

Multi-site characterization of an fMRI working memory paradigm: Reliability of activation indices

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Introduction

We investigated the reliability of a working memory (WM) task, an adaptation of the Sternberg Item Recognition Paradigm¹⁰, for use as a clinical imaging biomarker for The Mental Illness Neurosciences Discovery Institute (www.theMINDinstitute.org) multi-site, longitudinal study of schizophrenia. This study was designed, implemented and analyzed in close collaboration with the Function BIRN project (www.nbirn.net). Results of fBIRN preliminary calibration study guided procedures.

- Rationale for the Sternberg Item Recognition Paradigm (SIRP):**
- Well-characterized & used in the experimental psychology field since 1966¹⁰.
 - Paradigm constrains strategy & requires WM.
 - Performance is impaired in schizophrenia.
 - Better than chance performance in schizophrenia.
 - Using different memory loads allows matching of groups for performance.
 - Allows a separation of cognitive & motor reaction times (RT).
 - Reliably activates dorsolateral prefrontal cortex (DLPFC) in healthy & schizophrenia subjects^{8,9}.
 - Parametric increase in DLPFC activity with increasing WM load⁹.
 - Suggested as a measure of cortical efficiency for genetic studies.
 - Relatively free of practice effects³.

- Goals:**
- Evaluate **reliability of fMRI activation indices across acquisition sites** with different field strengths (1.5T & 3T).
 - Evaluate **reliability of load dependence of fMRI activation indices** for use as a probe of disease effect in future clinical studies of schizophrenia.

Methods

- Ten healthy subjects** (5 males, 5 females, aged 30-63 yrs, mean 46±10)
- Four participating sites** (3T Siemens Trio: University of Minnesota & Massachusetts General Hospital; 1.5T Siemens: University of New Mexico & 1.5T GE: University of Iowa)
- Four scans** of the SIRP task paradigm at each site on each of **two visits**. The probe digit sets varied for each scan to eliminate learning effects
- Behavioral outcome measures were response accuracy and slope and intercept of reaction time (RT) plotted by WM load
- Whole-brain, gradient echo, EPI data (TE/TR/FOV 40/2000msec/22cm) for 27 5mm thick contiguous slices along an oblique axial, parallel to the AC-PC line. 177 image time points for each scan (duration 5:54 sec).

Task

Subjects retained a **memory set of 1, 3 or 5 digits** and then indicated whether the probe digits were targets (members of the memorized set) or foils.

