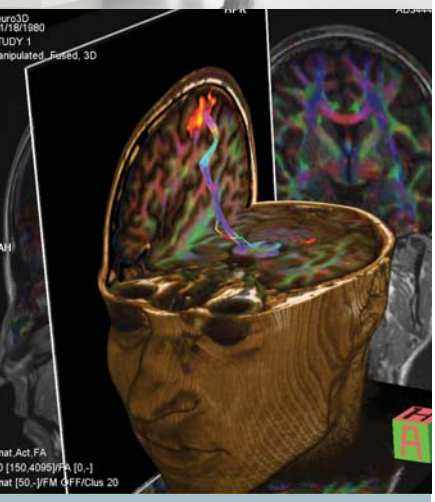

Clinical fMRI

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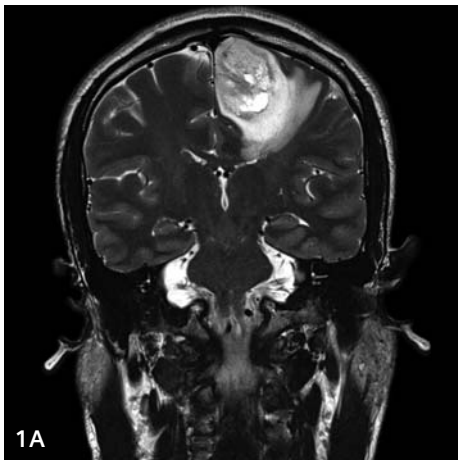
Clinical fMRI

Keith Heberlein, PhD, Siemens Medical Solutions USA, Inc.

All images courtesy of Sun Yat-Sen Hospital, Guangzhou, P.R. China.



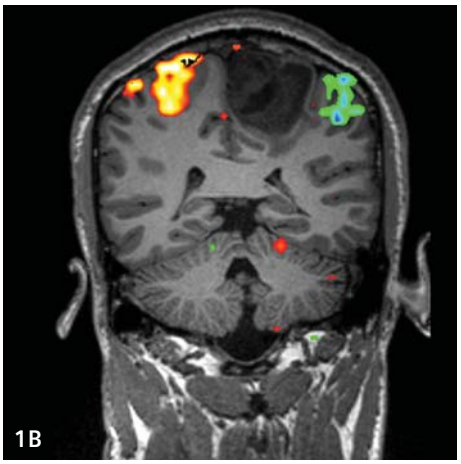


Figure 1A: T2W Coronalc. Figure 1B: Motor brain activation in a case of Meningioma.

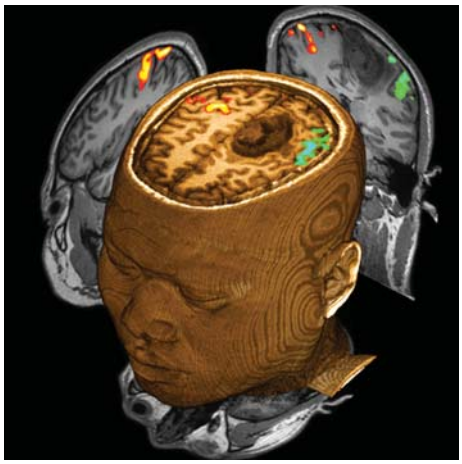


Figure 2: Anatomical and fMRI corelation with Nuero 3D task card.

Introduction

Magnetic resonance imaging of the brain can provide both structural and functional information of brain physiology, making this technology a versatile tool for neuroscience research and clinical evaluation. The most common tool for investigating brain function is Blood Oxygenation Level Dependent (BOLD) contrast, which relies on the inherent magnetic properties of the endogenous contrast agent deoxyhemoglobin. Since its discovery 16 years ago, there has been an explosion in basic neuroscience work and disease characterization using functional magnetic resonance imaging (fMRI). Direct clinical applications are stymied by a lack of sensitivity (SNR) in BOLD fMRI studies, where group averaging is often employed to increase sensitivity. Group analysis can characterize a disease process in general, but is not typically useful for making diagnosis and disease management decisions.

