

# Thalamocortical diaschisis: positron emission tomography in humans

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## Abstract

To investigate further the relations between cortical energy metabolism and neuropsychological impairment after unilateral thalamic lesion, 55 patients underwent positron emission tomography studies of either cortical oxygen consumption or glucose utilisation, including eight repeat studies, at times ranging from 4 days to 98 months after the onset of the lesion [stroke (n = 44) or stereotaxic VL-Vim thalamotomy performed for movement disorders (n = 11)]. Patients with thalamotomy were also studied preoperatively and the surgery induced a significant fall in cortical metabolism on both sides (more so ipsilaterally); post-operatively the magnitude of the ipsilateral cortex hypometabolism was positively correlated to the severity of global neuropsychological impairment; similar but less significant findings were obtained for the ipsilateral/contralateral cortical metabolic asymmetry. With respect to the whole patient sample, the cortical metabolic asymmetry was initially pronounced, with subsequent mono-exponential recovery, in the cognitively impaired study group, but it was only mild and showed no meaningful trend for recovery in the cognitively unaffected study group; yet even soon (<3 months) after thalamic lesion there was a noticeable overlap of individual asymmetry values among the two study groups. These results lend further support to the view that the neuropsychological impairment that frequently follows unilateral thalamic lesions is reflected in a depression of synaptic activity in both the overlying and the contralateral cerebral cortices. For individual patients, this study also illustrates the potentially misleading nature of the measured cortical metabolic asymmetry with respect to neuropsychological status, especially at late times after lesion, in part because side to side metabolic ratios do not reflect bilateral changes.

(*J Neurol Neurosurg Psychiatry* 1992;55:935-942)

In patients with subcortical stroke positron emission tomography (PET) commonly shows reduced metabolic rates of glucose or oxygen in the ipsilateral cerebral cortex relative to the contralateral side.<sup>1</sup> Although this functional effect on the ipsilateral cortex may partly underlie neuropsychological deficits of sub-

cortical origin,<sup>2</sup> support for this hypothesis to date is inconclusive.<sup>3-9</sup> Specifically, discrepancies have been reported between neuroimaging and neuropsychological status, such as the presence of cortical metabolic asymmetry in neuropsychologically intact (or recovered) patients<sup>3,7</sup> or its lack in neuropsychologically impaired patients.<sup>8,9</sup> This unresolved issue is of some importance because if "subcortical" neuropsychological impairment is indeed partly subtended by cortical hypometabolism (diaschisis<sup>10</sup>), brain metabolism could be manipulated pharmacologically, with the aim of enhancing the rate and extent of functional recovery.<sup>11</sup>

Unilateral thalamic stroke is a suitable model to test this hypothesis because the overlying cortex has a different arterial supply and is anatomically distant from the damaged area, thus reducing potentially confounding issues; previous follow up studies of patients with thalamic stroke have shown a significant trend for progressive normalisation of cortical hypometabolism and side to side asymmetry.<sup>3,8</sup> In addition, comparison with healthy controls suggested that not only the ipsilateral but also the contralateral cerebral cortex was hypometabolic<sup>3</sup>; if confirmed, these bilateral effects could possibly account for the above mentioned discrepancies between side to side metabolic asymmetry and neuropsychological status.

The goal of this study was to investigate further the relation between neuropsychological impairment and cortical metabolism after unilateral thalamic lesions. To this end, two complementary approaches were used. In the first, patients with movement disorder in whom a stereotaxic thalamotomy was planned were evaluated cognitively and by PET both before and after surgery; because this approach allows each patient to act as his/her own control it is ideally suited to investigate directly the brain metabolic effects of unilateral thalamic lesion in humans, as well as their relations to cognitive impairment. In the second approach we further investigated the controversial issue of the relations between the occurrence of cognitive impairment and the magnitude and time course of cortical metabolic asymmetry in a large sample of patients with thalamotomy or unilateral thalamic stroke.

## Patients and methods

### Patients

From 1983 to 1988, 55 consecutive patients were included in this study (tables 1 and 2)

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Received 19 December 1990  
and in final revised form  
5 May 1992.