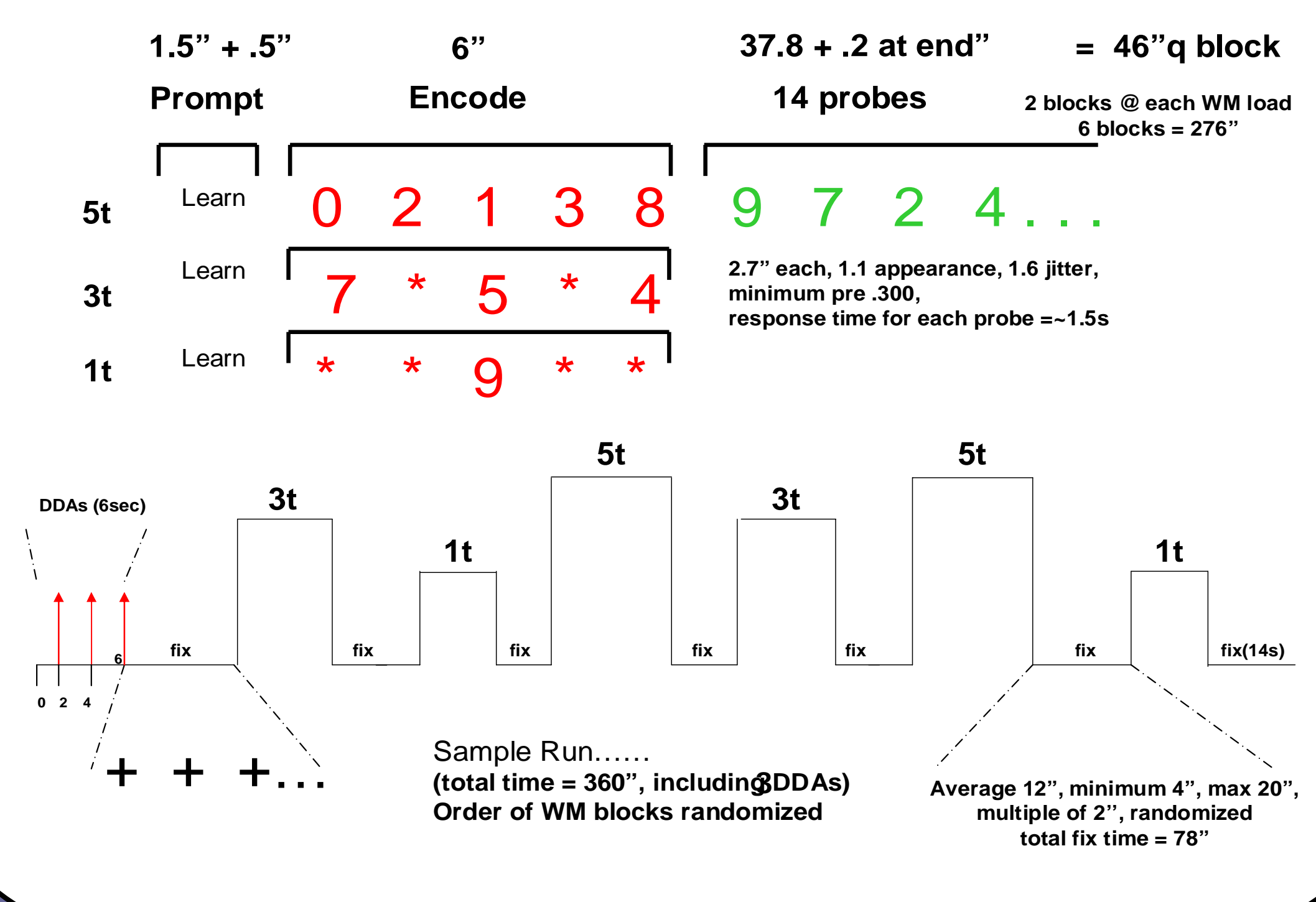
