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Motor recovery after stroke
Morphological and functional brain alterations

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Summary
The aim of this study was to evaluate the relationships of morphological and CBF patterns with both the severity and the evolution of the motor deficit in the late phase of stroke and, in particular, to identify morphological and/or functional brain alterations associated with a persistent severe motor deficit or a poor, delayed motor recovery. We analysed CT/MRI and single photon emission tomography (SPET) findings from 37 patients studied in the chronic phase of stroke (mean duration±SD=3.6±1.6 months), whom we were able to follow clinically for a period of 3 months. The eventual degree of motor recovery correlated significantly (negatively) with the time since stroke at entry, but not with the severity of neurological impairment at entry. The volume, side and location (cortical or subcortical) of the infarct did not correlate with either the severity or the evolution of the motor deficit. Patients with a CT/MRI lesion of the parietal lobe (n = 8) showed a more severe motor deficit than those with other cortical locations. The severity of the motor deficit correlated significantly (negatively) with CBF values in the supplementary motor area (SMA) and parietal areas of the damaged hemisphere, and in the contralateral undamaged primary motor cortex. The degree of motor improvement correlated significantly (positively) with CBF values in the contralateral undamaged thalamus, lentiform and caudate nuclei, and premotor cortex. In the late phase of stroke, the severity of the motor deficit may be positively associated with the functional impairment of associative parietal and frontal areas of the damaged hemisphere. The functional impairment of the basal ganglia–frontal network in the undamaged hemisphere seems to be related to a poor, delayed motor recovery.

Keywords: motor deficit; motor recovery; stroke; single photon emission tomography; cerebral blood flow

Abbreviations: CBF = cerebral blood flow; SPET = single photon emission tomography; SMA = supplementary motor area

Introduction
Recovery from a motor deficit caused by stroke is a complex, multifactorial process. Following the acute phase of stroke, in which regression of oedema and reperfusion of areas of ischaemic penumbra are probably the decisive factors, other mechanisms such as neuronal rearrangements and adaptive responses have been hypothesized to explain the slow but steady improvement in motor function, which may go on for many months (Goldstein and Davis, 1990).

Recent studies, using activation PET methodology, suggest that motor recovery is in part due to the extension of motor areas in the affected hemisphere, and in part to the recruitment of ipsilateral motor pathways (Chollet *et al.*, 1991; Weiller *et al.*, 1992). It should be borne in mind, however, that these studies were conducted on selected groups of patients who, a few months after stroke, had made an almost complete recovery.

Only a small percentage of patients are left with no, or minimal, disability after a stroke (Stallones *et al.*, 1972; Gresham *et al.*, 1975; Gresham *et al.*, 1979). Most patients show a more severe and persistent motor deficit which affects their daily activities in varying degrees (Duncan *et al.*, 1992). Classical studies report that the restitution of motor function occurs spontaneously within the first 2 months after injury (Twitchell, 1951; Van Buskirk, 1954). The motor improvement may go on for up to one year, albeit to a lesser degree (Ahlsio *et al.*, 1984; Kotila *et al.*, 1984). If we assume that spontaneous motor recovery is generally completed within the first 2 months, we need to address the question of

which processes subsequently lead to the further improvement observed in some patients.

In a previous work, we observed a significant correlation between motor deficit severity at 2–6 months after stroke and the hypoperfusion of the structurally intact contralateral SMA (Pantano *et al.*, 1995). Similarly, motor recovery was found to be associated with the metabolic improvement in associative motor areas of the damaged hemisphere in patients studied by PET in both the acute and chronic phases of stroke (Di Piero *et al.*, 1992). These findings could be meaningful for the prognostic evaluation of hemiplegic stroke patients. If regression of the hypometabolism observed in the acute phase of stroke is due to the resolution of ischaemic penumbra, be it spontaneous or therapy-induced, the hypoperfusion in undamaged cerebral areas in the chronic phase may be due to diaschisis, which is potentially reversible as well.

For these reasons, we analysed CT/MRI and SPET findings from 37 patients studied in the chronic phase of stroke (2–7 months), whom we were able to follow clinically for a period of 3 months.

The aim of this study was to evaluate the relationships of morphological and CBF patterns with both the severity and the evolution of the motor deficit in the late phase of stroke, and, in particular, to identify morphological and/or functional brain alterations associated with a persistent severe motor deficit or a poor, delayed motor recovery.

