QIBA Profile:

Mapping of Sensorimotor Brain Regions using Blood Oxygenation Level Dependent (BOLD) Functional MRI as a Pretreatment Assessment Tool.

5

Version 1.0 rev1

Stage A: Initial Draft

Table of Contents

Change Log:

Date	Sections Affected	Summary of Change

Open Issues:

The following issues are provided here to capture associated discussion, to focus the attention of reviewers on topics needing feedback, and to track them so they are ultimately resolved. In particular, comments on these issues are highly encouraged during the Public Comment stage.

Q. Are the extent and edges of a focus of activation important to specify? **A**.
Q. Optimal thresholding – What is the optimal threshold for accurately delineating the area of activation? **A**.
Q. Assessment of Neurovascular Uncoupling as a data qualification step. – How does one determine if there is NVU for areas other than the hand motor representation which is addressed in this profile? **A**:
Q. Revisit terms for tSNR and SNR based on David Soltysik's upcoming paper? **A**.
Q:Revisit the new motion parameter estimation formulas and the DRO verification for the subsequent profile. **A:**
Q: Better characterize impact of task-correlated motion on profile compliance. **A**:
Q: Rationale for Contrast-to-Noise (CNR) ratio limit? **A:**

Closed Issues:

The following issues have been considered closed by the biomarker committee. They are provided here to forestall discussion of issues that have already been raised and resolved, and to provide a record of the rationale behind the resolution.

1. Executive Summary

This profile provides guidance for using functional magnetic resonance imaging (fMRI) to map the central brain components of the motor system for use in planning and guiding brain surgery or radiation treatment. The current focus is on using fMRI as a location biomarker for the center-of-mass of brain areas supporting hand movement that may be at risk of damage from invasive treatments. Accordingly, the goal of this QIBA Profile is to help the user to achieve a useful and specified level of performance of the biomarker.

The **Claim** (Section 2) describes the biomarker and its performance.

The **Activities** (Section 3) contribute to generating the biomarker. Requirements are placed on the Actors that participate in those activities as necessary to achieve the Claim.

Assessment Procedures (Section 4) for evaluating specific requirements that should help the user in assessing conformance with this profile.

This QIBA Profile (Mapping of Brain Motor Regions using Blood Oxygenation Level Dependent (BOLD) functional MRI as a Pretreatment Assessment Tool) has been developed to provide a systematic approach for optimizing Blood Oxygen Level Dependent (BOLD) fMRI brain mapping for treatment planning prior to surgery or invasive treatment intervention. It places requirements on Acquisition Devices, Technologists, Radiologist, Post-Processing Software and Image Analysis Tools involved in Subject Handling, Image Data Acquisition, Image Data Processing, Image QA and Image Analysis. Note users who plan to bill for imaging services using this profile should also consult the current procedural terminology (CPT) codes which may have additional requirements. Please refer to the ASFNR website for further information (http://www.asfnr.org/cpt-codes/).

1.1 Background

Task-induced BOLD fMRI (Thulborn K, 1982, Ogawa S et al, 1990) can be used clinically as a biomarker for functionally eloquent brain tissue that might be at risk of damage from invasive procedures used to treat

brain cancer or other focal pathologies (Medina LS et al 2005, Mahdavi A, et al 2015, Petrella JR et al 2006, Ulmer J et al 2004, Belyaev AS et al 2013). The clinical utility and professional acceptance of BOLD as a biomarker is dependent on the reproducibility and validity of task-induced BOLD response patterns - the primary measure produced by BOLD exams and from which secondary quantitative measures are derived (Friedman L et al 2006, Soltysik DA 2011). Current methodology is quite variable at all stages from exam administration, data acquisition, analysis and report of results. This reflects the use of a wide variety of MRI scanners, data acquisition systems, analysis platforms and software components (Glover et al, 2012, Gountouna V, 2010, Chen JE, Glover G, 2015). Due to this great variation, a current priority of the QIBA BOLD fMRI Technical Committee is to characterize the current state of the art and to identify significant sources of methodological variability which can negatively affect quantitative fMRI measures.

Our initial studies of BOLD signal reproducibility provide quantitative measures that are used in the statement of claims presented below. Note that this document only states requirements to achieve the claim, not 'requirements on standard of care.' Conformance to this profile is secondary to properly caring for the patient.

This QIBA BOLD Profile 1.0 provides specifications that may be adopted by users as well as equipment developers (hardware and software devices) to meet targeted levels of clinical performance in identified settings. This profile makes claims about the precision with which fMRI responses in eloquent cortex can be measured and displayed under a set of defined image acquisition, processing, and analysis conditions.

This document is intended to help clinicians basing decisions on this biomarker, imaging staff generating this biomarker, vendor staff developing related products, purchasers of such products and investigators designing research studies with functional brain imaging as a focus or major component.

Limitations of current profile and roadmap for future development: This version 1.0 of the profile is intentionally focused narrowly on the precision of fMRI as a biomarker for locating brain sites responsible for the voluntary movement of the hand. This narrow focus was adopted to minimize the number of methodological factors and issues that must be addressed to ensure that the claims can be achieved routinely in clinical practice using the procedures outlined herein. Future versions will seek to extend this profile to additional functional sites including those supporting motor function of additional body parts (feet, legs, mouth), to vision and language, and to additional imaging technologies such as resting state fMRI. Moreover, future versions will likely extend the claims from the location of the center-of-mass of fMRI activation to the location of the activity boundary and to the volume and amplitude of activation. The authors of this profile have been impressed with the time and effort required to create a precise and informative document and hope that this has established a strong base for future extensions of this profile to cover the full range of fMRI utility as a clinical imaging biomarker.

This QIBA Profile and others addressing additional imaging biomarkers using CT, MRI, PET and Ultrasound can be found at qibawiki.rsna.org.

2. Clinical Context and Claims

BOLD fMRI is used as a tool for pre-treatment planning and intraoperative guidance in individual patients with brain lesions, including tumors, vascular malformations and epileptogenic foci. For such patients, fMRI can identify and spatially map healthy brain tissue that is potentially at risk of damage from surgical or radiation treatment of a neighboring pathology site. The presenting symptoms and location of the pathology determine the region or regions of the brain to be mapped and the behavioral paradigm(s) selected (e.g. motor task, language task) to evoke a BOLD response. This profile primarily focuses of the use of fMRI to map brain regions controlling hand movements. The change in BOLD signal elicited by specific hand movements (relative to a control condition) provides information about the brain region(s) controlling those movements and about the proximity of this eloquent cortex to the brain site(s) to be treated. Bold fMRI mapping near a site of pathology can reveal the potential for damage to eloquent brain tissues and the potential for post-operative deficits. The goal of this QIBA profile is to specify the procedures and quantitative parameters under which BOLD fMRI is an accurate and reliable predictor of brain function, that is, as a valid imaging biomarker for medically meaningful changes in brain activity elicited by a behavioral task.

Assumptions concerning the application of BOLD fMRI follow:

Assumption 1 – fMRI neuro-vascular-coupling: A BOLD fMRI signal that is temporally synchronized with the onset/offset of a sensory stimulus or behavioral task is a valid indicator (biomarker) of the local hemodynamic response to that stimulus/task. Furthermore, the hemodynamic response is assumed to be an indicator of the local neuronal response. (See Appendix B for background support for this assumption.)

Assumption 2 – Functional specificity: Increased BOLD signal within brain area A produced by paradigm P is a valid indicator of the function of area A (which can be extended to imply that excision or damage of area A could produce a functionally related neurological deficit.) It is also assumed that a focus of interest can be uniquely identified relative to other potential foci. (See Appendix B for background support for this assumption.)

Biomarker measurand: Local T2* MRI contrast change (reflecting a hemodynamic response to change in brain activity) – commonly referred to as the BOLD fMRI signal. The primary measurement of interest is the location of the weighted center-of-mass of a focus of fMRI activation (wCMA) in sensorimotor cortex elicited by task-prescribed hand movements. A voxel is considered part of the activation focus if it's fMRI signal amplitude or T-statistic exceeds a preselected threshold criterion. The fMRI signal amplitudes of all

voxels that are part of the activation focus are then used as the weighting factors in the computation of the weighted center-of-mass. (See section 3.9 and Appendix I for details of the wCMA calculation.)

Conformance to this Profile by all relevant actors and equipment is required to ensure the validity of the following claim:

160 **Claim 1: If X,Y,Z is the measured location of the weighted center-of-mass of a single focus of fMRI hand motor activation (wCMA), then the 95% confidence interval for the X,Y,Z of the true wCMA is +/-5mm in any direction (assuming no systematic bias).** (The **+/-**5 mm precision value represents 1.96 x within-subject standard deviation).

3. Profile Activities

This Profile is documented in terms of "Actors" performing "Activities". "Actors" can be individuals (e.g. technologist), devices (e.g. MRI scanner, video display) or software (e.g. post-processing software). Actors and activities for fMRI are summarized in Table 1 which also lists sections of this profile in which specific activities are described in detail. Those sections also provide activity requirements that must be met to qualify for compliance with this profile and that should allow the practitioner to achieve the profile claims (See Assessment Procedures, section 4). The general clinical workflow of activities specified in Table 1 is outlined in Figure 1.

Table 1: Actors and Activities

Actor	Activity	Section
N/A	Predelivery	3.1
MR Scanner Vendor /Physicist /Peripheral System Vendor	Installation	3.2
Vendor /Technologist /Scientist	Periodic Q/A	3.3
Physician /Scientist /Technologist	Subject Selection	3.4
Physician /Scientist /Technologist	Subject Handling	3.5
MR scanner Vendor /Technologist /Physician /Scientist	Image Data Acquisition	3.6
Technologist /Scientist /Image Analyst	Image Q/A	3.7
Vendor /Technologist /Scientist /Image Analyst	Image Data Processing	3.8
Vendor /Technologist /Scientist /Image Analyst	Image Analysis	3.9
Physician /Scientist /Technologist	Image Interpretation & Distribution	3.10

Conformant Actors shall support the listed Activities by conforming to all requirements in the referenced

Section. The requirements in this Profile do not codify a Standard of Care; they only provide guidance intended to achieve the stated Claim. Failing to conform to a "shall" in this Profile is a protocol deviation. Although deviations invalidate the Profile Claim, such deviations may be reasonable and unavoidable and the radiologist or supervising physician is expected to do so when required by the best interest of the patient or research subject. How study sponsors and others decide to handle deviations for their own purposes is entirely up to them.

