

Clinical fMRI: Where do I start?

Victoria Sherwood, Ph.D.; and Tina Pavlin, Ph.D.

NordicNeuroLab AS, Bergen, Norway

Introduction

There have been many developments in technology in recent years which have seen functional MRI gain popularity and acceptance within clinical practice. The most common use for functional MRI (fMRI) remains to be pre-surgical mapping of motor and language areas of the brain, which can help guide the neurosurgeon in their approach. Despite its steadily increasing use, many clinicians still see fMRI as a tool for the large teaching hospital, and something unachievable for a smaller center with less of a support network. Although expertise in neuroradiology is paramount to success, there are fewer barriers to setting up an fMRI service than is often believed. Sites equipped with a motivated multi-disciplinary team can easily navigate the learning curve with support from equipment manufacturers. Increasing the number of centers performing fMRI will aid hugely in future standardization. Siemens Healthineers and NordicNeuroLab provide an easy to use system of hardware and stimulus presentation software, which can ease users into this subject with confidence.

The BOLD signal

fMRI is based on the detection of a Blood Oxygenation Level Dependent (BOLD) signal change when a person is presented with a stimulus. Rapid imaging using a

T2*-weighted sequence allows an increased signal to be detected due to the increase in blood flow in the stimulated brain area. An experiment, or paradigm, is based on stimuli which target a certain neurological process, such as language production. These measurements make it possible to both lateralize and localize the part of the brain controlling that process on an individual basis. This is incredibly important for planning an approach for tumor resection, or temporal lobectomy in epilepsy, for example. There is a vast amount of literature available for the interested reader [1–4]. This article outlines the requirements for reliable paradigm delivery and measurement of the BOLD response.

Use cases

In the first instance, a clinical referral guides the choice of paradigms to be used. In tumor or stroke cases, the location of the pathology will dictate which functions the clinician would choose to map. Temporal lobe epilepsy is a rapidly growing area in terms of fMRI referrals, and in this case lateralizing the patient's language function has historically been the most important motivation [5]. Recently more and more groups are investigating the possibility of directly mapping memory centers [6], although memory activation is somewhat more difficult to achieve. In addition, there are a surprising number of topics in research where fMRI is of interest, relating to myriad



1 fMRI hardware (left to right): SyncBox, InRoomViewingDevice, VisualSystem HD (VSHD), and ResponseGrips.

neurological disorders [7–11] and extending to psychology, economics and marketing, to name but a few [12–16]. Resultingly there is a demand for facilities that can conduct high quality fMRI.

Standardization

As with many quantitative MRI techniques, standardization is a difficult subject due to a lack of sufficient clinical evidence. A brief search of the literature will uncover so many paradigm designs and discussions of post processing approaches that it can be overwhelming to a clinician who is looking into the possibility of setting up a service [17]. However, there are some basic motor and language paradigms that are very commonly used, such as tapping the fingers on one or the other hand to activate the primary motor area, and asking the patient to think of words starting with a given letter to activate the Broca's area associated with language production. Typically, multiple motor and language paradigms would be run within a session. For the motor cortex, this might be due to the need to map areas associated with different motor functions such as feet, toes, even the tongue. With regards to language, it is useful to overlap results from at least three paradigms to gain further confidence in the results. The American Society for Functional Neuroradiology have published recommendations for language [18] and motor [19] paradigms where they also address the need for some flexibility depending on the patient. It is crucial that the radiographer understands each patient and their capabilities and can adapt accordingly (see "Patient preparation and setup").

Basic requirements

Hardware overview

An fMRI system normally consists of 5 components:

1. A device for synchronization of stimulus presentation with MR image acquisition
2. A high-resolution MR compatible visual display (screen or goggles) for presenting visual stimuli inside the MR scanner
3. A powerful PC running stimulus presentation SW, such as NordicNeuroLab's *nordicAktiva* solution
4. High-precision pneumatic, electrostatic, or piezoelectric headphones/earplugs for auditory stimulus presentation, along with a communication console in the MR control room
5. A pair of hand-held button devices or grips for collecting subject feedback during the fMRI experiment

These are described in more detail below, and are shown in Figure 1.

Synchronization

One of the challenges in fMRI is synchronizing stimulus presentation with MR image acquisition. The accuracy and verification of timing information is critical to the validity of results. The synchronization device from NordicNeuroLab is called a *SyncBox* (Fig. 1). It detects the optical trigger pulse (or alternatively, the TTL pulse or the RS 485/422 signal) from the MRI scanner at the start of each acquisition and then sends the signal (either ASCII code or key press) to the stimulus-presentation computer via a USB connection (green connection Fig. 2). One useful feature of NNL's *SyncBox* is a so-called simulation mode: by simulating trigger signals coming from the MR scanner during image acquisition, paradigms can be developed and tested outside the MR environment, thus minimizing the need for expensive scanner time.

