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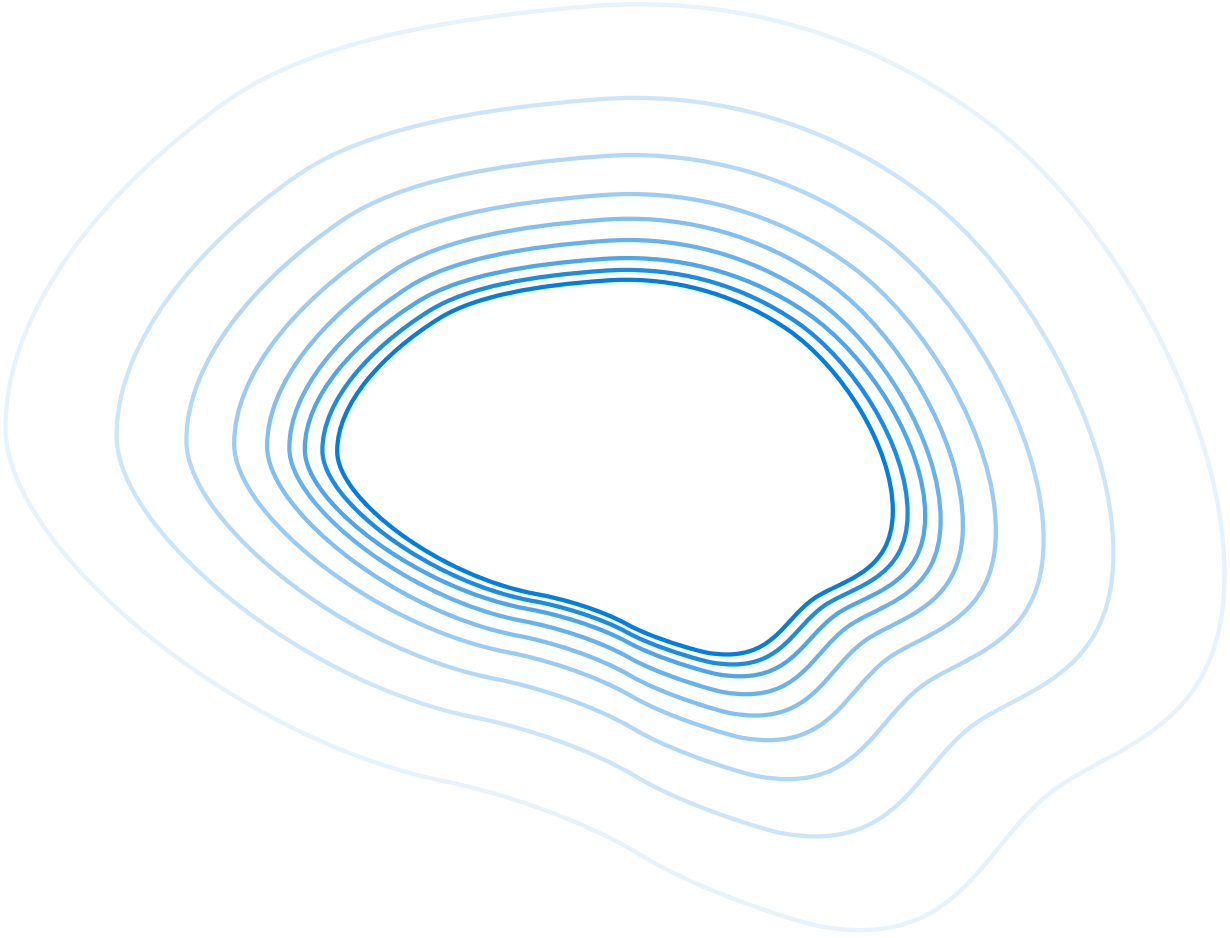
fMRI Solutions

Clinical fMRI: Where do I start?



Clinical fMRI: Where do I start?

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1 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 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 centre 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 centres performing fMRI will aid hugely in future standardisation. NordicNeuroLab provides an easy-to-use system of hardware and stimulus presentation software, which along with the available support, can ease users into this subject with confidence.

1.1 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 T_2* 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 lateralise and localise the part of the brain controlling that process on an individual basis. This is incredibly important for planning an approach for tumour 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.

