Analysis of longitudinal neuroimaging data with OLS & Sandwich Estimator of variance

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Reading workshop lifespan neurobiology
27 June 2014

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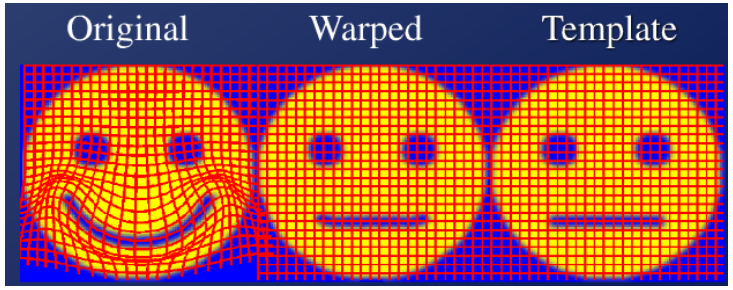
An example of longitudinal studies in neuroimaging
The ADNI study

- Tensor-Based Morphometry (TBM) images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (Hua et al., 2013; Guillaume et al., 2014)
- Available scans:

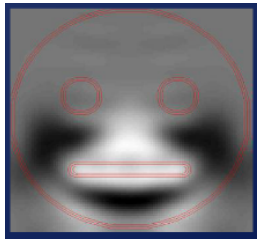
	AD	MCI	N	Total
0 month	188	400	229	817
6 months	159	346	208	713
12 months	138	326	196	660
18 months	n/a	286	n/a	286
24 months	105	244	172	521
36 months	n/a	170	147	317

TBM images?



Determinant of the deformation matrix:

$det(J)$

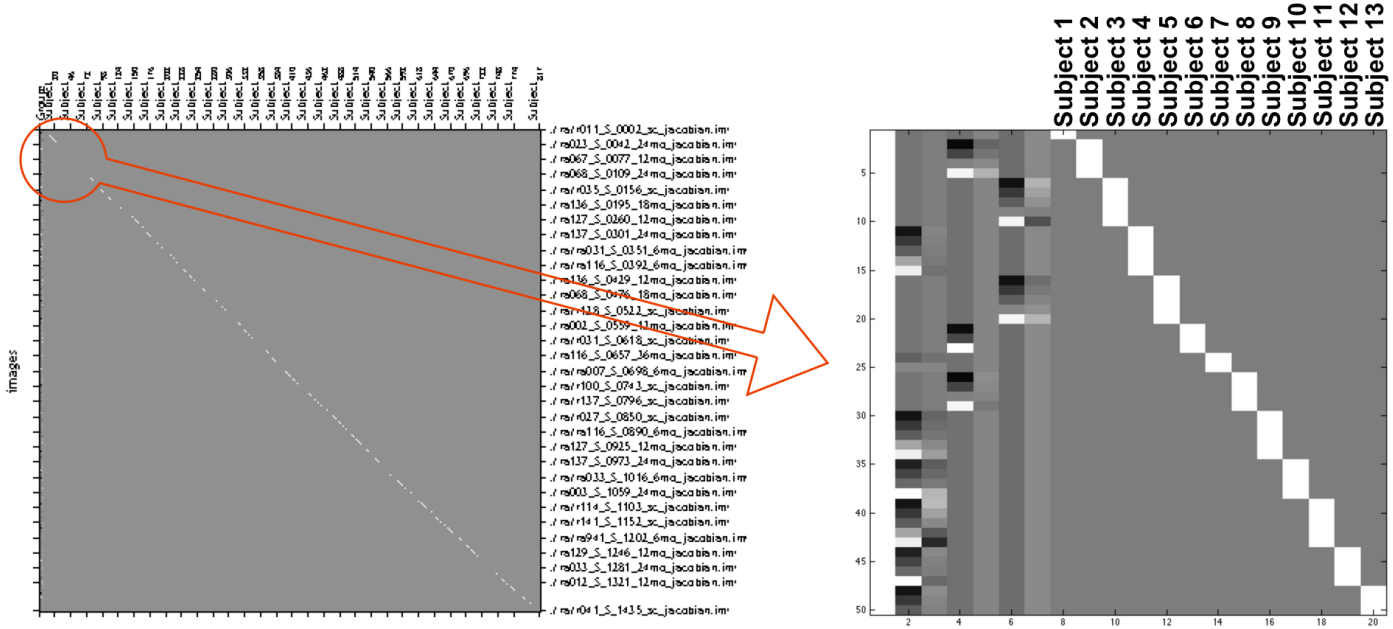


$det(J) > 1$: expansion

$det(J) < 1$: contraction

The Naive Ordinary Least Squares (N-OLS) model

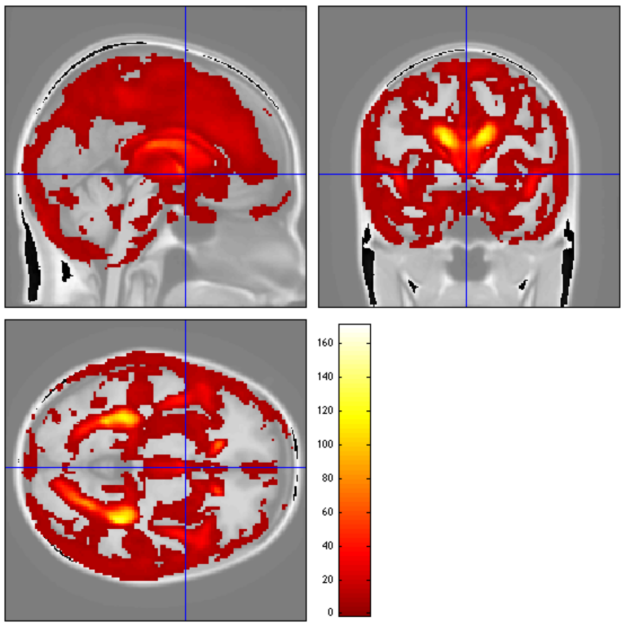
- Design matrix in the ADNI design



- Assumes Compound Symmetry (CS):
  - Equal intra-visit variances
  - Equal intra-visit correlations
- No inference possible on between subject effects (e.g., group intercept, gender, age at first visit)

Compound Symmetry (CS) in the ADNI dataset?

- Box's test of Compound Symmetry (Box, 1950) image thresholded at 5% after Bonferroni correction:



- 56% of the in-mask voxels survived the thresholding!!!

The Summary Statistics OLS (SS-OLS) model

- Procedure
  1. Extraction of summary statistics for each subject
     - E.g., intercept, slope
  2. Use of an OLS model for each summary statistic
- Transformation of correlated data into uncorrelated data
- Important loss of information
  - Will affect negatively the power
  - In general, misbehaviour in unbalanced design
    - E.g., subject with 2 visits vs. subject with 6 visits

Linear Mixed Effect (LME) models

For each subject i:

$$y_i = \underbrace{X_i\beta}_{\text{Fixed effects}} + \underbrace{Z_i\alpha_i}_{\text{Random effects}} + \underbrace{\epsilon_i}_{\text{Random error}}$$

Pros

- The gold standard in the biostatistic literature
- Accurate if correctly specified
- Subject-specific inferences on the random effects possible

Cons

- Difficult to specify and validate
  - Only random intercepts? Also, random slopes?
  - Best model may vary across the brain
- Generally not robust against misspecification
  - E.g., random-intercept LME assumes CS like the N-OLS method
- Iterative method
  - Generally slow
  - May fail to converge

References: Bernal-Rusiel et al. (2013a,b); Chen et al. (2013); Guillaume et al. (2014)

Other methods could also be considered

- The “SPM procedure"
  - Assumption of a common covariance structure for the whole brain
- Generalised Methods of Moments (Skup et al., 2012)
- Generalised Estimating Equations (Li et al., 2013)
- . . .

The Sandwich Estimator (SwE) method

- Use of a simple OLS model (without subject indicator variables)
- The fixed effect parameters β are estimated by

$$\hat{\beta}_{OLS} = \left(\sum_{i=1}^{M} X_i' X_i \right)^{-1} \sum_{i=1}^{M} X_i' y_i$$

- The fixed effect parameters covariance var$(\hat{\beta}_{OLS})$ are estimated by

$$S = \underbrace{\left(\sum_{i=1}^{M} X_i' X_i \right)^{-1}}_{\text{Bread}} \underbrace{\left(\sum_{i=1}^{M} X_i' \hat{V}_i X_i \right)}_{\text{Meat}} \underbrace{\left(\sum_{i=1}^{M} X_i' X_i \right)^{-1}}_{\text{Bread}}$$

Property of the Sandwich Estimator (SwE)

$$S = \left(\sum_{i=1}^{M} X_i' X_i \right)^{-1} \left(\sum_{i=1}^{M} X_i' \hat{V}_i X_i \right) \left(\sum_{i=1}^{M} X_i' X_i \right)^{-1}$$

If $m^{-1} \sum_{i=1}^{m} X_i' \hat{V}_i X_i$ consistently estimates $m^{-1} \sum_{i=1}^{m} X_i' V_i X_i$, the SwE tends **asymptotically** (Large samples assumption) towards the true variance var$(\hat{\beta}_{OLS})$. (Eicker, 1963; Eicker, 1967; Huber, 1967; White, 1980)

