Clinical Functional Magnetic Resonance Imaging for Pre-surgical Planning – the Singapore General Hospital Experience with the First 30 Patients

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Abstract

Introduction: Functional magnetic resonance imaging (fMRI) is a neuroradiological technique for the localisation of cortical function. FMRI made its debut in cognitive neuroscience and then eventually to other clinical applications. We report our experience with pre-surgical fMRI on a high field scanner, based purely on a clinical platform. Materials and Methods: The protocols included motor, auditory, visual and language fMRI. The choice of protocols was dependant on clinical request and lesion locale. Results: Retrospective analysis and audit of the first 30 consecutive patients over a 12-month period revealed that about 85% of patients had a successful examination. In a pictorial essay, we demonstrate that patients with weakness in performing a motor task showed abnormal activations of the pre-motor and supplementary motor areas. Conclusion: FMRI data greatly enhances the pre-surgical planning process and the conduct of surgery when it is incorporated into the surgical navigation system in the operating theatre.

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Key words: fMRI, Pre-surgical planning, Task activation

Introduction

It is pertinent to mention Pierre Paul Broca's historical report from 1861 and state-of-the-art functional neuronavigation in the same sentence as it illustrates the continuous efforts expended by investigations in refining the golden rules for identifying locations of functional areas.[1] One remarkable example is the visualisation of the omega-like shape of the part of the primary motor cortex that involves hand movement. Susceptibility-weighted imaging (SWI), one of the latest developments in magnetic resonance imaging (MRI), monitors sensitively the amount of iron in the brain which is presumably higher in gray matter compared to white matter, and thus provides increased contrast between the two tissues compared to conventional images.[2] The 'omega' in SWI, identifies the motor hand area with ease (Fig. 1), in contrast to the 'knob' on the precentral sulcus, which may be visualised with difficulty in T1-weighted studies.[3]

Functional MRI (fMRI) was initially designed to map changes in blood volume in the region of the brain while it responds to a stimulus. The patient or volunteer usually rests and receives specific stimuli in a repeated manner.[4] Further major milestones for fMRI were mapping of changes in blood oxygenation and perfusion,[5,6] and most recently the quantitative measures of oxygen metabolism. This article deals with blood oxygen level-dependent (BOLD) contrast that originates from changes in the amount of oxyhaemoglobin in the capillaries close to the source of neuronal activity. This is referred to as a positive BOLD response as there is an increase in oxygenated blood flow to the active brain area outweighing the additional demand on oxyhaemoglobin. Oxyhaemoglobin is diamagnetic (no net unpaired electrons) while deoxyhaemoglobin is paramagnetic (suggesting at least one unpaired electron in the complex). BOLD fMRI takes advantage of this difference by means of susceptibility (T2*) weighted MRI sequences that result in higher signal intensities where the oxyhaemoglobin level is higher.

Based on a myriad of similar developments,[7] fMRI has become the most widely used method for imaging brain areas activated by a task in cognitive neuroscience, and on a slower timescale, in clinically related research such as neurological and psychiatric disorders, and in routine pre-surgical clinical cases.