Accepted 13 May 1992

Table 1 Clinical features of patients with thalamic stroke

Case (No/age/sex)	Nature of lesion	Side	CT scan	MRI scans	Approximate location	Initial clinical findings	Interval since onset	Neuropsychological impairment*		
								Language	Memory	Neglect
1/52/M	I	L	1	1	M	Coma	12 Days	+	O	O
2/54/M	H	L	1	1	M	Coma, aphasia	28 Days	O	++	O
3/50/M	H	L	1	1	M	Headache-obtundation, diplopia, right hemiparesis	2 Months	++	++	O
4/58/M	H	L	1	1	M	Headache, stupor, right hemiplegia	{ 2 Months 5 Months	O	+	O
5/61/M	I	R	1	U	M	Left hemiparesis and hypesthesia	24 Days	O	O	++
6/48/M	I	L	1	U	PL	Right hemiparesis and aphasia	13 Months	+	+	O
7/59/M	I	L	1	U	PL	Right hemiparesis, RLHH	7 Days	++	O	O
8/59/M	I	R	1	1	PL	Left hemitaxia and hemiparesthesiae	9 Months	O	O	O
9/59/M	H	R	1	1	PL	Left sided paresthesiae	4 Days	O	O	O
10/38/M	I	L	1	1	PL	Right hemiparesis and hypesthesia, dysarthria, aphasia, stupor	14 Days	+	+	O
11/47/M	H	L	1	U	CT	Right cerebellar ataxia	7 Days	O	O	O
12/64/F	H	L	1	1	CT	Stupor, right hemiparesis, amnesia-dysarthria	50 days	O	++	O
13/40/F	H	L	1	1	CT	Right ataxia, right hemiparesis, amnesia	{ 34 Days 7 Months	+	+++	+
14/51/F	H	L	1	1	CT	Right hemiparesis and hypesthesia, aphasia-amnesia	{ 38 Days 5 Months	++	++	O
15/53/F	H	L	1	U	CT	Right hemiparesis	27 Days	+	+	O
16/53/F	H	L	1	1	CT	Right sided paresthesiae	19 Months	O	O	O
17/76/M	H	R	1	1	CT	Left hemiparesis and hypesthesia	24 Days	O	++	+
18/64/M	H	R	1	1	CT	Coma, Left hemiparesis	1 Year	O	+	O
19/70/M	H	R	1	1	CT	Left hemiparesis and hypesthesia, amnesia	14 Months	O	O	O
20/61/M	H	R	1	1	CT	Left hemiparesis, LLHH, aphasia	{ 2 Months 8 Months	++	+	++
21/63/M	H	R	1	U	CT	Left hemiparesis and hypesthesia	7 Months	+	+	+
22/78/F	H	R	1	1	CT	Left hemiparesis, LLHH, neglect	10 Days	O	O	+
23/58/F	I	L	1	1	AM	Left hemiparesis, diplopia—mild language impairment	18 Days	+	O	O
24/45/M	I	L	1	1	AM	Left cerebellar ataxia, diplopia amnesia	5 Years	O	O	O
25/40/F	I	R	1	1	AM	Dizziness, vomiting, left lateropulsion, diplopia, paraesthesiae right face	22 Days	O	O	O
26/74/M	I	L	1	1	AM	Left Horner's syndrome, aphasia, amnesia, right hemiparesis	1 Month	+	+	O
27/76/F	I	R	1	1	AM	Stupor, III <sup>rd</sup> nerve palsy	1 Month	O	++	+
28/41/M	I	L	1	1	AM	Obtundation, aphasia	9 Days	++	++	O
29/63/M	I	R	1	U	AM	Headache, stupor, left hemiparesis, LLHH	20 Days	++	+	O
30/72/F	I	L	1	1	VPL	Painful paresthesiae	4 Years	O	O	O
31/57/F	I	R	1	1	VPL	Left painful paresthesiae	9 Years	O	O	O
32/53/M	I	R	1	1	VPL	Left sided paresthesiae, LLHH	5 Years	O	O	O
33/76/F	I	L	1	1	VPL	Right sided paresthesiae	21 Days	O	O	O
34/51/F	I	R	1	1	VPL	Left hemiparesis and hypesthesia	2 Months	O	O	O
35/72/F	I	R	1	1	VPL	Left hemiparesis and hypesthesia	11 Days	O	O	O
36/62/M	I	L	1	1	VPL	Right hemihypesthesia	37 Days	O	O	O
37/55/M	I	L	1	1	VPL	Right sided paresthesiae	9 Months	O	O	O
38/64/M	I	R	1	1	VPL	Left sided paresthesiae	7.5 Months	O	+	O
39/54/F	I	R	1	1	VPL	Left sided paresthesiae	7 Months	O	+	O
40/60/F	I	L	1	U	A	Left ptosis, left Horner's syndrome, amnesia, confusion, aphasia	20 Months	O	++	O
41/57/F	I	L	1	U	A	Stupor, right facial paresis, diplopia	2 Months	+	+	O
42/59/F	I	L	1	U	A	Right hemiparesis, aphasia	42 Days	+++	?	O
43/70/M	I	R	1	1	A	Stupor, left visual and sensory neglect, amnesia	5 Years	O	+	+
44/86/F	H	R	1	U	P	Left visual and sensory neglect	40 Days	O	O	+

M = male; F = female; I = infarct; H = haemorrhage; L = left; R = right; MRI = magnetic resonance imaging; 1 = available; U = unavailable; M = medial; PL = posterolateral; CT = capsulo thalamic; AM = anteromedial; VPL = ventroposterolateral; A = anterior; P = pulvinar; LLHH = lateral homonymous hemianopia; O = no deficit; +, ++, +++ = mild, moderate, and severe deficit, respectively; ? = impairment impossible to evaluate.  
\*Rated at time of PET scan.

Table 2 Clinical features of patients with thalamotomy

Case (No/age/sex)	Side	CT scan	MRI	Clinical findings (post-thalamotomy)	Interval since surgery	Neuropsychological impairment*		
						Language	Memory	Neglect
45/50/M	Left	1	1	Memory impairment	15 Months	O	+	O
46/64/M	Left	1	1	Right motor neglect, confusion	{ 10 Days 2.6 Months	++	+	O
47/48/M	Left	U	1	Right hemi-hypesthesia	{ 22 Days 8 Months	O	O	O
48/66/F	Right	U	1	Left hemiparesis and hypesthesia, amnesia	{ 63 Days 10 Months	++	++	O
49/58/M	Right	U	1	Neglect	3 Months	O	O	+
50/66/F	Left	1	1	—	7 Days	O	O	O
51/54/M	Left	U	1	Amnesia	70 Days	O	++	O
52/55/M	Right	U	1	Hypesthesia, left hand	56 Days	O	O	O
53/60/M	Left	U	1	—	1 Month	O	O	O
54/53/M	Left	1	1	Confusion, aphasia	{ 16 Days 13 Months	++	+++	O
55/59/M	Right	I	U	—	1.5 Months	?	?	?