1.2 Use cases

In the first instance, a clinical referral guides the choice of paradigms to be used. In tumour 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 lateralising 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 centres [6–9], although assessing the impact on clinical outcomes from providing such data to the neurosurgeon e.g., for epilepsy patients is still an emerging



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

area of research. In addition, there are a surprising number of topics in research where fMRI is of interest, relating to myriad neurological disorders [10–14] and extending to psychology, economics and marketing, to name but a few [15–19]. Resultingly there is a demand for facilities that can conduct high quality fMRI.

1.3 Standardization

As with many quantitative MRI techniques, standardisation 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 [20]. 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 or 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 [21] and motor [22] 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").

2 Basic requirements

2.1 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 compatible 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 quality headphones (nordicAudio*) for auditory stimulus presentation, along with a console in the MR control room to allow for patient communication;
5. Hand-held button devices or grips for collecting subject feedback during the fMRI experiment.

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

*nordicAudio is only available in EU

Clinical fMRI: Where do I start?

2.2 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 the *SyncBox* (figure 1). It detects a trigger pulse from the MRI scanner, either via optical, TTL or RS 485/422 connection, 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 in figure 2). Whenever the scanner transmits subsequent trigger pulses, which could be at the start of every acquired EPI volume or every block of the paradigm (see section 'Stimulus Presentation Software'), the *SyncBox* again forwards that to the stimulus presentation computer. One useful feature of NNL's *SyncBox* is a so-called simulation mode: by simulating the MR scanner trigger signals using the *SyncBox*, paradigms can be developed and tested outside the MR environment, thus minimizing the need for expensive scanner time.

2.3 Visual display

The most common clinical solution for presenting visual stimuli to a patient inside the MR scanner is a shielded LCD screen, such as the *InRoomViewingDevice* from NordicNeuroLab (figure 1), 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 NNL *InRoomViewingDevice*, 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 *nordicComfortSolution* 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 paediatric 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, due to the need for the subject to focus on their task, it is a very beneficial feature to use during associated structural and tractography sequences, as it helps to ease patient anxiety or even claustrophobia, minimising patient motion and scan interruptions [23-24].

An alternative to a shielded LCD screen is a coil-mounted display in the form of goggles, for example NordicNeuroLab's high-definition *VisualSystem HD* (*VSHD*, figure 1). These use dual HD OLED technology to display the visual stimuli to the patient. One advantage is full visual immersion, with a large 60° diagonal 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 can help the subjects feel better equipped to complete tasks presented visually. Finally, the integrated eye-tracking functionality provides feedback to the radiographer on the patient's level of alertness as well as stress. Despite the advantages of the *VSHD*, the LCD screen may be preferable in clinical settings due to its ease-of-use and minimal set-up time, which allows for high patient throughput.

As shown in figure 2, visual stimuli are first transmitted from the stimulus PC using an HDMI (video) output. To avoid RF interference inside the MR room, a *Fibre Transmitter* converts the digital video signal into an optical signal which is then fed through the waveguide (red connection in figure 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.