The classical (uncorrected) SwE method

- V_i estimated from the residuals $e_i = y_i - X_i\hat{\beta}$ by

$$\hat{V}_i = e_i e_i'$$

and the SwE becomes

$$S_{\text{classic}} = \left(\sum_{i=1}^{M} X_i' X_i\right)^{-1} \left(\sum_{i=1}^{M} X_i' r_i r_i' X_i\right) \left(\sum_{i=1}^{M} X_i' X_i\right)^{-1}$$

- Asymptotic test:
  $H_0 : C\hat{\beta} = 0, H_1 : C\hat{\beta} \neq 0$
  C: contrast matrix of rank q

$$\frac{(C\hat{\beta})'(CSC')^{-1}(C\hat{\beta})}{q} \sim \chi^2(q)$$

- Works well in large samples
- But not in small samples

Small sample adjustment of the SwE method

- Several adjustments exists
- One of the best combination of adjustment (Guillaume et al., 2014):
  - Use of corrected residuals $e_{ik}/(1-h_{ik})$ in the estimation of V_i
  - Assumption of homogeneity across subjects within groups (e.g., same covariance structure for all the AD subjects)
  - Use of a statistical test assuming small samples
    $H_0 : C\hat{\beta} = 0, H_1 : C\hat{\beta} \neq 0$
    C: contrast matrix of rank q

$$\frac{\nu - q + 1}{\nu q}(C\hat{\beta})'(CSC')^{-1}(C\hat{\beta}) \sim F(q, \nu - q + 1)$$

Simulations: setup

- Designs considered:
  - ADNI design and 4 of its subsets (817, 408, 204, 103 and 51 subjects)
- Monte Carlo Gaussian null simulation (10,000 realizations)
- For each realization,
  1. Generation of longitudinal Gaussian null data (no effect) with intra-visit covariance structures:

Compound Symmetry

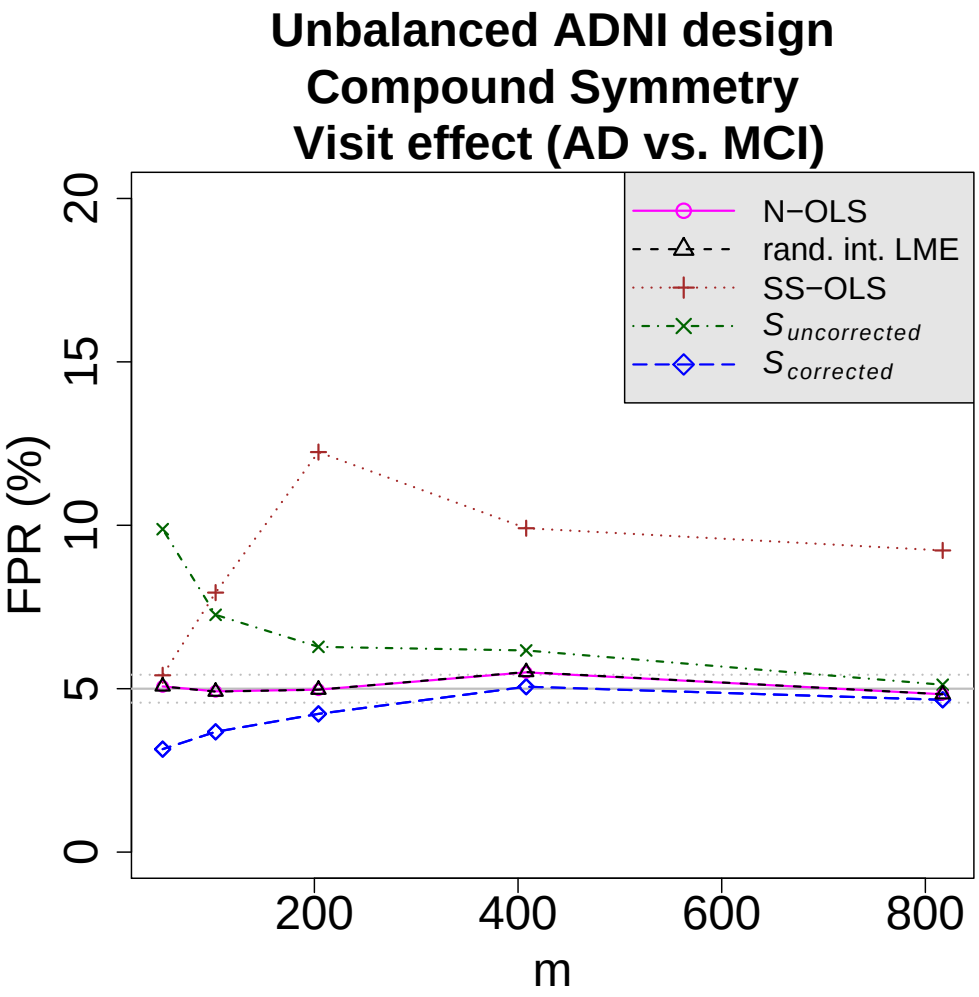
$$\begin{pmatrix} 1 & 0.95 & 0.95 & 0.95 & 0.95 \\ 0.95 & 1 & 0.95 & 0.95 & 0.95 \\ 0.95 & 0.8 & 1 & 0.95 & 0.95 \\ 0.95 & 0.95 & 0.95 & 1 & 0.95 \\ 0.95 & 0.95 & 0.95 & 0.95 & 1 \end{pmatrix}$$

