MICCAI ‘04

Cerebral damage in epilepsy: longitudinal quantitative MRI

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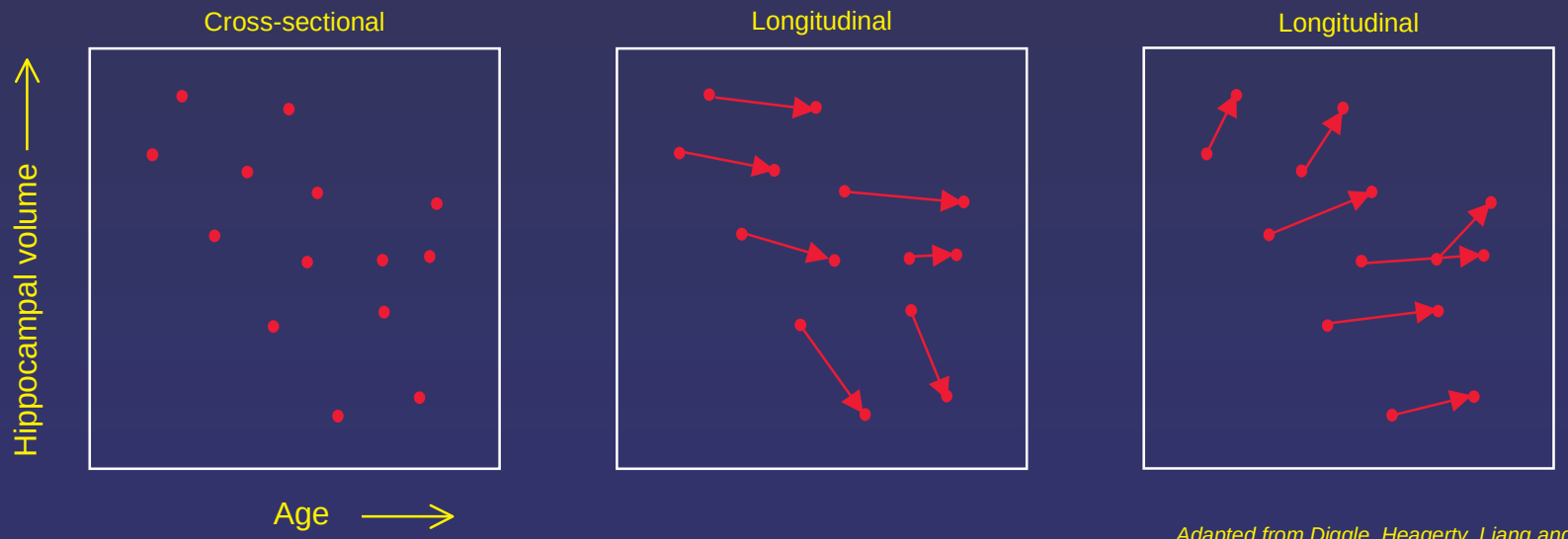
Outline

- Introduction
- Principles & methods of serial MRI analysis
- Application: prospective population-based longitudinal study
- 3T
- Conclusions & prospective

Longitudinal studies: why?

- Time is an essential aspect of disease
- Longitudinal vs Cross-sectional:
  - Subject as own control
  - Time (ageing) / cohort effects: baseline value?



Adapted from Diggle, Heagerty, Liang and Zeger

Longitudinal: a necessary condition to assess causality

Analysis of change: Brain

- Repeated measures:
  - ‘High-res’ T1 volumetric sequence
  - Fully automatic GM, WM, CSF segmentation: *Exbrain*
  - Sequential measures of:
    - Total grey matter
    - Total white matter
    - Total intracranial CSF
  - Tissue density distributions
- Difference image analysis:
  - Genuine change maps (structured noise map)
  - Visual, ROI analyses

Automatic segmentation – *Exbrain* Method

- Fully automatic and 3D
- Data preparation: Non-uniformity correction - *N3* [Sled *et al*. IEEE-MI 1998]
- Main steps:

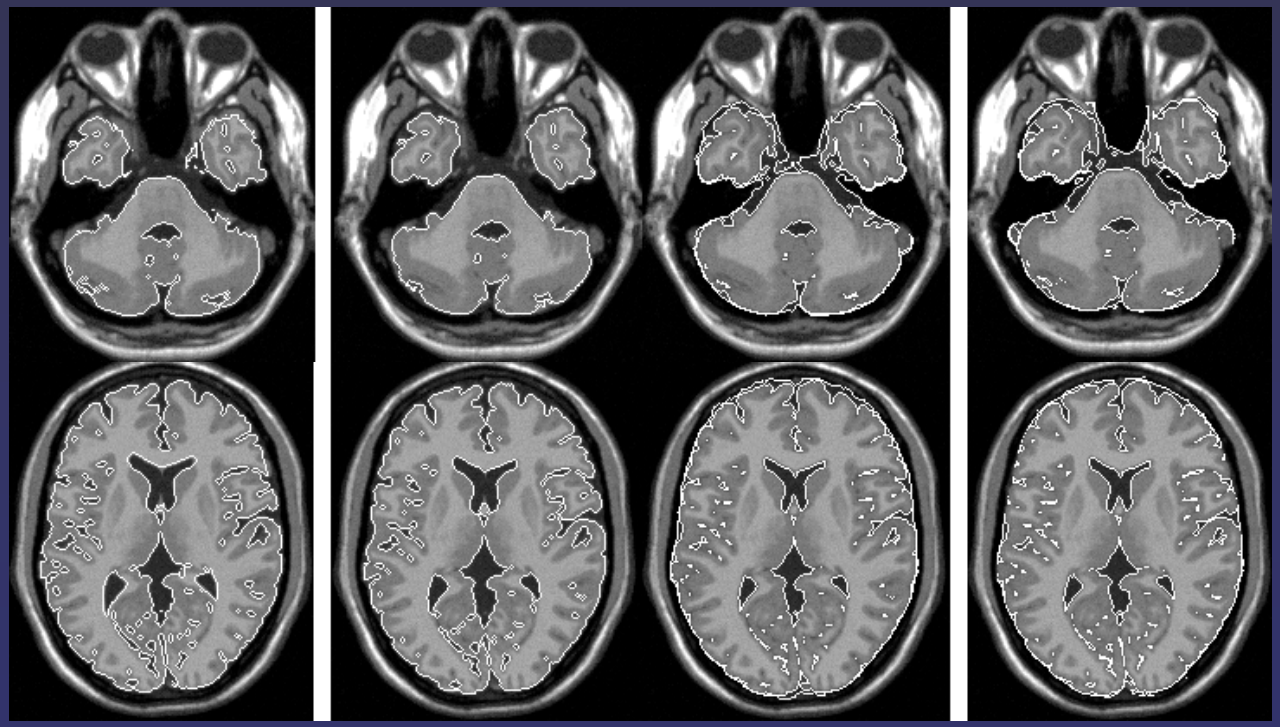
  0: Initial brain segmentation: rough ‘scalp’
  1: Segmentation of intra-sulcal & ventricular CSF
  2: CSF and background intensity characterization
  3: Final CSF segmentation
  4: Refinement of the GM-CSF boundary
  5: Connectivity: brain and intra-cranial (IC) masks
  6: Brainstem & CSF cutting in axial plane
  ⇒ **CSF and brain binary masks**

  Volumetry: penta-Gaussian fitted to IC mask IPD

  ⇒ **CSF, GM and WM volumes**

  Fuzzy classification

Automatic segmentation – *Exbrain* Accuracy (1)