Visual display

The most common clinical solution for presenting visual stimuli to a patient inside the MR scanner is a shielded LCD screen mounted on a stand ideally at the back of the scanner, allowing for a large visual field and unobstructed view of the patient from the MR control room. If space is limited, the LCD screen can alternatively be placed at patient's feet. The patient can see the display through mirrors mounted on the head coil assembly, and the placement of the LCD screen and the mirror configuration will determine the required orientation of the visual display. The display orientation of the *InRoomViewingDevice* from NordicNeuroLab (Fig. 1), can be adjusted via an in-built settings menu. However, a much more user-friendly solution is to adjust the screen rotation remotely from the control room. NordicNeuroLab has developed a *nordic-Comfort* software that not only enables the radiographer to control the LCD functionality (display orientation and an in-built camera) remotely, but also includes a library of content-appropriate entertainment for adult and pediatric¹ patient populations, as well as the possibility to stream entertainment content from a number of popular streaming services. Although the patient entertainment functionality cannot be utilized during a task-based fMRI scan, it is a very beneficial feature to use during the structural and DTI acquisitions as it helps to ease patient anxiety or even claustrophobia, minimizing patient motion and scan interruptions [20–21].

An alternative to a shielded LCD screen is a coil-mounted display in the form of goggles, for example NordicNeuroLab's high-definition *VisualSystem (VSHD)*, (Fig. 1). These use dual HD OLED technology to display the visual stimuli to the patient. One advantage is full visual immersion, with

¹MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.

a large field-of-view. This can be especially beneficial for patients with claustrophobia or children who often resist being prepped for scanning due to the unfamiliar environment. Another advantage of the *VSHD* is that it allows dioptric correction of patient vision, which is often a problem in the aging population. Finally, the integrated eye-tracking functionality provides feedback to the radiographer on the patient's level of alertness as well as stress. Despite these advantages, the LCD screen may be preferable in clinical settings due to its ease-of-use which allows for high patient throughput.

As shown in Figure 2, the paradigm is first transmitted from the stimulus PC using an HDMI (video) output. To avoid RF interference inside the MR room, a *Fiber Transmitter* converts the digital video signal into an optical signal which is then fed through the waveguide (red connection Fig. 2) and connected to either the LCD screen or the coil-mounted goggles. The LCD and *VSHD* both require a power source. NordicNeuroLab uses a *Shielded Interface Unit* which resides in the far-corner of the MR room to convert the AC voltage to a DC voltage required to power the displays without producing RF interference.

Audible stimulus presentation

There are several MR-compatible audio solutions on the market today, utilizing different technology for providing the auditory stimuli to the patient. The most common are pressure waveguide headphones that keep speakers outside of the magnet bore and the sound is carried through semi-rigid tubing into the headphones [22]. Although robust and integrated with the scanner's communication console in the control room, the downside is the inability to provide a stereo input and a rather compromised sound quality due to signal losses along

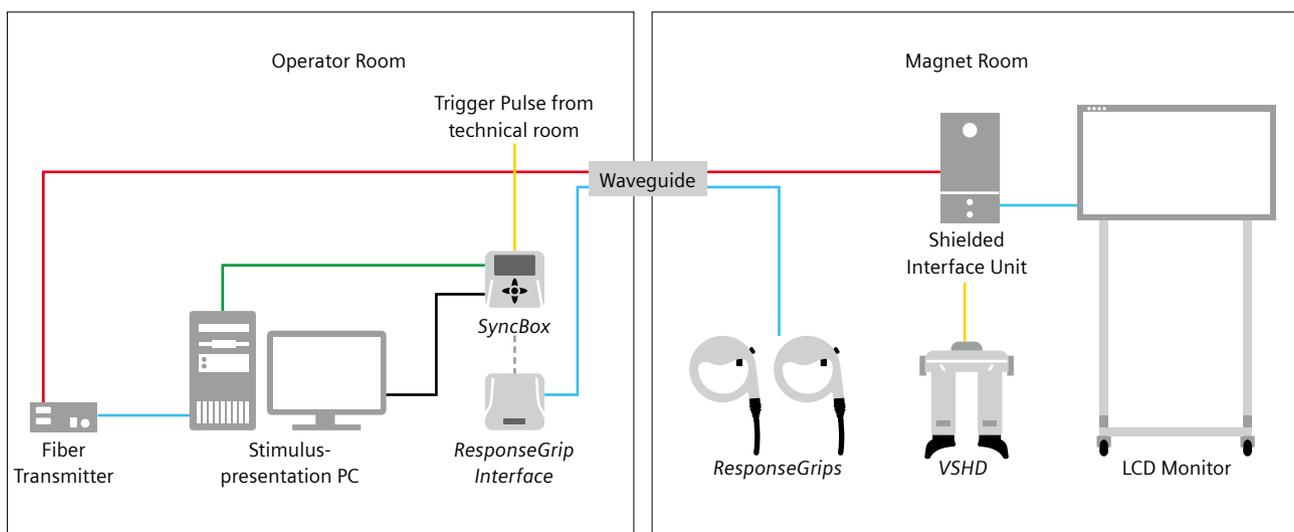
the waveguide. A better sound quality is achieved using either electrostatic or piezoelectric headphones. Furthermore, space restrictions within the latest head coils can be prohibitive, therefore in-ear headphones can be advantageous.

