Quantitative In-vivo Imaging of the Impact of Cancer Therapy on the Normal Pediatric Brain

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St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.

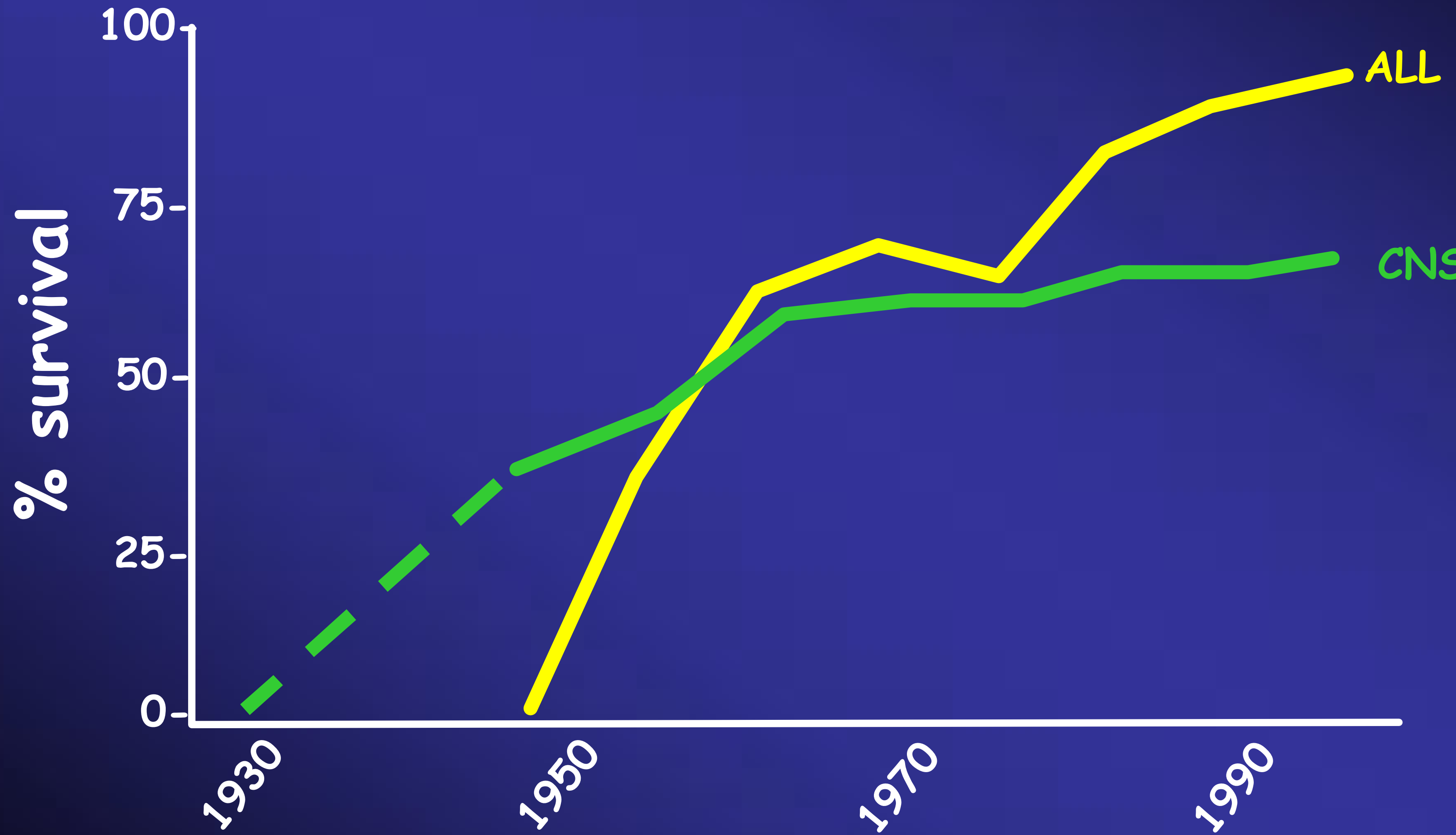
The Clinical Problem

- Acute lymphoblastic leukemia (ALL) is the most common childhood cancer
  – Affecting 2,400 children annually in the US
  – Young age at diagnosis and high survival rate
- Brain Tumors are the most common solid tumors of childhood
  – Affecting 3,110 children annually in the US
  – Most common cause of cancer related death in children
  – High rate of severe morbidity

RJ Gilbertson

Source: CBTRUS and SEER

Increasing Importance of Neurotoxicity



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Source: CBTRUS and SEER

Independent Research Program

Probing Substrates of Neurotoxicity

Basic Research Focus: Development of innovative algorithms and methods to quantify the structure and integrity of cerebral white matter *in vivo*

Clinical Research Focus: Use non-invasive imaging technology to quantify neurostructural changes resulting from radiological or pharmacological insult

Ultimate Goal: To assist in the development of therapy that would prevent, mediate, or intervene to minimize impact of neurotoxicity in survivors of pediatric cancer

Translational Imaging Research

- Basic Research
  - Image Registration and Fusion
  - RF Correction
  - Segmentation
  - Volume of Interest Analyses
  - Diffusion and Perfusion
- Clinical Research (BT)
  - Historical Background
  - Most Recent Results
  - Ongoing Studies
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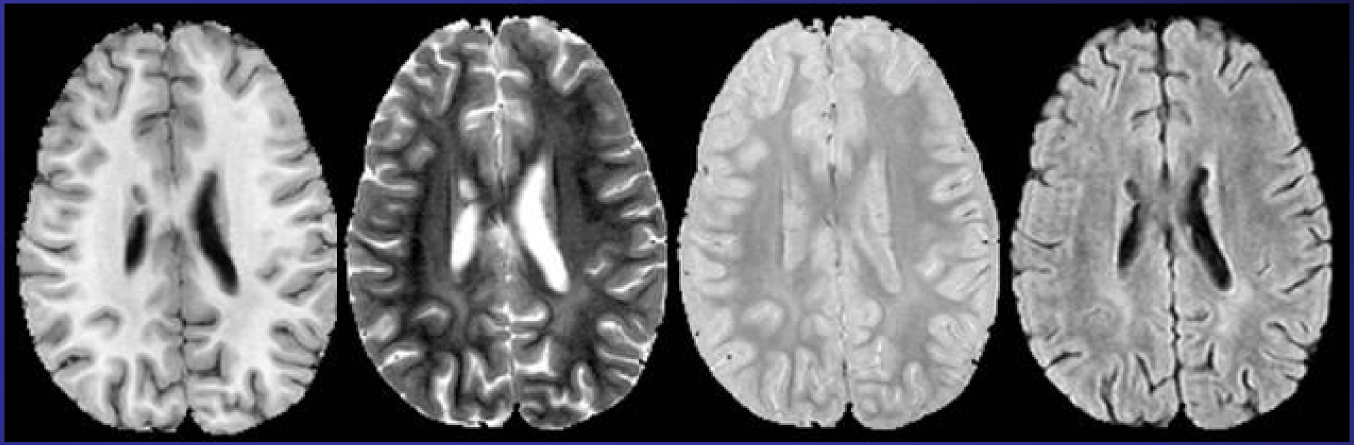
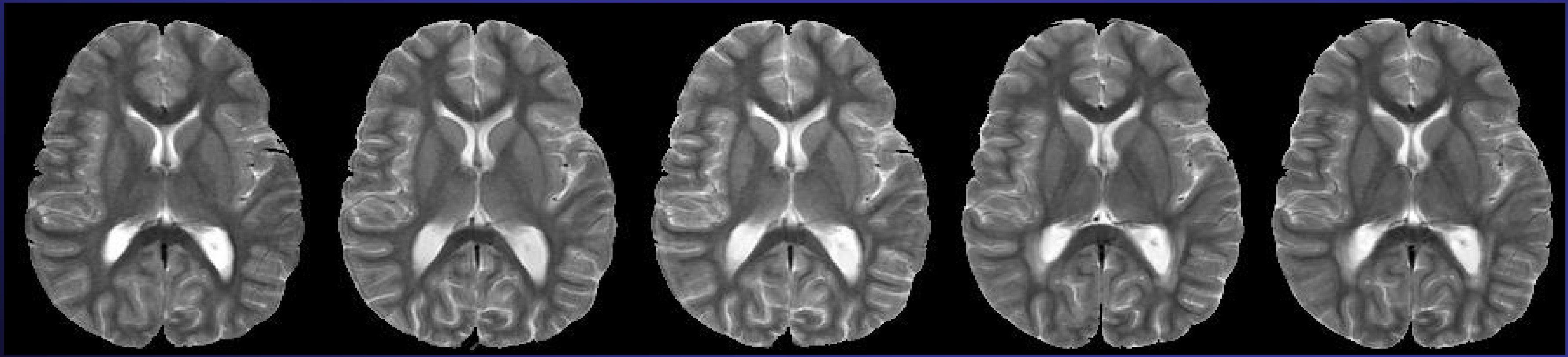
3D Affine Registration

