Functional imaging in stroke

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Recent advances in magnetic resonance techniques make it possible to image physiological parameters such as molecular diffusion, tissue perfusion and cortical activation. These techniques greatly contribute to the early detection and to the understanding of the pathophysiological evolution and recovery from ischaemic stroke.

Computed tomography (CT) has been the mainstay of the imaging of stroke owing to its wide availability and high sensitivity in differentiating cerebral haemorrhage from acute ischaemic stroke. Conventional magnetic resonance imaging (MRI) improves visibility and earlier detection of ischaemic changes compared to CT, particularly in lacunar and posterior fossa strokes. Functional MRI (fMRI) provides additional information on physiological parameters not available with conventional MRI. It is an umbrella term, which includes imaging of microscopic water motion (MR diffusion imaging), microvascular haemodynamics (MR perfusion imaging) and blood oxygen-level dependent (BOLD) imaging of cerebral activation (which can also be assessed using positron emission tomography (PET)). This article briefly describes the technical principles behind these methods and discusses the current clinical applications of functional imaging in the acute and recovery phase of stroke.

TECHNICAL PRINCIPLES

MR perfusion imaging

MR perfusion imaging exploits magnetic susceptibility effects within the brain tissue during the first pass of an intravenously injected gadolinium-based contrast agent. During its first pass the contrast medium causes a transient signal drop on T2*-weighted (susceptibility-weighted) MR images (Sorensen et al, 1996; Beauchamp et al, 1999). Images are typically acquired with a temporal resolution of one image every 1–2 seconds and the use of single shot echoplanar imaging allows multi-slice imaging with full brain coverage. MR perfusion imaging is at present only semiquantitative and cannot provide absolute values of cerebral blood flow (CBF). The sequential changes in signal intensity can by plotted as a time–signal intensity curve of a chosen region of interest or represented as pixel-based colour maps of specific haemodynamic parameters such as relative cerebral blood volume (rCBV), bolus arrival time (T_0) and mean transit time (MTT) (*Figure 1*). The relative CBF can be estimated by dividing rCBV by MTT (Beauchamp et al, 1999).

MR diffusion imaging

Diffusion-weighted MRI exploits the presence random motion (brownian motion) of water molecules to produce image contrast, thus providing information not available on standard T1- or T2-weighted images (Provenzale and Sorensen, 1999). This is achieved by applying a pair of 'diffusion' gradients around a 180° refocusing radiofrequency pulse of a T2-weighted MR sequence. Mobile molecules acquire phase shifts, which prevent their complete rephasing and result in signal loss. The loss of signal is proportional to the degree of microscopic motion and regions of relatively stationary water molecules appear much brighter than areas with a higher molecular diffusion.

The degree of phase shift and signal loss depends also on the strength and duration of the diffusion gradient, which is expressed by the 'b value'. For imaging of acute stroke the b values used are typically around 1000 sec/mm^2. Quantitative analysis of the apparent diffusion coefficient (ADC) requires scanning with at least two different b values and additional postprocessing. ADC maps are solely based on differences of tissue diffusion, independent of any T2 effects. Areas with a decreased ADC appear dark on ADC maps, which is the converse to diffusion-weighted images where areas of decreased diffusion appear bright (Provenzale and Sorensen, 1999) (*Figure 2*).

Diffusion is a truly three-dimensional process. In certain tissues, such as cerebral white matter, molecular mobility is not the same in all directions. This directional dependence or diffusion anisotropy can be examined and characterized with diffusion tensor imaging (DTI), which pro-