Response devices

Visual and auditory stimuli are used to instruct the patient to perform a task during MR acquisition. The patient may be asked to perform a simple motor or language task, such as finger-tapping or word generation, in which case there is little need to monitor patient responses. However, in instances when the patient is performing a task which requires a decision, such as a rhyming or a verbal memory task, then the fMRI hardware should also include a set of Button Response Devices (BRD). NordicNeuroLab supplies *ResponseGrips* (Fig. 1) for this purpose. These consist of a pair of ergonomically made 2-button grips, and a *ResponseGrip Interface* which converts each button press, detected as an interruption of optical signal (light blue connection Fig. 2), into a distinct ASCII character code output. This is detected by the stimulus-presentation software, *nordicAktiva* (black connection Fig. 2), and stored in a log file of the fMRI experiment.

Stimulus presentation workstation

The stimulus-presentation software should be installed on a dedicated workstation in the control room. This workstation must have at least one HDMI video port (or equivalent), an audio port, and one or more USB ports for detecting the ASCII character code input from the trigger box and the BRD. In addition, it must have a powerful graphics card for fast video transmission and a fast processor to minimize signal delays.



2 Connection diagram of fMRI hardware in the control room and magnet room.

Stimulus-presentation software

Stimulus-presentation software controls the selection and timing of paradigms. Paradigms used in clinical fMRI are most commonly based on a block design, which means periods of active tasks are interlaced with periods of either rest or non-relevant tasks (Fig. 3), and the fMRI analysis then looks at the BOLD signal differences between the two conditions.

The most basic solution for paradigm display is Microsoft PowerPoint®. Slides containing text, video or audio content can be designed easily, and slide timing can be controlled using the slide-timing feature. However, using PowerPoint has its limitations – the biggest one being that it is challenging to detect the scanner trigger signal from within the software, so the presentation and the MRI acquisition must be started simultaneously by the radiographer. In addition, the internal clock of the PowerPoint presentation is not as accurate as in a dedicated SW, so the presentation can over time become out-of-sync with the MRI acquisition. Finally, PowerPoint cannot detect patient responses.

There exist more powerful and flexible paradigm-presentation software options including E-prime® (Psychology Software Tools, Sharpsburg, PA, USA), Presentation® (Neurobehavioral Systems, Albany, CA, USA), PsychoPy (based on Python language) and Psychophysics Toolbox (based on Matlab). These packages are designed for research use and require some effort and time to learn. *nordicAktiva* from NordicNeuroLab, on the other hand, is a clinically approved software designed specifically for pre-surgical motor and language assessment in the treatment of patients with brain tumors, epilepsy and other conditions. *nordicAktiva* is delivered with a library of ready-to-use standard clinical paradigms that are designed according to ASFN recommendations [18–19]. Although these recommendations need constant revision and improvement due to developments in the field, they provide a common frame of reference by which inter-institutional

