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Session: An Update on fMRI

Title: Clinical Applications of fMRI: from Presurgical Planning to Functional Connectivity

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Highlights:

- Neurosurgical decision-making critically revolves around current and potential Quality of Life.
- Greater understanding of key functional systems in the brain, and their adaptive potential, dramatically increases the relevance of brain mapping techniques to optimise individual patient outcomes.
- fMRI allows mapping of key functional regions and related networks that can assist the clinician in determining surgical risks and boundaries, predicting cognitive outcome/recovery, and selecting patients for surgery previously considered inoperable.
- Improved knowledge of how functional systems are organised and interact, based on task, resting and diffusion MRI, promises a great step towards individualized medicine.

Target Audience

Translational neuroscientists, psychologists, physicists, radiologists and clinicians involved in the development and/or application of research fMRI methods for personalised treatment of neurosurgical patients, who already have an understanding of the basis of BOLD- fMRI and general analysis principles.

Outcomes/Objectives

This teaching session lecture aims to outline the current primary applications of functional MRI in neurosurgical settings, providing an overview of

- Neurosurgical questions for which fMRI offers a direct clinical utility as well as those for which fMRI is not currently useful / indicated
- Key methodological and interpretative limitations facing fMRI applications to presurgical planning
- Current promises and challenges for clinical applications of fMRI connectivity

Purpose

In the 2 decades since the introduction of functional MRI has provided researchers with a unique window onto human brain function, the majority of translational research efforts have focused on 3 main areas: (i) measuring and predicting effects of therapy (drug or rehabilitative), (ii) early diagnosis of neurodegenerative risk factors, and (iii) planning neurosurgery. The application of fMRI to diagnostic and therapeutic areas primarily aims to uncover mechanisms of disease / drug action and its functional consequences. Where fMRI has come the closest to directly impacting clinical decision-making is in the field of neurosurgical planning.

When a patient presents with seizures or sudden focal neurological deficit and a clear, resectable lesion is diagnosed as the cause, the clinical question of *whether and how to treat* will depend on weighting the likely benefit of neurosurgical intervention against the potential risk of producing or exacerbating a deficit for the patient. Improvements in diagnostic imaging techniques over the years have enabled earlier diagnosis of low-grade tumours, often before neurological deficits are seen. Long-term outcome studies demonstrate a significant clinical benefit from larger resections for both seizure control[1] and low-grade gliomas[2]. Thus, the clinical dilemma is escalated, since large resections would carry a greater risk of producing impairments in young patients who are overall behaviourally intact at the time of diagnosis. In these cases, functional mapping may help clinical decision-making to determine a) what functions are most at risk, b) planning the safest possible surgical route and c) whether/where to perform intraoperative mapping for an individual patient.

<u>Approach [Methods & Results]</u>
The motor, visual and auditory cortices have a highly characteristic and largely rigid anatomico-functional mapping. Surgical damage to motor and visual cortex risks producing profound and irreversible deficits. Outside these primary zones, high inter-individual variability in functional organization, especially in the presence of brain pathology such as epilepsy or a tumour, makes it essential to consider functional mapping to determine the risk-benefit ratio of neurosurgery to an individual patient. Pre-surgical functional MRI has demonstrated high sensitivity, as evaluated against intra-operative cortical stimulation, to identify motor and language regions[3] relevant to planning surgical approaches around an isolated lesion. In addition to basic motor mapping [Figure 1A], pre-surgical language mapping in many epilepsy centres has replaced invasive temporary lesion tests (the “Wada test”) to identify the hemisphere dominant for language [Figure 1B] due to the relative ease, repeatability and non-invasiveness of fMRI compared to the clinical alternative Wada test and direct cortical stimulation during surgery.