M = male; F = female; MRI = magnetic resonance imaging; 1 = available; U = unavailable; O = no deficit; +, ++, +++ = mild, moderate and severe deficit, respectively; ? = impairment impossible to evaluate.  
\*Rated at time of PET scan.

according to three inclusion criteria:

(1) Patients had a first thalamic or thalamocapsular stroke (either ischaemic or haemorrhagic) or had undergone stereotaxic thalamotomy (aimed at the nucleus ventralis lateralis (VL) and the nucleus ventralis intermedius (Vim)) for control of disabling tremor.<sup>12</sup> Associated infarction in the cortical territory of the posterior cerebral artery (four patients) or in one cerebellar hemisphere (two patients) was not a reason for exclusion. Candidates for thalamotomy were excluded from the protocol if they were cognitively impaired or if multiple sclerosis or head trauma was the cause of tremor.

(2) Patients had a lack of detectable lesion in the contralateral thalamus as assessed by computed tomography (49 patients) or magnetic resonance imaging (MRI), or both (44).

(3) Patients had negative results on cervical Doppler ultrasonography. This excluded patients with significant disease of the carotid artery.

Overall, 44 patients with thalamic stroke (ischaemic in 27 and haemorrhagic in 17) and 11 with VL-Vim thalamotomy (performed for right sided hemiparkinsonism in seven patients, for left sided hemiparkinsonism in three, and for severe bilateral action tremor in one who was operated on the right side) were enrolled in this study (which included the 10 patients with stroke initially reported on<sup>3</sup>). A follow up PET study was obtained in eight patients, four with stroke and four with thalamotomy. In addition, 10 of the 11 patients with thalamotomy underwent a PET study before surgery. Thus the total number of PET studies was 73—63 initial post-lesion (including eight patients studied twice) and 10 pre-thalamotomy studies. Overall, 48 studies involved patients with stroke and 25 patients with thalamotomy. The time between thalamic lesion and PET ranged from 4 days to 98 months, but the studies were performed more often early than late after the lesion (thus 40 studies were performed within the first five months and 23 later). The clinical and neuropsychological data are summarised in tables 1 and 2.

#### *PET studies*

##### METHODS

Because of the protracted time (six years) over which this large patient sample was recruited, consistency of the PET procedure could not be ensured. Thus two different PET cameras were used successively: the ECAT II single ring device (about 19 mm axial and 16 mm lateral resolution) in the 20 initial studies, and the LETI-TTV01 camera four ring (seven slices about 13 mm resolution, both axial and lateral) in the subsequent 53 investigations. The PET studies were performed with reference and parallel to the orbitomeatal (OM) line, centred at levels OM + 15, + 35, and + 55 mm with the ECAT II camera, and at levels OM - 5, + 10, + 25, + 40, + 55, + 70, and + 85 mm with the LETI-TTV01 camera. Each study involved attenuation correction using measured <sup>68</sup>Ge-<sup>68</sup>Ga transmission scans,

and radial artery catheterisation for measurement of blood and plasma radioactivities, blood gas tensions, oxygen saturation, and plasma glucose concentrations. Cerebral energy metabolism was measured according to the in vivo autoradiographic method using <sup>18</sup>F-fluoro-2-deoxy-D-glucose<sup>13</sup> (FDG) or the steady state method using oxygen-15<sup>14</sup>; these methods measure the cerebral metabolic rates of glucose (CMR Glu) and oxygen (CMR O<sub>2</sub>) respectively, according to standardised procedures implemented in our laboratory and detailed elsewhere.<sup>15 16</sup> Overall, FDG and oxygen-15 studies were performed in 43 and 30 investigations, respectively. A previous study of thalamic stroke found that the cortical metabolic asymmetry is of the same magnitude regardless of the method used,<sup>3</sup> in agreement with earlier investigations that had shown that the normal coupling between CMR Glu and CMR O<sub>2</sub> is not disrupted in hypometabolic remote structures-diaschisis<sup>17</sup>; likewise, there was no significant difference in the cortical metabolic changes measured by either CMR Glu or CMR O<sub>2</sub> (also obtained using two different PET cameras) in progressive supranuclear palsy, a "subcortical" dementia.<sup>18</sup> In our current study PET studies of patients with thalamotomy were exclusively carried out with the LETI-TTV01 camera in conjunction with FDG (in case 47, however, only CMR O<sub>2</sub> could be obtained preoperatively).

##### PET DATA ANALYSIS

For each side of the brain we measured the effects of unilateral thalamic lesions on whole cortex metabolic rates as earlier work has shown that thalamic stroke induces an essentially diffuse cortical hypometabolism.<sup>3 19 20</sup> Thus two brain levels, obtained in all studies regardless of the PET device used, were selected: at the level of the basal ganglia level (OM + 35–40 mm) and corona radiata (OM + 55 mm). On these images sets of circular (about 3 cm<sup>2</sup>) regions of interest were visually positioned over the cortical rim, tangentially to each other as well as to a 30% computer derived isocontour lining the outer contour of the cortex<sup>21</sup> (in the four patients with associated occipital infarction, the regions of interest overlying the infarcted area and the contralateral homologous regions were excluded from analysis). From the original values obtained on both brain levels two weighted average cortical metabolic values were obtained, one for the side ipsilateral and one for the side contralateral to the lesion; this allowed ipsilateral/contralateral cortical metabolic ratio (MR) to be calculated.

