Clinical review

Science, medicine, and the future

Functional magnetic resonance imaging in neuropsychiatry

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The ability of functional magnetic resonance imaging to provide high quality imaging of brain function without the need for radioactive tracers is rapidly making it the technique of choice for research into neuropsychiatric disorders and their treatment. The future is likely to bring a closer involvement in clinical practice, with the technique being used for early detection of dysfunction, assessing the clinical efficacy of drug treatments, and as an alternative to invasive preoperative procedures requiring localisation of function.

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Predicted developments

Improved understanding of the relation between neural dysfunction and symptoms in neuropsychiatric disorders that are currently diagnosed on the basis of behaviour and self reports (such as schizophrenia and depression)

Repeated scans of individuals will allow development of profiles of patients likely to respond well, or poorly, to particular drugs

Non-invasive early diagnosis of disorders such as Alzheimer's disease

Almost immediate localisation of brain function with real time imaging, allowing replacement of invasive preoperative procedures to localise functions in conditions such as vascular malformations, tumours, and intractable epilepsy

Combination of imaging with electrophysiological techniques such as electroencephalography will enhance understanding of transitory neuropsychiatric phenomena such as single hallucinations

Functional magnetic resonance imaging

The development of anatomical neuroimaging enabled the in vivo visualisation of neuropathology in conditions such as stroke, facilitating differential diagnoses and early treatment. Since then scanning techniques have gone beyond structural detail to provide images relating to human brain function, and in the past decade these techniques have been joined by an impressive new imaging tool, functional magnetic resonance imaging (functional MRI). This has a spatial resolution within the millimetre scale and can capture responses in the brain occurring over a few seconds, although reconstruction and processing of the raw data commonly occur after scanning. Functional MRI is non-invasive and safe. It does not require radioactive tracer substances, unlike positron emission tomography (PET) or single photon emission tomography (SPET), and uses the brain's natural haemodynamic response to neural activity as an endogenous tracer. It can be carried out during the same session as routine magnetic resonance imaging in a clinical scanner. These features are making it increasingly popular in neuropsychiatric research.

The commonest form of functional MRI is blood oxygenation level dependent (BOLD) imaging.[1] The BOLD signal depends on the ratio of oxygenated to deoxygenated haemoglobin. In regions of neuronal activity this ratio changes as increased flow of oxygenated blood temporarily surpasses consumption, decreasing the level of paramagnetic deoxyhaemoglobin. These localised changes cause increases in magnetic resonance signal, which are used as markers of functional activation (fig 1). Ultrafast scanning can measure these changes in signal, which are mapped directly onto a high resolution scan of the subject's anatomy. In addition, data from several subjects can be combined to provide group averaged images mapped into standard neurological coordinates.

Most functional MRI involves measuring the BOLD signal while people are engaged in carefully controlled tasks. During a scan subjects lie within the bore of the magnet, and their behavioural responses to presented stimuli are monitored. A wide range of stimuli can be presented across sensory modalities. It is possible to examine covert phenomena such as thinking, planning, or hallucinating as well as overt motor responses, such as generating a specific movement or signalling the answer to a question by pressing a button. Sophisticated methods of data analysis are used to test whether changes in signal during performance of a task are statistically reliable.[2]

In several direct comparisons functional MRI has been able to replicate findings from positron emission tomography,[3] suggesting that the non-invasive functional MRI should be used whenever possible to avoid

