

Introduction

Multi-scanner/multi-site fMRI trials are performed to increase the sample size in order to probe a subtle effect and/or to increase the pool of rare or unusual subjects. The interest in multi-site fMRI has increased in recent years (e.g., [1-4]); however, researchers are still investigating the best way to perform multi-site studies. The purpose of the functional Biomedical Informatics Research Network (fBIRN, www.nbirn.net) is to create a test bed for evaluating multi-site fMRI studies. Using test bed data, we investigated methods to reduce the effect of site on the fMRI hemodynamic response amplitude. Amplitude bias is important because it represents systematic differences between sites that may contaminate the results of a multi-site study. In this study, we assess the amount of bias between four 3T fBIRN sites (two GE and two Siemens).

Processing Method Manipulations:

1. B0 Distortion Correction – With and Without
2. EPI – Structural Registration Method
 - a) Correlation Ratio (CR, [5]) – sensitive to spatial intensity fluctuations
 - b) Boundary-based Registration (BBR, [6]) – insensitive.
3. EPI – Structural Registration Degrees of Freedom (DOF)
 - a) DOF = 6 (translation and rotation)
 - b) DOF = 9 (additional scaling)

Note: registration to MNI152 done with 12 DOF
4. Intensity Normalization
 - a) Global (rescale entire volume to achieve same mean intensity)
 - b) Voxel-wise (rescale each voxel by its mean)

Method 1: No B0 + CR + DOF=6 + Global Intensity Normalization

Method 2: B0 + BBR + DOF=9 + Voxel-wise Intensity Normalization

Evaluation:

1. Volume of task activation ($p < .01$)
2. Volume of site effect (Repeated Measures ANOVA, $p < .01$)
3. Volume of visit effect (Paired-t, $p < .01$)
4. Scale Registration Parameters

MRI Methods

Scanners: four, all 3T, two GE and two Siemens (see below)

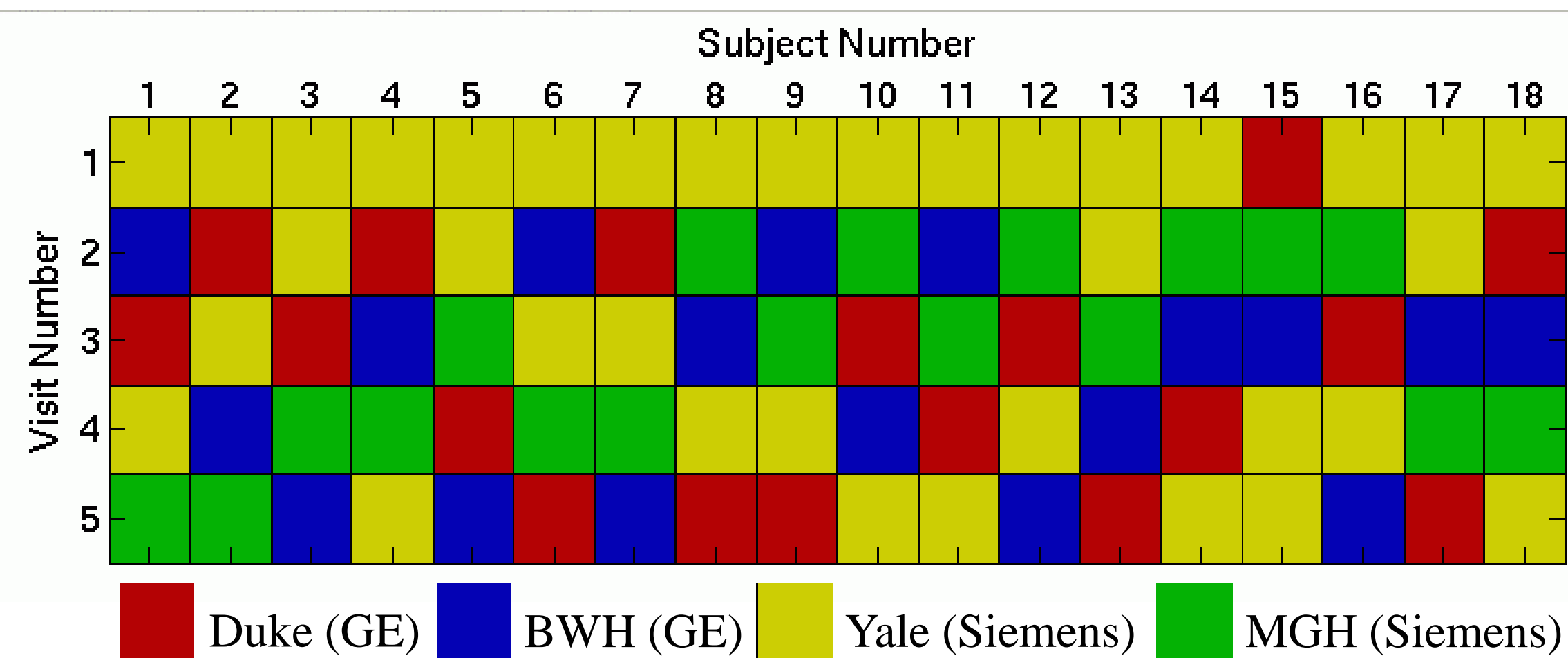
fMRI Protocol: acquisition parameters were matched as closely as possible across sites, though there are some unavoidable differences due to manufacturer (eg, ramp sampling and ghost correction).