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Table 1

Patient	Age/Gender	Histology	Location	fMRI for localisation of:	Notes
1	45/M	Gliosarcoma (WHO grade IV)	left temporal lobe	Motor: finger, ankle Speech	Premotor/SMA activation of ankle task Broca and Wernicke activation
2	35/M	Fibroblastic meningioma	parafalcine	Motor: ankle	Premotor/SMA activation of ankle task
3	57/M	Metastatic carcinoma (lung primary)	left frontal lobe	Motor: finger, lip, ankle Speech	Activation of Broca's area only
4	22/M	Arterio-venous malformation	left frontal lobe	Motor: finger, ankle Speech	Activations of Broca's and Wernicke's areas
5	37/M	Arterio-venous malformation	right parietal-occipital	Vision	
6	55/M	Vascular malformation (negative for malignancy)	right parietal lobe	Motor: finger, lip, ankle	
7	69/F	Metastatic adenocarcinoma (GI tract primary)	right frontal lobe	Motor: finger, ankle	
8	31/M	Astrocytoma (WHO grade II)	left frontal lobe	Motor: finger, ankle	
9	44/M	Arterio-venous malformation	left parietal lobe	Motor: finger, ankle	Right motor activation undetected at threshold >4 but premotor/SMA activation of ankle task
10	56/M	Metastasis (No operation/biopsy)	left fronto-parietal	Motor: finger, lip	
11	59/M	Metastatic adenocarcinoma (lung primary)	right frontal lobe	Motor: finger, ankle	
12	48/M	Mixed oligodendroglial-astrocytic tumour (high grade)	right fronto-parietal	Motor: finger, lip Auditory	Right fMRI activities of auditory and lip areas are masked
13	20/F	Tumour (No operation/biopsy)	right postcentral gyrus	Motor: finger, ankle	Left motor activation undetected at threshold >4 but premotor/SMA activation of ankle task
14	50/F	Anaplastic glioma (WHO grade III)	right frontal lobe	Motor: finger, lip, ankle	Premotor/SMA activation of ankle task
15	32/F	Demyelinating pseudotumour	right parietal lobe	Motor: finger, lip	Auditory
16	49/F	Right temporal lobe epilepsy		Speech	Activations of Broca's area and right hemisphere homologue and Wernicke's area
17	18/F	Astrocytoma (WHO grade II)	left parietal lobe	Motor: finger, ankle	Right motor activation undetected at threshold >4 but premotor/SMA activation of ankle task
18	13/F	Arterio-venous malformation	right frontal lobe	Motor: finger, lip, ankle	
19	38/F	Oligodendroglioma (WHO grade II)	right fronto-parietal	Motor: finger, lip, ankle	SMA activation of finger task
20	21/F	Anaplastic ependymoma (WHO grade III)	right parietal lobe	Motor: finger	
21	38/F	Astrocytoma (WHO grade IV)	right frontal lobe	Motor: finger, ankle	Premotor/SMA activation of ankle task
22	33/F	Supratentorial primitive neuroectodermal tumour (WHO grade IV)	left frontotemporoparietal lobe	Motor: finger	
23	38/M	Glioblastoma multiform	left precentral gyrus	Motor: finger, ankle	Premotor/SMA activation of ankle task
24	47/F	Meningioma	left parieto-occipital	Motor: finger, lip Vision	
25	44/F	Glioblastoma multiform	high right parietal	Vision	
26	24/M	Adenoid cystic carcinoma	right frontal lobe	Motor: finger, ankle Auditory	

fMRI: functional magnetic resonance imaging; SMA: supplementary motor area

Visual fMRI was performed at 1.5T (Magnetom Avanto Siemens)

What is common and different when comparing fMRI as a tool for studying brain function in cognitive neuroscience versus pre-surgical planning? Firstly, the choice of a paradigm depends on the objective of a study. While cognitive processes are generally complex and may require more than one type of stimulus,[8] the aim for pre-surgical planning is to identify areas of the brain that affect the patient's ability to function with regard to speech, vision, hearing and muscle control, which are either perceptive or motor processes. In these cases, the paradigms are quite simple, such as rest-task block paradigms.[8] Another aspect is the subject group. Volunteers who participate in research studies are focused and are able to concentrate on a strict protocol. On the other hand, the patient's awareness of an impending life-threatening disease may impair their attention. For example, the question 'Am I going to lose all these functions?' may recur in their mind and impair the performance of the task. In addition, the task may be difficult for those with compromised functions due to the underlying disease.

The objective of this study is to illustrate our experience with fMRI in patients undergoing imaging for pre-surgical planning in our institution.