Patients and methods

Thirty-seven stroke patients (18 male and 19 female, mean age±SD = 62.7±11.7) who were hospitalized for motor deficit rehabilitation, were included in the study. Inclusion criteria were: (i) age ranging between 40 and 85 years; (ii) first-ever stroke causing a moderate to severe facio-brachio-crural hemiparesis/hemiplegia; (iii) persistence of the motor deficit which required hospitalization in a rehabilitation centre; (iv) interval since stroke >2 months; (v) single ischaemic lesion in the internal carotid artery territory at CT/ MR scan; (vi) absence of other neurological or psychiatric diseases. At entry, the time elapsed since stroke was 3.6±1.6 months (range 2–7).

All patients were submitted to a neurological evaluation, including the assessment of motor deficit severity by means of the Adams' scale (score from 0 = normal to 28 = hemiplegia; Adams *et al.*, 1987), CT and/or MRI and SPET–CBF study. The Adams' scale was again used to assess the patients' motor deficit after 3 months ($Adams_{(2)}$); an index (%) of motor recovery was then calculated from this and the score ($Adams_{(1)}$) obtained at entry as:

$$[100 \times (Adams_{(1)} - Adams_{(2)})/Adams_{(1)}].$$

All the patients were treated with physical therapy and, when necessary, with specific treatment for neglect or aphasia. Clinical data are shown in Table 1. A Siemens-Somatom CR high-resolution scanner was used for CT scans in 27 patients, while MR images were recorded with a 02 T ESA-TOM Ansaldo PM 5000 in the remaining 10 patients. The extent of the ischaemic lesion was quantified by using a dedicated software that allows the measurement of the lesioned area from CT or MR (T_1) images using a video-display and cursor system, according to a method previously described (Pantano *et al.*, 1993).

Patients were divided into two groups depending on whether the infarct was circumscribed to subcortical structures or also affected the cerebral cortex. A Tomomatic 564 (Medimatic, Denmark) equipped with a high resolution collimator was used for brain activity recording after i.v. injection of 20 mCi of Tc^{99m} hexa methyl-propylene amine oxime. The patient's head was positioned with the orbito-meatal line perpendicular to the floor by using a laser reference system and ink dots on the skin. The head was then fixed to the head holder by tape. The SPET studies were performed at rest (eyes closed, ears unplugged) in a dimly lit room, with external stimuli reduced to a minimum. The scan started 5 min after tracer administration and lasted 25 min. Six to nine transverse slices were obtained from each patient, from the cerebellum to the cortical mantle (slice thickness = 10 mm; interslice centre to centre distance = 20 mm; spatial resolution in the transverse plane = 9 mm).

Data analysis was restricted to 10 cerebral areas involved in motor control (primary motor cortex, premotor cortex, SMA, prefrontal cortex, superior and inferior parietal cortices, caudate nucleus, lentiform nucleus, thalamus and cerebellum), identified on SPET slices on the basis of a reference atlas (Damasio and Damasio, 1989), according to a method previously described (Pantano *et al.*, 1995). In these cerebral areas, an asymmetry index was calculated from the ratio between counts in homologous regions in the damaged (d) and undamaged (u) hemisphere as ($1 - d/u$). For the cerebellum, the side which was contralateral to the supratentorial lesion was considered the damaged one.

However, since this method assumes that the areas of the undamaged hemisphere are normally perfused, whereas evidence exists both of remote effects of the infarct on the contralateral hemisphere (Lenzi *et al.*, 1982; Seitz *et al.*, 1994) and of a possible involvement of the undamaged hemisphere in motor recovery processes (Chollet *et al.*, 1991; Weiller *et al.*, 1992), we completed our analysis by normalizing counts in the 'motor' areas (in both the damaged and undamaged hemisphere) to the visual cortex of the undamaged hemisphere.

Ten age-matched patients with no history of cerebrovascular disease and normal CT scans were used as controls.

Statistical analysis was performed using analysis of variance (ANOVA), simple and stepwise regressions, and non-parametric tests. Owing to the exploratory nature of this study, we decided not to apply any correction for multiple comparisons.

Table 1 *Clinical and neuroradiological data of 37 patients with hemiplegic stroke*