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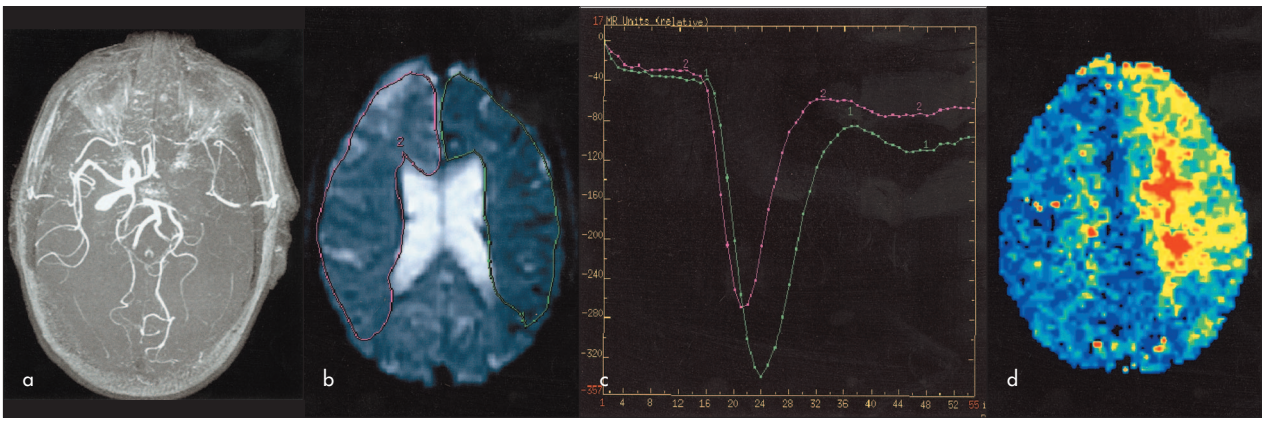

Figure 1. a. Magnetic resonance (MR) angiography and (b,c) MR perfusion study in a patient with left internal carotid artery occlusion. a. The intracranial MR angiography shows occlusion of the left internal carotid, middle and anterior cerebral arteries with collateral circulation from the left middle meningeal artery. b. Axial image of perfusion scan with delineation region of interests (ROI) corresponding to the anterior cerebral circulation territory of the right (red) and left (green) hemispheres and (c) time–signal intensity curves of these ROIs. The y-axis represents signal intensity and the x-axis time in seconds. There is a decrease in signal intensity during the first pass of the gadolinium bolus, which is delayed in the left hemisphere (green) compared to the right (red). The area under the curve, which corresponds to the relative cerebral blood volume, is larger on the left, indicating compensatory collateral circulation. d. A pixel-by-pixel colour map (d) of the bolus arrival time shows delayed arrival in the territory of the left anterior and middle cerebral arteries (red and yellow) compared to the right side and both occipital artery territories.

vides more detail about the tissue microstructure and can be used to assess the course and integrity of white matter tracts (Gillard et al, 2001).

Cerebral activation studies

Cerebral activation studies provide one way of studying the changes in cerebral brain function accompanying plasticity in humans. These techniques rely on the assumption that neuronal activity is closely coupled to a local increase in CBF secondary to an increase in metabolism. PET maps the distribution of radioactive tracers, whereas fMRI relies on the fact that during an increase in neuronal activation there is an increase in local CBF, but only a small proportion of the oxygen is used. There is therefore a net increase in the tissue concentration of oxyhaemoglobin and a net reduction in the tissue concentration of deoxyhaemoblobin. This results in an increase in signal intensity on T2*-weighted images, measured as the BOLD signal.

FUNCTIONAL IMAGING IN ACUTE STROKE

In acute stroke fMRI methods can help rapidly to establish the diagnosis and to identify potentially salvageable tissue. They have the potential of influencing patient selection for thrombolysis.

Pathophysiological considerations

The pathophysiology of acute stroke can be simplified into three consecutive stages in order to explain the evolution of imaging findings:

1. Flow abnormalities
2. Cellular dysfunction
3. Structural breakdown (Ueda et al, 1999a).

Flow abnormalities can be detected immediately after the onset of stroke by MR perfusion imaging. Cellular dysfunction occurs if the CBF falls below