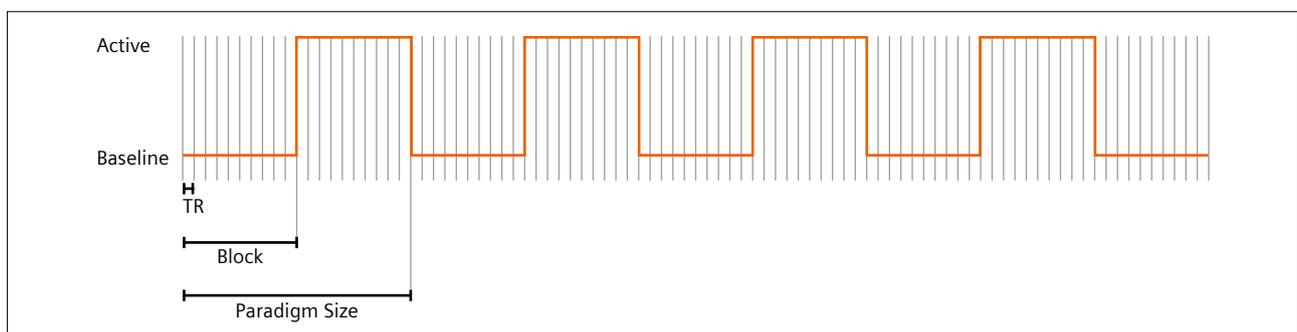
standardization of clinical fMRI becomes a possibility.

This in turn can lead to meaningful comparison of clinical fMRI outcomes between institutions and, eventually, to advancement of our knowledge and improved patient care.

Even though the standardization of fMRI paradigms is at the core of *nordicAktiva*, the user can modify the paradigms to better suite their needs. A typical modification could be to shorten the TR within the paradigm to make it compatible with acquisition protocols utilizing Simultaneous Multi-Slice (SMS; see “Scanning protocol”) or to make simple changes to the slide content, such as changing the text, picture, or sound presented to the patient. *nordicAktiva* also includes patient and operator instructions in multiple languages and allows the user to easily add new languages to the standard paradigm library.

Post-processing software (BOLD and DTI)

After the functional data are acquired, they must be processed through calculations of statistical *t*-maps using the General Linear Model (GLM). This model compares the signal time course in each voxel with what is expected based on the paradigm design and hemodynamic response (see “Processing”) to determine whether signal changes during stimulation are significantly greater than those at rest. These maps are examined by neuroradiologists before being passed on to neurosurgeons. The user has a plethora of post-processing software packages to choose from, such as *syngo.via* Neuro 3D and NordicNeuroLab's *nordicBrainEx*, each with its strengths and limitations. In the context of clinical fMRI and DTI, it is essential to choose a software that allows for the export of BOLD overlays and diffusion fiber groups to presurgical planning stations and neuro-navigational systems used by neurosurgeons, such as BrainLab (Munich, Germany), Stryker (Kalamazoo, MI, USA), Medtronic (Dublin, Ireland) or Surgical Theatre (Los Angeles, CA, USA). Furthermore, the software should have an intuitive workflow for easy adoption in the clinics, and fast processing capabilities to handle large data



- 3** Schematic representation of a block design paradigm: Red curve represents blocks of active (Task ON) and baseline (Task OFF) state. Periods between vertical lines represent measurements of brain volumes which take one TR time to acquire. Here there are ten measurements per block, a total of 90 measurements. Paradigm Size is a vector parameter in the BOLD sequence tab card representing an OFF+ON state. In the example above, the Paradigm Size would contain ten baseline measurements and ten active measurements (= 20).

throughput as well as the increasing need to examine the data shortly after scanning. Most importantly, it should be based on modern post-processing algorithms that have been validated against existing gold standards, such as cortical mapping using electrocortical stimulation, and which aim at minimizing the number of false positive and false negative findings [23].

Patient preparation and setup

One of the most important factors determining success of an fMRI examination is proper patient preparation which relies on good and efficient communication between patient and radiographer. It is paramount that the radiographer evaluates the patient's functional capacity and ability to perform a specific task. Very often, stroke or tumor patients have functional deficits, for instance difficulty reading, speaking, and/or understanding instructions, or compromised motor function. Epilepsy patients can be sensitive to certain colors or color combinations which can trigger an epileptic seizure. Older patients often have compromised vision and/or hearing, while children have a large spread of reading proficiency. Basic useful information can be gathered via a standard questionnaire. Patients should be asked what their mother tongue is, whether they are left/right-handed for certain tasks, whether they wear glasses or contact lenses, whether they suffer from seizures, and whether they have issues with particular colors. Furthermore, patients should be asked whether they take any medication (such as sedation, relaxant), whether they have taken any medication on the day of the scan, and whether they feel tired.

It is very beneficial to do a 'practice-run' through the paradigms in the patient preparation room. The patient can be given a document describing the paradigms and asked to rehearse each task, then shown the paradigms on a workstation or laptop as they will appear on the screen during the MRI scan. *nordicAktiva* can be run in a so-called Simulate Mode, without requiring a trigger from the scanner. This way the patient can see the entire paradigm before the actual exam. The patient should also be told explicitly that they should not read the text on the slides out loud, but silently in their head.

