Imaging after brain injury

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Head injury remains an important cause of death and disability in young adults. This review will discuss the role of structural imaging using computed tomography (CT) and magnetic resonance imaging (MRI) and physiological imaging using CT perfusion, $^{131}$Xe CT, MRI and spectroscopy (MRS), single photon emission computed tomography, and positron emission tomography (PET) in the assessment, management, and prediction of outcome after head injury. CT allows rapid assessment of brain pathology which ensures patients who require urgent surgical intervention receive appropriate care. Although MRI provides greater spatial resolution, particularly within the posterior fossa and deep white matter, a complete assessment of the burden of injury requires imaging of cerebral physiology. Physiological imaging techniques can only provide ‘snap shots’ of physiology within the injured brain, but they can be repeated, and such data can be used to assess the impact of therapeutic interventions. Perfusion imaging based on CT techniques (xenon CT and CT perfusion) can be implemented easily in most hospital centres, and provide quantitative perfusion data in addition to structural images. PET imaging provides unparalleled insights into cerebral physiology and pathophysiology, but is not widely available and is primarily a research tool. MR technology continues to develop and is becoming generally available. Using a complex variety of sequences, MR can provide data concerning both structural and physiological derangements. Future developments with such imaging techniques should improve understanding of the pathophysiology of brain injury and provide data that should improve management and prediction of functional outcome.

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Imaging modalities

Structural imaging

CT is routinely used to assess all patients with acute head injury who require admission and observation within hospital. Such imaging provides early assessment of the extent of the injury and can be obtained quickly using modern multi-detector high resolution scanners which are widely available. Patients admitted via emergency departments within neurosurgical centres and general hospitals can be transferred to the radiology suite and images reviewed on-line or transferred electronically for specialist review. The short imaging time and ease of acquisition is of considerable benefit in agitated patients and those who are ventilated but unstable due to severe trauma. Image slices that are degraded by motion artifact can easily be repeated. Imaging data can be visualized using brain or bone contrast windows and reconstructed into three-dimensional (3D) CT.
data sets in order to demonstrate bony injury\textsuperscript{58} (Fig. 1) and intracranial pathology.

Imaging data sets demonstrate the differences between normal and abnormal brain in terms of the degree of X-ray attenuation. Blood clot, which has a high degree of X-ray attenuation, appears as a hyperdense or white area, whereas oedematous or ischaemic regions with increased water content and lower electron density appear dark due to reduced attenuation. Acute CT is useful in identifying those individuals in whom deterioration is a result of a mass lesion and demonstrate extradural, subdural or intracranial haemorrhage, and midline shift (Fig. 2), or traumatic subarachnoid haemorrhage and ventricular abnormality (Fig. 3). The ease of access and speed of data acquisition ensures that, where appropriate, patients benefit from early surgical management which has been shown to improve outcome.\textsuperscript{68}

Despite its usefulness, CT imaging is limited by beam hardening effects, which can partially obscure the posterior fossa, temporal and frontal regions, and partial volume errors. The latter occur when a region of injured tissue has one or more dimensions that are smaller than the resolution of the acquired data.\textsuperscript{46} This can mean that haemorrhage or other evidence of intracranial pathology may remain undetected. Such issues are of particular concern within the brain stem and spinal cord, where a small area of pathology can result in devastating injury, and in many patients who exhibit evidence of diffuse axonal injury (DAI) after trauma. DAI is a frequent finding after TBI, accounting for up to 50% of trauma patients.\textsuperscript{29} The regions of the brain that are commonly injured include the grey–white matter interface, corpus callosum and deep white matter, periventricular and hippocampal areas, and brainstem.\textsuperscript{29} Such regions are best visualized using MRI,\textsuperscript{63} and increasingly patients undergo acute MRI after TBI. Access to the MR suite has been improved through the provision of integrated monitoring and anaesthetic equipment suitable for critically ill patients. Patients, staff, and equipment must be verified to be safe before transfer, and contraindications prevent imaging in some cases.\textsuperscript{14 73} Despite the obvious advantages of MRI in terms of delineating the extent and severity of brain injury, the MRI suite is not immediately accessible, and CT remains the modality of choice in the acute phase.

