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Clinical Overview

Making sense of neuroimaging in psychiatry

Malhi GS, Lagopoulos J. Making sense of neuroimaging in psychiatry.

Objective: Neuroimaging of psychiatric disorders has increased exponentially in the last decade; however, much of the uptake thus far has been in the realm of research. We anticipate that clinical use of neuroimaging modalities in psychiatry will increase dramatically in the near future and suggest that clinicians need to be aware of the potential applications.
Method: The authors conducted an extensive MEDLINE, EMBASE, PubMED and PsychInfo search of the published literature (1965–2007) using a variety of search terms to find relevant articles. Bibliographies of retrieved papers were further scrutinised for publications of interest, as were indices of books. Articles that reported clinically significant findings and research reports conducted using pertinent neuroimaging modalities were reviewed in detail.
Results: The review suggests that exciting neuroimaging advances are being made that have relevance to psychiatry. Novel neuroimaging applications with potential clinical utility are rapidly emerging and the accessibility and use of these technologies will increase in coming years. Clinically meaningful findings have begun to emerge in mood disorders, post-traumatic stress disorder, schizophrenia and dementia. Coupling multimodal imaging with genetics and pharmacotherapeutic studies will further assist in understanding the pathophysiology of neuropsychiatric disorders.
Conclusion: It is important that clinicians understand the benefits and limitations of modern neuroimaging techniques and are also suitably equipped to appraise future developments. The use of neuroimaging in evaluating psychopathology is likely to impact upon the future nosology of psychiatric disorders, and assist in diagnosis and clinical management. The integrated use of neuroimaging in conjunction with clinical assessments promises to improve clinical care and markedly alter psychiatric practice.

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Clinical recommendations

- Neuroimaging advances thus far have produced potentially useful clinical tools for the structural and functional assessment of psychiatric disorders such as dementia.
- Findings from neuroimaging research studies of psychiatric disorders are viewed with both scepticism and awe are however an accurate appraisal that recognises both the strengths and weaknesses of neuroimaging studies of the brain is necessary.
- A basic knowledge of the capabilities of modern neuroimaging techniques and their limitations will become increasingly necessary for practicing psychiatrists as imaging modalities are integrated into the clinical management of psychiatric disorders.

> **Additional comments**
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> - The combination of neuroimaging technologies with other methods of investigation is likely to become commonplace in the near future and holds much promise with respect to unravelling the neurobiology of psychiatric disorders.
> - Neuroimaging has emerged as a valuable research tool in the study of many psychiatric illnesses; however, translation into clinical practice will require further substantial technical and statistical advances.
> - The clinical future of neuroimaging is most likely to be linked to therapeutic choices and interventions. Important developments in this regard include molecular imaging and neuroimaging genomics.

Introduction

In the 20th century, psychiatry attempted to define itself by linking the mind to the brain and developing a medical model for the study of psychological disorders. Overlapping with neurology, neurosurgery and psychology with respect to psychopathology, psychiatry has attempted to maintain its connections with these disciplines but at the same time delineate its boundaries. To some extent it has succeeded, however, the emergence of new disciplines, such as cognitive neuroscience and neuroimaging genomics and the subdivision of psychiatry into specialities, poses a new threat to its identity. The core problem with the 'house' of psychiatry has been its foundations. The apparent lack of a biological basis for the majority of psychiatric disorders and the inability to achieve universal clinical consensus, as regards syndromic definitions has diminished its status as a medical specialty. The advent of new technologies, however, has provided some reprieve, with many researchers seeking to refine current diagnostic categories by identifying neurobiological substrates. At the same time, these developments have also ushered in the possibility of dramatic change, with some researchers pursuing a totally different basis for the classification of psychiatric disorders; one that is based solely on diagnostic biomarkers. In this regard genetic research has perhaps made the greatest advances thus far, and in psychiatry, neuroimaging appears to be equally promising. Hence, the focus of this clinical overview article is neuroimaging as applied to psychiatric disorders; explicating both the science and salience of findings to clinical practice.

In recent years, the research of brain structure and function using modern neuroimaging techniques has increased exponentially (1). In this journal alone, several recent articles have featured neuroimaging findings in psychiatric disorders (2, 3).

Technological advances across biomedical engineering and computing have enhanced our ability to dissect the 'working brain' and better understand its neurobiology. Progress in the field has been accelerated through iteration between an increasing knowledge base and methodological developments. Indeed, neuroimaging today is seemingly able to 'capture our ideas' and provide unique insights into mentation and psychopathology. In psychiatric practice the focus of aetiopathological models has shifted from the mind to the brain with interventions in the psychotherapeutic realm also pursuing a neural basis. Not long ago psychiatrists would routinely explain behavioural dysfunctions solely in terms of psychological constructs, however, increasingly psychiatrists are beginning to provide explanations of disorders with reference to the structure and function of the brain.

Aims of the study

It is against this rapidly changing background that this clinical overview article has been written to provide a basic understanding of the neuroimaging technologies that are currently available and explain the meaning behind the pictures. Key neuroimaging findings across a number of psychiatric disorders are then briefly reviewed and the likely future developments in brain imaging and implications for psychiatry are discussed.

Material and methods

The authors conducted an extensive search of the published literature (1965–2007) employing a number of databases (MEDLINE, EMBASE, PubMED and PsychoInfo) and relevant terms, exemplars of which include neuroimaging, psychiatry, radiology, magnetic resonance imaging (MRI), structure, function and mental illness. Bibliographies of articles were scrutinised for further publications of interest as were indices of

books and other sources of literature known to the authors. Articles that reported clinically significant neuroimaging findings or used a novel modality as judged by the authors were reviewed in detail.

This article is therefore divided into two sections. The first deals with neuroimaging modalities and provides a basic overview of available techniques. Detailed information is provided in boxes, and figures have been used to furnish examples. The second section highlights significant findings across a select number of psychiatric disorders. A comprehensive review of all the neuroimaging findings across all psychiatric disorders is clearly beyond the scope of this article and even within each phenotype, only findings of research interest or clinical salience can be addressed. Hence in this article a number of common and contrasting neuropsychiatric disorders have been chosen namely post-traumatic stress disorder (PTSD), mood disorders, schizophrenia, mild cognitive impairment (MCI) and Alzheimer's disease (AD). In addition each of these conditions has been selected by virtue of being amenable to investigation using neuroimaging and because a significant number of studies have been conducted examining each disorder.

Results

Brain neuroimaging modalities

Neuroimaging of the brain has advanced at a tremendous pace because of technological innovations and developments in computing. Concurrently, new statistics have been developed to interrogate neuroimaging data. We initially consider the clinical technologies that are currently available and then discuss the potential research applications of novel neuroimaging techniques.

Presently there are essentially three neuroimaging modalities that are commonly used in clinical settings. These are computerised tomography (CT), MRI and perfusion studies that typically examine regional cerebral blood flow (rCBF), (although, perfusion-MRI is increasingly being utilised in both clinical and research settings). Hence, these will be discussed in detail with respect to methods and interpretation of findings.