Adapting to your patient

In case a patient has difficulties executing a task, adaptations should be considered. For visually impaired patients, a simple solution could be to increase font sizes; if a patient cannot read, their language function can be tested using picture naming or auditory stimuli (such as a Story Listening paradigm); if they cannot tap each finger individually for a motor task, they can tap all the fingers at the same time, or clench them into a fist; if they are completely paralyzed on one side, then one can test their

sensory input by stroking their hand. Having a range of different paradigms based on written text, pictures or audible stimuli, and accounting for varying levels of proficiency, can go a long way to ensuring the success of the examination.

Positioning

Once prepared, the patient is positioned on the MR scanner table with the appropriate head coil. Immobilization of their head using memory foam is recommended, and they should be made as comfortable as possible (e.g., padding their knees, covering them with a blanket). An appropriate mirror should then be attached to the head coil, and the patient instructed to look at the LCD screen. Are the letters oriented correctly (up/down, left/right)? Can they see sharply or are the words blurred? Can they see the entire screen? At this point it might be necessary to modify the size of the letters, re-orient the LCD display or reposition the LCD screen (Fig. 4).

Communication during the scanning session is key. The radiographer should encourage and motivate the patient by giving positive feedback, thereby relaxing the patient, increasing their confidence and improving task performance. Specific task instructions should be repeated before each paradigm, as these can easily be forgotten.

After the completion of the scan, the patients should be asked about their performance, whether they felt they executed the tasks well, and whether they remained alert during the scan. This information can be very useful for quality control purposes.

All patients are unique, and radiographers are faced with new and unforeseen challenges almost daily. However, with proper training they can become experts in evaluating patient's ability and needs, and thus greatly contribute to the success of an fMRI session.



4 Patient positioned with double mirror and LCD screen behind the scanner. At this point correct orientation of the screen should be confirmed by the patient.

Scanning protocol

Suggested core sequences for a functional study and important parameters to consider can be found in Table 1. These are by no means hard and fast rules, but should be considered as a starting point for optimization.

Anatomical data

A high-quality 3D isotropic structural scan of the whole brain is the first step. This will provide a detailed anatomical reference for the statistical activation maps and tractography data. Functional data will be co-registered to and overlaid on the structural data, providing a sense check that the fibers and areas of activation are in the expected locations and aiding in localization.

The BOLD sequence

BOLD images are usually obtained using a gradient-echo EPI sequence. The BOLD tab card (Fig. 5) contains information relevant to the paradigm design and pre-processing steps.

A whole-brain volume is acquired within each TR, and each volume makes up one measurement (Fig. 5, A) within the experiment. Continuous measurements are made for the entirety of the paradigm duration (Fig. 3). When setting up each BOLD sequence, the TR and the total number of measurements must match exactly the paradigm. These can be compared with *nordicAktiva* before starting the paradigm. Note: the scanning time will be a few seconds longer than the duration of the paradigm due to the acquisition of dummy scans. It is recommended

Sequence	Resolution, mm	TR, ms	TE, ms	Acceleration	Directions	b-value, s/mm ²
T1 MPRAGE	1 x 1 x 1 (Distance factor = 0)	As per Siemens Healthineers library protocol	As per Siemens Healthineers library protocol	As per Siemens Healthineers library protocol	–	–
BOLD (EP2D) (without SMS)	3 x 3 x 3 (Distance factor = 0)	3000	20–30	GRAPPA 2–3	–	–
BOLD (EP2D) (with SMS)	2 x 2 x 2 (Distance factor = 0)	2000	20–30	GRAPPA 2, SMS 3	–	–
DTI (EP2D MDDW) (with or without SMS)	2.5 x 2.5 x 2.5 (Distance factor = 0) or as close as possible, remaining isotropic	Depending on SMS, coverage, etc.	Lowest possible	GRAPPA 2, SMS 3 where possible	≥ 32	1000–2000

Table 1: Recommendations of core sequences and various scanning parameters for an fMRI examination.



5 BOLD tab card in syngo MR XA11 software, including most important parameters: Number of measurements (A), GLM statistics for inline processing (B), motion correction (C), spatial smoothing filter activation (D), and paradigm block design specification (E).

that the 'Introduction' feature is switched off to avoid further confusion about the timings. Spatial resolution is also an important consideration, particularly for pre-surgical planning where visualization in 3D is the endpoint, and isotropic acquisitions with no slice gap are highly recommended.