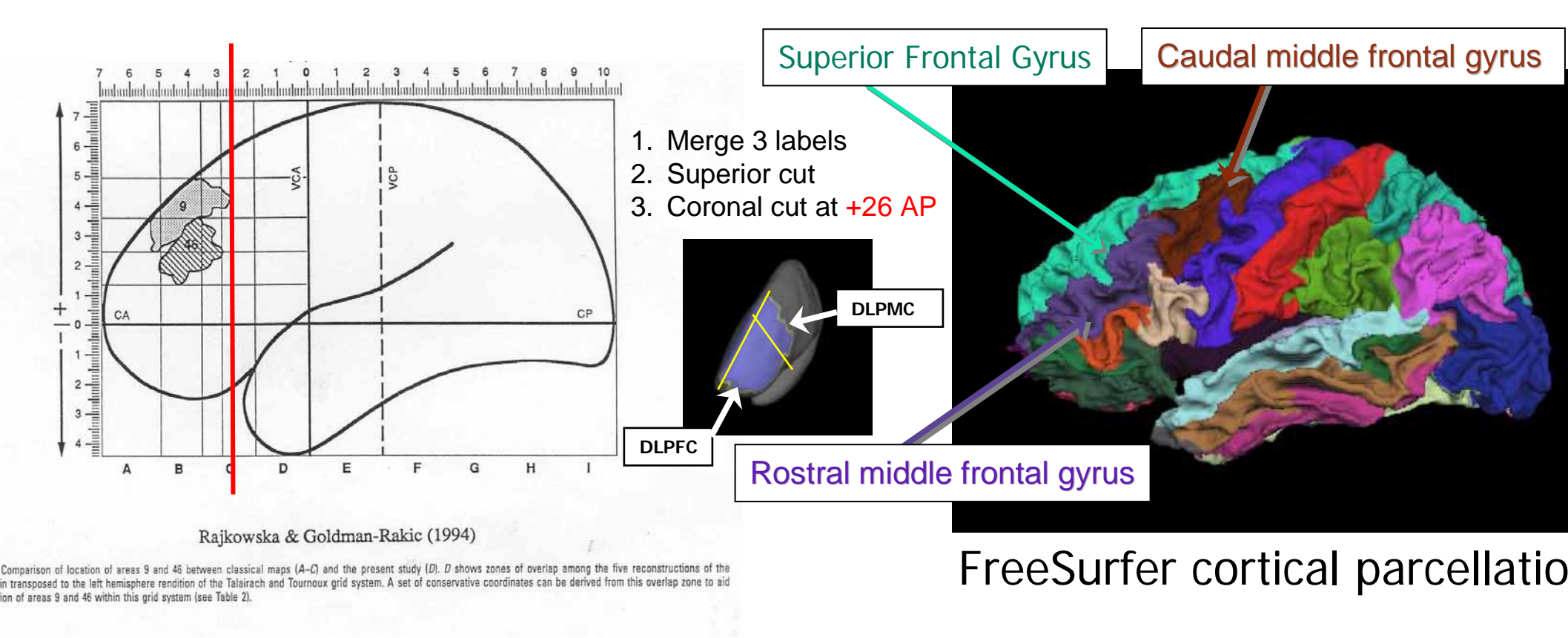


