Progress in imaging stroke: emerging clinical applications

JV Guadagno, C Calautti and J-C Baron

Department of Neurology and Stroke Unit, Wolfson Brain Imaging Centre, University of Cambridge, Cambridge, UK

Recent years have seen major advances in the imaging of cerebrovascular disease. Although quantitative positron emission tomography (PET) has continued to be the gold standard in acquiring functional imaging data, with recent developments continuing to bear fruit, it remains a complex, costly, and not readily available technique. The emphasis in this overview is in the development of the newer magnetic resonance (MR) techniques, such as diffusion-weighted (DWI) and perfusion-weighted imaging (PWI), which allow rapid assessment of the underlying pathophysiology in acute ischaemic stroke. This is of major importance in classifying patients according to pathophysiology rather than clinical and structural imaging data, which may be essential in deciding therapy such as thrombolysis (which has proven benefit within 3–6 h of clinical onset, but can also lead to harmful haemorrhagic transformation) and/or neuroprotection, as well as patient selection in clinical trials. In conjunction with magnetic resonance angiography (MRA), DWI-PWI has been shown to improve the diagnosis and clinical management of stroke. Other novel MR techniques which have yet to reach the clinician, such as spectroscopic imaging, diffusion tensor imaging (DTI) and blood oxygenation level-dependent functional MRI (BOLD-fMRI), are currently established research tools which provide data about infarct evolution, fibre disruption and the mechanisms of stroke recovery. Electrophysiological methods including transcranial magnetic stimulation (TMS) and magneto-encephalography (MEG) will not be addressed here.

A detailed overview of the methods used in functional imaging can be found elsewhere in this volume (Turner & Jones) and in published reviews1,2, so only a brief summary of the techniques used in cerebrovascular disease are listed in Table 1. Diffusion and perfusion MR techniques are explored in more detail below.

Magnetic resonance imaging

Diffusion-weighted imaging

Diffusion-weighted hyperintense lesions indicate a restriction in the
Table 1 Physiological imaging as applied to CVD

<table>
<thead>
<tr>
<th>Method</th>
<th>Technique</th>
<th>Uses</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT perfusion</td>
<td>Bolus injection of iodinated contrast medium</td>
<td>CBV, MTT and CBF</td>
<td>CT availability Absolute quantification theoretically possible</td>
<td>Ionizing radiation Doubt about accuracy Limited slices</td>
</tr>
<tr>
<td>Xe-CT</td>
<td>Freely diffusible stable gas inhaled</td>
<td>CBF</td>
<td>Uses existing equipment, washes out fairly rapidly</td>
<td>Ionizing radiation Small signal-to-noise ratio Limited amount of brain cuts possible Anaesthetic effect</td>
</tr>
<tr>
<td>Helical CT angiography</td>
<td>Vascular anatomy</td>
<td>Vascular occlusive disease, aneurysms and AVMs</td>
<td>CT availability Quick to create images</td>
<td>Ionizing radiation</td>
</tr>
<tr>
<td>Single photon emission CT (SPECT)</td>
<td>99mTc HMPAO</td>
<td>Perfusion</td>
<td>Widely available</td>
<td>Ionizing radiation Quantitation difficult Tracer’s behaviour can deviate in pathophysiological situations Debate about findings in clinical setting</td>
</tr>
<tr>
<td></td>
<td>99mTc-ECD</td>
<td>Perfusion and cell homeostasis</td>
<td>Can provide haemodynamic, chemical and functional imaging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzodiazepine radioligands</td>
<td>Neuronal density</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positron emission tomography (PET)</td>
<td>[15O]-tracers – H2O, CO2, CO and O2</td>
<td>CBF, CBV, CMRO2, OEF</td>
<td>Haemodynamic, chemical and functional imaging Quantifiable results Absolute physiological variables can be determined</td>
<td>Ionizing radiation Arterial line required in some techniques Complex equipment Limited access</td>
</tr>
<tr>
<td></td>
<td>[18F]-fluoro-2-deoxy D-glucose (FDG)</td>
<td>Activation mapping</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[11C]-flumazenil</td>
<td>Neuronal integrity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[11C]-PK 11-195</td>
<td>Glial inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[18F]-fluoro-misonidazole</td>
<td>Tissue hypoxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>[13C]-aspartate (NAA), a specific neuronal marker</td>
<td>Metabolic activity – lactic acid Neuronal density</td>
<td>Non-invasive analysis of tissue pathology Improvements currently with high-field new generation magnets</td>
<td>Most applications so far with single-volume MRS Resolution previously poor but improving Quantitation unstable</td>
</tr>
<tr>
<td>Functional MRI</td>
<td>BOLD effect uses deoxyhaemoglobin (which is paramagnetic) as an endogenous contrast agent</td>
<td>Activation maps to investigate mechanisms of recovery from motor deficits and aphasia</td>
<td>Non-invasive Less person and facility intensive than PET Easily repeatable</td>
<td>Neurovascular coupling may be affected in pathology</td>
</tr>
</tbody>
</table>
diffusional movement of water. It reliably identifies severely ischaemic tissue within minutes of stroke onset, whereas T1 and T2 weighted images may be normal. The degree of water proton mobility can be quantified by a parameter known as the apparent diffusion coefficient (ADC). On ADC maps, areas of restricted diffusion appear as low ADC (hypo-intense). The reason for the early decline in ADC is thought to be cytotoxic oedema as a result of cellular energy failure causing a loss of ion homeostasis and subsequent shift of water to the intracellular compartment where diffusion is thought to be more restricted.