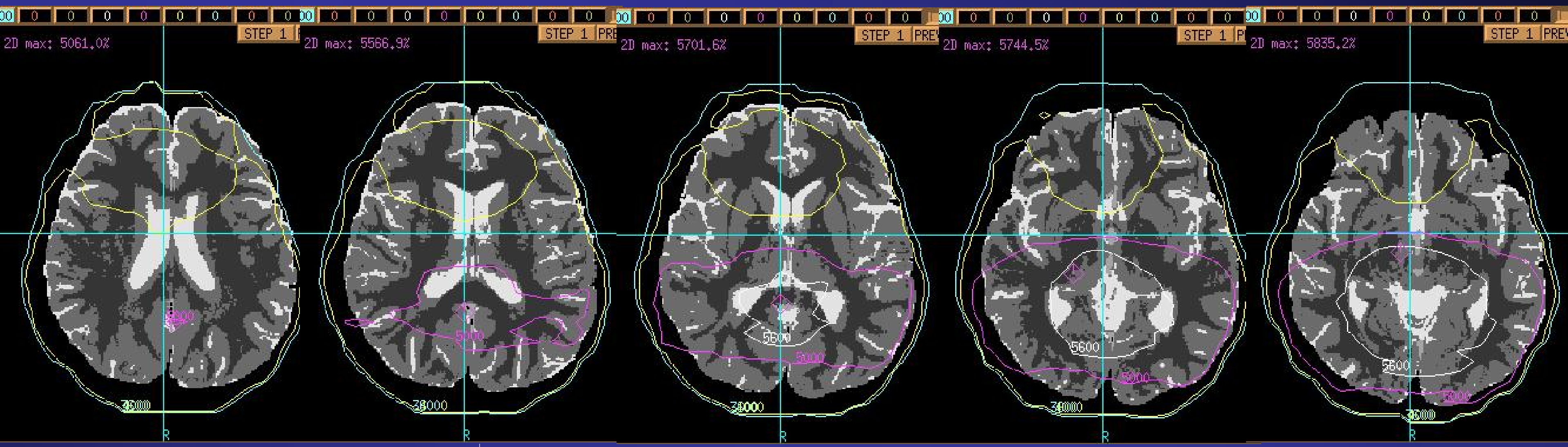


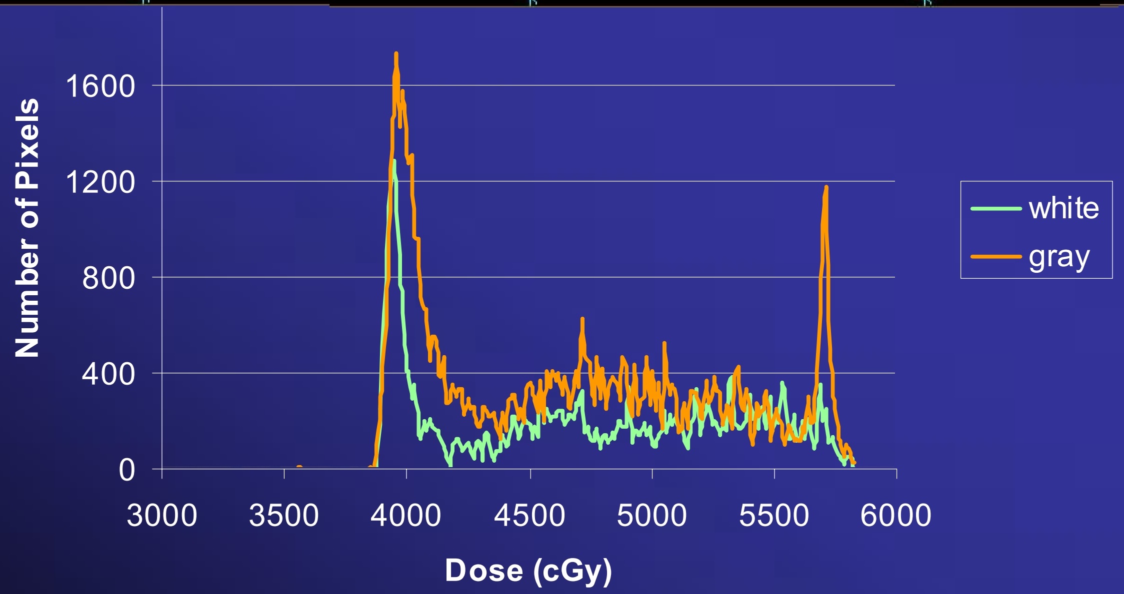
Within an examination



Between examinations

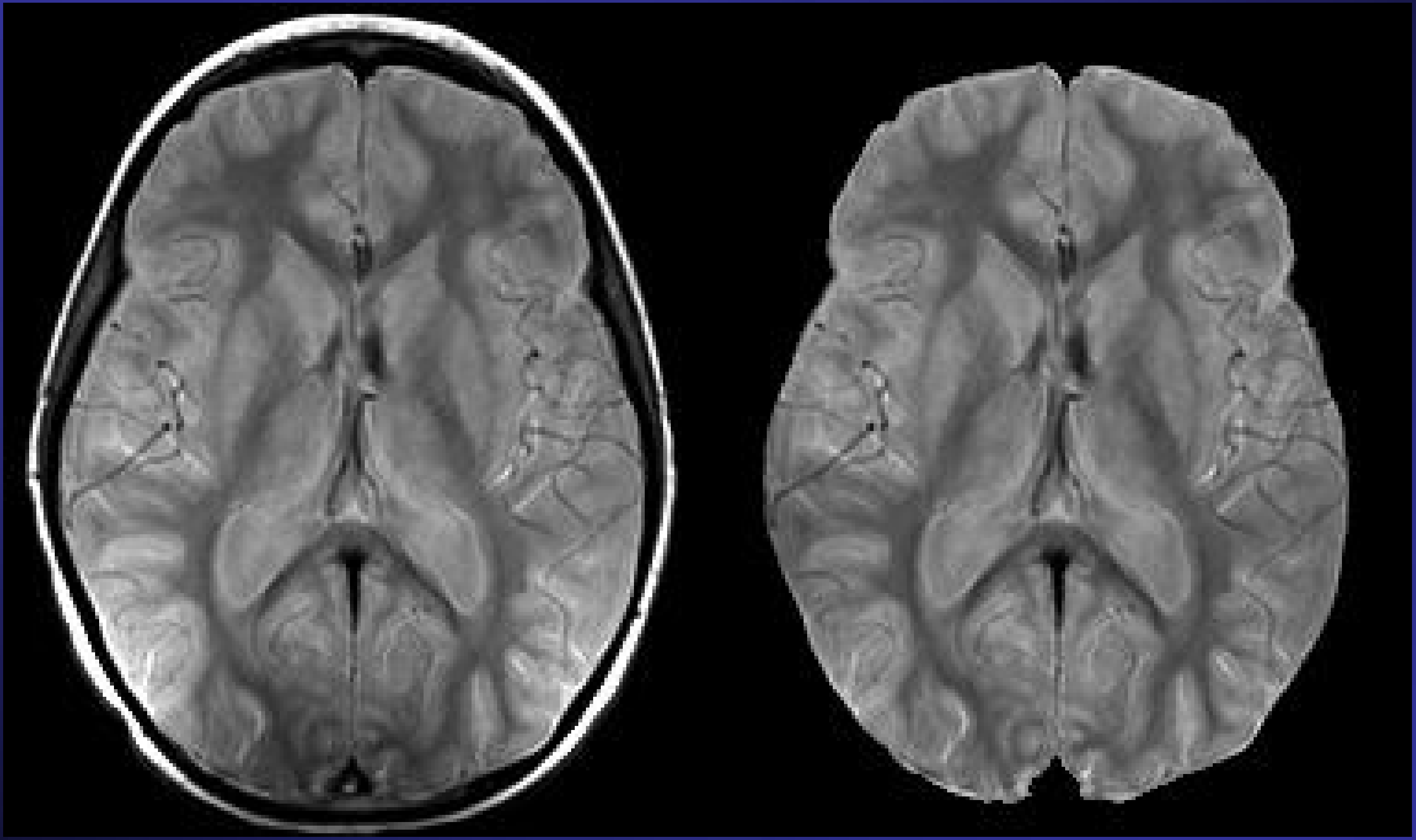
Fusion of RT Dose with Segmented MR





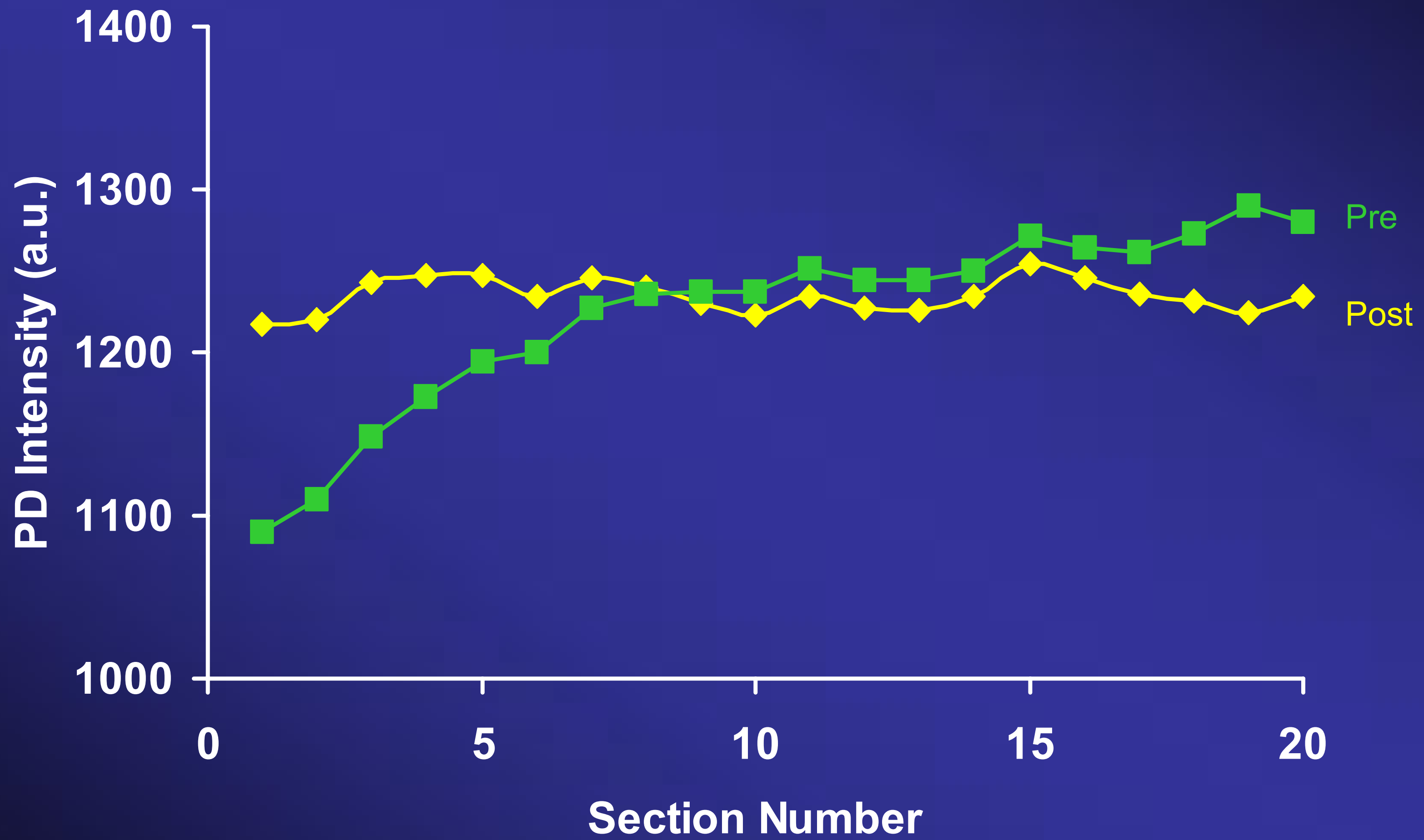
TE Merchant

Bias Field Correction (in plane)

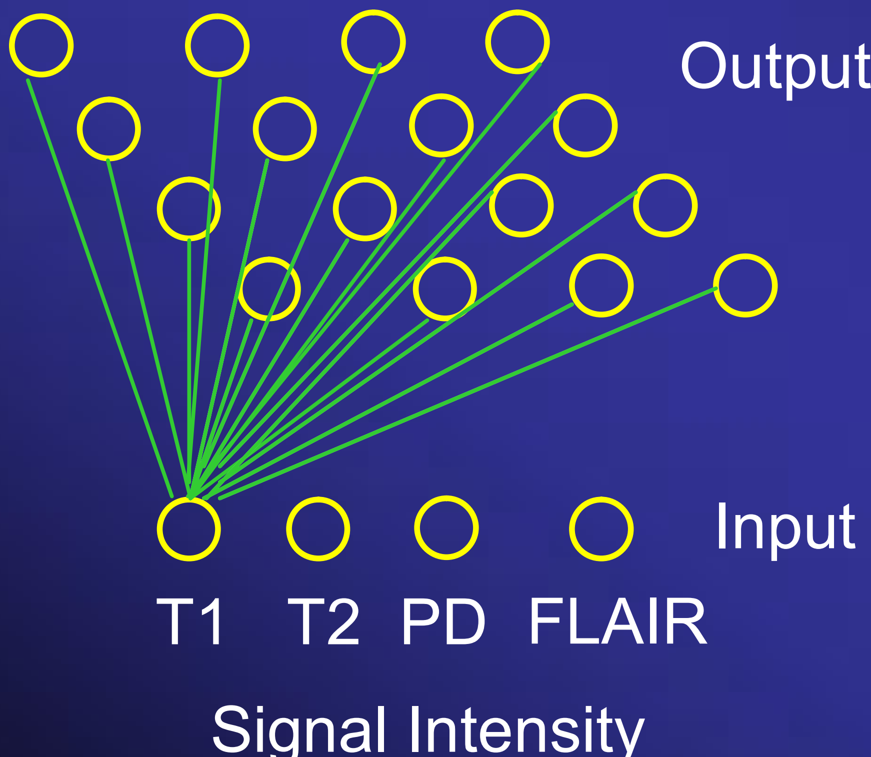


(Ji et al. *MRM* [in prep], 2005)