Additional parameters in the BOLD tab card allow for optimal inline processing, which has two main benefits. Firstly, statistical *t*-maps are created automatically (GLM series), so for sites where pre-processing requirements are well known and tested, it is possible to avoid any offline processing of the data beyond a visual check and thresholding of the maps, for example in the fMRI tab of the *syngo.via* Neuro 3D workflow. Secondly, and perhaps more importantly, thumbnails of the inline statistical maps can be viewed in real time during the scan. Although these do not provide the complete picture available after post-processing, they can make a useful guide for the radiographer to indicate that some activation is visible in the relevant brain areas. The 'GLM Statistics' check box (Fig. 5, B) should be used to provide the inline statistical processing. Retrospective motion correction is available here (C), as are some other pre-processing options. For ease of inline visualization of activations by the radiographer, it is recommended that a spatial (smoothing) filter (D) of at least 1.5 times the in-plane resolution of the sequence is used (see "Processing"). Defining the extent of spatial smoothing is possible once the box is checked. Finally, the BOLD tab card contains details of the block design of the paradigm (E). 'Paradigm size' refers to one full cycle (active and rest) of the paradigm (Fig. 3). For example, a simple 'On/Off' paradigm with ten measurements per block would have a paradigm size of 20. Each measurement must be specified as 'Baseline' or 'Active' via a series of drop-down tabs. A more complex paradigm with two different active conditions such as Rest – Right-hand finger tapping – Left-hand finger tapping, also with ten measurements per block, would have a total paradigm size of 30. Note: Inline processing only accounts for a single active condition, so the GLM series must be re-calculated for any experiment involving multiple different active conditions.

It is advisable to create a library protocol with correct parameters for all required paradigms, to minimize the potential for errors during a session.

The impact of SMS

Simultaneous multi-slice (SMS) sequences can have a big impact on fMRI. The additional acceleration can be used in a number of ways:

- If the paradigm timings are kept the same, a larger slice coverage or higher spatial resolution can be achieved within the same TR.
- Maintaining the same spatial resolution, the TR can be significantly reduced. Either this can provide time savings by making the entire experiment shorter, or the total number of measurements can be increased accordingly to improve statistical power [24, 25].

In the latter case, the paradigm itself will require modification. *nordicAktiva* v1.3 includes different TR options to cater for customers with or without SMS capabilities.

Motion correction

There are two options in the Siemens library for inline motion correction of BOLD EPI data. 'Moco' is a retrospective motion correction using *k*-space interpolation to correct for motion after the acquisition of data and can be activated using a check box in the BOLD tab card (Fig. 5, C). PACE is a prospective technique where motion is detected, and the image position shifted in real time for the next measurement. The two techniques can be used independently or together, however, it should be noted that for PACE protocols both the motion correction and spatial smoothing (see "Processing") are applied prior to reconstruction of the base EPI images and cannot be removed. With Moco there is a separate motion corrected 'MocoSeries' generated in addition to the original images. For applications where the user may wish to apply their motion correction during the processing stage (a common request for research studies, for example), PACE would not be appropriate, but Moco could still be used to improve the inline maps. Some form of motion correction is of course recommended, however, and in the clinical setting a PACE approach may give a cleaner result in the presence of significant motion [26].

Log and design files

nordicAktiva writes any detected responses from *ResponseGrips* to a log file. This describes all events occurring during the experiment and their exact timings, including details of the slides presented and incoming trigger signals from the scanner. Afterwards, this file can be saved alongside a design file. The design file describes the block design of the presented paradigm for later importing into *nordicBrainEx* post-processing software.

DTI

It is common to use tractography alongside BOLD in pre-surgical planning, and some thought should be given to optimization for this purpose. SMS can provide significant time savings for DTI and should be used where possible.

Processing

An overview of the steps

There are several strategies that may be taken when processing fMRI data, depending on the preferences of the site. The main recommended steps are summarized in Table 2.

Conditions and contrasts

For statistical calculations one must specify whether a paradigm block should represent an active condition (e.g., 1) or baseline (e.g., 0). Next, the required contrasts are specified. In a basic On/Off paradigm such as unilateral finger tapping with one active and one baseline condition, one would specify a contrast of [1 0] to compare the active condition with baseline. If two active conditions are included (such as right hand (condition 1) and left hand (condition -1) finger tapping), there are a few options. One can compare each hand separately with the baseline condition, resulting in contrasts of [1 0]

and [-1 0], and/or one can compare each hand with the other, resulting in contrasts of [1 -1] or [-1 1]. In the latter case, any brain regions which are activated by both stimuli will be cancelled out, so for inclusion of the supplementary motor area, the two hands should be analysed separately.