MRI is more sensitive at detecting white matter abnormalities than CT.\textsuperscript{27} In addition, Gradient echo\textsuperscript{47} and fluid attenuation inversion recovery (FLAIR) MR sequences\textsuperscript{1} demonstrate high sensitivity for DAI, and may help predict outcome.\textsuperscript{39 40} Differences in imaging contrast within both normal and injured brain are dependent on the particular MRI sequence employed. FLAIR sequences generate images in which areas of tissue T2 prolongation are bright whereas normal CSF signal is nulled and appears dark. This allows the detection of periventricular and superficial cortical lesions. Gradient echo MRI is sensitive to changes in magnetic susceptibility which results in lesions of low intensity after haemorrhage within the brain due to local magnetic field inhomogeneities caused by the paramagnetic properties of haemosiderin. By employing a variety of different MR sequences, the extent of brain injury can be demonstrated with high resolution across the brain (Figs 4 and 5).

Head injury can also lead to damage to the cerebral vasculature and result in cerebral ischaemia and infarction. Traumatic vascular injury is commonly associated with basal skull fracture, neck trauma, or penetrating head injury. Such injuries can result in cerebral ischaemia within the affected vascular territory and early assessment using cerebral angiography, CT or MR angiography is essential since prompt repair of treatable causes will prevent infarction and poor outcome. It would clearly be beneficial if imaging data could be used to predict patient outcome. Although imaging findings, based on CT and MR data,\textsuperscript{50 51 63 72 80} can predict survival, they do not provide sufficient information to allow accurate prediction of functional recovery. Indeed, although patients with lesions within the deep white matter and brain stem are more likely to suffer poor outcome, a consistent relationship based on the assessment of CT and MRI data remains elusive.\textsuperscript{46}

**Functional imaging**

Although structural imaging enables early diagnosis, directs initial management, and helps to predict eventual outcome, imaging of cerebral function is desirable. It can define the early pathophysiological processes responsible

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\textbf{Fig 1} 3D CT reconstruction. This patient sustained injury after collision with the knee of a fellow cricketer while fielding the ball. The reconstruction allowed operative planning of the cranial and facial fractures.
for neuronal injury, assess the efficacy of therapeutic interventions, and potentially direct the design and implementation of future therapeutic interventions aimed at reversing or preventing neuronal injury. Several imaging techniques are available which can measure aspects of brain physiology, including cerebral blood flow (CBF) and metabolism. Xenon-enhanced computerized tomography (xenon CT), CT perfusion, and SPECT provide measurements of cerebral perfusion, whereas PET, MRI, and MRS are able to assess both perfusion and cerebral metabolism. These imaging modalities are helpful in defining the extent of injury, evidence of cerebral ischaemia, and predicting outcome.\textsuperscript{14, 18, 44}

\textbf{Xenon-enhanced CT}

This technique uses stable non-radioactive \textsuperscript{131}Xe, which is a radio opaque, highly lipid soluble, diffusible indicator capable of crossing the blood brain barrier.\textsuperscript{14, 44} It provides a measure of tissue perfusion with quantification based on a modification of the Fick principle.\textsuperscript{41} Data are acquired during inhalation of a gas mixture containing 28\% \textsuperscript{131}Xe and oxygen.\textsuperscript{44} Acquisition of a baseline structural scan without xenon inhalation is followed by serial scans at regular intervals after beginning xenon inhalation. Typically, up to six slices of data are acquired over 4.5 min, with a further 10 min for data processing. Alveolar xenon concentration is measured by end-tidal sampling and assumed to be equal to arterial concentration. The degree of tissue enhancement of CT images [Hounsfield units (HU)] is calculated, and relates to an increase in the tissue \textsuperscript{131}Xe concentration which is proportional to the blood flow.\textsuperscript{22, 44} Movement artifacts can be troublesome in patients due to the known sedative effects of xenon. However, such problems have been lessened by the gradual reduction in the concentration of xenon required, and are irrelevant in patients who are already sedated and ventilated. Although xenon can induce CBF increases of up to 30\% and increase

