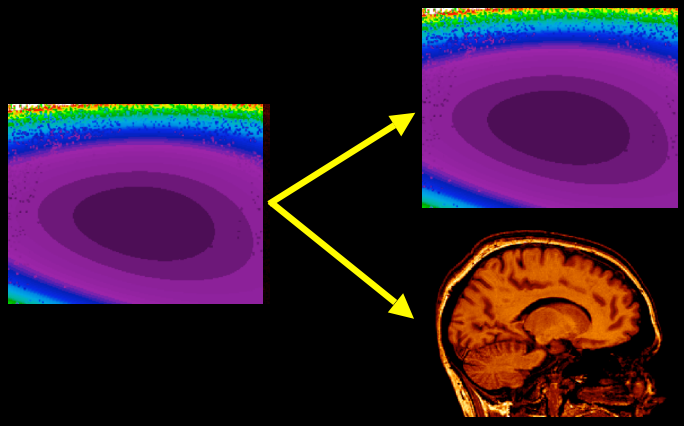


Image Alignment

- unaligned images

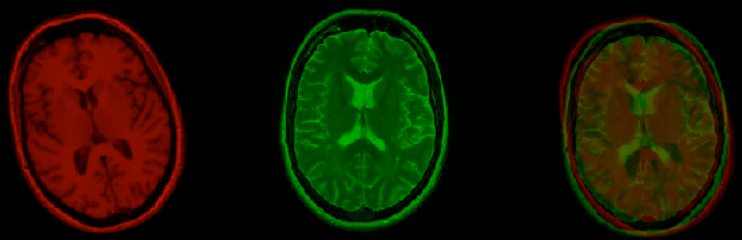
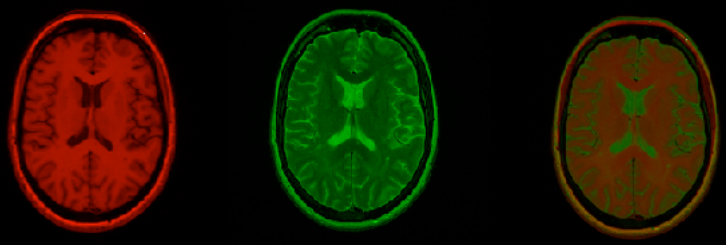


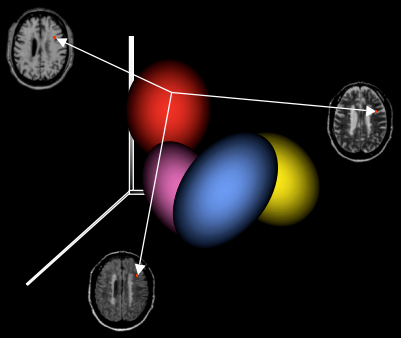
Image Alignment

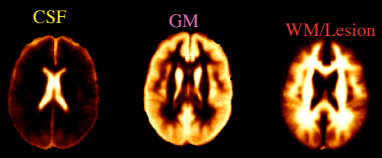
- aligned images



- voxel-anatomy synchrony
- multi-modal data
- longitudinal anatomical information

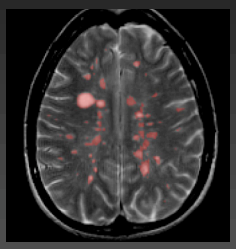
Tissue Classification



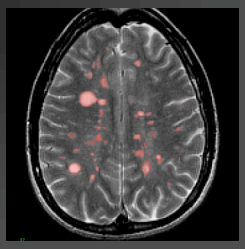


Probability of a tissue class is based on MRI intensities & anatomical prior knowledge

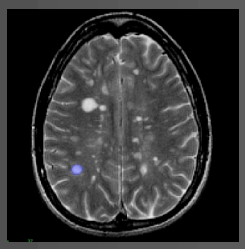
T2w & New/enlarging T2w lesions



T2w Lesion volume
1st time-point



T2w Lesion volume
2nd time-point



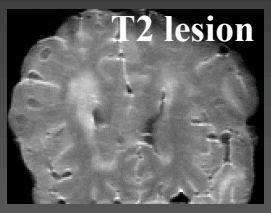
New T2 label

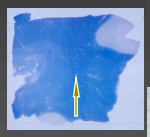
Value of imaging outcome measures

- Increased precision & sensitivity to change
  - smaller, more efficient studies
- Can be related to pathophysiology:

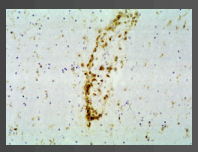
T2 = sensitive, not specific

lesions can have variable severity

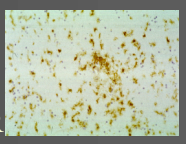




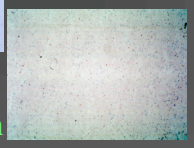
Inflammation



LCA

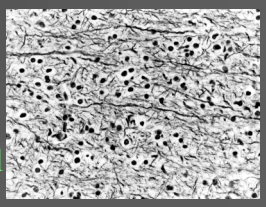


HLA-DR



ORO

Myelin breakdown

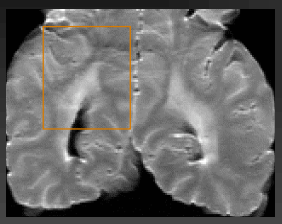


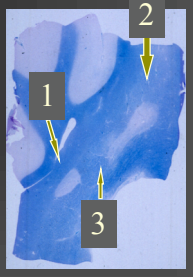
Bodian Axonal loss

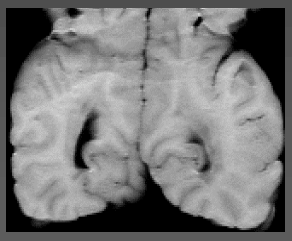
Courtesy of F. Barkhof

T1 lesions *(chronic)*:

less sensitive, more specific





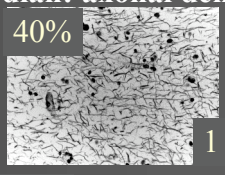


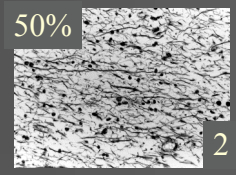
1: strongly hypointense

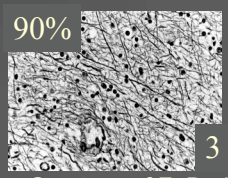
2: mildly hypointense

3: slightly hypointense

Bodian: axonal density





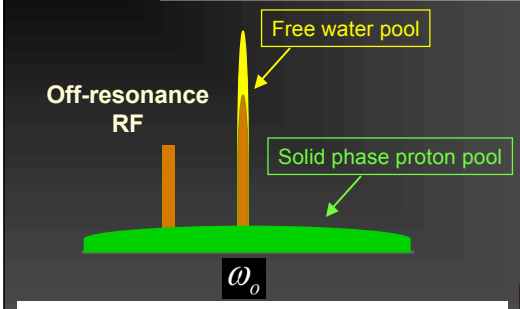


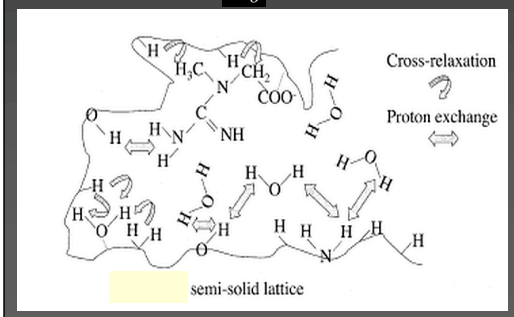
Courtesy of F. Barkhof

“Non-conventional” & quantitative MRI for increased pathhological specificity

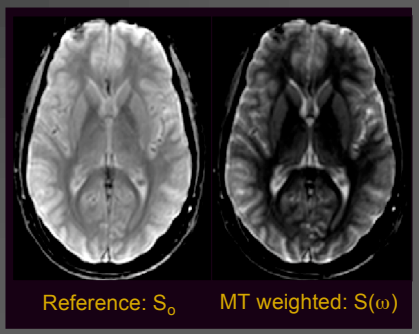
- MTR
  - myelin content / tissue integrity / remyelination
- MRS
  - axonal damage / repair
- Atrophy
  - tissue loss (swelling)

Magnetization transfer (MT Effect)