Advances in gradient performance and RF coil technology, such as Tim, and the availability of high field MR systems (1.5T and 3T) have significantly closed the gap on sensitivity. The combined spatial and temporal resolution of fMRI, the simple-to-use MR scanners and wide range of activation paradigms present distinct advantages over positron emission tomography (PET) and magnetoencephalography (MEG). The exciting recent trend is the movement of fMRI into clinical practice as a result of several emerging applications with an emphasis on presurgical planning.

fMRI helps mapping of brain functions in relationship to intracranial tumors, epileptic foci, or vascular malmorfations before surgical excision. The goal of fMRI is to maximize resection of pathological tissue, spare eloquent cortices which improves patient rehabilitation, and reduce surgical risk.

Presurgical planning is the most widespread use of clinical fMRI. For cases of tumor resection, eloquent areas of functional cortex are navigated around to remove the greatest amount of cancerous tissue with minimal functional deficit (see Figures 1 and 2). Functional mapping can be performed intra-operatively, yet often requires a large craniotomy to have access to large areas of cortex. Presurgical mapping of eloquent areas using fMRI can reduce the need for large craniotomies. In some cases, localization of gyri and sulci provide localization of eloquent areas, although patient variability exists in these functional roadmaps, especially in the presence of disease states. This situation is shown in Figure 3, where a patient with a large left temporal lobe tumor underwent language mapping using BOLD fMRI. Both Broca's and Wernike's areas are evident in the functional map, yet a profound displacement of Wernike's area is observed, which is critical information for surgical planning.

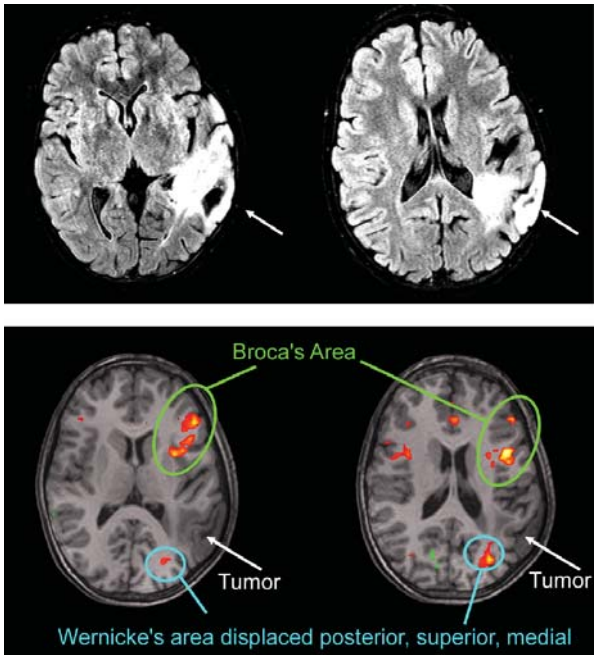


Figure 3: Presurgical planning requires knowledge of eloquent areas of cortex. This example presents a case where a left temporal lobe tumor, conspicuous on the FLAIR images, has displaced Wernicke's area (Images courtesy of Tim Roberts, PhD, Children's Hospital of Philadelphia).