##### *Neuropsychological assessment*

A neuropsychological evaluation was obtained in all instances within two weeks of the PET study and was repeated in patients with follow up PET studies. It consisted of both a comprehensive standard test battery and tests more sensitive to thalamic related deficits. The standard test battery comprised (a) the Wechsler memory scale, the verbal scale (from the Wechsler adult intelligence scale), and Raven's

progressive matrices, which provided the memory, verbal, and performance IQs, respectively; (b) Visuospatial and visual memory tests (Rey's figure); and (c) standard language (fluency, denomination, comprehension) and calculation tests. The specific tests consisted of (a) the differential assessment of visual and verbal memory, as described in Baron *et al.*,<sup>3</sup> and (b) the assessment of hemi-neglect in right thalamic lesions, using standard tests for visual, sensory, and motor neglect, as well as tachistoscopies and dichotic listening tests in patients with uncertain clinical findings. With respect to patients with thalamotomy ( $n = 10$ ; the preoperative PET study was unavailable in case 45), the values for memory IQ, verbal IQ, performance IQ, verbal memory, and visual memory were normalised to a standard control value of 10; this allowed a "neuropsychological composite score" to be calculated as the average of these five normalised items. Then we calculated the percentage change in the composite score, as well as that in the verbal IQ, verbal memory, and visual memory, before and after thalamotomy (in three patients in whom a preoperative neuropsychological assessment was unavailable the corresponding scores were estimated by using the average performance obtained in controls of similar age range and educational level). With respect to patients with thalamic stroke, only a qualitative neuropsychological assessment could be obtained in the severely affected subjects, and items of the quantitative battery were missing in a few others. Thus in the global data analysis that included both stroke and thalamotomy cases (see below), only a semiquantitative approach was possible. Based on the neuropsychological-clinical evaluation performed at the time of the PET study, the status with respect to language, memory, and neglect was rated as impaired (mild, moderate, or severe impairment) or intact by two investigators (JCB and ML) unaware of the subject's metabolic data (tables 1 and 2). This in turn allowed the overall cognitive status to be classified as impaired if impairment was present in at least one of these three items and as intact otherwise. Out of 63 post-lesion PET studies, and using this simple binary classification, there were 41 PET studies carried out in patients with a neuropsychologically impaired state and 21 in patients with a neuropsychologically intact state. One study could not be classified, that of an uneducated, non-French speaking patient with thalamotomy, (case 55), whose cognitive status was impossible to assess. With respect to the eight patients studied twice post-lesion, only one of the seven initially impaired patients had fully recovered at follow up PET study and thus had shifted category (case 4) while the single subject initially intact remained so at repeat PET study (case 47).

#### Statistical data handling

##### THALAMOTOMY SAMPLE

The early post operative values (obtained 7 days to 3 months after surgery, mean 41 days) were compared with the corresponding pre-

operative values obtained in the same subjects using standard paired  $t$  tests (two tailed); this was applied to the absolute metabolic rates on the lesioned and on the opposite side, as well as to the lesioned/contralateral metabolic ratios. Percentage changes (from preoperative to post-operative) in CMR Glu both on the lesioned and on the opposite side, as well as changes in lesioned/contralateral metabolic ratios, were calculated and compared with the corresponding percentage changes in the composite neuropsychological score. Finally, percentage changes in verbal IQ, verbal memory, and visual memory were tested against corresponding changes in left or right hemisphere CMR Glu.

Significant correlations were sought using both Pearson's linear regressions and the more conservative Spearman's test, in which linearity is not an assumption, using two tailed  $p$  values.

##### WHOLE SAMPLE

For the whole patient sample (both thalamotomies and strokes), the MR values were plotted against the time elapsed since the lesion occurred; this was done separately for the neuropsychologically impaired and the neuropsychologically intact studies. Because previous work suggests a time dependence of the cortical metabolic asymmetry after thalamic lesion,<sup>3,8</sup> a simple comparison of mean metabolic asymmetries (obtained at widely different times after the lesion) between neuropsychologically impaired and intact studies would be statistically inadequate. Thus to compare these two samples, the time from lesion was taken into account by fitting the PET data to a monoexponential model of recovery, which accurately describes the cortical metabolic recovery that follows lesions of the nucleus basalis of Meynert (NbM) or anterior callosotomy in baboons<sup>22,23</sup>; monoexponential models are also widely used to describe recovery of neuropsychological function.<sup>24</sup> Thus the unweighted ipsilateral/contralateral MRs in neuropsychologically impaired and neuropsychologically intact studies were separately subjected to least square fitting according to the following model of metabolic recovery.<sup>22</sup>

$$MR = MR_{\text{final}} + (MR_{\text{initial}} - MR_{\text{final}})e^{-t(\ln 2)/T_{1/2}}$$

where MR is the fitted metabolic ratio at time  $t$ ,  $MR_{\text{final}}$  and  $MR_{\text{initial}}$  the fitted metabolic ratios at  $t = a$  and  $t = 0$ , respectively, and  $T_{1/2}$  the fitted half recovery time. With this approach, we hypothesised that the data from the neuropsychologically impaired studies would be fitted to this model with clinically meaningful results—that is, substantial increment of the fitted MR within a clinically reasonable recovery period. To this end, the fitted MR at  $t = 2$  years ( $MR_{2 \text{ years}}$ ) was calculated based on the fitted parameters, and compared with  $MR_{\text{initial}}$ . Only if clinically meaningful (according to the above definition) would a set of data then be subjected to the bootstrap procedure,<sup>25</sup> which is designed to assess the variance in the fitted parameters; this procedure is based on repeated fits on subsets