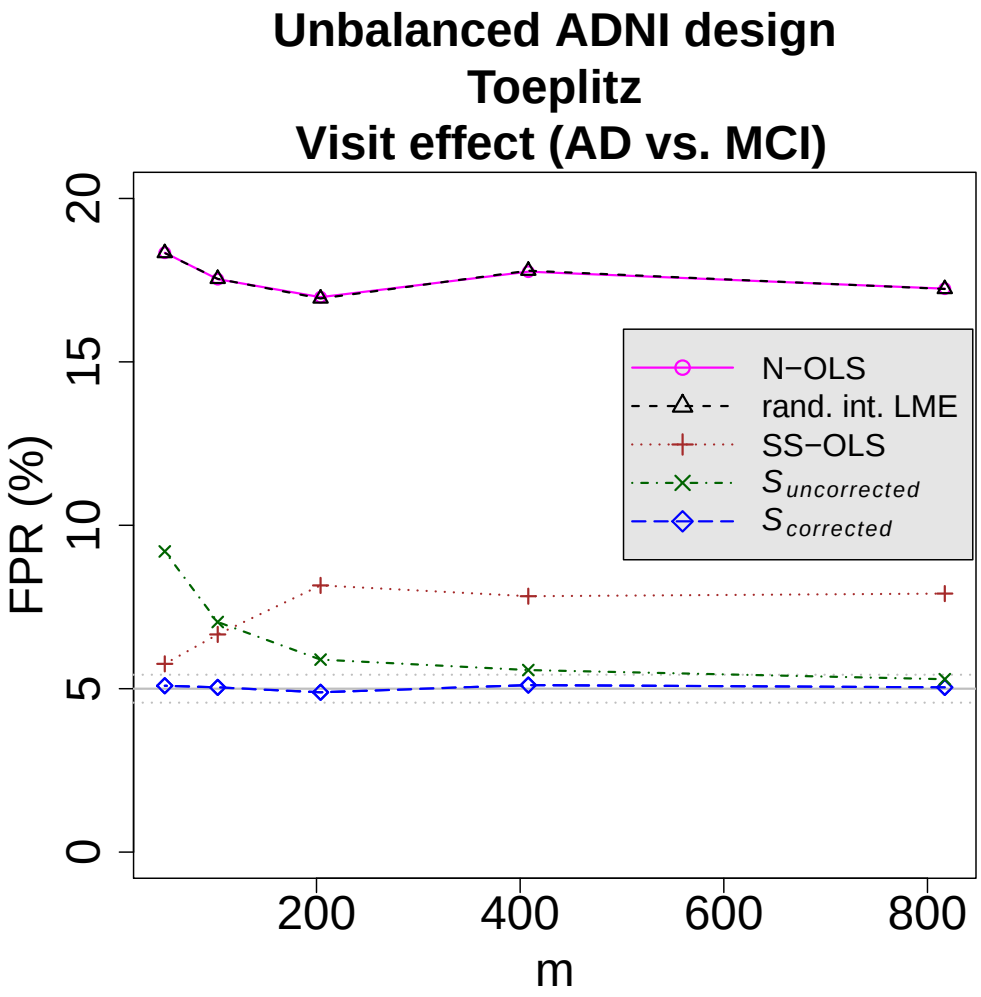
Toeplitz

$$\begin{pmatrix} 1 & 0.9 & 0.8 & 0.7 & 0.6 \\ 0.9 & 1 & 0.9 & 0.8 & 0.7 \\ 0.8 & 0.9 & 1 & 0.9 & 0.8 \\ 0.7 & 0.8 & 0.9 & 1 & 0.9 \\ 0.6 & 0.7 & 0.8 & 0.9 & 1 \end{pmatrix}$$