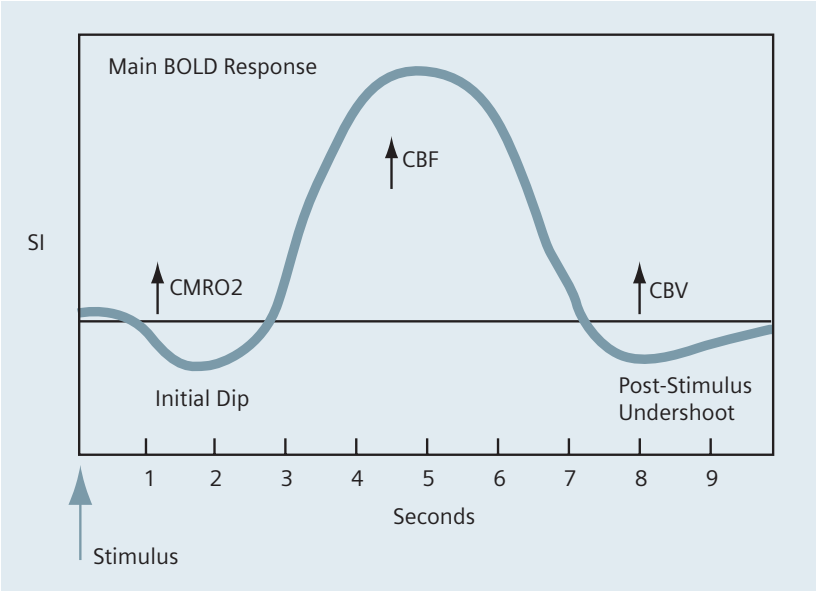


Figure 4: The timecourse of the BOLD response due to a short stimulus is shown with three distinct phases. The most robust signal change occurs approximately 5 seconds after the stimulus and is readily detected by MRI.

In cases of intractable epilepsy, the epileptogenic area can be removed surgically. These areas can be identified using fMRI as well as guiding the surgeon around important speech and language centers of the brain. As fMRI makes inroads into clinical practice, future applications become increasingly apparent. There is great potential for fMRI to be part of the drug discovery process, which may then translate fMRI into a therapy monitoring role. Development of specific fMRI biomarkers could provide measures for tracking the disease progression of Alzheimer's disease, multiple sclerosis, or Parkinson's disease, in addition to tracking the recovery process following stoke.

The BOLD Mechanism

Figure 4 shows the typical BOLD response due to a short stimulus. Initially oxygen is locally consumed (CMRO2) due to increased oxygen demands of the brain tissue. Since deoxyhemoglobin is paramagnetic, this causes a short lived (<2 sec) signal decrease in the MR signal intensity (SI) on T2*-weighted images termed the "fast response" or "initial dip". Increased synaptic activity due to the stimulus triggers a cerebral blood flow (CBF) and cerebral blood volume (CBV) increase causing a much larger increase in SI due to washout of deoxyhemoglobin. This large positive response is attributed to local brain activation and is generally used to detect the activated state, although the response is coupled to the neuronal activation by a mechanism still not fully understood. Following the large positive response, a post-stimulus undershoot persists for several seconds, which can be attributed to persistent CBV effects. Figure 4 presents a commonly held theory of the BOLD response, but the actual physiological response may be more complicated. The main BOLD response is the most commonly used signal characteristic of the BOLD timecourse used for functional mapping due to the more robust signal change. Additionally, the response can be enhanced using a longer stimulus. For the alternate case of a prolonged stimulus, on the order of 10 to 30 seconds, a sustained BOLD response is observed. Two experimental designs are then possible, either using short stimuli or long stimuli, which are differentiated as "event related" or "block design" paradigms.

BOLD Imaging

Detection of the BOLD response typically uses a fast gradient echo MR pulse sequence which is sensitized to susceptibility (T2*) effects. Most commonly used is the echo-planar technique (EPI) with an echo time near 55 ms for 1.5T and 35 ms for 3T. Often the TE can be shortened slightly to mitigate susceptibility artifacts. The temporal dynamics of the BOLD response are on the order of seconds (see Figure 3), which requires a relatively high emporal resolution (2 to 3 sec) dynamic scan of the brain. Ultra-fast EPI scans