Traditionally, imaging has been divided into *structural* and *functional* neuroimaging; however, some novel neuroimaging modalities provide an admixture of the two and do not fit pristinely into this dichotomy (see Fig. 1). These techniques such as spectroscopy, diffusion tensor imaging (DTI)
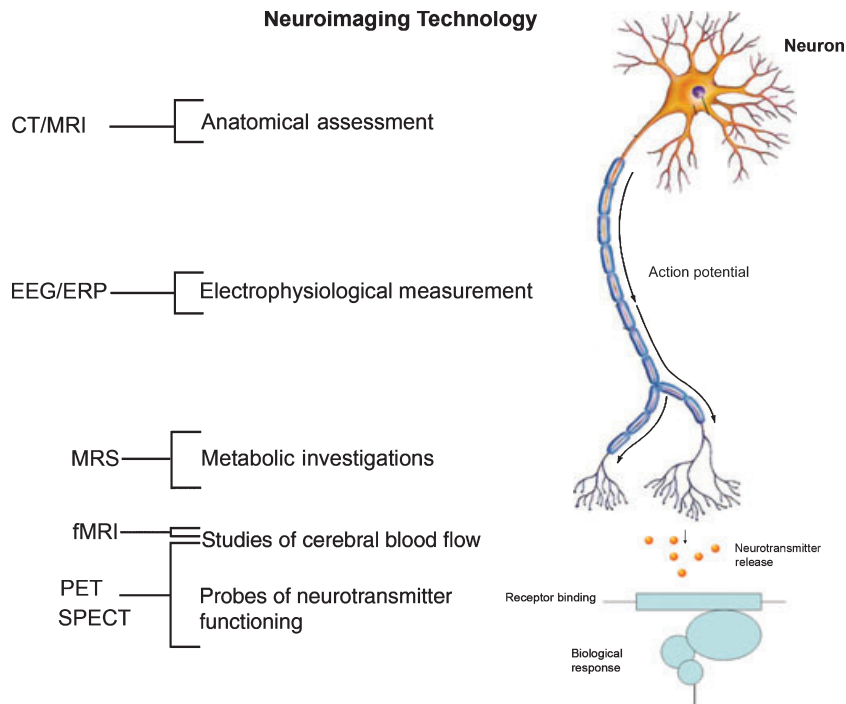

Fig. 1. The neurobiological processes assessed by neuroimaging modalities. This is a schematic representation of a neuron depicting an action potential travelling along its axon and resulting in neurotransmitter release at the axon terminal bouton. The neurotransmitter then migrates across the synapse and binds with the receptor to initiate a biological response. The middle column indicates the parameters that can be measured throughout this process from action potential to biological response. The first column indicates the neuroimaging technology best suited to measure the various parameters of neurobiological activity.

and other innovative means of scanning the brain will be discussed separately.

Structural neuroimaging

CT and MRI provide a powerful means by which to map the anatomy of the brain. Both techniques yield images with excellent spatial resolution and contrast and are widely used to assess cerebral pathology in neuropsychiatric disorders. From the perspective of practicing psychiatrists both techniques are important and they are now readily available and increasingly affordable.

Computerised tomography. In CT imaging of the brain a thinly calibrated beam of X-rays is used to irradiate the head of an individual. The beam encounters various tissues the properties of which determine the degree of attenuation that occurs as the X-rays travel through the brain onto a scintillation crystal that acts as an image receptor and makes a record. During a CT scan the beam is rotated around the head and the pattern of attenuation changes is collated by a computer program that reconstructs the individual measures into a 2D image (see Box 1 and Table 1).

Box 1: CT imaging basics

CT uses ionising X-ray radiation. A highly collimated beam of X-rays is transmitted through the head of the subject and recorded by specialised detectors. The degree of X-ray attenuation determines the final image and is dependent on tissue properties. Dense tissues such as bone attenuate X-rays more so than soft tissues such as fat. On a CT image air appears very dark or almost black as it is less dense than fat and attenuates X-rays the least. Soft tissues such as cerebrospinal fluid and fat are also dark but appear slightly lighter than air, whereas dense tissues such as bone and blood appear white. An iodinated contrast is also used to identify blood vessels as it increases the attenuation of X-rays and appears white in CT images and is also used to detect leakage through the blood brain barrier.

Magnetic resonance imaging. MRI takes advantage of the fact that certain atoms when placed in a magnetic field align with the direction of the field. In an MRI scanner this pattern of alignment is predictably disrupted by radio-frequency (RF) waves that are turned on and off systematically to yield pulses of energy that are then measured and processed into images (see Boxes 2 and 3).

Table 1. Appearance of cerebral tissues on computerised tomography (CT) images

Scanned tissue	Appearance on CT image
Air	Intense black
Fat/lipids	Black
Water/cerebrospinal fluid	Grey–black
White matter	Grey
Grey matter	Grey–white
Blood (acute bleeding)	White
Calcification	White
Bone	Intense white

Box 2: magnetic resonance imaging basics

Hydrogen is the most commonly imaged element in MRI because of its abundance and because it gives the strongest signal. The nucleus of a hydrogen atom is a single spinning proton with a positive charge that generates a tiny magnetic field. Normally the field surrounding hydrogen atoms is orientated randomly and together the fields of many hydrogen atoms cancel out. However, when in a large external magnetic field (B_0) such as that of the MRI scanner the protons align with the direction of the field and *precess* about B_0 at a frequency called the Larmor frequency, and lie in the RF range. If then an RF pulse of this frequency is directed into the tissue the spinning protons resonate and precess in phase. This generates a transverse magnetic field that precesses at the same Larmor frequency. When the RF pulse is switched off the precessing protons induce an electromagnetic field in a detector coil outside the tissue that can be measured and subsequently powerful computers process this raw data to produce the MRI images.

Box 3: MRI sequences and terminology

The appearance of the brain on an image from an MRI scan is dependent on a number of inter-related factors (see Table 2). These include innate tissue properties that are described using parameters such a relaxation time and proton density and are referred to as T1 and T2. Imaging techniques and protocols also determine the exact nature of the image obtained and terms that are frequently used in this context include sequences such as spin-echo, fast spin-echo, gradient-echo and echo-planar imaging with varying echo times (TE), flip angles and repetition times (TR). A T1-weighted image has a short TR and short TE such that tissues with a short T1 relaxation time appear bright and those with a long T1 appear dark. On a T2-weighted

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image that has long TR and long TE, tissues with a short T2 relaxation time are dark and those with a long T2 are bright. Fluid attenuation inversion recovery sequences provide T2-weighted images with cancellation of fluid signal (black fluid and black cerebrospinal fluid). Intravenous contrast shortens the T1 relaxation time and increases the T1 signal intensity.