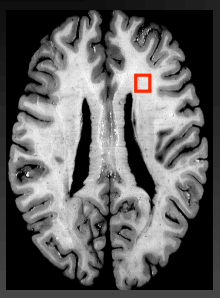


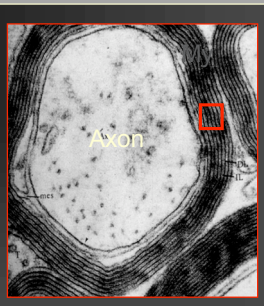


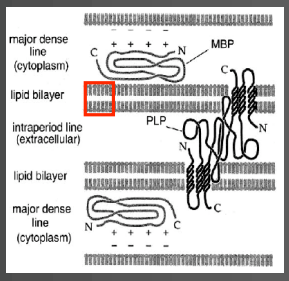
$$MT = f(T_1, T_2, k, F, B_1, etc)$$

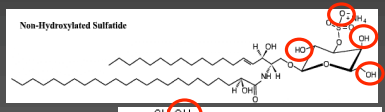


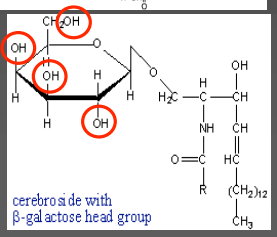
What are these Semi – solid Protons?

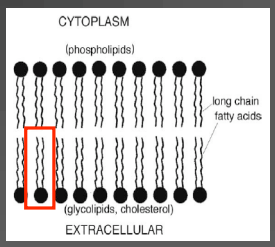






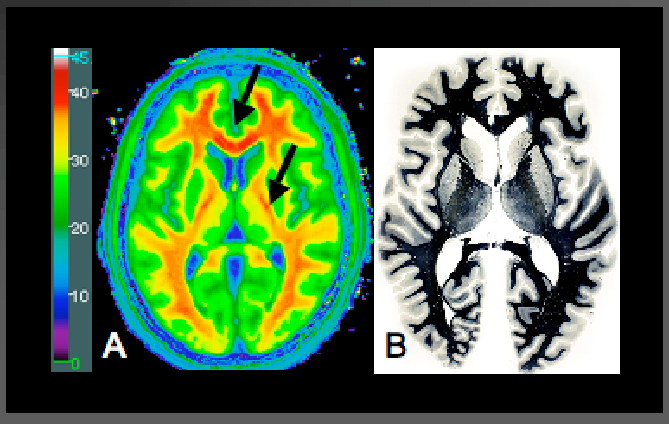




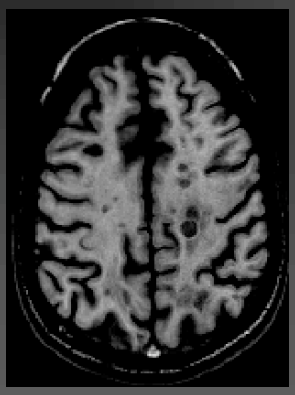


Barkovich, A. J. Inherit. Metab. Dis. 28 (2005) 311

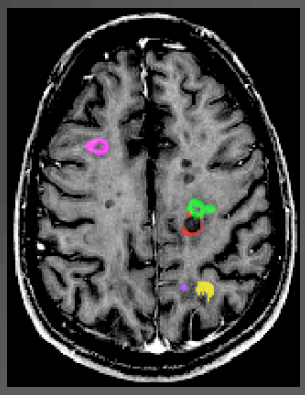
MTR: WM Anatomy:
Axial slice - Basal ganglia



