Motor recovery after acute ischaemic stroke: a metabolic study

V Di Piero, F M Chollet, P MacCarthy, G L Lenzi, R S J Frackowiak

Abstract

The metabolic changes occurring after ischaemic stroke were measured to investigate the functional anatomy of clinical motor recovery. Positron emission tomography (PET) and the steady-state 15O technique was used to compare resting relative metabolic distributions at the onset of functional deficit with those following recovery. Ten patients were studied with repeat scans. Motor recovery was associated in some patients with an increase of relative oxygen metabolism in anatomical structures normally involved in motor function in the affected hemisphere, particularly in the cortical motor areas. In those patients without such metabolic changes in the cortex of the diseased hemisphere, relative increases in cortical metabolism in the contralateral hemisphere were associated with better motor recovery than in patients with no relative cortical metabolic increase in either hemisphere. There was no correlation between the degree of improvement in motor function and the severity of motor deficit at onset, the size and site of the lesion and the metabolic changes in the infarcted zone. No particular pattern of global metabolic changes was observed after recovery. Thus different relative patterns of metabolic recovery were seen in patients with different lesions and evidence was found for the participation of contralateral structures in the recovery process in some patients.

Materials and methods

We studied 5 male and 5 female patients, mean (SD) age 54.3 (8.7) years, presenting with motor dysfunction due to acute ischaemic infarction in a cerebral hemisphere. Comatose patients or those suffering from other neurological conditions were excluded. The study had the approval of the Hammersmith Hospital ethics committee and the Administration of Radioactive Substances Advisory Committee of the Department of Health, UK. Written informed consent was obtained in each case from the patient or the nearest relative. All but one patient (case 8—table 1) had no history of cerebrovascular disease. Clinical evaluation included a full neurological examination, an assessment of motor function using the motricity index (MI) of Demeurisse et al,12 of general function using the Barthel scale,13 a Mini Mental State test14 and a formal neuropsychological evaluation. The MI is a published scale based upon the MRC grading of muscle strength, especially designed to evaluate "patients' progress in motor recovery ... and correlations with other clinical data".12 The scale reflects motor performance using three movements in each limb with appropriate weighting to give a 0–100 scale, with 100 representing normality. Scores from 0 to 32
indicate a severe plegia, from 33–64 a moderate paresis and 65–99 mild disability. Improvement in motor function was assessed by the raw score increment obtained at follow up examination relative to the initial assessment during the acute phase of the illness. Ratings were performed by one assessor throughout to obviate added variance resulting from interrater variability.

All patients had CT or MRI scanning on admission and, if necessary, this was repeated following recovery. Delayed CT or MRI scans were used to delineate the extent of the infarction. All images were reoriented so that the transverse slices lay parallel to the intercommisural plane. All the patients received standard medical treatment for their stroke—patients 4, 5, 7, 8 and 10 received anti-hypertensive medication, none received Ca channel blockers, anticonvulsants, sedatives or anti-psychotics. Clinical data are summarised in table 1.

**PET studies**

PET was performed at a mean (SD) 4·9 (4·6) days from symptom onset and was repeated in the chronic phase [95·1 (48·7) days], following appreciable recovery of function. The 15O inhalation method was used to measure cerebral blood flow (CBF), cerebral blood volume (CBV) and oxygen extraction (OER), from which the rate of oxygen consumption (CMRO2) was calculated.14-16 Studies were carried out with an ECAT 931/8/12 (CTI, Knoxville) and performed at rest, in a quiet and dimly lit room with the patients’ eyes closed and ears unplugged. During each study, head position was maintained by an individually moulded thermoplastic head holder. A short 21 g arterial line was placed into the radial artery at the onset of each study. The intrinsic spatial resolution of the scanner was 5·5 × 5·5 × 7·0 mm full-width at half maximum (FWHM), allowing the simultaneous collection of 15 contiguous transaxial planes.17 Reconstruction, attenuation correction (by measurement) and filtering resulted in images with a resolution of 8·5 × 8·5 × 7·0 mm (FWHM). The set of data was then expanded by linear interpolation in the axial dimension to produce 43 transaxial slices with near cubic voxels of 2·05 × 2·05 × 2·5 mm allowing three dimensional inspection of scans visually. The scans were analysed on a computer (SUN 3/60) with image analysis software (ANALYZE, BRU, Mayo Clinic), which allowed them to be displayed relative to the intercommissural line (AC-PC line) and to be scaled for precise anatomical localisation by standard stereotactic coordinates based on the Talairach atlas.18-19 The procedure of reorienting PET scans was developed for normal studies but has been used successfully in studies of patients with cerebral infarcts.