Table 2. Appearance of cerebral tissues on magnetic resonance imaging (MRI) images

Scanned tissue	Appearance on MRI image	
	T1 sequence	T2 sequence
Air	Intense black	Intense Black
Fat/lipids	White	Black
Water/cerebrospinal fluid	Black	White
White vs. grey matter	Lighter	Darker
Bleeding (subacute<acute<chronic)†	Light: dark: darker	Light: dark: darker
Bone and calcification	Intense black	Intense black

†A subacute bleed is lighter than an acute bleed, which in turn is lighter than a chronic bleed. However, it is important to note that haemorrhage has a complex signal that varies considerably with time.

CT vs. MRI. Images of the brain on MRI achieve a high degree of resolution and have several advantages over other means of assessing brain structure. Necrosis, haemorrhage, cysts, tumours and white-matter changes are readily discernible with MRI as are changes in brain regions that are difficult to image with CT, such as the brain stem and cerebellum. However, cerebral CT is more sensitive than MRI with respect to identifying acute haemorrhage and calcification and is better for characterising bony anatomy. Whilst the soft tissue contrast obtained by CT is not as high in resolution as that of MRI, CT remains the imaging modality of choice for assessing acute trauma and instances where an acute subarachnoid haemorrhage is suspected. Hence, in clinical practice CT does offer some advantages. It is still more widely available than MRI, and much less expensive. It is also generally more accessible, as it has fewer contraindications. It is important to note, however, that some older style electronic or metallic implanted devices that include cardiac pacemakers, aneurysm clips, cochlear implants and neurostimulators may not be MRI compatible (4). However more recently, advances in materials engineering have made some neurostimulators and metallic implants compatible.

Functional neuroimaging

In its broadest sense functional neuroimaging can denote electrophysiological assessment of brain processing however, in this article it is used to refer to functional MRI (fMRI) and emission tomography.

Functional magnetic resonance imaging. Functional MRI makes use of the same hardware as MRI but exploits the paramagnetic properties of deoxy-haemoglobin (see Box 4 and Fig. 2). Typically, fMRI is used to identify brain regions that are activated by a specific task performed by an individual whilst in the scanner. It is important to note, however, that it does not detect actual neuronal transmission but instead relies on the presumed coupling of neural responses to local blood flow. It is therefore used to assess neuro-cognitive processes, and the concurrent acquisition of structural MRI allows the regions of activity to be accurately mapped onto images of the brain. The advantages of fMRI over other techniques is that it is non-invasive and allows the study of brain function without the use of ionising radiation or the injection of radiopharmaceuticals that are used by other methodologies [see positron emission tomography (PET) and single-photon emission computed (SPECT)]. In practice, fMRI can be conducted on most clinical 1.5 Tesla MR scanners, using conventional hardware, although some additional software is often needed. Nowadays high field scanners (3 Tesla) are more common and are the preferred choice as they afford greater signal-to-noise ratio. In comparison to other modalities fMRI offers the best spatial resolution, however, it is susceptible to a number of artefacts, the most limiting of which is caused by movement. Hence, in most fMRI experiments it is necessary for subjects to lie extremely still for up to 40 min and this makes it difficult to apply to some psychiatric disorders such as panic disorder and mania.

Box 4: fMRI basics

fMRI relies on the variations in signal intensity that occur as a consequence of altered levels of cerebral blood oxygenation. This technique is called blood oxygen level-dependent (BOLD) contrast. Regional neural activity results in increased local CBF producing an increase in oxyhaemoglobin carrying red blood cells. This essentially leads to a net decrease in de-oxyhaemoglobin. The two molecules oxyhaemoglobin and de-oxyhaemoglobin have different magnetic properties (diamagnetic and paramagnetic respectively) and the relative change in concentrations of the two results in a change in signal intensity.
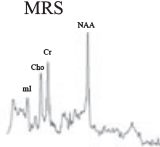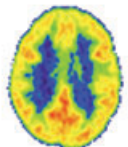
Imaging Modality	Advantages	Disadvantages
MRS	* Identifies location and concentration of active brain metabolites * Non-invasive * Permits chemical biopsy of the brain	* Not all metabolites are relevant to disease processes * Many metabolites cannot be measured * Need specific hardware to assess nuclei of interest
PET/SPECT	* High sensitivity and specificity of radioligands * Can visualise brain function - Especially with PET	* Invasive - involves radiation * High cost * Availability and stability of short acting radioligands * Poor spatial and temporal resolution
fMRI	* Non-invasive and no radiation * Detects changes in regional cerebral blood volume * High spatial resolution * Widely available hardware	* Poor temporal resolution * Anaiysis is complex and time consuming * Very sensitive to movement artifact * Many contraindications
DTI	* High spatial resolution * Non-invasive * Able to identify white matter fibres	* Difficult to conduct group comparisons

Fig. 2. The images of differing neuroimaging modalities. A graphical display of the actual data output obtained from magnetic resonance spectroscopy (MRS), positron emission tomography (PET), functional MRI (fMRI) and diffusion tensor imaging (DTI) neuroimaging modalities. The output for MRS takes the form of a spectral graph that depicts the relative concentration of metabolites present in the region of the brain sampled. PET output consists of a slice of whole brain at a specified level that depicts the uptake of radioligands via a gradation of colour. Warm colours such as red/orange depict increase uptake whereas cooler colours such as blue/green indicate little or no uptake. The fMRI output is depicted by an MRI slice with the coregistered BOLD activations present and indicated in red/yellow. Finally, DTI tractography shows the actual arrangement of white matter fibres.

Functional MRI experiments utilise stimuli (visual, auditory, motor or sensory) in the form of a task that is presented to the subject in the scanner so as to probe a specific function of interest. Baseline images are acquired with the subject in a resting or control state and then subsequently, when the subject responds to stimuli, another set of images is acquired. Typically, tasks across a number of domains are used to form a cognitive paradigm that can be used to assess complex functions. However, fMRI data requires sophisticated analysis to produce images that allow brain activation to be visualised (see Fig. 3) (5). Reports from fMRI studies usually provide regional coordinates and statistical scores that indicate the robustness of activations (6). Clinically, fMRI is most widely used for preoperative brain mapping in patients about to undergo neurosurgery. With respect to psychiatric disorders, fMRI has limited clinical utility but remains a useful tool within the realm of research.

Emission tomography. Two techniques are subsumed under this term namely, PET and SPECT. Both are nuclear imaging techniques that involve the injection of short half-life radio-pharmaceuticals and the detection of emitted radiation using scintillation cameras. SPECT detects gamma rays that are produced as radio-nuclides decay, whereas PET detects gamma rays that are emitted following the collision of positrons and electrons. The information these gamma rays impart is used to recreate a 3D image of the brain regions emitting the rays. In general, PET tracers are able to map a broader range of brain activity than SPECT tracers (see Box 5 and Fig. 2); however, the latter have longer half-lives and do not require a cyclotron to be

situated in close proximity for generation. This is a significant limitation of PET and makes it comparatively expensive. For imaging the brain, however, PET offers much better spatial and temporal resolution than SPECT. Consequently, it is increasingly preferred for studies of cerebral function and is steadily becoming more widely available especially in combination with CT in the form of PET/CT.