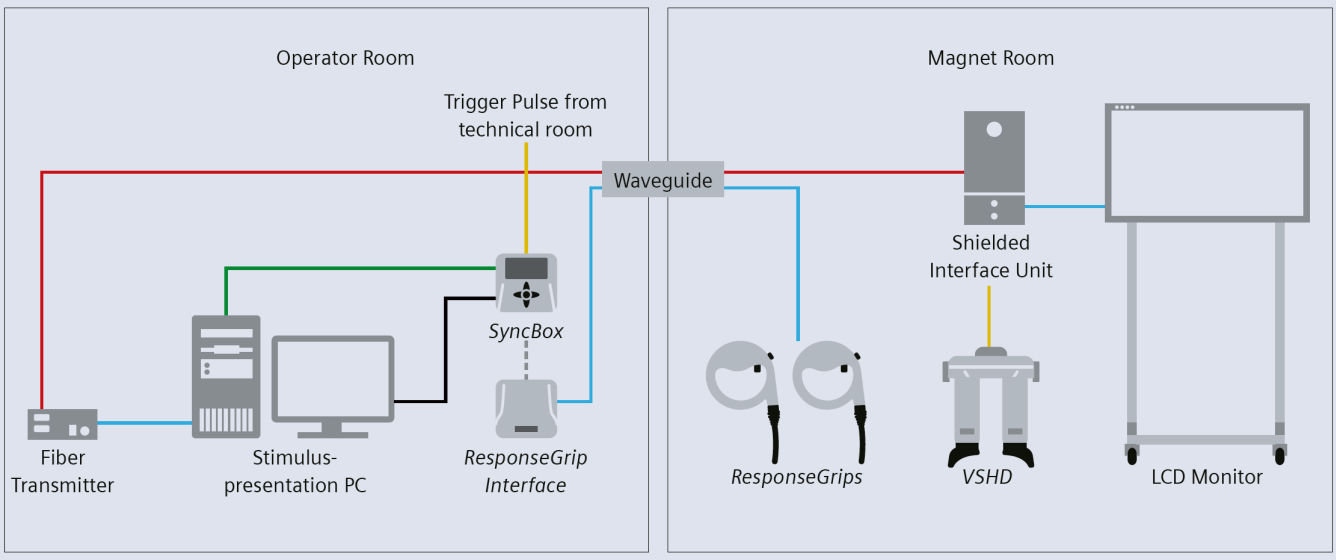


Figure 2: Connection diagram of fMRI hardware in the Control Room and Magnet Room.

Clinical fMRI: Where do I start?

2.4 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 [25]. 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.

Current commercial offerings in this space can be limited due to space restrictions imposed by modern head coils, or the inability to effectively reduce scanner noise. A solution is currently under development by NordicNeuroLab for slim, high-quality headphones using state-of-the-art microelectromechanical system (MEMS) speakers with active noise cancellation. These will be a significant enabler in improving the patient experience and widening the scope for fMRI tasks to be delivered audibly. For some patients this will mean the difference between success and failure of an fMRI exam.

2.5 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 opportunity to gather responses from the patient during the scan. However, in instances when the patient is performing a task which requires a decision, such as whether two words displayed on the screen rhyme with one another, then the fMRI hardware should also include a set of Button Response Devices (BRD). NordicNeuroLab supplies *ResponseGrips* (figure 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 in figure 2), into a distinct ASCII character code output. This is detected by the stimulus presentation software, *nordicAktiva* (purple connection in figure 2), and stored in an event log of the fMRI experiment.

2.6 Stimulus-presentation workstation

The stimulus presentation software should be installed on a dedicated workstation in the control room. In the case of the NordicNeuroLab fMRI hardware, 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 *SyncBox* and the *ResponseGrips*. In addition, it must have a powerful graphics card for fast video transmission and a fast processor to minimise signal delays.

2.7 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 (figure 3), and the fMRI analysis then compares the MR signal change with the pattern of activation which would be expected from that paradigm.

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 manually pressing two buttons at once. In addition, the internal clock of the PowerPoint presentation may not be entirely accurate, so the presentation may over time become out-of-sync with the MRI acquisition. Finally, PowerPoint cannot detect patient responses.

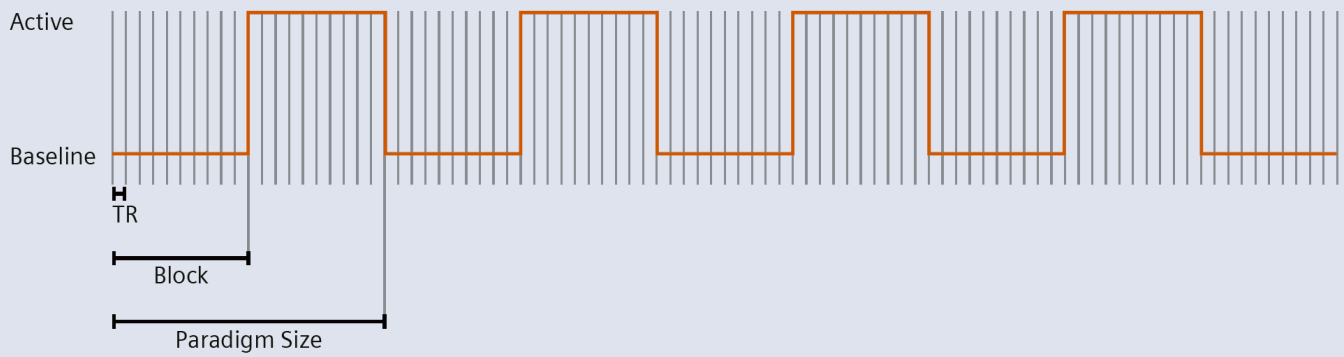


Figure 3: Schematic representation of a block design paradigm: Red curve represents blocks of active (Task ON) and baseline (Task OFF) state. Periods between blue vertical lines represent measurements of brain volumes which take one TR time to acquire. Here there are ten measurements per block, a total of 90 measurements.

Clinical fMRI: Where do I start?