fMRI Task: Subjects performed a working memory task.

fMRI Analysis: MC, Smooth 5mm, GLM Fit (performed in FSL [7]).

Group Analysis: performed in MNI152 space. All analyses used a single resampling step and weighted least squares (WLS).

Subjects: 18 healthy, all traveled to each site



References: [1] Friedman L; Glover GH. 2006. JMRI 23:827-839. [2] Friedman, L, Glover, G, Krenz, D., and Magnotta, V. NeuroImage 32, 1656-1668. [3] Friedman L; Glover GH NeuroImage 33 471-481. [4] Suckling, et al, 2008, HBM 10, 1111-22. [5] Roche, et al, 1998. [6] Greve & Fischl, Neuroimage, 2009. [7] Woolrich, M., et al, 2001. Neuroimage 14, 1370-1386.

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Intersite Variability: Causes and Consequences

There are many ways in which a scanner may impart a unique signature to the data it produces. Here, we are addressing three of these effects: (1) B0 Distortion, (2) Spatial Intensity Variation, and (3) Scanner Metric Calibration. Differential B0 distortion (Figure 1) can cause the registration to the common space (eg, MNI152) to have site-specific aspects both in and away from the B0 distortion regions. The registration can also be systematically different if an area of the brain is systematically brighter in one site than in another (Figure 2). This spatial intensity variation can also systematically effect the amplitude of the hemodynamic response. Finally, the definition of “1mm” in one scanner might be different than “1mm” at another due to differences in the way the scanners were calibrated or due to differences in EPI ramp sampling. These systematic effects may be misinterpreted as population differences in a multi-site study.

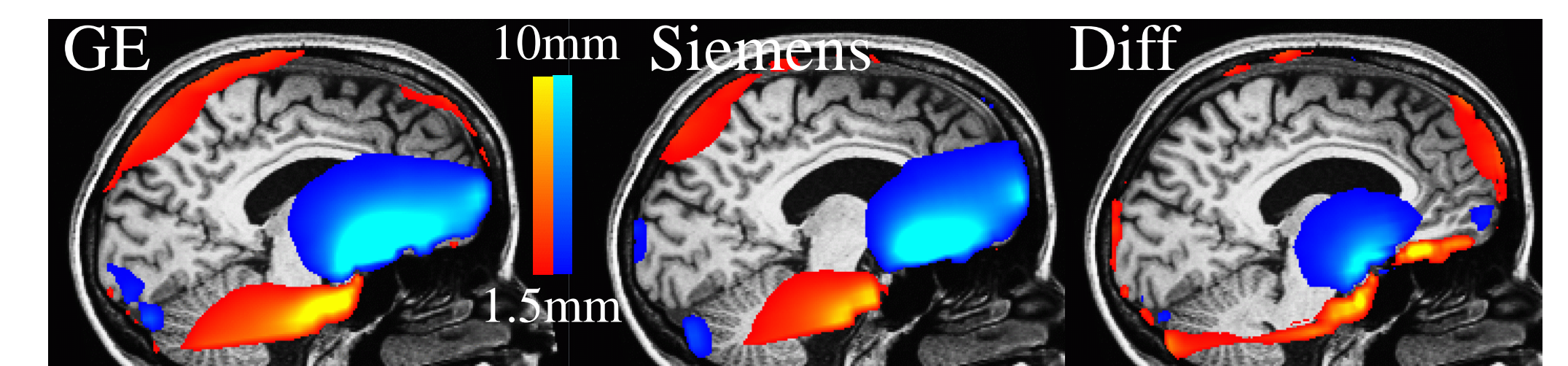


Figure 1. Differences in B0 distortion at two sites. While they show similar patterns, there are substantial differences (over 10 mm).