No.	Sex/ age (years)	Months since stroke	Adams score (1)/(2)	Motor recovery (%)	Sensory loss (D/S)	Aphasia/ neglect	Lesion volume (cm^3)	Side	Location
1	M/59	4	7/7	0	−/−	−/−	1.3	R	wm
2	F/70	6	9/9	0	−/−	−/−	38.6	R	wm-Ro
3	M/77	3	9/8	11.1	−/−	−/−	59	R	Ro
4	F/61	6	9/7	22.2	−/+	+/−	25.2	L	wm-bg
5	F/67	7	11/11	0	−/−	+/−	7.9	L	wm
6	M/60	5	12/12	0	−/−	+/−	5.8	L	wm-bg
7	M/72	4	12/12	0	+/+	−/−	2.2	L	wm
8	M/64	2	12/12	0	−/−	+/−	3.8	L	wm
9	M/65	3	12/8	33.3	+/−	−/−	NA	L	NA
10	M/60	2	16/12	25	+/+	−/−	5.3	R	wm
11	M/71	3	16/8	50	−/−	−/−	13.1	R	wm-bg
12	M/43	7	18/18	0	−/−	+/−	108.7	L	wm-bg-Ro
13	M/41	3	18/18	0	+/+	+/−	77.3	L	wm-bg-Ro
14	M/43	4	19/19	0	−/+	−/+	16.5	R	wm-bg-Ro
15	M/62	2	19/13	31.6	+/+	−/+	35.7	R	wm-bg-T
16	M/52	2	20/16	20	−/+	+/−	18.6	L	wm-bg
17	F/65	3	21/18	14.3	−/+	−/−	2.1	L	wm
18	F/49	4	21/21	0	+/+	+/−	34.8	L	wm-bg
19	F/47	2	21/20	4.8	−/+	−/−	7.7	R	wm-T
20	M/56	2	21/19	9.5	+/+	+/−	132	L	wm-bg-Ro
21	F/65	2	21/15	28.6	−/−	−/−	1.3	L	wm
22	F/83	7	21/21	0	−/+	−/+	18.3	R	wm-bg
23	F/73	3	22/22	0	+/+	−/+	121	R	wm-bg-Ro-pF-T-P
24	M/43	3	23/18	21.7	+/+	−/+	94.2	R	wm-bg-Ro-P
25	F/53	2	23/20	13	+/+	+/−	194	L	wm-bg-Ro-pF-P
26	F/60	3.5	23/23	0	+/+	−/+	165.9	R	wm-bg-Ro-T-P
27	M/80	6	23/19	17.4	−/+	+/−	23.1	L	wm-bg
28	F/62	5	25/25	0	−/−	+/−	6	L	wm
29	M/54	2	25/21	16	+/+	+/−	103	L	wm-bg-Ro-P
30	F/73	4	26/26	0	+/+	+/−	6.3	L	wm
31	F/55	3	26/24	7.7	+/+	−/+	35.4	R	wm-bg-Ro-pF-T-P
32	F/61	3.5	27/21	22.2	+/+	+/−	9.4	L	wm-bg
33	F/79	5	27/27	0	+/+	−/+	NA	R	NA
34	F/73	2	28/26	7.1	−/−	−/−	31.5	R	wm-bg
35	M/83	3	28/28	0	+/−	−/+	44.9	R	Ro-P
36	F/62	2.5	28/27	3.6	+/+	−/+	18	R	Ro
37	M/80	3	28/28	0	+/−	−/+	28.6	R	wm-bg-T-P

The Adams score (range 0–28) was assessed at the patient's first neurological evaluation (1) and after 3 months (2). M = male; F = female; D = deep; S = superficial; − = absent; + = present; R = right; L = left; wm = white matter; bg = basal ganglia; Ro = rolandic cortex; T = temporal cortex; pF = prefrontal cortex; P = parietal cortex; NA = images not available.

Results

Clinical features

Detailed clinical data are shown in Table 1. The score obtained using the Adams' scale at entry for the evaluation of the motor deficit was 19.6±6.3 (range 7–28). There was no significant correlation between the severity of motor deficit and the patient's sex or age, or with the time elapsed since stroke.

The motor deficit was associated with visuo-spatial neglect in 11 patients, with aphasia in 15, and with deep and/or superficial sensory loss in 26. The presence of either neglect or deep sensory loss was associated with a more severe motor deficit (P = 0.005 and 0.03, respectively, by Mann–Whitney U test). After 3 months, the Adams' score was significantly lower than at the first evaluation (P = 0.0001 by Wilcoxon signed-rank test). The extent of motor recovery was 10±12%. However, in 18 patients no motor improvement was observed at the second evaluation when compared with the first; in the remaining 19, the extent of motor recovery ranged from 4% to 50%. The group with no motor improvement did not contain patients with significantly more severe motor deficit at entry or a significant higher proportion of cases with sensory disturbances, aphasia or neglect than the group of patients who improved. However, the time elapsed between stroke and the first Adams' evaluation was significantly longer in patients without any motor improvement (4.8±1.5 versus 2.8±1.2 months, $P < 0.001$ by Mann–Whitney U test). The extent of motor recovery, in fact, correlated significantly (negatively) with the time elapsed since stroke (r = –0.326; $P < 0.05$).