Bias Field Correction (between planes)



Kohonen Self-Organizing Map
(Segmentation)



Learning Algorithm

$$\Delta weight_{i,j} = \left(neigh(iter)\right)^2 \left[input_j - weight_{i,j}\right]$$

$$neigh(iter) = \eta * \exp\left[\frac{-\left(x^2 + y^2\right)}{2 * \sigma^2}\right]$$

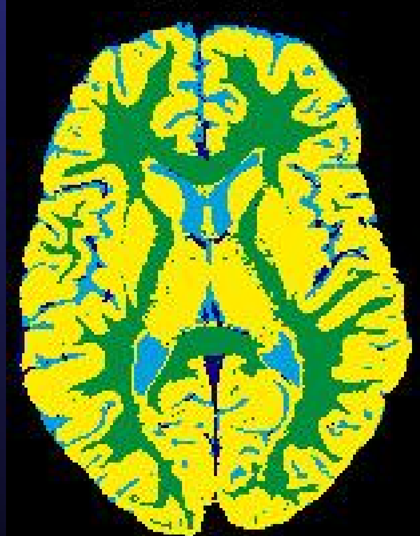
$$\eta = 0.005^{\frac{iter}{iter_{\max}}}$$

$$\sigma = 3\left(0.4^{\frac{iter}{iter_{\max}}}\right)$$

(Reddick et al. *IEEE-TMI*, 1997)

SOM of Normal Examination

T1 T2 PD FLAIR



SOM

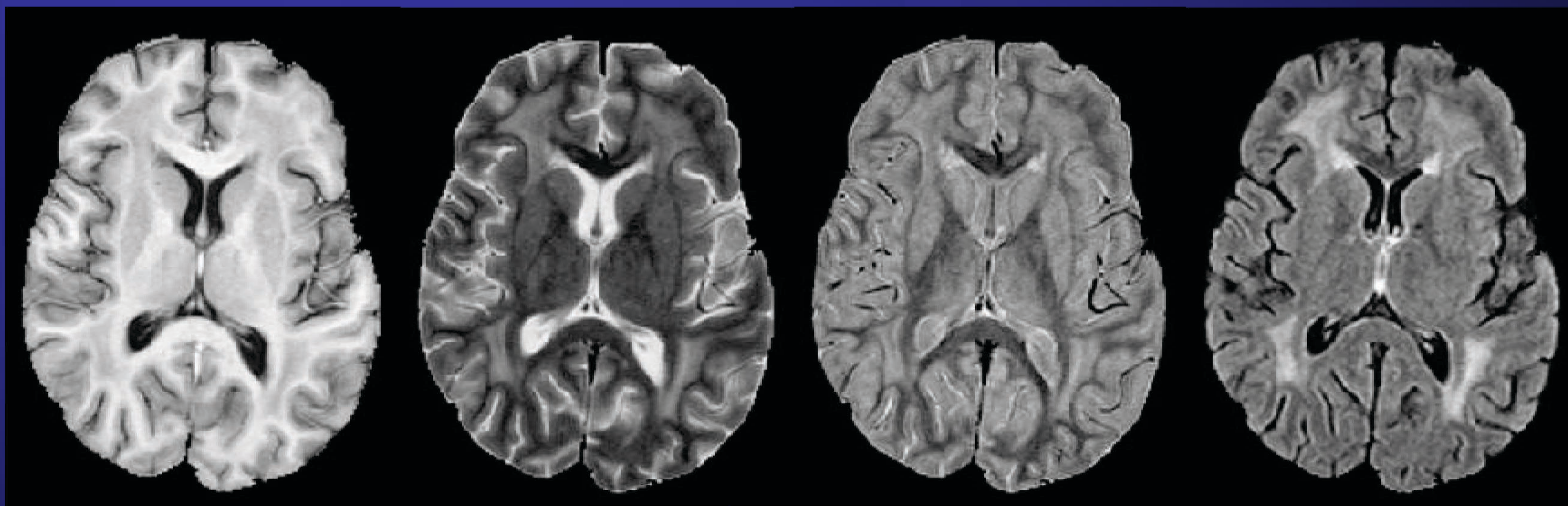
Intra-class correlations for N =14

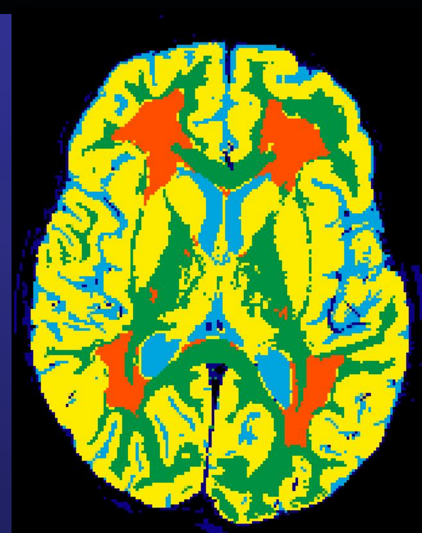
White matter	ri = 0.91	($p < 0.01$)
Gray matter	ri = 0.95	($p < 0.01$)
CSF	ri = 0.98	($p < 0.01$)

(Reddick et al. *MRM*, 2002)

SOM of Abnormal Examination

T1 T2 PD FLAIR



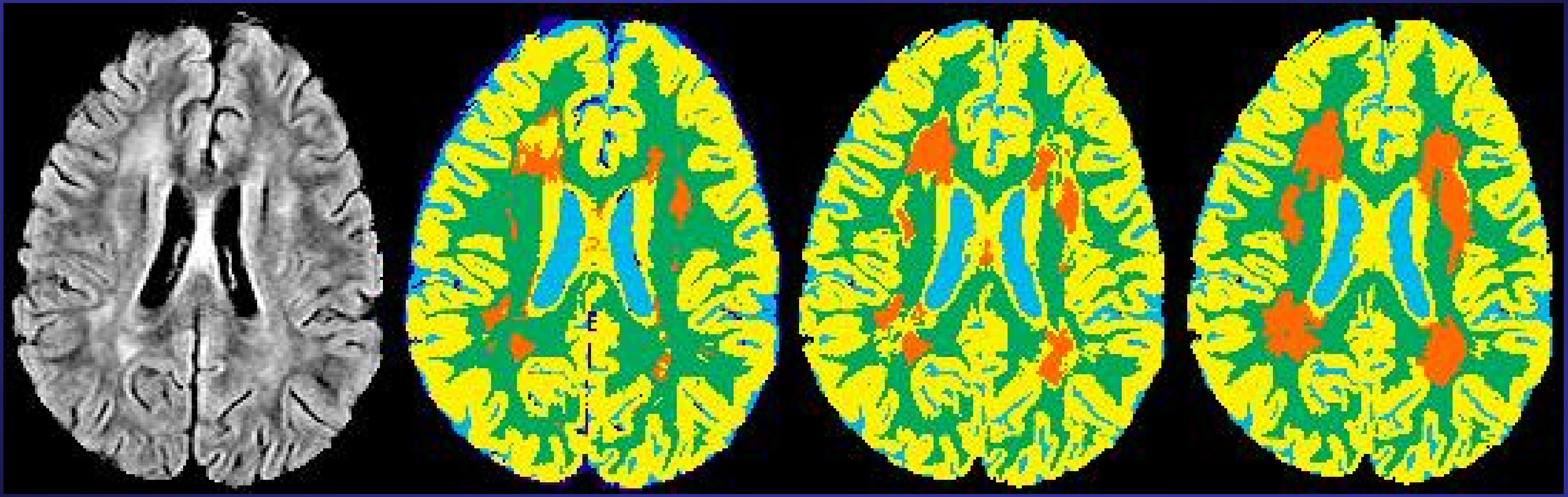


SOM

(Reddick et al. *MRM*, 2002)

Additional Refinements

FLAIR	SOM-02	SOM-03	SOM-04

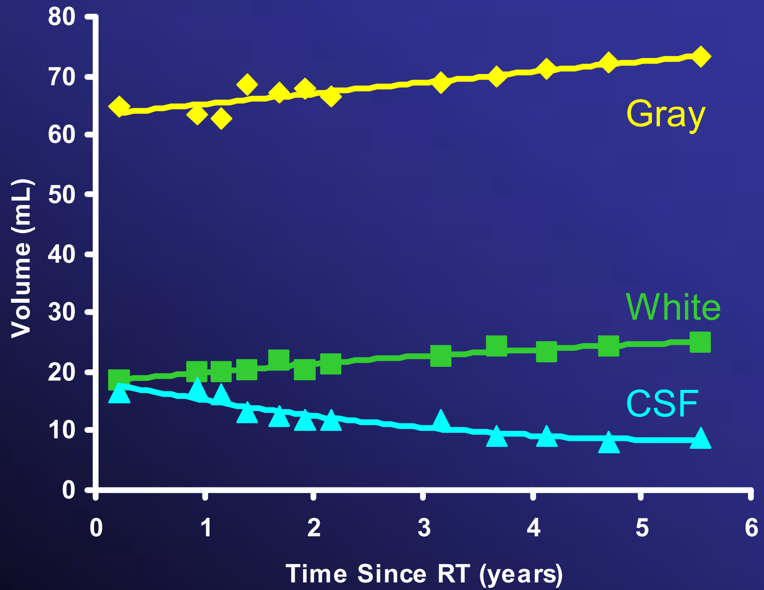


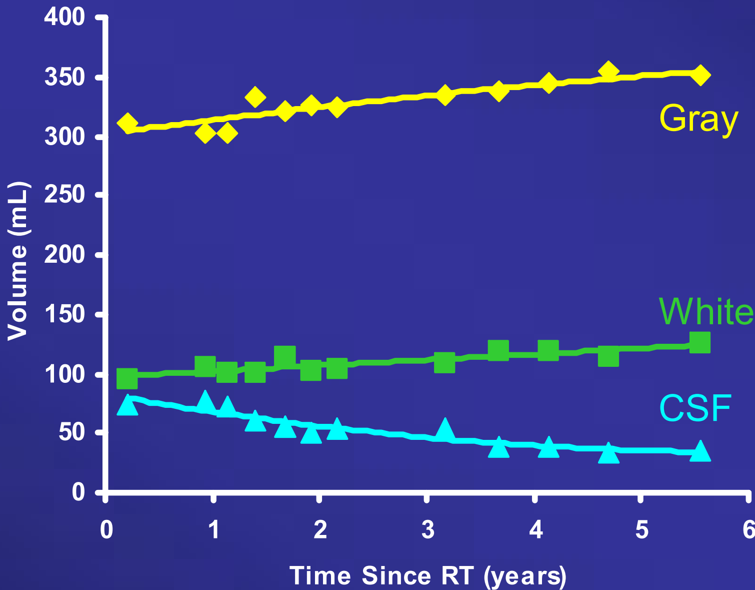
Kappa measure of agreement (N = 15)