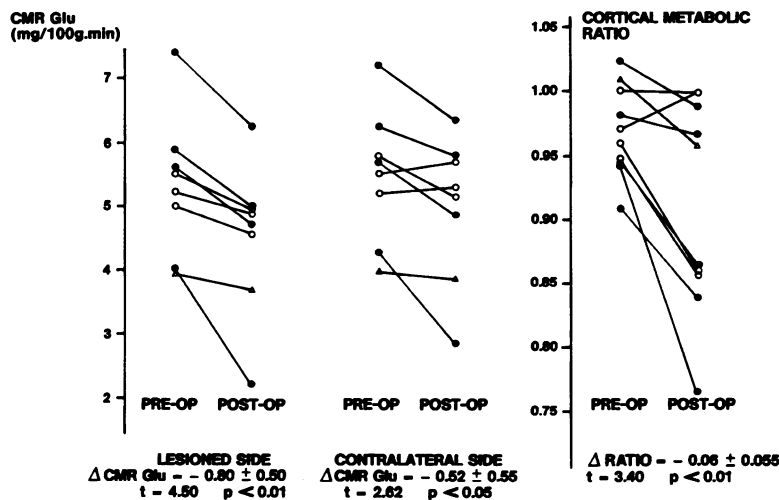


Figure 1 Absolute rates of glucose utilisation (CMR Glu) measured in the cerebral cortex ipsilateral (lesioned) and contralateral to stereotaxic thalamotomy, and cortical metabolic ratio (lesioned/contralateral) in the preoperative and first postoperative (0.2 to 13.6 months post-op) PET studies, respectively. The lines join the pre-op and post-op values measured in the same subject (of the series of 10 patients, the pre-op and post-op CMR Glu values of eight are shown, as in one case the oxygen consumption was measured preoperatively because of technical failure, and in another the postoperative FDG-PET study was non-quantitative; however, the cortical metabolic ratios of these two patients could be used for comparing pre-op and post-op values). The statistical analysis by paired two tailed t test showed significant reductions of CMR Glu on both sides, (indicated as  $\Delta$  CMR Glu, in units of mg/100 g.min) as well as significant appearance of cortical metabolic asymmetry, in the post-op study. Black circles represent the patients who were cognitively impaired after thalamotomy, open circles represent cognitively unaffected patients, and open triangles the single patient whose cognitive performance was impossible to assess (case 55).

of experimental data and takes account of the heterogeneity of data sampling over time.

The above procedure was not applied to the CMR O<sub>2</sub> and the CMR Glu data because of the well known variability in these measurements and the lack of strict control on time since onset in the present series. In contrast, because it is assumed close to unity before occurrence of thalamic lesion (see fig 1), the ipsilateral/contralateral metabolic asymmetry

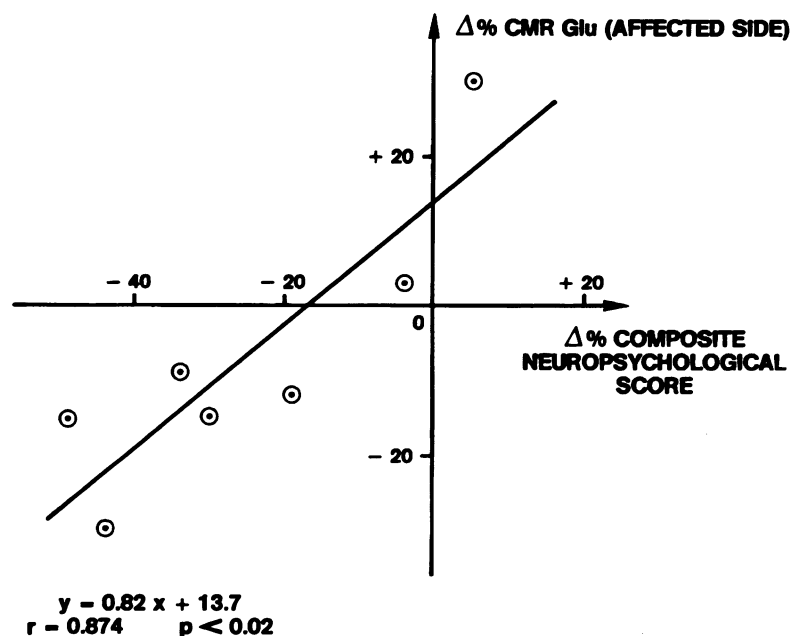


Figure 2 Significant linear correlation between percentage changes (before and after stereotaxic thalamotomy) in glucose utilisation of the ipsilateral cerebral cortex and in composite neuropsychological score, as measured in seven patients (see results).

normalises for this variability and allows all PET studies to be combined regardless of the metabolic parameter measured and PET camera used; this procedure thus allows comparison of the two patient samples (cognitively intact/impaired) in terms of initial metabolic asymmetry and subsequent recovery.

