NEUROIMAGING

Applications of fMRI in translational medicine and clinical practice

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Abstract | Functional MRI (fMRI) has had a major impact in cognitive neuroscience. fMRI now has a small but growing role in clinical neuroimaging, with initial applications to neurosurgical planning. Current clinical research has emphasized novel concepts for clinicians, such as the role of plasticity in recovery and the maintenance of brain functions in a broad range of diseases. There is a wider potential for clinical fMRI in applications ranging from presymptomatic diagnosis, through drug development and individualization of therapies, to understanding functional brain disorders. Realization of this potential will require changes in the way clinical neuroimaging services are planned and delivered.

Positron emission tomography
(PET). A technique that images the distribution of positron-emitting tracer isotopes (for example, ^{11}C-choline) incorporated into compounds of interest by tomographical mapping that is based on photons emitted from positron collisions.

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Modern imaging has transformed practice in the clinical neurosciences by providing information about structural abnormalities in the brain and spinal cord rapidly and non-invasively. However, many chronic neurological or psychiatric complaints confronted in the clinic (for example, pain, movement disorders, depression and psychosis) are not associated with structural abnormalities that can be detected in an individual patient with current clinical technologies. In response to these needs, clinical imaging is incorporating new methods that are able to define brain function. Single photon emission computed tomography (SPECT) and positron emission tomography (PET), which use radiolabelled tracer molecules to define physiological measures (for example, tissue blood flow or substrate consumption) or specific molecular interactions, are already well integrated as clinical tools in specific areas of application. However, neither has been as important as MRI-based investigations, because of the safety, wide availability and extraordinary flexibility in terms of the application of this non-ionizing imaging approach. Most recently, functional MRI (fMRI) has emerged as a promising new extension of the technology for clinical neuroimaging[1].

Conventional (structural) MRI defines the borders between different tissues (for example, grey and white matter in the brain) on the basis of their water content and on the physical properties of water related to differences in its association with macromolecules, its diffusion or the content of magnetically interactive compounds such as iron. fMRI makes use of contrast mechanisms related to physiological changes in tissue. The imaging of brain perfusion by observing the time course of changes in brain water signal as a bolus of injected, paramagnetic gadolinium DTPA (diethylenetriaminepentaacetic acid) contrast moves through the brain provided the first fMRI images[2], but applications of this approach are limited by dose restrictions for the contrast agent used. During the last 10 years in particular, with the widespread availability of high field (1.5–3 Tesla) MRI systems, intrinsic contrast related to local changes in blood oxygenation with brain activity (blood-oxygen-level-dependent (BOLD) contrast) has been used to provide a rapid, non-invasive approach to functional assessment[3,4] (BOX 1).

BOLD fMRI is still in the earliest stages of translation from research laboratories to clinical applications. Nonetheless, it is already beginning to make some clinically meaningful contributions to neurosurgical planning, the understanding of clinical syndromes and the development of new therapies. Here, we will review examples of these applications, highlighting some of the challenges that will be faced in validation, standardization and routine implementation. An initial problem faced for the effective, routine use of this or any functional tool is the need to change the types of question that are asked in therapeutics development and application. These will be explored through discussions of fMRI-guided neurosurgery (an application of fMRI that is already widely appreciated) and functional characterization of disease (a direct extension of pre-clinical pathophysiological studies into the clinical environment). We also will discuss how pharmacological fMRI (phMRI) can be used to define drug action, and how related approaches can provide objective measures that are predictive of long-term outcomes of complex interventions such as neurorehabilitation, which have been difficult to assess using conventional approaches.

Box 1 | **Blood-oxygen-level-dependent functional MRI**

Increased neuronal activity is associated with a local haemodynamic response involving an increase in both cerebral blood flow and blood volume. Recent studies suggest that this is predominantly a consequence of presynaptic neurotransmitter release and therefore reflects local signalling[162]. The haemodynamic response has a magnitude and a time course that also depend on relative inhibitory and excitatory input[85].

The haemodynamic response might act to match substrate provision to increased energy consumption[163]. However, the increase in blood flow is greater than is necessary simply for oxygen delivery to match increased consumption. Therefore, an alternative hypothesis is that the haemodynamic response is driven more directly by specific neuronal–glial interactions after neurotransmitter release[164]. There are several possible mediators, including nitric oxide and eicosanoids[100,165].

Deoxyhaemoglobin is paramagnetic and distorts an applied static magnetic field. Therefore, magnetic field inhomogeneities are found around blood vessels, and their magnitude increases with the amount of paramagnetic deoxyhaemoglobin. These field inhomogeneities increase the rate of intravoxel spin dephasing (measured as the apparent spin–spin relaxation time, T2* (REF. 166)) and reduce the MRI signal with a gradient echo image-acquisition sequence. A consequence of the increase in blood flow above that required for the increased tissue demands in response to neuronal activation is that the oxygen extraction fraction decreases. The lower ratio of deoxy- to oxyhaemoglobin in draining blood is associated with a small (typically 0.5–5% at 3 Tesla) increase in MRI signal.

Blood-oxygen-level-dependent contrast functional MRI relies on this phenomenon[3,4]. A series of brain images are acquired over the course of a changing cognitive state. Regions of significant signal increase are then defined by statistical analysis of the time series of data, providing a spatial 'map' that indirectly reflects neuronal activation changes. Qualitatively similar data can be acquired using direct measures of cerebral perfusion and blood volume, although these are more challenging to implement robustly in human MRI[167].

fMRI is a relatively young technique, and this review necessarily emphasizes promise more than progress. However, if even part of this promise can be achieved, the applications of fMRI in translational medicine and clinical practice will have a substantial impact on future approaches to neurological and psychiatric disease.

fMRI-guided neurosurgery

The most common type of fMRI study currently conducted is for the characterization of functional anatomy in the brain[5]. In a typical application, signal changes in a long (100 or more) series of rapidly (for example, one brain volume image every 2–3 seconds) and serially acquired brain images are correlated with the time course of a motor, sensory or cognitive probe task. 'Activation' is defined as a region showing statistically significant changes in BOLD signal that are strongly correlated with the time course of changes in performance through the probe task (for example, cycles of movement versus rest with hand tapping). The length of the series of images and the length of time that the patient performs the task are determined by the extent of averaging of the small signal changes associated with each task change that is needed to provide statistically significant measures of correlation.