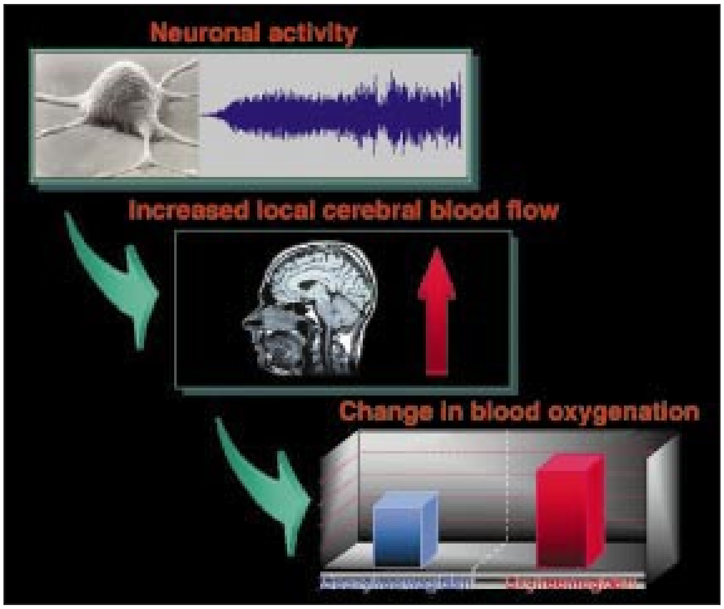

Fig 1 Principles involved in converting neuronal activity into a blood oxygenation level dependent (BOLD) signal, which can be measured with functional magnetic resonance imaging

exposure to radiation and the need for an expensive cyclotron unit on site. Unlike positron emission tomography, functional MRI is not limited in the number of scans that can safely be performed on a single person, which means that repeated scans of the same patient can track the course of a disorder and, potentially, its response to treatment. The safety of the technique also facilitates the recruitment of research subjects and enhances compliance, as well as extending the range of people who can be scanned to vulnerable groups such as children.

Like all neuroimaging methods, functional MRI has limitations. Movement of subjects during scanning can produce artefacts, although these can be resolved to a certain extent by corrective data procedures.[4] The magnetic resonance properties of the anterior skull base and petrous bone are another source of artefacts, causing a relative loss of signal in the medial inferior frontal lobe and inferior temporal lobe.[5] This problem can be reduced through careful choice of orientation of the scan, but it must be considered when interpreting results. There are also issues of a practical nature, such as the careful screening necessary to ensure that candidates for a scan can tolerate the noise of the scanner and close confinement within the magnet bore, as well as being free of metallic implants.

Applications to neuropsychiatric disorders

The infrastructure necessary for conducting functional MRI is already available in the magnetic resonance imaging departments of district general hospitals. It can be carried out on standard clinical MRI scanners with upgraded software. However, as with any new technology, established findings and standardised techniques will be required before functional MRI can make the transition from research to routine use in clinical practice. Its main applications to neuropsychiatry at present are to increase understanding of a wide range of disease states and the effects of treatment.

Functional MRI can provide a window into disease states, such as depression or schizophrenia, that, because of the lack of biological markers, are currently diagnosed on the basis of behavioural signs and self reported symptoms such as auditory hallucinations. Functional MRI has the potential to change our understanding of these conditions by demonstrating how neural dysfunction manifests itself in behaviour and symptoms.

Unipolar depression

One study compared depressed patients and healthy volunteers in their neural response to film clips designed to evoke transient sadness.[6] The brain activation recorded during emotionally neutral film clips was compared with that occurring during sad films. This revealed that, although many brain regions were activated similarly by both groups, the depressed subjects activated additional regions, namely the left medial prefrontal cortex and the right anterior cingulate gyrus, during the processing of transient sadness. These brain structures are thought to be involved in the attribution of emotional importance and the conscious experience of emotion. The investigators postulated that in depression abnormal frontal activity might disconnect the limbic system from normal modulatory influences.

Schizophrenia

Patients with schizophrenia show specific deficits in language processing, which are classically considered a cardinal feature of the illness. Functional MRI has begun to reveal the neural dysfunction underlying these deficits.[7] We found that patients performing a language task showed a broadly similar pattern of neural activation, though with an attenuated power of response, compared with controls.[8] However, we observed specific regions of hypoactivity in the frontotemporal cortex (fig 2). These may be related to deficits in language processing that can be observed at a cognitive level.

The extrapyramidal symptoms and neurological "soft signs" prevalent in schizophrenia have prompted the use of functional MRI to investigate brain function during psychomotor tasks. For example, Wenz et al reported functional abnormalities associated with motor processing during performance of a sequential

