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Contents

1 INTRODUCTION 4

2 fMRI WORKFLOW 4

3 fMRI WORKFLOW STEPS 6

3.1 ORDERING 6
3.2 PATIENT ASSESSMENT AND TRAINING 6
3.3 DATA ACQUISITION 7
3.4 POST-ACQUISITION DATA PROCESSING 7
3.5 REPORTING 7

4 fMRI DATA 8

4.1 DATA KNOWN AT THE TIME OF AN fMRI ORDER 8
4.1.1 Statistical Model 8
4.1.2 Stimulus Presentation Model 9
4.1.3 Acquisition Parameters 9
4.1.4 Processing Parameters 9
4.1.5 An Example of GLM-based Statistical and Stimulus Presentation Model 9
4.2 DATA KNOWN PRIOR TO CONDUCTING THE IMAGE ACQUISITION 10
4.2.1 Statistical Model 10
4.2.2 Stimulus Presentation Model 11
4.2.3 Acquisition Parameters 11
4.3 DATA PRODUCED DURING THE IMAGING EXAMINATION 11
4.3.1 Image Data 11
4.3.2 Patient Responses 11
4.3.3 Statistical Model 11
4.3.4 Performance Logs 11
4.4 DATA PRODUCED DURING POST-ACQUISITION DATA PROCESSING 12
4.4.1 Modified structural data 12
4.4.2 Statistical Maps 12
4.4.3 Records or Reports 12

5 CONCLUSIONS 12

1 INTRODUCTION

Functional MR Imaging (fMRI) is performed to determine which part of the brain is handling critical functions such as thought, speech, movement, and sensation. This is referred to as brain mapping[1]. Following establishment of CPT codes in 2007, fMRI-based brain mapping is finding increased use in the management of patients undergoing tumor resection surgery, surgery for patients with intractable epilepsy, and surgery to repair brain arteriovenuous malformations.

DICOM WG 16 has recently decided to undertake an investigation of using DICOM 'tools' (data representations, services, etc) to address the data management needs of clinical fMRI examinations. One notable problem that exists is the lack of clinical knowledge and insight on the part of the members of DICOM WG-16. At a recent meeting, WG-16 expressed their need for input from the community of 'experts'.

The purpose of this paper is to forward the views of one such group of 'experts'.

In this paper we described a clinical workflow for conducting fMRI examinations that we think is emerging in the imaging department. This document also contains a description of the data consumed and produced in the process of execution of a clinical workflow. Scope is limited to departmental activities of the associated workflow; activities start by placing an order for an examination, and end with the dissemination of the study results. Patient management activities that precede the placement of the examination order (such as patient physical and neurological evaluation, other imaging studies, etc.) are considered outside the scope and not described. Similarly, those activities which occur following the analysis and distribution of results (treatment planning, etc) are outside the scope of this workflow and not described.

It is our opinion that investigations of WG-16 should proceed in the following manner: initial activities should focus on creating one or more candidate models for the workflow and data to be managed during the performance of an fMRI examination. The resulting 'candidate' workflow and data can then be represented (in part or in total) using DICOM's current toolset. If the candidate model cannot be represented in total, then an analysis of the 'gap' or difference between the representation using DICOM's current toolset and a desired, or 'ideal', representation should be established. Once the gap is understood for each of the candidate models, the gaps can be evaluated to aide in the decision about how WG-16 should proceed. With this information, the choice of a candidate workflow model and DICOM representation can be chosen and work can begin to fill the gaps.

2 FMRI WORKFLOW

The majority of fMRI has been conducted in the research setting. Research workflows can be highly variable and focused upon results which differ from the clinical use of the same or similar technology. As pointed out by Nakai et al[2]:

> 'Although scientific and clinical neuroimaging will share the majority of resources, the annotation of concepts and instances will be slightly different, which can be explained by the contrast of "research flow" and "clinical flow" (see figure).'

[1] RadiologyInfo Functional MR Imaging (fMRI) – Brain (see http://www.radiologyinfo.org/en/info.cfm?PG=fmribrain)
[2] Nakai T, Bagarinao E, Tanaka Y, Matsuo K, and Racoceanu D. Ontology for fMRI as a Biomedical Informatics Method. Magn Reson Med Sci, 7:3, 141-155, 2008.