Lesion MTR Dynamics:
Demyelination & Remyelination



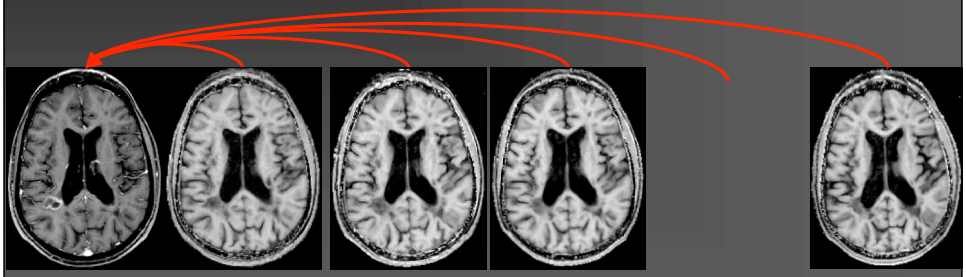
T_1w



$Gd+T_1w$

The evolution of mean MTR in Gd-lesions

- register images



baseline: time-point #1

time-point #2

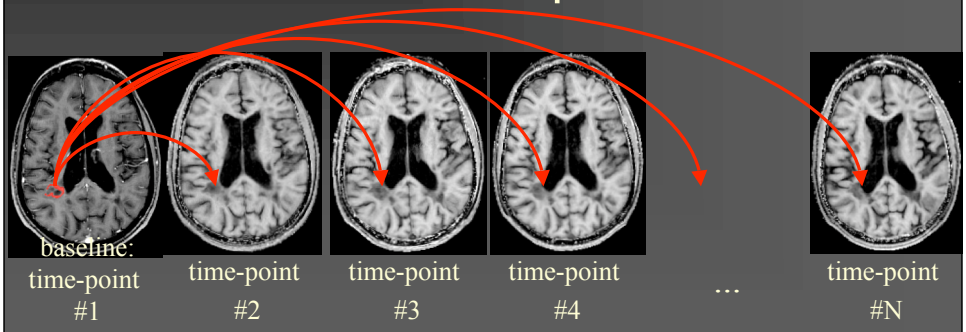
time-point #3

time-point #4

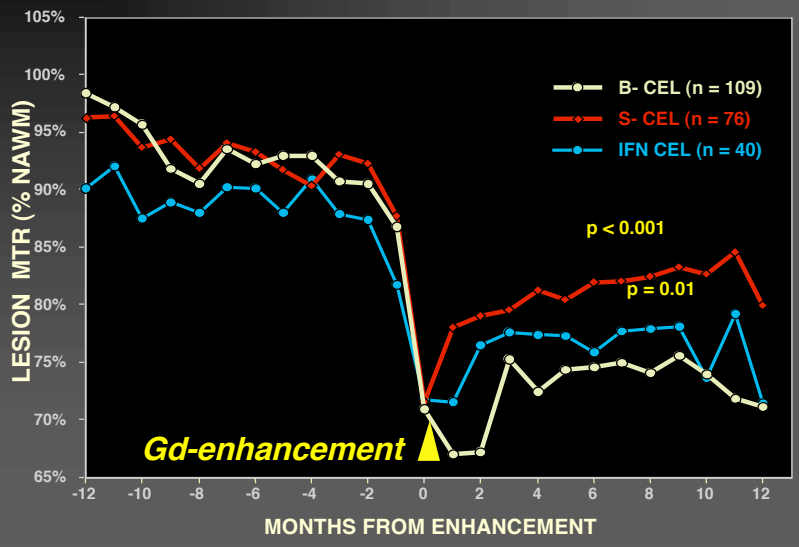
…

time-point #N

- propagate the initially enhancing lesion to other time-points

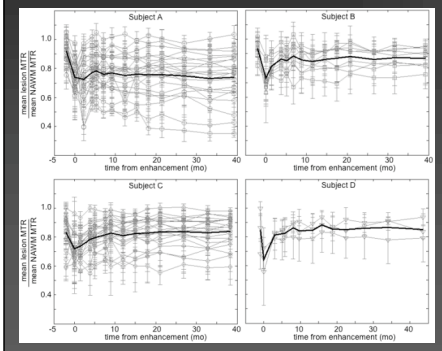


Quantifying mean MTR recovery in acute lesions

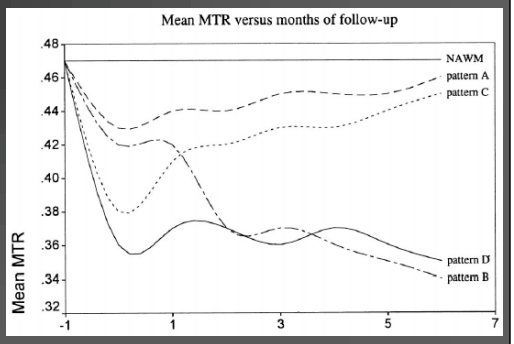


Richert et al. Mult Scler 2001

The evolution of **mean** MTR in initially Gd-enhancing lesions averages a heterogeneous processes



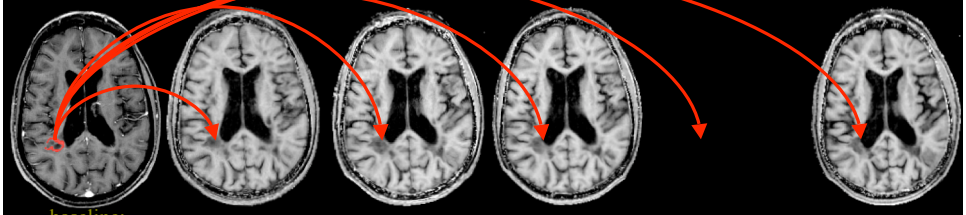
Chen et al., 2008



van Waesberghe et al., 1998

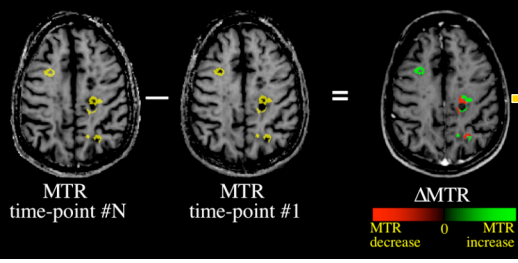
Linear non-brain-constrained symmetric registration
Non-linear, non-lesional tissue-based registration
Propagation of Gd-lesion labels:

%GdLV



baseline: time-point #1 | time-point #2 | time-point #3 | time-point #4 | ... | time-point #N

Calculation of voxel-wise MTR change:

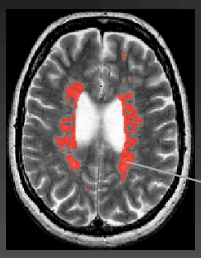


apply objective thresholds to exclude noise & partial-volume effects

%GdLV with MTR changes suggestive of remyelination

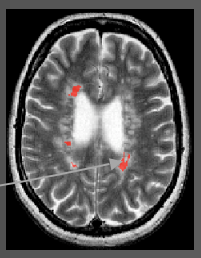
%GdLV with MTR changes suggestive of demyelination

Error analysis



T2w lesions

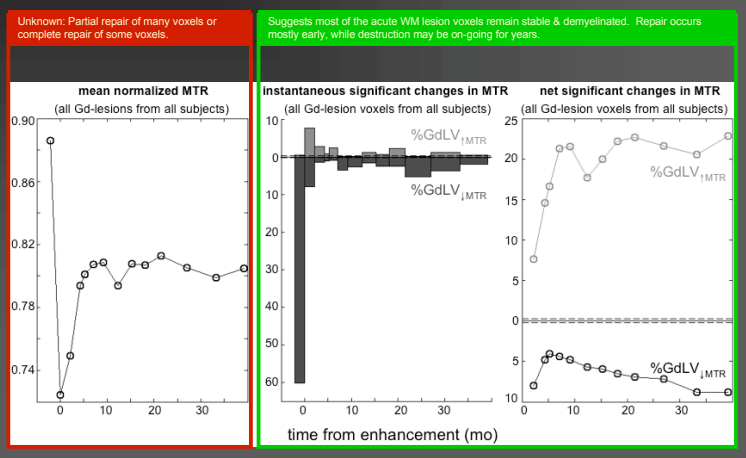
erosion of T2w lesion mask & removal of remaining isolated voxels



model Gd-lesions

Error < 0.02cc

Canadian MS/BMT study: Results from 4 SPMS patients



(Chen et al., 2008)

MTR: Sample size

Gd **voxels** that undergo increases in MTR suggestive of remyelination

- Canadian BMT trial
  - mean %GdLV per patient
- 20 % Rx-effect
  - 70 subjects/grp
- 25 % Rx-effect
  - 40 subjects/grp

- assumptions:
  - independent subjects, 2 groups, 0.05 significance level, ~80 % power, equal groups, lognormal probability distribution of the outcome, placebo mean=0.2079 SD=0.098 (from Canadian MS/BMT study)
- Wilcoxon Rank Sum test, 1000 iterations:
- Unpublished

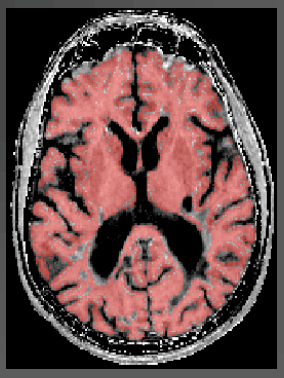
Myelin content:

Degeneration in normal-appearing tissue

MTR

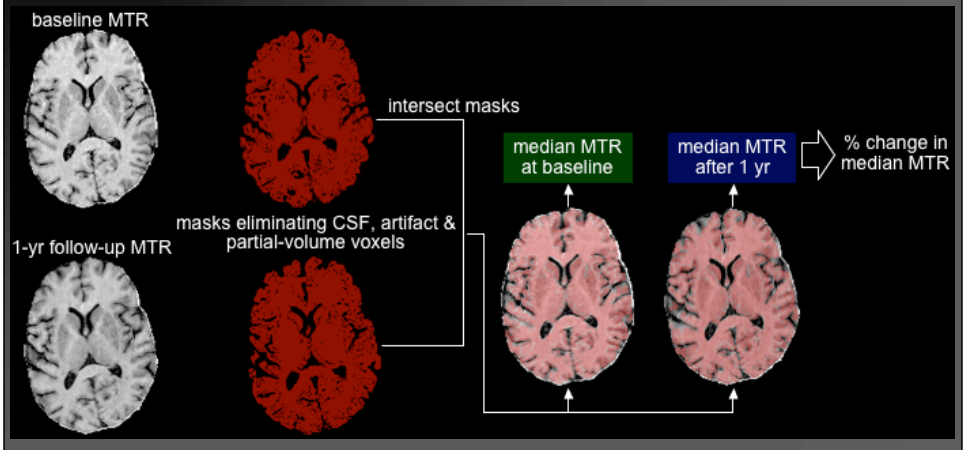
mean MTR in NABT

- The mean MTR in normal-appearing brain tissue is associated with the average myelin content in the non-lesional brain.
- Variable



NABT volume labeled in red overlayed on MTR image

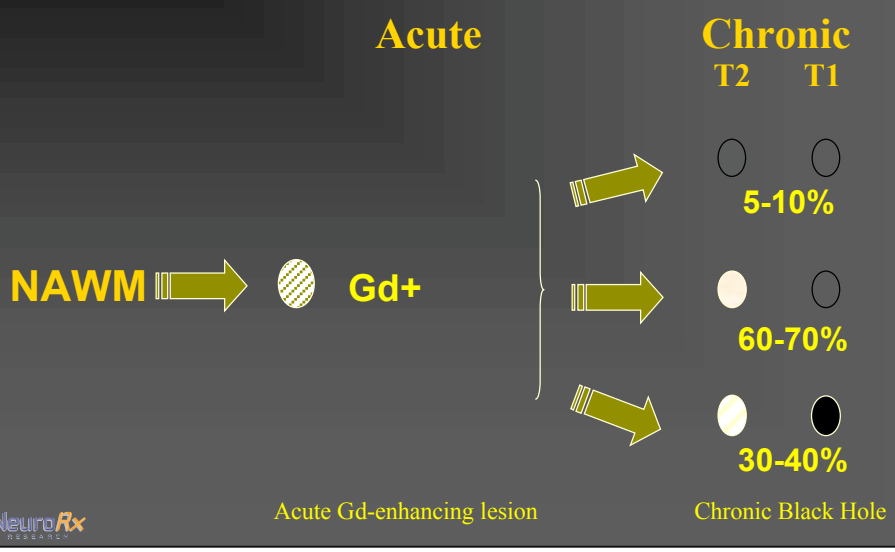
"Global" MTR change over time:



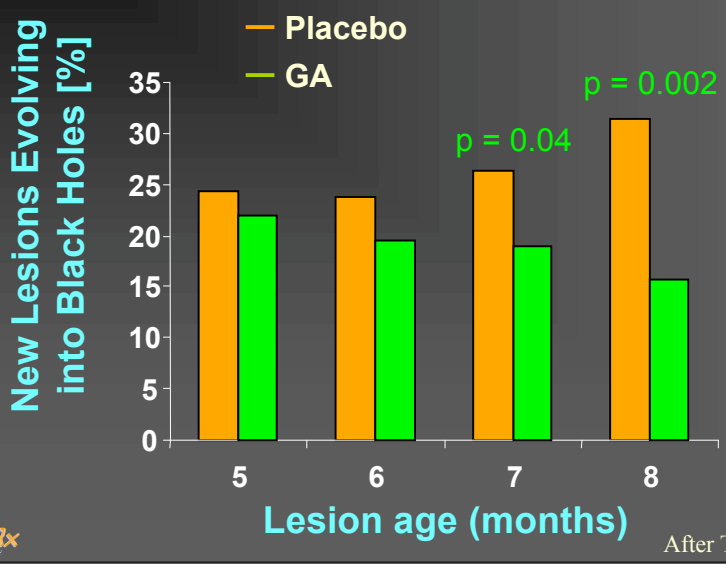
- Reproducibility error <0.64 %
- Sample size ?
- Attenuation of demyelination vs remyelination ?

