

## Introduction

There have been recent advances in neuroimaging longitudinal modelling [1,7,8], however all of these methods entail numerical optimisation at each voxel. While the current versions of the two most widely used packages (i.e. SPM and FSL) are computationally efficient, they can only model longitudinal data with more than two time points using restrictive assumptions. Indeed, FSL v5.0 must assume compound symmetry (constant variances and constant correlations over time) and a fully balanced design, and SPM12 unrealistically assumes a unique longitudinal correlation structure for the whole brain.

The gold standard method used in longitudinal data analysis is the Linear Mixed Effects (LME) modelling [6]. Unfortunately, it requires iterative algorithms that can be prohibitively slow and often fail to converge. One possible alternative is the Summary Statistics Ordinary Least Squares (SS-OLS) approach which first extracts summary statistics for each subject and then fits a separate OLS model for each of the summary statistics. Another alternative is the Naïve OLS (N-OLS) modelling where subject indicator variables are used to fit subject-specific slopes. The N-OLS approach *can* give equivalent inferences to LME with a random intercept, but only for a balanced 1-way repeated measures ANOVA with compound symmetric (all equal) variances and correlations. However, real data analyses often have unbalanced designs and, for more than 3 time points, a compound symmetric assumption is probably not realistic. Here, we demonstrate the use of our alternate approach [4] using OLS and the so-called 'Sandwich Estimate' of variance; this approach is computationally efficient and allows the use of within/between-subject covariates.

## Methods

We use an OLS model for the marginal model (i.e. no subject indicators) to create estimates of the parameters of interest; standard errors of these estimates are obtained with the Sandwich Estimator (SwE) in order to account for the longitudinal correlation [2,3]. In order to assess the methods (LME with a random intercept, N-OLS, SS-OLS and SwE methods), we consider a dataset obtained after using tensor-based morphometry on structural MRI from the Alzheimer's Disease Neuroimaging Initiative (ADNI) [5]; the data consists of 3314 images from 817 subjects divided in 3 groups, AD, MCI and Normal, with a maximum of 6 visits per subject. We use Monte Carlo simulations to simulate data respecting the ADNI design under 4 different types of subject covariance structure: (1) Compound Symmetry (CS), (2) Toeplitz assuming a linear decay of the correlation over time, (3) heterogeneous variance over time and (4) heterogeneous variance between groups. For all the methods, we evaluate the False Positive Rate (FPR) and the Power. Finally, we analyse the real dataset using the N-OLS (SPM), SS-OLS (SPM) and SwE (SPM SwE toolbox) methods. We consider, for each group, an intercept, the inter-subject effect of average age, the intra-subject effect of visit (time), and their interaction (sometimes called "acceleration").

## Results

We focus on the contrast for differences in visit effect between the 3 groups. In the simulations, Fig. 1 shows that only the SwE method is able to give accurate inference (FPR  $\approx$  5%) in all settings while the other methods can become invalid, mainly when CS does not hold. Fig. 1 also shows that the SwE method has similar power as the N-OLS, LME methods under CS (i.e. when the 3 methods are accurate); while the SwE method sometimes seems less powerful than the N-OLS and LME methods, these other methods are not usable as they do not control the FPR in these settings. Moreover, Fig. 1 shows that the SS-OLS method tends to be less powerful than the SwE method, even when it exhibits inflated FPR. In the real analysis, Fig. 2 shows that the N-OLS method exhibits larger t-values than the SwE method, which we attribute to a lack of FPR control, and the SS-OLS method exhibits smaller t-values likely due to the lack of power of the method (see Fig. 1). Finally, Fig. 3 shows the results of the analysis with the SwE method at three particular voxels demonstrating the capability of our marginal model to account for the inter-subject effect of average age, the intra-subject effect of visit, and the acceleration effect. In the right posterior cingulate, there is evidence of a stronger atrophy rate in the AD subjects compared to the Normal subjects; in the right anterior cingulate, the atrophy seems to be only due to ageing and independent of the subject condition. Acceleration effects, illustrated by short lines, are greatest in AD, but suggest *slowing* longitudinal effects with age.

## References

- [1] Bernal-Rusiel et al. (2012), NeuroImage; [2] Eicker (1963), The Annals of Mathematical Statistics; [3] Eicker (1967), Proceedings of the Fifth Berkeley Symposium on Mathematical Statistics and Probability; [4] Guillaume et al. (2012), OHBM, Beijing; [5] Hua et al. (2008), NeuroImage; [6] Laird and Ware (1982), Biometrics; [7] Li et al. (2013), NeuroImage; [8] Skup et al. (2012), Biometrics.