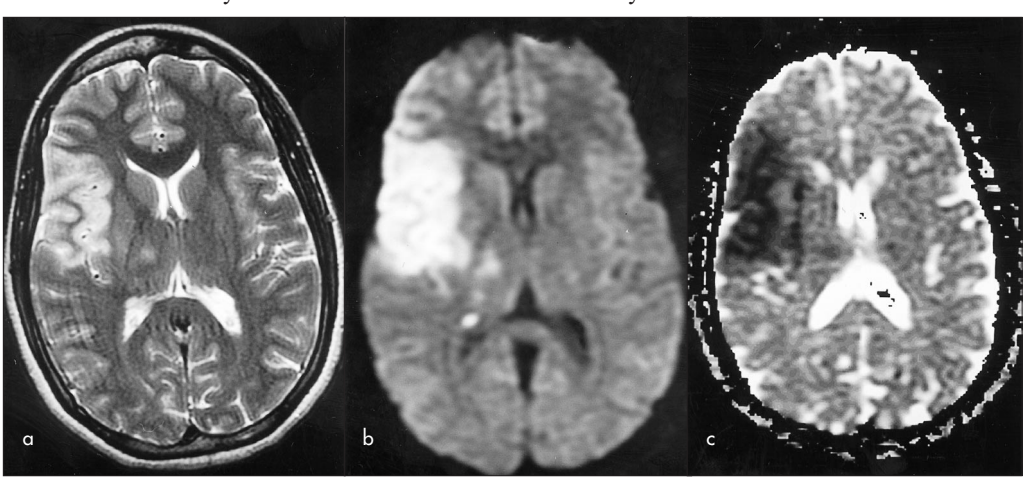

Figure 2. a. T2-weighted magnetic resonance image (MRI), (b) diffusion-weighted MRI and (c) apparent diffusion coefficient (ADC) map of a 30-year-old patient with an acute right hemisphere stroke. a. The T2-weighted image shows some high signal in the right insular cortex and internal capsule. There is a more extensive area of restricted diffusion which appears bright on (b) the diffusion-weighted image and dark on the ADC map (c). Note that the lesion is most obvious on the diffusion-weighted image but the ADC map is a more accurate reflection of the diffusion abnormalities, independent of any T2 effects.

a critical level. At 20–30 ml/100 g/min the electrical activity in the brain ceases, and at 10–15 ml/100 g/min failure of the energy-dependent sodium pump leads to an accumulation of intracellular sodium and watershift into the intracellular compartment causing swelling of neurons (cytotoxic oedema). Cytotoxic oedema predominates during the first 6 hours and can be detected with diffusion-weighted MR. As time proceeds, structural breakdown of the blood–brain barrier occurs with leakage of intravascular fluid and protein into the extracellular space (vasogenic oedema). Vasogenic oedema develops after 6 hours and reaches its peak between 24–48 hours. It causes brain swelling and produces high signal on conventional T2-weighted MR images.

MR perfusion and diffusion imaging

MR perfusion imaging provides immediate and direct evidence of the repercussions of a proximal vessel occlusion on the microcirculation (Ueda et al, 1999a). Prolongation of T_0 or MTT is the earliest and most consistent sign of impaired perfusion (Beauchamp et al, 1999). The rCBV may be normal or show a compensatory increase in the presence of adequate collateral supply. rCBV is decreased if the collateral circulation is insufficient resulting overall in decreased CBF.

Sorensen et al (1996) initially studied patients in the first 10 hours and showed the abnormalities on MTT maps to be more extensive than on rCBV maps. Later they showed that the final infarct size in untreated patients corresponded more closely to the blood volume maps (Sorensen et al, 1999), which has been confirmed by others.

MR diffusion imaging can detect parenchymal damage within 1 hour of an ischaemic insult. Areas of ischaemic damage have restricted water diffusion and appear consequently bright on diffusion-weighted images ('light bulb sign') and dark on ADC maps (*Figure 2*). The precise mechanisms leading to a reduction in diffusion are actively debated, but redistribution of extracellular water into the intracellular compartment (cytotoxic oedema), resulting in shrinkage of the extracellular space, appears the most likely explanation (Provenzale and Sorensen, 1999).

Diffusion-weighted imaging (DWI) is generally regarded as highly sensitive and specific for the early detection of cerebral ischaemia and as a marker of irreversible tissue damage. The latter and the fact that abnormalities on MR perfusion imaging are often more widespread than on DWI has led to the assumption that the difference between the perfusion and diffusion image (perfusion–diffusion mismatch) represents the ischaemic penumbra, a potentially salvageable tissue (Beauchamp et al, 1999; Ueda et al, 1999b). This concept, although valid in many cases, has subsequently proven to be somewhat simplistic.

