Montreal Neurological
Institute/Hospital

McGill University

Change Detection and Quantification
in Multiple Sclerosis

D. Louis Collins

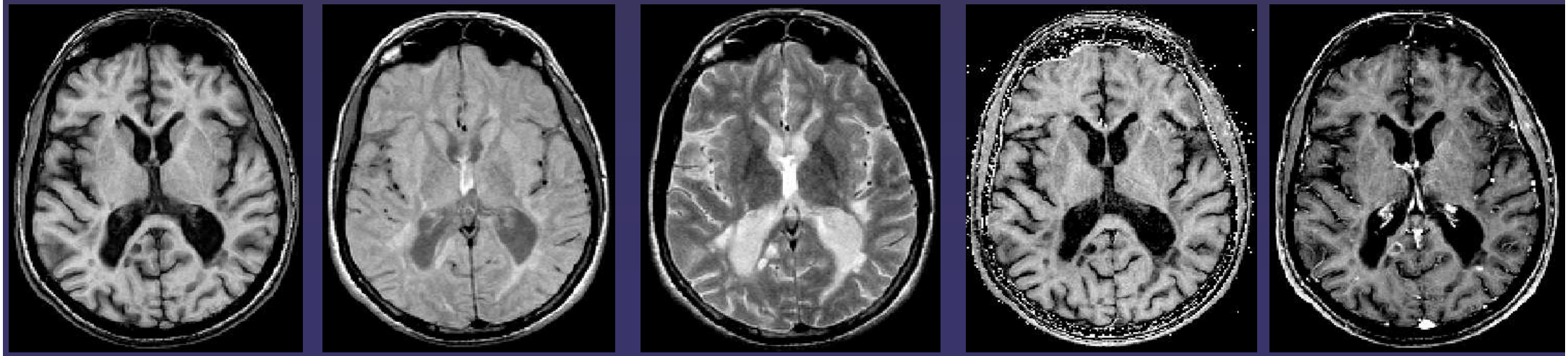
Sept 26, 2004

Multiple Sclerosis

- Motivations
- Volume change
  - Global (BICCR)
  - Regional (GM, ventricels, lobes)
  - Local (around lesions)
- Clinical trial
  - BICCR results
  - VBM results
- Deformation modeling
  - Where and When?

Motivation

- **Clinical surrogates of disease burden in MS are highly variable (EDSS, MSFC)**
- **MRI shows lesions in vivo**

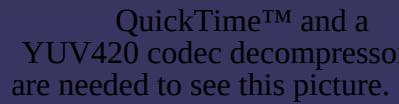


T_1-w PD T_2-w MTR Gado

Motivation

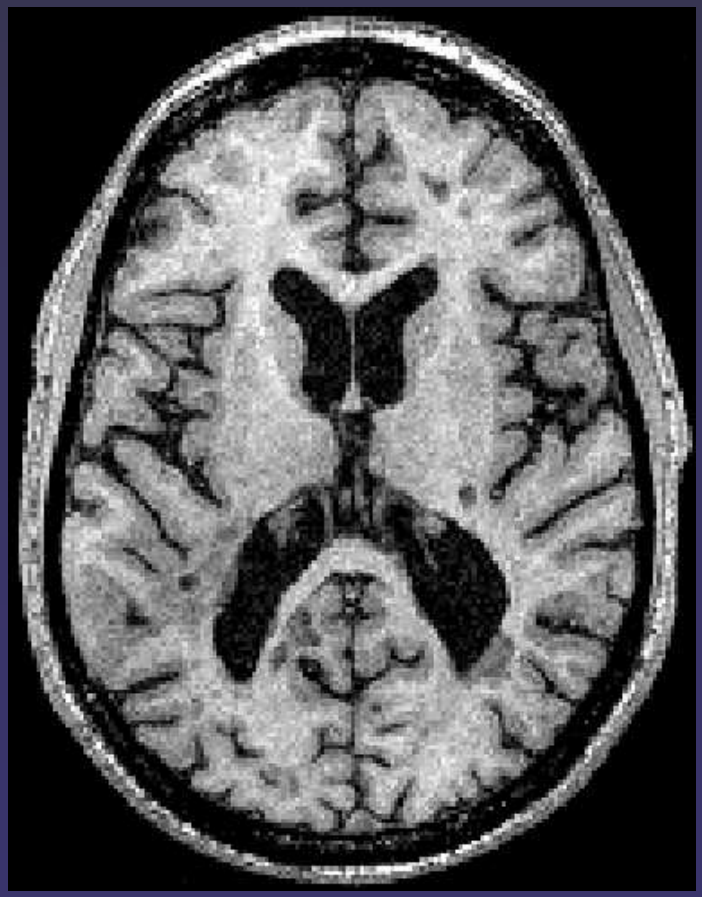
- Clinical surrogates of disease burden in MS are highly variable (EDSS, MSFC)
- MRI shows lesions in vivo
- MRI = 10 * clinical activity

MRI activity



MRI shows brain atrophy in MS

normal



MS

Motivation

- **Clinical surrogates of disease burden in MS are highly variable (EDSS, MSFC)**
- **MRI shows lesions in vivo**
- **MRI = 10 * clinical activity**

> **MRI-based surrogates of disease burden**

MRI-based surrogates

- **T2 and Gado-based lesion metrics**
  - **have shown treatment effects**
  - **are weakly correlated with disability**
- **CNS atrophy**
  - **associated with neuronal/axonal loss**
  - **associated with irreversible neurological impairment**
  - **strong correlations with disability**

⇒ **CNS atrophy may be a better surrogate**

Methodological Requirements

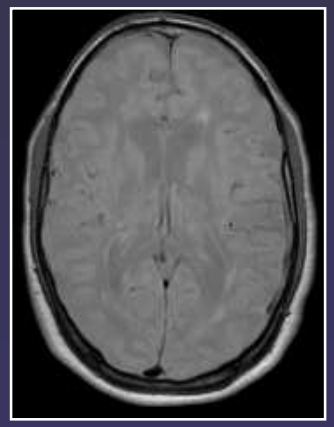
- Reproducible
- Sensitive to change
- Accurate
- Practical

Data acquisition issues

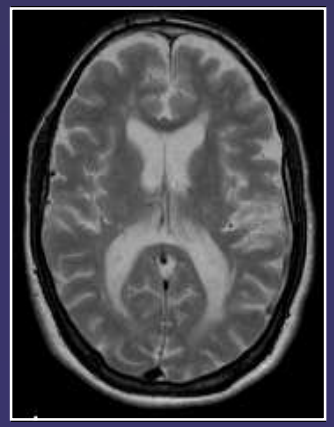
- Resolution requirements
  - Thin slices to reduce partial volume effects
  - Contiguous acquisitions (no slice gap)
  - Prefer 3D acquisitions over 2D
- Contrast
  - T1 with or w/o T2/PD
- Time constraints
  - Short acquisition to minimize motion artifacts

BICCR: Brain to IntraCranial Capacity Ratio

PDw MRI



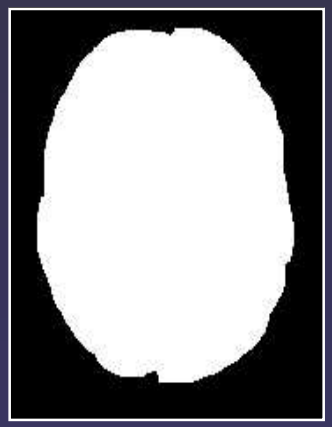
T2w MRI



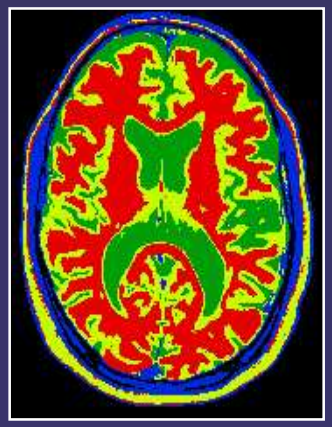
threshold, followed by erosion + dilation

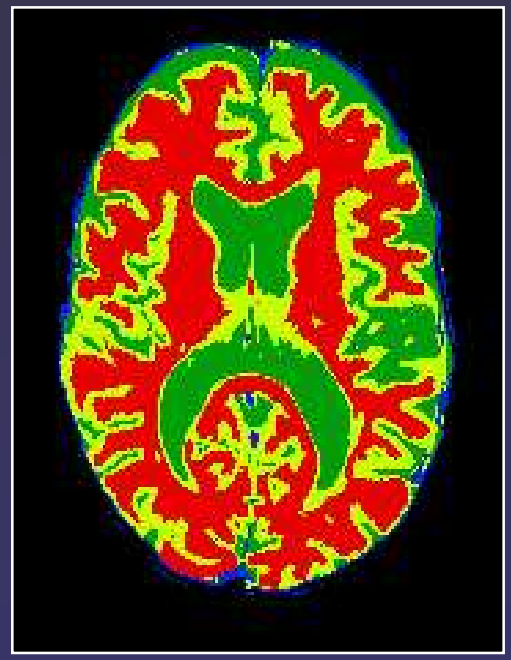
Tissue classification

ICC mask



classified data



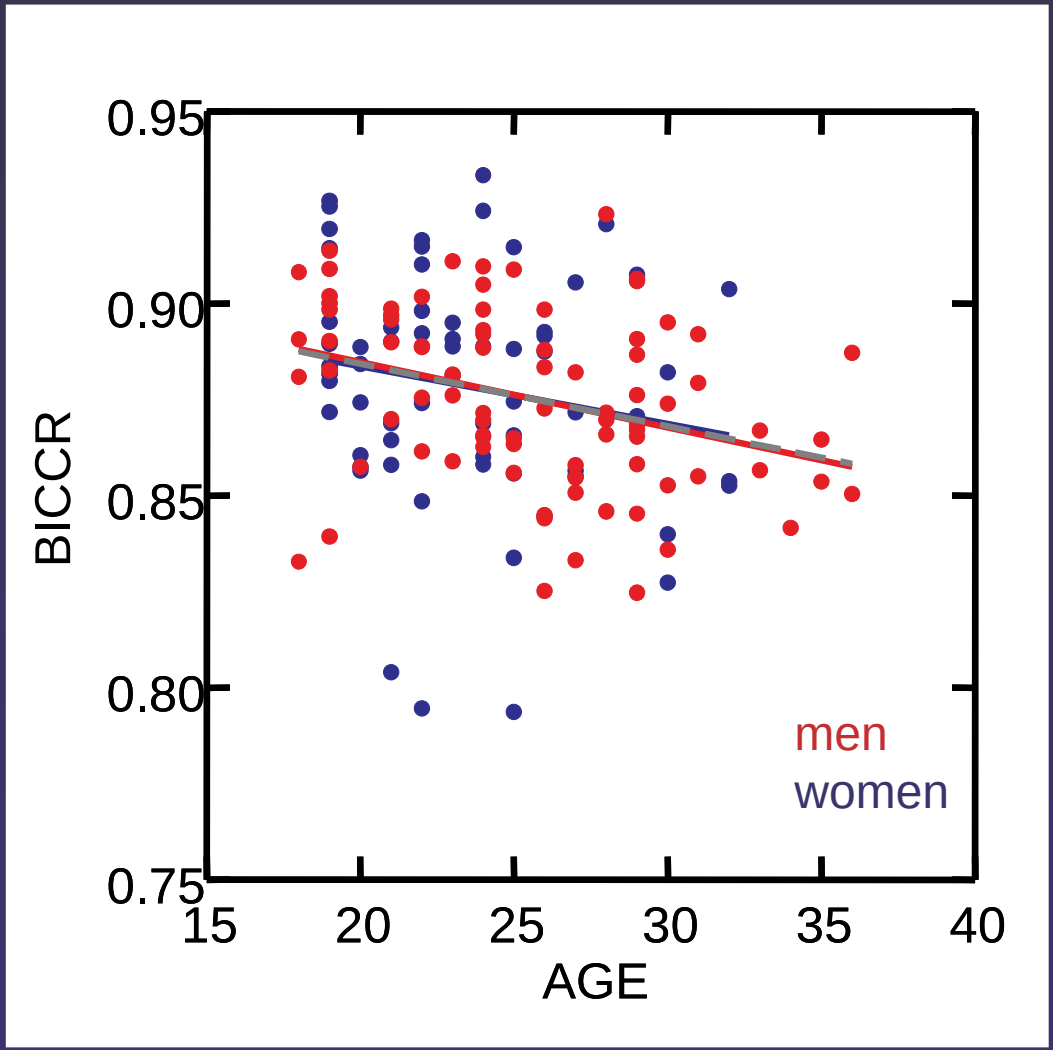


$$BICCR = \frac{GM + WM + LESION}{GM + WM + LESION + CSF}$$

Measuring Changes in Brain Volume Atrophy

- Scan-rescan COV of BPF, BICCR = 0.2%
- Smallest detectable change ~0.5%

BICCR by Age: Normal Controls



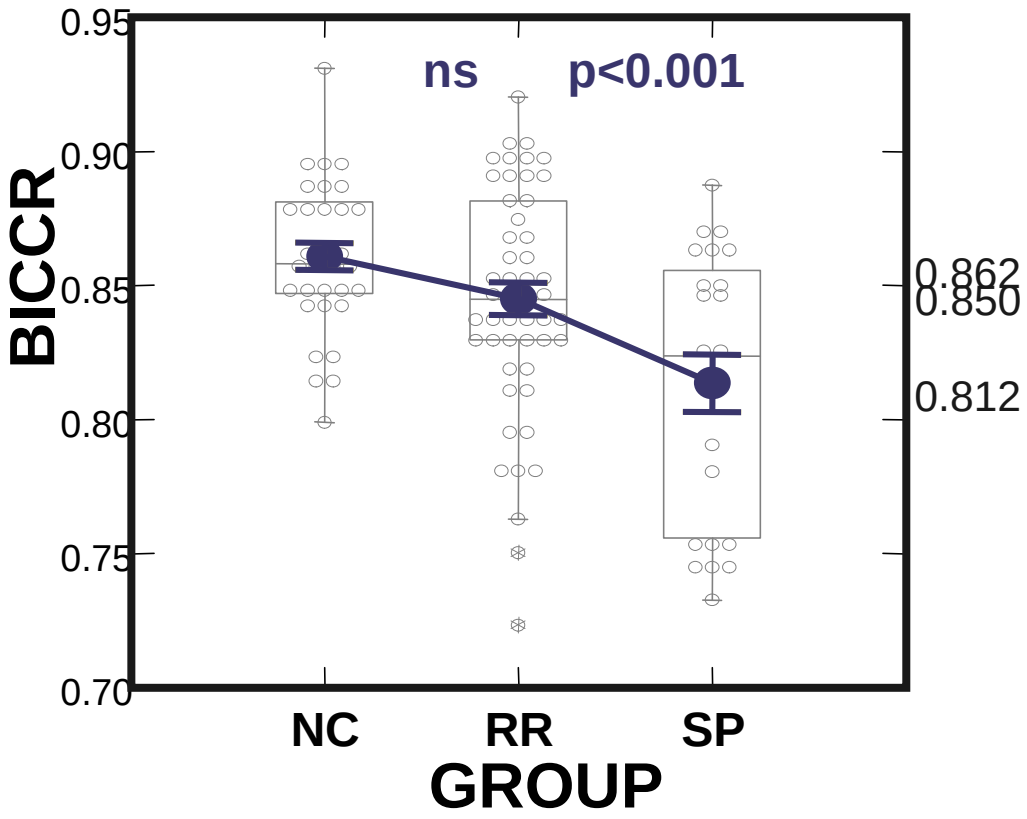
Data from ICBM project, courtesy A Evans