Materials and Methods

Patients underwent fMRI on a 3T scanner (Magnetom Verio, Siemens Erlangen, Germany). The system was equipped with a 12-channel headcoil. The examination protocol consisted of 3 steps. The first involved 3D-MPRAGE with isotropic resolution of 0.9 mm: TR/TE/TI 1900/2.48/900, flip angle 9 degrees, iPAT 2. In the second step a gradient field map was collected to display areas of high magnetic susceptibility and possible geometric distortion. The last step involved the T2*-weighted EPI measurement and 3D-PACE real time motion correction using parameters of TR/TE 3000/30, slice thickness 3 mm, 64 times 64 matrix, slice orientation to the inter-commissural line (anterior commissure to the centre of the posterior commissure).

Paradigm parameters: Block design with either stop-go commands or music off-on. Three cycles, 60 seconds per cycle. Twenty volumes scanned per complete cycle. The Neuro3D task card within the syngo application software was used interactively during the fMRI examination to evaluate the progress of the examination. It combined morphological or structural imaging with functional MRI information. In particular, 3D-MPRAGE dataset was overlaid by both the gradient field map and the BOLD images. Online analysis of the fMRI times-series including General Linear Model (GLM) statistics[9] and *t*-score thresholding >4 (on significance of activation[10]) and a clustering size of 16 voxels enabled real-time assessment and facilitated the decision either to continue with the next task or to repeat the last task.

The protocols included motor, auditory, visual and language fMRI. Motor: tapping fingers against thumb, using both hands, lip puckering, ankle turning one side at a time. Auditory: non-lyrical music. Vision: flashing checkerboard presentation. Language: Sentence generation when given nouns via auditory input. Choice of protocols was dependant on clinical request and lesion locale, for example, vision for lesions close to visual cortex, speech for lesions close to eloquent temporal cortex.

Results

Thirty patients were referred for pre-surgical planning between April 2008 and March 2009. Four patients could not perform the fMRI tasks, and thus pre-surgical fMRI and diagnosis were made in the remaining 26 patients. The results of the entire patient group comprising both clinical and fMRI data are summarised in Table 1. This retrospective review has been approved by our Institutional Review Board.

We opted to illustrate 5 cases of different fMRI tasks in a pictorial essay, namely Patient 8 (Fig. 2), Patient 26 (Fig. 3), Patient 2 (Fig. 4), Patient 1 (Fig. 5) and Patient 16 (Fig. 6).

In patients with weakness in performing a motor task, robust activation of the supplementary motor area (SMA) is observed at high *t*-score thresholds of >7 compared to volunteers of a t-score threshold of 4.5 ± 0.5 (group size n = 8). Patients with abnormal SMA activations are listed in the column 'Notes' in Table 1. Figure 7 depicts a representative case (Patient 19).

Discussion

The challenge in brain neurosurgery is to remove a lesion as extensively as possible while preserving as much as possible primary functions (motor, language, auditory, vision) if these are functions of the surrounding areas.[11] Perceptual and cognitive deficits remain inevitable risks of lesion removal.

Clinical fMRI differs from neuroscience fMRI research studies as paradigms must be:

simple, to be feasible for patient with neurological deficits,

fast, to be compatible with heavy clinical load, and

sensitive, to perform single subject analysis.

Establishing standards for clinical fMRI is an evolving process not only between institutions, but also within the same Radiological Department. Trying not to do too many things at the same time might be the first step. For example, we use the lip task to illustrate the face area (inferior part of the motor cortex), finger tapping task for the arm and hand area (middle part of the motor cortex), and ankle

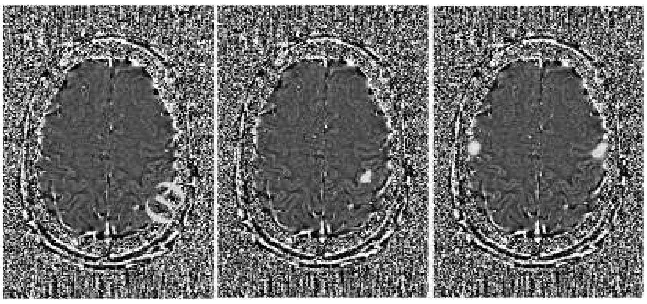

Fig. 1a.