Although still not routine, the best-established current clinical application of fMRI is for pre-surgical mapping to localize cerebral functions in tissue within or near regions intended for neurosurgical resection. The goal is to allow surgeons to spare tissue that, if injured during the surgery, would cause new clinical deficits or limit good recovery (FIG. 1). With a notional linear spatial resolution of a few millimetres (as usually implemented), fMRI localizes regions of the brain in which changes in activity occur during the probe task relative to a chosen baseline. Regions identified with motor or language tasks, or somatosensory stimulation[6–8] agree well with classically localized regions of the brain that are specialized for processing these activities. As measurements can be made on single individuals, borders between functionally and anatomically distinct regions (which can vary substantially between different people[9]) can be defined to allow precise and safe neurosurgical planning.

Clinical reports on the use of fMRI with relatively large surgical series are beginning to appear. These suggest that technically adequate fMRI can be acquired in the neurosurgical context, and that the proximity of resection to functionally active cortical regions predicts the likelihood of post-surgical deficits[10]. In general, good correlations between fMRI results and 'gold standard' clinical tools have been reported[11–13]. Direct integration of fMRI with surgical navigation tools is possible[14]. Initial evidence argues that functionally guided surgical navigation using fMRI (and other methods, such as magnetoencephalography[15]) can improve clinical outcomes, but the subject base for the study is small[16]. fMRI is also a tractable alternative to awake electrophysiological cortical mapping in children or other populations that are unable to undergo this demanding and invasive procedure[17]. This application is genuinely addressing an otherwise unmet need.

An important advantage of fMRI in applications for surgical planning is that it provides information at no cost to surgical theatre time. As the morbidity of surgery (as well as the cost) is related to the time that any procedure might take, there is a powerful clinical drive for the use of fMRI. Invasive intra-operative direct electrical stimulation methods for functional mapping are slow and expensive, demanding specialized personnel and resources.

Integrating fMRI with conventional imaging and other outcomes can still add value to current presurgical investigative protocols[18]. New developments indicate the potential for relating neocortical functional maps to the anatomy of the larger white matter pathways (which can be defined by diffusion MRI[19]). This adds additional information that can improve the prognostication and planning of tumour resections in a way that was impossible using conventional techniques[20].

A small but emerging extension of neurosurgical fMRI is to use functional–anatomical localization to help define targets for functional neurosurgery, in which specific regions are ablated or stimulated to relieve symptoms or impairments. Therefore, an important concern for functional neurosurgery is to define which specific brain regions to target, given the substantial inter-individual variation in surface anatomically defined borders between functional areas. A potentially powerful strategy to control for inter-individual variations in anatomy is to combine information from fMRI functional activation with grey matter parcellation that is based on diffusion MRI[21–23]. Intra-operative fMRI has

Functional MRI
(fMRI). An application of magnetic resonance to image physiological changes rather than structure. Use of blood-oxygen-level-dependent (BOLD) contrast is currently the most popular type.

Diffusion MRI
An application of magnetic resonance to image the moility (diffusion) of tissue water, an index of microstructure sensitive to many pathologies.

Functional neurosurgery
Neurosurgical procedures directed towards altering brain function through the ablation of tissue or implantation of stimulation electrodes.

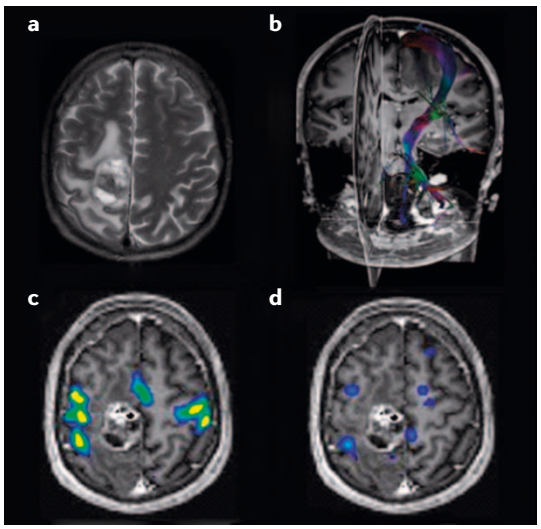

Figure 1 | **Applications of multimodal MRI to brain lesion characterization.** These images were acquired from a 52-year-old patient with a right solitary metastatic tumour in the post-central gyrus, associated with paresis of the left foot. **a** | A T2-weighted MRI hyperintense paramedian lesion was found. **b** | Diffusion tensor MRI fibre tractography[19] defined the corticospinal tract (colour), which was displaced laterally by the mass effect of the lesion. **c** | Functional MRI (fMRI) during finger tapping identifies the brain regions associated with hand movement. Injury to these regions during tumour resection could be expected to lead to functional impairments of the left hand. **d** | fMRI with sensory stimulation of the left foot identifies regions that, if injured during tumour resection, could be expected to lead to greater functional impairments of the left foot. On the basis of this imaging data, a neurosurgical removal of the lesion was performed from a medial surface approach with good outcome. Images courtesy of S. Sunaert, Department of Radiology, Catholic University, Leuven, Belgium.

been used to guide the placement of electrodes for deep brain stimulation (DBS)[24,25]. If this can be made a safe and practical procedure, it could substantially refine the way in which this therapy is applied, by providing new information concerning the mechanisms by which the effects of DBS are mediated and by providing rapidly available data on the differential effects of different stimulation protocols[24].

However, it is important not to place more confidence in these outcomes than is justified at present. Major problems remain to be resolved. For example, the definition of activation is based on the notion of an arbitrary measure of statistical significance, a measure determined not just by the magnitude of the signal, but also by noise contributions. These contributions are influenced by factors irrelevant to the pathology, such as patient movement during the study (even movements in the order of fractions of a millimetre can confound fMRI results)[26]. Therefore, many of the details of study implementation such as patient preparation, the nature of the head holder in the imaging system and the duration of the experiment influence fMRI measures.

Signal intensity in even the voxel of maximum change shows substantial variation between sessions and between individuals because of physiological changes[27]. Averaging is needed to achieve a sufficient signal-to-noise ratio for statistical significance, but the number of averages that will be sufficient to reliably obtain the definition of the relevant functional–anatomical pattern is difficult to estimate. Note that in other applications of signal averaging in medicine (for example, evoked potentials), the primary diagnostic information comes from the time course, and amplitudes are rarely interpreted except in the crudest fashion.