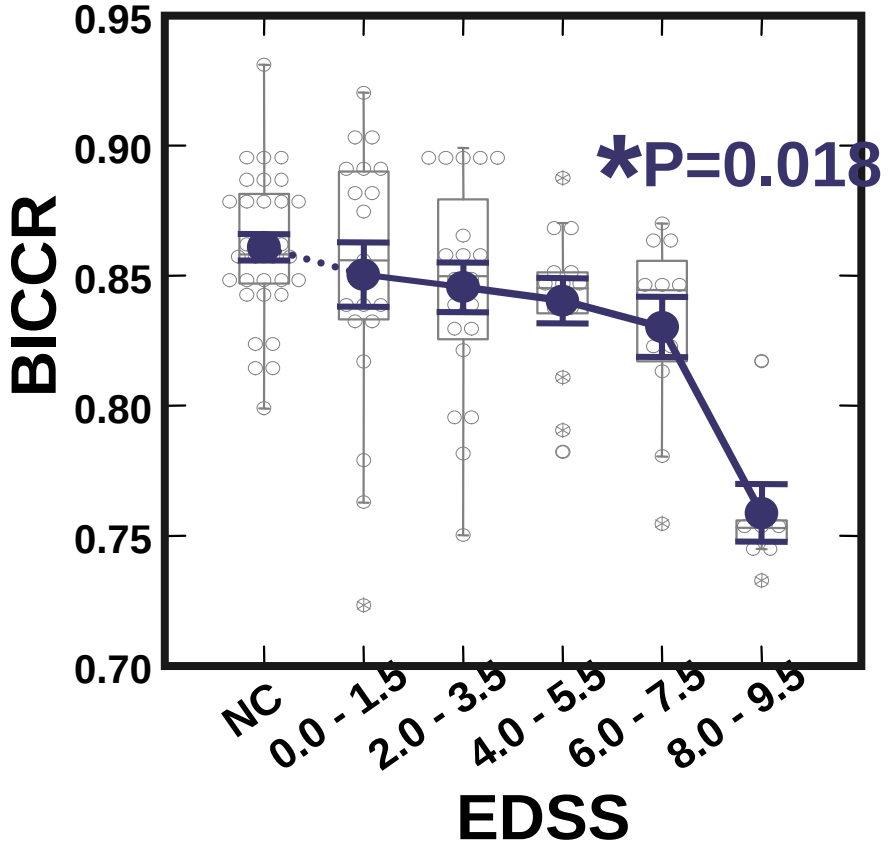
	Pearson	p	coef.	R^2
all (n=149)	-0.27	.0021	-0.175%/y	7%
women (n=64)	-0.18	.30	-0.215%/y	4%
men (n=85)	-0.34	.0028	-0.167%/y	11%

In agreement with the work of

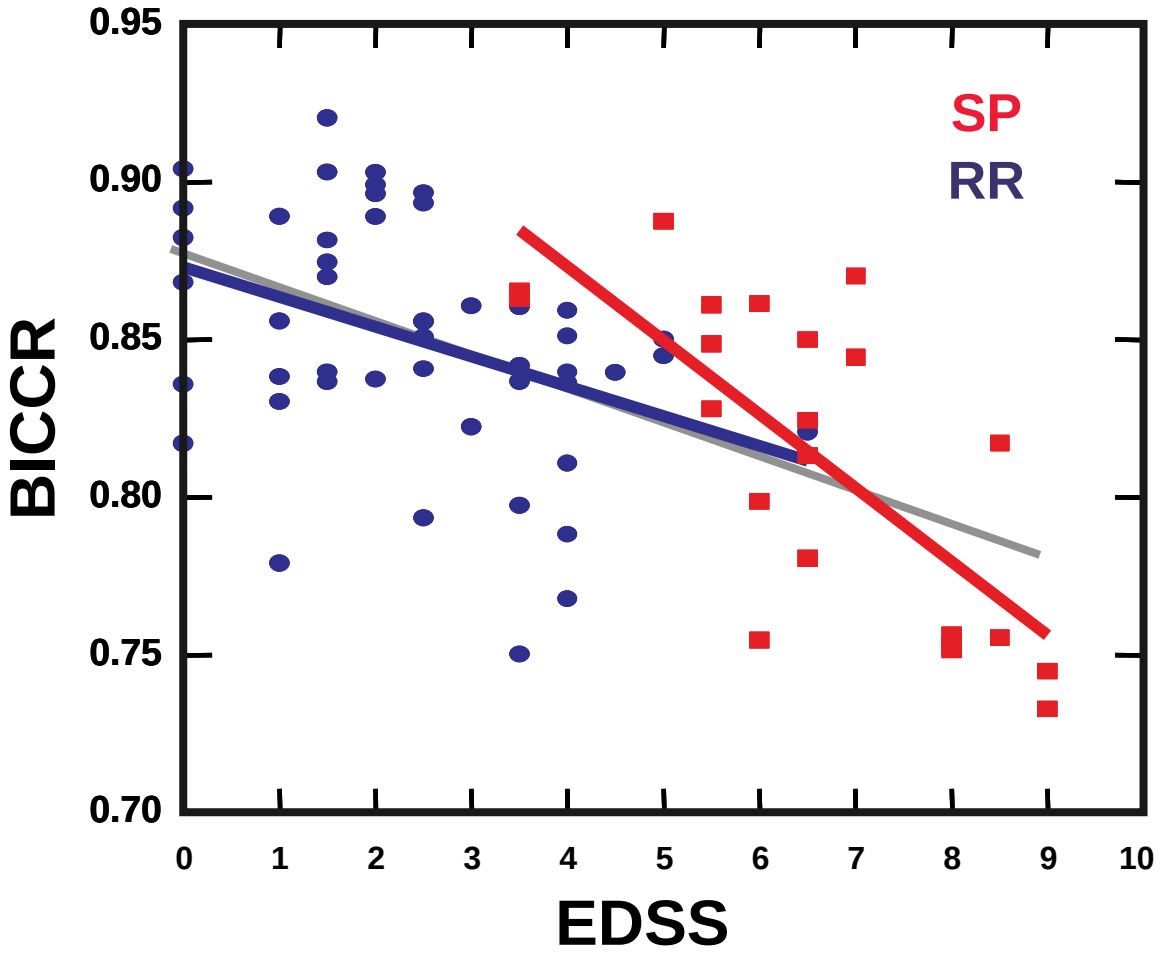
- Jernigan (1990) aging associated with ↑ CSF, ↓ GM
- Gur (1991), Blatter (1995), Coffey (1998) larger loss in men than in women

BICCR in MS


0.95
0.90
0.85
0.80
0.75
0.70
BICCR
ns
p<0.001
0.862
0.850
0.812
NC
RR
SP
GROUP

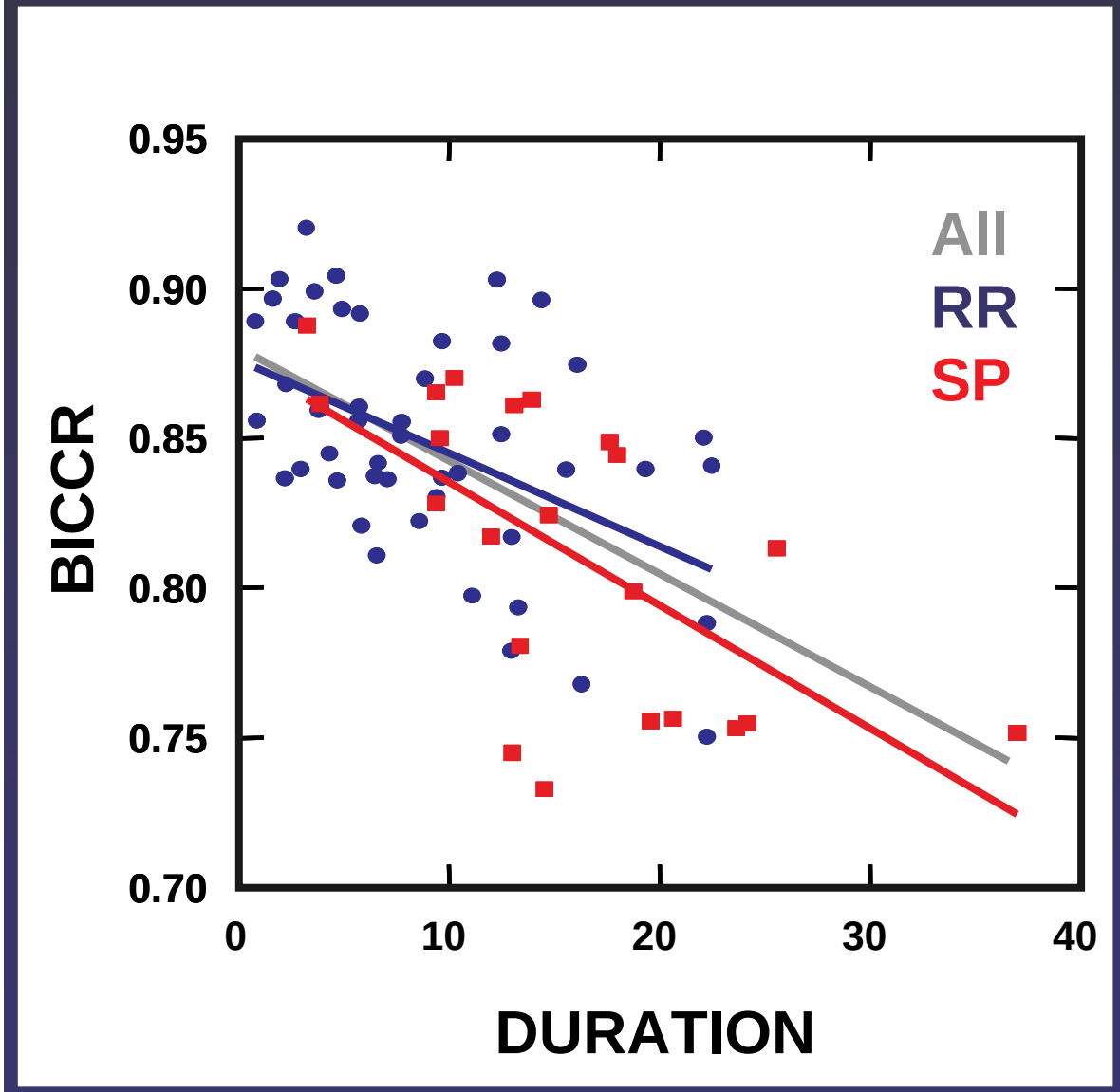

0.95
0.90
0.85
0.80
0.75
0.70
BICCR
*P=0.018
NC
0.0 - 1.5
2.0 - 3.5
4.0 - 5.5
6.0 - 7.5
8.0 - 9.5
EDSS

BICCR by EDSS



	Spearman	P	R^2
ALL (n=28)	-0.496	.0005	24%
RR (n=48)	-0.321	.01	9%
SP (n=22)	-0.682	.0005	46%

BICCR by Duration of Disease



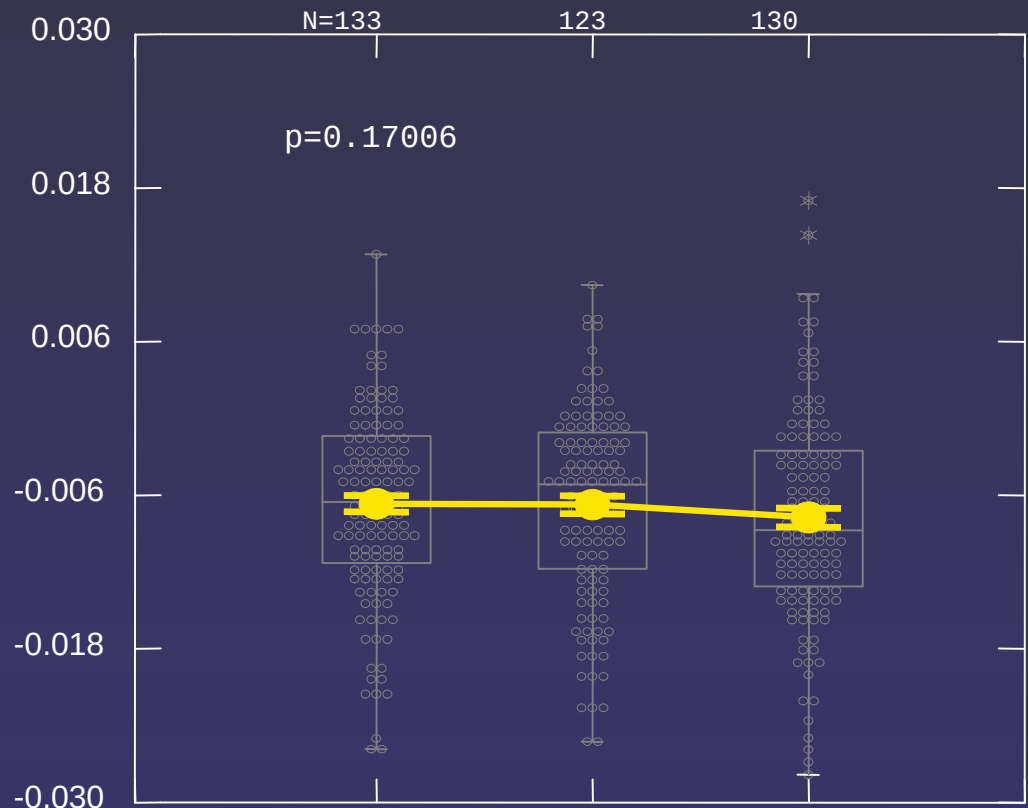
	Pearson	P	coef.	R^2
all (n=70)	-0.611	.0000	-0.393%/y	37%
RR (n=48)	-0.488	.0004	-0.273%/y	24%
SP (n=22)	-0.636	.001	-0.418%/y	40%

Clinical Trial Analysis

Analysis of PRISM baseline-year 2 data

- **No differences between groups when comparing the BICCR value at baseline, year 1 or year 2.**
- **Repeated measures ANOVA showed no differences between groups for year 2 or for the entire 2 year period.**

BICCR: total loss over 2 (all data)