**Data analysis**

In the acute phase of stroke a mismatch may occur between CMRO2 and CBF which manifests as a change in OER.7 For this reason, we analysed CMRO2 data which give a more direct reflection of tissue metabolism than CBF. Variability in the absolute levels of global CMRO2 between patients and between successive measurements in individuals averaged 9·4 (4·8)%). Such variability was present in both the lesioned and unlesioned hemispheres and is in accordance with previous data.20-22 Even such small interscan variability may mask

<table>
<thead>
<tr>
<th>N</th>
<th>Age</th>
<th>Sex</th>
<th>Days from stroke onset</th>
<th>Clinical presentation</th>
<th>GT or MRI scan lesion</th>
<th>Time interval to second scan</th>
<th>Residual deficit</th>
<th>Mortlicity Index</th>
<th>Other clinical data</th>
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<td>Minor difficulties</td>
<td>88, 100</td>
<td>Doppler normal previous myocardial infarct</td>
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<td>Increased tone and hypoaesthesia</td>
<td>92, 100</td>
<td>High blood pressure doppler I int carotid stenosis</td>
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<td>53</td>
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<td>Internal capsule</td>
<td>1 121</td>
<td>Mild weakness I finger abduction</td>
<td>71, 100</td>
<td>Angina</td>
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<td>58</td>
<td>f</td>
<td>5</td>
<td>1 arm paresis</td>
<td>Internal capsule and thalamus (MRI)</td>
<td>1 60</td>
<td>Increased tone and paresesia</td>
<td>72, 86</td>
<td>High blood pressure</td>
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<td>White matter lesions (MRI)</td>
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<td>Emparegesis</td>
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<td>Angio: occ I supramarginal lusus anticoagulant</td>
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<td>53</td>
<td>m</td>
<td>7</td>
<td>1 Hemi paresis</td>
<td>Anterior white matter</td>
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<td>1 Hemi paresis</td>
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<td>1 63</td>
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<td>87, 100</td>
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<td>86, 100</td>
<td>High blood pressure</td>
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<tr>
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<td>52</td>
<td>m</td>
<td>3</td>
<td>1 Hypothesis paresis</td>
<td>Fronto-temporo-parietal</td>
<td>1 55</td>
<td>Mild hemiparesis</td>
<td>44, 90</td>
<td>High blood pressure</td>
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</tbody>
</table>

**Table 1 Clinical presentation**
significant regional (r)CMRO₂ changes. To circumvent this problem, and because we were primarily interested in variations in the regional profile of metabolism between the acute and recovered phases, we normalised the rCMRO₂ data of the second scan of each patient to the average CMRO₂ of the patient's first scan. Three features were analysed in the PET scans: 1) relative rCMRO₂ changes in the anatomical area of the ischaemic lesion; 2) global CMRO₂ changes occurring between the first and second scans in the group of patients; 3) relative rCMRO₂ changes in individual patients.

1) Changes in the area of the lesion: To study the variations occurring in the area of the lesion, each pair of studies was aligned parallel to the AC–PC line.¹⁸ Irregular regions of interest (ROI) were drawn interactively, using the anatomical boundaries of the lesion shown on the similarly reoriented CT or MRI scan, onto the PET scan planes. The same ROIs were then automatically placed on the homologous slices of the follow up study. The average of the rCMRO₂ value for the whole lesion so defined was compared with the average normalised rCMRO₂ from the same region on the second scan for each patient.

2) Changes as a group: We used a descriptive and exploratory statistical approach to look for any general metabolic pattern associated with motor recovery. All the studies, irrespective of the site of the lesion were considered. The scans were flipped about the midsagittal plane such that all the ischaemic lesions were analysed as though left sided. All the scans were also resized by linear scaling into standardised brain dimensions. Data were smoothed by a square low-pass filter of size 9 pixels to improve the signal to noise and reduce variance due to differences in gyral anatomy between individuals. The presence of significant relative increases in rCMRO₂ was assessed by constructing average pixel-by-pixel maps of the normalised rCMRO₂ and associated variances for the first and the second scans and then comparing them by a t test. In this way, areas of significant change were shown as an image of r values thresholded for descriptive purposes at two levels: p < 0.01 and p < 0.001. The anatomical localisation of significantly changed areas was performed by simple cross reference to coordinates in the stereotaxic atlas of Talairach and Tournoux.¹⁹