**Results**

**THALAMOTOMY SAMPLE**

Absolute CMR Glu values were obtained both before and after surgery in eight patients. There was a significant fall in cortical metabolic rates on both sides after thalamotomy, more conspicuous on the operated ( $p < 0.01$ ) than on the contralateral side ( $p < 0.05$ ). This asymmetrical effect resulted in the significant appearance of cortical metabolic asymmetry in the postoperative period ( $p < 0.01$ ) in 10 patients (including case 47 with a preoperative CMR O<sub>2</sub> study and case 51, in which CMR Glu could not be measured postoperatively and the linearly proportional asymmetry in FDG uptake was used instead; the significance of results was not altered when these two cases were omitted). These results are shown in figure 1.

The percentage changes in ipsilateral cortical CMR Glu were positively correlated with the corresponding changes in composite neuropsychological score (fig 2) in a significant way ( $p = 0.01$  and  $p < 0.05$  by Pearson's and Spearman's test, respectively); no significant relation was obtained for the contralateral hemisphere. The changes in ipsilateral/contralateral metabolic ratio were also positively correlated (though less strongly) with the changes in composite neuropsychological score ( $p = 0.03$  and  $p = 0.06$  by Pearson's and Spearman's tests, respectively) (fig 3). The percentage changes in left hemisphere cortical CMR Glu were positively, but weakly, correlated with the corresponding changes in verbal memory, verbal IQ, and visual memory ( $p = 0.015$ ,  $p < 0.05$ , and  $p < 0.05$  respectively, by Pearson's test; none significant by Spearman's test); no significant correlations were observed when changes in right hemisphere CMR Glu were considered.

*Metabolic ratios (whole sample)*

There was a clear cut difference in the initial time course of MR values between neuropsychologically impaired and intact studies. For instance, 16 out of 28 and 3 out of 11 MRs measured in the first three months after lesion were below 0.90 (which represents the lower 95% limit for the MR in controls<sup>3</sup>) in the impaired and intact groups, respectively (fig 4). After this time, differences were less clear, indicating a trend for gradual recovery of the MR from initially low values in the neuropsychologically impaired group, compared with only slightly reduced MRs that were stable over time in the neuropsychologically intact group.

Fitting a monoexponential recovery model to the data confirmed these differences between the neuropsychologically impaired and the neuropsychologically intact studies

(fig 4). In the neuropsychologically intact studies, the fitting procedure yielded clinically meaningless results, with  $MR_{initial}$  only mildly reduced (0.950) and showing essentially no change at 2 years ( $MR_{2\text{ years}} = 0.953$ ); the fitted  $T_{1/2}$  was 38 months. Conversely, the findings in the neuropsychologically impaired group were clinically meaningful; thus the  $MR_{initial}$  was significantly reduced (0.884, 95% confidence interval 0.82 to 0.95) and there was a clear cut recovery at 2 years ( $MR_{2\text{ years}} = 0.930$ ); the fitted  $T_{1/2}$  was 3.5 months (2.7 to 4.3 months) and the  $MR_{final}$  was 0.935 (0.93 to 0.94). However, despite those clear cut differences in MR values between the two sets of data, there was a considerable overlap in the experimental data (fig 4). Thus, in the first three months after thalamic lesion many neuropsychologically impaired patients had symmetrical cortical metabolism, while several neuropsychologically intact patients showed a notable metabolic asymmetry; beyond a value for asymmetry of about 0.85, however, neuropsychological impairment was a consistent feature. At later times this overlap became increasingly more pronounced as an effect of recovery in the cognitively affected group; at the longest times a mild metabolic asymmetry of almost similar magnitude persisted in both groups (fig 4).

### Discussion

This study demonstrates (a) that unilateral electrocoagulation of the VL-Vim nucleus induces a widespread, but preferentially ipsilateral, depression of cortical energy metabolism and (b) that the magnitude of these metabolic effects in the cerebral cortex is proportional to the degree of postoperative neuropsychological impairment. The issue of recovery of these cortical metabolic effects in relation to cognitive impairment was evaluated by analysing in a large sample of patients with thalamotomy or stroke, the ipsilateral/contralateral cortical metabolic ratio as a function of both time since lesion onset and the

presence or absence of cognitive impairment; this ratio was initially more reduced in the cognitively impaired group and tended subsequently to slowly recover in a monoexponential fashion. Overall, therefore, this study lends further support to the concept that initial cognitive impairment after thalamic lesion is related to synaptic dysfunction in the overlying cerebral cortex and that recovery of the synaptic dysfunction may underlie or reflect the subsequent cognitive improvement.

Our findings in patients with stereotaxically placed thalamic lesions confirm that damage to the thalamus itself is capable of inducing cortical hypometabolism<sup>9</sup> and point to a role for the cortical afferents originating from the VL-Vim nucleus in the development of thalamocortical diaschisis. In addition, our study experimentally confirms previous data on humans indicating that unilateral thalamic damage induces bilateral metabolic depression,<sup>3</sup> analogous to the effects of stereotaxic NbM lesions in baboons.<sup>22</sup> The favoured hypothesis for such contralateral, presumably indirect, effects classically implies a transcallosal spread of the ipsilateral metabolic effects,<sup>10</sup> but this mechanism has been disputed recently.<sup>23</sup>