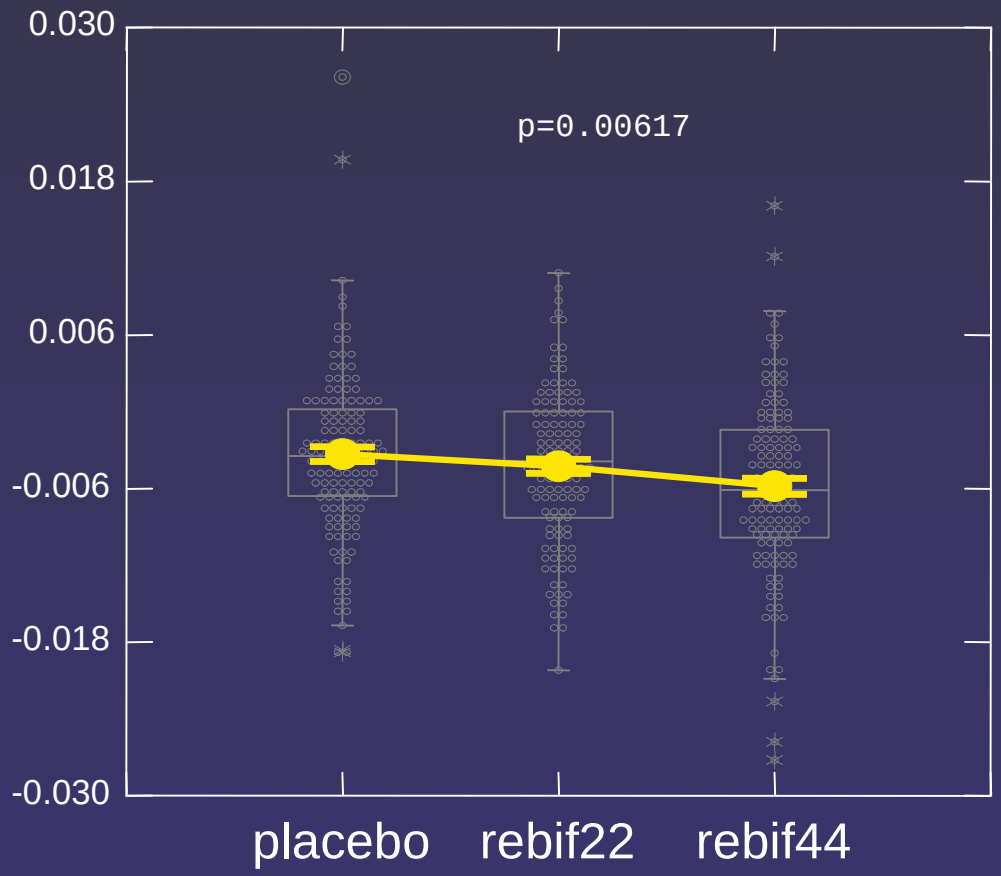


Post-hoc Tukey:

1.00000		
0.86135	1.00000	
0.15724	0.40519	1.00000

- **However, there was a slight difference (p=0.00448) between rebif44 and placebo in year 1, with rebif44 causing a larger brain volume loss than placebo (or rebif22, but the latter was not significant).**

BICCR: loss year 1
All data



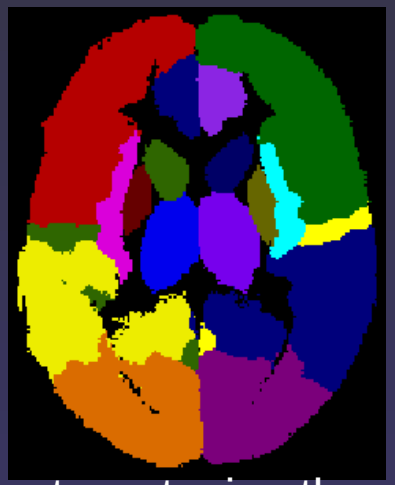
Post-hoc Tukey:

1.00000		
0.48267	1.00000	
0.00421	0.11984	1.00000

Detection of Regional Atrophy


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

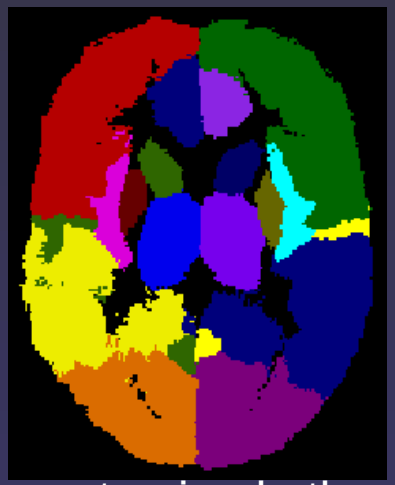
ANIMAL+INSECT



stereotaxic atlas

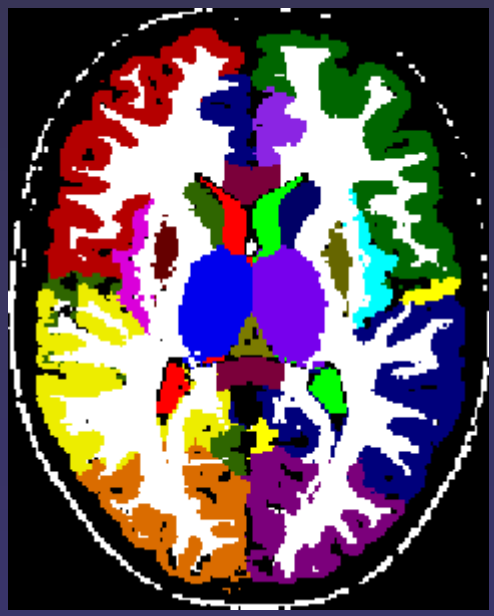
ANIMAL

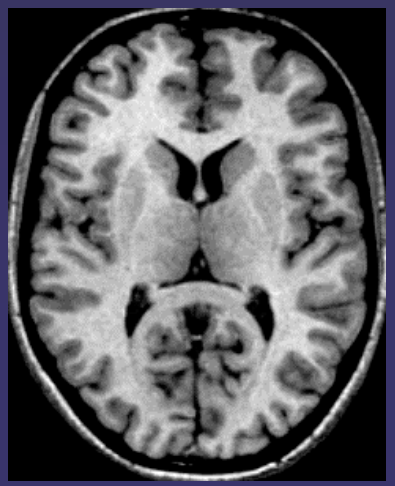
Inverse nonlinear



customized atlas

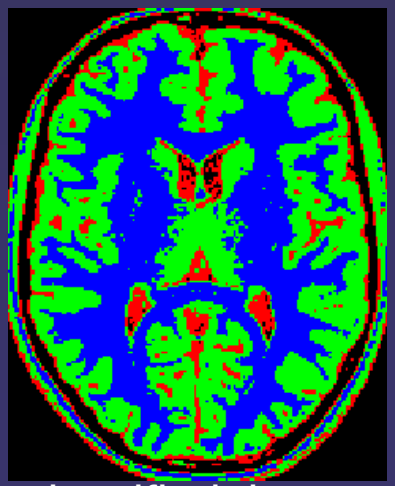
Anatomical masking





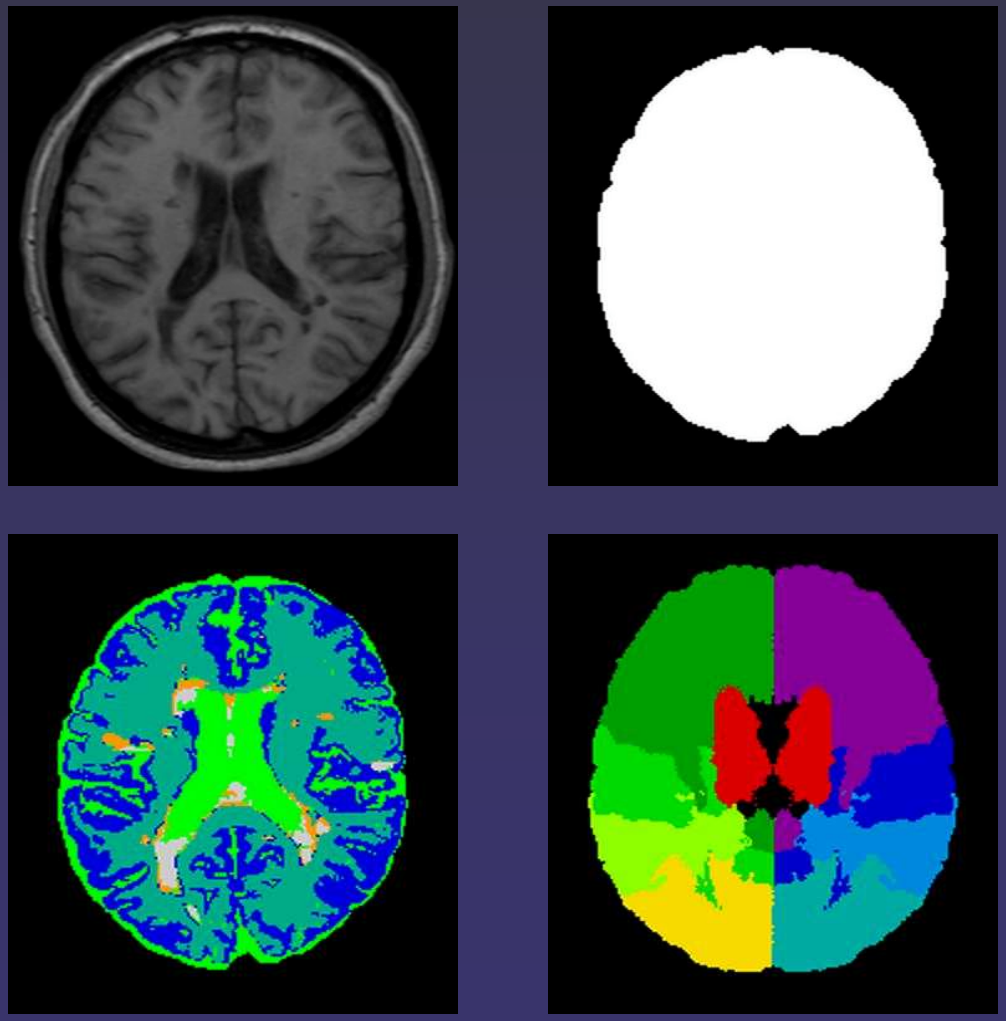
INSECT

classification



classified tissues

Regional GM Quantification - Method

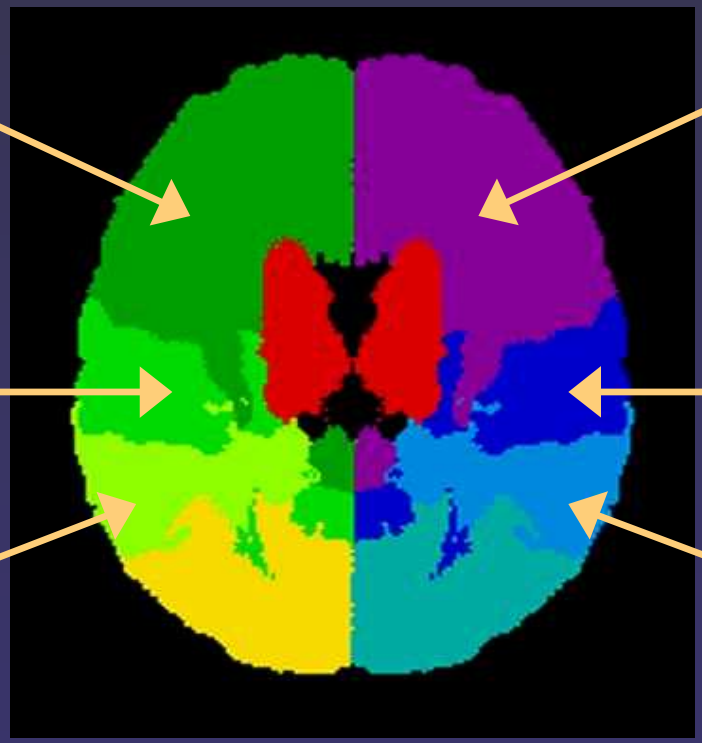


Regional GM Volumes

whole brain:
NC > MS, t = 4.4, p < .0001
NC > RR, NC > SP, F = 12.3, p < .0001

NC > RR > SP
F = 21.5, p < .0001

NC > RR > SP
F = 16.2, p < .0001



NC > SP
F = 6.8, p = .0003

NC > SP
F = 8.2, p < .0001

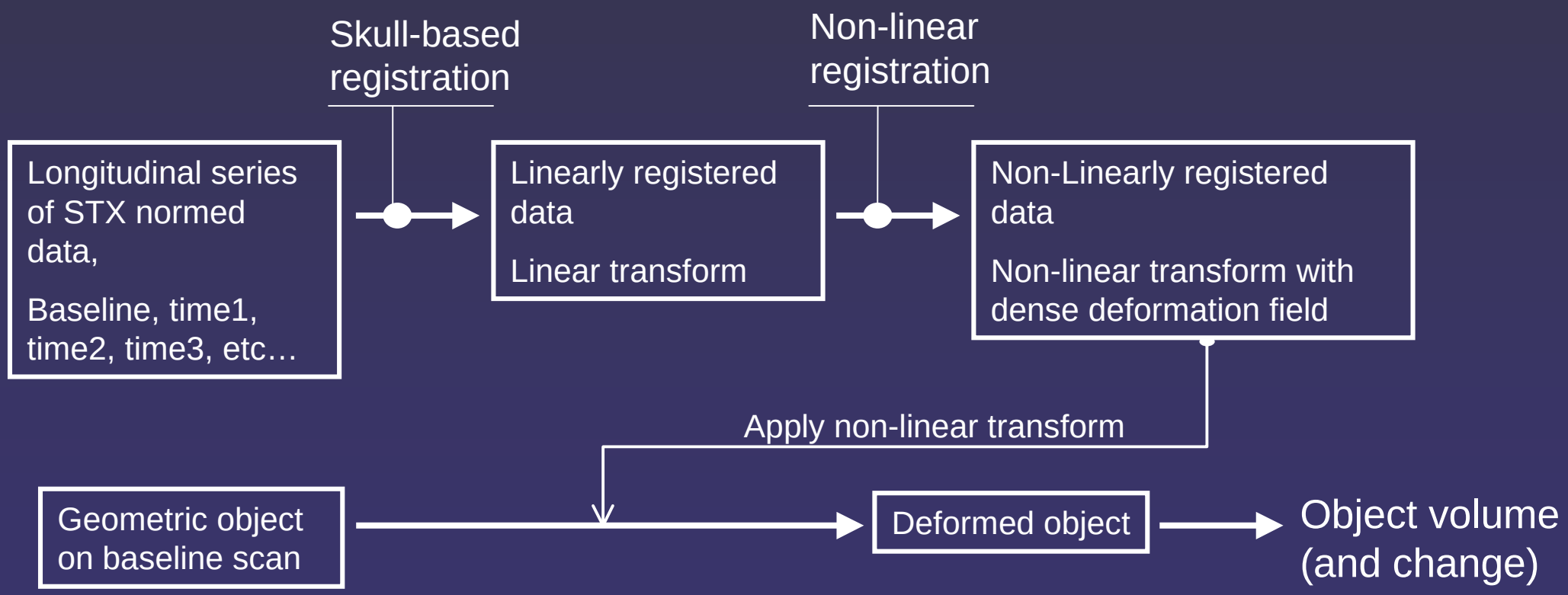
NC > SP
F = 9.9, p < .0001

NC > SP
F = 8.5, p < .0001

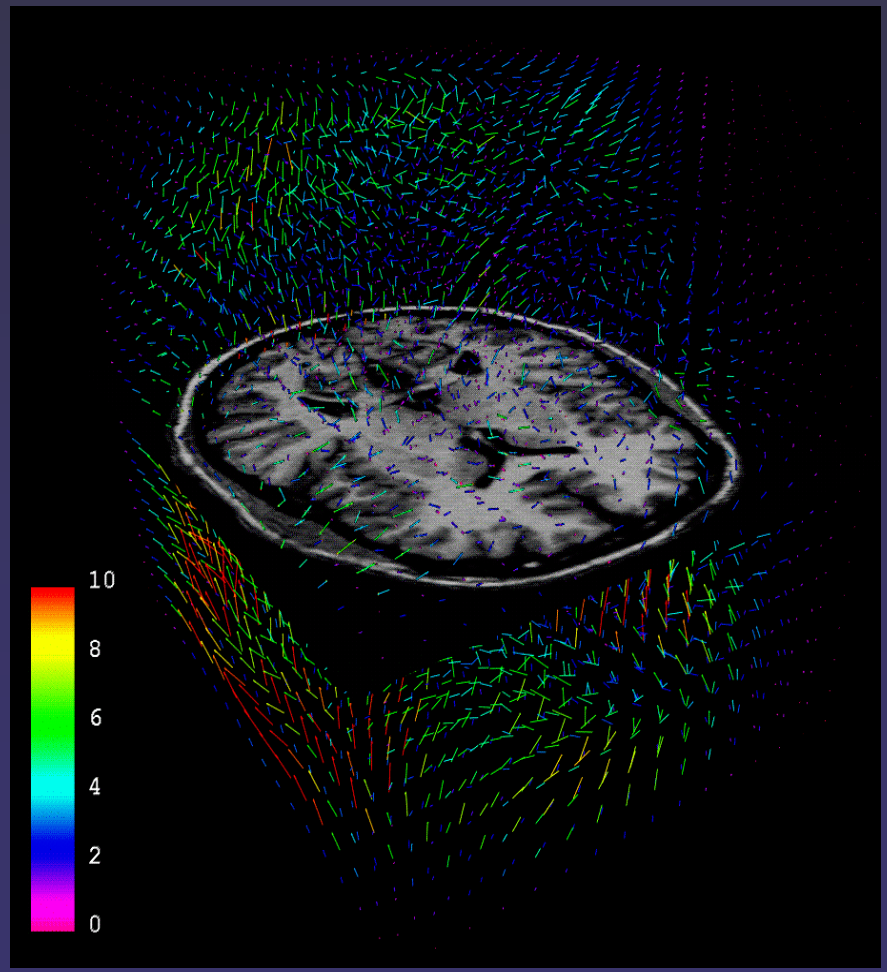
I Kezele, HBM 2004

Local atrophy estimation

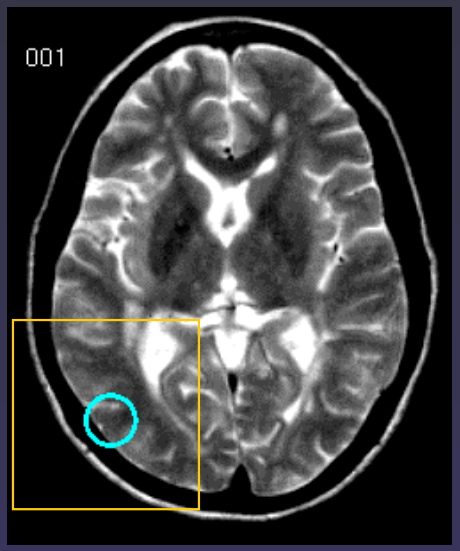
Longitudinal registration



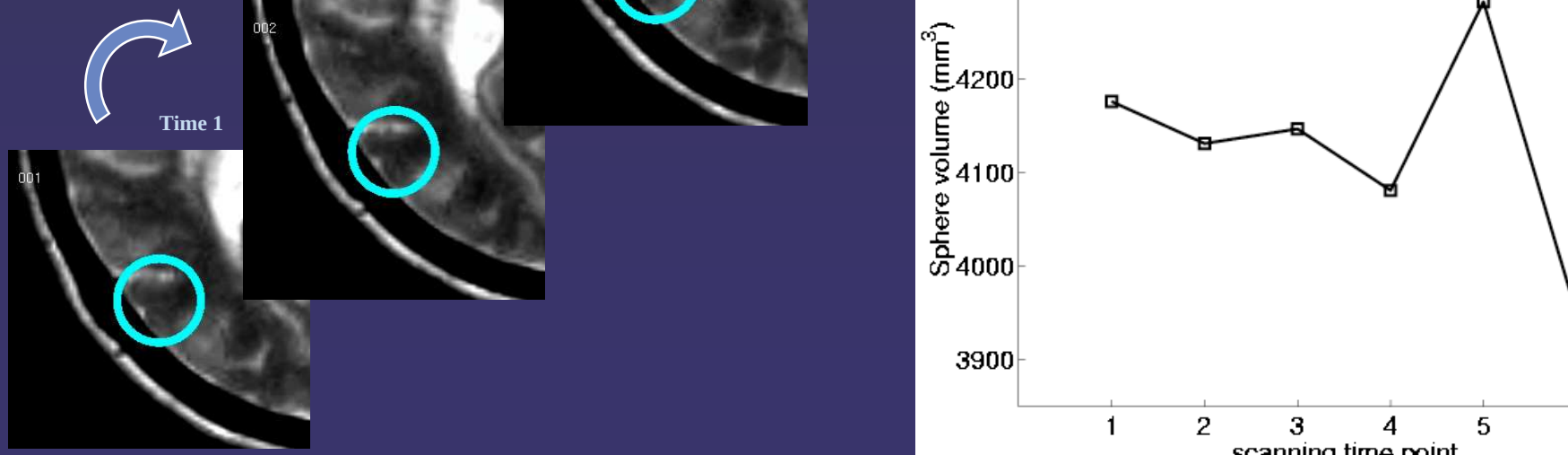
3D Deformation field



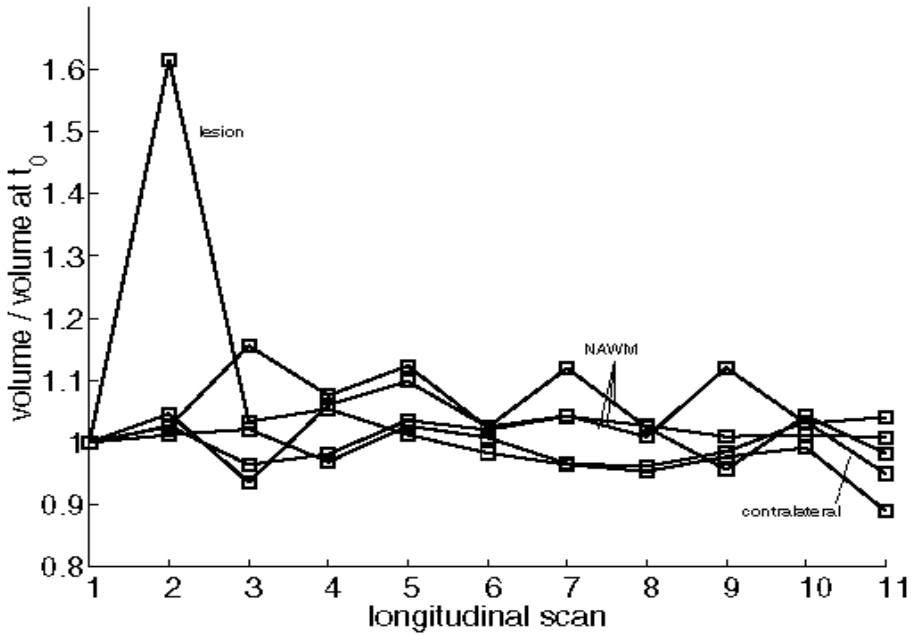
Local atrophy

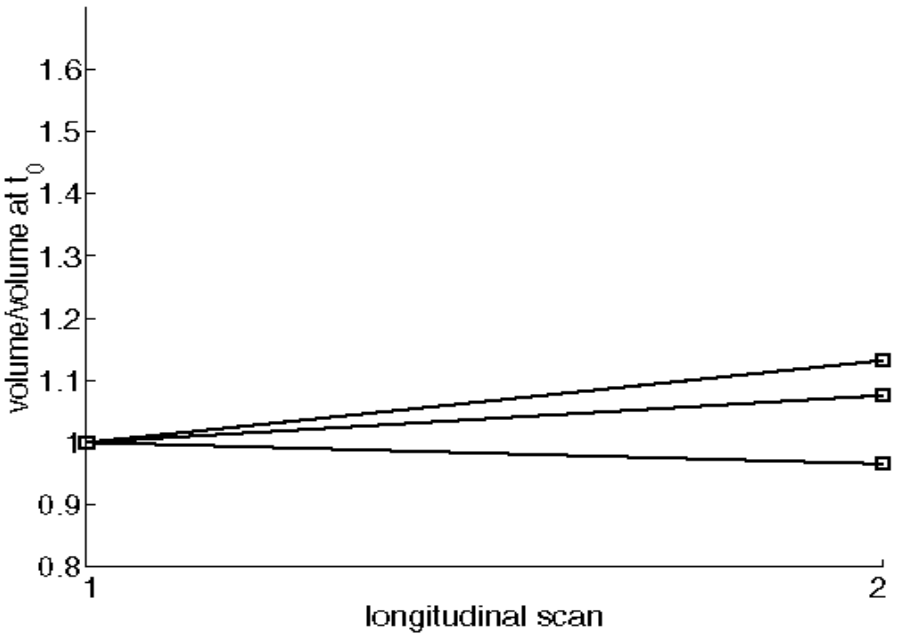


Successive Non-linear Registration



Results-Local Atrophy





patient

control

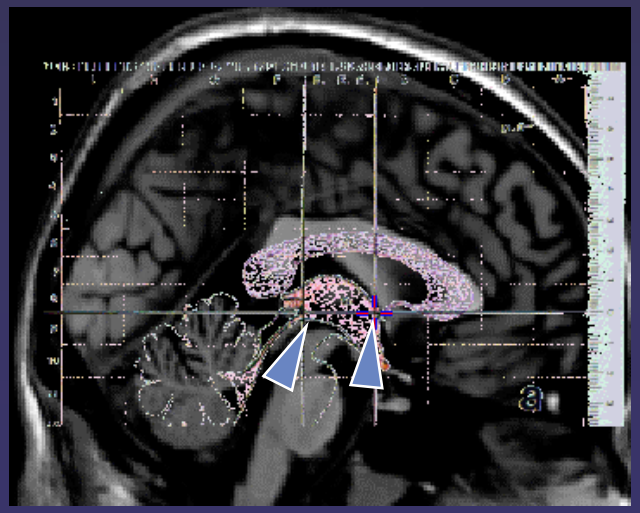
What about voxel-based image analysis of groups?

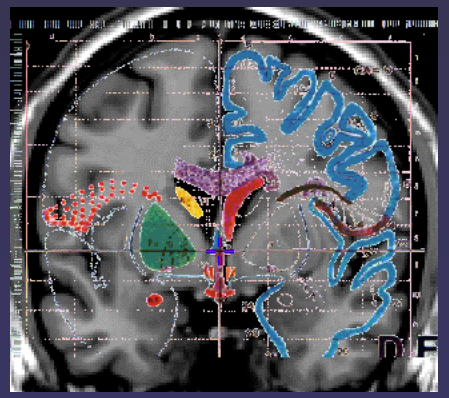
(SPM, VBM)

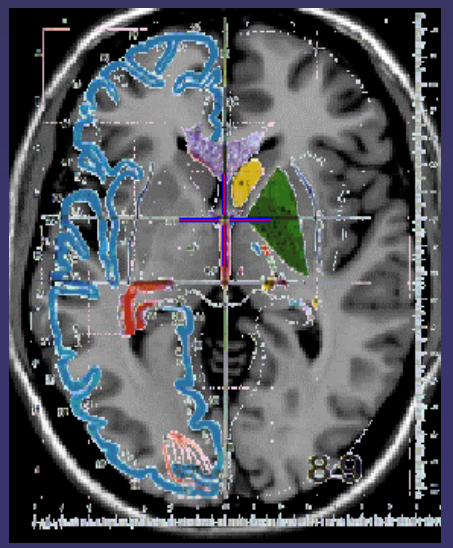
Stereotaxic Space

J. Talairach and P. Tournoux, Co-planar stereotactic atlas of the human brain: 3-Dimensional proportional system: an approach to cerebral imaging, Stuttgart, Georg Thieme Verlag, 1988

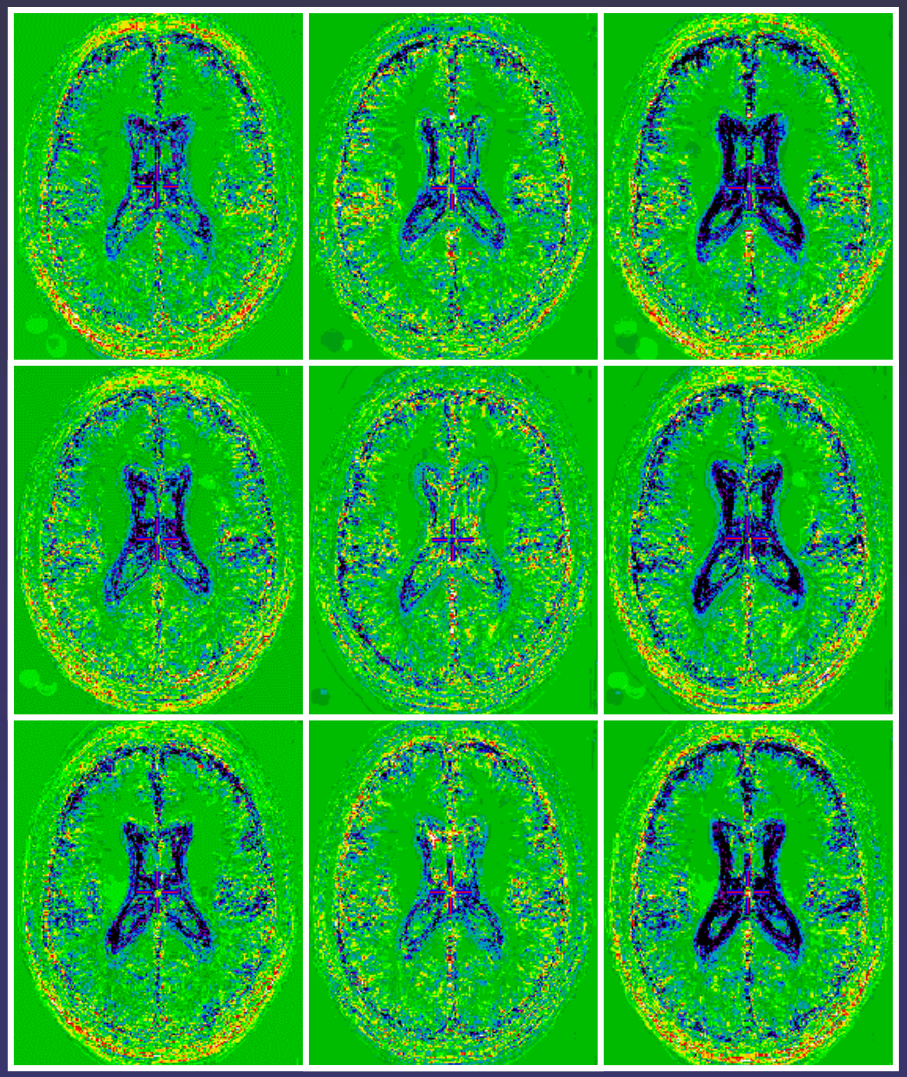
- based on anatomical landmarks (anterior and posterior commissures)
- originally used to guide blind stereotaxic neurosurgical procedures (thalamotomy, pallidotomy)
- now used by NeuroScientific community for interpretation and comparison of results







Difference images

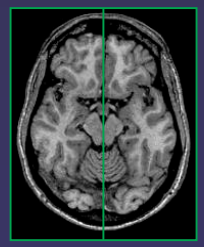


But what is really significant?