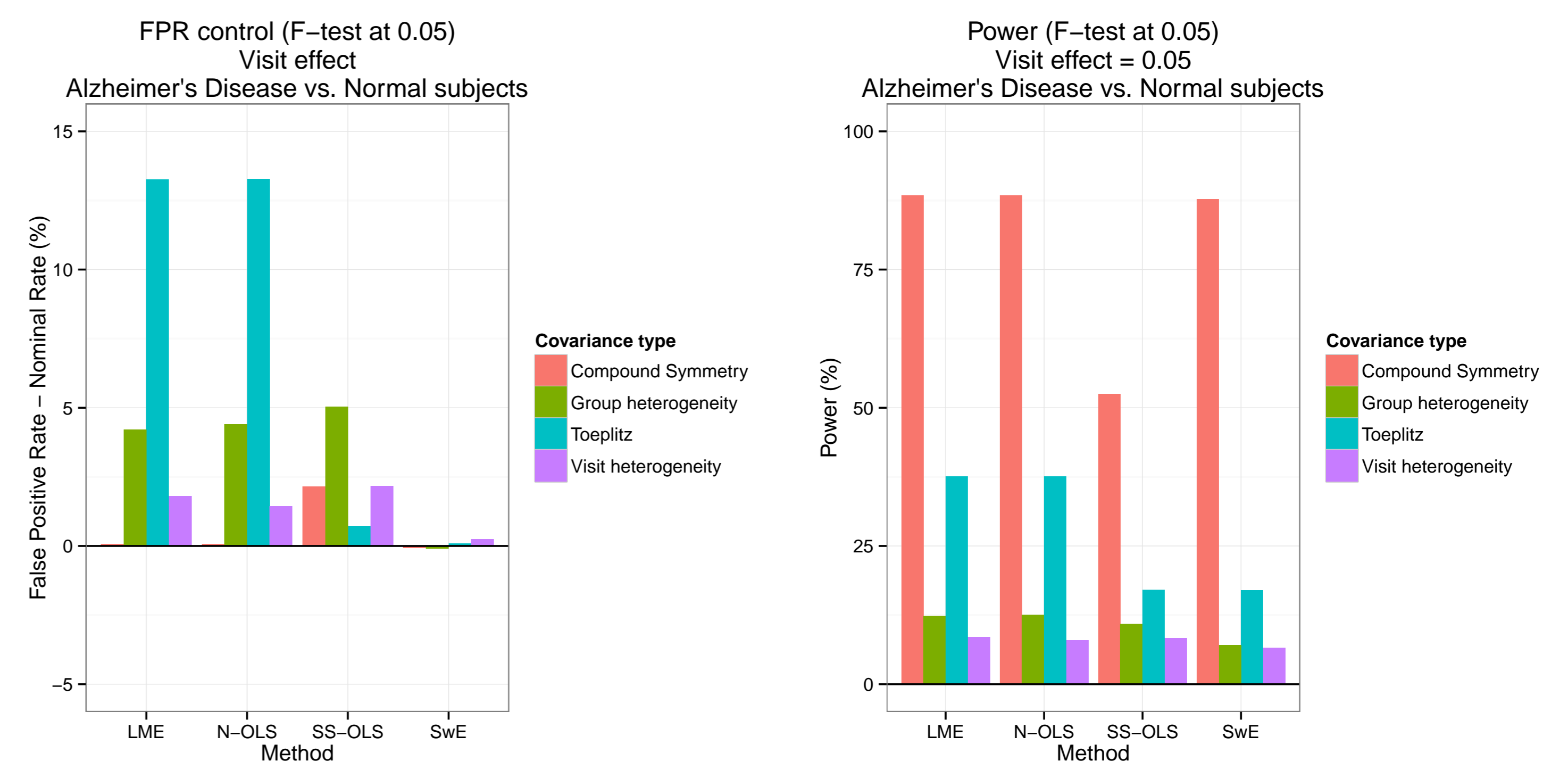


Figure 1: Simulation results: FPR and Power comparison with the design of the ADNI dataset; Compound Symmetry with a correlation of 0.8, group heterogeneity with MCI (AD, resp.) subjects variances twice (three times, resp.) larger than the Normal subjects variances, Toeplitz with a linear decay of the correlation of 0.1/year and visit heterogeneity with a variance increase of 1/year. Left figure shows that SwE's competitors suffer severe inflation of FPR for any setting other than Compound Symmetry. Right figure shows that, for methods that control FPR, SwE is as or more powerful.

