The impact of advanced brain imaging procedures in the field of human memory disorder is reviewed, with particular emphasis on current and potential applications that may impact upon the diagnosis and management of memory-disordered patients. While both advanced structural, resting physiological and functional physiological brain imaging procedures have been applied to conditions where memory disorder is a major feature, the specific implications of research findings for diagnosis and treatment in routine clinical practice remain tentative and promising, but not yet substantive enough to inform clinical decisions to a significant degree. In terms of diagnostic applications, several promising areas include dementia, epilepsy, and transient amnesic states. In the case of applications in treatment settings, advanced brain imaging procedures may help to monitor neural correlates of spontaneous recovery or progression of memory function, and may also help in the planning and monitoring of therapeutic intervention.

Not everything that can be measured counts, and not everything that counts can be measured.

---

Advances in science and in the application of science have tended to go hand-in-hand with advances in measurement procedures. For example, in the case of atmospheric physics the ability to obtain accurate measurements and images via satellite technology has revolutionized our understanding of climate and climate change. In the area of medicine, similar examples abound – the introduction of ways to measure polymer chain reactions and to decipher genetic signatures has had, or is beginning to have, major impacts in clinical practice. In the field of clinical neuroscience, advances in brain imaging procedures have been no less successful in revolutionizing our ability to understand and to treat brain disease. For a history of clinical brain imaging up to the early 1990s, the reader is referred to the excellent review by Burrows1.
Symptoms of memory impairment represent one of the most common manifestations of brain pathology – they are usually one of the earliest features of degenerative brain disease, they represent some of the deficits that are most likely to persist as the permanent sequelae of a brain insult, and they also comprise deficits that are particularly likely to result in impaired functioning in everyday domestic, social and work settings. There are many reasons for this relatively unique status of memory in brain disease, and they include the large number, extent and distributed nature of brain areas that exercise a direct or indirect role in human memory functioning.

In this paper, we review the application of advances in brain imaging to the diagnosis and management of human memory disorder, primarily those resulting from specific forms of cerebral pathology. We will consider each form of imaging in turn and, in the final section of this article, address possible future developments in imaging procedures and in their application to human memory disorder in clinical practice. With the huge explosion in human brain imaging research in recent years, our review will of necessity be selective, and we apologise in advance to any readers who feel we should have made reference to particular papers that have not been included.

**Advanced qualitative structural imaging**

While the emphasis in recent years has been on newly developed quantitative structural brain imaging protocols and on functional brain imaging procedures, it is worth noting that advanced magnetic resonance imaging (MRI) can now provide the clinician with valuable, high quality images. This may arise from the use of MR sequences to produce novel representations of tissue integrity – allowing lesions to be more readily detected, permitting areas of abnormality to be displayed in three dimensions, and enabling the automated demarcation and annotation of specific anatomical structures.

The initial advantages of MRI over conventional CT images rested in the generation of high quality *in vivo* brain images. At least three features of magnetic resonance images rendered them particularly valuable for providing improved anatomical definition of cerebral lesions: (i) the high resolution of images, such that structures and lesions as small as 1–2 mm across could be readily visualized; (ii) the ability to obtain clear views of structures from coronal, sagittal and axial views, and at most locations in the brain, though this is now possible with CT procedures; and (iii) the well-defined demarcation of abnormal signals that reflected underlying brain pathology, particularly lesions such as inflammatory changes, white
matter abnormalities and discrete micro-infarcts. T₂-weighted MR scans have allowed clinicians to visualise subtle changes in the early stages of an acute condition that, with prior brain imaging procedures, might well have escaped detection; for example, medial thalamic abnormalities in Wernicke-Korsakoff syndrome² and hippocampal lesions in hypoglycaemia³. Recent years have seen enhancement of the ability to detect lesions, due to the introduction into routine clinical practice of sequences such as fluid attenuated inversion recovery (FLAIR) sequences. For neuropsychologists dealing with memory disordered patients, this means that lesions in conditions such as multiple sclerosis⁴ and Creutzfeldt-Jakob disease⁵ may be more readily detected, allowing for links to be drawn between the presence of lesions and the pattern and severity of memory disorder. The ability to form three-dimensional images of lesions such as brain tumours, and to visualize their location in relation to key anatomical structures⁶ and in relation to critical white matter tracts⁷, may provide the physician and the neurosurgeon with a clearer idea of the size of a lesion and of its location vis-à-vis critical anatomical regions that have a role in memory functioning. Specific anatomical structures, such as the mammillary bodies⁸,⁹, mammillo-thalamic tract¹⁰, fornix¹¹,¹², basal forebrain¹³, and specific thalamic nuclei¹⁴ can now be characterized on brain imaging with greater confidence than before the MR imaging era. The demarcation and labelling of anatomical regions has been shown to be amenable to automated procedures¹⁵–¹⁷, and this may be particularly useful when considering memory functioning in patients such as those with primary degenerative dementia.