> **Box 5: PET radionuclides**
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> Available radionuclides for PET include nitrogen 13 (^{13}N), carbon 11 (^{11}O), oxygen 15 (^{15}O) and fluorine 18 (^{18}F). Clinically, the latter is the most widely used PET radionuclide. ^{18}F has the longest half-life and is used to label flouro-2-deoxyglucose (FDG). This is a glucose analogue. Glucose metabolism increases in areas of brain activity. Hence ^{18}F-FDG-PET is used to assess brain function.

Perfusion MRI. Perfusion MRI (pMRI) is becoming increasingly popular, as it enables measurements of the rate at which blood is delivered to tissue at microscopic levels of blood flow without the need for intravenous administration of an MR contrast agent. Perfusion MRI has inherent high spatial and temporal resolution, which makes it the technique of choice in the diagnosis of vascular diseases. Recently it has been used more widely in psychiatry, as it is provides a powerful means of studying the physiological events that accompany neural activation. One form of pMRI is arterial spin labelling (ASL), which uses magnetically labelled arterial blood water, as the endogenous tracer. Blood flowing into the imaging slice exchanges with tissue water, altering the tissue magnetisation to provide estimates of haemodynamic parameters such as cerebral blood volume, CBF or perfusion, and the mean transit time. To generate a perfusion image the image in which inflowing spins have been labelled is subtracted
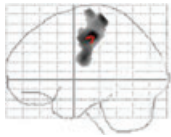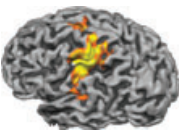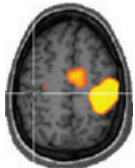
Display Type	Advantages	Disadvantages
Glass brain	Rapid reveiw of results	Poor spatial localisation
3D Render	Whole brain perspective	Deep brain structures unable to be displayed
MRI slice	Good spatial localisation	Limited whole brain perspective

Fig. 3. The representation of functional magnetic resonance imaging (fMRI) data in images. This figure depicts the three most commonly used methods for displaying fMRI data. The *glass brain format* is often used in conjunction with statistical parametric mapping data. The greatest advantage associated with viewing data using the glass brain is that it provides an instant appreciation of the extent of the activations present. However, this comes at the expense of accuracy in spatial localisation. The glass brain format crudely informs the reader about activations present in frontal, temporal, posterior or occipital regions without any specificity and as such should not be used as a reference to spatial localisation. *3D rendered brain.* Its strongest attribute is that it provides the reader with a whole brain perspective, however the 3D format is only able to display activations on the cortical surface and therefore activations, which may be present in deep subcortical regions, are not represented. Some groups have displayed deep subcortical activations as 'projections' to the cortical surface. In these instances caution needs to be exercised so as not to confuse cortical with subcortical activity as both are presented side-by-side on the cortical surface. *The MRI slice* comprises a co-registered structural MRI together with the BOLD signal. This is by far the most commonly used format as it provides the reader with good spatial localisation. However, similar to the glass brain format, the MRI slice does not provide a whole brain perspective. With all three display types, the issue of *laterality* requires careful consideration as there is still no universally accepted convention. Data can appear in *radiological orientation* in which case when viewing an image: *left* on the image denotes the *right* anatomically. Data displayed in *neurological orientation* follows a different convention: *left* on the image denotes the anatomical *left*.

from a corresponding image in which spin labelling has not been performed. The ASL technique utilises standard MRI equipment with specialised sequences and can be coupled with fMRI to study aberrant neural networks in the brain thought to contribute to psychiatric symptoms. However, despite its advantages, ASL has a low signal-to-noise ratio and the quantification of these parameters can be complex.

Magnetic resonance spectroscopy

Based on the principles of nuclear MR, MRS extracts chemical and metabolic information that in essence allows 'chemical sampling' of the brain (see box 6). MRS is non-invasive and permits the relative quantification of metabolites in specific brain regions (*single voxel*) as well as across a slice of the whole brain (*chemical shift imaging*). The data from MRS is not depicted as an image but instead as a spectrum (see Fig. 2). The type of MRS used for a particular study is dependent upon a number of factors namely, the specific nuclei of interest and the metabolites to be measured. In MRS perhaps more so than other areas of MR, higher field strength magnets offer significant advantages, particularly with respect to sensitivity, signal-to-noise-ratio and spatial resolution. Measurement of metabolites that are of interest to psychiatric disorders, such as gamma-amino butyric acid (GABA) and glutamate, benefits from the use of higher magnetic fields (7, 8). An advance in MRS that assists in measuring these metabolites further is the use of ^{13}C-labelled glucose, which is taken up into glutamate and then subsequently into GABA thus permitting the metabolism of the latter to be studied. Similarly, studies using ^{31}P-MRS can be used to study membrane dysfunction in schizophrenia (9).

Diffusion tensor imaging

A more recent brain imaging technique, which has emerged from advances in MRI, is that of DTI. Where, conventional MRI provides overall anatomical detail and fMRI a measure of cerebral activity in the grey matter, DTI provides a method for estimating the paths followed by water as it diffuses within the white matter (10, 11). This allows the identification of white matter tracts in the brain with respect to location and orientation. (see box 7 and Fig. 2) A further advance of DTI is its ability to non-invasively construct 3D trajectories of neural tracts *in-vivo* (12). Tractography then allows the

Box 6: MRS basics

In Magnetic Resonance Spectroscopy (MRS) a number of nuclei are studied. These include proton (^{1}H), phosphorous (^{31}P), lithium (^{7}Li), carbon (^{13}C), fluorine (^{19}F) and sodium (^{23}Na). The most widely used is proton spectroscopy which permits the identification of a number of metabolites including *N*-acetyl aspartate (NAA), creatine (CR), choline (Cho), myoinositol (MI), glutamate and glutamine (GLX), which often cannot be differentiated at lower field strengths. MRS provides relative quantification and for this purpose either water or CR serve as internal references because of their relative consistency both in health and across disease states. Moreover, the use of dedicated software programs such as LCModel makes it possible to obtain absolute quantification of metabolites. An MRS spectrum consists of the various peaks plotted along an axis of varying frequency. The resonant frequency and height of each peak characterises a specific metabolite and the area under the peak provides a measure of its relative concentration. The largest signal in proton MRS is understandably from water. In processing the data this signal has to be suppressed so as to achieve a steady baseline. The largest spectral peak is usually that of NAA and this is considered to be a reliable marker of neuronal integrity. Cho is also usually readily discernible and in the brain is associated with cell membrane turnover. Spectral peaks of MI, GLX and GABA are much smaller and can be enhanced using specific pulse sequences. In proton MRS two pulse sequences are used, namely stimulated echo acquisition method (STEAM) and point-resolved spectroscopy (PRESS). In general, STEAM (which is better suited to shorter TE) has better water suppression and can identify a broader range of metabolites, however it is more sensitive to motion artefacts. PRESS (can be used with short or long TE) provides greater signal-to-noise than STEAM (for an equivalent TE) and using a long TE it is able to identify Cho, CR, NAA, lactate and lipids. Using a short TE metabolites such as MI, glucose and the glutamate/glutamine (Glx) complex can be identified.

modelling of white matter neural connectivity, a method that is currently the subject of intense investigation as it can provide information relating to neuronal connections subserving brain function. At this point in time the ability of DTI

to characterise the white matter architecture of the brain is unparalleled by any other imaging modality.