3) Individual changes: To assess individual changes in relative rCMRO₂ we considered each pair of studies matched anatomically by reference to the AC–PC line. Scans were smoothed, again to increase signal to noise, though less severely because of the absence of interindividual anatomical variation. Subtraction images were generated by taking the CMRO₂ values of the first scan from the second, pixel-by-pixel. Only regions with increases spread over 4 contiguous pixels and anatomically associated with the motor system were considered further, that is, the primary motorsensory area, the premotor area, the supplementary motor area, the basal ganglia and the thalamus. Increases in normalised rCMRO₂ were quantified and expressed as percentage changes. The localisation of areas with an rCMRO₂ increase was performed as above. Data from the cerebellar regions were not available from all patients and therefore are not analysed further in this paper.

In an attempt to describe with one variable both the extent and magnitude of relative rCMRO₂ changes, we defined an index (oxygen metabolism index: OMI) from the product of the per cent normalised rCMRO₂ increase in the region (calculated as the ratio of the average rCMRO₂ between the second and the first scans) and the size of the contiguous area over which change was demonstrated (in pixels).

**Statistical analysis**
Changes in rCMRO₂ and OMI values and clinical scores were analysed by intergroup comparisons using Student's t test for paired and unpaired observations, linear regressions and Spearman rank correlations. Bonferroni corrections were used to adjust the threshold of significance for multiple comparisons.

**Results**
At the second examination, all patients demonstrated some recovery of motor function. The mean (SD) index of motor recovery (RI = MI at follow up — MI at entry), was 22 (15) (+33%), ranging from +5 to +46. The MI at entry was positively correlated to the MI at follow up (r = 0.91; p < 0.0001), but there was no correlation between the RI and both the MI at entry or at follow up scanning. Three patients (1, 6 and 10) had large cortical lesions on CT or MRI, while the remaining seven had small infarcts with a maximum diameter less than 2·5 cm. There were no statistically significant differences between the MI at entry or follow up, or of the RI between patients with small and large lesions.

In the lesion, a relative rCMRO₂ increase was observed in all but three patients (1, 4 and 5). On average, the rCMRO₂ increase was 9 (17%). There was no correlation between the rCMRO₂ changes at the site of lesion and the RI (fig 1). Statistical analysis failed to reveal a single pattern of rCMRO₂ change for the

![Figure 1](http://jnnp.bmj.com/) Variations of CMRO₂ in the area of the anatomical lesion, as a ratio between the second and the first scan (abscissa) and the degree of improvement in motor function (RI).
Motor recovery after acute ischaemic stroke: a metabolic study

Table 2 Image subtraction analysis: CMRO₂ changes after motor recovery evaluated as increases in the oxygen metabolism index (OMI) in cerebral regions normally associated with the generation of movements

<table>
<thead>
<tr>
<th>Case number</th>
<th>CT or MRI scan</th>
<th>RI</th>
<th>Affected hemisphere regions</th>
<th>I/II</th>
<th>n* pixels</th>
<th>OMI</th>
<th>Unaffected hemisphere regions</th>
<th>I/II</th>
<th>n* pixels</th>
<th>OMI</th>
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<tbody>
<tr>
<td>1</td>
<td>r Fronto-temporo-parietal</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>supplementary motor area</td>
<td>1/35</td>
<td>33</td>
<td>44-55</td>
</tr>
<tr>
<td>2</td>
<td>r Internal capsule</td>
<td>8</td>
<td>basal ganglia</td>
<td>1/63</td>
<td>20</td>
<td>32-56</td>
<td>—</td>
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</tr>
<tr>
<td>3</td>
<td>r Internal capsule</td>
<td>29</td>
<td>l motorosensory area</td>
<td>1/28</td>
<td>80</td>
<td>102-40</td>
<td>l motorosensory area</td>
<td>1/25</td>
<td>16</td>
<td>20-00</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>supplementary motor area</td>
<td>1/16</td>
<td>16</td>
<td>18-56</td>
<td>supplementary motor area</td>
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<td>16</td>
<td>18-88</td>
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<td>basal ganglia</td>
<td>1/26</td>
<td>16</td>
<td>17-26</td>
<td>premotor area</td>
<td>1/38</td>
<td>32</td>
<td>44-16</td>
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<tr>
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<td></td>
<td></td>
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<td>1/37</td>
<td>16</td>
<td>21-92</td>
<td>thalamus</td>
<td>1/62</td>
<td>32</td>
<td>51-84</td>
</tr>
<tr>
<td>4</td>
<td>r Internal capsule and thalamus (MRI)</td>
<td>14</td>
<td>—</td>
<td>—</td>
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<tr>
<td>5</td>
<td>l corona radiata</td>
<td>35</td>
<td>l motorosensory area</td>
<td>1/23</td>
<td>16</td>
<td>19-68</td>
<td>l motorosensory area</td>
<td>1/26</td>
<td>32</td>
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<tr>
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<td>r white matter “lucencies” (MRI)</td>
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<tr>
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<td>l fronto-parietal</td>
<td>45</td>
<td>supplementary motor area</td>
<td>1/75</td>
<td>112</td>
<td>195-84</td>
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<td>16</td>
<td>19-36</td>
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<td>—</td>
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</tr>
<tr>
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<td>1/31</td>
<td>64</td>
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A correlation was found between the RI and the OMI in cerebral regions associated with motor control, which was observed in the affected hemisphere (RI = 0.75; p < 0.01) (fig 2). No correlation was found between motor recovery and metabolic increases in the unaffected hemisphere or in the motor areas of both sides of the brain pooled. There was no significant difference in the OMI between the two cerebral hemispheres.