Volumetric and other morphometric procedures

The use of volumetric measures in the study of brain-behaviour relationships was one of the earliest research applications of magnetic resonance imaging in clinical neuroscience. In recent years, volumetrics as a morphometric measurement tool has been supplemented by new techniques, such as voxel-based morphometry, deformation-based morphometry and tensor-based morphometry¹⁸.

In the case of volumetrics, studies have related volumetric measures of memory-related anatomical structures with memory test performance across a range of populations including those suffering from primary degenerative dementia¹⁹–²³, epilepsy²⁴–²⁹, head injury³⁰,³¹, alcoholism³²,³³, and amnesia³⁴–³⁷. In general, correlations have been found between volumes of key structures such as the hippocampus and memory test performance, though there is significant variability in the strength of these correlations. In addition, there is variability in reported
hippocampal volumes even within control subjects. Volumetric and related procedures have also been used to measure extent of lesion pathology and to relate this with memory performance in conditions such as multiple sclerosis. Volumetric procedures have also proved useful in single-case studies of amnesic patients.

The limitations of volumetric procedures include technical ones relating to correcting for individual differences in brain volume, uncertainties in the precise demarcation of specific structures, and the relative crudeness of anatomical volume as an index of tissue integrity. There is of course the general proviso that volumetric indices do not necessarily reflect the neural network nature of human memory.

The closest approximation to the use of volumetric procedures in clinical practice is the attempt by some authors to use volumetric procedures to assist in the differentiation of conditions such as primary degenerative dementia, or to offer guidance on the laterality of cerebral pathology in temporal lobe epilepsy (TLE). While these indices probably represent valuable additional pieces of information, they do not in themselves provide decisive guidance and have to be considered in the context of other sets of clinical, imaging, laboratory and neuropsychological data.

Voxel-based morphometry, deformation-based morphometry and tensor-based morphometry are still very much experimental procedures. Voxel-based morphometry has been used with certain memory disordered patients (e.g. those with herpes simplex encephalitis and those with a primary degenerative dementia) and has largely confirmed the known lesion profiles associated with these conditions. These experimental procedures need to be seen in the context of other procedures, such as planimetry and stereology, and it is still an open question as to which morphometric techniques are best for assessing anatomical integrity in diseased brains.

**Spectroscopy**

Magnetic resonance spectroscopy (MRS) enables the identification and quantification of the concentration of various brain metabolites. MRS values may be sampled from single regions (single-voxel MRS) or from multiple regions at the same time (MRS imaging). The most common cerebral metabolite that has been sampled to date is N-acetylaspartate (NAA). Concentrations of NAA are often represented as ratios with other metabolites, such as choline-containing compounds.

One of the first studies to relate spectroscopic measures to memory function in neurological patients was that by Incisa della Rocchetta et al. They found abnormal proton spectroscopic values on the...
unoperated side of 50% of 34 patients who had undergone surgery for unilateral TLE. While such an abnormality was not related to seizure outcome after surgery, it was related to verbal memory performance – those right-sided TLE patients who underwent surgery were more likely to show postoperative verbal memory impairment if they had abnormal MRS values on the unoperated side. In a more recent study, Pauli et al\textsuperscript{50} found that side of hippocampal pathology in TLE patients, as indicated by proton spectroscopy, was closely related to verbal/non-verbal memory performance. Sawrie et al\textsuperscript{51} also reported verbal memory functioning in TLE patients to be related to left hippocampal spectroscopic values, and noted that this relationship was stronger than that between memory and volumetric measures. The same research group\textsuperscript{52} noted that a measure of ‘semantic memory’, picture naming, was closely related to left hippocampal integrity as indexed by MRS values and, in addition\textsuperscript{53}, a relationship was found between right hippocampal integrity and performance on a faces matching task. In a group of TLE patients, Namer et al\textsuperscript{54} observed that by themselves hippocampal spectroscopic values were not related to memory performance, but a relationship was apparent when the values were combined with T\textsubscript{2} measures (discussed below).

