Syllabus contribution – 23rd ISMRM Annual Scientific Meeting, Toronto, Canada 2015

Specialty area: Introduction to fMRI

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Highlights

- Informing functional risks associated with neurosurgery remains the most direct clinical application of fMRI.
- Research into neurophysiological correlates of fMRI is allowing improved selection of complex epilepsy patients likely to benefit (or not) from neurosurgery.
- Basic neuroscience investigations are refining clinical applications in the areas of disease prognostication and patient stratification.
- Longitudinal studies are needed to assess the impact of treatment-related fMRI signal changes on disease courses and long-term symptom control.
- Quick, simple and standardized methods to supplement fMRI are much needed to facilitate interpretation of metabolic and haemodynamic characteristics in individual patients.

TALK TITLE: Example applications of fMRI in basic & clinical neuroscience

TARGET AUDIENCE

Neuroscientists and psychologists interested in gaining a broad overview of basic neuroscience applications of non-invasive functional MRI techniques to gain mechanistic insight into brain function, with a focus on translation.

Clinical neuroradiologists, neurologists and neurosurgeons desiring an update on the targeted areas in which fMRI techniques have / are beginning to make a direct impact on clinical care.

OUTCOMES/OBJECTIVES

This talk aims to review developments in the application of fMRI techniques, with a focus on translational research, in areas with potential impact on clinical care.

Following this talk, it is hoped the listener will have gained an overview of

- Areas of basic neuroscience research offering promise for translational application in the near – to – medium future.
- Clinical applications for which fMRI is presently informing clinical care and those for which it remains a mechanistic tool.
- Key methodological and interpretative limitations facing fMRI translations to the clinical setting, especially for pre-surgical planning.

PURPOSE

Although an *indirect* marker of the complex processes involved in brain activity, functional MRI offers a safe, sensitive, non-invasive and reliable method to study and map the organization of complex functional systems in the living human brain. Without doubt, its introduction in the early 1990s enabled huge leaps in understanding of how the brain

processes and distributes information under normal and pathological conditions. The ability, through fMRI, to map differences in the diseased brain, however, remains many steps removed from directly assisting in the treatment or prevention of disease.

This talk will describe translational research efforts applied primarily to (i) planning neurosurgery, (ii) diagnosis and prognosis of disease processes and (iii) assessing and predicting effects of therapy.

APPROACH [METHODS & RESULTS]

The first applications of BOLD-fMRI, without the use of contrast agents, demonstrated detectable signal changes associated with stimulation of the visual (Ogawa et al., 1992, Kwong et al., 1992) and motor (Kwong et al., 1992, Bandettini et al., 1992) systems. Within 2-3 years, the accuracy of fMRI was already being assessed against intra-operative direct brain stimulation mappings in both adult (Jack et al., 1994) and paediatric (Chapman et al., 1995) patients undergoing neurosurgery. Evaluations of the potential for fMRI to replace invasive Wada testing for language lateralization in epileptic patients rapidly followed (Benson et al., 1994, Desmond et al., 1995, Binder et al., 1996). As basic neuroscience investigations continue to unravel the specific contributions made by individual medial temporal lobe structures to memory, it seems likely that greater confidence in fMRI memory mapping will eventually allow replacement of Wada testing altogether.

Informing pre-operatively and non-invasively the ***functional risks associated with neurosurgery*** to help decide whether and how to best treat an individual patient remains the most direct, active clinical application of fMRI. When applied in the correct context, fMRI can assist the surgeon to weigh the risk/benefit trade-off of neurosurgical intervention and decide upon additional clinical testing that may be required during surgery (e.g. awake direct brain stimulation mapping) (Figure 1). FMRI may also be useful to predict, in the same patients, those who may have a transient deficit following surgery (for example, SMA syndrome, Krainik et al 2001, 2003) so as to appropriately consent and plan timely rehabilitative treatment. Conversely, fMRI relies upon a number of statistical and physiological assumptions. Applications in the neurosurgical setting, therefore, require careful and considered interpretation. As with all fMRI studies, the quality and interpretability of activation maps depends on many factors including patient compliance, head motion, medication confounds, and pathological processes that may disrupt neurovascular coupling. Both model-based and data-driven analysis methods, minimizing *false negative* results are strongly recommended (Haller & Bartsch 2009). Direct cortical stimulation remains strongly advocated where-ever possible and especially when the clinical question concerns activation within or bordering pathological tissue.

