The SwE Toolbox: a Toolbox for the Analysis of Longitudinal and Repeated Measures Neuroimaging Data

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Introduction

Neuroimaging software packages like SPM and FSL currently model longitudinal and repeated measures neuroimaging data using restrictive assumptions. In particular, SPM assumes a common covariance structure for all the voxels in the brain and FSL assumes Compound Symmetry (CS), the state of all equal variances and all equal covariances. While more accurate methods have been recently proposed to analyse such data [1,2,4,5,7,8], there remain few easy-to-use implementations of these methods. Here, we present an SPM toolbox allowing the use of the Sandwich Estimator (SwE) method, a fast, non-iterative tool for longitudinal and repeated measures data [5], and illustrate its use on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

Methods

The SwE toolbox estimates parameters of interest using an Ordinary Least Squares (OLS) model and their variances/covariances using the so-called Sandwich Estimator [5]. The toolbox consists of a set of Matlab scripts designed to work in conjunction with the most recent versions of SPM (i.e. SPM8 or SPM12). The toolbox offers a user interface (Figure 1) allowing an easy specification of the design and data, and a display of results similar to standard SPM analyses. The use of the toolbox can be divided into 3 stages: the model setup, the model estimation and the display of results. The setup stage calls the Matlab batch system (Figure 1, top left) with a dedicated module for the SwE toolbox, which can be used to easily specify the data and design of the analysis. The second stage estimates the model. Finally, the third stage allows the specification of contrasts of interest to make inference and display results (Figure 1, middle and right) in a similar way as standard SPM analyses. Regarding the inferences, the current release version of the toolbox only allows for the use of parametric uncorrected and voxel-wise False Discovery Rate (FDR) inferences based on results in [5]; methods for non-parametric uncorrected, FDR, and Family-Wise Error (FWE) inferences based on a Wild Bootstrap [9] resampling method are forthcoming.

Here, we demonstrate the toolbox on a highly unbalanced longitudinal dataset (i.e. with many missing visits) consisting of Tensor Base Morphometry images obtained from the ADNI project, where 229 healthy elderly Normal control, 400 Mild Cognitive Impairment (MCI) and 188 Alzheimer's Disease (AD) subjects were scanned up to 6 times over a period of 3 years [6]. As comparison, we also analyse the same dataset using 2 alternative methods: the Naive-OLS (N-OLS) method which includes subject dummy variables in an OLS model and assumes, by construction, Compound Symmetry (CS), and the Summary Statistic OLS (SS-OLS) method which first fits a regression model for each subject to obtain subject-specific estimates of the parameters of interest, and then computes a simple model on these summary measures. In addition, we conducted a Box's test of CS [3] on the largest subset of the ADNI dataset without missing data to check the validity of the CS assumption.

Results

Figure 2 shows the Box's test F-score image (centred at the anterior commissure) thresholded at 5% after using a Bonferroni correction. 56% of the in-mask voxels survived the thresholding, indicating a strong evidence of non-Compound Symmetry in the brain and challenging the validity of the N-OLS method.

Figure 3 and 4 show a comparison of thresholded t-score images (centred at the anterior commissure) obtained with the N-OLS, SS-OLS and SwE methods on the difference in (longitudinal) atrophy effects between the AD vs. the Normal subjects. In figure 3, an uncorrected threshold ($p < 0.001$) was used while, in Figure 4, a FWE-corrected threshold ($p < 0.05$) was obtained using Random Field Theory for the N-OLS and SS-OLS method, and the new non-parametric Wild Bootstrap (with 999 bootstrap samples) approach for the SwE method. The three methods seem to be qualitatively similar, but with greater significance for the N-OLS method and less for the SS-OLS method. As the assumption of CS is not tenable (see Figure 2), the results obtained with the N-OLS approach are however difficult to trust and likely represent inflated significance (see [5]).

Discussion

We have described and demonstrated the SwE toolbox for longitudinal and repeated measures data, allowing more flexible and appropriate models than currently available in SPM and FSL. The toolbox has been made freely available at `http://warwick.ac.uk/tenichols/SwE`. We have also presented a new feature (available soon) of the toolbox implementing the Wild Bootstrap method for non-parametric uncorrected, FDR and FWE inferences.

