# fMRI Biomarker Development: Progress Report 2017

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Quantitative Imaging Biomarkers Alliance RSNA

## BOLD fMRI as a Quantitative Biomarker

The aim of the QIBA fMRI Biomarker Committee is to establish detailed Profiles for using functional MRI as a quantitative biomarker for imaging brain function. The Profile is a document describing claims for the quantitative precision that can be achieved with fMRI, along with equipment and procedure specifications for how to achieve those claims. The Profile also specifies assessment procedures whereby users of the Profile can assess their ability to conform with the Profile's data quality conditions and specifications. The primary context of use for the fMRI biomarker Profile is diagnostic fMRI to map critical brain areas for neurosurgical planning. An important aspect of the biomarker Profile is identifying standardized imaging procedures for reliably obtaining reproducible quantitative fMRI results in a clinical context. The focus of Profile v1.0 is mapping of hand motor regions. Profile v2.0 will address mapping of brain regions involved in language processing.

The QIBA fMRI biomarker committee has established working groups with weekly teleconferences to focus on specific issues (i.e., reproducibility, bias, DICOM standards, Profile writing). The committee has also undertaken several RSNA-funded groundwork projects to clarify specific issues critical to creating fMRI biomarker Profiles for mapping motor and language function. Completed projects include:

1) Establishing metrics for assessing scan-rescan reproducibility and procedures for improving reproducibility of results
2) Characterizing neuro-vascular uncoupling (NVU) affecting BOLD signals and QA methods for detecting NVU
3) Developing realistic, standardized, synthetic digital reference objects (DROs) for comparison of fMRI analysis methods in common use and for testing specific sources of variance in fMRI (e.g., head motion, behavioral performance, etc.)

## Profile Status

**fMRI Profile v1.0 on motor fMRI** has been released for public comment. It establishes the claim that the center of mass of activation (CMA) for a motor task can be localized reproducibly in brain activation maps. Specifically:

Biomarker measurand: Local T2* BOLD fMRI signal

Context of use: Mapping motor cortex for preoperative planning

Cross-sectional measurement: Location of BOLD signal as a biomarker of motor cortex

Index: The intensity-weighted center of mass of activation (CMA) evoked by a hand movement task

Precision profile: If XYZ is the measured location of the CMA of a single focus of fMRI hand motor activation, then the 95% confidence interval for the true CMA is XYZ +/-5mm (assumes no systematic bias).

**fMRI Profile v2.0 on language fMRI** is under development. Its claims will include center of mass of activation and spatial extent of language systems, as well as laterality index (LI) calculation.

## Groundwork Project: fMRI Variability by Analysis Site

**Compare analyses of same data at different sites:** As fMRI analysis methods vary from site to site we compared activation maps produced when 8 different sites analyzed the same raw fMRI data. All 8 sites were experienced at analyzing clinical fMRI scans. One site used 2 different methods, resulting in 9 analyses for comparison.

**Sample data sets:** The task data were synthesized as Digital Reference Objects (DROs), based on empirically-derived MRI scans of human volunteer subjects. Each DRO was created by adding a "rest" time-series of EPI images to an EPI time-series of empirical task signal, to produce realistic fMRI data sets with known activation signals. Ten sets of DROs were generated, where each DRO set consisted of a bilateral hand motor task, a silent sentence-completion language task, and a high-resolution T1-weighted anatomical scan, all from the same subject (Figure 1)

## Methods

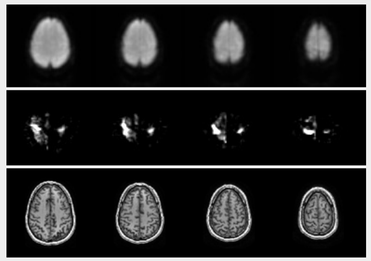


**Fig. 1 Sample DRO**

EPI rest time series without task signal
+
EPI task signal
= Task DRO

T1-weighted reference images

**Analysis of site activation maps:** Each site used their own methodology for analyzing clinical fMRI scans. For each DRO they generated an unthresholded ("raw") activation map, plus a thresholded map using a "standard" objective threshold setting (no manual adjustments) typical of that used for clinical scans. All maps, with methods description, were sent to a central site for comparison.