In the case of other memory-disordered neurological populations, MR spectroscopy has been shown to detect abnormalities in a wide range of patients with dementia (for a general review of such studies, see Hsu et al\textsuperscript{55}, and for reviews of those studies dealing with Alzheimer’s disease see Valenzuela and Sachdev\textsuperscript{56} and Chen et al\textsuperscript{57}). However, there appear to have been only a few MRS studies that have specifically related brain integrity to memory functioning. In patients with Parkinson’s disease, Hu et al\textsuperscript{58} found evidence of MRS changes in temporoparietal cortex, but did not find any correlation with performance on a verbal learning test. In a study of recovery of function after excessive alcohol consumption, Bendszus et al\textsuperscript{59} reported that recovery of MRS values was associated with improved performance on memory tests. In a group of patients with multiple sclerosis, Pan et al\textsuperscript{60} noted that left periventricular NAA concentrations correlated with performance on a word-list learning task. Frederick et al\textsuperscript{61} found changes in parietal lobe cytosolic choline levels to be related to changes in memory functioning in a group of Alzheimer’s disease patients in a drug treatment trial.

In summary, it does appear that certain MRS measures may yield information that parallels memory-related indices of brain integrity. Difficulties that remain in the use of such measures include those of sampling – since whole brain sampling was not technically feasible in the studies reported to date, findings in published studies may be dependent on the particular regions that were sampled. It is also important for future research to shed some light on the relationship between
spectroscopic values from different regions, and whether one value is dependent on the other. From the point of view of clinical practice, one of the more promising angles of the findings so far is the possibility that pre-operative spectroscopic measures may have predictive value in estimating degree of postoperative memory impairment, as in patients undergoing temporal lobe surgery. If this is borne out by future studies, it will add to the clinician’s armamentarium when faced with advising patients on the risks of brain surgery.

**T₂ mapping**

T₂ relaxation times reflect the state of brain tissue protons and are particularly sensitive to the dynamic structure and amount of brain water. In some cases, they may reflect the degree of gliosis in brain tissue. Several studies have related memory functioning to T₂ relaxation measurements. Incisa della Rocchetta et al. found that postsurgical memory deficits in right TLE patients were more likely if T₂ abnormalities were present in the left temporal lobe. Similar observations were made by Wendel et al., who noted that T₂ abnormalities were associated with memory ability independently of volumetric measures. Baxendale et al. did not find any significant correlations between memory performance and T₂ relaxometry in TLE patients, though there was some evidence that such measures from the left temporal lobe could have some predictive value for story retention scores. Both Kalviainen et al. and Wood et al. found a negative correlation between left temporal lobe T₂ relaxometry and verbal memory functioning in TLE patients. As noted earlier, Namer et al. found that T₂ relaxation times alone in TLE patients did not correlate with memory performance, but that such a relationship was found when T₁ measures were combined with spectroscopic indices.

Few other neurological populations appear to have been studied as extensively as epilepsy patients for relationships between T₂ measures and memory functioning. Diehl et al. found increased T₂ relaxation times in the region of the thalamus in patients shortly after they received ECT, and also reported a relationship between left thalamic values and verbal memory impairment.