The requirements included herein are intended to establish a baseline level of fMRI capability. Providing higher performance or advanced capabilities is both allowed and encouraged and the profile is not intended to be limiting in any way with respect to capabilities. This profile is not intended to specify the medical rationale for conducting an fMRI exam for the patient. It is assumed that the patient's referring physician(s) will determine the appropriateness and utility of an fMRI exam based on the patient's medical history, symptoms, treatment options, prognosis and other relevant information. It is further assumed that the physicians will anticipate the likelihood that an fMRI exam will provide information that will be useful to the assessment, diagnosis, and treatment of the patient's medical condition.

The sequencing of the Activities specified in this Profile is outlined in Figure 1:

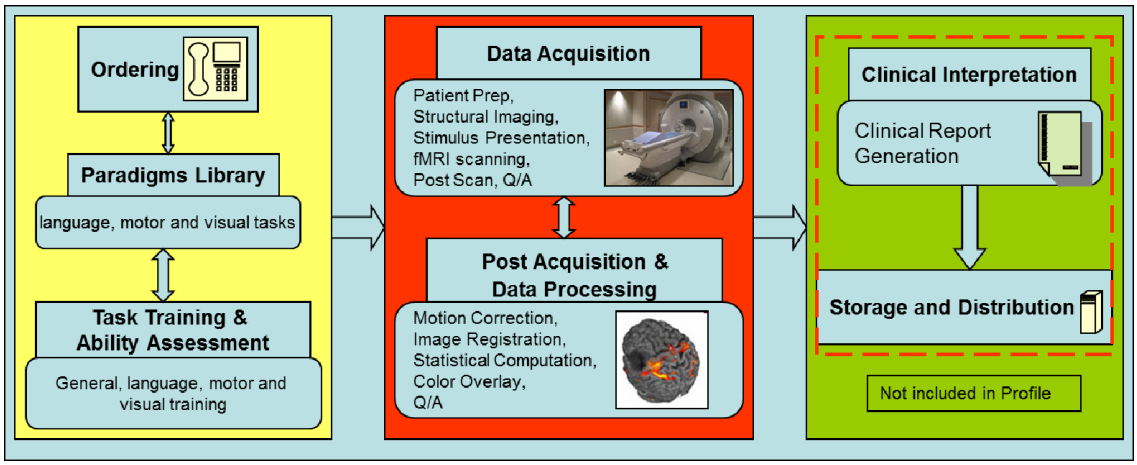


Figure 1: Mapping of Brain Regions using Blood Oxygenation Level Dependent (BOLD) functional MRI as a Presurgical Assessment Tool – Activity Sequence.

3.1. Pre-delivery

No specific pre-delivery activities are required by this profile.

3.2. Installation

3.2.1 Discussion

A performance site that is likely to be capable of achieving conformance with the profile claims will typically include the following:

- Magnetic resonance imaging scanner equipped for functional MRI
- Peripheral devices for delivery of visual and/or auditory stimuli to cue performance of the fMRI motor task and to record the patient's performance of the task.
- MR technologist, physician or scientist trained and experienced in fMRI acquisition procedures including training patients to perform the fMRI motor task
- Image post-processing and display software/hardware and technician trained to conduct post-processing.
- Demonstrated ability to comply with the specifications outlined below.

A complete fMRI study typically includes acquisition of anatomical/structural images plus several fMRI scans, depending on the set of behavioral tasks needed to ensure coverage of the brain regions of interest. Ideally all images are acquired in a single session during which time the patient is asked to move as little as possible to minimize misregistration of the different imaging series with each other.

During fMRI data acquisition, brain image volumes are acquired repeatedly (e.g. every 2 sec.) during the MR scan, which typically lasts several minutes or more. During the scan, the patient performs a behavioral task. Data documenting the patient's performance must be obtained. The complete data record will include the brain images, a description of the fMRI imaging pulse sequence and parameter settings, a record of synchronization trigger signals, a description of the task paradigm with actual performance data as well as any incidental observations of the MRI technologist. It is essential that all data are included in the clinical record and are passed on to post-processing, archiving, and to the physician for clinical interpretation.

MRI scans for fMRI analysis shall be performed on qualified equipment. Use of a field strength of 1.5 Tesla or higher with fMRI capabilities is recommended. It is also important to have appropriate personnel present during the scan to meet insurance CPT code requirements.

It is highly recommended that sites perform quality assurance tests on their devices to verify hardware function and consistency (see section 3.3.1 for more details). These hardware tests should include daily SNR and tSNR measurements to test scanner signal and image quality, as well as operational tests of the fMRI-specific equipment (i.e., response devices, projector, goggles, audio, etc.) prior to placing the patient in the scanner. (Glover et al 2012, Greve et al, 2011). Note that hardware tests alone are not sufficient to guarantee overall data quality due to the important contribution of non-hardware sources of variance.

Stimulus Display/Response Devices - A visual stimulus/cue can be displayed via MR compatible equipment such as binocular goggles or projector-based systems (LCD Monitor, or Projector). An audio stimulus can be

presented using audio delivery systems provided with the MR scanner or via a third-party system designed for the MR environment. Monitoring task performance (direct observation of finger/hand/foot movement) as well as recording patient responses (e.g. button box or other device) is essential.

It is critical to properly adjust the fMRI stimulus presentation devices (e.g., goggle device or mirror/display system) to correctly adjust for visual acuity and ensure that the entire visual display is visible to the patient. This minimizes squinting and movement of the eyes/head during scanning. Occlusion of portions of the visual display by glasses frames or improper positioning can degrade fMRI results. It is strongly recommended that the scanner technologist or an assistant view test stimuli from the position of a patient within the scanner since maladjustment can be difficult to assess from outside the bore. If stimuli are presented aurally, placement and adjustment of headphones is important for establishing appropriate volume control. For monitoring motor responses MR compatible button boxes, grip devices or trackballs should be positioned such that the patient is able to operate the device easily, without hindrance or inadvertent movement of the head. It is advisable to use foam padding to reduce head motion, and use foam ear plugs to reduce interference from scanner noise when a proper audio presentation system is not used.

Once positioned in the MR scanner, a quick review of the task is recommended to be sure that the patient is still familiar with what they will see or hear, and what they are asked to do during the task.

The following specifications are capable of meeting the Profile claims. Alternate specifications may also meet the claims but demonstrating conformance with this profile is then the responsibility of the actor (See Assessment Procedures, section 4).

Scan Synchronization/Triggering - The temporal sequence of task performance must be synchronized with the fMRI imaging sequence. This is best done using electrical trigger pulses to initiate software presentation of a visual and/or auditory cue. This permits accurate automated detection of fMRI responses and permits averaging of multiple scans to obtain better signal quality. Online recording of actual timing and trigger signals during acquisition can be included as part of the permanent data record and is highly recommended.

3.2.2 Specification

Parameter	Actor	Requirement
Stimulus Display Specification (Audio/Video)	Stimulus Presentation Device/Software	Shall provide stimuli of appropriate quality such that display size easily seen/read by the patient, and/or audio that can be easily heard and understood by patient
Response Device Specification	Response Device Or Technologist	Shall be capable of automatically recording behavioral measures (e.g. button presses, finger movements) or technologist shall observe and confirm that patient complies with task instructions.

Synchronization of MRI scan and task	Synchronization Device	Shall be capable of synchronizing MR image acquisition and stimulus task presentation, accurate to within +/- 100 msec or better.

3.3. Periodic QA

3.3.1 Discussion

It is advisable to perform QA scans on a large water phantom or any other appropriate head phantom provided by the vendor to assess factors listed in Table **3.7.2.** below as well as the following (Friedman L et al , 2006, Olsrud J, et al, 2008, ACR QC Manual, 2015):

- Ghost intensity in EPI scans for functional BOLD scans.
- Potential interference from other equipment
- Gradient spiking
- Gradient non-linearity and image distortion

3.3.2 Specification

Parameter	**Actor**	**Requirement**
Scanner Performance	Vendor	Shall ensure scanner meets specifications by performing periodic scanner testing as recommended by the vendor.
Response Device	Technologist	Shall confirm the response device is operational at time of exam (if used).
Stimulus Delivery Device	Technologist	Shall confirm the stimulus delivery hardware is operational at the time of exam.
Signal to Noise Ratio (SNR)	Technologist	Shall confirm that SNR is at least 200:1 (Friedman L et al , 2006; fBIRN Study).
Temporal SNR (tSNR)	Scientist	Shall confirm that tSNR >= 0.71 x average SNR of the phantom using procedure specified in section 4.5. Shall confirm that the instability noise is less than the raw noise (Greve, et al, 2011).

3.4. Subject Selection

3.4.1 Discussion

Task-fMRI signals are evoked by the patient's performance of a sensorimotor task during the fMRI scan. A patient's pathology and associated deficits may affect their ability to perform the task, and can significantly

affect the measured signal specificity, sensitivity and reproducibility. The patient's skills and abilities, as well as associated pathology, should be considered when selecting a task paradigm and establishing performance expectations. For this reason, consistent use of criteria for patient skill assessment and corresponding task selection will help ensure that the resulting fMRI data can meet the claims of this Profile.

3.4.2 Specification

Parameter	Actor	Requirement
Patient abilities prior to scanning	Physician or Scientist	Shall determine that the patient is at least able to minimally perform a functionally appropriate task.

3.5. Subject Handling

3.5.1 Discussion

Task Paradigm Selection - The task paradigm should be simple yet sufficiently challenging to adequately engage the patient in performance of the task. Radiologists and supervising physicians may modify tasks or relax performance criteria when required to accommodate a patient's abilities, but in such cases the fMRI data may not be conformant with the Profile procedure and thus may not achieve the Claims. The task should be functionally specific, which means that the paradigm has been shown to reliably activate those brain areas that are necessary for the performance of the task while minimizing the activation of non-essential brain areas. The task should produce BOLD signals of sufficient amplitude to meet the specifications below. If fMRI data will be acquired and compared over multiple imaging sessions (i.e. pre- and post-surgery), then identical task paradigms shall be used in each session to enhance reproducibility of results. A more complete discussion of paradigm design with a detailed specification of the bilateral hand motor paradigm used to establish the claims of this profile is provided in Appendix D.