Non-conventional use of conventional images

Evolution of Newly-Formed MS Lesions



Glatiramer acetate MRI trial: Evolution of lesions into Black Holes

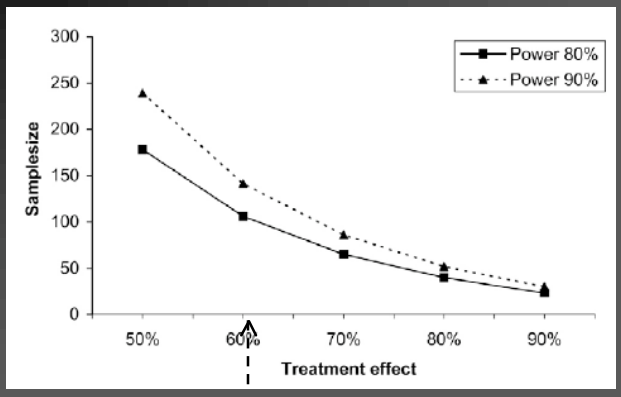


NeuroRx RESEARCH

After TEVA / Filippi

T1: Sample size

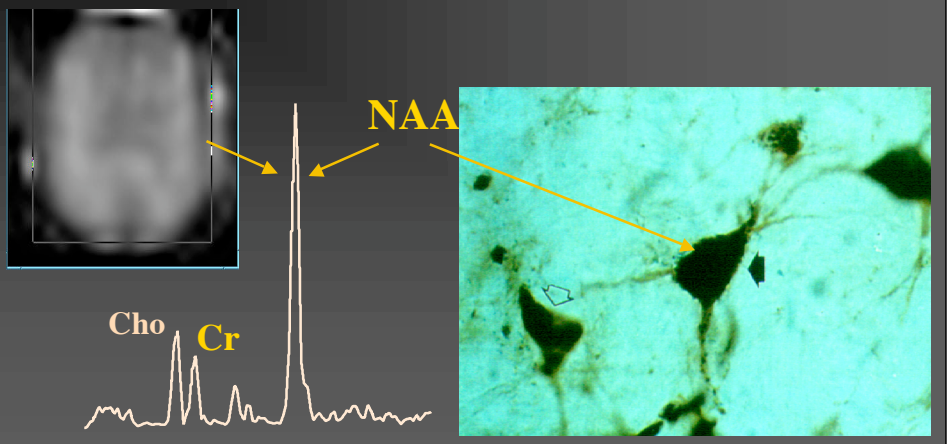
Gd **lesions** evolving to BH after 3 months



Dalton et al 2004 - Natalizumab

Van den Elskamp 2008

MR Spectroscopy: Imaging axonal injury & loss



From Coyle, JT. et al., 1989

MRS Protocol - Voxel size & position

Changes in NAA/Cr in NAWM over time

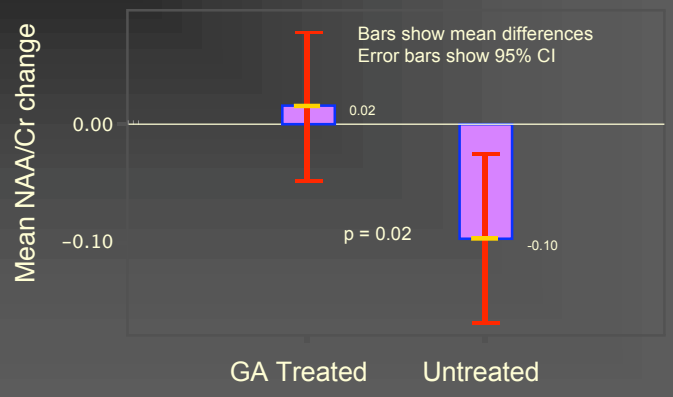
(adjusted for lesion volume evolution)

Model:

NAA/Cr = Subgroup + **Time** (yrs) + Subgroup x Time (yrs) + **Lesion** + Subgroup x **Lesion**

Independent Variable	*Estimate of Coefficient (β)*	*Std Error*	*Compared to NAWM in RR*	*Significance of Changes (p-value)*
Time (in RR)	-0.3	0.05	**-5.8%[a]**	< 0.001
Time (in SP)	0.07	0.03	**1.4%[a]**	ns
Lesion (in RR)	-0.6	0.1	-12.7%[c]	<0.001
Lesion (in SP)	0.4	0.2	-8.0%[c]	<0.1

NAA/Cr maintained by GA



Narayanan S, et al. Mult Scler 2004 (suppl)

Power: MRS (RRMS)

metric	mean change in placebo group	SD change in GA group	total sample-sizes required to detect:			Observed effects	
			25% Rx-effect	50% Rx-effect	75% Rx-effect	observed	total sample-size to detect observed Rx-effect
MTR NABT	-5.47 %/yr [8]	1.8 %/yr [8]	56	16	10	256% increase Rx group	4

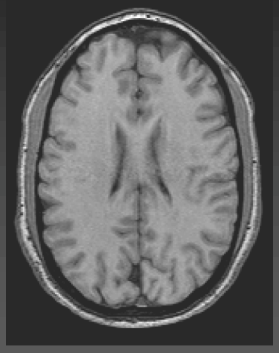
Khan et al, 2005, based on differences in group means