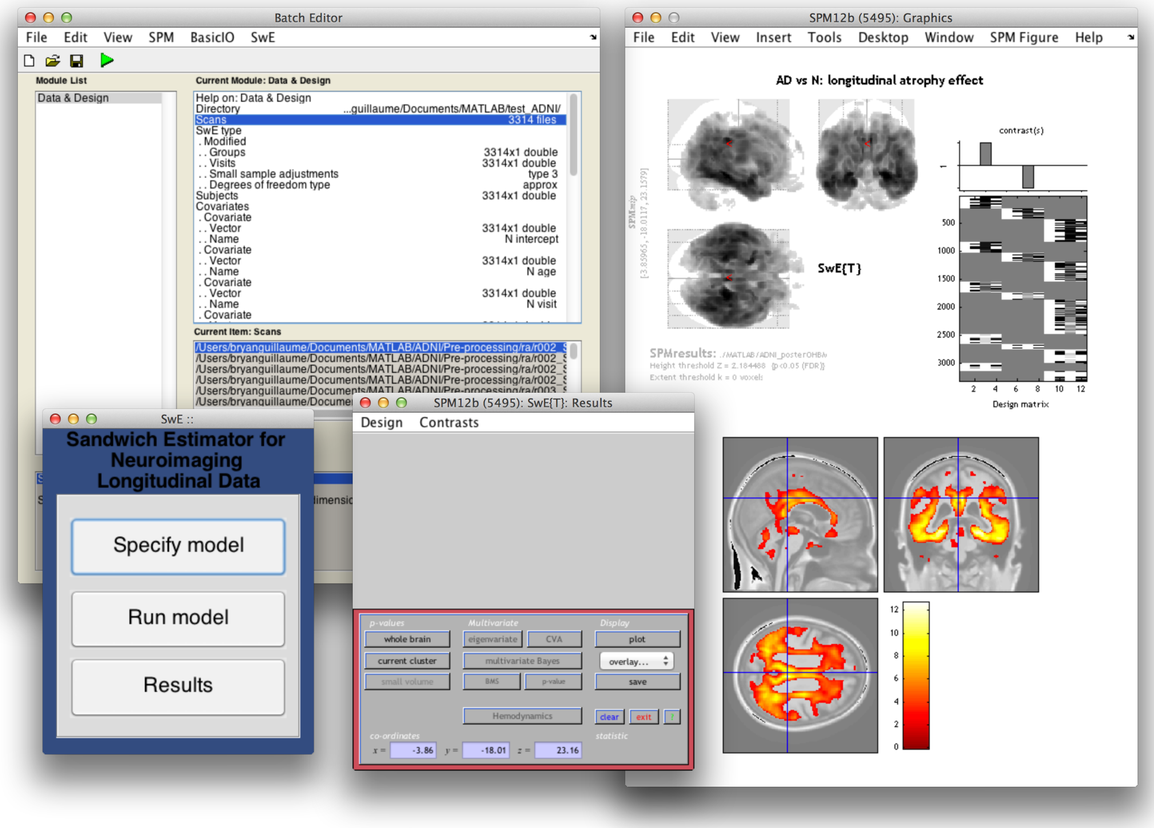

Figure 1: User interface of the SwE toolbox. Bottom left: the main interface window, top left: the batch system used to specify the model, middle and right: interface windows for the analysis of results.

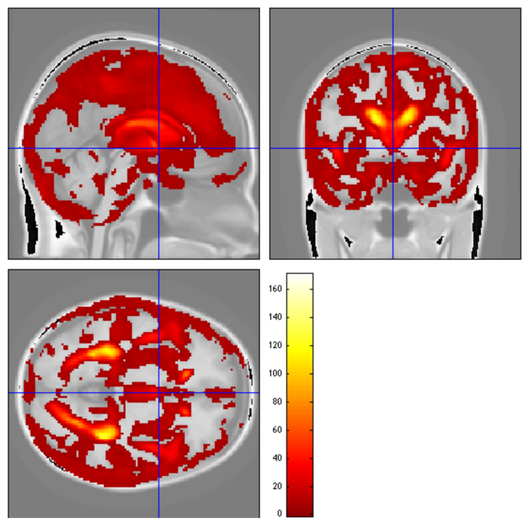

Figure 2: Box's test of Compound Symmetry F-score image on the ADNI data thresholded at 5% after using a Bonferroni correction. 56% of the in-mask voxels survived the thresholding, indicating extensive regions incompatible with the CS assumption.