Obs 1	0.651	0.653	0.744
Obs 2	0.602	0.615	0.699

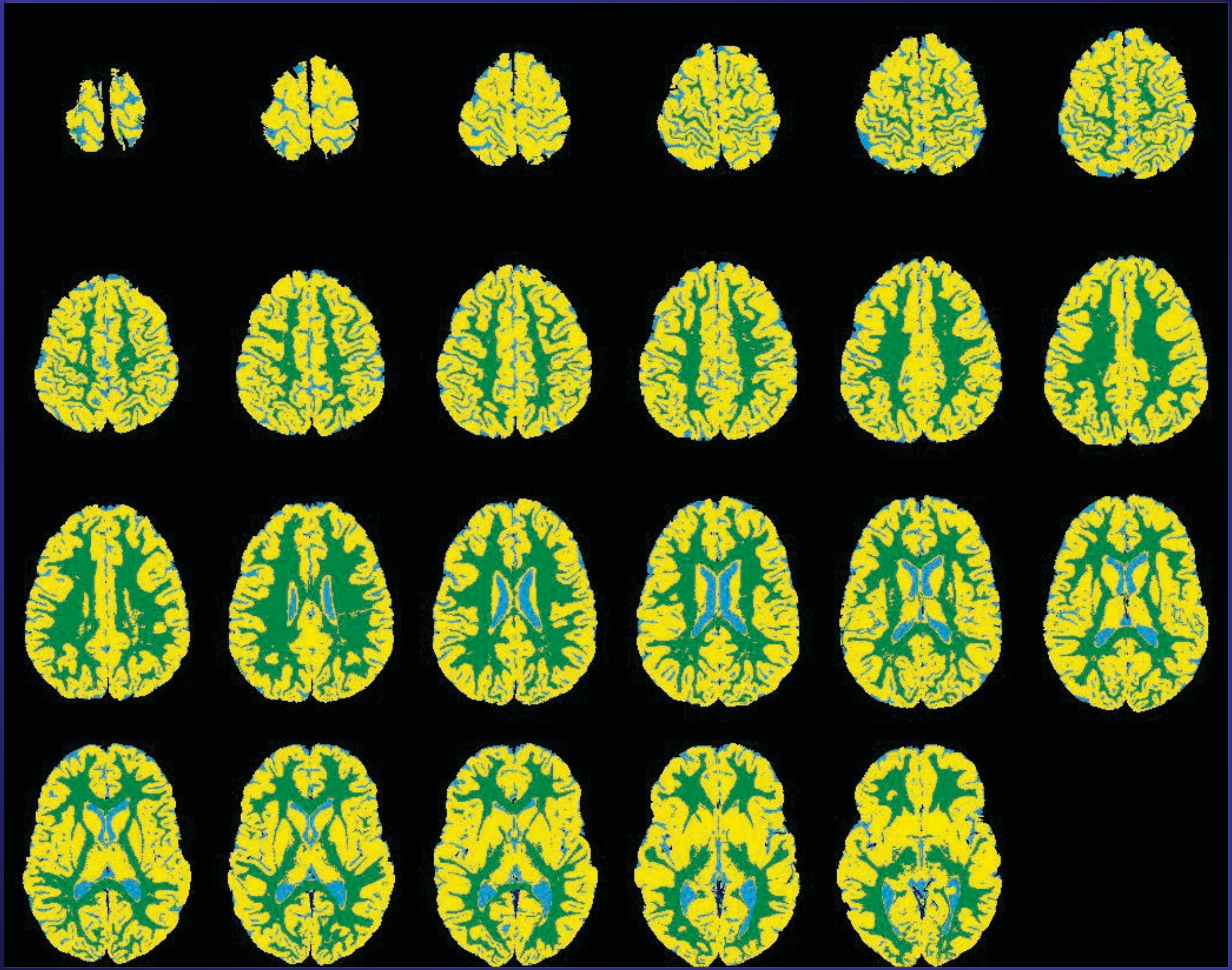
(Glass et al. *MRM*, 2004)

Index vs Expanded Sampling

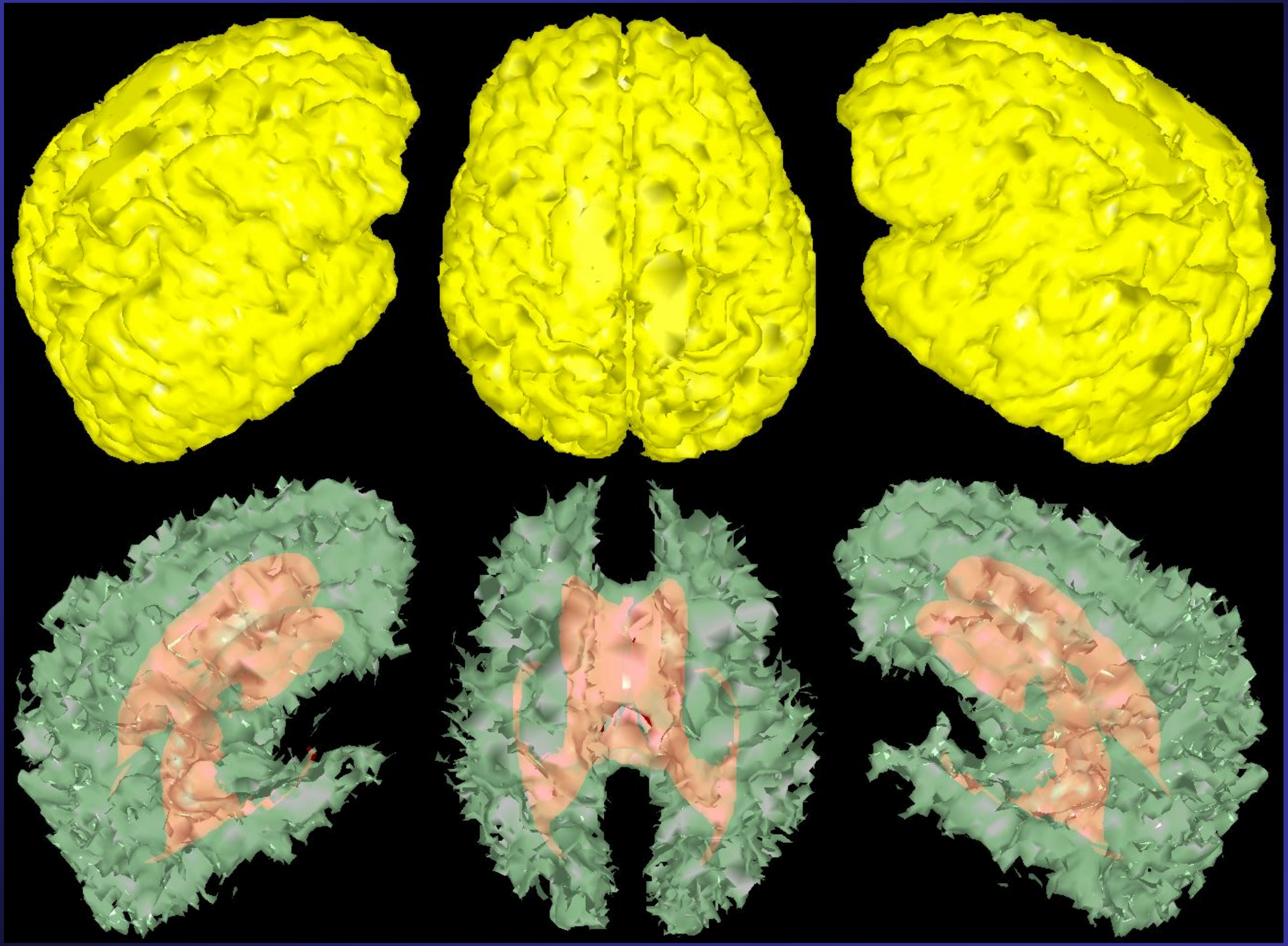




Expand Coverage



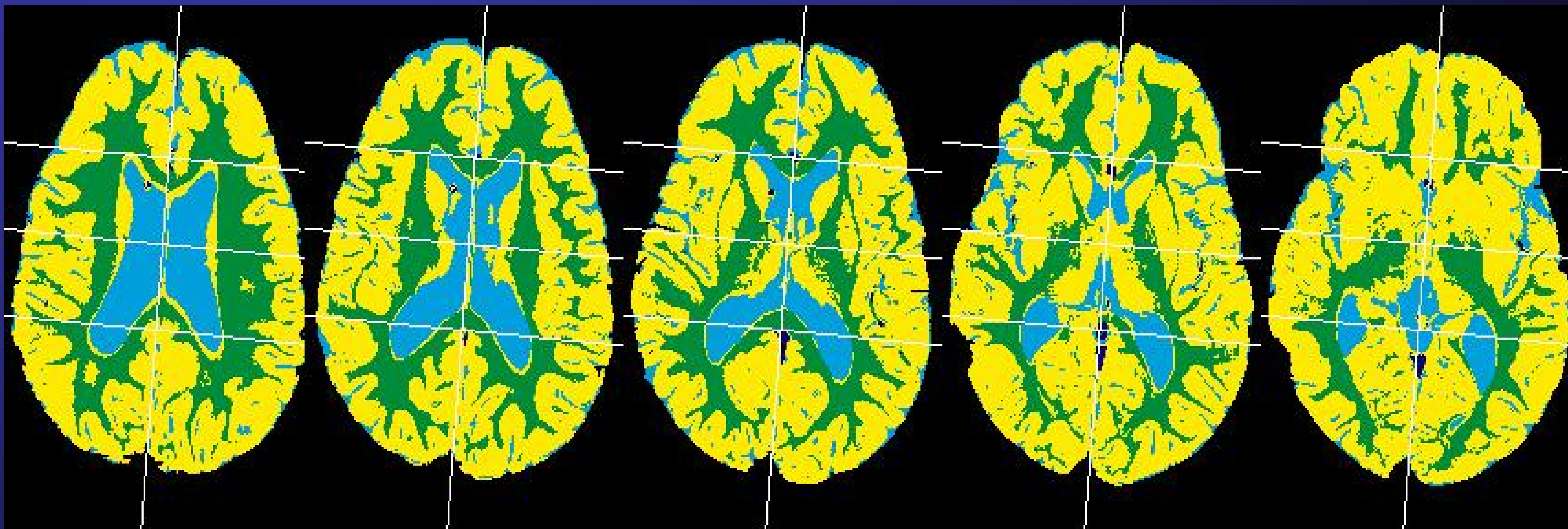
3D Visualization

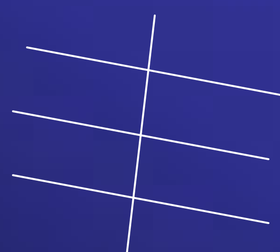


ZY Shan

(Mulhern et al. *Lancet Onc*, 2004)