Box 7: DTI basics

Diffusion weighted imaging is an MRI modality that enables the quantification of the diffusion of water in tissue making it possible to identify white matter within the brain. It is predicated on the fact that anatomical structures such as cell membranes, myelin sheaths, as well as intracellular micro-organelles act as barriers to the diffusion and free movement of water thus limiting the spatial flow of these molecules. The arrangement of axons in parallel bundles with myelin sheaths facilitates the diffusion of water molecules longitudinally. By acquiring a conventional diffusion weighted MRI in at least six non-collinear directions it is possible to reconstruct the brain's underlying neuronal microstructure that is normally 'invisible' using conventional MRI. This is called DTI. Often fractional anisotropy is used to describe the shape of the diffusion tensor and it provides a scalar measure for the degree of anisotropy in a given voxel. This measure can be used clinically to localise white matter lesions that do not appear on other forms of clinical MRI. The technique remains very much in the research realm, as hardware and analysis expertise are not readily available. However, the potential for it to be used clinically for lesion and trauma cases is high as evidenced by recent clinical applications (2, 13).

Voxel-based morphometry

Voxel-based morphometry (VBM) is an MRI technique that measures brain tissue concentrations and makes inferences about the brain on the basis of differences in tissue classifications. Strictly speaking, it is a post-processing method of morphological images, however, it is considered separately here as it is used widely in neuropsychiatric research. Indeed, the technique has been reliably used in psychiatric research for many years (14–16), however it has not made a transition into the clinical arena. The VBM technique is heavily dependent on statistical and computational evaluation of differences in tissue classes (see box 8). Large sample sizes are needed for identifiable changes to achieve statistical significance.

Hence, currently it is not a technique that can be used to investigate changes in grey and white matter composition in individual patients. Another limitation of VBM is that it assumes the brain consists purely of grey matter, white matter and cerebrospinal fluid. This makes analysis of groups with pathologies such as tumour and stroke using normalisation and segmentation procedures very difficult (17).

Box 8: VBM basics

VBM is a computationally and time intensive neuroimaging technique that can provide detailed information relating to changes in grey-white matter composition within the brain. The technique is based on a series of computational steps that correct the MR images for large-scale differences in gross anatomy prior to statistical evaluation. The computational steps include: (i) spatial normalisation of all the images to a common reference space or template. The purpose of this step is to correct for global differences in brain shape; (ii) the segmentation of tissue classes into grey matter, white matter and cerebrospinal fluid. To assist the segmentation process, the intensity of the structural images is often corrected for inhomogeneities caused by technical issues relating to the MRI head coil; and (iii) the final step involves smoothing the segmented grey and white matter images, which helps to compensate for the inexact nature of the normalisation process.

Multimodal imaging

An emerging field within the neuroimaging of psychiatric disorders is that of multimodal imaging (MMI). Unlike individual techniques such as fMRI, DTI and spectroscopy, MMI seeks to integrate one or more technologies to achieve a better understanding of brain function. Techniques such as electroencephalography (EEG) and magnetoencephalography have been used with modest success. These techniques record electric and magnetic fields at the scalp and provide information on electrical events that occur within the brain. These techniques have excellent temporal resolution that is in the range of milliseconds, however their spatial resolution is poor and thus they do not provide detailed whole brain patterns of activity. As alluded to earlier, advances in physics and

computing have led to the development of brain imaging techniques that examine complementary aspects of structure and function with excellent spatial resolution. Techniques such as fMRI identify metabolic activity that tracks neural activity, on the basis of changes in blood flow. In the case of fMRI, whilst the spatial resolution that can be attained is excellent, the associated temporal resolution is poor as the haemodynamic response accompanying metabolic changes can be relatively slow. To overcome the respective spatial limitations of EEG and temporal limitations of fMRI, there has been significant interest in combining technologies to maximise the advantage that each affords. The combination of EEG–fMRI is popular and is now increasingly used in the presurgical assessment of patients with intractable epilepsy (18). Integration of these neuroimaging techniques is clearly a further advance on using EEG and fMRI alone, however, the coupling of these two technologies where the dependant variables are electrical perturbations (EEG) and blood flow (fMRI), does not provide the optimal combination for studying brain function. To address this issue some researchers have combined functional transcranial Doppler (fTCD) sonography, which provides a high temporal resolution measure of blood flow, with fMRI. In this case as both fTCD and fMRI determine blood flow-dependant imaging parameters as surrogate parameters of neural activity, the coupling of the temporal millisecond resolution of fTCD with the spatial millimetre resolution of fMRI provides an extremely accurate representation of neural activity.

MMI also encompasses the combination of neuroimaging with neuropsychological measures (19). A novel example of such integration is the combination of galvanic skin response (GSR) with fMRI. The GSR has been widely used as an objective index of emotion-related activity exploiting the fact that this form of autonomic arousal is tightly coupled to emotional behaviour. The acquisition of simultaneous fMRI-GSR is particularly pertinent in psychiatric research as it enables the objective identification and partitioning of neural events that have emotional salience (20) and takes advantage of the close links between autonomic activity and mood.

As yet, MMI is still very much in its infancy, however, it is poised to provide significant insights into the workings of the brain. Currently much of the hardware required to conduct MMI is at a prototypic stage but as the integration of the various technologies becomes more mainstream, commercially available hardware will emerge and its application in clinical settings will eventuate.

Clinical neuroimaging in psychiatry

It is important to note before embarking upon a journey through the numerous neuroimaging studies that have been conducted in psychiatry, the premise upon which much of this research is based. The science of cognitive neuropsychiatry relates psychopathology to neuropsychological constructs that are ultimately linked to structural and functional aspects of the brain. The research applications of neuroimaging in psychiatry can be broadly viewed as having either a 'restructuring' or 'refining' role. *Restructuring* involves dispensing with the current psychiatric phenomenological entities and replacing these with biologically driven explanations based on neuroscientific findings. In contrast, *refining* involves generally maintaining the current categories of psychiatric disorders but validating their essential elements by providing a neural substratum. Both approaches find support in the many studies that have been conducted in psychiatric populations; however, in this clinical overview article only a handful of noteworthy findings can be discussed. Psychiatric disorders that are common and have been subjected to scrutiny using a number of neuroimaging modalities form the focus and include PTSD, mood disorders, schizophrenia, MCI and AD. Findings from studies that have clinical salience have been highlighted, along with those that are especially interesting from a neuroimaging perspective.

