**Applications of fMRI in Experimental and Clinical Medicine**

**P. M. Matthews**[1]
[1]GlaxoSmithKline, Middlesex, United Kingdom

Relatively recently, functional magnetic resonance imaging (fMRI) has emerged as a promising new neuroimaging tool for clinical applications.

While still not routine, the largest current clinical application of fMRI is for pre-surgical mapping prior to neurosurgical resection. The goal is to allow the surgeon to spare tissue that, if injured in the surgery, would cause new clinical deficits or limit good recovery. Clinical reports from relatively large surgical series suggest that the proximity of resection to functionally active cortical regions predicts the likelihood of post-surgical deficits. A complementary set of applications uses fMRI to localises spontaneous foci, e.g., in epilepsy or migraine. At present, this remains relatively insensitive, but it could provide some insight into disease processes by allowing, for example, dynamic observation of spatial-temporal patterns of propagation.

One of the exciting clinical-research frontier areas for fMRI is in the characterisation of the neurophysiologically-based *intermediate phenotypes* for functional disorders (e.g., those diseases in which structural changes are not macroscopically apparent, such as depression). Intermediate phenotypes are quantitative traits not defined by direct observation of the subject and more proximal to underlying disease mechanisms than classical clinical phenotypes. In Williams syndrome, for example, (studied by Meyer-Lindenberg and colleagues among others) structural abnormalities of the orbitofrontal cortex are evident and associated with impaired interaction of orbitofrontal and dorsolateral prefrontal regions, but reduced activation of amygdala to threatening faces also is found. For other, clinically much more heterogeneous disorders, imaging endophenotypes can provide markers for disease or disease sub-types. In these applications, fMRI is providing substantial new disease insight.

The ease of application is rapidly increasing understanding of *behavioural* disorders. A specific hypothesis that has been able to be increasingly strongly tested in recent years using fMRI is that common neural mechanisms are responsible for addictive behaviours across a wide range of substances, for example. fMRI also can help to understand the genesis of individual types of symptoms to guide better symptom-oriented treatment. For example, fMRI has allowed dissection of the *subjective experience* of pain into anatomically distinct activities of different functional systems (including arousal and the somatosensory and limbic systems).

A major potential driver for future clinical applications lies in applications of fMRI to the direct assessment of interventions. Pharmacological MRI (pHMRI) can provide neurophysiological indices of drug response which, because of the inherent functional-anatomical information, provide information relevant to understanding the cognitive basis for treatment response. FMRI also is contributing to a change in perception of the potential impact of adaptive brain functional changes that occur in response to disease.

Translation of fMRI from basic cognitive neuroscience to clinical investigation has begun. As implemented at present, there are practical limitations limiting routine use of fMRI as a diagnostic tool. However, it already is having some impact in *specific* applications. There is an expectation that fMRI will contribute to improving the efficiency of early phase drug development.