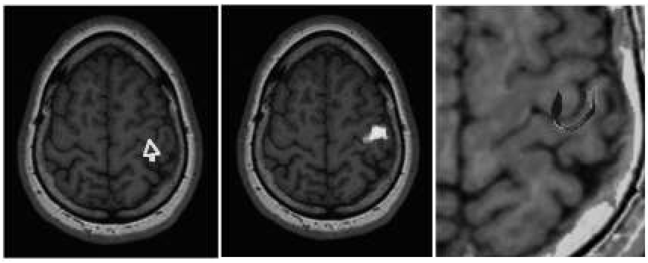

Fig. 1b.

Fig. 1. Volunteers' data.

a) Susceptibility-weighted image of the motor hand area. Left: SWI Filtered Phase Image; middle: tapping fingers against thumb of right hand showing activation within the 'omega'; right: Listening to a piece of piano music. Activation of pre-motor hand area.

b) FMRI of tapping fingers against thumb reveals subject's variations in the proportion of pre-to-post central activation based on different tactile sensations. Left: 'arrow' indicates the knob on the precentral gyrus (motor hand area). Middle: Pronounced activation of the somatosensory cortex. Right: Association fibers (U-fibres) connecting the activation area of b) with the motor hand area.

turning task for the leg area (superior part of the motor cortex). Since the motor hand areas are well lateralised over each cerebral convex side, finger tapping of both hands is performed simultaneously. Unlike finger tapping, ankle turning is done one side at a time because the cortex which corresponds to the legs is paramedian in location, lying on either side of the medial longitudinal fissure. Thus, activation patterns may have merging borders if the tasks were performed simultaneously. In our observation, single ankle turning tasks also induced less activity of the adjacent supplementary motor cortex for a better delineation of the different activation areas.

It is well reported that activation of non-motor primary areas such as pre-motor cortex and SMA is regularly visible during a complex finger movement task while for simple finger movement without further coordination requirements such as tapping fingers against thumb activation of the sensorimotor cortex is the dominant signal[12] (Fig. 1). However, when a patient encountered weakness in a particular movement, such as ankle turning, this was generally associated with activations of the pre-motor cortex and SMA (Table 1). In some cases of severe weakness in the ankle movement, involuntary movements of the other

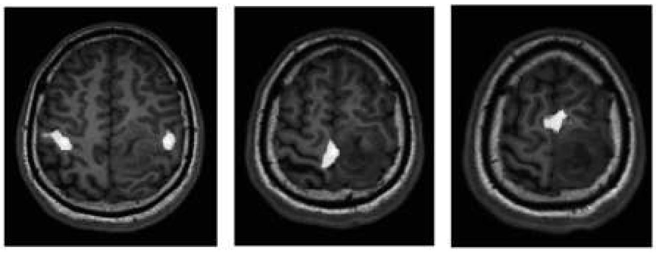

Fig. 2a. Fig. 2b. Fig. 2c.

Fig. 2. Low grade glioma located in the left perirolandic area with thickening of the associated gyri. a) The right finger/hand activation is just located lateral to the areas of gyral swelling. FMRI activation of motor cortex for b) left ankle turning while c) right ankle turning shows only SMA activation. Activation within the affected motor cortex is undetected at t-score threshold >4.

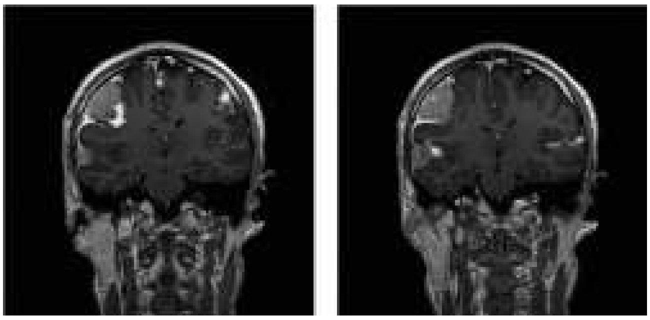

Fig. 3a. Fig. 3b.