Table 2 *Correlation between Adams' score and CBF at entry in 37 stroke patients*

Region	CBF asymmetry		Normalized CBF			
			Damaged hemisphere		Undamaged hemisphere	
	r	*P*	*r*	*P*	*r*	*P*
Cerebellum	0.201	0.23	−0.285	0.09	−0.129	0.45
Thalamus	0.077	0.65	−0.223	0.20	−0.201	0.25
Lentiform nucleus	0.268	0.12	−0.306	0.08	−0.174	0.32
Caudate nucleus	0.230	0.18	−0.250	0.15	−0.178	0.31
Primary motor cortex	0.174	0.30	−0.300	0.07	−0.455	0.005*
Premotor cortex	0.183	0.28	−0.229	0.18	−0.199	0.24
SMA	0.322	0.05*	−0.320	0.05*	−0.107	0 55
Prefrontal cortex	0.245	0.14	−0.279	0.10	−0.141	0.41
Superior parietal cortex	0.344	0.03*	−0.410	0.01*	−0.166	0.33
Inferior parietal cortex	0.470	0.005*	−0.428	0.01*	−0.045	0.80

Cerebral perfusion calculated both as regional asymmetry (1 − *d*/*u*), where (*d*/*u*) is the ratio of CBF in the damaged and undamaged hemisphere and normalized CBF. *Significant correlation.

Since the evaluation of the degree of motor recovery may be affected by a 'ceiling' effect when considering patients with a mild motor deficit at entry, we decided to analyse our data again, excluding patients who showed an $Adams_{(I)}$ score of <12. A score <12 on the Adams' scale is indicative of a mild motor impairement which means such patients have a good degree of autonomy in daily activities.

This further analysis, performed on 28 patients with a moderate to severe motor deficit at entry ($Adams_{(I)}$ score range 16–28), showed the same results, the time since stroke being the only clinical variable which correlated significantly (negatively) with the degree of motor recovery ($r = -0.395$, $P = 0.003$).

CT/MRI findings

The volume of the ischaemic lesion varied greatly (range 1.3–194 cm^3). The lesion was located on the right side in 18 patients and on the left in 19. Two patients, for whom neuroradiological images were not available, were evaluated by means of written reports. Infarcts were purely subcortical in 18 cases, and also affected the cerebral cortex in the remaining 17 cases. Detailed neuroradiological findings are also shown in Table 1.

The volume and the side of the ischaemic lesion did not influence the severity of the motor deficit. Patients with pure subcortical infarcts did not show significant differences in motor deficit severity when compared with patients presenting lesions also affecting the cerebral cortex ($Adams_{(I)}$: 18±6.4 versus 21±5.6). However, a significant difference in motor deficit severity was observed when patients with damage to the cerebral cortex were divided according to whether only the motor areas were affected or whether the damage extended to the parietal lobe. While patients with damage limited to the motor areas ($n = 7$) had values [$Adams_{(I)}$: 17.4±6] which were similar to those of patients with subcortical infarcts, patients with parietal involvement ($n = 8$) had significantly higher values ($P = 0.02$; $Adams_{(I)}$: 24.7±2.3).

The lesions affecting the parietal cortex were not significantly larger than cortical lesions sparing the parietal lobe. A significant association was found between the damage to the parietal lobe and both visuo-spatial neglect and deep sensory loss ($P = 0.001$ and 0.01, respectively, by χ^2).

No patient had a lesion purely of the parietal cortex, and in seven out of eight patients the rolandic area was also damaged. A two-factor ANOVA of the effects of a 'rolandic lesion' and a 'parietal lesion' on $Adams'_{(I)}$ scores showed that the lesion in the parietal cortex, but not in the rolandic one, had a significant effect [$F(1) = 6.16$, $P = 0.01$] without any interaction between the two factors.

The volume and the side of the ischaemic lesion did not influence the evolution of the motor deficit either. No significant differences in the degree of motor recovery were observed between patients with pure subcortical lesions and patients with damage to the cerebral cortex. The coexistance of damage to the parietal cortex did not influence the possibility of further recovery in the following 3 months. This finding was consistent even if the analysis was restricted to the 28 patients with a moderate to severe motor deficit at entry.

CBF findings

In the entire group of 37 patients, the mean values of normalized CBF in the 10 cerebral areas of the damaged hemisphere were significantly lower than the corresponding values in the undamaged hemisphere ($P < 0.005$ by Wilcoxon test) and than control values ($P < 0.01$ by Mann–Whitney *U* test).