**Diffusion tensor imaging and anisotropy**

Because of the structure of fibre tracts, water diffusion will appear less restricted along fibre tracts, i.e. water diffusion in brain tissue displays anisotropy. To correct the ADC for anisotropy, DWI sequences have three diffusion gradients placed in three orthogonal directions (x,y,z) with the average of the 3 images giving the diffusion trace image from which the final ADC is calculated. DTI is a more sophisticated form of DWI. The diffusion sensitizing gradients are applied in at least 6 different directions in space to fully define the diffusion tensor. This allows determination of the directionality as well as the magnitude of water diffusion and so the anisotropy is readily quantifiable with DTI. DTI has been used to investigate stroke where it displays an early reduction in fractional anisotropy, which may be helpful as an early indicator of the breakdown of neuronal membranes. Knowledge of the directionality of diffusion may be used to non-invasively track neuronal projections and, therefore, brain connectivity. This can be used to understand better the recovery process following stroke and other disconnection-related phenomena.

**Perfusion-weighted imaging**

Two types of PWI can be used: DSC (dynamic susceptibility contrast) MRI usually referred to as ‘bolus tracking’, and arterial spin labelling (ASL). In the clinical setting, only the former has been extensively used. In bolus tracking, the first pass of an intravenously injected gadolinium-based contrast agent causes a transient signal drop on T2*-weighted MR images. Relative cerebral blood volume (rCBV) is proportional to the area under the tissue signal change–time curve. Other measurements can be derived such as time-to-peak (TTP) and mean transit time (MTT). Using tracer kinetics, the relative cerebral blood flow (rCBF) can be estimated by dividing the relative blood
volume by the mean transit time \( (rCBF = rCBV/MTT) \). However, absolute quantification of CBF and CBV is feasible using deconvolution with the arterial input function (obtained from pixels in the origin of the middle cerebral artery, MCA) and is thought to be more representative of tissue perfusion. Although probably the technique of choice at the moment, an awareness of its current limitations is essential as recently pointed out by Calamante et al.\(^3\).

ASL techniques are completely non-invasive and are being assessed in cerebrovascular disease. The difference between a ‘tag’ image in which inflowing blood is labelled by an inversion pulse, and a control image without previous inversion pulse, is obtained. However, multiple tag and control images need to be acquired for signal averaging because of the small signal difference. Also, in very low flow states such as in stroke, the signal may have ‘decayed’ before entering the image plane (may be partly overcome by using a more powerful magnet, e.g. 3T MRI).

### Imaging of acute ischaemic stroke

In contrast to structural imaging, which is relatively unambiguous, functional imaging maps physiological variables and thus interpretation is less straightforward. Yet, applying this type of imaging has resulted in a considerable leap forward in the understanding of the mechanisms involved in clinical stroke, and has allowed a scientific rationale and logical approach to the management of acute stroke. The PET findings lay the foundations of this scientific rationale, with the newer MRI techniques continuing in the same vein, delving further into the underlying mechanisms.