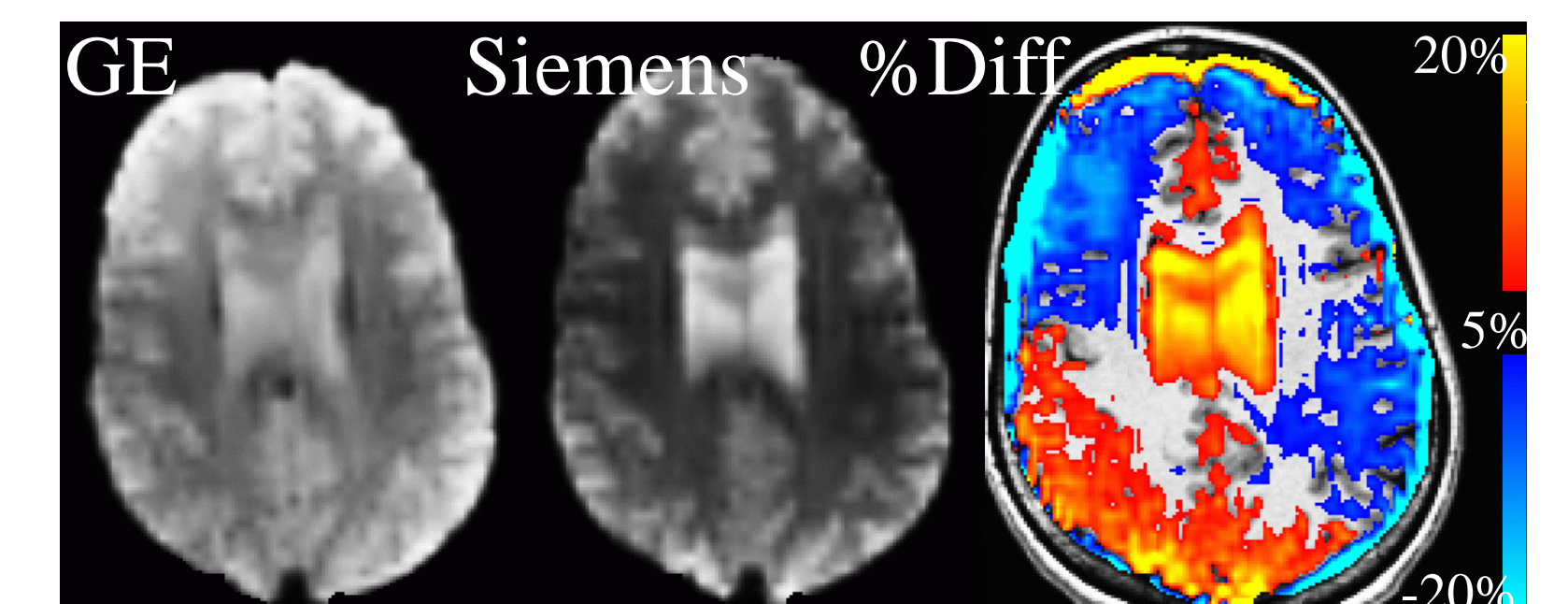
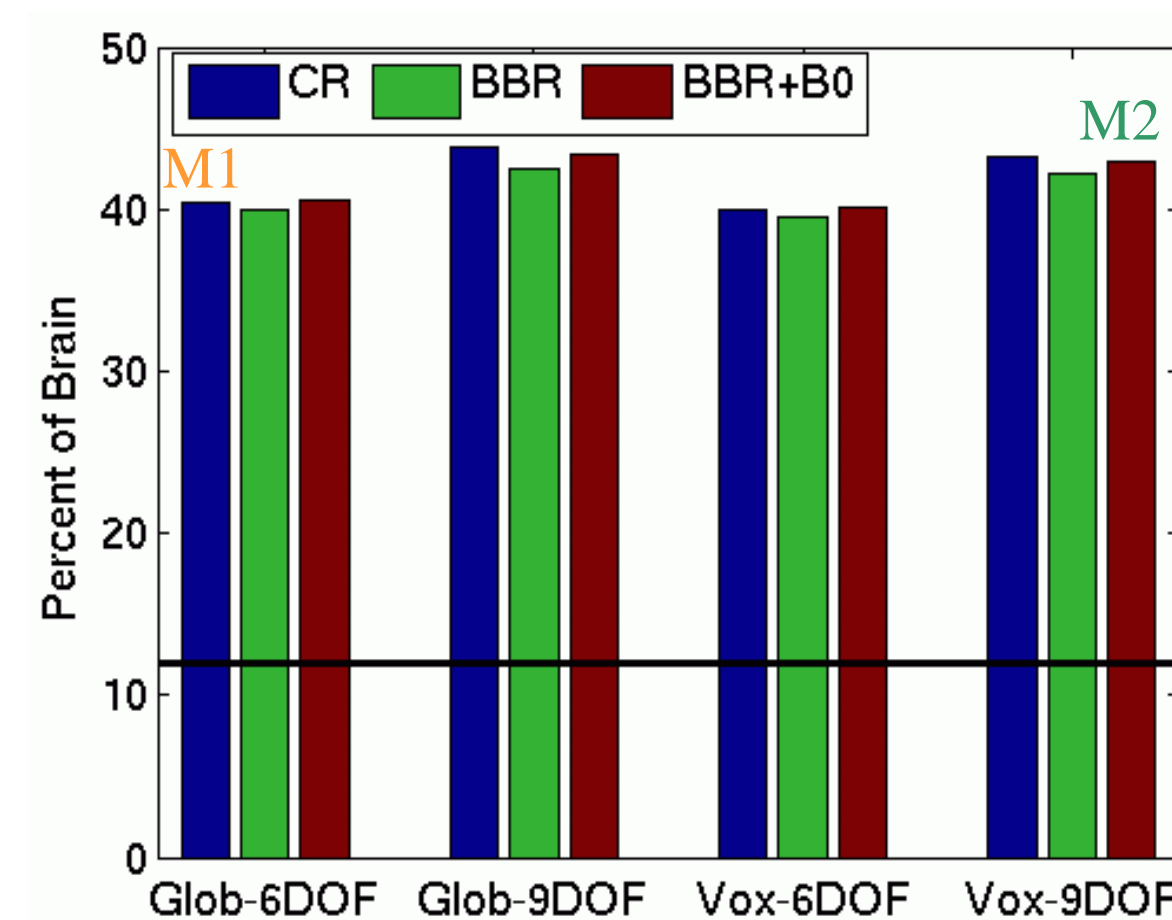