Regional Analysis





Right Left

Prefrontal

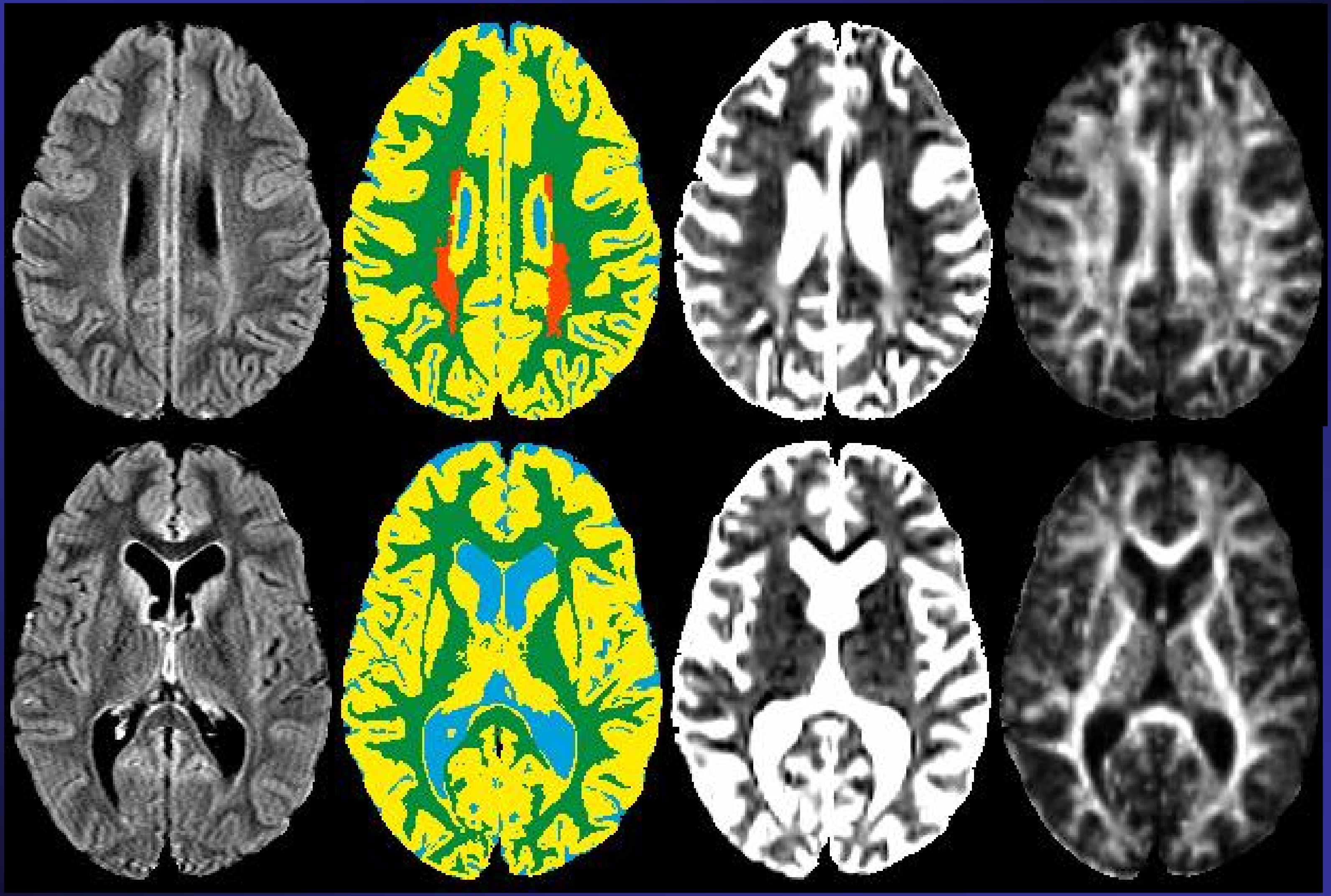
Frontal

Parietal / Mid-Temporal

Parietal / Occipital

(Mulhern et al. *JINS*, 2004)

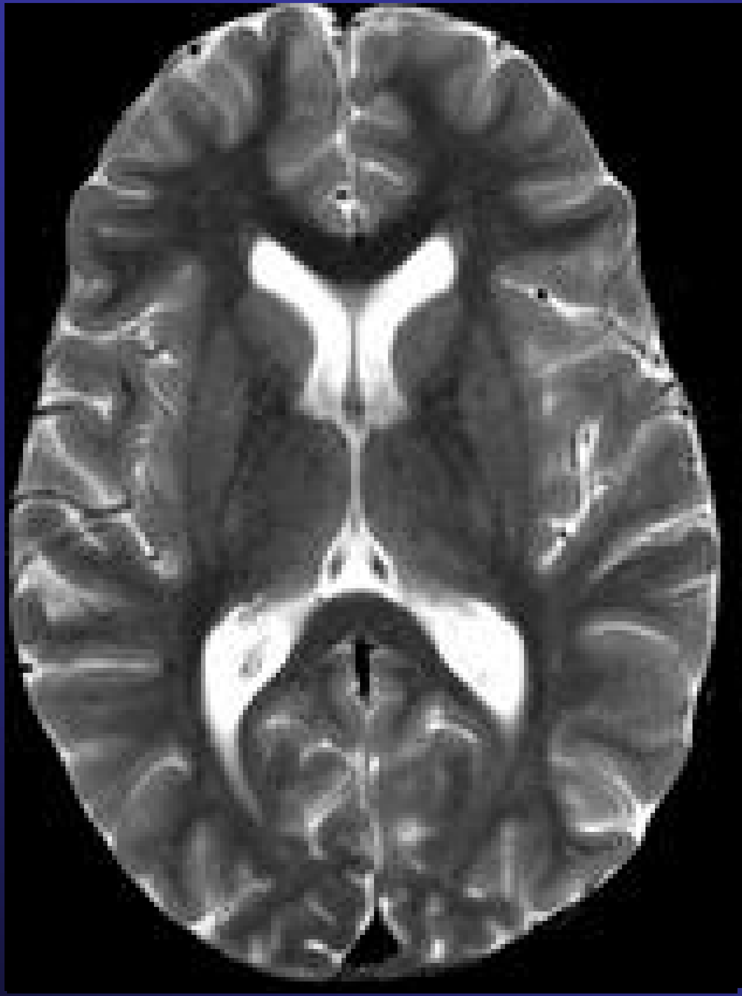
Quantifying White Matter Integrity



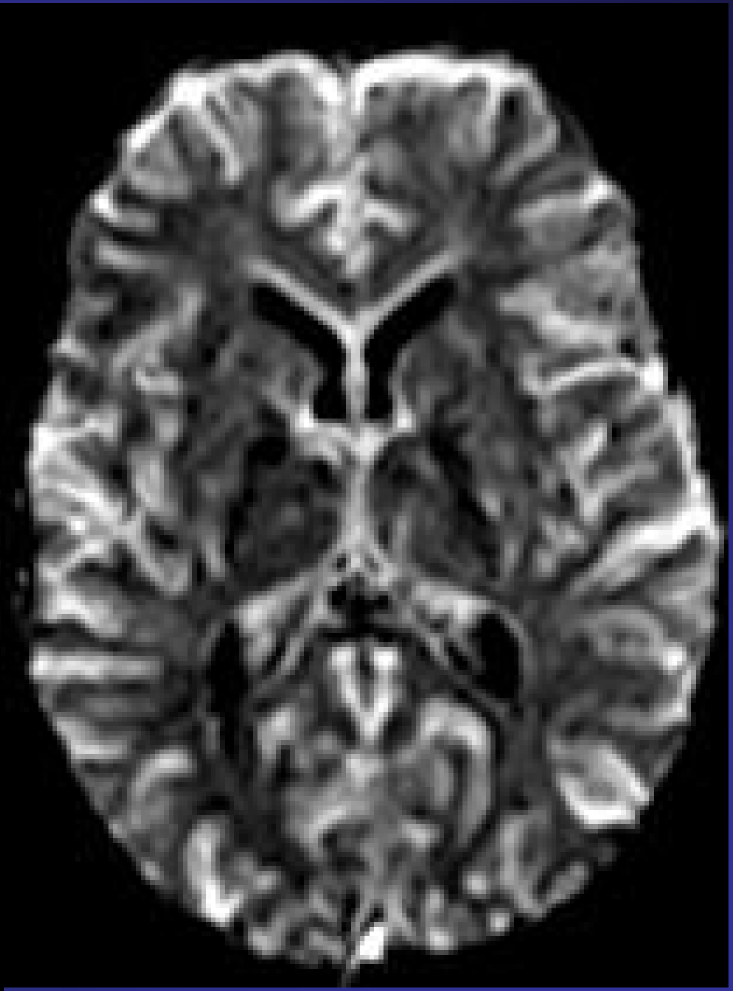
FLAIR SOM ADC FA

RJ Ogg

Quantifying White Matter Perfusion



T2



CBV

RJ Ogg

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Why Normal-Appearing White Matter?

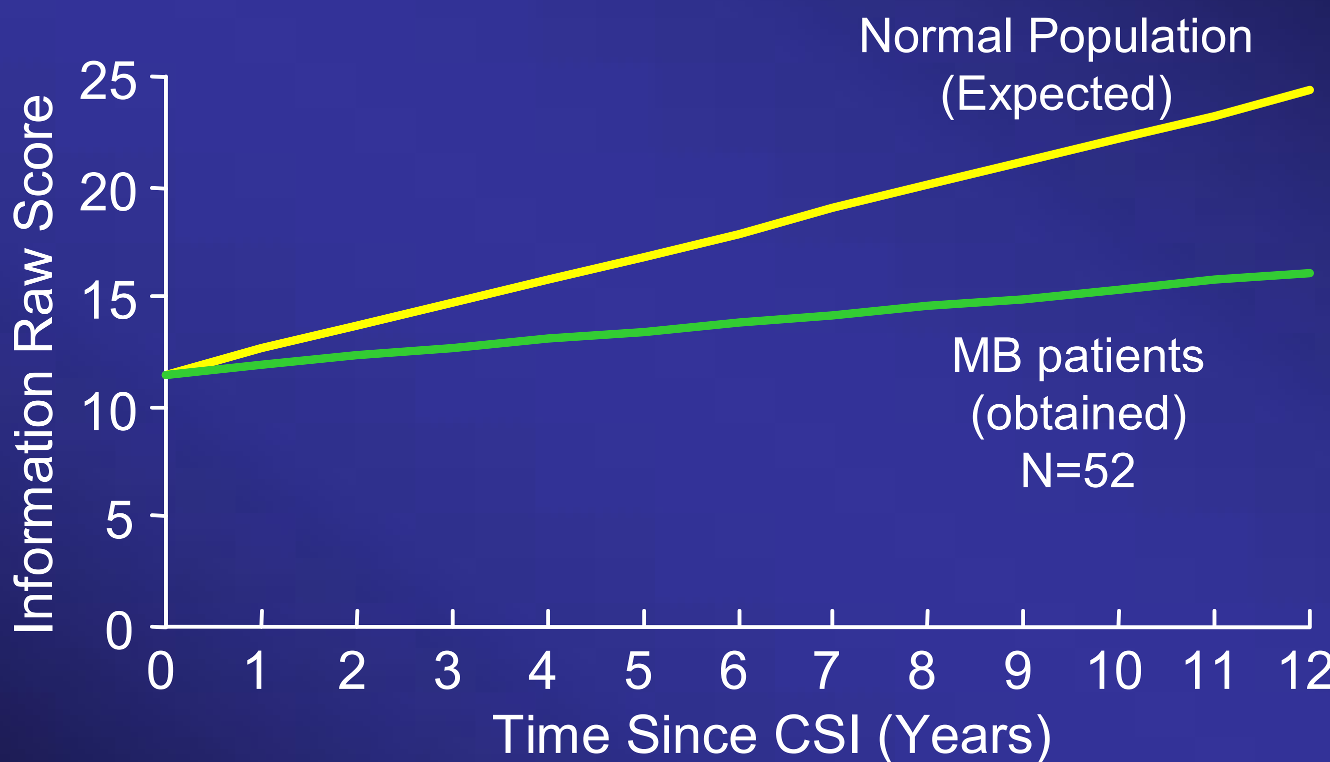
Two age-matched groups treated for brain tumors of the Posterior Fossa

Variable	MB (N=18)	LGA (N=18)	Significance
FSIQ	82.0 $\pm$ 10.9	92.9 $\pm$ 15.7	P=0.026
ICV	82.5 $\pm$ 5.4	85.2 $\pm$ 6.0	NS
White	21.4 $\pm$ 4.4	24.7 $\pm$ 5.7	P=0.008
Gray	52.6 $\pm$ 5.1	54.3 $\pm$ 6.1	NS
CSF	8.1 $\pm$ 4.0	6.1 $\pm$ 4.5	NS