Post-traumatic stress disorder

The pathophysiology of PTSD is linked to four mechanisms that include the fear response, a failure of fear extinction, behavioural sensitisation and memory problems. The structures involved in these processes include the sensory cortex, the dorsal thalamus, the lateral and central nucleus of the amygdala, the medial prefrontal cortex and hippocampus. These brain structures can be readily accessed using a variety of neuroimaging techniques and the phenomenology of PTSD clearly lends itself to neurocognitive scrutiny.

Structural neuroimaging. Structural changes that have been identified in PTSD patients involve the anterior cingulate cortex (a component of the medial prefrontal cortex), and the hippocampus. The latter is reduced in size by a number of types of trauma including physical and sexual abuse (21, 22). Despite these changes a causal relationship between reductions in hippocampal volume and a traumatic stressor is difficult to substantiate. Structural MRI studies of patients with PTSD

have centred on the hippocampus with few specifically examining the amygdala.

Functional neuroimaging. Functional neuroimaging has been particularly useful in investigating and understanding the pathophysiology of PTSD and hence studies of PTSD have used PET, SPECT and fMRI. Functional neuroimging studies suggest that metabolic activity in the medial prefrontal cortex–amygdala circuit is significantly altered (23). The most consistent findings have been those of increased amygdala and decreased medial prefrontal cortex activation (24), whereas functional imaging responses in the hippocampus and parahippocampal gyrus have been much less consistent (25). However, overall the findings support the hypothesis that there are two acute trauma response subtypes, one that is mainly dissociative and the other that is characterised by hyperarousal and intrusions (26).

Mood disorders

Mood disorders include primarily major depression and bipolar disorder; however, neuroimaging research of these disorders has been confounded by a lack of consistency in phenotypic grouping. This is further compounded by comorbid anxiety, substance misuse and the need to continue medication, especially in patients with bipolar disorder. However, limbic and cortical circuits that are implicated in the generation and regulation of emotion can be readily visualised using functional neuroimaging techniques, and paradigms that reliably modulate emotional tone can be created. Hence, mood disorders neuroimaging research is now a substantive field.

Structural neuroimaging. Even with grey and white matter differentiation, the majority of neuroimaging studies that have compared total brain volume in unipolar or bipolar disorder patients with healthy controls have found no significant differences (27–33). However, studies that have correlated changes to age and onset of illness (34, 35) indicate that neurodegenerative processes perhaps play a role, especially in the pathophysiology of bipolar disorder. The most consistent structural neuroimaging finding in studies of patients with mood disorders is that of increased white matter hyperintensities (WMH) in unipolar patients (36). WMH are T_2 signal hyperintensities that signify a change of water content in the brain. A similar finding is noted in patients with bipolar disorder especially in subcortical grey, periventricular and deep white matter (37, 38). However, signal hyperintensities lack anatomical and diagnostic specificity. They occur with ageing and are found in a variety of neuropsychiatric disorders including schizophrenia and dementia, hence their pathophysiological significance remains unclear.

Studies in unipolar depressed patients that have examined prefrontal cortical volume suggest a reduction as compared with healthy subjects (27, 31, 39–41). Further, structural MRI VBM analysis in patients with chronic treatment-resisitant depression (42), has identified reduced temporal lobe grey matter density in the anterior hippocampus. In bipolar disorder, temporal lobe changes are far less consistent with reports of both decreases (43, 44) and increases (45, 46). Amygdala enlargement, however, is a more consistent finding (47, 48) supporting its role in emotional processing. Thus, temporal lobe changes seem to distinguish unipolar and bipiolar disorder such that the hippocampus is reduced in size in unipolar depressed patients but largely unaltered in patients with bipolar disorder, whereas the reverse is true for the amygdala.

In addition to cortical changes, striatal pathology is strongly implicated in the pathophysiology of mood disorders, however the findings of decreased caudate and putamen volumes in unipolar depression and basal ganglia enlargement in bipolar disorder are inconsistent (49, 50). Similar observations have been made in other brain regions, including the cerebellum, corpus callosum, pituitary and brain stem. Recent studies examining anterior cingulate architecture in bipolar disorder suggest reductions in size and changes in morphology (51, 52).

Functional neuroimaging. A consistent finding in CBF studies of patients with depression or bipolar disorder is that of decreased anterior paralimbic and cortical activity. In major depression this finding of diminished blood flow reverses with successful treatment of the illness. Further, in depressed bipolar patients there is additional increased subcortical paralimbic metabolism (53) and together these findings support a limbic-cortical dysregulation model of depression (54). This model posits dorsal neocortical hypofunction that results in ventral paralimbic over activity along with reciprocity in this inverse relationship (55).

Proton spectroscopy studies in depressed patients with mood disorders show modest increases in the concentration of basal ganglia and anterior cingulate Cho (56). These changes are more marked in patients that respond to antidepressants and, although in need of further replication, it is likely that basal ganglia Cho

concentration is mood-state related (1). Proton spectroscopy studies of bipolar patients also suggest state-dependent changes in metabolism (3). Specifically, studies report diminished dorsolateral prefrontal NAA and CR (57, 58) indicating a decrement in neuronal density. Basal ganglia NAA is also diminished in patients with bipolar disorder (3), especially in patients with a late onset of illness and more fine-tuned MRS studies have identified a reduction of orbito-frontal grey matter NAA (59). Interestingly, the pattern of metabolite changes varies with age and similar findings to adults have not been replicated in adolescents and children with bipolar disorder (60). In comparison with proton spectroscopy, phosphorus spectroscopy findings in bipolar disorder have in general been less consistent, however, given the pivotal role of second messenger systems in the pathophysiology of mood disorders – further research is needed.

A novel *in vivo* application of MRS is its use for the measurement of cerebral psychotropic drugs such as lithium and fluorinated drugs such as the serotonin-specific reuptake inhibitors. Lithium is used as a mood stabiliser in the treatment of bipolar disorder (61), however, its serum and cerebral levels are poorly correlated and a significant proportion of patients with seemingly therapeutic lithium levels relapse or develop toxicity. In this regard ^{7}Li-MRS provides a non-invasive means of measuring brain lithium and although this technique is used largely for research at present, it clearly has clinical potential. Similarly, ^{19}F-MRS can be used to measure cerebral levels of fluorinated medications and their metabolites (62), an application that has significant clinical potential that will no doubt be realised in the near future.

Key to the pathophysiology of mood disorders is the central neurotransmitter serotonin, the investigation of which has been significantly facilitated with PET imaging and the development of specific ligands (63). Dysfunction of the serotonin transporter (SERT) that is located presynaptically has been implicated in the pathophysiology of depression (64) and its *in vivo* availability can be determined using selective PET radioligands that image the human 5HT transporter site. Binding to the SERT, serves as a proxy for the level of intrasynaptic serotonin, such that diminished binding is indicative of a decrease in intrasynaptic serotonin, or a reduction in the number of serotonin nerve terminals (65). In essence, it denotes diminished serotenergic functioning. A recent study that utilised $[^{11}C](+)$ McN5652 (a selective PET radioligand for the human 5HT transporter site) compared unipolar and bipolar patients that were antidepressant naïve with healthy controls.