Image analysis

- Image processing with FEAT (fMRI Expert Analysis Tool) version 5.43, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl)
- Automated by the Functional Image Processing Stream (FIPS) developed by the Function BIRN
- Motion-corrected, intensity-normalized, smoothed by FWHM of 5mm
- The HRF of each load was fit separately to a gamma function
- Anatomically defined ROIs registered to functional scans (see below)
- Indices of activation** in each scan at each level of WM load for each ROI:
 - Average percent signal change (Avg%Δ)** over the voxels where the contrast of the mean of all loads vs. fixation exceeded a threshold of p=0.023
 - Number of voxels (NVox)** where the contrast of each load vs. fixation exceeded a threshold of p=0.023
- Two way fixed-effects ANOVA for Subject, Site and interaction

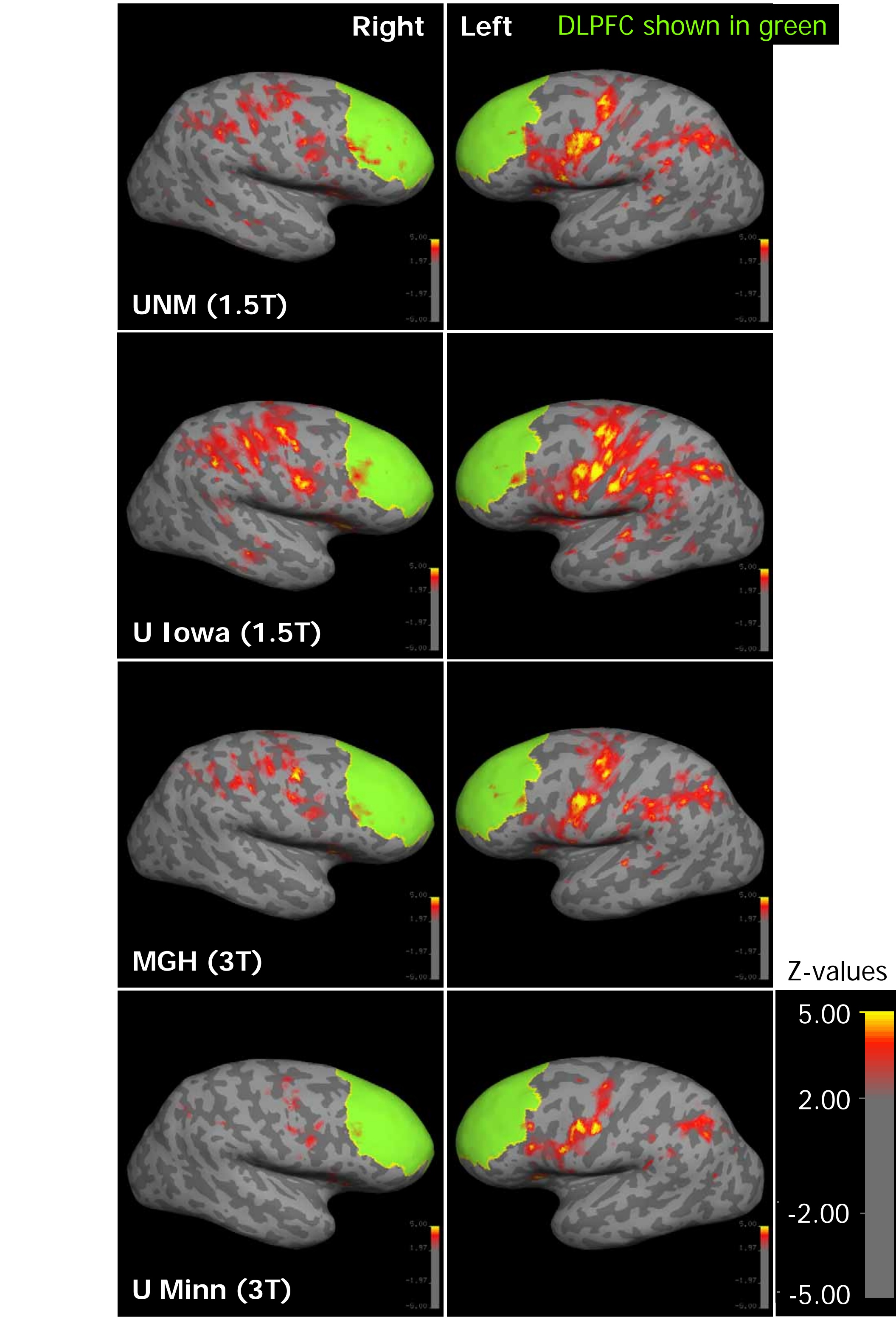
DLPFC & DLPFC ROI definition



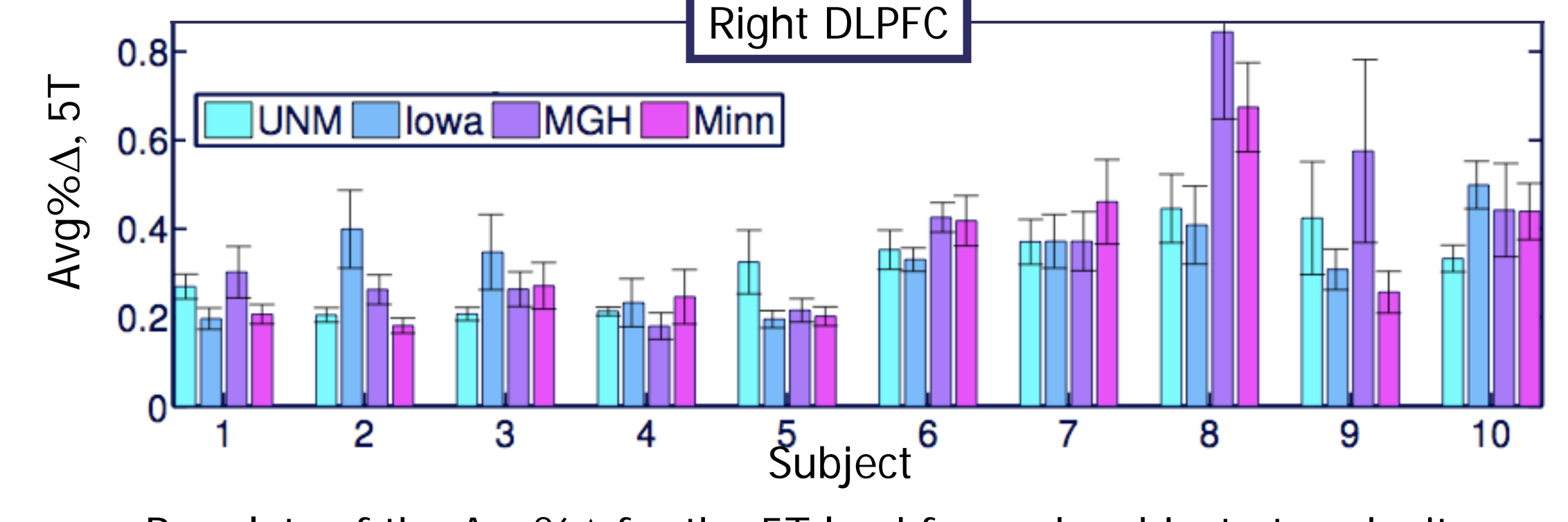
- Dorsolateral pre-frontal cortex (DLPFC)** ROIs derived from FreeSurfer cortical parcellations¹ edited to conform to conservative Talairach criteria⁹.
- Additional ROIs included:
 - The network previously identified to be activated during performance of the task for cognitive function: **Intraparietal sulcus (IPS)**, insula.
 - For motor function: **Dorsolateral pre-motor cortex (DLPMC)**, supplementary motor area, primary motor cortex in the hand area (M1).
 - A control region: **Middle temporal gyrus**.

Reliable activation of DLPFC

Z-maps of the **mean of all WM loads vs. fixation** (random effects average over 10 subjects, 2 visits; threshold: z=2) displayed on the inflated cortical surfaces of a representative subject.