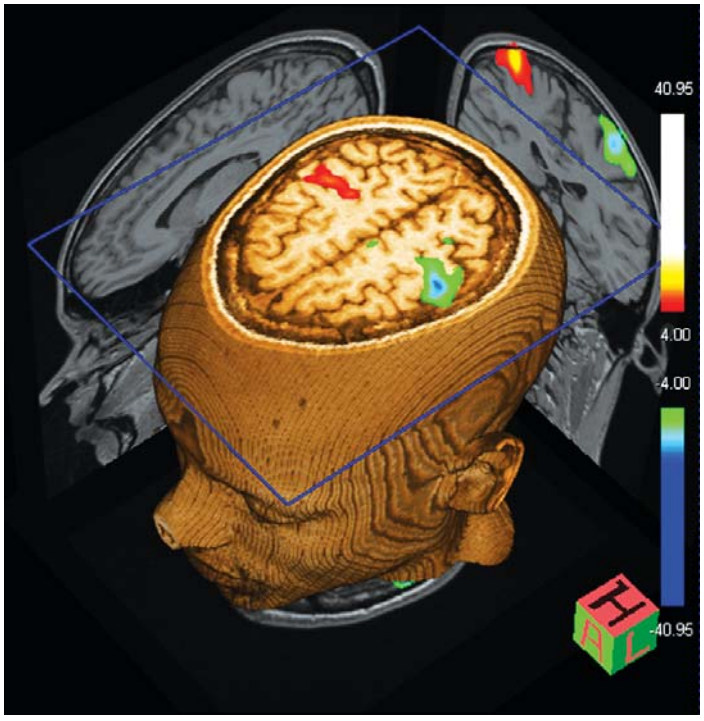


Figure 5: Mapping primary motor areas in Neuro 3D.

are repeated during the course of the examination for anywhere from 3 to 10 minutes depending on the type of stimulus presentation used. The imaging study results in a large volume of 4D data which must be post-processed for automated detection of activated regions of the brain.

The Functional Paradigm

Depending on the particular application various stimulus presentations can be used during the examination. For instance, mapping the primary motor areas of the brain can be performed using simple hand flexion or finger tapping tasks. Visual areas can be identified by appropriate visual stimulus via video presentation. Higher level cognitive tasks such as word generation and reading can be employed to evaluate frontal areas of the brain for eloquent cortex. Eloquent cortex refers to areas of the brain that when injured cause severe functional deficits such as loss of motor function, memory loss or speech deficits. There are two major classifications of functional paradigms, those that are "block design" and "event related". A block design consists of long 10–30 sec stimuli alternating with either a resting condition or control condition. The BOLD signal due to these long blocks is a sustained response that persists during the course of the stimulus block and returns to baseline during the control condition. An event related design instead uses a succession of short (~1 sec) repeating stimuli interspersed by a stimulus interval of 5-10 sec. An event related design captures the BOLD response shown in Figure 3. In practice, block designs are often chosen for simplicity and increased sensitivity, yet lack the specificity of a well designed event related paradigm. Choice of the control condition is often the most demanding task of the experimenter, often requiring a detailed knowledge of the underlying neuroscience. Complex tasks recruit multiple areas of the cortex, generating distributed areas of activation. Designing a proper control task can localize the activation to specific areas of interest, such as the primary motor area. A simple example is shown in Figure 5, where right hand finger tapping is alternated with left hand finger tapping in a block design, localizing both left and right motor areas while averaging out most pre-motor and SMA effects which are often bilateral. In practice, the results depend on the handedness of the subject and can show significant inter-subject variation.

Post-Processing fMRI

Functional imaging studies result in large volumes of 4-D imaging data which are not readable by human eye. Detection of brain activation must employ statistical analysis which can reduce the dimensionality of

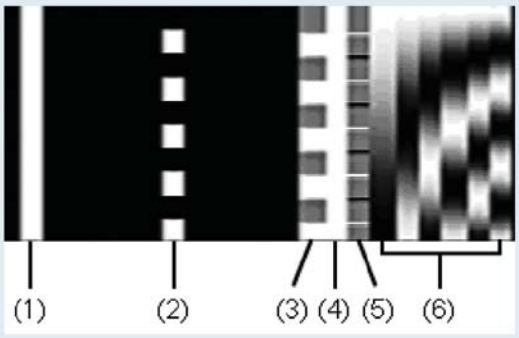


Figure 6. A typical GLM design matrix for fMRI analysis. The model includes the functional paradigm (2) folded with the hemodynamic response (3) and basis functions for removal of low frequency components (6).