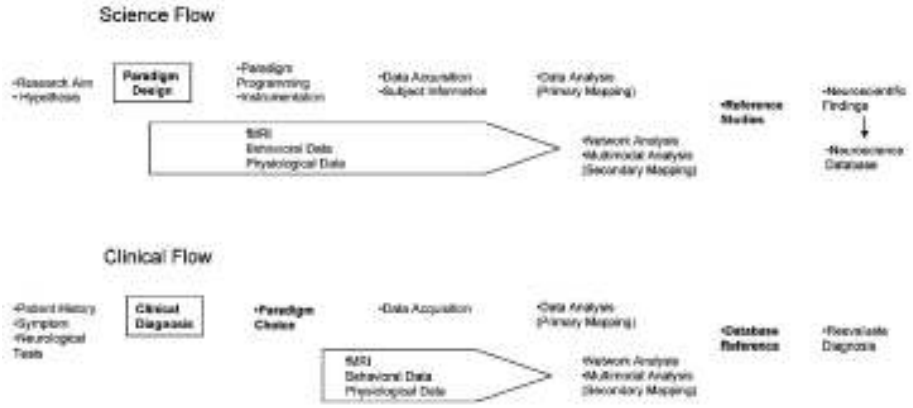

Figure 1. (Copied from Nakai et al.) Comparison of "clinical" and "scientific" neuroimaging.

The large body of literature exists about research workflows[3], and a body of literature describing efforts to transform research-oriented tools and services into clinically useful equivalents[4][5] is developing.

With the emergence of fMRI as a viable tool in the clinical management of patients with neurological disorders, a clinically oriented fMRI workflow is being established. There appears to be a lack of literature describing this workflow. In this paper we attempt to fill that gap by describing our understanding of this emerging clinical fMRI workflow.

For the purposes of this paper we suggest that the relevant scope for the fMRI workflow starts with an order for an fMRI examination and ends with results interpretation, and largely corresponds to the steps described above by Nakai. With this scope, the workflow is largely contained within the imaging department. We see conducting an fMRI procedure to include separate steps, or exam states, corresponding to the activities related to procedure ordering, patient assessment and training, data acquisition, post-acquisition data processing, and interpretation and results distribution (Figure 2).

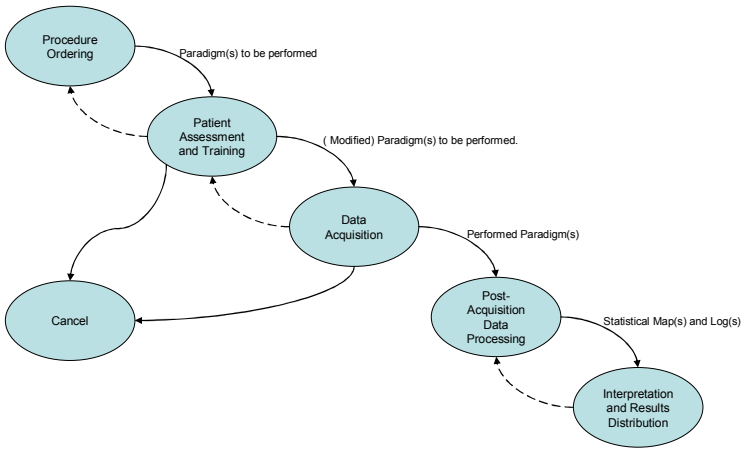

Figure 2. High-level representation of proposed clinical workflow.

[3] See, for example, http://frontiersin.org/neuroscience/neuroinformatics/specialtopics/12/.
[4] Karmonik C, York M, Grossman R, Kakkar E, Patel K, Haykal H, King D. An image analysis pipeline for the semi-automated analysis of clinical fMRI images based on freely available software. Comp Bio and Med, 40, 279-287, 2010.
[5] See, for example, Olabarriaga SD, de Boer PT, Maheshwari K and Belloum A. Virtual Lab for fMRI: Bridging the Usability Gap (authors can be contacted at {f*silvia,adam,ptdeboer,kmaheshw*g}*@science.uva.nl).*

3 fMRI Workflow Steps

3.1 Ordering

The ordering physician initiates the fMRI workflow by making a choice of one or more fMRI tests to be performed during the fMRI examination. Ordering may involve selecting individual tests from a list of available test, or selecting pre-defined 'packages' of tests (for example, the 'pre-surgical evaluation of motor function' which may include several individual tests of motor function). Individual tests may have order selectable features related to conducting the exam, processing of the data, or presentation of the results.