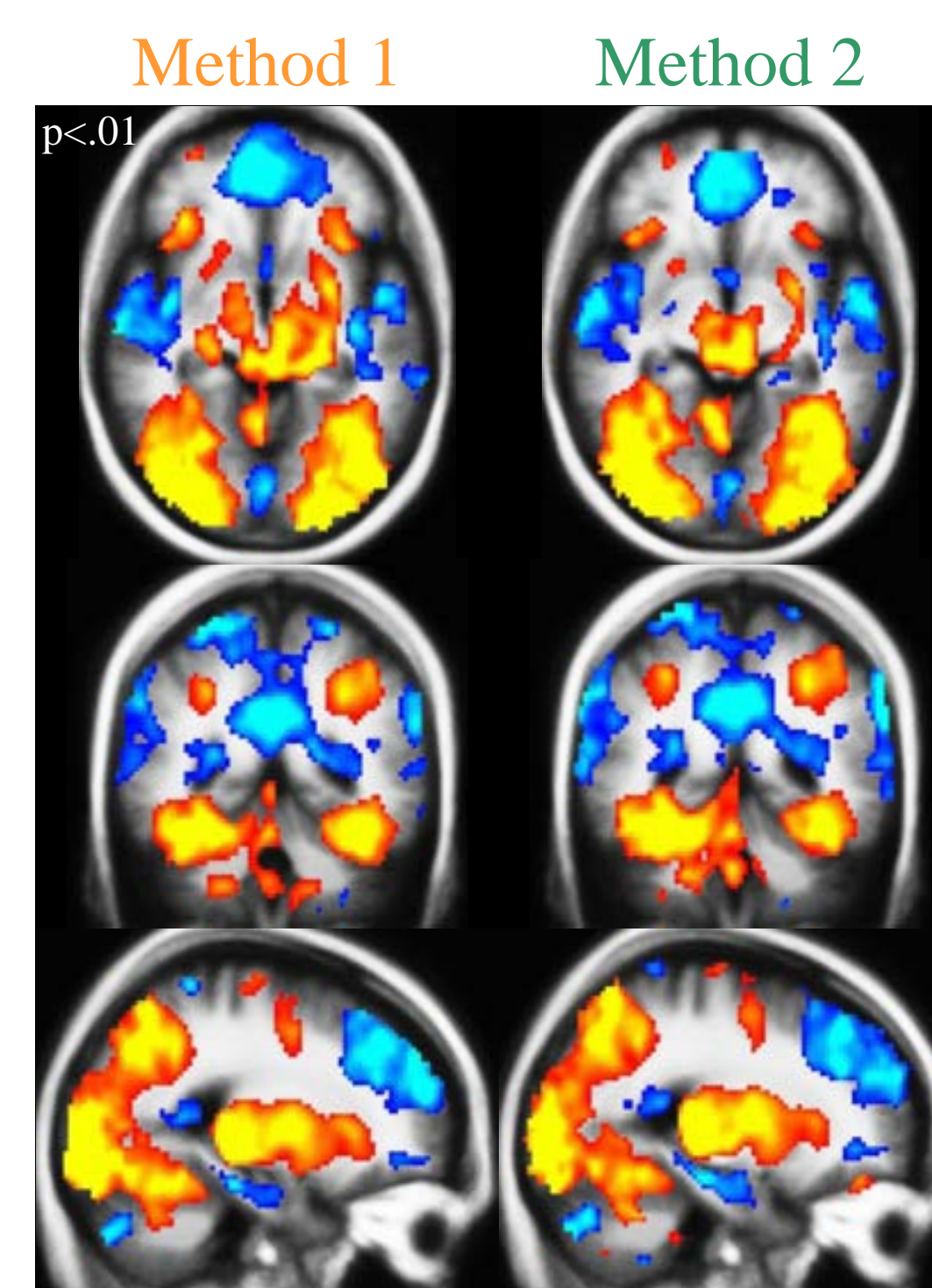