the data to visualize the results. While there are a large number of techniques available, most can be classified as model-based approaches, while several model-free approaches are still under development. A common example of a model based approach is the general linear model (GLM) where a priori knowledge of the functional paradigm, or design matrix (see Figure 6), is fitted to the data using an approximation of the hemodynamic response shown in Figure 3. Alternatively, for block designs a simple t-test between on-off conditions will also suffice. The results of either analysis yield statistical parametric maps which can be thresholded and displayed over co-registered high resolution anatomic images. The display threshold is chosen to minimize the chances of both false positives and false negatives for the detection of activity in each voxel. Typical steps for fMRI post-processing include: motion correction, registration, filtering, and statistical analysis. Motion during the fMRI exam creates a spatial misregistration of the time series. These artifacts usually appear near the edges of the brain in the functional maps and can be disastrous if the motion coincides with the functional paradigm. Thus, motion compensation techniques must be employed during the exam and afterwards to the raw data. The raw EPI images used for BOLD detection lack sufficient contrast and resolution for interpretation. These images must be registered with a separately acquired anatomical scan. In research studies often the data is warped to a standard brain atlas, however for clinical use the results should be registered to the patient's clinical scans. Spatial and temporal filtering may also be applied to smooth or detrend the data. For GLM analysis, the spatial filter is required to ensure meaningful statistical results.

Interpretation of fMRI clusters should be made carefully, as there are sources of potential artifacts. Always present is the fact that the BOLD response represents a coupling to the neuronal response via hemodynamics as described in Figure 4. Additionally, a greater portion of the BOLD signal is attributed to draining veins from the region of activation. These confounds generally place the localization abilities of BOLD fMRI at around 3 to 5 mm. Quantification of the BOLD response proves difficult, as there exists great heterogeneity across subjects as well as spatial and temporal variations within a subject. Advanced techniques related arterial spin labeling (ASL) mitigate these issues by measuring CBF directly. The ASL signal intensity is weighted more to the arterial input side and allows for quantification, however temporal resolution and sensitivity are significantly reduced compared to BOLD. These shortcomings still make BOLD detection preferred over ASL for most applications.

Tips and tricks

For maximum value, fMRI scans often require the coordination of the neuroradiologist, and communication with the neuro surgeon if the studies purpose is for pre-surgical planning. The functional paradigm must be designed to be robust on a patient by patient basis, which requires a high level of patient compliance. Standards for functional paradigms may be difficult to obtain due to varying abilities in patient populations, as the experimental design may need to be tailored to the functional level of the patient. For instance, a stroke patient may not be able to perform a motor task on their affected side. In this case, even imagined movements can be used for the functional task. For block designs, long rest periods used as a control task should be avoided as the patient may loose attention to the

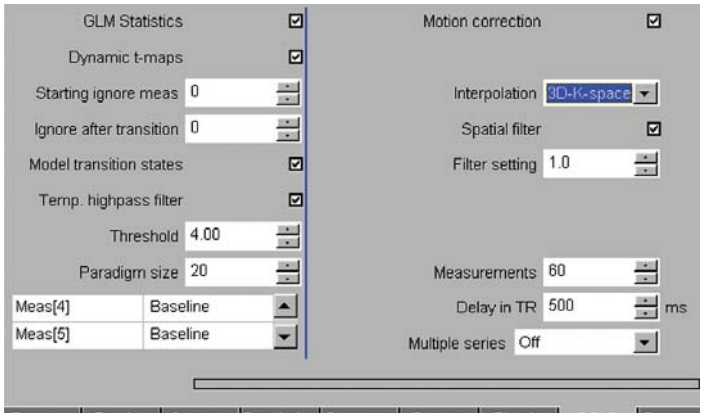


Figure 7: The BOLD sequence card.