There exist more powerful and flexible paradigm-presentation software options including E-prime, Presentation, PsychoPy (based on Python language) and Psychtoolbox (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 with the radiographer and their workflow in mind. *nordicAktiva* is delivered with a library of ready-to-use standard clinical paradigms including motor, language, visual and auditory tasks, that are designed according to ASFNR recommendations [21-22]. 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 standardisation 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 Repetition Time (TR) within the paradigm to make it compatible with accelerated acquisition protocols, 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.

2.8 Post-processing software

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 a model based on the paradigm design and haemodynamic response (see "Processing") to determine whether signal changes during stimulation are likely to have arisen due to brain activation caused by the presented stimulus. These maps are examined and reported by neuroradiologists before being passed on to neurosurgeons. The user has a plethora of post-processing software packages to choose from, including MR vendor solutions, as well as NordicNeurolab's *nordicMEDiVA**. In the context of clinical fMRI and DTI, it is essential to choose a software like *nordicMEDiVA* that allows for the export of BOLD overlays and diffusion fibre groups to presurgical planning stations and neuronavigational systems used by neurosurgeons, such as BrainLab, Stryker, Medtronic or Surgical Theater. Furthermore, the software should have an intuitive workflow for easy adoption in the clinics, and fast processing capabilities to handle large data throughput. 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 [26].

*nordicMEDiVA is only available in the US

3 Patient preparation and setup

3.1 Preparation for the exam

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. In addition to the usual MR safety considerations, it is paramount that the radiographer evaluates the patient's functional capacity and ability to perform a specific task. Very often, stroke or tumour patients have functional deficits, for instance difficulty in reading, speaking, and/or understanding instructions, or compromised motor function. Epilepsy patients can be sensitive to certain colours or colour 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 colours. 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 or scanner control room. The patient should be taken through what to expect for each of the paradigms and asked to rehearse each task to demonstrate their understanding and ability to complete it. *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 load, or respond covertly, but silently in their head.



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

Clinical fMRI: Where do I start?

3.2 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 a picture naming task, or a language task delivered audibly (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 auditory stimuli, and accounting for varying levels of proficiency, can go a long way to ensuring the success of the examination. Paradigm offerings within *nordicAktiva*, for example, include simplified versions for paediatric or impaired patients, but these could be used for anyone who finds the nature of the tasks difficult in any way. The factor which most contributes to success or failure of an fMRI exam is whether the subject fully understands the tasks they are being asked to complete.

3.3 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 once they are positioned at isocentre? At this point it might be necessary to modify the size of the letters, re-orient the LCD display or reposition the LCD screen (figure 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 briefly 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. Furthermore, the operator should consider asking the participant after each task how they felt it went. If the expected areas of activation are not seen, it can be valuable to simply repeat the paradigm.

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 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.

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

Sequence	Resolution, mm	TR, ms	TE, ms	Acceleration	Directions	B-value
3D T1-weighted structural scan	1 x 1 x 1	As per vendor library protocol	As per vendor library protocol	As per vendor library protocol	-	-
BOLD (without slice acceleration)	3 x 3 x 3 (Distance factor = 0)	3000	20–30	Parallel imaging with 2 or 3 times acceleration	-	-
BOLD (with slice acceleration)	2 x 2 x 2 (Distance factor = 0)	2000	20-30	Parallel imaging with 2 or 3 times acceleration; Three times acceleration	-	-
DTI (With or without slice acceleration)	2.5 x 2.5 x 2.5 (Distance factor = 0) or as close as possible, remaining isotropic	Shortest allowable (dependent on acceleration, coverage, etc.)	Lowest possible	Parallel imaging with 2 or 3 times acceleration; Three or more times slice acceleration where possible	≥32	~1000-2000

4.1 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 fibres and areas of activation are in the expected locations and aiding in localisation.

4.2 The BOLD sequence

BOLD images are usually obtained using a gradient-echo EPI sequence. For vendor supplied BOLD sequences, specific parameters will be available to ensure accurate timing as well as to optimise the inline processing, if available on the scanner.

Clinical fMRI: Where do I start?

The illustration in figure 5 outlines some of the most important BOLD-specific parameters and options to consider when setting up the protocol on the scanner. In addition to the below, spatial resolution is also an important consideration, particularly for pre-surgical planning where visualisation in 3D is the endpoint, and isotropic acquisitions with no slice gap are highly recommended.

