Is use of a site-specific EPI template still beneficial for group fMRI studies?

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Introduction: We have become aware of a trend for reviewers of fMRI data to express concern if co-ordinates and associated standard atlas labels are not provided in group results. This unfortunately can be determined only if data is spatially normalised to a standard template. We and others often prefer using an analysis stream that involves spatial normalisation to a site-specific template. The site-specific template can itself be spatially normalised to the standard template so that it is close to, but by definition not the same as, the standard template. The benefit of a site-specific template is better inter-subject registration (particularly in higher field-strength systems where image distortion and signal non-uniformity can be substantial). The superior registration ultimately yields greater study power compared to spatial normalisation to a standard template. The downside of a custom template is that co-ordinates, whilst close to MNI space, will systematically differ compared to co-ordinates obtained using a standard template. Obtaining an accurate mapping of co-ordinates from one space to the other is far from trivial. A desire for co-ordinates to be quoted in strict MNI space or Talairach space leaves one in a dilemma. Does one maximise study power, or co-ordinate accuracy? We wondered whether improvements in the latest popular SPM software package might make the argument moot. We therefore directly compared the results of the same data analysed in two different streams using SPM8, one using spatial normalisation to a site-specific template and the other to the standard SPM8 EPI template.

Methods: We analysed data from 26 subjects (mean age of 31.7 years (SD = 12.4), 15 female). Functional MRI was performed using a 3T GE Signa LX whole body scanner. Each subject performed a standard language fMRI study. This behavioural paradigm involved four 30-second blocks of task alternating with blocks of rest (visually presented cross hair). During task blocks subjects performed covert orthographically-cued lexical retrieval (OLR) – a verbal fluency task where the subject was required to generate words beginning with each of a series of displayed letters. The fMRI acquisitions were pre-processed using Statistical Parametric Mapping software (SPM8 release 3408; Wellcome Department of Imaging Neuroscience, London, UK). Images were first slice-time corrected, then realigned to a single target image within each time series. Two different normalisation schemes were tested in separate analyses. In the **standard-template analysis stream**, slice-time-corrected, realigned images in a session were spatially normalised to a common space by co-registering to the standard EPI template supplied with SPM8. We incorporated an advanced explicit intensity non-uniformity (bias) correction step as without it we found some subject's images were not adequately normalised to the standard template (this is despite the standard normalisation procedure including a form of bias correction). Specifically, the mean of the slice-time-corrected, realigned images was approximately registered (affine normalisation) to the standard EPI template, then bias corrected using the Segment module of SPM8. The resultant bias-corrected mean image for the subject was then non-linearly spatially normalised to the standard EPI template. The spatial transformation matrices were combined in the deformations toolbox of SPM8 and applied to the original slice-time-corrected, realigned images. In the **site-specific-template analysis stream**, a similar strategy was employed so that the only difference between the two analyses was the template used (even though the bias correction step did not appear to be as important to obtaining a reasonable spatial normalisation to the site-specific template). **Finally, images in both analysis streams** were smoothed with an isotropic Gaussian kernel of full-width-at-half-maximum (FWHM) = 8.0 mm and statistically analysed using the general linear model. In addition to the effects of interest (task and rest), effects of no interest consisting of the six rigid-body transformation parameters estimated during image realignment pre-processing were included in the model. Prior to estimation, the fMRI data and design matrix were high-pass filtered (cut-off = 128 s), and pre-whitened to correct for autocorrelation in the data, modelled as a first-order autoregressive process. The BOLD response of the task compared to rest state was modelled assuming the SPM canonical hemodynamic response function (HRF). A second-level (random effects) group analysis was undertaken and assessed using a Students t-test, thresholded at $P<0.05$ corrected for multiple comparisons. The statistical significance of activations was then examined to see whether one analysis stream outperformed the other.

Results: Results of the spatial normalisations are summarised in the figures. As noted above, without an additional bias correction step the standard-template analysis stream failed to adequately spatially normalise many subjects (fig. 1). A bias correction step was not required to obtain adequate registration to the custom template (fig. 2), although to keep the analysis streams identical except for the template we did use the bias correction step anyway for both streams. The results of the statistical analyses predominantly favoured the site-specific template, as can be seen from table 1.

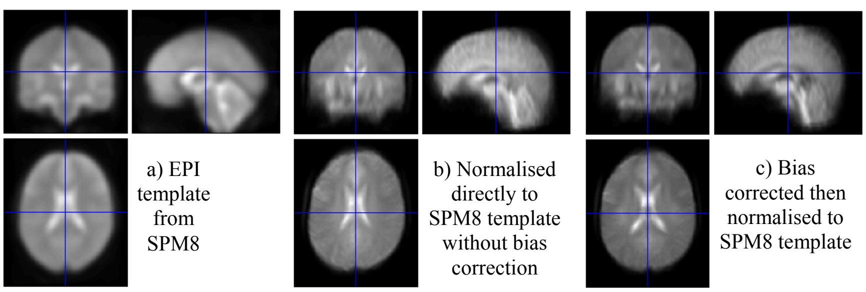

Figure 1: a) Standard EPI template. b) Directly normalised images averaged across the group; the normalisation failed to adequately normalise to the SPM8 template in many cases, as evident by the shear distortion in the axial view of the group average. c) images bias-corrected via the SPM8 segment toolbox then normalised and averaged across the group. The more sophisticated bias correction step in the segment toolbox has substantially improved the fidelity of the spatial normalisation.

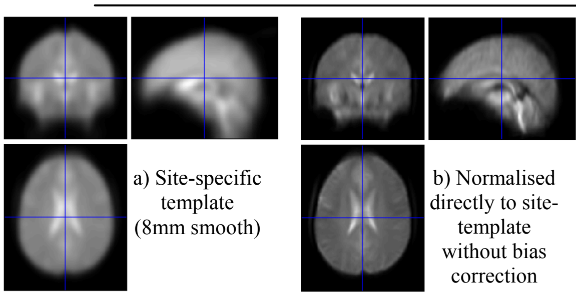

Figure 2: a) Site-specific EPI template created from 30 independent controls. b) Average of the 26 normalised images from the present study.

Table 1: Maximum Z-scores and k = region sizes for the top 5 activation blobs from each analysis. Z-scores were most often higher and there were considerably more activated voxels detected in the site-specific analysis.

MNI coordinate	Z (SPM8 template)	k (voxels) (SPM8 template)	Z (site-specific)	k (voxels) (site- specific)
-6, 6, 64	6.20	478	6.69	818
-34, 16, -2	6.06	370	6.05	1656
-50, 0, 34	6.06	989	6.27	in region above
-18, -2, 12	5.70	189	5.56	188
38, 20, -6	5.48	88	5.43	89

Conclusion: Use of a site-specific template can still be superior to direct spatial normalisation to a standard template if the ultimate aim is to maximise study power to detect an effect.