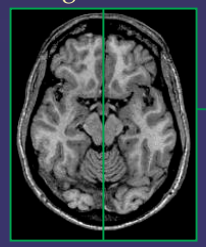
Voxel based morphometry

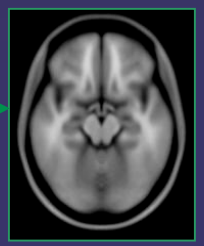
Volume from scanner to Talairach space

Intensity inhomogeneity correction and normalization



Global LIN registration

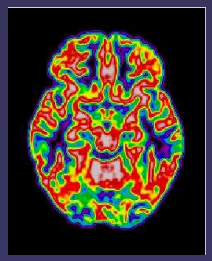




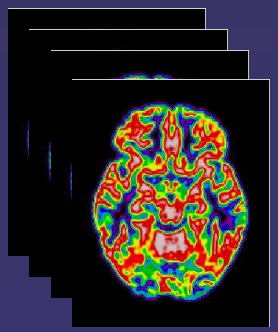
ICBM 152 avg in stereotaxic space

Classification [13]

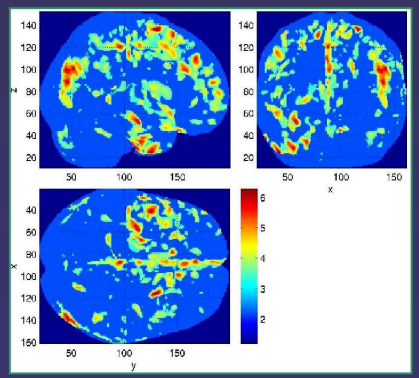
Concentration map smoothing



Generalized Linear modeling [2]

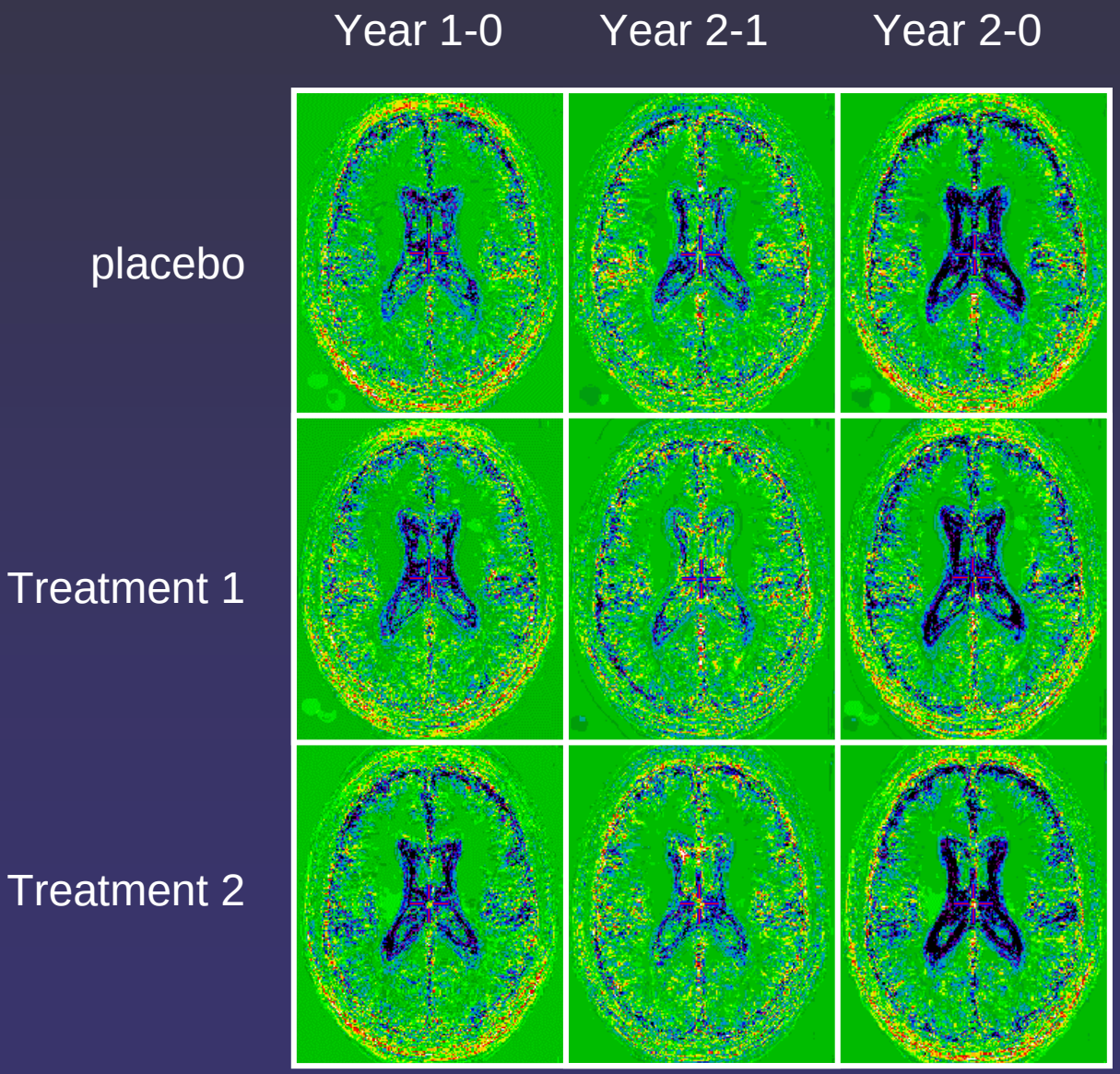


Thresholded T-stat image

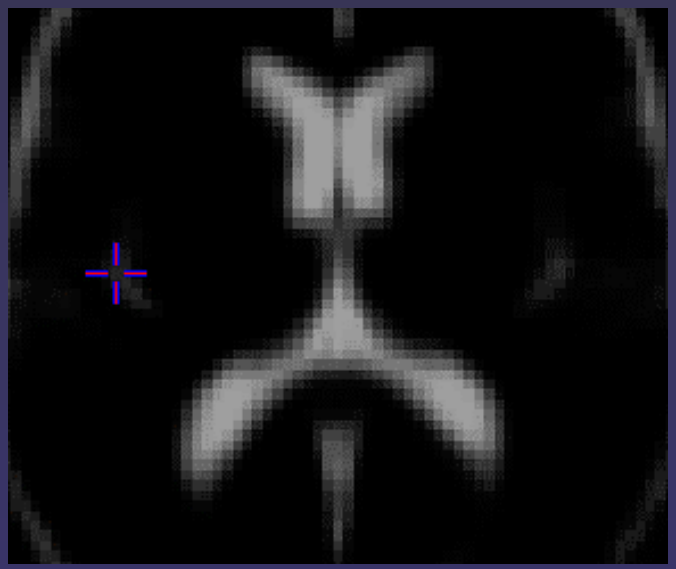


Ashburner , *NeuroImage*, 2000

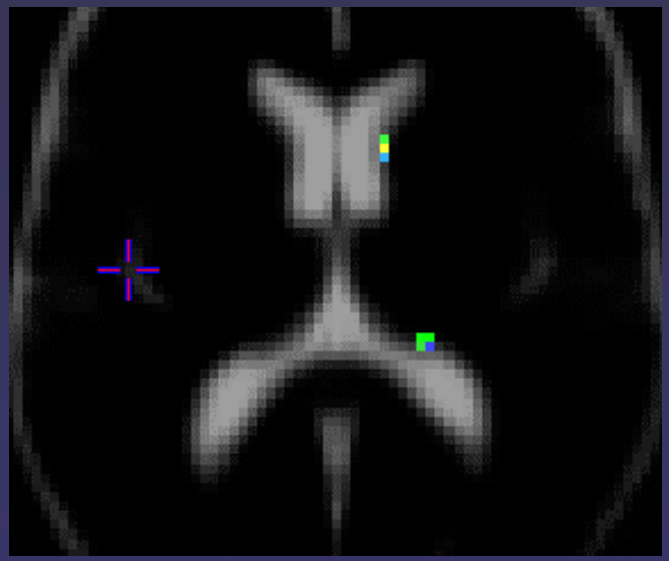
Difference images



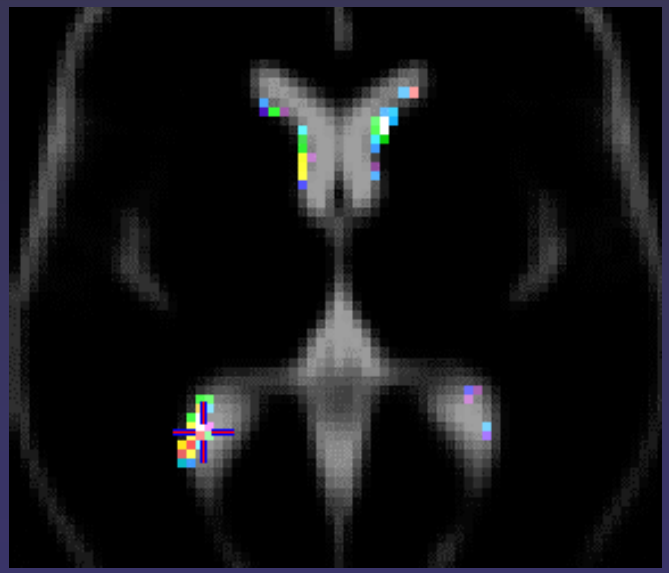
Voxel-based morphometry



placebo



Treatment 1



Treatment 2

Deformation Modeling and the ms-mni database

(a.k.a. pretty blobs)

Andrew L Janke
<rotor@cmr.uq.edu.au>

MINC
Medical Image NetCDF

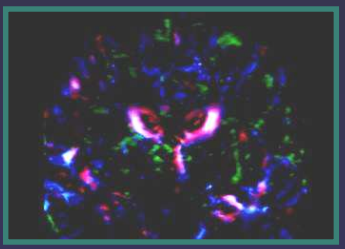
THE CENTRE FOR MAGNETIC RESONANCE

Why?

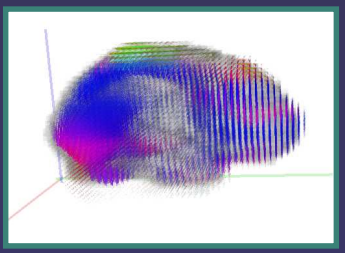
- Provides a wealth of preliminary information on where to direct further processing
- “VBM with a time dimension”
- Possible prediction on novel patients

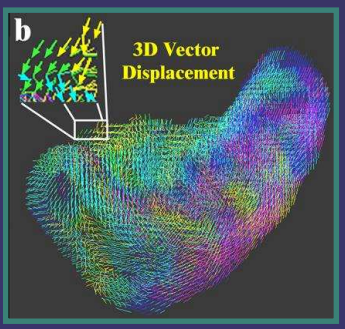
Previously investigative techniques

- VBM - Voxel based morphometry
  - Wright et al,. NeuroImage. 1995
  - Ashburner et al, NeuroImage. 1999
- Deformation based morphometry
  - Ashburner et al, Human Brain Mapping. 2000
- Vector deformations analyses
  - Ashburner J et al, Human Brain Mapping. 1998
  - Gaser C et al, NeuroImage. 1999
  - Thompson et al, Cerebral Cortex. 1998