Finally, because it provides a general measure of changing cognitive function during the probe task, fMRI can be surprisingly sensitive to variations in the context in which a probe task is implemented. For example, in a recent multi-centre fMRI study using a simple, visually cued hand-tapping task, significant differences in visual cortex activation were found in one centre relative to all the others (P.M.M., unpublished observations). After further investigation it was found that this centre had used a visual cue with a greater luminence change and size than any of the other centres. Controlling the way in which probe tasks are implemented across sites demands considerable attention to the detail of the psychophysical environment (for example, distracting stimuli in the magnet room, ambient sound level), as well as the more conventional aspects of the imaging technology. At present, it is still necessary for each site to develop site-specific control procedures and validation data sets — an unsatisfactory state of affairs for an examination that is expensive and is used for relatively few patients.

The clinical interpretation of fMRI studies is also complex. For example, the functional significance of activation changes outside anatomically well-established brain regions is not often certain. Activation changes associated with task performance might not be necessary, in the sense that functional interference with the region would not impair behaviour[28] or because the regions are responding to a remote change rather than processing information that is crucial to a primary aspect of the associated behaviour[29]. Without complementary information from independent methods (for example, a previous lesion or combined fMRI and transcranial magnetic stimulation interference studies[28]), caution could be needed in making this distinction. Although it might be reasonable to assume that activation changes in functional–anatomical regions that are responsible for fundamental levels of processing (for example, primary sensory or motor cortices) have a high likelihood of being essential for normal behaviour (and therefore more likely to cause a deficit with injury), the clinical effect of activity in other regions (for example, the association cortex) might be less clear.

Caution also needs to be exercised concerning the interpretation of the absence of activation changes. fMRI defines only the regions of brain in which there is a statistically significant change in BOLD contrast as the applied task modulates brain activity. The BOLD response is an indirect measure and does not characterize all brain processes contributing to the behaviour;

Voxel
A voxel is the three-dimensional (3D) equivalent of a pixel; a finite volume within 3D space. This corresponds to the smallest element measured in a 3D anatomical or functional brain image volume.

Transcranial magnetic stimulation
A method by which a single or series of brief magnetic pulses that are applied externally to the skull focally modulate brain function through the generation of intracortical electrical currents. Effects can be stimulatory or inhibitory depending on the approach.

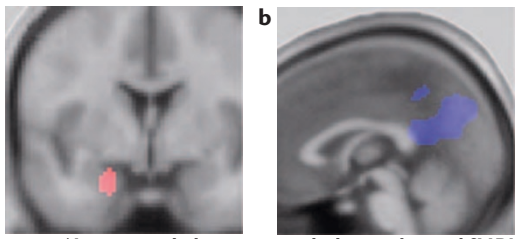

Figure 2 | **Integrated electroencephalography and fMRI for epilepsy.** To generate these images, combined electroencephalography (EEG) and functional MRI (fMRI) has been applied to the localization of the generators for interictal electrographic spikes. **a** | The common blood-oxygen-level-dependent (BOLD) activation in response to focal interictal spikes of a group of patients with different types of left-sided temporal lobe epilepsy who were studied with EEG–fMRI at rest. Despite heterogeneous EEG features and histopathology, the mesial temporal region, which is typically affected in temporal lobe epilepsy, shows common activation across the group. **b** | Typical deactivations in response to focal interictal spikes in the retrosplenium and the precuneus — brain areas that are characteristically more active during conscious rest[169]. These deactivations suggest that even interictal focal discharges widely affect ongoing brain functions. Images courtesy of H. Laufs, K. Hamandi, A. Salek-Haddadi, A. K. Kleinschmidt, J. S. Duncan and L. Lemieux, University College London, UK.

potentially widespread regions that are involved in a cognitive process, but are not changing activity significantly between the states being tested, will not be distinguished as active[30]. It is therefore possible that injury to regions not activated with the task modulation could lead to clinically significant deficits. In addition, because BOLD signal changes are small (in the order of 0.5–5%), they are easily confounded by noise arising from patient- and instrument-related factors. fMRI shows an exquisite sensitivity to artefacts — for example, from movement — and therefore clinical applications demand a new level of attention to the control of patient behaviour during scanning. With care, image acquisition requirements for some forms of head motion can be relaxed, such as with the use of pauses or silent intervals in volume acquisition to allow overt speech[31].

Mapping spontaneous brain activity

In the surgical applications outlined above, fMRI was performed using externally applied stimuli to drive changes in brain state. The time course of these stimuli then defines the statistical model used for defining activation changes in the brain. An alternative is to use spontaneously generated shifts in brain state to define the model of physiological change that is then correlated with the fMRI signal. In this way, the generators of spontaneous functional changes that underlie periodic events can be localized in the brain. A rare but highly illustrative example is provided by migraine[32,33]. Patients with inducible migraines can signal (for example, by squeezing a rubber bulb) the onset of the aura while being imaged, allowing a baseline and active state to be defined for the statistical comparison of images in the time series. The progression of the migraine can be assessed from the time-dependent modulation of the response to visual stimuli (for a visual aura). Using a physiological measure (the BOLD fMRI signal), this approach allows mapping of the functional–anatomical progression and timing of state changes associated with the migraine.

A clinically more important application of this concept is for the localization of ictal foci (the surgical removal of tissue, which in some instances can cure epilepsy) using interictal epileptiform activity on an electroencephalogram (EEG) acquired simultaneously with imaging data[34] (FIG. 2). In the simplest application, a patient lies at rest in the imaging system as images and the EEG are acquired. The EEG data are then used to define a model with which signal changes in the fMRI image series are correlated: the goal is to identify regions of the brain that show signal changes immediately following each epileptic spike. This approach has clinical utility because it provides more refined localizing information than is available from the EEG. In situations in which brain structural changes are ambiguous or absent (as is often the case with complex partial seizure disorders), such a study could have a great influence on the consideration of treatment options (for example, surgical cure rates for temporal lobe epilepsy are much higher in patients with well-lateralized, well-localized ictal foci).