This ordering process assumes the existence of a set of fMRI tests with certain characteristics. To support a clinical workflow, individuals test will have been designed and tested to elicit responses within certain parts of the brain (i.e. the motor strip), which should be made apparent to the ordering physician. Each available test should have available documentation and instructions to ensure proper conduct of the examination. The tests should be well understood by the departmental personnel who will perform the examination, including well understood patient training requirements. Each test will have its own physical requirements (stimulation hardware, etc); the department must have the necessary equipment to conduct the exam.

At the time the fMRI test is ordered, the test is considered 'unmodified' and represents the intent of the test designer. Departmental personnel should understand the demands the test places on the patient, and what, if any, modifications of the test can be made 'on the fly' to accommodate patient variability.

There should be a mechanism to expand the list of orderable fMRI tests, but doing so is outside the scope of this workflow. The list of paradigms should not include a 'design your own' selection. This is a clear difference between the clinical workflow and the research workflow, where in the latter case the purpose may be to design or validate new tests.

3.2 Patient Assessment and Training

In order to familiarize the patient with the fMRI tasks to be performed and to confirm the patient's ability to perform the task, the clinical workflow includes one or more patient training sessions. Patient training should be conducted for all patients, no matter how trivial the task.

Patient training should be closely aligned to the test being performed, and designed so as not to interfere with the results of the test. It is important to avoid patient habituation in certain testing scenarios.

Patient training may occur in a variety of different setting. In order to maximize MR scanner utilization, training is typically performed before beginning the image acquisition, and outside of the bore of the magnet. It is not, however, uncommon to conduct some (re-)training while the patient is in the bore of the magnet.

Patient training provides an opportunity to assess the patient's ability to perform the fMRI tasks as designed. Patient assessment results in one of several outcomes; it may be determined that:

a) the examination can be conducted as designed,

b) the examination should be canceled due to the patient's inability to perform the tasks, or

c) the examination should be altered (within pre-defined limits) to suit the patient needs and/or capabilities.

Alteration of a paradigm may be done for several reasons, including but not limited to reducing the duration of the examination to accommodate patients with attention deficits, or alteration of the response (say, from finger tapping to wrist movement) for patients with limited dexterity. These changes need to be recorded and made available to actors involved in subsequent steps of the workflow.

3.3 DATA ACQUISITION

Once the patient is familiarized and deemed capable of performing the test, data acquisition begins. Image acquisition typically consists of localizing images, followed by acquisition of a high-resolution (structural) dataset and one or more lower-resolution (functional) datasets. It is not uncommon for fMRI data to be acquired with other study data (e.g. diffusion imaging, etc).

Beyond the routine responsibilities of image acquisition, the MR technologist has additional responsibilities during an fMRI examination. During the acquisition of the functional data the patient may be engaged in mental and/or physical tasks designed to evoke specific forms of neuronal activity. The performance of these tasks may result from the patient being subjected to external stimuli delivered inside the magnet. If this is the case, the MR technologist must ensure that the image acquisition corresponds to the stimulation sequences specified by the paradigm designer as possibly modified for the patient during training. Managing a stimulus delivery system includes steps to ensuring that the proper hardware and software systems are available and operating, that the proper stimuli are loaded onto the stimulus delivery system, and to ensure that the operation of the stimulus delivery system is coordinated with the image acquisition.

Some paradigms record patient activity (in the form of simulated keyboard input, physiological measurements, etc). This represents additional management issues for the MR technologist, and the fMRI examination system.

The data acquisition phase can have one of three possible outcomes:

a) data acquisition may be successful and all images collected as expected,

b) data acquisition may be canceled due to a variety of patient or technology related issues, or

c) data acquisition may be partially successful with less than all expected images collected.

In the case of c), the decision to continue the examination should be made based on the cost of continuing versus the value and risk of producing an incomplete or inconclusive result.