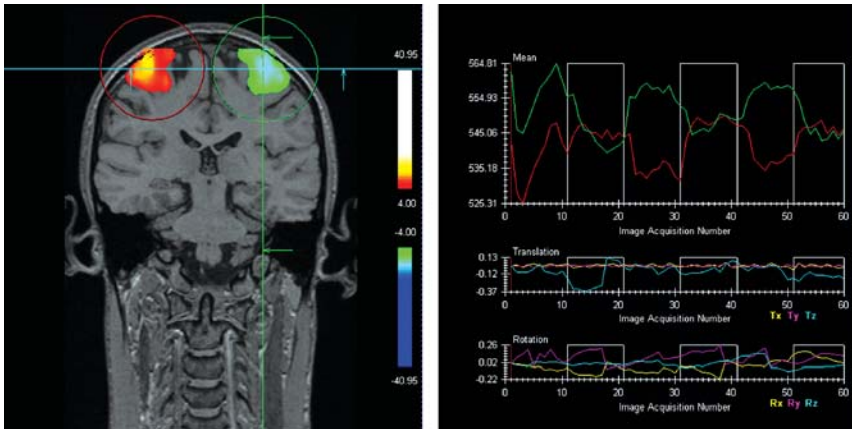


Figure 8: Volume of interest analysis and BOLD timecouse information shown in Neuro-3D. Inline mode provides realtime fMRI display during the exam.

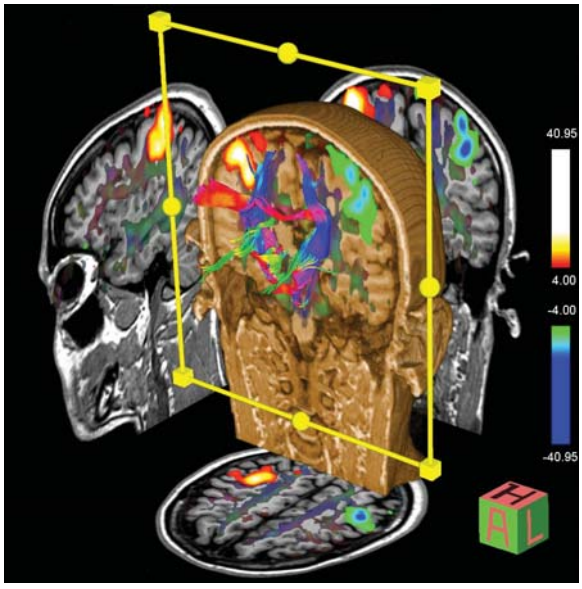


Figure 9: A hybrid display in Neuro-3D with fMRI and DTI integration.

task. In addition, rest may not always be an appropriate control condition. Steps should be taken to prevent head motion during the scan using appropriate head restraint and/or motion compensation techniques. In the context of surgical planning, care must be taken to account for brain displacements after craniotomy. Bringing additional equipment to the MR suite may be needed to perform certain functional tasks and behavioral recording. Care should be taken that these devices do not act as an electrical noise source to the scanner environment.

syngo can fMRI

syngo provides a complete set of tools for fMRI workflow from data acquisition through post-processing. The options available for Symphony and all Tim systems include Inline BOLD Imaging (or BOLD imaging), *syngo* 3D PACE, and *syngo* 3D Bold Evaluation* (*note the names of the packages have changed effective December 2006.) Imaging