Applications of combined EEG and fMRI mapping to idiopathic primary generalized seizure disorders have also been particularly exciting because of the new information that the combined methodology can provide. Accurate subcortical localization of the causative 'generators' for these seizures was difficult to prove in human epilepsies without combined EEG/fMRI mapping, because the conventional electrophysiological approaches as used in animal model studies are highly invasive[35,36].

However, despite the promising results from leading centres, the full value of the combined methodology is still difficult to realize. Safety issues for combined EEG and fMRI are a concern, although they can be resolved[37]. More difficult is optimal filtering of the EEG data, obtained from the combined observations, to remove the imaging artefacts from electromotive forces generated in the EEG leads by the shifting magnetic fields that are used for generating MRI images. Although the freely available methods are improving[38], there is a risk that signal filters will degrade the quality or otherwise bias the signal. A more fundamental concern in implementation is that many events must be averaged to give a sufficient signal, which limits applications to highly inter-ictally active epileptic foci. Of course, at the same time care must also be taken to ensure that the epileptic activity is not allowed to trigger a generalized seizure in the patient, the consequences of which would create severe movement artefacts and compromise patient safety.

Functional characterization of disease

Functional brain disorders can be defined empirically as those that are not associated with clear focal structural abnormalities, or those in which the structural

abnormalities are subtle or have an uncertain relationship to clinical deficits. A frontier area for fMRI is in the characterization of the neurophysiologically based intermediate phenotypes for such disorders — quantitative traits that are not defined by direct observation of the subject and that are more proximal to underlying disease mechanisms than are classical clinical phenotypes. A subset of the intermediate phenotypes are endophenotypes, which are quantifiable biological traits that are associated with complex genetic disorders. These can potentially be used as markers for identification and for a better understanding of genetic factors in aetiology[39]. Intermediate phenotypes and endophenotypes can define distinct subtypes of clinical disease syndromes, and can be used more generally as markers of disease[40,41]. They can be modulated by disease state and therefore also provide measures of treatment response[42].

Studies of Williams syndrome illustrate how intermediate phenotypes can be defined using fMRI. Williams syndrome has a range of characteristic clinical features, such as cognitive impairment with well-preserved verbal ability, hypersociability, and visuospatial and other focal sensory processing deficits, but only rather subtle structural brain changes[43–46]. This developmental disorder is associated with the deletion of a segment of one copy of chromosome 7, which can cause profound focal behavioural deficits in the context of normal intelligence. Such observations have the potential to inform neuroscience regarding the way in which genes determine specific aspects of cognitive potential and related behaviours. Simultaneous acquisition of data concerning structure and function allows a better understanding of how a particular behavioural deficit can be expressed in a way that emphasizes the interaction between local deficits and altered responses in a larger neurocognitive system. For example, structural abnormalities of the orbitofrontal cortex are evident and associated with impaired interaction of orbitofrontal and dorsolateral prefrontal regions[47,48], but reduced activation of the amygdala in response to threatening faces is also found. This intermediate phenotype suggests a functional hypothesis regarding the aetiology of a symptom in the disorder: that hypersociability results from a relative lack of negative social feedback processing. In the longer term, direct clinical relevance of such information could lie in better predicting long-term prognosis, or better tailoring behaviour modification interventions.

For other, clinically more heterogeneous disorders, imaging endophenotypes provides markers for disease or disease subtypes. Establishing patterns from the diversity of psychophysical and brain functional deficits that are associated with schizophrenia and relating these to clinical presentation promises to provide an objective approach to subtyping the illness[49,50], and could aid in clinical diagnosis and management. For example, predicting clinical course is a major concern on first presentation with psychosis. The right prefrontal fMRI response in untreated patients could provide an approach to differentiating schizophrenia from both non-schizophrenic psychosis[51] and depression[52] at the first outbreak of illness. If confirmed and validated as a marker, such information, by defining prognosis, would help in more rational treatment planning. It also could be predictive of treatment responses and guide therapy directly.

If an intermediate phenotype is abnormal in clinically unaffected relatives of patients who could carry a disease-related genetic trait, but do not clinically express it, then it might become useful as an endophenotype. For example, similar to the patients themselves, the relatives of patients with schizophrenia can show abnormal prefrontal fMRI activation[53–55] or reduced functional connectivity (a measure of the temporal correlation between activity in different brain regions) in fronto-thalamo-cerebellar and fronto-parietal networks[56]. Regional brain functional abnormalities that are predictive of the development of psychosis, identified by the longitudinal fMRI follow-up of high-risk patients, have potential diagnostic value[57].

In a genetically complex disease such as schizophrenia, understanding the relationship between such imaging traits and individual genes will facilitate the distinction of causative from associated pathology. Because the functional pathology is defined by fMRI relatively precisely compared with usual clinical measures, the informative direct testing of candidate genes in schizophrenic populations is possible using fMRI as a quantitative trait measure with even relatively small groups. This can be important, as significant associations with conventional phenotypes, which depend on multiple genetic and epigenetic factors, are often difficult to replicate between different populations.

A current hope is that an advantage of such imaging genomics over conventional phenotype–genotype correlations will lie in the ability to focus the search for candidate genes by using endophenotypes defined more precisely by specific biological functions. Some justification for this hope comes from recent studies in which plausible allelic associations have been reported on the basis of sample sizes of roughly an order of magnitude less than those required in conventional association studies. For example, disrupted in schizophrenia 1 (*DISC1*), glutamate receptor metabotropic 3 (*GRM3*)and catechol-*O*-methyltransferase (*COMT*) have been related to schizophrenia expression and associated with altered hippocampal structure and function[58], glutamatergic fronto-hippocampal function[41] and prefrontal dopamine responsiveness[40], respectively.

In similar ways, fMRI is beginning to assist the understanding of how genetic risk factors for depression contribute to the clinical expression of this highly heterogeneous and complex disease. It is well accepted that serotonin contributes to the generation and regulation of emotional behaviour, and that modulating serotonergic neurotransmission within the limbic system can be therapeutic. Therefore, one logical approach to understanding vulnerability to depression involves the identification of genetic mechanisms that have an effect on serotonergic transmission. The combined application of fMRI and genetics can be a powerful approach. For example, carriers of the short allele (*S*) in the 5′ promoter region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*) have an exaggerated fMRI response to environmental threat in the amygdala

Functional connectivity
A measure typically derived from the relative temporal correlation of brain regions in a physiological image that is interpreted to express the degree to which regions are functionally interacting.