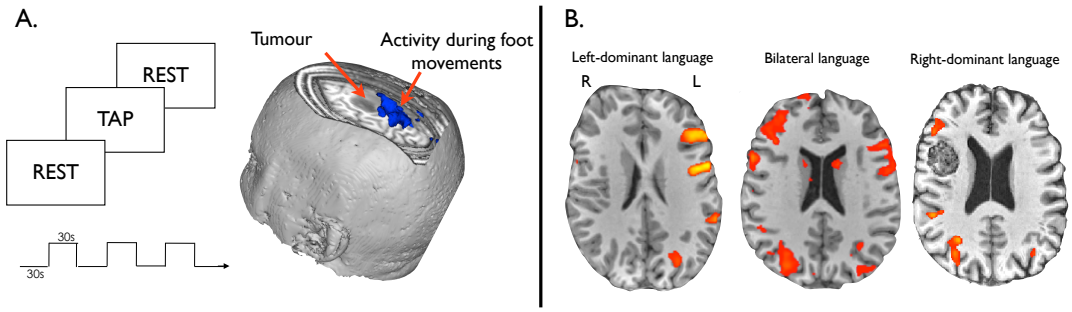

Figure 1. Mapping basic functions. A. Left: diagram of task paradigm using a standard block design during which a patient is visually instructed to rest or tap a specified limb in alternating blocks of 30-seconds. Right: T1-weighted scan of brain tumour rendered in 3D, displaying statistically threshold 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.

FMRI has also gained increasing attention as a supplemental tool to ***identify patients most likely to benefit from neurosurgery***. The whole-brain high spatial resolution afforded by fMRI has been shown to offer valuable complementary information in certain patients with complex drug-resistant epilepsy. When used simultaneously with compatible electroencephalography recordings, fMRI may identify a focal source of epileptic discharges that have been corroborated with invasive electrode recordings (Benar et al. 2006). Alternatively, EEG-locked BOLD fMRI signal changes may reveal widespread activity indicative of lower likelihood of surgical success (Thornton et al 2011). Unfortunately, the specificity of BOLD changes in this context is low and the neural processes measured in this context remain debated. One difficulty in establishing the direct clinical impact of fMRI is the relative lack of studies that report the extent to which fMRI has changed clinical care. However, two studies demonstrated direct utility for fMRI in deciding whether, or how, further invasive testing should be performed (Medina et al., 2005), and identifying avenues for treatment in patients previously declined for surgery (Zijlmans et al 2007). Similar applications in cochlear implants demonstrate utility of fMRI in determining the placement of implanted devices to optimize treatment response (Bartsch et al., 2006).

In most other clinical settings, an acute injury has already occurred (e.g. stroke/Traumatic Brain Injury), or evidence for a **latent chronic disease process** has emerged (e.g. Multiple Sclerosis / Alzheimer's Disease). Here, the clinical emphasis shifts away from *prevention* of decline and moves instead to functional *preservation*. The focus of fMRI research in this context has been to identify which systems have been disrupted as well as the most appropriate treatment to stabilize symptoms and prevent future decline. Basic neuroscience fMRI research, identifying both ***neurophysiological processes*** associated with symptoms and the brain's remarkable potential to redistribute neural resources following injury, has provided tools with which to assess potential ***rehabilitative treatments***. Following stroke, dynamic reorganization has been shown on repeated fMRI assessments (Johansen-Berg et al., 2002), and shows sensitivity to manipulation through exogenous influences on brain activity such as transcranial direct current stimulation (Stagg & Johansen-Berg 2013) or repetitive transcranial magnetic stimulation (Thiel et al., 2013).