Subject Training - The patient should be trained to perform the required behavioral task(s) prior to entering the MRI scanner. Consistent training and assessment avoids performance anxiety and/or poor performance which negatively affect exam results. It is important to provide information to the patient regarding the flow of the exam (e.g. order of the tasks, what can be expected in terms of time for each paradigm administered). If the patient has never been in an MR scanner, the technologist should review what is to be expected in terms of noise, discomfort, etc. After training, the patient should be familiar with the task and comfortable with performance expectations.

Recording/documentation of paradigm type, any modifications, and patient performance is essential for

proper interpretation of the fMRI scan results. Note that assessment and recording of task performance during training can be helpful but should not replace recording of task performance in the scanner during fMRI scan acquisition.

Subject Positioning - Consistent body positioning avoids unnecessary changes in attention, changes in gravity induced shape and fluid distribution, or changes in anatomical shape due to posture, contortion, etc. Appropriate positioning that is comfortable and requires no overt muscle tension to maintain helps minimize patient movement during the scan. Automatic recording in the image header of subject position and table height is recommended for auditing and repeating baseline characteristics, so is a desirable feature of the MRI scanner acquisition software. Significant details of subject body positioning include the position of the arms, the anterior-to-posterior curvature of the spine as determined by pillows under the back or knees, and the lateral straightness of the spine. The hands should be positioned separately and not contacting each other to avoid creation of a conductive loop to minimize the potential for artefactual muscle stimulation by magnetic gradients. When the patient is supine, the use of positioning wedges under the knees and head is recommended so that the lumbar lordosis is straightened and the scapulae are in contact with the table. However, the exact size, shape, etc. of pillows is not expected to significantly impact the Profile Claim. Clinical trial documentation or local clinical practice may specify the preferred patient positioning.

Head motion can significantly degrade or even destroy fMRI data quality. Positioning of the head within any close fitting local gradient or RF coils can be critical to achieve patient comfort, to minimize head movement, and to permit viewing of a visual stimulus display and/or use of headphones/ear buds. Head coils should provide adequate allowance for this. It is important to use restraints such as foam pads to minimize head movement. Head padding should be used to align the head so that its dorsal-ventral axis is parallel to the scanner Z axis with minimal side-to-side twist.

Subject preparation should also include correction of visual acuity to assure clarity of visual stimuli, as well as adjustment of the volume of auditory stimuli. It is expected that clinical trial documentation or local clinical practice will outline the method for determining if stimulus delivery equipment has been positioned properly per manufacturer/vendor guidelines.

The technician should frequently communicate with the patient between scans to assess comfort and attention, and to provide intermittent instruction/encouragement. It is also helpful to provide frequent reminders to the patient to avoid head movements once scanning has begun, stressing that movements between scans are also to be avoided to maintain head alignment across scans.

3.5.2 Specification

Parameter	Actor	Requirements
Task paradigm selection	Physician/Scientist/Technologist	Shall use the paradigm described in Appendix C or similar paradigm that is: ● appropriate for the subject's performance abilities ● functionally specific for the motor areas (e.g. primary motor cortex, premotor cortex, SMA, cerebellum, basal ganglia) and subdivisions (e.g. hand representation) of interest) ● capable of generating fMRI signals meeting the quality specifications indicated below in section 3.7.2
Subject Training	Technologist/Physician/Scientist	Shall train the subject on the task paradigm to be performed during the exam and observe/record performance.
Subject Positioning	Technologist	Shall position the subject supine if possible, with devices such as positioning wedges to immobilize the head as described above.
Peripheral Equipment Adjustment	Technologist	Shall confirm that the patient can see and/or hear stimuli clearly, e.g. not obstructed by peripheral equipment. Shall confirm the patient's ability to manipulate the response device (if present) without causing head movement.
Task	Technologist/ Physician/Scientist	Shall confirm that the patient is capable of performing the task specified in Appendix C.
Task Timing	Technologist/ Physician/Scientist	Acceptable: 180 sec., (9-30 sec. ON, 9-30 sec. OFF) x 5, Ideal: 4 min, (20 sec. ON, 20 sec. OFF) x 6
Scan Duration	Technologist/ Physician/Scientist	Shall match duration of the task plus initial scanner equilibration scans (latter are discarded).
Task Performance	Technologist/ Physician/Scientist	Acceptable: Shall manually observe and evaluate response adequacy/consistency Ideal: Automated hardware recording of response timing, amplitude speed via response device interface. Assess recorded performance data, noting any lapses or non-compliance.

Subject Interview (Post)	Technologist/ Physician/Scientist		
		Acceptable	Shall confirm with the subject that they performed task
		Ideal	Interview patient and record self-assessment of task performance

3.6 Image Data Acquisition

3.6.1 Discussion

Anatomical/Structural Images

MRI scan acquisition typically starts with a shim scan and localizer scan to correct magnetic field inhomogeneity and to prescribe slice positioning respectively. This is typically followed by T1- or T2-weighted anatomical scans to cover the whole brain. The anatomical series can be acquired before, after or in the middle of the functional series.

Functional MR images typically lack sufficient anatomical detail. So, it is essential to acquire a high resolution anatomical scan in the same scan session that functional MRI scans are obtained and, ideally, with no intervening patient motion. Between-scan head movement can potentially degrade registration of functional images with the anatomical data.

Functional Images

An fMRI series typically consists of a series of image volumes acquired at regular temporal intervals, typically 1-3 sec. duration. Each image volume contains a set of image “slices” covering the anatomical area specified by the user (typically whole brain) though this can be a smaller region than is covered by the anatomical images. The total imaging time to acquire an fMRI series (typically several minutes) is dependent on the repetition time (TR) and the total number of measurement periods acquired during the scan. The BOLD T2* images are typically reconstructed on the scanner as individual images or as mosaics. On many systems, the images and fMRI signal time series can be viewed during or shortly after acquisition to verify the presence of good quality fMRI signals.

Behavioral Task - During an fMRI scan, the patient performs a motor task, (e.g. repetitive movement - finger tapping) sustained for 10-30 second epochs alternating with comparable epochs of rest for a minimum of 3 cycles. It is the alternation of movement and rest that causes corresponding changes in neuronal activity within the central motor system that, in turn, drives the local hemodynamic changes that generate the BOLD T2* fMRI signal. (See Appendices C and D for detailed specification of the bilateral hand motor task used to establish the claims of this profile.)

Monitoring Task Performance - Monitoring the patient's performance of the task during scan acquisition is highly recommended. Performance failure/inconsistency can degrade the fMRI data or even render it unusable. This may be particularly true for certain types of fMRI tasks such as motor tasks. It is also recommended to record an assessment of task performance after each scan. Some recommended methods to monitor performance are described below.

Behavior Qualitative Assessment - It is helpful to record a qualitative assessment of both the subject's performance and the overall scan success immediately following each scan. Any departures from optimal can be noted and used to alert the physician of any potential issues which could affect clinical interpretation of the scan results.

Resolution of anatomical data can affect the fMRI data if the latter is eventually resampled to match the anatomical data. To avoid loss of fMRI resolution, an acceptable anatomical resolution should be at least comparable to the fMRI but is typically higher.

B1/B0-field Map: Under ideal conditions it will be beneficial to acquire B1/B0-field map images in the same anatomical plane as the fMRI images. Although acquisition of B0-field maps are not a required part of the protocol they can used in certain cases to correct for geometric distortions in the fMRI raw data.

3.6.2 Specification

3.6.2.1: Representative anatomical image acquisition parameters.

Parameter	Actor	Requirement
Image Type	Technologist	Shall acquire at least one of the following: T1-weighted, T2-weighted, FLAIR
Anatomic Coverage	Technologist	Shall acquire images to provide coverage of whole brain
Field of View	Technologist	Shall acquire whole brain (required), isotropic voxels (recommended)
Resolution	Technologist	Shall acquire anatomic images with resolution that is the same or better than fMRI – (1 mm^3 recommended)
Scan Plane (Image Orientation)	Technologist	Shall acquire in any orientation relative to anatomy (See Resolution above) - optimized for tumor location/orientation and for whole brain coverage

3.6.2.2: Representative fMRI acquisition parameters

Parameter	Actor	Requirement	
BOLD Pulse Sequence	Technologist		
		Acceptable	Shall acquire images using a T2* weighted Echo Planar Gradient Echo Sequence (see appendix D for specific parameter
Anatomic Coverage /Field of View	Technologist		
		Acceptable	Shall acquire images which cover the area of interest (match anatomical orientation)
		Ideal	Whole brain

3.7 Image QA Check

595 3.7.1 Discussion

Following processing of the fMRI data, an overall quality assessment should be performed by an analyst with experience in assessing fMRI image data and identifying data quality problems that could affect the clinical interpretation. The analyst should look for excessive head motion or other signal artifacts and should assess the patient's task performance record for lapses or non-compliance even if the subject claims
600 otherwise.

Neurovascular Uncoupling - The potential for neurovascular uncoupling (NVU) in or near a site of operable pathology should always be evaluated. This is essential for presurgical planning since NVU-related loss of fMRI signals associated with healthy tissue could result in a debilitating post-operative neurological deficit (Pillai J et al, 2011). If a breath-hold or other test for NVU was acquired, the results should be examined
605 and highlights included in the report to the interpreting physician. (Pillai AJNR 2015, Pillai & Zaca 2012) See section 4.3 for assessment procedure.

Patient Motion - Patient head motion is one of the most prevalent sources of variance in the fMRI signal. In the extreme, it can render an fMRI data useless. More moderate levels may prevent profile compliance or limit accuracy and sensitivity. Head motion whose timing is temporally correlated with the fMRI task is
610 particularly disruptive, whereas more randomly timed movements often can be tolerated. Consequently, quantitative measurement of head motion for each fMRI scan is highly recommended. This typically can be computed from the fMRI image data themselves using scanner or 3rd party software. Appendix J provides a more detailed discussion of this topic including compensatory strategies and methods.

Contrast to Noise Ratio (CNR; Task Dependant) - CNR expresses the quality of the task induced fMRI signal

relative to ongoing fMRI noise. A minimum CNR is need to attain a reliable measurement such as center of mass. Various image processing software packages (e.g. AFNI) can be used to perform the CNR calculation on a voxel-by-voxel basis. To assess conformance, an fMRI activation focus of interest (e.g. in the hand representation of the motor cortex) is identified at a user selected activation threshold and the CNR is computed for all suprathreshold voxels in the focus of interest. To be conformant, all such voxels should have a CNR greater than or equal to the minimum specified in Table 3.7.2. This can computed using the assessment procedure described in section 4.2.