Two assumptions regarding diffusion-weighted MRI have been challenged by research (Kidwell et al, 2000; Sunshine et al, 2001). First its sensitivity in detecting hyperacute ischaemia: anecdotal case reports of negative findings on diffusion-weighted images in acute stroke have been followed by an analysis of perfusion- and diffusion-weighted MRI in 62 patients with hyperacute stroke (Sunshine et al, 2001). In approximately a quarter of these patients MR perfusion imaging provided the only evidence of large vessel occlusion and in seven of these MR diffusion imaging was entirely normal.

Second the specificity of diffusion-weighted MRI as a marker of irreversible damage has been called into question by reports describing a resolution of diffusion abnormalities, particularly after intra-arterial thrombolysis (Kidwell et al, 2000). A likely explanation is that the severity of reduction in blood flow necessary to produce abnormalities on diffusion-weighted images lies somewhere between the threshold of electrical failure (20 ml/100 g/min) – which leads to clinical symptoms – and the threshold of irreversible tissue damage (which lies below 10 ml/100 g/min). New efforts are directed towards a more quantitative analysis of diffusion changes by looking at ADC values (Desmond et al, 2001) and anisotropy changes. Isotropic diffusion is more reduced in white matter than gray matter and DTI may be more sensitive than DWI to white matter ischaemia (Mukherjee et al, 2000).

FUNCTIONAL IMAGING IN THE RECOVERY PHASE OF STROKE

In the subacute phase of stroke, the emphasis shifts from the rescue of potentially salvageable tissue to secondary stroke prevention and influencing recovery. Understanding the mechanisms which led to the stroke and which govern the recovery process is crucial and may be aided by functional imaging methods.

MR perfusion and diffusion imaging

Abnormalities on MR perfusion imaging tend to regress fairly rapidly in the early subacute phase. In untreated patients, delays in T_0 and MTT may reverse to normal within 48 hours as a reflection of spontaneous vessel recanalization (Beaulieu et al, 1999).

MR perfusion imaging can also be used to identify patients with severe carotid artery stenosis or occlusion who are at risk from haemodynamic rather than embolic infarction. In the former MR

perfusion imaging may follow a borderzone distribution or be normal at rest and show impairment following a challenge of the vascular reserve with acetazolamide. Normally the cerebral flow increases following acetylcholamine administration. Some patients with severe steno-occlusive disease have a decreased response to the acetylcholamine challenge (Gückel et al, 1996), with a higher risk of a future stroke.

Appearances on MR diffusion imaging are strictly time-dependent. ADC values are low within the first week, leading to bright lesions on diffusion-weighted images. During the second week ADC values become pseudonormal and thereafter they are higher than in normal brain parenchyma and so appear dark on diffusion-weighted images. Low ADC values indicate that an infarct is less than 10 days old with good sensitivity and specificity (Lansberg et al, 2001).

MRI diffusion imaging can therefore be useful in identifying subacute infarcts. In the presence of several abnormalities on T2-weighted images, diffusion-weighted images can pinpoint the acute lesion and determine its vascular territory. This was felt to be clinically relevant in 48% of the cases in a study by Albers et al (2000).

DTI in the subacute phase can provide information about the integrity of white matter tracts. One can distinguish whether white matter tracts are distorted around the infarct or disrupted by it, which may have implications for functional recovery (Gillard et al, 2001).

Cerebral activation studies

The natural history of motor recovery following stroke is for a variable degree of functional improvement to occur over time. Recovery during the acute stage may be related to a number of factors including resolution of oedema and survival of the ischaemic penumbra. What is remarkable, but is often taken for granted, is that recovery may continue for several months after the acute event. There is increasing evidence that the acutely damaged brain is more plastic, and that these changes occur at the level of the synapse (either increased number or efficacy) and are consequently reflected at the level of neuronal circuits (Cramer and Chopp, 2000). The increase in interest in this area is thus fuelled by the notion that if we can understand these processes then we will be able to facilitate functional recovery following brain injury.