This study found that the availability of thalamic SERT in patients was significantly increased as compared with control subjects (66). In addition to implicating the thalamus in the pathophysiology of mood disorders this study suggests that there is altered serotonergic functioning in patients with mood disorders, specifically within thalamic nuclei. Another study that used the same PET ligand to examine drug-free depressed patients in a very small sample, found significantly greater right cingulate and left frontal 5HT transporter site binding as compared with healthy controls (67).

The PET studies in patients with bipolar and major depression examining 5-HT$_{1A}$ receptor function have found significant reductions in receptor binding in limbic, frontal and temporal cortical regions (68, 69). Similarly, 5-HT$_{2A}$ receptor PET studies also report a decrement (70–72) in patients with major depression relative to controls, however, some studies find no difference (73, 74).

In recent years fMRI has been increasingly used to investigate mood disorders. With respect to unipolar major depression a relatively consistent finding across fMRI studies is that of diminished activation in the dorsal prefrontal cortex (BA9) that can be rectified with effective treatment (54, 75). Responses in this region have also been identified in healthy subjects during memory driven sadness and happiness suggesting that the right prefrontal cortex (BA9) is an important destination for limbic projections and that it perhaps plays a role in modulating mood states (76). Specifically, responses in BA9 may indicate emotional awareness that entails attention to internal emotional states (77) and involves greater cognitive emotional processing. The medial prefrontal cortex may therefore have a general role in emotional processing that involves the modulation and evaluation of emotion and emotion-dependent decision-making (78, 79). Another region that appears to be integral to emotional decisions and is functionally pivotal to the experience of emotion, perhaps by virtue of its reciprocal connections to the orbital frontal cortex, amygdala and insula, is the anterior cingulate (80). Functional activation and resting-state treatment studies (39, 75, 76) along with neuropsychological and lesion studies (81, 82) strongly implicate the subgenual cingulate (BA25) in the pathogenesis of clinical depression, a region that is activated by autobiographical script-induced sadness (75, 76, 83). However, the latter is not definitive as it may simply process the cognitive aspects of internally generated emotion rather than sadness *per se*. The amygdala is also a region of great interest and is activated across a wide range of functional imaging

studies but especially those that impinge upon the detection of environmental threat and the experience of fear (84). It is possible that its function is more general, determining for instance the dangerousness of affective stimuli or indeed their salience irrespective of valence. Hence, in addition to fearful and averse stimuli (85, 86), sad and happy affect (87) can also produce amygdala activation in functional imaging experiments in healthy volunteers and patients with major depression and bipolar disorder (88).

In examining bipolar disorder, fMRI studies have employed a variety of stimuli enlisting executive function and affective paradigms such as the STROOP, facial affect discrimination, and emotionally valenced pictures and words. Studies have shown reduced activation notably in the left rostral ventral prefrontal cortex (89) (a region that approximates to BA10 and 47). Interestingly, hippocampal (3, 90) and amygdala activation (3, 91) have been found in both unipolar and bipolar patients resulting in a pattern of diminished prefrontal activation in major depression, and state-related subcortical activation in bipolar disorder (92–95).

Clearly, there are functional abnormalities in mood disorders that can be identified using fMRI, however, the interpretation of these findings in a clinical context is as yet limited partly because of a number of confounds, such as the effects of medication and the heterogeneity of functional imaging stimuli, but also because of the complexity of emotional networks and our incomplete understanding of the integration of these networks with higher cognitive processes. A critical question in functional imaging research of mood disorders is that of whether neuroimaging findings are state or trait related. Trait-related changes have the potential to provide a biological marker of the illness, which in practice may precede the manifestation of symptoms, and state-related changes offer potential means for monitoring treatment response.

Schizophrenia

Structural neuroimaging. It is now widely accepted that schizophrenia is a neurodevelopmental disorder with neuropathological evidence from macroscopic and histological studies of the brain. The fact that structural changes occur and are discernible with neuroimaging has assisted in unravelling the pathophysiology of schizophrenia. Functionally, there are clear neurocognitive deficits, the neuropsychological underpinnings of which have been usefully modelled. Schizophrenia has therefore been an ideal candidate for both structural

and functional neuroimaging research. In addition, the dominant dopamine hypothesis that has driven drug development in schizophrenia has fostered neuroimaging receptor studies that have examined many aspects of dopaminergic function.

As described earlier MRI is better able to depict white matter than CT and as such has been particularly useful in examining white matter connectivity in schizophrenia. In patients with schizophrenia WMHs are common and occur particularly in late life schizophrenia. Such reductions in prefrontal cortical white matter volume have been associated with negative symptoms (96), and have also been found in first-episode schizophrenia and twin studies. Interestingly, structural changes are only apparent in the cotwins with the disorder but not in those that are healthy (97).

Volumetric MRI of schizophrenia patients has been used successfully to better characterise the widely documented finding of enlarged lateral cerebral ventricles. The latter, discovered using CT, was initially thought to be associated with diffuse brain atrophy, however, more recently it has been associated with focal decreases in brain parenchyma in specific brain regions and nuclei, such as the putamen, thalamus and superior temporal gyrus (98). This finding has been corroborated by another study that identified diminished mediodorsal and pulvinar thalamic nuclei volume in schizophrenia (99).

Structural deficits in schizophrenia have been further delineated by DTI. For instance, a recent study of patients with schizophrenia localised executive function deficits to the left cingulate bundle and declarative-episodic verbal memory deficits to the left uncinate fasciculus (100). In this regard DTI has been used successfully to corroborate structural imaging findings with reports of white matter tract changes in prefrontal and temporal brain regions (101).

Functional neuroimaging. Examining the dopamine hypothesis of schizophrenia, PET and SPECT studies have used amphetamine-induced reduction of raclopride binding to identify changes in dopamine D2 receptors. These neurotransmitter function studies suggest that there is increased dopamine release in schizophrenia (102). Further, spectroscopy studies in schizophrenia have consistently reported a reduction in frontal and temporal cortex NAA concentrations suggesting neuronal loss that is in keeping with a localised reduction of grey matter (103).

Akin to PET/CT fusion that permits the synchronous acquisition and accurate coregistration of functional (PET) and anatomical (CT) imaging

data, PET can also be coregistered with MRI as demonstrated in a recent ^{18}F-FDG PET study of glucose metabolism. This study examined thalamic subdivisions in patients with schizophrenia and coregistered axial T1-weighted MRI images and PET images in 41 unmedicated patients and compared these with 60 matched healthy controls. It found that in comparison with controls glucose metabolism in the mediodorsal nucleus and centromedian nucleus of the thalamus in patients with schizophrenia was significantly diminished, whereas in the pulvinar it was significantly enhanced. Interestingly, diminished mediodorsal nucleus glucose metabolism correlated with negative symptoms whereas diminished pulvinar glucose metabolism correlated with positive symptoms and hallucinations (104). The partitioning of thalamic regions with contrasting changes in glucose metabolism and the correlation of these abnormalities to clinical phenomenology in this study demonstrates clearly how sophisticated neuroimaging can inform our understanding of complex psychiatric illnesses such as schizophrenia.