3.7.2 Specification

Parameter	Actor	Requirement
Magnetic Field inhomogeneity	Technologist/ Physician/Scientist/Image Analyst	Shall assess field distortion by comparing raw EPI functional images to anatomical images in order to determine if distortions are so severe as to displace foci of activation more than a voxel dimension away from their true anatomical positions.
Neurovascular uncoupling	Physician/Scientist/Image Analyst	Shall evaluate ROI in contralesional primary sensorimotor activation to determine if there is a comparable focus in the opposite hemisphere. See section 4.3 for methodology to formally assess NVU.
Head Motion	Technologist/ Physician/Scientist/Image Analyst	Shall monitor head motion throughout the scan and confirm the maximum momentary head motion calculated as SSDrms is less than 1 mm, and MCMrms is less than 3 mm. See Appendix H for details.
Contrast-to-Noise (Task dependent)	Technologist, Physician/Scientist/Image Analyst	Shall confirm that contrast-to-noise ratio > 1 for all activated voxels within each activation cluster of interest. See section 4.5.2.

3.8 Image Data Processing

3.8.1 Discussion

Post-acquisition image processing is required to convert the raw (K-space) data from the MRI scanner into a

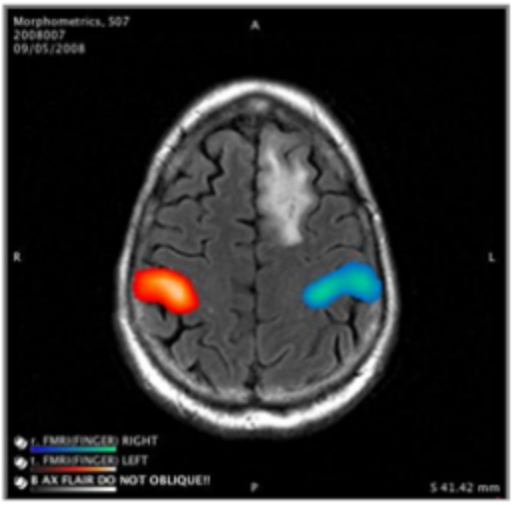
time series of images, to correct for a variety factors such as B-field inhomogeneity and subject motion and to convert the fMRI time-course signals into a brain activation map.

Appendix F outlines the processing steps used in the analysis of the data supporting the claims of this profile. This sequence is representative of many used in the field but does not necessarily represent the most optimal analysis nor is it necessarily preferred by all practitioners. Alternate processing methods are used by many sites and may achieve the profile claims but have not been verified by this committee. FMRI processing/statistical analysis can be performed with software provided by the scanner manufacturer or by third party vendors. A variety of software and algorithms are available for this purpose (Friston K et al, 1995, 2007; Hyde JS 2012, Poldrack R et al, 2011; Smith SM et al, 2004; Jenkinson M et al 2012).

The following discussion highlights key steps in the analysis and provides some discussion of issues that can arise with specific steps. Raw fMRI acquisition data are typically converted to DICOM compliant image-based data using computational software supplied by the scanner vendor. Although some advanced users may use alternate methods that they prefer, this is not common for routine clinical use. Accordingly, the post-processing sequence outlined in Appendix Table F begins at the point that DICOM images are obtained from the MRI scanner.

The fMRI data consist of 3D image volumes acquired repeatedly (every TR period) during an fMRI scan. Thus, the fMRI signal for each brain voxel is represented as a temporal waveform varying in magnitude over time. A valid task-related fMRI response will tend to have a waveform that reflects the timing of the task epochs, typically being high during performance of the task (e.g. finger tapping) and low during intervening rest periods. However, legitimate but weak responses can be obscured by noise and artifacts, so post processing methods are used to reduce such effects by selective filtering or signal conditioning. Each voxel's signal is typically smoothed in 3-dimensional space using a spherical Gaussian kernel to improve SNR. The resulting signals are then de-trended which includes removal of any DC, linear and possibly additional low order trends. Artifacts identified manually or automatically may be removed, and slice timing differences corrected. Head motion during the scan is typically identified, measured and corrected through image co-registration within the BOLD scan as well as registration with T1 or T2 structural images. The registration transform is saved for later Q/A checks and to document any significant patient motion. A variety of statistical methods (GLM, correlation, etc.) can be used to detect valid responses and provide statistical metrics. Finally, the

Figure 2. An illustration of an fMRI BOLD activation map showing motor cortex activation on both the hemispheres in two colors. A site of pathology is visible in the left frontal lobe.



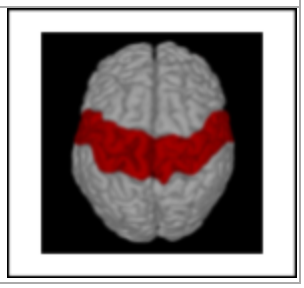
fMRI activation data are used to create pseudocolored functional brain maps (Figure 2). Such maps are usually viewed superimposed on 2-D structural images or as volumetric 3D brain maps for visualization by the end users. Individual maps pertaining to different behavioral tasks are created. These maps can be saved in DICOM, generic formats on the scanner or PACs and archival systems. The fMRI data are then typically accompanied by additional data that aid clinical interpretation (See section 3.10).

Functional Image Processing Software - It is recommended that fMRI image post-processing be accomplished using automated software when possible to promote consistency and to promote rapid availability of results for clinical interpretation. However, it is also recommended that the post-processing be performed by a knowledgeable technologist who can monitor the analysis, detect problems and determine if the computations are executing accurately. In general, it is the technologist's responsibility to detect any computational issues that could adversely affect the results and document those issues so they are available to the physician who will interpret the study results.

Field Inhomogeneity Correction/Compensation - Local magnetic field inhomogeneity affects BOLD t2* echo planar images by introducing localized spatial distortions and signal drop-out in brain regions close to bony structures or air, as often occurs in the medial temporal lobe and inferior frontal lobe (Belaroussi B et al 2006). To some degree it is possible to compensate for these effects by acquiring a B-field map shortly before or after fMRI data acquisition and using it to correct distortions with appropriate software. If a B-field map is unavailable, the raw BOLD images can be manually checked for major geometric distortions and partially corrected using manual manipulations such as image nudging and warping. Any corrections for field inhomogeneity effects should be documented and included in any report to physicians who will perform clinical interpretation. There are special pulse sequences one can use such as z-shim BOLD sequences if one is particularly interested in fMRI signals in regions typically affected by field inhomogeneities (Hoge et al, 2013).

Use of Motion Correction - Correction of head motion can be done by co-registering fMRI image volumes obtained throughout an fMRI scan or using regression or other techniques. See Appendix H for more details. Although motion correction is widely used in practice, under some conditions it can result in spurious false positive activations and its use is still debated (Freire L et al 2001). Although, correction often can improve valid signal detection, it has also been found to occasionally degrade signal detection in some subjects/scans. The ideal strategy for dealing with head motion is to try to eliminate such motion during acquisition. However, when working with patients some head motion may be unavoidable, in which case use of motion correction may make a marginal dataset usable. (Cox RW et al 1999; Friston KJ et al, 1996; Jiang A 1995; Oakes TR et al 2005; Soltysik DA et al 2006, 2011; Mazaika PK 2007).

730 3.8.2 Specification

Parameter	Actor	Specification
Coregistration of Functional & Anatomical Images	Physician/ Scientist/Vendor/Image Analyst	Shall coregister the functional images to the anatomical images of the patient.
Spatial Smoothing	Physician/ Scientist/Vendor/Image Analyst	Shall use a FWHM of twice the acquired voxel size of the functional data (add reference to SPM manual).
Statistical Parametric Map Generation	Physician/ Scientist/Vendor/Image Analyst	Shall compute whole brain statistical parametric using either General Linear Model or Cross Correlation (student t or r correlation coefficient).
BOLD Map Thresholding	Physician/ Scientist/Vendor/Image Analyst	Shall identify a peak of fMRI activation in the vicinity of the motor cortex and set the threshold to 50% of the peak value. See Appendix F.
Region of Interest Identification.	Physician/ Scientist/Vendor/Image Analyst	Shall identify the motor cortex in the vicinity of the central sulcus if identifiable otherwise between the posterior frontal lobe and anterior parietal lobe. 

3.9 Image Analysis: Calculating the weighted center-of-mass biomarker

780 3.9.1 Discussion

The main claim of this profile (Section 2) specifies the precision for the measured 3-dimensional brain location of the weighted center-of-mass of a focus of fMRI activation (wCMA). The formula for computing the wCMA is presented below. Precision claims are provided in Section 2 based on repeatability of the wCMA measurements within- and across-imaging sessions. The latter incorporate the effects of variation
785 in the exact positioning of the patient within the MRI scanner (and relative to the imaging voxel matrix)

and, so, tend to be more variable than the within-session measures.

It is important to note that calculation of the wCMA for an activation focus requires specification of a criterion (threshold) for identifying brain voxels that exhibit statistically significant activation and that are, thus, included or excluded from the fMRI focus of interest. This is an inherently statistical criterion that sets the probabilities of including/excluding false positive and false negative signals given the signal-to-noise of the fMRI data for a particular patient. For guiding surgical resection of a brain tumor, this choice can affect the potential risk of inadvertently resecting viable brain tissue vs the risk of failing to fully resect the tumor. Normalization of the fMRI amplitude metric (e.g. T-statistic) can make the metrics and, consequently, the threshold criterion more consistent across sessions and patients thus helping to minimize variation in the wCMA measurements due to these factors (Voyvodic, 2009,2012). See Appendix F for additional information. Also, note that it is assumed that a single fMRI focus of interest has been identified and the location coordinates of its constituent active voxels obtained. This is typically accomplished by setting a region of interest (ROI) surrounding only the fMRI focus of interest and then reading out the coordinates of voxels within the ROI that meet the threshold criterion. A variety of software packages provide tools to do this.