(an endophenotype) relative to long allele (*L*) homozygotes[59,60]. *S* allele carriers also have lower amygdala and perigenual cingulate volumes, and correlations between activity in these regions are reduced relative to healthy controls[61] whereas the functional connectivity between the amygdala and ventromedial prefrontal cortex is increased[62]. Elucidation of these functional–anatomical features suggests physiological hypotheses for symptoms (for example, susceptibility to affective disorders arises with a biasing of amygdala responsiveness). By relating brain functional changes directly to behaviour in a relatively unbiased fashion, fMRI studies can generate new information in ways that can challenge conventional thinking[63].

A crucial clinical issue is the selection of optimal treatment for patients with psychiatric diseases. Responses are highly variable; for example, only ~70% of patients respond well to a given antidepressant[64]. Identifying a first-line treatment-responsive population at presentation would allow more effective treatment planning and optimization of follow-up for patient needs and safety. The abnormally high fMRI BOLD response in the amygdala during a facial expression probe task in depressed patients is normalized with effective treatment[42,65]; therefore, a higher BOLD signal in the amygdala at baseline might be predictive of treatment response[66]. However, the responsiveness of this circuit to treatment is unlikely to be unique; other fMRI functional markers change with treatment, such as signal change in the ventromedial prefrontal and anterior cingulate cortices[67], or the modulation of cortico-limbic functional connectivity[68].

Appreciation of a neurobiological basis for complex experiences, such as motivation or reward, is leading to a better understanding of important behavioural disorders. Because this demands the dynamic correlation of brain functional states directly with the associated human behaviours, fMRI (and related non-invasive functional imaging tools) has a role in the elucidation of these disorders. For example, a specific hypothesis that has been tested more rigorously in recent years using fMRI is that common neural mechanisms are responsible for addictive behaviours across a wide range of substances. Studies of cue-elicited craving define an apparently common, central role of the mesolimbic reward circuit in addictions to nicotine[69], alcohol[70], gambling[71], amphetamines[72], cocaine[73] and opiates[74]. The combination of fMRI with PET receptor mapping can relate systems-level dysfunction directly with the molecular targets of drug therapies in ways that enhance target validation for new pharmacological treatments faster and more cheaply than conventional clinical designs allow[75]. Results from studies such as this suggest that therapeutic interventions that target dopaminergic pathways could have an impact across addictions. Moreover, building on the association of fMRI responses with specific probe tasks and addictive behaviour, short-term fMRI responses with a controllable probe task can now be exploited for their potential to predict longer-term and more variable clinical outcomes. Confidence in such predictive potential would enhance new proof-of-concept treatment trial power by providing a rational approach to the selection of responders with treatment interventions[76], or in assessing the potential for relapses after treatment[72]. People at a higher risk of developing addictive behaviours could also be identified[77,78].

Clinical fMRI has great promise for the more accurate diagnosis and better understanding of functional disorders that are as yet without any certain 'organic' basis. Conversion disorders provide a good example. The clinical management of these disorders is often compromised by an extended period of diagnostic uncertainty, and there is an unmet need for paraclinical tests that are useful in their evaluation[79]. Functional imaging with PET has suggested impairments in higher order motor control in an individual patient, but the significance of this finding has been difficult to assess, as control cognitive states in healthy participants cannot be defined confidently[80,81]. More recent fMRI studies of non-dermatomal somatosensory conversion syndrome deficits are more easily interpreted[82] because the stimuli can be applied identically to healthy controls and patients. The identification of different patterns of brain activation in these patients relative to controls suggests that functional imaging might be able to predict ultimate clinical distinction between feigned symptoms and a true conversion disorder[83]. A recent study of a patient with visual conversion disorder (hysterical blindness) emphasizes that fMRI might be able to define physiological abnormalities even when conventional neurophysiological investigations have been non-diagnostic[84].

However, as discussed above with respect to neurosurgical applications, there are major general challenges to the meaningful clinical interpretation of fMRI measures in neuropsychiatric applications. First, the relationship of blood-flow changes with altered presynaptic activity depends on the physiological context[85]. Secondly, it is an empirical observation that relatively increased activation in disease is associated with both relative functional impairment (in which case it could be interpreted as an index of physiological 'inefficiency')[86] and normal behaviour (suggesting interpretation as evidence for compensatory recruitment to maintain performance)[87]. Similarly, relatively reduced activation might represent functional pathology[88] or improved efficiency[89], depending on the context in which it is observed. With any of these situations, the clearest interpretation demands the matching of performance between the groups (for example, patient and healthy control), as differences in performance are an additional mechanism for altered patterns of brain activation[90]. The latter problem imposes special limitations on the types of information that can be derived from clinical applications of fMRI to patient groups, who, by definition, generally have clinical deficits.

As noted above, a central issue for consideration in the practical clinical implementation of fMRI as a diagnostic or monitoring tool is whether adequate standardization of studies between centres is possible. Because there are so many potential contributions to variance, care must be taken to limit the number of confounds, as in many cases the cognitive context for their application can have an impact on the results. As a minimum, fMRI protocols that

Box 2 | **New methods in functional imaging**

Future methodological developments will make functional MRI (fMRI) more informative. Computational advances already allow robust analyses in real time[160,168], which could enable full quality control during an examination or more precise tailoring of the protocol to the question being asked about an individual patient. Intra-operative scanners (either 'open' scanners that permit surgery within the magnetic field or configurations that allow the patient to be quickly moved to the scanner or the scanner to the patient) allow direct functional localization of cortical functional markers, even in the anaesthetized patient, which could improve functional localization for neurosurgery[169].

Limitations to the interpretation of the BOLD response can be addressed by using complementary forms of MRI contrast, or through the integration of BOLD MRI and other measures in simultaneous data acquisitions. Direct measures of brain blood flow can be made using non-invasive arterial spin labelling (ASL) MRI methods, which have greater stability over time for better assessment of slow (in the order of a minute or more) changes in brain responses[27]. Combined ASL and BOLD measures can be used to determine cerebral metabolic rate of oxygen consumption ($CMRO_2$) quantitatively[170,171], although current approaches are technically demanding. With care for safety issues and the correction of the artefacts induced by the shifting magnetic field gradients used for MRI, high-quality electroencephalograms can now be obtained simultaneously during an fMRI examination[34]. Combined evoked potential and fMRI studies promise to lend greater pathological specificity and sensitivity than evoked potential measurements alone for characterizing the diseased brain[172].