**Findings with PET**

Based on validated thresholds for CBF, OEF, CMRO\(_2\), or FMZ uptake\(^1,4\), PET classifies the abnormal brain tissue into four subtypes: (i) the core (defined as the irreversibly damaged tissue already present at time of imaging); (ii) the penumbra (defined as that severely hypoperfused tissue at risk of, but that can still be saved from, infarction); (iii) the oligaemia (defined as mildly hypoperfused and not at-risk of infarction under normal circumstances); and (iv) the hyperperfused tissue (defined as that tissue with CBF higher than that in the contralateral homologous tissue, and taken to represent effective reperfusion).

Consistent with its end-artery vascular system, the striato-capsular area exhibits irreversible damage very early in many patients with MCA stem occlusion. This contrasts with the cortical mantle, which
demonstrates penumbra. In some patients, however, the core may widely extend into cortical areas as early as 4–6 h after stroke onset, probably resulting from inadequate pial collaterals and/or proximal carotid occlusion. The volume of core correlates with both the severity of admission neurological deficit and the final infarct volume, as assessed by structural imaging in the chronic stage. Mapping the ischaemic core in the acute stage of stroke, therefore, helps predict final infarct volume.

Both the incidence and the extent of penumbra tend to decrease with elapsing time since stroke onset. Substantial cortical penumbra has been reported in 90% of patients studied within 6 h from onset, in over 50% of the patients studied within 9 h, and in about one-third of patients studied between 5–18 h, suggesting that closure of the therapeutic window of opportunity may be delayed in a subset of patients. In one study, up to 52% (average, 32%) of the ultimately infarcted tissue still exhibited penumbra as late as 16 h after symptom onset.

The penumbra can progress to or escape from infarction in part or in all, depending on subsequent events such as reperfusion – either spontaneous or therapeutic. Survival of the penumbra is the most important determinant of recovery after ischaemic stroke. The volume of penumbral tissue that eventually escapes infarction, either spontaneously or after successful thrombolysis, has high correlation with the extent of spontaneous neurological recovery. Thus, saving the penumbra has definite and predictable benefit on subsequent neurological recovery in man. Interestingly, the best correlation in the data of Furlan et al was observed with 2-month recovery scores, suggesting that survival of the penumbra influences not only early, but also late, recovery (i.e., it provides an opportunity for subsequent peri-infarct neuronal re-organization).

By definition, the oligemic tissue is hypoperfused but, in principle, not at risk of infarction. It displays a mild degree of misery perfusion (reduced CBF with high OEF), but its perfusion stands above the penumbra threshold. Furlan et al documented that while in some patients the high OEF area was largely penumbral, in others it was virtually entirely oligemic. Because it has lost its autoregulation, the oligemic compartment, though not at risk of infarction in uncomplicated circumstances, may become incorporated in the penumbra, and hence potentially into the core, as a result of secondary events that tend to reduce the local cerebral perfusion pressure (CPP) such as vasogenic oedema and systemic hypotension. It is also possible that cells in the oligemic tissue are sensitive to systemic factors that aggravate the flow-to-metabolism mismatch, such as hyperglycaemia and pyrexia. These considerations are important because they explain the benefits from avoiding secondary events and maintaining systemic blood pressure in the early days after stroke.

Spontaneous hyperperfusion has been observed in about one-third of the cases studied 5–18 h after stroke. It is associated with reduced OEF
and increased CBV, indicating luxury perfusion with abnormal vasodilatation. In most instances, the hyperperfused tissue exhibits normal or mildly increased CMRO₂ and integrity at late structural imaging. This pattern suggests that re-canalization spontaneously occurred prior to PET and resulted in efficient reperfusion of the penumbra, consistent with the well-established experimental notion that infarct size is reduced by early re-canalization. Thus, the experimental concept according to which sudden tissue re-oxygenation might exacerbate ischaemic brain damage (so-called ‘reperfusion injury’) may not apply to man. However, hyperperfusion developing after therapeutic thrombolysis occasionally heralds poor tissue outcome. One interpretation of this discrepancy with spontaneous re-canalization is that thrombolysis may force reperfusion into an already irreversibly damaged vascular tree.

