Analysis of multi-site structural neuroimaging data using VBM: a case study in childhood absence epilepsy

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Introduction

The voxel-based morphometry (VBM) approach to analysis of structural MRI data is widely utilised for the detection of subtle changes in regional tissue distribution. Incorporating MR data collected from different MR scanners would confer a number of benefits to clinical researchers, not least of which is the potential to substantially increase study power due to higher numbers of subjects. A potential confounding factor in the use of MRI data from multiple sites is the existence of subtle systematic differences between images acquired on different scanners. Such differences can include, for example, spatial sensitivity, intensity uniformity and degree of anatomical distortion. The analysis methodology therefore needs to account for inter-scanner differences in order to identify real differences between subject groups. In this study we investigate structural neurological differences between subjects with childhood absence epilepsy (CAE) and controls using structural MRI data from two sites. The study demonstrates that differences in the images obtained from the two sites are spatially heterogenous and therefore may manifest as highly significant regional differences in the statistical parametric map (SPM) output of the VBM analysis. By grouping controls and subjects from the two sites, and including the site as a covariate in the analysis, we demonstrate that the site-specific differences may be removed from the VBM analysis and a more accurate image of structural difference between the two patient populations can be obtained.

Methodology

13 subjects with CAE (N = 13, 12 female) were imaged at Site A. Details of the recruitment can be found in [1]. 213 controls (115 female) were imaged at the same site. The CAE subjects and controls were imaged on a 3T GE LX Horizon scanner using an inversion-recovery 3D Gradient Echo MR imaging sequence (voxel size 0.48 x 0.48 x 2 mm). 15 subjects with CAE (6 female) were imaged at Site B. 33 controls (16 female) were imaged at the same site. The CAE subjects and controls were imaged using a 3D Gradient Echo MR imaging sequence on a 1.5 T Siemens Sonata MR scanner (voxel size 0.86 x 0.86 x 1.5 mm). VBM analyses were carried out using the SPM2 software package and the "optimised VBM" protocol. In all analyses the age, gender and total intracranial volume are included as covariates of no interest.

Results

Figure 1 shows regions of putative decreased gray matter volume in control subjects scanned at site B compared with controls scanned at site A. The SPM output is thresholded at $p < 0.05$ using family-wise error (FWE) correction for multiple comparisons. Extensive changes are observed in the retrosplenial area, thalamus, brainstem and other areas. Figures 2 and 3 show regions of decreased gray matter volume in CAE subjects compared to controls from sites A and B respectively. Figure 3 D shows the same analysis as Figure 3 A – C but displayed with a lower threshold. The primary region of gray matter decrease in both figures is the thalamic nuclei. The results are displayed without correcting for multiple comparisons. Figure 4 shows regions of decreased gray matter volume in CAE subjects compared to controls grouping data from both sites. In addition to age, gender and intracranial volume the site is included as a covariate of no interest. Figure 4 demonstrates significant bilateral gray matter volume decrease in the thalamus, thresholded at $p < 0.05$ with family-wise error correction for multiple comparisons. All images are displayed in neurological orientation.

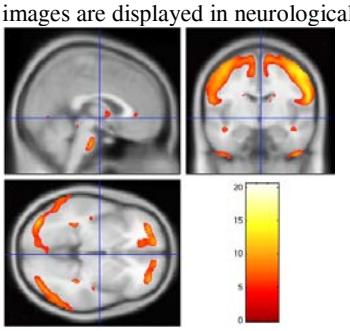

Figure 1. VBM comparison of controls scanned at site A with controls scanned at site B ($p < 0.05$, FWE).

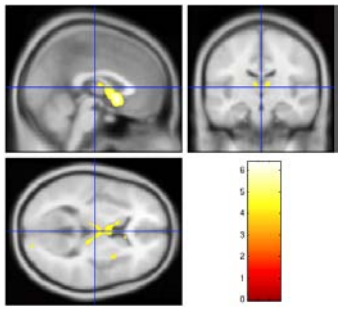

Figure 2. VBM comparison of controls and CAE subjects scanned at site A ($p < 0.001$, uncorrected)

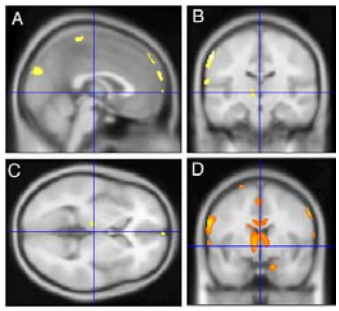

Figure 3. VBM comparison of controls and CAE subjects, both scanned at site B (A, B, C: $p < 0.001$, D: $p < 0.05$, uncorrected).

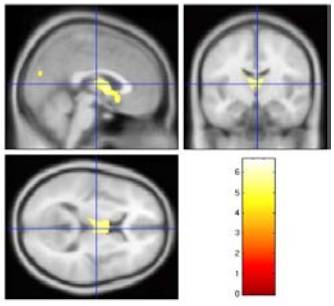

Figure 4. VBM comparison of controls with CAE subjects from both sites ($p < 0.05$, FWE).

Conclusions

The study results suggest that significant regional differences may be observed in the output of a VBM analysis that reflect site-specific differences in the MRI scans rather than pathology-specific differences. The comparison of control data from one site with control data from another site reveals significant regional variation (Figure 1). It is possible that the differences may be explained by systematic differences in neurological structure due to the different racial and socio-economic backgrounds of the subjects imaged at both sites, although in any case the methodology outlined in this study will account for these differences. Previous research [2] suggests that differences in RF coil characteristics, acquisition parameters and other instrument-dependent effects are also significant sources of variation in the SPM images. It is also highly likely that the different field strengths of the two scanners contribute to the observed regional differences. Although the comparison of the CAE subject group with the controls from the same site gives an indication of the regions affected, these regions do not survive correction for multiple comparisons at a reasonable significance level ($p < 0.05$), whether the correction method is family-wise error correction or false discovery rate. If the two groups are pooled and the site included as a covariate of no interest, the specific regional change suggested by the individual site analysis is statistically significant using a significance level of $p < 0.05$ with family-wise error correction, a conservative correction method for multiple comparisons. Also the presumed artifactual regions that appears highly significant when comparing control images from different sites are no longer seen in the SPM output. The results of this study suggest that voxel-based analysis of structural MRI data from multiple sites is feasible, but it is crucial to incorporate control data from each of the sites to avoid incorrectly identifying regions as morphometric differences between groups of subjects.

References

[1] Chan, C.H., Briellmann, R.S. *et al* Thalamic Atrophy in Childhood Absence Epilepsy, 2006 *Epilepsia* 47(2), 399-405

[2] Pell, G.S., Pardoe, H.R. *et al* Investigation of sources of variance in the analysis of structural data with voxel based morphometry, ISMRM 2006 abstract # 5629