3.4 POST-ACQUISITION DATA PROCESSING

Following acquisition of the image data, processing is required to extract the fMRI signal and to prepare the entire dataset for subsequent evaluation and reporting.

Processing of the structural data typically includes steps to remove non-brain structures (such as the skull) and to reposition and resample the brain images into a canonical orientation.

Processing of functional data is more elaborate than the processing of the structural data. Multi-step processing of the functional data is employed to extract the functional results. Broadly, the processing can be categorized into data conditioning (smoothing, motion correction, etc) followed by signal extraction, followed by further data conditioning (alignment and blending with structural data, etc).

The specific steps, their order and characterization are initially specified by the paradigm designer (and thus known at the time the order is placed). Processing parameters may be altered by the processing technologist during the processing episode. The specific steps used to derive a particular set of results is commonly recorded and associated with the results, since the details of processing may have bearing on the interpretation of the results.

The output of this processing includes modified structural data and functional data sets. The functional data consist of voxel-wise datasets that correspond to the statistical analysis (so-called *Z-maps*).

3.5 REPORTING

Results from fMRI examinations typically enter the imaging department's routine reporting, results distribution and billing processes.

Some variability may exist, however. fMRI results are frequently used in treatment planning systems, which require specially prepared data be exported from the imaging department to the treatment department. Examples include surgical planning and navigation systems (as sold by Medtronic, Stryker, BrainLabs and others) and radiotherapy treatment systems (as sold by ADAC, GE and others).

4 FMRI DATA

In this section we describe the different 'types' of data used and produced during the fMRI examination, and tie their usage and production to the steps specific workflow steps. In Figure 3 we represent the 'flow' of this data along the fMRI examination workflow.

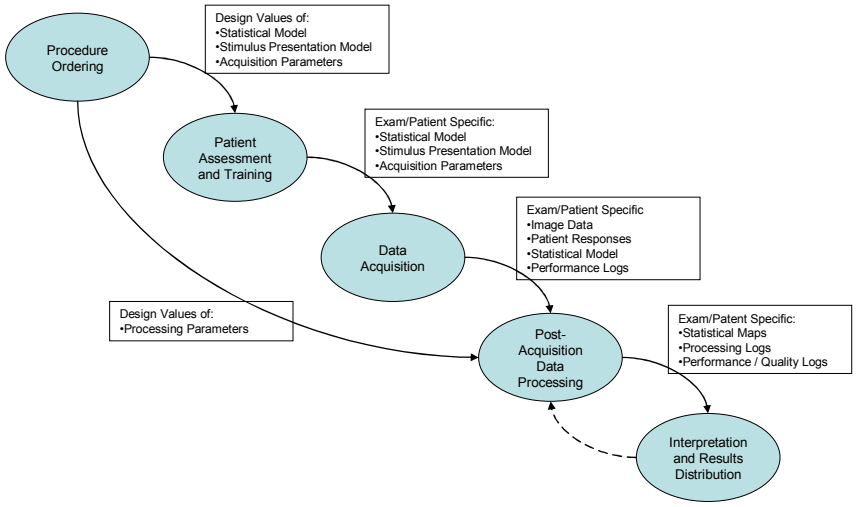

Figure 3. Data associated with workflow steps.

4.1 DATA KNOWN AT THE TIME OF AN FMRI ORDER

fMRI tests, commonly referred to as *paradigms*, are designed for the purpose of measuring specific brain activity. The design process used to create a particular paradigm is beyond the scope of this document. For the purposes of this paper, we assume the existence of one or more paradigms that can be ordered and performed.

We define a paradigm to consist of four related parts, or sets of data: the *statistical model*, the *stimulus presentation model*, the *acquisition parameters*, and the *processing parameters*. The following sections describe each part of the paradigm; it is not the purpose of this document to describe how the data might be represented.

At time of the fMRI is ordered, the design values of the data sets are know. By design value we mean the values of the data the paradigm designer intended to be used during the performance of the examination.

4.1.1 STATISTICAL MODEL

The statistical model represents the underlying statistical hypothesis for the fMRI examination.