Fig. 3. Multiple metastases from primary adenoid cystic carcinoma. The largest mass is present in the right frontal region and a smaller mass in the right temporal region. a) The lip puckering activity lies just deep to the anterior margin of the tumour; b) Auditory activation of right transverse temporal gyrus of Heschl shows the activity to lie close to the dural metastasis in right temporal region.

ankle and even of shoulder/elbow in an attempt to move the weak ankle were noted. Cases of hand-, ankle-, lip-, and auditory-fMRI are shown in Figures 2 to 4.

Several approaches for evaluating language localisation and lateralisation in Broca's area (inferior frontal lobe) and Wernicke's area (posterior superior temporal gyrus) are well described, namely word generation,[13] verb generation, sentence generation, simple object naming, passive listening, noun-verb semantic association task, and other language comprehension tasks. All are based on the block design with either visual or auditory stimulus presentation. In summarising the different tasks, the results of activation and the success rate in localisation of the 2 language domains are inconsistent, especially for mapping Wernicke's area. On the other hand, this overview shows that tasks which stress comprehension of sentences and phrases yield stronger activation in Wernicke's area than do fluency and single word semantic decision tasks as it is a combination of speech production (articulation) and speech perception (understanding the spoken word).[14] Sentence formulation contains properties of spontaneous speech,

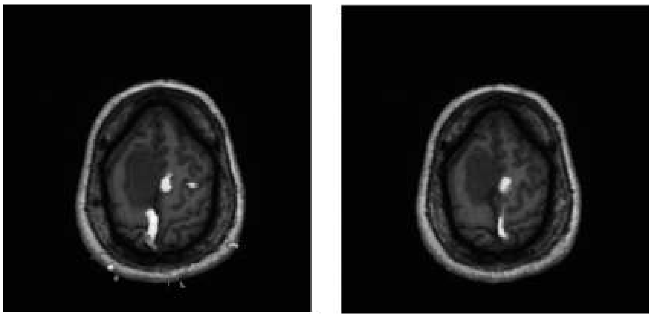

Fig. 4a. Fig. 4b.

Fig. 4. Falx meningioma. FMRI activations of motor cortex (posterior) and SMA are delineated for both a) left ankle turning and b) right ankle turning. Functional motor activation for leg/foot movements noted to be superior and posterior to the mass.

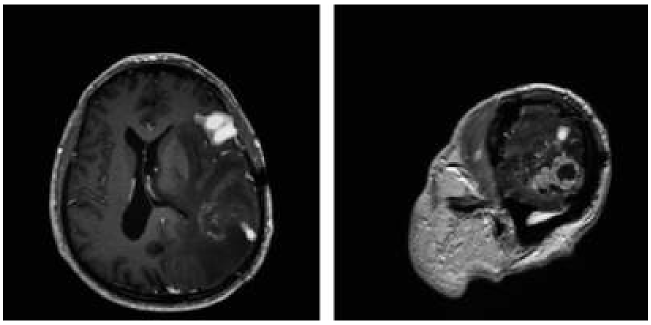

Fig. 5a. Fig. 5b.

Fig. 5. Gliosarcoma located in the temporoparietal region in the left hemisphere. There is significant perilesional vasogenic oedema, midline shift and mass effect. Language fMRI shows a) left frontal lobe activation in Broca's area, located just anterior to the area of oedema, while b) Wernicke's area appears displaced superiorly.

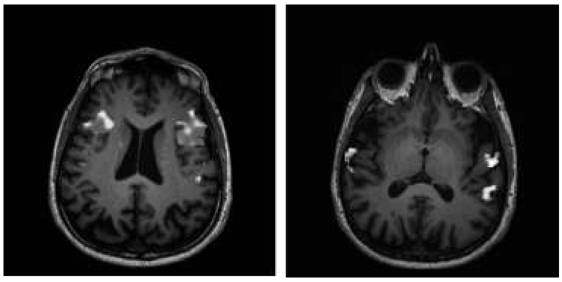

Fig. 6a. Fig. 6b.