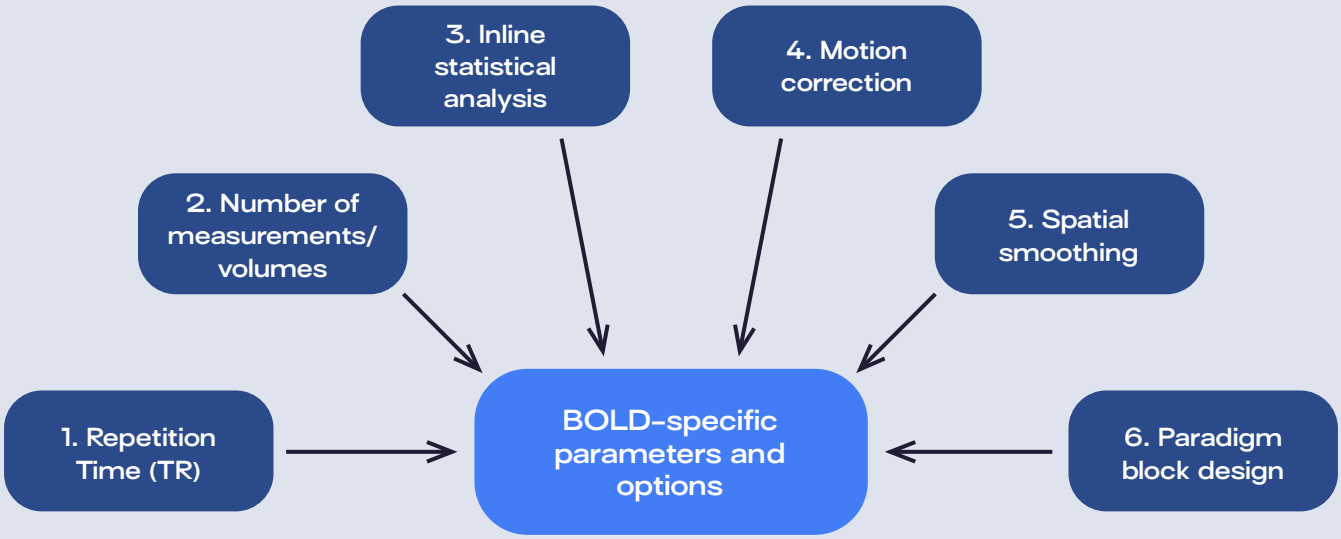


Figure 5. An illustration of the factors specific to a vendor supplied BOLD sequence, which should be set up to ensure timing accuracy and optimal in-line image presentation.

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

Whilst the scan is running, the scanner can perform some basic processing inline. This has two main benefits. Firstly, statistical t-maps can be created automatically, 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. Secondly, and perhaps more importantly, some visualisation of the inline statistical maps is typically available in real time during the scan. Although these previews 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. Furthermore, retrospective motion correction is often available, although it needs to be considered whether the post processing software will also be performing motion correction, as this should not be applied twice. For ease of inline visualisation of activations by the radiographer, it is recommended that a spatial (smoothing) filter of at least 1.5 times the in-plane resolution of the sequence is used (see 'Processing'). Finally, in order to ensure the accuracy of the inline processing, it is necessary to set up the block design of the paradigm. Depending on the MR vendor, this may be set up within the sequence cards, or in a separate application. It is common to specify which measurements are active (during the task) and which are baseline (during rest) for one 'cycle' of the paradigm, i.e., baseline & active blocks. For example, for a simple 'On/Off' paradigm with 10 measurements per block, one cycle would be 20 measurements. Each of these 20 measurements must be specified as 'Baseline' or 'Active'. For a more complex paradigm with two different active conditions such as Rest – Right-hand finger tapping – Left-hand finger tapping, also with 10 measurements per block, one cycle would be 30 measurements. Here, if it is not possible to specify two different active conditions on the scanner (e.g., left and right), then all measurements during finger tapping can be marked 'active', but the operator will expect bilateral activation from the inline results, and the data will need to be re-processed offline to separate out the two active conditions.

It is advisable to create a library protocol with correct parameters for all required paradigms, labelled with the paradigm name, to minimise the setup time and the potential for errors during a session.

4.3 The impact of slice acceleration techniques

Multiband (MB) or 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 [27-28].

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

Clinical fMRI: Where do I start?

4.4 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 describing the block design of the presented paradigm for archiving purposes. The design can be easily entered into *nordicMEDiVA* post-processing software.

4.5 DTI

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

5 Processing

5.1 An overview of the steps

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

Table 2. A summary of common processing parameteres used in fMRI.