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Fig2.png}
\caption{CT imaging of space-occupying lesions. (a) Right extradural haematoma. Bleeding occurs within the potential epidural space and is usually associated with a fracture. The expanding lesion has resulted in compression of the ipsilateral ventricle and midline shift. (b) Left subdural haematoma. Bleeding occurs between the arachnoid and inner meningeal layer of the dura. The underlying brain is swollen with cortical haemorrhagic contusion, compression of the ipsilateral ventricle, and midline shift. In addition, there is a right frontal haemorrhagic contusion. (c) Large right intracerebral haemorrhage secondary to brain contusion with evidence of compression and midline shift. (d) Bilateral haemorrhagic contusions with evidence of left subdural haematoma.}
\end{figure}
ICP, the available data suggest that both CBF and ICP data are not affected adversely during the short-term inhalation of xenon required for CBF imaging using this technique.\textsuperscript{44–48} Xenon CT provides rapid access to both structural and quantitative CBF data using equipment that is readily available. Studies can be repeated within a short period of time allowing assessment of clinical therapy, such as hyperventilation, CPP augmentation, or hypertonic saline.\textsuperscript{12, 71, 76} Such data have been used to demonstrate early hyperperfusion consistent with ischaemia after head injury, predict cerebral infarction, raised ICP secondary to hyperperfusion and abnormal CO\textsubscript{2} reactivity and autoregulation.\textsuperscript{18, 37, 52, 64} Despite these advantages, quantitative CBF studies can be difficult to perform in patients with associated pulmonary pathology since the technique is based on the assumption that the end-tidal xenon concentration is identical to the arterial concentration.\textsuperscript{14, 60, 83}

CT perfusion

The development of high-speed helical CT scanners and the availability of image reconstruction software have allowed this technique to become clinically available. CT perfusion involves sequential acquisition of axial data during the i.v. administration of iodinated contrast material. Since the change in CT enhancement (HU) is proportional to the concentration of contrast, perfusion is calculated from the time course of contrast enhancement profiles for each pixel in relation to the profile of arterial contrast enhancement (the arterial input function).\textsuperscript{44, 54} On the basis of the central volume theorem, CT perfusion is able to provide parametric images of cerebral blood volume (CBV), mean transit time (MTT), CBF, and CT angiography alongside structural data.\textsuperscript{14, 44, 67} It is a widely accessible, rapid, and accurate technique which can provide a means for directing therapy and predicting outcome after head injury,\textsuperscript{32, 54} and assessing cerebral vasospasm after subarachnoid haemorrhage.\textsuperscript{30, 82} A typical protocol allows acquisition of two 10 mm slices of data covering a region of interest within the brain.\textsuperscript{56}

However, the number and location of selected brain slices is limited due to radiation exposure,\textsuperscript{28, 44, 83} and repeat imaging after a therapeutic intervention is limited by the volume of contrast agent that can be safely administered.

Single photon emission computed tomography and positron emission tomography

SPECT uses conventional $\gamma$-emitting nuclear medicine isotopes with multiple detectors to generate tomographic images.\textsuperscript{133}Xe and technetium-99 m-hexamethylpropylene-oxide (99Tc-HMPAO) have been commonly employed to investigate blood flow within the brain.\textsuperscript{44, 77} SPECT is a relatively simple and inexpensive technique which can be used to assess cerebral perfusion,\textsuperscript{55} but the images produced are of relatively low resolution and generally non-quantitative.\textsuperscript{44, 77}