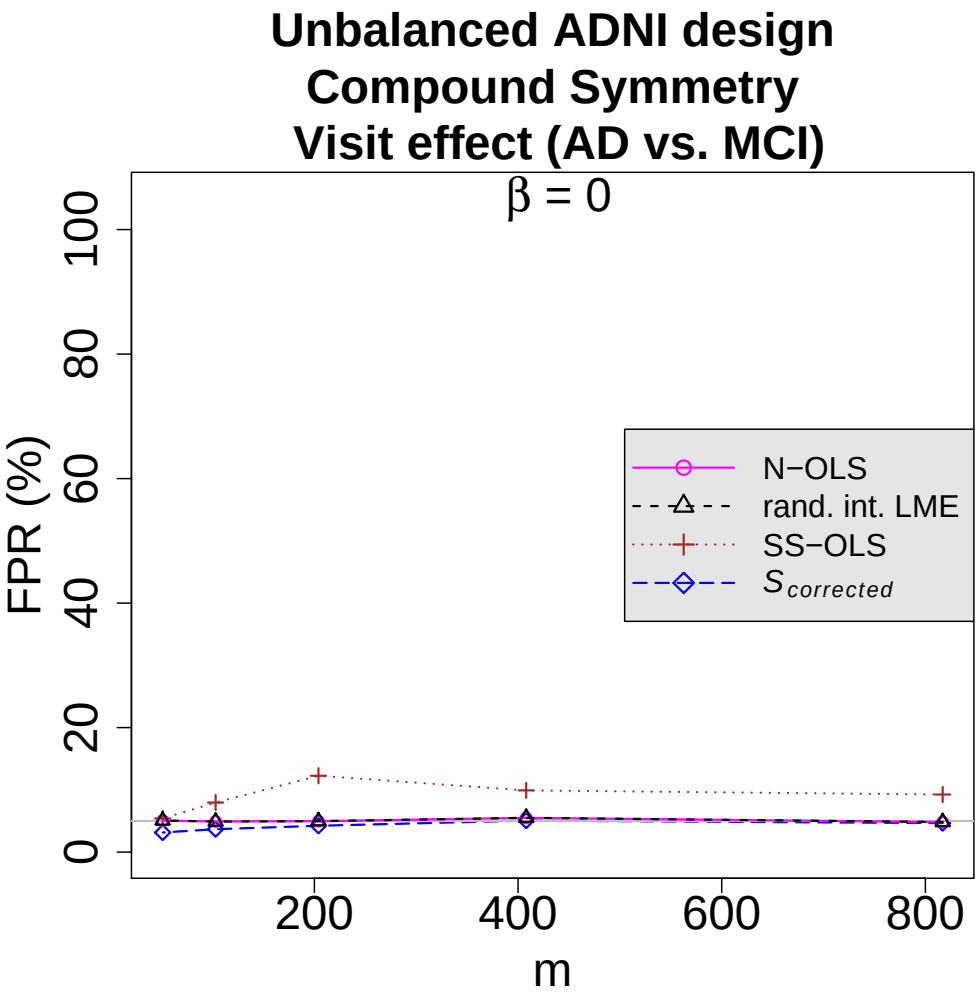
  2. Statistical test (F-test at 5%) on the parameters of interest and estimation of the FPR