3.9.2 Specification

Formula for computing the weighted center of mass:

Given N voxels with a criterion level of activation, their location coordinates [x_i y_i z_i] and fMRI amplitude metrics [T_i], then the coordinates of the weighted center-of-mass [X Y Z] are:

$$(1) \qquad X = \frac{[\sum_{i}^{N} x_i * T_i]}{\sum_{i}^{N} T_i} \quad \ldots \qquad \textit{similarly, for Y, Z}$$

Parameter	Definition
wCMA coordinates (XYZ)	Weighted-center-of-mass coordinates, expressed in millimeters, of an fMRI focus in sensorimotor cortex elicited by a task prescribed hand movement.
Voxel coordinates (x_i y_i z_i)	Location coordinates in millimeters of voxels having amplitude metrics greater than or equal to the threshold criterion
fMRI amplitude metric	T-statistic or normalized T-statistic of the task-related fMRI signal component

(T_i)	
Threshold criterion	Minimum acceptable fMRI amplitude metric

3.10 Image Interpretation & Distribution

3.10.1 Discussion

The complete fMRI study package should include all information useful to the physician for performing image interpretation. It should consist of at least the data listed in table 3.10.2.

Typically, study data will be transferred to a workstation and/or PACs system equipped with software for viewing the fMRI image data superimposed on the anatomy (Figure 2) thereby permitting assessment of the proximity of fMRI activation (indicating healthy tissue) to a site of operable pathology and surrounding anatomical features. The images typically will be in standard DICOM Secondary Capture (SC) format either as a full-volume series or as selected slices/montages but may also be provided in a format compatible with any specialized viewing software used at a given site. Often, an experienced analyst may create a technical report summarizing the study and highlighting issues that the interpreting physician may want to consider, especially any factors that may have degraded the quality or accuracy of the images. The study results are then made available to the physicians who will perform the medical interpretation. Finally, the data will be archived and should include storage of all items listed below in case the study is to be re-interpreted at a future date.

3.10.2 Specification

Parameter	**Actor**	**Requirement**
fMRI image time series files	Physician/Technologist	Report shall include DICOM time series
Anatomical image files	Physician/Technologist	Report shall include DICOM anatomical Images
Post-processed fMRI image file(s)	Physician/Technologist	Report shall include the fMRI activation maps as secondary capture, DICOM or other format files compatible with PACS or other 3D visualization software.
Summary of Q/A statistics and any issues	Physician/Technologist/ Scientist	Report shall include secondary capture compatible with PACS or as note attached to the patient record sheet preferably displayable on PACS.
Record of	Physician/Technologist/	Report shall include button press data captured as text or as note

behavioral performance	Scientist	attached to the patient record sheet preferably displayable on PACS.
Description of the fMRI task and its timing	Physician/Technologist/ Scientist	Report shall include a note attached to the patient record sheet preferably displayable on PACS.
Study acquisition & post-processing record sheet(s)	Physician/Technologist	Report shall include documentation of patient name or identifier, time, date, site, study personnel, tests run, data file names and locations, and key parameter settings. Include comments by study staff documenting issues that arose during acquisition.

Additional items that can be helpful to the interpreting physician include: (1) a subject's self-assessment of their alertness during each fMRI scan (e.g. scale of 1-5, obtained by querying the patient after each scan), (2) eye position and blink recording synchronized to the fMRI task timing.

4. Assessment Procedures

To conform to this Profile, participating staff and equipment ("Actors") shall support each activity assigned to them in Table 1. To support an activity, the actor shall conform to the requirements (indicated by 'shall language') listed in the specifications table of the activity subsection 3. Conformance with many of the requirements described in Section 3 can be assessed simply by direct observation. For other more quantitative requirements, appropriate assessment procedures are described in relevant subsections (4.1-4.4) below.

Formal claims of conformance by the organization responsible for an Actor shall be in the form of a published QIBA Conformance Statement. Vendors publishing a QIBA Conformance Statement shall provide a set of "Device-specific Parameters" (as illustrated in Appendix E) describing how their product was configured to achieve conformance. Vendors shall also provide access or describe the characteristics of the test set used for conformance testing.

Actors publishing Conformance Statements shall also provide access to, and fully describe the characteristics of, fMRI data sets and test results used to demonstrate conformance. It is recommended that conformance be established using data from healthy individuals and/or synthetic fMRI data to avoid interpretational complications related to potential effects of pathology.

Digital Reference Objects (DROs, synthetic datasets): QIBA provides synthetic fMRI datasets to assist actors in establishing profile compliance for post-processing and display hardware/software. These datasets are available online at the QIDW website https://www.rsna.org/QIDW/. The datasets have known signal properties (waveforms, spatial distributions) that can be compared with signals extracted using

post-processing hardware/software provided by a performance site or other actor.

4.1 Assessment Procedure: MRI Equipment Specifications and Performance

Conformance with this Profile requires adherence of MRI equipment to U.S. federal regulations (Delfino, 2015) or analogous regulations outside of the U.S., MRI equipment performance standards outlined by the American Association of Physicists in Medicine (Jackson et al, 2010) and/or by the American College of Radiology (1) as well as quality control benchmarks established by the scanner manufacturer for the specific model. These assessment procedures include a technical performance evaluation of the MRI scanner by a qualified medical physicist or MRI scientist at least annually. Evaluated parameters include: magnetic field uniformity, patient-handling equipment, gradient and RF subsystems safety, calibration and performance checks. Periodic MR quality control must monitor image uniformity, contrast, spatial resolution, signal-to-noise and artifacts using specific test objects and procedures (e.g., ACR phantom and QA procedure). In addition, preventive maintenance at appropriate regular intervals must be conducted and documented by a qualified service engineer. A pulse sequence that is suitable for BOLD functional MRI (e.g., echo planar imaging (EPI)) must be available on the scanner.

(1) https://www.acr.org/~/media/ACR%20No%20Index/Documents/QC%20Manual/2015_MR_QCManual_Book.pdf

4.2 Assessment Procedure: Technologist

Radiologic technologists shall fulfill the qualifications required by the ACR MRI Accreditation Program (2) or analogous non-U.S. accreditation programs for non-U.S. facilities. These include certification by the American Registry of Radiologic Technologists (ARRT) or analogous non-U.S. certifying organization, appropriate licensing, documented training and experience in performing MRI, and compliance with certifying and licensing organization continuing education requirements. The technologist shall be capable of setting up, performing, and saving QA and EPI acquisition protocols for their specific system to be consistent with this Profile. The technologist must be trained to conduct fMRI studies on the scanner, and to recognize when patient behavior (compliance, body movement, etc.) may compromise fMRI quality.

(2) http://www.acraccreditation.org/~/media/ACRAccreditation/Documents/MRI/Requirements.pdf?la=en

4.3 Assessment Procedure: Physician

Radiologists shall fulfill the qualifications required by the ACR MRI Accreditation Program (3) or analogous non-U.S. accreditation programs for non-U.S. facilities. These include certification by the American Board of Radiology or analogous non-U.S. certifying organization; appropriate licensing; documented oversight, interpretation, and reporting of the required ABR minimum number of MRI examinations; and compliance

with ABR and licensing board continuing education requirements. Performance of fMRI does not specifically require additional certification of the radiologist, but best practices for clinical fMRI should be understood and followed (4). Specific training opportunities are available through professional societies, e.g. the American Society of Functional Neuroradiology (ASFNR, https://www.asfnr.org/).

(3) http://www.acraccreditation.org/~/media/ACRAccreditation/Documents/MRI/Requirements.pdf?la=en

(4) https://www.acr.org/~/media/83D4D6452E9E4FC1B451D20CFB52D77A.pdf

4.4 Assessment Procedure: Image Analyst

In clinical practice, it is expected that the radiologist interpreting the examination often will be the image analyst. In some clinical practice situations, and in the clinical research setting, the image analyst may be a non-radiologist professional such as a medical physicist, biomedical engineer, MRI scientist or 3D lab technician. While there are currently no specific certification guidelines for image analysts, a non-radiologist performing the analysis shall be trained in technical aspects of fMRI including: understanding key acquisition principles of EPI; procedures to confirm that fMRI-related DICOM metadata content is maintained along the network chain from scanner to PACS and analysis workstation. The analyst must be expert in use of the image analysis software tools and computations, including fMRI activation map generation from EPI time series and recognition of image artifacts. In addition the image analyst should have expertise in neuroanatomy for locating relevant ROI and selecting activation sites. (see figure above in table 3.8.2).

4.5 Assessment Procedure: Image Processing & Analysis Software

The image processing and analysis software produces activation maps in clinically useful forms, as well as summarizing technical information about the study (e.g. patient compliance, image quality). In addition the software should facilitate the performance of specific assessment procedures that establish compliance with the technical claims of this profile (below).

4.5.1 Assessment Procedure: fMRI center-of-mass reproducibility (Claim)

This procedure can be used by an manufacturer or a site to assess the fMRI center-of-mass reproducibility of an acquisition device or post-processing software. The fMRI center-of-mass reproducibility is assessed in terms of the mean variance. The following procedure was employed by QIBA to originally establish the profile claims. Additional details are provided in Appendix G.

1. Obtain 30* within- and across-day test-retest pairs of fMRI datasets using the hand movement task specified in Appendix D. (The data sets used to establish the claims of this profile are available through the Quantitative Imaging Data Warehouse (QIDW) website at: https://www.rsna.org/QIDW/) (* See Appendix G

for rationale.)

2. Post-process the resulting data with appropriate software to yield statistical parametric brain maps displaying the fMRI amplitude or normalized amplitude T-statistic.

3. Select an appropriate statistical threshold for identifying significantly responsive voxels.

4. Identify a region of interest (ROI) containing an fMRI activation focus in or near the primary motor cortex of the precentral gyrus.

5. Obtain the 3-dimensional position coordinates of the active voxels within the fMRI focus for each test-retest pair.

6. Compute the weighted center-of-mass of the active voxels using the formula described above in section 3.9.2. Then compute the variance of the spatial difference in the center of mass for each test-retest pair.

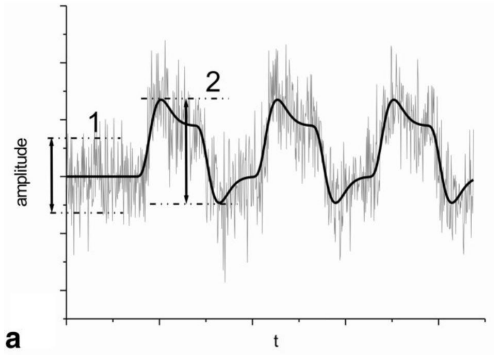
7. Compute the mean variance over all the subjects. Compare the result with the profile claim. A mean variance $\leq$4.0 demonstrates conformance with this requirement.

4.5.2 Assessment Procedure: Contrast-to-Noise Ratio

fMRI response quality is assessed in terms of the Contrast-to-Noise Ratio (CNR) of voxels within the focus of interest. This procedure can be used by a vendor or an imaging site to assess the of an activation focus of interest in an fMRI dataset.