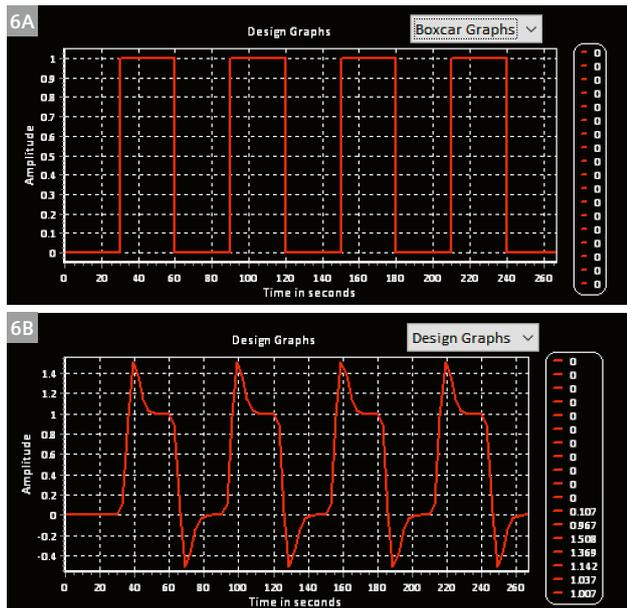
The use of inline processing

Using the BOLD tab card, it is possible to specify pre-processing steps and the block design. This allows for inline calculation of statistical maps, in which case the post processing may only involve thresholding and exporting the maps. Although this process is the most streamlined, it removes the ability to explore different pre-processing options and adapt them to the patient. Variability between seemingly similar patients can be extremely high, and for patients with low activation, particularly in language paradigms, visualization can be difficult. Increasing the spatial filter and applying clustering can greatly help in these cases, especially for lateralization. The user has a lot

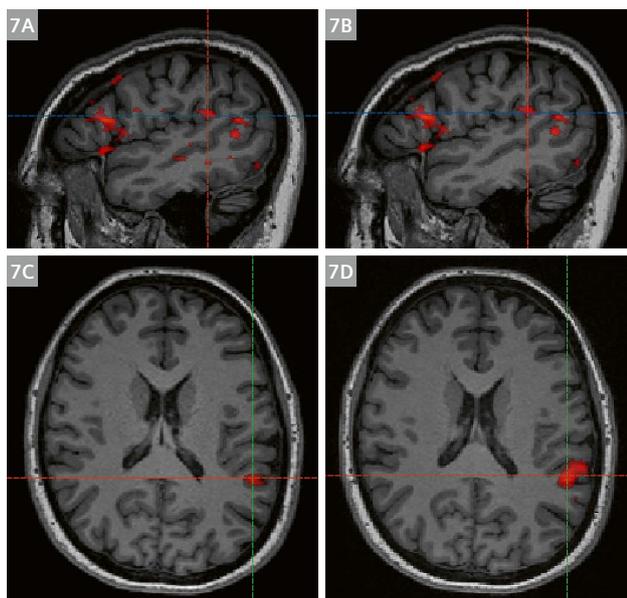
Processing step	Description
Co-registration	3D rigid registration of BOLD and DTI data with structural data.
Motion correction	Registration of each frame in the functional series to the first. Applies to both BOLD and DTI data.
Slice timing correction	A correction for BOLD data to account for the fact that slices are not all acquired simultaneously. This cannot be applied to SMS data.
Spatial filtering	A smoothing kernel is commonly applied to help improve visualization of activation over noise. This does also reduce the spatial localization accuracy so should be used appropriately depending on the importance of localization versus laterality.
Temporal high pass filtering	High pass filtering can be applied to remove slow signal drifts over time.
Temporal smoothing	Data can be smoothed in the time domain to reduce inherent rapid noise fluctuations. This should also be used with caution to prevent smearing out of the responses over time.
Convolution of the stimulus with the hemodynamic response function	The effect of a stimulus on the blood flow in the brain is not immediate but is characterized by a hemodynamic response function (HRF). A model of the HRF should be included in the analysis (Fig. 6).
Calculation of statistical maps using the General Linear Model	The statistical significance of signal changes is calculated based on knowledge of the expected signal change due to the paradigm. Pixelwise maps of the t -statistic are created for overlay onto the structural data.
Thresholding of t -maps	Whilst viewing as an overlay, a threshold is applied to each t -map and adjusted manually such that only pixels above a certain value are displayed. This is a subjective process and requires knowledge of the neuroanatomy involved. Thresholding can significantly impact the apparent size of activation regions, so radiologists should be involved in this process. <i>nordicBrainEx</i> provides automated thresholding to 40% of the maximum t -value as a starting point to assist with standardization [27].
Clustering	To remove small regions of noise from the t -maps, clustering can be applied such that activation regions are only displayed when x number of adjacent voxels are above the chosen threshold (Fig. 7). Clustering is applied in 3D and may typically be set to 20 or 30 voxels.