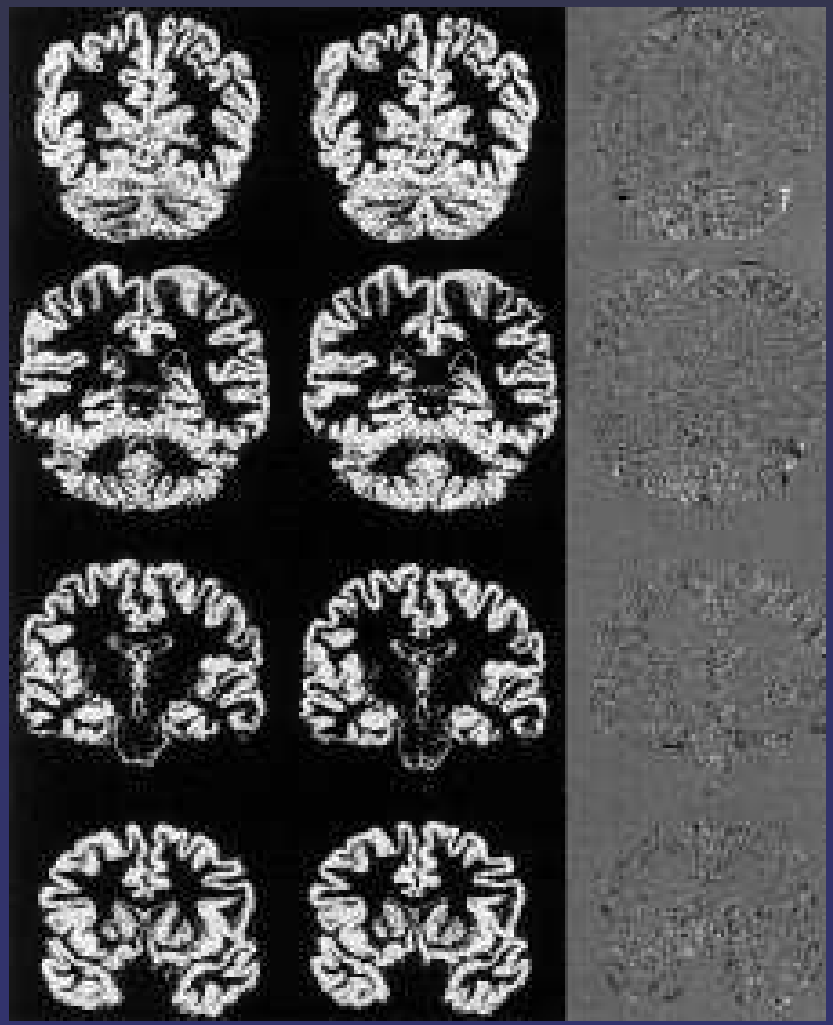
Automatic segmentation – *Exbrain* Accuracy (2)

Comparison with *Brainweb*:

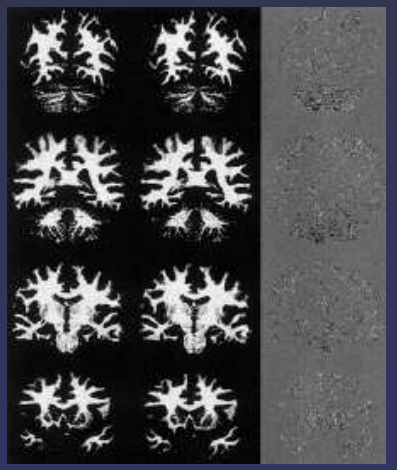
	Similarity	*Vol error*
Brain binary mask:	98%	+0.1%
GM:	95%	+2.0%
WM:	96%	-1.4%
CSF:	86%*	-5.0%
Intra-cranial:	96%	-1.3%

*: reference MNI CSF mask has ‘imperfections’

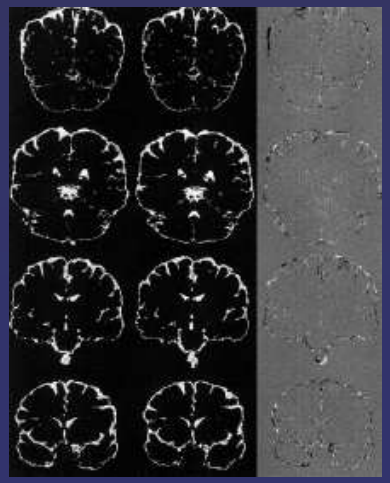
Automatic segmentation – tissue distribution reproducibility (repeat scans; rigid-body registration)



GM



WM



CSF

[Lemieux et al. MRM 2003]

Automatic segmentation – volume reproducibility

Assess impact of following on registration reproducibility:

- Registration,
- Registration, intensity matching and ‘recycling’ of baseline values

IPD-Derived Tissue Volume Changes in 20 Normal Controls Scanned 8.2 Months Apart

	dGMV		dWMV		dTBV[a]		dCSFV		DICV[b]	
	Mean	CR	Mean	CR	Mean	CR	Mean	CR	Mean	CR
cm^3										
Repeat-baseline	+0.83	24.0	+0.98	25.4	+1.82	35.2	+0.58	22.0	+2.39	29.0
Registered repeat-baseline	+2.72	26.4	+0.51	20.2	+3.24	24.2	+1.36	25.8	+4.59	20.8
Registered and matched repeat-baseline	+7.77	29.0	−3.96	9.50	+3.81	25.2	+0.75	24.0	+4.56	17.1
% of baseline volume										
Repeat-baseline	+0.10	3.06	+0.19	5.0	+0.15	2.80	+0.27	10.42	+0.16	1.98
Registered repeat-baseline	+0.35	3.36	+0.10	3.98	+0.26	1.94	+0.64	12.20	+0.31	1.42
Registered and matched repeat-baseline	+0.99	3.70	−0.77	1.86	+0.30	2.02	+0.35	11.36	+0.31	1.16