The assessor shall select a single focus within the motor cortex region of interest described in table 3.7.2.

$$CNR = \frac{\Delta S}{\sigma_{t-noise}}$$



The assessor shall then compute (e.g. using software such as AFNI) the CNR of all suprathreshold voxels in the focus of interest using the formula described by Geissler et al (2007) and shown in Figure 4.2-1.

Where ΔS is the peak to peak estimate of the true task-evoked signal (#2 in Fig **a**) and the denominator is the standard deviation over time of the noise (#1 in Fig **a**), which may be estimated from a scan period preceding the initiation of the task (as shown in Fig **a**) or from the fMRI signal after regressing out the task-evoked signal, S.

4.5.3 Assessment Procedure: Head motion

The head motion specification in Table 3.7.2 was computed using AFNI's 3dvolreg routine which employs an "iterated linearized weighted least squares" algorithm to compute the translation and rotation transform that when applied to a new image volume acquired at time t makes it maximally similar to a base image volume (typically acquired at t=0). This is repeated for each successive time point to yield a head motion vector spanning the duration of the fMRI scan. Analogous vectors are computed for each of 3 orthogonal directions of translation and each of 3 orthogonal axes of rotation. The maximum 3-dimensional deviation (computed from the individual vectors) over the duration of the scan should be less than or equal to the maximum head motion (translation or rotation) specified in Table 3.7.2. Note that the maximum rotation specification in Table 3.7.2 is only a rough estimate since the effect of rotation on a specific focus of interest will vary depending on the distance of the focus from the axes of rotation.

4.5.4 Assessment Procedure: Neurovascular Uncoupling

To achieve the profile claims, evaluate via ROI comprising contralesional primary sensorimotor activation to determine using a 50% AMPLE threshold the primary cluster of activation (using a task that generates bilateral symmetric activation: caveats: 1. Patient adequately performs the task, 2. No other artifacts, 3. absence of other confounding factors). The maximal T-value voxel in this cluster defines the threshold used for assessing ipsilesional activation. If at 50% of this maximal T-value, no activation is seen ipsilesionally, this constitutes moderate to severe (i.e., clinically relevant) NVU. In this case, the Profile claims do not hold. (Based on empirical data from Dr. Pillai).

Additional approaches may be used for indirect assessment of NVU such as cerebrovascular reactivity mapping (CVR) using a breath hold (BH) task. In this case ipsilesional prominent decreases or frank absence of CVR in cortex directly affected by or immediately adjacent to lesions, relative to contralateral homologous regions, may be considered a qualitative surrogate marker of NVU, but the above-described more quantitative approach is preferable.

4.5.5 Assessment Procedure: TSNR (Specification Table 3.3.2)

To achieve the profile requirement regarding the tSNR values shown in Table 3.2.2 the following formula can be used. tSNR is a measure of the signal to noise over the course of the entire fMRI time series. For a time series x_i. (Murphy K et al, 2007)

$$TSNR = \frac{\mu}{\sigma} = \frac{\mu}{\sqrt{\frac{1}{N}\sum_{i=1}^{N}(x_i - \mu)^2}}$$

where N is the number of time points, μ is the mean of the time series and σ is its standard deviation.

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6. Appendices

Appendix A: Acknowledgements and Attributions

This imaging protocol is proffered by the Radiological Society of North America (RSNA) Quantitative Imaging Biomarker Alliance (QIBA) Functional MRI (fMRI) Technical Committee. The fMRI technical committee is composed of scientists representing the imaging device manufacturers, image analysis software developers, image analysis laboratories, biopharmaceutical industry, academia, government research organizations, professional societies, and regulatory agencies, among others. All work is classified as pre-competitive. A more detailed description of the fMRI group and its work can be found at the following web link: http://qibawiki.rsna.org/index.php?title=FMRI_tech_ctte

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The fMRI Technical Committee is deeply grateful for the support and technical assistance provided by the staff of the Radiological Society of North America.

Appendix B: Conventions and Definitions

Acquisition vs. Analysis vs. Interpretation: This document organizes acquisition, reconstruction, post-processing, analysis and interpretation as steps in a pipeline that transforms data to information to knowledge. Acquisition, reconstruction and post-processing are considered to address the collection and structuring of new data from the subject. Analysis is primarily considered to be computational steps that transform the data into information, extracting important values. Interpretation is primarily considered to be judgment that transforms the information into knowledge. (The transformation of knowledge into wisdom is beyond the scope of this document.)

Bulls-eye Compliance Levels Acquisition parameter values and some other requirements in this protocol are specified using a “bulls-eye” approach. Three rings are considered from widest to narrowest with the following semantics:

ACCEPTABLE: failing to meet this specification will result in data that is likely unacceptable for the intended use of this protocol.
TARGET: meeting this specification is considered to be achievable with reasonable effort and equipment and is expected to provide better results than meeting the ACCEPTABLE specification.
IDEAL: meeting this specification may require unusual effort or equipment, but is expected to provide better results than meeting the TARGET.

An ACCEPTABLE value will always be provided for each parameter. When there is no reason to expect better results (e.g. in terms of higher image quality, greater consistency, lower dose, etc.), TARGET and IDEAL values are not provided.

Some protocols may need sites that perform at higher compliance levels do so consistently, so sites may be requested to declare their “level of compliance”. If a site declares they will operate at the TARGET level, they must achieve the TARGET specification whenever it is provided and the ACCEPTABLE specification when a TARGET specification is not provided. Similarly, if they declare IDEAL, they must achieve the IDEAL specification whenever it is provided, the TARGET specification where no IDEAL level is specified, and the ACCEPTABLE level for the rest.

Appendix C: Paradigm Specification – Hand Motor Task

The ability of an fMRI paradigm to generate BOLD signal changes is strongly dependent on the selection and design of the behavioral task to be performed by the patient during an fMRI scan. The task should be functionally specific and sufficiently challenging to ensure robust fMRI activation but must not be too challenging to prevent adequate performance or to cause generation of correlated head movement. The table below describes the movement sequence of a bilateral hand motion task suitable for mapping brain regions related to hand movement. However, it is important to bear in mind that seemingly minor variation in task design or performance may alter the fMRI results. For example, changing the task from finger-to-thumb opposition to simultaneous finger flexion can potentially alter the center of mass of the activation maps. Typically, the range of values that are acceptable in clinical practice will be broader than those used to establish the claims.

Behavioral Task Paradigm Description

Paradigm	Parameter Settings to Achieve Compliance Levels	
Hand Movement (ASFNR procedure)	Epoch0 task (to be discarded)	No movement
	Epoch0 duration	6-8 sec
	Epoch1 task	Self-paced, fist clenching, left hand
	Epoch1 duration	9-15 sec (used in claim), 20 sec (recommended).
	Epoch2 task	Self-paced, fist clenching, right hand
	Epoch2 duration	9-20 sec
	Epoch3 task	No movement
	Epoch3 duration	9-20 sec
	Number of repetitions	4 (Epochs 1,2,3 in order in each rep)

Appendix D: Device-specific Parameters to Achieve Claim Conformance

Variation in MR scanner settings can affect reproducibility of the fMRI results. Increasing or decreasing in-plane and slice resolution, choice of receiver bandwidth, the type of RF coil used, and the optimal echo time can all have an impact on the signal and noise characteristic of the BOLD signal. To obtain consistent results, it is desirable to use a fixed array of parameter settings with minimal variation as necessary to accommodate different subjects (e.g. field of view, number of slices, slice positioning.)

NOTE: Scanner make and model: This profile is based on test-retest reproducibility studies performed on clinically-rated MRI scanners. Both Siemens and GE MRI scanners were involved, and data were compared at 1.5T and at 3.0T. All data are based on use of 8-channel receive-only head coils. The inclusion of specific product models/versions in the following data shall not be taken to imply that those products are necessarily fully compliant with this QIBA Profile. Similarly, omission of other hardware or software models does not imply that such products would not be compliant. Use of devices and settings outside the range shown are unverified as of this writing. (Conformance statement to be provided by the scanner manufactures as well as the post-processing software manufacturers).

MR Acquisition Parameters:

Description	Parameter Settings used in QIBA reproducibility study to achieve claim	
Imaging Parameters	Field strength	1.5T and 3.0T

Scan type	BOLD T2* weighted gradient echo, echo-planar
Field of view (FOV)	240 mm
Slice thickness	3 - 5 mm
Number of slices	20 – 36
Repetition time (TR)	1.5 - 3 sec
Echo time (TE)	30-35ms at 3T; 40-50ms at 1.5T
Repetitions (# TR periods)	90-256
Flip angle	90
NEX	1
Parallel Imaging Factor	not used

Appendix E: fMRI Processing

The entries in the following table reflect processing steps used in a QIBA sponsored study used to establish the current profile claims. Some steps were either used or not used in separate analyses to help assess the step's influence on the claim reproducibility.

Processing Step	Setting to Achieve Claim Compliance	
Data Consolidation	Used	Combine DICOM images into 4D volumetric dataset (e.g. AFNI BRIK or NIFTI format)
Co-register fMRI and structural images	Used	AFNI or fScan (see Voyvodic et al., 2009)
Remove initial transient	Used	Remove first 3-12 seconds
Motion Correction	Used	Align all images in time series to a reference time point
Spatial Smoothing	Used	4-6 mm.
Zero mean, detrend	Used	Linear or low-frequency trend removal
Normalization (e.g. AMPLE)	Not Used	(Study compared with and without normalization)
	Used	Divide voxels by smoothed peak fMRI amplitude in active area
Detect and measure task-related fMRI signals	Used	t-test or general linear model (GLM)

Threshold	Used	tested with t-stat cutoff = 3, 4, 6, 8 and 10; AMPLE threshold cutoff = 40% 60% and 80%

Appendix F: Selecting a threshold criterion for identifying active voxels

The fMRI contrast-to-noise ratio (CNR) of voxels comprising an fMRI focus of activation is typically a maximum near the weighted center-of-mass (wCM) and then falls off at greater distances. Consequently, voxels near the periphery of the focus may have signals that are only fractionally larger than the fMRI noise. To compute the wCM thus requires selection of a statistical threshold criterion to allow identification of the voxels that are considered "active" and, thus, part of the activation focus. If the spatial distribution of CNR values surrounding the wCM was perfectly symmetric, a wide range of thresholds could be used with little effect on the computed wCM. However, this is rarely the case in practice, so selection of a consistent threshold criterion is desirable to help reduce threshold-dependent variation in the measured wCM. Unfortunately, use of a fixed conventional T-statistic based on the amplitude of the fMRI task-driven response can still yield unacceptably high variation in the extent, shape and wCM of an fMRI focus especially across MRI scan sessions and across patients. One method to reduce this variability is to normalize the fMRI response amplitude using an algorithm such as AMPLE (Voyvodic JT, 2009). This helps make fMRI foci more consistent in size, shape and wCM compared to using a fixed threshold criterion. A universally validated threshold criterion that maximizes the accuracy of fMRI as a biomarker of the location of the function–specific neurons has yet to be fully established but see Voyvodic et al, 2009 for relevant data.