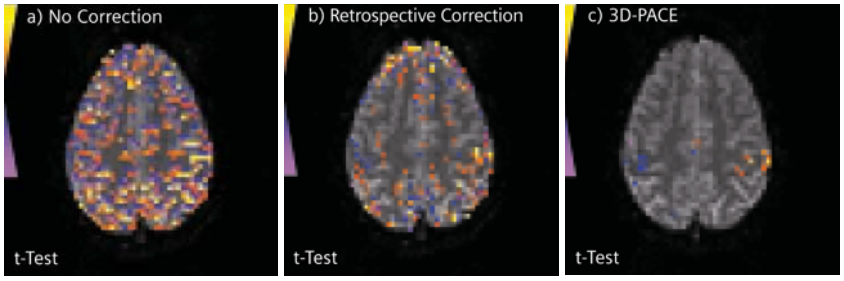


Figure 10: Activation maps of a fMRI study, while the volunteer performs nodding head motions of 1.5 degrees in correlation with a stimulus. Data were acquired without motion correction at all (a), with retrospective motion correction only (b), and with 3D PACE (c). The 3D PACE image (c) clearly shows how the technique helps to virtually eliminate pixels incorrectly showing activation as compared to (a).

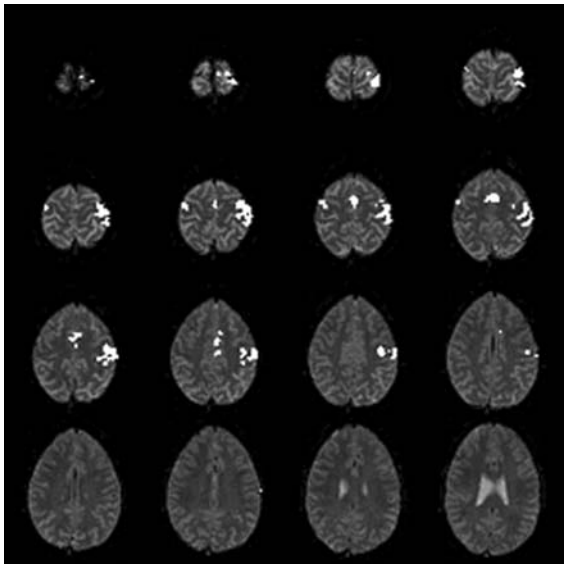


Figure 11: Mosaic format provides efficient use of storage space and data mobility.

sequences and optimized protocols are provided for BOLD fMRI are provided with the Inline BOLD Imaging option. The BOLD sequence card (Figure 7) allows functional paradigm specification and controls the attributes the user desires for inline processing of statistical maps using GLM analysis (GLM model was implemented with B13 software. B13 is for Tim systems only).

The InLine functionalities include real-time calculation of z-score maps and an overlay of Inline t-test results on the images being acquired. A t-test may be observed simultaneously for all slices during the measurement in progress (see Figure 10). This is beneficial for judging patient compliance during the study, from both a response and motion aspect.

The most subtle movement will cause significant degradation in the quality of the examination; as a result motion correction is applied to the dataset. Post-processing of the data for motion is accomplished with the Advanced Retrospective Technique (ART). In addition to retrospectively correcting for motion, the optional *syngo* 3D PACE package, a Siemens exclusive, can be added to the acquisition capabilities of Inline BOLD. This technique detects and corrects rotations and translations in all 6 degrees of freedom. This technique can account, in real-time, for any so-called "rigid-body motion" ensuring accurate results.
As thousands of images may be generated, the images are stored in a mosaic format (see Figure 11), providing efficient use of storage space and data mobility.

The Neuro3D task card included with *syngo* 3D Bold Evaluation provides for color overlay of the fMRI results on co-registered T1 anatomic images. InLine mode is able to monitor patient motion through visualization of the activation map built in real-time. Additionally, realtime volume of interest analysis is possible (Figure 8). When considering diffusion information, overlay functionality permits the merging of tensor and fMRI information on the anatomical images (Figure 9). All of these features are able to be implemented directly on the scanner which improves workflow by avoiding data transfer to fMRI workstations typically designed for research purposes.

Synchronization to external devices for controlling stimulation systems is provided via scan triggers from the hardware cabinet. This permits 3rd party devices that deliver stimuli to be synchronized to the data acquisition.

Conclusion

Taking fMRI from the research lab to the clinic has become a hot topic in MR. Siemens has identified the need for robust tools to support clinical workflow using fMRI and we are working rapidly to meet this demand.

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