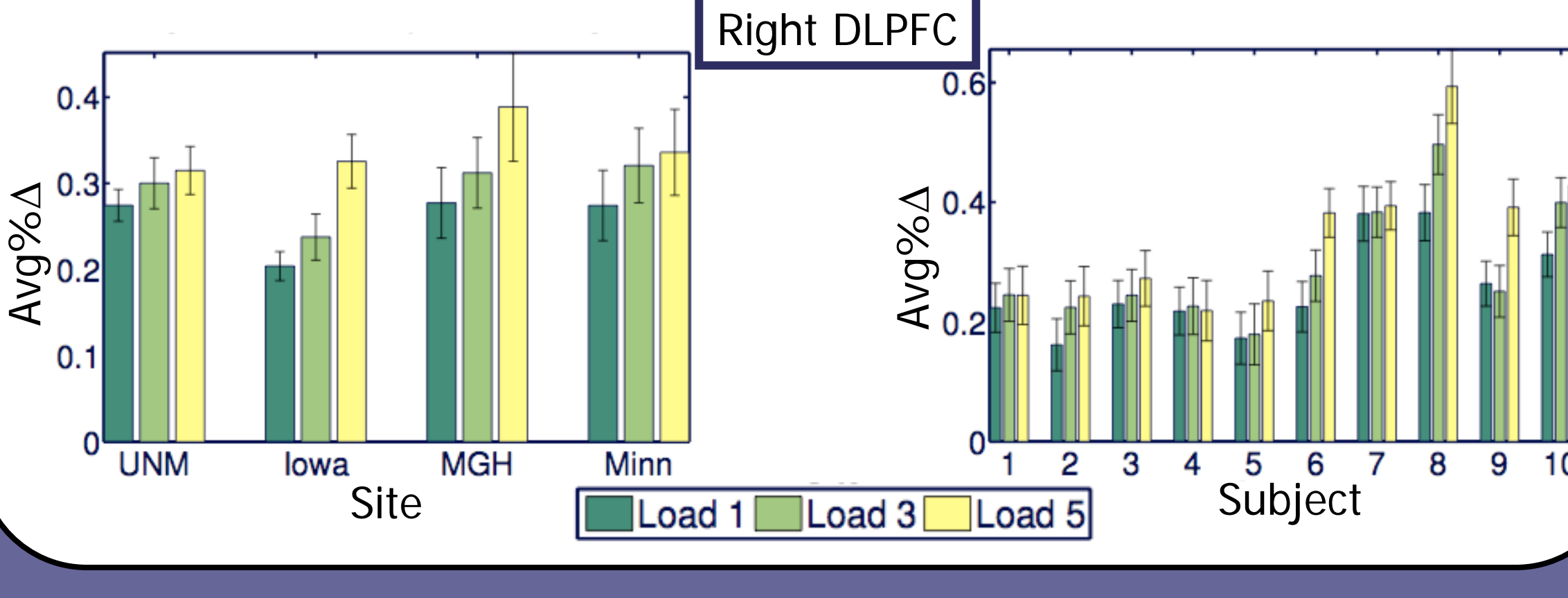


We found **comparable activation in the DLPFC and the rest of the WM network across sites**. The site effect was not significant: Left DLPFC F(9,39)=1.072, p=0.372; right DLPFC F(9,39)=0.748, p=0.529.



Bar plots of the Avg%Δ for the 5T load for each subject at each site. Subject effect: Left DLPFC F(3,39)=3.830, p=0.00154; right DLPFC F(3,39)=6.612, p<0.0001. **Between-subject variability is greater than between-site variability.**

Load effect shown by site/subject



Estimation of error variance

To assess the relative contributions of SIRP load, subject differences and site effects to the total variance, we analyzed the data using mixed-model ANOVA fit by restricted maximum likelihood. Fixed effects included Load, Visit, and their interaction. We modeled Subject, Site, and their interaction as random effects. We found no significant difference between Visits within Subject and Site and no significant interaction of Visit with Load. Consequently, the Visit and Visit by Load interaction were dropped from the model for the final analysis.

Table 1: DLPFC Fixed Effect Coefficients ± SD for the SIRP WM task

Index	Hemisphere	Intercept	Slope	P
Avg%Δ	Left	0.23 ± 0.03	0.0126 ± 0.00001	<0.01
Avg%Δ	Right	0.23 ± 0.03	0.0208 ± 0.00001	<0.01
NVox	Left	31.90 ± 7.06	2.9581 ± 0.56675	<0.0001
NVox	Right	38.48 ± 12.14	5.0047 ± 0.95681	<0.0001

The Load effect is highly significant bilaterally for Avg%Δ in the DLPFC (P<0.01), DLPFC (P<0.001) and IPS (P<0.0001) and for NVox in the DLPFC (P<0.0001), DLPFC (P<0.0001) and IPS (P<0.0001, Z- tests).