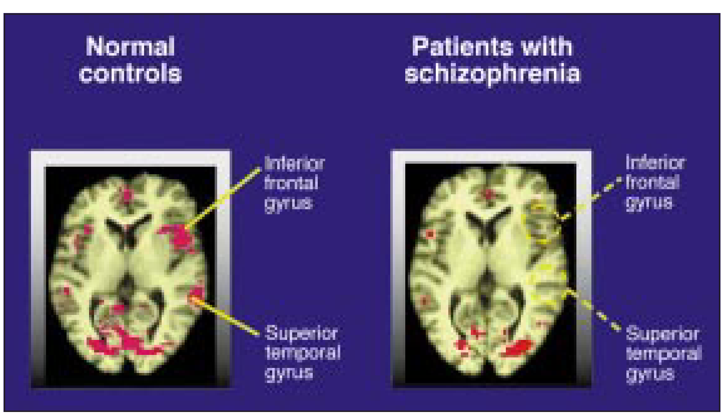

Fig 2 Functional MRI images showing reduced activation of language areas during a linguistic task in patients with schizophrenia (from Honey et al[8])

thumb to digit task in patients with schizophrenia compared with controls.[9] These results suggested that interhemispheric communication is disturbed in schizophrenia. The concept of anomalous cerebral asymmetry in schizophrenia is supported by results from other studies using functional MRI (fig 3).[10 11]

An alternative approach has used functional MRI to investigate temporary states such as specific symptoms rather than comparing patients with healthy volunteers. Howard et al found that photic stimulation of a patient experiencing visual hallucinations produced a significantly less extensive pattern of response in the visual cortex than when the patient was rescanned after successful resolution of symptoms with risperidone treatment.[12] Similarly, patients who are experiencing auditory hallucinations show inhibited activation of the auditory association cortex in response to external auditory stimuli.[13] These studies indicate that processing of endogenous and exogenous stimuli may compete for common neural resources.

The potential of functional MRI for conducting repeated scanning of an individual patient has important clinical applications. Characterisation of the functional neuroanatomy of cognitive processes will provide a framework for research into the longitudinal effects of pharmacological treatments on cognitive function. We have followed drug induced changes in the brain function of patients with schizophrenia after switching them to newer atypical antipsychotic drugs.[14 15] Such research raises the possibility of developing profiles of patients likely to respond well to particular drugs, allowing doctors to assess the probability of a positive response before embarking on lengthy and expensive courses of treatment. It could also be used to develop treatment profiles outlining which disease related cognitive deficits are enhanced by particular drugs. Repeat scanning with functional MRI would also allow physicians to track changes in a patient's brain function during the course of an illness. For example, schizophrenia is characterised by psychotic episodes and periods of remission. Repeat scanning could be used to differentiate between those neural deficits underlying the illness and those associated with exacerbation of symptoms during acute psychotic episodes.

Alzheimer's disease

In disorders where neural correlates have been identified, such as Alzheimer's disease and epilepsy, research has focused on establishing that functional MRI can adequately replicate existing clinical findings from more invasive techniques. For example, Sandson et al used a variant of functional MRI to investigate cerebral hypoperfusion in patients with Alzheimer's disease.[16] They replicated previously demonstrated temperoparietal hypoperfusion and found it to correlate with the severity of the dementia. Indeed, Harris et al reported that, with a non-radioactive magnetic contrast agent, functional MRI could detect such hypoperfusion at an early stage in the disorder when symptoms were still mild.[17] Together, these studies indicate that functional MRI shows promise as a clinical tool for the early detection of Alzheimer's disease.

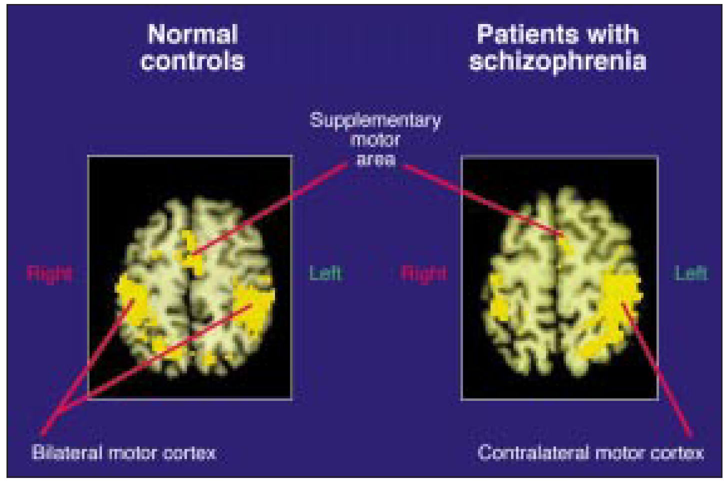

Fig 3 Functional MRI images showing abnormal cerebral asymmetry during a psychomotor task performed by people with schizophrenia (Honey et al[11])