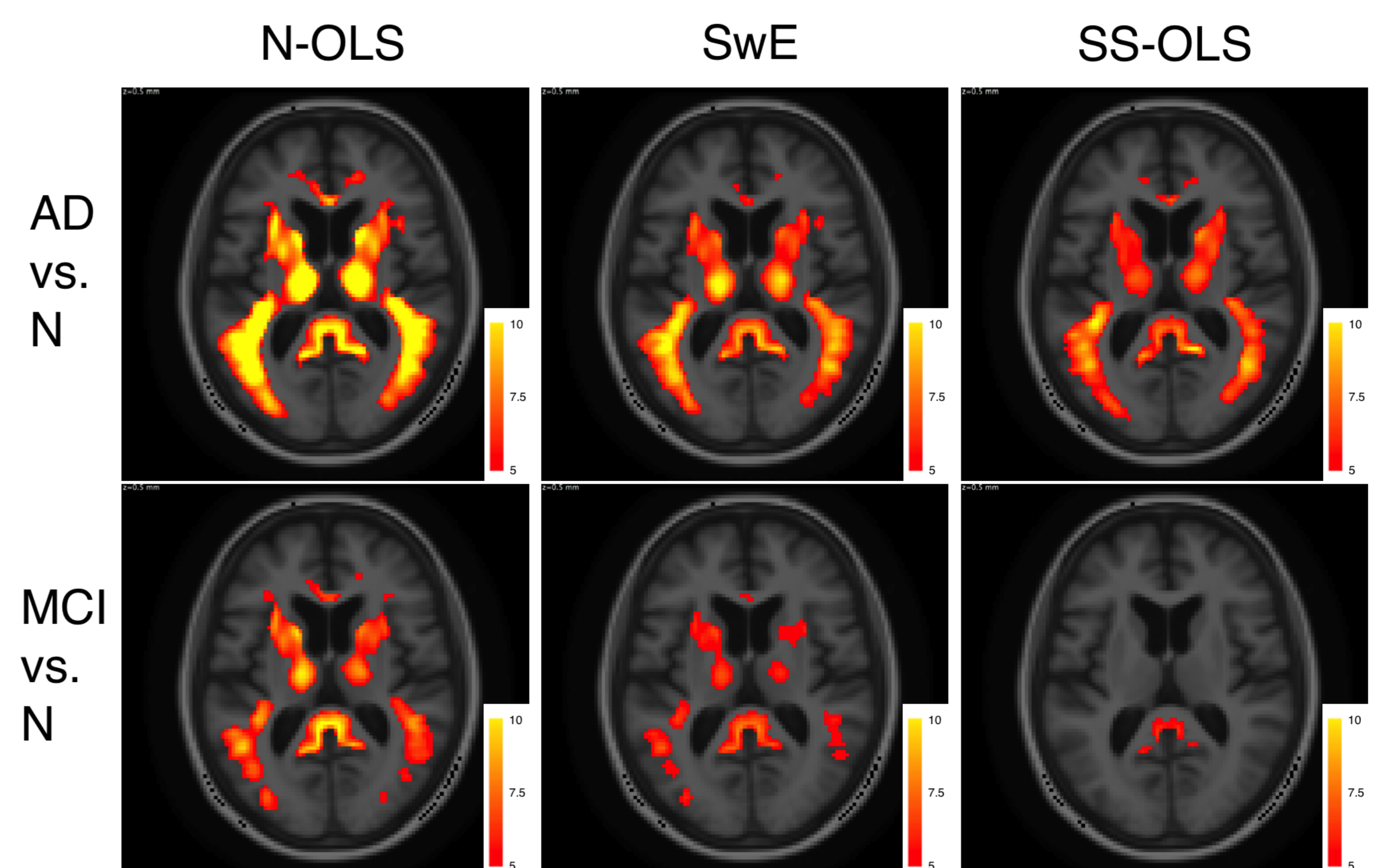


Figure 2: t-scores images ( $T > 5$ ) for the difference in visit effect between groups on the brain atrophy for the N-OLS, SwE and SS-OLS methods. While N-OLS shows more significant voxels, this may be attributed to inflated FPR; SS-OLS suffers worse power than SwE (see Figure 1).