Pathophysiological heterogeneity and clinical correlates

In patients investigated in the 5–18 h post-stroke interval, the relationships between acute-stage PET findings and clinical outcome were prospectively assessed⁵. There was considerable pathophysiological heterogeneity, largely unpredictable from neurological status. The sample could be classified into one of three patterns, one-third in each pattern, namely: (i) extensive subcortico-cortical core (pattern 1); (ii) presence of penumbra without extensive core (pattern 2); and (iii) hyperperfusion without extensive core (pattern 3). There was a highly significant relationship between these patterns and subsequent neurological course. Thus, all pattern 1 patients did poorly (malignant infarction with early death or poor outcome), whereas all patients classified as pattern 3 did well (complete or nearly complete recovery in all). Consistent with the penumbra concept, pattern 2 patients had an unpredictable course, ranging from death to full recovery. Importantly, the PET patterns had significant independent predictive value for recovery over and above that of clinical scores alone.

Overall, SPECT with [⁹⁹mTc]-HMPAO and [⁹⁹mTc]-ECD in acute stroke has yielded findings consistent with PET, although with substantially lower accuracy due to lower spatial resolution, uncertain interpretation in terms of perfusion, and at best indirect metabolic information⁹.

Findings with DWI and PWI

**DWI lesion**

Already within minutes after onset of stroke (or transient ischaemic attack), some patients exhibit DWI hypersignal. DWI detects nearly 100% of ischaemic strokes regardless of size and location, making it the
most sensitive technique of all\textsuperscript{10}, although other acute conditions such as seizure or encephalitis can exhibit a DWI lesion. DWI also detects multiple small strokes, pointing to a proximal source of emboli, and discriminate acute extension of previous infarcts. DWI combined with PWI and MRA of neck and intracranial vessels permits precise diagnosis of stroke mechanism, such as carotid or MCA occlusion, dissection, distal branch occlusion, perforator stroke, and small vessel disease.

The DWI–PWI ‘mismatch’

PWI maps haemodynamic disturbances, which together with DWI provides important pathophysiological information. A mismatch between hypoperfusion extending over the entire MCA territory but DWI lesion restricted to, for example, the striatocapsular/insular area is found in up to 70\% of patients with acute (\(< 6\) h) MCA territory stroke\textsuperscript{10}. Presence of aphasia or neglect in patients with subcortical DWI lesion is associated with hypoperfusion affecting the cortex. In reference to earlier PET data, the ischaemic penumbra has been operationally defined as tissue with normal diffusion but reduced perfusion, around the core of diffusion abnormality. One source of confusion, however, stems from the fact that the ‘hypoperfused area’ as seen by PWI is variably defined (\textit{e.g.} prolonged MTT or time-to-peak, reduced CBV or reduced CBF), yet only the latter would reflect true hypoperfusion. Basic physiology predicates that MTT and CBV will increase in regions where perfusion pressure is decreased but CBF is maintained (\textit{i.e.} normally autoregulated), but CBV will tend to decline with severe ischaemia. Thus, neither MTT nor CBV abnormalities reliably reflect the extent of hypoperfusion. Even the latter does not equate with penumbra as it also comprises the oligaemic area. Accordingly, studies that have attempted to define a penumbra threshold based on PWI maps have provided conflicting results, although a delay of the MTT between 4–6 s relative to the unaffected side may represent tissue at-risk of infarction (\textit{i.e.} penumbra).

The volume of DWI abnormality correlates with both admission and outcome neurological deficit as well as with final infarct volume, which would suggest that the DWI lesion equates with irreversible damage. Accordingly, several studies suggest there may be a threshold of ADC below which tissue is irreversibly infarcted\textsuperscript{11}. However, consistent with animal studies, the initial DWI lesion contains not only infarcted but also penumbral tissue, and reversal of DWI hyperintensity following spontaneous or thrombolysis-induced re-canalization has now been clearly documented\textsuperscript{12,13}. In addition, there is heterogeneity of ADC values within the ischaemic area, with the lesion rim having only marginally reduced values, which may represent penumbral tissue. Confounding
factors in the interpretation of DWI changes include timing of scans post symptom onset, and patient population studied, i.e. either all the hemispheric stroke patients imaged or only those that show a perfusion/diffusion mismatch. Overall, therefore, DWI–PWI does not allow unequivocal and direct visualization of the penumbra and the core.