**Diffusion and perfusion magnetic resonance imaging**

A study by Strupp et al. provided evidence to show that diffusion-weighted imaging (DWI) can reveal focal medial temporal lobe abnormalities in patients up to 38 h after an attack. Of the 10 patients...
studied, 3 showed bilateral hippocampal abnormalities, but in 4 patients the lesion was restricted to the left hippocampus. One of the patients with bilateral hippocampal changes was studied 2 h after the onset of the attack. Strupp and co-workers hypothesized that the changes seen on scanning may have reflected cell oedema, and that their findings provided support for a particular mechanism, ‘spreading depression’, as underlying transient global amnesia (TGA). It is worth pointing out that although discrete hippocampal lesions, possibly of an ischaemic nature, have been noted on DWI in patients with episodes resembling TGA70,71, and may be present up to 44 h after the onset of an attack72, subsequent reports73–75 did not find distinctive DWI medial temporal lobe abnormalities in patients who were studied during the acute stages of a TGA episode. It remains possible, therefore, that findings such as those reported by Strupp and colleagues may have been: (i) specific to their imaging procedures; (ii) specific to their particular patients; or (iii) artefactual. A further ‘negative’ finding of note is that of Zorzon et al76, who carried out MRS during and after a TGA episode, and did not find any changes that would have been consistent with neurochemical abnormalities in the hippocampus, in particular those relating to N-acetylaspartate. Greer et al77 were able to detect focal left medial temporal lobe abnormality on DWI, but normal T2, and perfusion imaging, in a patient with apparent transient global amnesia. On recovery, this lesion remained, and was presumed to reflect a discrete infarct in the region of the left uncus.

**PET/MRI functional brain imaging**

A number of earlier studies of ‘functional’ brain imaging of neurological patients used positron emission tomography (PET) and single photon emission tomography (SPECT) measures while patients were resting in the scanner. The reader is referred to other sources for detailed consideration of findings relating to resting level PET and SPECT studies in patients with Alzheimer’s disease78,79 or transient global amnesia80.

In patients with a specific memory disorder or amnesic syndrome, Fazio et al81 reported hypometabolism throughout limbic-diencephalic circuits (including the thalami and hippocampi) in 11 patients. These patients had varying underlying aetiologies, and separate analyses for these aetiological subgroups were not given. However, Aupee et al82 examined three Korsakoff patients and two hypoxic patients, finding hypometabolism bilaterally in the thalami, posterior cingulate/retrosplenium, and mesial prefrontal cortex, and unilaterally in the left supramarginal and middle temporal gyri for the group as a whole, with broadly consistent findings in individual subjects. Findings in other studies of the Korsakoff syndrome
have varied from wide-spread hypometabolism\textsuperscript{83} to minimal change\textsuperscript{84}, and have included hypometabolism in the medial temporal lobes\textsuperscript{85,86}; this probably relates to diagnostic issues and inclusion criteria. Reed \textit{et al}\textsuperscript{87} found relative white matter hypermetabolism in frontal/temporal/parietal regions and relative grey matter hypometabolism in the thalamus, retrosplenium, and medial temporal lobes. In hypoxia, there are also reports of hypometabolism in the thalamus and/or medial temporal lobes\textsuperscript{88–90}. Thalamic hypometabolism was also reported in a severely amnesic patient with structural changes in the hippocampi\textsuperscript{91}, and thalamic, retrosplenial, and medial temporal hypometabolism were found in a patient profoundly amnesic following MDMA (‘Ecstasy’) toxicity, either as a direct consequence of serotonin toxicity or of resulting hypoxia/ischaemia\textsuperscript{92}.

The major source of recent research has emerged from studies that have employed functional activation brain imaging paradigms\textsuperscript{93–95}. In patients with epilepsy, the major potentially therapeutic application has been in respect of presurgical assessment of patients, with the aim of obtaining information that complements or substitutes that which has been obtained by the Wada procedure to determine the integrity of the brain in respect of language and memory functioning. While the area of language functioning is covered elsewhere in this volume, we briefly note that fMRI studies have generally been successful in lateralising language functions, using tasks such as picture naming and verbal fluency/verb generation\textsuperscript{96,97}, and have been successfully applied to neurological populations\textsuperscript{98–100}. Bellgowan \textit{et al}\textsuperscript{101} reported the very interesting finding of greater left medial temporal lobe activation during a semantic decision task in patients with right TLE compared to those with left TLE. Billingsley \textit{et al}\textsuperscript{102} have demonstrated functional re-organization of language in patients with left TLE, with enhanced involvement of frontal and right temporal structures.