RK Mulhern

(Reddick et al. *MRI*, 1998)

A New Understanding of Decreasing IQ



(Palmer et al. *JCO*, 2001)

Linking Therapy & Neurocognitive Deficits

Cross sectional study of Medulloblastoma survivors (N=42)

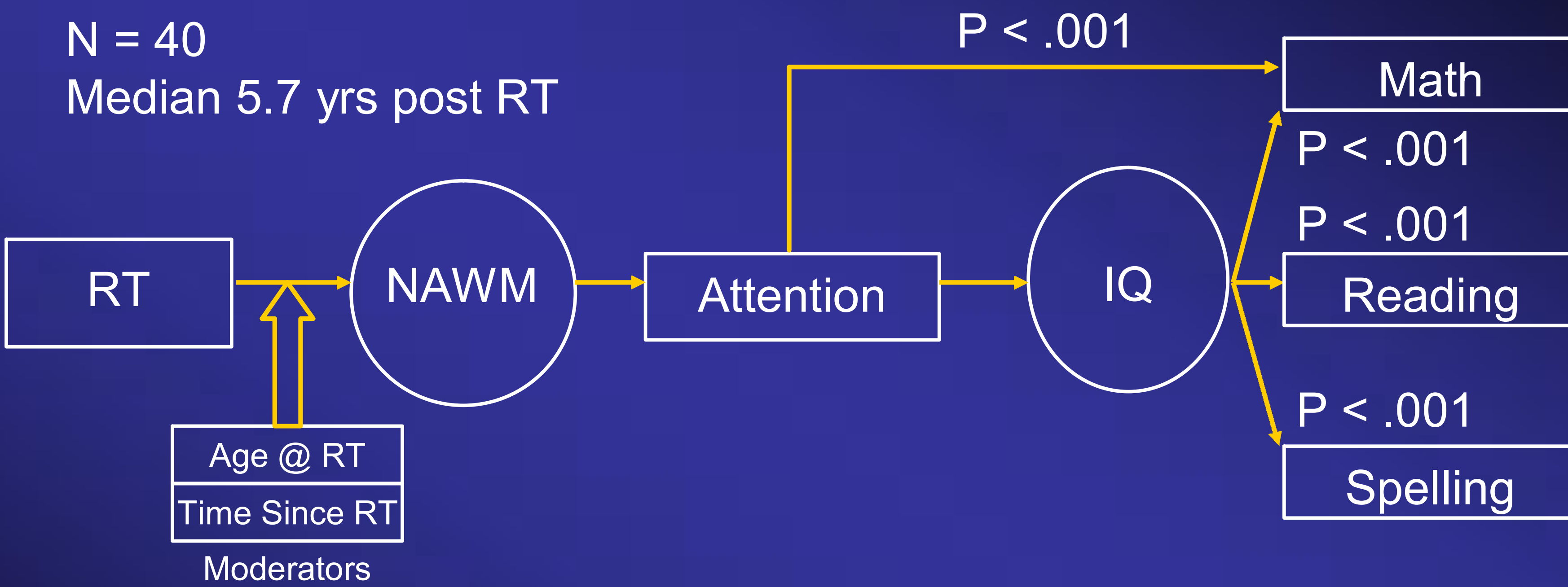
Age at irradiation significantly associated with FSIQ
($R^2 = 0.170$; $P = 0.006$; controlled for time since irradiation)

Mediational model: ~70% of association explained by Normal Appearing White Matter

(Mulhern et al. *JCO*, 2001)

Developmental Model

N = 40
Median 5.7 yrs post RT



Model explains:
~ 60% of variance in reading
~ 60% of variance in spelling
~ 80% of variance in math

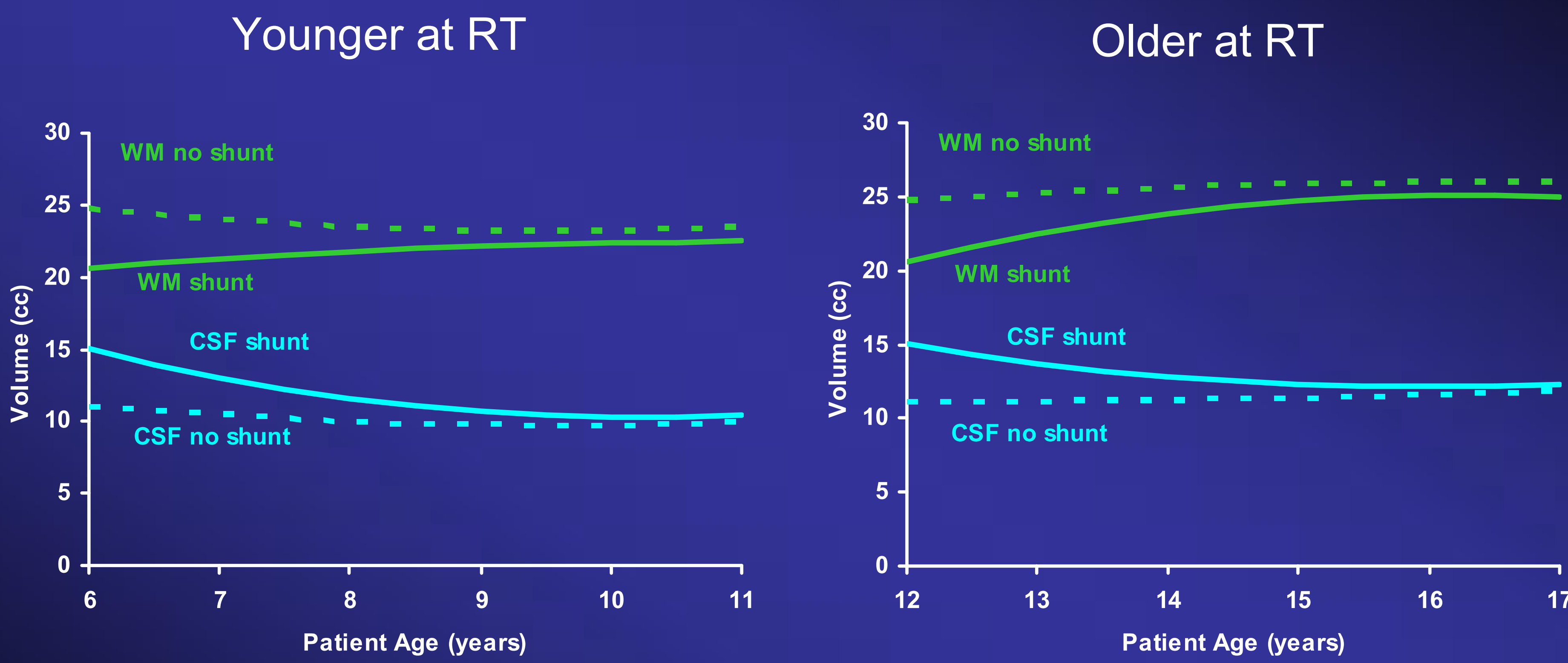
(Reddick et al. *Cancer*, 2003)

Most Recent Results

- Longitudinal study of 324 MR exams from 52 subjects treated for Medulloblastoma
  - All received 36 Gy CSI
  - 19 had shunts placed
  - Median age @ irradiation 8.3 yrs (3.4 to 20.0 yrs)
  - Median time since irradiation 2.5 yrs (-0.2 to 7.9 yrs)
- Cross-sectional study of a subset of 19 patients age similar to controls and without shunts
  - Single most recent MR
  - Age at examination 13.0 ± 3.1 yrs
- 26 healthy sibling controls imaged once
  - Age at examination 12.6 ± 3.4 yrs

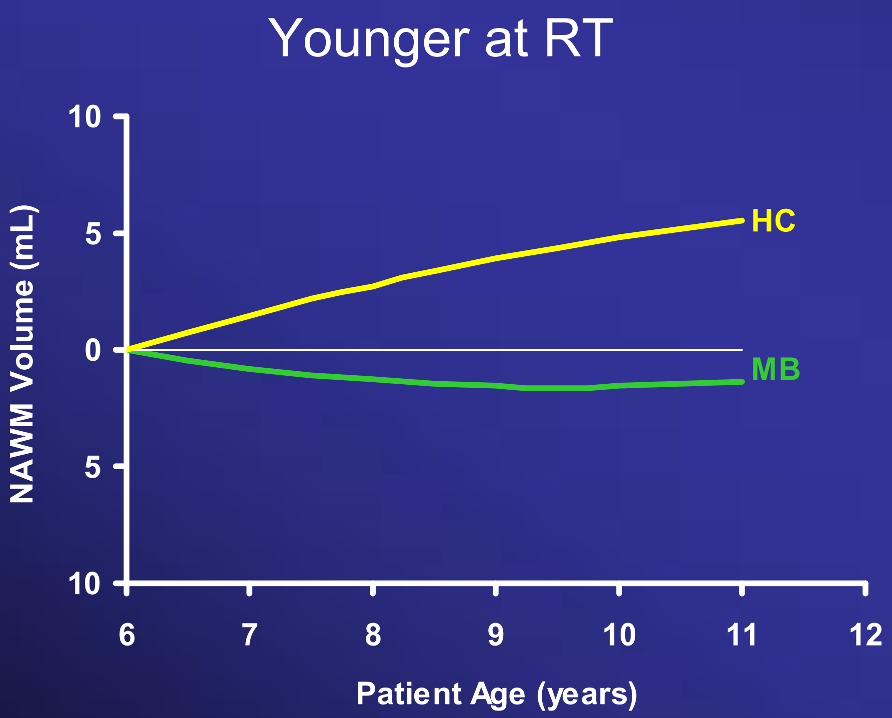
A Gajjar

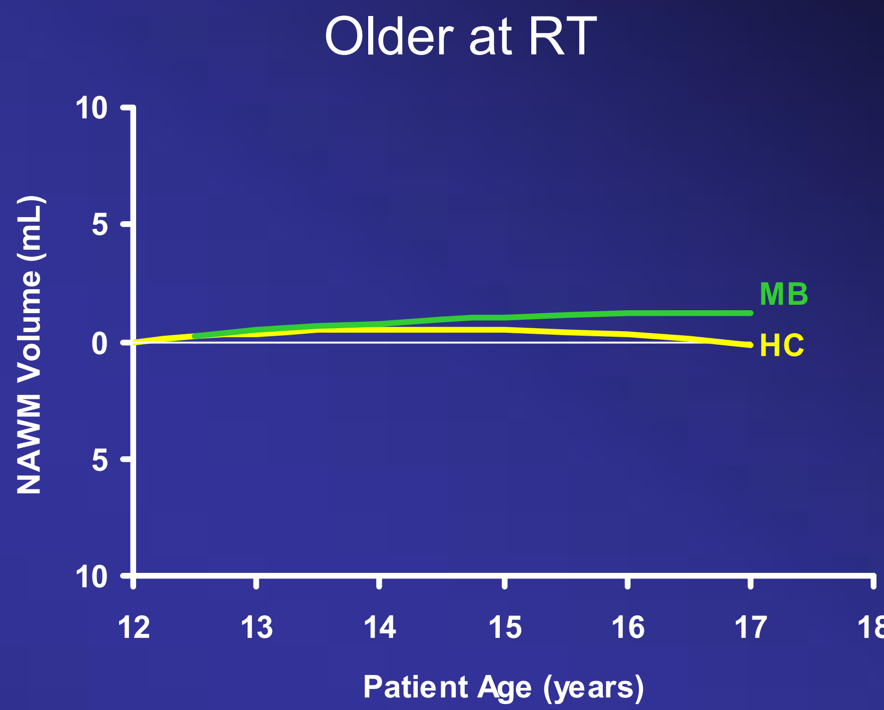
Longitudinal Brain Volume Development



(Reddick et al. *Neuro Onc*, 2005)