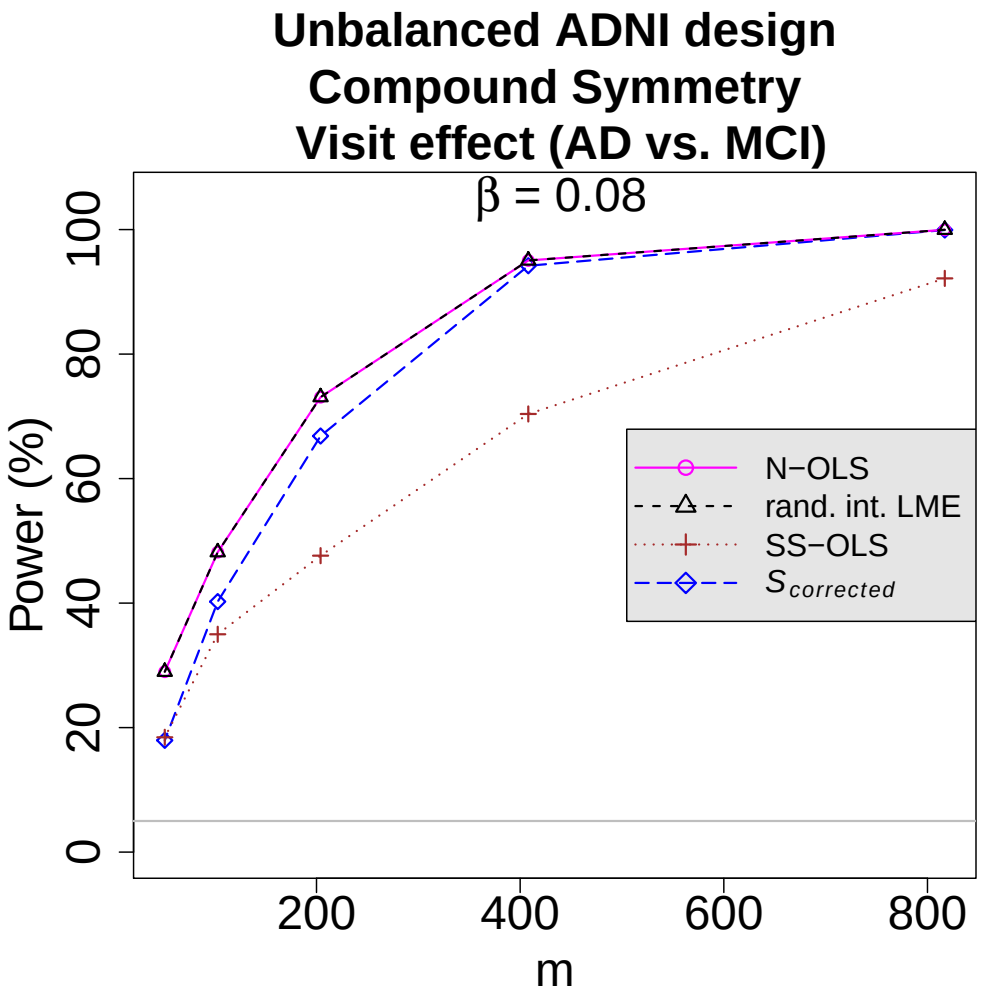
False Positive Rate (FPR) control



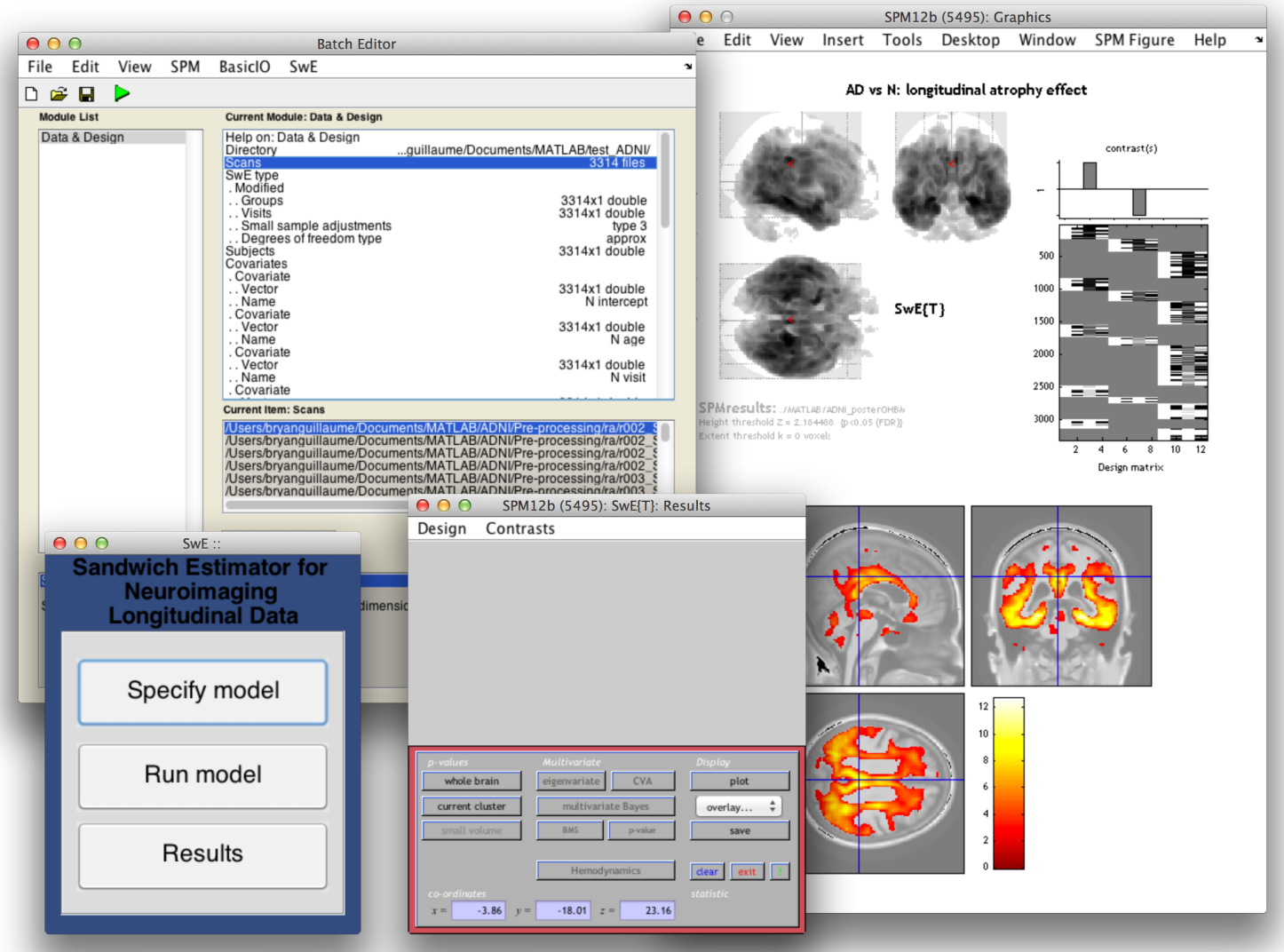


Power analysis





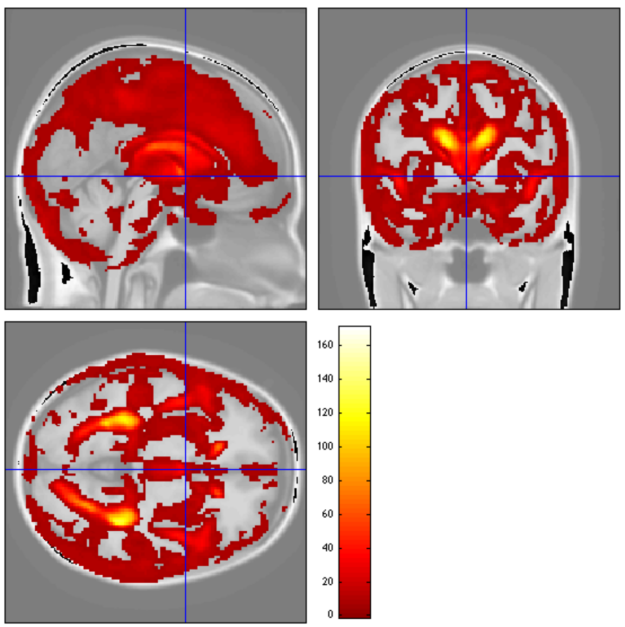