In the case of memory functioning, there are now some promising findings in normal subjects that show left–right lateralisation of memory, depending on the verbal nature of stimuli\textsuperscript{103}. The application of such paradigms to clinical populations is the next step, and some preliminary findings have been reported. Detre \textit{et al}\textsuperscript{104} showed that presentation of a complex scene activated posterior parahippocampal cortex bilaterally in normal subjects, but asymmetric activation was found in unilateral TLE patients, and that this asymmetry corresponded to the results of sodium amytal Wada testing. Using a non-verbal memory task where subjects had to mentally navigate along personally familiar landmarks, Jokeit \textit{et al}\textsuperscript{105} also found bilateral medial temporal lobe activation in control subjects, but asymmetric activation in patients with TLE. This asymmetry was more closely related to memory test scores obtained during neuropsychological testing than to performance
on visuospatial tasks. Dupont et al\textsuperscript{106} studied pattern of functional activations during both verbal encoding and retrieval episodic memory tasks. In patients with left medial TLE, less marked left occipito-temporo-frontal activation was seen than in control subjects together with reduced bilateral parahippocampal activation. However, they also reported increased dorsolateral frontal activation in the epilepsy patients compared to control subjects. In a follow-up study\textsuperscript{107}, where they examined retention over longer (24 h) intervals, Dupont and colleagues found reduced activation of bilateral parietal and right hippocampal activation in left TLE patients compared to control subjects at the time of 24-h retrieval.

Turning to other neurological conditions, in mild head injury patients McAllister et al\textsuperscript{108,109} found that in certain working memory tasks, mainly those with a moderate processing load, patients showed greater bilateral frontal and parietal activation when examined 1 month after injury, even though actual levels of task performance were similar to those of control subjects. Christodoulou et al\textsuperscript{110} gave a verbal working memory task, involving serial addition, to head injury patients and control subjects. Across both groups, functional imaging during task performance showed similar involvement of diverse areas in frontal, temporal and parietal areas; however, there was evidence that the task generated greater left hemisphere activation in the control group, but greater right hemisphere activation in the head injury group.

In the case of patients with dementia, there have been a large number of studies which have applied functional brain imaging paradigms to patients with primary degenerative dementia, usually those with presumed Alzheimer’s disease\textsuperscript{78,111}. Many of these studies will have been reviewed elsewhere in this volume, but a few recent studies will be noted here. Grön et al\textsuperscript{112} found that patients with probable Alzheimer’s disease failed to show right hippocampal activation during a pattern learning task, this activation being present in normal control subjects and in patients with major depression. Greater bifrontal activation compared to controls was also seen in Alzheimer patients, presumably reflecting some form of compensatory activity in the form of greater concentration that was required of them. An interesting adjunct to studies with clinical populations of patients with dementia is to carry out functional brain imaging with those who are at risk of developing a dementing illness. Bookheimer et al\textsuperscript{113} found greater activation of left hippocampal, parietal and prefrontal regions during a verbal memory task in carriers of the apolipoprotein E (APOE) gene, a genetic risk marker for Alzheimer’s disease. Of particular interest was the further observation that greater activation in these patients was correlated with greater decline in memory functioning when subjects were re-assessed after 2 years.

Several single-case studies using functional brain imaging paradigms with memory disordered patients have provided information of possible
theoretical and clinical significance. Maguire et al\textsuperscript{114} assessed autobiographical memory in a developmental amnesic patient (Jon) with circumscribed hippocampal damage. Jon activated similar temporal lobe structures during memory retrieval as control subjects, both medial and lateral on the left. In contrast to controls, Jon also activated homologous regions in the right temporal lobe. In spite of having 50\% volume loss bilaterally in his hippocampi, retrieval activity in their patient was associated with increased activation of the hippocampi. Of particular interest was the fact that Jon made a distinction between events that the control subjects did not make, namely he clearly remembered some of the autobiographical and public events, while he knew about others but did not truly remember them. His hippocampi and medial frontal cortex were significantly more active during retrieval of events for which he had clear and conscious recollection compared with those he knew as much about, but could not remember experiencing. Maguire and co-workers also showed that although Jon activated the same general network of brain regions as controls (albeit bilaterally), and with the same pattern of response in the hippocampus, the communication between regions differed from controls with regard to hippocampal-cortical connectivity. During retrieval of autobiographical events, in control subjects there was increased effective connectivity between parahippocampal cortex and hippocampus, In contrast, this increase was not apparent in Jon, in whom retrieval of autobiographical events elicited greater interaction between the hippocampus and retrosplenial cortex, and also increased interaction between retrosplenial and medial frontal cortex.