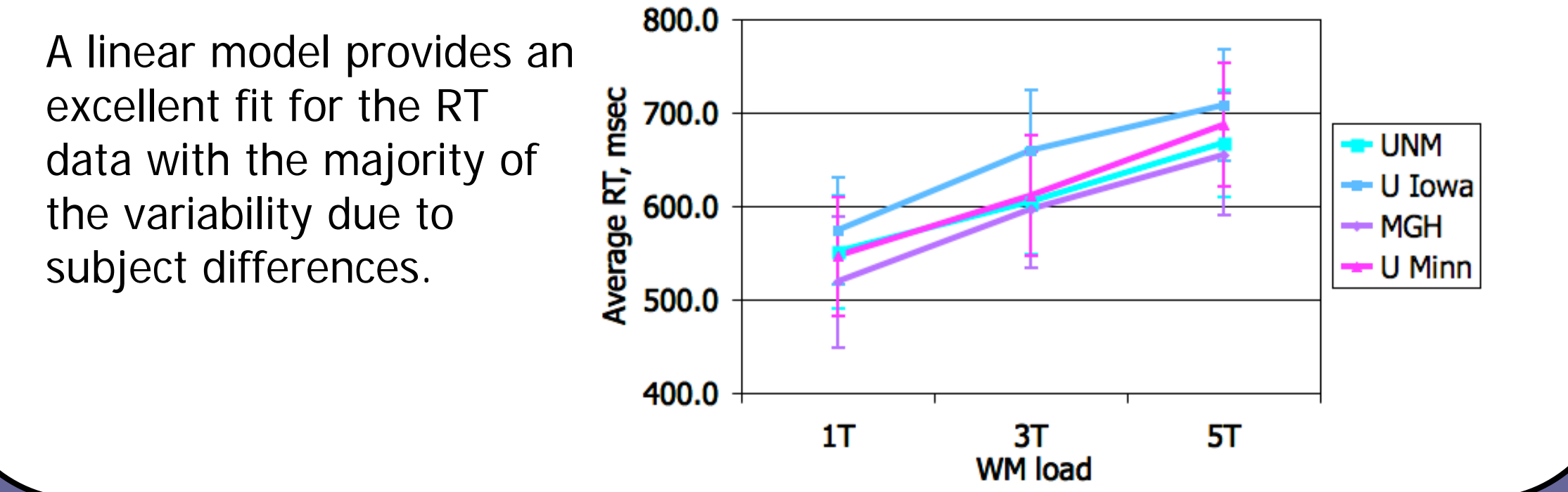
Table 2: DLPFC Percentages of Error Variance Attributable to Each Source

Index	Hemisphere	Subject	Site	Subject x Site	Residuals
Avg%Δ	Left	11.7	1.5	7.7	79.2
Avg%Δ	Right	9.6	1.3	5.4	83.7
NVox	Left	13.9	3.8	9.1	73.2
NVox	Right	24.4	2.8	11.5	61.3

Residual variance is greater than all other sources in the DLPFC for both indices of activation. The next greatest source is Subject followed by the Subject by Site interaction. Site is the smallest source of error variance. This overall pattern of results held for the DLPFC, the IPS and the other ROIs in the network.