Real ADNI data: use of the SwE toolbox



- Freely available at `http://warwick.ac.uk/tenichols/SwE`

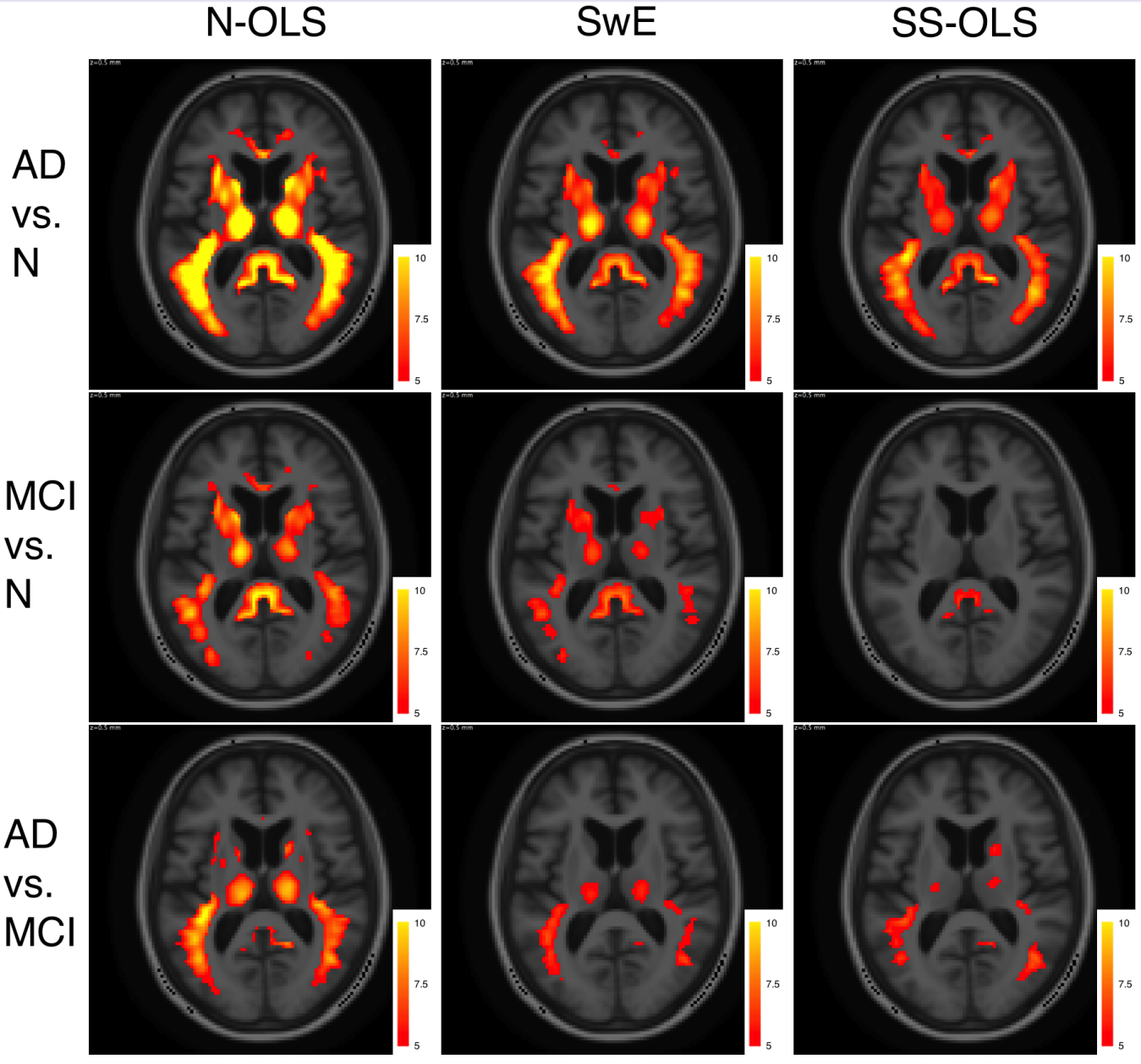
Real ADNI data: reminder of the Box's test of CS