Consistent with earlier PET studies, perfusion changes precede the development of DWI lesions and, in the absence of reperfusion, the area of restricted diffusion spontaneously progresses within the region of perfusion abnormality, although some areas of decreased perfusion can remain free of DWI signal change. Conversely, spontaneous or therapeutic re-canalization tends to arrest this process\(^\text{14}\). Consistent with PET findings, Beaulieu et al\(^\text{15}\) showed that, despite the increase in DWI lesion volume during the initial week, the neurological deficit improved in all patients who displayed reduction of volume of perfusion deficit; in other words, the hypoperfused area included functionally impaired but still viable tissue (i.e. penumbra). In approximately 50% of patients, the acute DWI lesion was smaller than the final infarct volume. In some patients, lesions enlarged beyond 24 h, suggesting that penumbra extended beyond the hyperacute phase.

By mapping the growth of the DWI abnormality into the contours of the final infarct, it is possible to identify retrospectively that part of the penumbra that progresses to pan-necrosis. Studies that attempted to define thresholds of either diffusion or perfusion to predict infarct growth have differed in their techniques and data analysis methods. Overall, it appears at present that a single physiological threshold cannot predict with certainty infarct growth – if this is possible at all – but that a combination of both diffusion and perfusion values\(^\text{16}\) with a clinical assessment may be more accurate\(^\text{17}\).

Plate V (see end of file p.*158) illustrates some of the concepts discussed above in an acute ischaemic stroke PET and MR study.

**DWI–PWI patterns**

As with PET, about 30% of acute MCA patients do not exhibit ‘mismatch’, but rather either a more or less extensive area of matched DWI abnormality and PWI hypoperfusion, suggesting completed infarction, or a DWI lesion with PWI being unremarkable or showing hyperperfusion, suggesting early spontaneous recanalization. Less than 5% of patients exhibit no significant abnormality (DWI nor PWI), possibly reflecting transient ischaemia, or a non-ischaemic process (e.g. migraine).

**Implications for patient management**

Demonstration of high OEF or ‘mismatch’ in the setting of acute stroke implies that arterial occlusion is still present and that the autoregulation
of CBF is superseded in the affected territory. Thus, any lowering of the systemic arterial pressure (SAP) is likely to reduce further the CBF in the affected tissue, which can be harmful not only for the penumbra – which may precipitate into necrosis – but also for the oligaemia – which may become penumbral and thus, in turn, at risk. Accordingly, reductions in SAP in acute stroke have frequently been associated with worse outcome. This issue is especially important in view of the frequent occurrence of reactive hypertension in this setting. Conversely, treating excessive arterial hypertension would not pose substantial risk if hyperperfusion with low OEF were observed.

Fig. 1 Possible reference framework for the management of acute stroke.

Acute focal neurological deficit within 6 h of symptom onset

T2* GRE/susceptibility-weighted MRI (or CT)

No evidence of acute haemorrhage

Acute haemorrhage

DWI / PWI / MRA

No thrombolysis BP monitoring

Consider clot removal if bleeding continues

PWI lesion > DWI lesion

If DWI lesion is small, dismiss thrombolysis If extensive DWI lesion, treat vasogenic oedema and consider brain decompression.

MCA branch occlusion (or normal MRA)

Consider i.v. thrombolysis and/or neuroprotection

Distal ICA or proximal MCA occlusion

Consider i.a. thrombolysis (in addition to or instead of i.v.) especially if 3–6 h from symptom onset, and/or neuroprotection

Acute focal neurological deficit within 6 h of symptom onset

T2* GRE/susceptibility-weighted MRI (or CT)

No evidence of acute haemorrhage

Acute haemorrhage

DWI / PWI / MRA

No thrombolysis BP monitoring

Consider clot removal if bleeding continues

PWI lesion > DWI lesion

If DWI lesion is small, dismiss thrombolysis If extensive DWI lesion, treat vasogenic oedema and consider brain decompression.