In a single-case study of a patient with a left frontal vascular lesion, and evidence of psychogenic retrograde amnesia, Costello et al\textsuperscript{115} found that brain monitoring during presentation of stimuli for which the patient was amnesic elicited specific activation in the precuneus. A further single-case study of dense retrograde amnesia, where it was thought that the memory loss may have been wholly neurological in nature, was reported by Levine et al\textsuperscript{116}. Their patient, who had suffered a severe head injury, was studied in a functional brain imaging paradigm which included assessment of activation at encoding and retrieval of semantically-related word pairs. Levine and colleagues found that, compared to control subjects, their patient showed reduced right frontal activation and enhanced left medial temporal lobe activation. They suggested that a form of frontotemporal disconnection, due to lesioning of the uncinate fasciculus, may have contributed to the patient’s unusually focal retrograde amnesia and to the pattern of activation seen during functional brain imaging. Right frontotemporal hypometabolism has also been noted in cases of psychogenic retrograde amnesia\textsuperscript{117}.

Since the time window available for brain imaging in transient global amnesia is short, the opportunity to carry out fMRI with cognitive
probes may only occur very rarely. LaBar et al did seize one such opportunity, and they found that during a scene-encoding task a TGA patient, imaged 6 h after the onset of the attack, showed greater activation of parietal areas, suggesting a possible compensatory mechanism in operation. Compared to a post-recovery session, there was decreased activation in left retrosplenial cortex, bilateral parahippocampal cortex, right inferior temporal sulcus and right temporal pole. Compared to control subjects, there was also decreased activation in the posterior cingulate cortex in the initial TGA imaging session.

**Mapping of brain electrical and magnetic activity**

The possible clinical application of investigations using advanced EEG mapping/evoked potential procedures has been reviewed by Philpot, who noted that there is as yet little firm evidence to substantiate their role as specific diagnostic markers in settings such as the investigation of dementia. The P3-evoked potential marker, which has been associated with memory mechanisms, was not found to be abnormal in a study of a patient who was assessed during an episode of transient global amnesia. Event-related potentials (ERP) associated with repetition priming were studied by Schnyer et al in a group of patients with presumed Alzheimer’s disease. While control subjects displayed behavioural and ERP repetition priming with words repeated at long delays, this priming was absent in Alzheimer’s disease patients. A few researchers have used magneto-encephalography (MEG) in memory-disordered populations, but these studies have been both preliminary and experimental in nature, and it is too early to draw any conclusions relating to the use of MEG in clinical practice.

**Other imaging modalities**

While in recent years the emphasis has been on PET and fMRI technologies, it should be borne in mind that other long-standing and emerging technologies exist that may shed light on the nature of memory disorder in neurological populations. In the case of brain stimulation of human subjects in intra-operative settings, the work of Penfield, which started in the 1930s, and more recent studies by other researchers, have high-lighted the specific contribution of particular cortical regions to memory functioning. Sampling considerations – both in terms of the patient group that is studied (usually patients with epilepsy), and also the population of nerve cells that is targeted – mean that such findings need to be considered with caution, though there have
been promising correlations with imaging data from other sources such as fMRIs. At present, while intra-operative brain stimulation has occasionally been used in clinical practice to identify ‘eloquent’ areas that play a role in language or motor functioning, it does not yet appear to have been widely used to guide surgical ablation with a view to reducing the likelihood of memory dysfunction after surgery.

A parallel technique to intra-operative brain stimulation is brain recording under similar conditions. Intra-operative hippocampal electrocorticography has been used in clinical settings to guide the location and extent of surgical ablation. Evidence relating to the neocortical fractionation of specific memory functions has been offered, and pattern of neuronal firing in medial temporal lobe structures has been correlated with subsequent retention. However, here again there has been little direct application of such methodologies into routine clinical practice.