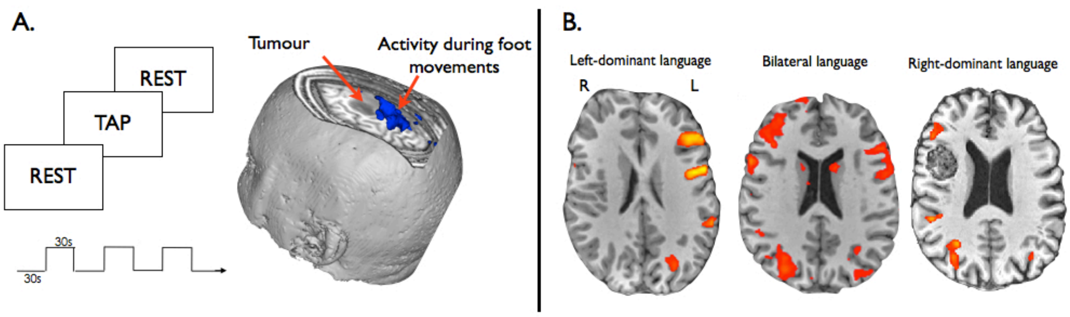

Figure 1. Mapping basic functions. A. Left: diagram of task paradigm using a standard block design during which a patient is visually instructed to rest or tap a specified limb in alternating blocks of 30-seconds. Right: T1-weighted scan of brain tumour rendered in 3D, displaying statistically threshold map of activation resulting from foot tapping around a low-grade tumour subsequently successfully removed. B. Variable fMRI language activation patterns in right-handed patients with left temporal lobe epilepsy (left and middle column) and in a left-handed patient with a right inferior frontal lobe cavernoma.

Given the widely acknowledged *potential* of fMRI, why is it not yet an intrinsic part of neurosurgical practice? Aside from limited resources (access to clinical MRI time and expertise), a number of interpretative challenges arise when considering functional activation maps for clinical decision-making. As with all fMRI studies, the quality of data acquired is influenced by factors such as patient head movement during the scan and potential pharmacological confounds (e.g. antiepileptic medication). If respiratory and cardiac cycle data are recorded using a simple respiratory bellows belt and a pulse monitor, physiological confounds that may produce false positive activation can often be successfully removed using dedicated and freely available post-processing software.

Additional issues arise specifically in neurosurgical populations. Unlike healthy volunteer studies, where interpretations are based on group-average activation maps, the neurosurgeon is concerned with reliable, relevant activity occurring in the individual patient's brain. The choice of which functions to map should therefore reflect what matters most for *that patient's* quality of life, their current performance and compliance levels. Depending on the nature of the lesion / pathology to resect (e.g. hippocampal sclerosis, tumour, cavernoma), the BOLD signal - on which the majority of fMRI studies are based - can be affected in unpredictable ways by pathological processes affecting the very regions we wish to map. As a result, standard statistical approaches may not be appropriate. Both model-based and data-driven analysis methods, minimizing *false negative* results and considering both increases and decreases in BOLD signal during the task are strongly recommended[4]. However, these do not overcome the limitation that fMRI is an *indirect* marker of neuronal activation and altered neurovascular coupling may reduce sensitivity to *true* functional activity. Direct cortical stimulation is therefore strongly advocated where possible and especially when the clinical question concerns activation within or bordering pathological tissue rather than basic hemispheric lateralization of function.

The true added benefit of fMRI to neurosurgical decision-making is difficult to establish objectively. Longitudinal pre-and post-operative fMRI assessment is critical in order to relate behavioural outcomes to pre-surgical fMRI activation maps. In the case of supplementary motor cortex, studies of surgery-induced transient impairments find direct correlations between the volume of fMRI 'activity' removed and post-operative deficits[5 & 6]. Fascinatingly, these and other longitudinal studies indicate that dynamic reorganization occurs not only in response to epilepsy and tumour growth, but is further modulated by neurosurgery. These plasticity-related processes, at least for some functions, might facilitate much greater recovery following neurosurgery than following stroke affecting the same regions[7]. If this proves to be a general feature of the chronic disease-affected brain, it has been suggested that 'multi-stage' interventions, halting surgery when functional borders are reached and continuing after some period to allow for 'plasticity', might allow resection of lesions in regions classically considered inoperable[8].