Epilepsy

Another potential use of functional MRI is in the presurgical testing of patients with intractable epilepsy. In cases where temporal lobe resection is considered patients undergo lateralisation testing of temporal lobe functions to establish the risk of permanent neurological damage. This is commonly achieved by testing language and memory abilities after an injection of sodium amylobarbitone into an internal carotid artery to anaesthetise one hemisphere or by direct electrical stimulation. Research has shown that functional MRI can replicate the results of these tests, raising the possibility of replacing distressing and potentially harmful procedures.[18] In the United States, functional MRI of sensorimotor and language functions has been used to assess whether a patient is a candidate for surgery and to guide surgical planning in cases of vascular malformations, tumours, intractable epilepsy, and lesions near critical cortical areas.[19]

Clinical implications of technological advances

Functional MRI is still in its infancy. This decade we have seen many technical developments, and we can expect to see further improvements. Currently, functional MRI is mainly used in neuropsychiatry to investigate static aspects of disorders. Improving the temporal resolution of scanning extends the range of disease processes that can be investigated to include even momentary phenomena such as individual psychotic hallucinations. Researchers have begun to achieve this by combining functional MRI with electrophysiological techniques such as electroencephalography and magnetoencephalography.[20]

Another new development, real time functional MRI, displays the course of neurological activation during the scan rather than processing the data after scanning. This is particularly useful for clinical practice as it allows immediate assessment of brain activation and movement within the scanner, thus adding to the potential of functional MRI as a useful presurgical tool.[21] It might also be possible to use real time scanning in treatments based on biofeedback—that is, the self modulation of physiological parameters in response to simultaneous feedback of biological information. For example, in cases of intractable epilepsy it has been found that training patients to alter the pattern of their electroencephalogram reduced seizure rates over a six month period.[22] With real time functional MRI, it might become possible to show patients images of their own brain function while they are in the scanner in order to facilitate biofeedback.

Competing interests: None declared.

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Lesson of the week

Hyponatraemic seizures and excessive intake of hypotonic fluids in young children

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Afebrile seizures in young children may be caused by hyponatraemia—take a dietary history and measure serum electrolytes

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The differential diagnosis of afebrile seizures in children with normal development includes epilepsy and metabolic disorders. Children admitted to hospital with seizures (febrile or afebrile) of unknown cause are often treated with antibiotics and antiviral agents for suspected infection of the central nervous system while investigations are undertaken. Afebrile seizures caused by hyponatraemia associated with excessive intake of hypotonic fluids was first reported in 1967.[1] This is a common problem in the United States,[2–8] but it has rarely been reported in the United Kingdom.[9 10] We describe four cases (table).

Case reports

Case 1

A 20 month old girl presented with a short history of vomiting, cough, and anorexia. She had attended the accident and emergency department on four occasions—with a viral illness, urinary tract infection, pertussis, and breath holding. She was admitted for observation, and a provisional diagnosis of viral illness was made. The girl refused solid food but took fluids well over the next 48 hours. At this time she had a tonic seizure associated with apnoea but responded to treatment with rectal diazepam. Biochemical investigations showed serum sodium concentration 116 mmol/l, chloride 84 mmol/l, potassium 2.8 mmol/l, urea 2.8 mmol/l, and creatinine 35 mmol/l.

The patient's fluid intake was restricted to 60% of the maintenance requirement, but four hours later she had a further tonic seizure associated with decerebrate posturing. She was intubated and ventilated and given intravenous mannitol and phenytoin. Computed tomograms of the brain showed diffuse cerebral oedema (figure). Her urine output over the next 12 hours was approximately 12 ml/kg per hour, and with fluid restriction her serum electrolyte values returned to normal. Repeat computed tomography 24 hours later showed appreciable improvement, with normal basal cisterns and ventricles (figure).

The girl was considered to have encephalitis and was ventilated for six days, during which time her electrolyte values remained normal. However, analysis of cerebrospinal fluid removed by lumbar puncture was normal, blood cultures were sterile, and viral serology failed to show infection. Dietary inquiry showed that