A major challenge is to correlate molecular events that are relevant to the interactions of therapeutic drugs to systems-level changes that can be related to behaviour. Advances in positron detection methods herald the advent of combined human positron emission tomography and MRI scanners[131]. In some instances, the molecular targeting of MRI contrast agents might be possible[173], although the time frame for practical clinical applications of this technology still seems medium- to long-term.

demand active participation of the subject need to be carefully tailored to limit variance in outcomes arising from variable task compliance or differences in strategies[91].

Because very small signal changes are measured, standardization also demands careful control over sources of noise and the approach to analysis. With modern scanners, remarkably little noise arises from scanner sources[92]. Most comes from physiological noise, which might be patient group- or disease-related. For example, normal ageing and Alzheimer's disease have both been shown to increase low-frequency or long-memory properties of resting fMRI noise[93]. New methods for perfusion imaging ultimately might provide alternatives that are more robust, particularly for observations over longer periods (BOX 2). Different problems are encountered for patients and for control groups; for example, patients with amyotrophic lateral sclerosis, who have bulbar symptoms, have difficulties remaining supine for prolonged periods because of problems with clearing saliva. Care must be taken to control such factors to prevent undesirable biases in the data[94]. Reassuringly, after these acquisition-related confounds are considered, and although the statistical model used for the analysis and the nature of the data preprocessing can have substantial effects on results, a recent comparative study shows that the specific statistical analysis package used has minimal influence[95].

fMRI applications potentially demand a new type of quantitative radiology that considers results from any single subject in an appropriate context. For example, age-related changes in BOLD responses demonstrate the need for age-normalization of results[96]. There also is a need to consider variability in the relationship between neuronal activation and BOLD response as a consequence of drugs[97]. For example, common drugs (such as caffeine, nicotine and indomethacin)[98–100] have significant effects on the neuronal haemodynamic response.

Understanding disease symptoms

A main goal of the examination in clinical practice is to define objective signs that are related to specific symptoms. However, objective validation of the patient's experience of major classes of symptoms, particularly those related to perception or sensation, is impossible.

fMRI can help to understand the genesis of individual types of symptom to guide better symptom-orientated treatment. Two broad experimental approaches have been adopted for symptom-related studies, involving the measurement of brain activity while the symptom of interest is experienced, or during the performance of tasks that engage cognitive processes putatively related to the symptom. Applications to understanding pain and psychosis, respectively, provide good examples of these complementary approaches.

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)[101]. The clinical importance of such a dissection is that it rationally defines distinct targets for therapeutic modulation. fMRI studies have also indicated that common physiological mechanisms are shared between pain that is directly experienced and pain that is imagined, and between exteroreceptive and affective pain[102,103].

Provision of objective, fMRI-based measures for neurophysiological mechanisms of pain might also increase sensitivity to detect intervention effects in therapeutic trials[101,104] (FIG. 3). fMRI can capture the variability of responses even on a single subject level; for example, inter-individual differences in pain responses can be found in the primary somatosensory, anterior cingulate and prefrontal cortices[105]. fMRI studies have been able to objectify neurophysiological correlates of reductions in pain intensities reported after analgesic interventions following noxious stimuli[104,106,107]. To our knowledge, so far only preliminary data from one phMRI study of pain in a patient population has been reported[108], but the applications of fMRI to exploratory therapeutic and Phase II trials of new analgesics are certain to expand. Better definition of the general anticipatory system responses that distinguish placebo[109–111] from active treatment responses are also needed, as is an understanding of how the brain encodes differences in qualities of pain[112,113].

A different approach can be taken with perceptions that are basically qualitatively abnormal (for example, hallucinations), which can be considered as a form of misattributed sensory response. Increases in primary auditory[114–116] and potentially language-related[116] cortical activity are evident during auditory hallucinations in schizophrenic patients. By contrasting these responses in schizophrenic patients with responses to inner speech

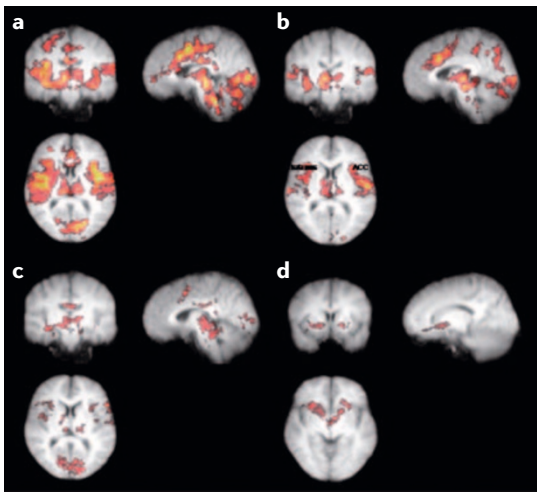

Figure 3 | **Pharmacological functional MRI (phMRI) allows drug effects in the brain to be defined from their modulation of activity.** In this example, brain activity with a noxious thermal stimulus applied to the skin relative to that with a non-painful warmth was mapped during the infusion of increasing concentrations of remifentanil, an opiate analgesic saline placebo (**a**); 0.5 ng/ml (**b**); 1.0 ng/ml (**c**); 2 ng/ml (**d**). The decrease in the functional MRI signal provides an objective measure of decreasing central pain response with higher doses of the drug. This provides a tool for both pharmacokinetics and pharmacodynamic studies[106]. Images courtesy of I. Tracey and R. Wise, Oxford Centre for Functional Magnetic Resonance Imaging of the Brain.

in healthy controls (attributed appropriately to an external source), specific hypotheses can be made concerning the brain dysfunction in schizophrenia responsible for psychotic features[117]. Regional differences in activity between healthy controls and patients could potentially provide new, short-term measures of response to anti-psychotic medication.