Such recent conceptual shifts in neurosurgical treatment from purely anatomy-based to function-based decision-making raise critical questions about the true nature and efficiency of reorganised neocortical activity for sustaining normal behavior. fMRI evidence of altered neural activation patterns does not automatically reflect *efficient* functional reallocation. In the context of neurosurgical decision-making, it is crucial therefore to consider all potential contributions to atypical fMRI activations, ideally using multiple tasks to establish reliability. Intraoperative direct electrical stimulation offers a powerful validation of fMRI activation, at least surrounding a lesion to be resected. Direct stimulation can assess function not only at the cortical level, but also subcortical structures and, critically, can be used to delineate essential functional *pathways*. But not all functions are suitable for awake mapping in the surgical theatre, which additionally requires a high level of cooperation from the patient. As such, cortical stimulation is not feasible in all patients, and does not allow validation of *contralateral* fMRI activations, which instead should be interpreted in the context of detailed neuropsychological assessments both before and after surgery. The combination of fMRI with techniques that disrupt or enhance neural activity, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), is therefore gaining increasing interest to study the consequences of disrupting one area of fMRI "activity" on related brain regions in widely distributed functional *networks* (see[9]).

Studies based on imaging and disrupting brain activity show that focal lesions affect remote brain areas within functional *systems* involving widespread regions of the brain[10]. In several of these systems, longitudinal outcome studies identify specific white matter pathways that must be preserved to sustain normal performance and facilitate post-operative recovery[8]. These findings have a number of direct clinical implications. Firstly, better knowledge is needed of neocortical and white matter communication within but also between functional networks to develop surgical approaches for patients with lesions in regions associated with high-level cognition. The inclusion of diffusion tensor imaging based fibre tractography when interpreting fMRI activation results is therefore strongly supported. Second, neurosurgical intervention should aim to preserve as far as possible functional regions and functional pathways not already affected by disease in order to preserve patients' quality of life[11]. Third, detailed studies are needed of neural changes underlying post-operative recovery in order to maximize surgical resections and tailor rehabilitative strategies. However, large-scale functional networks cannot readily be mapped using single (or even several) fMRI tasks in individual patients, who often cannot tolerate lengthy testing sessions. Instead, "resting fMRI" - which measures how strongly BOLD signal in one brain region correlates with that of another region during a relatively short (5-10 minute) scan – offers a valuable means of measuring functional connectivity within and among functional systems in the brain, particularly in children and patients less able to comply with fMRI task instructions. Basic sensorimotor and visual networks measured from resting fMRI closely match those derived from task fMRI as well as intraoperative cortical stimulation mapping[12]. However, the correspondence between specific cognitive functions and resting networks involving association cortices remains the subject of active research.

Beyond mapping of basic functions, resting fMRI has received great interest for its potential to map areas disrupted by pathology, particularly in the context where structural abnormalities are subtle or undetected, such as certain epileptogenic lesions. In this context, resting fMRI shows exciting promise to provide clinical value, for example in uncovering potential surgical resection zones undetected using conventional clinical tools (surface EEG, structural MRI, PET). However, as resting fMRI is correlational, not causal, extensive validation is required to differentiate brain regions containing primary brain pathology (which must be removed in order to control seizures) from regions secondarily affected by it. For example, grey matter density and white matter coherence, both known to be affected by chronic seizures, also change resting fMRI signal correlations within and outside of the epileptic zone[13] [Figure 2]. Additionally, as with task-based fMRI, statistical challenges arise in defining both regions of relevant BOLD signal correlations and their alteration in disease[14,15]. Here again, intraoperative stimulation and modulation of brain activity using TMS/tDCS will be invaluable to determine the accuracy, reliability and specificity of resting fMRI as a clinical tool.