While there are other experimental techniques that may hold promise in future work with memory disordered patients, including transcranial magnetic stimulation, optical imaging, transcranial Doppler ultrasonography, near-infrared spectroscopy, functional brain imaging, novel ways of representing resting oxygen levels using MR imaging, and functional magnetic resonance spectroscopy, it is worth bearing in mind that post mortem imaging and quantitative analyses of brain tissue remains an important and somewhat neglected tool in the neuropsychologists’ research armamentarium for understanding brain–behaviour relationships. In patients with TLE, histological analyses of ablated brain tissue has enabled investigators to relate their findings to pre-operative neuropsychological and imaging observations. To the extent that such studies help to validate pre-operative measurement procedures, it remains important for clinical neuroscientists to be aware of the potential value of histopathological imaging procedures, and to be aware of developments such as the use of stereological procedures.

Possible future developments

As can be seen from this review, the clinical application of advanced neuroimaging procedures in the field of human memory disorder is in its relative infancy, but the future holds considerable promise for meaningful contributions to patient care. While it is impossible to foresee which basic and applied developments in neuroimaging will be most beneficial, we have highlighted a few that we consider to be important.

1 The combination of fine spatial and fine temporal resolution, as when fMRI is used together with cognitive evoked potentials, should allow a
better overall view of the precise mechanisms underlying particular normal and abnormal states of cognitive processing by offering both spatial and dynamic temporal maps of the various stages of cognitive activity\textsuperscript{146}. In general, information from a variety of sources – be they functional brain imaging, brain stimulation, signal alteration on structural scans secondary to brain lesions, advanced quantitative structural imaging, \textit{etc.} – should be integrated to provide a coherent set of evidence with which to inform clinical decisions. Each source has its own limitations and advantages, and can make a particular contribution in specific clinical problems. Moreover, the use of a combination of imaging modalities allows mapping of the distal effects of a specific (structural) brain lesion\textsuperscript{90}. 

2 A greater understanding of anatomical connectivity, including the introduction of structural equation modelling to provide information on functional and effective connectivity, combined with the use of connectionist models to help understand and explore particular areas of cognitive functioning, should give a more realistic picture of the complexity of brain processes in normal and memory disordered populations. 

3 While it is implicitly accepted that any given cognitive operation, even a relatively simple one, probably involves a synchrony of excitatory and inhibitory activity, there are at present no clear functional brain imaging markers that distinguish excitatory from inhibitory activity. It is possible that animal studies\textsuperscript{147} may yield some useful insights in this respect, and that we will see a greater integration of animal and human functional brain imaging studies to provide detailed clues regarding the particular neural mechanisms underlying normal and pathological cognitive states. It is also important that researchers using advanced brain imaging procedures with memory disordered populations bear in mind conceptual issues involved in designing appropriate paradigms and evaluating functional brain imaging data in such settings – such issues have been discussed in detail elsewhere\textsuperscript{148–150}. 

4 Advanced imaging techniques will continue to be important in localizing lesions with greater precision in surgery for epilepsy and tumours in memory-disordered patients, and in avoiding adverse effects upon memory or other cognitive functions by localizing critical structures and fibre pathways. These techniques will also continue to be important in diagnosing unusual dementias. 

5 One of the ultimate goals of advanced imaging procedures is to change the management of patients for the better. Those imaging procedures that shed light on the neurochemical basis of normal and abnormal memory processing should help in the more rational development of novel drug therapies for memory-disordered patients. An analogous strategy, which may hold promise in the future, is to assess patients in functional brain imaging settings during naturally occurring variations of their pharmacological status, and to use.
this as a means of exploring the neurochemical basis of human memory\textsuperscript{151}.

6 Functional brain imaging procedures can be used to monitor recovery processes and the effects of pharmacological or rehabilitation-based treatments. This may prove informative in indicating to clinicians which therapeutic procedures, if any, are most likely to be effective, and such strategies have been employed in other cognitive disorders\textsuperscript{152–155}.