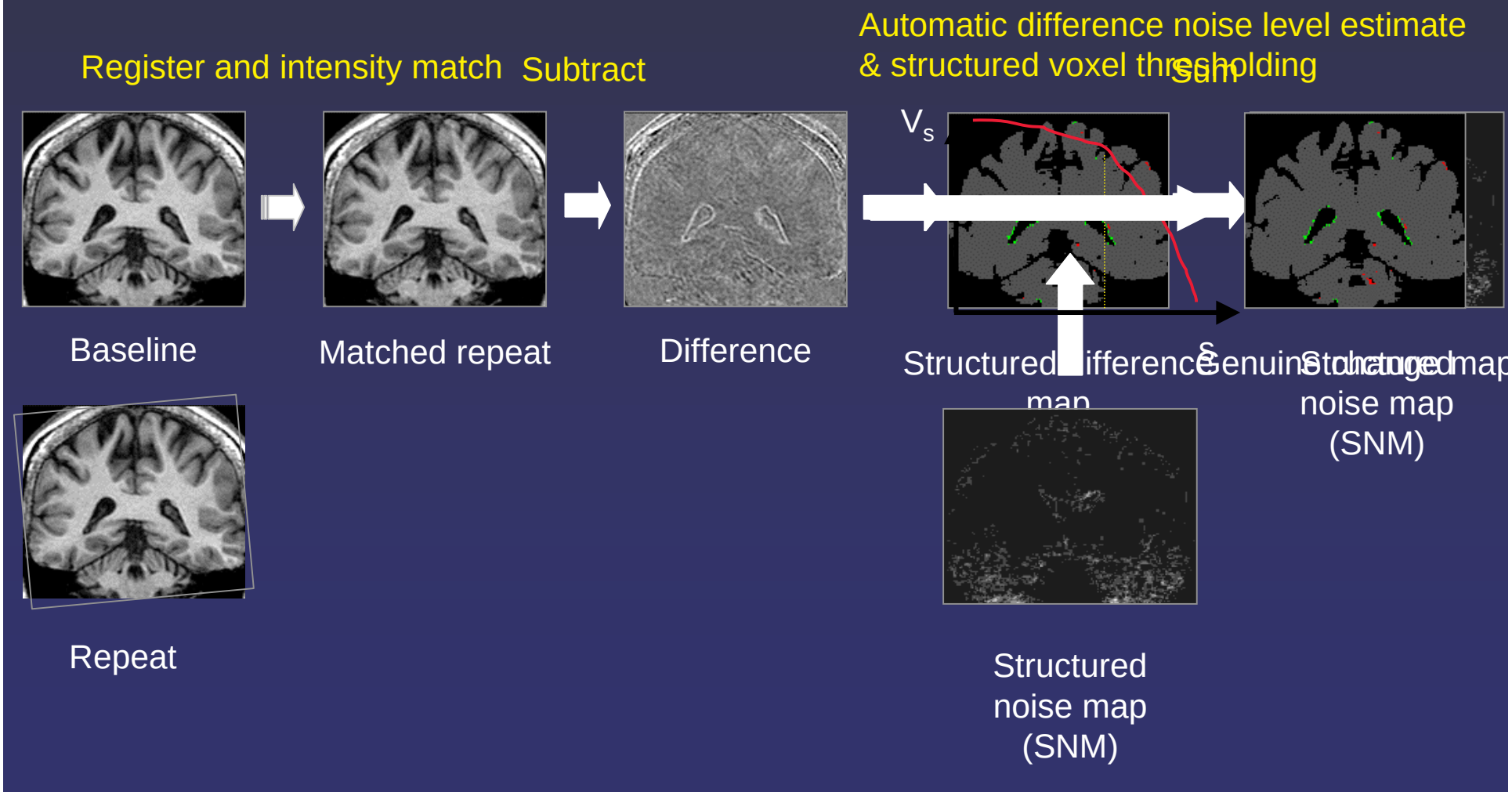
[a]TBV is the sum of GMV and WMV.

[b]ICV is the sum of TBV and CSFV. CR, Coefficient of repeatability = 2 × SD.

[Lemieux et al. MRM 2003]

Algorithm reality check: ‘Double cortex’

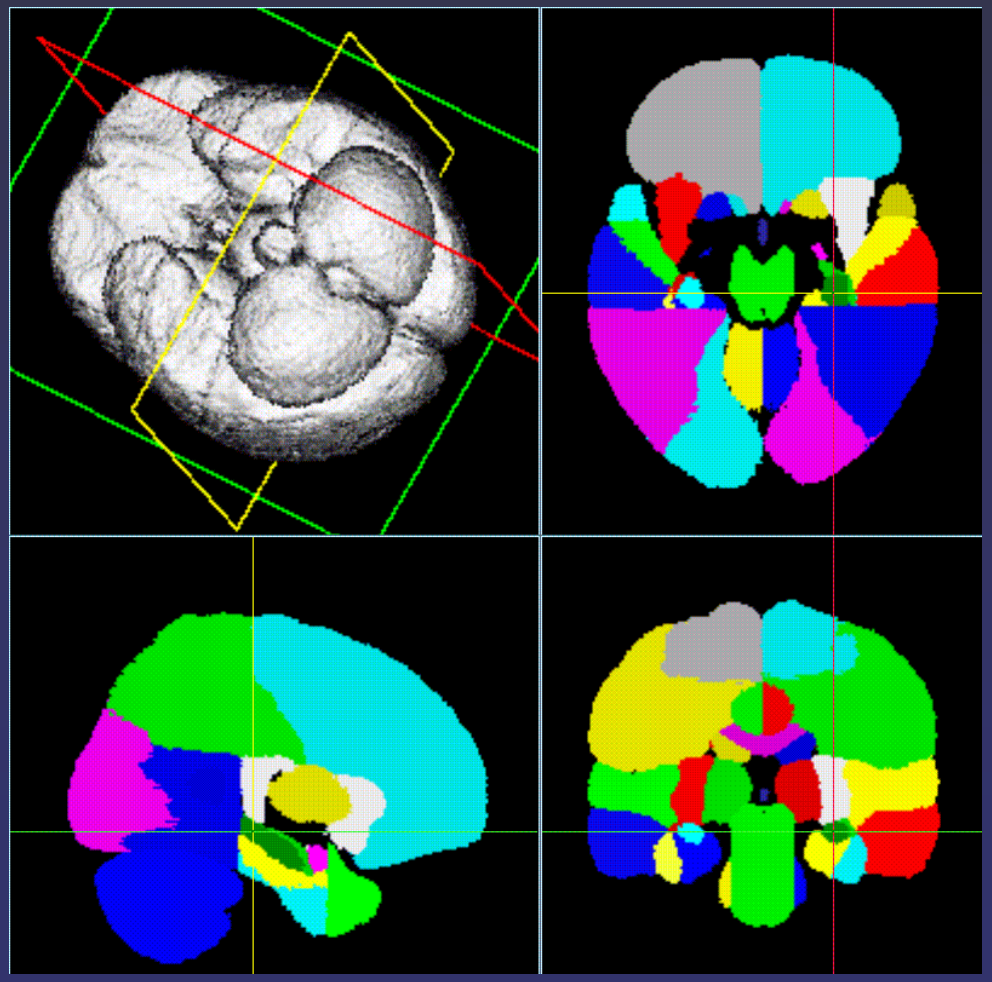
Serial volumetry - difference image analysis



[Lemieux et al., Med Imag Anal 1998]