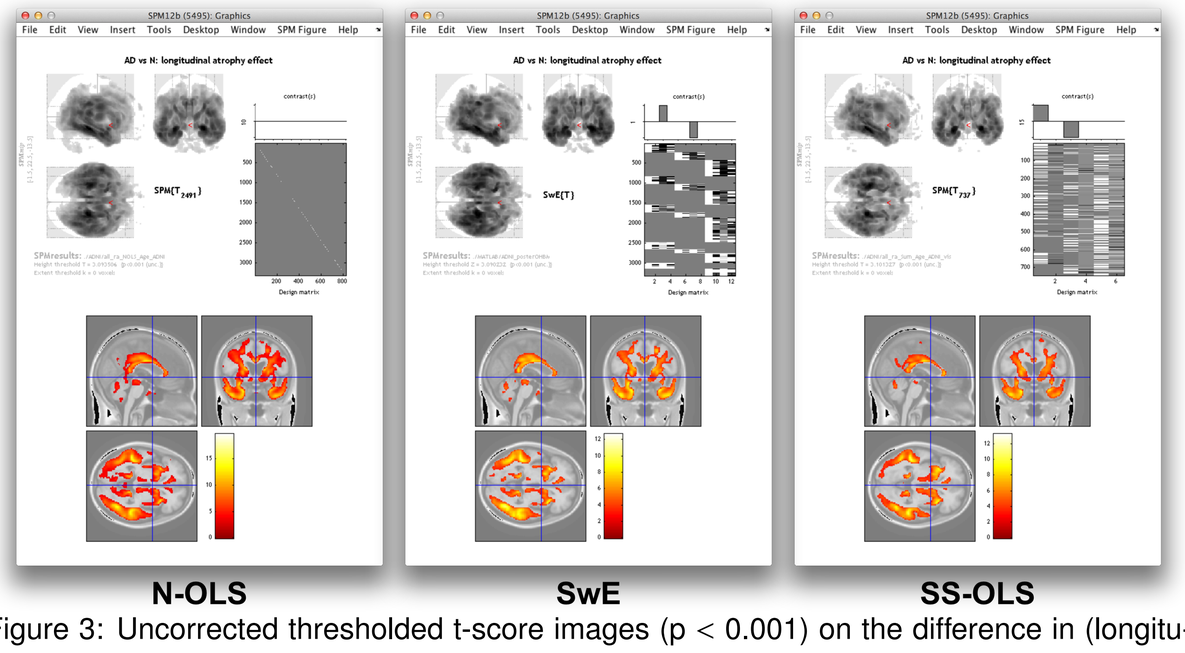

Figure 3: Uncorrected thresholded t-score images ($p < 0.001$) on the difference in (longitudinal) atrophy effect (AD vs. N) obtained with the uncorrected parametric N-OLS, SwE and SS-OLS methods.

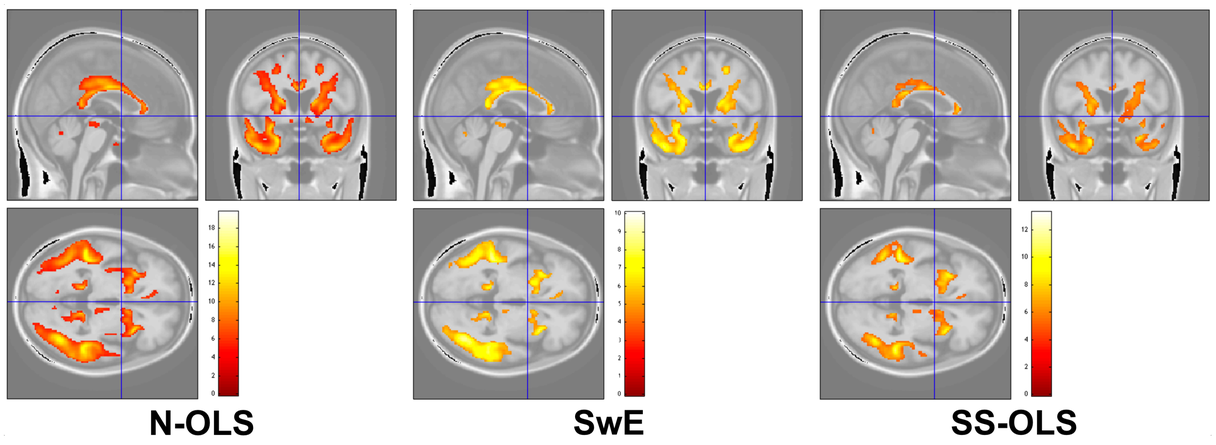

Figure 4: FWE-corrected thresholded t-score images ($p < 0.05$) on the difference in (longitudinal) atrophy effect (AD vs. N) obtained with the parametric N-OLS and SS-OLS methods (using both Random Field Theory), and the non-parametric SwE method (using Wild bootstrap with 999 bootstrap samples).

References

[1] Bernal-Rusiel et al. (2013a). Neuroimage, 66, 249-260. [2] Bernal-Rusiel et al. (2013b). NeuroImage, 81, 358-370. [3] Box (1950). Biometrics, 6 (4), 362-389. [4] Chen et al. (2013). NeuroImage, 73, 176-190. [5] Guillaume et al. (2014). NeuroImage, 94, 287-302. [6] Hua et al. (2013). NeuroImage, 66, 648-661. [7] Li et al. (2013). NeuroImage, 72, 91-105. [8] Skup et al. (2012). Biometrics, 68 (4), 1083-1092. [9] Wu (1986). Annals of Statistics 14, 1261-1295.