In parallel, fMRI has uncovered deviations in normal brain function in normal-performing people at genetic risk of subsequent neurodegenerative decline (Filippini et al 2009), as well as neural signatures predictive of likely disease course in patients with mild cognitive impairment (Petrella et al., 2011). In particular, there is increasing agreement that up-regulated fMRI activity may be seen in early, but not late stages of memory dysfunction,

predicts hippocampal failure, and is a poor prognostic marker (see Sperling 2011 for review). Much interest has therefore focused on task and resting fMRI measures as potential ***prognostic markers*** of Alzheimer's disease.

The development of such prognostic markers presents tangible new opportunities for fMRI as a measure to assess the ***efficacy of pharmacological interventions*** aimed at halting or even reversing disease processes. In Alzheimer's disease, preliminary longitudinal fMRI scans in amnestic patients demonstrated normalization of hippocampal hyperactivity and concurrent improved memory performance following active treatment but not placebo (Bakker et al., 2012). Naturally, longitudinal studies will need to demonstrate the consequent effect on distributed memory networks and on the natural course of disease progression of pharmacological intervention in the early stages of MCI.

A particularly powerful example from basic neuroscience is the identification, using positron emission tomography and fMRI neuroimaging techniques, of inter-related but dissociable systems involved in pain perception. This discovery of biological rather than subjective "targets", in turn, triggered directly clinically motivated research to understand how dissociable affective and nociceptive brain networks may be modulated to reduce the individual's pain experience and improve early assessment of novel analgesic drugs (Duff et al., 2015). While this research remains largely mechanistic at this time, converging evidence from pharmacological studies supports an increasing potential role for fMRI to monitor and even predict individual patient responses to pharmacological intervention to minimize the personal and financial cost of trial and error approaches to drug administration.

DISCUSSION

Twenty years on from the seminal localisation mappings of primary sensory cortices that enabled clinical applications in neurosurgical planning, fMRI applications have extended to all major neurological and psychiatric conditions. Huge advances in data acquisition, task design and analysis techniques have provided novel insight into the detailed and distributed organization of brain functions, stages of consciousness, normal and abnormal brain development, and the brain's response to disease and its treatments. However, despite two decades of active research, direct clinical applications of fMRI still remain limited.

Partly, this slow pace of translation reflects rapidly expanding methodological advances in data processing and ongoing efforts to understand the emergence of symptoms, time-scale of disease processes, and inherently large variability among individual patients presenting with the same over-arching 'disease'.

The utility of fMRI in the clinical, and especially surgical, setting depends heavily on appropriate patient selection and the clinical question posed. FMRI has shown value in pre-operatively identifying functional risks of surgery, and, increasingly, to determine rehabilitative needs and response. However, the rationale and interpretation of fMRI mapping results should be carefully considered in patients with likely altered neurovascular coupling or impaired neurocognitive performance, especially when mapping results are negative. This remains one of the central criticisms of fMRI, and further research developments providing quick, simple and standardized supplemental methods in the clinical setting are very much needed to facilitate interpretation of baseline metabolism and haemodynamics in individual patients (Pike 2012).

Further, emerging applications in predicting disease course and pharmacological response remain currently limited by our poor understanding of the tremendous variability in normal

brain function, hindering the discrimination between what is normal or abnormal at the individual level. Critically, the real impact of fMRI clinically will be at the individual subject level, where what matters is not how the *average* person would respond, but how a given individual patient will.

CONCLUSION

As early as 1995, a NIH conference on fMRI concluded that "Repeated testing of a single patient will allow clinicians to follow changes in cerebral activity over the course of a progressive disease, during recovery from injury or stroke, and in response to treatment." (Le Bihan et al., 1995). Now, exactly 20 years later, large progress has been made towards fulfilling each of these predictions. Without doubt, ever-continuing advances in data analysis and basic neuroscience research are beginning to open new avenues for clinical applications especially in the area of disease prognostication and patient stratification. Large-scale prospective studies are now required to determine not only the sensitivity and specificity, but, critically, the added value of fMRI relative to other imaging modalities and established clinical tests to improve patient care and reduce disease burden.

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