**Threshold normalization:** Unthresholded fMRI maps were compared using the AMPLE threshold normalization method (Voyvodic et al., 2009; Voyvodic, 2012) to identify voxels above 50% activation based on a custom anatomical ROI mask of clinically-relevant brain areas in standard MNI space (Figure 2c).

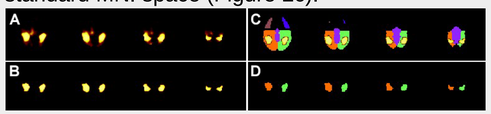
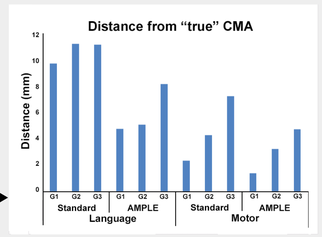



**Fig. 2 Comparison of fMRI maps** Sites provided raw (A) and standard-thresholded (B) maps. Clinical reference ROI masks were used for AMPLE analysis (C). BOLD regions underwent cluster analysis to identify largest cluster in each clinical ROI (D).

**Fig. 4 Comparison of CMA locations across sites**
Each blue bar is the average distance across all DROs per group (9 DROs x 3 sites in each group).




## Results: Comparing maps

**Qualitative comparison of standard-threshold versus AMPLE-threshold maps:** Comparing the "standard" threshold maps from different site analyses for each DRO showed similar patterns of activation but with significantly different spatial extents (Fig. 3 A & C). AMPLE-normalized versions of those site maps resulted in more similar maps (Fig. 3 B & D).

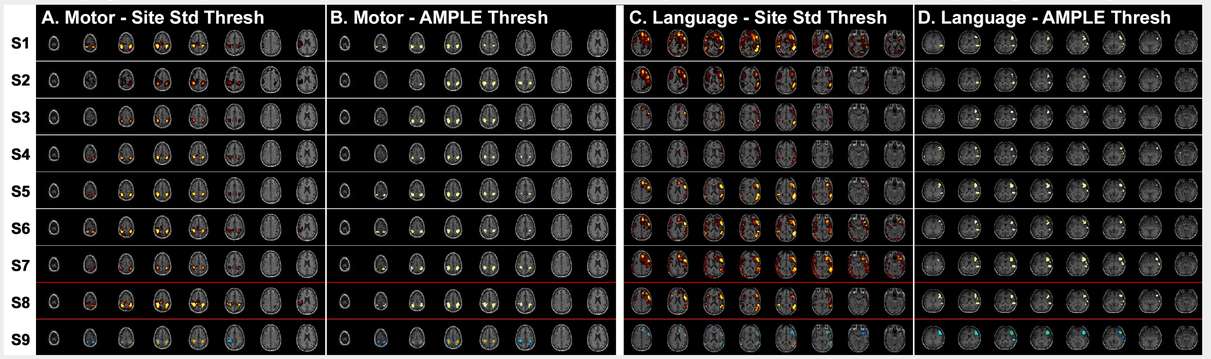



**Fig. 3 Comparison of fMRI maps from DRO #1, both motor and language, for all sites.** All 9 site analyses (S1-S9) are shown at both the site's own "standard" threshold and after automated AMPLE normalization of the "raw" unthresholded map.

**Quantitative comparison of localization of center-of-mass of activation (CMA):** We calculated the distance between the "true" CMA and the CMA of each fMRI activation region detected in the different site maps, using an automated cluster-based analysis. For this, the 9 site analyses were separated into 3 groups (G1, G2, G3) based on how they performed coregistration of EPI and T1 images. G1 maps had not been re-registered (relative to original DRO DICOM images), G2 maps had converted oblique-axial to straight axial slices, and G3 maps had performed active coregistration of EPI and T1 images. For both motor and language maps, CMA distances were best (smallest) for G1 sites, then G2 sites, then G3 sites. CMAs of AMPLE-normalized maps were consistently closer to true than sites' "standard" thresholded maps (Fig. 4).

## Conclusions:

1) The same fMRI scan data analyzed at different clinical fMRI sites yield significantly different activation maps.
2) EPI/T1 coregistration differences cause some inter-site variability.
3) Threshold normalization (e.g. using only voxels in the upper half of the BOLD signal range) greatly reduces inter-site variability.
4) These DRO results support our Profile v1.0 Claim.

**References:**
Voyvodic, Petrella, & Friedman (2009), JMRI, 29:751-759
Voyvodic (2012), JMRI, 36:569-580

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