Appendix G: Estimating the weighted center-of-mass and its precision (variability)

The formula for computing the location coordinates for the weighted center of mass of an fMRI focus is presented above in section 3.9.2. The following formulas were used to estimate its precision/variability of the wCM based on M repeated measures obtained either within- or across imaging sessions. The input data consist of the individual mean center-of-mass coordinates, X_j Y_j Z_j for each measurement repetition (obtained from each of M fMRI imaging scans).

Within session variability – having M within-session repeated measurements [X_i Y_i Z_i]

(2) $\overline{wCM} = [\overline{X}\ \overline{Y}\ \overline{Z}]$ *grand mean coordinates within session*

(3) $[\Delta X_j\ \Delta Y_j\ \Delta Z_j] = [X_j\ Y_j\ Z_j] - [\overline{X}\ \overline{Y}\ \overline{Z}]$ *difference from within session mean*

(4) $\Delta D_j = \sqrt{\Delta X_j^{\,2} + \Delta Y_j^{\,2} + \Delta Z_j^{\,2}}$ *distance from within session mean*

(5) $wSD^2 = \sum_j^M \Delta D_j^{\,2} \,/\, (M\text{-}1)$ *within-session variance*

Across sessions variability - Same as above except M is replaced by L = # sessions

(There is an across session measure for each within session repetition and for each subject)

Sample Size - In the assessment of actors' within-session standard deviation (wSD) (to be sure that their wSD is < or = to 2.55, which is what the claim is based on), actors must do a test-retest study with 30 subjects. Then they must calculate their wSD. If their wSD is 2.0 or smaller, then they have passed this requirement. The 2.0 is the maximum allowable wSD that an actor can have (with a sample of N=30) to be 95% confident that their wSD is good enough to meet the claim.

Appendix H: Head motion as a source of fMRI variance

Head motion during an fMRI scan can be one of the most important sources of signal variability and consequent inaccuracy in quantitative measures derived from the fMRI data (Friston, K.J., et al., 1996, Wu, D.H., et al 1997, Oakes, T.R., et al., 2005, Johnstone, T., et al., 2006, Hutton, C., et al., 2011). In the specific context of this profile, head motion can contribute to variation in the center-of-mass of an fMRI focus and, in the extreme, can invalidate the profile claims regarding the center-of-mass. Consequently, real-time or post-acquisition assessment of a subject's head motion during an fMRI scan is highly recommended. To some degree, post-acquisition computational algorithms can help minimize the deleterious effects of head motion. But, depending on the amplitude and characteristics of the head motion, complete compensation/correction may not be possible. Consequently, the only certain remedy may be to re-acquire the fMRI data after taking steps to further stabilize the head.

Head motion characteristics and effects: Head motion characteristics can vary significantly over time within an MRI scan session, across sessions, and across subjects. Motion can manifest as slow drifts or rotations, cyclic movements related to respiration or task performance, or short jerks perhaps as the subject awakens after dozing. Some subjects, especially children, can have difficulty remaining completely immobile for long periods of time and patients experiencing physical pain may also move as they become uncomfortable.

Head motion can affect the BOLD fMRI signals in a variety of ways. As the head moves relative to the fixed voxel matrix the contents of a voxel can change, especially if the voxel is positioned near a tissue boundary such as the edge of the brain or a ventricle. Moreover, depending on the fMRI pulse sequence (e.g., echo planar) different brain "slices" are acquired at slightly different times so that brain movement effects can reflect an interaction of both time and space. One might suppose that the signal from an active fMRI brain site could be reconstructed if one knows the spatio-temporal pattern of movements and then reconstructs the signal by concatenating the moment-by-moment signals from the imaging voxels that the brain site successively occupied over time. However, due to partial volume effects, nonlinear warping, susceptibility artifacts (Wu, D.H., et al 1997) and the "history" of spins occupying a voxel (Friston, K.J., et al., 1996) such reconstructions may only be partially successful (Oakes, T.R., et al.,2005, Siegel, J.S., et al., 2014).

Task-correlated head movements that are synchronized with the performance of a behavioral task during an fMRI scan can be particularly problematic because the movement effects can mimic the timing of the legitimate task-evoked fMRI signals. Thus, some motion-induced effects can be nearly indistinguishable from true task-evoked signals. For example, repeated toe "curling" alternated with "rest" is a common task used to activate the foot representation of motor cortex. But, if the movements are too vigorous, movement can be transmitted along the body to the head and cause motion artifacts. Visual inspection of both the fMRI time course data and the image sequence can often reveal such effects. After post-processing, task-correlated head motion may appear as an apparent "fMRI halo" along the edge of the brain. At other locations, such "false positive" fMRI responses may be more difficult to detect and can intermix with voxels containing legitimate task-evoked responses thereby altering the size and/or apparent center-of-mass of the activation site. Head motions that are un-correlated with the fMRI task can degrade the sensitivity for detecting legitimate fMRI responses while task-correlated movements can create spurious "false positives" that may increase or displace a legitimate focus of activation.

Acceptable head motion limits: It is virtually impossible for a subject to be completely motionless, since respiration and even cardiac motion can affect an fMRI scan. Consequently, we have attempted to provide some guidelines for acceptable levels of head motion in Table 3.7.2. Unacceptable degradation of fMRI signals may still occur despite meeting these criteria. It must be stressed that these criteria are not hard limits and that the severity of the effects can depend critically on the relative locations of spurious and legitimate fMRI signals and the response metric of interest (e.g. amplitude vs size vs center-of-mass). The criteria in Table 3.7.2 reflect estimates from simulations (described briefly below) conducted by members of the QIBA fMRI subcommittee as well as the substantial working experience of fMRI practitioners on the committee.

Minimizing head motion: A successful fMRI study typically includes strategies to minimize the effects of head motion. Here we provide some recommendations based on our collective experience with the caveat that most of these procedures are either common sense or have been developed through experience. First, it can be beneficial to discuss the head motion problem with the subject prior to entry into the scanner to streamline the setup procedure and allow for questions. Some sites employ a "mock" scanner to allow the subject to become familiar with lying supine in the scanner bore, arranging padding and supports for maximum comfort, and to practice keeping the head motionless while performing any requisite behavioral tasks. Screening for susceptibility to claustrophobia or other emotional reactions can be helpful at this point since a negative emotional reaction to the MRI scanner can contribute to increased head motion during the scan. Coughing, sneezing or nasal congestion/dripping and bodily elimination should also be addressed. Placing the subject in the scanner and arranging padding/supports requires practice to enable the subject to achieve a comfortable, immobile position that will not slowly "drift" as the subject relaxes into the padding. It is particularly helpful to ask the subject to "fully relax, letting go of all muscle tension in

any part of the body". Stress that the patient should not try to hold their head rigidly in place but, rather, should let all their muscles "go limp". Padding under the knees and on either side of the head should be added. It is also important to place a pad (e.g. rolled up towel) under the neck and foam under the top/back of the head to minimize head "nodding" motions, one of the most common artifacts. Potential pressure points, especially at the back of the head should be well padded. Typically, the feet should be resting freely without the bottoms of the feet pushing on a solid support since inadvertent movement of the feet against a solid surface is readily transmitted to the head. The subject should be given behavioral response buttons and then asked to find a comfortable position for the hands that can be maintained throughout the scan. If multiple scans are to be obtained during the scan session and careful alignment is important, the subject can be asked to remain motionless even when the scanner is not operating. Depending on the hardware and software installed at an MRI site, it may be possible to monitor head motion signals during acquisition and thereby provide feedback to the subject when unacceptable movements occur. Sometimes if subjects are made aware that the scanner operator can monitor head motion, it acts as a deterrent to "careless" movements.

Correcting for head motion: Despite the best efforts to minimize head motion during scan acquisition, such motions can still invade the resulting data. A variety of techniques and algorithms are available to try to reduce the deleterious effects of head motion (Friston, K.J., et al., 1996, Oakes, T.R., et al.,2005, Siegel, 2014, Bullmore, E.T., et al., 1999, Glover, G.H., 2000, Birn, R.M., 2004, Diedrichsen, J. Neuroimage, 2005, Birn, R.M., et al., 2006, Lemieux, L., et al., 2007, Huang, J., et al 2008. Churchill, N.W., et al., 2012) but none are entirely effective in all cases. A variety of software packages provide motion correction algorithms that are roughly equivalent as far as improving fMRI analysis results (Oakes, T.R., et al.,2005, Morgan, V.L., et al.,2007). Manual visual inspection of the fMRI signals is recommended, ideally, during acquisition, but at least as a first stage in post-processing. Momentary (spike-like) motions can be identified and manually "censored" (removed/replaced) if relatively infrequent. Slow "drift" changes in head motion can be reduced by computationally removing the mean and low order trends (typically 1-3rd order) in the time course data. If an independent estimate of the head position and rotation in all 3 dimensions is available (provided by many software packages such as AFNI, AIR, Brain Voyager, FSL, SPM2 (Oakes, T.R., et al.,2005,)), the resulting signals can be removed from the recordings using regression techniques (Friston, K.J., et al., 1996, Morgan, V.L., et al.,2007). However, if the head motion is temporally correlated with the fMRI task, "regressing out" the presumed head motion may also regress out the true fMRI signal. Alternately, if the motion is not task-correlated, some methods for detecting fMRI responses, such as temporal correlation with the task timing waveform, can be relatively immune to random head motion.

Simulation of head motion effects: Quantitative empirical assessment of the effects of head motion on the ability to detect valid fMRI activation is problematic since the true pattern of activation is not known independently. Use of simulations can be instructive in this respect since the pattern of fMRI activation and

noise properties can be controlled and specified precisely. But, the degree to which a simulation accurately mimics all empirical signal and noise properties obtained with real subjects is an important interpretational concern. The QIBA fMRI committee is conducting several simulation studies of head motion effects. Full accounts of these studies will appear in published scientific papers but some initial insights are described here.