Results of regression analysis between Adams' scores and SPET findings are shown in Table 2: significant negative correlations were found with CBF values in the SMA and parietal areas of the damaged hemisphere, and in the primary motor cortex of the undamaged hemisphere.

Figures 1 and 2 show the highly significant negative correlations between the CBF ratios (damaged/undamaged

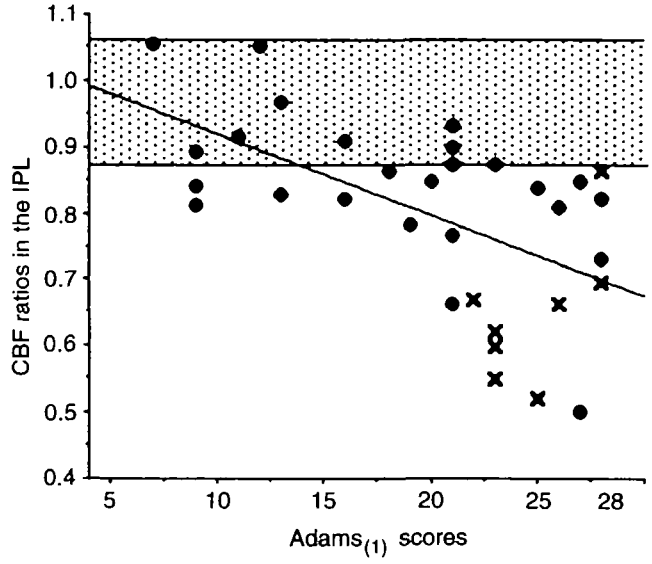

Fig. 1. Simple negative regression between motor deficit, as assessed by the Adams' scale at entry, and CBF ratios in the inferior parietal lobule (IPL) (damaged/undamaged hemisphere) of 37 stroke patients. Crosses indicate patients with structural damage to the parietal lobe. The hatched area represents the 95% confidence intervals of the mean of CBF ratios in the inferior parietal lobule in controls.

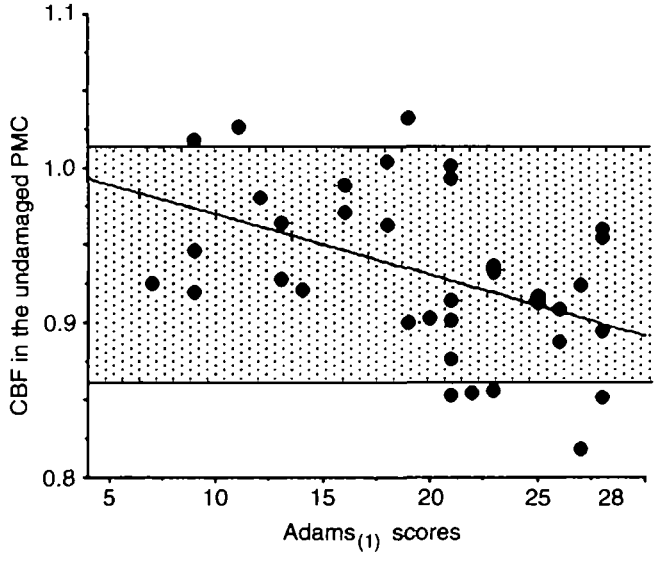

Fig. 2 Simple negative regression between motor deficit, as assessed by the Adams' scale at entry, and normalized CBF values in the primary motor cortex (PMC) of the undamaged hemisphere of 37 stroke patients. The hatched area represents the 95% confidence intervals of the mean of normalized CBF values in the primary motor cortex in controls.

hemisphere) in the inferior parietal lobule and the normalized CBF in the undamaged primary motor cortex and motor deficit severity. Stepwise regressions of normalized CBF in these two regions with all the other 19 regions of both hemispheres showed significant positive associations between the inferior parietal lobule of the damaged hemisphere and the ipsilateral premotor area (coefficient $\beta = 0.664 \pm 0.117$, $P < 0.001$) and contralateral inferior parietal cortex ($\beta = 0.742 \pm 0.35$, $P < 0.02$) and between the primary motor cortex of the undamaged hemisphere and the ipsilateral superior parietal cortex ($\beta = 0.546 \pm 0.104$, $P < 0.001$).

The extent of motor recovery in the group of 37 patients (taken as a whole) did not correlate with the values of cerebral perfusion in the 10 brain areas analysed. However, when we excluded patients with a mild motor deficit at entry from the analysis, the CBF values from the thalamus, lentiform nucleus, caudate nucleus and premotor cortex of the undamaged hemisphere were found to correlate significantly (positively) with the motor improvement. The results of linear regression between the degree of motor recovery and the normalized CBF values (in the 28 patients with an $Adams_{(I)}$ score of >12) are shown in Table 3.