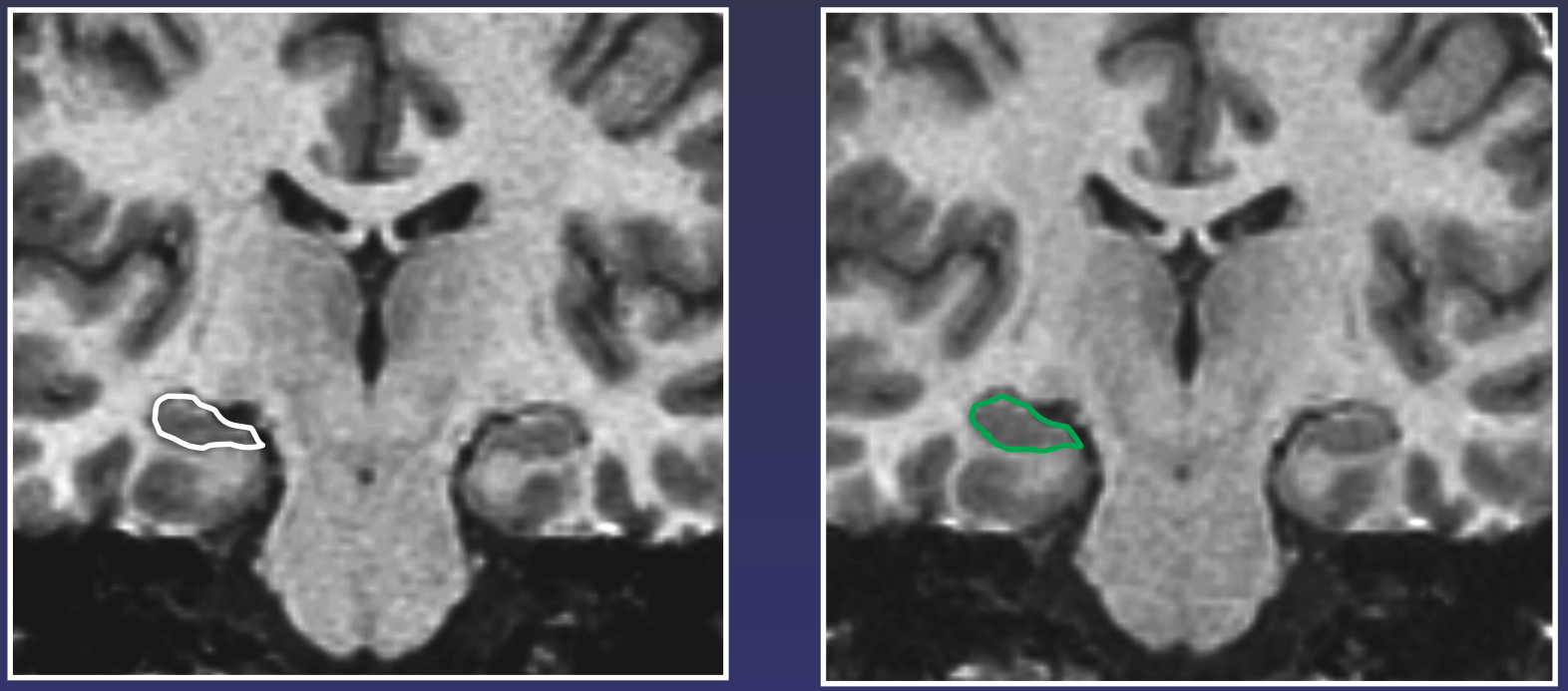
ROI difference analysis: Hammers atlas

- 49 ROIs
- 20 brains
- *Exbrain*
- Manually delineated ROI's
  - 2 observers
- SPM99/MNI space
- Maximum probability



[Hammers et al., *Human Brain Mapping* 2003;
Hammers et al., *Human Brain Mapping* 2002]

Serial hippocampal volumetry



Coefficient of reliability: 78mm^3

[Lemieux et al. MRI 2000]

The Wellcome II population-based study

Aims:

- To address the brain/hippocampal damage chicken & egg question:
  - To determine whether recurrent seizures are associated with secondary damage to the hippocampus and neocortex over 3.5 years
- To identify risk factors associated with cerebral damage in epilepsy

[See Liu RSN et al 2000-2003; Lemieux L et al. 2000, 2003]

Wellcome II study - Experimental design

PHASE 1

153 chronic active epilepsy

90 newly diagnosed epilepsy

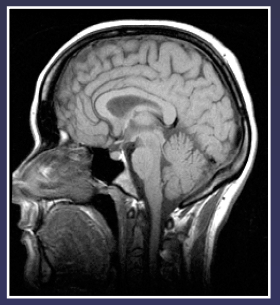
90 control subjects

3.5 years

Clinical data collected:

- head injuries
- alcohol consumption
- steroid use
- medical / psychiatric history
- seizure types + frequency
- status epilepticus
- AED usage, and episodes of intoxication