Janke et al 2000



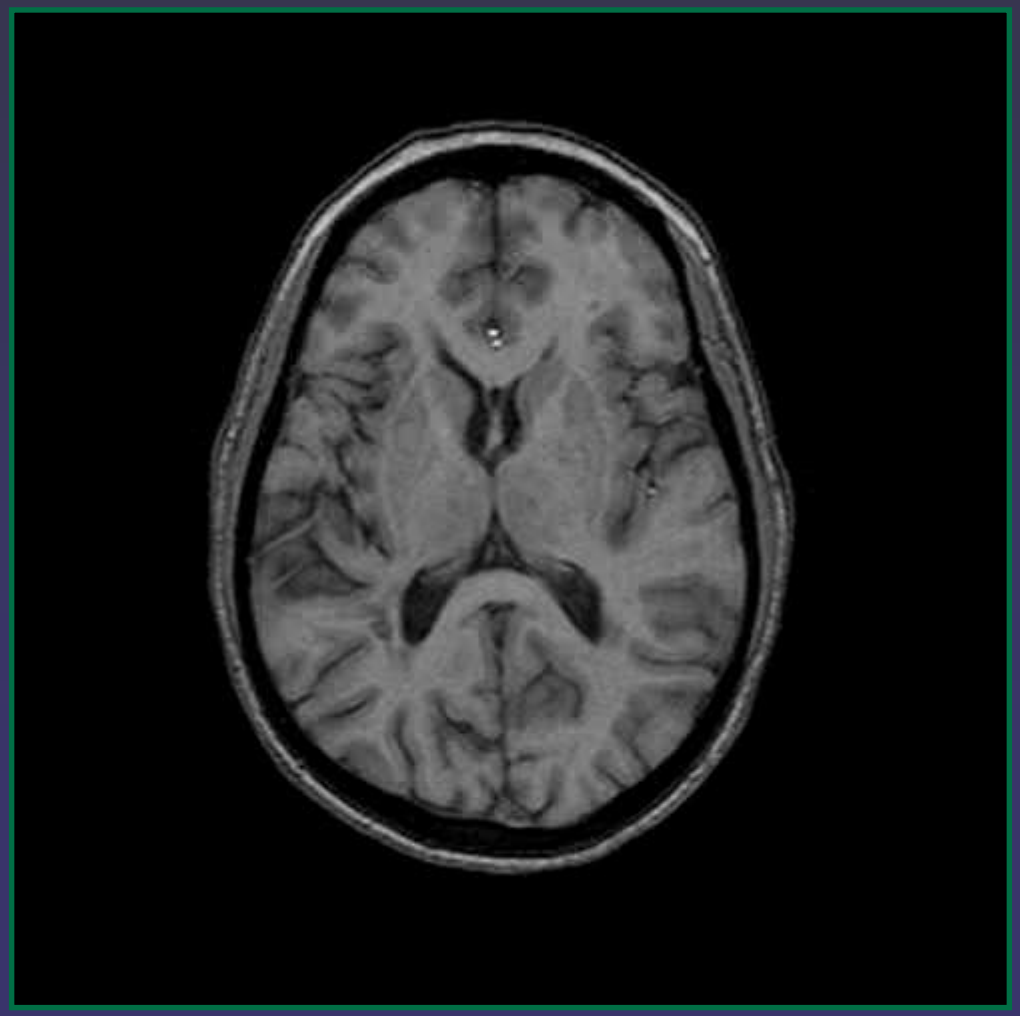


Thompson et al 2000

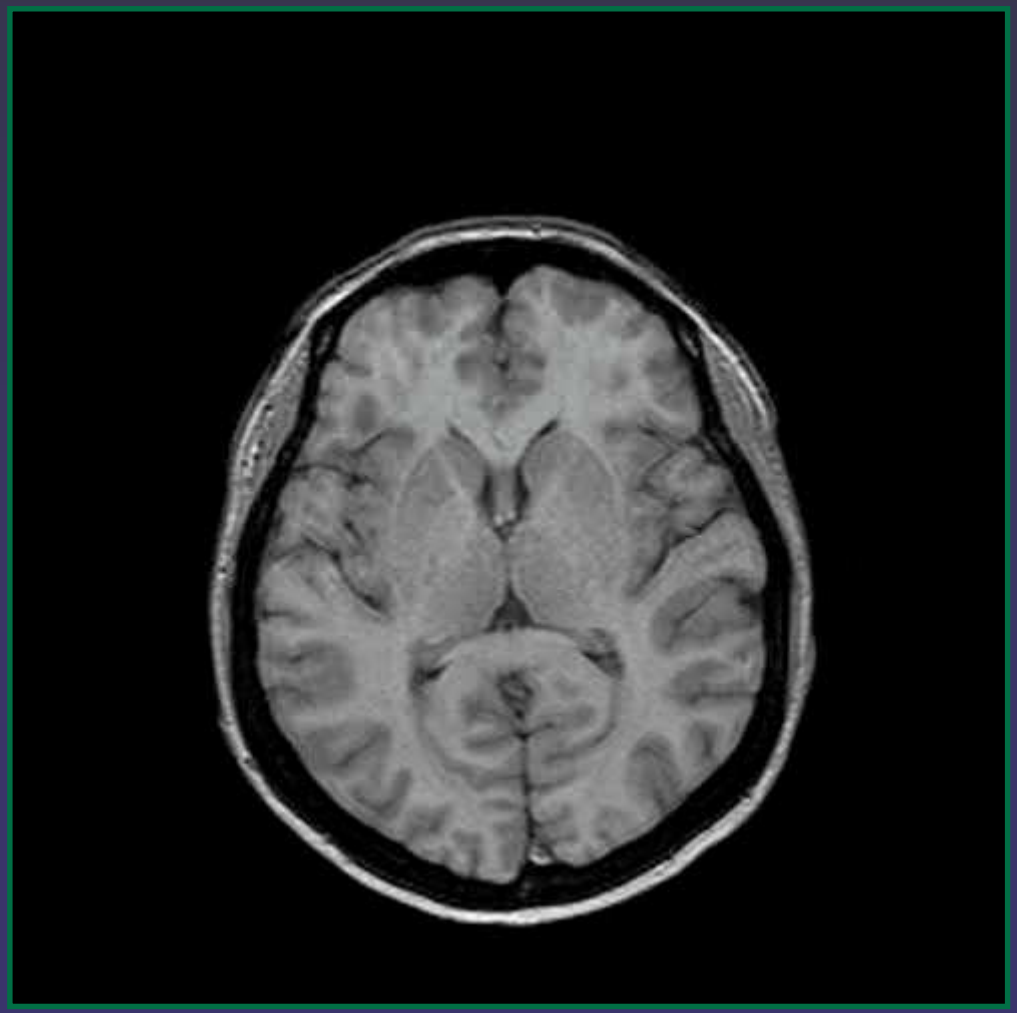
The Processing Pipeline

- **Data**
  - **~4200 data sets, 780 scanning points, 230 patients**
- **Pre Processing**
  - **Rough inter-scan normalisation via clamping between histogram thresholds**
  - **Intensity corrected (N3)**
- **Registration**
- **Modeling**

MS patient progression #1



MS patient progression #2



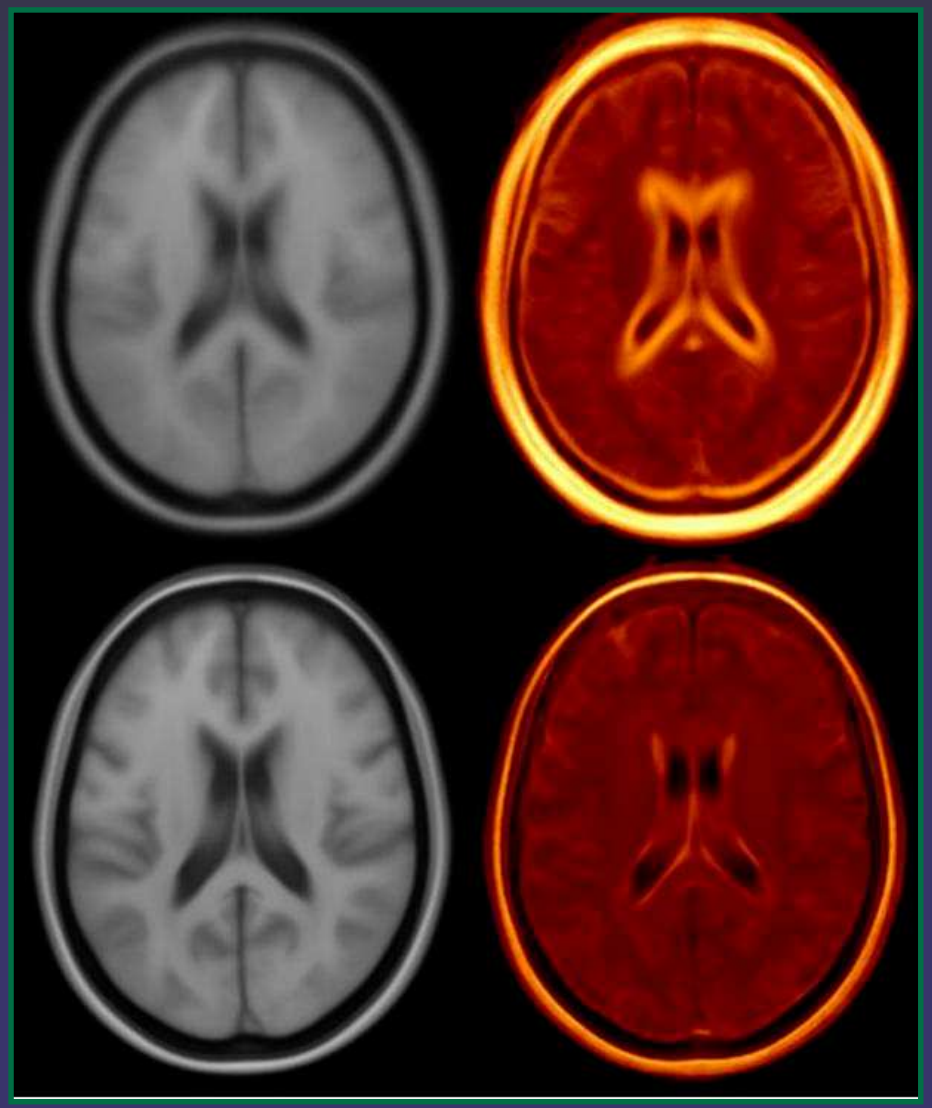
It’s average space Jim …

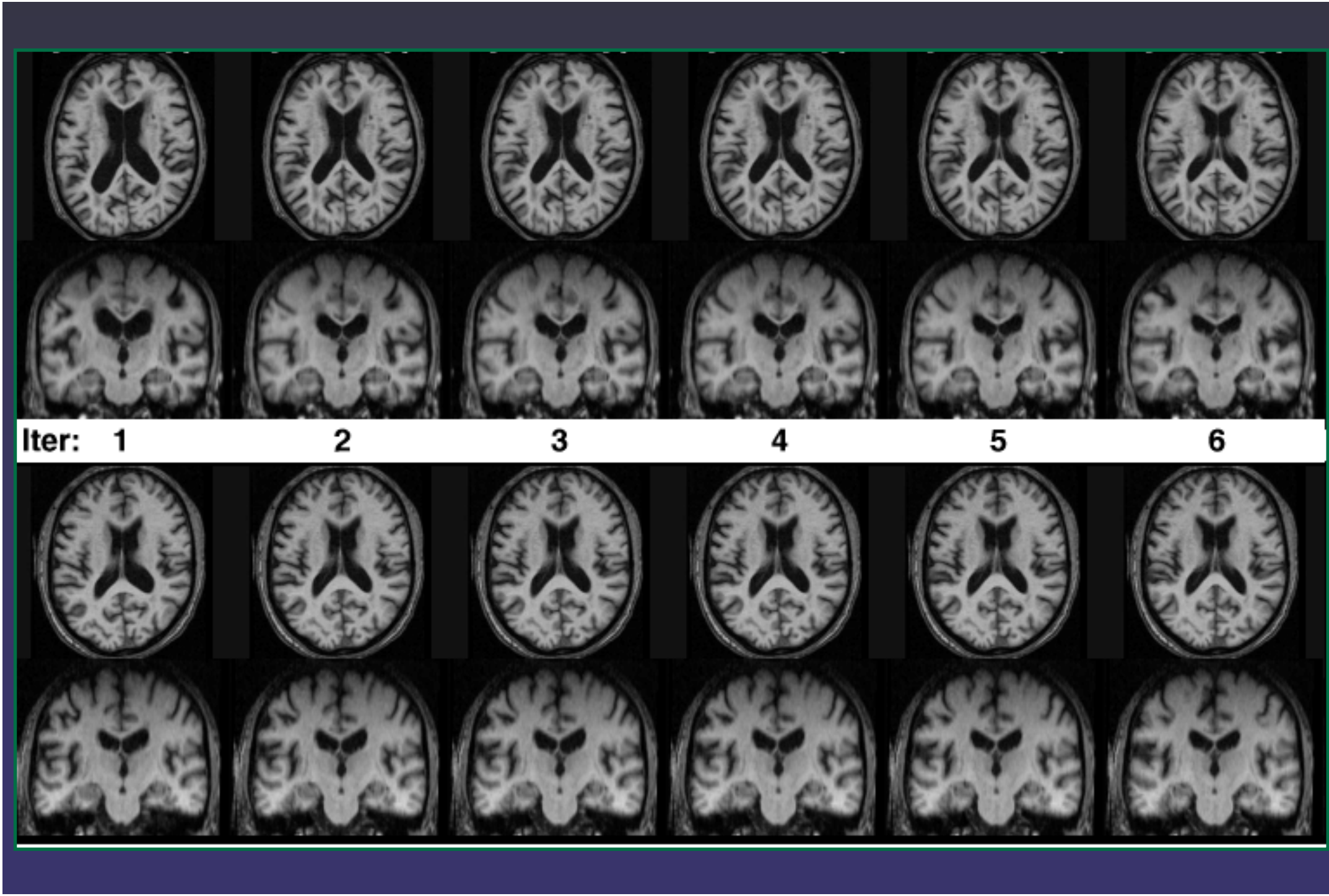
(but not as we knew it)

- Linear averaging is not good enough for abnormal structure
- Need custom targets on a per-disease or even per-study basis
- Also need non-linear average targets to register to.
  - Chickens and eggs….

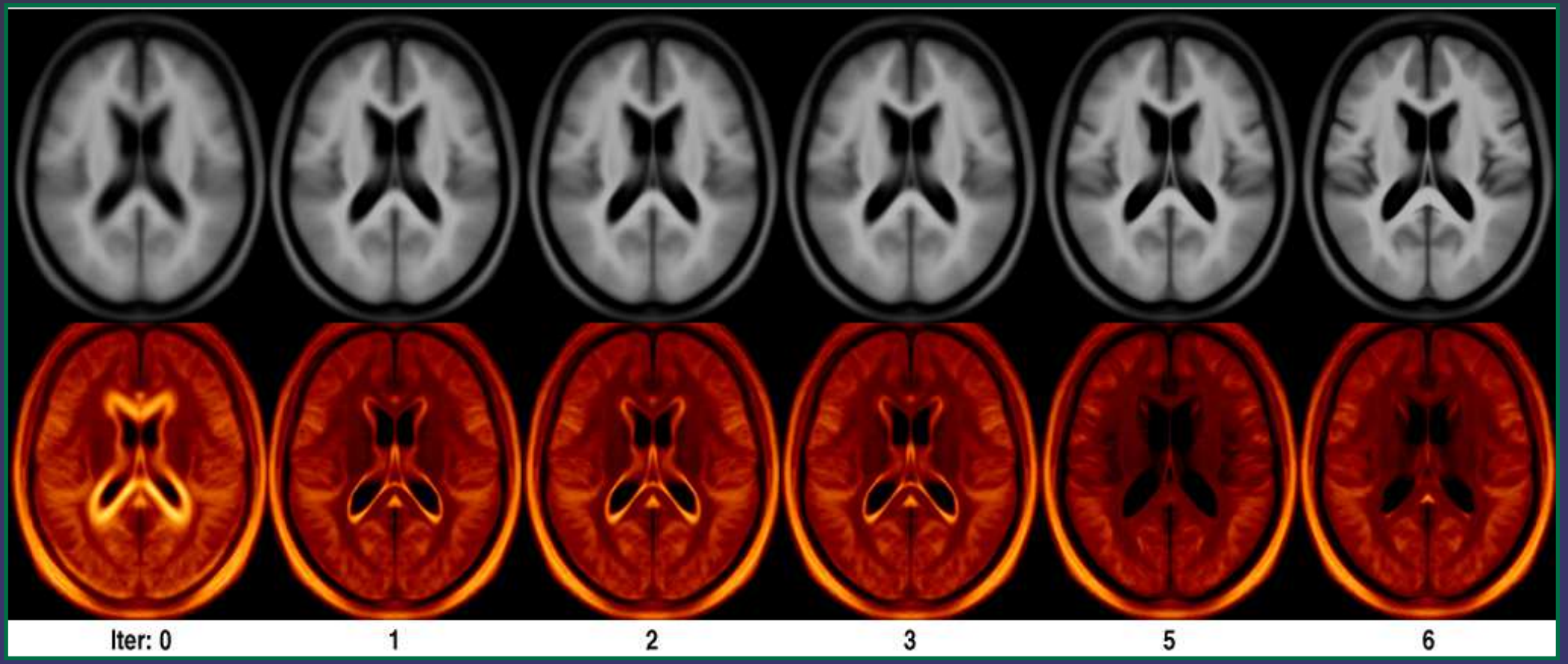
Target creation

- First register all linearly to a model (icbm_152)
- Build a new model (ms01lin)
- Nonlinearly register all to this model again
- Repeat….