Table 2: A summary of common processing parameters used in fMRI.

of flexibility in their choice of pre-processing parameters, depending on the chosen software, and this can sometimes be overlooked. The Neuro3D workflow in Numaris X or *syngo.via* will automatically load the maps produced inline and display them for thresholding and will assume



6 (6A) Boxcar diagram of a straightforward On/Off paradigm, and (6B) the design graph incorporating a model of hemodynamic response function.



7 Visualization of language areas (7A) without and (7B) with clustering of 30 voxels, showing the ability to remove spurious noisy areas of false positive activation. Wernicke's area with (7C) no spatial smoothing filter and (7D) with 6 x 6 x 6 mm smoothing.

the paradigm followed the block design specified in the BOLD tab card. However, it also includes an optional 'BOLD Calculation' step which can be used to change the paradigm design, add contrasts, change pre-processing parameters and implement clustering. As mentioned, this feature is required in the case of multiple active conditions (e.g., rest – left hand – right hand) which the inline processing cannot facilitate.

The use of design files and *nordicBrainEx*

nordicBrainEx provides an automated GLM calculation using a design file. Firstly, a design file can be sent to *nordicBrainEx* from *nordicAktiva* which describes exactly the paradigm design that was displayed during the experiment, thus removing the potential for error. It also contains default values for the pre-processing steps and contrasts, which are then easily editable prior to calculation, if desired. Once a design file has been imported, it will be saved and can be selected for subsequent patients for whom the same paradigm has been used. Either the original EPI images can be imported, or the MocoSeries – in the latter case, both motion correction and spatial filtering can be switched off in *nordicBrainEx*.

Multiple overlapping activation maps

Particularly for language or memory paradigms, it can be difficult to clearly visualize the areas of true activation over and above false positive regions. Overlapping multiple *t*-maps from different paradigms can really increase confidence in the true positive results, and it is recommended that for language area mapping, at least three paradigms are used.

Processing of DTI data alongside BOLD

Where DTI data is desired, it can be very useful to display both BOLD and DTI simultaneously. Importantly BOLD activation regions can be used to guide tractography.

Conclusions – Setting up an fMRI service

Most commonly fMRI is used for neurosurgical planning/navigation. This requires a multi-disciplinary team, within which the importance of communication cannot be underestimated. Central to this team is a motivated radiologist with the time, interest, and support to develop the service. Another key person is the neurosurgeon, both as the end user of the information, and potentially as a source of funding. Neurosurgeons should be educated on the capabilities of the software to produce data sets of various formats (both from BOLD and DTI data), to optimize the integration with the neuronavigational system. Feedback from the neurosurgeon on the format, quality, and usefulness of the data should be sought regularly to aid further optimization. The responsibility for feedback on image

quality lies with the radiologist, and often it takes several trial sessions to ensure the available scanning tools are being used to their fullest. Practically the scanning is up to the radiographers, who should be specifically designated staff members who have undergone appropriate training to build confidence in patient preparation, image sequences and paradigms. Whilst the support of an MR physicist with knowledge of fMRI is not essential, it can help both the radiographers and radiologists become more proficient in their respective roles more quickly.

When getting started, support from applications specialists is paramount, for sequence and workflow optimization as well as paradigm delivery. It can be beneficial for the multi-disciplinary team to discuss with the applications specialists the plans and possibilities for the service, to ensure every person is clear about the overall goals, and to set expectations. Variability in equipment, paradigms, sequence parameters and patients themselves all impact on the success of an investigation. There may be instances where little or no activation is seen simply due to the patient. Accepting occasional failure and learning how to adapt to difficult situations are important steps in the learning curve.

Even once the service is up and running, additional applications support should be sought, even as far as sharing data for discussion. It is within everyone's best interests to establish an efficient workflow using equipment which integrates and communicates effectively.

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Contact

Vicky Sherwood, Ph.D.
Application Specialist
NordicNeuroLab AS
Møllendalsveien 1
N-5009 Bergen
Norway
Mobile: +44 7367 190 271
vicky@nordicneurolab.com



Vicky Sherwood Tina Pavlin