We found that after unilateral VL-Vim thalamotomy changes in the composite neuropsychological score (an index of global cognitive performance) correlated significantly with alterations in both ipsilateral CMR Glu and, less strongly, cortical metabolic asymmetry (figs 2 and 3). However, the search for more specific cognitive-metabolic correlations was less fruitful; thus, although changes in verbal IQ and verbal memory were associated with parallel reductions in left cortical metabolism, the actual correlations were only marginally significant, while the visual memory score paradoxically tended to correlate with the left but not the right hemisphere CMR Glu. Although these findings may partly reflect the fact that our study design did not allow for investigating hypometabolism in functionally selective zones of cerebral cortex, they nevertheless imply that the cortical metabolic effects of unilateral thalamic lesions, which are widespread and bilateral, presumably underlie global cognitive impairment. This may account for the often poorly specific memory and behavioural impairment that characterises unilateral thalamic lesion in the acute stage (table 1).<sup>26</sup>

This finding of a significant relation between cortical hypometabolism and global neuropsychological impairment after unilateral thalamic lesion is consistent with previous cognitive-metabolic investigations. Thus, significant linear correlations between cortical metabolic and corresponding neuropsychologic right-left asymmetries or anteroposterior gradients have been reported in studies of dementia of the Alzheimer type.<sup>27-29</sup> In progressive supranuclear palsy Blin *et al* found a weak but significant correlation between relative frontal hypometabolism and a clinically assessed frontal lobe score.<sup>18</sup> After subcortical stroke both Metter *et al*,<sup>6</sup> and Karbe *et al*,<sup>4</sup> found sig-

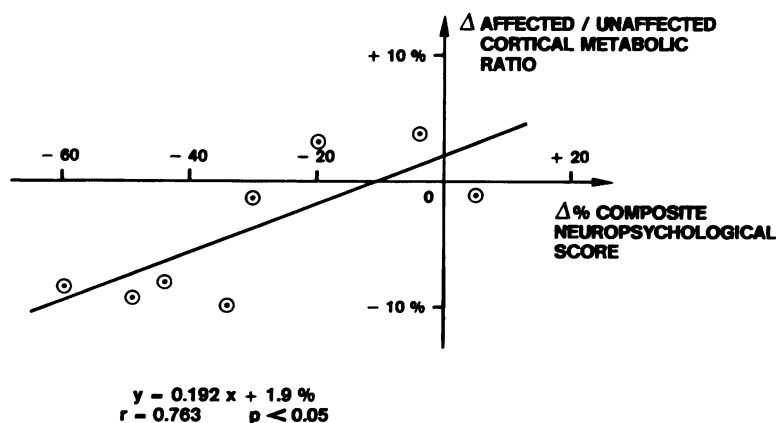


Figure 3 Significant linear correlation between change (before and after thalamotomy) in the affected/unaffected cortical metabolic ratio and the percentage change in composite neuropsychological score, measured in eight patients with stereotaxic thalamotomy (see results).