Iter: 1
2
3
4
5
6

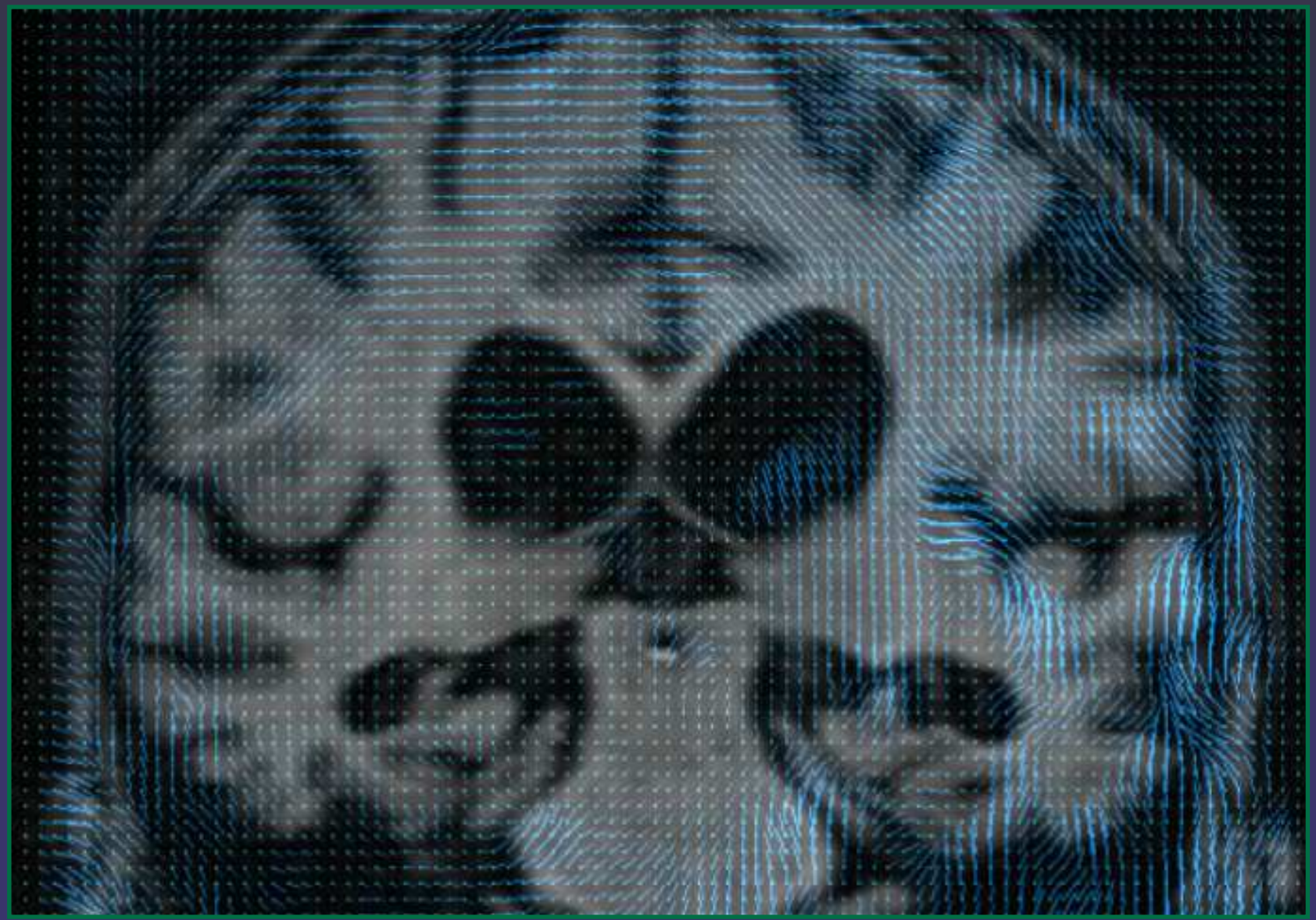
Mean and SD Evolution



Once finally in average space..

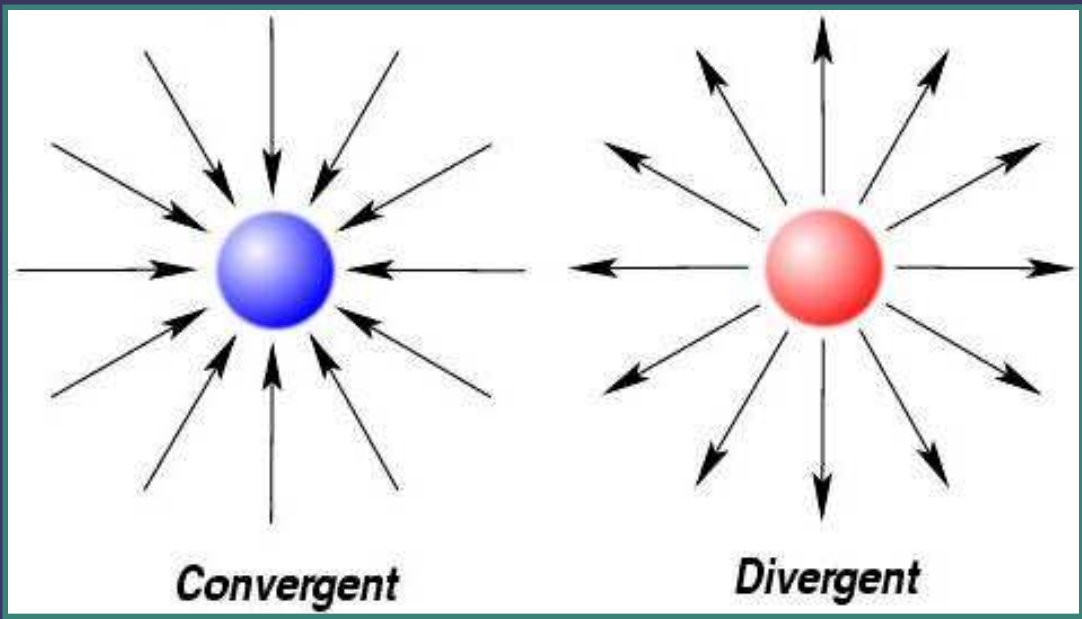
- Non-linear deformations are computed between each of the time points
- The non-linear grids and then resampled to the average space
  - Yes, transforming a non-linear transform with a non-linear transform.
  - Or, just compute them in average space (less clean but probably easier to understand)

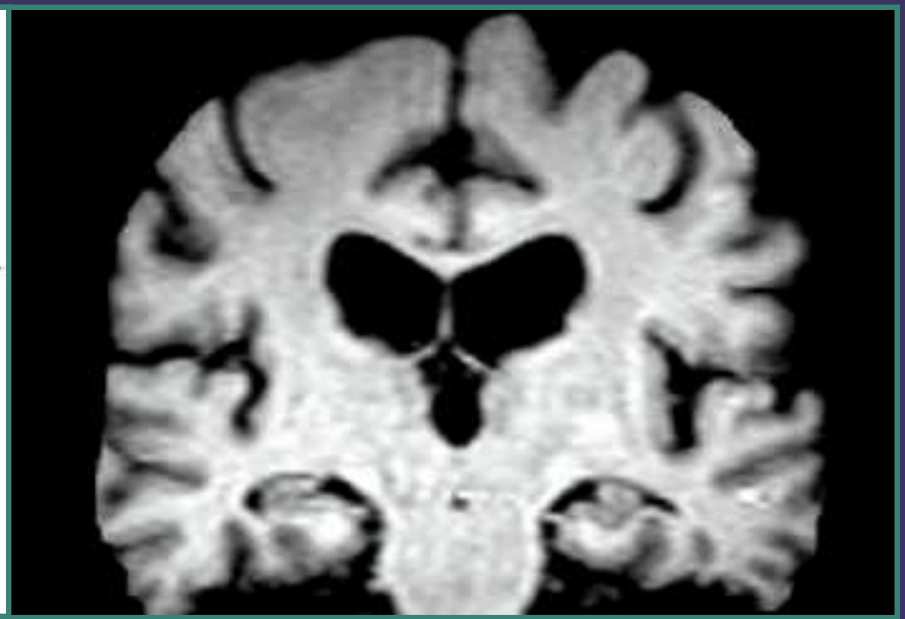
Deformations for an Individual

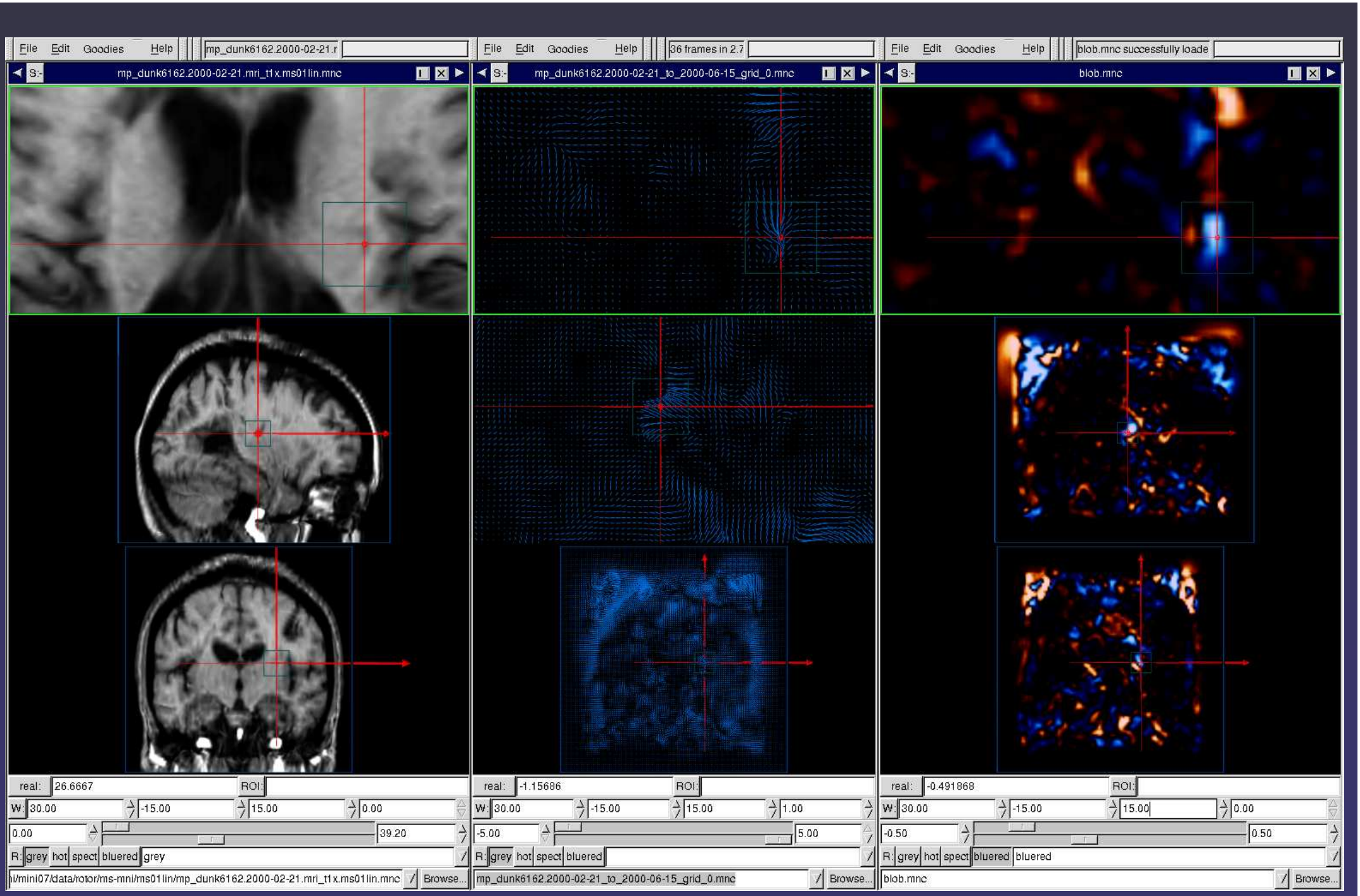


Deformation Metrics 1

- **Volume Loss / Increase**
  - Volume dilation - Trace of the deformation field. (Worsley & Chung 1999)
  - Intensity encodes the magnitude of the dilation