We also analysed the different individual patterns of rCMRO₂ change (table 3). In the cortex one patient showed an increase in the

The results of individual analyses of changes in motor associated areas are reported in table 2. The magnitude and extent of metabolic improvement did not correlate with MI scores at entry or at follow up. The change in OMI did not differ between patients with large and small ischaemic lesions in either the affected or unaffected cerebral hemispheres, neither regionally nor globally.

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We also analysed the different individual patterns of rCMRO₂ change (table 3). In the cortex one patient showed an increase in the

Figure 2 Correlation between the increase in the oxygen metabolism index (OMI) in motor areas of the affected cerebral hemisphere and the degree of improvement of motor function (RI).
Table 3  CMRO₂ changes in the brain after motor recovery expressed as increases in the oxygen metabolism index (OMI). The subcortical structures included the basal ganglia and thalamus.

<table>
<thead>
<tr>
<th>Case number</th>
<th>Global Affected hemisphere</th>
<th>Global Unaffected hemisphere</th>
<th>Cortical Affected hemisphere</th>
<th>Cortical Unaffected hemisphere</th>
<th>Sub-cortical Affected hemisphere</th>
<th>Sub-cortical Unaffected hemisphere</th>
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Discussion

Restoration of function is a complex phenomenon that depends on various factors such as the nature of the affected function, the location and extent of the lesion, residual neuronal viability in damaged brain structures and the capability of other anatomical structures to assume the functions of damaged regions. We did not observe a unique pattern of relative metabolic changes at rest that were related to motor recovery in our group of patients or in subgroups based on the size of the ischaemic lesions. This is not surprising because of heterogeneity in the patient population which represents one of the main problems in the investigation of stroke patients in general. To partially circumvent this, we focused our analysis on the motor deficit and the relative metabolic changes in brain areas primarily involved in motor function. We were aided in interpreting the metabolic changes by the absence of correlation between the extent of motor recovery (RI) and the severity of initial motor dysfunction in our patients. This allowed use of the RI as an index of motor recovery, whatever the initial clinical presentation. Likewise, motor recovery was not related to any relative metabolic changes at the site of the lesion. Similar results were obtained by Hakim et al.²¹ who reported rCMRO₂ changes occurring in the core of the ischaemic lesion and in the "penumbra" area, in a randomised study of the effects of nimodipine in patients with acute stroke. Despite different patterns of metabolic changes in these two areas (+24.4% and +18.8% in the treated group and in −17.1% and −12.4% in the untreated one), the authors did not observe any differences in outcome between the two groups. Our study and that of Hakim et al scanned patients relatively acutely, but at a stage when low OER indicated that ischaemic infarction had already occurred. It is therefore not surprising that we found no significant correlation between functional recovery and relative metabolic changes in the infarct itself.