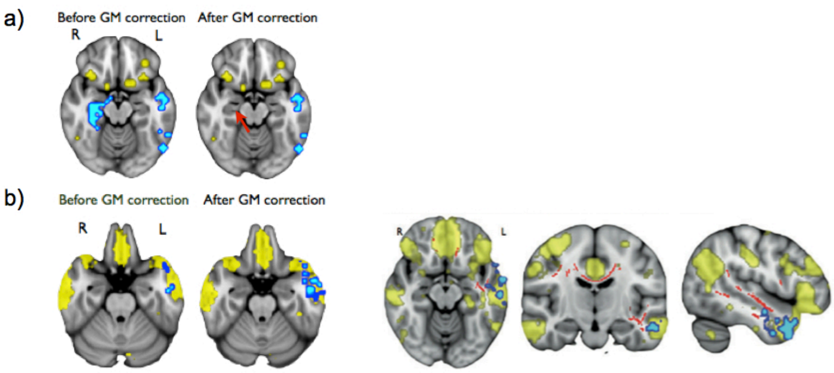

Figure 2. Altered resting fMRI signal 'connectivity' in temporal lobe epilepsy (TLE). a) Reduced ($p<0.05$) resting 'connectivity' in right-TLE patients compared with healthy controls between the right hippocampus (blue) and posterior default mode network (yellow) (left image) is explained by variability in right hippocampus volume (right image). b) reduced resting 'connectivity' between the left lateral neocortex (blue) and anterior default mode network (yellow) is not explained by variability in grey matter density (images on left), but instead by coherence of fibre pathways in the left temporal lobe (significant correlation with voxels represented in red, images on the right). From Voets et al. 2012 (reference 13). GM = grey matter.

Discussion

Although an indirect marker of neuronal activity, fMRI offers a safe, sensitive, non-invasive and reliable method to study and map the organisation of complex functional systems in the living human brain. The contribution of fMRI in the neurosurgical setting, however, depends heavily on the clinical question posed. Thus, in patients with relatively preserved functional baselines and stable (e.g. seizure-inducing hippocampal sclerosis or focal cortical dysplasia) or slow-growing pathology (e.g. benign or low-grade tumours) in whom a clear and testable functional concern arises, fMRI can offer a valuable tool to assess surgical risks, plan surgical routes, identify regions for intraoperative stimulation mapping and, to some extent, predict rehabilitative potential. Conversely, the rationale for functional mapping and interpretation of results should be carefully considered in cases of altered neurovasculature or impaired baseline neurocognitive performance. Crucially, as diagnostic tools continue to improve and neurosurgeons accordingly are faced with opportunities to intervene earlier in chronic disease courses, the challenge facing the neuroscience and neuroimaging communities is to develop a comprehensive understanding of the organisation and consequences of damage to brain systems supporting "higher-order" functions. It is likely that such knowledge will come not only from considering local functional activity in cortex adjacent to a lesion, but also in wider, inter-linked brain networks as measured through combined task-based fMRI, resting fMRI and diffusion tensor imaging and validated through cortical interference techniques and longitudinal outcome monitoring with detailed neuropsychological observation.

Conclusion

Why should we continue to focus on mapping brain functions? As the contribution of individual brain structures to key functional circuits in the brain uncovered with increasing detail (e.g.[16]), the combination of fMRI and clinical mapping techniques is enabling aggressive treatment of potentially life-shortening disease with very minimal functional risks. Aside from very general principles, however, our knowledge about how the brain processes information remains limited. Technological and analytical advances in very recent years provide the level of temporal and spatial resolution that could offer key information about systems-level functional organization / communication that holds great promise for advancing neurosurgical practice.

By the same token, without doubt a key determinant of the success of fMRI integration within neurosurgical applications is an excellent understanding and communication of what it is hoped that fMRI will inform in the individual patient. Not every fMRI scan in every patient will be successful and for mapping of motor cortex may in fact not be as clinically informative as detailed anatomical assessment[17]. Conversely, in the context of statistical and technical considerations, even robust and anatomically specific fMRI-based functional mapping cannot absolutely guarantee that surgery will not induce (transient) deficits especially in lesser-understood functional systems. Having demonstrated the feasibility of task and resting fMRI to safely and reliably map networks in the brain supporting functions essential for normal human behaviour, the challenge now remains to determine the real clinical benefit gained from the application of fMRI, in terms of preservation of quality of life relative to neurosurgical gain for individually-tailored clinical treatment.

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