The idea that intact areas of the brain become functionally disconnected from the sites of focal lesions, and that this might have an impact on both the clinical presentation and on recovery, was first discussed in 1914 by Von Monakow (1969) and termed diaschisis. There is some evidence to support the idea that improvement in diaschisis has functional significance and that areas of the brain remote from the site of damage may subserve recovery. In particular, it appears that a better outcome can be gained if certain deep structures, particularly the thalamus, maintain their functional connections with cortical motor structures (Pantano et al, 1996).

Studies performed at rest might provide prognostic information, but to understand the reorganization that is often assumed to underlie functional recovery, empirical data are required from stroke patients while they are performing a task, often a motor task. The problem of comparing normal controls with patients unable to perform the task with the same degree of precision was initially avoided by studying only patients having made a good recovery.

Chollet et al (1991) and Weiller et al (1992) scanned patients using PET while performing a finger opposition task some months after recovery from first ischaemic subcortical stroke. In both studies, the normal lateralized pattern of activity in cortex and cerebellum associated with this task became bilateral with movement of the recovered hand. In addition activations were seen in areas of the brain normally only recruited in more complex motor tasks involving the whole limb.

Weiller et al (1993) were able to perform a similar experiment and analyse individual results rather than just those of a group. Contralesional primary sensorimotor areas were activated in only four out of eight patients, each of whom displayed mirror movements, and so it was felt that this finding in particular could not be attributed to reorganization of the motor system. Investigators using fMRI to perform similar experiments have also demonstrated a greater degree of activation in the contralesional sensorimotor cortex compared to controls. In these studies, the bilateral activation pattern was only occasionally accompanied by mirror movements, and in one patient with mirror movements, there was exclusively contralesional activation during recovered hand movement, suggesting that the contralesional hemisphere was mediating movement in both left and right hands (Cao et al, 1998). Although always a possible confound in the interpretation of these results, mirror movements are unlikely to be the sole explanation for this change in activation pattern.

As well as bilateral motor cortex activations, there are also data which support the notion that surviving peri-infarct cortical tissue may be helpful to the recovering patient. Cao et al (1994) studied teenage patients who had suffered a perinatal infarct, each with only moderate recovery.

Sequential finger movements of the affected hand were associated with bilateral activations, as well as peri-infarct cortical rim. Peri-infarct cortical rim activations in recovered stroke patients were seen by Cramer et al (2000) during similar tasks, and other groups have subsequently reported shifts in cortical maps in patients studied during simple motor tasks in fMRI (Pineiro et al, 2001).

These alterations in activation patterns are often interpreted as representing alternative cortical areas taking over the function of the damaged area, but a correlation between changes in activation patterns and the degree of recovery has yet to be made. One approach would be to study the time course of these changes in relation to recovery. Marshall et al (2000) and Calautti et al (2001) performed early and late scans in small groups of patients after stroke. Although there were differences in experimental design, both studies tended to show a shift from bilateral activation to a more normal unilateral pattern of sensorimotor cortex activation over time. All patients made good recoveries, so without comparison to patients with different degrees of recovery, it is not possible to determine whether these changes are related to recovery.

Functional imaging techniques have proved a useful tool with which to study brain reorganization after stroke, but further studies will be required before we know whether it will prove to be useful in a clinical setting. **HM**

Conflict of interest: none.

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KEY POINTS

- Advanced magnetic resonance imaging techniques allow imaging of physiological parameters such as molecular diffusion, tissue perfusion and cortical activation.
- Magnetic resonance perfusion and diffusion imaging allow early detection of hypoperfusion and ischaemic injury. Used in combination, they have the potential to identify tissue at risk from infarction, which is potentially salvageable.
- Magnetic resonance diffusion and perfusion in the subacute stage contribute to the understanding of stroke mechanisms and pathophysiology.
- Positron emission tomography and functional magnetic resonance imaging will contribute towards the understanding of functional reorganization in the brain that underlies recovery from stroke