Figure 3 shows the highly significant positive correlation between the CBF in the caudate nucleus of the undamaged hemisphere and the degree of motor recovery. None of the many variables analysed, i.e. motor deficit severity, time elapsed since stroke, volume, side and location (cortical or subcortical) of the infarct, structural damage to the cortical motor or parietal areas, was significantly associated with low CBF values in the caudate nucleus of the undamaged hemisphere. Stepwise regression of normalized CBF in the caudate nucleus of the undamaged hemisphere with all the other 19 regions of both hemispheres showed a significant positive association with CBF levels in the ipsilateral thalamus ($\beta = 0.492 \pm 0.07$, $P < 0.001$) and prefrontal cortex ($\beta = 0.757 \pm 0.19$, $P < 0.001$).

Discussion

The processes underlying motor function recovery are not yet completely known. It is possible to use PET activation studies to show which cerebral areas are involved in movement execution in patients who have recovered from motor stroke (Chollet *et al.*, 1991; Weiller *et al.*, 1992; Weiller *et al.*, 1993). However, the question remains whether some patients, in whom the improvement of motor function is absent or partial, have any structural or functional brain alteration which may be incompatible with recovery.

From a clinical point of view, the possibility of identifying those patients who can benefit from rehabilitation in the late phase of stroke is relevant to the costs of hospitalization and rehabilitation therapy (Feigenson *et al.*, 1978; Oster *et al.*, 1994; Smurawska *et al.*, 1994). At the present time, there are no data to guide selection of stroke patients for specific interventions (Wade, 1992).

Clinical features

The age of the patient, considered to be a good prognostic indicator in the acute phase of stroke (Fiorelli *et al.*, 1995), was not found to be associated with either the severity or the improvement of the motor deficit in our patients who

Table 3 Correlations between motor improvement and CBF at entry, in 28 stroke patients with moderate to severe motor deficit at entry (Adams' score >12)

Region	CBF asymmetry		Normalized CBF			
			Damaged hemisphere		Undamaged hemisphere	
	r	*P*	*r*	*P*	*r*	*P*
Cerebellum	−0.233	0.23	0.331	0.09	0.154	0.44
Thalamus	−0.086	0.67	0.328	0.10	0.426	0.02*
Lentiform nucleus	−0.282	0.16	0.332	0.09	0.375	0.05*
Caudate nucleus	−0.249	0.21	0.336	0.09	0.607	0.001*
Primary motor cortex	−0.309	0.10	0.346	0.07	0.251	0.20
Premotor cortex	−0.251	0.20	0.312	0.11	0.372	0.05*
SMA	−0.272	0.17	0.185	0.36	0.111	0.59
Prefrontal cortex	−0.148	0.45	0.205	0.30	0.302	0.12
Superior parietal cortex	−0.230	0.23	0.244	0.22	0.069	0.73
Inferior parietal cortex	−0.203	0.33	0.242	0.21	0.304	0.15

Cerebral perfusion calculated both as regional asymmetry and normalized CBF. *Significant correlation.

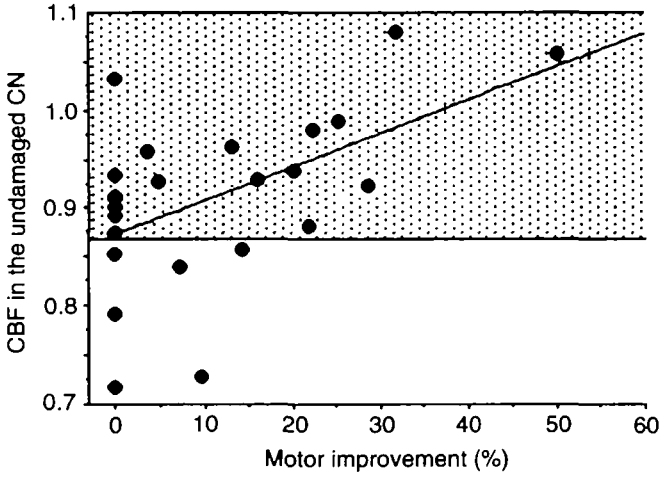

Fig. 3 Simple positive regression between motor improvement and normalized CBF values in the caudate nucleus (CN) of the undamaged hemisphere in 28 stroke patients with a moderate to severe hemiparesis at entry (Adams' score >12). The hatched area represents the 95% confidence intervals of the mean of normalized CBF values in the caudate nucleus in controls.

were studied in the late phase of stroke; our observation is in agreement with other studies (Hier *et al.*, 1983; Schenkman *et al.*, 1983).