PHASE 2



122 chronic active epilepsy

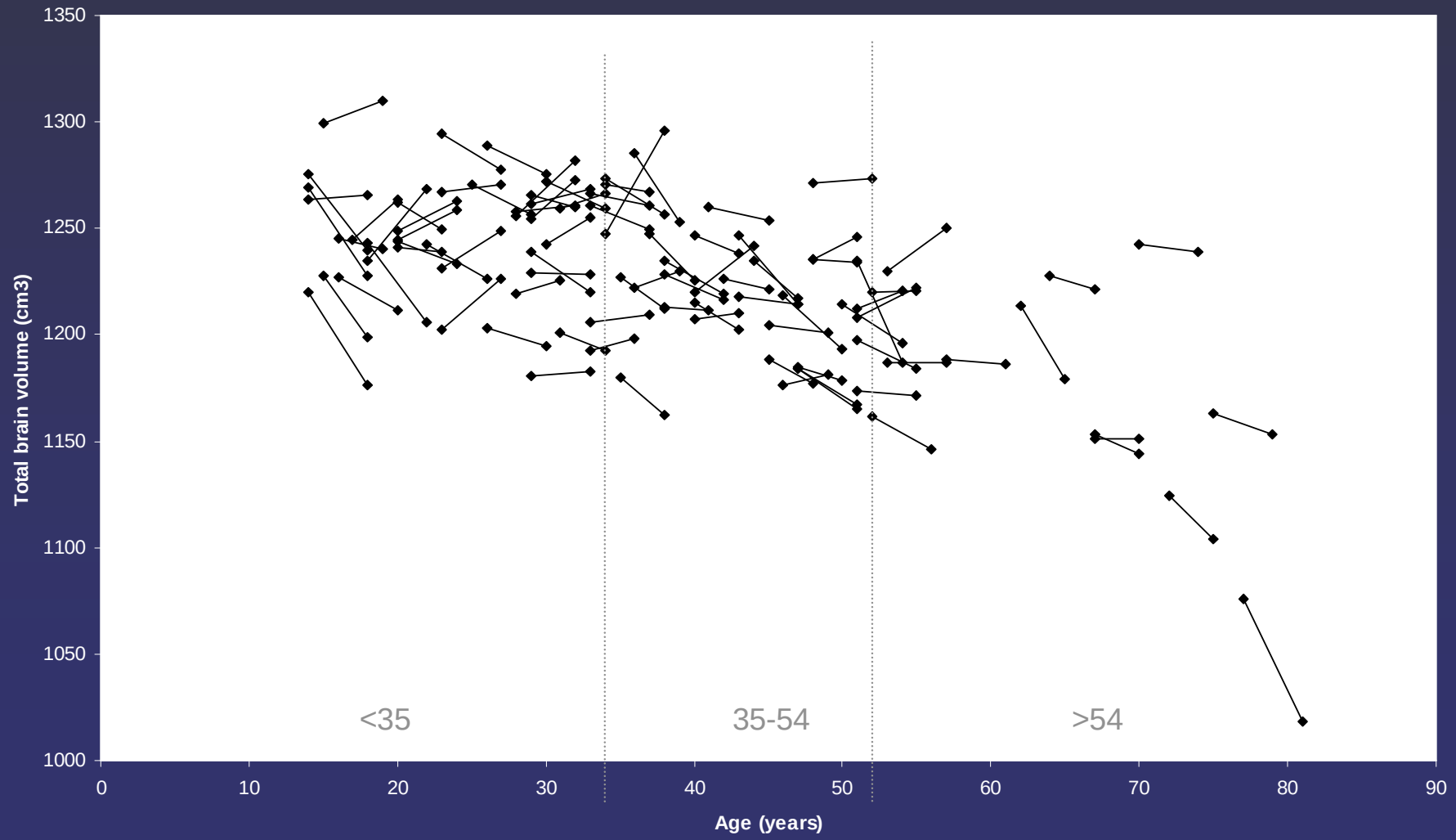
68 newly diagnosed epilepsy

90 control subjects

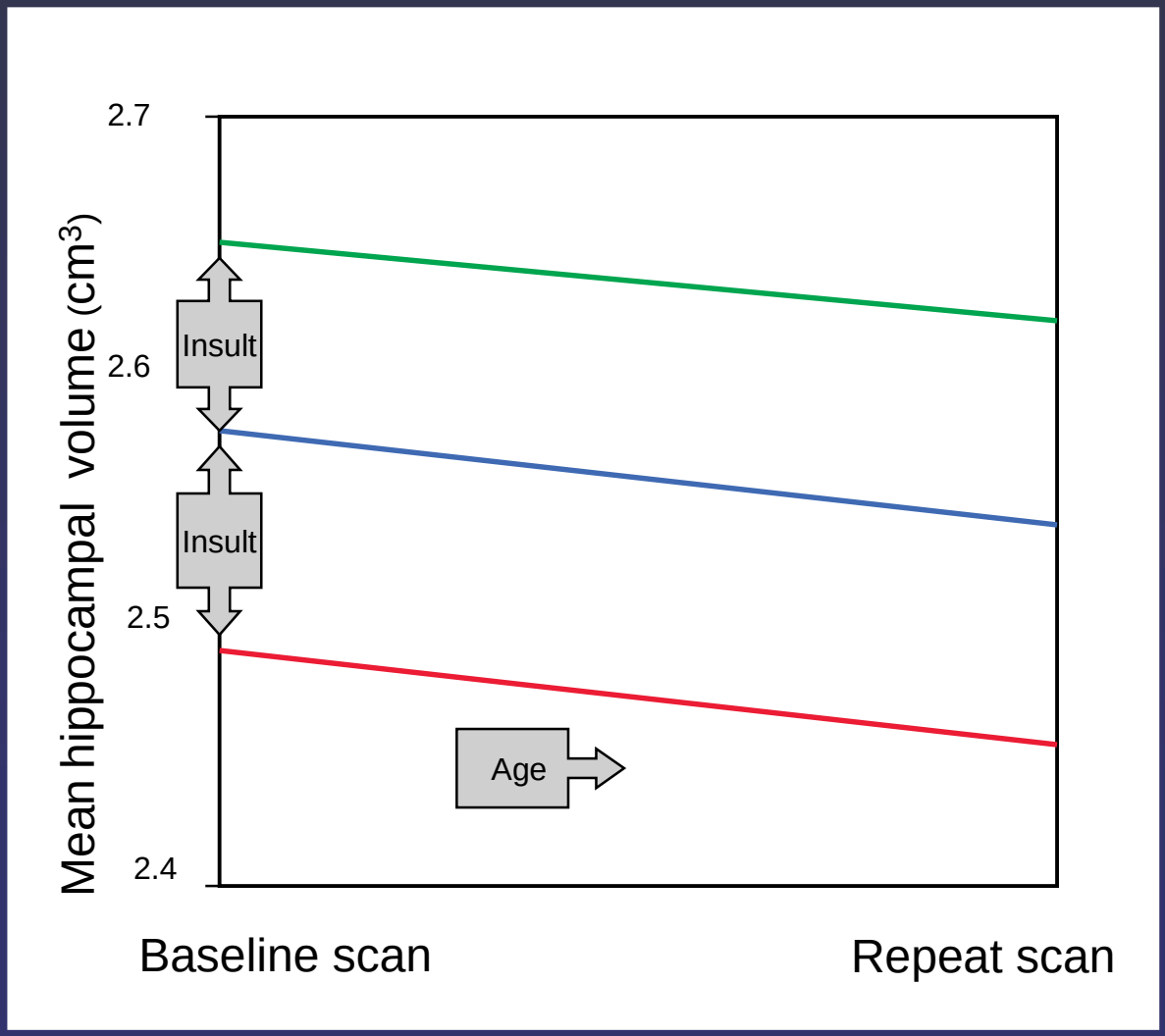
- Baseline and repeat MRI scans performed on same scanner using identical acquisition sequences

Total: 560 T1 scans

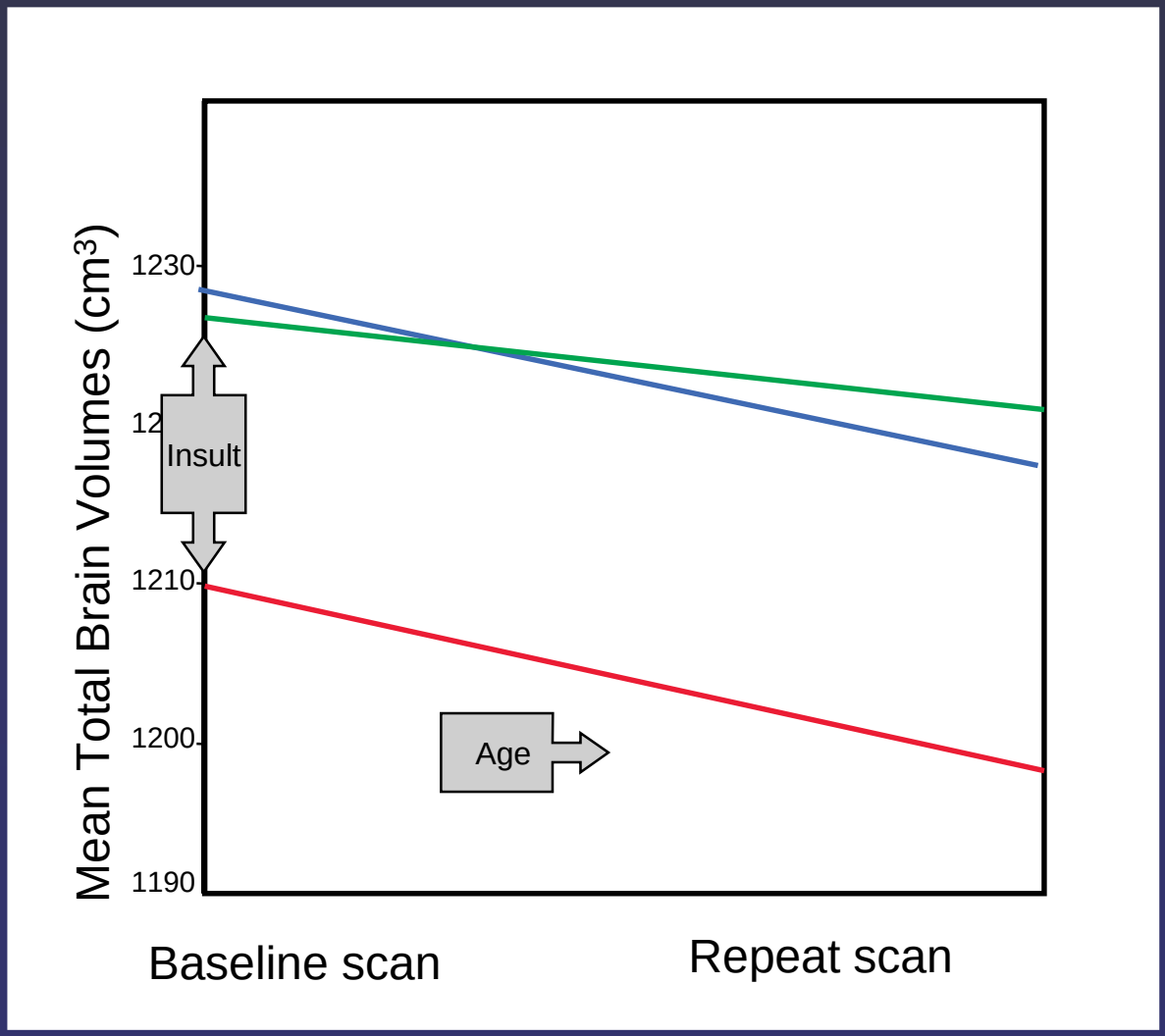
Wellcome II study – Controls: change in total brain volume with age