Fig. 6. Temporal lobe epilepsy. a) Language fMRI reveals bilateral inferior frontal lobe activation in Broca's areas and b) auditory activation in bilateral temporal lobe and in left Wernicke's area (activity denoted posterior to temporal lobe). Activation in bilateral Broca's areas is a common finding in subjects forced to change from left-handedness to right-handedness in their childhood, as was the case in this patient.

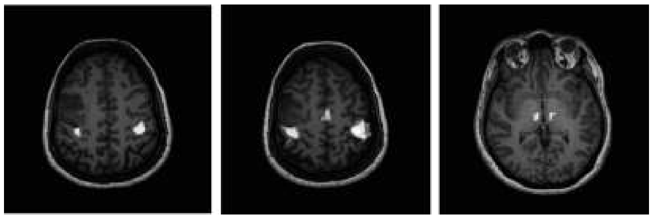

Fig. 7a. Fig. 7b. Fig. 7c.

Fig. 7. Low grade oligodendroglioma. FMRI of tapping fingers against thumb shows a) a smaller area of activation in the hand area of the right hemisphere (posterior to the tumour) compared to the left hemisphere, b) SMA at *t*-score threshold of 7, c) thalamus activation at *t*-score threshold of 4. Increased SMA and thalamic activations (compared to volunteers) may indicate a higher coordination hurdle in performing the task for this patient.

such as speech errors, hesitations, self-repairs and correct usage of grammar, for example, 'dogs bite' or 'a dog bites'. Thus it has a higher complexity of language function than for example the 'verb generation' task.

Both auditory and/or visual presentations are possible ways to activate language tasks.[15] We used a paradigm of sentence generation based on nouns presented as an auditory paradigm. In our experience, auditory presentation appears to have an advantage over visual stimulus presentation. During visual stimulus presentation, there is a possibility that the patient may abandon himself to his thoughts. Thus, instead of monitoring task performance, for example, by pressing buttons on a keypad, which is sometimes confusing, keeping the patient attentive with periodic task commands will be a better way. This in turn results in greater effectiveness of the underlying task activation. We intend to validate this observation in future studies. Thorough training in the task prior to fMRI is mandatory. The patient has to become familiar with the voice of the technician performing the fMRI examination. Initially, the patient has to say aloud the sentences when nouns are given. Depending on the patients' individual linguistic abilities, the frequency of presented nouns is varied from 4 to 6 per 30 seconds. Subsequently the procedure is repeated, but the patient now generates the sentence silently. However, the auditory stimuli may result in an overlap of auditory and language associated activity in the region of the superior temporal gyrus in some cases, as inter-subject variability of location of Wernicke's area is high.[16]

While single fMRI paradigms are used for the assessment of language laterality in preoperative brain tumour patients, different aspects of language processing such as verbal fluency, reading comprehension and auditory comprehension should be tested in a combined analysis of pre-surgical epilepsy evaluation. However, fMRI does not have the accuracy in determining hemisphere language dominance compared to the intracarotid amobarbital test (Wada test).[17]

This is demonstrated in Figures 5 and 6. The benefit-to-risk ratio is different for these 2 cases. The first case (Fig.

5) involves a recurrence of a glioblastoma multiforme in which surgery is mandatory. The goal of fMRI was to identify eloquent areas in the distorted pathological brain. The other case (Fig. 6) is a patient suffering from temporal lobe epilepsy, who in childhood, was forced from left-handedness to right-handedness. Language fMRI done according to our protocol showed activations of Broca's area and its right hemisphere homologue bilateral activation of Broca's area, but left lateralised activation of Wernicke's area. This result does not clearly provide an answer as to which is the dominant hemisphere for language and indicates that further testing needs to be done.

In conclusion, our neurosurgeons have found the addition of functional MRI data to greatly enhance the pre-surgical planning process and the conduct of surgery when it is incorporated into the surgical navigation system in the operating theatre, which also comprises high resolution structural scans and diffusion tensor imaging.

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