4.1.1.1 Generalized Linear Model (GLM)

The vast majority of fMRI data processing being performed today employs a multiple-regression-based statistical analysis based on the Generalized Linear Model (GLM). GLM models represent (a) one or more statistical conditions of interest that model "active" mental states (i.e., the neuronal activities of interest) and "baseline" mental states; and (b), zero or more statistical conditions of no interest that model statistical confounds, such as DC bias, linear signal drift over time, low-frequency noise, etc. In a well-designed fMRI experiment, each condition of interest models the onset and duration of one specific type of neuronal activity throughout the course of the experiment. From a mathematical perspective, each statistical condition, whether it is a condition of interest or a condition of no interest, is used to generate a regressor, which is a quantity employed in the multiple regression analysis.

4.1.1.2 Other Statistical Models

TBD.

4.1.2 STIMULUS PRESENTATION MODEL

The stimulus presentation model represents the specific sequences of *external* sensory stimuli delivered to the patient during image acquisition.

Presentation of stimuli to the patient may require dedicated hardware and software systems compatible with the MR environment. A number of such systems and components exist in the marketplace. Stimuli and control logic are represented by these systems, and little standardization or interoperability of exists.

4.1.3 ACQUISITION PARAMETERS

The acquisition parameters provide information about how the MR image data should be acquired. These parameters represent desirable default values specified by the paradigm designer prior to the performance of the experiment, such as TR, Group Delay, etc.

4.1.4 PROCESSING PARAMETERS

Processing and statistical analysis of the acquired brain images require specification of parameters that govern how the fMRI image data is to be treated. Examples of such parameters include statistical contrast vectors, the width of the Gaussian smoothing kernel, and hemodynamic response function parameters. We refer to these parameters, in general, as the processing parameters.

4.1.5 AN EXAMPLE OF GLM-BASED STATISTICAL AND STIMULUS PRESENTATION MODEL

Although frequently confused, and often used incorrectly in an interchangeable manner, the statistical model and the stimulus presentation model are two very different concepts, and convey different information. In some cases it is possible to derive a portion of the statistical model from the stimulus presentation model, but this does NOT generally hold true. We provide here a simple paradigm, and describe both the statistical model and the presentation model in an effort to clarify the differences.

Let us consider an fMRI paradigm designed to identify regions of the brain involved in a certain cognitive processes. The paradigm designer may decide to engage those processes by having the patient perform mental arithmetic. In this case, the statistical condition of interest is in the active state when the patient mentally solves simple arithmetic problems, and is in the baseline state when the patient observes strings of random numbers.

In Figure 4 below, we present a diagram of both the statistical model and stimulus presentation model for our example. The statistical model is represented by the statistical conditions labeled SC1, SC2, SC3, and SC4. The stimulus presentation model is represented by the sequence of stimulus delivery events labeled SM1.

In our simple paradigm, the statistical condition of interest is represented by SC1. It begins with 30 seconds of the baseline state and is followed by 30 seconds of the active state. This cycle of baseline/active state is repeated 10 times (although only the first 2.5 cycles are shown in the diagram).

Statistical condition SC2 represents a condition of no interest that removes the effects of a DC signal bias from the statistical results. Likewise, statistical condition SC3 represents a condition of no interest that removes the effects of linear signal drift from the statistical results. Statistical condition SC4 is a sinusoidal condition of no interest that removes the effects of low-frequency noise from the statistical results. Our simple paradigm uses only one sinusoid; in practice, anywhere from 4 to 10 sinusoids are often used.

Stimulus delivery sequence SM1 consists of stimulus delivery events that occur every 5 seconds. During the baseline state of statistical condition SC1, the stimuli display strings of random numbers to the patient through an MR-compatible display apparatus; these events are represented by the slightly shorter blue arrows in the diagram. During the active state of SC1, the stimuli display equations representing arithmetic problems to be solved, such as “28 – 5 = ??”; these events are represented by the black arrows in the diagram. Visual stimuli are presented throughout the experiment so that the visual cortex is constantly activated, and thus has a signal that does not vary in conjunction with SC1, and therefore cannot confound the statistical results.