Our study suggests that in patients still presenting a motor deficit 2–7 months after stroke, the possibility of motor recovery in the 3 months following the enrolment in the study, is independent of the severity of the residual motor deficit but is significantly negatively correlated with the time elapsed since stroke. This finding further supports the need to start rehabilitation in stroke patients as soon as possible, and also suggests that little or no improvement can be expected after 4 months; this is in keeping with studies indicating that motor recovery has reached its final level 8–12 weeks after a stroke (Andrews *et al.*, 1981; Skillbeck *et al.*, 1983).

Clinical studies suggest that the concomitant presence of visuo-spatial deficits have an influence on outcome (Kotila *et al.*, 1984; Formisano *et al.*, 1993). This finding was confirmed by the present study in which patients with a persistent visuospatial neglect and/or deep sensory loss showed a more severe motor deficit at entry. Motor improvement in nine out of 11 patients with neglect was either absent or minimal (<10%). These findings, together with the close association with parietal damage, suggests that the lack of information on the left-side intra- and extrapersonal space and/or the orientation and position of the body parts in the space can constitute a further obstacle to the reorganization of movement. This interpretation is supported by experimental evidence that sensory inputs are integrated in the posterior parietal association cortex of the monkey with behavioral acts in the immediate extrapersonal space (Mountcastle *et al.*, 1975).

Morphological findings

We found that the volume, side and location (cortical or subcortical) of the lesion did not correlate with either the severity or delayed improvement of motor function. The relationship between CT findings and clinical recovery has been previously studied. Kotila *et al.* (1984) reported that in their series of 154 stroke patients, the outcome at 3 and 12 months did not differ between patients with left and right hemispheric lesions.

In recent studies, no association between cortical or subcortical site, or lesion size, and clinical outcome was observed (Schenkman *et al.*, 1983; Dromerick and Reding, 1995). In a clinical study on recovery of function after lesions restricted to the right hemisphere, Hier *et al.* (1983) found that recovery from constructional apraxia and visuo-spatial neglect was more rapid in patients without injury to the frontal lobe, whereas patients without injury to the parietal lobe recovered more quickly from extinction and leg weakness. These authors concluded that the sparing of

anatomical structures adjacent to the site of injury is important in the recovery from certain deficits, whereas damage to them may delay the emergence of compensatory mechanisms. Similarly, our results indicate that damage to the parietal lobe is associated with a more severe motor deficit 2–7 months after stroke, which would be expected in patients with a poor recovery in the first phase of stroke. Parietal damage did not, however, preclude the possibility of a delayed improvement in motor function, observed in four out of eight patients with an infarct also affecting the parietal cortex.

Functional findings

In our attempt to identify other factors of importance in predicting the possibility of motor recovery in the chronic phase of stroke, we also analysed SPET–CBF findings. We observed that patients with motor deficit following stroke had many cerebral areas which were hypoperfused even if spared by the structural lesion, as previously demonstrated by emission tomography studies in stroke patients (Baron *et al.*, 1986; Pantano *et al.*, 1986; Metter *et al.*, 1987; Perani *et al.*, 1988). However, only the CBF in the SMA and parietal areas in the damaged hemisphere, and in the primary motor cortex in the undamaged hemisphere, were significantly correlated (negatively) with the severity of the motor deficit. Moreover, the undamaged hemisphere seems to play an important role in motor recovery, as is suggested by the fact that the CBF in the thalamus, caudate nucleus, lentiform nucleus and premotor cortex was significantly positively correlated with the improvement observed during the 3 month period of study.

In the damaged hemisphere, the primary motor and premotor cortices were probably functionally compromised in all the patients by lesions in different sites, as shown by CT/MR images. Consequently, the additional impairment of other structures, such as the SMA and the parietal lobe, assumes a special role in the persistence of a severe motor deficit.

The importance of the SMA in motor recovery is supported by studies showing its role in the motor system both in a hierarchic and parallel organization, through efferents both to the primary motor cortex (Strick, 1988) and directly to the spinal cord (Biber *et al.*, 1978; Fries *et al.*, 1993). Moreover, the functional involvement of the SMA, which has been demonstrated in the reorganization of cortical motor areas after damage of the primary motor cortex (Aizawa *et al.*, 1991), may explain the negative correlation between CBF in the SMA and motor deficit severity.