In this context fMRI has also been useful in examining frontal lobe dysfunction that is thought to be at the core of schizophrenia. A consistent finding across a number of imaging modalities in schizophrenia has been that of *hypofrontality*, namely an inability to generate a frontal cerebral response to a specific task (105). Neuroleptic naïve patients with schizophrenia have been shown in fMRI studies to have reduced activation in the left temporal lobe, right frontal lobe and left cerebellum. This hypofrontality on fMRI is consistent with early PET and SPECT findings (106) and can be reversed, as shown by a verbal working memory fMRI study (107). This showed that after 6 weeks of treatment with an atypical antipsychotic, patients with schizophrenia had enhanced prefrontal function (107).

Mild cognitive impairment and Alzheimer's disease

The neuropathology of AD is perhaps the best characterised of all psychiatric disorders, and clinically neuroimaging is of increasing importance in the diagnosis and management of dementia. Similarly, MCI is a growing clinical problem that psychiatrists have to deal with. Fortunately, it too is an area where neuroimaging can make a significant contribution.

Functional neuroimaging. The diagnosis of MCI is based on the assessment of a number of cognitive functions, however, neuroimaging methods are now enabling risk stratification of MCI patients so as to identify patients with preclinical AD and in individual cases perhaps even anticipate and predict short-term conversion to AD. In this regard, a number of studies have shown that cerebral (^{18}F)-FDG-PET is a valuable diagnostic tool for determining clinical outcome in patients with MCI (108, 109). MRI-based morphometry studies of patients with MCI have shown that accelerated atrophy, possibly because of both neurofibrillary tangle accumulation and functional alterations in brain regions, such as the posterior cingulate, can be assessed longitudinally and thus provide a means of monitoring the effects of treatment on brain architecture (110, 111). These studies that identify atrophy in the entorhinal cortex, superior temporal gyrus and inferior frontal gyrus, along with changes in the hippocampus, indicate that there are multiple forms of MCI and that each of these has distinctive neuropathology further suggesting that there may be more than one aetiological process that culminates in dementia (112).

Functional MRI studies of MCI have shown that neurodegeneration discernibly alters response patterns. A study that investigated entorhinal and hippocampal function in patients with very early MCI and AD, using a learning paradigm found significantly greater hippocampal activation in the MCI group as compared with controls. In comparison, AD patients had entorhinal and hippocampal atrophy and reduced activation. A similar gradation of performance was noted with respect to the recognition memory task with AD patients performing poorly and the MCI patients performing as well as controls (113).

Another issue of concern in the assessment of dementia is the differential diagnosis of AD. Current diagnostic criteria based on clinical assessment have limited accuracy for dementia with Lewy bodies (DLB) with up to 50% of cases failing to be identified. It is of note that in DLB there is severe nigrostriatal dopaminergic degeneration, a feature that does not occur in most other dementia subtypes including AD. A recent study that used SPECT brain imaging with ^{123}I-FP-CIT to differentiate DLB from other causes of dementia (114), demonstrated a high correlation between low binding to dopamine reuptake sites, as measured with SPECT, and a clinical diagnosis of DLB. This study suggests that this neuroimaging technique is of sufficient accuracy to be useful clinically in distinguishing AD and DLB. Another study that used the same SPECT probe also showed that ^{123}I-FP-CIT SPECT scans improved the accuracy of diagnosis of DLB as compared with using clinical judgement alone (115). Interestingly, a separate

group that used ^{18}F-FDG PET in patients with AD and DLB evaluated a computer assisted fully automated diagnostic system for mild DLB to distinguish this from mild AD. This study that compared visual inspection by experts in the field to the automatic system of differential diagnosis found similar accuracy across the two methodologies suggesting that it may have potential for clinical use (116).

Discussion

The desire to understand the brain in terms of its structure and function has led to the development of sophisticated technology making it possible to 'see' the brain in action. The examination of diffuse processes such as metabolism and blood flow using PET has evolved to encompass receptor studies mapping neuronal localisation within brain regions. In the rapidly growing field of cognitive neuroscience, fMRI has emerged as an exciting and pivotal tool that has enabled investigators to probe the mind and anchor their findings within the brain. Similarly, MRS has opened a neurochemical window, that permits *in vivo* sampling of chemical activity. Collectively, in addition to better understanding the architecture of the brain and its changes through neurodevelopment and neurodegeneration, these technologies have made it possible to draw meaningful links between brain biology and human behaviour, both in health and disease. More recent developments permit the partitioning of grey and white matter regions in the cerebral cortex thus making it possible to analyse precisely the constituents of brain matter (117). Add to this the fact that white matter fibres can be individually tracked using DTI tractography and it becomes apparent that researchers can now literally 'join the dots' (118). These marvellous developments have made it possible to investigate neural connections and the complex functional relationships between specific brain regions.

The ability to combine neuroimaging modalities and integrate neuroimaging with neurochemical and genetic probes, has prompted the development of new fields of research such as molecular imaging and neuroimaging genomics. It is clear that the risk of disease for many psychiatric disorders is mediated by multiple genes that individually have small effect but through interactions exert significant influence. Recent research that combines genetics and neuroimaging is providing a means of potentially 'genotyping function'.

Currently, the majority of psychiatric neuroimaging is research oriented; however, as we gain a better understanding of the utility of these technologies clinical applications will gradually emerge. Ultimately, neuroimaging will be viewed as a routine clinical investigation alongside psychiatric mental state examination and neuropsychological evaluation. Indeed, with respect to the diagnosis and management of dementia this is already happening.

It is important, however, to add a cautionary note because despite the many wonderful achievements of researchers the reality remains that at present neuroimaging is limited in what it can offer clinically. Many structural and functional findings for instance relate to comparisons across groups of subjects and have little relevance to an individual with a psychiatric disorder. In reality neuroimaging is just beginning to categorise the basic neurobiology of the brain. This is perhaps not surprising as the neurobiology of cognition and the neural substrates of behaviour are necessarily complex and do not lend themselves easily to scientific investigation. Added to this are the complexities of clinical populations such as the effects of medication and the ubiquity of comorbidity across psychiatric disorders.

It is equally important, however, to acknowledge the rapid advances that have been made in neuroimaging in psychiatry. In a comparatively short period of time neuroimaging has made a tremendous impact upon our understanding of the neural processes that form the basis of psychiatric disorders, and no doubt this will continue. In the not too distant future it is likely that psychiatrists will routinely need to make sense of neuroimaging findings and therefore as clinicians, it is important that we are aware of the potential applications of modern neuroimaging and that we are suitably equipped to make full use of the technologies at hand.

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