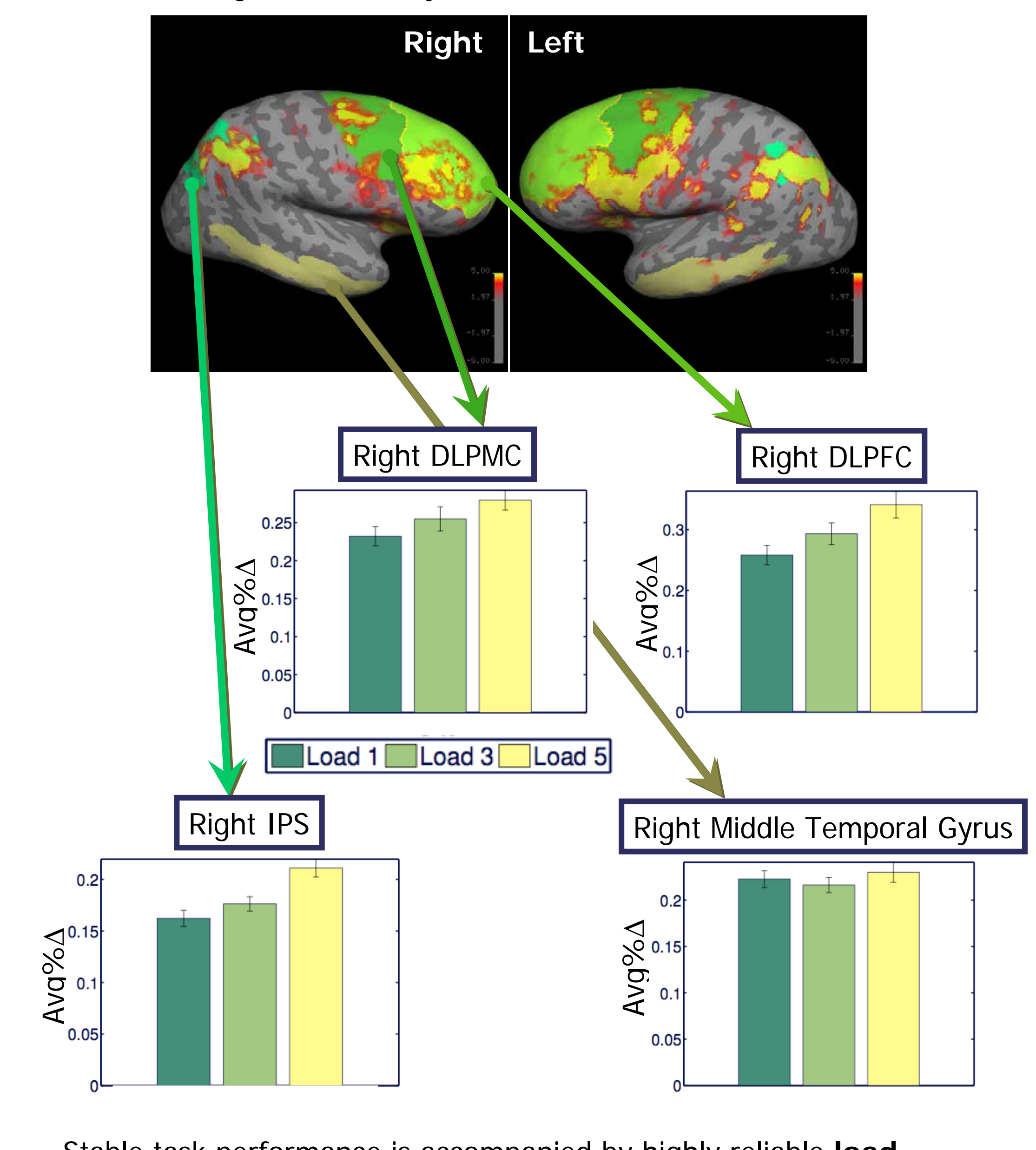
Reliable WM performance

All subjects performed at or near ceiling accuracy (range 86-99% correct, mean 94.4 ± 3.2% correct) for all sessions. The **RT slope and intercept were highly reliable** within subject across visits within site and across sites².



Reliable load dependence

Z-maps of the **highest (5T) vs. lowest (1T) WM load** (random effects average over 10 subjects, 4 sites, 2 visits; threshold: z=2).



Stable task performance is accompanied by highly reliable **load-dependent fMRI activation indices** in *a priori* ROIs including bilateral DLPFC, DLPFC and IPS; but not in areas outside the predicted network such as the middle temporal gyrus.

Summary and conclusions

- Healthy subjects perform the SIRP WM task during fMRI scanning with a high degree of reliability over repeated sessions at multiple sites. This was a prerequisite for achieving reliable activation in the WM network.
- Using matched fMRI data acquisition methods fMRI activation was reliable in the DLPFC and other *a priori* ROIs in the WM network.
- Activation was load dependent in all *a priori* ROIs.
- Variability due to field strength was significantly less than variability between subjects.
- Current analysis methods explain only a small portion of the overall variance in fMRI data. In collaboration with fBIRN, additional approaches to decreasing this noise are being explored.
- Further investigation of the details of fMRI response in the rest of the activation network, the reliability of the spatial distribution of the activation and the temporal characteristics of the activation using event-related analyses are ongoing.
- This validates the use of the SIRP as a stable and reliable probe of WM performance and functional brain activation for multi-site, longitudinal studies. Functional brain activation indices are reliable when experimental paradigm, image acquisition and data processing factors are well-controlled.

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