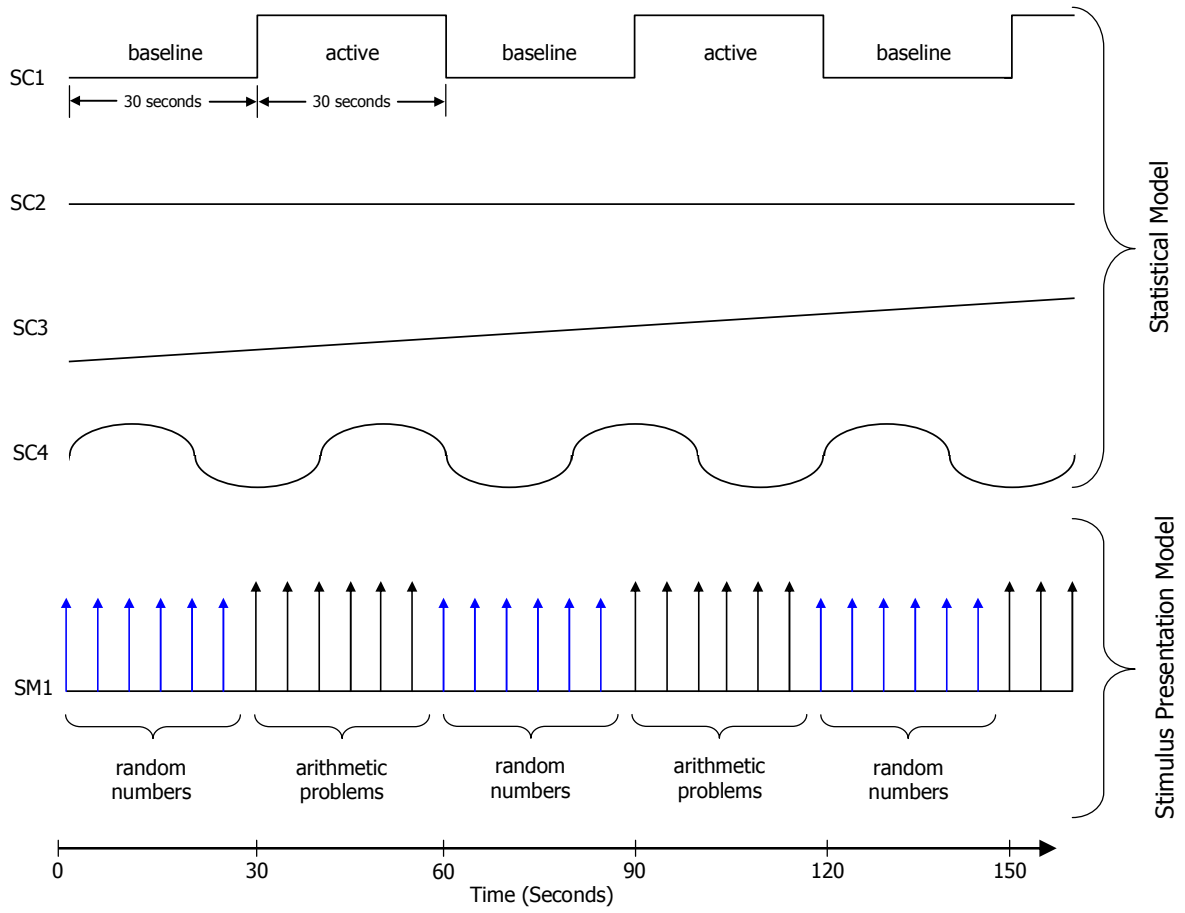

Figure 4. Graphic representation of Statistical and Stimulus Presentation Models.

It is very important to note that the statistical model contains information necessary to derive the statistical results for the experiment. The statistical model, when combined with the acquisition data and processing parameters, provides all information required to perform the statistical analysis.

On the other hand, the stimulus presentation model describes only the delivery of individual stimuli to the patient. Even in our simple example, it cannot describe the statistical condition of interest SC1 without including some higher level semantic that describes the "meanings" of the individual stimulus delivery events. It cannot describe the other statistical conditions, and is therefore insufficient on its face for performing the statistical analysis.

4.2 Data Known Prior to Conducting the Image Acquisition

4.2.1 Statistical Model

In the case of a paradigm with a *deterministic* statistical model, the complete statistical model is known prior to image acquisition. The paradigm designer specifies the default model, which corresponds to default values of the stimulus presentation model and data acquisition parameters. Through the course of the fMRI examination leading up data acquisition (particularly during training and assessment), the statistical model may be modified to reflect specific patient capabilities. These changes must be fixed prior to the start of data acquisition.