PET measures the accumulation of positron-emitting radioisotopes within the brain.\textsuperscript{5, 14} These positron-emitting isotopes can be administered via the i.v. or inhalation route, and for imaging of the brain, 15-oxygen (15O) is employed to measure CBF, CBV, oxygen metabolism (CMRO\textsubscript{2}), and oxygen extraction fraction (OEF), whereas 18-fluorodeoxyglucose (\textsuperscript{18}FDG) is used to measure cerebral glucose metabolism. The emitted positrons are annihilated in a collision with an electron resulting in the release of energy in the form of two photons (gamma rays) released at an angle of 180$^\circ$ to each other. This annihilation energy can be detected externally using coincidence detectors, and the region of each reaction localized within the object by computer algorithms. Although PET is clearly capable of defining many complex aspects of cerebral physiology and pathophysiology, it is a research tool which is relatively expensive and not universally available.\textsuperscript{14} Despite this, PET has been successfully used to investigate changes in physiology after head injury.\textsuperscript{15–18, 53, 59, 62, 78} These demonstrate that early reductions in cerebral perfusion can result in cerebral ischaemia that is associated with poor outcome, despite optimal management of ICP and cerebral perfusion pressure (CPP) (Fig. 6). However, other PET studies have failed to find conclusive evidence of cerebral ischaemia.\textsuperscript{20, 21} Indeed, brain-injured patients commonly demonstrate evidence of global hypometabolism and metabolic stress which fails to recover in patients who have a poor outcome.\textsuperscript{7, 78, 84} PET studies can be repeated and used to assess changes in physiology with commonly applied therapeutic manoeuvres, such as hyperventilation and CPP augmentation. Such studies have helped to demonstrate that the efficacy of such therapies should be determined by
measurement of cerebral perfusion and metabolism within individual patients and across the injured brain (Fig. 7).\textsuperscript{16} 17 Blood flow and metabolism varies dramatically across the traumatized brain and different regions may require different therapeutic approaches. Although this is obviously not possible using global therapeutic manoeuvres, it is clear that the effect of common therapeutic interventions should be measured and only continued where benefit is demonstrated.\textsuperscript{16} 17

Although several PET studies have sought to define thresholds for tissue viability and ischaemia after ischaemic stroke\textsuperscript{4} and head injury,\textsuperscript{18} a recent review highlights the difficulties with such published thresholds.\textsuperscript{2} Although brain regions with dramatic reductions in CBF are clearly incapable of surviving, patients also demonstrate functional cognitive deficits in regions without clear evidence of structural injury. One possible cause for such findings is that a region which appears structurally intact may have suffered patchy neuronal injury which results in selective neuronal loss and functional deficit. Early PET studies of CBF and metabolism clearly help to predict outcome, but further studies using markers of such selective neuronal injury, such as MRS\textsuperscript{31} and Flumazenil PET,\textsuperscript{31} may improve the predictive power of such thresholds after head injury.

**Fig 4** (a) MR imaging after head injury. (a) Proton density. (b) T2 weighted. (c) Fluid-attenuated inversion recovery. (d) Gradient echo sequences. Images from a patient who sustained a severe head injury after an assault and underwent left frontal lobectomy and decompressive craniectomy for management of raised ICP. (a) and (b) demonstrate multiple high signal areas in the left frontal, left temporal, and right temporo-parietal region. These abnormalities are more clearly defined in (c) since the CSF signal has been nulled. In (d), the right temporo-occipital lesion has a haemorrhagic component since there is signal loss within this region.
Fig 4 (a) MR imaging following head injury. (a) Proton density. (b) T2 weighted. (c) Fluid attenuated inversion recovery. (d) Gradient echo sequences. Images from a patient who sustained a severe head injury following a road traffic accident. All the images demonstrate subcutaneous swelling on the right side of the head, while the collection of fluid (hygroma) over the right frontal cortex is best demonstrated in (b) and (d). (a) and (b) demonstrate mixed signal abnormality within the deep white matter, particularly within the corpus callosum, suggestive of haemorrhagic confusion. Due to its proximity to the ventricles this abnormality is more clearly demonstrated on the FLAIR image (c). In (d) the presence of haemorrhage within these confused regions is confirmed.