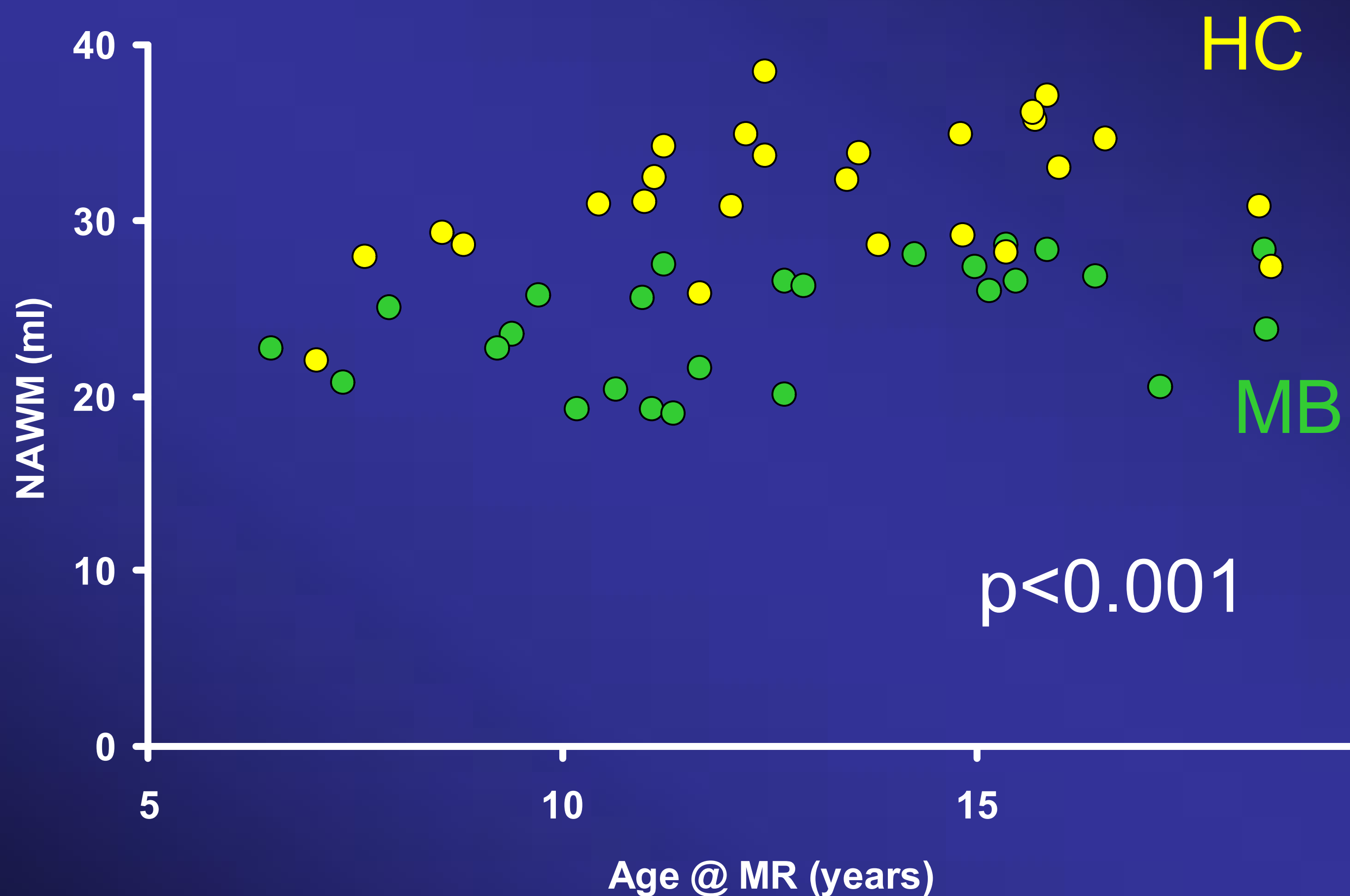
Longitudinal Brain Volume Development





(Reddick et al. *Neuro Onc*, 2005)

Longitudinal Brain Volume Development



(Reddick et al. *Neuro Onc*, 2005)

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Most Recent Results

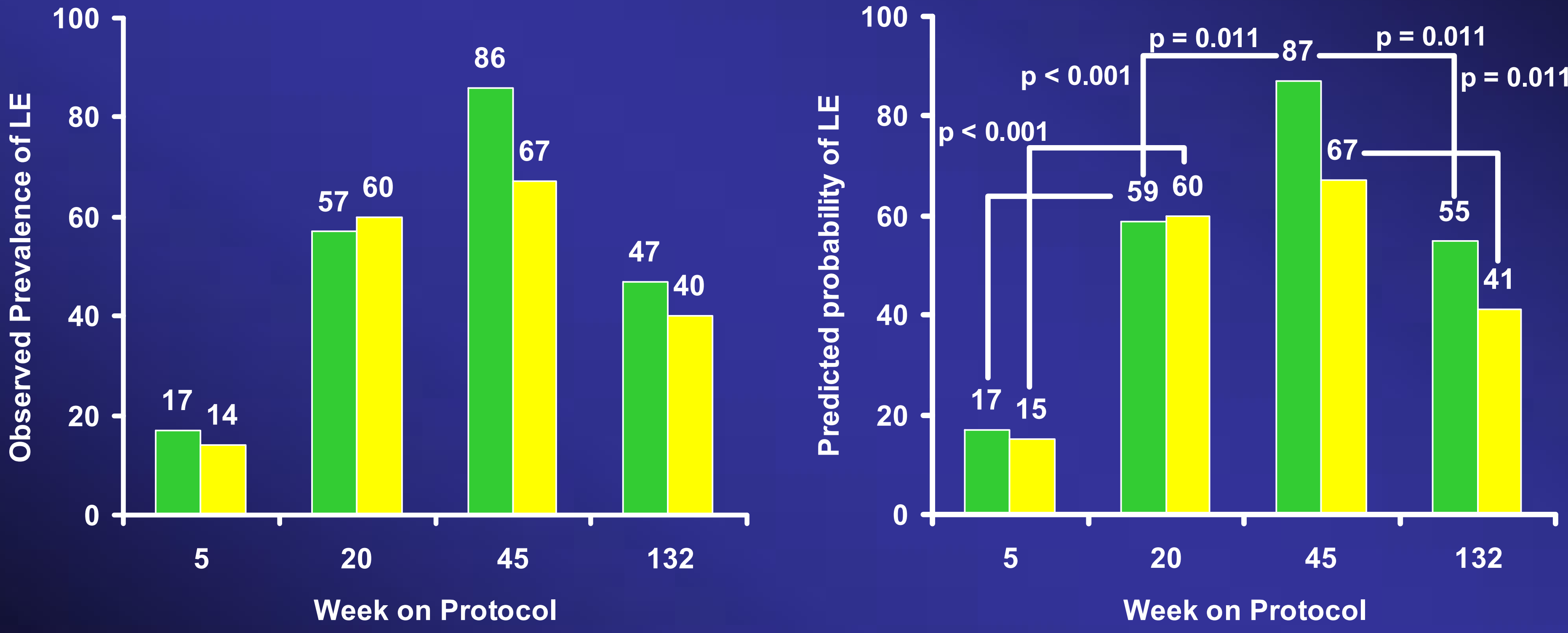
Longitudinal study of 164 MR exams from 45 subjects treated for ALL on Total 14

	Low Risk	Standard / High Risk
Number of Subjects		
Post 1 IV-MTX	21	23
Post 4 IV-MTX	20	21
Post 7 IV-MTX	21	21
End of Therapy	20	17
Gender		
Male	10	11
Female	12	12
Age at Diagnosis (years)	5.0 ± 2.7	9.2 ± 4.8

C-H Pui

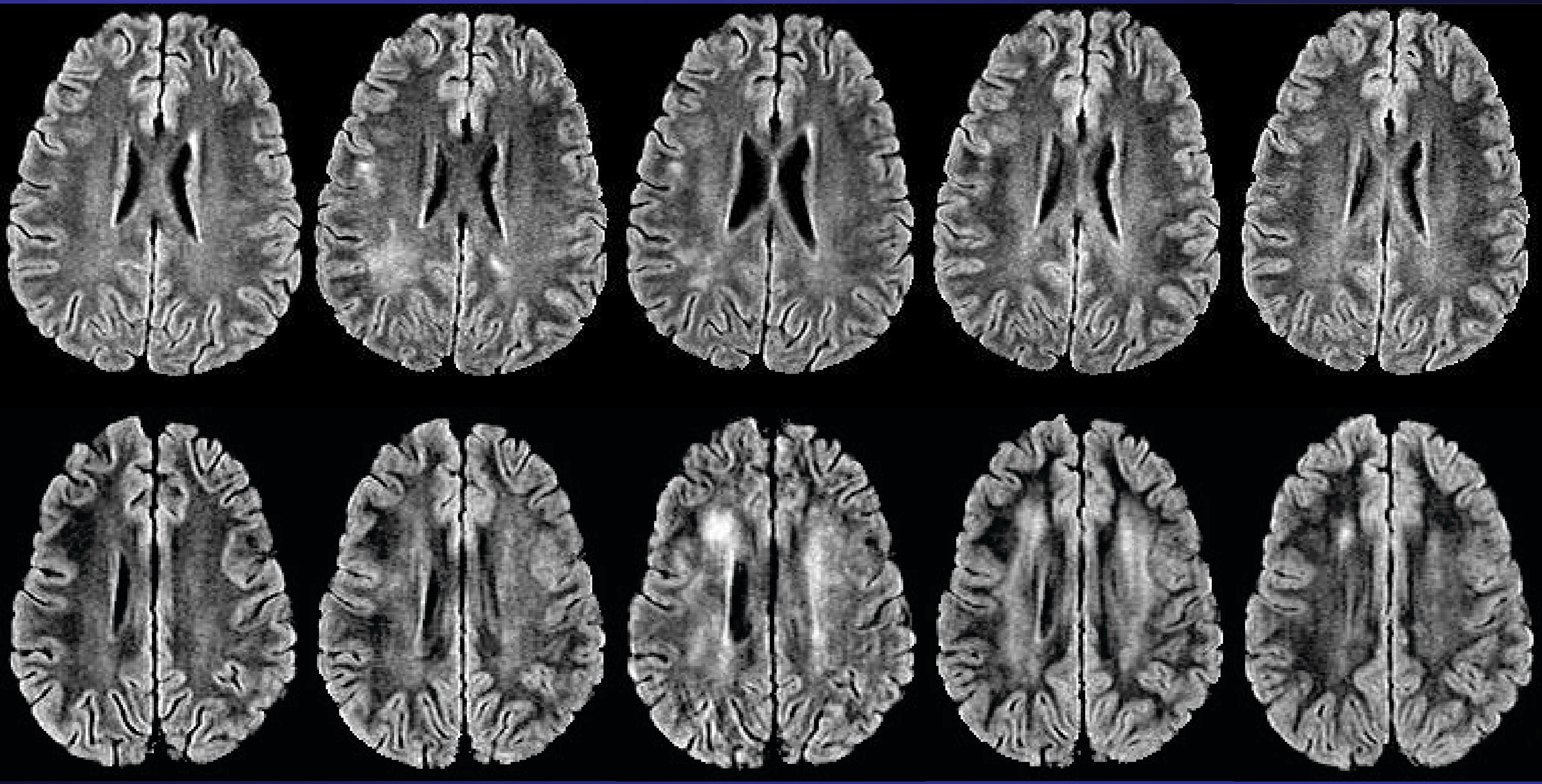
Prevalence of LE

Standard / High-Risk
Low-Risk



(Reddick et al. *AJNR* [in press], 2005)