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 image slices are not all acquired simultaneously within indvidual volumes. This cannot be applied to slice accelerated data.
Spatial filtering	A smoothing kernel is commonly applied to help improve visualisation 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, for example.
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 haemodynamic response function	The effect of a stimulus on the blood flow in the brain is not immediate but is characterised by a haemodynamic response function (HRF). A model of the HRF should be included in the analysis (figure 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. *nordicMEDiVA* provides automated thresholding to 40% of the maximum t-value as a starting point to assist with standardisation [29].
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 (figure 7). Clustering is applied in 3D and may typically be set to 30 or 50 voxels, depending on resolution and SNR.

Figure 6: (a) Boxcar diagram of a straightforward On/off paradigm, and (b) the design graph incorporating a model of the haemodynamic response function.

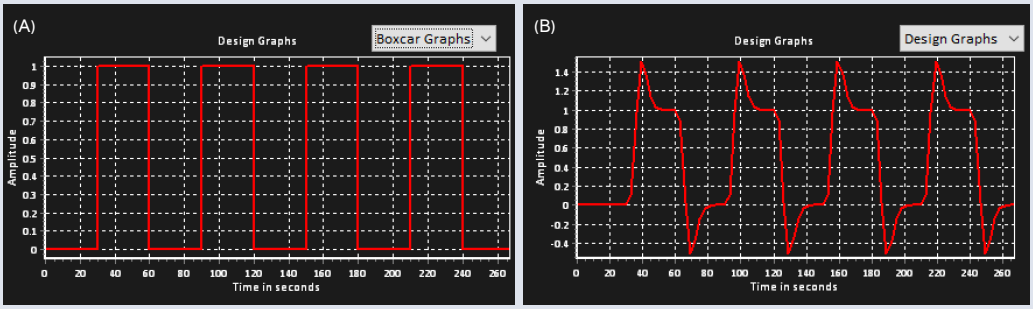
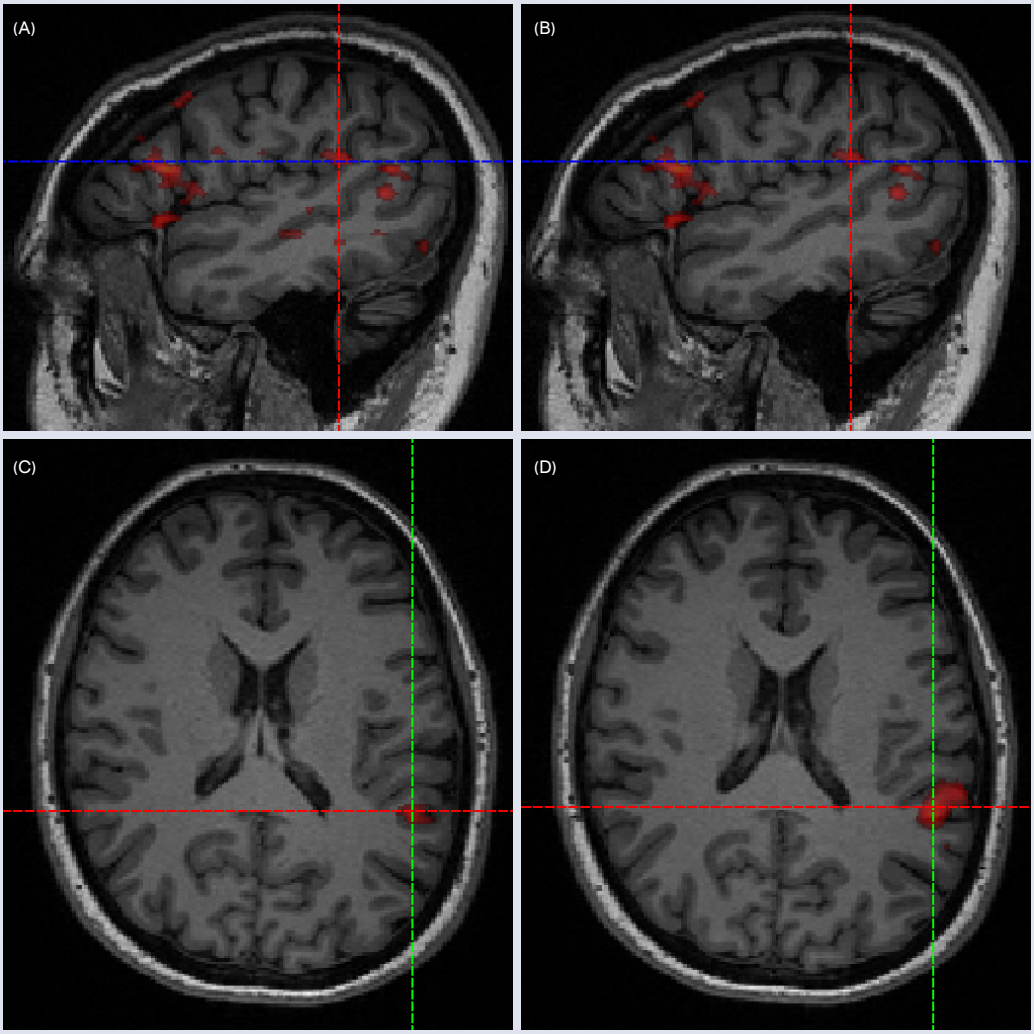