7 While memory processing is a crucial area of cognitive functioning, it is not impervious to emotional and motivational influences\textsuperscript{156,157}. How these influences interact with neural processing, and how this interaction may be mapped by functional brain imaging procedures, is an important topic for the future, and it may also help our understanding of purely ‘psychogenic’ amnesias. Recent studies have examined functional brain imaging correlates of malingering\textsuperscript{158,159}, and are useful steps in this direction.

8 Finally, it is possible, as Bigler\textsuperscript{160} has speculated, that neuropsychological assessments of the future will involve testing a neurological patient while in a scanner that is monitoring brain activity. The introduction of upright MR scanners\textsuperscript{161} certainly brings closer the utopian scenario where one is testing a patient and simultaneously viewing the areas of the brain that are being engaged by the task in question!

**Key points for clinical practice**

- There is a wide range of advanced brain imaging procedures – structural, resting physiological and functional activation – which have a potential impact in the field of human memory disorder.
- The successful application of these procedures into routine clinical practice remains a potential development rather than a current reality.
- Advanced brain imaging procedures appear to hold particular promise in the diagnosis of conditions such as primary degenerative dementia, epilepsy, and transient amnesic states.
- Advanced brain imaging procedures may be helpful in planning treatment, and in monitoring the effects of therapeutic intervention.

**Acknowledgement**

We thank Pat Abbott for her help in the preparation of this manuscript.

**References**

3 Holemans X, Dupuis M, Misson N et al. Reversible amnesia in a type 1 diabetic patient and bilateral hippocampal lesions on magnetic resonance imaging (MRI). Diabet Med 2001; 18: 761–3
6 Makela JP, Kirveskari E, Seppa M et al. Three-dimensional integration of brain anatomy and function to facilitate intraoperative navigation around the sensorimotor strip. Hum Brain Map 2001; 12: 180–92
8 Shogry MED, Curnes JT. Mammillary body enhancement on MR as the only sign of acute Wernicke encephalopathy. AJNR Am J Neuroradiol 1994; 15: 172–4
11 Aggleton JP, McMackin D, Carpenter K et al. Differential cognitive effects of colloid cysts in the third ventricle that spare or compromise the fornix. Brain 2000; 123: 800–15
26 Trenerry MR, Jack CR, Cascino GD et al. Gender difference in post-temporal lobectomy verbal memory and relationships between MRI hippocampal volumes and preoperative verbal
50 Pauli E, Eberhardt KWE, Schäfer I et al. Chemical shift imaging spectroscopy and memory
function in temporal lobe epilepsy. Epilepsia 2000; 41: 282–9


70 Ay H, Furie KL, Yamada K et al. Diffusion-weighted MRI characterizes the ischemic lesion in transient global amnesia. Neurology 1998; 51: 901–3


82 Aupee AM, Desgranges B, Eustache F et al. Voxel-based mapping of brain hypometabolism in permanent amnesia with PET. Neuroimage 2001; 13: 1164–73
87 Reed LJ, Lasserson D, Marsden P et al. FDG-PET findings in the Wernicke-Korsakoff syndrome. Cortex 2002; In press
90 Reed LJ, Lasserson D, Marsden P et al. FDG-PET analysis and findings in amnesia resulting from hypoxia. Memory 1999; 7: 599–612
92 Kopelman MD, Reed LJ, Marsden P et al. Amnesic syndrome and severe ataxia following the recreational use of 3,4-methylenedioxymethamphetamine (MDMA, ‘Ecstasy’) and other substances. Neurocase 2001; 7: 423–32
95 Detre JA, Floyd TF. Functional MRI and its applications to the clinical neurosciences. Neuroscientist 2001; 7: 64–79
98 Benson RR, Fitzgerald DB, LeSueur LL et al. Language dominance determined by whole brain...
101 Bellgowan PSF, Binder JR, Swanson SJ et al. Side of seizure focus predicts left medial temporal lobe activation during verbal encoding. *Neurology* 1998; 51: 479–84
149 Price CJ, Warburton EA, Moore CJ et al. Dynamic diaschisis: anatomically remote and context-
161 Nagada T, Tasaka N. Human brain imaging in the upright position. Neurology 2001; 57: 1720–2