Figure 2. Differences in EPI spatial intensity fluctuations at two sites. Volumes are globally intensity normalized

Results

Effect of Task

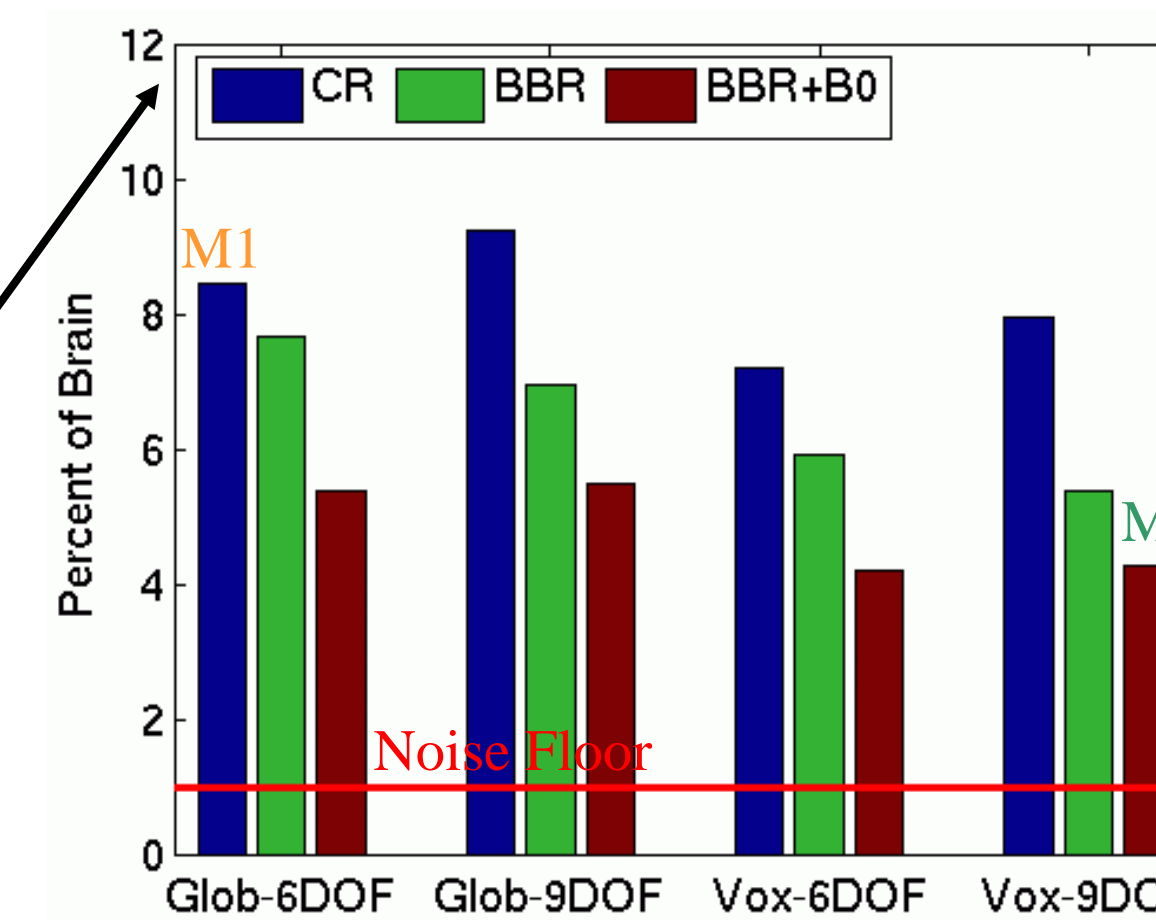
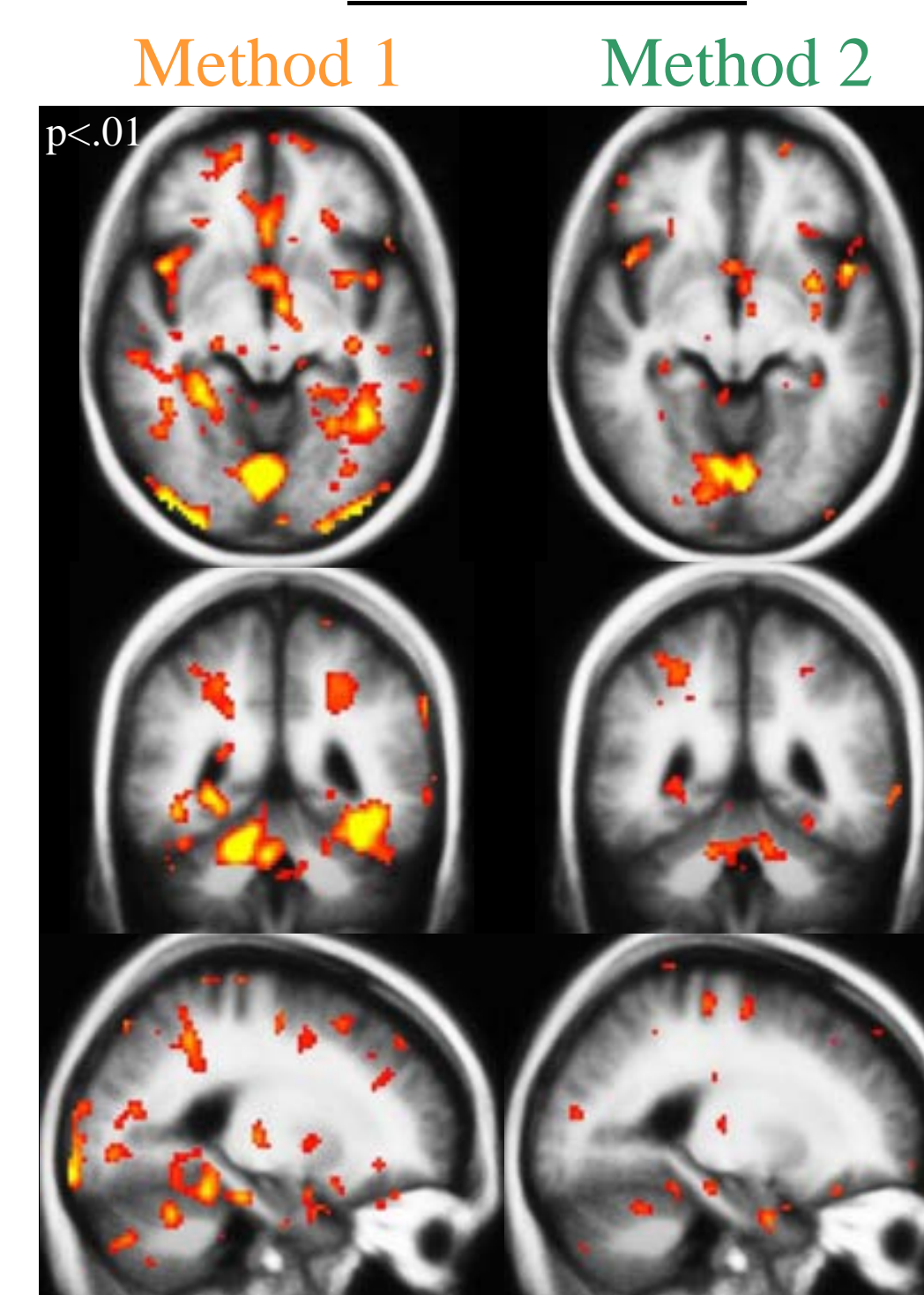


1. Very large main effect of task – about 40% of brain voxels show task activation. Important because Site Effects may only show up where there is a task effect.
2. Not a strong effect of method, which means that the method manipulations are not making it more difficult to detect activation.