Wellcome II - Group analysis: Hippocampal volume



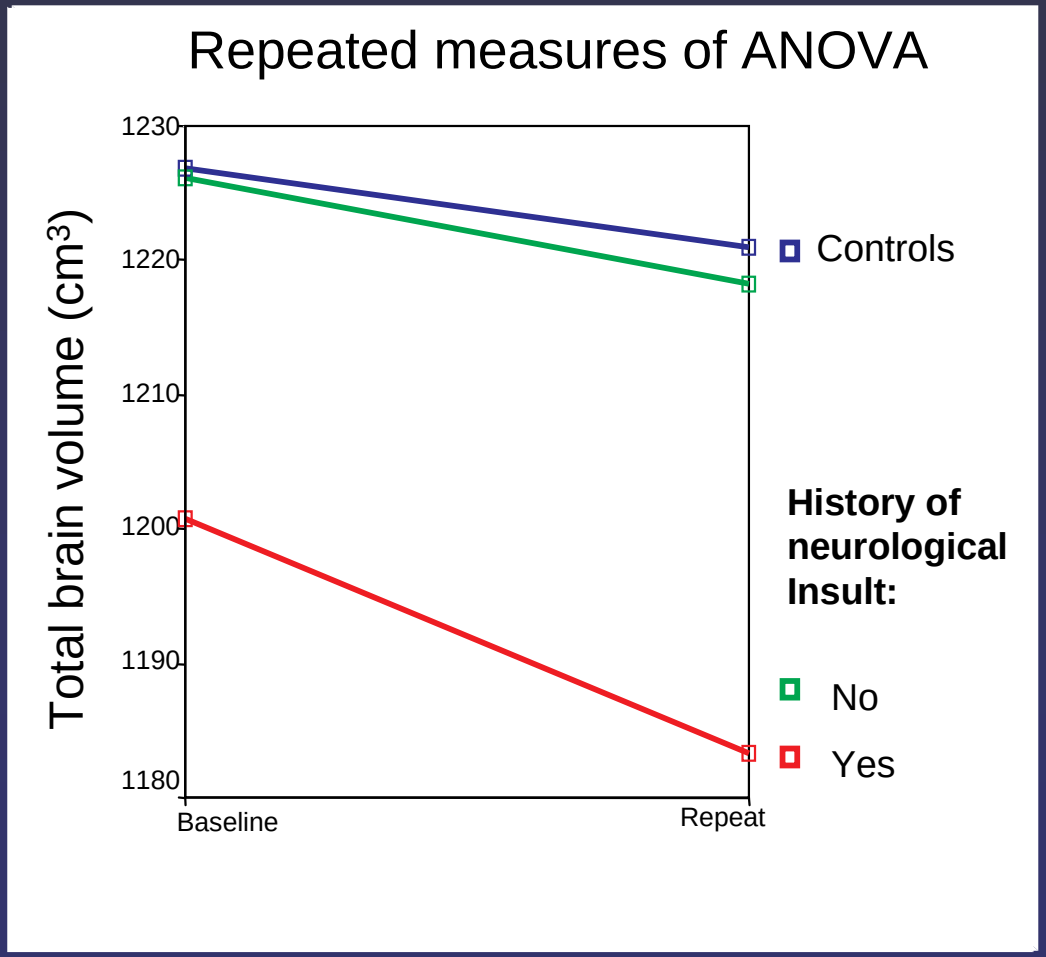
Wellcome II - Group analysis: Total brain volume



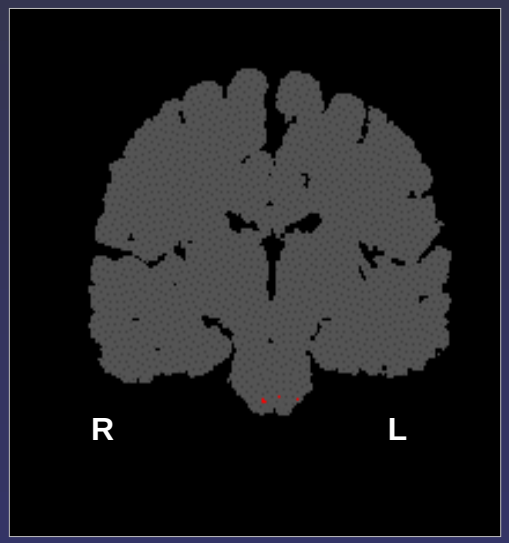
Wellcome II - Group analysis: Total brain volume

F=4.58

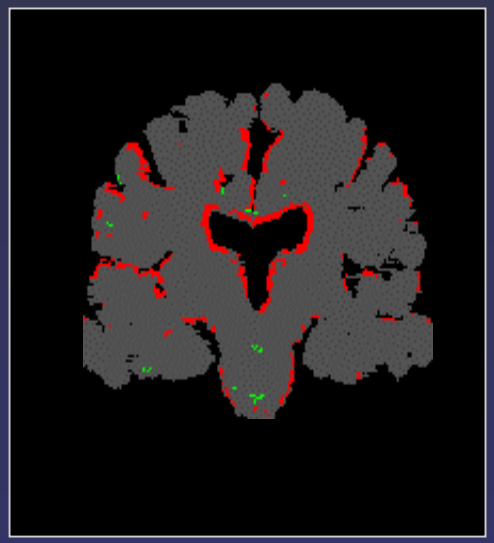
p=0.02



Wellcome II – Difference image analysis: Patterns of neocortical change



No change



Generalized volume loss

Focal neocortical volume loss

Focal / generalized neocortical signal change / volume loss:

- 54% of chronic epilepsy cases
- 39% of newly diagnosed cases
- 24% of controls

Wellcome II – Main biological conclusions

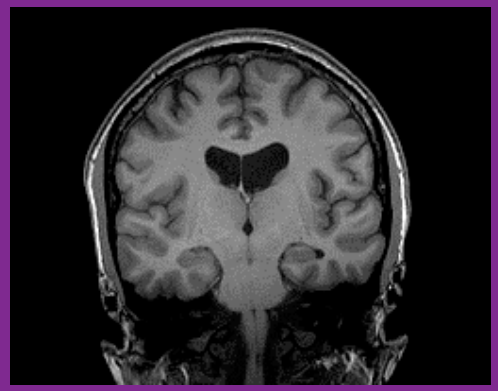
- Baseline reductions in hippocampal and neocortical volumes could be attributed to **antecedent** neurological insults.
- The rate of hippocampal and neocortical volume loss was strongly associated with **age** but **not** overt **seizures**.
- A prior neurological insult was associated with an increased rate of cerebral atrophy.
- Structural damage primarily the result of an **initial precipitating insult**.
- Continuing loss of brain volume can occur but is subtle and often remote from the putative epileptic focus.

See: Liu RSN et al. *NeuroImage*, **14**(1): 231-243, 2001. Liu RSN et al. *NeuroImage*,**20**:22-33, 2003. Liu RSN et al. *Ann. Neurol.*, **52**: 573-580, 2002. Liu RSN et al. *Ann. Neurol.*, **53**(3): 312-324, 2003.

