fMRI Biomarker Development: Progress Report 2015

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BOLD fMRI as a Quantitative Biomarker

The aim of the QIBA fMRI technical committee is to establish a detailed profile 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 with equipment and procedure specifications for how to achieve those claims. The profile also specifies conformance procedures whereby users of the profile can assess their ability to meet the profile's data quality conditions. 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 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 an fMRI biomarker profile. 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

Profile Status

The first version of the fMRI profile 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* MRI contrast change – commonly referred to as the BOLD fMRI signal (the biomarker is a measurable physical property)
Context of use: Preoperative mapping of eloquent cortex for treatment planning/guidance
Cross-sectional measurement: Location of BOLD signal as a biomarker of motor cortex
Index: The center of mass of activation evoked by a hand movement task
Precision profile: There is a 95% probability that the measured CMA, +/- 5mm, encompasses the true CMA.
Conformance: Procedures and specifications for how to achieve the claim. For example:

Imaging site requirements:
- Appropriate imaging equipment satisfying QA specifications (duty cycle, SNR, stability)
- Appropriate peripheral equipment and stimulus delivery methodology,
- Appropriate image acquisition and analysis software for fMRI
- Experienced MR technologists for the imaging procedure

Tasks and patient performance:
- Availability of appropriate behavioral tasks for eliciting brain activation of interest
- Procedures for training patients on task and verifying satisfactory pre-scan performance
- Procedures for verifying task performance during fMRI imaging

Data quality assurance (QA)
- Procedures for assessing image QA metrics (head motion, NVU, signal consistency, etc)
- Specifications for acceptable QA values consistent with achieving the profile claims

Image analysis procedures
- A standardized statistical image processing protocol known to be able to meet the claims

We will use QIBA funding from NIH in 2015-16 on groundwork studies to begin developing a biomarker profile for language mapping.

DICOM WG-16 Collaboration - Update

Goal: Add storage and transmission of fMRI data to the DICOM standard.
Progress in 2015: WG-16 (fMRI) has focused on the storage of activation maps utilizing Enhanced MR objects including Real World Values (RWV) and Parametric Maps. The group held its first face-to-face meeting in Milwaukee, WI and presented its proposed course for review at the WG-06 meeting in Arlington, VA in September.
Current Plans: WG-16 will incorporate suggestions from the WG-06 review and finalize a change proposal (CP) for supporting activation maps. Next it will address other fMRI data requirements including representation of task paradigms, task results, and processing results.
Input from the QIBA fMRI Biomarker Committee will be sought as needed.

Digital Reference Object (DRO) Development & Results

Over the past year, the fMRI groundwork project has focused on creating realistic synthetic DROs to study how the profile's claim is affected by:
1)head motion
2)variable task performance
3)neurovascular-uncoupling (NVU)

Approach: Synthetic DRO data sets were created with different brain activation and noise properties. Brain activation maps obtained from analysis of each DRO are compared to the known "true" activation signal for that DRO.

Methods: DROs were created by isolating and extracting multiple different signal components from empirical fMRI data sets and then recombining selected components in different ways to create synthetic data sets with realistic properties. Individual components included: T1 and T2*-weighted images of brain structure, background BOLD signal fluctuations, task-dependent BOLD signals, spatial weighting maps of active brain voxels, head motion, task performance fluctuations, and NVU maps.

Here we present preliminary results for head motion DROs (2 types of motion DROs) and variable task performance; these represent major sources of variance in fMRI.

Head motion DROs

Motion DROs were created using 2 different approaches: Both used synthetic time series of EPI images in which individual images were moved by a known amount of translation or rotation and then resampled and analyzed using AFNI. Center of mass (CM) of activation derived for each DRO was compared to true CM.
Approach 1: used 2.5mm cubic voxels and added gaussian white noise plus an ideal fMRI response (Fig 1, red) adjusted for a maximum SNR of 2. Synthetic head motion was introduced by creating a normalized motion vector over time (Fig 1 blue graph). Five amplitudes of the motion vector were applied as both a translation or rotation of the brain along/around each 3D head axis yielding 30 (6x5) new fMRI datasets that each incorporated a single type and amplitude of head motion. For head motions such as shown in Fig 1, that are not correlated with the fMRI task, significant deviations from the true CM were not observed below 6 mm or 6 degrees of translation/rotation (Fig 2).
Approach 2: used high resolution 1mm cubic voxels and added translational head motion (e.g. Fig 3) at a 2s TR slice acquisition frequency (15 Hz) and resampled to 4mm cubic voxels to account for partial volume effects. In this approach, even small amounts of head motion reduced detection of true active voxels (Fig 4) and reduced the accuracy of CM localization (Fig 5). Motion correction did not make much difference.
Conclusion: Synthetic DROs can be used to assess the effect of different types and amounts of head motion of fMRI as a quantitative biomarker. More work is needed to identify the optimal methodology for creating motion DROs and for sampling the full parameter space of realistic types of head motion.

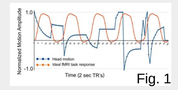


Fig. 1

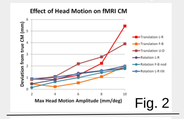


Fig. 2

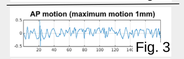
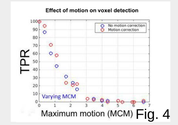


Fig. 3



Maximum motion (MCM) Fig. 4

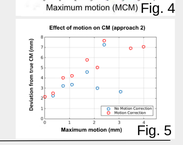


Fig. 5

Variable performance DROs

Problem: Clinical fMRI scans use repeated block-design tasks that, ideally, result in regular sinusoidal BOLD signal oscillations (Fig 6A). Actual patients, however, have variable task-dependent BOLD oscillations (eg. Fig 6B). We introduce a "consistency index" QA metric, as the correlation between observed oscillation and an ideal sinusoidal oscillation.
Performance DROs: 400 synthetic DROs were created using 400 different empirical performance-related waveforms (eg. Fig 6B) as activation weighting factors.
ROC analysis: Each DRO was analyzed to create an activation t-map, which was then compared to the known true activation pattern to create receiver-operator characteristic (ROC) curves for detection as a function of threshold. (Ideal detection curves approach the upper left corner of ROC plots.)
Results: The 400 DROs that differed only in performance weighting curves yielded variable t-maps and associated ROC curves (Fig 7). Using the automated AMPLE normalization algorithm (Voyvodic 2006, MRI 24:1291-61) to ignore voxels below 20% of peak activation improved detection as shown by increased area under the ROC curves (Fig 8). Plotting the area under each ROC curve in Fig 8 as a function of the performance consistency index showed a very strong correlation (Fig 9).
Conclusion: DRO analysis shows that consistency index (which can be easily calculated for any real patient fMRI scan) can be used as a conformance QA parameter for fMRI.

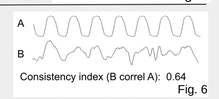


Fig. 6

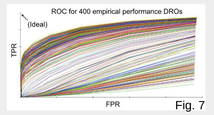


Fig. 7

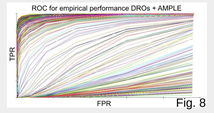


Fig. 8

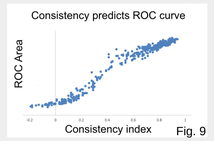


Fig. 9

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