Figure 7: Visualisation of language areas (a) without and (b) with clustering of 30 voxels, showing the ability to remove spurious noisy areas of false positive activation. Wernicke's area with (c) no spaitial smoothing filter, and (d) with 6x6x6 mm smoothing.



Clinical fMRI: Where do I start?

5.2 Conditions and contracts

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, if using *nordicMEDiVA*, one would specify a contrast matrix with one element, e.g. [1]. This means that the software will check for voxels where the signal is greater during the active measurements than during baseline. If two active conditions are included, such as right hand (first condition) and left hand (second condition) finger tapping, the contrast matrix would have two elements. One can compare each hand separately with the baseline condition, resulting in contrast matrices of [1 0] (right hand greater than baseline) and [0 1] (left hand greater than baseline), and/or one can compare each hand with the other, resulting in contrasts of [1 –1] (right hand greater than left hand) or [–1 1] (left hand greater than right hand). 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 (SMA), the two hands should be analysed separately.

5.3 The use of inline processing

As previously described, it is possible to specify pre-processing steps and the block design timings within the scanning protocol, which allows for inline calculation of statistical maps. In this 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, visualisation can be difficult. Increasing the spatial smoothing and applying clustering can greatly help in these cases, especially for lateralisation. The user has a lot of flexibility in their choice of pre-processing parameters, depending on the chosen software, and this can sometimes be overlooked.

5.4 The use of nordicMEDiVA for BOLD processing

nordicMEDiVA provides automated GLM calculation through predefined image processing routes. These routes are configured to exactly match the paradigm design presented during the experiment, ensuring consistent and reproducible processing across all patients undergoing the same paradigm. Each route includes default parameters for preprocessing and contrasts, which can be easily modified if desired. Once a processing route has been created in nordicMEDiVA, it can be set to automatically trigger for subsequent patients based on the same

5.5 Multiple overlapping activation maps

Particularly for language or memory paradigms, it can be difficult to clearly visualise 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 3 paradigms are used.

5.6 Processing of DTI data alongside BOLD

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

6 Conclusions – Setting up an fMRI service

Functional MRI is most commonly 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 datasets of various formats (both from BOLD and DTI data), to optimise 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 optimisation. 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 under-gone 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 application specialists is paramount, for sequence and workflow optimisation as well as paradigm delivery. It can be beneficial for the multi-disciplinary team to discuss with the application 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.

Clinical fMRI: Where do I start?

Even once the service is up and running, additional application 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. Enough high-quality training should be provided by the manufacturers of MRI scanners and fMRI equipment to enable hospitals with many or few resources to at least succeed in reliable motor and language mapping.

Need support?

Are you interested in learning more about functional MRI? NordicNeuroLab can offer training to suit your needs. If you would like to discuss how we might help you via onsite or online support, please contact our team of dedicated scientists at

applicationsupport@nordicneurolab.com

Clinical fMRI: Where do I start?