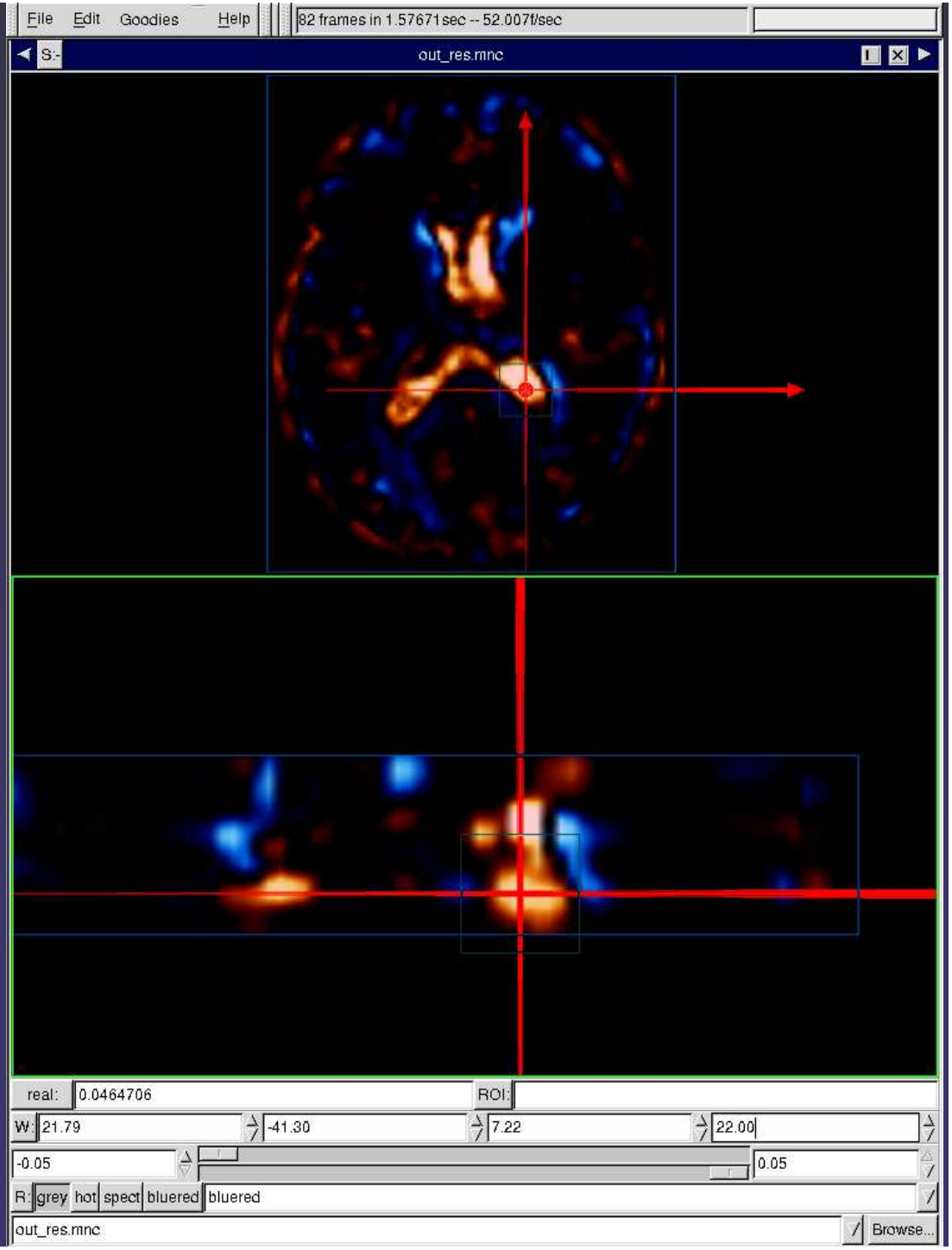




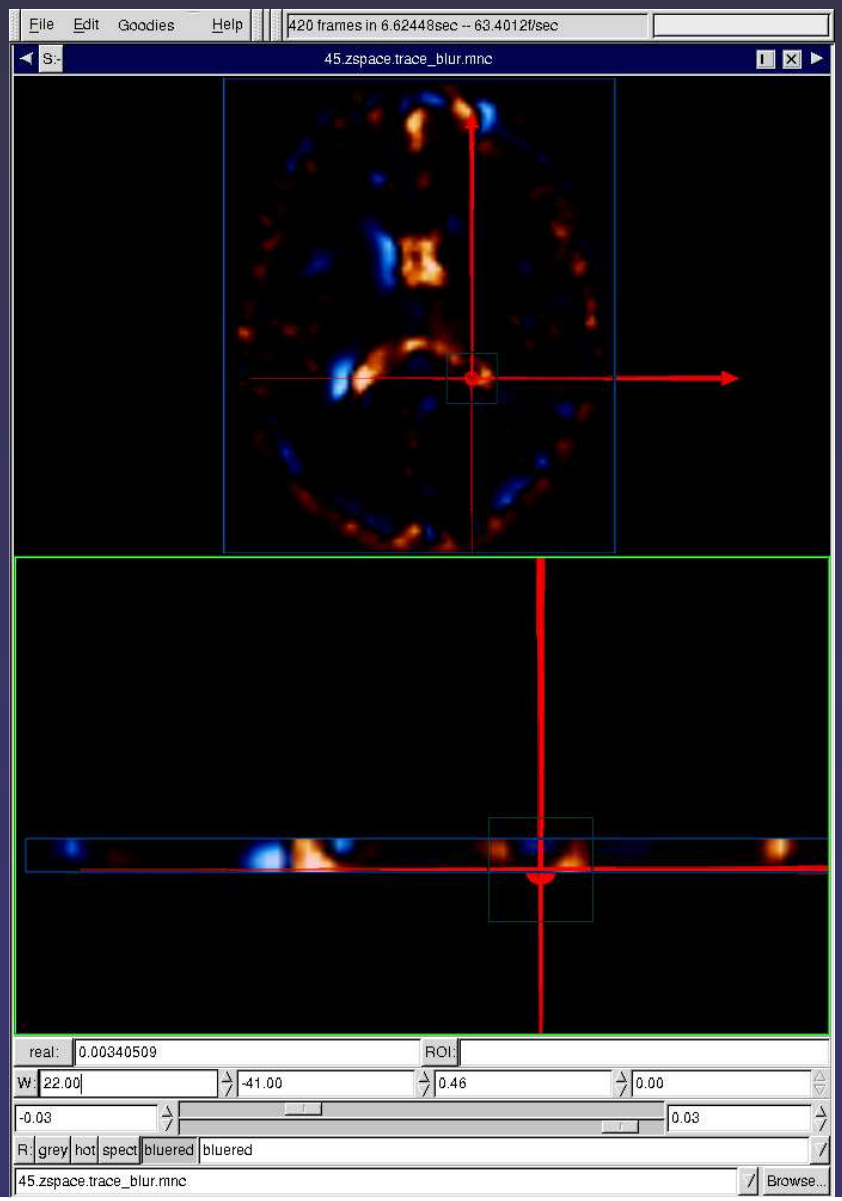

File Edit Goodies Help
mp_dunk6162.2000-02-21.r
mp_dunk6162.2000-02-21.mri_t1x.ms01lin.mnc
File Edit Goodies Help
36 frames in 2.7
mp_dunk6162.2000-02-21_to_2000-06-15_grid_0.mnc
File Edit Goodies Help
blob.mnc successfully loade
blob.mnc
real: 26.6667
ROI:
W: 30.00 -15.00 15.00 0.00
0.00 39.20
R: grey hot spect bluered grey
/mini07/data/rotor/ms-mni/ms01lin/mp_dunk6162.2000-02-21.mri_t1x.ms01lin.mnc
Browse...
real: -1.15686
ROI:
W: 30.00 -15.00 15.00 1.00
-5.00 5.00
R: grey hot spect bluered
mp_dunk6162.2000-02-21_to_2000-06-15_grid_0.mnc
Browse...
real: -0.491868
ROI:
W: 30.00 -15.00 15.00 0.00
-0.50 0.50
R: grey hot spect bluered bluered
blob.mnc
Browse...

Results are 4D..

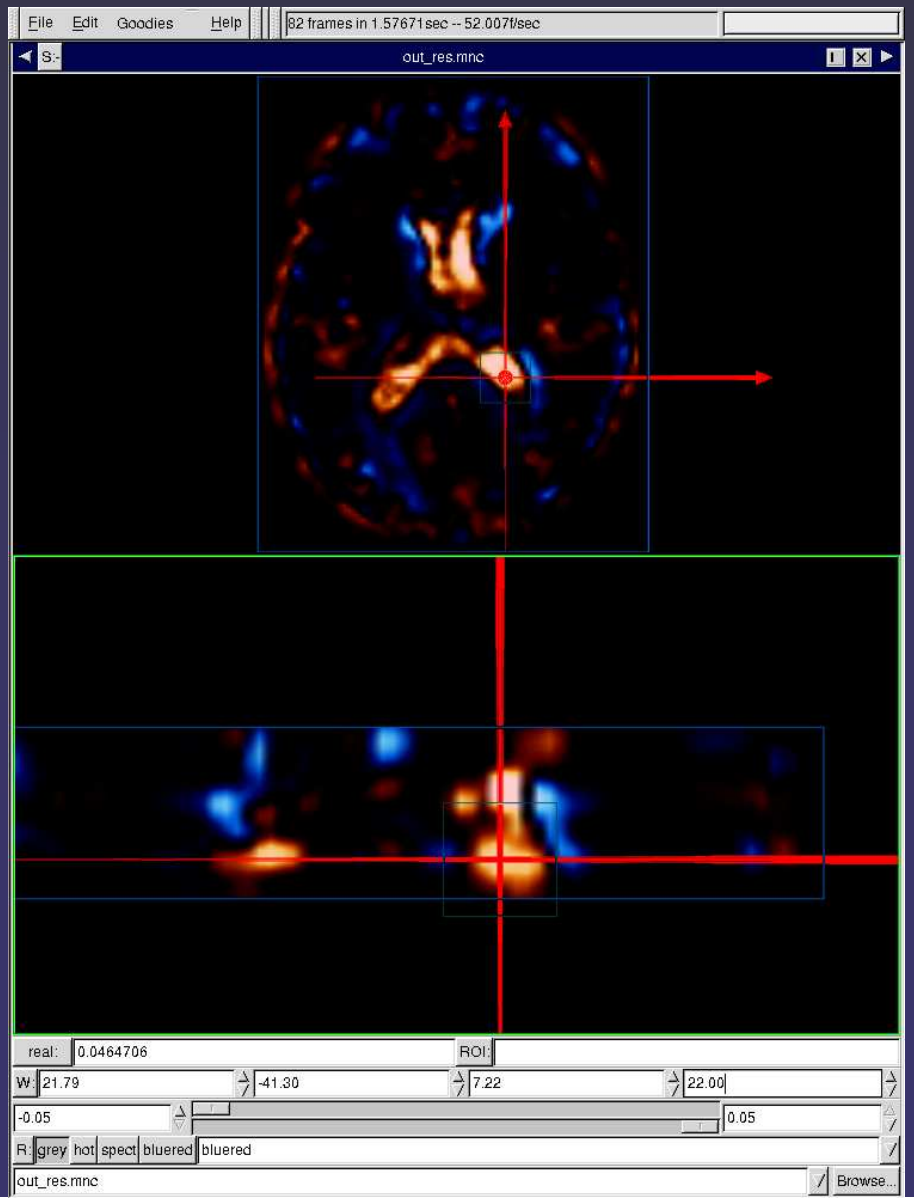
- RR average results
- Top
  - Std transverse determinant image
- Bottom
  - Y vs Duration slice
  - ‘z dimension’ is actually duration



EDSS

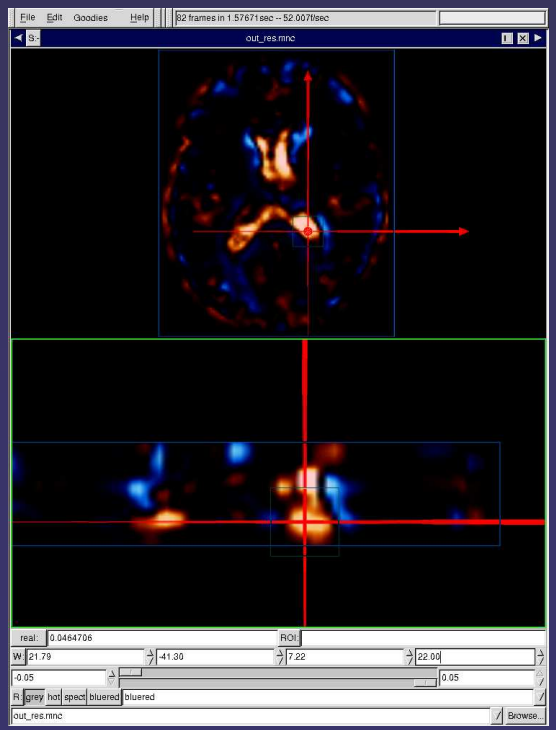


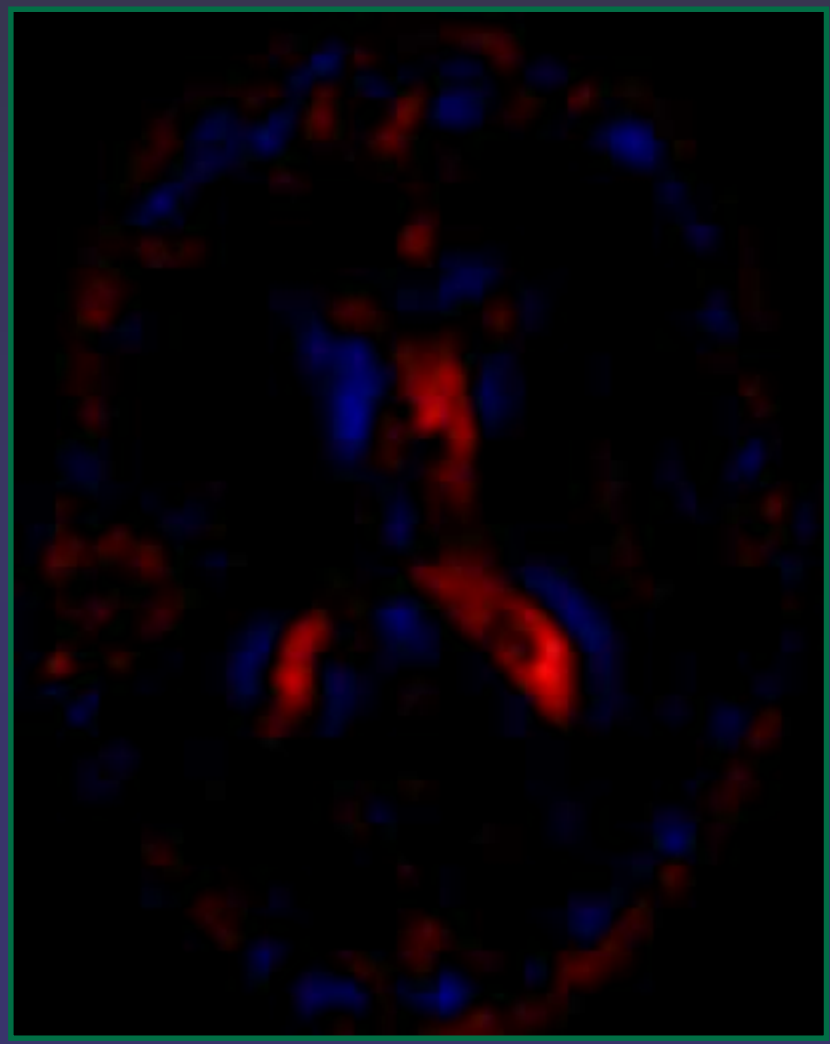
Duration



Changing change and change progression

Cheat Sheet





Conclusions

- **Ability to follow longitudinal change**
  - **Methodology is not limited to any particular score**
- **Characterisation and localisation**
- **Caveat Emptor**
  - **Choice of deformation metric and Interpretation**
  - **A *physiological process* should be easily inferable**