Wellcome II – Main methodological conclusions

- Automatic registration & segmentation successful for all 280 scan pairs
- Automated brain and IC segmentation provides objective baseline values and normalisation data
    - Time saving, too
- Repeat brain volume measures adequate for group analyses
- Manual segmentation of hippocampi: very time consuming
- Difference image analysis much more sensitive

3D IrpFSPGR @ 3T
GE 8-channel (RX) headcoil

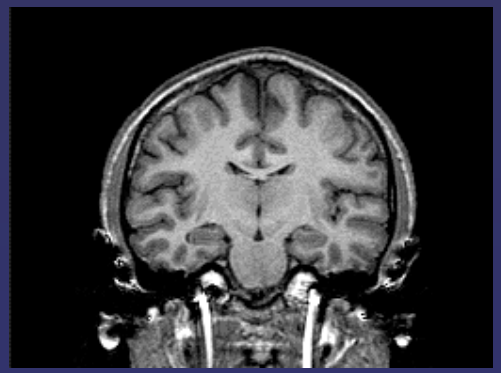


Slice thickness: 1.1mm
Scan time: 7:27

	μ	s	SNR
WM:	**2800**	**(65)**	**43**
GM:	**2200**	**(65)**	**34**
CSF:	**1000**	**(50)**	**20**
Bkgnd:	**125**	**(30)**	

CNR_{GM-WM}=9 CNR_{GM-CSF}=22

1.5T ‘standard’ TX/RX headcoil:



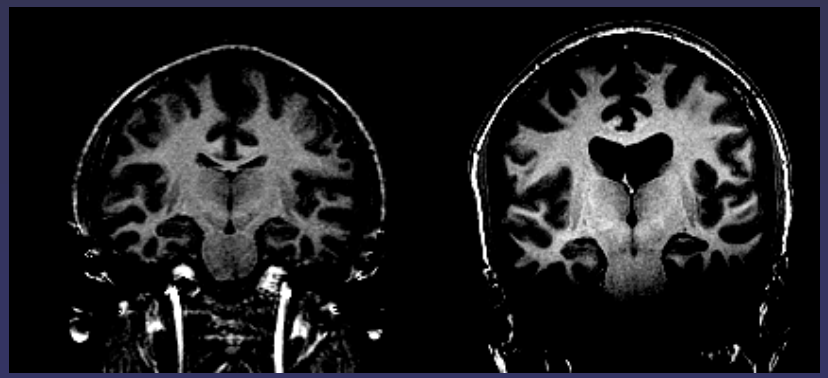
Slice thickness: 1.5mm
Scan time: 6:56

	μ	s	SNR
WM:	**105**	**(4)**	**26**
GM:	**90**	**(4)**	**23**
CSF:	**20**	**(4)**	**5**
Bkgnd:	**4**	**(3)**	

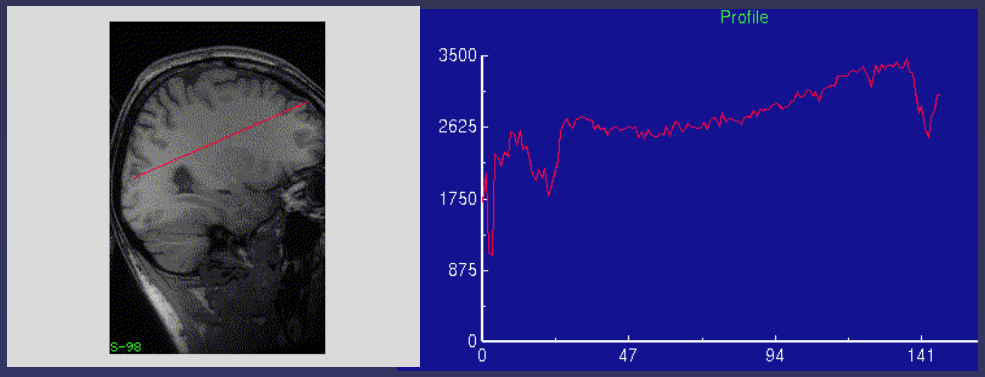
CNR_{GM-WM}=4 CNR_{GM-CSF}=18

3T multi-channel headcoil: non-uniformity

Problem:

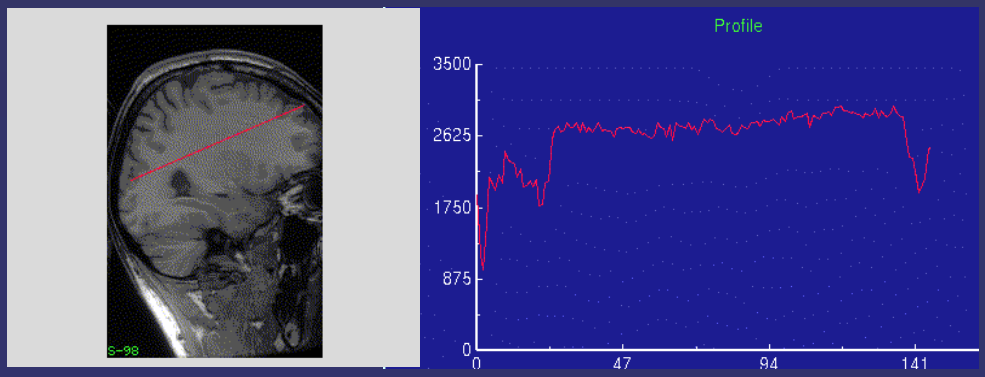


1.5T Q-HC 3T MC-HC

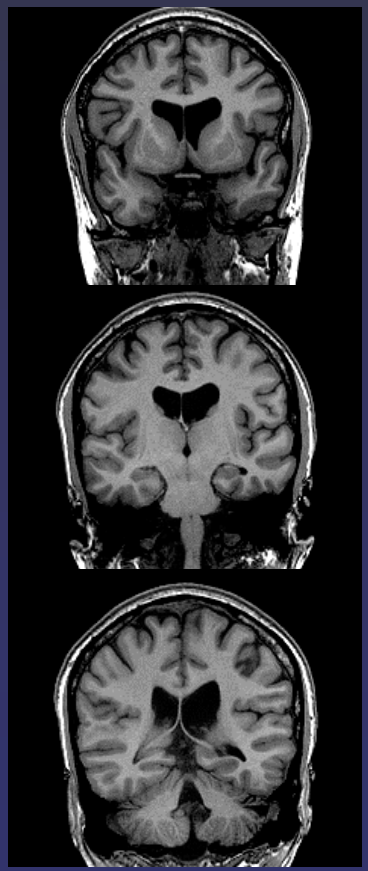


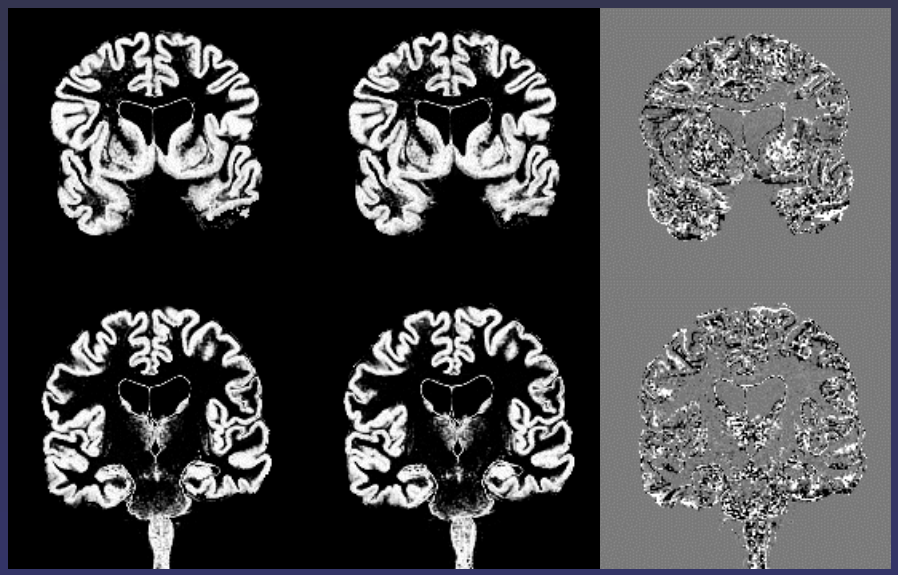
Solution:

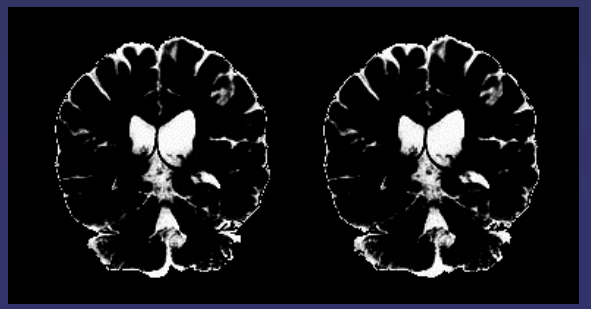
N3:



Tissue maps @ 3T: repeat scan results







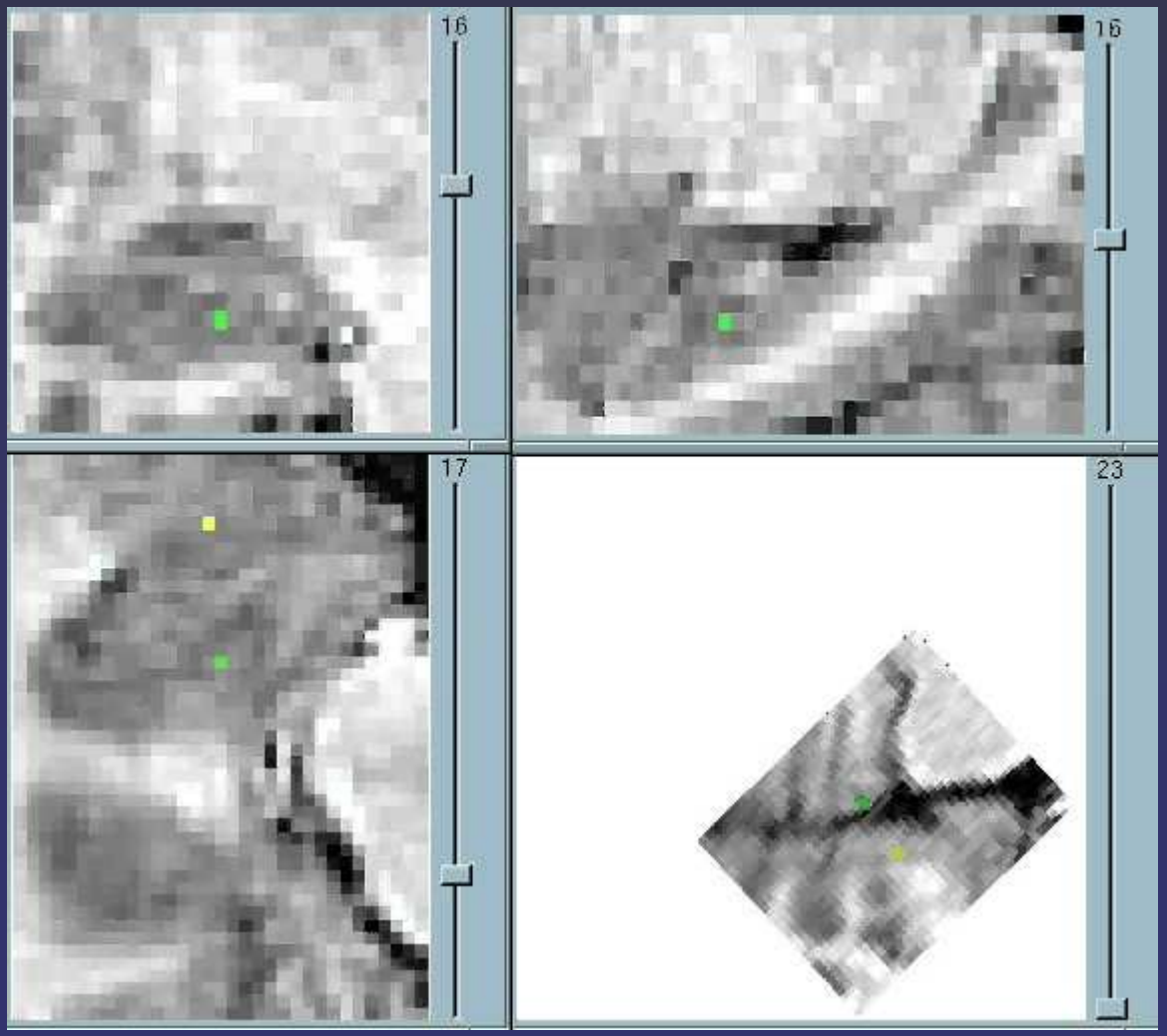
GM

CSF

Prospective

- Increase sensitivity: other sequences *[Bosc et al], etc*
- Theoretical
  - Increase sampling
  - Identify optimal inter-scan interval
  - Modelling of change?
- Methodological developments:
  - Hippocampal segmentation automation (differential)
  - Improve patient repositioning
  - Differential analysis of other sequences
  - Difference volume analysis by tissue type
    - Whole brain; ROI atlas
  - Long term studies:
    - Adapt to scanner changes

Automated hippocampus (& amygdala) segmentation: Fast algorithm



hippocampus
amygdala

Execution time: ~ 2 min

Cognitive Neuroscience and
Brain Imaging Laboratory, Paris

[Chupin M et al, submitted]

Acknowledgements

RSN Liu

SM Sisodiya

SD Shorvon

J Burdett

G Bell

B Kendall

J Stevens

A Hammers

JS Duncan

PA Bartlett

JWA Sander

The Wellcome Trust

National Society for Epilepsy

Wellcome II - main publications

- Lemieux L et al. Hippocampal and cerebellar volumetry in serially acquired MRI volume scans. *Magn. Reson. Imaging*, **18**(8): 1027-1033, 2000.
- Liu RSN et al. Increase in brain size with abstinence from alcohol *Lancet*, **355**: 1969-1970, 2000
- Liu RSN et al. A longitudinal quantitative MRI study of community-based patients with chronic and newly diagnosed seizures: methodology and preliminary findings. *NeuroImage*, **14**(1): 231-243, 2001.
- Liu RSN et al. A longitudinal study of normal ageing using quantitative MRI and difference image analysis. *NeuroImage*,**20**:22-33, 2003.
- Liu RSN et al. The structural consequences of newly diagnosed seizures. *Ann. Neurol.*, **52**: 573-580, 2002.
- Liu RSN et al. Progressive neocortical damage in epilepsy. *Ann. Neurol.*, **53**(3): 312-324, 2003.
- Lemieux L et al. Automatic, accurate segmentation of the brain and intracranial cerebrospinal fluid in T1-weighted volume MRI scans of the head and its application to serial cerebral and intracranial volumetry. *Magn. Reson. Med.*, **49**: 872-884, 2003.