Fig 5 MRI of brain stem injury. This patient presented with a Glasgow Coma Score of 4 after a road traffic accident and failed to improve, despite maximal medical therapy, and therefore underwent MRI to assess the extent of injury. The T1 weighted images are displayed in axial (a) and coronal (b) section. These demonstrate a high signal abnormality within the pons (arrow) which extended from the basal ganglia through the midbrain and into the pons.
MRI techniques

Blood flow can be measured using two different measurement techniques. Perfusion MRI uses rapid sequential susceptibility-weighted imaging after injection of a bolus of MRI contrast medium [typically Gadopentate dimeglumine (Gd-DTPA, Magnevist)] that induces a change in intravascular magnetic susceptibility to produce images of MTT, and relative CBF and CBV. Another MR technique uses an endogenous diffusible tracer to measure CBF by applying magnetic resonance pulses to tag in-flowing water protons. In this ‘arterial spin labelling’ approach, the changes in the amplitude of the MRI signal are used to construct quantitative images of cerebral perfusion. Although such techniques are now being successfully applied to clinical settings, there are outstanding issues regarding absolute quantification.

Diffusion-weighted MRI (DWI) images the microscopic movement of water using powerful gradient coils that undergo rapid switching in polarity on either side of a 180° excitation pulse. The random motion of diffusion leads to phase shifts and signal loss, whereas regions with decreased motion show little or no signal loss and appear relatively bright on DWI images. Early hypointensity on apparent diffusion coefficient (ADC) DWI occurs after acute ischaemia and is associated with the movement of water into the intracellular compartment where it is relatively restricted (cytotoxic oedema). A region demonstrating an acute decrease on ADC maps is assumed to have suffered irreversible injury (core), whereas the presence of reduced perfusion but normal diffusion is representative of tissue at risk of ischaemic injury (ischaemic penumbra). For these reasons, a so-called perfusion/diffusion mismatch has been used to diagnose early cerebral ischaemia and direct therapy. DWI data can also be reconstructed to provide imaging of white matter tracts using diffusion tensor imaging (DTI) since the direction and magnitude of water diffusion is highly constrained within such regions (Fig. 8). Such data are useful in delineating the extent of brain injury, and evidence suggests that disruption of white matter tracts has important implications for cognitive recovery.

Fig 6 PET imaging of cerebral ischaemia. X-ray CT, PET CBF, OEF, oxygen metabolism (CMRO₂), and glucose metabolism (CMRgluc) images obtained after evacuation of a subdural haematoma. Note the small amount of residual subdural blood with minimal midline shift. The cerebral hemisphere underlying the evacuated subdural haematoma displays a marked reduction in CBF, slight decrease in CMRO₂, and large increase in OEF suggestive of cerebral ischaemia. In addition, the substantial increase in CMRgluc implies a switch to non-oxidative metabolism of glucose in order to meet underlying metabolic need.

Fig 7 Assessment of the efficacy of acute hyperventilation using PET imaging. Gray scale PET CBF images obtained from a head injury patient at relative normocapnia (A) and hypocapnia (B). Voxels with a CBF less than 20 ml 100 ml⁻¹ min⁻¹ are picked out in red. Baseline ICP was 21 mm Hg and supports the use of hyperventilation to lower PaCO₂ and improve ICP control. Hyperventilation did result in a reduction in ICP to 17 mm Hg but, in this individual, led to a substantial increase in the volume of hypoperfused brain.

Magnetic resonance spectroscopy is a non-invasive imaging technique that allows the investigation of biochemical pathology within the brain. Although both proton (¹H-MRS) and phosphorus (³¹P-MRS) spectroscopy are frequently used to study cerebral metabolism and ischaemia,¹H-MRS is the prominent technique in humans. ¹H-MRS provides data on several biologically relevant molecules, including lactate, N-acetyl aspartate (NAA), total creatine [creatine and phosphocreatine (Cr+PCr)], glutamate/glutamine (Glx) and choline (Cho). Increased lactate suggests deranged energy metabolism and is consistent with cerebral ischaemia. NAA is located primarily within neurones, and a reduction in NAA can be indicative of neuronal death or dysfunction. A decrease in NAA has been found after head injury, and although this may represent neuronal loss, it may also be the consequence of mitochondrial dysfunction and metabolic depression.
Although it is clear that MRS can provide important information regarding the metabolic state and potential viability of ischaemic brain tissue, at present, there are limitations to the technique. MRS imaging is hampered by limited coverage of the brain, poor spatial resolution, and the necessity for long imaging times. Despite this, MRS has been shown to be clinically useful in head injury, and promises to become widely available since it can be readily implemented on existing MRI machines.