Brain volume (Atrophy):

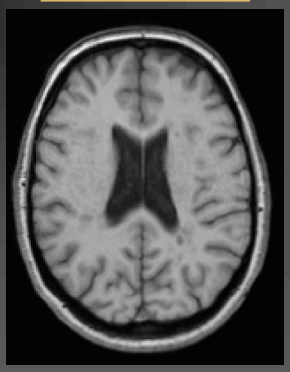
SIENA

Atrophy in MS

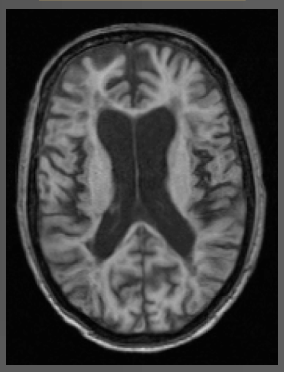
Normal Control



Patient with RR-MS



Patient with SP-MS



SIENA

Skull-based registration

Skull image from first scan

Skull from follow-up scan

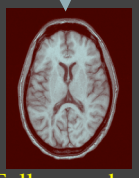
Register skull images *with scaling*

Transform

Apply skull transform to F/U MRI brain

Register *transformed* F/U brain to initial brain *without scaling*

Transform

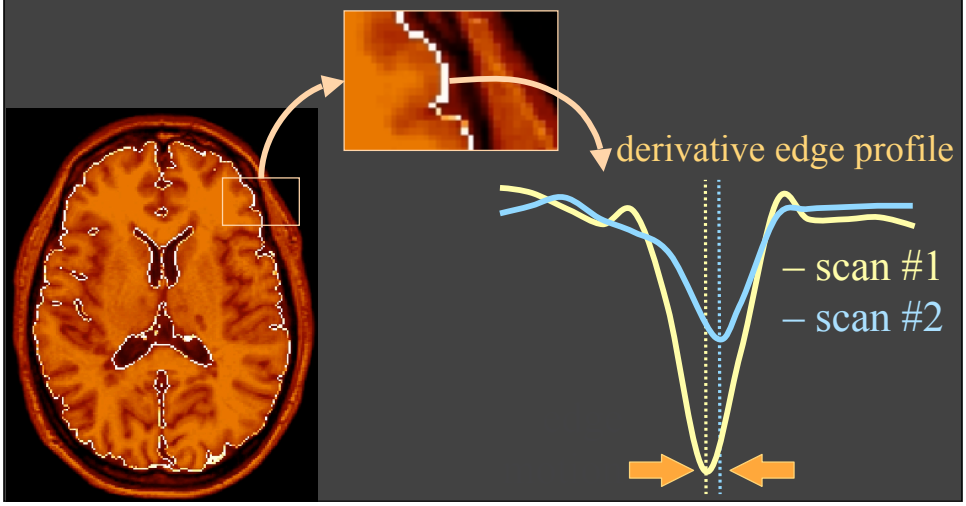


Follow-up brain registered to initial brain

Courtesy of Steve Smith and Paul Matthews, FMRIB

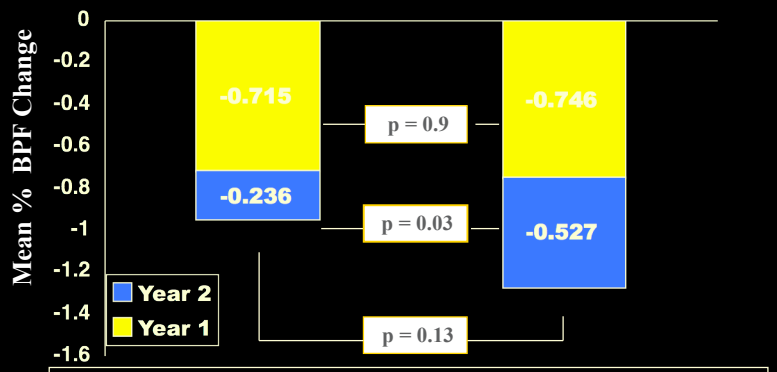
SIENA: Atrophy over time

Automatic longitudinal edge detection



IFNβ-1a IM for RR MS:

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)

R. Rudick and E. Fisher

Atrophy: Sample size

- ~100 patients per arm
- 1-2 years

What we need to use MRI biomarkers in multicenter trials

- Precision
- Automation
- Robustness