MCA branch occlusion (or normal MRA)

Consider i.v. thrombolysis and/or neuroprotection

Distal ICA or proximal MCA occlusion

Consider i.a. thrombolysis (in addition to or instead of i.v.) especially if 3–6 h from symptom onset, and/or neuroprotection

British Medical Bulletin 2003;65

153
Pathophysiological heterogeneity suggests that, in acute stroke, blind inclusion of patients into trials may blur any beneficial effects of the agent being tested. Thus, physiological imaging should be used to depict each patient’s pathophysiology before aggressive therapy is considered. The framework in Figure 1 might be considered.

**Remote metabolic effects of stroke**

Coupled reductions in resting-state perfusion and metabolism in brain structures remote from, but connected with, the area damaged by the stroke, is commonly observed with techniques such as PET and SPECT\textsuperscript{18}. Spectacular examples of structures so affected are the cerebellum contralateral to MCA stroke, and the cerebral cortex overlying deep-seated (e.g. thalamic) infarction or haemorrhage\textsuperscript{19}, but the cortex contralateral to stroke can also be affected to some degree. Thus, mapping of these remote effects allows identifying disrupted networks from focal damage. Often referred to collectively as ‘diaschisis’, the remote metabolic effects represent depressed synaptic activity as a result of disconnection (either direct or transneural), and are the single imaging expression of various cellular derangements, from reversible hypofunction to evolving Wallerian or trans-synaptic degeneration. Importantly, some of them reflect purely functional, potentially recoupable synaptic derangement, which may participate in both the acute clinical expression of stroke\textsuperscript{20} and subsequent recovery\textsuperscript{21}.

Following subcortical stroke, ipsilateral cortical metabolic depression tends to recede over the ensuing months, in parallel with recovery of language or hemineglect, suggesting some process of synaptic reorganization takes place within the de-afferented cortex. Although language recovery within the first year appears to be linked primarily to metabolic recovery in the dominant hemisphere, long-term language improvements seem to be related to slow metabolic recovery in the contralateral hemisphere, specifically in the homotopic frontal and thalamic areas\textsuperscript{22}. Taken together, the available evidence suggests that recovery of cortical metabolism, both ipsilateral and contralateral, partly subtends functional recovery after stroke and is one expression of neuronal re-organisation after network damage.

**Cortical map changes and network re-organisation**

Functional imaging with PET and fMRI during execution of behavioural tasks has provided important new information about re-organisation of cortical maps and neural networks after stroke, and its relationships
Taking recovery of hand motor function as a model, several robust findings have emerged. Firstly, there occurs a displacement of ipsilesional primary motor cortex (M1) activation focus, in the caudal and posterior direction after subcortical stroke, and towards the infarct rim in cortical stroke\(^23,24\). Displacement of cortical representations may reflect the ‘unmasking’ or disinhibition by the lesion of pre-existing but normally inactive connections (intrinsic redundancy), or ‘recruitment’ of neurons/connections not normally devoted to this function (i.e. vicariance), representing plasticity in the adult human brain. However, there is no data to indicate, as yet, that such displacements are beneficial to recovery of function.

A second major finding is bilateralisation of M1 activation, and increased activation in the primary and secondary motor areas, as well as in some non-motor areas\(^25\). The significance of recruitment of the unaffected primary motor cortex is still a matter of debate. Although some relationship with mirror movements is apparent across patients, this clearly is not a one-to-one relationship. It may also represent recruitment of the direct (uncrossed) cortico-spinal tract to compensate for damage of the ipsilesional (crossed) cortico-spinal tract. Execution of even simple movements after a stroke may require bilateral recruitment of the motor network, known to engage with difficult tasks only in healthy subjects. Excessive recruitment of the cortical fields would allow the stroked brain to perform the task despite established cortico-spinal tract damage. Finally, recruitment of areas normally not engaged in the execution of simple movement, such as the prefrontal, posterior parietal and anterior cingulate, might reflect the bringing into play of compensatory cognitive strategies (e.g. visuo-spatial), in order to carry out the task\(^25\).