References

1. Castellano A et al. (2017), Functional MRI for Surgery of Gliomas. *Current Treatment Options in Neuroradiology*, 19:34.
2. Orringer D et al. (2012), Clinical Applications and Future Directions of Functional MRI. *Seminars in Neurology*, 32(4):466–475.
3. Bizzi A (2009), Presurgical Mapping of Verbal Language in Brain Tumours with Functional MR Imaging and MR Tractography. Neuroimaging Clinics of North America, 19:573–596.
4. Tieleman A et al. (2009), Preoperative fMRI in tumour surgery. *European Radiology*, 19:2523–2534.
5. van Heereden J et al. (2014), Functional MRI in clinical practice: A pictorial essay. *Journal of Medical Imaging and Radiation Oncology*, 58:320–326.
6. Towgood K et al. (2015), Bringing Memory fMRI into the Clinic: A Comparison of Seven Memory fMRI Protocols in Temporal Lobe Epilepsy, *Human Brain Mapping*, 36:1595–1608.
7. Massot-Tarrus et al. (2019), Comparing the Wada Test and functional MRI for the presurgical evaluation of memory in temporal lobe epilepsy. *Current Neurology and Neurosience Reports*, 19:31
8. Benjamin CFA et. al. (2018). Presurgical language fMRI: Clinical practices and patient outcomes in epilepsy surgical planning. *Human Brain Mapping*, 39:2777–2785.
9. Goldstein HE et al. (2022). Precision medicine in pediatric temporal epilepsy surgery: optimization of outcomes through functional MRI memory tasks and tailored surgeries. *Journal of Neurosurgery Pediatrics*, Jul 1:1–12.
10. Sirnsek F et al. (2017), Neural activation during cognitive reappraisal in girls at high risk for depression. *Prog Neuropsychopharmacol Biol Psychiatry*, 77:49–56.
11. Zhang B et al. (2017), Altered task-specific deactivation in the default mode network depends on valence in patients with major depressive disorder. *Journal of Affective Disorders*, 207:377–383.
12. Wang X et al. (2017), Early Changes in Cortical Emotion Processing Circuits after Mild Traumatic Brain Injury from Motor Vehicle Collision. *Journal of Neurotrauma*, 34(2):273–280.
13. Szabo AG et al. (2017), Impaired mixed emotion processing in the right ventrolateral prefrontal cortex in schizophrenia: an fMRI study. BMC Psychiatry, 17(1):391.
14. Amgrim N et al. (2019), Effect of hypoxia on BOLD fMRI response and total celebral flood flow in migraine with aura patients. Journal of Celebral Blood Flow and Metabolism, 39(4):680–689.
15. Dimoka A et al. (2012), How to conduct a functional magnetic resonance (fMRI) study in social science research. *MIS Quarterly*, 36(3):811–840.

nordicMEDiVA is only available in the US

16. Lambert B et al. (2017), A functional MRI study on how oxytocin affects decision making in social dilemmas: Cooperate as long as it pays off, aggress only when you think you can win. *Hormones and Behaviour*, 94:145-152.
17. Bethlehem R et al. (2013), Oxytocin, brain physiology, and functional connectivity: a review of intranasal oxytocin fMRI studies *Psychoneuroendocrinology*; 38(7):962-74.
18. Gawda B et al. (2017), Valence of Affective Verbal Fluency: fMRI Studies on Neural Organization of Emotional Concepts Joyand Fear. *Journal of Psycholinguistic Research*, 46(3):731-746.
19. Hsu CT et al. (2018), How mimicry influences the neural correlates of reward: An fMRI study. Neuropsychologica, 116(Pt A):61-67.
20. Amaro E & Barker GJ et al. (2006), Study design in fMRI: Basic principles. *Brain and Cognition*, 60:220-232.
21. Black DF et al. (2017), American Society of Functional Neuroradiology-Recommended fMRI Paradigm Algorithms for Presurgical Language Assessment. *American Journal of Neuroradiology*, 38:E65-E73.
22. American Society for Functional Neuroradiology. Available: https://www.asfnr.org/wp-content/uploads/ASFNR-BOLD-Paradigms.pdf
23. Siemens Healthineers (2019), MRI Patient Experience Accessories. Available: https://www.siemens-healthineers.com/en-uk/magnetic-resonance-imaging/patient-experience
24. Lemaire C et al. (2009), Impact of audio/visual systems on pediatric sedation in magnetic resonance imaging. Journal of Magnetic Resonance Imaging, 30(3):649-655.
25. *fMRI Techniques and Protocols*, 2nd ed. Ed. Massimo Filippi, Neuromethods 119, Springer Protocols.
26. Unadkat P et al. (2019), Functional MRI Task Comparison for Language Mapping in Neurosurgical Patients. Journal of Neuroimaging, 29:348-356.
27. Hoge R et al. (2015), Improving Sensitivity and Specificity in BOLD fMRI Using Simultaneous Multi-Slice Acquisition. Magnetom Flash, 63: 65-69.
28. Bouchard LO et al. (2017), Simultaneous Multi-Slice: a Case-based Presentation of Pre-Operative Brain Tumor Evaluation. Magnetom Flash, 68:19-21.
29. Voyvodic JT (2012), Reproducibility of single-subject fMRI language mapping with AMPLE normalization. Journal of Magnetic Resonance Imaging, 36(3):569-580.

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