Table I: Registration Scale Factors (Site Effect for all $p < 10^{-16}$)

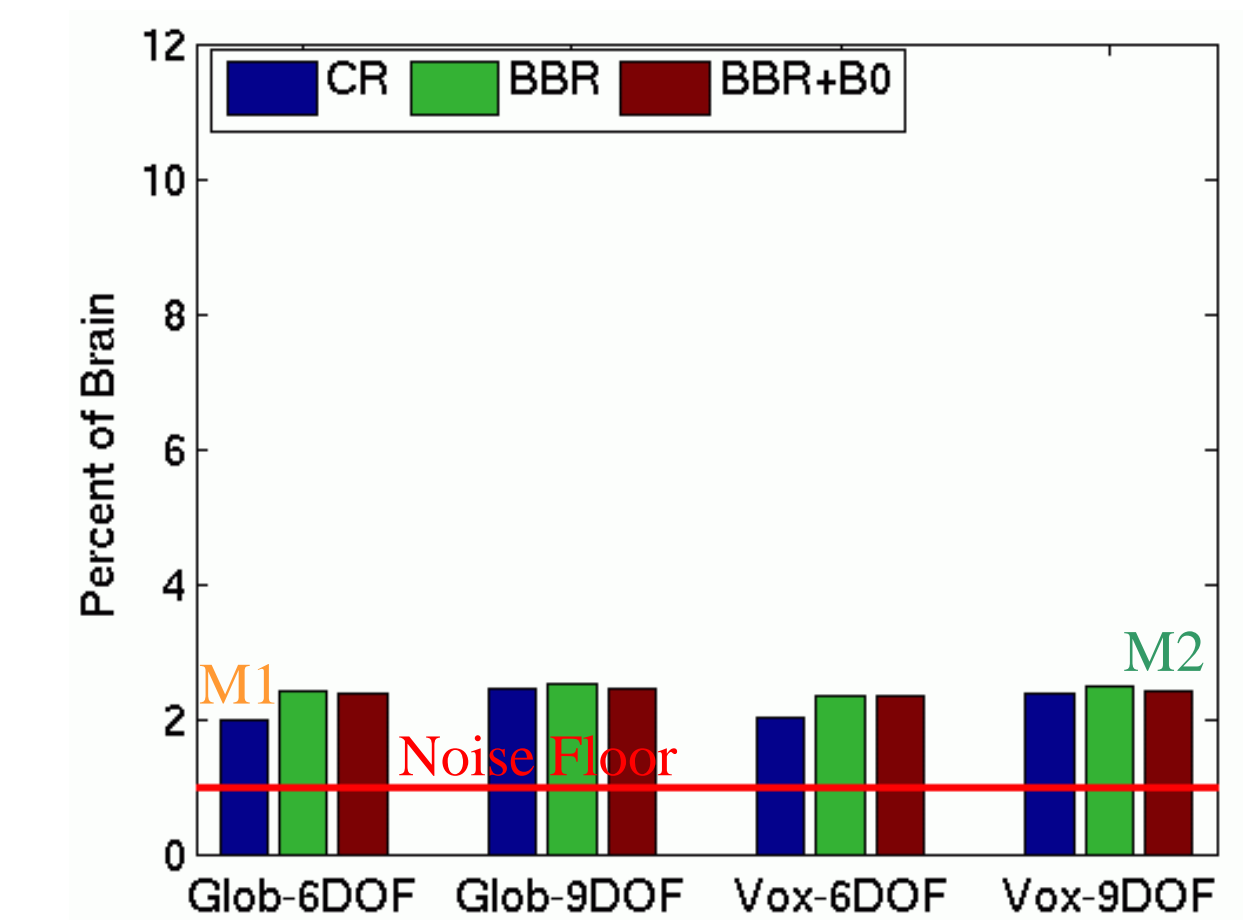
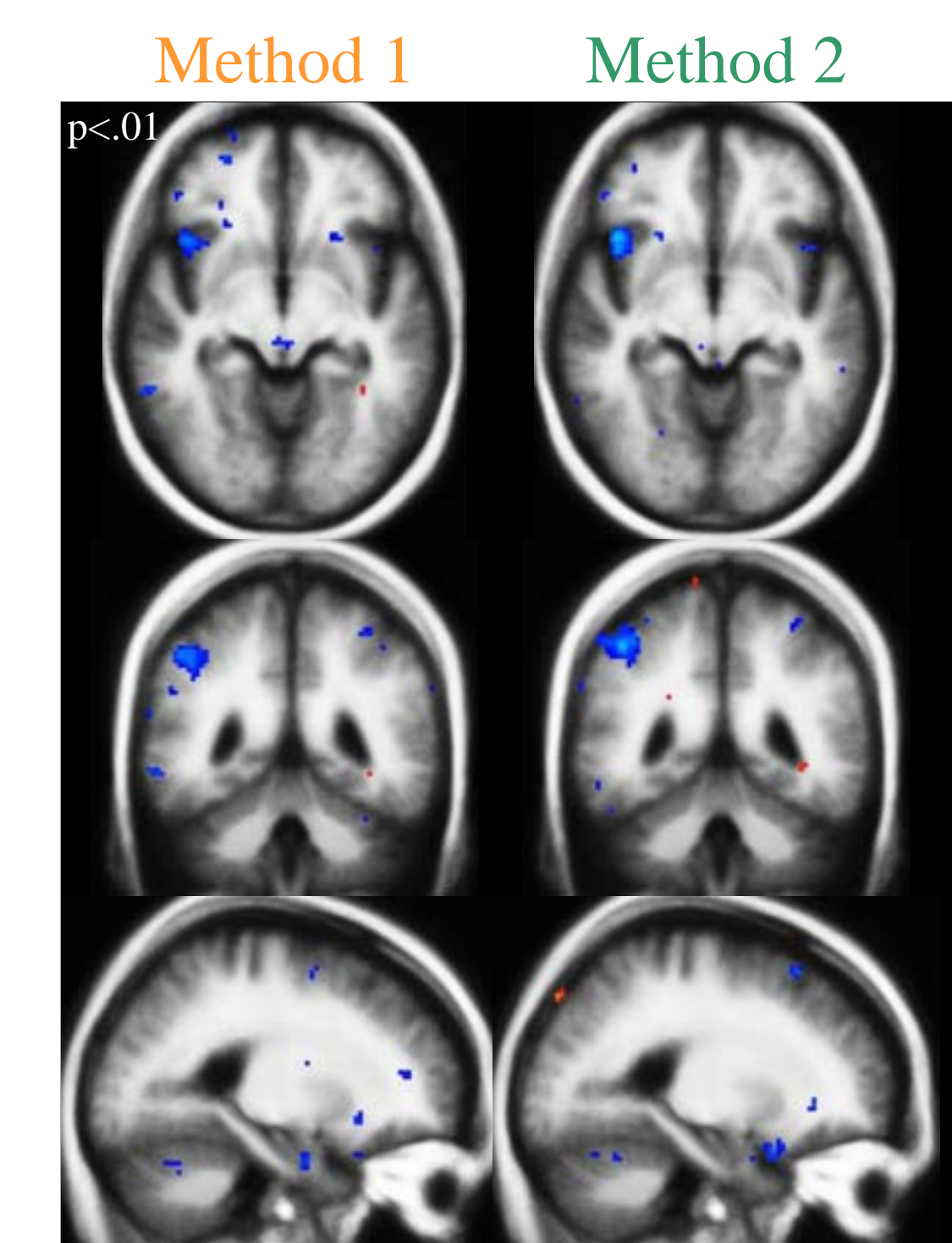
	R-L	A-P	S-I
Duke (GE)	0.9685	0.9836	0.9537
BWH (GE)	0.9816	1.0014	0.9613
MGH (Si)	0.9705	0.9922	0.9671
Yale (Si)	0.9716	1.0109	0.9712