Longitudinal studies while the patient recovers are difficult, but necessary to assess the brain correlates of measured recovery of function. These studies have shown that the altered patterns of activation are not static over time, but dynamically change even to achieve the same motor performance (Plate VI see end of file p. 159). During recovery following subcortical stroke, there may occur a change in balance of activation between the affected and unaffected hemisphere, and a decrease in total amount of activated voxels in both hemispheres. Preliminary correlations with motor performance show that recovery is worse when activation becomes predominant over the non-affected side M1 with elapsing time\(^26\), in agreement with descriptive studies in aphasia\(^22\). This observation would be consistent with TMS studies in adult stroke showing that stimulation of contralesional M1 is inefficient. Although early on contralesional activation may be useful, its relative contribution appears to decline as recovery proceeds. Conversely, recovery would be optimal when the primary motor cortex not only is
preserved structurally (i.e. de-afferented rather than destroyed), but also is capable of enhanced workload and thus not completely disconnected. In the case of cortical stroke, that the peri-infarct area may be crucial for early recovery would be consistent with the PET findings described above regarding the fate of the penumbra.

These findings have important implications for therapy. They indeed suggest that enhancing the use and activity of M1 (or of what is left of it in case of partial M1 infarct), and more generally of the cortex normally in charge of the impaired function (e.g. the left temporal cortex in aphasia) should result in improved recovery. Accordingly, two recent reports document enhancement of contralateral SM1 activation by active re-habilitation and fluoxetine, two interventions that are thought to improve motor recovery27,28.

New avenues

Major gaps in our knowledge of the mechanisms underlying early deterioration after, and recovery from, stroke still remain, especially regarding the relationships among the saved penumbra, diaschisis and re-organization of cortical maps. Important questions that might be addressed by imaging are whether the surviving penumbra is affected by selective neuronal loss and the role of the latter in the process of recovery, and what is the role of peri-infarct inflammation in the scarring process. Important new methodological developments may soon allow unprecedented approach to acute stroke, such as the non-invasive mapping of OEF and CMRO₂ with MR, new derivatives of F-MISO for improved mapping of brain hypoxia, and PET ligands of apoptosis and inflammation. Regarding the study of brain plasticity and its role in long-term recovery, precise mapping of the chronic lesion and subsequent fibre degeneration with voxel-based morphometry and DTI, respectively, together with combined fMRI, TMS and EEG coherence studies, should allow major breakthroughs, especially in the context of re-habilitation and pharmacological interventions.

References

18 Feeney DM, Baron J-C. Diaschisis. Stroke 1986; 17: 817–30
Plate V  Magnetic resonance and PET study in the same acute ischaemic stroke patient. A 51-year-old previously well gentleman with no vascular risk factors presents with an expressive and receptive dysphasia, right hemiparesis (face, arm and leg), right homonymous hemianopia and right sided neglect, i.e. a total anterior circulation syndrome (TACS). Investigations revealed a left carotid artery dissection. Top row of images are from a ‘triple O2’ PET scan carried out 9 h after symptom onset. Bottom row are from a diffusion and perfusion MR study carried out 7 h after symptom onset on the same patient. Some patchy MR defined perfusion–diffusion mismatch is present. The MR perfusion parameter defined here is mean transit time which, as noted, may not represent true physiological perfusion. Within the PET-derived true perfusion deficit, there is reduced CMRO₂ with increased areas of OEF indicating potentially viable tissue at 9 h. CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate of oxygen consumption; OEF, oxygen extraction fraction; DTI, diffusion tensor imaging; ADC, apparent diffusion coefficient; MTT, mean transit time.
Plate VI  Group analysis of PET activations in the primary and secondary motor areas in controls and patients with left capsular stroke at PET1 (2 months) and PET2 (8 months), during the execution of a right auditory-cued thumb to index finger tapping. The significant voxels (P < 0.05, corrected) are projected onto a rendering surface of a standard MRI template. The neurological convention is used. The data illustrate the dynamic changes of activations in both extent and spatial distribution from PET1 to PET2 in patients and at one time-point in controls. Briefly, activation mainly concerned in controls the contralateral hemisphere primary motor cortex (M1) but also the bilateral cingulate cortex and cerebellum. In contrast, in patients the activation of M1 was bilateral though strongly in favour of the left hemisphere at PET1 and still bilateral but more balanced between the two hemispheres at PET2. Note at PET1 the left M1 activation covers a more extensive area (and was of greater amplitude – not obviously visible on these images) than in controls.