We have, however, observed a correlation between motor recovery and the mean relative increase of metabolism in cerebral regions involved in motor function in the affected hemisphere and in particular in the cortex. Thus our data suggest that the degree of relative metabolic improvement in intact areas functionally connected to the site of ischaemic damage may be correlated with the magnitude of clinical improvement. The occurrence of functional changes in the nervous system at sites remote from the primary lesion has been named diaschisis.²² Feeney and Baron²³ reviewed the occurrence of diaschisis with various brain lesions and discussed its contribution to the clinical deficit. Evidence suggests a correlation between reversal of remote effects and recovery. After selective cortical ablations Dauth et al.²⁴ and Deuel²⁵ observed hypometabolism in a number of cortical and subcortical areas undamaged by lesions and subsequent regression with recovery. Many authors²⁶⁻²⁸ have described clinical recovery and concurrent increases of cortical metabolism or blood flow in patients with subcortical lesions. Finally, in acute stroke, Kushner et al.²⁹ have shown that the degree of glucose hypometabolism in the infarct and the surrounding, structurally intact cortex (as judged by structural imaging) is inversely related to the extent of eventual recovery.

Our results also suggest that in some cases there may be a role for the unaffected hemisphere in the recovery process. Generally we observed similar relative metabolic increases in the cerebral hemispheres between the first and the second scans, but patients without an increase in the lesioned, but an increment in the unaffected hemisphere seemed to recover more than patients without cortical metabolic changes in either. There is clinical and experimental evidence to suggest a role for the ipsilateral hemisphere in recovery and there are also dramatic clinical reports of functional recovery following hemispherectomy.³⁰⁻³³ Other investigators have demonstrated deficits in fine motor control and speed of execution of hand movements on the side ipsilateral to cortical lesions.³⁴⁻³⁷

A direct ipsilateral corticospinal projection has been suggested by experimental studies with unilateral spinal cord or cerebral peduncular lesions.³⁸ This phenomenon is evident.
Motor recovery after acute ischaemic stroke: a metabolic study

only after a lesion because the ipsilateral pathways are probably suppressed when the crossed contralateral system is intact. The role of cross-talk between the hemispheres may be a crucial component of this mechanism. Crowne et al. found that monkeys which recovered from acute neglect after frontal eye field lesions redeveloped neglect after callosal section. Watson et al. demonstrated that neglect after unilateral frontal lesions was more severe in monkeys who had previously undergone callosal section. Steiner and Mamelé observed that ipsilateral eye deviation from unilateral hemispheric stroke usually persists for a few days, but may persist for weeks if there has been previous damage to the other hemisphere.

Further evidence for the role of ipsilateral structures in the recovery of function comes from the work of Yamaguchi et al. who showed a focal rCBF increase in the right hemisphere in a region homologous to Broca's area during verbalisation following recovery from aphasia. Levine et al. showed that the rate and extent of improvement from left spatial neglect in patients was dependent on the integrity of remaining areas in both cerebral hemispheres, as assessed by the presence of atrophy at CT scan. Recently, Chollet et al. have performed PET CBF activation studies in patients with recovery from ischaemic hemiparesis. They demonstrated strict lateralisation of focal cortical responses when the normal hand was used, but bilateral foci on movement of the recovered, previously paretic hand.

In conclusion, we observed a relative increase of oxygen metabolism in the lesioned hemisphere in all our patients, affecting the primary lesion and/or areas apparently undamaged by the primary ischaemic insult. The cortical increases correlated with recovery. Motor recovery was least pronounced in those without demonstrable increase in relative cortical oxygen metabolism, intermediate in those with increases in the cortex of the unlesioned side alone and most marked in those with increases in the appropriate, but lesioned hemisphere also. This pattern suggests that motor recovery may be due to the development of new functional connections between brain areas generally associated with motor function. Thus motor recovery is a complex phenomenon in which the lesioned site and other cortical and subcortical areas (in ipsilateral and contralateral hemispheres) that together constitute the distributed neuronal network that normally subserves movement, interplay to help reverse the deficit caused by the infarct. The conclusions of our study must be qualified by the number of patients, the heterogeneity of clinical presentation and the use of steady-state techniques which permit only single estimations of metabolism at one scanning session.

Metabolism is a more direct index of transynaptic activity than cerebral blood flow. However, rCBF can be used effectively to monitor changes of metabolism during activation, whereas rCMRGlu appears uncoupled from local glucose metabolism (rCMRGlutan) under these conditions. In addition rCMRGlu cannot be measured rapidly. This explains why this is the first attempt at a regional analysis of the relative profiles of resting rCMRO₂ in patients recovering from stroke.

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Motor recovery after acute ischaemic stroke: a metabolic study.

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