In the case of a *non-deterministic* statistical model, the complete model will not be known prior to beginning image acquisition. What is known is how the *non-deterministic* model will be created.

4.2.2 STIMULUS PRESENTATION MODEL

The paradigm designer specifies the default stimulus presentation model, which is reflected in the ordered test. The default stimulus presentation model corresponds to default values of the statistical model and data acquisition parameters. Through the course of the fMRI examination leading up data acquisition (particularly during training and assessment), the stimulus presentation model may be modified to reflect specific patient capabilities. These changes must be fixed prior to the start of data acquisition.

Like the statistical model, stimulus presentation models may be classified as *deterministic* (where the set and timing of stimuli are completely known prior to beginning data acquisition) and *non-deterministic* (where the set and timing of stimuli are not completely known prior to the beginning of data acquisition). An example of a deterministic stimulus presentation model is the simple paradigm we presented above. An example of a non-deterministic paradigm might be a maze solving paradigm, where the path followed by the subject, and the resulting stimuli, evolves during the performance of the paradigm.

4.2.3 ACQUISITION PARAMETERS

The paradigm designer specifies the default acquisition parameters, which corresponds to default values of the statistical model and stimulus presentation model. Through the course of the fMRI examination leading up data acquisition (particularly during training and assessment), the acquisition parameters may be modified to reflect specific patient capabilities. These changes must be fixed prior to the start of data acquisition.

4.3 DATA PRODUCED DURING THE IMAGING EXAMINATION

4.3.1 IMAGE DATA

The image data acquired during an fMRI examination typically includes high-resolution structural images and (low-resolution) volumetric data-sets acquired while the patient performs the tasks specified by the stimulation model.

In clinical use, high-resolution structural data sets may be T1, T2 or proton density images, with 256^2 or 512^2 matrix sizes, 1.0 to 0.5mm slice thickness, and sufficient number of slices to image the anatomical region of interest. Functional datasets can consist of 64x64x10 up to 256x256x40 slice volumes, and cover similar anatomical region of interest. Individual volumes may be acquired once per one- to two-seconds. Acquisitions may last as briefly as 10's of seconds or extend for 10's of minutes.

Other data sets may be acquired (e.g. diffusion weighted images), but they are of no consequence to the results of the fMRI study.

4.3.2 PATIENT RESPONSES

Patient responses may be collected during the performance of the fMRI examination. Collecting patient responses may require dedicated hardware compatible with the MR environment as discussed above.

Examples of responses include physiological data (such as respiratory rates, eye motion, EEG data, etc.), and voluntary responses, such key presses on an MR-compatible keypad in response to stimulus events.

Response data may be used for a variety of purposes, including the assessment of patient performance and related study quality factors. Patient responses may also be used during data analysis.

4.3.3 STATISTICAL MODEL

In the case of a paradigm with a *non-deterministic* statistical model, the complete statistical model is completely known only after the conclusion of the imaging.

4.3.4 PERFORMANCE LOGS

Records of what was actually collected, and technologist notes, may be collected and recorded for later review.

4.4 DATA PRODUCED DURING POST-ACQUISITION DATA PROCESSING

4.4.1 MODIFIED STRUCTURAL DATA

Structural data may be modified during post-acquisition processing. Typical modifications include removing structures (such as hair, boney-tissue, etc) which would otherwise obscure visualization of results. Processing may also include re-orientation of the data into a standardized, or canonical, orientation.

4.4.2 STATISTICAL MAPS

During statistical processing to extract functional signal, *t*- and F-tests are performed to identify voxels with time-varying signals that are strongly correlated with an expected hemodynamic response function represented in the statistical model. The results of this processing include voxel-wise datasets that correspond to the statistical analysis (so-called *Z-maps*, which are images of *Z-scores*).

4.4.3 RECORDS OR REPORTS

Records, reports or logs of the processing performed may be produced.

5 CONCLUSIONS

In this paper we present a workflow model that we think describes the clinical fMRI examination. We further describe significant data objects, and identify when those are produced, used and modified during the workflow.