Effect of Site:



1. Overall site effect is not huge ($< 10\%$)
2. Several strong site effects, predominantly in occipital/fusiform cortex, cerebellum, frontal inferior medial, and brain stem (not shown).
3. Method manipulations have a strong impact on site effect:
 - a) BBR reduces site effect compared to CR
 - b) B0 distortion correction reduces site effect
 - c) Voxel-wise intensity normalization reduces site effect
 - d) Using DOF=9 has a small effect which is lost when using B0 distortion correction.
 - e) There is a small but very consistent difference in scale factor (Table I)
4. Method 2 reduces site effect by 65% with respect to Method 1.
5. Occipital/fusiform not reduced much.

Effect of Visit:



1. Overall visit effect is very small ($< 3\%$), near the noise floor.
2. Very little effect of manipulation, indicating that the manipulations are truly affecting the inter-site variability and not inter-visit variability.

Conclusions

1. We examined bias in the hemodynamic response across site as impacted by several processing methods.
2. B0 distortion correction reduced site bias substantially.
3. The use of a registration method that is insensitive to intensity fluctuations reduced site bias.
4. Using voxel-wise intensity normalization reduced site bias.
5. There was a small but very systematic site bias in metric scale. Compensating for this helped, but the improvement was overridden with B0 correction.
6. All processing enhancements combined reduced the site effect by 65%.
7. Site bias does not invalidate a multi-site study, but its reduction makes us more confident in the results.