Fibre connections between motor areas and parietal association areas are well documented (Godshalk *et al.*, 1984; Petrides and Pandya, 1984; Cavada and Goldman-Rakic, 1989). Our stepwise analysis seems to assign particular importance to the connections between the inferior parietal lobule and the ipsilateral premotor cortex, in agreement with experimental results indicating that the arcuate premotor area in macaques receives inputs from parietal area 7 (Strick, 1988). This area, equivalent to the human inferior parietal lobule (Mountcastle *et al.*, 1975), has been shown to participate in the control of visually guided arm movements (Lynch *et al.*, 1977).

In 10 patients who recovered from their striato-capsular motor stroke, Weiller *et al.* (1992) found that CBF at rest was decreased in many areas of the damaged hemisphere and increased in some areas of the undamaged hemisphere when compared with normals. The existence of these abnormal CBF patterns at rest, however, was not clearly associated with motor deficit since all their patients had recovered well and could move their previously paretic hand at the time of the PET studies.

The movement of the recovered hand induced a significant CBF increase in many areas of both cerebral hemispheres, some of which, such as the lower parietal cortex of the damaged hemisphere, had normal CBF at rest. It is interesting to compare the role of the inferior parietal lobule in our study with that in the study of Weiller *et al.* (1992); they found that CBF in this area in patients who had recovered was normal at rest, but increased during the movements of the recovered hand. We found, in patients who had not recovered, a low CBF at rest in the inferior parietal lobule. It could be argued that the inferior parietal lobule plays an essential role in the improvement of motor function in the first months after stroke, while its structural and/or functional involvement may be associated with the persistence of a severe motor deficit. In our data the blood flow in the parietal areas of the undamaged hemisphere was not correlated with either the severity or the degree of improvement of the motor deficit, indicating that the CBF at rest in this region is not predictive of motor recovery, despite the fact that this same area was found to be activated during the movement of the previously paretic hand by Weiller *et al.* (1992).

Our results are quite different from those obtained by Seitz *et al.* (1994), who found that the depression of glucose metabolism in the putamen of the lesioned hemisphere and in the contralateral cerebellum was significantly correlated with motor impairment in 28 patients with a first-ever hemiparetic stroke. In our previous work (Pantano *et al.*, 1995), we found that hypoperfusion in these structures was associated with the persistence of muscular flaccidity after stroke, regardless of the motor deficit severity. In the present work, both the lentiform nucleus and cerebellum showed low CBF levels not significantly associated with either a more severe hemiparesis or a less marked motor improvement. These data are in accordance with those reported by the Caen PET group on the relationship between cerebellar hypometabolism and stroke outcome (Serrati *et al.*, 1994). They found that in the acute phase (within 5–30 h of onset) the cerebellar metabolism and the neurological outcome (or recovery at day 60) were neither strongly nor consistently correlated; they were correlated in the subacute phase (13–56 days later), but this finding became non-significant when the effect of lesion size was taken into account.

Our data also point to a link between the functional activity of the undamaged hemisphere and motor function. The CBF levels in the primary motor cortex of the undamaged hemisphere correlated negatively with the severity of the motor deficit, while CBF in the deep grey structures, i.e. the thalamus, caudate and lentiform nuclei, and the premotor cortex correlated positively with the motor improvement after 3 months. The role of the ipsilateral cortico-spinal pathways in the recovery processes has already been suggested by experimental (Bucy *et al.*, 1966), clinical (Glees, 1980) and emission tomography (Chollet *et al.*, 1991; Weiller *et al.*, 1992; Sabatini *et al.*, 1994) studies.

The possibility of delayed motor improvement seems to be related to the functional activity of deep grey structures, particularly the caudate nucleus and its cortical projections to the frontal lobe. It is interesting to note that these areas, i.e. the caudate nucleus, premotor and prefrontal cortices of the undamaged hemisphere, were also found to be activated during movement execution in patients who made an early complete recovery (Weiller *et al.*, 1992).

The caudate nucleus and the associative frontal cortex, which are linked by well-defined anatomical connections (Goldman and Nauta, 1977; Yeterian and Hasen, 1978; Alexander *et al.*, 1986), might represent a functional cognitive network whose functional integrity is necessary in both early spontaneous and delayed rehabilitation-induced motor recovery after stroke. This concept is further supported by the fact that striatal dysfunction in humans appears to affect aspects of mood, motivation, attention, learning and behavioural programming (Cummings and Benson, 1984). The reason for the reduction of CBF in the caudate nucleus of the undamaged hemisphere in some patients, however, remains poorly understood.

Our work may provide useful information on brain alterations associated with motor deficit in the late phase of stroke, when some improvement in motor function is still possible. Many points, however, need to be elucidated and further studies are necessary, especially in selected groups of patients in whom a better motor recovery is observed.

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