Pre-symptomatic diagnosis of disease

An important new challenge for clinical neuroimaging is being set with the availability of therapies that could delay the onset or expression of chronic neurological diseases[118]. The clinical problem is to identify early disease specifically and with confidence. Structural imaging must be interpreted in an appropriate context (for example, clinical suspicion and atrophy of the caudate nucleus for Huntington's disease[119], or mesial temporal atrophy and memory loss in mild cognitive impairment[120]), and has limited sensitivity to pathology. Investigation of altered patterns of brain activation in patients with an increased genetic risk of disease suggests that fMRI could contribute to the identification of early or pre-symptomatic disease expression; for example, in Huntington's Disease[121], Alzheimer's disease[122,86] or schizophrenia[54]. As fMRI responses are related to specific cognitive activities, they promise increased specificity that can be related directly to neuropsychological indices. In well-chosen clinical situations, structural and functional MRI could have useful, complementary roles to improve disease staging or to assess therapeutic responses. However, fMRI would have to show substantial additional value to be adopted as a clinical routine given the availability of other less expensive and complex adjunctive functional assessment tools (for example, in mild cognitive impairment[123]). Alternatively, examinations could be made simpler, making them easier to undergo for impaired patients (BOX 3).

Pharmacological fMRI

Applications of fMRI to the direct assessment of drug action are expanding[124] and phMRI could soon assume important roles in drug development. Pharmacodynamic data (that is, establishing that a drug has an effect on brain function) can be obtained from: the analysis of brain changes with the administration of drugs (for example, nicotine)[125]; the correlation of brain activity with the behavioural effects of drug administration (for example, methamphetamine)[126]; or the characterization of the way in which the activity of a probe task is modulated by a drug[127–130] (FIG. 3). In early drug development this can inform dose-ranging studies. The functional–anatomical information also shows sites of drug action to provide biological proofs of principle (although these fMRI responses need to be interpreted cautiously, as they could be either direct or indirect[29]). Correlations between fMRI measures of system responses and drug receptors or receptor occupancy measurements by PET are possible[75,131].

The kinetics of the fMRI signal change reflect the convolution of neuronal responses with the much slower haemodynamic response[132], but they can also provide useful pharmacokinetic data (that is, data describing the time course of drug action)[106]. A special feature of this type of pharmacokinetic information is that it is functionally and anatomically specific.

phMRI can provide neurophysiological indices of drug response that, because of the inherent functional–anatomical information, provide information relevant to understanding the cognitive basis for treatment response[130,133–135] and test alternative hypotheses regarding mechanisms[136]. phMRI might be useful for defining the effects of treatment in populations that are too small to allow behavioural effects to be discerned, or in cases in which routine tests are simply insensitive to drug effects[90,137]. Therefore, fMRI could be adapted to allow rapid individualization of treatments for specific populations or even for individual patients. A strong signal from the fMRI endophenotype relative to usual clinical measures would facilitate pharmacogenomic studies[77].

The suitability of fMRI methods will need to be considered carefully with each potential pharmacological application, as they are associated with unique confounds. In some instances, short- and long-term pharmacological responses could be different. Where an indirect phMRI effect is studied through modulation of activity associated with a probe task, the choice of probe task might determine not only sensitivity, but also the nature of response to the drug. An issue affecting all such studies is the differentiation of changes that are due to the modulation of blood flow by effects on the vasculature

from the modulation of neural activity and secondary vascular response effects. However, there are potential approaches for testing this distinction — for example, by relating fMRI and behavioural responses to conventional EEG or evoked potential studies, which will not be affected simply by the modulation of blood flow.

Recovery of brain function: plasticity in disease

The functional plasticity intrinsic to brain development and learning appears to be an important mechanism limiting the expression of disease and promoting recovery[138]. The extent to which the developing brain can reorganize in response to injury has long been recognized, but its potential importance in the adult brain was not widely appreciated. fMRI is contributing to a change in the perception of the importance of adaptive functional changes in the brain for recovery and maintenance of normal function after brain injury or during disease.

One of the most striking illustrations of this potential for altered use in the brain is in the tactile perception of braille in the blind. Whereas the sensorimotor cortex is activated by tactile stimuli in sighted controls, blind individuals reading Braille by touch show robust activation of the primary, secondary and higher visual cortices[139,140]. Considerable evidence for brain functional plasticity has been presented for other functional systems and in other disease states; for example, with chronic focal lesions from tumours[141] or after stroke[142], and with multifocal pathology such as multiple sclerosis[11,143]. Distant regions of the brain can be recruited to apparently compensate for dysfunction from injury. Transient interference with activity in some of these areas impairs performance, confirming their behavioural significance[28]. The changes are dynamic[144], and aspects of this functional recruitment are rapid and can be pharmacologically modified[90].

Functional plasticity
Changes in the functional association of activity in a brain region, provoked by alterations of intrinsic brain function rather than by the context of the activities alone.

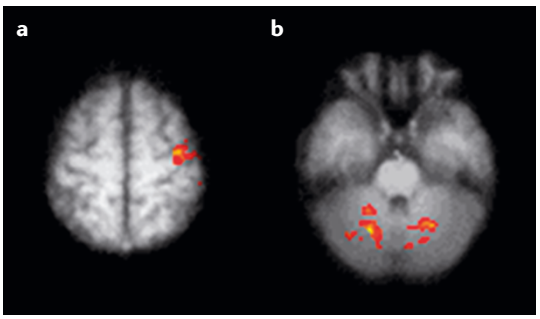

Figure 4 | **Monitoring of long-term brain activity changes with a chronic treatment intervention.** Patients with hemiparesis after stroke were given a period of standardized rehabilitation. Functional MRI (fMRI) studies with movement of the affected hand were performed before and after rehabilitation. A statistical contrast of the fMRI images was performed to assess regions of the brain that show increases in activity with recovery in order to define brain regions that potentially mediate the therapeutic response. Increased activity in the premotor cortex (**a**) and bilaterally in the dentate region of the cerebellum (**b**) were identified, suggesting that functional changes in these regions mediate clinically important aspects of recovery with rehabilitation[153].

The systems involved depend on the severity[145,146] and distribution of pathology[146,147], and on subsequent experience[148]. However, although information can be acquired easily, meaningful characterization of these phenomena by fMRI will depend on understanding disease, as well as therapy-related, age-related and other relevant effects on neurovascular coupling for fMRI[97].