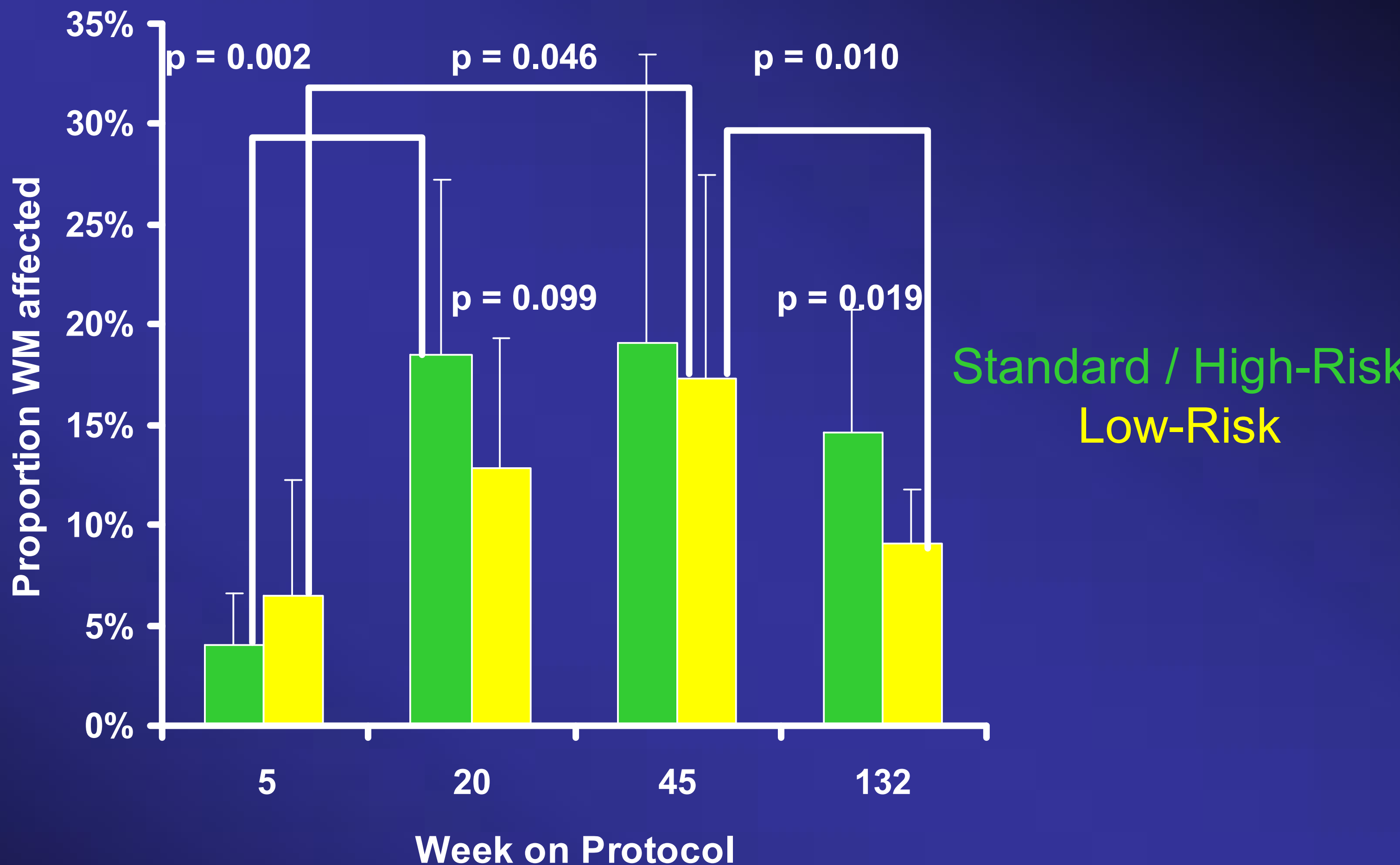
Transient vs. Persistent



Week 5 | 20 | 45 | 132 | 240

KJ Helton

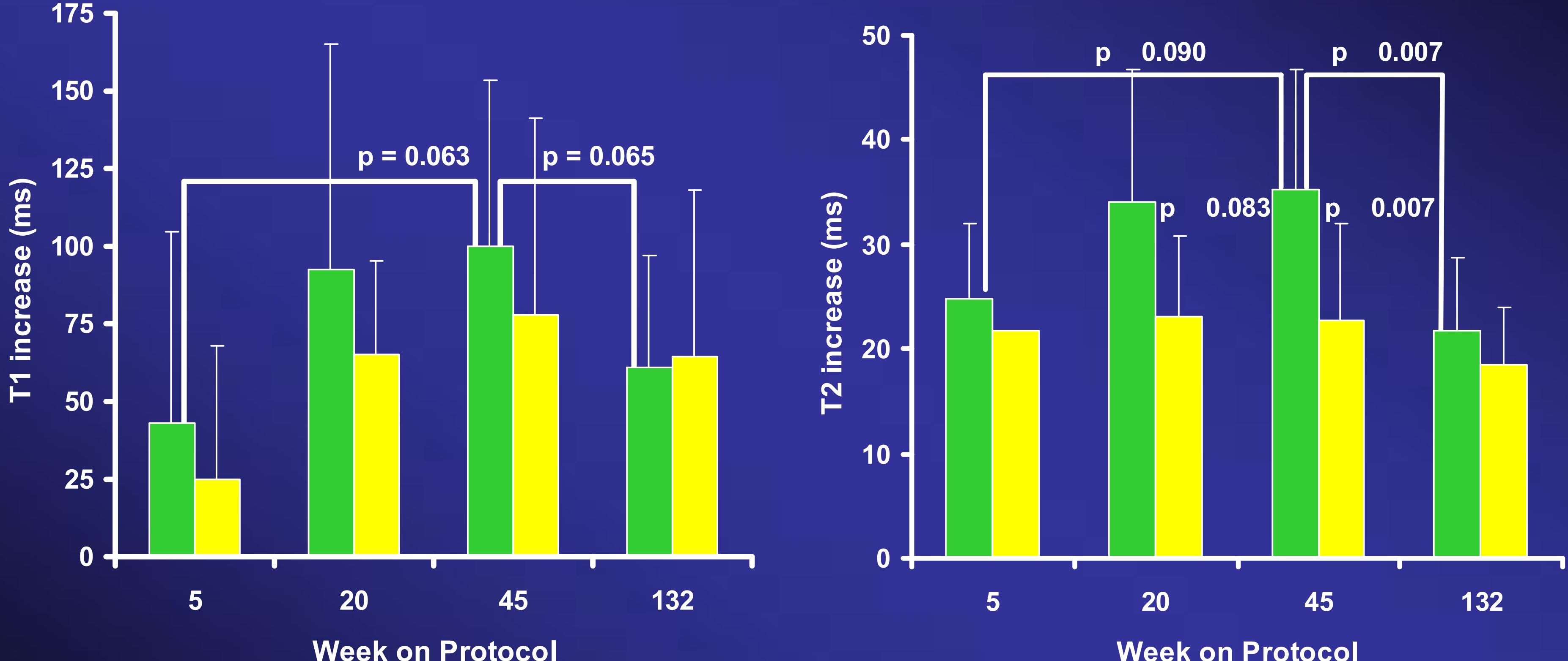
Extent of LE



(Reddick et al. *AJNR* [in review], 2005)

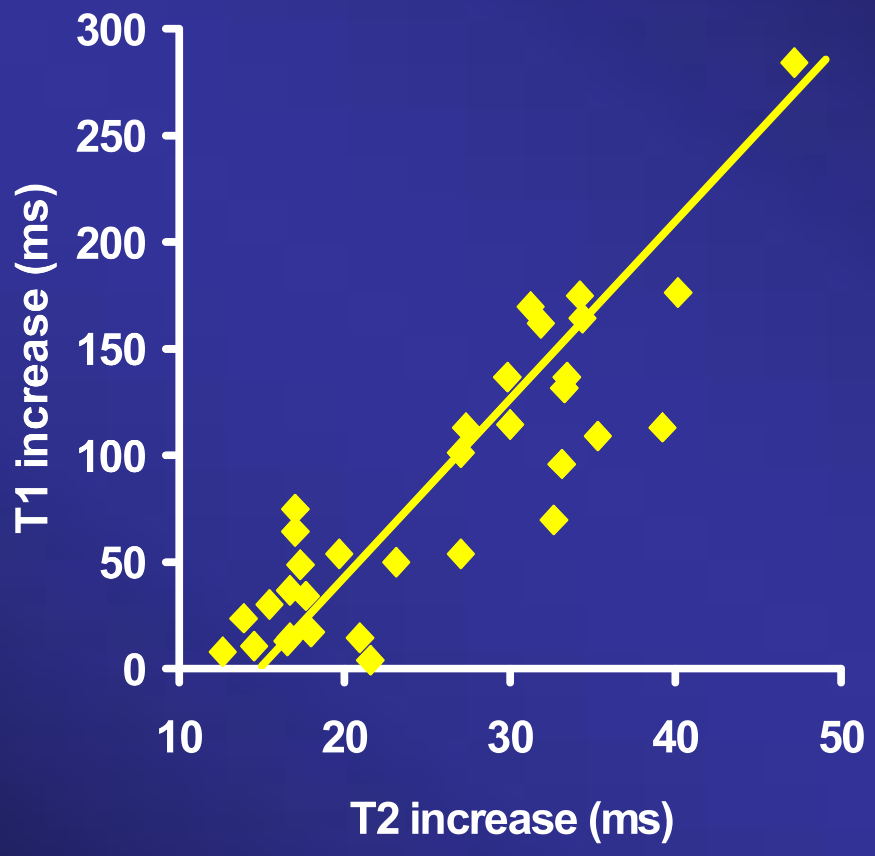
Intensity of LE

Standard / High-Risk
Low-Risk



(Reddick et al. *AJNR* [in review], 2005)

Relationship Between Intensity Measures



(Reddick et al. *AJNR* [in review], 2005)

Translational Imaging Research Summary

Basic Research

- Developed essential novel image processing capabilities which were optimized for specialized clinical research applications
- Continue to develop innovative algorithms and methods to quantify the structure and integrity of cerebral white matter *in vivo*

Clinical Research

- Used non-invasive imaging technology to quantify neurostructural changes resulting from radiological or pharmacological insult and related these changes to neurocognitive performance

Translational Imaging Research Summary

Building on extensive experience with MB

- New studies designed to combine radiation dosimetry maps with MR imaging measures of perfusion and diffusion
- Investigate the integrity of white matter microvasculature and axonal myelin
- Changes in these measures is hypothesized to precede more global changes in cerebral white matter volume
- 120 subjects with 1560 MR exams

Translational Imaging Research Summary

Building on preliminary experience with ALL

- Ongoing ALL study designed to test hypotheses that early changes in MR imaging measures are:
- predictive of later white matter changes
- proportionate to exposure to HDMTX
- related to CSF and plasma homocysteine
- predictive of treatment-induced neurocognitive deficits and diminished quality of life in survivors
- 300 subjects with 1200 MR examinations

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