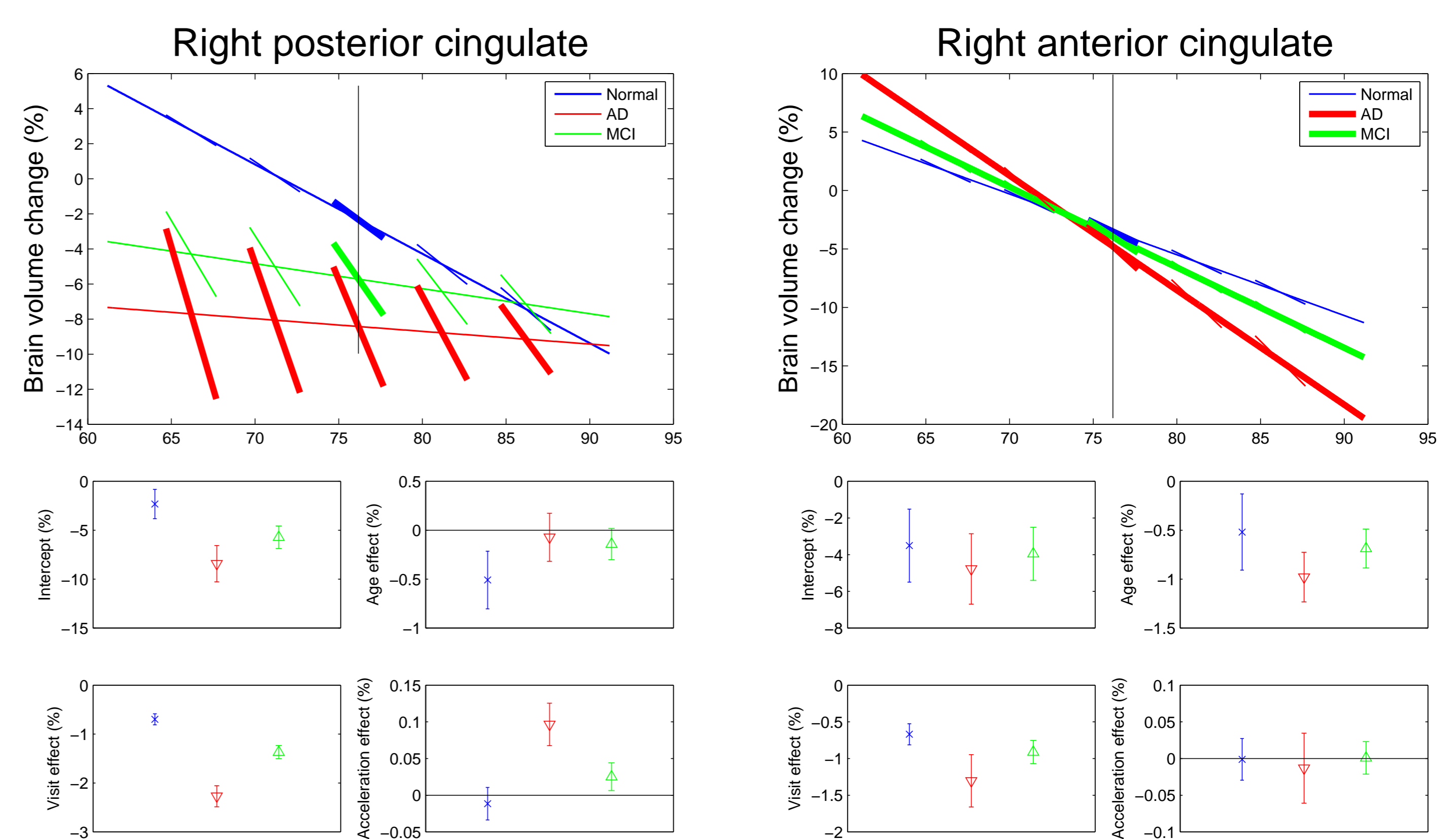


Figure 3: Plots of the fitted models with the SwE method for 2 selected voxels. Long lines show the inter-subject effect of average age and short lines show the intra-subject effect of visit. An acceleration effect is indicated by non-parallel short lines.

## Discussion

We have shown that the standard methods can lead to very inaccurate inferences when, mainly, Compound Symmetry does not hold. In contrast, the SwE method has been shown to be very accurate in a large range of settings. By eliminating subject-indicator covariates, the SwE method is easy to specify, allows the use of within/between-subject covariates and is fast since it does not require any iterative computation. A SwE toolbox is under development for release later in 2013.