Neurobiologically informed neurorehabilitation

Appreciation for the potential importance of brain functional plasticity in recovery has provided a new context for understanding neurorehabilitation[149]. Neurorehabilitation is still the main intervention for promoting recovery after serious brain or spinal cord injury. However, it is expensive and can be logistically demanding. An immediate practical problem is to better define patients who could benefit most from interventions, so that greater resources can be directed to them. Longitudinal fMRI studies post-stroke suggest the possibility that patterns of movement-related brain activation relatively early after a stroke could better define patients with a potential for substantial recovery, and who might benefit from more intensive therapy[150]. However, optimism that this will provide a practical tool that can be applied in a straightforward way needs to be guarded, given the complexity of interaction between the severity, anatomical location and extent of the lesion and the time since injury[147,151].

A second major problem in neurorehabilitation is that the standardization of therapy is difficult for multi-centre, randomized trials that are able to provide outcome measures in which clinicians can have confidence[152]. The heterogeneity of pathology and patient responses, the difficulties of defining functional rating scales that are sensitive to changes across a broad range of disability and the conceptual challenges of defining appropriate intervention placebos have limited the number of

Box 3 | **Resting state networks**

One approach to simplifying clinical functional imaging approaches could be to study the functioning of the human brain during rest[174,175]. Functional MRI (fMRI) images obtained using blood-oxygen-level-dependent (BOLD) contrast show signal fluctuations at rest that occur at low-frequencies (0.01–0.05 Hz), with coherent changes between widely-separated brain regions (for example, bihemispheric sensorimotor cortices)[174,176]. Although the resting state is an ill-defined condition, consistent spatial, frequency and coherence patterns between individuals suggest that there is common default or 'idling' activity within each of these resting state networks (RSNs)[175,177].

The low sampling rate for fMRI images (typically one brain volume every 2–3 seconds) causes temporal aliasing of variations of the BOLD fMRI signal induced by cardiac and respiratory cycles into a low-frequency range, similar to that of the RSN signal fluctuations. Some low-frequency coherences in conventionally acquired resting BOLD fMRI data are a consequence of this physiological noise[176]. Additional low-frequency fluctuations in resting fMRI data that are related directly to vascular processes independent of cortical neuronal function have been identified[178,179]. By contrast, RSNs appear to be a direct consequence of slow coherences in faster neuronal activity[180–182]. The specific spatial patterns suggest that they might be related to the functional integration of distributed nodes in well-recognized brain processing networks[177]. They have 'small world' properties (a local clustering of connections between neighbouring regions and a short path length between any pair of interacting regions), which are theoretically optimal for information transfer[183,184]. The observation of changes in specific RSN pattern with neurological disease (for example, Alzheimer's disease[185]) suggests possible clinical applications.

Box 4 | **Clinical applications of fMRI**

fMRI-guided neurosurgery
- Localization of functional brain anatomy to enhance resection safety[10].
- Localization of specific brain functions to guide functional neurosurgical ablation or stimulation[24].
- Localization of ictal foci for surgical resection in epilepsy[34].

Applications of fMRI for understanding disease
- Localizing generators for primary generalized epilepsy[36].
- Imaging the progression of migraine aura[32].
- Definition of phenotypes in cognitive–behavioural disorders, such as Williams syndrome[43].
- Characterizing mechanisms of disease[49].
- Markers of disease-related traits[56].
- Endophenotypes for genetic characterization of disease[58].
- *In vivo* assays for functional polymorphisms[59].

Potential applications of fMRI for clinical management
- Characterization of disease risk; for example, Alzheimer's disease[86].
- Diagnostic marker of disease; for example, schizophrenia[51].
- Predicting treatment response[64].
- Assessing potential for relapse after treatment[72].
- New paraclinical tests supporting the diagnosis of functional disorders; for example, conversion syndrome[84].

Applications of fMRI for the discovery and development of new therapies
- Relating molecular targets to behaviours; for example, addiction[75].
- Enrichment of study populations with treatment responders[76].
- Differentiating strong placebo responders[111].
- Pharmacodynamic markers[126].
- Pharmacokinetic markers[106].
- Potentially more sensitive measures of treatment response; for example, in analgesia development[108].

informative clinical trials for even the more popular neurorehabilitation approaches. By contrast, fMRI can be relatively sensitive to change after intervention because responses in specific functional systems can be assessed (FIG. 4). These, in turn, can be related to behaviour[153], and their significance for recovery can be tested directly using complementary methodologies, such as transcranial magnetic stimulation[28,150]. This approach allows underlying neurobiological mechanisms to be better understood[138] and offers a new way of assessing the relative efficacy of different rehabilitation methods in small, informative trials[128,151,154]. The concept can be extended to the assessment of the potential for drugs to enhance rehabilitation[128]. With a better understanding of imaging markers of heterogeneity in developmental[155,156] or acquired[157] disorders of language, and the dynamics of functional brain changes with cognitive training[158], similar approaches hold promise for cognitive rehabilitation[159].

The limited access to MRI scanning resources excludes the realistic consideration of fMRI as a clinically useful routine approach for monitoring neurorehabilitation in individual patients, or for providing biofeedback[160] that might itself be part of therapy. However, it is conceivable that even in the near future fMRI could be used to guide and calibrate responses from a less information-rich imaging methodology such as near infrared spectroscopy[161], which is portable and relatively inexpensive.

Conclusions and future perspectives

The translation of fMRI from basic cognitive neuroscience to clinical investigation has begun. At present, there are practical considerations limiting the routine use of fMRI as a clinical tool. However, it is already having some impact in specific clinical applications, such as in neurosurgical planning, disease characterization, drug pharmacokinetics and pharmacodynamics, and in the better prediction of treatment outcomes (BOX 4). This potential leads many to expect that fMRI will contribute to improving the efficiency of early phase drug development. It might also contribute to an earlier, more specific and more confident diagnosis of functional brain disorders. It is clear that widespread introduction of clinical fMRI will demand new skills and an even closer integration of neuroimaging with medical care. It should help to hasten the introduction of more quantitative approaches in neuroradiology. Potentially, the greatest long-term impact could be the ability of fMRI to define disorders of mind and cognition in the context of the range of human behaviours in the broader population. This will foster more effective approaches to addressing problems associated with the management of personally or socially limiting behaviours (for example, addiction, compulsive behaviours and autistic syndromes), on the basis of an appreciation of potentially modifiable consequences of the interaction between individual neurobiology and the environment.

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Competing interests statement
The authors declare competing financial interests: see web version for details.

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