- Box's test of Compound Symmetry (Box, 1950) image thresholded at 5% after Bonferroni correction:



- 56% of the in-mask voxels survived the thresholding!!!

Real ADNI data: Visit effect on the brain atrophy



Summary

- Longitudinal standard methods not really appropriate to neuroimaging data:
  - N-OLS & LME with random intercepts: issues when CS does not hold
  - Difficulties to specify and validate LME models
  - Convergence issues with LME models
  - Under unbalanced design, SS-OLS may be inaccurate and its power quite poor
- The SwE method
  - Accurate in a large range of settings
  - Easy to specify
  - No iteration needed
    - Quite fast
    - No convergence issues
  - Can accommodate pure between covariates
  - SPM toolbox available
  - But, careful in small samples:
    - Adjustments essential
    - Typically, less powerful than N-OLS or LME models

Acknowledgement

- Thomas E. Nichols (Warwick University)
- Lourens Waldorp (Amsterdam University)
- Paul M. Thompson (UCLA)
- Xue Hua (UCLA)
- ADNI

Bibliography

J. L. Bernal-Rusiel, D. N. Greve, M. Reuter, B. Fischl, and M. R. Sabuncu. Statistical analysis of longitudinal neuroimage data with linear mixed effects models. *Neuroimage*, 66:249–260, 2013a.

J. L. Bernal-Rusiel, M. Reuter, D. N. Greve, B. Fischl, and M. R. Sabuncu. Spatiotemporal linear mixed effects modeling for the mass-univariate analysis of longitudinal neuroimage data. *NeuroImage*, 81(0):358 – 370, 2013b. ISSN 1053-8119. doi: http://dx.doi.org/10.1016/j.neuroimage.2013.05.049.

G. E. Box. Problems in the analysis of growth and wear curves. *Biometrics*, 6(4):362–389, 1950.

G. Chen, Z. S. Saad, J. C. Britton, D. S. Pine, and R. W. Cox. Linear mixed-effects modeling approach to fmri group analysis. *NeuroImage*, 2013.

B. Guillaume, X. Hua, P. M. Thompson, L. Waldorp, and T. E. Nichols. Fast and accurate modelling of longitudinal and repeated measures neuroimaging data. *NeuroImage*, 94:287–302, 2014.

X. Hua, D. P. Hibar, C. R. Ching, C. P. Boyle, P. Rajagopalan, B. A. Gutman, A. D. Leow, A. W. Toga, C. R. J. Jr., D. Harvey, M. W. Weiner, and P. M. Thompson. Unbiased tensor-based morphometry: Improved robustness and sample size estimates for alzheimer's disease clinical trials. *NeuroImage*, 66(0):648 – 661, 2013. ISSN 1053-8119. doi: 10.1016/j.neuroimage.2012.10.086.

Y. Li, J. H. Gilmore, D. Shen, M. Styner, W. Lin, and H. Zhu. Multiscale adaptive generalized estimating equations for longitudinal neuroimaging data. *NeuroImage*, 2013.

M. Skup, H. Zhu, and H. Zhang. Multiscale adaptive marginal analysis of longitudinal neuroimaging data with time-varying covariates. *Biometrics*, 2012.

Thanks for your attention!