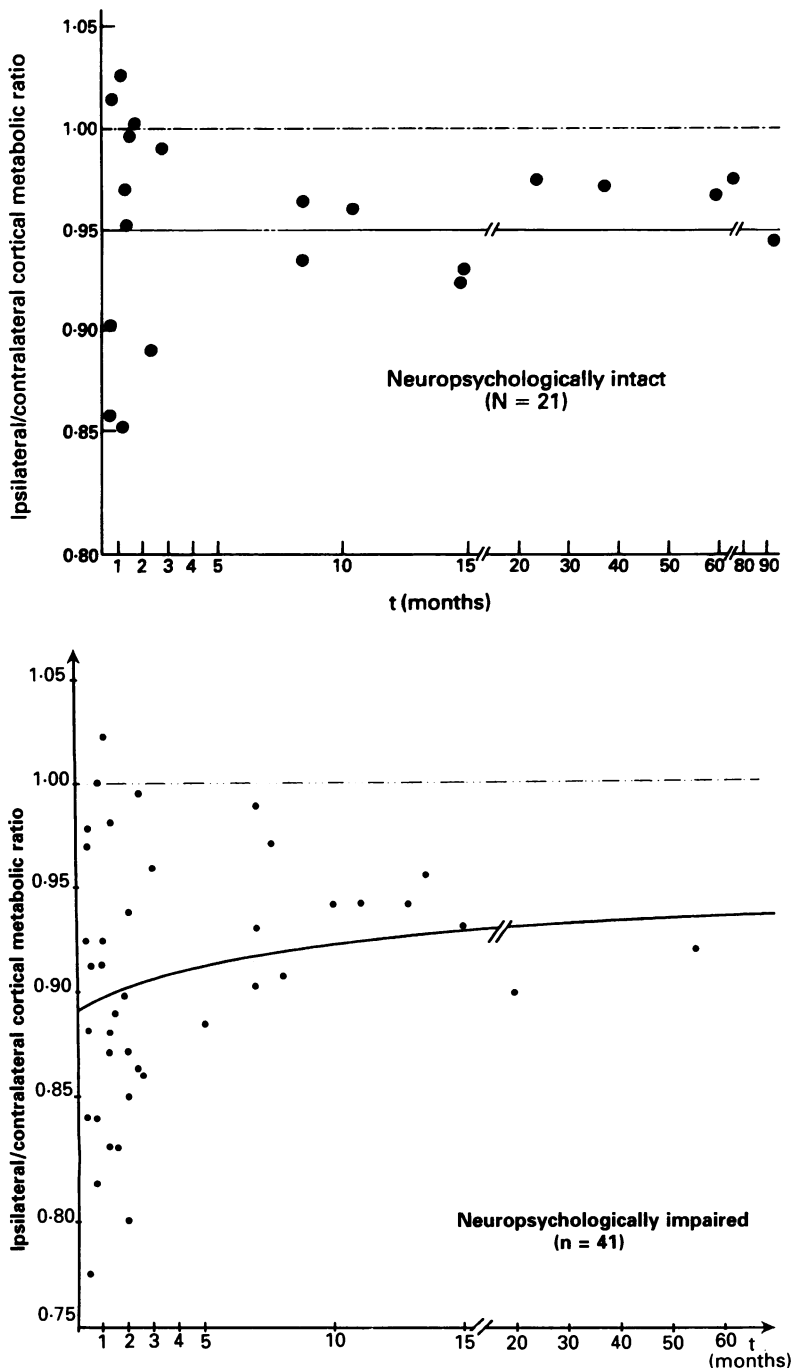


Figure 4 Plot of the affected/unaffected cortical metabolic ratio as a function of time from onset of thalamic lesion, obtained in 21 and 41 studies while patients were either neuropsychologically intact (top) or neuropsychologically impaired (bottom). The continuous lines represent the best fit according to a monoexponential model (see methods), showing clinically meaningful recovery in the neuropsychologically impaired but not the neuropsychologically intact study groups. Note large overlap among data from the two patient groups, except for ratios below 0.85 seen only in the cognitively affected studies.

nificant correlations between left parietotemporal and lateral-frontal metabolic rates or asymmetries and measures of language comprehension and fluency. In a study of single photon emission computed tomography of left thalamic stroke Rousseaux *et al* found significant correlations between verbal fluency and perfusion in the left frontal cortex, as well as between verbal comprehension, object naming, and paraphasias and left temporooccipital cortex perfusion.<sup>5</sup> Thus in various clinical situations cortical metabolic depression is

associated with neuropsychological/behavioural impairment. However, non-proportionality and threshold effects may well exist, and the issue of specificity has rarely been addressed. In support (of a negative nature), Pappata *et al*,<sup>9</sup> and Chabriat *et al*,<sup>30</sup> have documented unaltered cortical metabolism in cognitively intact patients with small internal capsule (posterior limb) and posterolateral thalamic infarcts, respectively.

Although the present as well as earlier studies of subcortical lesions indicate that cortical hypometabolism participates in the mechanism of neuropsychological impairment, the important and direct role of the subcortical structures should not be overlooked. Thus, significant correlations have been reported between intellectual performance and caudate metabolism in Huntington's disease,<sup>31</sup> and between some aspects of language dysfunction and caudate or thalamic hypometabolism in brain infarction.<sup>32,33</sup> Using PET and pathway analysis in aphasic patients, Metter *et al* showed both a direct and an indirect (through frontal hypometabolism) role of structural damage to left thalamus and basal ganglia in impaired verbal fluency.<sup>6</sup> Thus, in subcortical lesions the observed cortical hypometabolism is but part of a more widespread synaptic derangement and presumably reflects dysfunction in the highest order element common to several distributed parallel neuronal networks.<sup>34</sup>

Although it would ideally have to be definitively established by a large scale longitudinal evaluation, the gradual recovery of initial cortical metabolic asymmetry documented here in the cognitively affected group confirms our preliminary reports on thalamic stroke;<sup>3,8</sup> it is also reminiscent of findings in baboons subjected to unilateral NbM lesion that indicated a monoexponential recovery from initial cortical metabolic asymmetry.<sup>22,35</sup> The fact that the appreciable cortical metabolic asymmetry present initially in cognitively impaired subjects tended to recover subsequently in conjunction with improvement in cognitive status, compared with the lack of such changes in cognitively intact subjects, expands our initial reports<sup>3,8</sup> and that of others.<sup>26</sup> Overall, these findings suggest that recovery of cortical metabolism underlies the often prominent cognitive improvement induced by unilateral subcortical lesions.

In the individual subject, however, the results of the present study clearly illustrate the lack of strict concordance between cortical metabolic asymmetry and cognitive status. Thus, even early (<3 months) after thalamic lesion there was a considerable overlap in whole cortex metabolic ratios among cognitively affected and unaffected studies (fig 4), with several cognitively affected patients showing no metabolic asymmetry, and vice versa (this should not detract from the fact that there exists a weakly significant linear relation between cortical metabolic asymmetry and global cognitive changes in the initial post-thalamotomy stage, as shown in fig 3). At later times this overlap became even more pronounced,

reflecting recovery of metabolic asymmetry in the cognitively impaired group. Finally, in the long term a mild cortical asymmetry of almost similar magnitude was present in both groups, a metabolic "scar" possibly reflecting irreversible degeneration of some thalamocortical terminals. Thus in individual cases the degree of cortical metabolic asymmetry is not a good marker for neuropsychological impairment, in agreement with previously reported discrepancies such as cognitively unaffected patients showing a significant cortical metabolic or perfusional asymmetry<sup>3, 18, 37</sup> and affected patients having normal images.<sup>8, 9</sup> Such discrepancies may be partly related to the fact that the depression in cortical metabolism that occurs after unilateral thalamic lesion is bilateral and recovers at a slower rate than does the metabolic asymmetry.<sup>37</sup> Thus the need to obtain quantitative physiological values to evaluate bilateral effects on brain function when using imaging techniques such as PET and single photon emission computed tomography must be emphasised. Yet, simple assessment of individual side to side asymmetry may retain some value in the early stages (< 3 months) after thalamic stroke because pronounced reductions in the ipsilateral contralateral metabolic ratio below a value of about 0.85 were consistently associated with cognitive impairment in our sample.

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