MR has become an extremely useful clinical tool after head injury, since it combines the ability to image perfusion, the status of tissue (DWI and MRS), vascular patency (MR angiography), and white matter tracts (DTI) across the whole brain with high-resolution structural imaging. This thorough assessment of the derangements induced by brain injury can be used to predict the mechanism of injury, the likely response to therapeutic intervention and the degree of eventual functional recovery (Fig. 9).

Functional MRI
Functional MRI (fMRI) can be used to measure neural activation by measurement of changes in blood oxygenation using the blood oxygen level dependent technique which is sensitive to local changes in the magnetic field induced by the presence of deoxygenated haemoglobin. This technique uses a rapid MRI sequence capable of demonstrating change after performance of a particular cognitive task aimed at inducing activation within a region of the brain. Neural activation results in an increase in regional blood flow and influx of oxygenated blood which causes a decrease in the level of deoxygenated haemoglobin. Such techniques have been used in the assessment of patients who appear to be in a vegetative state after brain injury and can demonstrate that some patients may remain cognitively aware and capable of some degree of recovery. Although such positive findings have clear implications for predicting outcome after brain injury, a negative response in a particular cognitive task does not confirm that a patient is, or will remain, in a persistent vegetative state. Despite this, the technique has significant implications for the assessment of patients recovering from various forms of brain injury that appear to be in a vegetative, minimally conscious or locked in state.

Conclusions
Imaging is an important clinical tool used in the management of patients with brain injury. CT allows rapid assessment of the extent and type of brain pathology which ensures patients who require urgent surgical intervention receive such care at the earliest opportunity. Access to high field MRI is improving and patients benefit from its greater spatial resolution, particularly within the posterior fossa and deep white matter, and its ability to combine imaging of structure and function across the brain. Although the extent and distribution of structural lesions within the brain is associated with outcome, such data do not allow accurate prediction of functional outcome. A more complete assessment of the burden of injury within the brain requires imaging of cerebral physiology, both in the acute phase and into the recovery period. Several techniques are currently available which provide imaging of cerebral blood flow and metabolism. Although such imaging techniques can only provide ‘snap shots’ of physiology within the injured brain, they can be repeated and used to assess the impact of therapeutic interventions. Perfusion imaging based on CT techniques (xenon CT and CT perfusion) can be implemented easily in most hospital centres, and provide quantitative perfusion data in addition to structural images. PET imaging provides unparalleled insights into cerebral physiology and pathophysiology, but is not widely available and is primarily a research tool.
MR technology continues to develop and is becoming generally available. Using a complex variety of sequences, MR can provide data concerning both structural and physiological derangements. Future developments with such imaging techniques should improve understanding of the pathophysiology of brain injury and provide data that might improve management and prediction of functional outcome.

**Fig 9** MR imaging of physiology after head injury. (A) FLAIR images from two levels in a patient who sustained a severe head injury after a road traffic accident. The left image appears unremarkable except for a thin collection of subdural fluid and loss of volume within the underlying right temporo-parietal cortex. The right image demonstrates high signal within the right internal carotid (arrow) consistent with dissection and thrombosis secondary to basal skull fracture. (a) ADC (left), multivoxel spectroscopic imaging of the lactate to creatine ratio (middle) and data from a single voxel from the right temporo-parietal region (right). The ADC image demonstrates hypodensity in the right temporo-parietal region and there is an increased lactate in the adjacent voxels from the spectroscopy image suggesting cytotoxic oedema and ischaemia, respectively. The data from a representative voxel confirm the presence of a lactate peak, and the persistence of the NAA peak suggests the region remains viable at this stage. (c) FLAIR image from the same patient obtained 24 h later. There is an increased signal within right temporo-parietal region consistent with cerebral infarction, despite active management.
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