1. Task-correlated motion can significantly degrade the ability to recover a true focus of activation, potentially even invalidating the profile claims (Field, A., et al, 2000).

2. Head motion effects can differ significantly for different axes of motion/rotation.

3. Head motion effects are not uniform throughout the brain and can be particularly prominent at abrupt tissue boundaries (eg., edge of brain or ventricles).

4. The effects of head motion on a brain region of interest will likely reflect an interaction of the site's size, shape, orientation, and location relative to the preceding factors (#2,3). State which types of motion have the greatest effects and any other concise additions that provide a bit more detail.

Improving head motion assessment: Traditional assessment of head motion in fMRI has relied upon measuring the scan-to-scan translations and rotations resulting from motion correction algorithms (Cox & Jesmanowicz, 1999). The maximum cumulative translation and rotation across a time series of motion parameters can then be calculated. Commonly applied thresholds for motion have included setting limits to the maximum cumulative translation of 1 or 2 mm and limits to the maximum cumulative rotation of 1 or 2 degrees. These limits have never been justified by experiment, however. Furthermore, these limits are problematic due to the complicated nature of rotation on voxels of interest. Mathematically, the translation caused by a rotation can be estimated by using the angle of rotation, θ, and the distance from the axis of rotation to the region of interest, *d*:

$$x \approx d \cdot \tan(\theta).$$

For rotations where the axis of rotation is in proximity to the region of interest, the translation due to rotation will be small. Conversely, for rotations where the axis of rotation is far from the region of interest, the translation due to rotation of an identical angle will be large. Therefore, it is unwise to set limits of motion that are equal across different types of rotation (i.e., pitch, yaw, and roll). Both pitch and yaw are rotations with axes of rotation in the neck region, far from the primary motor cortex, while roll is defined as rotation about the inferior-superior axis, which is close to the motor cortex. For this reason, rotations in pitch and yaw will yield worse translations in the motor cortex than matching rotations caused by roll.

To compute distances from the axes of rotation to the region of interest, you need to acquire the coordinates for each axis of rotation and the center of the region of interest (e.g., the primary motor cortex). Taking pitch, for example, you need to acquire the *y* and *z* coordinates for the axis of rotation (y_i, z_i)

and the center of the primary motor cortex (y_j, z_j). The *x* coordinate can be ignored because pitch rotates the brain about the x-axis. The distance between these two points can then calculated as:

$$d_{pitch} = \sqrt{(y_i - y_j)^2 + (z_i - z_j)^2}.$$

The distance for roll can be calculated using x and y, while the distance for yaw can be calculated using x and z. See Table 1 for example calculations of rotational displacements using the Talairach atlas brain. Clearly, a 1° pitch or yaw will have a much worse effect than a 1° roll.

Table 1. Examples of rotations and calculated rotational displacements

	Rotation	Estimated distance from axis of rotation to center of M1	Rotational Displacement
Pitch	1°	114 mm	2.0 mm
Yaw	1°	118 mm	2.1 mm
Roll	1°	32 mm	0.6 mm

With this information in mind, new head motion metrics have been developed to account for both translation and rotational displacement (Soltysik, 2017). The first head motion metric is called the sample standard deviation of motion root mean square:

$$SSDM_{RMS} = \sqrt{SSDM_x^2 + SSDM_y^2 + SSDM_z^2 + SSDM_{roll}^2 + SSDM_{pitch}^2 + SSDM_{yaw}^2},$$

which is the root mean square of six sample standard deviations of motion:

$$SSDM_x = \sqrt{\frac{\sum_{i=2}^{N}(x_i - x_{i-1})^2}{N-1}},$$
$$SSDM_y = \sqrt{\frac{\sum_{i=2}^{N}(y_i - y_{i-1})^2}{N-1}},$$
$$SSDM_z = \sqrt{\frac{\sum_{i=2}^{N}(z_i - z_{i-1})^2}{N-1}},$$
$$SSDM_{pitch} = \sqrt{\frac{\sum_{i=2}^{N} d_{pitch}^2\left(tan(\alpha_i) - tan(\alpha_{i-1})\right)^2}{N-1}},$$
$$SSDM_{yaw} = \sqrt{\frac{\sum_{i=2}^{N} d_{yaw}^2\left(tan(\beta_i) - tan(\beta_{i-1})\right)^2}{N-1}},$$
$$SSDM_{roll} = \sqrt{\frac{\sum_{i=2}^{N} d_{roll}^2\left(tan(\gamma_i) - tan(\gamma_{i-1})\right)^2}{N-1}}.$$

Each term is computed using the *N* values in the motion parameter time series. Note that the SSDM equations for the rotations use the distance (d) from the axis of rotation to the region of interest to compute the rotational displacement. The SSDMrms head motion metric can be thought of as the standard deviation of all the volume-to-volume head motion displacements added in quadrature across the six degrees of motion.

The second head motion metric is the maximum cumulative motion root mean square:

$$MCM_{RMS} = \sqrt{MCM_x^2 + MCM_y^2 + MCM_z^2 + MCM_{pitch}^2 + MCM_{yaw}^2 + MCM_{roll}^2},$$

which is the root mean square of six maximum cumulative motions:

$$MCM_x = x_{max} - x_{min},$$
$$MCM_y = y_{max} - y_{min},$$
$$MCM_z = z_{max} - z_{min},$$
$$MCM_{pitch} = d_{pitch}\left(tan(\alpha_{max}) - tan(\alpha_{min})\right),$$
$$MCM_{yaw} = d_{yaw}\left(tan(\beta_{max}) - tan(\beta_{min})\right),$$
$$MCM_{roll} = d_{roll}\left(tan(\gamma_{max}) - tan(\gamma_{min})\right).$$

Here also, the MCM equations for the rotations use the distance from the axis of rotation to the region of interest to compute the rotational displacement. The MCMrms head motion metric can be thought of as the maximum extent of displacement added in quadrature across the six degrees of motion.

DRO study to assess head motion metrics

A simulation study using digital reference objects (DROs) was performed to assess the relationship between SSDMrms, MCMrms, and the deviation from the true center of mass of activation (Soltysik, 2017). Random head motions were applied that yielded translations in the motor cortex that ranged from 0 to 0.5 mm for in-slice motion (x, y, and roll displacement) and 0 to 4 mm for out-of-slice motion (z, pitch displacement, and yaw displacement), the worst case scenario. DROs had a spatial resolution of 4×4×4 mm^3 and a TR of 2 s. Results showed that the deviation from the true center of mass quickly rose to a plateau for small values of both SSDMrms and MCMrms (Fig. 1). For values of SSDMrms < 1.4 mm and values of MCMrms < 3.5 mm, the deviation from the true center of mass was less than or equal to 8 mm for 95% of the cases. It should be noted that a very small number of cases (not shown) resulted in deviations above the dashed line in Fig. 1.

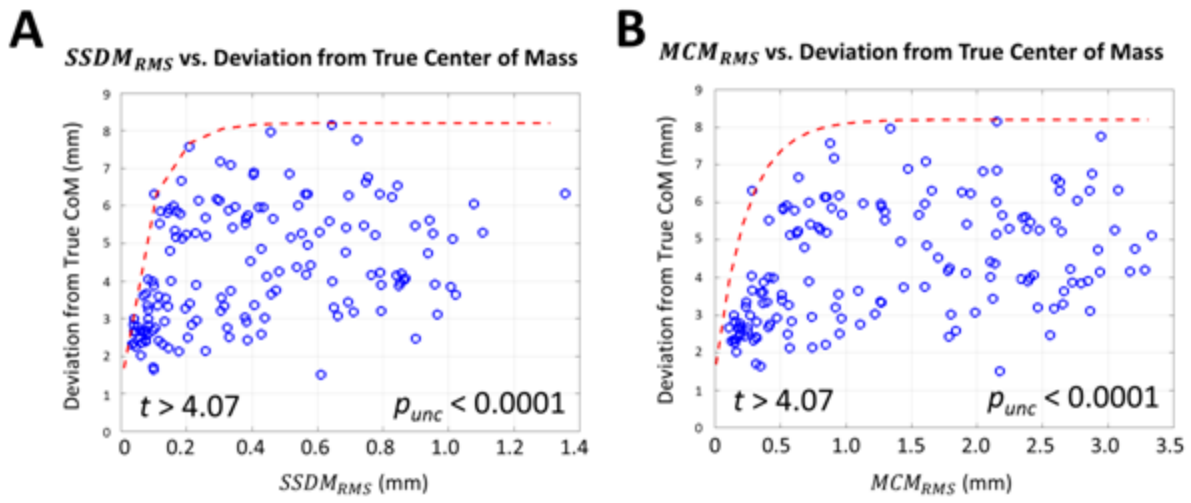

Figure 1. Deviation from the true center of mass plotted against two different head motion metrics. A) . B) . The dashed line was fit to show the maximum potential deviation for 95% of the cases.

The results of this simulation study showed that, unlike activation volume, the center of mass of the motor cortex activation was very stable for head motions up to those that exceed those typically observed in fMRI studies. In addition, according to Fig. 1, the only way to reduce the potential deviation from the true center of mass would be to completely restrict head motion. This goal is not realistic, however, even when using a bite bar (Diedrichsen, 2005). Therefore, as long as the SSDMrms is below 1.4 mm and the MCMrms is below 3.5 mm, the DRO study showed that the deviation from the true center of mass will be equal to or

less than a constant value of 8 mm. This value is slightly higher than the current profile's claim of a deviation of less than 5 mm resulting from our experimental studies. This discrepancy can be explained by the possibility that the DRO study may have slightly exaggerated the true effects of head motion. Mathematically, however, the DRO study revealed that the maximum potential deviation is roughly the same for a wide range of head motion where SSDMrms could be as high as 1.4 mm and the MCMrms could be as high as 3.5 mm. Therefore, there is no need to restrict the maximum motion to the overly conservative limits of 1 or 2 mm, as previous studies have done.

Based upon the results of the DRO study and including a conservative tolerance, we make the following QA recommendation for head motion metrics: To be assured that the QIBA fMRI profile claim can be made, the SSDMrms should be less than 1.0 mm and the MCMrms should be below 3.0 mm.

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